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ABSTRACT SUPPLEMENT

2013 ANNUAL MEETING

October 25–30, 2013
San Diego, CA

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

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AMERICAN COLLEGE OF RHEUMATOLOGY
ABSTRACT SUPPLEMENT

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

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

AMERICAN COLLEGE OF RHEUMATOLOGY
77th Annual Meeting

ASSOCIATION OF RHEUMATOLOGY HEALTH PROFESSIONALS
48th Annual Meeting

October 25-30, 2013
San Diego, CA

The supplement was not financed by profit-making organizations or by organizations representing for-profit interests. The editorial and peer review processes were handled entirely by the American College of Rheumatology (ACR) according to its peer review process for abstracts submitted for presentation at the ACR Annual Meeting.

ACR/ARHP 2013 Annual Meeting Overall Needs Assessment/Practice Gaps

The American College of Rheumatology and the Association of Rheumatology Health Professionals are committed to providing comprehensive education to improve the knowledge and performance of physicians, health professionals and scientists. Through evidence-based educational programs, the organization strives to enhance practice performance and improve the quality of care in those with or at risk for arthritis, rheumatic and musculoskeletal diseases. The 2013 annual meeting program has been developed independent of commercial influence.

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

Program Highlights

- Educational tracks to help attendees identify content targeted to them. Tracks include: basic science, business/administration, clinical practice and clinical science.
- Latest science and best-practices presented through peer-reviewed and selected clinical and scientific abstracts, and invited speakers providing clinical, evidence-based and quality focused content.
- Diverse formats of education delivery, including: didactic lectures, debates, and interactive sessions, such as poster tours, Meet the Professors and Workshop sessions.
- A larger forum for discussion of practical management issues such as the Curbside Consults – Ask the Professors session.
- Extensive learning opportunities in the basic science of rheumatology, an area of the program developed by a subcommittee of US and internationally prominent basic scientists.
- Clinical management sessions, including the Thieves' Market, Curbside Consults – Ask the Professors, The Great Debate and the ACR Knowledge Bowl.
- Specific pediatric rheumatology content integrated throughout the program designed to provide a high-level educational program to pediatric rheumatologists; and relevant updates to adult rheumatologists.
- Formal presentations of new practice guidelines provided to alert the membership and explain, in an open forum, the data supporting the guidelines and propose approaches for implementation.
- Over 35 workshops designed to provide hands-on skills training.

For additional details, refer to the session level learning objectives at www.ACRannualmeeting.org.

About The Annual Meeting

Participation Statement

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Global Learning Objectives

At the conclusion of the 2013 ACR/ARHP Annual Meeting, participants should be able to:

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

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ACR Poster Session A
Antiphospholipid Syndrome: Clinical Manifestations and New Biomarkers in Antiphospholipid Syndrome
Sunday, October 27, 2013, 8:30 AM–4:00 PM

1

Anti-β2GP1-Domain-1 Antibodies Are a Marker Of APS Severity. Nancy Agmon-Levin[1], Luciana Seguro[2], Cristina Rosário[3], Michael Mahler[4], Mariele Gatto[5], Nir Tomer[6], Elaine P. Leon[7], Andrea Doria[8], László Kovács[9], Nathalie Costedoat-Chalumeau[10], Boris Gilburd[11] and Yehuda Shoenfeld[12]. [1]The Zabludowicz Center for Autoimmune Diseases, Tel-Hashomer, Israel, [2]Division of Rheumatology, University of São Paulo School of Medicine, Sao Paulo, Brazil, [3]Internal Medicine Department, Hospital de Pedro Hispano, Rua Dr. Eduardo Torres Matosinhos, Porto, Portugal, [4]INOVA Diagnostics, San Diego, CA, [5]Department of Medicine, University of Padova, Padova, Italy, [6]The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel, [7]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [8]University of Padova, Padova, Italy, [9]University of Szeged, Szeged, Hungary, [10]Hopital Cochin, Paris, France, [11]The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel, [12]Sheba Medical Center, Ramat Gan, Israel.

Background/Purpose: Autoantibodies targeting Domain-1(D1) of beta-2-glycoprotein-1(β2GP1) are common among patients with the antiphospholipid syndrome (APS)[1]. However, few studies assessed their clinical relevance and correlation with other anti-phospholipid antibodies (aPLA). Thus, in the current study we evaluated the correlations between anti-β2GP1-D1 levels and APS clinical and serological parameters.

Methods: Serum samples of 178 APS patients, 50 healthy subjects and 47 patients diagnosed with sepsis were utilized to determine levels of IgG-antibodies to cardiolipin(aCL), β2GP1 and β2GP1-D1 (BIO-FLASH®, INOVA). Demographic, clinical and serological (i.e. Lupus anticoagulant (LAC)) data were analyzed.

Results: Among APS patients aCL, anti-β2GP1 and anti-β2GP1-D1 were present in 60%, 70% and 49%, respectively. The presence of anti-β2GP1-D1 antibodies correlated with the presence of LAC (91 vs. 67%; $p<0.001$), aCL (98 vs. 23%; $p<0.001$). Triple aPLA positivity was present in 89% of anti-β2GP1-D1 positive sample compared with 16% among anti-β2GP1-D1 negative samples ($p<0.001$). Anti-β2GP1-D1 antibodies correlated with higher titers of aCL antibodies ($p<0.001$) and anti -β2GP1 ($p=0.03$).

Anti β2GP1 antibodies correlated with the occurrence of venous thrombosis ($p< 0.009$). Anti-β2GP1-D1 positivity (>20CU) related to the occurrence of any thrombotic event (91% vs. 79% OR 2.54; 95% CI 1.05–6.15; $p=0.039$). Medium levels of anti-β2GP1-D1 (>30CU) correlated with arterial thrombosis (55% vs. 33% OR=2.5; 95%CI 1.37–4.67; $p = 0.006$). High levels of anti-β2GP1-D1 (>64CU) were associated with multiple thrombotic events (62% vs. 31% OR 3.58; 95%CI 1.49–8.61; $p=0.005$) arterial thrombosis (60% vs. 33% OR 3.04; 95%CI 1.61–5.73; $p=0.001$) and CNS manifestations (45% vs. 27% OR 1.99; 95%CI 1.03–3.81; $p=0.038$).

Conclusion: In our cohort of APS patients, anti-β2GP1-D1 antibodies were a marker of high risk aPLA profile. Moreover their presence, particularly in med-high levels correlated with repeated thromboses, arterial occlusion and CNS-related manifestations. Thus, anti-β2GP1-D1 may potentially serve as a biomarker of thrombosis in APS.

[1] Mahler M, et al Autoimmun Rev. 2012;12(2):313–7.

Disclosure: N. Agmon-Levin, None; **L. Seguro**, None; **C. Rosário**, None; **M. Mahler**, Inova Diagnostics, Inc., 3; **M. Gatto**, None; **N. Tomer**, None; **E. P. Leon**, None; **A. Doria**, None; **L. Kovács**, None; **N. Costedoat-Chalumeau**, None; **B. Gilburd**, None; **Y. Shoenfeld**, None.

2

Charaterization Of Micrornas Involved In The Regulation Of Atherothrombosis In Antiphospholipid Syndrome and Systemic Lupus Erythematosus. Chary Lopez-Pedrera Sr.[1], Patricia Ruiz-Limon[1], Raul Teruel[2], Ángeles Aguirre Zamorano[1], Rosario M. Carretero-Prieto[1], Nuria Barbarroja[1], Antonio Rodriguez-Ariza[1], Eduardo Collantes-Estevez[1], Rocio gonzalez-Conejero[2], Constantino Martinez[2], M[a] Jose Cuadrado[3] and Carlos Perez-Sanchez[1]. [1]IMIBIC-Reina Sofia Hospital, Cordoba, Spain, [2]Regional Centre for Blood Donation, University of Murcia, Murcia, Spain, [3]The Rayne Institute, London, United Kingdom.

Background/Purpose: miRNAs are key players in pathophysiological processes, but no previous studies have investigated their asscociation with the cardiovascular and atherothrombotic risks observed in primary antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE).

The aim was to characterize the miRNAs involved in pro-inflammatory, prothrombotic and pro-oxidative status in SLE and APS patients.

Methods: In silico search was performed and six putative miRNAs regulating factors involved in the proinflammatory and pro-oxidative status of APS and SLE patients (miR-124a, -125a, -125b, -146a, -155, and -222) were selected and quantified by RT-PCR in neutrophils and monocytes from 11 APS and 17 SLE patients, and 26 healthy donors. Pro-inflammatory and prothrombotic proteins and oxidative stress markers were evaluated by flow cytometry. Proteins related to the biogenesis of miRNAs were quantified by RT-PCR and Western Blot.

Results: Expression of selected miRNAs was significantly decreased in neutrophils from SLE and APS patients compared to healthy donors. However, only miR-124a was found significantly reduced in monocytes from SLE and APS patients. The expression of those miRNAs negatively correlated with autoimmunity-related parameters (anti-dsDNA and aCL-IgG), disease activity (SLEDAI), inflammation (IL-2, -6, -8 and MCP-1) and oxidative stress (peroxides). Low levels of specific miRNAs in neutrophils and monocytes from both SLE and APS were found further associated with thrombotic events and pathological carotid intima media thickness. This selective decrease miRNA expression was related to a significant reduction in the expression of miRNAs biogenesis genes (Xportin-5, Drosha, Dicer, Ago-1 and Ago-2) in neutrophils from APS and SLE patients compared to healthy donors. I*n vitro* treatment of healthy monocytes with purified antiocardiolipin antibodies from APS patients caused a significant decrease in the levels of miR-124a. Notably, when this miRNA was transfected into monocytic THP-1 cells a significant decrease (~30%) in MCP-1, STAT3 and p38 expression was observed, pointing at these proteins as potential targets of miR-124a.

Conclusion: 1. Decreased expression of a number of miRNAs in monocytes and neutrophils from APS and SLE patients correlates with autoimmunity, inflammation, thrombosis and oxidative stress and atherothrombotic markers. 2. A down-regulation of miRNA processing might explain the low expression of evaluated miRNAs in APS and SLE neutrophils. 3. Antiocardiolipin antibodies directly regulate miR-124a expression, which is directly involved in the proatherosclerotic profile of APS and SLE patients.

Disclosure: C. Lopez-Pedrera Sr., None; **P. Ruiz-Limon**, None; **R. Teruel**, None; **Aguirre Zamorano**, None; **R. M. Carretero-Prieto**, None; **N. Barbarroja**, None; **A. Rodriguez-Ariza**, None; **E. Collantes-Estevez**, None; **R. gonzalez-Conejero**, None; **C. Martinez**, None; **M. J. Cuadrado**, None; **C. Perez-Sanchez**, None.

3

The Global Antiphospholipid Syndrome Score (GAPSS) In Primary APS. Savino Sciascia[1], Giovanni Sanna[2], Veronica Murru[3], Dario Roccatello[1], Munther A. Khamashta[3] and Maria Laura Bertolaccini[3]. [1]Centro di Immunopatologia e Documentazione su Malattie rare, Torino, Italy, [2]Louise Coote Lupus Unit, St. Thomas' Hospital, London, United Kingdom, [3]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom.

Background/Purpose: Antiphospholipid Syndrome (APS) is a heterogeneous entity with a wide variation in clinical course and laboratory profile. We aimed to evaluate the clinical utility of GAPSS (Global APS Score) in a cohort of primary APS patients. GAPSS is derived from the combination of independent risk for thrombosis and pregnancy loss (PL), taking into account the antiphospholipid antibodies (aPL) profile, the conventional cardiovascular risk factors, and the autoimmune antibodies profile.

Methods: This study included 62 consecutive with primary APS. Data on clinical manifestations, conventional cardiovascular risk factors, and antiphospholipid antibodies profile were collected. GAPSS scoring system was calculated for each patient by adding together the points corresponding to the risk factors, based on a linear transformation of the corresponding β regression coefficient as follows: 3 for hyperlipidemia, 1 for arterial hypertension, 5 for aCL IgG/IgM, 4 for anti-β2GPI IgG/IgM, 3 for aPS/PT IgG/IgM and 4 for LA.

Results: Higher values of GAPSS were showed in patients who experienced thrombosis alone compared to those with pregnancy loss (PL) alone (11.5 ± 4.6 and 8.7 ± 3.2,$p=0.0378$). Patients with both thrombosis and pregnancy loss showed higher GAPSS compared to those pregnancy loss alone (12.5 ± 4.6 vs 8.7 ± 3.2,$p=0.0152$). Higher values were also shown sub-grouping for the site of thrombosis, compared to pregnancy loss alone

(12.2±5.2, for arterial thrombosis; 12.±4.0 for venous and 8.7±3.2, p=0.0214 and p=0.0472, respectively). Patients with thrombotic recurrences showed higher values of GAPSS compared to those without (13.7±3.1Vs 9.4±3.9,p=0.0205, respectively). Higher values were also seen when comparing recurrences Vs no recurrences according to the site of thrombotic event (13.9±3.6 and 11.0±4.3,p=0.0143 for arterial; 13.6±2.18 Vs 8.91±3.6,p=0.001, for venous events, respectively).

GAPSS values higher or equal to 11 were strongly associated with higher risk of recurrences (OR 18.27 [95%IC 3.74–114.5] for cut off 11, OR 20.64[3.92–185.92] for cut off 12, 21.64[3.89–189.56] for cut off 15, respectively. GAPSS values higher or equal to 11 seemed to have the best accuracy, in terms of sensitivity and specificity.

Conclusion: GAPSS is demonstrated to be a valid tool to a substantial improvement in risk stratification for thrombosis in primary APS, also in terms of recurrences.

Disclosure: S. Sciascia, None; **G. Sanna**, None; **V. Murru**, None; **D. Roccatello**, None; **M. A. Khamashta**, None; **M. L. Bertolaccini**, None.

4

Proteomic Analyses Of Monocyte Responses To IgG From Patients With Antiphospholipid Syndrome. Vera M. Ripoll, Anastasia Lambrianides, Wendy Heywood, Anisur Rahman, Yiannis Ioannou and Ian Giles. University College London, London, United Kingdom.

Background/Purpose: Antiphospholipid syndrome (APS) is an autoimmune disorder characterised by recurrent vascular thrombosis (VT) and/or pregnancy morbidity (PM) caused by antiphospholipid antibodies (aPL). Whilst aPL are known to activate monocytes by inducing production of tissue factor and pro-inflammatory cytokines, upstream mechanisms leading to this pattern of cellular activation are not fully understood. There is evidence that aPL from VT and PM patients stimulate different monocyte intracellular pathways but these have not been characterised in detail. We therefore carried out proteomic analysis of human monocytes treated with IgG from VT, PM and healthy controls (HC) using two different techniques.

Methods: Human monocytic cell line U937 and healthy monocytes were treated with 200 μg/ml of IgG purified from patients with VT, PM or HC. Proteomic analysis was performed using two dimensional difference gel electrophoresis (2D DiGE) and Label Free Quantitative LC-MS/MS. Differentially upregulated proteins were identified by mass spectrometry and validated using quantitative PCR (qPCR) and western blotting.

Results: The table shows the numbers of proteins whose expression in 2D DiGE analysis was regulated by at least two-fold (up or down) in cells exposed to VT IgG or PM IgG compared to HC IgG.

	U 937	Healthy monocytes
VT IgG	41 upregulated, 11 downregulated	119 upregulated, 21 downregulated
PM IgG	22 upregulated, 1 downregulated	105 upregulated, 22 downregulated

Monocytes showed more regulated proteins than U937 cells. Far more proteins were upregulated than downregulated in both cell types. 11 proteins showing the most significant regulation were identified by mass spectrometry analysis. Of these, vimentin and zinc finger CCCH domain-containing protein 18 (ZCH18) were the most significantly upregulated in both U937 cells and monocytes. Additionally, Myeloperoxidase (MPO) and CAP Gly domain-containing linker protein 2 (CLIP2) were significantly induced in monocytes. Upregulation of vimentin, ZCH18, MPO and CLIP2 was confirmed by qPCR. Induction of vimentin and MPO was also validated by western blotting. Anti-cardiolipin/vimentin antibodies have been reported in APS. We found anti-vimentin in serum of 35% of patients with APS but no correlation between anti-vimentin level and ability of IgG to up-regulate monocyte vimentin.

LC-MS/MS of healthy monocytes exposed to VT IgG revealed over 100 proteins that were differentially regulated compared to monocytes exposed to HC IgG. Pathway analysis showed that these proteins were involved in cytoskeletal, coagulation and integrin-signaling functions; all relevant to APS. S100 A11 and POTE ankyrin domain family member E were significantly upregulated whereas Plasminogen activator inhibitor 2 and Coronin 1 were downregulated. Targets were validated using qPCR.

Conclusion: Two different proteomic techniques were used to identify novel proteins involved in the actions of aPL on monocytes. Several of these proteins are strongly associated with autoimmune disease and coagulation and could become potential new therapeutic targets for APS.

Disclosure: V. M. Ripoll, None; **A. Lambrianides**, None; **W. Heywood**, None; **A. Rahman**, None; **Y. Ioannou**, None; **I. Giles**, None.

5

Plasma Levels Of PF-4var/CXCL4L1, A Non Allelic Variant Of Platelet Factor-4 (PF-4/CXCL4), Are Elevated In Patients With Antiphospholipid Syndrome (APS). Marina Sikara[1], Markos Patsouras[1], Elias Eliopoulos[2] and Panayiotis Vlachoyiannopoulos[1]. [1]School of Medicine, National University of Athens, Athens, Greece, [2]Agricultural University of Athens, Athens, Greece.

Background/Purpose: Platelet derived chemokines, such as PF-4 and a recently isolated protein product of its nonallelic variant gene PF-4var, are implicated in several aspects of vascular thrombosis and inflammation. The above chemokines present only 4.3% aminoacid divergence in the mature proteins; however they exhibit distinct platelet secretion mode and function. The precise role of PF-4var regarding the haemostatic balance is not yet studied.

Previous study from our group demonstrates a novel interaction between β2-glycoprotein I (β2GPI), the major autoantigen in APS, and PF-4 or PF-4var. This complex formation leads in the stabilization of β2GPI dimeric structure which facilitates the antibody recognition and platelet activation, as indicated by p38MAPK phosphorylation and thromboxane production.

To determine PF-4var plasma levels and platelet PF-4var expression (RNA level) in patients with APS and evaluate the correlation with clinical and laboratory parameters of the disease.

Methods: From 70 patients, who fulfill the revised diagnostic criteria for APS, blood samples were taken and separate samples of serum, plasma and platelets were isolated. Complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), aPTT, anti-cardiolipin (anti-CL) and anti-β2GPI antibodies were measured. A healthy control (n=30) and a disease control group (SLE, n=26) were included in the study.

Plasma levels of PF-4var were determined using a commercially available ELISA, which absolutely discriminates PF-4var from PF-4 protein. Statistical analyses were evaluated by Mann-Whitney t-test and Kruskal-Wallis test.

Platelet PF-4var and PF4 RNA levels were determined in RNA isolated from donor's and patient's platelet preparations using quantitative Real-Time PCR.

Results: APS patients showed higher levels of plasma PF-4var compared to healthy individuals (median 137 pg/ml; intarquartile range 66.4–200.5 pg/ml versus 79.03 [40.3–99.2] pg/ml, p=0.0052). In addition, RT-PCR revealed significantly higher PF-4var expression in platelets derived from patients comparing to healthy donors ($2^{-\Delta\Delta CT}$: 1.540; [1.020–1.943] versus 0.89 [0.705–1.203], p<0.001). PF-4var levels were significantly elevated in patients suffering from primary APS (PAPS) than those with APS secondary to SLE (SAPS), (197.7 [113.3–304.8] pg/ml versus 126.6 [49.94–170] pg/ml, p=0.0086). Regarding the clinical presentation of the disease, patients who experienced thrombotic events versus pregnancy morbidity or arterial versus venous thrombotic events do not show statistically significant difference in PF-4var levels. A positive correlation was also revealed between the presence of thrombocytopenia and the elongation of aPTT with the higher PF-4var levels (p=0.0048 and p=0.0195, respectively).

Conclusion: Preliminary results suggest that higher PF-4var levels are present in plasma of APS patients and especially in those with PAPS and these are associated with laboratory characteristics indicative for higher risk of thrombotic complications.

Disclosure: M. Sikara, None; **M. Patsouras**, None; **E. Eliopoulos**, None; **P. Vlachoyiannopoulos**, None.

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Researchers' Own Experience In Managing Obstetric Complications In Pregnant Women With Antiphospholipid Syndrome. Lidia Ostanek[1], Danuta Bobrowska - Snarska[1], Barbara Nestorowicz[2] and Marek Brzosko[3]. [1]Pomeranian Medical University, Szczecin, Poland, Szczecin, Poland, [2]Pomeranian Medical University, Szczecin, Poland, Szczecin, Poland, [3]Department of Rheumatology and Internal Diseases Pomeranian Medical University in Szczecin, Szczecin, Poland.

Background/Purpose: 1. To analyse risk factors for obstetric pathology in patients with antiphospholipid syndrome (APS).

2. To assess the effectiveness of treatment depending on pharmacotherapy.

Methods: The courses of 275 pregnancies and deliveries in patients with diagnosed APS (PAPS-68, SAPS-41 patients) were analysed. 101

pregnancies were treated according to current recommendations. The treatment was consistently followed up with both a rheumatologist and an obstetrician. A retrospective analysis of previous pregnancies and deliveries, both treated and untreated was conducted. The immunological profile of the patients (ANA, SS-A, SS-B, Ro52, lupus anticoagulant (LA), anticardiolipin antibodies (aCL), anti β2GPI (aβ2GPI), antiprothrombin antibodies (aPTR), anti-phosphatidylserine (aPS), complement component 3 and complement component 4) was investigated. Assessment of metabolic and environmental factors influencing pregnancy (smoking, arterial hypertension, lipid profile, hyperglycaemia, uric acid concentration) was carried out. Yate's chi-sqared test, Pearson's ch-sqared test, Spearman's rank correlation and logistic regression analysis were used to conduct the statistical analysis.

Results: Risk factors for unsuccessful pregnancy included: young age at the diagnosis and during pregnancy (p<0,001), presence of LA (p=0,0046), aPTR (p=0,034), arterial hypertension (p=0,012), hyperuricemia (p=0,005). Miscarriages were more frequent in patients with PAPS than with SAPS (p=0,007), in patients with aCL IgM (p=0,042) and in patients treated with glucocorticosteroid (GS) (p=0,027). Premature births were more frequent in young patients (p=0,002), with SAPS (p=0,005), with presence of ANA (p=0,0026), LA (p=0,045), low concentration of C3 (p=0,006), patients with smoking history (p=0,018) and those treated with GS (p=0,000). The presence of LA involved the risk of fetal death (p=0,027). Chances of successful pregnancy were enhanced by: the application of low molecular weight heparin (LMWH)(p=0,000), aspirin (ASA) (p=0,001), combined treatment: LMWH+ASA (p=0,002), and immunoglobulins iv (p=0,002).

Conclusion: 1. The occurrence of aPL and diagnosis of APS increase the risk of obstetric pathology.

2. Apart from immunologic factors (aCL, LA, aPTR, ↓ C3), there are other factors which determine the risk of pregnancy failure, i.e. demographic factors (age), environmental factors (smoking, hyperuricemia) and associated treatment (GS).

3. PAPS increases the risk of miscarriage, SAPS increases the risk of premature birth.

4. Treating APS patients with ASA, LMWH, and in justified cases with immunoglobulins iv, increases the chances of successful pregnancy.

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7

Prospective Validation Of The Global Antiphospholipid Syndrome Score (GAPSS). Savino Sciascia[1], M[a] Jose Cuadrado[2], Giovanni Sanna[3], Veronica Murru[4], Dario Roccatello[1], Oier Ateka[5], Munther A. Khamashta[4] and Maria Laura Bertolaccini[4]. [1]Centro di Immunopatologia e Documentazione su Malattie rare, Torino, Italy, [2]The Rayne Institute, London, United Kingdom, [3]Louise Coote Lupus Unit, St. Thomas' Hospital, London, United Kingdom, [4]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [5]Lupus Unit, London, United Kingdom.

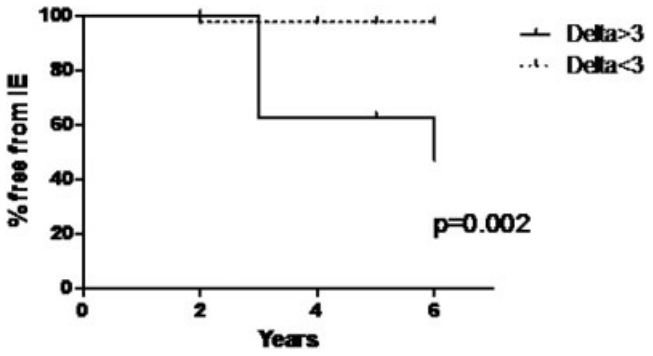
Prospective Validation of the Global Antiphospholipid Syndrome Score (GAPSS)

Background/Purpose: Backgrounds: This study was performed to prospectively and independently validate the GAPSS (1) (Global APS Score), a score system derived from the combination of independent risk factors for thrombosis, taking into account the antiphospholipid antibodies (aPL) profile and the conventional cardiovascular risk factors.

Methods: GAPSS were prospectively applied to 52 consecutive SLE patients with positive aPL (51 female, mean age 39.1±10.6, mean follow-up 47.53±19.15 months). GAPSS scoring system was calculated yearly for each patient by adding together the points corresponding to the risk factors.

Results: An increase in the GAPSS (entry Vs. last visit) was seen in patients who experienced thrombosis (n=5, 6±5.05 Vs 9.4±4.93, p=0.0388). No changes were observed in those without thrombotic event (n=47, 8.28±4.88 Vs 7.13±5.75, p= NS).

An increase of more than 3 points in GAPSS during the follow-up was strongly associated with higher risk of thrombosis (HR 25.00 [95%IC 3.74–189.1]). The risk of thrombosis was also evaluated by Kaplan-Meier analysis (fig.1; IE: ischemic event) and the cumulative proportion of thrombosis-free individuals was higher (p=0.002) in the patients whose GAPSS was not increased by 3 or more points.



Conclusion: We have prospectively demonstrated that GAPSS is a valid tool for accurate prediction of thrombosis in SLE patients with aPL.

1. GAPSS: the Global Anti-Phospholipid Syndrome Score. Rheumatology (Oxford). 2013 Jan 12. [Epub ahead of print]

Disclosure: S. Sciascia, None; **M. J. Cuadrado**, None; **G. Sanna**, None; **V. Murru**, None; **D. Roccatello**, None; **O. Ateka**, None; **M. A. Khamashta**, None; **M. L. Bertolaccini**, None.

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Clinical Evaluation Of Two Anti-Beta$_2$glycoprotein I Domain 1 Autoantibody Assays To Aid In The Diagnosis and Risk Assessment Of The Antiphospholipid Syndrome. Rohan Willis[1], Michael Mahler[2], Francesca Pregnolato[3], Charis Pericleous[4], Anisur Rahman[4], John Ioannou[5], Ian Giles[4], Gabriella Lakos[2], Roger Albesa[2], Navid Zohoury[2], Pier-Luigi Meroni[6] and Silvia S. Pierangeli[1]. [1]University of Texas Medical Branch, Galveston, TX, [2]INOVA Diagnostics, San Diego, CA, [3]Lab of Immunology, IRCCS Istituto Auxologico Italiano, Milan, Italy, [4]University College London, London, United Kingdom, [5]Rayne Institute, University College London, London, UK, London, United Kingdom, [6]University of Milan, Milano, Italy.

Background/Purpose: Antiphospholipid Syndrome (APS) is characterized by the presence of antibodies to phospholipids (aPL) and to $\beta_2$glycoprotein I (β_2GPI) in patients with thrombosis or pregnancy morbidity. Several studies provided evidence that antibodies to domain 1 of β_2GPI (β_2GPI-D1) represent a promising biomarker for the diagnosis and risk assessment of APS. Several immunoassays have been described to detect those antibodies, but harmonization of those tests as well as correlation of those assays has not been properly addressed. Here we aimed to compare two assays for the detection of anti-β_2GPI-D1 antibodies using clinically defined patients samples.

Methods: A total of 72 APS patients and 45 controls (including healthy individuals, patients with infectious or autoimmune diseases) were tested for anti-β_2-GPI antibodies by ELISA (in-house, London, UK and INOVA Diagnostics, San Diego, US) and for anti-β_2GPI-D1 by QUANTA Flash CIA (INOVA) and by ELISA (in-house, London, UK). History of thrombosis was known for 94 patients (39 with and 55 without history of thrombosis).

Results: Both anti-β_2GPI-D1 assays showed good qualitative (79.5%, 95% CI 71.0–86.4; *kappa*=0.60, 95% CI 0.46–0.74) and quantitative agreements (spearman's *rho*=0.76, 95% CI 0.67–0.83) as well as similar discrimination between APS patients and controls as shown by ROC analysis.

Comparison between assays

Qualitative (Total Agreement %/*kappa*) Quantitative (Spearman)	B2 ELISA (INOVA)	D1 ELISA (UK)	D1 CIA
B2 ELISA (UK)	88.9 (0.77) 0.82 (0.75–0.87)	86.3 (0.73) 0.83 (0.76–0.88)	89.7 (0.79) 0.84 (0.78–0.89)
B2 ELISA (INOVA)	/	82.1 (0.65) 0.68 (0.57–0.77)	85.5 (0.71) 0.76 (0.67–0.83)
D1 ELISA (UK)	/	/	79.5 (0.60) 0.76 (0.67–0.83)

Comparison between APS patients and controls

Assay	Area under the curve (95% Confidence interval)	LR+/LR− at cut-off	LR+/LR− at LR+ max	Sensitivity (95% Confidence interval)	Specificity (95% Confidence interval)
D1 CIA	0.89 (0.83–0.96)	9.69/0.15	13.8/0.71	86.1 (75.9–93.1)	91.1 (78.8–97.5)
D1 ELISA	0.83 (0.75–0.90)	4.02/0.44	11.25/0.77	62.5 (50.3–73.6)	84.4 (70.5–93.5)
B2 ELISA (UK)	0.90 (0.84–0.96)	6.25/0.19	9.69/0.60	83.3 (72.7–91.1)	86.7 (73.2–94.9)
B2 ELISA (INOVA)	0.93 (0.88–0.97)	7.5/0.19	24.4/0.47	83.3 (72.7–91.1)	88.9 (75.9–96.3)

Discrimination between patients with and without history of thrombosis

	D1 CIA	D1 ELISA	B2 ELISA (UK)	B2 ELISA (INOVA)
Sensitivity	89.7	64.1	87.2	79.5
Specificity	76.4	74.5	72.7	80.0
Likelihood ratio (+)	3.80	2.52	3.20	3.97
Likelihood ratio (−)	0.13	0.48	0.18	0.26

Conclusion: Anti-β_2GPI-D1 antibodies are a promising biomarker to aid in the diagnosis and risk assessment of APS patients. Confirmatory studies using multi-centric setups and large patient cohorts are necessary to confirm the data.

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Domain 1 Is The Main Specificity Of Anti-$\beta_2$glycoprotein I Antibodies In Systemic Autoimmune Diseases. Laura Andreoli[1], Cecilia Nalli[1], Maria-Orietta Borghi[2], Francesca Pregnolato[3], Alessandra Zanola[1], Claudia Grossi[4], Maria Gerosa[5], Flavio Allegri[1], Michael Mahler[6], Gary L. Norman[6], Pier Luigi Meroni[7] and Angela Tincani[1]. [1]Rheumatology Unit, University of Brescia, Brescia, Italy, [2]Lab of immunology, IRCCS Istituto Auxologico Italiano, Department of Clinical Sciences and Community Health, University of Milan, Milano, Italy, [3]Lab of Immunology, IRCCS Istituto Auxologico Italiano, Milan, Italy, [4]Laboratory of Immuno-rheumatology, IRCCS Istituto Auxologico Italiano, Milan, Italy, [5]Division of Rheumatology, Gaetano Pini Institute, Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, [6]INOVA Diagnostics, San Diego, CA, [7]Division of Rheumatology, Gaetano Pini Institute, Milano, Italy.

Background/Purpose: Anti-$\beta_2$glycoprotein I antibodies (a-β_2GPI) are involved in the pathogenesis of the Antiphospholipid Syndrome (APS). Antibodies to the domain 1 of β_2GP1 (a-β_2GPI-D1) have been suggested as a marker of thrombosis, while antibodies to domain 4/5 (a-β_2GPI-D4/5) have been described in non-thrombotic, non-autoimmune conditions. The clinical significance of these biomarkers is still evolving. We analyze different groups of patients affected by systemic autoimmune diseases and asymptomatic carriers of anti-phospholipid antibodies (aPL).

Methods: 154 patients with positive IgG a-β_2GPI at routine assay were enrolled in this multicenter study: A) 55 thrombotic (+/− obstetric) primary APS (PAPS); B) 31 women with pure obstetric PAPS; C) 42 Systemic Lupus Erythematosus (SLE)/Undifferentiated Connective Tissue Disease (UCTD) with positive aPL but without any APS event in their medical history; D) 14 asymptomatic aPL carriers; E) 12 Rheumatoid Arthritis (RA). As controls, 99 adult normal healthy donors (NHD) were included. IgG a-β_2GPI-D1 and IgG a-β_2GPI-D4/5 were tested on research ELISAs containing recombinant β2GPI domain antigens. The results were considered as optical density (OD) values.

Results: Table shows median OD values in each group. To define the preferential specificity of a-β_2GPI, the ratio between a-β_2GPI-D1 and a-β_2GPI-D4/5 was calculated. A p value less than 0.05 was considered as significant (ns=not significant).

	IgG a-β_2GPI (routine assay)	IgG a-β_2GPI-D1	IgG a-β_2GPI-D4/5	Mann-Whitney Test a-D1 vs a-D4/5	D1–D4/5 RATIO (median)
Thrombotic PAPS (n=55)	1.324	0.458	0.171	p<0.0001	2.3
Obstetric PAPS (n=31)	1.058	0.312	0.154	p=0.0003	2.4
SLE/UCTD with aPL (n=42)	0.953	0.497	0.204	p<0.0001	2.1
aPL carriers (n=14)	1.030	0.317	0.228	p=ns	1.2
RA (n=12)	0.917	0.202	0.519	p=ns	1.0
NHD (n=99)	0.041	0.109	0.080	p=ns	1.4

Conclusion: A-β_2GPI-D1 is the prevalent specificity of a-β_2GPI not only in PAPS with thrombosis, but also in PAPS with pure obstetric disease and in SLE/UCTD patients with no APS manifestations. In the latter group, the pathogenic potential of a-β_2GPI-D1 might be mitigated by the absence of additional risk factors and/or to the presence of adequate prophylaxis. aPL carriers appear not to have a polarized profile, suggesting that a-β_2GPI-D1 may be a fingerprint of systemic autoimmune diseases.

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Autoantibodies Targeting Domain 1 Of Beta 2 Glycoprotein I As Promising Marker In The Diagnosis and Risk Stratification Of The Antiphospholipid Syndrome. Navid Zohoury[1], Munther A. Khamashta[2], Tatsuya Atsumi[3], Jacek Musial[4], Toshiyuki Watanabe[5], Maria Papp[6], Concepción González-Rodríguez[7], Roger Albesa[1], Gary L. Norman[1], Pier-Luigi Meroni[8] and Michael Mahler[1]. [1]INOVA Diagnostics, San Diego, CA, [2]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [3]Hokkaido University Graduate School of Medicine, Sapporo, Japan, [4]Jagiellonian University Medical College, Krakow, Poland, [5]Hokkaido University Graduate School of Medicine, Hokkaido, Japan, [6]University of Debrecen, Debrecen, Hungary, [7]Virgen Macarena University Hospital, Seville, Spain, [8]University of Milan, Milano, Italy.

Background/Purpose: Antiphospholipid Syndrome (APS) is characterized by the presence of antibodies to phospholipids (aPL) and to $\beta_2$glycoprotein I (β_2GPI) in patients with thrombosis or pregnancy morbidity. Several studies provided evidence that antibodies to Domain 1 of β_2GPI (β_2GPI-D1) represent a promising biomarker for the diagnosis and risk assessment of APS patients. Here we aimed to analyze the diagnostic potential of β_2GPI-D1 antibodies and the value in risk stratification of APS patients using a large multi-centric cohort of patients.

Methods: A total of 273 APS patients and 1096 controls (including healthy individuals, patients with infectious or autoimmune diseases) were tested for anti-β_2GPI-D1 by QUANTA Flash CIA (INOVA). A reduced number of samples (n=622) were also tested on anti-β_2GPI by QUANTA Flash CIA (INOVA). Clinical data including the history of thrombosis was known in 89 APS patients (58 had a history of thrombosis).

Results: In the entire cohort, anti-β_2GPI-D1 antibodies differentiated APS and controls with a sensitivity and specificity of 49.8% and 99.6%, respectively. The likelihood ratios were LR+ 136.5 and LR- 0.5. The prevalence of anti-β_2GPI antibodies was higher in primary than in secondary APS and reach significance for anti-β_2GPI-D1 (p=0.0029), but not for anti-β_2GPI antibodies (p=0.06). When compared with the anti-β_2GPI assay, both assays showed good qualitative (79.8%, 95% CI 69.1–86.5; *kappa*=0.60, 95% CI 0.44–0.76) and quantitative agreements (spearman's *rho*=0.81, 95% CI 0.73–0.87) as well as similar discrimination between APS patients and controls as shown by ROC analysis. In the smaller sub-cohort (n=622), sensitivity/specificity were 50.2%/99.2% (β_2GPI-D1) and 72.8%/87.3% (β_2GPI), respectively.

Assay	Cut-off	Sensitivity (95% Confidence interval)	Specificity (95% Confidence interval)	LR+/LR− at cut-off
β_2GPI	20 CU	72.8 (66.6–78.4)	83.7 (79.7–87.3)	4.5/0.33
β_2GPI-D1	20 CU	50.2 (43.6–56.8)	99.2 (97.8–99.8)	64.8/0.50
β_2GPI	50.9 CU	62.1 (55.6–68.4)	96.9 (94.6–98.4)	20.0/0.39
β_2GPI-D1	7.3 CU	60.0 (53.4–66.3)	96.9 (94.6–98.4)	19.4/0.41
β_2GPI	91.1 CU	57.4 (50.9–63.9)	99.0 (97.4–99.7)	55.6/0.43
β_2GPI-D1	11.1 CU	56.2 (49.6–62.6)	99.0 (97.4–99.7)	54.3/0.44

When APS patients were stratified according to the history of thrombosis, anti-β_2GPI-D1 and anti-β_2GPI antibodies showed sensitivities/specificities of 37.9%/93.5% and 60.3%/67.7% respectively. At high specificity (96.8%), the sensitivity for thrombosis was significantly higher for β_2GPI-D1 than for β_2GPI (22.4% vs. 12.1%; p<0.05).

Assay	Cut-off	Sensitivity (95% Confidence interval)	Specificity (95% Confidence interval)	LR+/LR− at cut-off
β_2GPI	20 CU	60.3 (46.6–73.0)	67.7 (48.6–83.3)	1.87/0.59
β_2GPI-D1	20 CU	37.9 (25.5–51.6)	93.5 (78.6–99.2)	5.88/0.66
β_2GPI	4868 CU	12.1 (5.0–23.3)	96.8 (83.3–99.9)	3.74/0.91
β_2GPI-D1	286.9 CU	22.4 (12.5–35.3)	96.8 (83.3–99.9)	6.95/0.80

Conclusion: Anti-β_2GPI-D1 and anti-β_2GPI antibodies show similar performance characteristics in differentiation of APS patients and controls. The correlation with history of thrombosis appears to be stronger for anti-β_2GPI-D1 compared to anti-β_2GPI-antibodies. Therefore, anti-β_2GPI-D1 antibodies are a promising biomarker to aid in the diagnosis and risk assessment of APS patients, but further studies are needed to verify those preliminary findings.

Disclosure: N. Zohoury, Inova Diagnostics, Inc., 3; **M. A. Khamashta**, Inova Diagnostics, Inc., 5; **T. Atsumi**, None; **J. Musial**, None; **T. Watanabe**, None; **M. Papp**, None; **C. González-Rodríguez**, None; **R. Albesa**, Inova Diagnostics, Inc., 3; **G. L. Norman**, Inova Diagnostics, Inc., 3; **P. L. Meroni**, Inova Diagnostics, Inc., 5; **M. Mahler**, Inova Diagnostics, Inc., 3.

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Catastrophic Antiphospholipid Syndrome (CAPS): Clinical, Immunologic Features, and Outcome Of 441 Patients From The "CAPS Registry". Ignasi Rodriguez[1], Gerard Espinosa[2] and Ricard Cervera[3]. [1]Fellow, Barcelona, Spain, [2]Department of Autoimmune Diseases, Hospital Clínic, Barcelona, Barcelona, Spain, [3]Hospital Clinic, Barcelona, Spain.

Background/Purpose: To analyze the clinical and laboratory features as well as the precipitating factors, treatment and outcome of patients with catastrophic antiphospholipid syndrome (CAPS).

Methods: We analyzed the clinical and serologic features of the patients included on May 31, 2013, in the "CAPS Registry", a web-site based international registry of patients with this condition. Categorical variables are presented as frequencies and continuous variables are presented as mean ± standard deviation. Comparative analysis was performed with chi-square test for categorical variables and t-test for quantitative variables using non-parametric tests when parametric tests were not applicable.

Results: The entire series includes 441 patients (456 episodes). Thirteen (2.9%) patients recurred twice and 2 recurred three times. Three hundred (68%) patients were female and 136 (30.8%) were male. They had a mean age of 38.4 ± 17.0 years (range, 0–85). Male patients were older than female (43.4 years vs. 36.2 years; $p<0.001$). The main underlying conditions were primary APS (59.4%), systemic lupus erythematosus (SLE) (30.4%), and lupus-like disease (3.4%). The catastrophic episode was the first manifestation of the APS in 223 (50.6 %) patients. A precipitating factor was reported in 286 (62.7%) episodes, including infections (30.3%), malignancy (10.7%), surgery (10.5), oral contraceptive pills (7.2%), drugs (4.4%), cesarean section (4.2%), lupus flare (2.0%) and trauma (1.1%).

A variety of thrombotic manifestations involving the majority of organs were recorded, including renal (73.6%), lung (58.4%), cerebral (56.3%), heart (49.3%), hepatic (36.3%), gastrointestinal (24%), splenic (16.3%), adrenal (10.4%), and pancreatic (7.1%) manifestations.

Patients with APS associated with SLE had more episodes of *livedo reticularis* (29.1% vs. 15% $p=0.001$), heart valve lesions (22.1% vs. 10.4%; $p=0.01$), seizures (12.8% vs. 6.9%; $p=0.042$), pancreatitis (13.4% vs. 4.4%; $p=0.001$) and more frequently exhibited thrombocytopenia (72.4% vs. 62.5%; $p=0.05$). No differences in clinical manifestations were found between male and female patients.

Regarding immunologic features, IgG anticardiolipin antibodies (aCL) were positive in 81.6% of the patients, lupus anticoagulant in 81.3%, IgM aCL in 48.6%, IgM anti-β2GPI in 3.2% and IgG anti-β2GPI in 11.1%. Female patients had a higher frequency of hemolysis and schistocytes. One hundred and seventy-five (38.6%) patients died at the time of the CAPS event.

Conclusion: The CAPS is an uncommon but potentially life-threatening condition that needs a high clinical awareness. CAPS may affect any organ of the body and display a broad spectrum of manifestations.

Disclosure: I. Rodriguez, None; **G. Espinosa**, None; **R. Cervera**, None.

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Phosphatidiyserine-Prothrombin Complex (aPS/PT) IgG Antibodies Correlate With Lupus Anticoagulant and Specific Pregnancy Complications In Patients With Antiphospholipid Syndrome. Rohan Willis[1], Anne E. Tebo[2], Gabriella Lakos[3], Michael Mahler[3], Gary L. Norman[3], Ware D. Branch[4], Jane Salmon[5], Marta M. Guerra[5] and Silvia S. Pierangeli[1]. [1]University of Texas Medical Branch, Galveston, TX, [2]University of Utah, Salt Lake City, UT, [3]INOVA Diagnostics, San Diego, CA, [4]Univ of Utah, Salt Lake City, UT, [5]Hospital for Special Surgery, New York, NY.

Background/Purpose: Criteria laboratory tests for antiphospholipid syndrome (APS) include lupus anticoagulant (LAC) as well as IgG and IgM antibodies for cardiolipin and beta2 glycoprotein. Of these tests, only the LAC strongly predicts thrombosis. A recent study (PROMISSE) also showed that LAC was the primary predictor of adverse pregnancy outcome after 12 weeks gestation in aPL(antiphospholipid antibody)-associated pregnancies. Antibodies to phosphatidylserine-prothrombin complex (aPS/PT) have been suggested to strongly correlate with the presence of LAC. Anti-PS/PT antibodies are detected with immunoassay, which is more likely to be amenable to standardization than LAC testing, and can be performed on patients during anticoagulation therapy. Using the PROMISSE cohort we investigated if aPS/PT, similarly to LAC, can predict pregnancy outcomes.

Methods: A total of 97 samples from the PROMISSE study were analyzed at the APLS Laboratory using QUANTA Lite® PS/PT IgG and IgM ELISA kits (INOVA Diagnostics). LAC test results were obtained from PROMISSE investigators. Qualitative agreements, kappa scores, and univariate and multivariable logistic regression analyses were done with SPSS software.

Results: The prevalence of LAC positivity was 53/97 (54.6%), aPS/PT IgG was 35/97 (36.1%), aPS/PT IgM was 51/97 (52.6%) and any aPS/PT was 64/97 (66.0%). The inter-assay agreement between the aPS/PT and LAC is shown in Table 1. Both aPS/PT IgG and IgM showed significant correlation to LAC ($p<0.001$ and $p=0.015$). Anti-PS/PT IgG was significantly associated with any pregnancy morbidity ($p=0.002$; OR=6.2, 95% CI 1.7–22.8) and any pregnancy losses ($p=0.006$; OR=4.3, 95% CI 1.5–12.7). The correlation with preeclampsia did not reach significance ($p=0.061$; OR=3.4, 95% CI 1.0–11.3). Anti-PS/PT IgM was not correlated with adverse pregnancy outcomes. In a multivariable model, anti-PS/PT IgG remained a significant predictor of pregnancy morbidity and pregnancy losses.

Table 1. Inter-assay agreement and association of aPS/PT with LAC

	Total/Positive/Negative agreement (Kappa)	Chi squareP value OR (95% CI)
PS/PT IgG	67.0/63.6/69.8 (0.357)	P=0.000 5.920 (2.241–15.637)
PS/PT IgM	62.9/65.4/60.0 (0.254)	P=0.015 2.842 (1.243–6.496)
ANY PS/PT	68.0/73.5/56.7 (0.341)	P=0.001 4.710 (1.901–11.670)

Conclusion: Anti-PS/PT IgG antibodies show good correlation to LAC and association with pregnancy complications in APS patients. This suggests that aPS/PT may be a promising biomarker for obstetric risk assessment in APS given its advantages with respect to clinical applicability and standardization.

Disclosure: R. Willis, None; **A. E. Tebo**, None; **G. Lakos**, Inova Diagnostics, Inc., 3; **M. Mahler**, Inova Diagnostics, Inc., 3; **G. L. Norman**, Inova Diagnostics, Inc., 3; **W. D. Branch**, UCB, 5; **J. Salmon**, None; **M. M. Guerra**, None; **S. S. Pierangeli**, None.

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A MORE Specific Immunoassay For The Diagnosis Of APS. Claudia Grossi[1], Maria Borghi[1], Elizabeth Papalardo[2], Silvia S. Pierangeli[3] and Pier Luigi Meroni[4]. [1]Lab of immunology, IRCCS Istituto Auxologico Italiano, Milano, Italy, [2]Louisville APL Diagnostics, Inc, Seabrook, TX, [3]University of Texas Medical Branch, Galveston, TX, [4]Division of Rheumatology, Gaetano Pini Institute, Milan, Italy, Milan, Italy.

Background/Purpose: Anticardiolipin (aCL) antibody assays are sensitive for the detection of antiphospholipid antibodies (aPL) in patients with the Antiphospholipid syndrome (APS) but are known to have suboptimal clinical specificity due to cross-reaction with infectious diseases and other non-APS sera. The APhL ELISA® is an immunoassay that detects antibodies to negatively charged phospholipids in the presence of β_2GPI and has been shown to be more specific than the aCL in the diagnosis of APS. The objective of this study was to evaluate and compare the clinical sensitivity and specificity of the APhL ELISA® with two aCL

Methods: Serum samples from confirmed primary and secondary APS patients (n=54), syphilis (n=20), infectious diseases (n=30), hyperglobulinemias (n=15), paraproteinemias (n=15) and healthy controls (n=54) were evaluated for IgG and IgM aPL antibodies in the APhL ELISA® (Louisville APL Diagnostics) and in two aCL assays (Louisville APL Diagnostics, Inc; LAPL) and in a laboratory developed test (LDT). Samples were obtained from Prof Meroni's laboratory and kits were provided at no cost by the

manufacturer. Assays were considered positive when above the stated cut-off for each test. Clinical sensitivities, specificities, positive predictive (PPV) and negative predictive values (NPV) were calculated individually by isotype or combined (IgG and IgM) for each assay.

Results:

	APhL ELISA® IgG	APhL ELISA® IgM	APhL ELISA® IgG and IgM	aCL LAPL IgG	aCL LAPL IgM	aCL LAPL (IgG and IgM)	aCL LDT IgG	aCL LDT IgM	aCL LDT IgG and IgM
Clin Sens %	83.0	92.5	94	83.3	90.7	96	73.5	39.6	81.0
Clin Spec %	95.5	95.5	91	77.6	59.7	52.0	73.1	77.6	61.0
PPV %	88.0	89.0	81.0	56.9	52.6	44.0	52.0	42.0	45.2
NPV %	92.0	96.9	97.6	91.7	94.1	97.2	87.5	76.4	91.1

Conclusion: The APhL ELISA® showed better PPV, NPV, combined sensitivities and specificities whether analyzed for IgG or IgM independently or combined, when compared to the two aCL assays. The APhL ELISA® may be used as a first line of testing and certainly could be recommended as a confirmatory assay for the diagnosis of APS.

Disclosure: C. Grossi, None; **M. Borghi**, None; **E. Papalardo**, Louisville APL Diagnostics, 3; **S. S. Pierangeli**, Louisville APL Diagnostics, Inc, 4; **P. L. Meroni**, None.

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Isotype Dependent Performance Of Beta$_2$glycoprotein I Immunoassays In Two Diverse Patient Cohorts: Implications For Assay Harmonization and Standardization. Anne E. Tebo[1], Rohan Willis[2], Troy Jaskowski[3], Jane E. Salmon[4], Michelle Petri[5], Ware D. Branch[6] and Silvia S. Pierangeli[2]. [1]University of Utah, Salt Lake City, UT, [2]University of Texas Medical Branch, Galveston, TX, [3]ARUP Laboratories, Salt Lake City, UT, [4]Hospital for Special Surgery, New York, NY, [5]Johns Hopkins University School of Medicine, Baltimore, MD, [6]Univ of Utah, Salt Lake City, UT.

Background/Purpose: The presence IgG and/or IgM beta$_2$ glycoprotein I (β_2GPI) antibodies are associated with thrombosis and/or pregnancy-related morbidity in antiphospholipid syndrome (APS) and/or systemic lupus erythematosus (SLE). Some reports show that IgA β_2GPI antibodies may be of clinical relevance in certain patient groups. There are, however, concerns regarding the diagnostic performance of these assays probably due to lack of international calibration materials amongst other factors. This study was designed to determine isotype-specific prevalence and correlation between four different aβ_2GPI immunoassays in two cohorts of patients.

Methods: IgG, IgM, and IgA β_2GPI antibodies were determined in 97 pregnant women with positive antiphospholipid (aPL) antibodies (PROMISSE cohort) and 204 SLE patients ('HOPKINS' cohort) with 4 commercial kits (Bio-Rad, Corgenix, INOVA, Phadia). Results were expressed in kit-specific arbitrary units (AU) for IgG, IgM, and IgA as well as in the recently established international consensus units (IU) for IgG and IgM isotypes. Isotype-specific prevalence, Kappa and Spearman's Rho correlation coefficients were calculated using Analyse-it™.

Results: The positivity rates of the aβ_2GPI tests ranged from 1.0–10.2% and 40.6–63.2% (IgG); 3.9–6.3% and 32.3–47.4% (IgM); and 10.7–20.0% and 18.8–85.3% (IgA) in the HOPKINS and PROMISSE cohorts, respectively. The overall agreement between any two assays ranged from 92.2–99.6% (IgG), 95.4–98.8% (IgM) and 77.6–92.2% (IgA) in both cohorts. While the Kappa coefficients (k) showed moderate-to-almost-perfect agreement for IgG and IgM (0.54–0.98), the analysis revealed fair-to-substantial correlations for IgA β_2GPI tests (0.24–0.75). Despite differences in the positivity rates and varying agreements, good quantitative Rho Spearman's correlation was observed for the IgG and IgM in all 4 kits. Rho correlations were significantly improved when results of the IgG and IgM β_2GPI determinations were expressed in IU. However, suboptimal correlations were obtained for the IgA β_2GPI assays, with better agreement observed between the Phadia and INOVA kits and between the Bio-Rad and Corgenix assays, respectively.

Conclusion: Overall, our study demonstrates good qualitative agreements between these immunoassays for the determination of IgG and IgM antibody isotypes. The use of consensus IU clearly indicates an improvement in the harmonization of the IgG and IgM β_2GPI. Further standardization of the IgA β_2GPI assays is warranted.

Disclosure: A. E. Tebo, None; **R. Willis**, None; **T. Jaskowski**, None; **J. E. Salmon**, Biogen Idec, BMS, J and J, Merck, Quest, 1, Roche Pharmaceuticals, 2, Alexion, Regeneron, Movartis, BMS, 5, Alliance for Lupus Research, RRF, Kunkel Society, 6; **M. Petri**, None; **W. D. Branch**, UCB, 5; **S. S. Pierangeli**, None.

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Establishment Of Standardized International Units For IgM ANTI-$\beta_2$glycoprotein Antibody Measurement. Rohan Willis[1], Claudia Grossi[2], Maria Borghi[2], Pier Luigi Meroni[3], Gabriella Lakos[4], Tammy Buckner[5], Fernando S. Cavalcanti[6], Maria Crisostomo[7], Corina Dima[8], Kerrie Jaskal[9], Matthias Kast[10], Luis R. Lopez[11], Nina Olschowka[10], Sarah Paul[12], Tony Prestigiacomo[7], Josep Puig[6], Wendy Vandam[7], Alfredo Villarreal[12], Roger Walker[7], Mike Watkins[12] and Silvia S. Pierangeli[1]. [1]University of Texas Medical Branch, Galveston, TX, [2]Lab of immunology, IRCCS Istituto Auxologico Italiano, Milano, Italy, [3]Division of Rheumatology, Gaetano Pini Institute, Milan, Italy, Milan, Italy, [4]INOVA Diagnostics, San Diego, CA, [5]Corgenix, Broomfield, CO, [6]Biokit, Barcelona, Spain, [7]Bio-Rad Laboratories, Hercules, CA, [8]Theratest Laboratories Inc, Lombard, IL, [9]Instrumentation Laboratories, Bedford, MA, [10]Phadia Thermofisher, Freiburg, Germany, [11]Corgenix Inc, Broomfield, CO, [12]Bio-Rad Laboratories, Benicia, CA.

Background/Purpose: Recurrent IgG or IgM anti-$\beta_2$glycoprotein (ab$_2$GPI) antibody positivity is a key laboratory indicator for classification of antiphospholipid syndrome (APS). Considerable inter-laboratory variation still exists for both isotyopes hindering efforts at standardization. At the 13th International Congress on Antiphospholipid Antibodies in 2010, the "Criteria aPL Testing" task force recommended both the development of international units (IU) and of suitable polyclonal and monoclonal reference material (RM) for aβ_2GPI measurement. As such, we sought to prepare polyclonal RM and establish IU for the measurement for IgM aβ_2GPI antibodies.

Methods: IgM aβ_2GPI fractions were affinity-purified (AP) from the sera of 3 APS patients using a combination of ion exchange and affinity chromatography. Purity was confirmed using SDS-PAGE; high-activity fractions were pooled, concentrated and sterile-filtered. The Bradford assay was used to assign IU values (1 IU/ml = 1μg/ml AP- aβ_2GPI). The RM serum was assigned an IU value using the AP- ab$_2$GPI material and sent with 30 samples to six commercial companies (INOVA, Bio-Rad, Corgenix, Phadia, Human and Instrumentation Laboratory) for testing in their kits (eight total) according to an approved protocol to evaluate linearity, unit equivalency and commutability (CLSI guidelines EP14-A2 and C53-A).

Results: The pooled AP material had a protein concentration of 15.125 μg/ml and was assigned a value of 15 IgM aβ_2GPI IU/ml. The RM had a value of 220.3 IgM aβ_2GPI IU/ml. The linearity (R^2) of the RP curve for the various assays ranged from 0.9649 to 0.9996. The value of the RM in the various arbitrary kit units ranged from 71.6 to 568 units. Commutability among the different assays was confirmed as demonstrated in figure 1 (representative of all assays) in which dilutions of the IgM RM fell within the 95% prediction interval limits of the regression curve created by the 30 native serum samples. Commutability was also demonstrated using principal components analysis.

Table. Performance of IgM RM in various IgM aβ_2GPI assays

Kit	Method	Cut-off	Linearity	RM in kit units
Bio-Rad Bio-plex	ELISA	<20 M units	R^2: 0.99	93.8 M Units
Bio-Rad ELISA	Multiplex	<20 M units	R^2: 0.96	96.4 M Units
Corgenix ELISA	ELISA	<20 M units	R^2: 0. 98	77.4 M Units
IL ACUSTAR	Chemiluminescence	<10 U/ml	R^2: 0.99	69.1 U/ml
INOVA ELISA	ELISA	<20 SMU	R^2: 0.99	98.4 SMU
INOVA Bio-Flash	Chemiluminescence	<10 U/ml	R^2: 0.99	72.5 CU
Phadia	Immunofluoroescence	<10 U/ml	R^2: 0.99	568 U/ml
Human GmbH	ELISA	<7 U/ml	R^2: 0.99	71.6 U/ml

Conclusion: The results of linearity and commutability studies suggest that this material can be used as a calibrant/reference in a wide array of assays of different formats and new international consensus are now available for IgM-aβ_2GPI measurement. These studies contribute significantly to the much-needed standardization of aβ_2GPI immunoassays and further characterization by international bodies (IRMM/IFCC) will be done Performance of IgM RM in various IgM ab$_2$GPI assays

Disclosure: R. Willis, None; **C. Grossi**, None; **M. Borghi**, None; **P. L. Meroni**, None; **G. Lakos**, Inova Diagnostics, Inc., 3; **T. Buckner**, Corgenix, 3; **F. S. Cavalcanti**, Biokit, 3; **M. Crisostomo**, Bio-Rad, 3; **C. Dima**, TheraTest Laboratories, 3; **K. Jaskal**, Instrumentation Laboratories, 3; **M. Kast**, Phadia, 3; **L. R. Lopez**, None; **N. Olschowka**, Phadia, 3; **S. Paul**, Bio-Iad, 3; **T. Prestigiacomo**, Bio-Rad, 3; **J. Puig**, Bio-Kit, 3; **W. Vandam**, Bio-Rad, 3; **A. Villarreal**, Bio-Rad, 3; **R. Walker**, Bio-Rad, 3; **M. Watkins**, Bio-Rad, 3; **S. S. Pierangeli**, None.

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Only IgG and IgA $\beta_2$glycoprotein I Antibody Isotypes Are Associated With Venous Thrombosis In Systemic Lupus Erythematosus. Anne Tebo[1], Rohan Willis[2], Troy Jaskowski[3], Laurence S. Magder[4], Silvia S. Pierangeli[2], Ware Branch[5] and Michelle Petri[6]. [1]University of Utah, Salt Lake City, UT, [2]University of Texas Medical Branch, Galveston, TX, [3]ARUP Laboratories, Salt Lake City, UT, [4]University of Maryland, Baltimore, MD, [5]Univ of Utah, Salt Lake City, UT, [6]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: The current APS Classification Criteria recommend testing for IgG and IgM antibodies for $\beta_2$glycoprotein I (β_2GPI), and do not differentiate between primary and secondary APS. This study was designed to investigate the clinical performance of different β_2GPI IgG, IgM and IgA antibody tests in a SLE with arterial and/or venous thrombosis.

Methods: IgG, IgM, and IgA anti-β_2GPI antibodies were determined in 200 patients from a lupus cohort with 3 ELISA (Bio-Rad, Corgenix and INOVA) and 1 fluoro-enzyme immunoassay commercial kits (Phadia), following the manufacturers' instructions. Kits were provided at no cost by the manufacturers, and assays were performed at ARUP laboratories. The degree of agreement between the different kits was quantified using a Kappa statistic. Univariate and multivariate analyses were performed to assess the association between kit results and lifetime history of venous or arterial thrombosis.

Results: The pairwise agreement between the different kits was high for IgG and IgM with Kappa coefficients ranging from 0.64 to 0.98 and 0.74 to 0.93 respectively. This measure was somewhat lower for IgA with Kappa coefficients ranging from 0.24 to 0.78. Twenty-seven (14%) had a history of venous thrombosis. For all assays and all kits, those with a positive assay result were more likely to have a history of venous thrombosis than those with a negative assay result. These differences reached statistical significance in univariate and multivariate analyses of IgG and IgA, adjusted for age, race, and anti-htn medications. The observed differences were not statistically significant for IgM, in part due to the relatively small number of patients positive for IgM. Thirty-four patients (17 %) had a history of arterial thrombosis. There was not strong evidence of an association between the assay results and arterial thrombosis.

Table 1. Proportion(%) with a history of Venous Thrombosis by antibody status.

		Proportion(%) with history of Venous Thrombosis (n=27)			
Assay	Company	Antibody-positive	Antibody-negative	P-value[1]	Adjusted P-value[2]
IgG	Phadia	6/20 (30%)	21/180 (12%)	0.04	0.015
	Bio-Rad	4/9 (44%)	23/191 (12%)	0.02	0.016
	Corgenix	4/10 (40%)	23/190 (12%)	0.03	0.019
	INOVA	2/2 (100%)	25/198 (13%)	0.02	1.0
	Any	6/22 (27%)	21/178 (12%)	0.09	0.025
IgM	Phadia	3/10 (30%)	24/190 (13%)	0.10	0.29
	Bio-Rad	4/10 (40%)	23/190 (12%)	0.03	0.097
	Corgenix	4/13 (31%)	23/187 (12%)	0.080	0.14
	INOVA	3/8 (38%)	24/192 (13%)	0.08	0.23
	Any	5/18 (28%)	22/182 (12%)	0.08	0.17
IgA	Phadia	9/36 (25%)	18/164 (11%)	0.03	0.0055
	Bio-Rad	8/29 (28%)	19/171 (11%)	0.03	0.031
	Corgenix	9/41 (22%)	18/159 (11%)	0.10	0.037
	INOVA	7/21 (33%)	20/179 (11%)	0.01	0.0049
	Any	12/56 (21%)	15/144 (10%)	0.06	0.0080
Any Assay		13/65 (20%)	14/135 (10%)	0.08	0.021

[1] Fisher's Exact Test
[2] Based on Logistic Regression, controlling for age and race, and anti-htn medications.

Table 2. Proportion (%) with a history of Arterial Thrombosis by antibody status

		Proportion(%) with history of Arterial Thrombosis (n=34)			
Assay	Company	Antibody-positive	Antibody-negative	P-value[1]	Adjusted P-value[2]
IgG	Phadia	2/20 (10%)	32/180 (18%)	0.50	0.40
	Bio-Rad	2/9 (22%)	32/191 (17%)	0.70	0.70
	Corgenix	2/10 (20%)	32/190 (17%)	0.70	0.80
	INOVA	0/2 (0%)	34/198 (17%)	1.0	Too few
	Any	3/22 (14%)	31/178 (17%)	1.0	0.70
IgM	Phadia	2/10 (20%)	32/190 (17%)	0.70	0.90
	Bio-Rad	4/10 (40%)	30/190 (16%)	0.070	0.20
	Corgenix	4/13 (31%)	30/187 (16%)	0.20	0.30
	INOVA	3/8 (38%)	31/192 (16%)	0.10	0.30
	Any	4/18 (22%)	30/182 (16%)	0.50	0.90
IgA	Phadia	9/36 (25%)	25/164 (15%)	0.20	0.20
	Bio-Rad	4/29 (14%)	30/171 (18%)	0.80	0.40
	Corgenix	6/41 (15%)	28/159 (18%)	0.80	0.50
	INOVA	6/21 (29%)	28/179 (16%)	0.20	0.20
	Any	10/56 (18%)	24/144 (17%)	0.84	0.80
Any Assay		12/65 (18%)	22/135 (16%)	0.70	0.80

[1] Fisher's Exact Test.
[2] Based on Logistic Regression, controlling for age, race, and anti-htn medications.

Conclusion: Only IgG and IgA isotypes were associated with venous thrombosis in SLE, using the p-value adjusted for age and ethnicity. Although the IgA kits showed variable agreements, our data indicate that testing for β_2 GPI IgA isotype may be of clinical relevance in the evaluation of venous thrombosis in APS associated with SLE.

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Autoantibodies Against Component Of Complement One Contribute To The Complement Activation and Clinical Manifestation Of Antiphospholipid Syndrome (APS) Especially In Refractory Cases. Kenji Oku[1], Olga Amengual[1], Ikuma Nakagawa[1], Toshiyuki Watanabe[2], Yusaku Kanetsuka[1], Toshiyuki Bohgaki[1], Tetsuya Horita[1], Shinsuke Yasuda[1] and Tatsuya Atsumi[1]. [1]Hokkaido University Graduate School of Medicine, Sapporo, Japan, [2]Hokkaido University Graduate School of Medicine, Hokkaido, Japan.

Background/Purpose: In the pathogenic mechanisms of antiphospholipid syndrome (APS), it is recognized that pathogenicity of antiphospholipid antibodies (aPL) has dominant effects. Complement is the part of the innate immune system and is one of the main effector mechanisms of antibody-mediated immunity. We have previously reported that complement activation prevalently coexists in sera of antiphospholipid syndrome (APS) patients and functions as source of procoagulant cells activation. Recently, autoantibodies against C1q, the component of complement 1, were reported to correlate with complement activation in patients with systemic lupus erythematosus (SLE). They are not neutralizing antibodies but target the neoepitopes of deformed C1q bound to various molecules such as anionic phospholipids. The binding of anti-C1q antibodies to C1q induces accelerated activation of complement pathway. There are no previous studies discussing the involvement of anti-C1q antibodies in APS patients. The purpose of this study is to investigate the existence and significance of anti-C1q antibodies in APS patients.

Methods: This study was comprised of 40 consecutive primary APS patients that visited Hokkaido University Hospital rheumatology clinic from 2002 to 2013 that had more than 2 years history of APS. Informed consent was obtained from every patients and the study was approved by ethics committee of the Hokkaido University Hospital. All the patients were retrospectively analyzed of their clinical manifestations and laboratory data. Ten patients had refractory APS defined as a clinical status of relapsing thrombosis or pregnancy morbidity during adequate secondary prophylaxis. Twenty non-SLE connective tissue disease patients without APS and 20 healthy control subjects were also included. An enzyme-linked immunosorbent assays (ELISA) were used to measure serum levels of anti-C1q antibody titers and anaphylatoxins (C3a,C4a).

Results: Anti-C1q antibodies were more frequently detected in primary APS patients (14/40) than in non-SLE connective tissue disease patients (2/20) ($p<0.01$). In APS patients, anti-C1q antibodies titers were significantly correlated with serum C4a levels ($p=0.013$) and showed tendency of inverse correlation with serum C3a levels ($p=0.07$). The prevalence or the titers of anti-C1q antibodies were not associated with any of the specific clinical manifestations of APS or titers of aPLs. However, refractory APS patients, compared with APS patients without flare, had higher positivity (9/10 vs 3/20, $p=0.01$) and higher titers of anti-C1q antibodies ($32.9+/-6.95$ vs $10.9+/-1.89$, $p=0.01$). Using a cut-off level of 20, the hazard ratio of the anti-C1q positivity for the reoccurrences of the APS manifestation during adequate secondary prophylaxis were 80.0 (95%CI 7.45–880, $p=0.000007$).

Conclusion: These findings indicate that anti-C1q antibodies are associated with complement activation in APS and may contribute to the manifestation especially in the refractory cases.

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Clinical Correlates Of Positive Anti-Cardiolipin and β-2 Glycoprotein 1 Antibodies In a Cohort Of 110 Patients At Mayo Clinic. Uma Thanarajasingam, Cynthia S. Crowson, Melissa R. Snyder, Rajeev Pruthi, Harvinder S. Luthra and Kevin G. Moder. Mayo Clinic, Rochester, MN.

Background/Purpose: Testing for antiphospholipid antibodies is typically indicated for diagnosis and prognosis of antiphospholipid syndromes, however, selected patients undergo testing for other reasons. The clinical significance of positive antibodies in this subgroup of patients is unclear. In this study, we sought to identify patient characteristics and events associated with positive anti-cardiolipin (aCL) and anti-beta-2 glycoprotein 1 (anti-B2GP1) antibodies in a large cohort of patients. The patients with positive results were compared to age and gender -matched controls who had tested negative for the same antiphospholipid antibodies.

Methods: We included 110 adults and 110 age and gender-matched controls tested for aCL and anti-B2GP1 antibodies within the same calendar year (2009) at a large academic medical institution. Clinical and laboratory data was abstracted from 1998 through 2013.

Results: Of the 110 cases, the mean age was 54.1 years and 76 (69.1%) were female. The majority of patients (84) were positive for aCL-IgG (41), IgM (25) or both (18); 29 were additionally tested for anti-B2GP1-IgG (14 positive)and IgM (15 positive). ANA was positive in 52 patients (61%). Thrombotic events were seen in 64 patients (59%); these included 31 (29%) with DVT/PE, 29 (27%) with stroke/TIA, 18 (22%) with any fetal loss, and 6 (6%) with any peripheral arterial events. Thirty-six patients (33%) met criteria for APS and 23 (21%) had SLE. Compared to controls, those with positive antiphospholipid antibodies were significantly more likely to be ANA positive ($p<0.003$), experience a thrombotic event ($p<0.018$), suffer fetal loss ($p<0.022$) and have SLE ($p<0.001$). There were non-statistically significant trends towards increased prevalence for DVT/PE ($p=0.067$) and peripheral arterial events ($p=0.055$). No statistically significant differences were seen between the cases and controls with respect to total number of pregnancies, oral contraceptive and stroke/TIA.

Conclusion: Over one-half of patients who tested positive for antiphospholipid antibodies experienced thrombotic events. When compared to controls, those with positive antiphospholipid antibodies had a statistically significant increase in ANA positivity, any thrombotic event, fetal loss and a diagnosis of SLE. To our knowledge, this is the first study examining the frequency of clinically significant conditions and associated events in a large cohort of patients with positive anti-cardiolipin and anti-beta-2 glycoprotein antibodies as compared to age and sex matched controls with negative antibodies.

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Association Of Antiphospholipid Antibodied Detected In The Aphl ELISA With Clinical Manifestations Of The Antiphospholipid Syndrome In Two Lupus Cohorts. Silvia S. Pierangeli[1], Rohan Willis[1], Michelle Petri[2], Hong Fang[2], Monica Smikle[3], Karel de Ceulaer[4] and E. Nigel Harris[5]. [1]University of Texas Medical Branch, Galveston, TX, [2]Johns Hopkins University School of Medicine, Baltimore, MD, [3]University of the West Indies, Kgn 7, Jamaica, [4]University of the West Indies, KIngston, Jamaica, [5]The University of the West Ind, Kingston, Jamaica.

Background/Purpose: Antiphospholipid Syndrome (APS) is characterized by the presence of antibodies to phospholipid (aPL) and to $\beta_2$glycoprotein I (β_2GPI) in patients with thrombosis or pregnancy morbidity. Anticardiolipin (aCL) assays are used to confirm the diagnosis of APS. Although a sensitive assay, aCL is often found positive in a number of infectious, drug-induced and non APS related autoimmune diseases. The APhL ELISA is an immunoassay that detects antibodies to negatively charged phospholipids in the presence of β_2GPI and has been shown to be more specific and as sensitive as the aCL in the diagnosis of APS. Here we examined the association aPL antibodies detected in the APhL ELISA with clinical manifestations of APS in two lupus cohorts.

Methods: A total of 590 serum samples from patients with lupus (diagnosed according to ACR criteria) from the HOPKINS cohort (n=543) and from the University of the West Indies Rheumatology Department Jamaica cohort (n=47) were analyzed for IgG and IgM aPL antibodies using the APhL ELISA (Louisville APL Diagnostics), following the manufacturer's instructions. Samples were considered positive when above 15 GPL or MPL units for IgG and IgM, respectively. Association of venous thrombois, arterial thrombosis, any thrombosis, diagnosis of APS (Sapporo revised criteria), any miscarriage, any pregnancy morbidity or toxemia with a positive APhL test (either IgG or IgM) was assessed by univariate analysis, using the SPSS® v20.0 software.

Results:

IgG APhL	P	OR	95% CI
Venous thrombosis	0.000	3.5	1.9–6.3
Arterial thrombosis	0.070	1.8	1.0–3.5
Any thrombosis	0.000	3.1	1.7–5.8
Diagnosis of APS	0.000	5.8	2.7–12.1
Any miscarriage	0.022	2.2	1.1–4.1
Any pregnancy morbidity	0.007	2.5	1.3–4.7
Toxemia	0.007	3.1	1.4–6.8

Any APhL positive test was significantly associated with venous, arterial, any thrombosis and with diagnosis of APS, but no association of IgM APhL positivity with clinical manifestations was observed. There was no difference in the results when data were calculated combined or individually in each cohort.

Conclusion: The APhL ELISA is an excellent test to detect aPL associated with thrombosis and pregnancy morbidity in patients with lupus.

Disclosure: S. S. Pierangeli, Louisville APL Diagnostics, Inc, 4; **R. Willis**, None; **M. Petri**, Anthera, Gaxo, Medimmune, TEVA, UCB, Pfizer, 2, Anthera, UCB, Genentech-,Glaxo,Medimmune, Pfizer, 5; **H. Fang**, None; **M. Smikle**, None; **K. de Ceulaer**, None; **E. N. Harris**, Louisville APL Diagnostics, Inc, 5.

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Complement Deposition On Platelets Is Associated To Venous Thrombosis In Systemic Lupus Erythematosus. Christian Lood, Helena Tydén, Birgitta Gullstrand, Gunnar Sturfelt, Andreas Jönsen, Lennart Truedsson and Anders A. Bengtsson. Lund University, Lund, Sweden.

Background/Purpose: Anti-phospholipid (aPL) antibodies are associated with development of venous thrombosis and stroke in the autoimmune disease systemic lupus erythematosus (SLE). The underlying mechanism for aPL-mediated thrombosis is not known but may include activation of platelets and the complement system. The aim of this study was to investigate if aPL antibodies could interact with platelets and support complement activation. Furthermore, we investigated if this mechanism was operating in SLE patients and whether complement deposition on platelets was associated to venous thrombosis and specific for SLE.

Methods: Complement deposition was measured by flow cytometry in patients with SLE, rheumatoid arthritis, systemic sclerosis, myocardial infarction and healthy individuals. Associations to cardiovascular disease were analyzed with logistic regression analysis and adjusted for traditional risk factors. Anti-cardiolipin antibodies were used to investigate if aPL antibodies supported platelet activation and complement deposition

Results: Platelet deposition of C1q and C4d was increased in SLE as compared to healthy individuals ($p<0.0001$), but high levels were also seen in some patients with rheumatoid arthritis and systemic sclerosis. Complement deposition was clearly associated to venous thrombosis and aPL antibodies in SLE. In vitro, anti-cardiolipin antibodies increased platelet activation and supported C4d deposition on platelets.

Conclusion: Platelet C1q and C4d deposition are identified as markers of venous thrombosis in SLE patients. Several mechanisms are operating in SLE to amplify platelet complement deposition, of which anti-cardiolipin antibodies was identified as one important contributor. Further studies are needed to elucidate the role of platelet complement deposition in development of venous thrombosis.

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Factor Xa Reactive Antibodies In Patients With Systemic LUPUS Erythematosus and Antiphospholipid Syndrome Have Differential Effects Upon Coagulation Assays and Endothelial CELLS. Bahar Artim-Esen, Natalia Smoktunowicz, Charis Pericleous, Vera M. Ripoll, Ian Mackie, Rachel Chambers, David A. Isenberg, Anisur Rahman, Yiannis Ioannou and Ian Giles. University College London, London, United Kingdom.

Background/Purpose: Antiphospholipid antibodies have been shown to bind serine proteases (SP) involved in the coagulation cascade. Previously, we found that IgG anti-Factor(F)Xa antibody levels were higher in patients with the antiphospholipid syndrome (APS) and patients with systemic lupus erythematosus (SLE) but no APS compared with disease and healthy control (HC) groups. Given that FXa has important haemostatic and cellular effects we hypothesized that anti-FXa antibodies may be important in the pathogenesis of APS and SLE. Therefore, we investigated whether differences exist in the avidity and functional effects of APS and SLE anti-FXa IgG upon the coagulant and cellular functions of FXa.

Methods: IgG was purified from patients with APS (n=15) and SLE (n=15) who had medium or high serum levels of anti-FXa binding and HC (n=10) negative for anti-FXa IgG. The avidity of IgG-FXa binding was measured under chaotropic conditions using a NaCl gradient. We measured effects of anti-FXa IgG on FXa-activated clotting time (ACT) and on FXa enzymatic activity in a chromogenic assay in the absence and presence of antithrombin (AT)III. Cellular effects of IgG on FXa-protease-activated receptor (PAR) mediated intracellular calcium release in human umbilical vein endothelial cells (HUVEC) were measured using the fluorescent image plate reader (FLIPR).

Results: All SLE-IgG displayed significantly lower (less than 25 % binding) avidity compared to APS-IgG (25–70% binding) to FXa at 0.13 to 1M concentrations of NaCl ($p<0.05$). The mean residual binding of APS-IgG to FXa was significantly higher than that of SLE-IgG below 2M NaCl (26 vs 13 %; $p<0.05$ at 1 M). FXa enzymatic activity was significantly reduced by APS-IgG (90%) and SLE-IgG (92 %) compared to HC-IgG (98 %) (APS vs HC $p<0.05$, SLE vs HC $p<0.05$, APS vs SLE $p=0.04$). ATIII mediated inhibition of FXa however, was significantly reduced by APS-IgG (62%) compared with HC (79%) and SLE (81 %) ($p<0.05$). The greatest prolongation of FXa-ACT was observed with APS-IgG followed by SLE-IgG and HC-IgG (74, 63 and 26 sec respectively). In cultured HUVEC, APS IgG caused significantly greater enhancement of FXa-mediated Ca^{2+} flux compared to SLE and HC-IgG at the same concentration (400 μg/ml) (APS vs HC $p<0.05$, APS vs SLE $p=0.03$) and this effect was reduced at lower IgG concentration (200 μg/ml).

Conclusion: FXa reactive IgG isolated from patients with APS displayed higher avidity binding to FXa and had greater functional effects upon FXa activity, ATIII mediated inhibition of FXa and FXa-PAR mediated signalling in cultured endothelial cells than SLE-IgG. Further work is now underway to further characterise the cellular effects of these anti-FXa IgG.

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What Is The Prevalence Of Non-Criteria Antiphospholipid Antibodies in Patients With Antiphospholipid Syndrome? Veronica Rodriguez-Garcia[1], Yiannis Ioannou[2], D.A. Isenberg[2] and Ian Giles[2]. [1]Hospital Regional Universitario Carlos Haya, Malaga, Spain, [2]University College London, London, United Kingdom.

Background/Purpose: Increasing interest has focused upon assays which are not currently included in the Antiphospholipid syndrome (APS) classification criteria to detect antibodies directed against other phospholipids (PL), PL binding proteins, coagulation factors and a mechanistic test for resistance of Annexin A5 (AA5) anticoagulant activity. Therefore, we carried out a systematic review to try and establish the prevalence of each non-criteria assay in APS and control populations.

Methods: We searched PubMed and EMBASE using the keywords APS, antiphospholipid antibodies (aPL), non criteria, new assays, aCL, LA, anti-domain (aD)I, Ig A antiB2 GPI, antiphosphatidylserine (aPS), antiphosphatidylethanolamine (aPE), antiphosphatidic acid (aPA), antiprothrombin (aPT), antiphosphatidylserine-prothtombin (aPS-PT), anticardiolipin/vimentin (CL/Vm) and AA5 resistance. Each publication was systematically examined.

Results: We selected 15 (6 retrospective, 1 case-control and 8 cross-sectional studies from which we were able to extract original data on prevalence of non-criteria aPL in 1535 patients with APS and 1184 healthy and disease controls. We found the largest APS sample size from 3 studies of aDI, which found a prevalence of 34.26% of aDI in 645 patients with APS patients versus 3.3% in 30 healthy controls (HC). In reducing order of samples size. Three studies found an overall prevalence of 7.8% of IgM and 4.3% IgG aPE in 337 patients with APS compared with 3.9% IgM and 0.9% IgG aPE in 340 HC. IgA aCL were found in 37.46% of APS patients (n=262), 37.8% autoimmune disease (n=37) controls and 3.4% in healthy and atherosclerosis (n=527) controls. In contrast, 55% of 196 patients with APS were positive for IgA anti-B2GPI, versus 32.9% in 382 atherosclerosis and 13% in 145 healthy controls. The prevalence of AA5 resistance from 3 studies was 66.83% in 163 patients with APS compared with 0% in 80 HC. In 132 APS patients, 27.56% were positive for IgM aPT and 36% positive for IgG aPT versus 5% IgG and 0% IgM in HC.

All of the remaining studies contained less than 100 patients with APS. Studies of other non-criteria aPL identified: 24% IgM and 65.5% IgG aPA in 67 APS patients versus 0% IgM/G aPA in 104 HC; 36.6% IgM and 50.8% IgG aPS in 89 APS patients versus 1% IgM and 0% IgG aPS in 104 HC; 33.8% IgM and 38.8% IgG aPI in 89 APS patients versus 0% in HC; 25% IgM and 27.5% IgG aPS/PT in 44 APS patients versus 3% IgM and 0% IgG in 138 disease controls; and 80% IgM and 92.4% IgG anti-CL/Vm in 40 APS patients versus 0% IgM/G in 32 HC.

Conclusion: We found the highest prevalence of non-criteria aPL in the largest number of patients with APS in studies of AA5 resistance and aDI. Further prospective studies however are urgently required to confirm these findings.

Disclosure: V. Rodriguez-Garcia, None; **Y. Ioannou**, None; **D. A. Isenberg**, None; **I. Giles**, None.

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Seizures In Systemic Lupus Erythematosus Are Not An Inflammatory Manifestation Of Lupus Anticoagulant. Michelle Petri and Hong Fang. Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: About 50% of SLE patients make an antiphospholipid antibody and 10% develop classic antiphospholipid syndrome. Seizures are one of the components of the SLICC classification criteria, and can occur due to SLE itself or secondary to stroke. Because seizures have been proposed as an inflammatory (non-thrombotic) manifestation of antiphospholipid antibodies, we determined whether seizures in SLE were associated with the lupus anticoagulant.

Methods: 2206 SLE patients were enrolled in a prospective cohort. Their mean age was 43 years; 93% were female, 55% Caucasian, 38% African-American and 7% other ethnicity. 27% had a history of lupus anticoagulant, 9% stroke and 10% seizures. The association of seizure with lupus anticoagulant and then excluding those with stroke was determined using chi-squared analyses. The lupus anticoagulant was determined by dRVVT with confirmatory testing.

Results: Table One shows the association of seizure with the lupus anticoagulant ($p = 0.0017$).

Table 1. Association between Lupus Anticoagulant and Seizure (All Patient Analysis)

	LA Pos (N=591)	LA Neg (N=1615)	P-value
Seizure	13.03%	8.54%	0.0017

Table 2 shows the association of seizure with the lupus anticoagulant, but excluding those with stroke. The p-value was 0.22.

Table 2. Association between Lupus Anticoagulant and Seizure (Excluding Those with Stroke)

	LA Pos (N=493)	LA Neg (N=1515)	P-value
Seizure	9.33%	7.59%	0.22

Conclusion: The apparent association of the lupus anticoagulant is explained by the association with stroke. Thus, seizures in the absence of stroke should not be attributed to the lupus anticoagulant. Seizures should not be added to the classification criteria for antiphospholipid syndrome.

Disclosure: M. Petri, None; **H. Fang**, None.

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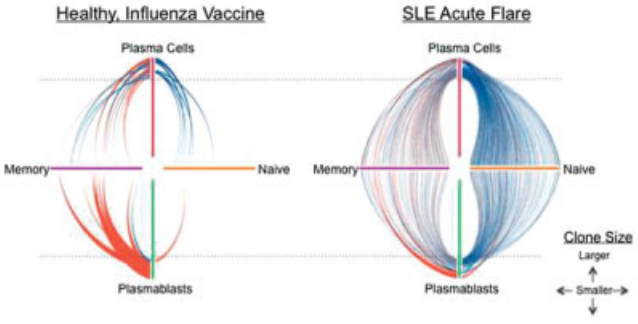
Plasma Cells In Acute Systemic Lupus Erythematosus Flares Are Characterized By a Highly Diversified Repertoire Accentuated By Clonal Expansions Of VH4-34 Antibodies. Christopher Tipton[1], Christopher Fucile[2], Alex Rosenberg[2], Scott Jenks[3], Jennifer Hom[1], F. Eun-Hyung Lee[1] and Inaki Sanz[1]. [1]Emory University, Atlanta, GA, [2]University of Rochester, Rochester, NY, [3]Emory University School of Medicine, Atlanta, GA.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is an autoimmune disease in which faulty B cell tolerance promotes the generation of multiple autoantibodies of which anti-ds DNA, anti-Sm and VH4–34-encoded 9G4 antibodies, are highly specific for this disease. Acute SLE flares are typically accompanied by a substantial expansion of circulating antibody-secreting plasmablasts (PB) and plasma cells (PC). Similar expansions of PB/PC populations in healthy subjects post-immunization are comprised of large clonal expansions of antigen-specific cells derived from pre-existing memory cells. To determine if SLE PB/PC expansions follow the same model, and to understand the diversity, origin and antigenic specificity of SLE PB/PC expansions, we used immunoglobulin heavy chain (IGH) deep sequencing to analyze sorted cells obtained from patients experiencing acute flares.

Methods: Peripheral blood lymphocytes were sorted into various B cell populations. Multiple VH family-specific primer sets were used to amplify the IGH gene from extracted RNA and then sequenced using the Illumina MiSeq platform. Sequences were analyzed using internally designed analysis software. Our software conducts quality filtering, detailed mutational analysis and identifies inter-population relationships between samples.

Results: PB/PC expansions in SLE acute flares are a highly diversified repertoire with lower VH mutation rates than memory cells. However, within this diverse pool significant clonal expansions accounting for 0.5% or more of the entire repertoire were regularly detected. Strikingly, VH4–34 sequences comprised the largest clones in all SLE samples. Also of interest, a substantial fraction of PB/PC in SLE were highly evolutionarily related to a pool of activated naïve precursors. This was in stark contrast to results obtained in PB/PC samples from healthy, vaccinated subjects, which contained large, clonal expansions, high VH mutation rates, were largely related to memory cells, and had an absence of autoreactive VH4–34 clonal expansions. Figure 1 shows clonal relationships between the top 20% of PB and PC sequences and Naive and Memory clones. Clones are arranged in increasing size from center to outer edge, and lines link matching clones.

Fig. 1



Conclusion: Combined, our data support a model of generalized naïve and memory activation underlying the activation phase of human SLE. This polyclonal activation is accentuated, and possibly promotes, antigen-selected clonal expansions dominated by VH4–34-encoded autoreactive 9G4 antibodies. Ongoing monoclonal antibody studies will clarify the nature of the selecting antigens.

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SLE Flares Are Characterized By Generalized Polyclonal Expansions Of Antibody Secreting Cells Without Preference For Autoimmune Responses. H. Travis Ichikawa Emory University, Atlanta, GA.

Background/Purpose: Increased circulating antibody secreting cells (ASC), including both CD138- plasmablasts and CD138+ plasma cells (PB/PC), correlate with SLE activity and are prominent during Lupus flares. We tested whether this expansion is predominantly driven by typical SLE autoreactivities including anti-dsDNA, -Sm and -Ro and 9G4+ antibodies.

Methods: Peripheral blood lymphocytes (PBL) were collected from SLE patients (n=12; 4 mild-severe flare patients defined by SELENA-SLEDAI) with high serum levels of ≥1 autoantibody (anti-dsDNA, anti-Sm or anti-Ro). PB/PC frequency was calculated as % of total B-cells by flow cytometry. Anti-dsDNA, anti-Sm and anti-Ro60, 9G4+ and anti-microbial (anti-tetanus toxoid and anti-influenza) IgG ASC were detected by ELISPOT and expressed as % of total IgG ASC. Memory cells were activated by stimulation with R848 and IL-2 for 7 days. Frequencies of antigen specific IgG memory cells were determined by ELISPOT as before.

Results: PB/PC frequencies were increased for up to 25-fold in SLE compared to HC and comprised up to 38 % of total B-cells. Of total IgG ASC, frequencies of each SLE specific IgG ASC responses (anti-dsDNA, anti-Sm and anti-Ro60) never exceeded 3.4% (mean ± SD, 0.25 ± 0.65%) in patients with high serum antibody levels. 9G4+ ASC, which include several SLE-specific autoreactivities including anti-dsDNA and anti-apoptotic cells, were the most abundant autoreactivity but did not exceed 6% (mean ± SD, 2.2 ± 1.7%). Combined, all the lupus–related autoreactivities accounted for <10% of all IgG ASC. No correlation was found between PB/PC frequencies and SLE specific or 9G4+ IgG ASC frequencies. Furthermore, anti-Tetanus and/or anti-influenza ASC, usually not found in healthy PBL, were found in SLE PBL in frequency similar to autoreactive responses (0.06 ± 0.09% and 0.37 ± 0.12%, respectively). Anti-Sm, anti-Ro and 9G4 as well as anti-tetanus and anti-influenza reactive IgG memory cells were present in frequencies typically higher than that found for ASC of the same antigenic reactivity. Notably, in 5 out of 6 patients with high anti-Ro serum titers, anti-Ro IgG memory cells represented > 2% of all IgG memory cells. In contrast, anti-dsDNA IgG memory cell frequencies (0.01 ± 0.02%) were as low as anti-tetanus memory cell frequencies (0.12 ± 0.31%).

Conclusion: Combined, conventional lupus autoreactivities only account for <10% of the greatly expanded numbers of circulating ASC characteristic of lupus flares. In addition, these frequencies are lower than the frequency of memory cells for the corresponding autoantigens. Moreover, antimicrobial responses are present in circulating ASC with frequencies similar to autoimmune responses. While our studies did not test for other potential SLE autoreactivities, our results are consistent with a polyclonal expansion of ASC during lupus flares that is not predominantly driven by conventional autoantigens even in patients with high titers of serum antibodies. These studies have important implications for our understanding of the mechanisms underlying lupus flares and the contribution of different cellular compartments to the generation of serum autoantibodies at different times in the course of the disease.

Disclosure: H. T. Ichikawa, None;

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Autoantibodies Directed Against Cell Surface Components In Autoimmune Disease Patients: Proposal Of a Novel ELISA For The Detection Of Anti-Endothelial Cell Antibodies. Keiji Miura[1], Ayako Kondo[2], Kazuo Takahashi[2], Daisuke Hirano[2], Yoshiyuki Hiki[1], Shunji Yoshida[2], Yukio Yuzawa[2] and Yoshikazu Kurosawa[1]. [1]Fujita Health Universtiy, Toyoake, Japan, [2]Fujita Health Universtiy School of Medicine, Toyoake, Japan.

Background/Purpose: Sera from patients with systemic vasculitis or inflammatory conditions have been reported to contain antibodies that bind to endothelial cells (EC), i.e., AECA (anti-endothelial cell antibodies). AECA are known to play immunogenic effects by triggering EC activation and vascular damage, but the immunopathological role of AECA is not clear. SDS-PAGE and Western blotting have previously been used for detecting target antigens of AECA. However, we assumed that these methods are not appropriate for searching genuine target antigens on cell surface, and developed a novel solubilized cell surface protein-capture ELISA (CSP-ELISA).

Methods: Antigens were obtained as cell surface proteins from the plasma membrane of human umbilical vein endothelial cells (HUVEC); these

cell surface proteins were biotinylated, solubilized with detergent, and captured on ELISA wells coated with NeutrAvidin biotin binding protein. AECA titers in serum from 126 autoimmune disease patients and 122 healthy controls (HC) were tested. Additionally, sera from 52 patients with biopsy-proven lupus nephritis (LN), 25 with systemic lupus erythematosus (SLE) without renal involvement (non-LN SLE), 10 disease controls (DC) and 81 healthy controls were tested for IgG- and IgA-AECA to human glomerular EC (HGEC) by CSP-ELISA.

Results: IgG-AECA were detected in 28 of 36 (78%) of SLE patients; in 13 of 16 (81%) of mixed connective tissue disease (MCTD) patients; in 5 of 9 (56%) of systemic sclerosis (SSc); and in 4 of 122 (3%) of healthy controls. Relatively weak denaturation of antigens on ELISA wells caused loss of binding of these autoantibodies. Titers of IgG- and IgA- AECA to HGEC were significantly higher in LN and non-LN SLE patients than in the combined DC and HC ($P < 0.001$) groups. The level of IgG-AECA did not correlate with active lesions, but the level of IgA-AECA to HGEC did correlate with histological evidence of active lesions in LN patients ($P < 0.001$). Immunocytochemical analysis showed AECA recognized membrane proteins on HGEC. The significant correlation of titer of AECA to both HGEC and HUVEC ($R = 0.95$ for IgG-, 0.93 for IgA-AECA, respectively) indicated AECA in LN patients recognize membrane proteins expressed on HGEC and HUVEC. To identify specific antigens against AECA, biotinylated CSPs were incubated with sera from LN patients with high titers of IgG-AECA, immunoprecipitated with immobilized protein G followed by immobilized avidin, and blotted with NeutrAvidin. A 150-kDa protein band that shifted to a 55-kDa protein band under reducing conditions was detected in patients with LN, but not in HC.

Conclusion: This newly developed CSP-ELISA method enables the detection of antibodies to the labile epitopes of autoantigens such as membrane proteins, and this method is generally applicable to various kinds of membrane proteins and the antibodies against them. IgA-AECA was observed to be associated with pathological activity in LN. These EC membrane components recognized by AECA may be linked with the pathogenesis of LN. We propose CSP-ELISA for measuring AECA in serum samples for routine laboratory testing.

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Specificity Of Autoantibodies In Patients With Rheumatologic Inflammatory Syndrome Following Mineral Oil Injections Is Similar To Those In Mice With Adjuvant Mineral Oil-Induced Autoimmunity. Minoru Satoh[1], Olga Vera-Lastra[2], Claudia Martínez[3], Jesús Sepulveda- Delgado[3], Luis J. Jara[4], Raúl Vargas-Ramírez[5], Beatriz Teresita Martin-Marquez[6], S. John Calise[1], Edward K.L. Chan[1] and Monica Vázquez-Del Mercado[7]. [1]University of Florida, Gainesville, FL, [2]MD, Mexico City, Mexico, [3]Hospital de Especialidades Centro Médico Nacional La Raza, IMSS, Mexico City, Mexico, [4]Hospital de Especialidades Centro Medico La Raza, México City, Mexico, [5]Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético, Universidad de Guadalajara, Guadalajara, Jalisco, México, Mexico, [6]Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético, Guadalajara, Mexico, [7]Universidad de Guadalajara, Guadalajara, Jalisco, México, Mexico.

Background/Purpose: Intraperitoneal injection of pristane or adjuvant mineral oil (incomplete Freund's adjuvant) in non-autoimmune strains of mice mainly induces autoantibodies to U1RNP and Su/argonaute2 (Ago2). Injection of mineral oil as a cosmetic procedure has been commonly performed in certain countries including Mexico, however, inflammatory syndrome among these subjects have been reported. In the present study, autoantibody specificity in patients who had mineral oil injection and inflammatory syndrome were examined and compared with data from animal models

Methods: Twenty-one cases of patients, who had mineral oil injections (17 buttocks, 9 breast, 5 thigh, 2 legs, 1 face) and developed rheumatologic symptoms after mineral oil injections were studied. Autoantibodies were tested by immunofluorescence antinuclear antibodies (ANA) using HEp-2 slide, immunoprecipitation (IP) of ^{35}S-methionine-labeled cell extract and anti-Ro52 and U1RNP-70kD ELISA. Autoantibody specificities were compared with those in BALB/cByJ mice that received a single 0.5 ml intraperitoneal injection of adjuvant mineral oils (incomplete Freund's adjuvant or pristane). Clinical information was from medical record

Results: By immunofluorescence ANA, 62% (13/21) were positive in nuclear (5 cases), nucleolar (3 cases), mitochondria-like (3 cases), or GW bodies (2 cases) pattern. By IP, one had anti-U1RNP, 2 had anti-Su/Ago2 (both had GW body staining in ANA) and 3 had anti-Ro60. Two were positive by anti-Ro52 ELISA and one was positive in anti-U1RNP-70kD ELISA (positive for U1RNP by IP). Among 6 cases with these autoantibodies (2 had more than one), a case with anti-Su+Ro52 had a diagnosis of SLE, however, other 5 cases had non-specific rheumatological symptoms only. It is of interest that anti-U1RNP and –Su/Ago2 that are the main autoantibody specificity induced by adjuvant mineral oils in animal models, was also seen in mineral oil injected human subjects. Prevalences of these antibodies was not as high as pristane-treated mice but similar to those in adjuvant mineral oil-injected mice.

Conclusion: Patients with rheumatologic inflammatory syndrome after mineral oil injections have autoantibody specificity similar to those in mice with adjuvant mineral oil-induced autoimmunity (anti-U1RNP and Su/Ago2). In addition, they also developed anti-Ro60 and Ro52.

Table. Prevalence of autoantibodies by immunoprecipitation

	Human	BALB/cByJ mice	BALB/cByJ mice
Chemical injected	Mineral oil	Adjuvant mineral oil (incomplete Freund's adjuvant)	pristane
Site of injection	buttocks, breast, thigh, leg, face	intraperitoneal	intraperitoneal
Features	rheumatologic symptoms		immune complex glomerulonephritis
N =	21	20	20
Anti-U1RNP	4%	10%	55%
Anti-Su/Ago2	10%	10%	45%
Anti-U1RNP or Su	14%	20%	85%
Anti-Ro60	14%	0%	0%

Disclosure: M. Satoh, None; **O. Vera-Lastra**, None; **C. Martínez**, None; **J. Sepulveda- Delgado**, None; **L. J. Jara**, None; **R. Vargas-Ramírez**, None; **B. T. Martin-Marquez**, None; **S. J. Calise**, None; **E. K. L. Chan**, None; **M. Vázquez-Del Mercado**, None.

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Differentiation, Activation, and Autoreactivity Of CD11c+ B Cells (ABCs). Alice E. Wiedeman, Natalia V. Giltiay, Lena Tanaka and Keith B. Elkon. University of Washington, Seattle, WA.

Background/Purpose: Recently, a population of CD11c+ age-associated B cells (ABCs) was identified in normal aged female mice. These cells could be expanded following activation by TLR7 agonists and their presence was associated with autoantibody production. The goals of the current study were to determine: a) when ABCs develop during B cell maturation in the spleen; b) how B cell intrinsic and extrinsic factors influence ABC generation; and c) how TLR7 expression influences ABC generation in a B cell receptor (BCR) transgenic (Tg) mouse with specificity for RNA (the TLR7 ligand).

Methods: Knock-in mice that overexpressed TLR7 on a B6 background (TLR7 Tg) were crossed with either IFNaR knockout (KO), RNAse Tg, HEL-specific BCR Tg, or RNA specific BCR Tg (H564) mice. Mixed chimeras were generated with combinations of wildtype B6 and TLR7 Tg bone marrow. Flow cytometry was used to identify splenic B cell subsets and analyze CD11c expression. CD11c+ (ABCs) and CD11c- (non-ABCs) B cells were sorted using a BD FACS Aria, and cultured for 6d with or without TLRs 4, 7, or 9 agonists. Ig production was quantified by ELISA.

Results: While in wildtype mice, CD11c+ ABCs were increased only in females greater than 6 months of age, TLR7 Tg mice had significantly expanded ABCs as young as 3 months in both males and females (1.1 ± 0.2 % in B6 versus 3.4 ± 1.1 % in TLR7 Tg, $p < 0.003$). ABC accumulation was greatest in the transitional B cell stages but the relative proportion of ABCs was also higher in marginal zone than follicular B cells. To address whether generation of ABCs was intrinsic or extrinsic we used WT:TLR7 Tg mixed bone marrow chimeras, and observed that ABC expansion of TLR7 Tg B cells had a definite cell-intrinsic component. However, when TLR7 Tg mice were crossed with RNAse Tg or IFNaR KO mice to remove the RNA ligand or response to IFN-I respectively, ABCs were modestly but statistically significantly reduced. In TLR7 Tg mice, serum levels of anti-RNA autoantibody correlated with % ABCs in spleen and we also observed that ABCs produced more antibody (including anti-RNA autoantibodies) in response to innate stimulation in vitro. Consistent with these findings, crossing TLR7 Tg and autoreactive H564 BCR mice further increased ABC accumulation, while

crossing to an HEL mouse resulted in expansion of ABCs in the polyclonal but not in the HEL-specific subset.

Conclusion: CD11c+ ABCs are B cells that appear early during B cell maturation, and are increased under conditions of TLR7 hyperreactivity. ABC generation is, in part, cell intrinsic but is also influenced by exposure to self antigen and to IFN-I. ABCs can be directly implicated in autoantibody production by comparing antibody concentrations following stimulation of ABCs and non-ABCs in vitro as well as by enhanced ABC expansion in a TLR7 Tg mice that has specificity to self antigen (RNA) but not to non-self (HEL). Since these results suggested that ABCs, at least in part, contribute to autoantibody production, CD11c+ B cells may be a good target for amelioration of autoimmunity without broadly impairing host defense.

Disclosure: A. E. Wiedeman, None; **N. V. Giltiay**, None; **L. Tanaka**, None; **K. B. Elkon**, None.

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A Novel CD27$^{(-)}$ B-Cell Subset Identified Based On Intracellular Characteristics Is Expanded In SLE. S.J. Fleischer[1], Capucine Daridon[2] and Thomas Dörner[3]. [1]Charité University Medicine Berlin, Berlin, Germany, [2]Charité University Medicine / German Rheumatism Research Centre Berlin (DRFZ), Berlin, Germany, [3]Charité university medecine/ German Rheumatism Research Centre Berlin (DRFZ), Berlin, Germany.

Background/Purpose: Several studies linked the emergence of autoimmunity to abnormalities of the B-cell receptor (BCR) due to disturbances of signaling molecules or its co-receptors. Therefore this study focused on spleen tyrosine kinase (Syk), a key molecule of early BCR signaling in autoimmunity. Our model is systemic lupus erythematosus (SLE) which is an autoimmune disease known to be associated with a breakdown of self-tolerance resulting in auto-antibody production, B-cell hyper-reactivity and disturbed B-cell homeostasis of peripheral B-cell subsets.

Methods: Peripheral blood was taken from 31 healthy, 61 SLE patients, 15 patients with rheumatoid arthritis (RA) and 16 primary Sjögren's syndrome (pSS) patients. The expression of Syk and basal / BCR-induced phosphorylation of Syk by B-cells were studied by phosphoflow analysis. To assess the localization of Syk within B-cells, immunofluorescence was performed and analyzed by confocal microscopy. In addition, characterization of B-cells was evaluated by flow cytometry using the following markers CD19, CD20, CD27, CD38, IgD, CD95 and Ki67. Finally, the capacity of B-cells to differentiate into antibody producing cells was evaluated by flow cytometry and Elispot after 5 days of *in vitro* culture.

Results: In this study, two different subsets according their expression of Syk (Syk^{bright} and Syk^{dim}) within the CD20^{+}CD27$^{(-)}$ population have been identified. The frequency of CD27$^{(-)}$Syk^{bright} B-cells were significantly increased in SLE compare to HD, however the disease activity (SLEDAI) do not correlate with the frequency of this subset. No significant increase in the frequency of this population was observed in others autoimmune diseases (*i.e.* RA and pSS). This subset showed an accumulation of Syk within the cytoplasm, a superior response to the BCR and plasma cell differentiation compared to CD27$^{(-)}$ Syk^{dim} B-cells. Finally, this subset exhibited a memory-like phenotype.

Conclusion: A novel subset of B-cells defined as CD27$^{(-)}$Syk^{bright} B-cells and carrying memory features has been identified in SLE patients. This population represents a prime candidate how peripheral check point control of conventional B cells can be possibly bypassed in SLE.

Disclosure: S. J. Fleischer, None; **C. Daridon**, None; **T. Dörner**, None.

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Gene Expression Profiling Analysis Of Human B-Cell Subsets In Health and Systemic Lupus Erythematosus. Chungwen Wei[1], Edward Ramos[1], Norm Allaire[2], Suzanne Szak[2], Susan Kalled[2], Ann Ranger[2] and Ignacio Sanz[1]. [1]Emory University, Atlanta, GA, [2]Biogen Idec Inc, Cambridge, MA.

Background/Purpose: SLE is an autoimmune disease, which exhibits multiple B cell abnormalities including expanded populations of plasmablasts and DN memory cells as well as a contracted unswitched memory subset. The transcriptional profiles that underlie these homeostatic changes are poorly understood. To remedy this knowledge gap and generate insight into the disease pathogenesis, we carried out transcriptome analysis of sorted B cell subsets.

Methods: B cell subsets were flow sorted from 12 healthy controls (HC) and 13 SLE patients with low disease activity (SLEDAI<6): naïve (IgD^{+}CD27^{-}), unswitched memory (IgD^{+}CD27^{+}), switched memory (IgD^{-}CD27^{+}), DN memory (IgD^{-}CD27^{-}) and plasmablasts (IgD^{-}CD27^{++}CD38^{++}). Total RNA was hybridized to Human Genome U133 Plus 2.0 GeneChip (Affymetrix). The scans were subjected to quality control measures and the resulting CEL files normalized with Robust Multi-array Average (RMA). All calculations and analyses were carried out using R/Bioconductor computational tools. To identify differentially expressed genes (DEGs) between groups of samples, a two-way ANOVA model using Method of Moments was applied. Gene that exhibited a FDR <0.05 and fold change >2 or <-2 were considered significantly different.

Results: Overall, there are fewer DEGs among the three memory B cell subsets than between naïve and each of the three memory subsets in both healthy subjects and SLE patients, suggesting that the gene expression program is quite similar among all the memory B cells in HC and SLE. IL4R and IL21R are upregulated in naïve cells whereas IL6R is over-expressed in memory cells. Also upregulated in naïve cells is TCL1A, which promotes Akt-mediated survival. TACI is upregulated in the switched and unswitched memory subsets compared to naïve cells in HC and SLE, and is higher in SLE DN B cells compared to the same population in HC. SLE DN cells had also higher levels of AICDA and FcRL4. Overall, most DEGs differentials between the two cohorts were identified in the DN subset. Within either cohort, thousands of DEGs were observed between plasmablasts and the other four B cell subsets.

Conclusion: The transcriptome of multiple B cell subsets was remarkably similar between HC and SLE patients with low disease activity suggesting that most differences in active disease may be due to extrinsic differences. Our results are consistent with the important role of IL-4 and IL-21 as growth factors for naïve cells and the known activity of IL-6 in memory differentiation into plasma cells. Of great interest is the upregulation of TACI, AICDA and FcRL4 in DN B cells, a population expanded in SLE. The implications for the potential germinal center origin and activation status of these cells, reported to represent exhausted cells in HIV infection, will be discussed.

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IgD- CD27- B Cells From Systemic Lupus Erythematous Patients Have Increased Expression Of Genes Involved In RNA Sensing and Toll-Like Receptor 3 Signaling Pathways. Scott Jenks[1], Edward Ramos[2] and Ignacio Sanz[1]. [1]Emory University School of Medicine, Atlanta, GA, [2]Emory University, Atlanta, GA.

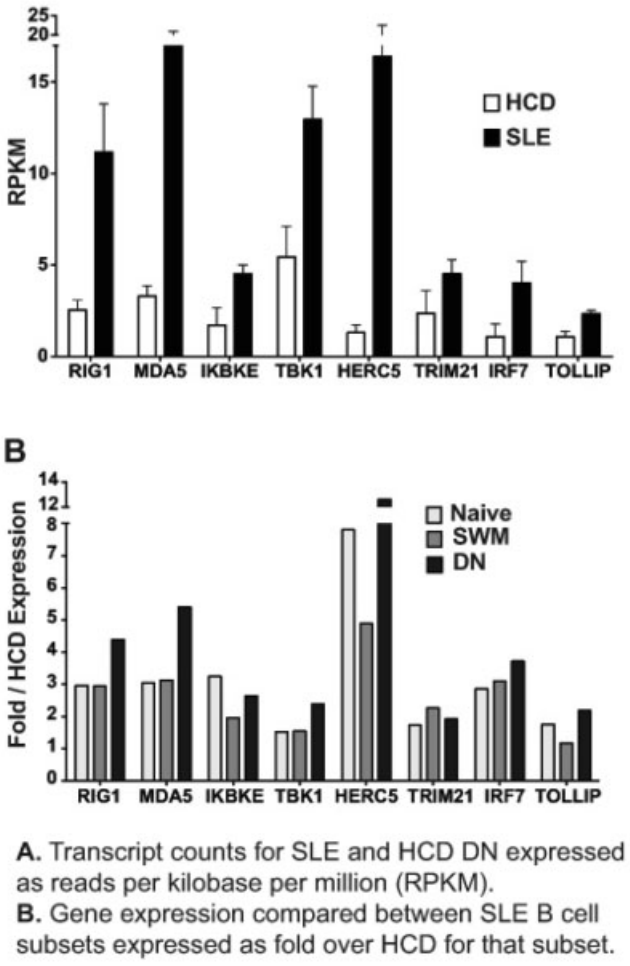
Background/Purpose: SLE patients have perturbations in B cell subsets including a large expansion of IgD-CD27- B cells (DN) in patients with active disease. Patients also have changes in PBMC gene expression, particularly increased expression of interferon regulated genes (IRG). However, data on gene expression in SLE B cells is limited. The purpose of this study was to understand the function and potential dysregulation of DN in SLE by comparing differences in gene transcription between B cell subsets from SLE patients and healthy control donors (HCD).

Methods: RNA was isolated from B cells from 3 HCD and 3 SLE patients with elevated DN sorted into naive (IgD+CD27-CXCR5+), switched memory (IgD-CD27+CXCR5+), and DN (IgD-CD27-CXCR5-) subsets. After amplification, high throughput sequencing of cDNA was used for transcriptional expression profiling. Sequencing data was processed and analyzed using the Tuxedo suite and EdgeR software package. Genes were tested for differential expression using a three way ANOVA model.

Results: 115 of the 249 genes differentially expressed in B cells between SLE patients and HCD were IRG. In addition to previously defined IRG, pathway analysis found several genes involved in TLR-3 and RNA sensing signaling pathways. These included RNA sensing molecules RIG1 and MDA5, downstream kinases IKBKE and TBK1, kinase substrate and transcription factor IRF-7, and HERC5 and TRIM21, molecules that regulate IRF stability. Of these only IRF-7 has been previously described as differentially expressed in SLE B cells. While, expression for most genes was increased in all B cell subsets, the DN subset showed the largest increase in expression for all genes except IKBKE and TRIM21. The DN subset also had increased expression and differential splicing of TOLLIP, an inhibitor of MyD88 mediated TLR signaling.

Conclusion: IKBKE and TBK1 are key signaling kinases for detecting RNA through the TLR3 and MDA5/RIG1 pathways. These pathways detect viral RNA but are also activated by endogenous RNA from apoptotic cells. Increased expression of IKBKE and TBK1 in SLE B cells is accompanied by the expression of both the upstream receptors and downstream kinase substrate. Furthermore, while TRIM21 mediates degradation of IRF-7, expression of TRIM21 was lowest in the DN and these cells expressed high levels of HERC5, which prevents IRF degradation. Coordinated expression of these genes strongly suggests these pathways are more active in SLE B cells and particularly in the DN population. In SLE, RNA from apoptotic cells can be internalized in RNP and Ro60 immune complexes through Fc receptors(FCR) and are thus available to MDA5/RIG1 and TLR-3. DN express high levels of FCR. This combined with increased expression of these signaling molecules likely results in RNA antigens having a powerful pro-inflammatory influence on DN.

Figure 1



A. Transcript counts for SLE and HCD DN expressed as reads per kilobase per million (RPKM).
B. Gene expression compared between SLE B cell subsets expressed as fold over HCD for that subset.

Disclosure: S. Jenks, None; **E. Ramos**, None; **I. Sanz**, Pfizer Inc, 5, Biogen Idec, 9.

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Understanding The Stimulatory Pathways Responsible For Naïve B Cell Activation In Systemic Lupus Erythematosus. Emily Blalock, Chris Scharer, Scott Jenks, Jeremy Boss and Ignacio Sanz. Emory University School of Medicine, Atlanta, GA.

Background/Purpose: Systemic lupus erythematosus (SLE) is a recurrent autoimmune disease characterized by multiple B cell abnormalities, including the activation of naïve B cells. However, gaps in terms of our knowledge regarding the extent and mechanisms of activation remain. We therefore investigated the expression of activation markers on activated naïve (aN) and resting naïve (rN) B cells of SLE patients as well as the stimulatory pathways responsible for their expression.

Methods: Multidimensional flow analysis was utilized to determine levels of B cell activation markers including CD21, CD23, CD24, CD25, CD69, CD80, CD83, CD86, and IgM on aN and rN B cells of SLE patients with active disease versus healthy controls (HC). In addition, total PBMCs from SLE and HC patients were stimulated *ex vivo* with B cell receptor (anti-kappa or anti-lambda), T cell (CD40L), or cytokine stimulation for 16 h, 48 h, and 4 days and compared via flow analysis. Lastly, we compared the epigenome of SLE aN and rN by analyzing their genome-wide DNA methylation status using MeDIP-Seq.

Results: Compared to HC, aN B cells, globally defined by Mitotracker green retention, from SLE patients exhibited low levels of CD21, CD24, CD69, and CD83, while CD86 levels were up-regulated. Following stimulation, aN B cells of SLE patients exhibited increased levels of CD21, CD25, CD69, CD80, CD83, and CD86 and decreased levels of CD24 at 16 h post-stimulation. Levels of CD21 and CD25 decreased at 48 h, followed by CD83 levels on day 4 post-stimulation. Expression of CD69, CD80, and CD86 remained high at all time points. However, aN B cells of SLE patients exhibited differential expression of CD23 and IgM based on stimulation type. Global DNA methylation analysis of aN B cells from an SLE patient revealed several genes, including interferon-regulated genes, were hypomethylated when compared to the HC. Interestingly, the CD83 gene was hypermethylated in aN B cells of the SLE patient; a result consistent with low CD83 levels observed via flow staining and RNASeq transcriptional analysis performed on several SLE patients.

Conclusion: Activated naïve B cells of SLE patients differentially express activation markers including CD21, CD24, CD83, and CD86. The stimulation of total PBMCs through distinct pathways reveals that activation markers are temporally expressed on aN B cells of SLE patients only to decrease with prolonged stimulation, as would be expected *in vivo*. Epigenetic analysis indicated hypermethylation of CD83, a result consistent with flow and transcriptional studies. Decreased expression of CD83 could help explain several phenotypic characteristics of lupus B cells including: decreased marginal zone maturation, decreased IL-10 production, and increased Ig secretion [1, 2]. Our results provide important clues regarding abnormal B cell function, highlighting the power of integrated experimental approaches to address this problem.

1. Kretschmer, B., et al., *CD83 modulates B cell function in vitro: increased IL-10 and reduced Ig secretion by CD83Tg B cells.* PLoS One, 2007. **2**(8): p. e755.

2. Luthje, K., et al., *CD83 regulates splenic B cell maturation and peripheral B cell homeostasis.* Int Immunol, 2008. **20**(8): p. 949–60.

Disclosure: E. Blalock, None; **C. Scharer**, None; **S. Jenks**, None; **J. Boss**, None; **I. Sanz**, Pfizer Inc, 5, Biogen Idec, 9.

33

B Cell Receptor Signaling As A Potential Clinical Parameter In Lupus. Michael Faludi, Christian A. Pineau, Evelyne Vinet, Ann E. Clarke, Sasha Bernatsky, Joyce Rauch and Emil P. Nashi. McGill University Health Center, Montreal, QC.

Background/Purpose: B cells are central to SLE. Signaling through the B cell receptor (BCR) controls critical processes at various stages of B cell development. Murine BCR manipulation and human genomic studies have implicated the BCR pathway in SLE, but few studies have assessed this pathway in patients.

Methods: Ethics committee approval was obtained. Blood lymphocytes were isolated from patients with SLE and other autoimmunities, and normal controls; cells were frozen in liquid nitrogen. Detailed clinical parameters were obtained. 100 000 B cells were stimulated with 20 ug/mL anti-IgM and anti-IgG for 0 or 5 minutes, and a 10-color flow cytometry panel was used to identify the following B cell subsets: naïve mature, transitional, IgM memory, IgG memory, IgG B1 and IgM B1. We assayed surface BCR levels, pSyk (early signaling), pPLC-γ2 (mid-point), pERK1/2 (late) and carboxy-pLyn (regulation). Triplicates of each assay, daily bead-based voltage adjustment, and replication of all experiments on separate days ensured signal stability.

Results:

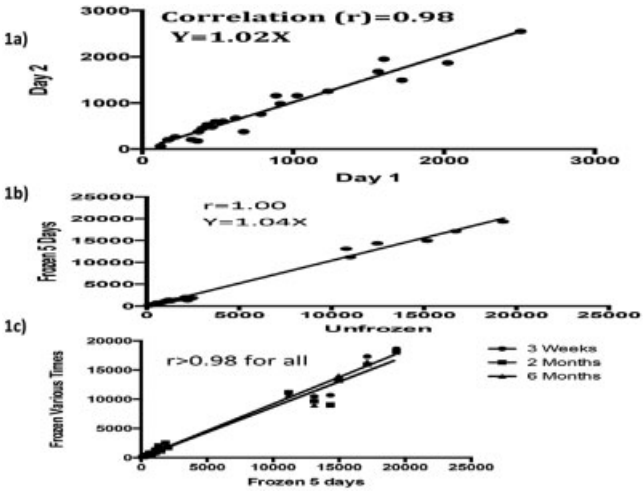

Fig 1. Stability of BCR signal. We found consistently high correlation between assays run on separate days (1a), between frozen and unfrozen cells (1b) and cells obtained at various times from the same person (1c). Each dot represents the fluorescence of one signaling parameter in a specific B cell subset.

2a)

pERK1/2	Transitional	IgM Memory	IgG Memory
Patient 1	1390 ↑	1200 ↓	1625 ←→
Patient 2	1244 ↑	1038 ↓	1613 ←→
Patient 3	1124 ↑	993 ↓	1718 ←→
Average for all patients	938	1859	1782

2b)

Transitional B cells	IgM	pSyk	pPLC-g2	pERK1/2
Patient 1	27334	381	1047	1390
Patient 2	16643	427	767	1895
Patient 3	16014	196	558	760
Average for all patients	17056	229	602	938

Fig 2. The importance of studying different B cell subsets and BCR stages. Some patients had increased signal in one subset but decreased or normal in other subsets (2a). Signaling deviation can occur at different stages (2b, yellow highlights).

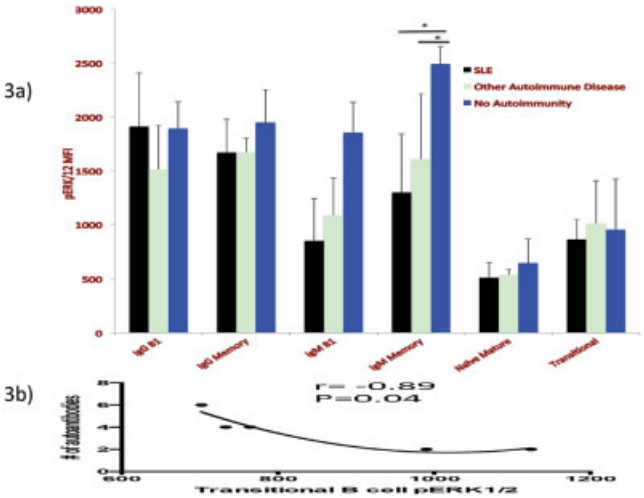

Fig 3. Signaling in 15 patients. Diminished IgM Memory BCR signal was found in SLE and other autoimmunities versus controls (3a). Among SLE patients, diminished signal in transitional B cells correlated with increased number of autoantibody specificities (3b).

Conclusion: We have optimized a flow cytometry-based technique that allows simultaneous study of BCR signaling in B cell subsets, at various stages of signaling, in a manner that yields stable results over time. We found that diminished BCR signaling in transitional B cells correlates with increased diversity of autoantibodies in SLE patients. We will study 150 patients. Clinical BCR measurement may inform SLE pathogenesis and guide emerging BCR-targeted therapies.

Disclosure: M. Faludi, None; **C. A. Pineau**, None; **E. Vinet**, None; **A. E. Clarke**, None; **S. Bernatsky**, None; **J. Rauch**, None; **E. P. Nashi**, None.

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Dichotomous Responses Of Human Systemic Lupus Erythematosus B Cell Subsets To B Cell Receptor Stimulation. Franziska Matzkies, Anthony DeFranco, Andrew J. Gross, Maria Dall'Era and Michelle Hermiston. University of California, San Francisco, San Francisco, CA.

Background/Purpose: Autoantibody production is a hallmark of Systemic Lupus Erythematosus (SLE), supporting a central role for B cells in disease pathogenesis. Prior studies have demonstrated augmented B cell receptor (BCR) signaling in a subset of SLE patients relative to healthy controls (HC). Both B cell intrinsic factors such as aberrant signal network wiring and B cell extrinsic factors such as excessive cytokines have been implicated in loss of B cell tolerance and B cell hyperactivity. However, previous studies have generally examined these parameters in total peripheral blood B cells rather than in well defined subpopulations. This is an important distinction because BCR signaling in mature naive B-cells leads to proliferation and survival, while these same signals lead to receptor editing, depletion or anergy in immature cells. We hypothesize that dysregulation of these signaling networks could contribute to SLE pathogenesis.

Methods: Peripheral blood was obtained from 12 patients satisfying ACR SLE criteria and 12 HC that lacked a family history of autoimmune disease. To minimize confounding influences of cytokines, patients had low disease activity (SLEADI$<$5). B cells were enriched with RosettespTM and ficoll, rested at 37°C for 1 hr, stimulated with 10 μg/ml (low dose) or 50 μg/ml (high dose) of F(ab')2 goat anti-human IgM or phorbal 12-myristate 13-acetae (PMA), immediately fixed, and processed for flow cytometry. Phosphorylation of intracellular signaling proteins (pSyk, pPLCg, pERK, pAKT, pS6) in transitional ($CD20^{+}CD27^{-}CD24^{Hi}CD38^{Hi}$) and naïve ($CD20^{+}CD27^{-}CD24^{Int}CD38^{Int}$) B cells was measured using FlowJo 8.8.7 and Cytobank software.

Results: The basal phosphorylation states of Syk, ERK, PLCg, and S6 were increased in both transitional and naïve B cells of SLE patients relative to HCs. Upon BCR ligation, both transitional and naïve SLE B cells demonstrated augmented phosphorylation of SYK, ERK, and PLCg relative to HC. Surprisingly, these same patients displayed hypo-phosphorylation of S6 in response to the same stimuli. Interestingly, hypo-activation of S6 was observed in mature naïve but not transitional B cells. The response to stimulation with PMA, which bypasses proximal signaling machinery, was equivalent in SLE and HC B cell subsets, indicating that the difference in signaling was upstream of S6.

Conclusion: We find that both transitional and naïve B cells obtained from SLE patients with well-controlled disease have increased activation of the MAPK pathway in the basal state and in response to BCR stimulation. Phosphorylation of S6, which is downstream of the PI3K/AKT/mTOR pathway, is also elevated in the basal state in SLE B cell subsets, but surprisingly *hypo*phosphorylated in naïve mature but not transitional B cells in response to BCR ligation in these same patients. While S6 is a target of the PI3K pathways after BCR ligation, it also receives inputs through growth hormone and cytokine receptors as well as the mTOR complex, which plays a key role in sensing energy and nutritional levels. Current investigations are under way to identify the mechanisms mediating these observations and their relation to SLE pathogenesis.

Disclosure: F. Matzkies, None; **A. DeFranco**, None; **A. J. Gross**, None; **M. Dall'Era**, None; **M. Hermiston**, None.

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Defective Regulatory Function Of Granzyme B-Producing B Cells In Patients With Systemic Lupus Erythematosus. Naoko Ueki, Hiroaki Niiro, Shun-ichiro Ota, Hirofumi Tsuzuki, Siamak Jabbarzadeh-Tabrizi, Yuri Hirosaki, Kumiko Noda, Naoyasu Ueda, Atsushi Tanaka, Masahiro Ayano, Sho Ueda, Satomi Hisamoto, Daisuke Oryoji, Mitsuteru Akahoshi, Yojiro Arinobu, Hiroshi Tsukamoto, Takahiko Horiuchi and Koichi Akashi. Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan.

Background/Purpose: The efficacy of B-cell depletion therapy highlights a pathogenic role of B cells in autoimmune diseases. In certain conditions, elimination of B cells can lead to exacerbation of these diseases, suggesting the existence of regulatory B cells (Bregs). Bregs are often referred to as IL-10-producing B cells, however it is possible that Bregs can exert a regulatory function by an IL-10-independent mechanism. Granzyme B (GzmB) is known to exert both cytotoxic and non-cytotoxic effects on various cell types. In this study, we have determined whether granzyme B (GzmB)-producing B cells could function as another type of Bregs in humans, and also have tested their functions in patients with systemic lupus erythematosus.

Methods: Levels of GzmB mRNA and protein in B cells were assessed using quantitative real-time PCR and intracellular staining, respectively. To evaluate the function of GzmB-producting B cells, they were co-cultured with activated T cells, and growth, survival and cytokine production of T cells were then assessed using flow cytometry.

Results: Among the stimulators tested, IL-21 was the potent inducer of GzmB in normal B cells and it acted synergistically with antigen receptor stimulation. Naive B cells produced higher levels of GzmB as compared with memory B cells. In addition, GzmB-producing B cells inhibited the growth, survival and cytokine production of T cells, which is in line with the idea that these cells function as Bregs in normal subjects. In SLE patients, naive B cells similarly produced more GzmB than memory B cells, however levels of its production in both subsets were apparently higher than those in normal subjects. Intriguingly, however, GzmB-producing B cells in SLE patients were without regulatory effects on T cell functions. A molecular explanation for these findings is now in progress.

Conclusion: Our current findings could help to better understand a role of Bregs in the pathogenesis of autoimmune diseases as well as to provide a novel clue to manipulate the generation of Bregs for therapeutic application in the future.

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IFN-α Induces Altered Transitional B Cell Signaling and Function In Systemic Lupus Erythematosus. Joan E. Wither[1], Nan-Hua Chang[2], Timothy Li[2], Julie Kim[2], Carolina Landolt-Marticorena[3], Paul R. Fortin[4], Dafna D. Gladman[5] and Murray B. Urowitz[5]. [1]Toronto Western Research Institute, Toronto Western Hospital, University of Toronto, Toronto, ON, [2]Toronto Western Hospital, Toronto, ON, [3]Toronto Western Hospital, University of Toronto, Toronto, ON, [4]Centre de Recherche du Chu de Québec et Université Laval, Quebec City, QC, [5]University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Previous experiments suggest that the B cells of lupus patients are hyper-responsive to B cell receptor engagement resulting in increased tyrosine phosphorylation and Ca^{2+}mobilization. However the precise B cell populations that are affected and the mechanisms leading to this hyper-responsiveness have yet to be determined. In this study we have used Phosflow to address these questions.

Methods: PBMC were isolated from 27 healthy controls and 39 SLE patients with $\geq$ 4 ACR criteria. Phosflow was used to assess the levels of p-SYK, p-PLCγ2, or p-ERK following Ig receptor engagement with goat anti-human IgM $F(ab')_2$in distinct B cell subsets defined by anti-CD19,-CD27, -IgD, -IgM and -CD38. B cell proliferation and apoptosis following anti-IgM stimulation were assessed by flow cytometry, using CFSE and annexin V staining, respectively. For some experiments, healthy control B cells were incubated with IFN-α, or 50% plasma $\pm$ anti-IFN or irrelevant Ab. Lupus associated SNPs were determined by TaqMan genotyping.

Results: There were increased basal levels of p-SYK and p-ERK in naïve B cells ($CD19^+CD27^-IgD^+$) from lupus patients as compared to controls. The levels of basal p-SYK correlated with CD86 expression suggesting that these cells had already been activated in-vivo. Following crosslinking with anti-IgM, there was a significant increase in the proportion of p-SYK^+ cells above basal levels in the naïve B cell population of lupus patients as compared to controls. Similar trends were seen for the proportion of p-PLC$\gamma2^+$ and p-ERK^+ cells. The increases seen in p-SYK^+ cells were most marked for the transitional B cell subset ($CD19^+CD27^-IgD^+CD38^{hi}IgM^{hi}$), where the levels of p-SYK correlated with enhanced proliferation and survival. There was no correlation between lupus associated SNPs in BLK, LYN, PTPN22, and CSK, and the proportion of p-SYK^+ cells following IgM crosslinking. The proportion of p-SYK^+cells in the transitional B cell subset fluctuated between visits, suggesting a possible role for pro-inflammatory factors. Consistent with this, incubation of lupus plasma with control B cells enhanced SYK phosphorylation following IgM crosslinking, which was blocked by pre-incubation of plasma with anti-IFN but not irrelevant Ab. Incubation of healthy control cells with recombinant IFN-α enhanced SYK phosphorylation, proliferation, and survival following IgM crosslinking, particularly of the transitional B cell subset.

Conclusion: IFN-α alters transitional B cell function leading to enhanced survival and proliferation. As purging of transitional B cells plays an important role in preventing autoreactive B cells from entering the mature B cell pool, it is likely that elevated levels of IFN-α exacerbate the breach of B cell tolerance in lupus.

Disclosure: J. E. Wither, None; **N. H. Chang**, None; **T. Li**, None; **J. Kim**, None; **C. Landolt-Marticorena**, None; **P. R. Fortin**, None; **D. D. Gladman**, Janssen, Abbvie, Amgen, Pfizer, UCB, Novartis, Lily, Celgene, 2, Janssen, Abbvie, Amgen, Pfizer, UCB, Novartis, Lily, Celgene, 5; **M. B. Urowitz**, None.

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Follicular Entry Of Lymphotoxin-Expressing B Cells Via Type I Interferon Disrupts Marginal Zone Barrier Integrity and Exacerbates Systemic Autoimmunity. Hao Li[1], Hui-Chen Hsu[2], Qi Wu[1], Jun Li[1], PingAr Yang[1], Yang-Xin Fu[3] and John D. Mountz[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Birmingham VA Medical Center, Birmingham, AL, [3]The University of Chicago, Chicago, IL.

Background/Purpose: Marginal zone macrophages (MZMs), a small subset of specialized splenic macrophages located in the MZ, act as final follicular entry barrier to clear apoptotic cells (ACs) to prevent AC antigens (Ags) entering to the spleen follicles. We recently reported reduced tolerogenic function, frequency and numbers of MZMs in the spleen of lupus prone BXD2 mice. Loss of MZMs were further confirmed in B6 Sle1.Sle2.Sle3 mice and lupus patients. Expression of lymphotoxin (LT) by B cells has been implicated as a critical factor to maintain MZMs. The present study investigated how type I interferons (IFNs) dissociated this interaction and induced MZM loss in lupus.

Methods: Confocal microscope and FACS analysis were carried out to determine the percentages and location of of MZMs, B cells and the distribution of LT and its receptor (LTβR) in the spleen. A mixed bone marrow (BXD2-GFP^+*Ifn$\alpha r^{+/+}$*:BXD2-GFP^-*Ifn$\alpha r^{-/-}$* =1:1) reconstitution in BXD2 *Rag2*$^{-/-}$ mice was carried out to determine if type I IFNs affect MZ integrity through direct action on MZMs or indirectly by affecting B cells. LT-LTβR interaction *in vivo* was disrupted by repeated injection of mice with a low dose of LTR fusion protein (LTR:Fc, 15 ug/mouse per week, 4 weeks) or by administrations of CpG (2.5 ug/mouse, every other day for 2 weeks).

Results: Repeated injections of CpG to B6, but not B6-*Ifn$\alpha r^{-/-}$* mice, induced loss of MZMs. Consistent with this, the spontaneous loss of MZMs and the elevated autoantibodies against MZM Ags, Marco and scavenger receptor A, in BXD2 mice were prevented in the absence of type I IFN signaling. Marginal zone B cells (MZs) are the major LT expressing cells in the marginal zone. Although there was comparable expression of LT, MZs were mainly localized in the follicles in BXD2 mice but in the marginal zone in both B6 and BXD2-*Ifn$\alpha r^{-/-}$* mice. BM reconstitution experiment further shows that the absence of type I IFNR did not directly affect MZM repopulation, but rather affected MZ B cell distribution. GFP^+*Ifn$\alpha r^{+/+}$* B cells mainly migrated to the follicles whereas GFP^-*Ifn$\alpha r^{-/-}$*B cells remained in the marginal zone and became the source of LT to support MZMs. Administration of a low dose of LTR:Fc to BXD2 mice selectively depleted MZMs and enhanced the spontaneous germinal center (GC) response without affecting follicular dendritic cell networks.

Conclusion: Our present study suggests a novel mechanism associated with type I IFN-promoted immune response against apoptotic self-Ags as a result of follicular migration of LT expressing and self-antigen carrier B cells. The shift of LT expressing B cells from the MZ to the follicles by type I IFNs

promoted apoptotic Ag delivery and LT stimulation to FDCs via breaking down the marginal zone barrier and finally exaggerated the production of pathogenic auto-antibodies.

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Use Of An In Vitro Whole Blood Depletion ASSAY To Compare The Efficacy Of B CELL Depleting Agents In Patients With Systemic LUPUS Erythematosus. Venkat Reddy[1], Geraldine Cambridge[1], D.A. Isenberg[1], Mark Cragg[2] and Maria Leandro[1]. [1]University College London, London, United Kingdom, [2]Southampton University, Southampton, United Kingdom.

Background/Purpose: Variability in clinical response to B-cell depletion therapy (BCDT) with the anti-CD20mAb rituximab (RTX) has been well described in Systemic Lupus Erythematosus (SLE). Poor clinical response is associated with incomplete depletion which suggests that improving the efficiency of depletion might result in improved therapeutic outcome. GA101 is a recombinant, afucosylated fully human type II anti-CD20 mAb that has shown more effective depletion and clinical response in phase II trials in lymphoma. We have therefore compared the in vitro B-cell cytotoxicity (cytotoxicity index, CTI) of BHH2 (glycosylated GA101) with RTX, in lymphocytes from patients with SLE.

Methods: We included 23 patients with SLE, who met the American College of Rheumatology revised classification criteria. An *in vitro* autologous whole blood depletion assay (WBD) was used to assess the CTI. Briefly, 100μl of heparinised blood was incubated with either RTX, BHH2 or without antibody, at a concentration of 1μg/ml at 37°C, 5% $CO_2$for 24hours. Samples were then analysed by flow cytometry for CD45 (all lymphocytes), CD3 (T cells) and CD19 (B cells). The CTI was calculated using the formula:CTI of mAb=100-[(number of B:Tcells in sample without antibody-number of B:Tcells with mAb)/number of B:T cells in sample without antibody) $\times$ 100] and the mean from triplicate well calculated. The relationship between the relative expression (mean fluorescence intensity;MFI) of CD20 and CD32B (FcgRIIB) on B cells and CTI was determined using spearman rank correlation. Concurrent clinical and laboratory parameters including anti-dsDNA and C3 were collected and assessed.

Results: The mean CTI of BHH2 was higher than RTX in all but one patient. Median CTI in 23 SLE patients was 20% (range9–70) and 15% (range 1–42), for BHH2 and RTX, respectively ($p=0.0002$). CTI was $<25\%$ in 5 (21%) and 16 (73%) patients, for BHH2 and RTX, respectively. The mean$\pm$SD MFI of CD20 and CD32B on SLE-B cells was 9079$\pm$4025 and 4223$\pm$1587, respectively. The CTI of neither mAb correlated with the expression of CD20 ($r^2=-0.332,0.204$, for BHH2 and RTX, respectively). Also, there was no correlation between the CTI of mAbs and lymphocyte-count, serum creatinine, total IgG, C3, positivity for ENAs or anti-dsDNA.

Conclusion: These results indicate that BHH2 is superior to RTX at inducing cytotoxicity *in vitro* in B cells from patients with SLE. This study provides the preliminary data to consider type II mAbs (GA101-like) as an alternative BCD agent for SLE in a clinical trial setting.

Disclosure: V. Reddy, None; **G. Cambridge**, None; **D. A. Isenberg**, None; **M. Cragg**, None; **M. Leandro**, None.

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Chaperone-Mediated Autophagy As a Target Of Therapeutic P140 Peptide Used In Lupus. Sylviane Muller. CNRS, Strasbourg, France.

Background/Purpose: In the pipeline of molecules with a potential for treating lupus patients, the P140 peptide/Lupuzor holds a lot of promise. P140 is a 21-mer linear peptide (sequence 131–151) that is derived from the small nuclear ribonucleoprotein U1–70K and that is phosphorylated at the Ser^{140}position. In a multicenter, randomized, placebo-controlled phase IIb study, Lupuzor was safe and met its primary efficacy end points in lupus patients (Zimmer et al., 2012). These results confirm data generated in MRL/lpr lupus-prone mice in which the preclinical studies were performed. The mechanism of action of P140 was further studied in this mouse model.

Methods: Immunocytochemical analyses were used to identify the way of P140 entry into B cells, and CMA activity was assessed in fibroblasts stably expressing a photoactivable CMA reporter. FACS analyses after LysoTracker and LysoSensor staining of isolated B cells were used to study the number and acidity of lysosomes in B cells from MRL/lpr mice.

Results: We found previously that P140 reduces autophagic flux in MRL/lpr B cells (Page et al., 2011) and that macroautophagy (the best characterized type of autophagy) is abnormally enhanced in T lymphocytes from lupus mice and patients (Gros et al., 2012). In this work, we show that a selective form of autophagy, chaperone-mediated autophagy (CMA), is a key target of P140 and demonstrate that the P140 inhibitory effect on CMA results from its ability to alter the integrity of the HSC70/hsp90 heterocomplex of lysosomal chaperones. Expression of HSC70 and LAMP-2A, the two main CMA components, which is increased in MRL/lpr B cells, is down-regulated after P140 treatment. P140 enters MRL/lpr B lymphocytes via a clathrin-dependent endo-lysosomal pathway and accumulates at the lysosomal lumen. There, it may act both by directly hampering HSC70 chaperoning functions and, as a result of loss of hsp90 function, by destabilizing LAMP-2A in lysosomes. This dual effect may interfere with the endogenous (auto)antigen processing and loading to MHCII molecules and as a consequence, lower activation of autoreactive T cells.

Conclusion: Our findings provide the first demonstration showing that P140 peptide acts directly on CMA. These results shed light on mechanisms by which P140 can modulate lupus disease and by which it may operate in humans affected by this disorder.

Disclosure: S. Muller, None.

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Preclinical Characterization Of a Humanized Antagonistic Anti-CD40 Mab. Kerry Ralph, Amy Nicoletti, Eunice Musvasva, Susan Cannan, Susan VanTongeren, Diann Blanset, Scott Brodeur, Jennifer Ahlberg, Hua Li, Steve Fogal, Sudha Desai, Kathy O'Shea, Rachel Kroe-Barrett, Gerald Nabozny, Helen Wu, Gale Hansen, Keith Canada, Sanjaya Singh, Meera Ramanujam and Christine Grimaldi. Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT.

Background/Purpose: CD40-CD40L interactions play a central role in T-B cell costimulation. Targeting this pathway has generated great interest; however early attempts to target CD40L failed mainly due to thrombotic complications observed in the clinic. In addition, developing antagonistic CD40 antibodies with suitable potency, favorable PK and no agonistic activity has proven to be challenging. BI 655064 is an anti-human CD40 mAb being developed for the treatment of autoimmune disorders. BI 655064 is engineered as a human IgG1 molecule with a mutated Fc region to abrogate effector function. Here we describe the preclinical characterization of BI 655064.

Methods: Binding of BI 655064 to CD40 expressed on primary B cells was measured by flow cytometry. The ability of BI 655064 to block CD40L-induced B cell proliferation *in vitro* was measured by tritium uptake. A subcutaneous PK/PD study in the cynomolgus monkey was performed to establish correlations between BI 655064 exposure, target coverage using a receptor occupancy assay and pharmacodynamic effects using an *ex vivo* CD54-induction assay. *In vivo* blockade of B cell function was also tested in a human-peripheral blood lymphocyte (huPBL) induced SCID mouse model of graft-versus-host disease (GvHD) and in cynomolgus monkeys immunized with keyhole limpet hemocyanin (KLH).

Results: BI 655064 binds human CD40 on B cells present in whole blood with an EC90 value of 6.85 nM $\pm$ 0.74. Blockade of CD40L-induced B cell proliferation was observed at an average IC50 of 0.4 nM. In the PK/PD study, cynomolgus monkeys dosed with greater than 1 mg/kg of BI 655064 exhibited complete blockade of *ex vivo* CD54 upregulation corresponding to full CD40 target coverage on B cells. *In vivo*, BI 655064 demonstrated clear effects on B cell function in the GvHD model where both human IgM and IgG responses were abrogated. As part of a repeat dose tolerability study, BI 655064 given to cynomolgus monkeys prior to immunization with KLH resulted in inhibition of KLH-specific IgM and IgG antibody responses. At doses of 5 mg/kg and above, germinal center size was decreased microscopically in Peyer's patches, lymph nodes, spleens and tonsils in treated monkeys.

Conclusion: BI 655064 is a humanized antagonistic anti-CD40 mAb which is to be tested in human clinical trials for autoimmune disorders to establish safety and efficacy. BI 655064 demonstrated relevant pharmacologic *in vitro* and *in vivo* activity, blocking CD40-related functions at clinical dosing levels of $>$ 1 mg/kg in animal models.

Disclosure: K. Ralph, Boehringer Ingelheim, 3; **A. Nicoletti**, Boehringer Ingelheim, 3; **E. Musvasva**, Boehringer Ingelheim, 3; **S. Cannan**, Boehringer Ingelheim, 3; **S. VanTongeren**, Boehringer Ingelheim, 3; **D. Blanset**, Boehringer Ingelheim, 3; **S. Brodeur**, Boehringer Ingelheim, 3; **J. Ahlberg**, Boehringer Ingelheim, 3; **H. Li**, Boehringer Ingelheim, 3; **S. Fogal**, Boehringer Ingelheim, 3; **S. Desai**, Boehringer Ingelheim, 3; **K. O'Shea**, Boehringer Ingelheim, 3; **R. Kroe-Barrett**, Boehringer Ingelheim, 3; **G. Nabozny**, Boehringer Ingelheim, 3; **H. Wu**, Boehringer Ingelheim, 3; **G. Hansen**, Boehringer Ingelheim, 3; **K. Canada**, Boehringer Ingelheim, 3; **S. Singh**, Boehringer Ingelheim, 3; **M. Ramanujam**, Boehringer Ingelheim, 3; **C. Grimaldi**, Boehringer Ingelheim, 3.

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Targeting Cereblon With The High Affinity Immunomodulatory Compound CC-220: A Novel Therapeutic Agent For Autoimmunity. Peter Schafer[1], Emily Rychak[2], Derek Mendy[2], Stacey Parton[1], Lori Capone[1], Antonia Lopez-Girona[2], Dorota Cedzik[1], Jolanta Kosek[1], Ling-Hua Zhang[1] and Rajesh Chopra[1]. [1]Celgene Corporation, Summit, NJ, [2]Celgene Signal Research, San Diego, CA.

Background/Purpose: Cereblon (CRBN) is a component of the E3 ubiquitin ligase complex including CUL4A, DDB1, and ROC-1. CC-220 is a novel immunomodulatory compound currently in development for the treatment of immune conditions. The effects of CC-220 on CRBN binding and ubiquitination, and on immune cell responses were profiled.

Methods: Binding studies to CRBN were conducted using endogenous CRBN from human U266 plasmacytoma cells and affinity beads in a competition assay by quantitative immunoblot determination. CRBN ubiquitination was measured in HEK293T cells transfected with a His-biotin-tagged CRBN construct, treated with the MG132 proteasome inhibitor (to arrest degradation of ubiquitinated proteins). Cells were lysed and processed to measure CRBN ubiquitination by SDS-PAGE and immunoblot analysis. T-cell costimulation was measured in purified primary human T cells stimulated using immobilized anti-CD3 antibody. Cytokine secretion was measured by ELISA. Immunoglobulin M and G (IgG and IgM) production was measured from normal donor peripheral blood mononuclear cells by culturing in the presence of the B cell differentiation factors IL-2, IL-6, IL-10, IL-15, CD40L, and TLR9 ligand. IgM and IgG were measured by ELISA. Cell proliferation studies were conducted in H929 plasmacytoma cells assessed by 7-aminoactinomycin D (7-AAD) staining. Toll-like Receptor 4 (TLR4) stimulation was performed in human PBMC from subjects with SLE and SSc using lipopolysaccharide (LPS).

Results: In the competitive CRBN binding studies, CC-220 had a 50% inhibitory concentration (IC_{50}) of approximately 0.1 μM, compared with 3 μM for pomalidomide. CRBN ubiquitination studies in the transfected HEK293T cells resulted in an IC_{50} of 0.19 μM. CC-220 costimulated IL-2 production by T cells with an EC_{50} of approximately 0.29 nM, compared with 10 nM for pomalidomide. CC-220 inhibited IgM and IgG production with an IC_{50} of 0.35 and 2.1 nM, respectively, compared to 17 nM and 63 nM for pomalidomide. The IC_{50} value for inhibition of proliferation by CC-220 was 0.01 μM in the H929 plasmacytoma cell line. A 50% decrease in cell cycle (S-phase) was evident after 24 hours of treatment of H929 cells with CC-220. At 48 hours, CC-220 decreased expression of survivin and retinoblastoma protein (pRB) and increased expression of the cyclin-dependent kinase inhibitor p27. In LPS-stimulated PBMC from systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) patients, CC-220 significantly reduced production of pro-inflammatory cytokines including TNF-α, IL-1α, IL-1β, and IL-6, and increased production of IL-10.

Conclusion: The results indicate that CC-220 binds to CRBN and inhibits CRBN ubiquitination CC-220 enhances T cell IL-2 production, but inhibits B cell production of immunoglobulin and reduces plasma cell line proliferation. This compound also reduces the production of several key inflammatory mediators by SLE and SSc patients cells stimulated via the TLR4 pathway. In summary, CC-220 is a novel high affinity CRBN ligand with immunomodulatory effects and is currently in development for the treatment of immune and inflammatory diseases.

Disclosure: P. Schafer, Celgene, 3; **E. Rychak**, Celgene, 3; **D. Mendy**, Celgene, 3, Celgene, 1; **S. Parton**, Celgene, 3; **L. Capone**, Celgene, 3; **A. Lopez-Girona**, Celgene, 3; **D. Cedzik**, Celgene, 3; **J. Kosek**, Celgene, 3; **L. H. Zhang**, Celgene, 3; **R. Chopra**, Celgene, 3.

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Inhibition Of B Cell Differentiation To The Plasmablast and Plasma Cell Lineage By CC-220, a Potent Modulator Of The Cereblon E3 Ubiquitin Ligase Complex. Peter Schafer, Lori Capone, Lei Wu and Rajesh Chopra. Celgene Corporation, Summit, NJ.

Background/Purpose: CC-220 is an immunomodulatory compound which binds to the CUL4 family E3 ubiquitin ligase complex protein cereblon (CRBN) with high affinity and modulates the ubiquitination of substrate proteins. To explore the effects of CRBN targeting on the differentiation of B cells to the plasmablast and plasma cell lineages, CC-220 was tested in an in vitro model of primary human B cell differentiation.

Methods: CD19+ peripheral blood human B cells from normal donors, or total PBMC for patients with systemic lupus erythematosus (SLE), were cultured in the presence of cytokines and stimulatory ligands for one week. Cells were counted, viability assessed, and expression of CD20, CD38, CD44, and CD83 were measured by flow cytometry. Plasmablast lineage factors IRF-4, BLIMP-1, XBP-1, and IgJ, and germinal center markers PAX-5 and BCL-6 were measured by qRT-PCR. Intracellular protein expression was measured by laser scanning cytometry. Secreted immunoglobulins IgG and IgM were measured by ELISA.

Results: In B cell cultures, CC-220 decreased the percentage of viable CD20-CD38+ plasmablasts on day 7 from 30.4% in control cultures in a dose-dependent manner to 27.3%, 2.1%, and 0.4% at 2 nM, 20 nM, and 200 nM CC-220, respectively. On Day 7, qRT-PCR analysis showed that CC-220 (20 nM) reduced expression of the plasmablast lineage factors IRF-4, BLIMP-1, XBP-1, and IgJ gene expression to 20.5%, 14.3%, 15.1%, and 31.5% of control, respectively ($P \leq 0.001$). By intracellular flow cytometry, CC-220 (20 nM) significantly decreased IRF-4 ($P<0.5$), BLIMP-1 ($P<0.05$), and XBP-1 ($P<0.05$) protein expression at Day 4, but significantly increased BCL-6 ($P<0.05$) protein expression on Day 7. By laser scanning cytometry on Day 7, CC-220 (20 nM) reduced CD38+ cell intracellular protein expression of IRF-4 ($P \leq 0.001$), and BLIMP-1 ($P \leq 0.001$), and increased BCL-6 expression ($P \leq 0.05$) (n=3). CC-220 inhibited secreted IgG production with an IC_{50}=1.8 nM (n=3).

In PBMC from SLE patients, CC-220 (20 nM) had similar effects as in normal B cells, reducing BLIMP-1, XBP-1, and IgJ gene expression to 52.8%, 49.2%, and 13.6% of control, respectively ($P \leq 0.001$, n=3). CC-220 (20 nM) significantly reduced CD38+ plasmablast intracellular protein expression of BLIMP-1 ($P \leq 0.01$) and IRF-4 ($P \leq 0.001$), and increased BCL-6 ($P \leq 0.05$) (n=3). CC-220 inhibited secreted IgM and IgG production by SLE patient PBMC with IC_{50}s of 0.9 nM and 3.2 nM, respectively (n=3).

Conclusion: These results demonstrate that targeting of the E3 ubiquitin ligase complex substrate co-receptor CRBN with the small molecule immunomodulator compound CC-220 results in potent inhibition of B cell differentiation to the plasmablast lineage, as shown by a reduction in the percentage of viable CD38+ cells, a decrease in BLIMP-1, XBP-1, IRF4, and IgJ gene and protein expression, and inhibition of secreted immunoglobulin production. These data implicate the CUL4-CRBN complex in the differentiation of B cells to the plasma cell lineage furthermore define a novel pathway for treatment of immune inflammatory conditions. CC-220 is currently entering clinical development for the treatment of immune diseases associated with autoantibody production.

Disclosure: P. Schafer, Celgene, 3; **L. Capone**, Celgene, 3; **L. Wu**, Celgene, 3; **R. Chopra**, Celgene, 3.

ACR Poster Session A
Biology and Pathology of Bone and Joint (Cartilage and Osteoarthritis)
Sunday, October 27, 2013, 8:30 AM–4:00 PM

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Overexpression Of Lamin A In Mesenchymal Stem Cells Compromises Chondrogenesis and Enhances Adipogenesis. Jesús Mateos[1], Arancha Landeira[1], Alexandre De la Fuente[1], Iván Lesende-Rodríguez[2], Pablo Fernández-Pernas[2], Maria Carmen Arufe[1] and Francisco J. Blanco[3]. [1]CIBER-BBN, Zaragoza, Spain, [2]Department of Medicine, Area of Anatomy and Human Embryology, University of A Coruña-INIBIC, A Coruña, Spain, [3]Department of Medicine. University of Santiago de Compostela, Santiago de Compostela, Spain.

Background/Purpose: Previous work by our group and others indicated that an accumulation of lamin A (LMNA) is associated with the osteoarthritis (OA) chondrocyte phenotype. Mutations of this protein are linked to laminopathies and specifically to Hutchinson-Guilford Progeria Syndrome (HGPS), an accelerated aging disease. Some authors have proposed that a deregulation of LMNA affects the differentiation potential of stem cells. In the present study, we examined the effect of the over-expression of LMNA, on the mesoderm and, specifically, chondrocyte differentiation potential of Mesenchymal Stem Cells (MSCs).

Methods: MSCs from human umbilical cord (UC) stroma have previously been isolated, expanded and differentiated towards mesoderm cell lineages. For efficient gene delivery of wt LMNA and GFP (Green Fluorescence Protein) as control, we used a lentiviral expression system. Osteogenic potential was studied by with alizarin red staining and Real-Time PCR of ALP, OC and Runx2 to assess early and late osteogenic differentiation.

Adipogenic potential was studied with Oil Red staining and Real-Time PCR of LPL, FABP and ADIPOQ, for early and late adipogenic differentiation. Chondrogenesis and hypertrophy were studied using immunohistochemistry and Real-Time PCR of Aggrecan, MMP-13, Type II Collagen, Type I Collagen and Type I Collagen. Reactive oxygen species (ROS) generation was measured by flow cytometry and oriented migration capacity was tested in a Modified Boyden′s chamber assay.

Results: We found that over-expression of LMNA by lentiviral gene delivery leads to alterations in differentiation potential. Adipogenic capacity is increased in LMNA-MSCs, accompanied by an accumulation of Fatty Acid Synthase, as revealed by Western-blotting. The chondrogenic potential is defective in LMNA-MSCs, showing a decreased COL2/COL1 ratio and an increase in hypertrophy markers. These cells present lower levels of manganese superoxide dismutase (MnSODM) and an increase of mitochondrial MnSODM-dependent reactive oxygen species (ROS). This stable extra ROS generation is accompanied by alterations in the oriented migratory capacity of these cells under the effect of pro-inflammatory cytokines. ROS synthesis was partially and totally reverted by incubation with the ROS scavenger N-Acetyl Cystein (NAC) for 1 hour in culture. In addition, defects in chondrogenesis detected by immunohistochemistry and Real Time-PCR are partially reversed by periodic incubations with NAC for 1 hour.

Conclusion: Overall, our results show that chondrogenic differentiation of UC-MSCs is compromised by Lamin A deregulation whereas adipogenic differenciation is enhanced. We also demonstrated that this deregulation alters the oxidative stress balance in MSCs, modifies their migratory properties and induces defects in their capacity to differentiate into chondrocytes in our in vitro model. Further experiments are necessary to determine the in vivo significance of those alterations and to explore putative key targets for stem cell therapies in OA and other aging syndromes.

Disclosure: J. Mateos, None; **A. Landeira**, None; **A. De la Fuente**, None; **I. Lesende-Rodríguez**, None; **P. Fernández-Pernas**, None; **M. C. Arufe**, None; **F. J. Blanco**, None.

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Suppressor Of Cytokine Signaling 3 Negatively Modulates Leptin-Mediated Catabolic and Proinflammatory Effects In Cartilage - New Potential Mechanism To Target Obesity-Induced Osteoarthritis. Anna Koskinen, Katriina Vuolteenaho, Riku Korhonen, Teemu Moilanen and Eeva Moilanen. The Immunopharmacology Research Group, University of Tampere School of Medicine and Tampere University Hospital, Tampere, Finland.

Background/Purpose: Adipocytokine leptin has been suggested to link obesity and osteoarthritis (OA). Initially leptin was found to regulate energy metabolism through central nervous system. More recent studies have shown that leptin is also a proinflammatory factor in arthritis and has detrimental effects on cartilage including upregulation of proinflammatory and catabolic factors. However, we and others have found a significant variation in the leptin responses in cartilage samples between different donor patients. One of the factors that regulate the metabolic effects of leptin in hypothalamus is suppressor of cytokine signaling 3 (SOCS-3). SOCS-3 is also known as an important negative feedback mechanism of inflammatory signals in leukocytes. The aim of the present study was to investigate SOCS-3 as a possible modulator of leptin's detrimental effects in cartilage.

Methods: Cartilage samples from 97 OA patients undergoing knee replacement surgery were collected. Cartilage explants were cultured with leptin (10 μg/ml) for 42 hours. The expression of SOCS-3, inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 were measured by Western blotting. Matrix metalloproteinase (MMP)-1, MMP-3 and IL-6 were measured in the culture media by ELISA, and nitric oxide (NO) by the Griess reaction. The results were analyzed in an ANOVA model allowing for intergel variation of SOCS-3, and adjusting for BMI and age. The role of SOCS-3 in leptin signaling was further studied in H4 chondrocytes by downregulating SOCS-3 with siRNA.

Results: Leptin significantly enhanced the expression of NO, IL-6, MMP-1, MMP-3, iNOS and COX-2 in the cultured cartilage samples (fold of increase: 2.7 (6.2); 8.3 (30.5); 2.8 (3.4); 1.8 (1.2); 11.7 (160); 6.9 (18); median (IQR), respectively). There was a considerable variation in these responses between the cartilage samples from different donor patients, which was not explained by any clinical factor measured (BMI, age, sex, diabetic status, radiographic scaling of OA or macroscopic scaling of cartilage defects). Leptin responses were significantly higher in the cartilage samples with low SOCS-3 expression than in the samples with high SOCS-3 expression. In the ANOVA model, SOCS-3 was confirmed to negatively explain leptin-induced expression of NO, IL-6, MMP-1, MMP-3, iNOS and COX-2 independently of BMI and age ($p = 0.008$; 0.009; 0.064; 0.008; 0.001; 0.006, respectively). Accordingly, downregulation of SOCS-3 by siRNA in H4 chondrocytes enhanced leptin-induced expression of NO, iNOS, IL-6, MMP-3 and MMP-13.

Conclusion: Previous studies have shown that leptin levels are increased in obesity and leptin has detrimental effects in cartilage. The present results show that SOCS-3 negatively regulates catabolic and proinflammatory effects of leptin in cartilage, suggesting that SOCS-3 could be a future drug target in the treatment or prevention of obesity-induced OA.

Disclosure: A. Koskinen, None; **K. Vuolteenaho**, None; **R. Korhonen**, None; **T. Moilanen**, None; **E. Moilanen**, None.

45 WITHDRAWN

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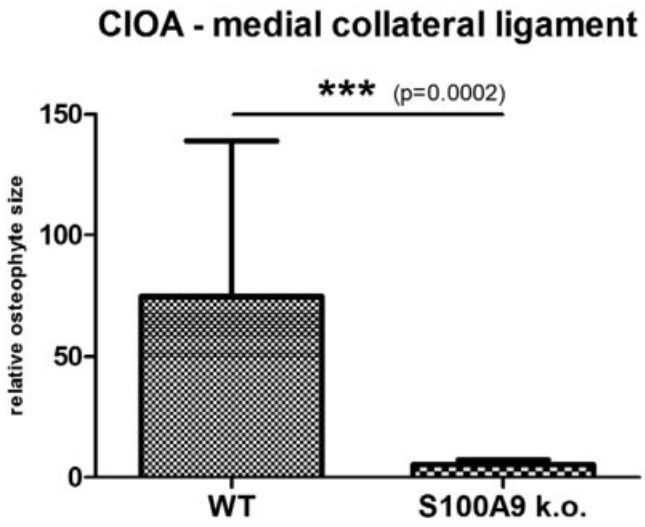
Alarmins S100A8/A9 Regulate Osteophyte Formation In Experimental Osteoarthritis With High Synovial Activation. Rik Schelbergen[1], Arjen B. Blom[1], Wouter de Munter[1], Annet W. Sloetjes[1], Thomas Vogl[2], Johannes Roth[2], Wim B. van den Berg[3] and Peter L.E.M. van Lent[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]University of Muenster, Muenster, Germany, [3]Rheumatology Research and Advanced Therapeutics, Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.

Background/Purpose: Osteophytes are cartilage capped, bony outgrowths that limit joint movement and originate from the periosteum or from ligaments during osteoarthritis (OA). There is increasing belief that the synovium contributes to OA joint pathology since a large subset of OA patients shows synovial activation. As shown recently in our lab, alarmins S100A8 and S100A9 (major products of activated synovial macrophages) are involved in cartilage degradation and synovial activation during human and murine OA. In the current study, we explored the involvement of S100A8/A9 in osteophyte formation in experimental OA

Methods: Experimental OA was elicited in C57Bl/6 (WT) mice and S100A9−/− mice (in which peripheral myeloid cells lack functional S100A8), either by intra-articular collagenase injection (CIOA), or by transsection of the medial anterior meniscotibial ligament (DMM). Osteophyte size was assessed by a blinded observer using image analysis software. Chondrogenesis was induced by bringing human fetal mesenchymal stem cells (hMSCs) in pellet or murine C3H10T1/2 in micromass culture and stimulating for 5 (hMSCs) or 21 days (C3H10T1/2) with BMP-2 and TGFβ1, with 1 or 5 μg/ml human or mouse recombinant S100A8. Proteoglycan content was quantified on SafO stained sections, expression of mRNA with RT-qPCR

Results: Synovial activation, which is high in CIOA, was significantly reduced in S100A9−/− mice. Osteophyte size at day 42 of CIOA was dramatically reduced in the S100A9−/− compared to WT in the medial collateral ligament (92,5% reduction, Figure 1), but also significantly at the medial side of both tibia and femur (68,2% and 64,6% reduction) (n=10). One explanation for the reduced osteophyte size in S100A9−/− mice may be a direct effect of S100-proteins on chondrogenesis. To investigate this, we first stimulated murine C3H10T1/2 MSCs in micromass culture with 5 μg/ml S100A8 (in the presence of BMP-2 and TGFβ1) and found a marked increase in MMP3 and aggrecan mRNA as well as a strongly altered morphology, indicating increased remodeling. In line with that, stimulation of human MSCs in pellet culture with 1 or 5 μg/ml S100A8 (again together with BMP-2 and TGFβ1) strongly increased proteoglycan deposition as measured by redness in SafO staining (27% and 71% increase respectively). Finally, we determined osteophyte size in the DMM model, in which synovial involvement is very low. At day 56, we observed no significant differences in osteophyte size between the S100A9−/− and WT at the medial femur and tibia (105% and 136% of WT, n=8).



Conclusion: S100A8/S100A9 play a crucial role in osteophyte formation in an OA model that shows high synovial involvement, probably by stimulating chondrogenesis. Considering also the deleterious effect of S100A8/A9 on joint destruction in OA, targeting these alarmins during OA may be very promising.

Disclosure: R. Schelbergen, None; **A. B. Blom**, None; **W. de Munter**, None; **A. W. Sloetjes**, None; **T. Vogl**, None; **J. Roth**, None; **W. B. van den Berg**, None; **P. L. E. M. van Lent**, None.

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Exogenous Hydrogen Sulfide Donors Show Anti-Catabolic and Anti-Inflammatory Properties But Limited Anti-Oxidant Capability On Human Articular Osteoarthritic Chondrocytes. Elena F. Burguera[1], Angela Vela-Anero[1], Rosa Meijide-Failde[2] and Francisco J. Blanco[1]. [1]Tissue Engineering and Cellular Therapy Group (CBTTC-CHUAC), CIBER BBN/ISCIII, A Coruña, Spain, [2]Department of Medicine, University of A Coruña, A Coruña, Spain.

Background/Purpose: Osteoarthritis (OA) is characterized by an imbalance between catabolism and anabolism, higher than normal levels of matrix metalloproteinases (MMPs), an increase in inflammatory markers (i.e. interleukins (ILs) or eicosanoids), and an increase in reactive oxygen species (ROS). Hydrogen sulfide (H_2S) is a novel endogenous gas and signaling molecule. Here we looked into the effects of H_2S donors as anti-catabolic, anti-oxidant and anti-inflammatory agents in human articular chondrocytes (hCs) from OA tissue.

Methods: We used an *in vitro* model in which hCs were stimulated with one of two H_2S donors: NaHS or GYY4137; 50mM to 1000mM; 48h; H_2S-only-treated (S)-group. In some tests, IL1β (5ng/mL) or Lipopolysaccharide (LPS, 1μg/mL) were also added. We chose MMP1, 3 and 13, collagen-II (COLII) and aggrecan (ACAN) as matrix degradation and synthesis markers. The prostaglandin E2 (PGE2) synthesis pathway and IL6, for inflammation. Superoxide dismutase(SOD)-2 and catalase (CAT) as scavenger enzymes. ROS synthesis (mitochondrial(M)-ROS and cytoplasmatic(C)-ROS) was measured with cell cytometry. Effects on gene expression were quantified with qRT-PCR and those on proteins with immunocytochemistry (ICC) or enzymatic immunoassays (EIA).

Results: 1. Catabolism: The two H_2S donors reduced MMP3 and MMP13 expression in the S-group, although $p>0.05$. On IL1β-group, MMP3 and 13 (Fig.1A) expressions in the IL1β condition (182 and 52 fold vs. the basal (B)), were reduced to 124 and 10 (1000mM GYY4137, respect.) and 91 and 13 (1000mM NaHS, respect.). There was a marked reduction in MMP3 protein levels (ICC). **2. Anabolism:** 200mM NaHS and GYY4137 counteracted COLII and ACAN repressed expression on the IL1β-group. **3. Inflammation:** H_2S donors reduced IL-6 (Fig.1B), cyclooxygenase (COX)-2 mRNA expression in the IL1β-group without significantly affecting COX-1. **4.ROS:** Only 200mM NaHS reduced C-ROS in the S-Group (from 27.7$\pm$5.7 to 21.5$\pm$1.9UA). On the IL1β-group, H_2S donors did not reduce ROS. SOD2 (Fig.1C) and CAT expression levels were unaffected ($p>0.05$) in either group. Only 200mM GYY4137 reduced M-ROS in the LPS-Group to B level.

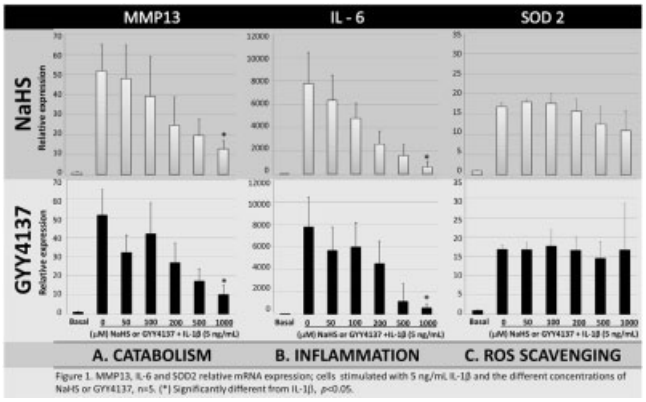

Figure 1. MMP13, IL-6 and SOD2 relative mRNA expression; cells stimulated with 5 ng/mL IL-1β and the different concentrations of NaHS or GYY4137, n=5. (*) Significantly different from IL-1β), $p<0.05$.

Conclusion: Exogenous H_2S donors NaHS and GYY4137 show anti-inflammatory, anti-catabolic and pro-anabolic properties in an *in vitro* model with human OA chondrocytes. However, in the conditions of the present study, they do not reduce pathological ROS levels found in OA chondrocytes and do not increase the anti-oxidant capacity of the cells.

Disclosure: E. F. Burguera, None; **A. Vela-Anero**, None; **R. Meijide-Failde**, None; **F. J. Blanco**, None.

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The In Vivo Role Of Bone Specific EphB4 Receptor Overexpression In Osteoarthritic Synovial Membrane. Gladys Valverde-Franco[1], David Hum[1], Bertrand Lussier[2], Koichi Matsuo[3], Jean-Pierre Pelletier[1], Mohit Kapoor[1] and Johanne Martel-Pelletier[1]. [1]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [2]Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Montreal, Saint-Hyacinthe, QC, [3]Laboratory of Cell and Tissue Biology, School of Medicine, Keio University, Tokyo, Japan.

Background/Purpose: Osteoarthritis (OA) is characterized by progressive destruction of all joint tissues including inflammation of the synovial membrane. The histological changes that occur in OA present a range of abnormalities in the synovial membrane including fibrosis. Members of the ephrin family, the EphB4 receptor and its specific ligand ephrin-B2, were found to positively impact the abnormal structure and metabolism of OA subchondral bone and cartilage. In the context of evaluating the in vivo effect of the EphB4 receptor, we further investigated in vivo in mice the effect of bone-specific EphB4 overexpression (TgEphB4) on synovial membrane during OA.

Methods: Knee OA was surgically induced by the destabilization of the medial meniscus (DMM) in 10-week-old male EphB4 homozygous (TgEphB4) and wild-type (WT) mice. Synovial membrane evaluations were performed at 12 weeks post-surgery using histology, immunohistochemistry, and real-time PCR.

Results: Data demonstrated a significant decrease in the synovial membrane thickness ($p\leq0.02$), pro-collagen type I ($p\leq0.01$), and fibrin ($p\leq0.04$) in DMM-TgEphB4 compared to DMM-WT. The expression of the fibrotic markers connective tissue growth factor (CTGF, $p\leq0.02$), smooth muscle actine α (SMAα, $p\leq0.03$) and serum cartilage oligomeric matrix protein (COMP, $p\leq0.03$) were all significantly reduced in DMM-TgEphB4 compared to DMM-WT. Although the TGF-β was decreased in the DMM-TgEphB4 mice, the difference did not reach statistical significance. However, the synthesis of a member of the heat shock protein family (HSP), HSP90β, known to have a crucial role in enhancing TGF-β signaling, was significantly decreased ($p\leq0.03$) in DMM-TgEphB4.

Conclusion: This is the first in vivo evidence showing that protecting the subchondral bone prophylactically reduces the severity of pathological changes in the synovial membrane during the OA process. This study thus stresses the in vivo importance of subchondral bone biology in OA tissues. It also provides evidence that changes in the synovial membrane are an integral part of the OA disease process. In addition, these data define the EphB4 receptor as a potential novel therapeutic avenue for the treatment of the disease.

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Chondrocyte-Specific Bone Morphogenetic Protein-2 Overexpression Results In Severe Aggravation Of Osteophyte Formation In Experimental Osteoarthritis Without Altering Cartilage Damage In Young Mice.

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Background/Purpose: In murine osteoarthritis (OA) models chondrocytes surrounding lesions express elevated levels of Bone Morphogenetic Protein-2 (BMP2). This growth factor is well known for its ECM inducing qualities and capability to induce new cartilage and bone. The functional consequence of these elevated BMP2 levels near OA lesions is unclear. We made a collagen type II dependent, doxycycline-inducible BMP2 transgenic mouse to investigate the consequence of elevated chondrocyte-specific BMP2 on experimental OA (DMM-model).

Methods: We cloned a lentivirus with BMP2 controlled by minCMV promoter coupled to a tet responsive element (Lv-TRE-BMP2).We crossed a Col2-cre with a floxed rtTA mouse and transfected homozygote embryo's with Lv-TRE-BMP2 to gain a mouse expressing collagen type 2 dependent BMP2 solely in chondrocytes only upon doxycycline (dox) exposure (Col2-rtTA-TRE-BMP2). Experimental OA was induced (DMM model) in Col2-rtTA-TRE-BMP2 mice with or without dox exposure in food starting one week before DMM, lasting until the end of the experiment (8 weeks after DMM). We isolated knee joints for histology. Left knee joints served as non-OA controls.

Results: Mice with DMM alone showed osteophyte formation predominantly on the medial side of the joint originating from the periost near the femoral-tibial joint and extruding from the medial meniscus. Upon chondrocyte-specific BMP2 exposure, DMM-induced osteophyte formation aggravated severely resulting in outsized osteophytes, enthesophytes on the enthesis of the medial collateral ligament, new bone formation within the collateral ligament near the extruded meniscus and osteophyte formation originating from the femoral growth plate, predominantly but not exclusively on the medial side of the joint. There were no significant differences in non-OA knee joints comparing dox versus non-dox treated transgenics. In contrast, dox treatment resulted in large osteophytes in thoracic or cervical area of the spine. Strikingly, despite apparent changes in knee joint morphology due to large osteophytes there was no detectible difference, with regard to structural damage and Safranin O staining intensity, in cartilage damage when comparing DMM with or without dox exposure.

Conclusion: Elevated BMP2 levels in chondrocytes did not induce structural changes in articular cartilage of young mice. Moreover, unchallenged dox treated joints had no structural alterations in cartilage. In DMM, BMP2 overexpression greatly enhanced de novo cartilage formation, eventually turning into bone (osteophytes), which was not seen in non-OA knee joints with BMP2. We postulate that newly-induced chondrocytes produce high BMP2 levels in dox-treated transgenics, that boost outgrowth of these structures. In spine however, osteophytes developed in dox-treated transgenics without additional triggers. This could rely on chondrocyte precursor subpopulation that is stimulated to undergo chondrogenesis under control of BMP2 alone.

Our data show that chondrocyte-specific elevation of BMP2 levels does not alter the course of cartilage damage in an OA model in young mice but results in severe aggravation of osteophyte formation.

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Cartilage Matrix Remodeling and Activation Of Canonical Wnt- Signaling Precedes Calcification and OA-Like Changes In Mice.

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Background/Purpose: Calcification of cartilage is a common finding during osteoarthritis (OA) and is directly linked to the severity of cartilage degradation. We have found in a previous study that NPP1 is an important player in OA associated cartilage calcification in mouse and humans. The observed cartilage changes resemble aspects of endochondral ossification. In this study we aim to investigate the matrix changes and calcification of cartilage during the development of OA- like changes in mice.

Methods: The tip-toe walking (ttw/ttw) mouse that carries a mutation in the *enpp1* gene encoding for NPP1 was used as a natural model of OA. Using von Kossa staining in combination with Safranin-orange staining of knee sections we assessed the calcification of articular cartilage and the severity of OA using the Mankin-Score over a time course from 4 to 22 weeks. We analysed the compostion of cartilage matrix using toluidine blue, alcian blue/PAS staining. To investigate cartilage matrix remodelling we performed immunohistological stainings for collagen II, collagen X and the aggrecan cleavage marker BC-3. We performed the same stainings in knee joint sections of wild type mice with induced OA (DMM model). The influence of basic calcium phospahe (BCP) crystals on neonatal chondrocytes was investigated in micro mass cultures with alcian blue and alizarin red staining. Using Western Blot for β- catenin and pCamKII we investigated the activation of WNT signalling.

Results: We found a loss of proteoglycans in the joint cartilage of ttw/ttw mice already at an age of 8 weeks, whereas no changes of cartilage matrix were detectable in wild type mice. An increased Mankin Score in ttw/ttw compared to wild type mice also reflected these changes. Early matrix remodelling in ttw/ttw cartilage was followed by an increased calcification starting at the border to the subchondral bone. The straight border of the tide mark gets broken down by multiple calcified chondrocytes that give the border a wave-like appearance. Looking at the matrix changes in more detail we found an increase in sulphated proteoglycans in the ttw/ttw cartilage as well as in the induced OA cartilage. The same pattern was observed in the growth plate in the area of hypertrophic chondrocytes. We found an increased expression of collagen X in the cartilage and collagen II was down-regulated with increasing age and OA severity. Using neonatal chondrocytes of wild type and ttw/ttw mice we found that BCP crystals induce production of highly sulphated matrix and reduce proliferation of chondrocytes. Chondrocytes of ttw/ttw mice show an increase in β- catenin, which was also observed in wild type chondrocytes stimulated with BCP crystals.

Conclusion: We conclude from our data that matrix remodelling precedes cartilage calcification. The calcification seems to be associated with activation of canonical WNT signalling. Taken together, the data support the notion that OA is characterized by the re-initiation of developmental programms associated with endochondral ossification.

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Collagen-Based Microspheres Delivering TGF-β3 For Mesenchymal Stem Cell Differentiation: An Innovative Strategy For Cartilage Engineering.

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Background/Purpose: Because of a poor self-healing ability, joint cartilage undergoes progressive degradation in the course of aging or following traumatic injuries. One promising therapeutic approach is the use of mesenchymal stem cells (MSC), which have the potential to differentiate into chondrocytes. However, anchorage of MSC to the sites of injury and their differentiation *in situ* require combining cells with a biomaterial releasing a differentiation factor such as TGFβ3. Our objective was to design and test a new scaffold to support chondrogenic differentiation.

Methods: Microspheres were formed using an acidic type I collagen solution and perfluorated oil, stabilized by a surfactant. Spherical microparticles of fibrillar collagen were obtained through a sol-gel transition induced in aqueous droplets in contact with ammonia vapors. Microspheres were impregnated with TGFβ3 and release of this factor was measured using a reporter gene assay. Impregnated microspheres were combined with human MSC and cultivated *in vitro* or subcutaneously injected into immunodeficient mice. Expression of chondrocyte markers was monitored by RT-qPCR and immunohistochemistry.

Results: Microspheres are constituted by a gel of striated collagen fibrils and are 300 ± 67 μm in diameter. Fibrils occupy ca. 5% of the total volume, forming an entangled network with pores of 1–10 μm. After MSC adhesion onto the microspheres and *in vitro* culture for 21 days, they differentiate into chondrocytes expressing the specific markers, such as collagen type II variant

B and aggrecan. The type I collagen matrix is progressively degraded and replaced by the cartilaginous matrix. *In vivo*, MSC form a tissue histologically resembling cartilage which stain positive for collagen II and aggrecan.

Conclusion: The biomaterial described here is promising for cartilage engineering. Future improvements aim at obtaining microspheres of smaller and more homogenous sizes, which will facilitate their injection; covalently linking the TGFβ3 to the microspheres to prevent its dispersal in the organism.

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Altered Lipid Metabolism In Osteoarthritis With Subsequent Proinflammatory Properties Of Apolipoprotein A-I. Dominique de Seny[1], Gaël Cobraiville[1], Edith Charlier[1], Sophie Neuville[1], Laurence Lutteri[2], Denis Malaise[3], Olivier Malaise[1], Jean-Paul Chapelle[2], Biserka Relic[1] and Michel G. Malaise[1]. [1]GIGA Research - University of Liège - CHU Liège, Liège, Belgium, [2]Medical Chemistry - CHU Liège, Liège, Belgium, [3]University of Liège, Liège, Belgium.

Background/Purpose: Osteoarthritis (OA) is associated with a local inflammatory process. It is now considered as a metabolic syndrome rather than due to aging or mechanical stress. Several evidences point to the direction of an altered lipid metabolism as an underlying cause for the development of OA. Recently, we have studied the role played by an apolipoprotein, the acute phase serum amyloid A (A-SAA), as a pro-inflammatory marker in OA joints (de Seny et al., Plos One, 2013). Apolipoprotein A-I (ApoA1) is another major protein component of high-density lipoprotein (HDL) cargo molecules in plasma, and both are playing a major role in back cholesterol transport from peripheral tissues to the liver.

Methods: Lipoproteins, anti-oxidized LDL antibodies, cholesterol, ApoA1 levels and inflammatory parameters (IL-6, MMP-1 and MMP-3) in blood and synovial fluids of OA (n=29) and rheumatoid arthritis (RA) (n=27) patients were quantified and compared to those in matched healthy volunteers (HV) (n=35). Primary chondrocytes and fibroblast-like synoviocytes (FLS) were isolated respectively from cartilage and synovial membrane obtained from OA patients during joint replacement. Cells were stimulated with purified human ApoA1 in the presence or not of recombinant human A-SAA (rhSAA) protein, and with lipoproteins at physiological concentration encountered in OA. IL-6, MMP-1 and MMP-3 expression levels were quantified by ELISA after stimulation.

Results: 1) In the serum of OA patients, LDL/HDL ratio was significantly higher compared to HV and RA but remained similar in both OA and RA synovial fluid.

2) Although LDL and cholesterol serum levels were higher in OA than in RA, both were lower in the OA synovial fluid than in the RA.

3) In the OA and RA synovial fluid, cholesterol levels were positively correlated to LDL, HDL and ApoA1 levels, and HDL levels were positively correlated to ApoA1 levels. But of interest, OA synovial fluid had the unique characteristic of LDL levels being positively correlated to HDL and ApoA1 levels, which was not observed neither in the synovial fluid of RA patients nor in the serum of OA, RA and HV.

4) LDL and ApoA1 levels were also significantly correlated to IL-6 levels, another uncommon characteristic of OA synovial fluid suggesting local dysregulated processes within lipidic and inflammatory parameters. We also observed using *in vitro* experiments that the purified human ApoA1 likewise rhSAA induced IL-6, MMP-1 and MMP-3 expression in primary chondrocytes and FLS obtained from OA patients. ApoA1-induced IL-6, MMP-1 and MMP-3 expression was downregulated by TAK242, a specific TLR4 inhibitor. Presence of HDL at OA physiological concentration did not abolished ApoA1-induced IL-6, MMP-1 and MMP-3 expression.

Conclusion: Lipid diffusion into the joint cavity is dependent on the degree of inflammation. If inflammation is largely superior in RA compared to OA, we can nonetheless hypothesize that local inflammatory process and lipid diffusion inside OA joint cavity can also occur. In this study, several arguments have been raised in favour of an abnormal lipid profile in OA synovial fluid. This abnormal lipid profile was linked to the local pro-inflammatory process.

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Adenosine A_{2A} Receptor As a Potential New Therapeutic Target For The Prevention/Treatment Of Osteoarthritis. Aranzazu Mediero[1], Tuere Wilder[1] and Bruce N. Cronstein[2]. [1]NYU School of Medicine, New York, NY, [2]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Osteoarthritis, the most common type of arthritis in the United States, results from trauma and other mechanical factors as well as metabolic changes in bone and cartilage. We have previously demonstrated that adenosine, acting via the A_{2A} receptor, inhibits inflammation and plays a critical role in regulating bone metabolism. Thus, adenosine A_{2A} receptor knockout mice are osteopenic as a result of increased osteoclast number and activity. We have observed that aging adenosine A_{2A} receptor knockout mice experience difficulty in movement, taking food and walking and so we determined whether changes in their bone or joint structure or function could explain these changes.

Methods: 4 month old C57Bl/6 wild type (WT) and A_{2A}KO mice (n=4) were sacrificed and knee joints were prepared for microCT analysis and histology. PAS (Periodic Acid Staining) and Trichrome staining of decalcified sections of leg were carried out. MicroCT analysis of knees of WT and KO mice were carried out and analysis of bone was performed on the distal femur below the growth plate.

Results: microCT analysis of the knees of A_{2A}KO mice showed osteophyte formation together with mild remodeling and subchondral sclerosis when compared to WT mice. As we have previously reported A_{2A} KO mice suffered from osteopenia; bone volume/total volume (BV/TV) was significantly decreased in A_{2A}KO mice when compared to control (33.324 ± 0.56 vs 35.782 ± 0.78, respectively, $p<0.01$). The same decrease was observed for trabecular thickness (0.0685 ± 0.0035 vs 0.081 ± 0.002, $p<0.05$) and bone mineral density (BMD) (0.3795 ± 0.003 vs 0.4265 ± 0.01, respectively, $p<0.5$), with no change in trabecular number (4.8795 ± 0.17 vs 4.646 ± 0.23, p=ns). H&E and trichrome staining showed a loss in collagen in the cartilage together with diminished subchondral bone and chondrocyte hypertrophy and proliferation. PAS staining correlated with these results showing a loss in proteoglycans both in the articular cartilage and in the growth plate in A_{2A}KO mice together with an increase in chondrocyte proliferation.

Conclusion: Deficiency in adenosine A_{2A} receptors leads to spontaneous osteoarthritis and suggests that adenosine receptors may be novel targets for development of therapies to ameliorate or prevent osteoarthitis.

Disclosure: A. Mediero, Filed a patent on use of adenosine A2AR agonists to prevent prosthesis loosening (pending)., 9; **T. Wilder**, None; **B. N. Cronstein**, Canfite Pharma, 1, NIH, Gilead, Takeda, AstraZeneca, 2, NYU School of Medicine, 3, Merck-SeronoBristol-Myers Squibb, Novartis, CanFite Biopharmaceuticals, Cypress Laboratories, Regeneron (Westat, DSMB), Endocyte, Protalex, Allos, Inc., Savient, Gismo Therapeutics, Antares Pharmaceutical, Medivector, 5, Multiple patents on adenosine receptors and bone metabolism, pharmacology, 9.

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Anti-Fibrotic and ANTI-Hypertrophic Effect Of Adipose Mesenchymal Stromal Cells On Osteoarthritic Chondrocytes. Marie Maumus[1], C. Manferdini[2], Karine Toupet[1], A. Piacentini[2], A. Gabusi[2], A. Facchini[2], G. Lisignoli[2], Christian Jorgensen[3] and Daniele Noel[4]. [1]INSERM U844, Montpellier, France, [2]IOR BOLOGNA, BOLOGNA, Italy, [3]Inserm U844, CHU Saint-Eloi, Université Montpellier 1, CHU Lapeyronie, Montpellier, France, [4]UM1, Montpellier, France.

Background/Purpose: Mesenchymal stem cells (MSC) isolated from bone marrow (MSC) or adipose (ASC) tissues secrete a large amount of trophic factors. The possibility that these cells, through their paracrine potential, may influence the course of chronic degenerative disorders and prevent cartilage degradation is promising for the treatment of osteoarthritis (OA). Indeed, the aim of our work was to evaluate the effects of these cells on OA chondrocyte phenotype.

Methods: OA ASC were isolated from intra-articular (Hoffa-ASC) or hip (hip ASC) subcutaneous adipose tissue and healthy ASC from subcutaneous abdominal depot (abdo-ASC). BM-MSC and chondrocytes were obtained from OA donors. ASC or MSC were co-incubated with chondrocytes cultured in monolayer during 7 days using cell culture inserts. Expression of markers specific for mature and hypertrophic chondrocytes or fibroblasts was quantified by RT-qPCR or ELISA. Isotypic or anti-HGF antibodies (100ng/ml) were added during the coculture.

Results: After 7 days of ASC or MSC co-cultures with chondrocytes, a stable expression of the markers specific for mature chondrocytes (Col IIB, Agg, link, Sox9) was observed, while expression of hypertrophic (MMP13,

AP) and fibrotic (Col I and III) markers was significantly decreased. Compared to abdo-ASCs, Hoffa- and Hip-ASC reduced less efficiently the expression of hypertrophic/fibrotic markers and some markers of mature chondrocytes were decreased with Hip-ASC. Finally, factors known to be involved in fibrosis and matrix remodeling (TIMP-1 and -2, MMP-1 and -9, IL1-RA) were not changed. On the contrary, HGF secretion was induced and addition of neutralizing anti-HGF antibody reversed the anti-fibrotic effect of ASC whereas the hypertrophic markers were not modulated.

Conclusion: ASC from abdominal subcutaneous fat and MSC were the most efficient to reduce hypertrophy and dedifferentiation of articular chondrocytes. This effect was at least partly due to the induction of HGF secretion confirming the interest of using ASC in therapies of osteo-articular diseases.

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Glucocorticoid Receptor Modulator Compound A Does Not Induce Leptin In Human Osteoarthritic Synovial Fibroblasts and In Dedifferentiated Chondrocytes. Olivier Malaise, Biserka Relic, Edith Charlier, Mustapha Zeddou, Florence Quesada-Calvo, Sophie Neuville, Dominique de Seny and Michel G. Malaise. GIGA Research - University of Liège - CHU Liège, Liège, Belgium.

Background/Purpose: Leptin is generally considered detrimental in osteoarthritis (OA) as it can induce IL-8 in synovial fibroblasts (SF) and matrix metalloproteinases in chondrocytes. We recently showed that SF themselves were able to produce leptin and express leptin receptor (Ob-R) *in vitro*, strongly induced by glucocorticoid (GC) prednisolone, through TGF-β pathway and Smad1/5 phosphorylation (Stem Cell Dev 2012; 21: 1948–55). It is generally believed that transrepression of transcription factors by monomeric GC receptor (GR) is associated with GC anti-inflammatory properties, whereas side-effects (mellitus diabetes, lipid abnormalities, osteoporosis) would be mostly resulting in GR dimer-dependent transactivation. Compound A (CpdA), a plant-derived phenyl aziridine selective GR agonist, is efficient to reduce inflammation in a murine arthritis model and does not induce mellitus diabetes nor osteoporosis, offering a better benefit/risk ratio than GC. The aim of this study is to determine, in human OA SF and dedifferentiated chondrocytes (DDC), whether CpdA, as prednisolone, is leptin and Ob-R inducer.

Methods: Human SF and chondrocytes were isolated from OA patients during knee or hip surgery. Cells were treated with prednisolone (1 μM), TNF-α (10 ng/ml) and/or CpdA (1, 5 or 10 μM). ELISA measured leptin and IL-6 production in culture supernatant. Ob-R, GR, TGF-βRII, phospho-Smad1/5, phospho-Smad2, Smad1, Smad2, GILZ and α-tubulin were analyzed in total cell extracts by Western Blot.

Results: 1. Like prednisolone, CpdA down-regulated endogenous and TNF-α-induced IL-6 secretion by SF and DDC in a dose-dependent manner, supporting its anti-inflammatory action. **2.** By contrast to prednisolone, CpdA did not induce leptin and further decreased endogenous Ob-R expression in a dose-dependent manner in the same cells. Moreover, unlike prednisolone, CpdA did not induce TGF-βRII expression nor Smad1/5 phosphorylation and did not reduce Smad2 phosphorylation. Lastly, also opposite to prednisolone, CpdA poorly induced GR degradation and did not induce GILZ expression.

Conclusion: Unlike prednisolone, CpdA, a dissociative glucocorticoid receptor agonist, did not induce leptin nor Ob-R in human OA SF and in DDC and could even decrease Ob-R expression. As leptin favors osteoblastic differentiation of mesenchymal stem cells, our findings might explain why CpdA also fails to induce such a differentiation. Leptin is a new target where dissociative properties of CpdA can apply.

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Age-Related Loss Of The Transforming Growth Factor Beta Receptor ALK5 Precedes Osteoarthritis Development In Cartilage. Arjan van Caam, Esmeralda N. Blaney Davidson, Eva Thijssen, Wim B. van den Berg and Peter M. van der Kraan. Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.

Background/Purpose: Osteoarthritis (OA) is the most common joint disease and (old) age is its main risk factor. One of OA's main hallmarks is degradation of articular cartilage. TGFβ-superfamily signaling plays an important role in cartilage homeostasis via induction of Smad phosphorylation (pSmad). pSmad2/3 is a potent inhibitor of chondrocyte terminal differentiation and cell death, whereas pSmad1/5/8 induces these processes. In cartilage, TGFβ receptors that induce Smad phosphorylation are ALK1 for Smad1/5/8 and ALK5 for Smad2/3. We showed an age-related shift in receptor balance towards dominant Alk1 expression compared to Alk5 expression, and linked elevated Alk1 levels to increased *Mmp13* and *ColX*expression and cartilage damage in mice. However, OA development and ageing are concurrent in mice, and possibly both processes interfere. To uncouple ageing and OA-related processes, we investigated if age-related changes in TGFβ-superfamily signaling occur without interference of the OA process, and if these changes result in an altered cellular response to growth factors. We chose healthy bovine cartilage explants as a model system because bovine samples can be obtained in a wide age range without concurrent OA development.

Methods: From the metacarpophalangeal joint of cows (*Bos Taurus*) ($<$ 3 h *post mortem*), full thickness cartilage explants were collected. Macroscopically none of the animals showed any signs of OA. Samples were either immediately frozen in liquid nitrogen or, after 24 h equilibration in serum free medium, stimulated with growth factors for 24 h. Subsequently, mRNA was isolated and gene expression was measured by qPCR, using cDNA specific primers and SYBR-green.

Results: Gene expression analysis of bovine explants ranging from 0.5 up to 12 years old showed a very significant 100-fold ($R^2 = 0.7$, $p < 0.0001$) decrease in *Col2a1* expression and a 3-fold decrease in *Tgfb1* ($R^2 = 0.3$, $p = 0.002$) expression with increasing age compared to 4 reference genes; *Gapdh*, *Rpl22*, *Rps14* and *Gusb*. Furthermore, *Alk5* expression decreased 4-fold ($R^2 = 0.3$, $p = 0.0004$) whereas *Alk1* expression remained unchanged. In 8 year old explants, expression of the Smad2/3p response gene *Serpine1* (*Pai1*) was 11-fold less ($p = 0.01$) responsive to 1 ng/ml of the ALK5 ligand TGFβ_1 compared to 1 year old explants. In contrast, the response of 8 year old cartilage to the ALK1 ligand BMP9 (5 ng/ml) was not significantly different compared to 1 year old cartilage as measured by expression of the Smad1/5/8 response gene *Id1*.

Conclusion: The loss of *Col2a1* and *Tgfb1* expression are two characteristics of ageing cartilage, and confirm our system as valid to study age-related changes in cartilage. Because no signs of OA could be detected on macroscopic level, changes in TGFβ-superfamily receptor expression appear to occur independently of the OA process. The observed decrease in *Alk5* expression results in loss of Smad2/3p signaling in response to TGFβ_1, indicating that TGFβ_1's cartilage protective function is lost with increasing age. We propose that this loss of response predisposes chondrocytes for the OA process.

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Role Of Procatabolic Cytokines In Dysregulation Of O-Linked N-Acetylglucosamine Modified Proteins In Human Osteoarthritic Chondrocytes. Raquel Largo[1], Ane Larranaga-Vera[2], Sandra Pérez-Baos[2], Gabriel Herrero-Beaumont[2] and Jessica Andrés-Bergós[3]. [1]Jiménez Díaz Foundation University Hospital, Madrid, Spain, [2]Joint and Bone Research Unit. IIS-Fundación Jiménez Díaz. UAM, Madrid, Spain, [3]Tissue Engineering Repair and Regeneration Program, Hospital for Special Surgery and Weill Cornell Medical College, New York, NY.

Background/Purpose: Nuclear and cytoplasmic protein glycosylation by the addition of O-linked N-Acetylglucosamine (O-GlcNAc) to serine and threonine residues is a widespread post-translational modification that has been described in degenerative and age-related diseases, such as Alzheimer's and diabetes. This modification is catalyzed by the O-GlcNAc transferase (OGT) which uses UDP-GlcNAc as a donor, and O-GlcNAc can be removed by the O-GlcNAc-glucosaminidase (OGA). We have seen that O-GlcNAc glycosylation levels in the articular cartilage of patients with OA were increased as well as the expression of the different isoforms of OGT and OGA was dysregulated. The goal of this study was to assess whether a procatabolic cytokine, IL-1α, can be responsible of the changes in O-GlcNAc system found in OA human cartilage.

Methods: OA knee articular cartilage was obtained during replacement surgery. Twelve OA patients were included in this study (6 woman/6 men; mean age 71$\pm$3 years), with a Mankin score for knee specimens between 11

and 14. Human osteoarthritic chondrocytes (HOC) were isolated by protease digestion for primary culture. At confluence, cells were stimulated with different concentrations of IL-1α for different doses and periods of time after they were deprived of serum for 48 h. The level of O-GlcNAcylation, OGT and O-GlcNAcase expression was assessed by western-blot employing specific antibodies.

Results: The amount of O-GlcNAcylated proteins was increased in HOC 24 h after stimulation with different doses of IL-1α (1, 10 and 100 ng/ml), showing the highest accumulation with 10 ng/ml. This concentration was chosen for stimulation of HOC during different periods of time (3, 6, and 24 h). The increase in O-GlcNAc proteins amount showed a peak of induction at 6 h. This accumulation occurs especially in proteins between 50 to 150 KDa therefore showing a similar O-GlcNAcylated proteins pattern to that observed in OA cartilage. We also observed an increased expression of the three OGT isoforms, nucleo-cytoplasmic (ncOGT), mitochondrial (mOGT) and small (sOGT) in HOC as early as 3 h, although the peak of induction was at 6 h. Three isoforms were increased in a similar grade, without prevalence of sOGT as found in OA cartilage. IL-1α also increased the presence of both OGA isoforms, long (OGA-L) and short (OGA-S) after 3 and 6 h of stimuli. A clear prevalence of long isoform was found along IL-1α stimulation whereas OGA-S had the highest prevalence in OA cartilage.

Conclusion: To our knowledge, this is first evidence of procatabolic cytokines involvement in O-GlcNAc modifications. IL-1α can induce accumulation of O-GlcNAc proteins in human OA chondrocytes. Although both regulatory enzymes of this modification, OGT and OGA, are also increased with IL-1α stimulation, characteristic distribution of the different isoforms in OA cartilage was not reached. IL-1α is in part responsible of a dysregulation in the O-GlcNAc proteins modification during OA although other processes must be involved.

Disclosure: R. Largo, None; **A. Larranaga-Vera**, None; **S. Pérez-Baos**, None; **G. Herrero-Beaumont**, None; **J. Andrés-Bergós**, None.

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Saturated Fatty Acids Act Synergistically With Interleukin 1 Beta To Increase Inflammation, Endoplasmic Reticulum Stress and Cell Death In Human Articular Chondrocytes. Oscar Alvarez-Garcia[1], Nicole H Rogers[2], Roy G Smith[3] and Martin K. Lotz[4]. [1]Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, CA, [2]California Institute for Biomedical Research (Calibr), La Jolla, CA, [3]Department of Metabolism and Aging, The Scripps Research Institute, Jupiter, FL, [4]The Scripps Research Institute, La Jolla, CA.

Background/Purpose: Obesity is a major risk factor for the development of osteoarthritis (OA). Altered biomechanics have been postulated as the main causative mechanism, but recent data showing a higher incidence of hand OA in obese patients suggest the existence of a systemic component. Obesity is commonly associated with a state of low-grade inflammation, increased circulating adipokines and free fatty acids (FFA) released by adipose tissue. Whereas low-grade inflammation has received some attention in the recent years, little is known about the role of FFAs in OA pathogenesis. The aim of this study was to analyze effects of saturated (palmitate) and monounsaturated (oleate) FFAs on articular cartilage and chondrocytes.

Methods: Human Articular Chondrocytes (hAC) obtained from young healthy donors (21.3$\pm$2.9 years) were grown in monolayer cultures until confluence. For cell viability and caspase 3/7 activation assays, hAC were treated with 0.5 mM palmitate, 0.5 mM oleate or vehicle, in the presence or absence of 1 ng/ml IL-1β for 72 hours. For gene expression studies, shorter treatment time (24-hours) and lower IL-1β concentration (10 pg/ml) were used. Levels of proinflammatory factors, extracellular matrix proteins, extracellular proteases and endoplasmic reticulum (ER) stress markers were measured. In addition, bovine articular cartilage explants were cultured with FFA for 72 with or without IL-1β and cartilage integrity was studied.

Results: Palmitate induced caspase 3/7 activation and cell death in IL-1β -stimulated hAC, and significantly upregulated IL-1β -induced IL-6 and Cox-2 gene expression as well as IL-6 protein secretion, whereas oleate had no additive effect. Exposure to FFAs did not modify type II collagen, aggrecan, ADAMTS-4, -5, and MMP13 gene expression after 24 hours. ER stress markers were potently increased by palmitate alone, but not oleate, and this effect was further enhanced by IL-1β. Preliminary experiments showed that palmitate accelerated cartilage destruction driven by IL-1β in bovine explants, as evidenced by a significant increase in cell death and glycosaminoglycan release.

Conclusion: Saturated fatty acids, specifically palmitate, have catabolic effects on articular cartilage and can accelerate its breakdown in the context of low-grade inflammation by synergizing with IL-1β to increase proinflammatory mediators, ER stress and caspase-associated cell death. Collectively, our data suggest that elevated levels of saturated FFA may contribute to OA pathogenesis in obese patients.

Disclosure: O. Alvarez-Garcia, None; **N. H. Rogers**, None; **R. G. Smith**, None; **M. K. Lotz**, None.

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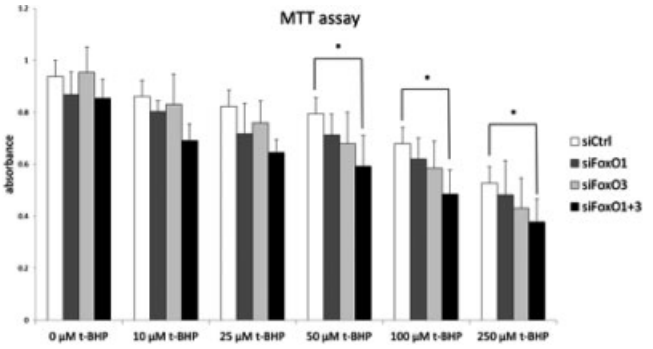
Downregulated Forkhead-Box Class O Transcription Factors Attenuate Oxidative Stress Resistance In Human Chondrocytes. Yukio Akasaki and Martin K. Lotz. The Scripps Research Institute, La Jolla, CA.

Background/Purpose: Aging-associated changes in articular chondrocytes represent a major risk factor for osteoarthritis (OA). The major signaling pathway that regulates cellular aging is the Insulin/IGF-1/Pl3k/Akt/forkhead-box class O (FoxO) transcription factor axis. The FoxO factors play a central role in oxidative stress resistance regulating antioxidants, autophagy and protein quality control. Previously, we observed that FoxO factors are dysregulated in aged and OA cartilage. FoxO expression is reduced during the aging process and phosphorylation of FoxOs (inactivation form) is increased in OA cartilage. However, the impact of downregulated FoxOs on chondrocytes is still unknown. The objective of this study was to investigate the role of FoxOs in anti-oxidative stress resistance in human chondrocytes

Methods: Normal human cartilage was obtained at autopsy from 4 adult donors. OA human cartilage was obtained from 5 patients undergoing knee replacement surgery. Small interference RNA for FoxO1 and FoxO3 were transfected into chondrocytes. The effects of down-regulated FoxO proteins on cell viability against the oxidant tert-Butyl hydroperoxide (t-BHP) were analyzed by MTT assay. Antioxidants and autophagy related proteins in FoxO-siRNA transfected cells were analyzed by Western blot. The changes in inflammatory mediators and extracellular matrix components following treatment with IL-1β or TGF-β were also examined

Results: FoxO1 and FoxO3 but not FoxO4 mRNA expression was significantly lower in OA cartilage compared to normal cartilage. MTT assay showed that the combination of siFoxO1 and siFoxO3 significantly reduced cell viability compared to control siRNA under treatment with t-BHP ($\geq$ 50 μM) (Figure 1). Knock-down of FoxO1 and FoxO1+3 resulted in significant reductions of GPX-1, catalase, LC3, Beclin1, p62, and Sirt1 proteins following treatment with t-BHP. Expression of iNOS was significantly increased in FoxO-siRNA transfected chondrocytes.



Conclusion: Down-regulated FoxO transcription factors in chondrocytes increased susceptibility to cell death induced by oxidative stress, and this was associated with reduced antioxidants and autophagy related proteins. Our data provide evidence for a key role of FoxO transcription factors as regulators of oxidative stress resistance in human chondrocytes.

Disclosure: Y. Akasaki, None; **M. K. Lotz**, None.

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O-Linked N-Acetylglucosamine Modified Proteome Of Human Osteoarthritic Cartilage: Biological Significance. Jessica Andrés-Bergós[1], María Luisa Hernáez[2], Miguel Otero[1], Ane Larranaga-Vera[3], Sandra Pérez-Baos[3], Mary B. Goldring[1], Gabriel Herrero-Beaumont[3] and Raquel Largo[4]. [1]Tissue Engineering Repair and Regeneration Program, Hospital for Special Surgery and Weill Cornell Medical College, New York, NY, [2]Proteomics Unit, Universidad Complutense de Madrid-Parque Científico de Madrid, ProteoRed ISCIII, Madrid, Spain, [3]Joint and Bone Research Unit. IIS-Fundación Jiménez Díaz. UAM, Madrid, Spain, [4]IIS-Fundación Jiménez Díaz, Madrid, Spain.

Background/Purpose: O-linked N-acetylglucosamine (O-GlcNAc) post-translational modifications have been implicated in the control of different signaling cascades and in the development and progression of degenerative and age-related diseases. We previously showed that accumulation of O-GlcNAc-modified proteins alters chondrocyte gene expression, leading to increased expression of chondrogenic markers in vitro and increased chondrogenic differentiation in vivo (Andrés-Bergós J, JBC 2012). We also showed that the total amount of O-GlcNAcylated proteins was significantly increased in human osteoarthritic (OA) cartilage compared to that of healthy cartilage (Tardío L, Arthritis Rheum, submitted). Here, we aimed to better profile and identify the O-GlcNAc-modified proteins in human OA cartilage.

Methods: Human OA cartilage was isolated from patients undergoing total knee replacement surgery (n=6), while healthy cartilage was obtained from age- and gender-matched donors (n=6). Wheat germ agglutinin (WGA) chromatography was used to selectively pull-down O-GlcNAc-modified proteins. To this end, equal amounts of proteins isolated from OA and healthy cartilage were loaded on WGA-affinity columns. The eluted fractions containing O-GlcNAc-modified proteins were processed by nano-LC-M/MS, using a 5500QTRAP mass spectrometer (AB Sciex), and subsequently analyzed using GeneCodis software, which grouped proteins based on predefined biological processes.

Results: Healthy and OA human cartilage shared a number of O-GlcNAc-modified proteins; however, our WGA-based analysis identified subsets of proteins O-GlcNAc-modified differentially in health and disease. Around a 26% of healthy cartilage specific proteins were involved in cytoskeleton organization, and more than 16% play an important role in cell adhesion. None of these biological processes were found in the analysis of OA differential proteins suggesting that these protein modifications may have an important role in preserving cell structural integrity in a healthy state. Interestingly, O-GlcNAc modifications in proteins involved in growth plate cartilage development, cartilage condensation, or inhibition of angiogenesis were absent in OA samples and prominent in healthy cartilage. More importantly, O-GlcNAc modifications of proteins implicated in extracellular matrix degradation, cell growth, or complement activation were higher in OA cartilage than in non-OA/healthy cartilage, clearly separating healthy and damaged tissue based upon biological processes and subsets of O-GlcNAc-modified proteins.

Conclusion: We report here for the first time subsets of differentially O-GlcNAc-modified proteins in healthy and OA human articular cartilage. Biological processes involving O-GlcNAc proteins are different in OA cartilage in comparison with the healthy one. Our results further highlight the contribution of this means of protein control to the development and progression of OA and, more importantly, may contribute to the identification of potential biomarkers and/or therapeutic targets in OA.

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Epigenome-Wide DNA Methylation Study Reveals Hypermethylated Collagen Genes and Suggests a Role for TGFβ in Osteoarthritis. Matlock A. Jeffries[1], Amr H. Sawalha[2] and Judith A. James[3]. [1]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]University of Michigan, Ann Arbor, MI, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: Osteoarthritis (OA) is the leading cause of chronic disability in the U.S., affecting 40% of individuals over the age of 70 and costing $128 billion annually in the US alone. Late-stage OA chondrocytes exhibit a host of gene transcription changes leading to upregulation of enzymes that contribute to cartilage breakdown. Herein, we characterize epigenome-wide DNA methylation changes in osteoarthritic compared to healthy cartilage from the same joints.

Methods: Twelve femoral heads were obtained at the time of hip arthroplasty for primary OA. Articular cartilage tissue was dissected from grossly affected and grossly normal areas, flash frozen in liquid nitrogen, and DNA was extracted. Following sodium bisulfite-treatment, DNA methylation was quantified at >485,000 CpG sites across the genome using Illumina HumanMethylation450 arrays. CpG sites with an absolute methylation difference between OA and normal cartilage (Db) $\geq$ 15%, and $P < 0.01$ after correction for multiple testing using a false discovery rate (FDR) of 5%, were considered statistically significant and used for subsequent analysis.

Results: We found 442 differentially methylated CpG sites in OA compared to normal cartilage from the same joints: 260 hypo- and 182 hypermethylated. Overrepresented gene sets included "Connective tissue disorder" (n=53, p=4.73E-6 to 7.36E-3), "Developmental disorder" (n=44, p=4.73E-6 to 7.36E-3), and "Skeletal & muscular disorder" (n=59, p=4.73E-6 to 7.36E-3). Particularly interesting methylation changes in OA include hypermethylation of *COL11A2*, which functions to maintain spacing and diameter of type II collagen and is mutated in patients with Stickler syndrome and OSMED. Additional DNA methylation changes detected include hypermethylation of *COL6A2*, hypomethylation of the fibrillar collagen gene *COL1A1*, and hypermethylation of *COL18A1*. Hypermethylation was also noted in multiple CpG sites within the WNT pathway co-receptor *LRP5*, which is associated with OA in mice and is a genetic susceptibility gene for OA in humans. Hypomethylation was found at multiple CpG sites in the transcription factor *RUNX1*. Upstream regulator analysis identified significant association of TGFβ1 with 44 differentially methylated genes. Finally, canonical pathway analysis identified enrichment of several pathways, most prominently the ERK signaling pathway among differentially methylated genes (p=1.51E-4).

Conclusion: We detected significant methylation changes in multiple collagen genes in OA. Our data suggest an epigenetic basis for defective collagen production in OA. Furthermore, we found evidence for epigenetic dysregulation of WNT signaling, and enrichment of genes associated with TGFβ- and ERK-pathway signaling, both of which are enticing targets for OA therapeutics. This work reinforces a role for genetic/epigenetic interaction in the pathogenesis of OA.

Disclosure: M. A. Jeffries, None; **A. H. Sawalha**, None; **J. A. James**, Pfizer Inc, 2, GSK, 5.

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Tenogenic Effect Of Homeobox Mohawk gene for Bone Marrow Mesenchymal Stem Cells. Koji Otabe, Hiroyuki Nakahara, Akihiko Hasegawa, Martin K. Lotz and Hiroshi Asahara. The Scripps Research Institute, La Jolla, CA.

Background/Purpose: Mohawk homeobox (MKX) has been demonstrated as a tendon and ligament specific transcriptional factor. MKX knock-out mice showed hypoplastic tendons throughout the body, due to reduced type I collagenproduction in tendon cells. Our group also demonstrated expression of MKX decreased in mature human knee ligament tissues, during joint aging and further decreased in osteoarthritis (OA). The aims of this study were to characterize factors that may promote tenogenic differentiation of bone marrow derived mesenchymal stem cells (BMMSCs) and to investigate the role of MKX in ligament/tenogenic differentiation of BMMSCs.

Methods: Human BMMSCs (n=9 from 3 donors) were purchased from Lonza, and treated with putative tenogenic factors (50ng/ml BMP12, 5ng/ml TGFbeta or 50ng/ml PDGF). Tendon/ligament related gene expression was analyzed by qRT-PCR at 1–5 days after treatment. BMMSCs were infected with adenoviruses expressing MKX or Scleraxis (Scx), also a tendon specific transcription factor and tendon related gene expression was analyzed levels at days 1, 2 and 7.

Results: Basal MKX and SCX expression levels were low in BMMSCs. BMP12 increased expression of MKX and SCX genes in BMMSCs at day 5 ($p<0.01$, n=6). COL1a1 levels were higher in BMP12 and TGFbeta treated groups ($p<0.01$, n=6). Decorin (DCN) and tenascin B (TNXB), important extracellular matrix (ECM) components of ACL, were also higher in BMP12 treated group ($p<0.05$, n=6). The expression of COL1a1 and TNXB were increased by overexpression of MKX in BMMSCs ($p<0.05$, n=9). Tenomodulin (TNMD), a marker of late stage tenogenic differentiation, was expressed at higher levels in Ad-Mkx and Ad-Scx groups than in Ad-Mock group ($p<0.05$, n=9).

Conclusion: This is the first report to compare several potential tenogenic factors in BMMSCs and to investigate the MKX expression and function in human BMMSCs. The present findings demonstrate that BMP12 most effectively enhanced tenogenesis related genes including Mkx, and overexpression of MKX was associated with increased tendon ECM production. Thus, MKX is represents a key factor for tenogenic differentiation of BMMSCs.

Disclosure: K. Otabe, None; **H. Nakahara**, None; **A. Hasegawa**, None; **M. K. Lotz**, Tanabe Research Laboratories, 4, Cargill, 2; **H. Asahara**, None.

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Investigations On The Role Of Delta/Notch Like EGF-Related Receptor In The Pathogenesis Of Osteoarthritis. Lucija Berninger[1], Anna Balkenhol[1], Clemens Baier[2], Stefan Rehart[3], Markus Rickert[4], Ulf Müller-Ladner[1], Elena Neumann[1] and Matthias Geyer[1]. [1]Justus-Liebig-University of Gieβen, Kerckhoff-Klinik, Bad Nauheim, Germany, [2]University of Regensburg, Bad Abbach, Germany, [3]Markus-Hospital, Frankfurt, Germany, [4]University Hospital Giessen and Marburg, Giessen, Germany.

Background/Purpose: Delta/Notch like EGF-related receptor (DNER) is a single-pass transmembrane protein with characteristic EGF-like repeats in the extracellular domain, similar to those of the Notch receptor and its ligand Delta. In our previous study, an overexpression of DNER mRNA was observed in lesional areas of human osteoarthritis (OA) articular cartilage compared to unaffected zones of the same tissue sample. Based on these findings and on the fact that Notch signaling pathway plays a major role in cell fate regulation and differentiation of human articular chondrocytes, we analyzed the role of DNER in the pathogenesis of OA.

Methods: Human articular cartilage was obtained from knee joint explants of OA patients undergoing total joint replacement surgery. The expression of DNER in human cartilage was analyzed by immunohistochemistry. Isolated primary chondrocytes were nucleofected with siRNA targeting human DNER or with a plasmid for DNER overexpression (pDNER), respectively. Knockdown and overexpression were confirmed by immunocytochemical staining for DNER in the nucleofected chondrocytes at different time points of cultivation. RNA was isolated and the effects of the artificially modified DNER expression on specific cartilage metabolic parameters (collagen type 2 and 1, Sox9, MMP9, ADAMTS4 and 5) analyzed using quantitative real-time PCR.

Results: Histologically, DNER was significantly increased in the affected cartilage of all patients (n=3) on the protein level compared to the intact zones of the same tissue. An overexpression of DNER in primary human OA chondrocytes peaked 24 h after nucleofection (increase: 50000 fold). 72 h after nucleofection, a down-regulation of collagen type 2 (−7,89 fold) and an up-regulation of collagen type 1 (2,07 fold) as well as Sox 9 (7.39 fold) mRNA was measured.The overexpression of DNER was detectable at different time points on the protein level. In contrast, following knockdown of DNER, its expression was significantly decreased ($p \leq 0.001$) but there was no significant change in the expression profile of collagen type 2 (0.94 fold; $p \leq 0.621$), collagen type 1 (0.74 fold; $p \leq 0.097$), Sox9 (0.83 fold), MMP9 (0.97 fold), ADAMTS4 (0.64 fold) and 5 (1.2 fold). The confirmation of the DNER knockdown on the protein level at different time points identified that DNER is still to be constitutively found in the membrane.

Conclusion: Since DNER overexpression led to a down-regulation of collagen type 2 in human articular chondrocytes whilst the expression of collagen type 1 and Sox9 were up-regulated, our preliminary results could lead to the assumption that DNER might contribute to the dedifferentiation of human OA chondrocytes within a "regenerative" attempt in order to de-organize and re-assemble adapted cartilage extracellular matrix to reconstitute physiological homeostasis and the ability to re-sustain to physical load during the course of human OA.

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Fibulin-3 In Joint Aging and Osteoarthritis Pathogenesis. Akihiko Hasegawa[1], Tomo Yonezawa[2], Noboru Taniguchi[2], Koji Otabe[2], Yukio Akasaki[2], Tetsuya Matsukawa[2], Masahiko Saito[3], Masashi Neo[4], Lihua Y. Marmorstein[5] and Martin K. Lotz[2]. [1]Osaka Medical College, Takatsuki, Osaka, Japan, [2]The Scripps Research Institute, La Jolla, CA, [3]Toho University Sakura Medical Center, Sakura, China, [4]Osaka Medical College, Osaka, Japan, [5]University of Arizona, Tucson, AZ.

Background/Purpose: Osteoarthritis (OA) is the most common joint disease. Among the earliest lesions during OA development is disruption of the superficial zone (SZ) of articular cartilage. The SZ of articular cartilage contains adult mesenchymal progenitor cells and is unique in extracellular matrix composition. Recently, we found that the EFEMP1 gene encoding fibulin-3 is specifically expressed in SZ. However, the expression pattern of fibulin-3 in articular cartilage and its role is unknown. The objectives of this study were to examine fibulin-3 expression patterns in joint aging and OA and to investigate the role of fibulin-3 in OA pathogenesis.

Methods: Immunohistochemical analysis was performed on human and mouse knee cartilage to determine changes in fibulin-3 expression during joint aging and in OA. To examine the role of fibulin-3 in cartilage homeostasis, experimental OA was induced in wild type and fibulin-$3^{-/-}$mice. The mice were euthanized 10 weeks after the knee surgery for histological analysis. To address whether fibulin-3 is involved in regulating chondrocyte differentiation, human articular chondrocytes were transfected with fibulin-3-specific siRNA. Cells were harvested at 48 hours and 72 hours for quantitative PCR and Western blot analyses. To further address the role of fibulin-3 during chondrogenesis, bone marrow mesenchymal stem cells (MSC) were transduced with lentivirus (LV) encoding EFEMP1 or control LV expressing LacZ, then MSC pellets were prepared and analyzed for chondrogenesis.

Results: Fibulin-3 was specifically expressed in the SZ of normal cartilage in human and mouse knee joints. Fibulin-3 expression was intracellular and in the extracellular matrix (ECM) and declined with aging. Both aging-related OA and experimental OA were significantly more severe in fibulin-$3^{-/-}$mice compared with wild type mice. Fibulin-3 expression was high in MSC and decreased during chondrogenesis. Suppression of fibulin-3 by siRNA in MSC significantly increased SOX9, collagen II and aggrecan in articular chondrocytes, while the overexpression of fibulin-3 inhibited chondrogenesis in MSC.

Conclusion: We found that fibulin-3 is specifically expressed in the SZ of articular cartilage and its expression is reduced in aging and OA. Fibulin-3 regulates survival and differentiation of adult progenitor cells and its aging-related decline is an early event in OA pathogenesis. Preventing or restoring aging-associated loss of fibulin-3 in SZ chondrocytes has potential to delay or prevent onset of OA.

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The Frequency Of Bone Marrow Oedema Adjacent To The Cruciate Ligament Peri-Entheseal Vascular Channels In Inflammatory and Degenerative Arthritis. Daniel Binks[1], Melissa Matzelle[2], Diane Bergin[3], Richard J. Hodgson[1], Ai Lyn Tan[1], Ellen M. Gravallese[4], Dennis McGonagle[5] and Aleksandra Radjenovic[1]. [1]University of Leeds, Leeds, United Kingdom, [2]University of Massachusetts Medical School, Worcester, MA, [3]Galway University Hospitals, Galway, Ireland, [4]UMass Memorial Medical Center, Worcester, MA, [5]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

Background/Purpose: We noted in mouse models of inflammatory arthritis (IA) that an early point of entry of inflammation into the marrow space occurred at sites where penetrating vessels entered the bone. The role of penetrating vessels in erosion formation in man has not been explored in IA, nor has the role of vascular channels in bone marrow oedema (BME) in osteoarthritis (OA) been explored. The purpose of this work was to investigate the frequency of BME in inflammatory and degenerative arthropathies in close proximity to the peri-entheseal ACL and PCL vascular channels

Methods: Normal microanatomy was defined in 21 cadaveric knees using 3T MRI and histology. MRI of 89 patients from the Osteoarthritis Initiative study and 27 patients with inflammatory arthritis were evaluated for BME at the same locations. An animal model of inflammatory arthritis was evaluated to ascertain whether the putative peri-entheseal vascular regions influenced the propensity of osteitis and bone erosion

Results: Data from the animal model of IA showed inflammation entering the marrow space along the adventitia of blood vessels that penetrate the cortical bone in close proximity to the cruciate ligament insertions. On 3T MRI, a vascular channel adjacent to the ACL tibial insertion was observed in 64% of cadaveric specimens examined. Similarly, a vascular channel adjacent to the PCL was seen in 71% of cases. BME was observed in the regions corresponding to the location of the vascular channel in 51% of knees for both

the anterior and posterior channel. Histological evaluation of 10 cadaveric specimens confirmed the location of the vascular channels along with the presence of associated subclinical microdamage including subchondral bone damage (80% of cases) and micro-cyst formation (50%). Evaluation of patient MRIs showed the prevalence of oedematous features in the same topographic locations in patients with early OA (41% ACL, 59% PCL) and IA (44% ACL, 33% PCL), (Figure 1).

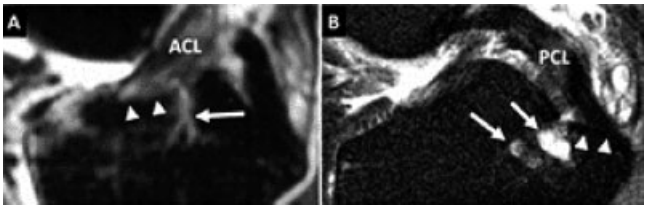

Figure 1. Sagittal fluid-sensitive MRI showing examples of **A,** tibial vascular channel (**arrow**) posterior to the anterior cruciate ligament insertion (**arrowheads**) in a patient with inflammatory arthritis and **B,** bone marrow lesions (**arrows**) seen in the region anterior to the PCL insertion (**arrowheads**) in a patient with osteoarthritis. Bone marrow lesions/oedema were seen adjacent to both cruciate ligament insertions in both inflammatory and degenerative types of arthritis.

Conclusion: Our findings show that the vascular channels adjacent to the anterior and posterior cruciate ligament entheses are common locations for erosion formation and damage in both inflammatory and degenerative arthritis. Furthermore, we have found a significant clustering of subclinical microdamage in these regions in normal cadaveric samples. Therefore, we conclude that peri-entheseal vascular channels are likely to present a common pathogenesis focus for both OA and IA.

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Follistatin-Like Protein 1 Is An Important Regulator Of Chondrogenesis. Yury Chaly[1], Sonja Smith[1], Daniel Bushnell[2], Brian Campfield[2], Harry Blair[3] and Raphael Hirsch[1]. [1]University of Iowa Carver College of Medicine, Iowa City, IA, [2]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [3]University of Pittsburgh School of Medicine, Pittsburgh, PA.

Background/Purpose: Chondrocytes play a pivotal role in osteoarthritis (OA) because they are the only cells in the articular cartilage that are responsible for maintenance of the extracellular matrix (ECM). Articular cartilage intrinsic regenerative capacity is strongly downregulated in humans with age. The use of mesenchymal stromal cells (MSC) is an attractive approach for cartilage repair because MSC are capable of proliferating and differentiating into chondrocytes in vitro. However, without detailed knowledge of how chondrogenic pathways are induced it has not been possible to produce true hyaline cartilage in vitro or in vivo, or to maintain cartilage growth. The present study was undertaken to determine whether follistatin-like protein 1 (FSTL1) regulates chondrogenic differentiation of MSC. We hypothesized that FSTL1 may enhance cell proliferation and anabolic activity in articular chondrocytes and, therefore, play an important role in maintaining cartilage homeostasis.

Methods: To study the role of FSTL1 in chondrogenesis, we made use of FSTL1 knockout (KO) mice generated in our laboratory. MSC were obtained from skulls of E18.5 embryos. Proliferative capacity of MSC was analyzed by flow cytometry using CFSE labeling. Differentiation of MSC into chondrocytes was carried out in a pellet culture system. Gene expression microarray analysis was performed on MSC isolated from FSTL1 KO and wild-type embryos. For signaling study, protein extracts from TGFb-stimulated MSC were analyzed for phospho (p)-SMAD3, p-p38 MAPK, p-AKT by Western blotting.

Results: Homozygous FSTL1 KO mice showed extensive skeletal defects, supporting a role for FSTL1 in chondrogenesis. FSTL1 KO embryos had decreased cellularity in the embryonic vertebral cartilage and FSTL1 KO MSC had reduced proliferative capacity. Microarray analysis of gene expression in FSTL1 KO MSC revealed dysregulation of multiple genes known to be involved in chondrogenesis, including COL1A2, COL2A1, COL10A1, SOX5, SOX9, TGFBR2, CTSK, GREM1, IGFBP4, WISP1. We also demonstrated that FSTL1-deficient MSC displayed defects in TGFb-induced differentiation into chondrocytes, including decreased production of ECM proteoglycans and reduced expression of type II collagen. TGFb-induced phosphorylation of SMAD3, p38 MAPK, and AKT were significantly decreased in FSTL1 KO cells.

Conclusion: These results demonstrate that FSTL1 is a crucial component of the regulatory mechanism controlling chondrocyte proliferation, differentiation, and expression of ECM molecules. Our findings may lead to the development of novel strategies for cartilage repair and provide new disease modifying treatments for OA.

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Heparin-Binding Epidermal Growth Factor-Like Growth Factor (HB-EGF) As a Potential Mediator In Osteoarthritis. Richard F. Loeser[1] and David A. Long[2]. [1]Wake Forest School of Medicine, Winston-Salem, NC, [2]Wake Forest University, Winston-Salem, NC.

Background/Purpose: We recently reported changes in gene expression in knee joint tissue from 12 week-old and 12 month-old mice after OA was induced by surgical destabilization of the medial meniscus (DMM). Heparin-binding EGF-like growth factor (HB-EGF) was found by gene array to be significantly up-regulated at 8 weeks after surgery in both age groups. HB-EGF is a known ligand for the EGF receptor (EGFR) which signals through MAP kinases and the small GTPase Rac. EGFR signaling has been implicated in OA pathogenesis but a potential role for HB-EGF has not been examined. The purpose of this study was to determine if HB-EGF was present in human OA cartilage and to test the ability of HB-EGF to stimulate production of chondrocyte MMP-13 which can contribute to matrix destruction in OA.

Methods: Real-time PCR was used to confirm the HB-EGF gene array results using RNA isolated from knee joint tissues (n=9 mice per surgical group) from 12 week-old and 12 month-old male C57/BL6 mice that had undergone DMM or sham control surgery. Immunohistochemistry for HB-EGF was performed using knee joint tissue collected from normal tissue donors or age-matched patients who had undergone knee replacement for OA (n=4 each). *In vitro* stimulation studies used cultured human articular chondrocytes isolated from normal donor tissue (n'3 independent donors for each experiment). Fibronectin fragments (FN-f) were used as a catabolic stimulus relevant to OA. Effects of recombinant HB-EGF, ± FN-F, on MMP-13 production were measured by immunoblotting and real time (RT)-PCR and on Rac activity using an activity assay.

Results: HB-EGF expression was about two-thirds lower ($p<0.05$) in the sham control joints of the older mice compared to young controls but increased by >6-fold ($p<0.001$) in the older DMM joints vs 1.4-fold in the young DMM when compared to the age-matched sham. Immunohistochemical staining revealed increased HB-EGF in human OA cartilage relative to age-matched normal where little to no staining was observed. Treatment of cultured human chondrocytes with FN-f increased HB-EGF expression which peaked at almost 60-fold (by RT-PCR) at 3 hours. Overnight FN-f stimulation increased HB-EGF secretion into conditioned media. We found that HB-EGF at 10ng/ml stimulated chondrocyte Rac activity and phosphorylation of the EGFR, ERK and p38 but not JNK. High dose (100ng/ml) but not low dose (10ng/ml) HB-EGF stimulated MMP-13 production in conditioned media, detected by immunoblotting. However, low dose HB-EGF enhanced the MMP-13 production induced by FN-F by 1.4-fold over FN-f alone and this was completely inhibited by blocking Rac1 with 100μM NSC23766 or EGFR with 250 nM AG1478.

Conclusion: HB-EGF was detected in human OA cartilage but not normal cartilage. FN-fs, known to be present in OA cartilage and to stimulate catabolic pathways, were found to stimulate HB-EGF production by normal chondrocytes. Given the finding that HB-EGF signals through the chondrocyte EGFR and promotes MAP kinase and MMP-13 production and that it is present in human OA cartilage, further evaluation of its role in OA is warranted.

Disclosure: R. F. Loeser, None; **D. A. Long**, None.

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Autophagy Activation Protects From Mitochondrial Dysfunction In Human Chondrocytes. Beatriz Caramés[1], Paloma López de Figueroa[1], Martin Lotz[2] and Francisco J. Blanco[3]. [1]Osteoarticular and Aging Research Lab, INIBIC–Complejo Hospitalario Universitario A Coruña, SPAIN, A Coruña, Spain, [2]The Scripps Research Institute, La Jolla, USA, La Jolla, CA, [3]Osteoarticular and Aging Res. Lab. CIBER-BBN. INIBIC- University of A Coruña, A Coruña, Spain.

Background/Purpose: A common feature of aging-related diseases, such as osteoarthritis (OA), is the progressive accumulation of damaged macromolecules leading to cell dysfunction and death. Autophagy, a key pathway for cellular homeostasis by removing such damaged molecules and organelles, including mitochondria, has a protective and survival-promoting function. Recent studies indicated that autophagy decreases with aging and OA contributing to the accumulation of damaged macromolecules. In addition, there is increasing evidence that mitochondrial dysfunction plays a critical role in accelerating the aging process and several lines of evidence demonstrated mitochondrial dysfunction in OA cartilage. *The objective of this study is to determine whether activation of autophagy protects from mitochondrial dysfunction in human chondrocytes.*

Methods: Human chondrocytes were treated with Rotenone (10 μg/ml), Antimycin (40 μg/ml) and Oligomycin (10 μg/ml), a mitochondrial respiratory chain (MRC) inhibitors of complex I, III and IV, respectively. Mitochondrial function and cell death were evaluated by Flow Cytometry (FC) and Fluorescence Microscopy (FM). Autophagy activation was analyzed by determination of LC3, a main marker of autophagy activation by Immunofluorescence (IF). To investigate whether autophagy protects from mitochondrial dysfunction, autophagy was induced by mTOR inhibition, using mTORC1 selective inhibitor Rapamycin (Rapa, 10 μM) and mTORC1 and mTORC2 inhibitor Torin 1 (50 nM). The effects on autophagy, mitochondrial function and chondrocyte viability were analyzed by IF, FC and FM.

Results: Mitochondrial dysfunction was induced by 6 h treatment with MRC inhibitors, which significantly decreased mitochondrial membrane potential ($\Delta\Psi$m) (ROT: 26.17 $\pm$ 5.9; AA: 18.21 $\pm$ 3.28; Oligo: 41.74 $\pm$ 7.59, expressed as % vs control; *$p < 0.01$). These results are consistent with increased ROS production (26.8 %, 44.6 % and 25.7 % for ROT, AA and Oligo, respectively; *$p < 0.001$) and cell death by apoptosis at 12 h (Control: 13.56 $\pm$ 1.83; ROT: 33.66 $\pm$ 5.55; AA: 29.05 $\pm$ 4.262; *$p<0.05$). Autophagy activity determined by LC3 expression significantly reduced in response to MRC inhibitors at 12 h. To evaluate whether autophagy regulates mitochondrial dysfunction, chondrocytes were pretreated with Rapa and Torin 1 for 4 h and then treated with the MRC inhibitors for 12 h. The results show an increase in LC3 expression compared to MRC inhibitors alone. Furthermore, autophagy inducers Rapa and Torin1 increased $\Delta\Psi$m (Rapa: 125.8 $\pm$ 20.74; Rapa+ROT: 44.67 $\pm$ 10.37; Rapa+AA: 30.71 $\pm$ 5.949; Rapa $\pm$ Oligo: 108.5 $\pm$ 55.03 and Torin 1: 90.34 $\pm$ 9.17; Torin 1+ROT: 35.24 $\pm$ 2.7; Torin 1+AA: 41.98 $\pm$ 6.49; Torin 1+Oligo: 98.19 $\pm$ 16.81; *$p<0.05$), decreased ROS production (*$p<0.05$) and reduced cell death, suggesting a protective effect of autophagy activation on pharmacologically induced mitochondrial dysfunction.

Conclusion: These data identify autophagy activation as a protective mechanism from mitochondrial dysfunction in human chondrocytes. Pharmacological interventions that enhance autophagy may have chondroprotective activity in articular cartilage with defects on mitochondrial function.

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Interconnected Cellular Projections and Gap Junctions Mediate Metabolic Coupling Between Chondrocytes Located In Different Layers Of The Tissue: Cell-To-Cell Communication In Normal and Osteoarthritic Cartilage. Maria Dolores Mayan[1], Paula Carpintero-Fernández[2], Raquel Gago-Fuentes[2], Patricia Fernández-Puente[3], Purificacion Filgueira-Fernandez[3], Noa Goyanes[3], Virgin Valiunas[4], Peter Brink[4], Gary Goldberg[5] and Francisco J. Blanco[6]. [1]Correspondence to: Ma.Dolores.Mayan.Santos@sergas.es and fblagar@sergas.es, A Coruña, Spain, [2]These authors contribute equally to this work, A Coruña, Spain, [3]Osteoarticular and Aging Research Group. Rheumatology Division, Biomedical Research Center (INIBIC). Hospital Universitario A Coruña, Xubias de Arriba 84, 15006, A Coruña, Spain, [4]Department of Physiology and Biophysics. State University of New York, Stony Brook, New York, SC, [5]Department of Molecular Biology. Medical Center Drive, University of Medicine and Dentistry of New Jersey, Stratford, NJ, [6]Osteoarticular and Aging Res. Lab. CIBER-BBN. INIBIC- University of A Coruña, A Coruña, Spain.

Background/Purpose: We have recently found that articular chondrocytes from human adults contain long cytoplasmic arms that cross the extracellular matrix and physically connect two chondrocytes located in distant lacuna. Besides, we have also demonstrated that primary chondrocytes from adults are able to communicate with each other via gap junctions (GJ) as evidenced by the intercellular transfer of tracer dyes.

Methods: For immunohistochemistry (IHC) assays, in situ cartilage was frozen immediately using Tissue-Tek O.C.T. and isopentanol in liquid nitrogen. For Scanning Electron Microscope (SEM), samples were embedded in cacodylate buffer before dehydratation. Dual Voltage-clamp methods along with the study of glucose and oligonucleotides transference and in situ electroporation were used for the study of gap junctional communication (InSitu Porator™ Cell Projects Ltd). Transwell co-culture system and mass spectrometry were used for the identification and quantification of transjuctional amino acids. Primary chondrocytes were previously cultured in SILAC® Dulbecco's Modiffied Eagle's Medium containing L-lisina [$^{13}C_6$] and L-arginina [$^{13}C_6$, $^{15}N_4$]. Prior to LC analysis amino acids were derivatized using the tEZ: faastTM kit. Detection of analytes was performed with a Thermo Scientific LTQ-Orbitrap.

Results: IHC, electrophysiology experiments and "metabolic capture" assays revealed that GJs play a metabolic function by exchanging nutrients including glucose and essential amino acids between cells. Microinjection of the fluorescent glucose derivative 2-NBDG showed a progressive fluorescence intensity increase in the contacted recipient cells during 22 and 35 minutes after dye injection. In situ electroporation of donor cells confirmed that adult chondrocytes efficiently exchange glucose between adjacent cells (18–20 cells deep). When cells were pre-incubated for 1 hour with 250μg/ml of the GJ inhibitor GAP27, the transference of glucose was severely reduced (1–2 cells deep). For Transwell co-culture system, donors previously cultured in "heavy medium" were allowed to settle for 4 hours, time enough to form cell projections on the membrane right side up containing receivers. Mass spectrometry analysis revealed the transference of 3,5 pmol/ml of [$^{13}C_6$]-L-lysina and 3 pmol/ml of [$^{13}C_6$, $^{15}N_4$]-L-arginina. The results were confirmed using in situ electroporation and fluorescent labelled amino acids. IHC experiments in cartilage from patients with osteoarthritis (OA) revealed significantly elevated levels of the GJ protein Cx43 in the superficial zone and down through the next 1000 μm of tissue. Besides OA condrocytes contain longer cytoplasmic projections.

Conclusion: The results here presented demonstrated that chondrocytes from human adult cartilage are physically connected to each other forming a three-dimensional cellular network, and are able to transfer nutrients such as glucose and essential amino acids through GJ channels. The levels of Cx43 protein and the length of cells projections suggest alterations in the normal homeostasis control and cell-cell communication between chondrocytes in cartilage of patients with OA.

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Chondrocyte Hypertrophy, Measured By The Secretion Of Collagen Type X, Is Associated With Cartilage Degradation and Systemic Inflammation In Osteoarthritis. Yi He[1], Natasja Stæhr Gudman[2], Niels Ulrik Hansen[1], Jianxia Wang[3], Di Su[3], Qinlong Zheng[3], Ole Simonsen[4], Kristian Kjaer Petersen[5], Moustapha Kassem[6], Morten Asser Karsdal[2] and Anne C. Bay-Jensen[2]. [1]Nordic Bioscience, Herlev, Denmark, [2]Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, [3]Nordic Bioscience China, Beijing, China, [4]Frederikshavn Hospital, Frederikshavn, Denmark, [5]Center for Sensory-Motor Interaction, Aalborg, Denmark, [6]Odense University Hospital and University of Southern, Odense, Denmark.

Background/Purpose: Osteoarthritis (OA) is the most common degenerative joint disease, of which the pathogenesis is inadequately understood. The hypertrophy-like changes, such as expression of hypertrophy markers and matrix calcification have been observed in the initiation and progression of OA. The aim of this study was to investigate the relationships of chondrocyte hypertrophy, cartilage degradation and systemic inflammation by measuring 3 biomarkers in serum of 283 OA patients.

Methods: i) A competitive ELISA, C-Col10, was developed as a marker of chondrocyte hypertrophy, through measurement of type X collagen (ColX). ii) C-Col10, C2M (matrix metalloproteinase-derived fragments of type II collagen) and hsCRP were quantified by ELISA in serum of the patients, stratified by Kellgren-Lawrence (KL) score 0–4. iii) Association between serum levels of the 3 biomarkers were analyzed (Pearson correla-

tions were done on log transformed data). The data is shown as mean [95%-CI]. iv) Full-depth cartilage biopsies from OA patients with different disease stages were immunostained with the C-Col10 and C2M antibodies.

Results: The C-Col10 assay was specific for the C-terminal of type X collagen. The measurement range of the C-Col10 assay was 22–500pg/ml, with intra- and inter-assay CVs of 4.2% and 13%. There was a trend towards increasing C-Col10 levels with increasing KL score: KL0 52[24–80] pg/ml, (n=10); KL1 67 [56–78] pg/ml, (n=59); KL2 87[74–99] pg/ml, (n=144); KL3 80pg/ml [60–101], (n=36), and KL87 [47–127] pg/ml, (n=22). There was significant correlation of levels between C-Col10 and hsCRP (r=0.23, P<0.0001), and C2M (r=0.55, P <0.0001). There was no correlation between C2M and hsCRP. Age and BMI adjustment didn't change the significant correlations. OA patients with above normal hsCRP (>5) levels showed increased C-Col10, however this was independent from cartilage degradation. These data was supported by immunoloclization of C-Col10 and C2M in the OA cartilage biopsies, which showed distinct staining patterns: C-Col10 was observed in the deep zone around the pre-hypertrophic chondrocytes in mild OA, and around chondrocyte clusters in severe OA. Whereas C2M was consistently observed in all layers of the OA cartilage.

Conclusion: Elevated C-Col10 levels were measured in OA patients and significantly higher in patients with above normal hsCRP levels, suggesting that inflammation is associated with chondrocyte hypertrophy. Correlation between C-Col10 and cartilage degradation indicated that chondrocyte hypertrophy may be involved in the cartilage degradation. All data show that chondrocyte hypertrophy is an essential step in the pathogenesis of OA and C-Col10 measurement can provide the critical information of OA disease status.

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Subchondral Bone Turnover and Osteophyte Formation Are Key Aspects In The Progression Of Osteoarthritis and May Be Assessed and Predicted By a-CTX. Morten Asser Karsdal[1], Janet L. Huebner[2], Virginia Byers Kraus[2], Diana J. Leeming[1], Edward Coleman[2], Gary E. McDaniel[2], Kim M. Huffman[2], Kim Henriksen[1] and Anne C. Bay-jensen[1]. [1]Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, [2]Duke University Medical Center, Durham, NC.

Background/Purpose: Osteoarthritis (OA) is the most common form of arthritic disease. It is characterized by pathological changes in both bone and cartilage turnover as well as structure in which subchondral bone remodeling is speculated to be both an initiator and driver of OA. The aim of the current study was to evaluate a biomarker of high localized bone resorption, a-CTX, previously used for bone metastasis. OA patients were characterized by; radiographic knee OA, severity, progression and localized knee bone turnover as assessed by bone scintigraphy, a dynamic and sensitive indicator of symptomatic knee OA.

Methods: A total of 149 participants (111 women, 38 men) were included who met ACR criteria for symptomatic OA and had the presence of Kellgren Lawrence (K/L) grade 1–4 radiographic OA in at least one knee. Late-phase bone scan images of both knees were obtained 2 hours after administration of ^{99m}Tc-MDP. The intensity of uptake was scored semi-quantitatively and summed for each joint site. Radiographic knee OA severity, based on the summed scoring of osteophytes (OST) and joint space narrowing (JSN) was assessed using the standardized OARSI radiographic atlas. Progression status was determined by calculating the sum of the change score in either JSN or OST between baseline and the 3-year follow-up assessment. The concentrations of urinary a-CTX and CTX-II were determined by ELISA and normalized to creatinine concentration.

Results: a-CTX was related to OST formation independent of the effects of age, gender, BMI, and HRT (p=0.009). a-CTX did not correlate with severity of knee OA based on OST and JSN, but did correlate with bone turnover assessed by intensity of ^{99m}Tc-MDP uptake in the medial knee compartment. Concentrations of urinary CTX-II were strongly associated with knee OA severity based on osteophyte, intensity of total knee ^{99m}Tc-MDP uptake, and joint space narrowing.

Conclusion: a-CTX was associated with subchondral bone turnover, and osteophyte formation, both central features of the pathogenesis of OA. CTX-II was correlated to JSN, and burden of disease as previously reported. The significant and strong association of a-CTX to bone turnover in the subchondral region suggests that this marker may be a non-invasive surrogate for active bone turnover in knee OA. Such markers may assist in the identification patients whom may benefit from strong anti-resorptives which inhibit bone and subchondral bone turnover.

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Autophagy Changes During Aging: A Study In GFP-LC3 Mice. Beatriz Carames[1], William B. Kiosses[2], Merissa Olmer[3] and Martin Lotz[4]. [1]Osteoarticular and Aging Research Lab, INIBIC–Complejo Hospitalario Universitario A Coruña, SPAIN, A Coruña, Spain, [2]The Scripps Research Institute, La Jolla, CA, [3]The Sripps Research Institute, La Jolla, CA, [4]The Scripps Research Institute, La Jolla, USA, La Jolla, CA.

Background/Purpose: Aging is a main risk factor for osteoarthritis (OA), the most prevalent musculoskeletal disorder. Aging-associated changes in autophagy, an essential cellular homeostasis mechanism, have recently been observed in several tissues, including articular cartilage. The objective of this study is to establish the patterns of autophagy in young and aging cartilage using GFP-LC3 mice.

Methods: In GFP-LC3 transgenic mice, GFP-LC3 is ubiquitously expressed under the control of CAG promoter, and the accumulation of GFP punctate, which represents autophagosome, is observed in almost all tissues after 24–48 h fasting period. Homozygous GFP-LC3 mice (tg/tg) were employed to monitore autophagy in liver and joint tissues in response to aging (6 months old and 28 months old mice) by confocal microscopy analysis of vibratome sections. Two sets of control mice were included: Wild-type C57BL/6J mice were used to determine the background level of green fluorescence and young homozygous GFP-LC3 mice (6 months old) to provide a baseline for autophagy activity in liver and joints. Morphological changes in the articular cartilage were examined by histology using a semiquantitative scoring system. Furthermore, cellularity was determined by Hematoxylin-Eosine staining (H&E) and expression of the autophagy proteins Atg5 and LC3 was analyzed by immunohistochemistry (IHC) in 6, 18, 24 and 28 months old mice.

Results: GFP-LC3 mice from 6 and 28 months old were employed to analyze the effect of aging on autophagy activation in liver and cartilage in the knee joints. In response to aging (28 months old mice), we observed a reduction in the GFP-LC3 signal in liver and cartilage. This reduction was statistically significant based on the total number of vesicles per cell ($P < 0.01$) and on the total area of vesicles per cell (um^2) ($P < 0.01$) compared to the control group (6 months old mice). In addition, the histological evaluation showed a significant decrease in cartilage score ($P < 0.01$) in the old mice compared to the young control group. These results were accompanied with a reduction on cartilage cellularity and with a decrease in the expression of Atg5 and LC3 in an age-dependent manner, indicating a correlation between autophagy defects and aging-related OA in mice.

Conclusion: These results support the hypothesis that autophagy is decreased with aging and that compromised autophagy represents a novel mechanism in the development of OA.

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Fibrillin-1 Expression and Function Is Needed For Normal Joint Function and Mutations Leads To Osteoarthritis. Wasabha Ramanayake[1], Helen Jones[1], Isabel Orriss[2], Tim Arnett[2], Andrew Pitsillides[3], Christopher P. Denton[1], David J. Abraham[1] and Blandine Poulet[1]. [1]UCL Medical School, London, United Kingdom, [2]University College London, London, United Kingdom, [3]Royal Veterniary College, London, United Kingdom.

Background/Purpose: Osteoarthritis (OA) is a common degenerative disease leading to pain and disability in >6 million british people. The TGFb signalling pathway has been shown to play a major role in joint homeostasis and in OA development. Fibrillin-1 is an extracellular matrix protein that may play a structural role in the matrix of articular cartilage, but also regulates the bioavailability of TGFb to the cell. Thus Fibrillin-1 mutations, such as those seen in the Tight Skin mouse (or TSK), have been shown to increase TGFb signalling. The aim of this study is therefore to determine changes in

fibrillin-1 expression during osteoarthritis in mice and to characterise the effect of Fibrillin-1 mutations in ageing-induced OA development in TSK mice.

Methods: Immunohistochemistry for Fibrillin-1 expression was performed in Str/ort mice, a known model of spontaneous OA, and in control aged-matched non-OA CBA mice, in knee joints with different degrees of OA severity. The knees of TSK and littermate control male mice of 60–80wks of age were fixed and microCT scanned. Abnormal ectopic calcified regions were analysed. After scanning, joints were decalcified and processed for paraffin embedding; serial coronal sections were cut at 6um and sections at regular intervals stained with Toluidine Blue.

Results: Fibrillin-1 was localised in the pericellular matrix of articular chondrocytes in normal joints. During the development of OA in Str/ort mice, however, Fibrillin-1 immunolabelling was decreased, in particular around articular cartilage lesions. TSK mice microCT images showed important ectopic calcification in various ligaments, as well as osteophyte formation on the margins of the joints. Preliminary data suggest that articulate cartilage degradation was increased in TSK mice compared to aged-matched control mice.

Conclusion: Our preliminary study shows that Fibrillin-1 protein expression is decreased during OA development in a well known model of spontaneous OA, suggesting TGFb bioavailability may be modified during this period. In addition, mutations in Fibrillin-1 in the TSK mouse lead to abnormal ossification in the knee joint as well as severe OA development. These data suggest that Fibrillin-1 plays an important role in joint homeostasis and that abnormal expression or mutations in its gene can lead to OA development.

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Terminal Uridyltransferase Enzyme ZCCHC11 Regulates Interleukin-6 Expression In Primary Human Osteoarthritis Chondrocytes. Abdul Haseeb[1], Mohammad Shahidul Makki[1], Ahmad Arida[2] and Tariq M. Haqqi[2]. [1]Northeast Ohio Medical University (NEOMED), Rootstown, OH, [2]North East Ohio Medical University, Rootstown, OH.

Background/Purpose: Non-template addition of nucleotides on the 3' termini of mRNAs acts as a mechanism that controls mRNA stability. ZCCHC11 is a member of the non-canonical poly A polymerase (ncPAP) family. It has been implicated in post-transcriptional regulation of various genes, including some cytokines, by modification of their poly A tails or by modification of microRNAs that target these mRNAs. Role of ZCCHC11 in chondrocyte physiology and in the pathogenesis of osteoarthritis (OA) has not been studied. In the present study we determined the expression of ZCCHC11 in damaged and undamaged cartilage obtained from OA patients. We also studied the effect of IL-1b on the expression of ZCCHC11 in primary human chondrocytes. We further investigated the effect of gene silencing of ZCCHC11 on the secreted levels of several cytokines.

Methods: Primary human chondrocytes were isolated from the deep zone of the cartilage obtained from OA patients who underwent total knee joint replacement surgery. Silencing of ZCCHC11 gene was carried out by using ON-TARGETplus siRNA pool (Thermo Fisher Scientific, Waltham, MA). Protein levels of 40 cytokines in culture supernatants after siRNA transfections were analyzed simultaneously using a glass-based human cytokine microarray (RayBio Human Cytokine Array). Poly A tail length analysis was performed by reverse transcription followed by PCR using an adaptor reverse primer and a forward primer specific for IL-6 mRNA. The PCR products were run on 2% agarose gel and visualized by EtBr staining. mRNA levels of ZCCHC11 and IL-6 genes were quantitated by using the TaqMan assays (Applied Biosystems, Carlsbad, CA). Data were derived using Origin 6.1 software and $P<0.05$ was considered significant

Results: There was higher expression of ZCCHC11 mRNA in damaged cartilage as compared to unaffected smooth cartilage obtained from OA patients. mRNA expression of ZCCHC11 was significantly up-regulated by treatment of human primary chondrocytes with IL-1b. Cytokine protein array analysis revealed a significant decrease in secreted levels of IL-6 and a subset of cytokines upon siRNA mediated silencing of ZCCHC11 gene. Quantitative PCR analysis showed that mRNA expression of IL-6 gene was also suppressed in human chondrocytes with depleted ZCCHC11 mRNA. Poly A tail length analysis showed a significant shortening of IL-6 mRNA poly A tail upon silencing of ZCCHC11 gene indicating that ZCCHC11 is required for IL-6 mRNA stability.

Conclusion: The data presented here for the first time show the expression of ZCCHC11 in human cartilage. Differential expression of ZCCHC11 in damaged and undamaged cartilage and its stimulation by IL-1b, a cytokine up-regulated during OA, point to a role of this enzyme in osteoarthritis. Furthermore, our gene silencing studies show the effect of ZCCHC11 on secretion of IL-6, an important cytokine involved in the pathogenesis of OA, via modifying its mRNA at the 3' end. Taken together, the present study reveals a novel RNA modifying enzyme ZCCHC11 as an important player in OA pathophysiology.

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Decorin-Deficiency Alters Cartilage Stiffness and Attenuates The Development Of Osteoarthritis In Mice. Tobias Gronau[1], Uwe Hansen[1], Daniela Seidler[1], Renato Iozzo[2], Attila Aszodi[3], Carina Prein[4], Hauke Clausen-Schaumann[4], Karsten Krüger[5], Frank Mooren[5], Jessica Bertrand[1], Thomas Pap[1], Peter Bruckner[1] and Rita Dreier[1]. [1]University Hospital Münster, Münster, Germany, [2]Thomas Jefferson University, Philadelphia, PA, [3]Ludwig-Maximilians-University Munich, Munich, Germany, [4]Munich University of Applied Sciences, Munich, Germany, [5]Justus-Liebig University Giessen, Giessen, Germany.

Background/Purpose: In articular (AC) and growth plate (GP) cartilage, the small leucine-rich proteoglycan decorin is mainly present within the interterritorial regions (ITs) of the extracellular matrix. Within the extracellular matrix it is associated with thick, well-banded collagen fibrils. Here we analyzed the impact of decorin-deficiency ($Dcn^{-/-}$) on the biomechanical properties of cartilage and the development of osteoarthritis via forced exercise.

Methods: Diverse cartilaginous tissues of $Dcn^{-/-}$ mice and wild-type (WT) mice were examined at different developmental time points by histology/immunohistochemistry and by atomic force microscopy (AFM). The levels of active TGF-β were analyzed by ELISA. Expression of glycosaminoglycan (GAG) modifing enzymes was assesed via semi-quantitave RT-PCR. Osteoarthritic changes (OA) were induced in 3 month-old $Dcn^{-/-}$ and WT mice via forced running on a treadmill. The severity of the disease was evaluated via a modified Mankin score.

Results: In P14.5 and adult $Dcn^{-/-}$ mice, Alcian blue (pH 1.0) stained highly sulfated GAGs intensely throughout the entire GP and AC. In WT mice, staining was weaker and mainly restricted to the pericellular/territorial zones. Likewise, antibodies to stubs of chondrotin-4-sulfate (ΔC4S) chains intensely labeled all zones of GP and AC in $Dcn^{-/-}$ but not in WT mice. Futhermore, mutant mice showed an increased expression of enzymes involved in GAG modification (PAPSS1, C4ST2). By contrast, the distribution and staining intensities of core proteins like aggrecan or biglycan were similar in both genotypes. AFM analysis of AC sections at 3 months of age revealed slightly altered fibril architecture and increased compressive stiffness of the ITs from $Dcn^{-/-}$ mice. Those abnormalities were accompanied by enhanced levels of TGF-β in mutant mice. Both genotypes exhibited osteoarthritic changes in knee joint cartilage after six weeks of forced running. However, the changes were less severe in $Dcn^{-/-}$ than in WT mice (Mankin score 4.5 versus 6.5).

Conclusion: We propose the following mechanism attenuating OA in $Dcn^{-/-}$ mice: Reportedly, decorin sequesters the cytokine TGF-β in the extracellular matrix. Higher levels of active TGF-β in cartilage of $Dcn^{-/-}$ mice are likely to prevent inappropriate chondrocyte hypertrophy and, hence, induction of osteoarthritis. TGF-β is also known to affect sulfation of GAGs. Probably an increased sulfation leads to an augmented immobilization of water, increased osmotic swelling pressure and accordingly a stiffer cartilage matrix. Therefore, $Dcn^{-/-}$ mice are less prone to develop osteoarthritis due to a combination of elevated active TGF-β levels and enhanced compressive stiffness of the articular cartilage.

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Protective Effect Of Intra-Articular Injection Of Alginate-Chitosan Beads In An Hydrogel Against The Development Of Experimental Osteoarthritis Lesions In Rabbit. Frédéric Oprenyeszk[1], Mickael Chausson[2], Véronique Maquet[2], Jean-Emile Dubuc[3] and Yves Henrotin[1]. [1]Bone and Cartilage Research Unit, Liège, Belgium, [2]KitoZyme SA, Herstal, Belgium, [3]Orthopaedic Department, Bruxelles, Belgium.

Background/Purpose: Today, there is no treatment to cure osteoarthritis (OA) or to delay effectively its progression. Current treatments are mainly based on the alleviation of painful symptoms but are unable to restore the cartilage. The development of biomaterial is a promising approach. Herein, we report the evaluation of a new biomaterial composed of alginate-chitosan (AC) beads dispersed in an (H) hydrogel derived from chitosan on OA rabbit model.

Methods: OA was surgically induced by the transection of the anterior cruciate ligament (ACLT) in HYLA albino rabbits. One week after surgery, animals were randomly divided into 3 groups: group I (n=7): mix of AC beads and H hydrogel; group II (n=7): H hydrogel alone; group III (n=7): saline solution (control). The treatments (900 μl) were injected intra-articularly. X-rays from the right knee were performed before surgery, at the time of injection and at sacrifice. The standard radiographs were acquired in extension and scored by the Kellgren and Lawrence (K&L) scale. After 6 weeks, animals were euthanized and the right joint was dissected. The macroscopic evaluation of cartilage from femoral condyles and tibial plateaus stained with India ink was done. Histological sections from bearing areas of each compartment and synovial membrane were stained with Safranine-O/fast green or hematoxylin/eosin. Histological evaluation was done according to the OARSI histological score where 0 represented a normal situation and 24 points the maximum severity score. Blood samples were collected the day of injection and prior the sacrifice. Prostaglandin E_2 (PGE_2) and C-reactive protein (CRP) were measured in serum using immunoassays.

Results: The X-rays analysis showed a significant decrease ($p < 0.05$) of the K&L score in group I (AC beads and H hydrogel; 1.5 ± 0.2) compared with group II (H hydrogel; 2.2 ± 0.5) and group III (saline solution; 3.0 ± 0.4). The size and the severity of the macroscopic OA cartilage lesion tended to decrease in group I compared to the other groups. The histological global score that refers to all compartments of the knee joint was significantly decreased in group I (11.0 ± 0.7) compared to group II (14.4 ± 0.6, $p < 0.01$) and group III (14.8 ± 0.6, $p < 0.001$). The injection of AC beads and H hydrogel also tended to reduce the synovial membrane inflammation. No significant variation of PGE_2 and CRP serum levels were observed in each after 6 weeks follow-up whatever the treatment injected.

Conclusion: Alginate-chitosan beads dispersed in H hydrogel prevented OA in rabbit after ACL transection. This effect was not observed with the hydrogel alone, suggesting that AC beads play a role in joint protection. The preventive effect was observed in all joint compartments indicating a global protective effect of this new injectable biomaterial.

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Human Mesenchymal Stem Cells Cultured On Collagen Scaffolds For Cartilage Tissue Engineering. Clara Sanjurjo-Rodríguez[1], Adela Helvia Martínez-Sánchez[1], Tamara Hermida-Gómez[1], Isaac M. Fuentes-Boquete[2], Francisco J. De Toro[2], Julia Buján[3], Silvia Díaz-Prado[2] and Francisco J. Blanco[1]. [1]Osteoarticular and Aging Res. Lab. CIBER-BBN. INIBIC- University of A Coruña, A Coruña, Spain, [2]INIBIC-Universidade da Coruña, A Coruña, Spain, [3]Department of Medical Specialties, Madrid, Spain.

Background/Purpose: Osteoarthritis is a degenerative disease without a treatment. Tissue Engineering could provide an alternative tool for cartilage repair. The aim of this study was to evaluate the neotissue formed using human bone marrow mesenchymal stem cells (hBM-MSCs) and collagen scaffolds.

Methods: hBM-MSCs were cultured on collagen (Col), Col+heparan sulfate (HS), Col+chondroitin sulfate (CHS) and Col+heparin (OLH3) scaffolds, in chondrogenic medium supplemented by TGFβ-3. Chondrogenic differentiation and the constructs were evaluated by histochemistry, immunohistochemistry, and molecular biology. Cellular morphology and ultrastructure were studied by electron microscopy. Culture supernatants were collected and the amount of secreted collagen was measured by ELISA.

Results: Haematoxilin-Eosin staining showed that hBM-MSCs have grown through the scaffolds. The cellular percentage respect the whole scaffold area was higher than 50% in all the biomaterials and it was observed a big amount of extracellular matrix (ECM) in all of them, except in Col+OLH3. The ECM showed proteoglycans, by means of safranin O (SO) staining, and immunopositivity for Col II in all the constructs, except in Col+OLH3 (Figure). By measurement of relative expression levels (REL) we observed that COLII were expressed by cells in Col I (0.63), Col I+Col II (1.00), Col I+3%HS (0.47), Col I+Col II+HS (0.93), Col I+Col II+CHS (3.57) and Col I+OLH3 (5.20). Moreover, REL of AGG were higher in Col I+Col II+HS (6.47) constructs than in Col I (0.00), Col I+Col II (0.95),Col I+3%HS (0.17), Col I+Col II+CHS (0.00) and Col I+OLH3 (0.00). Electron microscopy showed cells with a big amount of mitochondria and with spherical and oval shapes (Figure). Col released was detected in all supernatant cultures, obtaining the highest concentration (μg/total volume) at all times, in Col I+3%HS cultures except at day 21: Col I (137.33), Col I+Col II+HS (3.33), Col I+Col II (0.00),Col I+3%HS (0.00), Col I+Col II+CHS (13.90) and Col I+OLH3 (0.00).

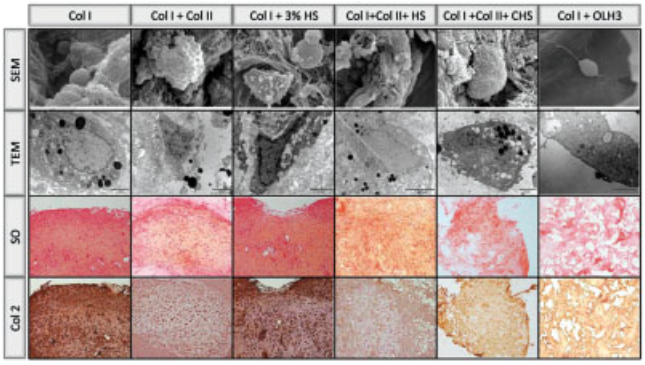

Figure. Images collected from the different constructs by electron microscopy analysis, histochemistry and immunohistochemistry. Vertically in columns are shown the constructs from the different types of collagen scaffolds. Ordered in rows are shown the different analysis: Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), Safranin O staining (SO) and Collagen type II immunostaining (Col 2).

Conclusion: Data showed that hBM-MSCs are capable of growing on collagen scaffolds. On HS enriched collagen scaffolds was kept the differentiated phenotype. The ECM characteristics and the gene expression showed the synthesis of a cartilage-like neotissue which could be useful for cartilage tissue engineering. *Acknowledgements*: Opocrin S.P.A.; CAM (S2009/MAT-1472); CIBER-BBN CB06-01-0040; SAI-UDC; REDICENT; Diputación de A Coruña; Jiménez Díaz Fundation.

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Norepinephrine (NE) Inhibits Mesenchymal Stem Cell (MSCs) Chondrogenesis By Accelerating Hypertophy – Relevance For Cartilage Regeneration. Zsuzsa Jenei-Lanzl[1], Peter Angele[2], Frieder Kees[3], Georg Pongratz[4] and Rainer H. Straub[5]. [1]Laboratory of Experimental Rheumatology and Neuroendocrine Immunology, Regensburg, Germany, [2]Department of Trauma Surgery, University Hospital Regensburg, Germany, Regensburg, Germany, [3]University of Regensburg, Regensburg, Germany, [4]University Hospital Regensburg, Regensburg, Germany, [5]Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, University Hospital of Regensburg, Regensburg, Germany.

Background/Purpose: The high potential of mesenchymal stem cells (MSCs) in cartilage regeneration is undoubtful. The presence of MSCs in healthy or arthritic cartilage has also been confirmed. In addition, MSCs migrating from synovium into the cartilage and differentiating into chondrocytes has been described, which might be the reason for increased MSC number in OA. Furthermore, it is known that sympathetic nerve fibers are present in healthy and osteoarthritic (OA) synovium and that the sympathetic nervous system mediates numerous effects on adult skeletal system. Therefore, the aim of this study was to investigate the effects of the most important sympathetic neurotransmitter norepinephrine (NE) on MSC chondrogenesis.

Methods: To find possible natural sources of local catecholamines in human joint material, we studied sympathetic nerve fibers (tyrosine hydroxylase (TH) expression), catecholamine biosynthesis and synovial fluid levels. Human bone marrow derived MSCs were expanded and chondrogenesis was initiated in a 3D aggregate culture. Endogenous catecholamine production of hMSCs was analyzed during proliferation and chondrogenesis via HPLC. Parallel to control conditions, aggregates were incubated with different NE concentrations and specific β-adrenoceptor agonist (isoproterenol) or antagonist (nadolol). After 21 days, chondrogenesis quality was evaluated macroscopically, histologically and biochemically. Furthermore, specific adrenoceptors (AR) were detected.

Results: In the human joint, TH-positive fibers and/or single cells were present in synovial tissue, meniscus, and subchondral bone marrow. In addition, knee-traumatized patients demonstrated high NE concentrations in synovial fluid. At various stages of human MSC chondrogenesis, βAR were expressed. No endogenous catecholamine synthesis was detected during chondrogenesis. Chondrogenic MSC aggregates treated with NE or isoproterenol synthesized lower amounts of type II collagen and glycosaminoglycans. NE and isoproterenol dose-dependently increased markers of cartilage hypertrophy (collagen type X and MMP-13). Nadolol reversed inhibition of chondrogenesis and up-regulation of cartilage hypertrophy.

Conclusion: The suppression of MSC-dependent chondrogenesis by high NE or isoproterenol suggests that the β-adrenoceptors mediate this effect. By inhibition of cartilage repair, these sympathetic influences can be important after multiple minor and major joint traumata. These findings can be a basis for novel neuro-chondrogenic therapeutic options.

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Synovial Activation In Experimental OA Drives Immuno suppressive Effects Of Adipose-derived Stem Cells After Local Administration and Protects Against Chondrogenesis In Ligaments. Peter L.E.M. van Lent[1], Rik Schelbergen[1], Menno C. ter Huurne[1], Arjen B. Blom[1], Johannes Roth[2], Thomas Vogl[2], Christian Jorgensen[3] and Wim B. van den Berg[4]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]University of Muenster, Muenster, Germany, [3]Inserm U844, CHU saint-Eloi, Université Montpellier 1, CHU Lapeyronie, Montpellier, France, [4]Rheumatology Research and Advanced Therapeutics, Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.

Background/Purpose: A substantial subpopulation of patients with early osteoarthritis (OA) show a thickened synovial lining layer comprising macrophages expressing an activated phenotype (reflected by production of IL-1β and S100A8/A9). Recently we have shown that adipose derived stem cells (ADSC) inhibit joint destruction after local application to knee joints with experimental OA. The goal of our study was to explore the effect of synovial activation on the immunosuppressive capacity of ADSCs to modulate joint destruction after local administration to experimental OA knee joints.

Methods: ADSCs were isolated from fat surrounding the popliteal lymph nodes and cultured for two weeks. Collagenase induced OA (CIOA) was induced by injection of collagenase into murine knee joints. ADSCs were injected into the same joints at day 7 after induction of OA. Joint destruction was measured within 6 weeks after induction. Total knee joints were isolated and processed for histology. Synovial thickening was measured using an arbitrary scale of 0–3. Synovium was isolated at various time-points after injection of ASC and washouts were measured for S100A8/A9 and IL-1 using Luminex. Chondrogenesis/bone formation inside ligaments was measured using image analysis.

Results: A single dose of ADSCs (20×10^3) was injected into the knee joint of mice, 7 days after induction of CIOA. Thickening of the synovial lining layer, which is characteristic for this model, was high (2,6+/−1) and was significantly inhibited by ADSC treatment at day 14 (9%) and day 42 (35%) when compared to control (serum) treated OA joints. Washouts of synovium taken at 6 hrs, 48 hrs, day 14 and day 42 after injection of ADSCs showed that protein levels of IL-1β and S100A8/A9 were significantly decreased already 48 hrs after injection of ADSC (IL-1β 57% and S100A8/A9 by 22%) and rapidly declined thereafter. Serum levels of S100A8/A9 were inhibited with 85% (from 794+/− 294 to 117+/− 29 ng/ml) at day 14 after ADSC treatment suggesting that the effect on synovial activation is very rapid. Strikingly, ADSCs had a protective effect on chondrogenesis in medial and cruciate ligaments at day 42 after treatment (inhibition 92% and 43% respectively). Next, we explored the effect in a condition with less synovial inflammation. Synovial thickness at day 42 was 62% lower when compared to the former study (from 2.6 +/−1 to 1 +/−0.2) which was reflected by lower S100A8/A9 serum levels (at day 14 around 50 ng/ml compared to 800 ng/ml). Injection of the same dose of ADSCs at day 7 after induction of OA, did not inhibit synovial thickening nor chondrogenesis in the collateral (1.3+/−0.2 versus WT controls 1.1+/−0.3) and cruciate ligaments (1.8+/−0.3 versus WT controls 1.9+/−0.2) when measured at day 42.

Conclusion: Our study indicates that synovial activation rapidly drives anti-inflammatory effects of ADSCs after local administration in murine knee joints with experimental OA and protects against development of ligament damage.

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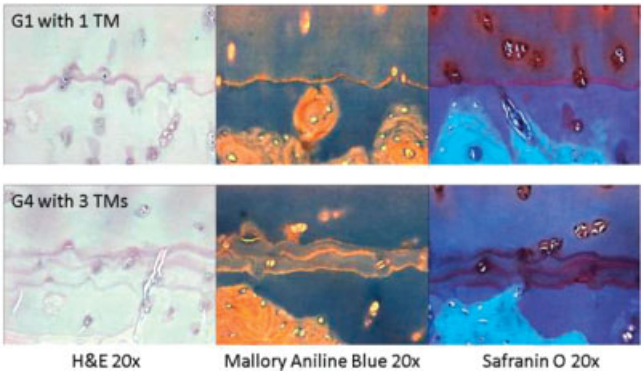
Tidemark Duplication In Osteoarthritis: Evidence Of Incremental Progression? Martine P. Roudier, Paul A. Manner and Peter A. Simkin. University of Washington, Seattle, WA.

Background/Purpose: Osteoarthritis (OA) is commonly envisioned as a gradual, relentlessly progressive process of "wear and tear" leading to eventual joint failure. As we see the tidemark (TM) between hyaline and calcified cartilage, we read a different message.

Methods: We studied the femoral condyles and tibial plateaux of 18 elderly body donors for evidence of tidemark duplication. We used 62 specimens representing at least 2 specimens per donor. Specimens were photographed, sampled, radiographed, decalcified using 10% formic acid, processed and embedded in paraffin, sectioned then stained with H&E, Safranine O and Mallory Aniline Blue. They were graded using the OARSI 2005 6 point-grading system (G0-G6). When two lesions existed in the same specimen, each lesion was individually graded. A TM number was recorded for each graded lesion. A Spearman correlation between the lesion grade and the number of tidemarks was determined using Graphpad Prizm software.

Results: TM number correlated significantly with OA histological grade ($r=0.81$, $p<0.0001$). Thirty three of the 62 specimens had 2 lesions generating 95 grades. Twelve grades were without visible TM (1 G5, 7 G6 and 4 technical issues) and were excluded from the study. Of the 83 remaining grades, 17 were G0 and had 1 TM, 27 were G1 and had 1 or 2 TMs, 22 were G2 and had 2 or 3 TMs, 9 were G3 and had 1, 2 or 3 TMs, and 8 were G4 and had 3 or 5 TMs.



Conclusion: The number of TMs correlated highly with the OARSI histological grade, suggesting that the TM number is a reflection of the OA disease stage. Since the TMs were distinct, we believe that duplication represents the legacy of abrupt, sequential changes leading to regional calcification of deep hyaline cartilage. The calcification buries the previous tidemark and causes the tidemark formation process to begin anew at a higher level. The most probable precipitating event would be a change in joint loading such as that resulting from a focal microfracture of subchondral bone.

Disclosure: M. P. Roudier, None; **P. A. Manner**, None; **P. A. Simkin**, None.

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Synovial Expression Of CCL19, MCP-1, and Their Receptors In Patients With Meniscal Injury: Variability and Relationship With Knee Symptoms. Justin B. Gan, Anjali Nair, Kanta Saha, Nikhil Verma, Charles Bush-Joseph, Matthew Tetreault, Anne-Marie Malfait, Kumar B. Rajan and Carla R. Scanzello. Rush University Medical Center, Chicago, IL.

Background/Purpose: Patients with meniscal injury are at increased risk for symptomatic knee osteoarthritis (OA), and often already have intraoperative signs of early-stage cartilage degradation. We previously reported that patients with meniscal tears often exhibit synovial inflammation, which is associated with more severe knee symptoms. We further demonstrated that synovitis was associated with expression of mRNA for CCL19, a lymphocyte chemoattractant, and its receptor CCR7. Others have reported a relationship between MCP-1, a macrophage chemoattractant, and knee pain in patients with knee injuries including meniscal tears. We sought to determine whether CCL19 and MCP-1 are measurable in synovial fluid (SF) of patients undergoing meniscal arthroscopies, and if protein levels are associated with knee symptoms or dysfunction. We also investigated expression patterns of CCR7 (CCL19 receptor) and CCR2 (MCP-1 receptor) within synovium to gain insight into the cell types that might be responsive to these factors.

Methods: We recruited subjects undergoing arthroscopy for meniscal tears. SF CCL19 and MCP-1 were measured by ELISA (R&D systems). Knee symptoms and dysfunction were preoperatively assessed using the Knee Injury and Osteoarthritis Outcome Score (KOOS), consisting of 5 subscales measuring pain, other knee symptoms, function in daily living (ADL), recreational activities, and quality of life. Associations with KOOS scores were tested using Pearson correlations. Multivariate linear regression models adjusted for age, gender, BMI, and degree of radiographic OA (Kellgren-Lawrence scores). Synovial CCR7 and CCR2 expression was characterized using immunohistochemical (IHC) staining, and compared to staining patterns in synovium from asymptomatic organ donors.

Results: 32 patients with meniscal tears were included. Median age (IQR) was 55 (47–61), and gender ratio M:F was 17:15. CCL19 was detectable in 25/32 (78%) while MCP-1 was detectable in all patients. Mean concentration+/−SD of CCL19 was 374.28+/−367.58 pg/mL, and MCP-1 was 450.13+/−273.85 pg/mL. CCL19 concentration correlated with worse KOOS-ADL subscores (Pearson r= −0.362, p=0.049), but was not independent of other factors in adjusted regression analyses. In the model, BMI was an independent predictor of KOOS-ADL subscores (p=0.01), and there was a correlation between BMI and CCL19 levels (Pearson r=0.430, p=0.02). MCP-1 levels did not correlate with KOOS subscores. IHC staining identified CCR7 expression in the synovial lining layer, endothelium, and perivascular inflammatory infiltrates, while CCR2 expression was identified primarily in the lining layer. CCR7 and CCR2 staining was more pronounced in patients with meniscal tears than in asymptomatic organ donors.

Conclusion: In patients with meniscal tears, CCL19 and MCP-1 are detectable in SF. Although SF CCL19 was not an independent predictor of knee symptoms, CCL19 may be related to increased BMI. CCR7 did appear increased in meniscal tear patients, and its expression by multiple cell types in synovium suggests that CCL19/CCR7 activity may be involved in development of synovial changes seen in these patients.

Disclosure: J. B. Gan, None; **A. Nair**, None; **K. Saha**, None; **N. Verma**, None; **C. Bush-Joseph**, None; **M. Tetreault**, None; **A. M. Malfait**, None; **K. B. Rajan**, None; **C. R. Scanzello**, U.S. patent pending for synovitis markers in osteoarthritis and joint injury, 9.

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Anatomical Variation In The Morphology Of The Posterior Cruciate Ligament Synovio-Entheseal Complex and Correlation With Degenerative Change. Daniel Binks[1], Diane Bergin[2], Tony Freemont[3], Aleksandra Radjenovic[1] and Dennis McGonagle[4]. [1]University of Leeds, Leeds, United Kingdom, [2]Galway University Hospitals, Galway, Ireland, [3]University of Manchester, Manchester, United Kingdom, [4]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

Background/Purpose: Ligament attachments are often found to form complex anatomical functional units involving the ligaments themselves as well as associated synovium and bony tuberosities. Furthermore, stress minimising accessory fibrocartilages are frequently observed in the immediately adjacent joint cavities. Collectively, these structures are termed synovio-entheseal complexes (SECs) and are subject to the full gamut of degenerative changes associated with the osteoarthritis (OA) disease process.[1] Here we have investigated the SEC formed at the posterior cruciate ligament (PCL) tibial insertion using high resolution magnetic resonance imaging (MRI) and matched histology to show the involvement of the PCL-SEC in the phenotypic expression of knee OA.

Methods: High-resolution 3T MRI and comparative histological evaluation were performed on 14 normal cadaveric knee joints. SEC microanatomy and OA features of the PCL tibial attachment were evaluated on serial histological sections stained with H&E and Masson's Trichrome. Bilateral 3T MRI images were evaluated in 49 patients with early OA from the Osteoarthritis Initiative cohort for SEC morphology and for lesions associated with the early OA disease process at the PCL tibial enthesis. Differences among groups were determined by calculation of chi-square values.

Results: Histological evaluation confirmed the SEC microanatomical structure comprising the PCL, adjacent tibial bone plateau and intervening synovium along with sesamoid, periosteal and enthesis accessory cartilages and the posterior horn of the medial meniscus. Evidence of microanatomical damage was observed throughout the PCL-SEC, including; neovascularisation, chondrocyte cell clustering, tide mark duplication and mild inflammatory changes. In the early OA cohort, 3T MRI showed a high prevalence of SEC related lesions including bone marrow oedema (BME) immediately anterior to the PCL insertion (seen in 61% of knees) and osteophytosis lateral to the PCL insertion (85%). Signal hyperintensity on fluid sensitive sequences compatible with posterior recess synovitis immediately adjacent to the PCL was seen in 48% of knees and correlated with SEC cartilage abnormality (χ^2 =7.25, p<0.01). Furthermore, the frequency of BME at the PCL insertion was associated with a medial meniscus posterior horn deficient SEC anatomical variant (χ^2 =10.02, p<0.05).

Conclusion: The PCL has a prominent SEC configuration that is associated with microscopic evidence of OA in normal tissue. In early knee OA, pathological features were commonly observed at the PCL-SEC and immediately adjacent locations on 3T MRI. Although the PCL rarely fails in OA, the PCL-SEC could play a hitherto unappreciated but important role in the phenotypic expression of early knee OA.

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Disclosure: D. Binks, None; **D. Bergin**, None; **T. Freemont**, None; **A. Radjenovic**, None; **D. McGonagle**, None.

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Oleuropein Or Rutin Consumption Decreases The Spontaneous Development Of OA In Hartley Guinea Pig. Christelle Sanchez[1], Marie-Noëlle Horcajada[2], Fanny Membrez Scalfo[2], Pierre Drion[3], Fanny Comblain[3], Elizabeth Offord[2] and Yves Henrotin[3]. [1]University of Liège, Liege, Belgium, [2]Nestle Research Center, Lausanne, Switzerland, [3]University of Liège, Liège, Belgium.

Background/Purpose: To assess the potential protective effect of oleuropein and rutin, two polyphenols found in olive oil, fruits or vegetables, on osteoarthritis development

Methods: Sixty 4 weeks old Hartley guinea pig were randomized in four groups and received daily during 31 weeks either standard guinea pig food (control group) or a standard guinea pig food enriched with oleuropein, rutin or rutin/curcumin association. Animals were weighted each week and blood sampled every 6 weeks and at the time of euthanasia (week 35). Biomarkers COLL2-1, COLL2-1NO2, Fib3-1, Fib3-2, as well as PGE_2, were quantified in the serum. Histological assessments of knee cartilage and synovial membrane were performed at week 35.

Results: At week 35, guinea pigs in the control group spontaneously developed important cartilage lesions with mild synovial inflammation. The histological scores of cartilage lesion and synovitis were well correlated with the increase of serum biomarkers level.. Histologically, all treated groups significantly reduced the cartilage degradation (p<0.01), and oleuropein group showed a significant decrease of the synovial modification (p<0.05) compared to the control group. Oleuropein decreased the PGE_2 levels found in serum at week 35 (p<0.01). Serum COLL2-1 and Fib3-1 were decreased by rutin and rutin/curcumin mixture, Fib3-2 was only decreased by rutin/curcumin mixture, while COLL2-1NO2 was significantly decreased by all treatments (p<0.05).

Conclusion: Oleuropein and rutin significantly slow down the progression of OA lesions in guinea pig developing spontaneously OA. Furthermore, oleuropein significantly decreased PGE_2 and COLL2-1NO2 serum levels, and reduced synovitis, indicating the potent anti-inflammatory properties of these compounds.

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New Formulation With Potential To Prevent and Treat Osteoporosis and Osteoarthritis. A. Torrent[1], E. Montell[1], J. Vergés[1], P. Dalmau[2], R. Ruhí[2], M.C. Carceller[3], A. Blanco[3], M.C. Terencio[3], M.L. Ferrándiz[3] and M.J. Alcaraz[3]. [1]Pre-Clinical R&D Area, Pharmascience Division, BIOIBERICA S.A., Barcelona, Spain, [2]Technological Extraction Dept, BIOIBERICA S.A., Palafolls, Spain, [3]Department of Pharmacology and IDM, University of Valencia, Burjassot, Spain.

Background/Purpose: Osteoarthritis (OA) is a multidimensional disease that affects all anatomical joint structures, particularly cartilage, synovium and subchondral bone. In turn, osteoporosis (OP) is a skeletal disorder characterized by a compromised bone strength which substantially increases the risk of fracture. In the past, attention was focused on a supposed inverse relationship between OA and OP, since both disorders usually affect the elderly, but were regarded to rarely coexist in a single person. However, recent studies have revealed several factors which contribute to the pathogenesis of both disorders (Bultink et al, 2013). Despite this, there is not any drug at the moment approved for the simultaneous prevention and treatment of osteoporosis and osteoarthritis.

The aim of this study was to investigate the effect of a new formulation in a combined rat model of OP and OA. The formulation (BIS076) contains Vitamin D3, Hydroxyapatite as a source of calcium and a natural extract from porcine cartilage. The latter is rich in bioactive substances due to the mild conditions used in the manufacturing process.

Methods: OP was induced by ovariectomy (OVX) in female Wistar rats and, two weeks after, OA was induced by Anterior Cruciate Ligament Transection (ACLT). Sixty female rats were assigned into the following groups: Sham Group, OVX + ACLT Group (Vehicle) and BIS076 Groups. BIS076 was administered daily during 12 weeks at two doses, 163.5 mg/kg/day and 245 mg/kg/day which correspond approximately to 1400 mg/day and 2100 mg/day in humans. For the assessment of OA, histology was performed and cartilage degeneration was evaluated by means of the OARSI score (Pritzker et al, 2006). Synovitis degree was estimated according to the score proposed by Krenn et al (2006). Bone microarchitecture and density were assessed by Micro-Computed Tomography (microCT).

Results: The preparation BIS076 has been shown to induce, at the 2 doses tested, a significant reduction (approximately 50%) of the cartilage degradation according to the OARSI score. Synovial inflammation was strongly reduced as well. In addition, microCT revealed that BIS076 treatment exerted a positive effect in bone structure, especially at the high dose: Significant increase in bone volume ($p<0.05$), bone surface density ($p<0.01$), trabecular number ($p<0.01$) and significant reduction in the trabecular bone pattern factor ($p<0.01$) compared to the Vehicle Group.

Conclusion: Our data demonstrate that treatment with BIS076 could be an effective strategy to control the progression of experimental Osteoarthritis and Osteoporosis. This approach holds promise for the development of improved therapies targeting these chronic and disabling diseases.

Disclosure: A. Torrent, BIOIBERICA, 3; **E. Montell**, BIOIBERICA S.A., 3; **J. Vergés**, BIOIBERICA S.A., 3; **P. Dalmau**, BIOIBERICA S.A., 3; **R. Ruhí**, BIOIBERICA S.A., 3; **M. C. Carceller**, None; **A. Blanco**, None; **M. C. Terencio**, None; **M. L. Ferrándiz**, None; **M. J. Alcaraz**, None.

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Cartilaginous Uric Acid Deposition In Advanced Osteoarthritis: Innocent Bystander Or Promotor Of Cartilage Destruction? Tim Bongartz, Andre M Oliveira, Rafael J Sierra, Arlen D Hanssen and Michael J Taunton. Mayo Clinic, Rochester, MN.

Background/Purpose: Recent studies have suggested that synovial fluid uric acid could contribute to tissue inflammation, disease severity and progression of osteoarthritis (OA). Intraarticular uric acid has been associated with OA disease severity and may promote cartilage destruction through inflammasome activation.We aimed to explore if intraarticular uric acid deposition does indeed occur in patients with osteoarthritis of the knee who have never experienced an episode of gout.

Methods: We recruited patients with advanced osteoarthritis of the knee and no history of gout who were scheduled to undergo knee replacement surgery. All subjects underwent dual-energy scanning of the target joint. CT images were screened for areas of uric acid deposition.During knee replacement surgery, samples of tibial and femoral condyle cartilage, menisci and synovium were obtained. Areas of possible uric acid deposition as identified through DECT were particularly targeted for sample collection.A musculoskeletal pathologist performed light (DeGalantha and H&E stains) and polarizing microscopy and recorded the presence of uric acid crystals in a descriptive manner.

Results: 5 patients with advanced osteoarthritis of the knee did undergo DECT. In all subjects, DECT indicated areas of uric acid deposition within the joint cartilage and the menisci. In 4 of these 5 patients, histopathology exam confirmed presence of uric acid crystal clusters in the cartilage and/or menisci. In 2 patients, uric acid deposition did also involve the synovium. Of note, synovial fluid in all patients was negative for MSU crystals as determined through polarizing microscopy. The mean serum uric acid level was 5.7mg/dl, range 5.0–6.4 mg/dl.

Conclusion: This pilot study did reveal evidence of cartilaginous uric acid deposition in the majority of patients with advanced osteoarthritis.Future studies will have to confirm this finding in a larger patient cohort and clarify if intracartilaginous urate crystals accelerate cartilage damage or are simply a result of matrix exposure and subsequent MSU crystallization without significant effects on disease progression.

Disclosure: T. Bongartz, None; **A. M. Oliveira**, None; **R. J. Sierra**, None; **A. D. Hanssen**, None; **M. J. Taunton**, None.

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The Role Of Meniscal Cells In Osteoarthritis Calcification. Andrea Roberts[1], David Mauerhan[2] and Yubo Sun[2]. [1]Carolinas Healthcare System, Charlotte, NC, [2]Carolinas Medical Center, Charlotte, NC.

Background/Purpose: Osteoarthritis (OA) is a disease that is characterized by the breakdown or loss of articular cartilage due to biomechanical and biochemical changes in the joints of the knees, hips and hands. Chondrocytes, the cells present in articular cartilage, have traditionally been thought to be exclusively responsible for inducing the calcification observed in OA, and therefore are believed to play an essential role in the development of OA pathogenesis. However, recent reports suggest that meniscal degeneration and calcification are correlated with articular cartilage degeneration in the knee of OA patients. Joint calcification correlates greatly with OA, as 70% of OA patients show an increase in calcium crystal deposition compared to non-OA patients. There are two main types of crystals present in advanced OA patients: calcium pyrophosphate dehydrate (CPPD) and basic calcium phosphate (BCP). However, it is still unclear which tissue (cartilage or meniscus) produce these calcium crystals. The role of meniscal cells in calcification is poorly understood at present, thus the purpose of this study is to determine the role of meniscal cells in the pathogenesis of osteoarthritis (OA) in the knee. Our central hypothesis states that meniscal cells play an unrecognized role in the development of OA in part by inducing calcification in the meniscus.

Methods: *Tissue was collected* from menisci and articular cartilage obtained from OA patients undergoing joint replacement surgery. *Calcium Crystals* were detected using alizarin red and Eosin Y staining. *Cell were isolated* from OA menisci and articular cartilage tissue. The cells were treated with and without extracellular ATP (a calcification inducer) and calcification medium for seven days in a monolayer culture. *Alizarin Red* staining was used to detect calcification present in a monolayer. Images were obtained using Sony Imaging software with an inverted scope and alizarin red was quantified measuring HCL absorbance at 405 wavelength using a microplate reader. *^{45}Calcium Assay* was used to quantify calcification induced by chondrocytes and meniscal cells in the presence and absence of extracellular ATP. The cells were cultured in a monolayer environment for 5 days. ^{45}Calcium was measured as counts per minute using a liquid scintillation counter.

Results: Our data, using a ^{45}Calcium assay and alizarin red staining, suggest that meniscal cells, similar to chondrocytes, induce the formation of calcium crystals in the presence of extracellular ATP and calcification medium, with meniscal cells inducing calcification at a slightly higher rate than chondrocytes. Additionally, OA patients have been shown to contain many types of calcium crystals in the knee cartilage, with BCP and CPPD crystals being the most abundant. Both of which have been implicated in the development and progression of knee OA. Our preliminary data shows the

meniscus of OA patients contains both BCP and CPPD crystals of which about 44% are CPPD crystals.

Conclusion: Our results suggest meniscal cells like chondrocytes induce calcium crystal formation and both BCP and CPPD crystals are present in the meniscus of OA patients.

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ACR Poster Session A
Epidemiology and Health Services I
Sunday, October 27, 2013, 8:30 AM–4:00 PM

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Global and Country Specific Burden Of Musculoskeletal Disorders:a Report From The Global Burden Of Diseases Musculoskeletal Expert Group. Lyn March[1], Damian Hoy[2], Emma Smith[3], Rachelle Buchbinder[4], Marita Cross[3], Peter Brooks[5], Theo Vos[2] and Anthony D. Woolf[6]. [1]University of Sydney Institute of Bone and Joint Research, Royal North Shore Hospital, St Leonards, Australia, [2]School of Population Health, University of Queensland, Brisbane, Australia, [3]University of Sydney, Insitute of Bone and Joint Research, Royal North Shore Hospital, St Leonards NSW, Australia, [4]Monash Department of Clinical Epidemiology at Cabrini Hospital, Department of Epidemiology and Preventive Medicine, Monash University, Malvern, Victoria, Australia, [5]Australian Health Workforce Institute, University of Melbourne, Melbourne, Australia, [6]Royal Cornwall Hospital, Truro Cornwall, United Kingdom.

Background/Purpose: The first Global Burden of Diseases (GBD) Study was conducted by the World Bank and WHO during the 1990's and ranked diseases by their contribution to burden as measured by disability adjusted life years (DALYs). All MSK disorders, with 2.1% of DALYs, ranked 12th. These were considered to be underestimates. The GBD 2010 Study aimed to repeat these DALYs to look for trends in diseases from 1990 to 2010 with updated disease definitions and literature review. The MSK Expert Group (EG) aimed to identify data for OA, RA, Back Pain, Neck Pain, Gout and Other MSK.

Methods: Systematic reviews of Medline, EMBASE, CINAHL, SIGLE and WHOLIS were screened from 1980 to 2010. Data were extracted from population-based studies using a Quality Assessment tool developed by the MSK EG. These prevalence and incidence data, together with estimates of possible covariates and relative risk of mortality, were entered into the DISMOD3 software developed by the IHME. Disability weights for health states related to MSK conditions were adjusted for distribution of severity and duration and frequency of each condition to calculate years lived with disability (YLDs) for each of the MSK conditions – OA of hip or knee, RA, Low Back Pain (LBP), Neck Pain (NP), Gout and Other MSK.

Results: Globally non-communicable chronic disorders were identified as the growing concern and of these MSK was highlighted.

In the overall global burden (DALYs) MSK disorders had increased from 4.7% in 1990 to 6.8% in 2010, and ranked 5th behind Cardiovascular (11.8%), Injuries (11.2%), All neoplasms (7.6%) and Mental and behavioural disorders (7.4%). For burden (DALYs) of specific disorders, LBP ranked 6th; NP 21st; and Other MSK 24th. In the global disability (YLD) estimates, mental and behavioural disorders combined at 22.7% ranked 1st, while combined MSK disorders at 21.3% was a close 2nd. Collectively MSK conditions affect 2,933,367,000 people, account for 166 million YLDs and represent a relative increase of 44.7% since 1990. For disease specific causes of disability (YLDs), LBP ranked 1st globally with 83.1 million; NP ranked 4th with 33.6 million; Other MSK 6th with 28.2 million; OA was 11th with 17.1 million; and RA was 6.7 million. OA was felt to be underestimated in this analysis. OA was identified as one of the most rapidly rising (64% increase) conditions with a rank of 15th in 1990 to 11thin 2010. When developed country level data are examined MSK conditions play an even greater role, for example in Australia where combined MSK conditions (15% of DALYs) were a close second only to combined Cancer (16% of DALYs) as the leading causes of disease burden, and LBP was estimated as the leading disease specific cause of total burden (DALYs). For disability in Australia MSK conditions were the leading cause with 27% of YLDs. Country level data are derived from ihme.org.

Conclusion: Data are lacking from the African nations, South America, Eastern Europe and Australasia. OA Knee is the most common MSK condition and is showing the greatest increase. Low back and neck pain account for the greatest proportion of MSK burden globally. In many countries MSK disorders are the leading cause of disability.

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Musculoskeletal Diseases Have The Worst Impact On Physical Health Compared With Other Diseases - Results Of The Dutch cross-Sectional Study. Antje van der Zee-Neuen[1], Polina Putrik[1], Sofia Ramiro[2], Andras P. Keszei[3], Rob de Bie[1], Astrid M. Chorus[4] and Annelies Boonen[5]. [1]Maastricht University, Maastricht, Netherlands, [2]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [3]School for Oncology and Developmental Biology, Maastricht, Netherlands, [4]Netherlands Organization for Applied Scientific Research, Leiden, Netherlands, [5]Maastricht University Medical Center, Maastricht, Netherlands.

Background/Purpose: Musculoskeletal conditions (MSKC) are among the most common chronic conditions. Increasingly, patients suffer from more than one disease. Moreover, the presence of a co-morbid disease adds to the burden of single diseases worldwide. The aim of this study was to understand 1) what is the impact of the number of morbidities on health and 2) whether MSKC has a higher impact on health compared with other diseases or has an important impact when being a co-morbidity.

Methods: In a Dutch cross-sectional study, 8904 subjects (>18 years old, random sample) completed a questionnaire on socio-demographic factors (age, gender, education, work status, origin and place of residence (postal code code)), BMI, self-reported physician-diagnosed diseases and the 12-Item Short-Form Health Survey (SF-12). Complete cases (n=7600) were analyzed. Multivariable linear regression was computed to identify 1) whether multimorbidity in terms of number of diseases was significantly associated with the SF-12 physical (PCS) and mental (MCS) subscales and 2)which diseases contributed the most to changes in health related quality of life (HrQol). Interactions of all diseases with MSKC were checked. Models were adjusted for age, gender, education (5 groups, from no education to university) origin (western vs. non-western) and BMI.

Results: Multimorbidity was present in 1432 subjects (19%). MSKC confirmed by a physician was reported by 1438 (19%) participants. 408 (5%) reported diabetes, 1460 (19%) CVD, 199 (3%) cancer, 547 (7%) a respiratory condition, 526 (7%) a skin condition, 462 (6%) a mental disorder, 334 (4%) migraine and 262 (3%) bowel disease. A linear relation between the number of diseases and health (both univariably and in fully adjusted model) was observed (Table 1). MSKC had the highest negative impact on PCS compared to other diseases (Table 2).

Table 1. Association of number of morbidities and health *(physical and mental component SF-12)*

	SF-12			
	Physical Component B[1] [95% CI]		Mental Component B[1] [95% CI]	
Number of morbidities	univariable	multivariable*	univariable	multivariable*
1	−4.83 [−5.01; −4.65]	−4.06 [−4.24; −3.87]	−1.62 [−1.82; −1.43]	−2.07 [−2.27; −1.87]
2	−9.66 [−10.03; −9.30]	−8.11 [−8.49; −7.73]	−3.25 [−3.63; −2.87]	−4.14 [−4.54; −3.74]
3	−14.49 [−15.04; −13.94]	−12.17 [−12.73; −11.61]	−4.87 [−5.45; −4.29]	−6.20 [−6.81; −5.59]
4	−19.32 [−20.05; −18.59]	−16.22 [−16.97; −15.47]	−6.50 [−7.27; −5.73]	−8.27 [−9.08; −7.46]
5	−24.15 [−25.06; −23.24]	−20.28 [−21.22; −19.34]	−8.12 [−9.08; −7.16]	−10.34 [−11.35; −9.33]

[1] understandardized coefficient
*adjusted for age, gender, education (5 groups, from no education to university), BMI
**adjusted for age, gender, education (5 groups, from no education to university), origin (western vs. non-western), BMI

Table 2. Association of type of morbidity and health *(physical and mental component SF-12)*

	SF-12			
	Physical Component B[1] [95% CI]		Mental Component B[1] [95% CI]	
Type of morbidity	univariable	multivariable*	univariable	multivariable**
CVD	−6.55 [−7.04; −6.05]	−2.60 [−3.07; −2.13]	−0.17 [−0.65; 0.30]	−0,91 [−1.40; −0.42]
Diabetes	−6.70 [−7.59; −5.81]	−2.05[−2.83;−1.281]	−0.20 [−0.63; 1.04]	−0.46 [−1.27; 0.34]
Cancer	−9.80 [−9.06; −6.54]	−5.24 [−6.29; −4.19]	−0.80 [−1.98; 0.38]	−1.05 [−2.146; 0.05]
Respiratory condition	−7.41 [−8.18; −6.64]	−3.92 [−4.57; −3.27]	−1.73 [−2.46; −1.00]	−0.62 [−1.30; 0.07]
Skin condition	−2.99 [−3.79; −2.19]	−0.49 [−1.15; 0.17]	−2.13 [−2.87; −1.39]	−1.17 [−1.86; −0.48]
Mental disorder	−4.13 [−4.98; −3.28]	−1.82 [−2.53; −1.11]	−14.82 [−15.54; −14.10]	−13.93 [−14.66; −13.19]
MSKC	−11.38 [−11.84; −10.92]	−8.93 [−9.37; −8.48]	−1.25 [−1.73; −0.77]	−0.30 [−0.76; 0.16]
Migraine	−4.56 [−5.54; −3.57]	−2.37 [−3.20; −1.55]	−3.73 [−4.65; −2.82]	−1.44 [−2.30; −0.58]
Bowel disease	−9.26 [−10.35; −8.17]	−4.68 [−5.61; −3.75]	−3.99 [−5.02; −2.97]	−1.42 [−2.39; −0.46]

[1] understandardized coefficient
*adjusted for age, gender, education (5 groups, from no education to university), BMI
**adjusted for age, gender, education (5 groups, from no education to university),origin (western vs. non-western),BMI

Conclusion: An increasing number of morbidities is negatively associated with physical and mental HrQol. MSKC are responsible for the largest decrease of physical health.

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Meta-Analysis of Randomized Controlled Trials Assessing the Effects of Vitamin D Supplementation On Skeletal Muscle Strength. Charlotte Beaudart[1], Fanny Buckinx[2], Véronique Rabenda[1], Sophie Gillain[3], Etienne Cavalier[3], Jean Petermans[3], Jean-Yves Reginster[1] and Olivier Bruyere[1]. [1]University of Liege, Liege, Belgium, [2]University of Liège, Liège, Belgium, [3]CHU de Liege, Liege, Belgium.

Background/Purpose: Currently, there is growing evidence that vitamin D plays a role on several tissues including skeletal muscle. Previous studies suggested that vitamin D deficiency is associated with low muscular strength. The objective of this meta-analysis is to summarize the effects of vitamin D supplementation on muscle strength

Methods: A systematic research of randomized controlled trials (RCTs), performed between 1966 and February 2013, assessing the effect of vitamin D supplementation on muscle strength has been conducted by two independent reviewers (data sources: Medline, Cochrane Database of Systematics Reviews, Cochrane Central Register of Controlled Trials, manual review of the literature and congressional abstracts). All forms and doses of vitamin D supplementation, with or without calcium supplementation, compared with placebo or control were included. Muscle strength was assessed either by grip strength and/or lower limb muscle strength. The quality of the RCTs was evaluated using the Jadad criteria.

Results: Out of the 214 potentially relevant articles, 19 RCTs involving 4824 individuals (mean age: 66.0 years) met the inclusion criteria. Studies show a mean quality score of 3.8/5 points. Results reveal a significant positive effect of vitamin D supplementation on global muscle strength *(Figure)* with a standardized mean difference (SMD) of 0.096 (95% CI=0.007–0.184; p=0.034). No significant between-study heterogeneity is found (Q-value= 23.6; p= 0.21; I^2= 19.6%). No publication bias was observed as shown with the Egger's regression analysis (p=0.13). Regarding the individual type of strength, 13 studies assessed the effect of vitamin D supplementation on grip strength and 15 on lower limb muscle strength. Results show no significant effect of vitamin D supplementation on grip strength (SMD=0.062, p=0.264), but a significant positive effect on lower limb muscle strength (SMD=0.169, p=0.03).

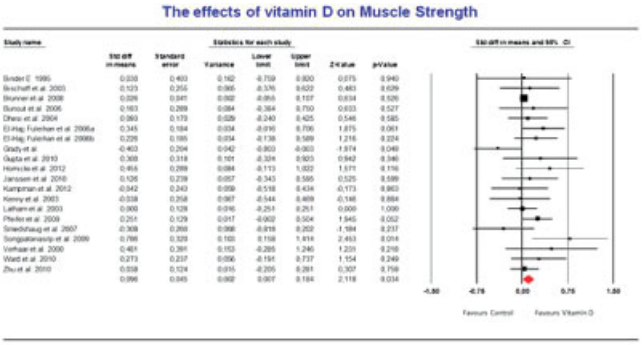

Figure: Forest plot for summary standardized mean difference for global muscle strength

Conclusion: Based on the studies included in this meta-analysis, vitamin D supplementation has a positive impact on global muscle strength, and more especially, on lower limb muscle strength.

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Insufficient Evidence For An Increase In Prevalence and Incidence Of Gout: A Systematic Review and Meta-Regression Analysis. José M.A. Wijnands[1], Wolfgang Viechtbauer[1], Kristof Thevissen[2], Ilja C.W. Arts[1], Pieter C. Dagnelie[1], Coen D.A. Stehouwer[2], Sjef van der Linden[2] and Annelies Boonen[2]. [1]Maastricht University, Maastricht, Netherlands, [2]Maastricht University Medical Center, Maastricht, Netherlands.

Background/Purpose: Estimates on the prevalence and incidence of gout in the general population vary widely and an increase is commonly reported. However, studies on the occurrence of gout have not been reviewed and appraised systematically. The aims of this study were: 1) to estimate the pooled prevalence and the incidence of gout in the general population; 2) to explore which factors contribute to the variation in estimated prevalence and incidence.

Methods: Pubmed, Embase and Web of Science were systematically searched for primary studies on the prevalence and incidence of gout in the general population. Two reviewers independently extracted data on prevalence and incidence as well as sources of clinical heterogeneity, methodological heterogeneity, and variation in outcome reporting. Prevalence rates were pooled using a random-effects model and were adjusted for a series of clinical and methodological study characteristics in a meta-regression analysis using the mixed-effects model.

Results: Of 1466 articles screened, 77 articles were included, of which 71 reported the prevalence and 12 the incidence of gout. The pooled prevalence based on a random effects model was 0.8% (95% CI 0.6; 1.0) with a high level of heterogeneity (I^2 =99.9%). Results from a mixed-effects meta-regression model indicated that gender (p<0.001), continent (p<0.001), consistency in data collection (p=0.003), and case definition (p=0.001) were significantly associated with gout prevalence and jointly accounted for 77.2% of the heterogeneity. Start of data collection was not associated with the prevalence. The incidence in the total population ranged from 0.06 to 2.68 per 1000 person-years and an increase in incidence was only seen in two studies.

Conclusion: The large variation in the prevalence data on gout in the general population is explained not only by well-known factors such as gender and continent on which the study was performed, but also by the case definition of gout. There was insufficient evidence for an increase in prevalence or incidence of gout in recent years.

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Risk Factors For Incident Hyperuricemia During Mid-Adulthood In African American and White Men and Women Enrolled In The Atherosclerosis Risk In Communities Study. Mara McAdams DeMarco[1], Andrew Law[2], Janet W. Maynard[3], Josef Coresh[1] and Alan N. Baer[4]. [1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [2]Johns Hopkins, Baltimore, MD, [3]Johns Hopkins University School of Medicine, Division of Rheumatology, Baltimore, MD, [4]Johns Hopkins University, Baltimore, MD.

Background/Purpose: Increased serum urate levels are associated with poor outcomes including but not limited to gout. Better understanding of which patients are at risk of developing hyperuricemia may aid in clinical decision-making about treatment of asymptomatic hyperuricemia. However, hyperuricemia risk prediction has been limited because previously published studies were not prospective in nature. The objective of this study is to identify risk factors for the development of hyperuricemia over 9 years in a population-based study, ARIC

Methods: This cohort recruited 15,792 individuals in 1987–1989 from 4 US communities and contained 9-years of follow-up; 8,212 participants who had serum urate levels <7.0 mg/dL were included in this analysis. Risk factors for 9-year incident hyperuricemia (plasma urate level of ≥ 7.0 g/dL at visit 4) were identified using an AIC-based selection approach in a modified Poisson regression model. We considered baseline, 3-year, and change in serum urate level over 3 years.

Results: The 9-year cumulative incidence of hyperuricemia was 4% and subgroup cumulative incidences were: 5% for men; 3% for women; 6% for African Americans and; 3% for whites. The final adjusted model included 8 predictors for incident hyperuricemia over 9 years: male sex (RR=1.78, 95% CI: 1.39–2.27), African-American race (RR=1.54, 95% CI: 1.19–2.00), current smoking (RR=1.36, 95% CI: 1.04–1.79), as well as basic education (RR=1.28, 95% CI: 0.99–1.64), hypertension (RR=1.73, 95% CI: 1.37–2.19), coronary heart disease (RR=1.57, 95% CI: 0.97–2.54), obesity (class I obesity: RR=2.82, 95% CI: 1.97–4.04 and ≥class II, RR= 3.93, 95% CI: 2.62–5.91) and eGFR<60 (RR=3.04, 95% CI: 1.73–5.34). In separate models, serum urate levels at baseline, 3 years after baseline, and change in serum urate level over 3 years in addition to demographic and clinical risk factors were all associated with the development of hyperuricemia (Table).

Table. Predictors of incident hyperuricemia over 9 years.

Risk Factor	Model 1: Baseline Serum Urate Adjusted	Model 2: 3 Year Serum Urate Adjusted	Model 3: Change in Serum Urate Adjusted
Male sex	1.09 (0.84, 1.42)	1.02 (0.80, 1.31)	1.57 (1.24, 2.01)
Black race	1.54 (1.20, 1.99)	1.38 (1.08, 1.77)	1.43 (1.11, 1.84)
High school education or higher	1.28 (0.99, 1.64)	1.16 (0.90, 1.50)	1.26 (0.98, 1.61)
Hypertension	1.49 (1.17, 1.90)	1.29 (1.01, 1.65)	1.51 (1.18, 1.93)
Coronary heart disease	1.56 (0.96, 2.54)	1.53 (0.94, 2.50)	1.52 (0.93, 2.48)
Smoking status			
Current smoker	1.34 (1.03, 1.75)	1.31 (1.00, 1.71)	1.34 (1.02, 1.75)
Former smoker	0.82 (0.62, 1.08)	0.78 (0.59, 1.03)	0.83 (0.63, 1.10)
Never smoker	*Reference*	*Reference*	*Reference*
Body mass index, kg/m^2			
BMI >= 35	2.14 (1.40, 3.27)	2.33 (1.54, 3.52)	3.75 (2.50, 5.63)
30 <= BMI < 35	1.92 (1.34, 2.77)	2.04 (1.42, 2.94)	2.72 (1.90, 3.89)
25 <= BMI < 30	1.72 (1.25, 2.36)	1.85 (1.35, 2.54)	2.19 (1.59, 3.00)
BMI < 25	*Reference*	*Reference*	*Reference*
eGFR, ml/min/1.73m^2			
<60	2.02 (1.15, 3.54)	2.10 (1.27, 3.45)	2.97 (1.75, 5.04)
60–90	0.94 (0.75, 1.19)	1.04 (0.83, 1.31)	1.19 (0.95, 1.50)
>=90	*Reference*	*Reference*	*Reference*
Serum urate level at baseline, 1 mg/dL	2.43 (2.02, 2.93)	–	–
Serum urate level at 3 year follow-up, 1 mg/dL	–	1.94 (1.80, 2.09)	–
3-year change in serum urate level, 1 mg/dL	–	–	1.62 (1.49, 1.76)

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Conclusion: Our results suggest that demographic and clinical risk factors that re routinely collected as part of regular medical care predict the development of hyperuricemia in middle-aged adults.

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Kidney Function and Alcohol Intake and The Risk Of Incident Gout In a Population-Based Cohort Of Adults: Atherosclerosis Risk In Communities Study. Mara McAdams DeMarco[1], Anna Kottgen[2], Andrew Law[3], Janet W. Maynard[4], Morgan Grams[3], Josef Coresh[1] and Alan N. Baer[5]. [1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [2]University Hospital Freiburg, Freiburg, Germany, [3]Johns Hopkins, Baltimore, MD, [4]Johns Hopkins University School of Medicine, Division of Rheumatology, Baltimore, MD, [5]Johns Hopkins University, Baltimore, MD.

Background/Purpose: Reduced kidney function is associated with higher urate levels as well as an increased risk of gout. Additionally, alcohol intake is known to increase serum urate levels and is associated with both kidney function and the development of gout. The interaction of modifiable risk factors for gout and kidney function on the development of gout is understudied. We estimated the risk of developing gout over a range of estimated glomerular filtration rate (eGFR) values and stratified by alcohol intake in participants enrolled in the Atherosclerosis Risk in Communities (ARIC) cohort study

Methods: ARIC is a prospective population-based cohort recruited in 1987–1989 from 4 US communities, consisting of 4 visits over 9 years. Participants were included in this analysis if they answered the gout query and were free of gout at baseline. Incident gout was defined as self-reported onset between baseline and visit 4 (9 years after baseline). Serum creatinine was estimated using a modified kinetic JaffŽ reaction. Glomerular filtration rate (eGFR) was estimated using the CKD-Epi equation and alcohol intake was ascertained using a food frequency questionnaire. Using a Cox Proportional Hazards model (age as time scale), we estimated the hazard ratio (HR) and 95% confidence intervals (CI) of incident gout by baseline eGFR (modeled as a linear function and a spline), adjusted for confounders (sex, race, and center) and clinical factors (diuretic use, diabetes, hypertension, and obesity) and stratified by alcohol intake.

Results: A total of 10,858 ARIC participants were included in the analysis. The study population was 43% male, 21% African American and the mean age at cohort entry was 54 years (SD=5.7). The mean eGFR was 92 (SD=14.9) ml/min/1.73 m^2. At baseline, 2% participants were classified as having eGFR<60 ml/min/1.73 m^2; 41% with an eGFR between 60 and 90 ml/min/1.73 m^2; and 57% with an eGFR >90 ml/min/1.73 m^2. The mean alcohol intake was 40.2 grams/week. There were 274 incident gout cases. There was slight evidence that the risk of gout by kidney function was higher in those who drank ≥50 g/week of alcohol (Table; P for interaction=0.08). For those with alcohol intake≥50 g/week and an eGFR<60, there was 1.65-times (95% CI: 1.10–2.48, P=0.02) the risk of gout for every 10 ml/min/1.73 m^2 decrease in eGFR. The risk of gout by eGFR was similar for those with alcohol intake <50 g/week.

Conclusion: There is slight evidence, potentially due to limited power, that the impact of reduced kidney function is greater for adults with alcohol intake ≥50 g/week than for those with lower alcohol intake.

Risk of Gout by eGFR stratified by alcohol intake

	Binary alcohol intake (>=50 g per week) HR (95% CI) N=2,542	p-value	Binary alcohol intake (<50 g per week) HR (95% CI) N=8,316	p-value
eGFR*	1.18 (1.03, 1.34)	0.01	1.12 (1.02, 1.23)	0.02
eGFR≥90*	0.92 (0.68, 1.25)	0.61	1.05 (0.85, 1.29)	0.64
60^{2}eGFR<90*	1.25 (0.96, 1.61)	0.09	1.17 (0.97, 1.41)	0.11
eGFR <60*	1.65 (1.10, 2.48)	0.02	1.16 (0.66, 2.07)	0.6

Adjusted for sex, race, center, diuretic use, hypertension, diabetes, and obesity.
* for each 10 unit decrease in eGFR.

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Higher Consumption Of Sugar-Sweetened Soft Drinks Increases The Risk Of Hyperuricemia In Korean Population: The Korean Multi-Rural Communities Cohort Study. Seong-Kyu Kim[1], Jisuk Bae[1], Jung-Yoon Choe[1], Byung-Yeol Chun[2], Pil Sook Park[3] and Dong Hoon Shin[4]. [1]Catholic University of Daegu School of Medicine, Daegu, South Korea, [2]Kyungpook National University School of Medicine, Daegu, South Korea, [3]Kyungpook National University, Daegu, South Korea, [4]School of Medicine Keimyung University, Daegu, South Korea.

Background/Purpose: The aim of this study is to clarify the association between sugar-sweetened soft drinks and fruit drinks made from oranges and apples and the risk of hyperuricemia in the Korean Multi-Rural Communities Cohort.

Methods: A total of 9400 subjects were enrolled in the Korean Multi-Rural Communities Cohort Study. Five quintiles (Q1 to Q5) according to consumption of soft drinks and other fruit/fruit juices were classified and then categorized into three groups (Q1-Q3, Q4, Q5) to assess the risk of hyperuricemia. Information on dietary intake was collected by well-trained interviewers using validated food frequency questionnaires.

Results: Higher consumption of sugar-sweetened soft drinks (Q5) increased the risk of hyperuricemia in males (adjusted OR 1.35, 95% CI 1.07–1.71) with a linear trend (p for trend = 0.01) and in females (adjusted OR 1.40, 95% CI 1.03–1.90) with no linear trend (p for trend = 0.09), compared to lower consumption (Q1-Q3). However, there were no significant differences of serum uric acid level according to the three categories of soft drink consumption, Q1-Q3, Q3, Q5, in males ($p = 0.21$) or in females ($p = 0.16$), whereas all subjects showed statistical significance of serum uric acid level within the categories ($p < 0.001$). Estimated amount of soft drink intake was associated with serum uric acid level in males (b = 0.001, $p = 0.01$) but not in females (b = 0.0005, $p = 0.10$).

Conclusion: Higher consumption of sugar-sweetened soft drinks increased the risk of hyperuricemia in the Korean population, showing a differential linear trend for hyperuricemia according to gender.

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Smoking and The Risk For Incident Gouty Arthritis. Weiqi Wang[1], Vidula Bhole[2] and Eswar Krishnan[3]. [1]stanford university, palo alto, CA, [2]EpiSolutions Consultancy Services, Thane, India, [3]Stanford University, Palo Alto, CA.

Background/Purpose: Historically, the published literature have suggested that smoking tobacco is associated with lower serum urate concentrations. However, whether smoking impacts the risk for incident gout or not has not been addressed in detail. Our aim was to test this hypothesis and assess if any such link is merely a reflection of the inverse relationship between smoking and obesity.

Methods: The analysis was based on Framingham heart study (FHS) visits 1 to 26, covering 52 years from 1948 to 2000. Gout was defined by presence of any of the following: self-report, physician diagnosis, gout medication use, and radiographic changes. Smoking was defined as any usage of tobacco. Hypertension was defined by presence of any of the following: systolic blood pressure >= 140 mm Hg or diastolic blood pressure >= 90 mm Hg or usage of anti-hypertensive medications. Diabetes were defined according to FHS official review. BMI was obtained from FHS raw data. Statistical analyses were performed using Cox proportional hazard regression models in STATA, where the dependent variable was the time from a patient first enrolled to his incident gout. All covariates that entered the multivariable models (smoking, sex, age, BMI, hypertension, diabetes, kidney disease and alcohol use) were treated as time varying in the regression models. Missing values were addressed by multiple imputations.

Results: There were 5079 participants that were included, among whom 3703 used tobacco. At the baseline the proportion of men was 45.17%. Overall there were 414 incident cases of gout during the follow up. The incidence rate per thousand person-years of gout in the smoking group was 2.55 and in the non-smoking group was 4.57. The unadjusted and age adjusted hazard ratio of smoking were 0.75 (95% confidence interval 0.58–0.99) and 0.73 (0.55–0.96) respectively. In multivariable Cox models, smoking was associated with a hazard ratio of 0.65 (0.44–0.96). The results were not different when men and women were analyzed differently.

Conclusion: Smoking was associated with lower risk for gout and this association was not confounded by obesity or other risk factors.

Disclosure: W. Wang, None; **V. Bhole**, None; **E. Krishnan**, Takeda, 2, takeda, 5.

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Hip Osteoarthritis and Risk Of All Cause and Disease-Specific Mortality Among Older Women: A Population-Based Cohort Study. Kamil E. Barbour[1], Li-Yung Lui[2], Charles G. Helmick[1], Kristina A. Theis[1], Michael C. Nevitt[3], Nancy E. Lane[4], Louise Murphy[1], Jennifer M. Hootman[5], Marc C. Hochberg[6] and Jane A. Cauley[7]. [1]Centers for Disease Control and Prevention, Atlanta, GA, [2]California Pacific Medical Center, San Francisco, CA, San Francisco, CA, [3]University of California, San Francisco, San Francisco, CA, [4]UC Davis School of Medicine, Sacramento, CA, [5]Centers for Disease Control and Prevention, Kennesaw, GA, [6]University of Maryland, Baltimore, MD, [7]University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: The morbidity of osteoarthritis (OA) is well documented; however few comprehensive studies have examined the effect of OA on mortality.

Methods: We used data from the Study of Osteoporotic Fractures, a US population-based cohort study of 9704 white women, ages 65 years or older. Hip radiographs were obtained at baseline (1986–1988) and visit 5 (1995–1996). A summary Croft grade of 0–4 for each hip was based on 5 individual radiographic features: joint space narrowing (JSN), osteophytes, subchondral sclerosis, cysts formation, and deformity of the femoral head. Radiographic hip OA (RHOA) was defined as having Croft grade of <2 in at least one hip (definite JSN or osteophytes plus one other radiographic feature). Clinical hip OA (CHOA) was defined as having both RHOA and self-report of hip pain "on most days for at least one month in the year" in the same hip. Mortality was confirmed through July, 2012 by death certificates and hospital discharge summaries, if available. All-cause mortality (cumulative incidence=64%) was analyzed along with three disease-specific causes of death (ICD-9-CM, cumulative incidence): cardiovascular disease (CVD) (390–459.9, 24.8%), total cancer (140–239.9, 11.5%), gastrointestinal disease (520–579.9, 1.8%), and all other causes (25.9%). Cox proportional hazards regression with time-dependent covariates (at baseline and visit 5) were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). All disease-specific mortality models accounted for competing risks of mortality.

Results: Mean follow-up time was 16.0 ± 6.1 years. The baseline prevalence of RHOA and CHOA was 7.4% and 3.2%, respectively, whereas the visit 5 prevalence was higher (9.7% and 3.9%, respectively). Having RHOA was associated with increased risk of all-cause [HR: 1.20; 95% CI: (1.10, 1.31)] and CVD [HR: 1.29; 95% CI: (1.13, 1.48)] mortality after adjusting for age, body mass index, health status, walking for exercise, diabetes, and stroke. Adjusting for potential mediating factors (i.e., physical function, falls, and disability) did not markedly attenuate these associations. CHOA was not associated with all-cause or any disease-specific mortality outcomes.

Conclusion: RHOA was associated with an increased risk of all-cause and CVD mortality in a cohort of older white women followed for a mean of 16 years.

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Epidemiology and Health Services Use For Osteoarthritis By First Nations People In Alberta, Canada. Cheryl Barnabe[1], Allyson Jones[2], Ed Enns[3], Don Voaklander[2], Christine Peschken[4], Joanne Homik[2], John Esdaile[5], Sasha Bernatsky[6], Brenda Hemmelgarn[1] and Deborah Marshall[1]. [1]University of Calgary, Calgary, AB, [2]University of Alberta, Edmonton, AB, [3]Alberta Bone and Joint Health Institute, Calgary, AB, [4]University of Manitoba, Winnipeg, MB, [5]University of British Columbia, Vancouver, BC, [6]Research Institute of the McGill University Health Ctre, Montreal, QC.

Background/Purpose: Self-reported survey data and a single provincial administrative data source have previously indicated that the First Nations (FN) population in Canada has a 1.5 fold higher prevalence of osteoarthritis (OA), but the health services use by this population is unknown. Our objective was to determine whether OA prevalence and healthcare use in Alberta, Canada varies by FN status.

Methods: Using population-based healthcare administrative data (years 1993 to 2010), we defined a cohort of patients with OA (2 physician claims within 2 years or 1 hospitalization with diagnosis code ICD9 715x, or ICD10 M15–19). FN patients were identified based on premium payer status and represent 3.8% of the Alberta population. OA prevalence (fiscal year 2007/2008) and outpatient visits for OA to primary care physicians, specialists (orthopedic surgeons and rheumatologists), and arthroplasty (hip or knee) are reported for FN and non-FN populations.

Results: The age and sex standardized OA prevalence in FN Albertans is twice that of the non-FN population (161.0 vs 78.2 cases/1,000 population, standardized rate ratio 2.06; 95%CI 2.00–2.12). Prevalence is highest in people residing in rural locations and in females (Table 1).

Table 1. Prevalence of Osteoarthritis in Alberta (/1,000 population)

		First Nations	non-First Nations
Overall Prevalence	Age and sex standardized	161.0	78.2
Location of Residence	Rural	186.7	88.5
	Urban	135.9	76.2
Sex	Females	184.9	93.1
	Males	148.8	72.3

Per year, FN persons had a mean of 3.4 primary care outpatient visits specifically for OA (20.3% of FN total primary care contacts) compared to 1.6 visits per year for non-FN persons (14.4% of non-FN total primary care contacts) ($p<0.001$). Contact with specialists was significantly lower for FN persons, with one-third fewer outpatient visits to orthopedics and rheumatology compared to non-FN persons (Table 2).

Table 2. Healthcare Use for Osteoarthritis in Alberta (/1,000 person-years)

	First Nations	non-First Nations
Primary Care Visits	3380.1	1557.4
Orthopedic Surgeons	218.3	405.0
Rheumatologists	39.0	51.4

FN with OA were two-thirds less likely to have arthroplasty of the hip or knee. This did not appear to be driven by the presence of other medical comorbidities (Table 3).

Table 3. Arthroplasty Rates for Osteoarthritis in Alberta (/1,000 person-years)

	First Nations	non-First Nations
Overall	8.1	26.4
Diabetes	8.6	23.5
Any Comorbidity	8.8	25.7

Conclusion: We demonstrate disparities in OA care in FN persons given an estimated 2-fold higher disease prevalence from administrative data sources. While this finding may be driven in part by an increased probability of diagnosis through frequent primary care contact, it is unlikely to account for the large gap in use of specialty services and arthroplasty in FN compared to non-FN persons. This care gap may be due to access barriers for FN patients.

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Incidence and Trend Of Osteoarthritis In An Administrative Database From British Columbia, Canada. M Mushfiqur Rahman[1], Jolanda Cibere[2], Charles H Goldsmith[3], Aslam H. Anis[4] and Jacek A. Kopec[2]. [1]Arthritis Research Centre of Canada, Richmond, BC, [2]University of British Columbia, VANCOUVER, BC, [3]Simon Fraser University, Burnaby, BC, [4]Centre for Health Evaluation and Outcome Sciences, Vancouver, BC.

Background/Purpose: Data on the incidence of osteoarthritis (OA) are limited and there is little information on the trend in incidence of OA over time. The objective of this study was to calculate the incidence rates and to describe the changes in OA incidence rates using two case definitions in 18 years of administrative health records.

Methods: We analyzed all visits to health professionals and all hospital admission records of a random sample (n = 540,000) from British Columbia, Canada for the fiscal years 1991/92 through 2008/09. Administrative OA was defined in two ways: 1) at least one physician diagnosis or one hospital admission (Def1) and 2) at least two physician diagnoses in two years or one hospital admission (Def2). Incidence rate was defined as the number of new OA cases during a fiscal year divided by the person-years at risk. New adult (age 20 years and older) OA cases were identified for the fiscal year 2008/2009 after deleting the prevalent cases from April 1991 to March 2008. To see the pattern of incidence, we have rates from 2000/01 through 2008/09, using nine years of run-in, that is, nine years was used to delete the prevalent cases. Both crude and age-standardized incidence rates for each sex were obtained after deleting prevalent cases for nine years. Finally, the annual relative change (ARC = (exp (β) – 1) × 100) was estimated from the weighted Poisson regression model for each sex.

Results: In 2008/09 fiscal year the overall incidence of OA using Def1 was 14.6 (12.7 in men and 16.5 in women) per 1000 person years, and 8.2 (7.2 in men and 9.3 in women) per 1000 person years in Def2. Between 2000/01 and 2008/09, crude incidence rates of OA based on Def1 varied from 11.8 to 14.2 per 1000 person years in men and from 15.7 to 18.5 per 1000 person years in women and the rates were lower to about 53–55% using Def2 (Table). For the crude rates, the ARCs were 3% ($p < 0.01$) and 2% ($p < 0.01$) for men and women respectively, in Def1, and the changes were similar in Def2. The age-standardized ARCs were not significantly different from 0% in both case definitions.

Table. Crude and age-standardized incidence of osteoarthritis per 1000 person years using nine years of run-in to delete the prevalent cases.

	Men Def1[1]		Men Def2[2]		Women Def1[1]		Women Def2[2]	
Year	**Crude**	**Standardized**	**Crude**	**Standardized**	**Crude**	**Standardized**	**Crude**	**Standardized**
00/01	11.8	12.7	6.3	6.8	15.7	17.0	8.5	9.2
01/02	11.6	12.3	6.1	6.5	15.7	16.7	8.8	9.4
02/03	11.7	12.1	6.2	6.4	15.4	16.0	8.5	8.9
03/04	12.5	12.7	6.6	6.8	16.9	17.2	9.3	9.5
04/05	12.6	12.6	6.7	6.7	17.3	17.3	9.7	9.7
05/06	13.6	13.2	7.1	6.9	17.8	17.4	9.7	9.5
06/07	13.5	12.8	7.5	7.1	18.1	17.3	9.8	9.3
07/08	13.9	12.9	7.4	6.8	18.1	16.9	10.2	9.4
08/09	14.2	12.9	7.9	7.1	18.5	16.8	10.2	9.2
ARC*	3%	1%	3%	1%	2%	0%	3%	0%
p-value	<0.01	0.43	<0.01	0.31	<0.01	0.71	<0.01	0.91

[1]Def1: one visit to a health professional or one hospital diagnosis. [2]Def2: two visits to a health professional in two years or one hospital diagnosis. *ARC stands for annual relative change = (exp (β) – 1) × 100 and was estimated from Poisson regression.

Conclusion: Our study suggests that physician diagnosed incidence of OA is higher in both men and women. Crude incidence rates of OA are increasing slightly over the years but the age-standardized rates do not show an increasing or decreasing pattern over the years. These data have implications in public health services for forecasting prevalence and costs of OA and in epidemiologic research.

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Prevalence Of Femoroacetabular Impingement Among Chinese Living In Vancouver, Canada: A Population-Based Study. Linda C. Li[1], Jacek A. Kopec[2], Hubert Wong[3], Jolanda Cibere[2], Charlie Zhang[4], Eric C. Sayre[2], Joanna Ye[2], Morgan Barber[2], Helen Prlic[5] and John Esdaile[6]. [1]Arthritis Centre of Canada, Richmond, BC, [2]Arthritis Research Centre of Canada, Richmond, BC, [3]St Paul's Hospital, University of British Columbia, Vancouver, V6Z 1Y6, Canada, Vancouver, BC, [4]University of British Columbia, Vancouver, BC, [5]Arthritis Research Centre of Canada, Vancouver, BC, [6]Arthritis Research Centre of Canada, University of British Columbia, Richmond, BC.

Background/Purpose: Femoroacetabular Impingement (FAI) is one source of hip pain in young adults and has been suggested as a major cause of hip osteoarthritis (OA). Studies have shown that the prevalence of FAI was over 50% in populations with established OA[1–3] and 45% in a primarily Caucasian population in Denmark[4]. Radiographic hip OA is extremely rare in Chinese; however, the prevalence of radiographic FAI in the Chinese population is unknown. The current study aims to estimate the prevalence of hip pain and FAI among Chinese living in Metro Vancouver, Canada (population=2.3 million, 2011 Census), where 19% of the population are ethnic Chinese. Over 25% of new immigrants to Vancouver in the past 5 years were from mainland China.

Methods: This study was conducted within IMPAKT-HiP*, a large multi-faceted study on the role of FAI and physical activity in cartilage damage and hip pain. Chinese participants were recruited in a cross-sectional telephone survey of a random sample of residents in Metro Vancouver. Individuals were eligible if they were between the age of 20 and 49, reported both parents were Chinese descent, and were available for an onsite assessment and x-ray session. Pregnant women were excluded. All calls were initiated in English. Non-English-speaking Chinese respondents received a second call by an interviewer fluent in Mandarin and Cantonese to assess eligibility. Participants were asked if they had any pain, stiffness or discomfort in the groin or the front of the upper thigh (i.e., hip pain) in the past 12 months. All hip x-rays were read by a trained reader using a standardized protocol. Pincer-type FAI was defined by: 1) presence of focal acetabular retroversion or 2) a lateral center edge angle >40°. Cam-type FAI was defined by an alpha angle >55°. Prevalence of hip pain and FAI were defined by participant, with a case represented by involvement of one or both hips.

Results: 201 eligible individuals (89 English-speaking, 112 Mandarin/Cantonese-speaking) were recruited between April 2012 and January 2013. The majority were women (n=134, 66.7%) with a mean age of 38.7 years (SD=9.0). 8 participants (4.0%) had been told they had hip OA by a health professional. Hip pain in the past 12 months was reported by 59 participants (29.4%; women=41, men=18). FAI was found in 76 individuals (37.8%; bilateral=55, 27.4%; unilateral=21, 10.4%). FAI was present in 44/134 women and 32/67 men. 58 participants (28.9%) had pincer FAI, 13 (6.5%) had cam FAI and 5 (2.5%) had mixed FAI.

Conclusion: Our findings contribute new information on the prevalence of FAI among Chinese living in North America. Further research to examine prevalence of FAI, using standardized methodologies, in populations with high (e.g., Aboriginal populations) vs. low hip OA prevalence may provide further insight into the cause of hip OA.

*IMPAKT-HiP=Investigations of Mobility, Physical Activity, and Knowledge Translation in Hip Pain

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Twenty-First Century Prevalence Of Frequent Knee Pain, Radiographic, Symptomatic and Clinical Knee Osteoarthritis According to American College Of Rheumatology Criteria In Southern Sweden.
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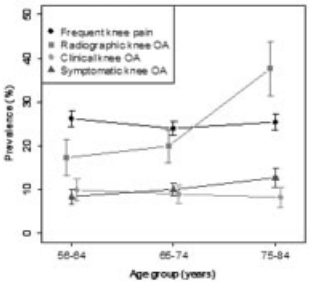
Background/Purpose: To provide current estimates of the prevalence of knee pain, radiographic, symptomatic, and clinical knee osteoarthritis (OA) in middle-aged and elderly in Sweden.

Methods: In 2007 a random sample of 10 000 56 to 84 year old Region Skåne residents from the Malmö Diet and Cancer Study (Manjer et al 2001) were sent a mailed questionnaire about knee pain in the last 12 months; this being the first part of the Malmö Osteoarthritis Study (MOA). We classified subjects reporting knee pain with duration of at least 4 weeks as having *frequent knee pain*. A random sample of 1300 subjects with frequent knee pain and a random sample of 650 subjects without (out of the 7737 questionnaire responders) were invited for a clinical and radiographic examination including assessment of *clinical knee OA* according to the American College of Rheumatology (ACR) clinical criteria. Participants underwent radiography of both knees in weight-bearing and semi-flexion. An independent radiologist who was blinded to clinical data assessed all frontal and patellofemoral radiographs. We considered subjects who fulfilled criteria approximating Kellgren and Lawrence (KL) grade 2 or worse to have *radiographic knee OA*. Those with frequent knee pain and having radiographic knee OA were classified as having *symptomatic knee OA*. We used weighting to adjust for different sampling probabilities depending on the knee pain status as well as for the nonresponse and volunteer bias in MOA study using data on age, sex, body mass index and highest education level collected within the Malmö Diet and Cancer Study and the knee pain status from the MOA survey.

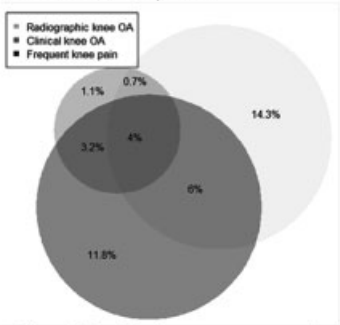
Results: The 10 000 random sample had mean (SD) age of 70.3 (7.6) years, mean (SD) body mass index was 27.1 (5.0) and 62% were women. The response rate in mailed questionnaire was 77.4% and 1527 invited subjects (78.3%) attended the clinical visit. The prevalence of *frequent knee pain* in one or both knees during the last 12 months was 25.1% (95%CI: 24.1 to 26.1), 20.8% in men and 27.7% in women and was similar in all age groups (Figure 1). The prevalence of *radiographic knee OA* (KL grade ≥2) was 25.4% (95%CI: 22.6 to 28.5), the prevalence of *symptomatic knee OA* was 10.5% and both increased with increasing age. The prevalence of *clinical knee OA according to the ACR criteria* was 9.0%. The prevalence of frequent knee pain in the subjects with radiographic knee osteoarthritis was 42.1%. Among those with symptomatic knee OA 40% fulfilled the ACR clinical knee OA criteria. In the study sample 11.8% of subjects reported frequent knee pain but did not fulfill OA criteria, neither for clinical ACR nor radiographic knee OA (Figure 2).

Figure 1. The prevalence of frequent knee pain, radiographic, symptomatic, and clinical ACR knee osteoarthritis (OA) in Swedish adults 56 to 84 years old.



Frequent knee pain – knee pain in one or both knees in last 12 months with duration of at least 4 weeks; Radiographic knee OA –changes on x-ray approximating Kellgren-Lawrence grade 2 or worse; Clinical knee OA – clinical knee OA according to the American College of Rheumatology clinical criteria, recursive positioning method; Symptomatic knee OA – frequent knee pain as defined above in combination with radiographic knee OA as defined above.

Figure 2. The prevalence and overlap of frequent knee pain, radiographic and clinical knee OA in Swedish adults 56 to 84 years old.



Radiographic knee OA –changes on x-ray approximating Kellgren-Lawrence grade 2 or worse, Clinical knee OA – clinical knee OA according to the American College of Rheumatology clinical criteria, Frequent knee pain – knee pain in one or both knees in last 12 months with duration of at least 4 weeks.

Conclusion: The prevalence of knee OA in southern Sweden in the age group 56 to 84 years varied from 9.5% to 25.4% depending on the definition used. The estimates from Sweden are lower than those from the United States. A lower body mass index in the Swedish population may be one explanation.

Disclosure: A. Turkiewicz, None; **M. Gerhardsson de Verdier**, Astra Zeneca, 1, Astra Zneca, 3; **G. Engström**, Astra Zeneca, 3; **S. Lohmander**, None; **M. Englund**, None.

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Myocardial Infarction and Mortality after Joint Surgery in Patients with Rheumatoid Arthritis Compared with the General Population.
Joanne Tropea[1], Mark Tacey[2], Megan Bohensky[2], Caroline Brand[2], Ian Wicks[1] and Sharon Van Doornum[2]. [1]Royal Melbourne Hospital, Melbourne, Australia, [2]The University of Melbourne, Melbourne, Australia.

Background/Purpose: Rheumatoid arthritis (RA) is associated with an increased risk of myocardial infarction (MI) and post-MI fatality compared with the general population. In a previous study examining post-MI treatment in RA compared with controls we noted that a higher proportion of the RA patients had experienced MI following a surgical procedure. The aim of this study was to compare the incidence of MI and mortality (all-cause and cardiovascular (CV)) at 6 weeks and 12 months following joint surgery in patients with RA compared with the general population.

Methods: Individuals who had undergone joint surgery in Victoria, Australia between 1 July 2000 and 30 June 2007 were retrospectively identified from routinely collected hospital administrative data. Individuals were classified as having RA using International Classification of Diseases codes recorded at the time of surgery or during any hospitalisation in the 2 years prior. Incidence of MI and mortality at 6 weeks and 12 months post-operatively was determined from hospital data and linked death registry data. Logistic regression analyses were performed with adjustment for age, sex, comorbidities, socioeconomic status and admission type (elective vs emergency).

Results: A total of 308,589 episodes of joint surgery occurred among 240,571 individuals, with 3654 (1.2%) occurring among patients with RA. The RA cohort was older (mean (SD) age in years 62.4(13.4) vs 52.5(18.6)), with a female preponderance (74.6% vs 45.6%) and had a higher burden of comorbidities, lower socioeconomic status and fewer elective admissions compared to the non-RA cohort. The number (prevalence) of events in the RA and non-RA cohorts respectively was as follows; MI at 6 weeks: 25 (0.68%) vs 838 (0.27%); death at 6 weeks: 22 (0.60%) vs 569 (0.19%); MI at 12 months: 59 (1.61%) vs 1968 (0.65%); death at 12 months: 93 (2.55%) vs 2411 (0.79%).

Figure 1 shows the adjusted odds ratios (OR) for each of these outcomes in the RA patients compared with the non-RA patients. At 6 weeks post joint surgery the adjusted OR of MI was 1.50 (95% CI 0.96–2.33), all-cause death was 1.87 (95% CI 1.12–3.11) and CV death was 1.93 (95% CI 1.10–3.39). At 12 months post joint surgery the

adjusted OR of MI was 1.71 (95% CI 1.28–2.29), all-cause death was 2.17 (95% CI 1.65–2.85) and CV death was 2.30 (95% CI 1.65–3.21).

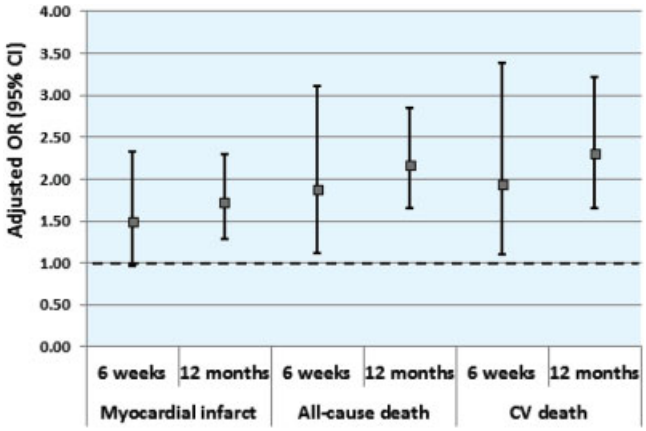

Figure 1. Risk of 6 week and 12 month myocardial infarction, all-cause death and cardiovascular death in patients with rheumatoid arthritis following joint surgery.

Conclusion: Following an episode of joint surgery RA patients have a significantly increased risk of death at 6 weeks, and MI and death at 12 months, compared to the general population. The reasons for this remain to be elucidated but in the meantime RA patients should be considered at higher risk in the peri-operative period.

Disclosure: J. Tropea, None; **M. Tacey**, None; **M. Bohensky**, None; **C. Brand**, None; **I. Wicks**, None; **S. Van Doornum**, None.

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Trends In Prescription Of Opioids From 2003–2009 In Persons With Knee Osteoarthritis. Elizabeth Wright[1], Jeffrey N. Katz[1], Stanley Abrams[1], Daniel H. Solomon[2] and Elena Losina[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Harvard Medical School, Brigham and Women's Hospital, Division of Rheumatology, Division of Pharmacoepidemiology, Boston, MA.

Background/Purpose: Osteoarthritis (OA) of the knee is a painful condition affecting ~13% of persons >65 years of age. OA is often accompanied by comorbidities. Effective pain control is important for managing this chronic disease. In the last decade, physicians have become increasingly aware of contraindications to NSAIDs due to comorbid conditions. We sought to examine whether physicians have begun to use opioids more frequently.

Methods: We assembled national cohorts of individuals with knee OA using data from waves of the Medicare Beneficiary Survey (MCBS) administered in the years 2003, 2006, and 2009. We examined temporal trends in opioid prescriptions in these cohorts over time. The MCBS survey consists of a nationally representative sample of Medicare beneficiaries. The MCBS survey data can be linked to Medicare claims. Survey respondents provided data on demographics, health status and prescribed medications. We selected knee OA cohorts from each of the three years from community-dwelling MCBS respondents aged 65 and older who had at least one outpatient visit in Medicare Parts A or B with an ICD-9-CM diagnostic code of a) 715.x6 (OA of knee) or b) ICD-9 code of 719.46 (knee pain) plus 715.x8, 715.x9 or 715.x0 (OA at other specified sites, at multiple sites and at unspecified sites, respectively). Functional status was categorized as poor if the survey respondent indicated "a lot of difficulty" or "inability" to walk ¼ mile or 2–3 blocks. The following six comorbidity categories were assigned from Medicare Parts A or B claims: cancer, cardiovascular disease, musculoskeletal disease other than OA, diabetes, depression and chronic obstructive pulmonary disease (COPD). We included all prescribed medication records classified as opioids under the MCBS antiarthritic or analgesic categories. The outcome was defined as receiving at least one prescription for an opioid in the year of study. We used multivariate logistic regression to establish whether opioid use changed over time and identify factors leading to greater utilization of opioids in elderly persons with OA.

Results: 488 (5%) subjects from the 2003 MCBS survey, 477 (5%) from the 2006 MCBS and 422 (5%) from the 2009 MCBS were identified with knee OA. Mean age and sex were similar across years (77 years, 70% females). We found a significant increase in opioid prescribing between 2003 and 2009, with 31% of the patients receiving opioids in 2003, 39% in 2006 and 40% in 2009 (OR 1.5, 95% CI 1.1, 2.0 for both years 2006 and 2009 compared to 2003). Across all time periods, independent correlates of opioids use included: female sex (OR 1.5, 95% CI 1.2, 2.0), functional limitations (OR 2.1, 95% CI 1.7, 2.7), poor self-reported health status (OR 1.6, 95% CI 1.2, 2.0), COPD (OR 1.4, 95% CI 1.0, 1.8) and musculoskeletal disease in addition to OA (OR 1.9, 95% CI 1.2, 2.8).

Conclusion: Opioid use in elderly persons with knee OA increased substantially between 2003 and 2009. The more frequent use of opioids is likely due to low efficacy and to toxicity of other classes of analgesics drugs currently used for pain relief in knee OA patients. As prevalence and incidence of knee OA continues to grow the public health impact of greater use of opioids should be monitored carefully.

Disclosure: E. Wright, None; **J. N. Katz**, OARSI, 6, JBJS, 9; **S. Abrams**, None; **D. H. Solomon**, Lilly, Amgen, CORRONA, 2, Lilly, Novartis, BMS, Pfizer, 6, Lilly, BMS, Novartis, 9; **E. Losina**, JBJS, 9.

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Association Of Area-Level Socioeconomic Status With Pain and Function At Presentation For Total Knee Arthroplasty. Candace H. Feldman[1], Yan Dong[2], Jeffrey N. Katz[2], Laurel Donnell-Fink[2] and Elena Losina[2]. [1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Prior studies suggest that individuals with lower socioeconomic status (SES) both under-utilize joint replacement procedures and present with increased pain and poorer function. Area-level SES is often used as a proxy when individual-level SES is unavailable and may also capture neighborhood-level effects. We examined the relationship between area-level SES and pain and function at presentation for total knee arthroplasty (TKA).

Methods: We examined a cohort of individuals undergoing TKA from 2010–2013 at an academic medical center. We obtained demographic information and measures of pain and functional status (WOMAC) and depression (MHI-5) from baseline surveys. We used the Geographic Information System (GIS) to geocode individual home addresses and linked these to U.S. Census data at the block group level. For P.O. Boxes, we used post office addresses. We constructed a previously validated composite area-level SES index that included occupation, income, wealth, education, and housing-related Census variables. We assessed bivariate associations between age (<65 or ≥65), sex, race (White or non-White), area SES (divided into quartiles, with highest two combined), BMI (<25, 25–30, 30–35, >35) and depression (MHI5>68 or less) and two outcomes –pain and functional status (WOMAC ≤30, 30–55, >55) –using Chi-squared tests. Linear regression models allowed us to identify independent correlates of high pain and low function (WOMAC >55). Covariates included age, sex, BMI, depression and area SES.

Results: Among 320 individuals, 181 (58%) were female. The mean age was 66 years (SD 10), and 282 (89%) were White. Addresses were geocoded for 297 street addresses and 20 P.O. Boxes. Our mean SES index score was 59 (SD 6, median 59, range 42–78); the U.S. population median SES is 51. In bivariate analyses, younger age, higher BMI, female sex, and higher depression scores were associated with higher pain and lower function ($p<0.05$). Higher BMI was also associated with lower area SES ($p<0.01$). Adjusted analyses showed striking associations between SES and baseline pain and functional status: 35% (95% CI 26–44) with the lowest area SES and 18% (95% CI 11–25) with the highest presented with high pain, while 31% (95% CI 22–40) with the lowest area SES and 18% (95% CI 11–25) with the highest presented with low function (**Figure**).

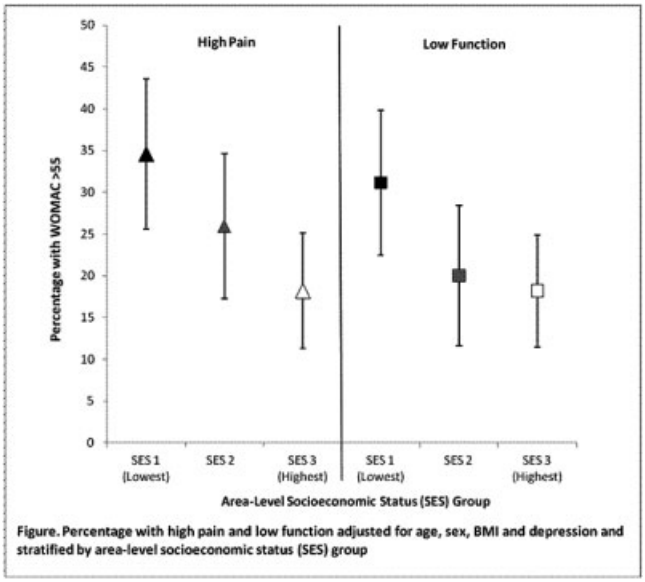

Figure. Percentage with high pain and low function adjusted for age, sex, BMI and depression and stratified by area-level socioeconomic status (SES) group

Conclusion: In this cohort of individuals with, on average, higher area-level SES than the general U.S. population, those from the highest SES areas presented for TKA with lower perceived pain and higher functional status than those from lower SES areas. Further research is needed to confirm these trends and understand why TKA appears to be utilized in higher socioeconomic status patients with relatively mild pain and high function.

Disclosure: C. H. Feldman, None; **Y. Dong**, None; **J. N. Katz**, OARSI, 6, JBJS, 9; **L. Donnell-Fink**, None; **E. Losina**, JBJS, 9.

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Proportion Of U.S. Older Adults Meeting Inclusion Criteria For 2010 ACR Recommendations On Glucocorticoid-Induced Osteoporosis. Robert A. Overman[1], Joshua C. Toliver[2], Jun-Yen Yeh[3], Margaret L. Gourlay[2] and Chad L. Deal[1]. [1]Cleveland Clinic, Cleveland, OH, [2]University of North Carolina, Chapel Hill, NC, [3]Long Island University, Brooklyn, NY.

Background/Purpose: Glucocorticoid-induced osteoporosis (GIO) is the most common cause of secondary osteoporosis. Fracture related to GIO increases a patient's mortality risk and reduces quality of life. The American College of Rheumatology (ACR) released updated guidelines on the prevention and treatment of GIO in 2010. For postmenopausal women (PMW) and men ≥50 years of age with past or anticipated oral glucocorticoid (GC) use of ≥90 days, treatment recommendations are stratified according to low (<10%), medium (10–20%) and high (>20%) 10-year risk of a major osteoporotic fracture calculated using the World Health Organization's FRAX® fracture risk assessment tool, with recommendations taking into account dose and duration of therapy. We estimated the proportion of the US population currently taking oral GC from the National Health and Nutrition Examination Survey (NHANES) and calculated the proportion of the US population that should be treated for GIO according to the ACR guidelines.

Methods: This study used 3 cycles between 2005 and 2010 of NHANES, a bi-annual US cross-sectional study designed to be representative of the entire non-institutionalized population. PMW aged ≥40 and men aged ≥50 with height and weight measurements who self-reported current use of an oral GC were included. FRAX® risk scores were calculated using NHANES risk factor data, and with femoral neck bone mineral density (BMD) when available. Anti-osteoporosis pharmaceutical treatment (AOP) was defined as reported use of a bisphosphonate, estrogen, raloxifene, or teriparatide. Results are presented as weighted percents (95% confidence interval) using interview weights and NHANES specific methodology for combining multiple cycles; population estimates are made from mid-year current population survey totals for 2005–2010.

Results: An estimated 825,284 PMW in the US population used GC and met inclusion criteria, with mean age 64.8 (62.5, 67.1) years. GC were used by 1.66% (1.19, 2.14) of PMW; based on ACR GIO risk categories, 0.5% were low-risk (0.2, 0.7); 0.3% medium-risk (0.1, 0.5); and 0.9% high-risk (0.5, 1.2).

An estimated 683,784 men aged ≥50 in the US population used GC and met inclusion criteria, with mean age 66.0 (63.1–68.8) years. GC were used by 1.65% of the men; based on ACR GIO risk categories 0.6% were low-risk (0.3, 0.9); 0.6% medium-risk (0.3, 1.0); and 0.4% high-risk (0.2, 0.7).

Chronic GC use (≥90 days) was reported by 81.2% (69.2, 93.3) of PMW GC users, of whom 55.5% (40.7, 70.3) would be recommended AOP treatment by ACR guidelines. Chronic GC use was reported by 75.8% (63.2, 88.5) of men aged ≥50, of whom 51.8% (38.3, 65.3) would be recommended AOP treatment by ACR guidelines. Of those who met ACR criteria for treatment, only 13.8% (2.2, 25.4) of PMW and 5.0% (0.0, 11.5) of men aged ≥50 reported AOP use.

Conclusion: Based on NHANES data, we estimate that greater than 1.5 million US PMW and men aged ≥50 were using an oral GC between 2005 and 2010. Using ACR guidelines, treatment would be recommended in greater than 50% of this population. However, less than 15% of PMW and 5% of men aged ≥50 reported use of an AOP medication. These results indicate a treatment gap in the management of GIO in the US.

Disclosure: R. A. Overman, None; **J. C. Toliver**, None; **J. Y. Yeh**, None; **M. L. Gourlay**, None; **C. L. Deal**, None.

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Incidence Of Osteoporotic Hip Fractures In Estonia Between 2005 and 2012. Mikk Jürisson[1], Anneli Uusküla[1], Riina Kallikorm[1], Sigrid Vorobjov[2] and Margus Lember[1]. [1]Faculty of Medicine, Tartu University, Tartu, Estonia, [2]National Institute for Health Development, Tallinn, Estonia.

Background/Purpose: Monitoring the incidence of hip fractures is essential to measuring population health and the value of improvements in health care. Data on recent trends in hip fractures from Eastern European countries is limited

Methods: Ecologic trend study uses data from the public health insurance fund covering the whole country to estimate the incidence of hip fracture. For the incident hip fracture case definition was based on the ICD 10 diagnosis code S72.0 on the health care bill for a person who had not been treated for the same cause in a preceding 12 months.

Age-specific fracture rates were calculated for males and females in 10 year age brackets and for population aged over 40 years. Age-standardized incidence rates were estimated using direct standardization method with the European population set as standard; trend in the rates over time was assessed using linear regression.

Results: In 2012, 833 patients were admitted for inpatient care for the incidence case of the hip fracture: 68% of the patients were women; the mean age was 76.7 years (SD 11.9; mean age for women 79.0 years, men 71.7 years; p-value<0.001). The age-specific incidence rates among women ranged from 9/100 000 (age group of 40–49) to 654/100 000 (age group 80+ years). The age-specific incidence rates among men ranged from 16/100 000 (age group of 40–49) to 577/100 000 (age group 80+). 57% and 34% of hip fracture cases were attributed to the oldest age group (80+ years) among women and men accordingly.

Unlikely for women and other age groups among men, age-specific incidence rates for men over 80 years were increasing between 2005 and 2012.

Over the period of 2005–2012 the estimated age-standardized incidence rates ranged from 102/100 000 (95%CI 89−114; in 2005) to 81/100 000 (95%CI 70−91; in 2012) among women, and from 91/100 000 (95%CI 83−100; in 2005) to 74/ 100 000 (95%CI 67−81; in 2012) among men. For both genders, the age-standardized incidence rates decreased over the period of 2005–2012 (men: p= 0.022; women; p- 0.02).

Conclusion: To our knowledge this is the first population-based analysis of hip fracture incidence in Estonia. There was no statistical difference between age-standardized incidence rates among women and men. The incidence among men was comparable to that reported from men from other European countries. However, the incidence observed among Estonian women is lower than that reported from their European counterparts. There was a decline in age-standardized incidence over the study period among both genders.

Disclosure: M. Jürisson, ICUROS, 2; **A. Uusküla**, None; **R. Kallikorm**, None; **S. Vorobjov**, None; **M. Lember**, None.

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Medication Use With Denosumab (Prolia®) In a Large Claims Database In The United States. Emily Durden[1], Lung-I Cheng[2], Elnara Eynullayeva[1], Christopher Gregory[1] and Bradley Stolshek[2]. [1]Truven Health Analytics, Washington, DC, [2]Amgen, Inc., Thousand Oaks, CA.

Background/Purpose: Persistence and compliance with osteoporosis therapies is associated with significantly fewer vertebral, nonvertebral and hip fractures. A number of studies have examined medication-taking behavior with oral bisphosphonates and teriparatide, and the 1-year persistence rates have ranged from 39.9% to 56.7%. Limited real-world data are available regarding persistence and compliance with newer osteoporosis therapies, such as denosumab, a RANK ligand inhibitor administered every 6 months as a subcutaneous injection. The purpose of this study is to assess persistence and compliance among patients treated with denosumab in a large claims database in the U.S.

Methods: In this retrospective, observational cohort study, patients 18 years of age and older newly initiating denosumab between January 1, 2012 and March 31, 2012 were identified for inclusion from the *MarketScan Research* Databases. The date of the denosumab claim was defined as the index date. Patients were required to have at least 24 months of pre-index continuous enrollment with medical and pharmacy benefits. Patients were also required to have at least 8 months of post-index continuous enrollment for the interim analysis and at least 12 months of post-index continuous enrollment for the final analysis. Patients with Paget's disease of the bone, osteogenesis imperfecta, hypercalcemia, malignant cancer and metastasis, HIV, and patients receiving preventive treatment for risk of breast cancer or denosumab in the pre-index period were excluded from the study. In the post-index period, patients with a cancer or metastasis diagnosis appearing prior to a medical claim for denosumab were also excluded. The current report contains results from the interim analysis. Persistence as indicated by continuous use of denosumab without a gap of 60 days or more between injections, medication coverage ratio (MCR) as the proportion of days covered by denosumab, switching to another osteoporosis therapy, and patients not returning for denosumab therapy were assessed during the 8-month follow-up period.

Results: 1,570 patients newly treated with denosumab (mean [SD] age: 69.6 [12.0] years; 98.2% female) were identified. In the pre-index period, an osteoporosis diagnosis as indicated by ICD-9-CM codes was identified in 76.1% of the patients, while 4.0% had a diagnosis code of osteopenia, 7.1% had a diagnosis code of renal insufficiency, and the mean (SD) Charlson Comorbidity Index score was 1.1 (1.5). Pre-index osteoporosis treatment was identified in 57.5% of the patients, and 17.6% had an osteoporosis-related fracture in the pre-index period. During the 8-month post-index period, 70.0% of patients were persistent with denosumab, 1.5% switched to another osteoporosis therapy, and 28.5% did not return for denosumab therapy. The mean (SD) MCR over 8 months was 89% (10%), with 67.4% of patients having an MCR greater than 80%.

Conclusion: Rates of persistence and compliance with denosumab observed in this study appear to be higher than those with other osteoporosis medications reported in previous studies. This study provides real-world evidence on denosumab utilization, and its high rates of persistence and compliance.

Disclosure: E. Durden, Amgen, 5; **L. I. Cheng**, Amgen, 1, Amgen, 3; **E. Eynullayeva**, None; **C. Gregory**, None; **B. Stolshek**, Amgen, 1, Amgen, 3.

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Antinuclear Antibodies Positive But No Autoimmune Disease. M Herold[1] and Werner Klotz[2]. [1]Medical University of Innsbruck, Innsbruck, Austria, [2]Innsbruck Medical University, Innsbruck, Austria.

Background/Purpose: Antinuclear antibodies (ANAs) are tested in sera of patients suspicious of an autoimmune disorder. ANAs are part in many classification criteria of autoimmune (AI) diseases. In healthy individuals ANAs may also be found and are most often anti-DFS70 antibodies (Mahler M et al. Autoimmun Rev 2012;11:642–5). The frequency of anti-DFS70 antibodies was tested in sera of patients who were hospitalized or attended our outpatient clinic.

Methods: 336 consecutive and ANA positive samples were screened on Hep-2 cells for the presence of a typical DFS70 pattern defined as dense fine speckled staining of nucleoli of interphase cells and intensive staining of the condensed chromosomal material in mitotic cells or similar immunofluorescence patterns (e.g. homogenous, fine speckled, combination of homogenous and fine speckled patterns, centromere and others). Presence of anti-DFS70 autoantibodies was confirmed using a new chemiluminescence immunoassay (CLI; BIO-FLASH - DFS70 Assay; kindly provided by Inova Diagnostics, USA, within an unrestricted research grant).

Results: A pattern indicative of DFS70 autoantibodies could be found in 103 samples; in 82 of them (80 %) presence of anti-DFS70 autoantibodies could be confirmed by the CLIA vs. 9 in 233 samples (4 %) with other patterns. Numbers of other patterns were 70 with fine speckled, 66 homogenous and fine speckled, 43 homogenous, 4 centromere and 50 with mixed or other patterns.

In 298 of 336 patients a clinical diagnoses was found in the medical records. An autoimmune disease was given in 12 out of 78 patients (15 %) with DFS70 pattern (6 with juvenile arthritis, 5 with rheumatoid arthritis, 1 SLE) vs. 86 out of 220 patients (39 %) with other patterns (31 with SLE, 28 with RA, 2 with ANCA-associated vasculitis, 6 juvenile arthritis, 4 Sjogren's syndrome, 4 UCDT, 11 other AI diseases) and 8 out of 71 patients (11 %) with DFS70 autoantibodies in specific immunoassay (3 with juvenile RA, 2 with RA, 2 SLE, 1 patient suspect of MCDT) vs. 88 out of 227 DFS70 negative patients (39 %) (31 with RA, 30 with SLE, 9 juvenile RA, 4 Sjogren's syndrome, 2 UCDT, 12 with other AI diseases).

Conclusion: Anti-DFS70 was most often found (85 %) in people without other signs of an autoimmune disorder.

Disclosure: M. Herold, None; **W. Klotz**, None.

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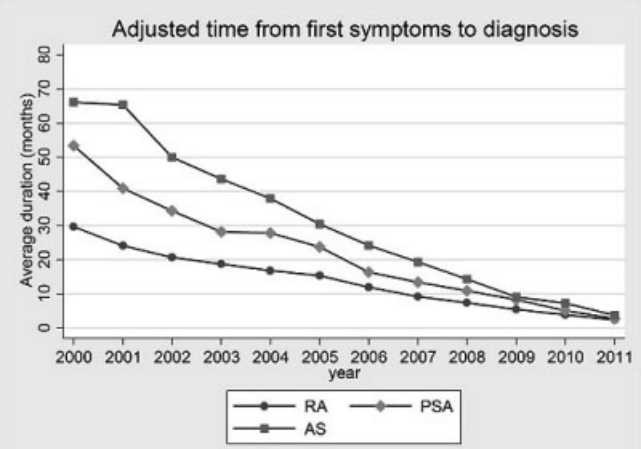
Duration Of Symptoms Before Diagnosis In Patients With Rheumatoid Arthritis, Psoriatic Arthritis and Ankylosing Spondylitis. Merete Lund Hetland[1] and Jan Sørensen[2]. [1]The Danish Rheumatologic Database (DANBIO), Glostrup Hospital., Copenhagen, Denmark, [2]Center for Applied Health Services Research, University of South Denmark, Odensen, Denmark.

Background/Purpose: Early diagnosis is important for the treatment of many rheumatic diseases. Little is known about the duration of symptoms before establishment of diagnosis, and if the delay in diagnosis has changed during recent years. We aimed to study the duration from onset of symptoms to diagnosis in patients with RA, PSA and AS using data from DANBIO from the last 12 years.

Methods: Month and year of initial symptoms and diagnosis, gender, year of birth, hospital and date of first entry into DANBIO were obtained for patients with RA, PSA or AS. Duration from symptom onset to diagnosis was modeled using generalized linear regression. Predicted values represent adjusted mean durations dependent of year of symptom onset. Sensitivity analyses including only patients who had symptom onset less than two (n=4,656) and five years (n=6,663) prior to first entry into DANBIO were performed and showed largely similar results (not shown).

Results: The figure shows the mean duration (in months) from initial symptoms to diagnosis adjusted for gender, age (10 year age groups), year of DANBIO entry, geographical region and social status. The duration from symptom to diagnosis for both RA, PSA and AS declined steadily during the period from 30, 52 and 68 months in year 2000, respectively, to 3–4 months by year 2011. The patients with valid data (RA: 10,737 (73%), PSA: 1,970 (68%), AS: 1,334 (65%)) did not differ significantly from the whole population, except for more missing data in the early years.



Conclusion: Since 2000, a dramatic reduction in the duration from symptoms to diagnosis was observed, probably reflecting a stronger awareness of the importance of early diagnosis.

Disclosure: M. L. Hetland, None; **J. Sørensen**, None.

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Cost-Effectiveness Analysis Of Diagnostic Tests In The Work-Up Of Patients With Intermediate Risk Of Developing Rheumatoid Arthritis. Jolanda J. Luime[1], Maureen Rutten[2], Leander Buisman[2], Mark Oppe[2] and Johanna M.W. Hazes[1]. [1]Erasmus Medical Center, Rotterdam, Netherlands, [2]Erasmus University, Rotterdam, Netherlands.

Background/Purpose: With technological improvements in genomics, cytomics and metabolomics many promising biomarkers for stratifying individuals at risk of developing Rheumatoid Arthritis will enter the market. However, research into the potential cost-effectiveness of applying these biomarkers in actual clinical settings has been lacking. This study shows an initial assessment of cost-effectiveness for 4 different technologies (MRI, il6-serum test, RNA B cell signature, genetic assay) applied to intermediate risk patients (3–5 points on the ACR/EULAR criteria for RA) using a one-year time horizon.

Methods: The cost-effectiveness of the 4 technologies was simulated with a decision model using data from the Rotterdam Early Arthritis Cohort (REACH; prevalence of RA 55%). The comparator was the 2010 ACR/EULAR classification criteria. Test properties (sensitivity, specificity and costs) were based on literature and expert opinion (see table 1). Patients were classified true positive (TP) if they score >=6 points on the criteria or were tested positive and used MTX at 12 months follow-up. True negative (TN) patients were those that scored <6 points, were test negative and did not use MTX at 12 months. Costs included test costs, rheumatology visits and treatment costs. Changes in utilities within 1 year were assigned to TP (+0.1), TN (+0.1), false positive (FP; +0.05) and false negative (FN; −0.05). Outcome assessment included changes in the TP and the FP rate, the diagnostic net reclassification benefit (NB) for intermediate patients, QALYs, costs and ICER.

Results: Table 1 shows the results of the new technologies as add-on test to the ACR/EULAR classification strategy. Given the current test properties, the largest net benefit would be achieved by adding RNA B cell signature with an incremental cost effectiveness ratio of €13,939. To stay below a willingness to pay (WTP) threshold of €20,000/QALY gained (given the current assumptions in utilities) the add-on test strategy for intermediate risk patients can cost €230 at maximum.

Table 1. Test properties and modeling results for the 4 technologies tested in intermediate patients only

	Se	Sp	Price	Δ TP*	Δ FP*	uNB#	QALY	COSTS	ICER
RA2010	0.65	0.76	-	-	-	-	0.66	€1,084	-
MRI	0.90	0.60	€488	13%	13%	0%	0.67	€1,334	€38,541
B cell	0.60	0.90	€150	9%	3%	45%	0.67	€1,163	€13,939
Il6	0.70	0.53	€100	10%	15%	−37%	0.66	€1,148	€17,343
SNP	0.75	0.85	€1000	11%	5%	37%	0.67	€1,571	€70,347

*Difference in TP or FP rate between ACR/EULAR RA2010 and the new test as a % of the total sample; #uNB is the unweighted net benefit ((Δ TP- Δ FP/ diseased intermediate patients)*100%)

Conclusion: When applying new biomarker technologies in patients with intermediate risk of developing RA the largest net benefit would be achieved for RNA B cell signature, a test assigned moderate sensitivity and high specificity. Under the current utility assumptions and a WTP of €20,000/QALY a test strategy would be cost-effective for intermediate risk patients if it costs no more than €230.

Disclosure: J. J. Luime, None; **M. Rutten**, None; **L. Buisman**, None; **M. Oppe**, None; **J. M. W. Hazes**, None.

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Comparison Of Characteristics In Rheumatoid Arthritis Between International and National Databases In Europe: A Systematic Literature Review. E. Gvozdenovic[1], R. Koevoets[1], J. Langenhoff[1], C.F. Allaart[1] and R. Landewe[2]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Academic Medical Center / University of Amsterdam, Amsterdam, Netherlands.

Background/Purpose: RA (Rheumatoid Arthritis) cohorts and registers are established for daily practice in clinical care. There are still differences between registries in disease activity and outcome, despite existing guidelines and international consensus about preferred drug therapies, which might be due to varying definitions for disease, inclusion criteria and variety in usage of biological agents. To improve collaboration between European rheumatologists, EULAR (European League Against Rheumatism) has recently started a repository of databases, which can be used as a platform for researchers to start collaborative projects. Our aim is to evaluate current European inter (national) databases and observational cohorts, and to compare inclusion criteria, aims, collected data and participation in the EULAR repository of databases.

Methods: An extensive search strategy was performed in Pubmed, Web of Science (WOS), Embase, Academic Search Premier, Wiley-Blackwell and LWW. Articles reporting on European inter (national) databases and prospective cohorts in RA with at least half a year of follow-up and >200 patients included were selected. We extracted data on national and international databases with details on aim, size, selection criteria, year of inception, frequency of data collection, physician/clinical evaluation, patient reported outcomes, laboratory information, funding and rheumatologic diseases captured.

Results: In total, 418 articles were included, which described 4 international and 39 national databases and cohorts. International databases were roughly similar and are mostly initiated to monitor and compare clinical patient care among countries. Also no restriction was present in frequency of data collection and selection criteria. The national databases differ in clinical features, such as aims (most registers aimed at efficacy and safety of treatment or monitoring disease activity in clinical practice), distribution among countries (not evenly distributed) and inclusion criteria (e.g. early RA registers versus routine care registers). Half of the national registers were connected to the EULAR repository of databases.

Conclusion: International databases have similar characteristics and the patients represent a large range of clinical activity (from inactive to active) and severity (from mild to severe). Regarding the national databases and cohorts heterogeneity is far greater, relevant differences exist in inclusion criteria, aims, frequency of data collection and distribution among Europe. Also only half of the databases are connected to the EULAR repository of databases. These differences may indicate that among researchers there is little awareness in guidelines to set up registers or cohorts and in the existence of the collaboration network of the EULAR.

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Differing Disease Expression In Latin American Mestizo and Spanish Caucasian Patients With Rheumatoid Arthritis With The Same Access To Healthcare and Antirheumatic Treatment. Virginia Ruiz-Esquide[1], Sonia Cabrera[2], Julio Ramirez[3], M. Victoria Hernández[4], José Inciarte[3], J. D. Cañete[3] and Raimon Sanmarti[4]. [1]Hospital Clinic of Barcelona, Barcelona, Spain, [2]Hospital Clínic, Barcelona, Spain, [3]Hospital Clinic, Barcelona, Spain, [4]Hospital Clínic of Barcelona, Barcelona, Spain.

Background/Purpose: Rheumatoid arthritis (RA) prevalence and clinical phenotype varies between ethnic groups. Few studies have analyzed differences in disease expression between Latin-Americans mestizos (LA) and Caucasians in a population with the same access to healthcare. The purpose of this study is to compare the activity, severity and prognostic factors, of RA in Spanish Caucasians and LA followed at the same Spanish health centre and with the same access to healthcare and antirheumatic therapy.

Methods: Cross-sectional case-control study of RA patients (ACR 1987 criteria) aged 18–65 years attending a specialized RA clinic of a tertiary Spanish hospital between September 2011 and December 2012. For each LA patient, 2 Spanish Caucasians matched by disease duration (± 12 months) were selected. Sociodemographic variables, disease activity, prognostic markers, serology and treatment were collected and compared between the two groups.

Results: Of a total of 314 patients with RA, a sample of 153 RA patients (51 LA and 102 Spanish Caucasians) were finally included. The mean age was 47.3 ± 10 years and 88% were female. Disease duration and age at disease onset was similar between groups. LA had more active disease than Spanish Caucasians as measured by DAS28, number of tender and swollen joints, patient global health assessment or ESR (see table). Remission or low disease activity defined by DAS28 was achieved less frequently by LA

patients (15.7% vs. 40.2%, p=0.002, OR 3.61, 95% CI: 1.54 – 8.47 and 31.3% vs. 56.8%, p=0.003, OR 2.88, 95% CI: 1.42– 5.86, respectively). Disability measured by mHAQ and erosive disease were similar in the two groups. There were no significant differences in the treatment received between groups, although LA patients more frequently received glucocorticoids, synthetic DMARDs and biologic therapy. LA patients more frequently had seropositive RA (rheumatoid factor and/or anti-CCP positive) and were less frequently current and past smokers. Other factors that may be related to disease activity, such as obesity and vitamin D deficiency, were significantly more frequent in LA patients.

Table. Disease activity and disability in Caucasian and Latin American patients with RA.

	Total n=153	Caucasian n=102	Latin American n=51	p
Age at diagnosis	40.11 ± 11.84	40.54 ± 12.04	39.24 ± 11.51	0.523
Disease duration (months)	91.25 ± 93.03	91.13 ± 92.94	91.5 ± 94.14	0.982
Disease duration < 2 years %	33.98%	22.55%	23.53%	0.892
Age at inclusion	47.30 ± 10.59	47.76 ± 10.73	46.37 ± 10.34	0.554
Sex % (female)	88.2%	87.25%	90.2%	0.595
Obesity (BMI > 25)	**57.7%**	**50%**	**72.92%**	**0.009**
Smoker	**51.4%**	**63.27%**	**27.08%**	**0.000**
Anti-CCP+	**84.1%**	**80%**	**92.57%**	**0.053**
RF +	**71.1%**	**65.35%**	**82.35%**	**0.029**
TJC	**3.42 ± 5.02**	**2.36 ± 3.38**	**5.53 ± 6.84**	**0.003**
SJC	**2.72 ± 3.91**	**2.29 ± 3.33**	**3.57 ± 4.8**	**0.057**
PGH	**37.71 ± 19.31**	**34.41 ± 17.89**	**44.31 ± 20.52**	**0.003**
DAS28	**3.5 ± 1.46**	**3.16 ± 1.33**	**4.17 ± 1.49**	**0.000**
Remission DAS28 < 2.6 %	**32%**	**40.2%**	**15.7%**	**0.002**
Low disease activity DAS28 < 3.2 %	**48.4%**	**56.86%**	**31.37%**	**0.003**
Pain VAS	**34.75 ± 26.97**	**30.16 ± 21.64**	**44.74 ± 34.24**	**0.027**
mHAQ	0.374 ± 0.474	0.373 ± 0.45	0.371 ± 0.52	0.986
CRP	0.82 ± 1.22	0.73 ± 1.2	1.01 ± 1.26	0.173
ESR	**21.52 ± 19.16**	**19.44 ± 19.89**	**25.71 ± 17.01**	**0.056**
Hemoglobin	**129.60 ± 12.93**	**132.04 ± 11.81**	**124.68 ± 13.65**	**0.001**
Glucocorticosteroids %	52.9%	48.04%	62.75%	0.086
DMARDs %	82.2%	81.2%	86.75%	0.355
Biologic therapy %	38.2%	36.63%	41.18%	0.586
Erosions %	51.9%	51.09%	53.49%	0.795
Vitamin D	**19.78 ± 10.75**	**21.69 ± 10.64**	**15.88 ± 9.98**	**0.003**

BMI: body mas index, RF: rheumatoid factor, TJC: tender joint count, SJC: swollen joint count, PGH: patient global health asessment, DAS: disease activity index, VAS: visual analogue scale, mHAQ: modified health asnessment quiestionnarie, CRP: C reactive protein, ESR: erythrocyte sedimentation rate, DMARDs: disease-modifying anti-rheumatid drugs.

Conclusion: Latin-American mestizo patients had differing prognostic factors and more active RA than Spanish Caucasian patients, despite having the same access to health care and receiving similar antirheumatic therapy.

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Identifying Groups At Increased Risk Of Developing Rheumatoid Arthritis Using Family History and Genetic Risk Scores. Jeffrey A. Sparks[1], Chia-Yen Chen[2], Xia Jiang[3], Johan Askling[4], Linda T. Hiraki[5], Lars Klareskog[6], Lars Alfredsson[3], Karen H. Costenbader[1] and Elizabeth W. Karlson[1]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Harvard School of Public Health, Boston, MA, [3]Karolinska Institutet, Stockholm, Sweden, [4]Karolinska University Hospital, Stockholm, Sweden, [5]Brigham and Women's Hospital, Harvard School of Public Health, Boston, MA, [6]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: The identification of high risk groups is crucial for RA prevention strategies. Individuals with family history (FH) of autoimmunity are at increased risk for RA. Genetic markers have been associated with RA and genetic risk scores (GRS) have incorporated these markers for RA risk. We aimed to identify groups at increased risk of RA using FH and GRS.

Methods: We investigated the association between FH and GRS and risk of RA in a nested case-control study in the Nurses' Health Study (NHS) and replicated in the Epidemiological Investigation of RA (EIRA). RA cases in NHS were validated by chart review and matched to controls. In EIRA, RA cases at diagnosis were matched to controls. All cases satisfied the 1987 ACR criteria for RA classification and were Caucasian. FH data were obtained from questionnaires (FH of RA or lupus for NHS) and registries (FH of RA for EIRA). Serologic status was defined as +RF/ACPA for NHS and by +ACPA for EIRA. Weighted genetic risk scores (GRS-HLA using 8 HLA shared epitope alleles, and GRS-39 using 8 HLA shared epitope alleles and 31 SNPs associated with RA) were calculated based on prior studies. GRS were dichotomized as high or low based on the 75th percentile of the GRS in controls. The joint effect of low/high GRS and no/any FH was examined using logistic regression models adjusted for matching factors and confounders (age, sex, smoking pack-years, body mass index, alcohol intake, education, parity, and occupational exposures) to estimate odds ratios (OR) and 95% confidence intervals (CI) for all, seropositive/ACPA+, and seronegative/ACPA- RA, with the reference of low GRS and no FH.

Results: We analyzed 492 cases and 501 controls among women in NHS and 1,752 cases and 1,361 controls among men and women in EIRA with available FH data. Compared to low GRS-HLA/no FH, the OR for high GRS-HLA and +FH was 8.56 (95% CI 3.87–18.93) in NHS and 6.17 (95% CI 3.86–9.85) in EIRA for all RA (**Table 1**). The OR for high GRS-39 and +FH was 6.63 (95% CI 3.30–13.31) in NHS and 8.24 (95% CI 4.64–14.64) in EIRA for all RA compared to low GRS-39/no FH (**Table 2**). There were no significant multiplicative interactions between GRS-HLA or GRS-39 and FH.

Table 1. Joint effect of family history (FH) and GRS-HLA for RA phenotypes in the Nurses' Health Study (NHS) and the Epidemiological Investigation of RA (EIRA) study.

		Low GRS-HLA		High GRS-HLA	
	FH	Cases/ controls	OR (95% CI)	Cases/ controls	OR (95% CI)
NHS					
All RA	**None**	252/367	1.0 (Ref)	120/96	1.84 (1.33–2.56)
	Any	78/30	4.04 (2.54–6.56)	42/8	**8.56 (3.87–18.93)**
Seropositive RA	**None**	140/367	1.0 (Ref)	72/96	1.93 (1.31–2.84)
	Any	41/30	3.93 (2.28–6.86)	23/8	**7.59 (3.17–18.16)**
Seronegative RA	**None**	112/367	1.0 (Ref)	48/96	1.72 (1.12–2.61)
	Any	37/30	4.41 (2.55–7.73)	19/8	**10.17 (4.16–24.88)**
EIRA					
All RA	**None**	580/783	1.0 (Ref)	1013/528	2.28 (1.95–2.76)
	Any	39/27	1.98 (1.18–3.32)	120/23	**6.17 (3.86–9.85)**
ACPA+ RA	**None**	214/783	1.0 (Ref)	699/528	4.32 (3.54–5.27)
	Any	22/27	3.04 (1.66–5.55)	93/23	**13.20 (8.03–21.71)**
ACPA-RA	**None**	366/783	1.0 (Ref)	314/528	1.16 (0.96–1.41)
	Any	17/27	1.34 (0.71–2.54)	27/23	**9.50 (3.95–22.83)**

All models are adjusted for age, smoking pack-years, body mass index, alcohol intake, education, and parity. EIRA models are also adjusted for sex and occupational exposures.

Table 2. Joint effect of family history (FH) and GRS-39 for RA phenotypes in the Nurses' Health Study (NHS) and the Epidemiological Investigation of RA (EIRA) study.

		Low GRS-HLA		High GRS-HLA	
	FH	Cases/ controls	OR (95% CI)	Cases/ controls	OR (95% CI)
NHS					
All RA	None	240/349	1.0 (Ref)	132/114	1.65 (1.20–2.27)
	Any	72/27	4.26 (2.63–7.07)	48/11	**6.63 (3.30–13.31)**
Seropositive RA	**None**	129/349	1.0 (Ref)	83/114	1.94 (1.33–2.82)
	Any	35/27	4.09 (2.29–7.39)	29/11	**6.73 (3.12–14.52)**
Seronegative RA	**None**	111/349	1.0 (Ref)	49/114	1.33 (0.87–2.02)
	Any	37/27	4.77 (2.72–8.48)	19/11	**6.39 (2.86–14.30)**
EIRA					
All RA	**None**	826/984	1.0 (Ref)	767/327	2.43 (2.06–2.87)
	Any	56/36	1.70 (1.09–2.66)	103/14	**8.24 (4.64–14.64)**
ACPA+ RA	**None**	370/984	1.0 (Ref)	543/327	3.86 (3.18–4.68)
	Any	35/36	2.43 (1.47–4.01)	80/14	**14.20 (7.82–25.75)**
ACPA-RA	**None**	456/984	1.0 (Ref)	224/327	1.32 (1.07–1.62)
	Any	21/36	1.17 (0.672.07)	23/14	**3.65 (1.83–7.26)**

All models are adjusted for age, smoking pack-years, body mass index, alcohol intake, education, and parity. EIRA models are also adjusted for sex and occupational exposures.

Conclusion: Using genetic risk scores and family history, we have identified groups at increased risk of developing RA. Genetic risk scores utilizing only HLA shared epitope alleles performed similarly to genetic risk scores incorporating a larger set of genetic markers for RA. Genetic testing, particularly HLA shared epitope alleles, among those with family history may identify groups at increased risk for RA.

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Sugar-Sweetened Soft Drink Consumption and Risk Of Developing Rheumatoid Arthritis In Women. Yang Hu[1], Karen H. Costenbader[2], Frank Hu[3], Daniel H. Solomon[4], Elizabeth W. Karlson[2] and Bing LU[5]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [3]Harvard School of Public Health, Boston, MA, [4]Harvard Medical School, Brigham and Women's Hospital, Division of Rheumatology, Division of Pharmacoepidemiology, Boston, MA, [5]Brigham & Women's Hospital and Harvard Medical School, Boston, MA.

Background/Purpose: Sugar-sweetened soft drink (SSSD) consumption is associated with weight gain, obesity, and increased risk of t*ype 2 diabetes (T2DM)* and cardiovascular disease (CVD). Previous studies have found that obesity may increase risk of rheumatoid arthritis (RA), while T2DM and CVD may share common pathways with RA development. We aimed to examine the relationship between SSSD intake and incident seropositive RA or incident seronegative RA in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II), two large prospective cohort studies.

Methods: The NHS was established in 1976 and enrolled 121,701 US female registered nurses, ages 30–55 years. The NHS II was initiated in 1989 and comprised 116,430 female registered nurses, aged 25–42 years. RA cases were initially self-reported then confirmed by medical record review for 1987 ACR criteria. Seropositive RA was defined as positive RF or ACPA. SSSD consumption (colas and carbonated non-cola, but not low-calorie soft drinks) was assessed with a validated food frequency questionnaire (FFQ) completed every 4 years from 1980–2006 in NHS and 1991 – 2009 in NHS II. To reduce the measurement error and the potential reverse causality bias, we calculated average values from the preceding SSSD measures excluding the most recent dietary record. Time-varying Cox models were used to study the association between SSSD consumption and risk of seropositive and seronegative RA after adjusting for potential confounders. Pooled hazard ratio estimates from the two cohorts were calculated using a fixed effects model

Results: During the 1,906,661 person-years of follow-up from 1980 to 2008 in NHS, 366 seropositive and 215 seronegative RA cases were confirmed, and during 1,524,433 person-years from 1991 to 2009 in NHS II, 197 seropositive and 105 seronegative RA cases were confirmed. In the pooled analysis after adjusting for age, smoking, alcohol, BMI, reproductive factors, physical activity, multivitamin use,, diet quality, and diabetes history, we found a significant positive association between SSSD and increased risk of seropositive RA (P for trend 0.005); women consuming ≥1 serving of SSSD per day had 1.71 (95% confidence interval 1.23–2.38) fold increased risk of developing seropositive RA compared to those consuming none or less than 1 serving per month (Table). However, we did not find any significant association between SSSD and seronegative RA in both cohorts.

Table. Hazard ratios for incident seropositive RA according to sugar-sweetened soft drink consumption in Nurses' Health Study (NHS, 1980–2008) and Nurses' Health Study II (NHS II, 1991–2009)

	<1 serving/ month	1–4 servings/ month	2–6 servings/ week	≥1 serving/ day	*p* for trend
		NHS			
Cases/person-years	144/757,671	75/376,048	116/539,330	31/97,461	
Age-adjusted model	1.00	1.06 (0.80,1.40)	1.17 (0.91,1.50)	1.82 (1.23,2.71)	0.015
Multivariable-adjusted model [a]	1.00	1.09 (0.82,1.45)	1.25 (0.96,1.62)	1.96 (1.29,2.98)	0.006
		NHS II			
Case/person-years	104/806,188	26/220,867	48/365,248	19/103,555	
Age-adjusted model	1.00	0.88 (0.57,1.35)	1.04 (0.74,1.46)	1.55 (0.95,2.53)	0.258
Multivariable-adjusted model [a]	1.00	0.96 (0.62,1.50)	1.10 (0.76,1.60)	1.34 (0.78,2.32)	0.351
		NHS and NHS II pooled [b]			
Age-adjusted model	1.00	1.00 (0.79,1.27)	1.12 (0.92,1.37)	1.71 (1.26,2.33)	0.009
Multivariable-adjusted model [a]	1.00	1.05 (0.82,1.33)	1.20 (0.97,1.49)	1.71 (1.23,2.38)	0.005

a. Adjusted for age, median income (quartiles), cigarette smoking pack-years (never, <20 pack years, ≥20 pack years), alcohol consumption (<5.0, 5.0–15.0, ≥15 grams/day), age at menarche (<12, 12, >12 years), parity and breast feeding (nulliparous, parous/no breastfeeding, parous/1–12 months breastfeeding, parous/ >12 months breastfeeding), hormone use (pre-menopausal, post-menopausal with never use, current use and past use), physical activity (0–3, 3–9, 9–18, 18–27, ≥27 METs/week), multi-vitamin use, healthy eating index (quartiles), body mass index (<20, 20–22.9, 23–24.9, 25–29.9, ≥30kg/m^2), diabetes history and total energy (Kcal, quintiles).
b. P-values for heterogeneity were non-significant (p>0.05) in all pooled estimates

Conclusion: Data from two large prospective cohort studies suggest that regular consumption of SSSD is associated with increased risk of developing seropositive RA in women.

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Posttraumatic Stress Disorder and Risk For Incident Rheumatoid Arthritis. Yvonne C. Lee[1], Susan Malspeis[1], Jessica Agnew-Blais[2], Katherine Keyes[3], Laura Kubzansky[2], Andrea Roberts[2], Karestan Koenen[3] and Elizabeth Karlson[4]. [1]Brigham and Women's Hospital, Boston, MA, [2]Harvard School of Public Health, Boston, MA, [3]Columbia University Mailman School of Public Health, New York, NY, [4]Brigham and Woman's Hospital, Boston, MA.

Background/Purpose: Posttraumatic stress disorder (PTSD) is associated with autoimmune dysfunction, but the relationship between PTSD and the incidence of autoimmune disorders has not been studied prospectively. We examined the prospective association between PTSD and rheumatoid arthritis (RA) risk and tested markers of adverse health behaviors, cigarette smoking and body mass index (BMI), as possible mediators

Methods: The Nurses' Health Study II (NHSII) is a longitudinal cohort of 116,430 female nurses enrolled in 1989 at ages 25–42 years. A subset (N = 50,347) completed the Brief Trauma Questionnaire and the Lifetime PTSD screen, validated questionnaires that include date of worst trauma (proxy for date of PTSD onset). Participants were categorized into 5 groups based on trauma exposure and PTSD symptoms: 1) no trauma (referent), 2) trauma but no PTSD symptoms, 3) trauma and 1–3 PTSD symptoms, 4) trauma and 4–5 PTSD symptoms and 5) trauma and 6–7 PTSD symptoms. Incident RA (N = 185) after 1989 was confirmed by medical record review. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between PTSD and RA risk, adjusted for age, questionnaire year, race and parental education. We also examined the association between PTSD and seropositive and seronegative RA risk. To assess whether BMI and smoking mediated these associations, BMI and smoking measured after PTSD onset were added to the models. To assess whether BMI and smoking were confounders, we performed a subgroup analysis, including variables assessed before PTSD onset (BMI at age 18 and smoking before age 19) among women who experienced PTSD onset after age 20

Results: Compared to women unexposed to trauma, women exposed to trauma and reporting more than 4 PTSD symptoms were at higher risk for incident RA. RA risk increased with increasing number of PTSD symptoms (4–5 PTSD symptoms: HR 1.78, 95% CI 1.03–3.09; 6–7 PTSD symptoms: HR 1.91, 95% CI 1.03–3.56) (**Table**). Results were similar for the association between PTSD and seropositive RA risk (4–7 PTSD symptoms: HR 1.90, 95% CI 1.09–3.33). This trend was also noted in a subanalysis predicting seronegative RA, but the HR was lower and did not reach statistical significance (1.68, 95% CI 0.69–4.08). Both BMI and smoking status attenuated the association between PTSD and incident RA. In secondary analyses among patients who developed PTSD at age > 20, the HR for association with PTSD was lower (HR 1.57, 95% CI 0.56–4.43), but neither BMI at age 18 nor smoking before age 19 changed the HR (HR 1.58, 95% CI 0.56–4.45).

Table. Reported PTSD in the NHSII cohort analysis through 2009 (N = 49,276, including 185 women who developed RA)

Variable	RA cases	Person Years	Age-adjusted PTSD* HR (95% CI)	Multivariate* HR (95% CI)
No trauma, no PTSD symptoms	36	239023	1.00 (REF)	1.00 (REF)
Trauma, no PTSD symptoms	92	462310	1.26 (0.85, 1.85)	1.26 (0.86, 1.86)
Trauma, 1–3 PTSD symptoms	23	107007	1.28 (0.75, 2.16)	1.27 (0.75, 2.15)
Trauma, 4–5 PTSD symptoms	20	65928	1.78 (1.03, 3.08)	1.78 (1.03, 3.09)
Trauma, 6–7 PTSD symptoms	14	42360	1.89 (1.02, 3.53)	1.91 (1.03, 3.56)

*P-value for trend: age-adjusted model: 0.0142, multivariate model: 0.0134
** Cox proportional hazards models, adjusted for age, questionnaire-year, race (Caucasian, non-Caucasian) and parental education (^{2} high school, > high school)

Conclusion: These results suggest that PTSD may increase RA risk. Additional studies are needed to elucidate the pathways by which PTSD is associated with RA risk, specifically to assess whether this association is due to adverse health behaviors, increased reporting and healthcare utilization or alterations in immune pathways due to dysregulated stress response.

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Patients With Regular Physical Activity Before Onset Of Rheumatoid Arthritis Present With Milder Disease. Maria E.C. Sandberg[1], Sara Wedren[2], Christina H. Opava[3], Lars Klareskog[4], Lars Alfredsson[1] and Saedis Saevarsdottir[4]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [3]Karolinska Institutet, Huddinge, Sweden, [4]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Physical activity is a crucial factor in human health; lack thereof is the third most important cause of preventable deaths today. Several biological mechanisms are affected by physical activity and decreasing markers of chronic inflammation have been shown in numerous studies. The aim of this study was to investigate whether the clinical presentation of rheumatoid arthritis (RA) might be affected by physical activity before disease onset.

Methods: Among the cases from the large, population-based, case-control study EIRA, with clinical data from the Swedish Rheumatology Quality Register, we compared patients with regular physical activity 5 years before diagnosis (N=288), to less active patients (N=329), we also investigated a possible dose-response relationship with physical activity in four levels. Logistic regression was used to calculate the odds of having above median level of 28-joint disease activity score (DAS28), physician assessment (5 categories), pain (visual-analog scale, VAS-pain) and activity limitation (health assessment questionnaire, HAQ). The analyses were adjusted for potential confounders (sex, age at diagnosis, period of diagnosis, smoking, body mass index, alcohol consumption, socioeconomic status, vegetable intake and physically demanding work (5 years before diagnosis).

Results: RA patients with *regular* physical activity before diagnosis had statistically significant decreased odds of having DAS28, physician assessment, and/or VAS-pain above median, while HAQ was not affected (see Table). We further found indications of a dose-response relationship for physical activity and DAS28, physician assessment and VAS-pain, for HAQ, however, only in the highest category of physical activity gave an effect (OR= 0.49 [95% CI: 0.24 – 0.99]). Further; statistically significant effects were found both for the combined objective components (swollen joint count, erythrocyte sedimentation rate, C-reactive protein) and combined subjective components (tender joint count, patient global assessment) of DAS28. Neither anti-CCP positivity, body-mass index, sex, physically demanding work nor socioeconomic status modified the observed associations.

	Physical activity at leisure time	Events (N)	OR	95% CI
DAS28 ≥5.3	No regular physical activity	189	1.00	Ref.
	Regular physical activity	122	**0.56**	**0.39–0–82**
Physician assessment >2	No regular physical activity	130	1.00	Ref.
	Regular physical activity	82	**0.62**	**0.42–0.92**
VAS-pain >50	No regular physical activity	181	1.00	Ref.
	Regular physical activity	127	**0.67**	**0.47–0.98**
HAQ ≥1	No regular physical activity	194	1.00	Ref.
	Regular physical activity	142	0.84	0.58–1.23

Conclusion: The findings of this study implicate that RA patients who were physically active before disease onset present with a milder disease according to both patient-reported, physician-reported and laboratory measures. No previous studies have evaluated the influence of physical activity on the clinical presentation of RA. However, DAS28 has been reported to improve after physical activity interventions among established RA-patients, and some trials also reported improvements in VAS-pain and/or HAQ. The results of the present study adds to the growing evidence of the general health benefits of physical activity, and might be an important, helpful message for individuals at increased risk of RA.

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Association Between History Of Periodontitis and Risk Of Rheumatoid Arthritis In Individuals With and Without Diabetes Mellitus: A Population-Based Cohort Study. Hsin-Hua Chen[1], D.Y. Chen[2] and Nicole Huang[1]. [1]National Yang-Ming University, Taipei, Taiwan, [2]Taichung Veterans General Hospital, Taichung, Taiwan.

Background/Purpose: To examine whether the association between periodontitis (PD) history and the rheumatoid arthritis (RA) risk differs between individuals with and without diabetes mellitus (DM)

Methods: We conducted a population-based retrospective cohort study using the 1997–2009 National Health Insurance (NHI) claims data of one million representative individuals from all NHI enrollees. Adults with DM (aged ≥20 years) newly treated during 2001–2009 were classified as DM subjects and those without a DM diagnosis during 1997–2009 were classified as non-DM subjects. We identified 7097 DM subjects with PD history within one year before initiating anti-diabetes treatment (index date). By matching these 7097 subjects for age on the index date, sex, and year of the index date, we randomly extracted 14,194 DM subjects without PD history, 14,194 non-DM subjects with PD history, and 28,388 non-DM subjects without PD history. Adjusted hazard ratios (aHRs) with a 95% confidence interval (CI) were calculated by applying Cox proportional hazards models to quantify the association between PD history and RA risk.

Results: Compared with subjects without PD history, the adjusted HR of RA among those with PD history was 2.26 (95%CI, 1.26–4.04). In subgroup analysis, this association was evident among DM subjects (aHR, 3.77; 95%CI, 1.48–9.60) but not among non-DM subjects (aHR, 1.56; 95%CI, 0.73–3.37; *P* for interaction 0.212).

Conclusion: The effect of PD exposure on RA risk was evident in newly treated DM subjects but not in non-DM subjects; no significant modifying effect of DM was observed.

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Lack Of Association Between Preclinical Markers For Cardiovascular Disease and Rheumatoid Arthritis-Related Autoimmunity In First-Degree Relatives Without Rheumatoid Arthritis. Jill M. Norris[1], Ryan W. Gan[1], Jan M. Hughes-Austin[2], Kevin D. Deane[3], M. Kristen Demoruelle[3], Elaine M. Urbina[4], Kerrie Moreau[3], Peter K. Gregersen[5], Michael H. Weisman[6] and V. Michael Holers[3]. [1]Colorado School of Public Health, Aurora, CO, [2]University of California, San Diego, La Jolla, CA, [3]University of Colorado School of Medicine, Aurora, CO, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]Feinstein Institute for Medical Research, Manhasset, NY, [6]Cedars-Sinai Medical Center, Los Angeles, CA.

Background/Purpose: Rheumatoid arthritis (RA) is characterized by systemic inflammation and immune dysregulation, including the presence of autoantibodies and elevated inflammatory biomarkers in subjects with classifiable RA as well as prior to the development of clinically-apparent RA. In addition, the risk for cardiovascular disease (CVD) is greatly increased in patients with RA, with autoantibodies and systemic inflammation believed to be major contributors to the pathogenesis of CVD. Furthermore, the increased risk for CVD may precede the development of classifiable RA, leading to the hypothesis that autoantibodies and systemic inflammation are influencing the development of CVD in subjects even prior to the onset of joint symptoms in RA. The Studies of the Etiology of RA (SERA) demonstrated previously an association between autoantibody positivity and increased levels of circulating cytokines in subjects without RA but at elevated risk for future RA, as they are first-degree relatives (FDRs) of probands with RA. We utilized SERA FDRs to test the hypothesis that CVD may be apparent in subjects at-risk for future RA, and related to the presence of RA-related autoantibodies.

Methods: Eighty-six autoantibody positive and negative FDRs from the larger SERA cohort were evaluated after a 10-hour fast for the following measures related to CVD: carotid intima media thickness (cIMT), carotid stiffness, flow-mediated dilation (FMD) of the brachial artery, abdominal adipose tissue using computed tomography (CT), blood pressure, lipids, lipoproteins and adipokines. Levels of these pre-clinical CVD phenotypes were log-transformed and compared by current autoantibody positivity status using mixed linear models to account for varying group sizes, adjusting for age, sex and ever smoked status.

Results: Nineteen FDRs were positive for anti-cyclic citrullinated peptide (either CCP2 or CCP3.1), 22 FDRs were positive for rheumatoid factor (RF) (either RF by nephelometry, or RF isotype-IgM, IgA, IgG), and 45 were negative for CCP and RF. The ApoB/ApoA ratio differed across autoantibody groups, with the Ab negative FDRs having the highest ratio, indicating increased CVD risk. Otherwise, there were no significant differences in CVD-related measures and current autoantibody status in FDRs (see Table).

Table. CVD-related measures between CCP positive, RF positive and Ab Negative FDRs. Adjusted for age, gender, race, and smoking status; values are back-transformed.

	CCP Positive n=19† Mean (SE)	RF Positive n=22 Mean (SE)	Ab Negative n=45 Mean (SE)	P
Age (years)*	51.42 (3.37)	49.86 (3.72)	53.44 (2.00)	0.67
Sex (% Female)	84.2	77.3	60.0	0.11
Ethnicity (% non-Hispanic white)	84.2	95.5	88.9	0.52
Ever Smoker (% Yes)	21.1	27.3	42.2	0.20
Blood Pressure				
Systolic (mm/Hg)	118.6 (4.1)	115.9 (4.9)	118.1 (2.8)	0.85
Diastolic (mm/Hg)	72.0 (2.5)	69.9 (2.9)	73.6 (1.8)	0.38
Lipids, lipoproteins and adipokines				
LDL (mg/dL)	93.2 (9.0)	82.2 (8.0)	91.2 (7.0)	0.33
HDL (mg/dL)	51.4 (3.8)	50.9 (4.6)	47.0 (2.6)	0.34
Cholesterol (mg/dL)	167.0 (11.3)	161.5 (8.5)	161.5 (8.5)	0.63
Triglycerides (mg/dL)	113.1 (15.5)	105.4 (18.5)	107.2 (11.3)	0.87
ApoB (mg/dL)	78.7 (5.5)	71.6 (4.8)	79.4 (4.3)	0.17
ApoA (mg/dL)	151.0 (6.5)	150.8 (7.1)	141.5 (4.5)	0.17
ApoB/ApoA	**0.53 (0.04)**	**0.48 (0.04)**	**0.58 (0.03)**	**0.02**
Adiponectin (ug/mL)	8.9 (1.6)	9.1 (1.9)	8.9 (1.2)	0.99
Leptin (ug/mL)	15.8 (4.4)	13.6 (4.7)	16.9 (3.5)	0.72
ICAM (ug/mL)	91.8 (11.9)	80.5 (10.6)	106.2 (11.3)	0.06
VCAM (ug/mL)	605.6 (64.3)	599.4 (71.6)	591.8 (59.0)	0.98
E-Selectin (ug/mL)	30.2 (4.3)	36.9 (6.1)	35.7 (3.3)	0.35
Adiposity				
BMI (kg/m^2)	28.8 (1.8)	28.4 (2.3)	29.9 (1.4)	0.68
Subcutaneous Fat Area (cm^2) at L4/5*	362.3 (110.0)	324.5 (74.3)	379.2 (55.0)	0.70
Visceral Fat (cm^2) at L4/5*	155.2 (90.0)	98.9 (36.7)	136.9 (27.0)	0.50
Carotid Intima Medial Thickness (averaged over left and right cIMT)				
cIMT, carotid bulb (max mm)	0.9 (0.07)	1.0 (0.09)	1.1 (0.07)	0.08
cIMT, carotid bulb (avg mm)	0.7 (0.05)	0.8 (0.06)	0.8 (0.05)	0.15
cIMT, common carotid artery (max mm)	0.7 (0.04)	0.7 (0.04)	0.7 (0.03)	0.85
cIMT, common carotid artery (avg mm)	0.6 (0.04)	0.6 (0.03)	0.6 (0.02)	0.69
cIMT, internal carotid artery (max mm)	0.6 (0.06)	0.6 (0.05)	0.7 (0.05)	0.16
cIMT, internal carotid artery (avg mm)	0.5 (0.04)	0.5 (0.03)	0.5 (0.03)	0.19
Measures of Carotid Stiffness				
Peterson's Elastic Model (mmHg)	413.4 (48.9)	379.3 (53.5)	423.4 (44.9)	0.66
Circumferential Arterial Strain (no units)	0.1 (0.01)	0.1 (0.02)	0.1 (0.01)	0.84
Beta Stiffness Index (no units)	4.3 (0.5)	4.1 (0.5)	4.4 (0.4)	0.75
Elastic Modulus, Incremental (mmHg)	1873.8 (286.3)	1688.2 (292.1)	1909.5 (270.5)	0.69
Young's Elastic Pressure Modulus (mmHg/mm)	355.2 (49.3)	327.0 (51.9)	361.4 (48.2)	0.75
Arterial Compliance (mm^2/mmHg)	0.1 (0.01)	0.1 (0.01)	0.1 (0.01)	0.34
Flow Mediated Dilatation (FMD) (Δ%)**	6.6 (1.7)	6.7 (1.4)	5.7 (0.9)	0.58

*Sample size reduced as not everyone participated in CT scan (CCP n=5, RF n=16, Ab- n=28).
**Sample size reduced as not everyone was measured for FMD (CCP n=11, RF n=13, Ab- n=20).
† 11 CCP positive cases were also positive for RF.

Conclusion: This analysis suggests that CCP and RF positive FDRs did not have worse biochemical, structural or functional indicators of vascular health compared to autoantibody negative FDRs, which is contrary to our *a priori* hypothesis. These results tentatively indicate that the increased risk for CVD that is seen in RA is not detectable in the early preclinical autoantibody phase of the disease, using the biochemical, structural or functional vascular changes measured herein. It is possible that the increased CVD risk seen in RA is manifested outside of these pathways and other mechanisms/measures should be explored.

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Postmenopausal Hormone Therapy and The Risk Of Rheumatoid Arthritis: Results From The Swedish EIRA Study. Cecilia Orellana[1], Saedis Saevarsdottir[1], Lars Klareskog[2], Lars Alfredsson[1] and Camilla Bengtsson[1]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden.

Background/Purpose: The importance of hormonal/reproductive factors has been hypothesized to contribute to the risk of Rheumatoid arthritis (RA), but the literature is somewhat contradictory. The use of postmenopausal hormone (PMH) has previously been observed to provide increased [1], decreased [2], as well as no association [3] with the risk of RA. The aim of the present work was to study the association between the use of PMH and the risk of developing RA in postmenopausal women (aged 50–70), by stratifying the cases according to presence/absence of antibodies to citrullinated peptides (ACPA).

Methods: Data from the Swedish population-based EIRA (Epidemiological Investigation of RA) case-control study was analyzed. In total, 380 incident postmenopausal female cases, aged 50–70 years, and 780 randomly selected controls (matched by age and residential area) were included between 2006–2009. Of the cases, 239 (62.9%) were ACPA-positive. The use of PMH was assessed by means of an identical questionnaire answered by the participating cases and controls. Current and past users of PMH were compared with never users to obtain odds ratios (ORs) with 95% confidence intervals (CI) by means of unconditional logistic regression models.

Results: A decreased risk of developing ACPA-positive RA was observed among current users compared with never users of PMH (OR 0.5, 95% CI 0.3–0.9). Among past users of PMH no association was found when comparing with never users (OR 1.2, 95% CI 0.8–1.7). For ACPA-negative RA no association was found among current (OR 1.0, 95% CI 0.6–1.8) or past (OR 1.2, 95% CI 0.8–2.0) users of PMH.

Conclusion: Our results indicate that current use of PMH is associated with a decreased risk of ACPA-positive RA in postmenopausal women aged 50–70, but has no association with the risk of ACPA-negative RA. The striking difference in the results for ACPA-positive and ACPA-negative RA adds further evidence to the notion that RA consists of two different entities with partly different etiology. Further research is needed in order to explore the biological mechanisms behind our findings.

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ACR Poster Session A
Fibromyalgia, Soft Tissue Disorders and Pain I
Sunday, October 27, 2013, 8:30 AM–4:00 PM

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The Controversies and Points Of Debate That Remain a Challenge For Fibromyalgia Care. Mary-Ann Fitzcharles[1], Peter A. Ste-Marie[1], Don L. Goldenberg[2], John X. Pereira[3], Susan Abbey[4], Manon Choinière[5], Gordon Ko[6], Dwight E. Moulin[7], Pantelis Panopalis[1], Johanne Proulx[8] and Yoram Shir[1]. [1]McGill University Health Centre, Montreal, QC, [2]Newton-Wellesley Hosp, Newton, MA, [3]University of Calgary, Calgary, AB, [4]University of Toronto, Toronto, ON, Canada, Toronto, ON, [5]University of Montreal, Montreal, QC, [6]University of Toronto, Toronto, ON, [7]University of Western Ontario, London, ON, [8]Patient Representative, Montreal, QC.

Background/Purpose: Fibromyalgia (FM) continues to present challenges for the health care community, with perceptions of disease and attitudes of physicians being highly polarized. Neurophysiologic studies provide reassurance of validity of FM, but clinical care remains dependant on the traditional "art of medicine". In the process of formulating Canadian guidelines for care of FM patients, debate was generated on a number of highlighted clinical issues (1). This report examines these contentious issues in order to provide insight regarding challenges surrounding FM.

Methods: In developing evidence based guidelines for the clinical care of FM, 11 of 60 recommendations did not achieve 80% approval at the first round of voting by a nationwide multidisciplinary health care panel. Modifications according to panel input were made and resubmitted for a second voting, at which time all passed, and form the basis of this report.

Results: Contention was seen in the following areas. *1. Criteria for diagnosis*: The healthcare community remains fixated on application of diagnostic criteria, the absence of which causes uncertainty. The tender point count (TPC) remains entrenched in clinical practice. Agreement was obtained by recommending that the 2010 ACR criteria *may be used* to validate a clinical diagnosis, and TPC may be done by choice, but neither is required for diagnosis. *2. Treatments*: Initial recommendation to *discourage use* of complementary and alternative medicine (CAM) treatments in absence of evidence for efficacy was modified to emphasize *lack of evidence to support* CAM use, thereby allowing for individual choice. Although antidepressants in all classes have shown some efficacy, individual bias favoured the newer serotonin norepinephrine reuptake inhibitors. Resolution was achieved by recommending that the specific choice be tailored to the patient according to physicians' knowledge and evidence for efficacy. *3. Terminology:* Recommendation to change the terminology of antidepressants and anticonvulsants to pain modulators was rejected in favour of promoting their pain modulating effects rather than a nomenclature change. *4. Past/triggering events:* Causation in FM is contentious with experts recommending acknowledgement of previous negative lifetime events, but without excessive emphasis on its importance. *5. Work and disability:* Recommendation to remain in the workforce was softened to state that continued work is ideal, with application of a rehabilitation program to improve function and *possible* return to work.

Conclusion: The healthcare community must adopt a rational and unified approach to the management of FM to dispel false notions that hinder management. The abundance of anecdotal literature, strong advocacy from various groups and the subjective nature of FM symptoms may all have played a part in diagnosis and treatment uncertainty. These guidelines reflect the available evidence with clinically applicable input from health care workers from various disciplines and adhere to strict standards of development. Continued dialogue will help dispel misperceptions and facilitate optimal patient care.

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Routine Assessment Of Patient Index Data 3 In Fibromyalgia: A Rapid and Reliable Instrument For Evaluating Disease Severity? Ece Kaptanoglu, Ozlem Sahin, Yunus Durmaz, Ahmet Kivanc Cengiz and Sami Hizmetli. Cumhuriyet University, Sivas, Turkey.

Background/Purpose: Routine Assessment of Patient Index Data 3 (RAPID 3) is a patient based questionnaire which was designed for evaluation of disease activity without formal joint counts for rheumatoid arthritis (RA) for busy clinical settings. Besides RA, it's usage is being serached for some other diseases, too. We aimed to search the effectiveness of RAPID 3 in evaluating severity of fibromyalgia (FM) which is a generalized pain syndrome sharing many symptoms of RA like stiffness and fatigue besides many somatic symptom.

Methods: 38 female volunteered patients with FM were involved in the study. All patients were requested to complete the RAPID 3, Fibromyalgia Impact Questionnaire (FIQ), Revised Fibromyalgia Impact Questionnaire (FIQR) and FM symptom severity scale.

Results: Mean age of the patients were 46±10,9 years and the mean disease duration was 4,8±3.8 years. There were significant correlations between RAPID 3 and FIQR (r=0.598 p=0.000), symptom severity (r=0.573 p=0.000), FIQ total (r=0.742 p=0.000) and subgroups of FIQ (FIQ physical impairment r=0.434 p=0.007, feel good r=0.524 p=0.001, work missed r=0.577 p=0.000, do work r=0.634 p=0.000, pain r=0.733 p=0.000, fatigue r=0.045 p=0.005, stiffness r=0.492 p=0.002, anxiety r=0.378 p=0.019, depression r=0.398 p=0.013 except rested r=0.197 p=0.236. The correlation of FIQR and FIQ total was also good (r=0.763 p=0.000). The correlations of FIQ total and FIQR with symptom severity were r=0.626 p=0.000 and r=0.481 p=0.005 respectively.

Conclusion: RAPID 3 has a good correlation with FIQ, FIQR and symptom severity scale which are gold standarts in follow up of FM. Though it is not a spesific questionnaire for FM, it successfully puts forward the severity of the disease in a quicker and easier way. These preliminary results justify further investigation of the usage of this questionnaire in FM.

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The Symptom Severity In Korean Patients With Fibromyalgia Is Associated With Socioeconomic Status, But Not With Obesity. Dong-Jin Park[1], Shin-Seok Lee[2], Seong-Ho Kim[3], Seong-Su Nah[4], Ji Hyun Lee[5], Seong-Kyu Kim[6], Yeon-Ah Lee[7], Seung-Jae Hong[7], Hyun-Sook Kim[8], Hye-Soon Lee[9], Hyoun Ah Kim[10], Chung-Il Joung[11] and Sang-Hyon Kim[12]. [1]Chonnam National University Medical School, Gwangju, South Korea, [2]Chonnam National University Medical School and Hospital, Gwangju, South Korea, [3]Division of Rheumatology, Inje University College of Medicine, Haeundae Paik Hospital, Busan, South Korea, [4]Soonchunhyang University Cheonan Hospital, Cheonan, South Korea, [5]Maryknoll Medical Center, Busan, South Korea, [6]Catholic University of Daegu School of Medicine, Daegu, South Korea, [7]Kyung Hee University, Seoul, South Korea, [8]Division of Rheumatology, Department of Internal Medicine, Soonchunhyang University of Korea, Seoul, Korea, Seoul, South Korea, [9]Hanyang University Guri Hospital, Guri, South Korea, [10]Ajou University Hospital, Suwon, South Korea, [11]Konyang university hospital, Daejeon, South Korea, [12]Division of Rheumatology, Department of Internal Medicine, Keimyung University School of Medicine, Daegu, South Korea.

Background/Purpose: Fibromyalgia (FM) is a chronic pain disorder characterized by widespread pain, tenderness, and various associated symptoms including sleep disturbances, chronic fatigue, depression, and other somatic symptoms. Several longitudinal and cross-sectional studies in western countries have shown that a high body mass index (BMI) is a strong and independent risk factor for future development of FM and is associated with higher levels of FM symptoms. In addition, obese patients have more physical and emotional impairments compared with nonobese patients. The purpose of this study was to determine whether obesity and socioeconomic factors influence symptom severity in Korean patients with FM.

Methods: A total of 343 patients with FM were recruited from outpatient clinics at 11 medical centers across the Republic of Korea. All patients met the ACR 1990 classification criteria for FM. We interviewed these patients using a structured questionnaire that included sociodemographic data, current or past FM symptoms, and current use of relevant medications at the time of enrollment. Tender point counts and scores were assessed by thumb palpation. Patients were asked to complete a Korean version of the Fibromyalgia Impact Questionnaire (FIQ), the Brief Fatigue Inventory (BFI), the SF-36, the Beck Depression Inventory (BDI), the State-Trait Anxiety Inventory (STAI), the Self-Efficacy Scale, and the Social Support Scale.

Results: Based on an obesity definition of a BMI of ≥25, 76 (22.1%) of the 343 patients were obese. Obese patients were not different from nonobese patients in terms of tender points and scores, FIQ, BFI, SF-36, BDI, STAI, Self-Efficacy, and Social Support scores. After age-, gender-, and symptom duration adjustment by propensity score matching, no significant differences were also found between obese and nonobese patients. However, socioeconomic status such as employment, insurance, and education were significantly associated with symptom severity of FM. The unemployed patients had higher FIQ scores ($p = 0.011$), higher BFI scores ($p = 0.013$), lower physical and mental component SF-36 scores ($p = 0.012$, $p = 0.005$), higher BDI scores ($p = 0.005$), and higher STAI II scores ($p = 0.041$). Lower-income patients had higher FIQ score ($p=0.040$), lower physical and mental SF-36 scores ($p = 0.047$, $p = 0.006$), higher BDI scores ($p < 0.000$), and lower Self-Efficacy scores ($p = 0.016$). Finally, patients with an education of <12 years had higher tender points ($p = 0.034$), higher BDI scores ($p = 0.007$), and higher STAI II scores ($p = 0.045$).

Conclusion: Our findings show that, contrary to Western patients, symptom severity in Korean patients with FM is associated with socioeconomic status, but not with obesity.

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Comparative Burden Of Chronic Widespread Pain and Fibromyalgia In The US Population. Caroline Schaefer[1], Rachael Mann[2], Elizabeth T. Masters[3], Joseph C. Cappelleri[4], Shoshana Daniel[5], Gergana Zlateva[3], Heather McElroy[6], Arthi B. Chandran[3], Edgar H. Adams[1], Annlouise R. Assaf[4], Michael McNett[7], Philip Mease[8], Stuart L. Silverman[9] and Roland Staud[10]. [1]Covance Market Access Services Inc., Gaithersburg, MD, [2]Covance Market Access Services Inc., San Diego, CA, [3]Pfizer Inc., New York, NY, [4]Pfizer Inc., Groton, CT, [5]Covance Market Access Services Inc., Conshohocken, PA, [6]Covance Market Access Services, Sydney, Australia, [7]Aurora Pain Program, Milwaukee, WI, [8]Swedish Medical Center, Seattle, WA, [9]Cedars-Sinai Medical Center, UCLA Center of Excellence, Beverly Hills, CA, [10]University of Florida, Gainesville, FL.

Background/Purpose: Few data exist on the comparative burden of chronic widespread pain (CWP) and fibromyalgia (FM) in the general population.

Methods: 8,382 nationally representative participants (≥18 years old) completed an online screener including sociodemographic questions and the London Fibromyalgia Epidemiology Study Screening Questionnaire (LFESSQ). Subjects who screened positive (bilateral pain, above/below waist, lasting ≥1 week in the past 3 months; CWP+), and a control group without CWP (CWP-) were invited for a site visit for physician evaluation of FM including a tender point exam. Of 1,331 CWP+ and 502 CWP- subjects who consented to be scheduled for a visit, mutually exclusive groups of CWP- (n=125), CWP+ (n=176) and confirmed FM subjects based on physician evaluation (n=171) completed a visit and an online questionnaire to assess clinical characteristics and patient-reported outcomes (including Brief Pain Inventory-short form [BPI-SF], Medical Outcomes Study Sleep Scale [MOS-SS], 12-Item Short Form Health Survey v2 [SF-12], EQ-5D-3L). Statistical significance was tested at the 0.05 level across the 3 groups using ANOVA for continuous variables and chi-square or Fisher's exact test for categorical variables.

Results: Age and race were similar among the 3 groups, but mean body mass index (kg/m^2) increased from CWP- (28.8) to CWP+ (30.7) to FM (32.1) (P=.0044). Among those reporting comorbidities, the mean (SD) number increased from 2.4 (1.6) to 3.2 (2.0) and 4.9 (3.0) for CWP-, CWP+, and FM, respectively (P<.0001), with a corresponding greater prevalence of specific physical conditions (e.g. arthritis, headache/migraine, irritable bowel syndrome; all P<.003) and affective disorders (anxiety, depression; both P<.0001). Pain severity and interference with function progressively increased from CWP- to CWP+ to FM (P<.0001) (Table), including all BPI-SF interference subscales. Sleep quantity and quality significantly differed across the groups as indicated by the MOS-SS total score (Table) and subscales. The EQ-5D-3L and SF-12 showed progressive reduction in health status, and physical and mental health, respectively (Table); all SF-12 domains scores were lowest with FM followed by CWP+ and CWP- (P<.0001). Relative to CWP-, higher proportions of CWP+ and FM groups were taking pain-related prescription medications, 32.8%, 52.8% and 62.6%, respectively (P<.0001); opioids were the single most frequently reported pain medication class.

Table. Comparative Burden in Subjects by Chronic Widespread Pain (CWP) and Fibromyalgia (FM) Status

	Mean (standard deviation)			
Measure	**CWP−**	**CWP+**	**FM**	***P*-value**
	(n=125)	**(n=176)**	**(n=171)**	
BPI-SF[a]				
Pain Severity Index	3.0 (2.1)	4.4 (2.1)	5.5 (2.0)	<.0001
Pain Interference Index	2.5 (2.5)	4.3 (2.6)	5.8 (2.4)	<.0001
MOS-SS total score[a]	32.8 (18.7)	48.2 (18.5)	59.6 (17.5)	<.0001
SF-12[b]				
Physical Component Summary score	48.1 (10.8)	38.9 (11.0)	33.7 (10.5)	<.0001
Mental Component Summary score	49.1 (10.4)	44.9 (10.8)	40.4 (10.8)	<.0001
EQ-5D-3L[b]				
Health state valuation	0.85 (0.13)	0.73 (0.18)	0.61 (0.21)	<.0001
Overall health status rating	79.8 (16.0)	68.7 (18.8)	58.7 (20.0)	<.0001

[a]Higher score=worse outcomes; [b]lower score=worse outcomes

Conclusion: In a nationally representative sample, CWP+ and FM were characterized by a high disease burden relative to CWP- including more comorbidities and pain-related medications, poorer sleep, and reduced function and health status; the burden was highest with FM. Health status observed in FM was lower than has been reported for chronic conditions, such as cancer and diabetes (Luo et al. *Health Outcomes Res Med.*2011;e203–14).

Disclosure: C. Schaefer, Covance Market Access Services, 3; **R. Mann**, Covance Market Access Services, 3; **E. T. Masters**, Pfizer Inc., 3, Pfizer Inc., 1; **J. C. Cappelleri**, Pfizer Inc., 1, Pfizer Inc., 3; **S. Daniel**, Covance Market Access Services, 3; **G. Zlateva**, Pfizer Inc., 1, Pfizer Inc., 3; **H. McElroy**, Covance Market Access Services, 3; **A. B. Chandran**, Pfizer Inc., 1, Pfizer Inc., 3; **E. H. Adams**, Covance Market Access Services, 3; **A. R. Assaf**, Pfizer Inc., 1, Pfizer Inc., 3; **M. McNett**, Pfizer Inc., 5, Lilly, 8, Pfizer Inc., 8; **P. Mease**, Forest Laboratories, 2, Lilly, 2, Pfizer Inc, 2, Forest Laboratories, 5, Lilly, 5, Pfizer Inc., 5; **S. L. Silverman**, Amgen, Lilly, Medtronics and Pfizer/Wyeth, 2, Amgen, Lilly, Pfizer/Wyeth, 8, Amgen, Genetech, Lilly, Novartis, Pfizer/Wyeth, 5, Cedars-Sinai Medical Center, 3; **R. Staud**, Pfizer Inc., 2, Forest Laboratories, 2.

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Rheumatologists Lack Confidence in Their Knowledge of Cannabinoid Molecules and Use in the Management of Rheumatic Disease Patients: Analysis of a Needs Assessment. Mary-Ann Fitzcharles[1], Peter A. Ste-Marie[1], Daniel J. Clauw[2], Shahin Jamal[3], Jacob Karsh[4], Sharon Leclercq[5], Jason J. McDougall[6], Yoram Shir[1], Kamran Shojania[3] and Zach Walsh[7]. [1]McGill University Health Centre, Montreal, QC, [2]University of Michigan, Ann Arbor, MI, [3]University of British Columbia, Vancouver, BC, [4]Ottawa Hosp Riverside, Ottawa, ON, [5]University of Calgary, Calgary, AB, [6]Dalhousie University, Halifax, NS, [7]University of British Columbia, Kelowna, BC.

Background/Purpose: The pharmacologic treatment of chronic rheumatic pain is often sub-optimal, leading patients to seek alternate treatments. Although herbal cannabis (marihuana) has had medicinal use for pain management for centuries, scientific study of cannabinoid effects is recent. With patient advocacy for access to cannabinoids, regulatory bodies worldwide are considering the merits of legalizing medical cannabis. As arthritis is cited as a common reason for medical cannabis use, rheumatologists should be better informed to advise patients. We have assessed rheumatologists' self-reported confidence in their knowledge of cannabinoids and their perceived competence in providing prescriptions.

Methods: Using a 19-question needs assessment survey, sent via email to the entire Canadian Rheumatology Association membership, we have examined rheumatologists' confidence in 1) knowledge of cannabinoids in general, including phyto-, syntheto- and endocannabinoids, and 2) perceived competence and ability to advise patients regarding indications, use and precautions for cannabinoids in general, and herbal cannabis specifically.

Results: 128 (25%) of all 510 members responded. Over three quarters were not confident in their knowledge of cannabinoid molecules, with two thirds reporting poor knowledge of the physiology of the endocannabinoid system. While 45 % of respondents stated no current role for any cannabinoid preparations for rheumatology patients, 70% believe this applies specifically to medical cannabis. Only 16 (13%) had ever previously recommended a trial of medical marihuana. Over 90% were not confident in writing a prescription for medical cannabis when required to indicate dosing, frequency and method of administration. When respondents were grouped as "Confident" in knowledge of cannabinoid molecules (n=33) vs. "Not-Confident" (n=95), the following were reported respectively: Current role for medical cannabis 48% vs. 23%; Previous prescription of pharmacological cannabinoid 33% v.12%; Previous recommendation for medical cannabis 27% vs.7%; No previous recommendation for either 39% vs. 81%; Would not recommend any cannabinoid in future 33% vs. 67%. Only 33% of knowledge confident respondents reported competence in prescribing medical cannabis. Concerns about risks of marihuana use were in line with current literature.

Conclusion: The overwhelming majority of rheumatologists reported lack of confidence in their knowledge of cannabinoids, and uncertainty about their competence to prescribe cannabinoid treatments and herbal cannabis in particular. This survey highlights a major disconnect between patients' advocacy, policy makers and physician need to provide competent patient care within the bounds of medical ethics and deontology. Guidance is required to inform rheumatologists on the prevailing evidence for the safe and effective use of cannabinoids in rheumatic conditions.

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Association Of Rheumatic Diseases With Symptom Severity, Quality Of Life, and Treatment Outcome In Patients With Fibromyalgia. Juan Jiao, John M. Davis III, Ann Vincent, Connie A. Luedtke, Stephen Cha and Terry H. Oh. Mayo Clinic, Rochester, MN.

Background/Purpose: Fibromyalgia is often associated with various comorbid conditions. A high prevalence of fibromyalgia in patients with rheumatic diseases has been reported. Previous studies showed that patients with rheumatoid arthritis (RA) and fibromyalgia had worse RA symptoms, greater disease activity, and worse physical and mental quality of life (QOL) compared with patients who have RA without fibromyalgia. How a comorbidity of rheumatic disease affects symptom severity, QOL, and treatment outcome in patients with fibromyalgia is unknown. This study aims to evaluate the association of rheumatic diseases with symptom severity, QOL, and treatment outcome in patients with fibromyalgia.

Methods: The initial study population consisted of 978 patients who were confirmed to have fibromyalgia and completed the brief multidisciplinary fibromyalgia treatment program (FTP), with emphasis on cognitive behavioral therapy (CBT). We based the present analysis on the 536 patients who returned survey questionnaires during the 6- to 12-month follow-up period (mean follow-up duration was 11.7 months; overall survey response rate, 54.8%). The Fibromyalgia Impact Questionnaire (FIQ) and the Short Form-36 Health Status Questionnaire (SF-36) were completed at initial evaluation and at 6- to 12-months follow-up period. Information about the presence or absence of inflammatory rheumatic disease (IRD) of each participant at initial evaluation in the FTP was collected retrospectively from the electronic medical record by an investigator. Presence of IRD was determined by physician diagnosis. Two-sample *t* test and multivariate regression analyses were performed to compare the rheumatic and nonrheumatic groups.

Results: Thirty-six patients (6.7%) had documented IRDs, with undifferentiated inflammatory arthritis and rheumatoid arthritis being the common IRDs. At baseline, the rheumatic group had poorer scores in SF-36 physical functioning ($P=.02$), pain index ($P=.01$), and physical component summary ($P=.009$) than the nonrheumatic group. After the FTP, both groups tended to improve; however, the rheumatic group had significantly less improvement in the FIQ subscales in pain ($P=.02$) and work missed days ($P=.02$), and in the SF-36 physical functioning ($P=.02$) compared to the nonrheumatic group.

Conclusion: Our findings suggest that IRD is a relatively common comorbidity among patients with fibromyalgia, with a prevalence of about 7% in the study population. Fibromyalgia patients with IRDs have worse SF-36–assessed physical health and pain but not for mental health at baseline compared to fibromyalgia patients without rheumatic diseases. In addition, the rheumatic group demonstrated lower treatment response to the FTP compared to the nonrheumatic group. Our study suggests that our brief FTP based on CBT is less efficacious in patients with fibromyalgia who have IRDs than in those who do not have IRDs. Further studies that seek to identify the relations and the pathophysiologic mechanisms linking fibromyalgia and IRDs will likely advance the understanding of these overlapping chronic conditions.

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Disability In Fibromyalgia Is Associated With Greater Self-Reported Symptoms and Functional Impairment. Emmanouil Rampakakis[1], Mary-Ann Fitzcharles[2], Peter A. Ste-Marie[2], John S. Sampalis[1] and Yoram Shir[2]. [1]JSS Medical Research, St-Laurent, QC, [2]McGill University Health Centre, Montreal, QC.

Background/Purpose: It is intuitive that disablement due to illness should be reflected in illness severity. When illness measurement is based on subjective report only, without objective validation, the reliability of symptom report is crucial and requires critical evaluation. Societal costs for fibromyalgia (FM) are high with disability rates up to 30% reported in the developed world. We have examined clinical characteristics of FM patients currently employed or receiving disability payments.

Methods: Of 246 participants in a tertiary care cohort study of FM patients, 90 were employed, 77 receiving disability payments. Demographic and disease severity measures included: pain visual analog scale (VAS), patient global assessment (PGA), Fibromyalgia Impact Questionnaire (FIQ), Health Assessment Questionnaire (HAQ), McGill Pain Questionnaire (MPQ), Pain Disability Index (PDI), Pain Catastrophizing Scale (PCS), anxiety and depression by Arthritis Impact Measurement Scale (AIMS). Between-group differences in discrete and continuous variables were assessed for statistical significance with the Chi-Square test and the independent-samples t-test, respectively. Linear regression was used to assess between-group differences in disease activity while adjusting for potential confounders.

Results: The prevalence of disablement was 30.8%. Disabled patients were significantly older (49.1 vs. 45.9; $P=0.020$), more likely to smoke cigarettes (33.8% vs. 15.6%; $P=0.006$) or use marijuana (13.0% vs. 3.3%; $P=0.020$). No significant differences were observed in pain duration (10.7 years) and gender (female: 91.0%). Prior/current occupation type differed significantly between groups: disabled patients were more likely previously employed in manual professions or service industry, with employed patients occupied in education/clerical/health fields ($P=0.001$). Significant between-group differences were observed for management strategies: disabled patients used a greater count of medications ($P=0.001$), more opioids ($P=0.001$), antidepressants ($P=0.032$), tranquilizers ($P<0.001$), and cannabinoids ($P=0.053$), and participated less in exercise activity ($P=0.009$). Those disabled demonstrated more allodynia ($P=0.027$) and pain related behaviour ($P=0.002$). Except for depression and anxiety, all other parameters were significantly higher in the disabled group: pain VAS ($P<0.001$), PGA ($P<0.001$), FIQ ($P<0.001$), HAQ ($P<0.001$), MPQ ($P<.0001$), PCS ($P=0.005$) and PDI ($P<0.001$). All associations remained significant except for HAQ, MPQ, and PCS when adjusted for age and education.

Conclusion: The results of this analysis suggest that a significant proportion of FM patients are unemployed due to disability. The subjective report of symptom severity for those disabled may be explained by true disease severity, negative impact of medications, or patient perception of illness and suffering. Alternately, justification for ongoing disablement may be the driver for augmentation of subjective illness report. As all measurements in FM are subjective, disabled patients may be an important confounder for understanding outcome in FM.

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Correlation Of Findings In Clinical and High Resolution Ultrasonography Examinations Of The Painful Shoulder. Raphael Micheroli[1], Diego Kyburz[2], Adrian Ciurea[2], Beat Dubs[3], Martin Toniolo[2], Samuel Bisig[4] and Giorgio Tamborrini[5]. [1]University of Zurich, Zurich, Switzerland, [2]University Hospital of Zurich, Zurich, Switzerland, [3]Sonography Institute Bethanien Zurich, Zurich, Switzerland, [4]Swiss Federal Institute of Technology Zurich, Zurich, Switzerland, [5]Bethesda Hospital Basel, Basel, Switzerland.

Background/Purpose: High resolution ultrasonography (HRUS) is a non-painful and non-invasive imaging technique which is increasingly used for evaluating patients with musculoskeletal disorders. In particular, HRUS is useful for an assessment of shoulder pain causes, as clinical examination often does not allow an exact diagnosis. The aim of this study was to establish the role of HRUS in the diagnosis of shoulder problems as well as to form an evidence base for clinical interpretation of most common clinical tests of the painful shoulder.

Methods: Non-interventional observational study of 100 adult patients suffering from unilateral shoulder pain. Exclusion criteria were shoulder fractures, prior shoulder joint surgery and prior shoulder injections (local anesthetics or steroids) in the past month. The HRUS examination was performed according to the guidelines of the Swiss Society of Ultrasound in Medicine (SGUM, musculoskeletal section). The clinical tests were: bursitis sign, Jobe's test, painful arc, drop arm sign, Hawkins and Kennedy impingement tests, lift off test, belly press test, m. infraspinatus test, acromioclavicular (AC) joint tenderness, Abbott-Saunders test, palm up test, Yergason test and Hueter sign. The physicians performing clinical and HRUS examination were blinded to each other. In the statistical analysis HRUS findings were used as the gold standard.

Results: In the HRUS examination pathologies of the bursa subacromialis were found in 87 %, of the m. supraspinatus tendon in 67 %, of the AC joint in 24 %, of the long biceps tendon in 20 %, of the m. subscapularis tendon in 11 %, of the m. infraspinatus tendon in 10 % and of the m. pectoralis major tendon in 1 % of all cases.

In order to detect pathology of the m. supraspinatus tendon, the Hawkins Kennedy impingement tests showed the highest sensitivity (0.86) whereas the Jobe's test showed the highest specificity (0.55). To identify m. subscapularis tendon pathology the lift off test showed a

sensitivity of 1, whereas the belly press test showed the higher specificity (0.72) as the lift off test (0.55). The m. infraspinatus test showed a high sensitivity (0.90) and specificity (0.74). All three AC tests (painful arc II[a], AC joint tenderness[b], cross body action[c]) showed low sensitivities ([a]0.25, [b]0.38, [c]0.38) but high specificities ([a]0.96, [b]0.99, [c]0.96). To evaluate the long biceps tendon the palm up test showed the highest sensitivity (0.47), the Yergason test showed the highest specificity (0.88).

Conclusion: Knowledge of sensitivity and specificity of various clinical tests is important for the interpretation of clinical examination test results and the identification of cases in which further imaging procedures are necessary to make a distinct diagnosis. Thus, clinical test results should be confirmed by HRUS examination, which allows a reliable differentiation of the various pathologies leading to a painful shoulder.

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Subgrouping Of Rheumatoid Arthritis Patients Based On Pain, Fatigue, Inflammation and Psychosocial Factors. Yvonne C. Lee[1], Michelle A. Frits[1], Christine K. Iannaccone[1], Michael E. Weinblatt[1], Nancy A. Shadick[1], David A. Williams[2] and Jing Cui[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Univ of MI Hlth System-Lobby M, Ann Arbor, MI.

Background/Purpose: Among rheumatoid arthritis (RA) patients, pain may be due to peripheral inflammation or other causes, such as central pain mechanisms. The objective was to use self-report measures and physical examination to identify clusters of RA patients who may have diverse causes of pain and different prognoses and treatment options.

Methods: Data were analyzed from 169 RA patients in a prospective observational study who had any pain > 0/10 and completed questionnaires about pain, fatigue, depression, anxiety, catastrophizing and sleep problems. Systemic inflammation was assessed using serum C-reactive protein (CRP) levels. A hierarchical agglomerative clustering procedure with Ward's method was used to obtain subgroups. Multivariate analysis of variance was used to determine the contribution of each variable in a cluster. General linear regression models were used to examine differences in clinical characteristics across subgroups. Discriminant analyses were performed to determine coefficients for linear combinations of variables that assigned cluster membership to individual cases.

Results: Cluster analyses identified three groups of RA patients (**Figure**). Cluster 1 consisted of the largest number of patients (N = 89, 52.7%) and was characterized by the lowest swollen joint counts and the lowest levels of fatigue and depression (**Table**). Cluster 2 consisted of 57 participants (33.7%), characterized by low swollen joint counts and high levels of fatigue, catastrophizing and sleep problems, indicative of a chronic widespread pain syndrome. Cluster 3 consisted of 23 participants (13.6%), characterized by high swollen joint counts and moderate levels of fatigue, catastrophizing and sleep problems, consistent with active inflammatory disease.

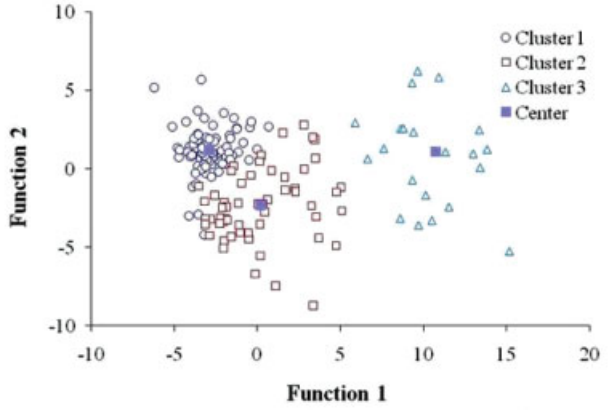

Figure 1. Cluster analyses identified three groups, which were distinguished by two discriminant functions, accounting for 88.3% and 11.7% of the variance (P <0.0001).

Table. Clinical characteristics used to define the clusters. Values are expressed as medians and interquartile ranges.[a]

Characteristic	Cluster 1 (N = 89)	Cluster 2 (N = 57)	Cluster 3 (N = 23)	*P*-value[b]
	0.0 (0.0–1.0)	2.0 (0.0–4.0)[c]	12.0 (10.0–14.0)[d,e]	<0.0001
BPI pain intensity	3.0 (2.0–4.0)	3.0 (2.0–5.0)[c]	3.0 (2.0–5.0)	0.03
Fatigue	20.0 (10.0–30.0)	70.0 (50.0–80.0)[c]	60.0 (25.0–80.0)[d]	<0.0001
Sleep problems	27.2 (16.1–41.1)	38.3 (27.2–46.7)[c]	35.6 (17.5–47.8)	0.009
HADS Depression	3.0 (1.0–5.0)	4.0 (1.0–7.0)[c]	5.0 (2.0–8.0)[d]	0.004
Illness burden[f]	1.0 (0.0–3.0)	2.0 (1.0–3.0)[c]	1.0 (0.0–2.0)[e]	0.06
Catastrophizing	6.0 (1.0–12.0)	12.0 (5.0–21.0)[c]	9.0 (3.0–18.0)	<0.0001

[a]BPI = Brief Pain Inventory, HADS = Hospital Anxiety and Depression Scale.
[b]*P*-value that any one cluster is different from the others.
[c]Cluster 2 is significantly different from cluster 1 at $P \leq 0.05$.
[d]Cluster 3 is significantly different from cluster 1 at $P \leq 0.05$.
[e]Clusters 3 is significantly different from cluster 2 at $P \leq 0.05$.
[f]Illness burden was quantified using a count of patient-reported symptoms of headaches, migraines, poor concentration, poor memory and poor word-finding.

Conclusion: Although most patients had low levels of inflammation, pain and fatigue, 47.3% continued to report moderate to high pain and fatigue. These results indicate that: 1) chronic widespread pain syndromes are common among patients with established RA; 2) active inflammatory disease does not explain all problems with pain, fatigue and psychosocial problems; and 3) chronic widespread pain syndromes are associated with significantly diminished quality of life (assessed by depression, fatigue and sleep problems), even compared to patients with active inflammatory disease.

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Clinical Application Of Pain Diagrams In Fibromyalgia. Amanda Steele[1], Dana Dailey[2] and Kathleen Sluka[2]. [1]University of Iowa Hospitals and Clinics, Iowa City, IA, [2]University of Iowa, Iowa City, IA.

Background/Purpose: Fibromyalgia is a condition characterized by chronic widespread pain. Accurately assessing the subjective experience of pain using objective measures remains a challenging clinical problem, particularly among patients with Fibromyalgia. Commonly utilized self-report pain measures are often time consuming (completing and scoring), potentially decreasing their clinical utility. The current study sought to establish a reliable scoring method of pain diagrams completed by patients with primary fibromyalgia.

Methods: Prior to data collection, IRB approval was received and written consent was obtained. 43 people with fibromyalgia (42 female, 1 male), aged 25–76 years, completed this study (duration of fibromyalgia 7.55 years; range 0.25 to 20 years). Subjects filled out the Fibromyalgia Impact Questionnaire (FIQ), McGill Pain Questionnaire (MPQ) and a visual analog scale (0–10) for pain at rest and movement (walking). Patients were instructed to mark a body diagram showing areas of pain. To assess inter-rater reliability, a scoring protocol, which included applying a transparent overlay to each patient's diagram, was designed and tested. A score of 0–46 was assigned to each diagram, based on the number of areas marked. Ten randomly selected diagrams were scored independently by two raters three times and inter-rater reliability assessed (intraclass correlation, ICC). The number of body areas was correlated with pain, FIQ, and MPQ scores (Pearson's, *p=0.05, **p=0.01).

Results: Means ± SEM: Average pain at rest was 4.39 ± 0.39, pain with movement was 5.23 ± 0.39, FIQ was 58.17 ± 2.24 and MPQ was 44.93 ± 2.5. Scores on the body diagram (n=43) averaged 16.55 ± 1.3 (95% CI 13.92 to 19.18) with the most common areas as neck (91%), shoulders (81%), and low back (63%). Inter-rater reliability for the body diagram scoring was excellent (ICC=0.952; 95% CI 0.912 to 0.974). Higher scores on the body diagram significantly correlated with higher scores on MPQ (R^2= 0.44**), pain at rest (R^2=0.324*), pain with movement (R^2=0.380*) but not FIQ (R^2=0.298).

Conclusion: Preliminary results indicate this protocol may be a reliable method of scoring pain diagrams among patients with Fibromyalgia and that higher scores significantly correlated with worse pain but not the impact of pain on function and quality of life (movement-pain,

FIQ). These diagrams provide a quick, simple and clinically applicable self-report measure that can be completed and scored in a very brief period of time. Thus, quantitative analysis of the body diagram may be useful to gain an understanding of the severity of pain but not the global impact of pain as measured by the FIQ.

Disclosure: A. Steele, None; **D. Dailey**, None; **K. Sluka**, None.

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Frequency Of Axial Spondyloarthropathy Among Patients Suffering From Fibromyalgia A Magnetic Resonance Immaging Study With Application Of The Assessment Of Spondylo-Arthritis International Society Classification Criteria. Jacob N. Ablin[1], Iris Eshed[2], Valerie Aloush[1], Irena Wigler[3], Dan Caspi[1], Maria Likhter[1], Mark Berman[1], Yonatan Wolman[1], Daphna Paran[4], Marina Anouk[5] and Ori Elkayam[3]. [1]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [2]Sheba Medical Center, Tel Hashomer, Israel, [3]Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [4]Tel Aviv Sourasky Medical Ctr, Tel-Aviv university, Tel Aviv, Israel, [5]Tel Aviv Sourasky Medical Ctr, Tel-Aviv University, Tel Aviv, Israel.

Background/Purpose: Fibromyalgia Syndrome (FMS), considered the result of increased processing of pain by the central nervous system, is a non-inflammatory condition characterized by chronic, widespread musculoskeletal pain and tenderness.

Axial spondyloarthritis (SpA) is the hallmark of Ankylosing Spondylitis (AS), an inflammatory joint disease primarily involving the sacroiliac joints and axial spine. Although FMS and axial SpA differ vastly in their pathogenesis, a considerable clinical overlap may exist between these conditions. Chronic nocturnal back pain and disturbed sleep may accompany either condition. We have previously described an increased prevalence of (secondary) FMS among female AS patients. The Assessment of Spondylo-Arthritis international Society (ASAS) has published updated classification criteria for axial SpA. These criteria are based on the evaluation of patients suffering from chronic back pain with an age of onset of less than 45.

Objective: To evaluate the prevalence of axial SpA among FMS patients, utilizing the 2010 ASAS criteria (1).

Methods: Patients suffering from FMS (ACR 1990 classification criteria) were recruited consecutively from a specialized FMS clinic. Patients were interviewed regarding the presence of SpA features, as defined by the ASAS group (Inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn's / colitis, good response to NSAIDSs, family history of SpA) and underwent HLA-B27 testing and CRP measurement. MRI examinations of the sacro-iliac joints were performed on a 1.5 T MRI unit using semicoronal T1-weighted, STIR and FSPGR pre- and post-contrast injection sequences. FMS severity was assessed by the FIQ and SF-36 questionnaires and physical examination of the tender points using a dolorimeter. SpA symptom severity was assessed by the BASDAI questionnaire

Results: 61unselected patients were recruited and MRI results were available for 56.

Table 1. Summarizes MRI findings, HLA-B27 results and ASAS criteria positivity among FMS patients (N=56):

Sacroiliitis (2)	Erosions	Sub-chondral sclerosis	Fatty replacement	HLA-B27	ASAS criteria positive
4 (7.1%)	11 (19.6%)	12 (21.4%)	4 (7.1%)	3 (5.4%)	4 (7.1%)

Sacroiliitis, based on ASAS definition (2), was found among 4 patients, 3 of which fulfilled ASAS SpA criteria. One additional patient fulfilled SpA criteria based on HLA-B27 positivity and additional SpA features.

Conclusion: Imaging changes suggestive of inflammatory SpA were common among patients presenting with a clinical diagnosis of FMS. Definite sacroiliitis and ASAS criteria SpA positivity were diagnosed among 7.1% of patients and additional changes typical of SpA were frequent. These findings suggest that FMS may mask an underlying SpA, a diagnosis with important therapeutic implications. Thus, physicians involved in the management of FMS should remain vigilant to the possibility of underlying inflammatory disorders and actively search for such co-morbidities.

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2. Rudwaleit M et al. Ann Rheum Dis 2009; 68(10):1520

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Identifying Predictors Of A Fibromyalgia Diagnosis: A Retrospective Electronic Medical Record Analysis. Elizabeth T. Masters[1], Jack Mardekian[1], Andrew Clair[1] and Stuart L. Silverman[2]. [1]Pfizer Inc, New York, NY, [2]Cedars-Sinai Medical Center, UCLA Center of Excellence, Beverly Hills, CA.

Background/Purpose: Fibromyalgia (FM) is a chronic pain condition characterized by a constellation of symptoms and comorbidities. Consequently, FM diagnosis can be challenging and it often goes undetected. This study used electronic medical record (EMR) data to identify factors associated with FM that may facilitate earlier identification and diagnosis.

Methods: Subjects ≥18 years old who had ≥1 diagnosis code for common pain conditions were extracted from the Humedica de-identified EMR database, which has broad geographic representation and includes information on demographics, diagnoses, inpatient/outpatient encounters, medications, procedures, lab results, and select data from physicians' notes. Records are linked using a unique patient identifier. Subjects with continuous enrollment in an integrated healthcare delivery system in 2010 and a first FM diagnosis in 2011 (cases) were compared with subjects without an FM diagnosis during 2011 (controls). Patients with an FM diagnosis prior to 2011 were excluded. FM diagnosis was based on ICD-9 code 729.1 (myalgia and myositis, unspecified). Sequential stepwise logistic regression was performed with FM diagnosis as the response variable, and demographic, clinical, and healthcare resource use as predictor variables. Variables with significant associations ($P \leq .05$) were retained in the model and expressed as odds ratios (OR) with their 95% confidence intervals (95% CI).

Results: Subjects were 2,823 individuals with an FM diagnosis and 210,495 without an FM diagnosis in 2011. Although mean (SD) age was similar between groups, 51.4 (15.3) years for cases and 51.4 (16.4) years for controls, the FM population had more females (72.3% vs 60.4%; $P < .0001$), and significant differences between groups were observed for other baseline characteristics including race and healthcare resource use (higher in cases; $P < .001$), and the presence of specific comorbidities (higher in cases; $P \leq .05$). The model identified 17 variables significantly associated with an FM diagnosis. The first variable (i.e., the variable with the smallest p-value when included as a predictor by itself) that made it into the model was the number of pain medication prescriptions (OR 1.03 (95% CI 1.02, 1.04), followed by the number of musculoskeletal pain conditions (OR 1.19 (95% CI 1.16, 1.23). Several clinical variables, including the presence of gastrointestinal and sleep disorders were also predictive: OR 1.38 (95% CI 1.26, 1.51) and 1.33 (95% CI 1.15, 1.55), respectively. Other healthcare resource utilization variables that entered into the model included number of outpatient visits and hospitalizations.

Conclusion: The model identified several demographic and clinical variables as significant predictors of an FM diagnosis. These results suggest analysis of EMR data can help identify variables associated with FM in a real world setting, and may inform earlier identification of FM patients.

Disclosure: E. T. Masters, Pfizer Inc, 1, Pfizer Inc, 3; **J. Mardekian**, Pfizer Inc, 1, Pfizer Inc, 3; **A. Clair**, Pfizer Inc, 1, Pfizer Inc, 3; **S. L. Silverman**, Amgen, Lilly, Medtronics and Pfizer/Wyeth, 2, Amgen, Lilly, Pfizer/Wyeth, 8, Amgen, Genetech, Lilly, Novartis, Pfizer/Wyeth, 5, Cedars-Sinai Medical Center, 3.

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Mindfulness Is Associated With Psychological Symptoms, Self-Efficacy and Quality Of Life Among Patients With Fibromyalgia. Nani Morgan[1], Lucas Morgan[2], Lori Lyn Price[3] and Chenchen Wang[4]. [1]University of Hawaii, Honolulu, HI, [2]University of Massachusetts, Honolulu, HI, [3]Tufts University, Boston, MA, [4]Tufts Medical Center, Boston, MA.

Background/Purpose: Mindfulness is the ability to observe, describe, or be aware of present moment experiences without judgment or reactivity. Preliminary evidence suggests that interventions aimed at increasing mindfulness may be effective in reducing chronic pain as well as symptoms of anxiety and depression commonly experienced among patients with fibromyalgia. Our objective was to evaluate whether mindfulness is associated with the overall impact of fibromyalgia on physical and psychological impairment, sleep quality, self-efficacy, and quality of life.

Methods: We conducted a secondary analysis of baseline data from our randomized trial comparing Tai Chi and aerobic exercise among patients with fibromyalgia as defined by the American College of Rheumatology criteria. Patients enrolled in the trial completed the Five Facet Mindfulness Questionnaire (FFMQ), a 39-item, self-report questionnaire, in which higher total

scores indicating higher levels of mindfulness in daily life. Patients also completed well-validated measures commonly used to assess patients with fibromyalgia (Revised Fibromyalgia Impact Questionnaire [FIQR], Perceived Stress Scale [PSS], Beck Depression Inventory Second Edition [BDI-II], Pittsburgh Sleep Quality Index [PSQI], Arthritis Self-Efficacy Scale Short Version [ASES-8] and Medical Outcomes Short Form-36 [SF-36]). We calculated Pearson's correlation coefficients to evaluate hypothesized associations between mindfulness and measures of fibromyalgia impact on physical and psychological impairment, sleep quality, self-efficacy, and quality of life.

Results: Our analysis included data from 81 patients with an average age of 52.04 (SD=11.92); 92% were female. All correlations were in the hypothesized direction. Patients reporting higher levels of mindfulness tended to report fewer symptoms of anxiety and depression as measured by the PSS ($r=-0.55$, $p<0.0001$) and BDI-II ($r=-0.49$, $p<0.0001$), respectively. They also tended to report higher self-efficacy as well as higher quality of life as measured by the ASES-8 ($r=0.26$, $p=0.02$) and SF-36 Mental Component Summary ($r=0.51$, $p<0.001$), respectively. There were no significant correlations between mindfulness and the FIQR, PSQI, or SF-36 Physical Component Summary.

Conclusion: Our results suggest that mindfulness is associated with psychological symptoms, self-efficacy, and quality of life among patients with fibromyalgia. Mindfulness may help to change patients' relationship to their symptoms and functional limitations through promotion of awareness and acceptance. Longitudinal studies are underway to evaluate whether changes in mindfulness are associated with changes in psychological symptoms, self-efficacy, and quality of life in patients with fibromyalgia and other chronic pain conditions.

Disclosure: N. Morgan, None; **L. Morgan**, None; **L. L. Price**, None; **C. Wang**, None.

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Prevalence and Antecedents Of Fibromyalgia In Elderly Women. Brian T. Walitt[1] and Frederick Wolfe[2]. [1]Washington Hospital Center, Washington, DC, [2]National Data Bank for Rheumatic Diseases, Wichita, KS.

Background/Purpose: Although epidemiological studies demonstrate that fibromyalgia (FM) prevalence increases with age, there have been no large-scale studies of FM in the elderly. In the clinic, elderly subjects usually receive treatment for common problems like diabetes, hypertension, back pain syndromes and other chronic illnesses; and the presence of FM is rarely recognized. In 2013 we performed a pilot study to estimate FM prevalence in the elderly by studying 882 women participants of the Women's Health Initiative (WHI). Because the WHI study is longitudinal, we used prior data to investigate factors that predicted subsequent FM development.

Methods: In 2013, we administered the 2010 modified American College of Rheumatology (ACR) survey criteria questionnaire to 882 randomly selected WHI participants. We utilized a wide range of questionnaire data that had been collected at WHI enrollment 16 years previously, including a range of questions from the SF-36, CESD depression scale, symptoms scales, and other questionnaires. We used logistic regression and baseline variables to predict current FM.

Results: In 2013, the age of participants was 78.4 (SD 6.0) and they had been followed by the WHI for 16.4 years. The (2013) prevalence of fibromyalgia was 6.6% (95% CI 4.9–8.2). The average questionnaire scores in the population were: widespread pain index (WPI, 2.8 (2.8)), the symptom severity scale (SS, 2.9 (2.3), and the polysymptomatic distress score (PSD - sum of WPI and SS) 5.7 (4.3). To identify predictors of FM at initiation, we first excluded possible FM cases (15%) at study onset from further analysis if they reported moderate or severe body pain during the past 4 weeks. Of the remaining 746 subjects, the 2013 FM prevalence was 4.7% (3.1–6.2). In univariate analyses the following variables predicted FM 16 years later: social function, physical function, body pain, pain interference, general health, energy/fatigue, sadness in last two weeks, upset stomach, depression, headaches, low back pain, neck pain, diarrhea, aches and pain, constipation, and tiredness. In multivariate analyses, the following variables were included after backward stepwise regression filtering: constipation, pain severity, general health, energy/fatigue, neck pain, pain interference, and aches and pains. The area under the ROC for the final logistic model was 0.85.

Conclusion: Fibromyalgia (by criteria) was common in WHI participants as they approached 80 years of age. FM appeared to develop primarily in those baseline pain, aching, fatigue, impaired general health, and GI symptoms. Psychological factors did not seem to be important predictors.

Table 1. Multivariable baseline predictors of fibromyalgia

Variable	Odds Ratio	P-Value	95% CI
Constipation (Y/N)	2.92	0.005	1.37, 6.25
Neck pain (Y/N)	3.57	0.002	1.59, 8.04
Pain interference (Y/N)	3.09	0.088	0.85, 11.30
SF-36 General Health	0.97	0.052	0.95, 1.00
SF-36 Energy/fatigue	0.98	0.019	0.96 1.00
SF-36 pain	1.05	0.042	1.00, 1.00
Aches and pains			
Aches and Pains-Mild	3.44	0.120	0.72, 16.39
Aches and Pains-Moderate or >	13.22	0.004	2.24, 77.99

Disclosure: B. T. Walitt, None; **F. Wolfe**, None.

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Relation Of Age With Symptom Severity and Quality Of Life In Patients With Fibromyalgia. Juan Jiao, Ann Vincent, Connie A. Luedtke, Stephen Cha and Terry H. Oh. Mayo Clinic, Rochester, MN.

Background/Purpose: The relationship of age and fibromyalgia symptom severity and quality of life (QOL) is still debated. Reports range from no differences between patients younger and older than 60 years, to less symptom burden in older patients, and worse symptoms as well as QOL in older patients with fibromyalgia. The goals of this present study were to examine the relationship of age with symptom severity and QOL in patients with fibromyalgia and to compare QOL in physical and mental health of our female patients with the female general population.

Methods: Nine hundred seventy eight patients with fibromyalgia who presented to a tertiary care fibromyalgia clinic were divided into 3 age groups: young (≤ 39 years), middle-aged (40–59 years) and older (≥60 years). They completed the Fibromyalgia Impact Questionnaire (FIQ) and the Short Form-36 Health Status Questionnaire (SF-36) at the time of their evaluation. A standardization of the SF-36 physical and mental component summaries of our female patients was made in accordance with the normative data from the US female general population. One-way ANOVA and Post Hoc pairwise *t*-tests analyses were performed to detect differences across age-groups.

Results: The mean age of 978 patients was 48.6 years (range, 19 to 87 years). Our patients age distribution in young, middle-aged and older were 233 (23.8%), 560 (57.3%), and 185 (18.9%), respectively. The young and middle-aged patients were more likely to be unmarried, employed, and current smokers, and to have a higher education level and more abuse history, a lower BMI, and a shorter duration of symptoms compared with the older patients. Pairwise comparison within 3 age-groups showed the young and middle-aged patients having worse fibromyalgia symptoms in the FIQ total score and all subscales except for the anxiety subscale when compared to the older patients ($Ps \leq 0.014$). Similarly, those young and middle-aged patients had worse QOL in the SF-36 mental component summary, as well as SF-36 general health perceptions, vitality, social functioning, and mental health index compared to the older patients ($Ps < 0.001$). When QOL of our female patients was compared to the U.S. female general population of similar age, all age groups had lower QOL in physical as well as mental health with more prominent reduction on physical health, particularly in the young patients.

Conclusion: Our study illustrates that symptom severity and QOL differs across age-groups in patients with fibromyalgia. Young and middle-aged patients had poorer QOL and worse fibromyalgia symptoms compared to older patients. When the QOL of our female patients was compared with the US female general population of similar age, all age-groups had lower QOL in physical as well as mental health, particularly on physical health in the young patients. Further studies are needed to demonstrate the physiologic and pathological mechanisms underneath this phenomenon in patients with fibromyalgia according to age.

Disclosure: J. Jiao, None; **A. Vincent**, None; **C. A. Luedtke**, None; **S. Cha**, None; **T. H. Oh**, None.

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Cross-Sectional Neurocognitive Data Do Not Support a Transition From Fibrofog To Alzheimer's Disease In Fibromyalgia Patients. Robert S. Katz[1] and Frank Leavitt[2]. [1]Rush Medical College, Chicago, IL, [2]Rush University Medical Center, Chicago, IL.

Background/Purpose: The issue of progressive decline in cognitive abilities is a source of concern to many patients with fibromyalgia. The fear

of progressing from fibrofog in middle age to Alzheimer's or other forms of dementia is central to the worries shared by many. To determine if cognitive impairment progresses over time in fibromyalgia, a cross sectional study of cognitive functioning was conducted with a battery of neuro-cognitive tests known to be sensitive to cognitive change.

Methods: In a cross-sectional study, cognitive disparities on 14 neuro-cognitive measures were evaluated in two cohorts of fibromyalgia subjects who met the new criteria for fibromyalgia. The first cohort contained 69 subjects with a short duration of cognitive problems (12 months or less). The second cohort contained 39 subjects with a long duration of cognitive problems (≥ 84 months or greater).

Results: The two groups were similar in terms of mean (±SE) education (15.0±2.2 vs. 14.9±2.5), Vocabulary Scale score (11.2 ± 2.3 vs. 11.9 ± 2.8), and depression (17.5±9.4 vs. 17.8±9.3). The Long Duration Cohort was significantly older (45.6 ± 10.8 vs. 52.3± 9.1 years; $p<0.001$). Cognitive data of the two cohorts are displayed in Table 1. No significant differences were found between the two duration derived cohorts on 13 of the 14 cognitive measures. Performance declined with the duration of cognitive problems on Trails A, a measure of spatial scanning and cognitive sequencing. However, the skills of Trails A are incorporated inTrails B, where performance of the two groups was essentially equivalent. Measures of episodic memory and processing speed, markers of preclinical Alzheimer's disease, are in the normal range for both cohorts

Conclusion: Fibromyalgia patients' fear of developing Alzheimer's or other forms of dementia was not borne out by the data. Duration of cognitive problems was not a determiner of cognitive severity. People with a duration of 84 months or greater were not significantly more cognitively disabled than those with a duration of 12 months or less. The data do not support later transitions to dementia. The fact that individuals suffering cognitive dysfunction from 7 to 26 years did not exhibit a broad based deficit relative to those suffering cognitive dysfunction for a duration of a year of less should allay the worries of many with fibromyalgia who fear that fibrofog in the middle years is the start of a dementing process.

Disclosure: R. S. Katz, None; **F. Leavitt**, None.

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Lower Socioeconomic Status Associates With Increased Symptom Severity and Functional Impairment In Fibromyalgia. Mary-Ann Fitzcharles[1], Emmanouil Rampakakis[2], Peter A. Ste-Marie[1], John S. Sampalis[2] and Yoram Shir[1]. [1]McGill University Health Centre, Montreal, QC, [2]JSS Medical Research, St-Laurent, QC.

Background/Purpose: Persons with lower socioeconomic status (SES) have poorer health status for many medical conditions. Reasons for this finding are multiple, but access to care, health related behaviours and adherence likely play a role. As fibromyalgia (FM) is a clinical construct with psychosocial implications, it is possible that SES may influence symptom expression and severity. We have examined the effects of SES (measured as proxy by level of education) for disease severity in a cohort of FM patients.

Methods: In a prospective cohort study of patients with FM followed at a tertiary care multidisciplinary clinic, patients were stratified according to education level: high school or less (Group 1; N=99), college (Group 2; N=84), and university (Group 3; N=63). Demographic and disease severity measures included pain visual analog scale (VAS), patient global assessment disease activity (PGA), Fibromyalgia Impact Questionnaire (FIQ), Health Assessment Questionnaire (HAQ), McGill Pain Questionnaire (MPQ), Pain Disability Index (PDI), Pain Catastrophizing Scale (PCS), and anxiety and depression by Arthritis Impact Measurement Scale (AIMS). Between-group differences in discrete and continuous variables were assessed for statistical significance with the Chi-Square test and one-way analysis of variance, respectively. Linear regression was used to assess between-group differences in disease activity while adjusting for potential confounders.

Results: The cohort comprised 246 patients with a mean ± SD age of 47.8 ± 10.4 years, disease duration of 10.8 ± 9.8 years, and 91.1% female. Baseline values were: pain VAS 6.5 ± 2.3, PGA 6.7 ± 2.1, FIQ 67 ± 17, HAQ 1.19 ± .59, MPQ 41 ± 15, PDI 38 ± 14, PCS 29 ± 12, AIMS anxiety 6.3 ± 1.8, AIMS depression 4.9 ± 1.8, with a mean medication count of 2.6 ± 1.3 per patient. There were no significant differences between groups for the following parameters: disease duration, marital status, cigarette smoking, previous eating disorder or alcohol abuse, current medication categories, and total number of medications used per patient. Higher education was associated with greater use of alternative medicines ($P<0.001$) and chiropractic, massage or osteopathic treatments ($P=0.021$). Lower education level was significantly associated with older age ($P=0.039$), previous drug abuse ($P=0.016$), current unemployment ($P<0.001$) and higher score in the following measures of symptom severity: PGA ($P=0.019$), FIQ ($P=0.002$), HAQ ($P=0.001$), MPQ ($P=0.026$), PDI ($P=0.031$), and PCS ($P=0.015$). These associations remained significant even upon adjusting for age and gender differences. No significant differences in pain severity, anxiety, and depression were observed between groups.

Conclusion: Similar to other health conditions, FM patients with lower SES reported greater symptom severity, functional impairment and unemployment, but not mood disorder. Although FM spans all socioeconomic groups, societal factors, rather than specific disease characteristics or mental status, appear to play an important role in patients' perception of illness.

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Evaluation Of The Quality Of Life and Sleep In Patients With Benign Joint Hypermobility Syndrome. Ilknur Albayrak[1], Halim Yilmaz[1], Ekrem Akkurt[1], Ali Salli[2] and Gulten Karaca[3]. [1]MD, Konya, Turkey, [2]MD, KONYA, Turkey, [3]Associate Professor, Konya, Turkey.

Background/Purpose: Traction injuries at tendon or ligament attachment sites, joint instability, low back, back and neck pain can be seen in patients with benign joint hypermobility syndrome (BJHS). The most important complaint of such patients is pain. Due to pain, impairment in the quality of sleep and life and fatigue resulting in effects on psychological condition. In this study, we aimed to evaluate pain, fatigue, quality of sleep, depression level and quality of life in patients with BJHS and compare these parameters with those of healthy controls.

Methods: 26 patients who had diagnosed with BJHS according to Brighton diagnostic criteria and 40 healthy controls were included in the study. In all patients and healthy controls, pain severity evaluation was performed using visual analog scale (VAS), fatigue severity was performed using Checklist Individual Strength Scale (CIS), quality of sleep was performed using Pittsburg Sleep Quality Index (PSQI), depression level was evaluated using Beck Depression Scale (BDS), and quality of life was evaluated using Short Form-36 (SF-36).

Results: Mean age was 31.4±7.6 years in the patient group, and 31.3±6.9 years in the control group. There were no statistically significant differences between the two groups with respect to age, gender, body mass index and marital status ($p>0.05$). In the patient group, VAS score during movement was 6.6±0.9. Total CIS scores were 4.3±1.09 in the patient group and 3.2±1.2 in the control group ($p=0.001$), global PSQI scores were 7.8±3.1 in the patient group and 4.9±2.9 in the control group ($p<0.001$), BDS scores were 17.6±8.8 in the patient group and 6.8±5.8 in the control group ($p<0.001$), SF-36 physical component scale scores were 52.7±14.6 in the patient group and 56.09±9.07 in the control group ($p>0.05$), and SF-36 mental component scale scores were 42.01±15.04 in the patient group and 54.3±10 in the control group ($p<0.001$).

Conclusion: This study shows that the levels of pain, fatigue and depression are increased and the quality of sleep and quality of life are adversely affected in patients with BJHS. Therefore, patients with BJHS should be evaluated in terms of pain, fatigue, depression, quality of sleep and quality of life during their diagnostic procedures and follow-up, and multi-faceted treatment programs should be planned.

Disclosure: I. Albayrak, None; **H. Yilmaz**, None; **E. Akkurt**, None; **A. Salli**, None; **G. Karaca**, None.

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The Detection Of Primary Hyperparathyroidism In Patients Diagnosed With Fibromyalgia. Michael Tsoukas, Peter A. Ste-Marie, Yoram Shir, Mary-Ann Fitzcharles and Elliot Mitmaker. McGill University Health Centre, Montreal, QC.

Background/Purpose: Some illnesses, such as hypothyroidism or small fiber neuropathy, may present similarly to fibromyalgia (FM), or may in turn lead to an augmented polysymptomatic distress, mimicking FM, by concomitant illness. Primary hyperparathyroidism (HPT), diagnosed biochemically by the measurement of parathyroid hormone in the context of serum calcium and phosphate levels, has a reported general population prevalence in the order of 0.1%. Its symptoms of musculoskeletal pain, fatigue, mood disorders, and sleep disturbances closely mimic those of FM. Given the commonality of

symptoms and possible underdiagnosis of HPT, we have examined the prevalence of HPT in a pilot study of FM patients.

Methods: A retrospective chart review of a convenience sample of FM patients attending a tertiary care multidisciplinary pain center was undertaken to assess parathyroid and calcium status. Consecutive patients attending the clinic between December 2012 and March 2013, had a primary diagnosis of FM as defined by clinical criteria, and had routine biochemistry screening during the preceding year. Routine blood tests included measurements for bone health, vitamin D, parathyroid hormone, calcium and phosphate levels. Hyperparathyroidism was diagnosed by the following biochemical parameters: parathyroid hormone (PTH) level > 9.3 pmol/L (93 pg/mL) with inappropriately non-suppressed calcium (true HPT or normocalcemic HPT), and/or an elevated serum ionized calcium > 1.32 mmol/L (5.3 mg/dL) with inappropriately high PTH levels (normohormonal HPT).

Results: Thirty-eight patients, 35 female, with a mean ± standard deviation of age 51.6 ±10.6 years, and similar disease duration comprised the cohort. Based on their constellation of biochemical indices, 4 patients of the cohort, representing 10.5% of subjects studied, were diagnosed with hyperparathyroidism.

Conclusion: In this small exploratory study, we have identified that unsuspected hyperparathyroidism in diagnosed FM patients has a prevalence of greater than 10%, as compared to 0.1% in the general population, representing a 100-fold difference. As no previous study has examined HPT in FM patients, these preliminary findings call for a more thorough study of parathyroid hormonal status in FM.

Disclosure: M. Tsoukas, None; **P. A. Ste-Marie**, None; **Y. Shir**, Purdue Pharma L.P., 8, Paladin Labs, 8, Paladin Labs, 5; **M. A. Fitzcharles**, Purdue Pharma L.P., 5, Eli Lilly and Company, 5, Pfizer Inc, 5, Valeant, 5; **E. Mitmaker**, None.

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A Population-Based Survey and Physician Assessment Of The Characteristics and Prevalence Of Fibromyalgia. Edgar H. Adams[1], Shoshana Daniel[2], Arthi B. Chandran[3], Heather McElroy[4], Caroline Schaefer[1], Rachael Mann[5], Gergana Zlateva[3], Joseph C. Cappelleri[6], Elizabeth T. Masters[7], Annlouise R. Assaf[6], Michael McNett[8], Stuart L. Silverman[9], Roland Staud[10] and Philip Mease[11]. [1]Covance Market Access Services Inc., Gaithersburg, MD, [2]Covance Market Access Services Inc., Conshohocken, PA, [3]Pfizer Inc., New York, NY, [4]Covance Market Access Services, Sydney, Australia, [5]Covance Market Access Services Inc., San Diego, CA, [6]Pfizer Inc., Groton, CT, [7]Pfizer Inc, New York, NY, [8]Aurora Pain Program, Milwaukee, WI, [9]Cedars-Sinai Medical Center, UCLA Center of Excellence, Beverly Hills, CA, [10]University of Florida, Gainesville, FL, [11]Swedish Medical Center, Seattle, WA.

Background/Purpose: No large-scale, national study estimating fibromyalgia (FM) prevalence in the United States (US) has been conducted involving physician evaluation. The study objective was to provide contemporary data on characteristics and prevalence of FM among a subset of a nationally representative sample of US adults who completed an online subject screener and physician evaluation.

Methods: This multi-stage study included an online subject screener, a site visit for physician evaluation of FM, and an online subject questionnaire. Subjects were required to be at least 18 years old. Nationally representative participants were invited to complete the online screener, which included the London Fibromyalgia Epidemiology Study Screening Questionnaire (LFESSQ) to identify those with chronic widespread pain (bilateral, above/below waist for ≥1 week in the past 3 months) (CWP) and sociodemographic questions. Subjects who screened positive (CWP+) and a control group who screened negative (CWP-) were invited to schedule a site visit at one of 20 sites for physician evaluation of FM including a manual tender point exam until the established cap was met. CWP+ subjects who were diagnosed with FM based on the physician's evaluation were designated as having FM and included in prevalence estimates. Point prevalence estimates of FM were calculated using an adjusted approach for a two-phase study design, and sampling weights reflecting the underlying screened population were used to refine estimates. Following the site visit subjects completed the subject questionnaire including validated patient-reported outcome instruments to measure FM impact, symptoms, and pain.

Results: 8,382 (1,939 CWP+, 6,443 CWP-) subjects completed the screener. A total of 475 subjects attended a site visit: 350 of 1,331 CWP+ and 125 of 502 CWP- who consented to be scheduled for a site visit. The mean age (years) of the screened sample was 44.1, and there was representation across racial groups with 75.1% white and 12.3% black/African American. Females were intentionally over-sampled (79.3%) in order to generate precise estimates. Estimated prevalence (95% CI) of FM was 9.5% (7.2, 11.7) after adjusting for CWP status, gender, age, and race in the screened sample and weighted by 2010 census results for gender to the US population. Gender-specific prevalence estimates were 12.4% (11.0, 13.8) and 6.8% (4.1, 9.5) among adult women and men, respectively. The majority (55.0%) of subjects with physician-confirmed FM were obese per WHO criteria (BMI ≥30 kg/m^2). Subjects with physician-confirmed FM had a mean (SD) of 14.4 (3.3) tender points, and 90.1% had ≥11 tender points.

Conclusion: Based on the results of this nationally representative sample, the FM prevalence among US adults was higher than previously estimated by regional prevalence studies. The higher prevalence estimate may be a function of changing demographic and clinical characteristics of the US population, increased awareness of FM among patients and providers, study design and factors that influenced study participation. Clinical characteristics of subjects with FM in this study are consistent with the FM clinical profile in the literature.

Disclosure: E. H. Adams, Covance Market Access Services, 3; **S. Daniel**, Covance Market Access Services, 3; **A. B. Chandran**, Pfizer Inc., 1, Pfizer Inc., 3; **H. McElroy**, Covance Market Access Services, 3; **C. Schaefer**, Covance Market Access Services, 3; **R. Mann**, Covance Market Access Services, 3; **G. Zlateva**, Pfizer Inc., 1, Pfizer Inc., 3; **J. C. Cappelleri**, Pfizer Inc., 1, Pfizer Inc., 3; **E. T. Masters**, Pfizer Inc, 1, Pfizer Inc, 3; **A. R. Assaf**, Pfizer Inc., 1, Pfizer Inc., 3; **M. McNett**, Pfizer Inc., 5, Lilly, 8, Pfizer Inc., 8; **S. L. Silverman**, Amgen, Lilly, Medtronics and Pfizer/Wyeth, 2, Amgen, Lilly, Pfizer/Wyeth, 8, Amgen, Genetech, Lilly, Novartis, Pfizer/Wyeth, 5, Cedars-Sinai Medical Center, 3; **R. Staud**, Pfizer Inc., 2, Forest Laboratories, 2; **P. Mease**, Forest Laboratories, 2, Lilly, 2, Pfizer Inc, 2, Forest Laboratories, 5, Lilly, 5, Pfizer Inc., 5.

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Long Term Outcomes In Fibromyalgia. Lesley M. Arnold and Thomas Blom. University of Cincinnati College of Medicine, Cincinnati, OH.

Background/Purpose: There are few studies on the long-term prognosis of fibromyalgia. This study assessed the natural history of fibromyalgia in patients receiving usual medical care and identified predictors of outcome.

Methods: Over about 3 years, patients from the Fibromyalgia Treatment Program completed questionnaires for demographics, pain, mood, fatigue, sleep, health-related quality of life, coping mechanisms, stressful life events, and global assessments. Clinicians evaluated pain thresholds, psychiatric comorbidity, medical history, and global assessments. Patient Global Impression of Improvement (PGI) at endpoint was used to define two groups: 1) definitely improved (much or very much better); and 2) not markedly improved (minimally improved, no change, or worse). Spearman correlation coefficients were calculated for baseline variables versus PGI endpoint scores. A general linear model was used to examine the relationship between baseline variables and PGI score at endpoint.

Results: Sixty-nine patients completed the baseline assessment and had at least 1 follow-up visit. About half (n=34) of the patients definitely improved. There were no significant differences in any demographic variable between the two groups. Among those who reported global improvement, there was significant improvement in fatigue. Having baseline maladaptive coping (catastrophizing), lower pain thresholds, more negative fibromyalgia impact, and impairment in quality of life were correlated with poorer global assessment at endpoint. In the regression analysis, only baseline catastrophizing remained a significant predictor of endpoint PGI.

Conclusion: Fibromyalgia patients who improved were less likely to use catastrophizing at baseline. Interventions directed at improving pain coping skills should be a major component of fibromyalgia management.

Disclosure: L. M. Arnold, None; **T. Blom**, None.

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Pain and Other Symptoms During The Childhood Of Fibromyalgia Patients. Robert S. Katz[1], Alexandra Small[2], Ben J. Small[3] and Susan Shott[4]. [1]Rush Medical College, Chicago, IL, [2]University of Illinois Medical School, Chicago, IL, [3]Rush University Medical School, Chicago, IL, [4]Rush University Medical Center, Chicago, IL.

Background/Purpose: We investigated the severity of pain and other symptoms during childhood, before age 12 and before age 18, that might be related to fibromyalgia (FMS).

Methods: 115 FMS patients and 63 control patients with other rheumatic diseases answered a rheumatology office questionnaire that included questions about symptoms experienced before the ages of 12 and 18. Patients were asked to rate each symptom as 1 = no problem, 2 = seldom, 3 = occasional,

4 = moderate, and 5 = severe problem. The chi-square test of association and Fisher's exact test were used to compare percentages, and the Mann-Whitney test was done to compare FMS and control patients with respect to age and symptom severity ratings. A 0.05 significance level was used and all tests were two-sided.

Results: The mean age was 48.1 ±12.3 years for FMS patients and 50.7 ±13.6 for rheumatic disease control patients ($p = 0.092$). 81.7% of the FMS patients and 61.9% of the control patients were women ($p = 0.004$). FMS patients had significantly worse severity ratings than did control patients for the following symptoms before age 18 (all with $p < 0.001$): "growing pains" (FMS 2.1± 1.5 vs. controls 1.4± 0.9), sleep problems (FMS 2.3± 1.4 vs. controls 1.3± 0.9), fatigue (FMS 2.2 ± 1.4 vs. controls 1.4 ±0.9), concentration problems (FMS 2.3 ±1.4 vs. controls 1.5± 0.8), memory problems (FMS 2.2±1.5 vs. controls 1.4 0.8), anxiety (FMS 2.1 ±1.4 vs. controls 1.4± 1.0), headaches (FMS 2.7 ±1.4 vs. controls 1.6 1.0), stomach aches (FMS 2.3 ±1.4 vs. controls 1.3 ±0.8), and depressed mood (FMS 2.1± 1.3 vs. controls 1.3± 0.7). Similar results were obtained for the same symptoms before age 12 (all with $p< 0.022$).

Conclusion: Pain, sleep problems, fatigue, concentration, and memory complaints were reported to be more common before the ages of 18 and before 12 in FMS subjects. Though recall bias could be a limitation of this study, the data suggest that fibromyalgia patients frequently have symptoms in childhood. Other studies have suggested that fibromyalgia may be related to a trait (fibromyalgianess). This study points out that the vulnerability to this illess might be manifested early in life.

Disclosure: R. S. Katz, None; **A. Small**, None; **B. J. Small**, None; **S. Shott**, None.

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Fibromyalgia and Pregnancy: Challenges Of The Savella® (Milnacipran) Pregnancy Registry. Damien Hirsch[1], Denise Leclair[1], Robert H. Palmer[1], Vikki Brown[2], Susan Sinclair Roberts[2] and Janice McLean[2]. [1]Forest Research Institute, Inc., Jersey City, NJ, [2]INC Research, LLC, Wilmington, NC.

Background/Purpose: During pregnancy, women with fibromyalgia (FM) often experience worsening of symptoms, which include widespread pain, fatigue, sleep disturbances, cognitive difficulties, and reduced daily functioning. Although the safety and efficacy of milnacipran in FM patients has been demonstrated in large clinical trials, these studies excluded pregnant women and milnacipran safety in this population is largely unknown. Milnacipran is a serotonin and norepinephrine reuptake inhibitor approved in the US for the management of FM. As with other drugs in this class, milnacipran is currently designated by the FDA as a Pregnancy Category C drug. As FM disproportionally affects women and, as a result, there is potential for exposure to milnacipran in women of child-bearing age, a pregnancy registry was established in October 2009.

Methods: This ongoing, voluntary, prospective, observational, US-based registry employs an exposure-registration cohort design that allows for the evaluation of birth defects and other pregnancy outcomes in women ≥18 years exposed to milnacipran at any time during pregnancy. Women are followed throughout pregnancy, with their infants followed until 1 year of age. Enrollment in the Registry is initiated by the woman or by her healthcare provider. Pregnancies with evidence of birth defects prior to enrollment are considered retrospective and excluded from the primary analysis to minimize selection bias. All data are reviewed at least yearly by the Registry's Scientific Advisory Committee.

Results: To date, 2 prospective subjects have enrolled in the Registry. Both gave birth to premature infants (at 32 and 35 weeks of gestation, respectively). No birth defects have been reported at this time. Enrollment is considerably lower than projected, and is far from the goal of 350 exposed pregnancies and 196 live births. Postmarketing surveillance data from 01Nov11 to 31Oct12 indicate that milnacipran was primarily prescribed to women (88.7%); however, only 21.5% of these women were 18–40 years of age (ie, women with the highest childbearing potential). Healthcare utilization data suggest that the pregnancy rate in women prescribed milnacipran may be <0.5% per year, well below the estimated general population rate of 7%. Other reasons for low enrollment may include pregnancy avoidance due to FM symptoms, the Category C classification, or lack of interest in participating in a voluntary registry.

Conclusion: Possibly due to the demographics of the target population, enrollment in the Registry has been challenging. The sample size is insufficient to reach conclusions about milnacipran safety in pregnancy. However, the Registry will continue to monitor milnacipran-exposed pregnancies for teratogenicity signals or other negative pregnancy outcomes. Increasing awareness of the Registry among pregnant women who have taken milnacipran and healthcare providers remains a major focus.

Disclosure: D. Hirsch, Forest Research Institute, 3; **D. Leclair**, Forest Research Institute, 3; **R. H. Palmer**, Forest Research Institute, 3; **V. Brown**, Forest Laboratories, Inc., 5; **S. Sinclair Roberts**, Forest Laboratories, Inc., 5; **J. McLean**, Forest Laboratories, Inc., 5.

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Skin Disease and Fibromyalgia: Dermatologic Diagnoses Encountered In a Series Of 845 Patients With Fibromyalgia At Mayo Clinic In 2008. Valerie Laniosz, David Wetter and Desiree Godar. Mayo Clinic, Rochester, MN.

Background/Purpose: To determine the common dermatological diagnoses and skin-related complaints in a cohort of patients with fibromyalgia seen in a tertiary referral center.

Methods: A retrospective chart review was performed of all patients with a diagnosis of fibromyalgia from January 1st, 2008-December 31st2008, whose diagnosis of fibromyalgia was confirmed in the Fibromyalgia Clinic at Mayo Clinic in Rochester, Minnesota. Charts were reviewed for dermatologic conditions and cutaneous symptoms. Demographic and clinical data were collected to assess for the frequency of skin-related issues in patients with fibromyalgia.

Results: Of 2233 patients screened, 845 patients met the inclusion criteria of having a confirmed diagnosis of fibromyalgia. Amongst these 845 patients with fibromyalgia, various dermatologic conditions and cutaneous complaints were identified including hyperhidrosis in 270 (31.8%); burning of the skin or mucous membranes in 29 (3.4%); and various unusual cutaneous sensations in an additional 14 (1.7%). Pruritus without identified cause was noted by 28 patients (3.3%); with another 16 (1.9%) with neurotic excoriations, prurigo nodules, or lichen simplex chronicus. 77 patients (9.1%) were found to have some form of dermatitis other than neurodermatitis.

Conclusion: Patients with fibromyalgia may have skin-related symptoms associated with their fibromyalgia. There does not appear to be any single dermatologic diagnosis overrepresented in this population with the exception of a subjective increase in sweating.

Disclosure: V. Laniosz, None; **D. Wetter**, None; **D. Godar**, None.

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Home Tender Point Measurement In Fibromyalgia Patients. Robert S. Katz[1], Hannah Bond[2] and Jessica L. Polyak[2]. [1]Rush Medical College, Chicago, IL, [2]Rheumatology Associates, Chicago, IL.

Background/Purpose: To determine whether: 1) patients with the fibromyalgia syndrome (FMS) can accurately evaluate their own tender points, similar to self-administered testing for other purposes (blood pressure and glucose), and 2) whether this might be helpful for monitoring the illness.

Methods: We enrolled 24 patients with a known diagnosis of FMS (meeting the 2010 ACR criteria) and 27 healthy controls. Dolorimetry was performed on each patient by a rheumatology nurse, who also instructed the patient in self-dolorimetry using a pressure gauge smaller than a standard dolorimeter, (Wagner Force Dial FDK/FDN Series Push Pull Force Gage).

Tender points were assessed using self-administered dolorimetry. Tender points were checked at 8 paired fibromyalgia tender point areas: occiput, lower cervical spine, chest wall, lateral epicondyles, knees, trapezius muscles, gluteus muscles, and greater femoral trochanters.

Results: FM patients' ages were 45 y.o. +/−20, 18F and 10M. Normal controls ages were 48 y.o. +/−15, 15F and 10M. Self-measured dolorimetry readings for fibromyalgia patients ranged from 3–20 pounds of pressure and for normal controls from 10–30. When we compared readings performed by a nurse with those done by patients, there were no significant differences. Dolorimetry exams of the trapezius muscle yielded the following results: 32 FMS patients recorded a mean reading of 5.86 pounds per pressure, while 32 controls had a mean reading of 12.05 pounds per pressure.

Conclusion: Using self-administered dolorimetry, our results show that tender points can be measured by patients easily and with reasonable accuracy. The sites providing the best discrimination between patients and controls were the occiput, trapezius muscles, and gluteal muscles. Currently, clinician rated VAS scales are used to monitor the efficacy of

treatment in FMS. Self-administered dolorimetry may also allow patients to assess treatment efficacy. This method of home monitoring would be a convient and inexpensive option for patients to monitor flares of disease.

Disclosure: R. S. Katz, None; **H. Bond**, None; **J. L. Polyak**, None.

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Rapid Infrared Microscopy (IRMS) For Differential Diagnosis Of Fibromyalgia and Other Central Sensitivity Syndromes. Kevin V. Hackshaw, Luis Rodriguez-Saona, Irving L. Rosenberg, Marcal Plans and C.A. Tony Buffington. The Ohio State University, Columbus, OH.

Background/Purpose: The aim of this study was to investigate the ability of a rapid blood-spot-based method for diagnosis of Fibromyalgia (FM) using mid-infrared microspectroscopy (IRMS) to differentiate patients with FM from those with osteoarthritis (OA) and rheumatoid arthritis (RA) as well as another central sensitization disorder – Interstitial Cystitis (IC) - and to identify molecular species associated with the spectral patterns.

Methods: Under IRB approval, blood samples were collected from patients diagnosed with FM (n = 14), RA (n = 15), or OA (n = 12) and IC (n = 20). Samples were prepared, placed onto a highly reflective slide, and spectra were collected using IRMS and compared using multivariate statistical modeling to differentiate groups. Aliquots of samples also were subjected to metabolomic analysis.

Results: IRMS separated subjects into classes based on spectral information with no misclassifications among FM, RA, OA and IC patients. Discriminating power was greatest based on spectral bands centered at 1560cm^{-1}, which are associated with indole ring vibrations of tryptophan or its derivatives. Metabolomic analysis revealed that RA and OA groups were metabolically similar, whereas biochemical differences were identified in the FM that were quite distinctive from those found in the other groups.

Conclusion: These results support the use of IRMS to differentiate patients with FM from those with other chronic pain or central sensitivity syndromes. The accuracy and simplicity of the test may make it useful for earlier diagnosis of these syndromes.

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Cytokines, Oxidative Stress Markers and Brain-Derived Neurotrophic Factor In Fibromyalgia Syndrome. Aline Ranzolin[1], Claudio Antônio da C. Neto[2], Bruna Maria Ascoli[3], Bianca Wollenhaupt-Aguiar[4], Angela Luzia B. Pinto Duarte[2], Markus Bredemeier[5], Flávio Kapczinski[3] and Ricardo M. Xavier[6]. [1]Programa de Pós-Graduação em Ciências Médicas da Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [2]Faculdade de Medicina, Universidade Federal de Pernambuco - Hospital das Clínicas de Pernambuco, Recife, Brazil, [3]Programa de Pós-Graduação em Ciências Médicas da Universidade Federal do Rio Grande do Sul: Psiquiatria, Porto Alegre, Brazil, [4]Programa de Pós-Graduação em Ciências Biológicas: Bioquímica, da Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [5]Hospital Nossa Senhora da Conceição - Grupo Hospitalar Conceição, Porto Alegre, Brazil, [6]Faculdade de Medicina, Universidade Federal do Rio Grande do Sul - Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil.

Background/Purpose: The pathophysiology of Fibromyalgia Syndrome (FMS) is incompletely understood. An imbalance of pro- and anti-inflammatory cytokines is assumed to play a role in the induction and maintenance of pain, but the many studies that have investigated cytokine levels in patients with FMS presented diverse results. The objective of our study was to analyze different cytokines, oxidative stress markers and brain-derived neurotrophic factor (BDNF) in patients with FMS. Considering that depression is also a possible cause of alteration in some of these markers, its presence was analyzed.

Methods: A total of 130 female subjects (69 FMS and 61 healthy controls) were included in the present study. The cytokines (IL-6, IL-10 and TNFα), oxidative stress markers (Thiobarbituric Acid Reactive Substances – TBARS – and carbonyl) and BDNF expression patterns were evaluated in all subjects. The Hamilton and Beck's depression scales, as well as the Fibromyalgia Impact Questionnaire (FIQ), were applied in FMS patients. BDNF serum levels were measured by sandwich-ELISA; the concentration of serum cytokines was determined by flow cytometry; levels of lipid peroxidation were measured by the method of TBARS and oxidative damage to proteins were analyzed by the determination of carbonyl groups content in proteins.

Results: Age was similar between groups (44.5 ± 6.4 years in FMS and 44.0 ± 6.7 in controls; p= 0.613). In the FMS group, the mean of FIQ was 70.3 ± 18.1 and almost all patients had depression (95.6 %) considering an abnormal score on specific scales. The majority of patients had mild/moderate depression (52.2% on Beck scale and 66.6% on Hamilton scale). IL-10 levels where significantly higher in FMS subjects, but other cytokines and biomarkers did not differ between the groups. (table). There was no correlation of any biomarker or cytokine with the FIQ and the Hamilton and Beck's depression scales.

Comparison of oxidative stress markers, BDNF and cytokines in FMS patients and healthy controls

	FMS patients (n=69) median (IQR)	Healthy controls (n=61) median (IQR)	p value*
Neuropsychiatric biomarkers			
TBARS (μM of MDA)	13.2 (9.8, 20.5)	14.4 (8.7, 29.2)	0.808
BDNF (ng/mL)	30.8 (21.8, 37.1)	30.7 (21.1, 35.4)	0.595
Carbonil (nmol/mg)	0.019 (0.015, 0.022)	0.021 (0.015, 0.027)	0.132
Cytokines (fg/mL)			
IL-6	1498.7 (743.5, 2595.6)	1077.1 (720.0, 2119.1)	0.128
IL-10	593.5 (348.4, 890.2)	441.4 (266.6, 569.8)	0.006
TNF-α	187.3 (145.7, 670.3)	187.3 (76.1, 352.9)	0.255

*Mann-Whitney test; the p value is not adjusted for multiple comparisons. IQR: interquartile range

Conclusion: The significant increase of serum IL-10 in patients with FMS found in this study may indicate a disregulation of antiinflammatory cytokines in this disease. This finding was also seen in patients with chronic fatigue syndrome, disease that is also characterized for chronic pain and tiredness.

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Autonomic Nervous System "Decomplexification" In Fibromyalgia. A Proof Of Concept Study Looking At The Fractality Of Heart Rhythms. Manuel Martinez-Lavin, Claudia Lerma, Laura Aline Martinez-Martinez, Oscar Infante and Angelica Vargas. National Institute of Cardiology, Mexico City, Mexico.

Background/Purpose: Prevailing linear-reductionist medical model seems unable to explain complex diseases like fibromyalgia (FM) and similar maladies. As consequence of this divorce, some physicians disparage the fibromyalgia concept. Paradigms derived from the new complexity theory may provide a coherent framework for these elusive illnesses. Along these lines is the proposal that FM represents a degradation of our main complex adaptive system (the autonomic nervous system), in a failed effort to adjust to a hostile environment (Semin Arthritis Rheum 2008;37:260).

Resilient complex systems have fractal structures (fractal is defined as an object or quantity that displays self-similarity at different scales). Fractality loss would signal degradation of a given system. Heart rate variability (HRV) fractal scaling index (alpha) is a novel non-linear method to assess autonomic nervous system resilience: high vagal influence produces less auto-correlated behavior (alpha values below 1.0) while increased sympathetic activity produces more auto-correlated and stiffer behavior (alpha greater than 1.0). Alpha values close to 1.0 indicate resilient fractal-like behavior (Open Cardiovasc Med J 2009;3:110).

The objective of this study was to estimate the HRV fractal scaling index in FM patients, and to correlate this scaling index with clinical symptoms.

Methods: We studied 30 women with FM (1990 ACR criteria) that were free from any medication that may affect the autonomic nervous system. Thirty age - matched healthy women served as controls. HRV was measured during 24 hrs with a Meigaoyi DSM-3 Holter monitor, while subjects were doing their routine activities. The fractal scaling index was estimated with the detrended fluctuation analysis method using custom computer programs which were previously validated. The scaling index was estimated in short-term scales or alpha 1 (4 to 11 heartbeats) and long-term scales or alpha 2 (greater than 11 heartbeats). Mean values between groups were compared with Student t test. Correlations between alpha indexes and symptoms scales were calculated with Pearson′s or Spearman′s correlations.

Results: Demographic features and main results are shown in the table. The short-term fractal scaling index (alpha1) was higher in FM patients when compared to controls (1.22 +/−0.10 vs. 1.16 +/− 0.10 p = 0.035). There was a positive correlation of fractal scaling index alpha 1 with total FIQ score (Rho=0.322, p=0.012).

	Group				
	FM n =30		Controls n = 30		
	Mean	Standard Deviation	Mean	Standard Deviation	*P*
Age	31	8	31	8	0.856 NS
BMI	23.8	4.4	24.4	3.2	0.550 NS
FIQ score	63.24	16.38	10.30	10.05	<0.0001
Fractal scaling	1.22	0.10	1.16	0.10	
index alpha 1	0.93	0.04	0.95	0.05	**0.035**
Fractal scaling index alpha 2					0.143

Conclusion: The short-term HRV fractal scaling index is altered in FM patients with values indicating stiffer autonomic behavior. This fractal index correlated with total FIQ score. This tangible non-linear finding supports the notion that FM represents a degradation of our main complex adaptive system, namely the autonomic nervous system.

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ACR Poster Session A
Genetics and Genomics of Rheumatic Disease I
Sunday, October 27, 2013, 8:30 AM–4:00 PM

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The Arthritis Severity Locus *Cia4* Is An Early Regulator of IL-6, IL-1β, and NFκB activators' Expression in Pristane-Induced Arthritis. Max Brenner, Teresina Laragione and Percio Gulko. Hosftra North Shore-LIJ School of Medicine, Manhasset, NY.

Background/Purpose: *Cia4* is a quantitative trait locus on rat chromosome 7 that regulates disease severity and joint damage in three models of rheumatoid arthritis including pristane-induced arthritis (PIA). To identify cellular and molecular processes regulated by *Cia4*, we studied the expression over 23,000 genes in synovial tissues from MHC identical DA (severe erosive disease) and DA.F344(Cia4) congenics (mild and non-erosive disease) rats.

Methods: Synovial tissues from DA and DA.F344(Cia4) congenics were collected at pre-clinical (day 10 and day 14 post-pristane administration; qPCR) and recent onset (day 18; microarray and qPCR) stages following the induction of PIA and analyzed for gene expression levels.

Results: *Il6* levels were 135-fold higher in DA compared with congenics at very early pre-clinical stages (day 10), and remained significantly increased. The *Il6* increase preceded the modest increase in *Il1b* (4.2-fold) suggesting that *Il6* could be driving cytokine expression and the early histologic inflammatory infiltration. 187 genes had significantly different expression and included inflammatory mediators expressed in increased levels in DA such *Slpi* (10.94-fold) and its receptor *Plscr1* (2.31-fold), *Cd163* (5.85-fold), *Ccl7* (5.17-fold) and *Litaf* (2.09-fold). *Syk* or NFκB pathway activating and interacting genes were increased in DA synovial tissues. Fifty-nine genes implicated in cancer-related phenotypes were increased in DA, while genes involved in cell metabolism, transport across membranes and tissue protection such as *Acat1, Dgat1, Dhcr7, Slc25a29*, and *Slc1a1* were increased in DA.F344(Cia4) congenics. 21 genes differentially expressed, or expressed in only one of the two strains were located within the *Cia4* interval, and could be the gene accounting for the arthritis effect.

Conclusion: The *Cia4* interval contains a new arthritis gene that regulates early *Il6*, *Il1b* expression, and other inflammatory mediators central to arthritis, and processes involved in cancer that could be mediating the development of synovial hyperplasia and invasion, and cartilage and bone destruction.

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Modular Analysis Of In Peripheral Blood Gene Expression In Rheumatoid Arthritis Captures Reproducible Gene Expression Changes In TNF Responders. Mark Curran[1], Michaela Oswald[2], Sarah Lamberth[1], Carrie Brodmerkel[1], Zhenya Cherkas[1] and Peter K. Gregersen[3]. [1]Janssen Research & Development, LLC., Spring House, PA, [2]The Feinstein Institute for Medical Research, Manhasset, NY, [3]Feinstein Institute for Medical Research, Manhasset, NY.

Background/Purpose: The use of whole blood gene expression to predict and follow the response to TNF inhibition therapy in RA has been challenging due to the complex nature of the data.

Methods: Here we employ an approach to gene expression analysis that is based on gene expression "modules" previously reported by Chassubel (Immunity 2:150–64, 2008). Whole blood RNA (PAXgene) was obtained at baseline and 12 or 14 weeks on two cohorts of rheumatoid arthritis patients beginning anti-TNF therapy.

Results: The initial cohort was enrolled by the ABCoN and contains 50 subjects stratified by EULAR Good Responders (N=14), Moderate Responders (N=21) and Non Responders (N=15) at 12 weeks after starting therapy. Good and Moderate Responders exhibited highly significant changes in multiple modules using a hypergeometric analysis. These included dramatic decreases in modules related to the myeloid lineage and inflammation, along with increases in B cell and plasma cell modules as well as in a number of modules related to the MHC and ribosomal proteins and other "undefined" module groups. Strikingly, Non Responders exhibited very little change in any modules. We have replicated these data in patients enrolled in a clinical trial of Simponi®, with full expression data available on 29 Good Responders, and 37 Moderate Responders. We observed nearly identical modular changes to those identified in the ABCoN Responders after 14 weeks of treatment. Only 6 Non Responders were available for study in this dataset, making convincing replication difficult for this subgroup. Several other replication datasets are currently being analyzed.

Conclusion: These data suggest that using gene expression modules related to inflammatory disease may provide a valuable method of characterizing the responder status of RA patients treated with TNF inhibitors or other biologic therapies.

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Microarray Analysis Of Synovial Specimen of Early Human (CHECK) and Experimental Osteoarthritis to Identify Pathways and Processes Associated with Pathology. Arjen B. Blom[1], Peter L. van Lent[1], Martijn H. van den Bosch[1], Hans Cats[2], Frank H.J. van den Hoogen[3], Peter M. van der Kraan[1] and Wim B. van den Berg[4]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Rheumatology Centre Sint Maartenskliniek, Nijmegen, Netherlands, [3]Rheumatology Centre Sint Maartenskliniek and University Medical Centre St Radboud, Ubbergen (Nijmegen), Netherlands, [4]Rheumatology Research and Advanced Therapeutics, Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.

Background/Purpose: The majority of osteoarthritis (OA) patients show synovial inflammation, even relatively early during the disease. We used microarray analysis of synovial tissue of early OA patients and of experimental OA, to identify common pathways that determine joint damage in this disease.

Methods: Expression analysis was performed on murine synovial tissue at day 7, day 21 and day 42 in collagenase induced OA (CIOA) and the surgically induced DMM model (destabilization of the medial meniscus). CIOA was induced by intra-articular injection of collagenase, which causes joint instability. From a subpopulation of patients (n= 25) that entered the CHECK Cohort study (Cohort Hip and Cohort Knee) and 7 controls, synovial biopsies were collected at year 0, 2 and 5. CHECK is a prospective 10-year follow-up study on participants with early osteoarthritis-related complaints (less than 6 months before inclusion) initiated by the Dutch Arthritis Association. Kellgren&Lawrence-score (KL) at inclusion was determined (n=18) and follow up measurements were performed at 2 and 5 years. Affymetrix was used for microarray, and pathway analysis was done using DAVID.

Results: Among the genes that were strongly upregulated on all 3 time points after induction of CIOA were MMP-3 (6-fold), MMP-13 (16-fold), MMP-14 (6-fold). Wound healing, phagocytosis, chemotaxis and metalloproteases were significantly enriched, as were the complement pathway, the TLR-, TGFβ, BMP and wnt-signaling pathways. Highly similar results were obtained in the DMM model for OA. However, at day 42 in this model very view genes were still regulated in the synovium compared

to other time points or CIOA, indicating that synovial activation differs late between the models. This was underlined by histological examination. All in all, the expression patterns in experimental OA showed compelling similarities with human OA synovium. Gene expression profiles of control synovia were compared to CHECK synovia. Analysis using DAVID indicated enrichment of several biological processes and signaling pathways, including macrophage presence, cell migration, TGFβ-, BMP- and wnt-signaling. This indicates activation of the synovium in the early OA versus controls. Next we compared synovial tissue of CHECK-patients with radiological damage (KL$\geq$1) with CHECK-patients without joint damage (KL=0). In the top 30 genes that were associated with cartilage damage were MMP-1 (18-fold), MMP-3 (10-fold) and S100A8 (6-fold), all of which have been associated with cartilage damage. FAC analysis further underlined response to wounding, chemotaxis, innate immune response and metalloproteases to be strongly enriched. In particular, complement-activation pathway, TGFβ- and BMP-signaling and TLR-activation were striking.

Conclusion: Activation pathways and processes in the two models for OA were highly similar. A major difference lies in the presence of late synovial activation. The data suggest an active role for the synovium in OA pathology, and identifies pathways that may be involved. Activation of the complement-pathway was strongly associated with damage. In addition, synovial MMP expression was associated with joint damage, underlining an active role of synovium in OA pathology.

Disclosure: A. B. Blom, None; **P. L. van Lent**, None; **M. H. van den Bosch**, None; **H. Cats**, None; **F. H. J. van den Hoogen**, None; **P. M. van der Kraan**, None; **W. B. van den Berg**, None.

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Comparative Proteomic Analysis Of Neutrophils From Patients With Microscopic Polyangiitis and Granulomatosis With Polyangiitis. Teisuke Uchida[1], Kohei Nagai[2], Toshiyuki Sato[3], Nobuko Iizuka[3], Mitsumi Arito[3], Yukiko Takakuwa[4], Hiromasa Nakano[4], Seido Ooka[4], Manae Kurokawa[3], Naoya Suematsu[3], Kazuki Okamoto[3], Shoichi Ozaki[4] and Tomohiro Kato[3]. [1]St. Marianna University School of Medicine, Kawasaki, Japan, [2]Kinki University, Wakayama, Japan, [3]St. Marianna University Graduate School of Medicine, Kawasaki, Japan, [4]St. Marianna University School of Medicine, Kawasaki, Japan.

Background/Purpose: Both microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) belong to ANCA-associated vasculitis (AAV), in which neutrophils are thought to be involved in their pathology. Clinically, it is often difficult to distinguish MPA from GPA. To discriminate between MPA and GPA, protein profiles of peripheral blood polymorphonuclear cells (PMNs) of MPA and GPA patients and healthy controls (HC) were analyzed.

Methods: Proteins extracted from peripheral blood PMNs of 11 MPA patients, 9 GPA patients, and 10 HC were separated by two-dimensional difference gel electrophoresis (2D-DIGE). Differentially expressed protein spots were identified by mass spectrometry analysis. Then, to find biomarker candidates which discriminate between MPA and GPA, the obtained protein profiles were subjected to the multivariate data analysis using SIMCA-P+ containing principal component analysis (PCA) and orthogonal partial-least-squares-discriminate analysis (OPLS-DA), and subjected to the receiver operating characteristic (ROC) analysis.

Results: In all the 864 protein spots detected, intensity of 55 spots was found to be significantly different ($p < 0.05$) among the three groups by an analysis of variance (ANOVA). 31 out of the 55 spots were identified by mass spectrometry. The OPLS-DA analysis revealed that the expression profile of the protein spots discriminated the AAV group from the HC group completely and also discriminated the MPA group from the GPA group completely. 13 protein spots were considered as biomarker candidates to distinguish between MPA and GPA. In those, spots whose intensity was higher in MPA than in GPA included actin with various p*I* values, while a considerable part of spots whose intensity was higher in GPA than MPA were proteins related with the activity of neutrophils. Among the candidate proteins, ROC analysis showed that a combination of neutrophil gelatinase-associated lipocalin and a kinase anchor protein 7 isoforms beta had a high diagnostic potential.

Conclusion: In the study, we determined that the protein profile of the neutrophil was clearly different between AAV and HC, and between MPA and GPA. In Particular, GPA was characterized by high expression level of the proteins associated with the activity of the neutrophil.

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A Subset Of Osteoarthritis Individuals Has Elevated IL-6 Pathway Activation Associated With Worse Symptoms. Michael Kuziora[1], Zheng Liu[1], Brandon W. Higgs[1], Philip Brohawn[1], Kim Lehmann[1], Fernanda Pilataxi[1], Katie Streicher[1], Lydia Greenlees[1], Meina Liang[2], Rozanne Lee[2], Amy Schneider[2], Raffaella Faggioni[2], Yihong Yao[1] and Koustubh Ranade[1]. [1]MedImmune, LLC, Gaithersburg, MD, [2]MedImmune, LLC, Hayward, CA.

Background/Purpose: Elevated levels of the pro-inflammatory cytokine IL-6 have been found in the affected joint of patients with osteoarthritis (OA), although the prevalence of OA patients demonstrating IL-6 pathway activation is not well-characterized. Our goal was to estimate the proportion of OA patients with increased IL-6 signaling in the diseased joint, and to correlate IL-6 pathway activation with Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores.

Methods: Synovial membranes were obtained from OA patients (N=101) undergoing knee replacement surgery. The WOMAC pain questionnaire was used to assess levels of pain on a visual analog scale of 100mm. Scores within each WOMAC subfunction (pain, stiffness and physical function) were averaged to derive a single composite subfunction score, and the WOMAC total score was calculated as the average of all subfunction scores. Synovial fluid and serum collected at the time of surgery was assayed for IL-6 and CCL8 proteins. Gene expression levels were measured using Affymetrix HG-U133Plus2 microarrays. Transcripts with >2-fold over-expression following treatment with IL-6 and IL6R in synovial fibroblasts were identified. Hierarchical clustering using expression levels of these inducible transcripts in synovial tissue was used to identify OA patients showing high levels of IL-6 activity. A signature score was calculated as the median expression intensities of IL-6 –inducible genes for each subject.

Results: CCL8 and SOCS3 were identified as IL-6 inducible genes in synovial fibroblasts and clustering of synovial membrane specimens from OA subjects revealed a cluster (19/101 subjects, 19%) with a 3.5-fold increase in the median expression of these two genes compared to the remaining subjects (388.4 ± 270.1 vs 111.4 ± 38.7, $p=3.0\times10^{-4}$) suggesting significantly elevated IL-6 pathway activation in this subgroup. These "IL-6 signature high subjects" also had significantly higher mean levels of IL-6 (155.2 ± 4.6 pg/mL vs 58.6 ± 4.1 pg/mL $p=7.4\times1-^{-3}$) and CCL8 (30.5 ± 2.5 pg/mL vs 14.4 ± 2.1 pg/mL $p=7.2\times10^{-5}$) proteins in synovial fluid. The levels of CCL8 and IL-6 proteins in synovial fluid were significantly correlated (rho=0.52, $p=1.6\times10^{-7}$). Compared to subjects with low levels of IL-6 inducible genes in the synovium, with those in the IL-6 signature high cluster were more likely to be women (Odds ratio 4.2 95% C.I. [1.1, 15.4] p=0.03), and had higher mean WOMAC scores for pain (65.6 ± 16.4 vs 55.6 ± 18.3, $p= 4\times10^{-2}$), stiffness (76.9 ± 17.0 vs 60.5 ± 24.8, $p=3.4\times10^{-3}$), physical activity (67.2 ± 15.8 vs 56.3 ± 18.2, $p=4.4\times10^{-2}$) and total score (69.9 ± 14.6 vs 57.5 ± 18.1, $p=8.9\times10^{-3}$).

Conclusion: An IL-6 inducible gene signature consisting of CCL8 and SOCS3 was used to identify a subgroup of OA subjects with elevated IL-6 pathway activation in the synovial membrane. OA subjects in this IL-6-signature high group were more likely to be women and had higher mean WOMAC pain scores. CCL8 is a potential biomarker of IL-6 pathway activation in the affected joint.

Disclosure: M. Kuziora, AstraZeneca, 1, MedImmune, 3; **Z. Liu**, MedImmune LLC, 3, AstraZeneca, 1; **B. W. Higgs**, MedImmune LLC, 3, AstraZeneca, 1; **P. Brohawn**, MedImmune LLC, 3, Astra Zeneca, 1; **K. Lehmann**, MedImmune, 3, AstraZeneca, 1; **F. Pilataxi**, AstraZeneca, 1, MedImmune, 3; **K. Streicher**, AstraZeneca, 1, MedImmune, 3; **L. Greenlees**, AstraZeneca, 1, MedImmune, 3; **M. Liang**, AstraZeneca, 1, MedImmune, 3; **R. Lee**, AstraZeneca, 1, MedImmune, 3; **A. Schneider**, AstraZeneca, 1, MedImmune, 3; **R. Faggioni**, AstraZeneca, 1, MedImmune, 3; **Y. Yao**, MedImmune, 3, AstraZeneca, 1; **K. Ranade**, AstraZeneca, 1, MedImmune, 3.

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The mtDNA Haplogroups Influence The Cartilage Integrity In Osteoarthritis. Data From The Osteoarthritis Initiative (OAI). Ignacio Rego-Pérez[1], Angel Soto-Hermida[1], Mercedes Fernández-Moreno[1], Sonia Pértega-Díaz[2], Juan Fernández-Tajes[1], María Eugenia Vázquez-Mosquera[1], Estefanía Cortés-Pereira[1], Sara Relaño-Fernández[1], Natividad Oreiro-Villar[1], Carlos Fernández-López[1] and Francisco J. Blanco[3]. [1]INIBIC-Hospital Universitario A Coruña. Rheumatology Division. Genomic Group, A Coruña, Spain, [2]INIBIC-Hospital Universitario A Coruña. Epidemiology and Public Health Unit, A Coruña, Spain, [3]Osteoarticular and Aging Res. Lab. CIBER-BBN. INIBIC- University of A Coruña, A Coruña, Spain.

Background/Purpose: Magnetic resonance imaging (MRI) is ideally suited for detect structural changes and degradation in cartilage against the limitations of radiographic common methods. Changes in volume and thickness are the most widely used variables to measure progression in OA with MRI. The aim of this study is to elucidate the influence of the mtDNA haplogroups on cartilage integrity based on MRI data obtained from different OAI projects.

Methods: We analysed the influence of the mtDNA haplogroups on quantitative measurements of cartilage morphology from MRI scans, mean cartilage thickness and volume of cartilage, in the whole knee joint by means of both cross-sectional and longitudinal studies during a follow-up period of 24 months. We selected for analysis 326 patients from project 18 (cross-sectional) and 358 from project 9 (longitudinal), all of them belonging to the progression subcohort of the OAI. Appropriate statistical analyses adjusting by gender, age and body mass index (BMI) at baseline were carried out using SPSS software (v.19) and R 2.10.0 (The R Foundation for Statistical Computing).

Results: The cross-sectional analyses showed that OA patients that carry the mtDNA haplogroup T had increased median values of cartilage volume in medial tibia (2.35×10^3 mm^3 vs 1.95×10^3 mm^3; $p=0.009$) and medial tibia femoral (3.56×10^3 mm^3 vs 3.02×10^3 mm^3; $p=0.015$) compartments, when compared with the most common mtDNA haplogroup H. In relation to mean cartilage thickness, OA patients that carry the mtDNA haplogroup T also showed higher mean cartilage thickness in medial tibia, however this difference borderline the statistical significance (1.85 mm vs 1.73 mm; $p=0.07$).

During the follow-up period of 24 months, OA patients that carry the haplogroup T suffered a significant smaller decline of volume in medial tibia femoral ($p=0.015$) and central medial femur ($p=0.016$) compartments when compared with the most common mtDNA haplogroup H. Even when the normalized cartilage volume of these two subregions was analysed, the results obtained were similar ($p=0.023$ and $p=0.031$ respectively). In relation to mean cartilage thickness, patients with the mtDNA haplogroup T suffered a significant smaller decline in central medial tibia femoral (weight bearing) ($p=0.011$), medial tibia femoral ($p=0.019$), medial tibia (anterior) ($p=0.007$) and central medial femur (center) ($p=0.013$) compartments when compared with the mtDNA haplogroup H.

The statistical models applied in the longitudinal approach showed both age and gender (female) as risk factors for volume loss ($p<0.02$ and $p<0.0001$ respectively) and thickness loss ($p<0.05$ and $p<0.0001$ respectively) in articular cartilage over time.

Conclusion: The mtDNA haplogroups manifest an intrinsic relation with OA progression in terms of cartilage integrity; carriers of this mitochondrial variant show a slower disease progression than haplogroup H carriers (most common in Caucasian population). The early haplogroup assignment could be crucial for an effective follow-up of the disease and a fit treatment.

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The Uncoupling mtDNA Haplogroup T Associates With Better Radiographic Progression Of Osteoarthritis. Data From The Osteoarthritis Initiative (OAI). Angel Soto-Hermida[1], Ignacio Rego-Pérez[1], Mercedes Fernández-Moreno[1], Sonia Pértega-Díaz[2], Juan Fernández-Tajes[1], María Eugenia Vázquez-Mosquera[1], Estefanía Cortés-Pereira[1], Sara Relaño-Fernández[1], Natividad Oreiro-Villar[1], Carlos Fernández-López[1] and Francisco J. Blanco[3]. [1]INIBIC-Hospital Universitario A Coruña. Rheumatology Division. Genomic Group, A Coruña, Spain, [2]INIBIC-Hospital Universitario A Coruña. Epidemiology and Public Health Unit, A Coruña, Spain, [3]CIBER-BBN-ISCIII, Madrid, Spain.

Background/Purpose: The Osteoarthritis Initiative (OAI) is a multicentre study focused on identifying and evaluating risk factors of knee osteoarthritis (OA). Previous studies carried out by our group showed the role of the mitochondrial DNA (mtDNA) haplogroups on the prevalence and severity of OA. The aim of this study is to replicate our previous findings about the influence of the mtDNA haplogroups on OA progression in the well characterized cohort of the OAI.

Methods: We assigned the mtDNA haplogroups in 891 Caucasian samples of the progression subcohort of the OAI to analyse their influence on radiographic OA progression attending to: KL grade, joint space narrow (JSN), presence of osteophytes and subchondral sclerosis in media tibial compartment between baseline and visit 6 (48 months). The progression criteria for KL grade consisted in an increase of at least one (KL or OARSI) grade at any visit and any knee; for JSN if an increase in score by a grade[3] 0.5 of the OARSI scale at any visit and any knee occurred. Additionally, we also analysed the four-year change in radiographic medial joint space width (mJSW) at $x=0.225$ in ($N=265$) patients with baseline unilateral JSN in both JSN knees (OARSI atlas grade ≥ 1) and non-JSN knees (OARSI atlas grade < 1).

Appropriate statistical analyses adjusting by gender, age and body mass index (BMI) at baseline were carried out using SPSS software (v.19) and R software v2.10.0 (The R Foundation for Statistical Computing).

Results: OA patients in the progression subcohort that carry the mtDNA haplogroup T showed the lowest significant cumulative probability of progression in terms of KL grade (Relative Risk (RR) = 0.490; 95% Confidence Interval (CI): 0.208–0.762; $p < 0.05$), osteophytes (RR = 0.490; 95% CI: 0.208–0.762; $p < 0.05$), subchondral esclerosis (RR = 0.490; 95% CI: 0.208–0.762; $p < 0.05$) and JSN (RR = 0.490; 95% CI: 0.208–0.762; $p < 0.05$) when compared with OA patients that carry the most common mtDNA haplogroup H.

Regarding to mJSW at $x=0.225$ in both knees of patients with unilateral JSN during the follow-up period of 48 months, the results obtained showed that carriers of the haplogroup T had a significant smaller decline in the mJSW at $x=0.225$ in non-JSN knees ($p = 0.033$). For JSN knees, though carriers of the haplogroup T showed the smallest decline too, the differences did not reach the statistical significance.

Conclusion: This work strength the hypothesis that mitochondrial genome is a key factor in the progression of the OA disease. The early identification and classification of patients with haplogroup T and the most common haplogroup H would permit to carry out a more personalized follow-up of the disease.

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Identification Of Autoimmune Disease Risk Alleles That Are Under Recent Selection In The Sea Island Gullah African Americans. Carl D. Langefeld[1], Satria Sajuthi[1], Jasmin Divers[1], Yiqi Huang[2], Uma Nayak[2], Wei-Min Chen[2], Kelly J. Hunt[3], Diane L. Kamen[3], Gary S. Gilkeson[3], Jyotika K. Fernandes[3], Ida J. Spruill[3], W. Timothy Garvey[4], Michèle M. Sale[2] and Paula S. Ramos[3]. [1]Wake Forest School of Medicine, Winston-Salem, NC, [2]University of Virginia, Charlottesville, VA, [3]Medical University of South Carolina, Charleston, SC, [4]University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: The reasons for the ethnic disparities in rheumatic and autoimmune diseases (AIDs) are largely unknown. Given the increasing evidence of selection at loci associated with human diseases, identification of alleles under selection may provide further insight into disease susceptibility. The Gullahs form a unique population of African ancestry in the U.S. In addition to their relative genetic and environmental homogeneity and low European admixture, a shorter genetic distance between the Gullahs and Sierra Leoneans has also been reported, suggesting that population genetic signals, such as regions under recent selection, may be more easily detected in the Gullahs than in other African American (AA) populations. We sought to capitalize upon the relative closeness between the Gullah and Sierra Leoneans to identify regions that differentiate both populations and may hence be under recent population-specific selective pressures. The goal of this study was to identify regions that might be under recent positive selection in the Gullah and that harbor risk loci for AIDs, which may help explain the higher prevalence of autoimmunity in AA.

Methods: We computed a linear regression model using the principal component of the HapMap Yoruba (YRI) population from Nigeria (PC2) as a quantitative outcome, using 277 Gullah and 400 Sierra Leonean samples genotyped on the Affymetrix Genome-Wide Human SNP Array 6.0. We adjusted for European admixture via inclusion of the HapMap Caucasian (CEU) population component (PC1) as a covariate. In total, 679,513 SNPs with MAF>5% were used in this analysis. In order to exclude spurious loci, only regions where at least one SNP met genome-wide significance (P<5E-10) and a second significant SNP (P<E-07) in LD with it were considered. We then checked for the presence of immune/autoimmune-related genes in these regions.

Results: Nine regions met our criteria as those that best differentiate the Gullah from the Sierra Leonean. The most significant was a ~2 Mb region at Xq22.2-q22.3 around the IL1RAPL2 gene, where 4 SNPs had P<5E-10. Of the other 8 regions, half encompass immune-function genes: TLR3 at 4q35.1, CD83 at 6p23, the extended HLA at 6p22.1-21.32, and RAPGEF5-IL6 at 7p15.3. The CD83 region is associated with rheumatoid arthritis, the HLA region with all AIDs, and the RAPGEF5-IL6 region with dialysis-related mortality in AA and CRP levels.

Conclusion: We have identified several regions that harbor immune function genes and differentiate the Gullah from the Sierra Leoneans, suggesting that recent selection may be operating at these loci. Given the relative homogeneity of the Gullah and their genetic proximity to Africans from Sierra Leone, identification of regions that might be under selection and harbor immune-related genes in the Gullah has the potential to elucidate AID risks in AA.

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Identification Of Autoimmune Disease Genes In Regions Under Selection In The Gullah African American Population Of South Carolina. Paula S. Ramos[1], Nathan Titus[2], Satria Sajuthi[2], Jasmin Divers[2], Yiqi Huang[3], Uma Nayak[3], Wei-Min Chen[3], Kelly J. Hunt[1], Diane L. Kamen[1], Gary S. Gilkeson[1], Jyotika K. Fernandes[1], Ida J. Spruill[1], W. Timothy Garvey[4], Michèle M. Sale[3] and Carl D. Langefeld[2]. [1]Medical University of South Carolina, Charleston, SC, [2]Wake Forest School of Medicine, Winston-Salem, NC, [3]University of Virginia, Charlottesville, VA, [4]University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Most autoimmune diseases (ADs) are more prevalent in specific ethnic groups. We hypothesize that one reason for the ethnic disparity may be an effect of population-specific selection influencing the allele frequencies at some loci. Selection for specific alleles that improves fitness and survival in a specific environment can lead to increased disease risk in a different environment. Given the growing number of disease-associated loci in regions that show evidence of selection, identification of alleles under selection may provide insight into disease susceptibility. Relative to other African-Americans (AA), the AA Gullah population has lower European admixture and higher ancestral homogeneity from the Sierra Leone area in Far-West Africa. The shorter genetic distance between the Gullahs and Sierra Leoneans suggests that population genetic signals, such as regions under recent selection, may be more easily detected in the Gullahs than in other African American (AA) populations. The goal of this study was to identify regions under recent positive selection in the Gullahs that may harbor risk loci for ADs.

Methods: We computed the cross population extended haplotype homozygosity test (XP-EHH) to identify alleles with higher than expected frequency relative to their haplotype length in one population relative to another. We compared 277 control Gullahs to 400 Sierra Leonean controls and to 203 HapMap Yorubans (YRI) from Nigeria. A total of 679,513 SNPs with MAF>5% met all statistical quality control criteria. Regions that met genome-wide significance ((|XP-EHH|>4, P<E-07) were followed to assess for overlap with regions known to be associated with ADs.

Results: We identified multiple regions with evidence of recent selection. Over 20 regions showed evidence of selection between the Gullah and the Sierra Leoneans (|XP-EHH|>4, P<E-07). They revealed an enrichment of genes involved in resistance to HIV infection (P-Bonferroni=0.017). Half of these regions showed evidence of selection in the Gullahs, including regions associated with ADs: *DAB1* (Kawasaki disease), *KCNH8* (Crohn's disease, psoriasis), and *LPP* genes (vitiligo, celiac disease). Twenty four regions showed evidence of selection between the Gullah and the YRI, revealing an enrichment of genes involved in cytokine/chemokine mediated immunity (P-Bonferroni= 0.0015), but only two regions were being selected for in the Gullahs, none of which has previously shown evidence of association with an AD. Regions associated with ADs showing evidence of selection in the YRI population include those of the the HLA region (all ADs), the *CCR2* (celiac disease), and *SMOC2* genes (vitiligo), with *CCR2* also showing evidence of selection in the Sierra Leone population. This scan also identified the region around the APOL1 gene, which has been shown to be under selection and associated with multiple kidney diseases in AAs.

Conclusion: We have identified several risk alleles for ADs that are targets of recent positive selection in an AA population. Given the increased prevalence of several ADs in AAs and the homogeneity of the Gullahs, identification of these regions in the Gullahs has the potential to elucidate AD risks in AAs and help explain the ethnic disparity.

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Exome Sequencing For Identification Of Potential Causal Variants For Diffuse Cutaneous Systemic Sclerosis. Angel CY Mak[1], M Kari Connolly[2], Tamiko Katsumoto[3], Paul Wolters[4], Clare Cleveland[3], Blanca M Herrera[1], Paul LF Tang[1], Simi Mathauda[1], Richard Lao[1], Pui-Yan Kwok[1] and Lindsey A. Criswell[3]. [1]University of California, San Francisco, Institute for Human Genetics, San Francisco, CA, [2]University of California, San Francisco, Department of Dermatology, San Francisco, CA, [3]University of California, San Francisco, Rosalind Russell Medical Research Center for Arthritis, San Francisco, CA, [4]University of California, San Francisco, Department of Medicine, Pulmonary Division, San Francisco, CA.

Background/Purpose: Scleroderma is a genetically complex autoimmune disease with substantial phenotypic heterogeneity. Previous genome-wide association studies (GWAS) have identified a large number of gene regions associated with disease risk. However, GWAS directly capture only common genetic variation that are presumably in linkage disequilibrium with causal variants, which may be rare in the general disease population. Our goal was to identify rare and potentially causal variants through performance of whole exome sequencing. We focused on patients with severe disease, and specifically those with diffuse cutaneous systemic sclerosis (dcSSc), to limit disease heterogeneity.

Methods: Our initial exome-sequencing studies were performed on 24 dcSSc patients using the Illumina HiSeq2500 platform and the Nimblegen SeqCap EZ v3.0 exome enrichment protocol. We also studied 60 healthy control subjects who underwent exome sequencing in the same laboratory using comparable methods. Exome sequencing reads were processed using the automated pipeline for next-generation sequencing data (bcbio-nextgen, https://github.com/chapmanb/bcbio-nextgen) and variants were annotated with ANNOVAR. We applied a gene burden test to identify genes that were enriched or depleted with rare (MAF≤0.01) and functionally deleterious (SIFT≤0.05) variants in dcSSc patients compared to control individuals.

Results: Paired 100bp end reads were generated with a mean coverage of 56X on the targeted exome regions (64Mb). We identified 31 genes that were enriched or depleted with rare and functionally deleterious variants in dcSSc patients. Among the 31 genes, 6 genes (*ADAMTS8, ALMS1, CHST15, DACH1, FMNL2, RELN*) were in previously identified scleroderma susceptibility loci or pathways implicated in scleroderma pathogenesis.

Conclusion: Using exome sequencing and gene burden analysis, we identified 31 genes that contain rare and potentially functionally deleterious variants that may contribute to the development of dcSSc. This pilot study demonstrates the potential value of whole exome sequencing for the identification of causal variants that contribute to scleroderma risk and/or severity.

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Cartilage Peptide Profiling: Identifying Novel OA Biomarkers For Early Disease Detection. Valentina Calamia, Lucía Lourido, Diego López, Jesus Mateos, Patricia Fernández-Puente, Carolina Fernández-Costa, Beatriz Rocha, Cristina Ruiz-Romero and Francisco J. Blanco. Osteoarticular and Aging Research Laboratory, Proteomics Unit-Associated Node to ProteoRed-ISCIII, INIBIC-CHUAC, A Coruña, Spain.

Background/Purpose: Cartilage secretome contains a complex matrix of proteolytically derived peptides that may provide useful information of the biological events occurring in the articular joint in normal and pathological condition. Moreover, the low-molecular-weight subset of the cartilage proteome may have a diagnostic potential in osteoarthritis (OA) research, not fully exploited yet. The aim of this study is to investigate cartilage secretome by means of peptidome analysis and to provide a novel source for OA biomarker discovery.

Methods: Tissue explants were obtained from the dissection of human OA cartilages, both from the wounded zone (WZ) and the unwounded zone (UZ). The study was approved by the local ethical committee. Cartilage shavings from each zone were cut into 6 mm discs and five discs/zone were placed into 96 wells plates and incubated (37 °C/5% CO2) in serum-free DMEM up to 6 days. Conditioned media from each condition were collected at day 1, 3 and 6. Selective extraction of endogenous peptides was realized by combining ultrafiltration and solid phase extraction. Then, the peptides were directly analyzed by nano reversed-phase liquid chromatography (RP-LC) in an Easy nLC II system coupled to an ion trap LTQ Orbitrap Velos Pro mass spectrometer (Thermo Scientific) without trypsin digestion. Protein/peptide identifications were searched against human database using the SEQUEST algorithm (Proteome Discoverer 1.3, Thermo Scientific).

Results: Firstly we compared the profiles of peptides released to the media at different times (0, 3, and 6 days in culture). At day 3 we detected the highest number of unique peptides and proteins, and the lowest serum contamination. Thus, we selected day 3 as the best point for the next proteomic analysis in which we compared peptide profiles from WZ and UZ. This study led to the detection of a panel of 262 peptides corresponding to 36 proteins that were differentially released from the WZ and UZ in OA cartilage. Most of them were cartilage ECM proteins or proteins with well-established matrix functions, such as collagens and proteoglycans, thus indicating the high cartilage-specific biomarker concentration present in our samples. 18 peptides were detected only in the WZ (corresponding to 5 proteins: K1C9, K1C10, PRPC, FIBA, and DCD) while 60 peptides only in the UZ (corresponding to 20 proteins: ACAN, CILP1, CILP2, COL11A2, COL1A2, COL25A1, LTBP2, MGP, and PRELP among others) (Table 1). 11 proteins (BGN, CLU, COL1A1, COL2A1, COL3A1, COL5A2, COMP, and FN1 among others) were detected in both zones but in all the cases the number of peptides was higher in the UZ than in the WZ.

Table 1. Examples of peptides detected at high levels (High) in UZ samples and not detected (ND) in WZ samples, potentially useful as early OA biomarkers.

Protein name	Accession no.	Sequence	MH+ [Da]	UZ	WZ
Cartilage intermediate layer protein 1 (CILP1)	O75339	ETNIIPLGEV	1084,58911	High	ND
		DWTPAGSTGQV	1118,51025	High	ND
		WTPAGSTGQV	1003,48511	High	ND
		SLPGGAPASGAA	955,48291	High	ND
Matrix Gla protein (MGP)	P08493	NANTFISPQQR	1275,64385	High	ND
		NANTFISPQ	991,48334	High	ND
		NPFINR	760,40991	High	ND
		VYGYNA	686,31451	High	ND

Conclusion: To our knowledge this is the first proteomic study specifically focused on cartilage peptidome analysis. In this work we analysed the cartilage endogenous peptides profile and highlighted its potential application as novel OA biomarker source for early disease detection.

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Application Of a Multiplex Gene Polymorphism Assay For Variants Associated With Rheumatoid Arthritis Susceptibility: Results Of 168 Single Nucleotide Polymorphisms In The Optima Study. Jeffrey F. Waring[1], Viswanath Devanarayan[2], Kenneth Idler[1], Feng Hong[2], Josef S. Smolen[3], Arthur Kavanaugh[4], Hartmut Kupper[5], Hendrik Schulze-Koops[6] and Alla Skapenko[6]. [1]AbbVie Inc., North Chicago, IL, [2]AbbVie Bioresearch Center, Worchester, MA, [3]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [4]University of California San Diego, La Jolla, CA, [5]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany, [6]University of Munich, Munich, Germany.

Background/Purpose: Genetic factors have been identified that may be associated with the development and severity of rheumatoid arthritis (RA), disease progression, or response to treatment. In-depth knowledge about RA susceptibility genes may thus prove useful for the development of future diagnostic tests or personalized therapeutics. Frequencies from previously investigated RA susceptibility gene polymorphisms from patients enrolled in the OPTIMA trial were compared to a control database to identify genetic risk factors for RA.

Methods: OPTIMA was a 78-week, multicenter, randomized study designed to assess adalimumab plus methotrexate therapy in early RA patients.(1) Of 1032 patients, genetic analysis was conducted on 921 patients who signed an additional informed consent for genetic analyses. Frequency rates for 168 identified RA susceptibility alleles from 88 genes were compared to the European cohort of the 1000 Genomes Project as a reference control.(2) Genotypic variants were assayed using the Illumina BeadXpress GoldenGate Assay. The largest deviations in the OPTIMA minor allele frequencies (MAFs), those > 0.05 compared to the control, were further investigated. Logistic regression was used to calculate odds ratios (OR) for RA susceptibility. Association of alleles with 28-joint count disease activity score (DAS28) and age were conducted using ANOVA comparing the OPTIMA cohort with the control cohort.

Results: The majority of single nucleotide polymorphism (SNP) MAFs from the OPTIMA study did not deviate > 0.05 from MAFs reported in the European cohort from the 1000 Genomes Project. Within known RA susceptibility genes or those with treatment response, 7 of 63 SNPs previously investigated as being associated with increased RA risk deviated > 0.05 from reference controls in OPTIMA patients and were investigated further; 11 SNPs that had not been previously associated with RA susceptibility had MAF differences > 0.05 comparing OPTIMA with the reference control. The BTLA SNP rs9288952 G allele displayed the highest OR for RA risk, 3.60 (95% CI, 2.49 – 5.20), was weakly associated with higher baseline DAS28, and also associated with patient age (mean ages were 50.9, 49.0, and 44.3 for genotypes A/A, A/G, and G/G, respectively), suggesting a potential association with onset at earlier or later age. STAT4 rs7574865 minor allele homozygosity was associated with higher baseline DAS28 scores. Of the previously unidentified RA susceptibility gene SNPs, only PDZD2 rs1532269 was significantly associated with higher baseline DAS28 scores.

	Gene	SNP	1000 Genomes MAF	OPTIMA MAF	Difference Between MAFs	Odds Ratio (95% CI)
Previously Investigated RA Susceptibility Gene SNPs	BTLA	rs9288952	0.04	0.15	0.11	3.60 (2.49–5.20)***
	FNDC1/TAGAP	rs394581	0.32	0.26	0.06	0.75 (0.62–0.90)**
	HLA-DPB1/HLA-DPB2	rs3117213	0.26	0.18	0.08	0.62 (0.51–0.76)***
	HLA-DQB1/HLA-DQA2	rs6457617	0.45	0.33	0.12	0.62 (0.52–0.73)**
	IL23R/IL12RB2	rs1495965	0.49	0.42	0.07	0.76 (0.64–0.90)***
	PTPN22	rs2476601	0.01	0.13	0.12	1.31 (0.99–1.72)#
	STAT4	rs7574865	0.23	0.29	0.06	1.37 (1.13–1.67)**
Previously Unidentified RA Susceptibility Gene SNPs	FAM167A/BLK	rs13277113	0.33	0.25	0.08	1.49 (1.23–1.81)***
	HLA-DPB1	rs3135021	0.36	0.28	0.08	1.48 (1.23–1.78)***
	NOS3	rs2070744	0.33	0.41	0.07	0.73 (0.61–0.87)***
	PDZD2	rs1532269	0.44	0.37	0.07	1.35 (1.14–1.61)***
	PTPN22	rs2488458	0.34	0.27	0.07	1.41 (1.17–1.70)***
	PTPRC	rs1326279	0.38	0.31	0.07	1.36 (1.13–1.63)***
	PTPRC	rs12144388	0.37	0.31	0.06	1.31 (1.09–1.57)**
	STAT4	rs12463658	0.47	0.40	0.07	1.35 (1.14–1.60)***
	STAT4	rs3024877	0.37	0.30	0.07	1.36 (1.14–1.64)***
	STAT4	rs1031509	0.20	0.27	0.07	0.70 (0.57–0.85)***
	STAT4	rs11693480	0.46	0.40	0.06	1.29 (1.08–1.53)**

MAF, minor allele frequency; SNP, single nucleotide polymorphism.
** and
*** denote statistical significance at the $p < 0.01$ and 0.001 levels, respectively.
# significant when homozygous for the minor allele.

Conclusion: Genes identified with increased RA risk have known roles in immune responses including mediation of lymphocyte signaling,

proliferation, and differentiation. The MAFs of 18 gene SNPs in the OPTIMA study differed from a healthy control population; further investigation into these SNPs will clarify their role in RA susceptibility and disease progression.

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The Use Of "Autoantigenomics" To Rapidly Identify Targets Of Human Autoantibodies. Wei-Hong Yang, Emily G. Bloch, Daniel F. Berenson, Rita L. Galdos, Pankaj Arora, Connie Wu and Donald B. Bloch. Massachusetts General Hospital and Harvard Medical School, Boston, MA.

Background/Purpose: The messenger RNA (mRNA) processing body (P-body) is a cellular structure that regulates the stability of cytoplasmic mRNA. Approximately 5% of patients with the autoimmune disease primary biliary cirrhosis (PBC) have antibodies directed against this structure and some patients have antibodies that react with several different known P-body components. In this study, we used a proteomic array and serum from a PBC patient to rapidly and efficiently identify a new P-body component.

Methods: Serum from patient 0081 was used to probe a high density protein macroarray which contains approximately 17,000 proteins. The proteins were produced *in situ* on a polyvinylidene difluoride (PVDF) membrane by *Escherichia coli* transformed with a prokaryotic expression cDNA library. This library was derived from mRNA prepared from phyto-hemagglutinin treated human T-lymphocytes. Human auto-antibodies that bound to the protein macroarray were detected using horse-radish peroxidase-conjugated rabbit anti-human IgG antiserum and chemiluminescence. Immunoreactive protein targets of these autoantibodies were determined by their locations on the PVDF membrane. Immunoblot was then used to confirm that serum 0081 contained antibodies that reacted with newly indentified auto-antigens. Human epidermoid cancer cells (HEp-2 cells) were transfected with plasmids encoding green fluorescent protein (GFP) fused to the new P-body component candidates, to confirm that the proteins localized to P-bodies.

Results: Serum 0081 reacted with fifty-six proteins on the protein macroarray membrane. One of these new proteins, Limkain B (LMKB), was chosen for further study because it was previously reported to localize to a "subset of peroxisomes", a staining pattern that might appear similar to the P-body pattern. Antibodies in serum 0081 reacted with glutathione *S*-transferase (GST)-LMKB, but not GST alone, by immunoblot. A plasmid encoding full-length LMKB fused to GFP was used to express the protein in HEp-2 cells. LMKB localized to cytoplasmic dots and co-localized with Ge-1, a known P-body component.

Conclusion: Our findings demonstrate that the combination of proteomic array technology and human autoantibodies provides a useful tool for identifying new autoantigens. "Autoantigenomics" can be used to rapidly and efficiently discover new proteins in cellular structures. Using this method, we identified LMKB as a novel component of mRNA processing bodies.

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Transcriptomic Blood Markers and Molecular Stratification In Sarcoidosis. Robert Su, Michael Li, Nirav Bhakta, Misha Agarwal, Prescott Woodruff and Laura Koth. University of California San Francisco, San Francisco, CA.

Background/Purpose: Sarcoidosis is a heterogeneous disease with diverse manifestations and varied clinical courses. Currently there are no reliable non-invasive biomarkers of disease activity or severity. The aim of this study was to identify "pathway-specific" blood gene expression signatures in subjects with sarcoidosis and to ascertain whether these signatures identify distinct subsets of patients and correlate with measures of disease severity.

Methods: We analyzed whole blood RNA (PAXgene RNA tubes) from 38 patients with sarcoidosis and 20 healthy controls using Affymetrix U133 Plus 2.0 microarrays (Affymetrix Inc., Santa Clara, CA). Correcting with the Benjamini-Hochberg method, we found differentially expressed (DE) genes that were upregulated in sarcoidosis compared to controls. We performed Ingenuity Pathway Analysis (IPA) and then hierarchical clustering (MultiExperiment Viewer) using selected genes representative of canonical pathways highly up-regulated in sarcoid. Standardized expression levels of DE genes were correlated with measures of pulmonary function testing (PFT). Whole blood DE genes expression levels were compared to levels found in publically available sarcoidosis tissue gene expression datasets (Gene Expression Omnibus GSE32887, GSE19976).

Results: 193 DE genes associated with a B-statistic > 0 (adjusted p value <0.006) were upregulated in sarcoidosis. These genes were associated with interferon (IFN), TNFα, and TGF-β1 signaling pathways. Hierarchial clustering of subjects using genes representative of IFN and TNFα pathways revealed different patient subsets, including subjects with IFN-high/TNFα-low or IFN-low/TNFα-high signatures, and subjects with dual IFN/TNFα-high or dual IFN/TNFα low signatures. Expression levels of TGF-β1-associated genes (*SKIL*, *USP15*, *LPCAT2*) correlated with PFT measures of restrictive lung volumes and decreased oxygenation, including FVC% predicted ($R^2 = 0.39$, $p<0.0001$), TLC% predicted ($R^2 = 0.26$, $p = 0.001$), and DLCO% predicted ($R^2 = 0.2$, $p = 0.004$). Expression levels of TNFα-inducible genes (*TNFAIP2, PLAUR, ICAM1*) correlated with degree of pulmonary obstruction as measured by FEV1/FVC ($R^2= 0.26$, $p = 0.001$). Expression of these pathway-specific genes was elevated in lesional sarcoid skin and progressive fibrotic sarcoid lung biopsy gene expression datasets.

Conclusion: Based on these data we hypothesize that IFN-, TNFα-, and TGF-β1-specific gene expression biomarkers reflect distinct subgroups of patients with sarcoidosis and signaling pathways that may play a pathogenic role in sarcoidosis. TGF-β1-associated DE gene expression levels may reflect severity of pulmonary fibrosis. We plan to test this hypothesis in a larger longitudinal cohort to 1) validate our groupings, 2) determine whether these signatures are stable over time or vary with disease activity, 3) determine whether these groupings have prognostic value.

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Association Analysis Of The Organic Anion Transporter 4 and Urate Transporter 1 Locus With Gout In New Zealand Case-Control Sample Sets Reveals Multiple Ancestral-Specific Effects. Tony R. Merriman[1], Amanda Phipps-Green[1], Jade E. Hollis-Moffatt[1], Marilyn E. Merriman[1], Ruth Topless[1], Grant Montgomery[2], Brett Chapman[2], Lisa K. Stamp[3], Nicola Dalbeth[4] and Tanya Flynn[1]. [1]University of Otago, Dunedin, New Zealand, [2]Queensland Institute of Medical Research, Brisbane, Australia, [3]University of Otago, Christchurch, Christchurch, New Zealand, [4]University of Auckland, Auckland, New Zealand.

Background/Purpose: There are genetic variants in urate transporters SLC22A11 (OAT4) and SLC22A12 (URAT1) that influence serum urate levels in European Caucasian. However, there is no consistent evidence for association with risk of gout. The aim of this study was to test genetic variation across the SLC22A11 and SLC22A12 locus for association with gout risk in New Zealand sample sets. The sample sets include Mβori and Pacific Island (Polynesian) participants, who exhibit higher prevalence and more severe gout than European Caucasian.

Methods: Twelve single nucleotide polymorphism (SNP) variants in four haplotype blocks were genotyped using TaqMan¨ and Sequenom MassArray in 1003 gout cases and 1156 controls. Gout was classified according to the 1977 American Rheumatism Association criteria. Association analysis of single markers and haplotypes was done using PLINK and STATA.

Results: SNP *rs17299124* (upstream of *SLC22A11*) in haplotype block 1 was associated with gout in the Polynesian sample sets with higher Polynesian ancestry, but not in Maori and Pacific with lower Polynesian ancestry and European Caucasian (OR=3.38, P=0.001; OR=0.94, P=0.54, respectively) (Table). A protective block 1 haplotype, rarer in Polynesian, was driving the association (OR=0.28, P=0.001). Within haplotype block 2 (*SLC22A11*) we could not replicate previous reports of association of *rs2078267* with gout in European Caucasian and people

with lower Polynesian ancestry (OR=1.00, P=1.00), however this SNP was associated with gout in people with higher Polynesian ancestry (OR=1.84, P=0.012). Within haplotype block 3 (including *SLC22A12*) there was evidence for association for SNP *rs3825018* in all ancestral groups (OR=1.27, P=0.002). Analysis of haplotypes revealed a haplotype with trans-ancestral protective effects (OR=0.80, P=0.004), and a second haplotype conferring protection in the less admixed Polynesian sample sets (OR=0.63, P=0.028) but risk in European Caucasian samples (OR=1.33, P=0.039).

Table. Allelic associations

SNP (haplotype block)	European Caucasian and low ancestry Polynesian			High ancestry Polynesian			All ancestries		
	OR [95% CI]	P	Het P[1]	OR [95% CI]	P	Het P[1]	OR [95% CI]	P	Het P[1]
rs475414 (1)	1.02 [0.85–1.22]	0.86	0.99	1.15 [0.92–1.43]	0.23	0.73	1.07 [0.93–1.23]	0.38	0.86
rs17299124 (1)	0.94 [0.76–1.16]	0.54	0.43	3.38 [1.69–6.79]	0.001	0.67	1.71 [0.89–3.28]	0.11	0.010
rs693591 (2)	0.99 [0.78–1.26]	0.94	0.56	1.25 [1.00–1.57]	0.051	0.053	1.12 [0.95–1.33]	0.17	0.087
rs17300741 (2)	1.08 [0.90–1.29]	0.40	0.45	1.04 [0.78–1.38]	0.79	0.17	1.07 [0.92–1.24]	0.40	0.39
rs2078267 (2)	1.00 [0.84–1.20]	1.00	0.50	1.84 [1.14–2.95]	0.012	0.80	1.08 [0.91–1.28]	0.37	0.17
rs3825018 (3)	1.24 [1.02–1.50]	0.028	0.66	1.33 [1.05–1.69]	0.020	0.57	1.27 [1.10–1.48]	0.002	0.82
rs475688 (3)	1.31 [1.06–1.60]	0.011	0.36	0.95 [0.76–1.20]	0.68	0.22	1.13 [0.97–1.32]	0.11	0.093
rs7932775 (3)	1.32 [1.05–1.66]	0.017	0.92	1.21 [0.97–1.51]	0.095	0.26	1.26 [1.08–1.48]	0.004	0.55
rs476037 (3)	1.05 [0.78–1.40]	0.77	0.87	1.25 [0.67–2.34]	0.48	0.014	1.08 [0.89–1.31]	0.42	0.070
rs478607 (3)	1.33 [1.05–1.70]	0.020	0.37	1.04 [0.79–1.36]	0.79	0.15	1.19 [1.00–1.43]	0.056	0.17
rs12289836 (4)	0.87 [0.72–1.05]	0.16	0.44	0.89 [0.70–1.13]	0.33	0.72	0.88 [0.76–1.02]	0.085	0.86
rs642803 (4)	0.97 [0.81–1.16]	0.73	0.27	0.95 [0.76–1.19]	0.66	0.86	0.96 [0.84–1.11]	0.59	0.82

[1]Heterogeneity P-value, $P < 0.05$ indicates significant heterogeneity.

Conclusion: Our analysis demonstrates several ancestral-specific effects across the SLC22A11/SLC22A12 locus indicating that multiple common variants influence the activity of both OAT4 and URAT1 in relation to risk of gout. These results clarify some of the previous inconsistent gout associations seen, and indicate that further fine mapping of the association signal is needed.

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H3K9 Demethylation By LSD1 Contributes To IL-1-Induced mPGES-1 Expression In OA Chondrocytes. Fatima Ezzahra El Mansouri and Hassan Fahmi. Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC.

Background/Purpose: Microsomal prostaglandin E synthase-1 catalyzes the terminal step in the biosynthesis of PGE_2, which plays a critical role in the pathophysiology of osteoarthritis. To investigate the role of histone H3 (H3K9) methylation in interleukin-1b (IL-1)-induced microsomal prostaglandin E synthase-1 (mPGES-1) expression in human osteoarthritic (OA) chondrocytes.

Methods: Chondrocytes were stimulated with IL-1 and the expression of mPGES-1mRNA was analyzed using real-time reverse transcriptase-polymerase chain reaction. H3K9 methylation and the recruitment of the histone demethylase LSD1 to the mPGES-1 promoter were evaluated using chromatin immunoprecipitation assays. The role of LSD1 was further evaluated using the the amino oxidase inhibitor tranylcypromine (a potent inhibitor of LSD1 activity).

Results: Treatment with IL-1 induced mPGES-1 expression in a time dependent manner. The induction of mPGES-1 expression by IL-1 was associated with H3K9 demethylation at the mPGES-1 promoter. These changes were concomitant with the recruitment of the histone demethylase LSD1. Treatment with tranylcypromine inhibited IL-1-induced H3K9 demethylation as well as IL-1-induced mPGES-1 expression.

Conclusion: These results indicate that H3K9 demethylation by LSD1 contributes to IL-1-induced mPGES-1 expression and suggest that this pathway could be a potential target for pharmacological intervention in the treatment of OA and possibly other arthritic diseases.

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Genotypic and Haplotypic Effects Of 7 Single-Nucleotide Polymorphisms In the *CRP* Gene On Levels Of C-Reactive Protein and DAS28 In a Cohort Of 180 Untreated Newly Diagnosed Rheumatoid Arthritis Patients (OPERA Study). Christian G. Ammitzbøll[1], Rudi Steffensen[2], Peter Junker[3], Mikkel Østergaard[4], Julia Johansen[5], Jan Pødenphant[6], Merete Lund Hetland[7], Hanne M. Lindegaard[8], Torkell Ellingsen[9] and Kristian Stengaard-Pedersen[1]. [1]Arhus University Hospital, Aarhus, Denmark, [2]Aalborg University Hospital, Aalborg, Denmark, [3]University of Southern Denmark, Odense, Denmark, [4]Copenhagen University Hospital Glostrup, Copenhagen, Denmark, [5]Copenhagen University and Glostrup Hospital, Copenhagen, Denmark, [6]Copenhagen University at Gentofte, Hellerup, Denmark, [7]The Danish Rheumatologic Database (DANBIO), Glostrup Hospital, Copenhagen, Denmark, [8]Odense University Hospital, Odense, Denmark, [9]Diagnostic Centre Region Hospital Silkeborg Denmark, 8600 Silkeborg, Denmark.

Background/Purpose: Single nucleotide polymorphisms (SNPs) in the *CRP* gene are implicated in the regulation of the basal C-reactive protein (CRP) expression and its response to pro-inflammatory stimuli. Previous reports suggest these effects may have an impact on clinical decision-making based on CRP, e.g. DAS28 (1). We aimed to investigate for the first time the possible association between 7 SNPs in the *CRP* and the serum level of CRP/ DAS28 in a cohort of 180 untreated inflammatory active early RA patients

Methods: 180 DMARD naïve RA patients with disease duration <6 months were included in a randomized double blind placebo-controlled trial (OPERA-study,NCT00660647) of methotrexate, intraarticular glucucorticoids + either adalimumab or placebo. SNPs were analyzed by the TaqMan OpenArray system. The 7 SNPs (Table 2) were selected based on previously reported effects on CRP levels(1). CRP was measured using CRP QUICK-READ (range 8–160 mg/l). The associations between SNPs (and haplotypes of SNPs) and CRP and DAS28 levels were evaluated using linear regression analysis adjusted for age, sex and treatment. For the analysis of genotypic and haplotypic effects, the common allele homozygous genotype/haplotype was selected as reference, and the effects are presented as percentage. 'Haplo.stats' package for R was used

Results: Baseline characteristics were similar in the two groups, Table 1. There were no significant genotypic or haplotypic effects of the 7 SNPs on CRP levels at baseline or one year (P≥0.080). Homozygosity for the minor allele of rs2808632 reduced borderline significant the baseline DAS28 levels to 54% P=0.055, and heterozygosity for rs1800947 increased DAS28 levels at one year to 158% P=0.03. Six haplotypes were constructed encompassing 94% of the cohort, Table 3. The H4 haplotype reduced baseline DAS28 score to 51% P=0.009, and the H6 haplotype increased the DAS28 score at one year to 168% P=0.02. No further haplotypic effect on DAS28 were observed at baseline or one year.

Table 1. Patient characteristics

	OPERA Placebo treated group (n=91)	OPERA Adalimumab treated group (p=89)	P value
Patient characteristics			
Female sex	69%	63%	0.46
Age, years	54 (28–77)	56 (26–78)	0.71
Disease duration, days	83 (42–150)	88 (42–162)	0.74
Anti-CCP positive	70%	60%	0.17
IgM-RF positive	74%	70%	0.67
DAS28	5.6 (3.8–7.3)	5.5 (3.8–7.8)	0.53
C-reactive protein, mg/l	15 (7–109)	15 (7–133)	0.54
Tender joint count(28)	11 (3–24)	10 (3–27)	0.78
Swollen joint count(28)	8 (2–22)	8 (2–26)	0.66
VAS-patient global, mm	65 (17–96)	70 (12–100)	0.27
Baseline x-ray erosions (ES≥1)	52%	54%	0.94
Disease activity, 1 year			
DAS28	2.6 (1.7–4.7)	2.0 (1.7–5.2)	0.009
C-reactive protein, mg/l	7 (7–44)	7 (7–21)	0.21

Values are medians with 5–95% percentile values in parentheses, unless otherwise stated. Anti-CCP = anti-cyclic citrullinated peptide, RF = rheumatoid factor, DAS28 = disease activity score 28 joints, VAS = visual analogue scale, ES = Sharp/van der Heijde Erosion Score.

Table 2. Linear regression analyses of the genotype effect on the mean CRP and DAS28 levels relative to the major genotype.

			CRP levels relative to major genotype in %				DAS28 levels relative to major genotype in %			
Rs-number	**Genotype**	**%**	**Baseline**	**P value**	**Year one**	**P value**	**Baseline**	**P value**	**Year one**	**P value**
rs11265257	CC	38	100 (ref.)	–	100 (ref.)	–	100 (ref.)	–	100 (ref.)	–
	CT	46	103 (75–141)	P = 0.87	99 (85–115)	P = 0.88	95 (67–136)	P = 0.78	99 (75–130)	P = 0.92
	TT	16	79 (51–122)	P = 0.29	105 (85–129)	P = 0.68	85 (52–139)	P = 0.52	98 (68–141)	P = 0.90
rs1130864	GG	49	100 (ref.)	–	100 (ref.)	–	100 (ref.)	–	100 (ref.)	–
	AG	41	92 (67–125)	P = 0.58	97 (84–113)	P = 0.73	119 (84–167)	P = 0.32	109 (84–142)	P = 0.51
	AA	10	119 (72–199)	P = 0.50	88 (69–112)	P = 0.30	117 (67–207)	P = 0.58	109 (71–167)	P = 0.71
rs1205	CC	46	100 (ref.)	–	100 (ref.)	–	100 (ref.)	–	100 (ref.)	–
	CT	44	105 (77–143)	P = 0.75	89 (78–101)	P = 0.08	101 (71–142)	P = 0.97	86 (66–113)	P = 0.28
	TT	10	69 (42–114)	P = 0.15	99 (81–123)	P = 0.96	103 (59–182)	P = 0.91	102 (66–157)	P = 0.93
rs1800947	CC	89	100 (ref.)	–	100 (ref.)	–	100 (ref.)	–	100 (ref.)	–
	CG	11	88 (55–140)	P = 0.59	96 (75–122)	P = 0.73	127 (76–213)	P = 0.37	158 (103–241)	P = 0.03
rs2808632	TT	46	100 (ref.)	–	100 (ref.)	–	100 (ref.)	–	100 (ref.)	–
	GT	46	115 (85–155)	P = 0.37	97 (84–112)	P = 0.65	113 (81–158)	P = 0.46	104 (81–135)	P = 0.75
	GG	8	113 (64–200)	P = 0.67	117 (89–154)	P = 0.26	54 (29–101)	P = 0.06	99 (61–161)	P = 0.98
rs3093077	AA	89	100 (ref.)	–	100 (ref.)	–	100 (ref.)	–	100 (ref.)	–
	AC	11	94 (58–151)	P = 0.79	110 (88–137)	P = 0.41	80 (47–136)	P = 0.41	80 (54–118)	P = 0.26
rs876538	CC	60	100 (ref.)	–	100 (ref.)	–	100 (ref.)	–	100 (ref.)	–
	CT	37	128 (94–174)	P = 0.12	101 (87–117)	P = 0.93	131 (93–184)	P = 0.12	111 (85–144)	P = 0.45
	TT	3	124 (55–281)	P = 0.60	85 (56–129)	P = 0.44	57 (23–140)	P = 0.22	79 (38–165)	P = 0.53

Numbers in parantheses are 95% confidence intervals. Calculated by linear regression, corrected for treatment (placebo/adalimumab), age and gender. ref.=reference

Table 3. Linear regression analyses of the haplotype effect on the mean CRP and DAS28 levels relative to the major haplotype.

			CRP levels relative to major genotype in %		DAS28 levels relative to major genotype in %	
Haplotype	**Frequency**	**SNPs#**	**Baseline**	**Year one**	**Baseline**	**Year one**
H1	30 %	C A C C T A C	100 (ref.)	100 (ref.)	100 (ref.)	100 (ref.)
H2	26 %	T G T C T A C	93 (72–121) P = 0.58	93 (72–121) P = 0.58	91 (68–121) P = 0.51	83 (67–103) P = 0.10
H3	21 %	C G C C G A T	115 (86–154) P = 0.35	115 (86–154) P = 0.35	95 (69–131) P = 0.77	99 (77–126) P = 0.93
H4	7 %	T G C C G A C	80 (51–126) P = 0.33	80 (51–126) P = 0.33	51 (31–84) P = 0.009	115 (80–165) P = 0.45
H5	5 %	C G C C T C C	96 (59–156) P = 0.87	96 (59–156) P = 0.87	78 (46–133) P = 0.36	75 (51–111) P = 0.15
H6	5 %	T G T G T A C	93 (56–153) P = 0.76	93 (56–153) P = 0.76	115 (66–200) P = 0.62	168 (108–261) P = 0.02

(#) The 7 SNPs defining the 6 haplotypes are listed as follows (rs11265257, rs1130864, rs1205, rs1800947, rs2808632, rs3093077, rs876538). ref.=reference

Conclusion: Seven selected *CRP* gene SNPs had no impact on pre- and one year post-treatment levels of CRP. Minor genotypic and haplotypic effects on DAS28 scores were observed, but these were not consistent between baseline and one year. This study shows that DAS28 can be used for clinical decision-making without adjustment for *CRP* gene variants.

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The Frequency Of Single Nucleotide Polymorphisms In Urate Transporter Genes and Their Association With Uric Acid Concentration Based On Data From Genome-Wide Association Studies In The Korean Population. Chan-Nam Son[1], So-Young Bang[2], Sang-Cheol Bae[1] and Jae-Bum Jun[1]. [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Hanyang University Guri Hospital, Guri, South Korea.

Background/Purpose: Gouty arthritis is characterized by hyperuricemia, which results from overproduction of, or impaired renal excretion of, uric acid. Recently, interest has increased in renal urate transporters, which control the excretion of uric acid. Genome-wide association studies (GWASs) are now identifying risk alleles among renal urate transporter genes. At present, few studies of factors affecting uric acid regulation have been conducted on Koreans. We therefore aimed, first, to investigate the minor allele frequencies (MAFs) of single nucleotide polymorphisms (SNPs) associated with serum uric acid (SUA) level in the Korean population, and compare these with data from other ethnic groups (Study 1). Second, to investigate whether the SNPs are associated with altered SUA levels (Study 2).

Methods: Study 1: We used datasets derived from two available GWASs. The first study was the Korean RA GWAS, including 800 rheumatoid arthritis (RA) cases and 757 controls, and the second was Korean systemic lupus erythematosus (SLE) GWAS, comprising 400 SLE cases (a total of 1957 subjects). We explored the GWAS results already obtained from subjects without gout to examine the frequencies of risk alleles, and investigated the MAFs of 40 previously described SNPs associated with SUA level in the Korean population, and compared results with data for other ethnic groups. Study 2: A total of 402 RA subjects satisfying the inclusion and exclusion criteria were selected from Study 1. The representative value of SUA level in this study was determined by the highest value among SUA levels, obtained by searching the medical records of subjects in the GWAS from December 2000 to October 2012. Subjects with renal insufficiency as well as SLE patients were excluded. Also, we used the highest SUA values obtained before use of drugs that could increase SUA concentrations, such as antituberculosis medication. We analyzed associations with serum uric acid concentrations based on data from GWASs in the Korean population, and also tested whether polymorphism of any of the 40 SNPs associated with SUA identified previously were associated with SUA levels.

Results: Study 1: We compared the MAFs of 13 SNPs in Koreans with those in other ethnic groups. Overall, the MAFs of SNPs associated with SUA level in the Korean population were quite similar to those among Japanese, but not in populations of European descent. Study 2: SNP rs12734001 (PPP1R12B) proved to have the most probable association with SUA concentrations (P_trend $= 2.29 \times 10^{-9}$). We also analyzed 13 SNPs shown previously by meta-analysis to be associated with SUA, and SNP rs3741414 (INHBC) was found to have ther strongest association with SUA level observed in the present study (P_trend $=$ 0.01).

Conclusion: The pattern of variants controlling SUA levels in the Korean population is quite similar to that in the Japanese population, but not in populations of European descent. SNP rs12734001 (PPP1R12B) is significantly associated with SUA level, and SNP rs3741414 (INHBC), previously identified SNP, is strongly associated with SUA levels among Koreans.

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Haptoglobin Chains As Potential Biomarkers In Serum Of Osteoarthritis Disease. Carolina Fernandez-Costa[1], Valentina Calamia[1], Patricia Fernandez-Puente[1], Jesus Mateos[1], Beatriz Rocha[1], Lucia Lourido[1], Jose Luis Capelo[2], Cristina Ruiz-Romero[3] and Francisco J. Blanco[1]. [1]Osteoarticular and Aging Research Laboratory, Proteomics Unit-Associated Node to ProteoRed-ISCIII, INIBIC-CHUAC, A Coruña, Spain, [2]BIOSCOPE Group, REQUIMTE, Departamento de Química, Faculdade de Ciências e Tecnologia, FCT, Universidade Nova de Lisboa,, Caparica, Portugal, [3]CIBER-BBN, INIBIC-CHUAC, A Coruña, Spain.

Background/Purpose: The aim of this study is to search for osteoarthritis (OA) biomarkers in human serum using an easy and fast approach and the validation of the potential biomarkers found with two independent methods.

Methods: The serum samples for the biomarker discovery experiment were obtained from 20 OA patients and 20 non-symptomatic controls. Samples were grouped into four pools of 10 samples each. The pools were subjected to a chemical sequential depletion protocol to reduce the high dynamic range of the proteins. Then, the proteomics comparison between OA and control sera was performed across two dimensional difference in-gel electrophoresis (2D-DIGE) experiment. The quantitative image analysis was performed using Same Spots software. For protein identification, gel spots were digested and analyzed by mass spectrometry (MALDI-TOF/TOF) and identified using Mascot with SwissProt knowledgebase.

Haptoglobin chains validation was performed with two different methods, immunoblotting and multiple reaction monitoring (MRM) technology with the QTRAP mass spectrometer.

Results: We studied the combination of a chemical sequential depletion method combined with 2D-DIGE for the search of OA biomarkers in 40 serum samples. The analysis resulted in 46 spots significantly and reproducibly altered between OA and control samples (29 increased and 17 decreased). These 46 spots correspond to 14 different proteins, Table 1. The most interesting result was the modulation of the protein haptoglobin (HPT), three different spots were opposite modulated and were identify as the three chains of haptoglobin. In human, HPT exists in two allelic forms that produce three known phenotypes. The presence of the different alpha chains in patients depends on which phenotype their express. Interestingly, HPT beta and HPT alpha-1 chains were increased in OA sera whereas HPT alpha-2 chain was decreased in OA sera versus control. Using western blot analysis and MRM mass spectrometry technique on 30 new individual samples from OA and control donors (15

from each condition), we confirmed the different modulations of the alpha and beta HPT chains.

Table 1. Proteins identified in this work as altered in Osteoarthritis (OA) vs Control (N) sera.

Protein ID	Proteins increased in OA	Ratio OA:N
A1AT	Alpha-1-antitrypsin	1,4
FETUA	Alpha-2-HS-glycoprotein	2
ANGT	Angiotensinogen	1,1
APOA1	Apolipoprotein A-I	2,2
HPT	Haptoglobin beta chain	2
HBB	Hemoglobin subunit beta	1,6
A2GL	Leucine-rich alpha-2-glycoprotein	1,5
TTHY	Transthyretin	2,2
HPT	Haptoglobin alpha-1 chain	1,4
	Proteins decreased in OA	
APOA2	Apolipoprotein A-II	0,7
APOA4	Apolipoprotein A-IV	0,6
APOC3	Apolipoprotein C-III	0,8
HPT	Haptoglobin alpha-2 chain	0,5
IGKC	Ig kappa chain C region	0,6
LAC2	Ig lambda-2 chain C regions	0,6
SAA	Serum amyloid A protein	0,8

Conclusion: We were able to identified 16 protein forms altered in the disease (9 increased and 7 decreased), and we verified for the first time the OA- dependent alteration of the haptoglobin chains. The haptoglobin protein provides two different OA biomarkers easily to measure in serum samples at the same time.

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New Insights Into The Metabolic Origin Of Osteoarthritis. Ignacio Rego-Pérez[1], María Eugenia Vázquez-Mosquera[1], Angel Soto-Hermida[1], Mercedes Fernández-Moreno[1], Juan Fernández-Tajes[1], Estefanía Cortés-Pereira[1], Sara Relaño-Fernández[1], Natividad Oreiro-Villar[1], Carlos Fernández-López[1] and Francisco J. Blanco[2]. [1]INIBIC-Hospital Universitario A Coruña. Rheumatology Division. Genomic Group, A Coruña, Spain, [2]INIBIC-Hospital Universitario A Coruña, A Coruña, Spain.

Background/Purpose: Metabolic alterations take place in osteoarthritis (OA) and the mtDNA haplogorups influence the prevalence and severity of the disease. The aim of this work is to analyze the metabolic behavior in OA from different points of view, including the analysis of gene polymorphisms, mitochondrial variants and gene expression.

Methods: The first approach consisted in the analysis of the influence of the mtDNA haplogroups in the body mass index (BMI) in a cohort of 638 OA patients and 474 healthy controls from Spain. This approach was followed by a second one that included the analysis of the expression levels of genes related to both lipid and glucose metabolism in RNA isolated from 24 OA and 22 healthy normal (N) cartilage samples; for this purpose we also used the chondrocyte cell line TC28a2 in order to analyse the glucose overload (at 1, 4.5 and 18 g/l) during 48 hours in the expression levels of these genes as well as of both MMP-3 and IL-6; finally, we search for possible interactions between the mtDNA haplogroups and the SNP -866C/T (rs659366) in the promoter region of UCP2 to assess their incidence in the prevalence of OA in a cohort of 137 OA patients and 133 healthy controls from Spain. Nucleic acid isolation was carried out using commercial kits following the manufacturer recommendations with some modifications. Appropriate data analysis was performed with SPSS software (v19) and qBase plus software (Biogazelle).

Results: The mtDNA haplogroup J and OA are independently associated with BMI, so that carriers of this mitochondrial variant show significant lower BMI values ($p=0.006$) meanwhile OA patients show significant higher values ($p<0.001$), being the BMI a risk factor for OA. The obtained OA/N expression ratio of GLUT1 (0.8 ± 0.26), GLUT3 (0.73 ± 0.01), GLUT5 (0.68 ± 0.19), HK1 (1.09 ± 0.02), HK2 (1.59 ± 0.21), INSR (0.99 ± 0.08), CPT1B (1.30 ± 0.1), ACADM (2.65 ± 0.36), HADHB (1.68 ± 0.09), PPARg (0.61 ± 0.11), PPARa (1.41 ± 0.33) did not show significant differences ($p > 0.05$). However, a significant increased expression of UCP2 (3.86 ± 0.12) as well as a decreased expression of PDK4 (0.20 ± 0.01) was detected in OA cartilage samples ($p<0.05$). Gene expression of OLR-1 was only observed in OA cartilage samples. The experiments of glucose overload carried out in the cell line TC28a2 showed a direct correlation between glucose concentration and the expression levels of UCP2 (correlation coefficient (c.c)$=0.965$; $p=0.102$), MMP-3 (c.c$=0.992$; $p=0.08$) and IL-6 (c.c$=0.996$; $p=0.05$) as well as an inverse correlation with PDK4 (c.c$=-0.914$; $p=0.265$). The analysis of the interaction between the mtDNA haplogroups and the SNP rs659366 showed that carriers of both haplogroups J or T (mtDNA cluster TJ) that also carry the T allele of rs659366 have a significant decreased risk of OA (OR$=0.581$; CI: 0.357 – 0.948; $p=0.029$).

Conclusion: This work provides strong evidence on metabolic alterations that occur in OA. These alterations involve the lipid and glucose metabolism, through the mitochondrial pathway, as well as the switch that modulates the balance between both metabolisms which, in turn, would lead to the increased inflammatory process that takes place in OA.

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The Potential Role Of Protein Tyrosine Phosphatase Receptor D (PTPRD) Gene Copy Number Variation In Susceptibility To Rheumatoid Arthritis. Su Jin Yoo[1], Mi Kyoung Lim[2], Donghyuk Sheen[2], In Seol Yoo[1], Jinhyun Kim[1], Seong Wook Kang[1] and Seung-Cheol Shim[3]. [1]Chungnam National University School of Medicine, Daejeon, South Korea, [2]Eulji University Hospital, Daejeon, South Korea, [3]Chungnam National University Hospital, Daejeon, South Korea.

Background/Purpose: Since it is important to explore genetic variations associated with rheumatoid arthritis (RA), genome-wide association studies (GWAS) have led to the identification of RA genetic variants putatively associated with susceptibility. Recently, copy number variation (CNV) may also affect susceptibility to diseases, which have been already observed in diverse autoimmune diseases. Protein tyrosine phosphatase receptor D (PTPRD) is a member of the receptor-like PTP which expresses in the B cell lines and thymus and could be involved in the pathogenesis of autoimmune diseases. In this study, we investigated whether the variation of the *PTPRD* gene copy number related with susceptibility to RA.

Methods: To investigate whether the variation of the *PTPRD* gene copy number influence the pathogenesis to RA, blood samples and clinical records were obtained from 217 RA patients (184 females, 33 males) and 205 healthy controls. The genomic DNA of RA patients and healthy controls was extracted from leukocytes in peripheral blood using the Genomic DNA Extraction kit (iNtRON Biotechnology, Korea). To measuring the copy number of *PTPRD* gene, the quantitative real-time PCR (QPCR) was carried out using Mx3000P QPCR system (Stratagene, La Jolla, CA) and each sample for each gene was assayed in triplicate. Western blot was conducted to detect expression levels of *PTPRD*.

Results: The copy number of *PTPRD* gene in RA patients was compared with that in healthy controls. The proportion of the individuals with <2 copy of *VPREB1* was significantly higher in patients than in controls, while that of the individuals with >2 copy was lower in patients than in controls. The average relative copy number of the *PTPRD* gene in RA patients (1.14, 95 % CI (1.12–1.16)) was significantly lower than that in healthy controls (1.65, 95 % CI (1.12–1.16), $p < 0.0001$). Furthermore, we also investigated association between copy number of *PTPRD* and RA phenotype such as RF factor and anti-CCP levels, which showed no association between copy number of *PTPRD* and both RA phenotypes. Western blot showed the lower expression of *PTPRD* in patients with RA compared to control subjects.

Conclusion: This is the first evidence showing the association between low copy number of the PTPRD gene and susceptibility to RA, which may help understanding the pathogenesis of RA and other autoimmune disorders like affecting maturation and differentiation of T cell and B cells.

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Association Of Functional Polymorphisms In *IRF2* With Systemic Lupus Erythematosus In a Japanese Population. Aya Kawasaki[1], Hiroshi Furukawa[2], Nao Nishida[3], Eiji Warabi[1], Yuya Kondo[1], Satoshi Ito[4], Isao Matsumoto[1], Makio Kusaoi[5], Akiko Suda[6], Shouhei Nagaoka[7], Keigo Setoguchi[8], Tatsuo Nagai[9], Shunsei Hirohata[9], Katsushi Tokunaga[10], Yoshinari Takasaki[5], Hiroshi Hashimoto[11], Takayuki Sumida[1], Shigeto Tohma[2] and Naoyuki Tsuchiya[1]. [1]University of Tsukuba, Tsukuba, Japan, [2]Sagamihara Hospital, National Hospital Organization, Sagamihara, Japan, [3]National Center for Global Health and Medicine, Ichikawa, Japan, [4]Niigata Rheumatic Center, Shibata, Japan, [5]Juntendo University, Tokyo, Japan, [6]Yokohama City University, Mecical Center, Yokohama, Japan, [7]Yokohama Minami Kyousai Hospital, Yokohama, Japan, [8]Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan, [9]Kitasato University School of Medicine, Sagamihara, Japan, [10]The University of Tokyo, Tokyo, Japan, [11]Juntendo University School of Medicine, Tokyo, Japan.

Background/Purpose: Interferon regulatory factor (IRF) families are transcription factors involved in type I interferon (IFN) pathway. Recent genetic studies identified association of IRF family genes, *IRF5*, *IRF7*, and *IRF8*, with systemic lupus erythematosus (SLE). IRF2 is thought to negatively regulate the type I IFN signals. In addition, IRF2 has a role in induction of Th1 differentiation and NK cell development. So far, association of *IRF2* with SLE has not been published. In this study, we conducted an association study to examine whether *IRF2* contributes to susceptibility to SLE in a Japanese population.

Methods: A case-control association study was performed in 501 Japanese patients with SLE and 551 healthy controls on 46 tag SNPs in the *IRF2* gene, selected based on linkage disequilibrium (LD) and minor allele frequencies ($r^2 \geq 0.8$, minor allele frequency≥ 0.05), using the DigiTag2 and the TaqMan allele discrimination assays. To identify functional SNPs, resequencing of the *IRF2* region was performed using the next-generation sequencing. Effect of *IRF2* SNPs on transcriptional activity was analyzed using a luciferase assay.

Results: Among the *IRF2* tag SNPs, rs13146124T in intron 1 was most significantly associated with SLE (dominant model, $P=7.4\times10^{-4}$, odds ratio [OR] 1.60, 95% confidence interval [CI] 1.22–2.11). Resequencing identified SNPs in LD with rs13146124. Eight SNPs including rs62339994 were in almost absolute LD with rs13146124 (r^2: 0.98–1), whereas rs66801661 showed moderate LD (r^2: 0.52).

We next examined association of rs66801661 with SLE. rs66801661A allele was significantly increased in SLE (allelic model, $P=3.7\times10^{-4}$, OR 1.75, 95%CI 1.29–2.39). Haplotype analysis identified three haplotypes constituted by rs66801661 and rs13146124, and the haplotype carrying both of the risk alleles, rs66801661A - rs13146124T, was significantly increased in SLE (SLE: 10.8%, control: 6.4%, permutation $P=2.0\times10^{-4}$). On the other hand, the haplotype formed by the non-risk alleles, rs66801661G - rs13146124C, was decreased in SLE (SLE: 83.1%, control: 87.9%, permutation $P=0.0014$).

To examine the functional significance of the risk haplotype, *IRF2* region containing the promoter region, exon 1 and the 5' part of intron 1 encompassing rs66801661 and rs62339994, which was in tight LD with rs13146124, were inserted upstream of the luciferase gene. Three constructs corresponding to the naturally-occurring haplotypes were transfected, and the luciferase activities were compared. The construct carrying both of the risk alleles, rs66801661A and rs62339994A (in LD with rs13146124T), was associated with the highest transcriptional activity in Jurkat cells under IFNγ stimulation (ANOVA, $P=1.3\times10^{-4}$).

Conclusion: *IRF2* polymorphisms are associated with susceptibility to SLE in a Japanese population. The SLE risk haplotype appeared to be associated with transcriptional activation of *IRF2*.

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Predicting The Severity Of Joint Damage In Rheumatoid Arthritis; The Contribution Of Genetic Factors. Hanna W. van Steenbergen, Roula Tsonaka, Tom W.J. Huizinga, Saskia le Cessie and Annette H.M. van der Helm-van Mil. Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: The severity of radiologic progression is variable between rheumatoid arthritis (RA) patients. Recently several genetic severity variants have been identified and replicated. This study determined the contribution of the established genetic severity factors to the explained variance in radiologic progression and evaluated whether genetic factors, in addition to traditional clinical and serological risk factors, improved the accuracy of predicting the severity of radiologic progression.

Methods: 417 early RA patients with yearly radiologic follow up were studied. The main outcome measure was the progression in Sharp-van der Heijde scores (SHSs) over six years. Genetic variants in the following genes were studied: HLA-DRB1, CD40, IL-15, DKK-1, IL2RA, GRZB, IL-4R, SPAG16, C5orf30, MMP-9 and OPG. Linear regression analyses were used to determine the explained variance and the net improvement in reclassifications of prediction models without and with genetic risk factors. For studying reclassification, the continuous outcome was categorized based on the severity of radiologic progression in progression in SHSs over six years $\leq$6, 7–30 and $>$30 units, indicating mild, moderate and severe radiologic progression.

Results: Treatment effects and a combination of traditional risk factors explained 7.1% and 31.2% of the variance in progression in SHSs over six years. The genetic factors together explained 18.1%. When added to treatment effects and traditional factors, the genetic risk factors additionally explained 7.4% of the variance. Compared to a prediction model without genetic factors, a prediction model also including genetic factors yielded a net correct reclassification of 5.9% of the patients; now 62% of those patients were correctly classified. Thus with a model including known traditional and genetic factors 38.1% of the patients were still not correctly classified. Evaluating the reclassifications per severity group, the net percentages of patients that were additionally correctly classified were 0%, 5.1% and 13.2% for the groups with mild, moderate and severe progression respectively. Hence, including genetic factors led to improved identification of patients with severe radiological progression in particular. Sensitivity analyses using imputation of missing radiographs yielded comparable results.

Conclusion: When added to a model consisting of traditional factors, genetic risk factors improved the predictive accuracy. Nonetheless, the predictive performance was still insufficient for use in clinical practice.

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Effects Of Chondroitin Sulfate On The Gene Expression Profile In Interleukin-1β Stimulated Synovial Fibroblast Cells Cultures. Cécile Lambert[1], Jean-Emile Dubuc[2], Eulalia Montell[3], Josep Verges[3] and Yves Henrotin[1]. [1]Bone and Cartilage Research Unit, Liège, Belgium, [2]Orthopaedic Department, Bruxelles, Belgium, [3]Pre-Clinical R&D Area, Pharmascience Division, BIOIBERICA S.A., Barcelona, Spain.

Background/Purpose: Chondroitin sulfate (CS) is one the most used molecules in the management of OA. Its mechanism of action remains to be detailed. In this study, we perform a microarray analysis to identify a differential expression profile between control and IL-1β stimulated synovial fibroblast cells cultures and to investigate the effects of CS on this gene expression profile

Methods: OA synovial specimens were obtained from 12 patients undergoing knee replacement. Synovial fibroblast cells (SFC) were enzymatically isolated and used after four passages (P4). SFC were pre-treated 1 hour with highly purified bovine CS (200 μg/ml, Bioibérica S.A., Barcelona, Spain) before treatment with IL-1β (1 ng/ml) for 24 hours. Gene expression profiling was performed using Illumina's multi-sample format Human HT-12 BeadChip (Illumina Inc.). Differential analysis was performed with the BRB array tools software. Class comparison test between control (Ctl) and interleukin (IL)-1β conditions, Ctl and Ctl/CS and IL-1β and IL-1β/CS conditions was based on paired t-test where Ctl and IL-1β, Ctl and Ctl/CS and IL-1β and IL-1β/CS were paired for each patient. The biological relevance of regulated genes was analyzed with Ingenuity Pathways Analysis (Ingenuity® Systems). Probes with a p-value below 0.001 were chosen and classified as up- or down-regulated.

Results: 3308 genes were identified as differentially expressed genes between Ctl and IL-1β conditions. A differential profile of expression of major pathways involved in OA pathogenesis was observed. In the inflammatory network, the most upregulated cytokines were IL-8 and IL-6 (fold change: 156.25 and 58.8 respectively). We identified several chemokines, enzymes and metallothioneins (MTs). Complement factor B (CFB) and complement component 3 (C3) are two factors upregulated in the inflamma-

tory complement cascade. We identified some genes implicated in the angiogenesis pathway. The most upregulated was Stanniocalcin 1 (STC1) (fold change: 9.09). The differential expression of intermediates in cartilage anabolism and catabolism revealed an imbalance in favour of catabolism. MMP-3 was largely upregulated (fold change: 62.5). Wnt 5A and low density lipoprotein receptor-related protein (LRP8) were significantly upregulated while frizzled homolog 2 (FZD2) and dickkopf homolog 3 (DKK3) were downregulated in the Wnt signaling. The class comparison test highlighted 660 differentially expressed genes between Ctl and Ctl/CS conditions and 241 genes between IL-1β and IL-1β/CS. Among them, our attention was focused on two genes upregulated in the presence of CS: lysyl oxidase-like 4 (LOXL4) and claudin 11 (CDLN11), two genes that negatively regulate cell invasion.

Conclusion: We here evidenced in synovial fibroblast cells the modulation of gene expression following IL-1β stimulation. We also demonstrated the modulatory effects of CS on gene expression and isolated several CS-modulated genes of interest such as LOXL4 and CDLN11, which could constitute new mechanisms of action of the molecule and contribute to explain the symptomatic efficacy of CS in the treatment of OA.

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Association Of BMI, 8 SNPs Reported To Be Related To Gout Phenotype and Their Interaction In Gout Incidence In Framingham Heart Study. Jasvinder A. Singh[1], Ana Vazquez[2], Richard Reynolds[2], Vinodh Srinivasasainagendra[3], S. Louis Bridges Jr.[2] and David Allison[2]. [1]University of Alabama, Tuscaloosa, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]University of alabama at birmingham, birmingham, AL.

Background/Purpose: We aim to assess the association of 8 serum urate SNPs and BMI and their interactions with incident gout in a population-based cohort study.

Methods: We used the Framingham Study including subject from the Original and the Offspring cohort (N=4,967). We assessed the effect of 8 SNPs in the recently described genetic urate score on incident gout. Subjects were genotyped with Affy500K platform, and two of the SNPs associated to gout rs1165196 and rs1106766 were present in that platform. The SNPs rs1967017, rs780093, rs13129697, rs2199936, rs675209 and rs2078267 were not present in the Affy SNP array, thus we imputed them with IMPUTE2. BMI was taken at the time of gout or, at the time of censoring if the subject is healthy or died without gout. We fitted logistic regression models to assess the associations. Estimated effects in the liability scale, odd ratios, and p-values are reported for all SNPs, covariates, and interactions. 408 patients had incident gout (74% males), with 169 from the FHS original cohort and 293 from the Offspring cohort.

Results: In a model with main effects of BMI and SNPs, three of eight SNPs and BMI were significantly associated with incident gout ($p<=0.008$ for all). Zero SNPs showed significant main effects on gout in the model that adjusted for all BMI*SNP interaction terms. However, BMI remained significant ($p=0.003$) and the rs2199936*BMI interaction was nearly significant ($p=0.06$). Gender and duration of follow-up were also significant predictors ($p<=0.009$) in all models.

Conclusion: SNPs known to predict urate levels moderated the association of BMI with gout, suggesting the possibility that the extent to which BMI increases the risk for got may depend on a person's a priori genetic risk for high urate levels.

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Effects Of Chondroitin Sulfate On The Gene Expression Profile In The Inflamed Synovial Membrane. Cécile Lambert[1], Jean-Emile Dubuc[2], Eulalia Montell[3], Josep Verges[3] and Yves Henrotin[1]. [1]Bone and Cartilage Research Unit, Liège, Belgium, [2]Orthopaedic Department, Bruxelles, Belgium, [3]Pre-Clinical R&D Area, Pharmascience Division, BIOIBERICA S.A., Barcelona, Spain.

Background/Purpose: Chondroitin sulfate (CS) is one the most used molecules in the management of OA. Its mechanism of action remains to be detailed. The aim of the present work is to identify the differentially expressed genes between the inflammatory (I) and normal/reactive (N/R) synovial areas using a unique ex vivo culture model and to investigate the genetic modulatory effects of CS in this model.

Methods: Synovial cells (SC) were isolated from OA synovial specimens from 12 patients undergoing knee replacement. The synovial membrane was dissected and SC from N/R and I areas cultured separately for a period of 7 days with or without highly purified bovine CS (200 μg/ml, Bioibérica S.A., Barcelona, Spain). Gene expression profiling was performed using Illumina's multi-sample format Human HT-12 BeadChip (Illumina Inc.). Differential analysis was performed with the BRB array tools software. Class Comparison test between N/R and I conditions, N/R and N/R-CS conditions and I and I-CS conditions was based on paired t-test where N/R and I, N/R and N/R-CS and I and I-CS were paired for each patient. The biological relevance of up- and down-regulated genes was analyses with Ingenuity Pathways Analysis (Ingenuity® Systems).

Results: From among 47000 probes, 18253 were filtered out. Probes with a p-value below than 0.005 were chosen and classified as up- or down-regulated ones. By this way, 465 differentially expressed genes between N/R and I areas were identified. Many inflammatory mediators appear differentially expressed. The interferon alpha-inductible protein 6 (IFI6) was the most up-regulated. We also identified the hydroxysteroid (11-beta) dehydrogenase 1 (HSD11B1), the cathepsin K (CTSK), the chemokine (C-X-C motif) ligand 1 (CXCL1) and the EBV-induced G-protein coupled receptor 2 (EBI2). The differential expression of intermediates involved in angiogenesis pathway was also revealed between N/R and I areas. Among them, R-spondin-3 (RSPO3), the secreted phopshoprotein 1 (SPP1) and aquaporin 9 (AQP9) were up-regulated whereas ADAMTS1 was down-regulated. Finally, in the Wnt signaling, RSPO3 was up-regulated unlike dickkopf homolog 3 (DKK3) which was in turn down-regulated. We next performed a class comparison test between N/R and N/R-CS in one hand and between I and I-CS the other hand. 489 genes were identified as differentially expressed genes between N/R and N/R-CS conditions while 219 genes were identified between I and I-CS conditions. In this latter, our attention was focused on the down-regulated genes. Among them, we identified a number implicated in angiogenesis and cell migration pathways. Thus, the endothelial cell-specific molecule-1 (ESM1), the Transmembrane-4-L-six-family-1 (TM4SF1), the 5'-Ectonucleotidase (NT5E) and the growth arrest-specific gene 6 (GAS6) were down-regulated by CS.

Conclusion: Our work demonstrates the differential gene expression profile between paired inflammatory and normal/reactive areas of synovial membrane as well as the modulatory effects of CS on gene expression in the inflammatory areas, especially regarding genes involved in both angiogenesis and cell migration.

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Transcript Profiling Of Kidney Biopsies From Chinese Patients With Lupus Nephritis Suggests a Prevalence Of Infiltrating CD8+ T Cells, Monocytes/Macrophages, and B Cells In ISN/RPS Class IV Disease. Zheng Liu[1], Chris Morehouse[1], Xinfang Huang[2], Philip Brohawn[1], Nan Shen[3], Gabor G. Illei[1], Yihong Yao[1] and Brandon W. Higgs[1]. [1]MedImmune, LLC, Gaithersburg, MD, [2]Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, [3]Cincinnati Children's Hospital Medical Center, cincinnati, OH.

Background/Purpose: Lupus nephritis (LN) affects ~60% of patients with systemic lupus erythematosus (SLE). The International Society of Nephrology and the Renal Pathology Services (ISN/RPS) classification system categorizes LN into 6 main classes based on the underlying renal pathology. Among these, Classes I and II rarely require immunosuppressive treatment and Class-VI is associated with irreversible glomerulosclerosis. Class-IV (diffuse proliferative nephritis) is the most severe form with the largest proportion of all diagnosed cases (~40%) followed by Class-III (focal proliferative nephritis), representing ~25% of all diagnosed cases. These classes have similar histopathological and clinical characteristics while Class-V (membranous nephritis) representing ~10% of LN cases is different both in its clinical course and histological appearance. We examined kidney biopsies from a group of ISN/RPS Class III, IV, and V LN subjects to evaluate molecular differences between these classes.

Methods: Kidney biopsies were procured from 6 healthy donor (HD) and 25 LN (8 Class-III, 6 Class-IV, and 11 Class-V) Chinese subjects. The

Affymetrix U133+ array was used to transcript profile specimens. Fold changes were calculated for each LN subject relative to the average HD expression. Previously defined cell type-specific gene signatures were identified to be differential between ISN/RPS classes.

Results: Several gene signatures were significantly over-expressed ($p<0.05$) in Class-IV subjects relative to both Class-III and -V subjects. These included: a chemokine, MHC class I, monocyte, macrophage, and CD8+ T cell gene signatures. An immunoglobulin (Ig) signature was also significantly over-expressed in Class-IV subjects compared to Class-V subjects, but not Class-III subjects. The following gene signatures did not significantly differ between the three classes: neutrophil, CD4+ T cell, and type I IFN.

Conclusion: Transcript profiling was used to correlate the molecular differences between LN disease classifications and cell infiltrate prevalence. In addition to pathways upregulated in all three forms of LN, we identified cell type-specific signatures which were over-expressed in Class-IV. The increased CD-8+ signature suggests that CD8+ effector T cell infiltration may correlate with more active disease status. Monocytes/macrophages are also more prevalent in this more active disease class, suggesting an increase in infiltration from damage caused by these CD8+ T effector cells, which may also lead to an increase in Ig products.

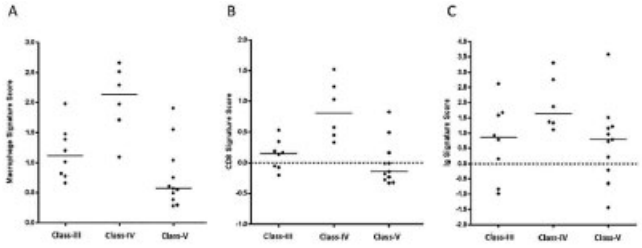

Figure 1. Distribution of A) macrophage, B) CD8+ T cell, and C) Ig gene signatures for LN patients with Class-III, -IV, or -V disease.

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***HLA-DRB1*08:02* Is Associated With Bucillamine-Induced Proteinuria In Japanese Rheumatoid Arthritis Patients: A Case-Control Study.** Hiroshi Furukawa[1], Shomi Oka[1], Kota Shimada[2], Shoji Sugii[2], Atsushi Hashimoto[1], Akiko Komiya[1], Naoshi Fukui[1], Taiichiro Miyashita[3], Kiyoshi Migita[3], Akiko Suda[4], Shouhei Nagaoka[5], Naoyuki Tsuchiya[6] and Shigeto Tohma[1]. [1]Sagamihara Hospital, National Hospital Organization, Sagamihara, Japan, [2]Tokyo Metropolitan Tama Medical Center, Tokyo, Japan, [3]Nagasaki Medical Center, National Hospital Organization, Omura, Japan, [4]Yokohama City University, Mecical Center, Yokohama, Japan, [5]Yokohama Minami Kyousai Hospital, Yokohama, Japan, [6]University of Tsukuba, Tsukuba, Japan.

Background/Purpose: Bucillamine (Buc) is one of the commonly used disease-modifying anti-rheumatic drugs (DMARDs) in Japan. Drug-induced proteinuria can occur in rheumatoid arthritis (RA) patients treated with Buc, and represents a drug hypersensitivity reaction. Striking associations of human leukocyte antigen (HLA) alleles with adverse reactions have recently been reported for many drugs.

Methods: We investigated the association of HLA class II with Buc-induced proteinuria (BI-Pro) in 485 Japanese RA patients treated with Buc, of which 25 had developed BI-Pro.

Results: This study showed a highly significant association of *DRB1*08:02* with BI-Pro ($P=1.09\times10^{-6}$, corrected P [Pc]$=1.96\times10^{-5}$, odds ratio [OR] 25.17, 95% confidence interval [CI] 7.98–79.38). *DQB1*04:02* was also significantly associated with increased risk of BI-Pro ($P=2.44\times10^{-5}$, $Pc=2.69\times10^{-4}$, OR 10.35, 95%CI 3.99–26.83).

Conclusion: We detected striking HLA class II associations with proteinuria induced by Buc in Japanese RA patients. This association merits confirmation in future large-scale studies for its potential clinical usefulness as a biomarker to prevent adverse reactions.

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Genetic Association On Disease Severity In Rheumatoid Arthritis: A Validation Study In Japanese Patients. Shinji Yoshida[1], Katsunori Ikari[1], Koichiro Yano[1], Yoshiaki Toyama[2], Atsuo Taniguchi[1], Hisashi Yamanaka[3] and Shigeki Momohara[1]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]Department of Orthopaedic Surgery, Keio University School of Medicine, Shinjuku, Japan, [3]Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: The disease severity of rheumatoid arthritis (RA) is objectively measured by radiographic joint destruction, which is reflective of the cumulative burden of inflammation. Recently, the heritability has been proven to be partly involved in progression of joint destruction in RA, and several genetic variants and gene-gene interactions have been reported to be associated with progression of joint destruction in European multi-cohort studies. However, the presence of genetic heterogeneity in RA susceptibility genes has been demonstrated in many population-based studies, and the genetic predisposition factors for progression of joint destruction remain to be poorly understood in Asian patients with RA. The purpose of this study was to identify genetic variants associated with progression of joint destruction in Japanese patients with RA.

Methods: This study included 865 Japanese patients with RA for whom Sharp/van der Heijde scores (SHS) of hands were available at a disease duration of 5 years. DNA samples of the subjects were obtained from the Institute of Rheumatology Rheumatoid Arthritis cohort study (IORRA) DNA collection. All of the patients who donated DNA samples consented to participate in this study in accordance with the process approved by the Tokyo Women's Medical University Genome Ethics Committee, and satisfied the American College of Rheumatology 1987 revised criteria for the classification of RA. Nine of the single nucleotide polymorphisms (SNPs) reported in European multi-cohort studies were selected and genotyped in the DNA samples: rs6821171, and rs1521761 which is in absolute linkage disequilibrium ($r^2=1$) with rs7667746, in *interleukin15 (IL15)*; rs8192916, in *granzyme B (GZMB)*; rs1896368, rs1896367, rs1528873, and rs10762715, in *Dickkopf-1 (Dkk-1)*; rs4792909, and rs6503475, in *sclerostin (Sost)*. SNP genotyping was performed by using the TaqMan fluorogenic 5' nuclease assay (Applied Biosystems, Tokyo, Japan). Univariate linear regression analyses were performed to examine the association of each SNP and several combinations of SNPs with progression of joint destruction in the first 5 years after onset of RA, calculated as SHS of hands at the 5-year disease duration. All SHS were log-transformed to obtain a normal distribution.

Results: Univariate linear regression analyses revealed that all of the SNPs and combinations of SNPs tested in this study were not associated with progression of joint destruction (Table 1).

Table 1

Gene	SNP	Allele (minor/major)	MAF	Tested model	β	P value
L15	rs6821171	C/A	0.30	additive	−0.05	0.48
				recessive	−0.13	0.36
	rs1521761	T/A	0.15	additive	−0.10	0.21
				recessive	−0.13	0.36
GZMB	rs8192916	A/G	0.45	additive	−0.01	0.91
				recessive	0.05	0.65
Dkk-1	rs1896368	A/G	0.42	additive	0.07	0.21
				recessive	0.12	0.16
	rs1896367	A/G	0.30	additive	−0.11	0.09
				recessive	−0.13	0.31
	rs1528873	C/A	0.22	additive	−0.07	0.28
				recessive	−0.02	0.90
Dkk-1	rs1528873	C/A	0.22	additive	−0.02	0.59
Sost	rs6503475	G/A	0.45			
	rs10762715	T/C	0.22	additive	0.01	0.78
	rs4792909	T/G	0.40			
	rs10762715	T/C	0.22	additive	0.02	0.59
	rs6503475	G/A	0.45			

Conclusion: Genetic variants in *IL15*, *GZMB*, *Dkk-1*, and *Sost* were not associated with progression of joint destruction in Japanese patients with RA.

These results indicate the presence of genetic heterogeneity in risk loci of progression of joint destruction in RA between Caucasian and Asian patients. The heritability of the rate of joint destruction might be different among ethnic populations.

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Dynamics Of The Inflammatory Response In Rheumatoid Arthritis Patients Following Traumatic Injury: Insights From *In Vivo*, *In Silico*, and Single Nucleotide Polymorphism Studies. Rajaie Namas[1], Rami Namas[2], Harpreet Sagar[3], Felix Fernandez-Madrid[3], Timothy Billiar[2] and Yoram Vodovotz[2]. [1]Wayne State University/ Henry Ford Health System, Detroit, MI, [2]University of Pittsburgh, Pittsburgh, PA, [3]Wayne State University, Detroit, MI.

Background/Purpose: Both traumatic injury/hemorrhagic shock (T/HS) and rheumatoid arthritis (RA) are inflammatory diseases that are major sources of morbidity worldwide. We hypothesize that RA modifies T/HS-induced dynamic inflammatory networks, and that anti-inflammatory therapy for RA may modify T/HS-induced inflammation and outcomes. Accordingly, we sought to compare a prolonged time course of post-injury inflammatory mediators and outcomes in T/HS patients with or without RA.

Methods: From a cohort of 472 blunt trauma survivors studied following IRB approval, 12 patients diagnosed with seropositive RA according to 2010 ACR criteria (8 males and 4 females; age: 65±4; ISS: 17±1, receiving Methotrexate and tumor necrosis factor-a [TNF-a]-inhibitors) were matched with 12 non-RA control patients (8 males and 4 females; age: 68±4, ISS: 17±2). Serial blood samples were obtained from all patients (3 samples within the first 24 h and then daily from days 1 to 7 post-injury). Twenty-three plasma inflammatory mediators were assayed using Luminex™, along with NO_2^-/NO_3^- assayed using nitrate reductase, respectively. Statistically significant differences ($P < 0.05$) between both groups were determined using the two-way analysis of variance (ANOVA) followed by the Holm-Sidak *post hoc* test. *In silico* Dynamic Bayesian Network (DBN) inference was utilized to infer causal relationships among inflammatory mediators based on probabilistic measures. Human genomic DNA was isolated and amplified for known TNF-α, IL-6, IL-10, and IFN-γ single nucleotide polymorphisms (SNPs) using PCR, along with TLR4 (Asp299Gly and Thr300I1e) SNPs using gel-DNA sequencing.

Results: There was no statistical difference in the ICU length of stay, total length of stay, days on mechanical ventilation, and Marshall score (a measure of organ dysfunction) in RA vs. non-RA patients. Plasma levels of TNF-α, IL-6, IL-10, IL-17, MIG, MIP-1β, and NO_2^-/NO_3^-were significantly elevated within the 24 h in the RA group and up to day 7 when compared to the non-RA group. In contrast, plasma IP-10 and MCP-1 levels were significantly lower in the RA group within the first 24 h when compared to controls. DBN suggested that the inflammatory response in RA trauma patients is mainly driven by MIG, whereas MCP-1 drives the inflammatory response via forward-positive loops with IP-10 and MIG in non-RA patients. The incidence of all of the measured SNPs was not significantly different between trauma patients with or without RA.

Conclusion: To our knowledge, this is the first pilot study that characterizes the inflammatory response in RA patients following blunt trauma. Our analysis suggested that different cytokine patterns emerge, particularly in the early events post-injury, in RA patients independent of the injury severity score on admission. Network analysis points to MIG as a key driver of this process. Larger cohorts are needed to clarify the role that T/HS plays in RA disease activity and therapy.

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Identification Of Major Histocompatibility Complex Class II Alleles Associated With Systemic Sclerosis Through Imputation Strategy. Jose Ezequiel Martin[1], Carmen P. Simeón[2], Norberto Ortego-Centeno[3], Patricia Carreira[4], Miguel A. Gonzalez-Gay[5], Nicolas Hunzelmann[6], Shervin Assassi[7], Filemon K. Tan[7], Frank C. Arnett[7], Xiaodong Zhou[7], T.R.D.J. Radstake[8], Maureen D. Mayes[7], Paul de Bakker[9], Javier Martin[10] and B. P. C. Koeleman[8]. [1]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Granada, Spain, [2]Hospital Valle de Hebron, Barcelona, Spain, [3]Hospital Clínico San Cecilio, Granada, Spain, [4]Hospital Universitario 12 de Octubre, Madrid, Spain, [5]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IFIMAV, Santander, Spain, [6]University of Cologne, Cologne, Germany, [7]University of Texas Health Science Center at Houston, Houston, TX, [8]University Medical Center Utrecht, Utrecht, Netherlands, [9]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [10]Instituto de Parasitologia y Biomedicina López-Neyra, IPBLN-CSIC, Granada, Spain.

Background/Purpose: Different alleles of MHC class II molecules have been associated either with risk to systemic sclerosis (SSc) or its subphenotypes. Due to the high cost of HLA typing, studies have been limited to small sample sizes, preventing definitive statements as to which HLA alleles are likely causal

Methods: We have imputed the MHC class I and II alleles of 2,296 cases and 5,356 controls from four countries with a method previously developed. Besides classical HLA alleles, we also imputed amino acid changes encoded by genetic variants within the different MHC molecules. We compared the frequencies of the different alleles between cases and controls for SNPs, amino acids and classical HLA alleles

Results: The accuracy of the imputations ranged from 84% to 94% depending on the alleles being imputed with an average of 92% for all alleles in both populations. We confirmed previous associations of HLA alleles with SSc or its auto-antibody positive subgroups (*e.g.* HLA-DRB1*0701, HLA-DPB1*1301, HLA-DRB1*1104, HLA-DQB1*0501). We define in deeper detail some of these associations down to the level of aminoacidic positions which affect epitope binding and relocate some previous SSc associations within auto-antibody positive subgroups. Furthermore, we describe new association of the HLA allele HLA-DRB1*0801 with the presence of anti-centromere auto-antibodies.

Conclusion: Our data indicate that most HLA associations are specific to the presence of auto-antibodies. Also, only MHC class II alleles are associated and not MHC class I.

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Differences and Overlap Of Immunological Pathways Implicated In The Aetiology Of Anti-Citrullinated Peptide Antibody Positive and Negative Rheumatoid Arthritis. Sebastien Viatte[1], Paul Martin[2], Andrew Brass[3], Mark Lunt[4], Anne Barton[4] and Stephen Eyre[4]. [1]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Sciences Centre, Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom, [3]School of Computer Science, University of Manchester, Manchester, United Kingdom, Manchester, United Kingdom, [4]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom.

Background/Purpose: Genome-wide association studies have been successful in identifying single nucleotide polymorphisms (SNPs) associated with disease. However, previous studies have been under-powered to detect differences between anti-citrullinated peptide antibody (ACPA) positive and negative patients. Using a custom Illumina® Infinium® array, the RA Consortium for Immunochip (RACI) allows comprehensive analysis of disease associations in both ACPA positive and negative patients. Pathway analyses can identify whether a molecular pathway is associated with disease by testing for enrichment of genes associated with disease. This involves mapping SNP associations to genes, which can often be subjective.

Objectives: The objectives of this study, therefore, were to develop a robust workflow-based method to assign SNPs to genes and to compare the pathways significantly enriched in ACPA positive and negative patients.

Methods: Excluding HLA, the top 100 most associated SNPs from the Immunochip analysis were selected for ACPA positive patients along with the top 100 most associated SNPs from the ACPA negative analysis. Genes were assigned to these SNPs using a Taverna workflow which defines an associated region using SNPs in linkage disequilibrium (LD) with the associated SNP. This prevents the bias introduced by researchers assigning SNPs to 'biologically plausible' genes and provides a robust, reproducible method for assigning genetic associations to genes. These genes were subsequently tested for enrichment in PANTHER pathways and Gene Ontologies (GO) using the Expression Analysis tool to calculate an enrichment binomial probability. To correct for the enrichment of genes with immunological functions present on the Immunochip, the statistical significance of enrichment binomial probabilities was calculated by permutation.

Results: Overall we show that the proportion of pathways shared between the two RA serological subtypes is significantly larger than expected by chance, indicating a high degree of overlap. On the other hand, we identified some pathways specifically and significantly enriched in the ACPA positive gene list (Interleukin Signalling Pathway: permutation p-value for enrichment = 7.0E-03, while in ACPA negative p = 0.46) and in the ACPA negative gene list (Interferon-Gamma Signalling Pathway: p = 1.2E-03, while in ACPA positive p = 0.33).

Conclusion: This study provides the first comparative pathway analysis of RA serological subtypes based on large numbers of RA cases. The methods developed here present a quantitative framework to compare different diseases at the pathway level. The findings not only suggest shared processes between the two disease sub-groups, but also identify serotype-specific pathways.

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Fc-Gamma Receptor Genetic Variation In Kawasaki Disease. Carline E. Tacke[1], Willemijn B. Breunis[2], Long T. Hoang[3], Eileen Png[3], Judy Geissler[2], Sietse Nagelkerke[2], Justine Ellis[4], Sonia Davila[3], Chiea Chuen Khor[3], Michael Levin[5], David Burgner[4], Chisato Shimizu[6], Jane C. Burns[6], Martin L. Hibberd[3] and Taco W. Kuijpers[2]. [1]Emma Children's Hospital/Academic Medical Center (AMC), Amsterdam, Netherlands, [2]Sanquin Resarch and Landsteiner Laboratory (AMC), Amsterdam, Netherlands, [3]Genome Institute of Singapore, Singapore, Singapore, [4]Murdoch Childrens Research Institute, Parkville, Australia, [5]Imperial College London, London, United Kingdom, [6]UC San Diego, School of Medicine, La Jolla, CA. Abstract on behalf of the International Kawasaki Disease Genetics Consortium.

Background/Purpose: Kawasaki disease (KD) is a pediatric vasculitis of unknown etiology with a substantial genetic contribution to susceptibility. KD is complicated by coronary artery aneurysms in 25% of untreated patients. Intravenous immunoglobulin (IVIG), a polyclonal IgG preparation, decreases the aneurysm rate to <10%. In our recent GWAS, a functional variant in *FCGR2A* (131H>R; rs1801274) was associated with KD at genome-wide significance. *FCGR2A* encodes the Fc-gamma receptor (FcγR) IIa, one member of a family of glycoproteins on leukocytes that bind the Fc-domain of IgG. The balance between the various activating and a single inhibiting FcγR (FcγRIIb) determines the level of cell activation. Hence, altered FcγR expression may result in unbalanced immunity or autoinflammation. *FCGR2A* is located within the *FCGR2/3* gene cluster. This cluster contains extensive gene copy number variations (CNVs) and several important single nucleotide polymorphisms (SNPs). We hypothesized that CNV and additional SNPs within the *FCGR* locus, regulating gene transcription and expression of the FcγRs, may be important in KD susceptibility.

Methods: The *FCGR*-specific Multiplex-Ligation Probe-dependent Amplification (MLPA) assay was performed in 426 patients and 710 controls of Caucasian origin, and in 510 patient-parent trios of mixed ethnic origin. First, the association between *FCGR* genotype status (including CNV, *FCGR2A-131H>R, FCGR2A-27Q>W, FCGR2C-ORF* and *FCGR2B -386G>C)* and KD susceptibility was analyzed. Second, the genetic variation at the *FCGR2/3* locus was correlated to the expression of these genes. Transcriptional expression data (pre-IVIG acute and post-IVIG convalescent samples) were available in a subset of 169 patients.

Results: An increased allele frequency of the open-reading frame (ORF) of *FCGR2C* encoding an additional activating FcγRIIc was found in patients as compared to controls (OR 1.4 [95%CI 1.1–1.7], p=0.016). We also observed a significant overrepresentation of *FCGR2A-27Q>W* (OR 1.5 [95%CI 1.1–1.9, p=0.006) and the -386G>C promoter polymorphism of *FCGR2B* and *FCGR2C* (OR 1.5 [95%CI 1.1–1.9], p=0.004) in KD. No significant difference was found in the allele frequency of *FCGR2A-131H>R* in KD patients and controls (43.8% versus 45.4%, p=0.467). The frequency of CNV in the *FCGR2C, FCGR3A* and *FCGR3B* genes was not significantly different between the groups. A positive correlation was observed between gene expression and dosage of *FCGR2C, FCGR3A* and *FCGR3B*, which may affect the activating FcγRs expression level on leucocytes. Results of the patient-parent trios data using transmission disequilibrium tests (TDT) will be used for further validation of our fine-mapping studies on the *FCGR2/3* genes in KD.

Conclusion: A significant overrepresentation of *FCGR2C-ORF*, as well as *FCGR2A-27Q>W* and the *FCGR2B/C*-386G>C promoter polymorphisms, was observed in Caucasian KD patients compared to the controls. Genetic variation at the *FCGR2/3* gene cluster may lead to a shift in the balance towards the activating FcγRs and may therefore contribute to the development of the inflammatory response in KD.

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The Association Between Single Nucleotide Polymorphism ABCG2 rs2231142 and Hyperuricemia: A Case-Control Study. Bingqing Zhang[1], Weigang Fang[2], Yun Zhang[2], Shufen Liu[2], Yuanjie Li[2] and Xuejun Zeng[2]. [1]Peking Union Medical College, Beijing, China, [2]Peking Union Medical College Hospital, Beijing, China.

Background/Purpose: The prevalence of hyperuricemia and gout in China increased markedly in the past decades. Genome-wide association studies in Caucasian population have identified multiple gene loci associated with hyperuricemia and gout, including single nucleotide polymorphism (SNP) of rs2231142 in the ABCG2 gene, which leads to an amino acid change from glutamine to lysine at position 141 of the membrane transporter. However, this association was not consistently observed in Asian population.

Methods: A case-control study was carried out to investigate the association between locus ABCG2 rs2231142 polymorphism and hyperuricemia in a Chinese cohort of faculty and staff members at an academic health center in Beijing. Blood samples were drawn and stored during their annual health examination in 2008. Physical examination and biochemical assay were performed for all participants at that time. Hyperuricemia was defined as serum urate ≥7 mg/dl in men or ≥6 mg/dl in women. Each case of hyperuricemia with glomerular filtration rate '30ml/min/1.73m^2 was matched with one or two controls that were randomly sampled from individuals with the same sex, age group, chronic kidney disease stage and body mass index classification as the case in the cohort. SNP rs2231142 was assayed for both cases and controls by amplification refractory mutation system polymerase chain reaction (ARMS-PCR) in 2013. Conditional logistic regression analysis was performed to study the association between SNP rs2231142 and hyperuricemia.

Results: A total of 198 subjects and 370 controls were identified in the cohort. The overall A allele frequency of the ABCG2 gene was 30.81% in the cohort, but it was significantly higher in the cases than the controls (38.38% vs. 26.76%, p<0.01). Compared to individuals with genotype CC, the Odds Ratios (ORs) of hyperuricemia in individuals with A allele (genotype AA + CA), genotype CA and AA were 2.89 (95% CI 1.91–4.37, p<0.01), 2.84 (95% CI 1.86–4.32, p<0.01) and 3.30 (95% CI 1.60–6.81, p<0.01), respectively. After adjustment of hypertension, hyperglycemia and dyslipidemia, the ORs of A allele, genotype CA and AA were 2.99 (95% CI 1.94–4.62, p<0.01), 2.99 (95% CI 1.93–4.66, p<0.01) and 2.99 (95% CI 1.39–6.48, p<0.01), respectively. Subgroup analysis showed the ORs of A allele, genotype CA and AA were higher in males (3.83, 3.62, and 6.34, respectively) than those in females (2.30, 2.34, and 2.04, respectively), but the interaction of allele and gender was not significant with OR 1.66 (95% CI 0.71–3.87, p=0.23).

Conclusion: ABCG2 SNP rs2231142 A allele is an independent risk factor of hyperuricemia in Chinese. The risk of hyperuricemia in individuals with A allele appears to be higher in males than that in females, but the interaction of allele and gender is not significant.

Disclosure: B. Zhang, None; **W. Fang**, None; **Y. Zhang**, None; **S. Liu**, None; **Y. Li**, None; **X. Zeng**, None.

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Familial Aggregation Of Female Premenopausal Gout –Monogenic, Polygenic Or Clinical Coincidence? Bingqing Zhang[1], Shufen Liu[2], Nuo Si[3], Yun Zhang[2] and Xuejun Zeng[2]. [1]Peking Union Medical College, Beijing, China, [2]Peking Union Medical College Hospital, Beijing, China, [3]Chinese Academy of Medical Science & Peking Union Medical College, Beijing, China.

Background/Purpose: Primary gout is a multifactorial disease, in which genetic background and environmental factors interact with each other. Genetic predisposition is particularly prominent in those seemingly low risk patients, such as the young and females. Women usually do not have gout until menopause, with menses as one of the most well-known protective factors of gout and hyperuricemia. We have found a rare family with three female gout patients, all of whom developed gout before menopause. The concentration of female patient with gout before menopause in this family highly suggests the involvement of genetic factors. The aim of this study is to explore the genetic factors related to gout in this female premenopausal gout family.

Methods: Medical history, physical examination and laboratory work-up of this family were collected. Allele sharing examination and exon sequencing were carried out to study the causative genes of familial juvenile hyperuricemia nephropathy, including UMOD, RENIN, HNF1B and FJHN3, as well as HPRT1 of Lesch-Nyhan syndrome. Serum uric acid concentration quantitative trait locus ABCG2, SLC2A9, and SLC22A12 were screened by exon sequencing

Results: The family was composed of 4 generations and 21 members (figure 1). All three patients were females; none of the male members had gout or hyperuricemia. The proband (III-5) was a female patient who had gout at the age 28; she started allopurinol since the second attack, but her renal function deteriorated. Her mother (II-5) had recurrent acute monoarthritis since the age of 16; she was diagnosed with gout at the age of 38, with obvious decreased renal function. The aunt of the proband (II-1) had gout at the age of 46, when she still had menses. None of the three patients had other known disease prior to gout attack.

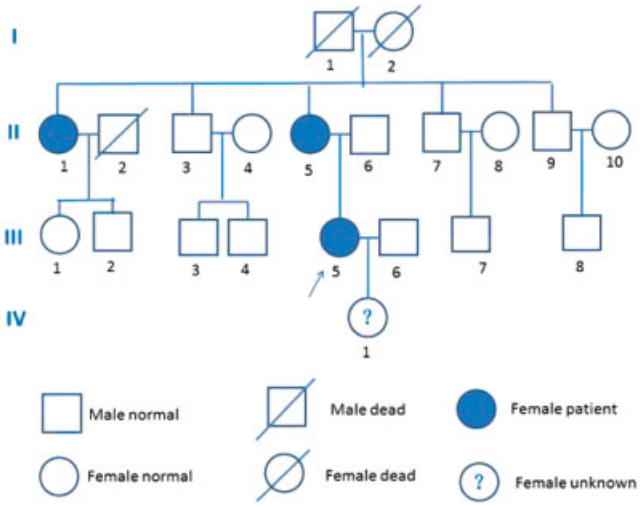

Figure 1. Pedigree of the family.

RENIN, the causative gene of Hyperuricemic Nephropathy, Familial Juvenile, type2 (HNFJ, MIM: #613092) was found to be shared in this family but not UMOD, HNF1B or FJHN3. Exon sequencing of RENIN and UMOD of patient II-5 was proved to be normal. HPRT1 of the rare Lesch-Nyhan syndrome was excluded by exon sequencing.

Multiple single nucleotide polymorphisms of gene ABCG2, SLC2A9 and SLC22A12 were found in patient II-5, including one locus known to be highly associated with gout, SNP rs2231142 (C>A) of gene ABCG2. Nearly all of the family members carry the risk A allele.

Conclusion: In this premenopausal gout family, all known causative genes of gout were found to be negative. ABCG2 rs2231142 (C>A) polymorphism was found in both female patients and male healthy members of this family.

Disclosure: B. Zhang, None; **S. Liu**, None; **N. Si**, None; **Y. Zhang**, None; **X. Zeng**, None.

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Rheumatoid Arthritis Quality Measure Results In a Large Managed Care Population. Roxanne Meyer[1], Lorie A. Ellis[2], Susan C. Bolge[2], Andrew Howe[3] and Yunping Zhou[3]. [1]Janssen Scientific Affairs, LLC, Horsham, NY, [2]Janssen Scientific Affairs, LLC, Horsham, PA, [3]Comprehensive Health Insights, Louisville, KY.

Background/Purpose: Improvement in quality of care is of growing interest to both physicians and payers. Both the American College of Rheumatology and National Quality Forum (NQF) recommend monitoring of quality measures in rheumatoid arthritis (RA) patients. The purpose of this study is to describe the proportion of RA patients in a large managed care population that achieved NQF quality measures specific to RA.

Methods: This is a retrospective analysis of Humana's Commercial and Medicare database. Claims were reviewed to evaluate compliance with four NQF quality measures in calendar year 2011. NQF definitions were used for the numerator (N) and the denominator (D) for each measure. Descriptive statistics were calculated on the specific measures.

NQF Measure	Definition
0054 Arthritis: disease modifying antirheumatic drug (DMARD) therapy in rheumatoid arthritis	Percentage of patients 18 years and older, diagnosed with rheumatoid arthritis who have had at least one ambulatory prescription dispensed for a DMARD
0590 Rheumatoid Arthritis New DMARD Baseline Liver Function Test	This measure identifies adult patients with a diagnosis of rheumatoid arthritis who received appropriate baseline liver function testing (AST or ALT) within 90 days before to 14 days after the new start of sulfasalazine, methotrexate, leflunomide, azathioprine, cyclosporine or cyclophosphamide during the measurement year.
0592 Rheumatoid Arthritis Annual ESR or CRP	This measure identifies adult patients with a history of rheumatoid arthritis who have received erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) lab tests during the measurement year
0601 New Rheumatoid Arthritis Baseline ESR or CRP within Three Months	This measure identifies adult patients newly diagnosed with rheumatoid arthritis during the first 8 months of the measurement year who received erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) lab tests either 4 months (3 months + 1-month grace period) before or after the initial diagnosis.

Results: The proportion of adult RA patients who received at least one prescription for a DMARD (measure 0054) was 72.8% (N=17,066, D=23,440). Liver function testing in patients with a new DMARD as defined by measure 0590 was achieved by 84.7% (N=3,130, D=3,694) of adult RA patients. The proportion of newly diagnosed adult patients receiving a baseline ESR or CRP (measure 0601) was 54.7% (N=2,595, D=4,742). For measure 0592 the proportion of adult patients receiving an annual ESR or CRP was 58.2% (N=13,125, D=22,538).

Conclusion: This analysis of an RA population in a large managed care population suggests that 15% to 45% of patients do not attain NQF quality measure standards. These findings suggest that improvements in patient care could be made with the goal of improving the proportion of patients achieving RA specific NQF measures. Further studies are warranted to understand whether attainment of these measures translates into better overall health or RA-related outcomes and may enhance physician and patient awareness about the benefits of quality of care.

Disclosure: R. Meyer, Janssen Scientific Affairs, LLC, 3; **L. A. Ellis**, Janssen Scientific Affairs, LLC, 3; **S. C. Bolge**, Janssen Scientific Affairs, LLC, 3; **A. Howe**, Janssen Scientific Affairs, LLC, 5; **Y. Zhou**, Janssen Scientific Affairs, LLC, 5.

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National Quality Forum Measures Among Rheumatoid Arthritis Patients In a Large Managed Care Population. Roxanne Meyer[1], Lorie A. Ellis[2], Susan C. Bolge[2], Joseph Tkacz[3], Peter Kardel[3] and Charles Ruetsch[3]. [1]Janssen Scientific Affairs, LLC, Horsham, NY, [2]Janssen Scientific Affairs, LLC, Horsham, PA, [3]Health Analytics, LLC, Columbia, MD.

Background/Purpose: The American College of Rheumatology and National Quality Forum (NQF) recommend monitoring quality measures among rheumatoid arthritis (RA) patients. This study describes the proportion of RA patients within a large managed care population meeting the criteria of RA specific NQF quality measures.

Methods: Definitions of NQF RA quality measures 0054, 0589, 0590, 0592, 0597–0599, and 0601 were applied to claims data of a commercially-insured population from Optum Insight's Clinformatics database for calendar years 2007–2011. NQF definitions may be found at www.qualityforum.org/Home.aspx.

Results: Measure 0054 defines the proportion of RA patients treated with a DMARD in a defined measurement year. At each year studied, approximately 70% achieved this measure.

Measures 0589, 0590 pertain to laboratory monitoring of adult RA patients with a new DMARD in the measurement year. Measures 0589 (baseline serum creatine) and 0590 (baseline liver function test; LFT) were achieved by only one-third of patients. The proportion of patients achieving these measures appeared to increase annually between years 2007 and 2010 but declined during 2011.

Measures 0597, 0598 and 0599 were designed to monitor adult RA patients within 12 weeks of a new methotrexate (MTX) prescription. Approximately one-third of patients met the criteria for Measure 0597 (LFT within 12 weeks), and 40% met the criteria for 0599 (serum creatinine within 12 weeks). In contrast, approximately 70% of new MTX-treated patients met the criteria for 0598 (complete blood count within 12 weeks). Slight variations in the proportions of patients achieving these measures were observed from year to year.

Measures 0592 and 0601 pertain to monitoring of ESR or CRP in adult RA patients. Measure 0601 (proportion of newly diagnosed RA patients who received an ESR or CRP measure within 3 months of diagnosis) was achieved by approximately 70% of patients. Proportions of patients achieving this measure were improved slightly over time. However, annual ESR or CRP (0592) was achieved in slightly more than half the patients.

NQF Measure Results 2007–2011	2007	2008	2009	2010	2011
0054 Arthritis: disease modifying antirheumatic drug (DMARD) therapy in rheumatoid arthritis					
Denominator (f)	21,156	26,514	27,034	24,852	26,420
Percent (%)	70.0%	71.2%	71.1%	72.1%	70.5%
0589 Rheumatoid Arthritis New DMARD Baseline Serum Creatinine					
Denominator (f)	2,438	3,868	3,388	3,181	3,160
Percent (%)	32.3%	31.3%	35.8%	38.3%	27.7%
0590 Rheumatoid Arthritis New DMARD Baseline Liver Function Test					
Denominator (f)	2,681	4,183	3,716	3,524	3,488
Percent (%)	29.7%	30.3%	36.5%	39.0%	26.7%
0592 Rheumatoid Arthritis Annual ESR or CRP					
Denominator (f)	14,792	21,702	25,474	25,416	26,776
Percent (%)	58.4%	57.7%	55.8%	54.9%	55.5%
0597 Methotrexate: LFT within 12 weeks					
Denominator (f)	7,126	8,743	8,589	7,977	8,285
Percent (%)	30.9%	33.2%	37.4%	37.3%	33.8%
0598 Methotrexate: CBC within 12 weeks					
Denominator (f)	7,126	8,743	8,589	7,977	8,285
Percent (%)	72.4%	72.7%	72.4%	72.8%	71.8%
0599 Methotrexate: Creatinine within 12 weeks					
Denominator (f)	7,126	8,743	8,589	7,977	8,285
Percent (%)	38.6%	41.0%	44.7%	45.0%	41.6%
0601 New Rheumatoid Arthritis Baseline ESR or CRP within Three Months					
Denominator (f)	3,249	4,144	4,283	4,540	4,709
Percent (%)	66.2%	67.8%	69.2%	71.6%	71.5%

Conclusion: This analysis of a large national health plan suggests that between 30% and 70% of RA patients do not meet NQF quality measure criteria. Further studies are needed to understand: 1) the relationship between NQF measures and health outcomes and cost; 2) drivers of meeting NQF quality standards; and 3) interventions that improve NQF scores within health plans.

Disclosure: R. Meyer, Janssen Scientific Affairs, LLC, 3; **L. A. Ellis**, Janssen Scientific Affairs, LLC, 3; **S. C. Bolge**, Janssen Scientific Affairs, LLC, 3; **J. Tkacz**, Janssen Scientific Affairs, LLC, 5; **P. Kardel**, Janssen Scientific Affairs, LLC, 5; **C. Ruetsch**, Janssen Scientific Affairs, LLC, 5.

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The Performance Of a Point Of Care Test For Detection Of Anti-Mutated Citrullinated Vimentin and Rheumatoid Factor In Early Rheumatoid Arthritis. Preeda Rojanasantikul[1], Prapa Pattrapornpisut[2], Kulvara Anuruckparadorn[3] and Wanruchada Katchamart[1]. [1]Division of Rheumatology, Department of Internal Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, [2]Department of Internal Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [3]Department of Transfusion Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Background/Purpose: Besides rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (ACPA), a newer serologic marker, was added to the new American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria 2010. Most commercially available assay used for detection of ACPA and RF is the ELISA-based method. This assay is a multi-step and time-consuming procedure requiring special equipments and experienced technicians. ACPA therefore may not be available worldwide. Moreover, the results of these tests may take too long to be of value in daily practice, leading to delayed diagnosis. Recently, a serological point-of-care test (POCT) for detection of anti-MCV and RF using a lateral flow immunochromatographic assay (LFIA) has been developed for a rapid result, and it also has wider availability. The diagnostic performance of this POCT was documented in established RA; however, its performance in patients with 'early' RA is still unknown. Our objective was to determine the diagnostic performance of a point of care test (POCT) for detection of anti-mutated citrullinated vimentin (MCV) and rheumatoid factor (RF) in early rheumatoid arthritis (RA) with 2 years of disease duration or less. Additionally, we evaluated the agreement of these tests when using EDTA whole blood and capillary blood.

Methods: Patients with RA and other rheumatic disorders were consecutively recruited from the Rheumatology outpatient clinic. The POCT for detection of anti-MCV and RF using capillary blood and EDTA whole blood was performed in 78 patients with early RA, 55 patients with other rheumatic disorders, and 55 healthy blood donors.

Results: The sensitivity and specificity of anti-MCV POCT in patients with early RA were 64% and 97%, respectively, while the sensitivity and specificity of RF POCT were 51% and 95% respectively. The positive likelihood ratio of the POCT for anti-MCV was higher than those for RF (23.5 vs.9.4). The negative likelihood was 0.37 for anti-MCV and 0.52 for RF. There were 3 cases with false positive for anti-MCV including a patient with psoriatic arthritis and the other two with systemic sclerosis. The agreement between capillary blood and EDTA whole blood testing for anti-MCV and RF was low to moderate with Cohen's kappa of 0.58 and 0.49, respectively.

Conclusion: This POCT for detection of anti-MCV and RF yielded high specificity and may be a valuable tool for the diagnosis of early RA. Using this POCT with EDTA whole blood instead of capillary blood is not recommended.

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Are Physician Gender, Age and Clinical Experience Associated With Discrepancy In Global Disease Score In Rheumatoid Arthritis, Ankylosing Spondylitis and Psoriatic Arthritis? Data From The Nationwide Danbio Registry. Cecilie Lindstrom Egholm[1], Niels Steen Krogh[2], Lene Dreyer[3], Torkell Ellingsen[4], Bente Glintborg[5], Marcin Kowalski[6], Tove Lorenzen[7], Ole Rintek Madsen[8], Henrik Nordin[9], Claus Rasmussen[10] and Merete L. Hetland[11]. [1]Regional Research Unit, Region Zealand, Roskilde, Denmark, [2]ZiteLab ApS, Copenhagen, Denmark, [3]Copenhagen University Hospital at Gentofte, Copenhagen, Denmark, [4]Diagnostic Centre Region Hospital Silkeborg Denmark, 8600 Silkeborg, Denmark, [5]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Glostrup Hospital, Glostrup, Denmark, [6]Aalborg University Hospital, Aalborg, Denmark, [7]Department of Rheumatology, Region Hospital Silkeborg, Silkeborg, Denmark, [8]Copenhagen University Hospital in Gentofte, Copenhagen, Denmark, [9]Department of Infectious Diseases and Rheumatology, Rigshospitalet, Copenhagen, Denmark, [10]Vendsyssel Teaching Hospital/ Aalborg University, Hjoerring, Denmark, [11]Copenhagen University Hospital Glostrup, Copenhagen, Denmark.

Background/Purpose: A global estimate on a 100 mm Visual Analogue Scale (VAS) assessed by patients (PATGL) and physicians (DOCGL) is commonly used to measure disease activity and to monitor treatment response in patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA). Several studies in RA have shown that PATGL and DOCGL are discordant (>20 mm difference) in about 1/3 of the encounters and have mainly focused on whether clinical measures and patient characteristics explain this. The influence of physician characteristics has not yet been examined across different arthritis diagnoses. Studies in other clinical areas suggest that treatment decisions are affected by physician gender and clinical experience. The aim of the study was therefore to assess whether physician characteristics are associated with discordance between DOCGL and PATGL in patients with RA, AS and PSA.

Methods: Physician characteristics were collected by a questionnaire sent to DANBIO physicians (n = 265). Patient characteristics and clinical measures as well as PATGL and DOCGL scores were obtained from DANBIO first encounters. A difference between DOCGL and PATGL of up to 20 mm was considered concordant, yielding three groups: PATGL>DOCGL, PATGL=DOCGL and DOCGL>PATGL. The two latter groups were merged due to few patients in DOCGL>PATGL. We used mixed effects logistic regression analyses with discordance (yes/no) as the dependent variable, performing independent analyses for each diagnosis. The model was adjusted for patient and clinical variables (e.g. age, gender, disease activity, treatment, disease duration), which were entered as covariates.

Results: 90 physicians (44% females, 61% rheumatologists, median age 52 years) returned the questionnaire (34%) and were pairwise matched with 7,619 RA, 1,291 PsA and 469 AS first encounters.

Discordance was independent of physician's gender and age, both for patients with RA, and for patients with AS or PSA, see table. Less experienced physicians (i.e. not yet specialized) had lower odds of discordance 0.69–0.92, although it only reached statistical significance in patients with RA, see table.

Table. Mixed effects logistic regression of predictors of discordance between patient and physician assessments of global disease activity.

	RA (N: 7,619 encounters)		AS (N: 469 encounters)		PsA (N: 1,291 encounters)	
	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Physician gender, male (female=1.0)	0.83 (0.69–1.01)	NS	1.25 (0.70–2.26)	NS	1.04 (0.73–1.49)	NS
Physician age >52 years (≤52 =1.0)	1.10 (0.89–1.37)	NS	1.16 (0.59–2.30)	NS	1.17 (0.79–1.74)	NS
Rheumatologist (specialized), no (yes=1.0)	0.72 (0.55–0.93)	*	0.69 (0.31–1.52)	NS	0.92 (0.56–1.51)	NS

Concordant group is reference group.
The model was adjusted for swollen and tender joint counts (0–28), C-reactive Protein, disease duration (years), biological treatment (yes/no), country of medical exam, and doctor's subjective rating of factors important for DOCGL (inflammation, fibromyalgia, structural joint damage, comorbidity and social factors). To account for clustering by physician and patient, these variables were included in the model as random effects.
***=p<0.001,
**=p<0.01,
*=p<0.05, NS=not significant

Conclusion: Data from clinical practice covering >9,000 DANBIO first encounters between 90 physicians and their patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis showed that, regardless of diagnosis, discordance (i.e. difference between patient's and doctor's global scores >20 mm) was independent of physician's age and gender. This is reassuring for the monitoring of patients in routine care. Having specialized in rheumatology seemed to be associated with increased odds of discrepancy compared to less experienced colleagues.

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No Secular Trends In Real Live Radiographic Progression Of Rheumatoid Arthritis In Recent Year. Miriam Gärtner[1], Farideh Alasti[1], Gabriela Supp[1], Josef S. Smolen[2] and Daniel Aletaha[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria.

Background/Purpose: Progression of joint damage as measured radiographically is a hallmark of rheumatoid arthritis (RA), and its reduction a key claim for traditional and novel antirheumatic drugs. Data from clinical trials may be interpreted to indicate that the observed progression of RA has decreased over the past two decades.[1] Although these observations mainly stem from clinical trials, it has been hypothesized that RA in general may have become a less destructive disease.

It was the aim of this study, to evaluate the frequency and degree of radiographic progression in real life routine RA patients over the past decade

Methods: RA patients of our outpatient clinic, who had two x-rays performed over a three to five year interval between the years 2000 and 2012 were included. X-rays of the hands and feet were scored according to the Sharp van der Heijde (SvdH; range 0–448) method.[2] Clinical and demographic data were collected from the patients' charts. Patients were separated into three periods of time (2000–2004, 2005–2008, 2009–2012) and the annual radiographic progression was calculated based on the observed progression in these periods. Disease activity was assessed using the time averaged clinical disease activity index (CDAI). The mean number of joints with radiographic progression per patient, as well as the mean grade of progression per joint (erosion/joint space narrowing, JSN) were evaluated. Lack of progression was defined as no progression in total SvdH

Results: Of the 444 patients included (mean duration of RA 7.4±9.4 years, 64.8% rheumatoid factor positive, 63.7% ACPA positive), 406 (91.4%) showed radiographic progression over a mean of 3.8±0.6 years. We found no significant difference neither in clinical nor in radiographic results comparing patients between the three time periods. In all progressors we found no difference in rates of annual radiographic progression, erosion score, or JSN, within the three different time periods (Figure 1). Although the annual rate of progression was stable, baseline SvdH scores decreased across the three periods (43.2±57.4 2000–2004 vs 43.0±49.7 2005–2008 vs 33.2±48.9 2009–2012).

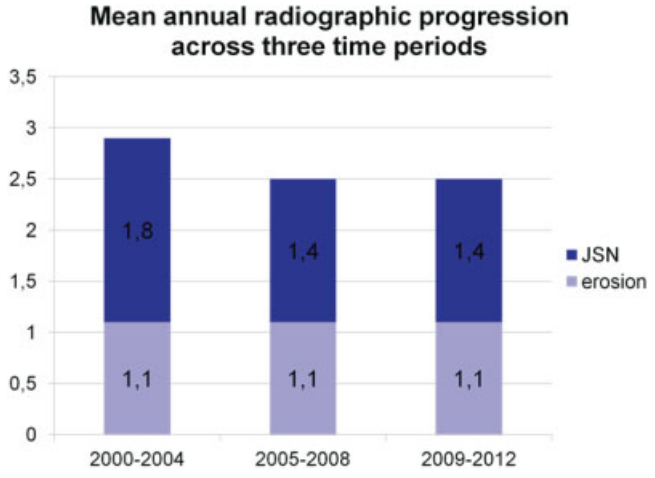

Figure 1. Patients with radiographic progression (n=406) during three time periods. The figure shows the mean annual radiographic progression rates for total SvdH-Score, erosions as well as JSN. There was no significant difference between the different time periods.

Conclusion: Only a minority of patients did not progress structurally over three to five years. The temporal trend analysis indicates that on the background of similar average disease activity and similar mix of treatment, the overall annual progression was constant during the last decade. However, in general progression of joint damage was low.

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Disclosure: M. Gärtner, None; **F. Alasti**, None; **G. Supp**, None; **J. S. Smolen**, None; **D. Aletaha**, None.

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Delay In Consultation and Starting Disease Modifying Anti-Rheumatic Drugs In Patients With Rheumatoid Arthritis In Argentina. How Early Arthritis Clinics Impact On Health Barriers? Natalia Zamora[1], Christian A. Waimann[1], Maria Florencia Marengo[1], Gustavo Citera[1], Amelia Granel[2], Ana Inés Marcos[2], Emilio Buschiazzo[3], Ricardo V. Juarez[3], Dora Pereira[4], Gisela Pendón[4], Andrea D'Orazio[5], Mariana Salcedo[6], Judith Sarano[7], María Victoria Collado[7], Graciela Gómez[7], Alejandra Medina[8], María Eugenia Lara[9], Juan C. Barreira[9], María Alicia Lázaro[10], Alejandra Cusa[10], Luciana González Lucero[11], María Silvia Yacuzzi[11], Raúl Nicolas Martínez[11] and Pablo Arturi[12]. [1]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [2]Hospital San Roque de Gonnet, La Plata, La Plata, Argentina, [3]Hospital Señor del Milagro, Salta, Argentina, [4]Hospital Ricardo Gutierrez, La Plata, La Plata, Argentina, [5]Hospital de la Asociacion Medica de Bahía Blanca, Bahía Blanca, Argentina, [6]Consultorio Privado, San Nicolás, Argentina, [7]Instituto de Investigaciones Medicas Alfredo Lanari, Buenos Aires, Argentina, [8]Hospital General de Agudos "Dr. E. Tornu", Ciudad Autónoma de Buenos Aires, Argentina, [9]Buenos Aires British Hospital, Buenos Aires, Argentina, [10]Hospital central de San isidro Dr A. Posse, San Isidro, Argentina, [11]Hospital Angel C. Padilla de San Miguel de Tucumán, San Miguel de Tucumán, Argentina, [12]Hospital Italiano de La Plata, La Plata, Argentina.

Background/Purpose: An early and intensive treatment has become the cornerstone in the treatment of Rheumatoid Arthritis (RA). For this reason, an early consult with a rheumatologist is crucial. The aim of our study was to evaluate the delay in consultation and starting disease modifying anti-rheumatic drugs (DMARDs) in patients with RA, and to assess the impact of early arthritis clinics and health barriers on such delay.

Methods: We carried out a retrospective multicenter study including patients with a diagnosis of RA of less than 5 years of disease evolution. Data collected included clinical, economic, sociodemographic characteristics, health insurance status and health care center (private vs. public hospital; early arthritis clinics vs. routine care hospitals). In addition, we evaluated the presence of health barriers in those patients with <2 years of disease duration, including geographical location, social support, family and work responsibilities, economics issues, accessibility to health care, self-treatment and patient-physician relationship. Three time-points were evaluated: time to first medical contact, time to rheumatologist and time to initiation of first DMARD. The association between variables and time-points were assessed using univariate and multivariate models.

Results: A total of 316 patients were included; 86% were female, mean age was 47 $\pm$ 14 years, disease duration 7 $\pm$ 5 years, 73% had a low income (less than 1000 dollars/month), and 11 $\pm$ 4 years of formal education. Two third were from public hospitals and one third from private sector, 8% lived alone and 23% were unemployed. The median time to first medical contact was 30 (IQR 10–60) days, being the clinician the initial physician (52%) followed by traumatologist and rheumatologist (24% for both). The total time to arrive to the rheumatologist was 90 (IQR 35–210) days, but 32% of the patients delayed more than six months to contact a rheumatologist. Twenty five percent of patients were never referred by their clinicians duplicating the access time to rheumatologists to 165 (IQR 30–365) days. The median time to start DMARDs treatment by the rheumatologist was 24 (IQR 6–365) days, which result on a total median time from onset of symptoms of five months. One quarter of patients took longer than 12 months to start a DMARD. Three health barriers were significantly associated with delay in consultation and treatment: geographical location, family and work responsibilities, and lack of economic issues. After adjusting for multiples confounders (health insurance, health care center, marital status, household members, comorbidities and age), the presence of health barriers was independently associated with increased delay to rheumatologist and initiation of the first DMARD. In addition, being attended in early arthritis clinics was significantly associated to shorter delay in receiving DMARD treatment.

Conclusion: The delay in starting treatment with DMARDs was about 5 months. However, one-quarter of patients took longer than one year to start the treatment. The implementation of early arthritis clinics, a fast referral system and limitation of health barriers could be a good strategy to optimize the prompt treatment of the patients with RA.

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The Health and Economic Consequences Of Delay In Starting Disease-Modifying Anti-Rheumatic Drugs In Australian Patients With Early Rheumatoid Arthritis. Danny Liew, Mark Tacey and Sharon Van Doornum. The University of Melbourne, Melbourne, Australia.

Background/Purpose: Several international studies suggest that the time between symptom onset and DMARD initiation in RA patients is longer than is considered optimal. We sought to assess the health economic impact of this delay in an Australian context.

Methods: The delay in DMARD initiation was estimated from a study of 135 Australian RA patients referred to hospital-based and community-based rheumatologists. RA-associated utilities and costs were sourced from published data. Patients not taking and taking DMARD therapy were assumed to have utilities of 0.59 and 0.64, respectively. The annual direct cost of DMARD therapy was assumed to be AUD$1200, consistent with the most expensive first-line agents in Australia. It was also conservatively assumed that DMARD therapy did not reduce non-DMARD RA costs. (NB: The Australian dollar is near parity with the US dollar.)

Results: The median time from time of symptom onset to initiation of DMARD therapy was 0.46 years. Over this time a mean of 0.27 quality-adjusted life years (QALYs). Had DMARDs been commenced at symptom onset, 0.30 QALYs would have been lived per patient, and AUD$555 of additional healthcare costs incurred. Hence early initiation of DMARDs would have saved 0.023 QALYs, equating to an incremental cost-effectiveness ratio (ICER) of AUD$24,000 per QALY saved. An additional AUD$600 could be spent per patient to reduce the time to DMARD initiation before the ICER breached the arbitrary cut-off of AUD$50,000 per QALY saved. Our analysis was conservative in it did not consider the long-term health and cost savings associated with avoidance of permanent joint damage.

Conclusion: The considerable delay in the initiation of DMARD therapy among patients with RA leads to significant health loss. Reducing the time to initiation of DMARDs represents a cost-effective means of reducing the burden of RA

Disclosure: D. Liew, Abbvie Australia, 2, Abbvie Australia, 9; **M. Tacey**, None; **S. Van Doornum**, AbbVie Pty Ltd, 2.

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Can MDHAQ/RAPID3 Be Used In Usual Care Of Patients With Systemic Lupus Erythematosus? Narender Annapureddy[1], Theodore Pincus[2], Joel A. Block[1] and Meenakshi Jolly[1]. [1]Rush University Medical Center, Chicago, IL, [2]NYU Hospital for Joint Diseases and New York University School of Medicine, New York, NY.

Background/Purpose: Disease-specific patient reported outcome (PRO) tools are uniquely informative for the management of systemic lupus erythematosus (SLE) patients. However, it is difficult to incorporate distribution of appropriate disease specific PRO measures in busy clinical settings. A single, simple PRO measure for all patients, irrespective of their underlying disease diagnosis, can easily be integrated into the clinic check-in processes without requiring additional processes/ personnel. Multi-Dimensional Health Assessment Questionnaire (MDHAQ) is a PRO tool developed for patients with musculoskeletal diseases; RAPID 3 (Routine Assessment of Patient Index Data) scores are easily and rapidly calculated from the MDHAQ. We compared RAPID3 and LupusPRO (a disease specific PRO tool for SLE) and disease activity indices in patients with SLE seen during usual care.

Methods: 78 consenting patients meeting 4 ACR criteria for SLE completed both MDHAQ and LupusPRO during a routine clinic visit. Disease activity was assessed using SELENA-SLEDAI (Physician Global Assessment-PGA 0–3), and demographic data were obtained. We compared

LupusPRO domain scores for 8 Health Related Quality of Life-HRQOL and 4 Non-Health Related Quality of Life-Non-HRQOL scales (all scored 0–100,higher scores=Better Quality of Life) and physician global assessment (DOCGL), SELENA-SLEDAI stratified by disease severity to RAPID3 scores in 4 categories,≤ 3 Remission; 3.1–6.0 Low severity; 6.1–12 Medium Severity and >12 High severity. Statistical significance was analyzed using Kruskall-Wallis non-parametric tests; a p value of ≤ 0.05 was considered significant on two tailed tests.

Results: Mean (SD) age, Physician global assessment (or DOCGL) and total SELENA-SLEDAI scores were 42.4 (13.8) yrs, 0.7 (0.7) and 3.9 (4.7) respectively. Mean (SD) RAPID3 score was 9.8 (7.6). Table 1 shows the median (IQR) disease activity and LupusPRO domain scores for the RAPID3 disease severity categories. Disease activity scores did not vary between RAPID3 disease severity categories. This phenomenon has been previously reported with all PRO tools (Generic or Disease Specific) used in SLE. Seven of the 12 LupusPRO domains differed significantly in patients in the 4 RAPID3 disease severity categories - lupus symptoms, cognition, physical health, pain-vitality, emotional health, body image, and desires- goals, while 5/12 domains - Procreation, Lupus Medications, Social Support, Coping and Satisfaction with Treatment, did not differ in the 4 groups. The composite HRQOL LupusPRO scores differed significantly in the RAPID3 disease severity categories, while the composite non-HRQOL did not differ.

Table 1. Disease Activity and LupusPRO scores stratified by RAPID3 Disease Severity.

	RAPID 3 Based Disease Severity				
Median (IQR)	**0–3**	**3.1–6**	**6.1–12**	**>12**	**P value**
Physician Global Assessment	0.0 (1.0)	0.25 (0.50)	1.0 (1.0)	0.5 (1.1)	0.101
Total SELENA-SLEDAI	2.0 (4.0)	2.0 (6.0)	4.0 (5.8)	4.0 (4.0)	0.130
LupusPRO-HRQOL					
Lupus Symptoms	91.7 (8.3)	90.6 (14.6)	66.7 (33.3)	50.0 (41.7)	<0.001
Cognition	100 (37.5)	81.3 (43.8)	56.3 (46.9)	50.0 (50.0)	<0.001
Procreation	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	0.120
Lupus Medications	100.0 (0.0)	75.0 (46.9)	81.3 (50.0)	87.5 (37.5)	0.030
Physical Health	100.0 (0.0)	100 (12.5)	80.0 (43.8)	55.0 (32.5)	<0.001
Pain-Vitality	95.0 (20.0)	75.0 (20.0)	50.0 (30.0)	30.0 (17.5)	<0.001
Emotional Health	83.3 (33.3)	75.0 (11.5)	79.2 (45.8)	45.8 (30.2)	<0.001
Body Image	100 (15.0)	97.5 (38.8)	77.5 (38.8)	50 (57.6)	<0.001
Composite HRQOL	91.7 (14.1)	86.7 (4.3)	76.3 (19.4)	57.9 (18.6)	<0.001
LupusPRO-Non-HRQOL					
Desires-Goals	93.8 (25.0)	78.1 (29.7)	68.8 (25.0)	46.9 (42.2)	<0.001
Social Support	100 (37.5)	100.0 (0.0)	87.5 (50.0)	93.8 (40.6)	0.227
Coping	83.3 (41.7)	91.7 (25.0)	66.7 (41.7)	75.0 (27.1)	0.314
Satisfaction Treatment	87.5 (62.5)	100 (0.0)	100 (34.4)	90.6 (31.3)	0.146
Composite Non-HRQOL	75.0 (26.0)	87.5 (9.9)	75.0 (30.7)	72.7 (12.9)	0.300

Conclusion: RAPID3 may be used as a PRO for HRQOL in busy clinical settings to add to management of SLE patients.

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Implementation Of a Methotrexate Self-Injection Education Video – Reducing Teaching Time While Maintaining Patient Confidence and Knowledge. Steven J. Katz and Sylvia Leung. University of Alberta, Edmonton, AB.

Background/Purpose: To compare the effect of standard nurse led methotrexate self-injection patient education to a methotrexate self-injection web based education video added to standard teaching on 1) Patient satisfaction with teaching 2) Patient self-confidence in performing the injection 3) Patient knowledge around injection technique & precautions & 4) nursing time required

Methods: Consecutive rheumatology patients at the University of Alberta Medicine Clinic seen by the Clinic Nurse for methotrexate self-injection education were asked to participate in the study. Each patient's pre-education confidence for self-injection (Visual Analog Scale 1–10), age, gender, & education level was ascertained. Patients were randomized 1:1 to either standard teaching or the intervention: a 12 minute video reviewing the steps before, during and after methotrexate self-injection, followed by further in-person nurse education with a focus on reviewing patient concerns and questions arising from the video, and practicing self-injection similar to the non-intervention group. At the end of the teaching session, patients recorded their post-education confidence for self-injection, their satisfaction with the teaching process (VAS 1–10), and answers to 4 specific knowledge based questions on methotrexate self-injection (graded as a score out of 6). The nurse recorded the number of minutes spent providing direct education to the patient

Results: 29 patients participated in this study: 15 had standard (S) teaching and 14 were in the intervention group (VS). Average age (49), gender (VS=6 males, S=5), & education level was similar in both groups. Both groups were very satisfied with the quality of teaching (9.9/10). There was no difference in pre-confidence (S=5.5/10 vs. VS=4.7/10, p=0.44) or post-confidence (S=8.8, VS=8.8, p=0.93) between the groups, although there was a trend to greater improvement in confidence in the video group (p=0.15). Further, there was a trend towards improved patient knowledge in the video group vs. the standard group, with an average of more correct answers in the video group (S=4.7/6, VS=5.5/6, p=0.15). Nurse teaching time was significantly less in the video group compared to the standard group (S=60 minutes, VS=44 minutes, p=0.012).

Conclusion: A web based education video may be a good supplement to standard in person nurse teaching for methotrexate self-injection. It has equally as good benefit on patient confidence and knowledge base while decreasing teaching time by 25%.

Disclosure: S. J. Katz, None; **S. Leung**, None.

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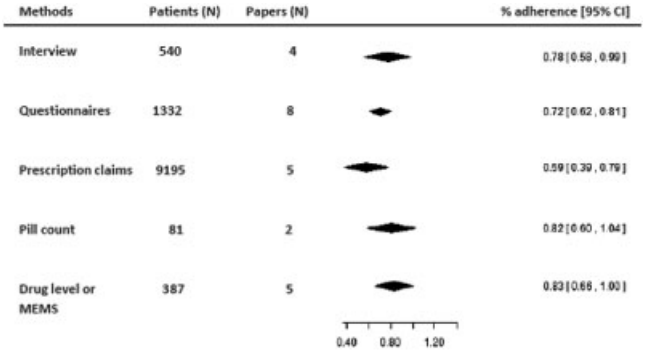
A Meta-Analysis and Systematic Literature Review: Effect Of The Method Used To Measure Adherence In Rheumatoid Arthritis On Its Rate, and Evaluation Of Associated Factors. Anat Scheiman-Elazary[1], Cortney Shourt[1], M. Cameron Hay[2] and Daniel Furst[3]. [1]Rheumatology UCLA, Los Angeles, CA, [2]Anthropology Miami University, Oxford, OH, [3]David Geffen School of Medicine, UCLA, Los Angeles, CA.

Background/Purpose: Adherence reported in the literature for RA varies widely (49.5–98%)[1]. This variability may result in part from different methods used to measure adherence. Our aim was to examine whether adherence is influenced by the method used to measure it through a meta-analysis. We also conducted a systematic literature review (SLR) on factors that are associated with adherence.

Methods: Systematic literature review was conducted using PubMed and Cochrane central database as well as associated reference lists from reviews from 1970 to Nov. 2012. Papers were included if they reported DMARD adherence data or factors associated with adherence in adult RA patients and if adherence was defined. Aspirin/NSAID or non pharmaceutical therapy were excluded. Papers were divided according to the method used to measure adherence. A Random effects model estimated adherence and a Binomial significance test was used to identify significant factors associated with adherence.

Results: Out of an initial 273 articles, 26 papers were included, including 34,700 RA patients. Figure 1 details the results of the meta-analysis for adherence, showing 2–8 articles for each method. Adherence rates were statistically similar when measured by interview, questionnaires, pill count, drug level or medication effect monitoring system (MEMS), although there was an 11% mean numerical range. There was a numerically but not statistically lower adherence when measured by prescription claims (0.59 for prescription claims versus 0.72–0.83 for the other methods).



Associated factors- Three factors were associated with increased adherence. 1. Patients belief about the necessity of medications and the ability to control pain, disease activity or negative mood related to arthritis. 2. Use of Infliximab compared to either Etanercept, Methotrexate or Anakinra. 3. Use of DMARDs prior to anti TNF therapy. Two factors were associated with decreased adherence, use of Sulfasalazine compared to Methotrexate and use

of Anakinra compared to Etanercept. Limitations- there were few articles using any one method and quality was variable, resulting in increased variability and decreased ability to separate the methods.

Conclusion: There was a numerical tendency for decreased rate of adherence when measured by prescription claims versus the other methods. Patient beliefs and specific DMARDs are associated with adherence.

Ref.

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Does Specific Joint Involvement In Rheumatoid Arthritis Patients Predict Patient Reported Outcomes? Implications For Clinical Practice.

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Background/Purpose: Assessment of functional (dis)ability in rheumatoid arthritis (RA) is subject to patient judgment when appraising their ability to do daily activities. The aim of this analysis was to describe the impact of specific joint involvement on patient reported outcomes (PROs) - functional activity, pain and patient global assessment of disease activity (PtGA) - and to identify joints most resistant to treatment over time.

Methods: Biologic Treatment Registry Across Canada (BioTRAC) is an ongoing, prospective, registry of patients initiating treatment for RA, AS, or PsA with infliximab or golimumab as first biologics or after having been treated with a biologic for less than six months. In this analysis, RA patients treated with infliximab between 2002 and 2012 or with golimumab between 2010 and 2012 were included. Based on joint involvement seven groups were created: shoulder(s), elbow(s), metacarpophalangeal (MCP), wrist(s), proximal interphalangeal (PIP), knee(s), and thumb(s). The impact of specific joints on patient outcomes was assessed with the independent-samples t-test. Linear regression was used in order to produce adjusted estimates.

Results: A total of 935 RA patients with 4854 assessments were included. Swelling, tenderness, and swelling and/or tenderness in all joint groups were associated with significantly ($P<0.001$) higher HAQ-DI, PtGA, and pain. Upon adjusting for age, gender and the total number of swollen (SJC28) and tender (TJC28) joints, swelling in all joint groups but the thumb(s) had a significant impact on PtGA, pain and HAQ. Similarly, tenderness in all joints but PIP had a significant impact on these parameters. Overall, swelling and/or tenderness at specific joints, shoulders, wrists and knees, had the greatest impact on HAQ-DI, PtGA, and pain ($P<0.001$). Swollen and/or tender PIP(s) did not have a significant effect on any PRO. At baseline, the MCP joint(s) and the wrist(s) were the most commonly swollen (86.4% and 67.9% of patients, respectively) or tender (82.9% and 73.1%, respectively) joints. Upon 12 months of treatment, the MCP joints were the joints most resistant to treatment, still remaining affected.

Table 1. Impact of Specific Joint Involvement on PROs

	Joint Group	HAQ-DI	PtGA	Pain
Swelling	Shoulder(s)	0.055*	0.049*	0.061*
	Elbow(s)	0.090*	0.059*	0.053*
	MCP	0.085*	0.103*	0.100*
	Wrist(s)	0.106*	0.113*	0.108*
	PIP	0.048*	0.032	0.044*
	Knee(s)	0.085*	0.098*	0.102*
	Thumb(s)	0.032	0.015	0.014
Tenderness	Shoulder(s)	0.114*	0.075*	0.090*
	Elbow(s)	0.075*	0.060*	0.065*
	MCP	0.042*	0.042*	0.049*
	Wrist(s)	0.100*	0.112*	0.109*
	PIP	0.014	0.002	0.007
	Knee(s)	0.102*	0.103*	0.106*
	Thumb(s)	−0.045*	−0.029	−0.034*
Swelling and/or Tenderness	Shoulder(s)	0.130*	0.082*	0.103*
	Elbow(s)	0.096*	0.069*	0.072*
	MCP	0.015	0.041*	0.043*
	Wrist(s)	0.105*	0.088*	0.086*
	PIP	0.008	−0.016	−0.015
	Knee(s)	0.095*	0.097*	0.101*
	Thumb(s)	−0.031	−0.034*	−0.040*

*$P<0.05$. Standardized coefficients upon adjusting for age, gender, and number of affected joints

Conclusion: Significant variability in PROs exists based on the presence of swelling and/or tenderness in specific joint groups. Swelling/tenderness of shoulders, wrists and knees were the main drivers of HAQ-DI, PtGA and pain. The results have important implications for the achievement of disease remission and would suggest that the joint type in addition to the number of affected joints has unique impact on PROs.

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Can Routine Assessment Of Patient Index Data (RAPID)3 Be Used As a Patient Reported Assessment Tool For Patients With Ankylosing Spondylitis?

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Background/Purpose: The assessment of disease activity in rheumatology is essential in both clinical trials and practice. The patient reported questionnaires have shown to reflect disease activity appropriately and is especially feasible in busy clinical settings. On the other hand, distribution of multiple questionnaires to patients with different diseases in a reception area might be difficult. A single questionnaire regarding to disease activity for all rheumatic diseases may present advantages to introduce quantitative measurement into routine care. Recently, a questionnaire that has been widely used and validated for rheumatoid arthritis, routine assessment of patient index data 3 (RAPID3), consists of patient function, pain, and patient global assessment, and has been suggested as suitable index for all rheumatic diseases. The aim of this study was to evaluate correlation of RAPID3 with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), AS Disease Activity Score (ASDAS), Bath AS Functional Index (BASFI), patient global assessment (PGA), and physician's global assessment (PhGA) in AS patients.

Methods: This single-centre, cross-sectional study was performed in a rheumatology department at a tertiary-care hospital. We included 341 consecutive AS patients who met the modified New York classification criteria. All patients completed BASDAI, BASFI, and MDHAQ at each visit, and their physicians completed physician global assessment. ASDAS scores were calculated using defined formulas. Spearman's rho correlation test was used to determine the linear association between RAPID3 and other disease activity measures.

Results: The median age of AS patients was 34.0 (21.0–69.0) years and the median disease duration 10.0 (2.0–35.0) years; 273 patients (80.1%) were male. Median scores for RAPID3, BASDAI, BASFI, ASDAS-CRP, ASDAS-ESR, PGA and PhGA were 13.0 (0.0–27.3), 4.7 (0.0–9.7), 3.0 (0.0–9.4), 3.0 (0.4–5.8), 2.5 (0.5–6.3), 5.0 (0.0–10.0) and

3.5 (0.0–9.5), respectively. RAPID3 was strongly correlated with PGA, BASDAI, and ASDAS-ESR (r=0.843, r=0.842, r=0.815; p<0.001, respectively) (Table 1).

Table 1. Correlation analysis between all disease activity measures.

	PhGA	PGA	ASDAS-ESR	ASDAS-CRP	BASFI	BASDAI
RAPID3	0.637	0.843	0.815	0.790	0.793	0.842
BASDAI	0.581	0.796	0.828	0.829	0.764	
BASFI	0.545	0.737	0.717	0.673		
ASDAS-CRP	0.672	0.824	0.888			
ASDAS-ESR	0.718	0.821				
PGA	0.606					

Conclusion: RAPID3 was found to have good levels of positive correlation with BASDAI, BASFI, ASDAS-CRP, ASDAS-ESR, PGA and PhGA and seems to be as informative as those established disease activity indices. One might conclude that this index can be replaced for them in the follow-up patients with AS and it may offer an additional advantage of being easier to implement in a routine care setting.

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Physician Variability In Rheumatoid Patients Not Receiving Biologics Or Non-Biologic Dmards: Implications For Quality Reporting. Dimitrios A. Pappas[1], Lang Chen[2], Leslie R. Harrold[3], George W. Reed[4], Joel M. Kremer[5], Jeffrey D. Greenberg[6] and Jeffrey R. Curtis[7]. [1]Columbia University, College of Physicians and Surgeons, New York, NY, [2]University of Alabama at Birmingham, Birmingham, AL, [3]University of Massachusetts Medical School, Worcester, MA, [4]CORRONA, Inc., Worcester, MA, [5]Center for Rheumatology, Albany Medical College, Albany, NY, [6]NYU Hospital for Joint Diseases, New York, NY, [7]University of Alabama at Birmingham, Division of Clinical Immunology and Rheumatology, Birmingham, AL.

Background/Purpose: Current quality of care guidelines recommend that all patients with Rheumatoid Arthritis (RA) be treated with biologic and/or non-biologic (nb) DMARDs. However, some RA patients are not treated with these agents for a variety of reasons, which may impact perceptions of the quality of care their physicians are providing.

To estimate physician-level variability on the proportion of RA patients who receive no biologic or nbDMARDs over a sustained period of time in a large U.S. Registry

Methods: Data from the Consortium of Rheumatology Researchers of North America (CORRONA) was used to identify rheumatologist-diagnosed RA patients. Patients were characterized as being on RA treatment (biologics and/or nbDMARDs, irrespective of glucocorticoids/NSAID/narcotics) based upon their most 3 consecutive visits in the registry. They were categorized as consistently on no treatment (0 of 3 visits), consistently on treatment (3 of 3 visits), and inconsistently on treatment (1–2 of 3 visits). Alternating logistic regression was used to evaluate physician-level clustering, controlling for patient-level factors including patient age, sex, RA disease duration, disease activity measured by CDAI, disability (by mHAQ), and comorbidities.

Results: A total of 361 CORRONA physicians and 22,889 of their RA patients contributed to the analysis (median [IQR] number of RA patients per physician 19 [4, 78]). Using data from the 3 most recent CORRONA visits, 3.5 % of patients were consistently on no treatment, 84.7% consistently on treatment, and 11.8% inconsistently on treatment. The proportion of physicians' patients on no RA treatment is shown (Figure) and ranged from 0 – 20%. For patients consistently on no RA treatment (n = 805), 31.4% were in remission, 37.1% were in low disease activity, and 31.4% were in moderate or high disease activity at the most recent CORRONA visit. After controlling for patient factors, physician clustering was independently associated with RA patients being on no RA treatment (adjusted OR = 1.81, 95% CI 1.17 – 2.80). Ongoing work is evaluating other potential reasons why patients may be untreated.

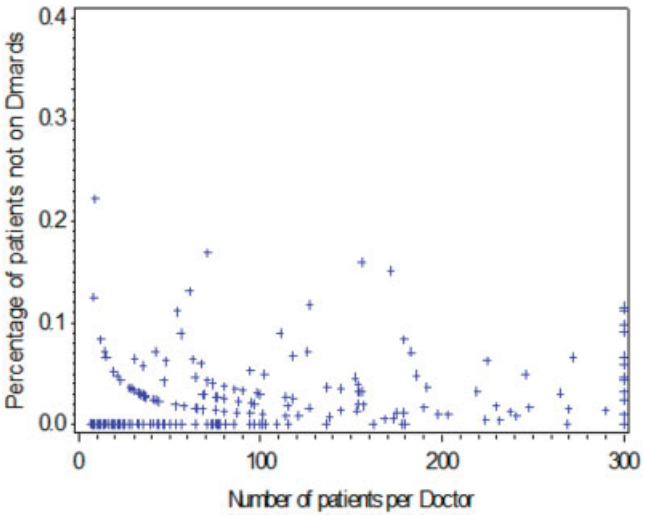

Figure. Proportion of Rheumatologists' RA patients consistently on no treatment

Conclusion: A modest proportion of RA patients are treated with no biologics or DMARDs over a sustained period of time. Even after controlling for RA-related and other patient characteristics, meaningful variability in the proportion of patients on no RA treatment was observed between physicians, suggesting the possibility of inappropriate variation in quality of care. Further efforts to explain and/or ameliorate quality gaps in RA appear warranted and have implications on reporting systems that judge rheumatologists' quality of care. Except in the circumstance where patients are in clinical remission, codifying other evidence-based reasons why offering no RA treatment is appropriate is likely to be useful.

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Team Managed Care From a Patient's Perspective: A Study Of Biological Patients At a Canadian Centre. Dawn Heap[1], Margaret Saldanha[1], Melissa Deamude[1], Cynthia Mech[1], Helena Ross[1], Kathy Kislinsky[1], Lauri Vanstone[2], Arthur N. Lau[3] and William G. Bensen[4]. [1]Rheumatology Health Team, St. Joseph's Hospital Hamilton, Hamilton, ON, [2]Rheumatology Health Team, Hamilton, ON, [3]McMaster University, Hamilton, ON, [4]St. Joseph's Hospital and McMaster University, Hamilton, ON.

Background/Purpose: In Canada, there is a widening care gap in Inflammatory Arthritis due to the increased aging population, higher disease prevalence, dwindling numbers of practicing rheumatologists and decreased access to care. As a result, there is delay in diagnosis, delay in initiating treatment, and delay in starting biological therapy. In 2008, our practice developed a team based program where trained Registered Nurses were assigned as the primary care nurse to patients receiving biological therapy in order expedite and more efficiently manage patient care. Currently more than 1300 biological patients are followed in this clinic.

In this unique to Canada practice, patients are first seen and assessed by a registered nurse who do a complete history, review medications, assess joints, and provide health teaching. The nurse then discusses the patient and their needs with the Rheumatologist, and together they devise a plan which the nurse then implements and follows through.

Methods: 175 consecutive patients with a confirmed diagnosis of inflammatory arthritis (Rheumatoid Arthritis, Ankylosing Spondylitis or Psoriatic Arthritis) receiving biological therapy between May and June of 2013 were sampled and given a confidential survey with 15 questions to determine their level of satisfaction with a multidisciplinary, team approach to care. They were asked questions regarding their general demographics, current treatment, and their confidence in the nurse that primarily follows them, whether or not the team addresses their questions or concerns, and treatment goals. 22 questionnaires had more than 2 questions left blank and therefore withdrawn from analysis.

Results: More than 150 patients surveyed were included in this analysis studying patient satisfaction using a team approach model of patient care. The majority of patients surveyed were middle aged (40–75) and predominantly female. 85 percent of patients strongly agreed that they felt comfortable discussing their health and issues centring on their arthritis treatment with the nurse and confirmed that these goals were discussed at each visit. 97 percent of patients were confident in the nurse's assessment skills and ability to manage their arthritis care and 99 percent of patients valued this team based model of care in comparison to seeing the physician alone.

Conclusion: Our results from this study demonstrate a high degree of confidence in team- based rheumatology care. Currently this practice manages the biological volume of about 10 clinical rheumatologists who practice independently. Nurses are able to establish a rapport with patients in a unique and different way than a physician, and are not only able to address the patient's physical needs but their psychosocial issues as well. Patients have the confidence that these highly trained specialty nurses are providing them with optimal care, allowing them to work toward achieving targeted treatment goals and better arthritis disease control. This study further affirms that team managed care is the only way we will be able to meet treat to target guidelines in our exponentially growing disease prevalence.

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Major Cost Savings Associated With Reduced Biologic Dosing Frequency In Inflammatory Arthritis. Claire-Louise Murphy[1], Miriam O'Sullivan[2], Sohail Awan[2], Shawn Chavrimootoo[2], Clara Bannon[2], Linzi Martin[2], Trevor Duffy[2], Eithne Murphy[2] and Maurice Barry[2]. [1]Connolly hospital, Dublin 15, Dublin, Ireland, [2]Connolly hospital, Dublin, Ireland.

Background/Purpose: Biologic agents are highly effective in Inflammatory Arthritis (IA) but are extremely expensive. A sustained reduction in biologic dosing frequency would lead to major cost savings. The purpose of this study was to explore whether patients with Inflammatory Arthritis would remain in remission following a reduction in biologic dosing frequency and therefore lead to cost savings.

Methods: This prospective non-blinded non-randomised study commenced in 2010. Patients with Inflammatory Arthritis (Rheumatoid Arthritis, Psoriatic Arthritis or Ankylosing Spondylitis) being treated with a biologic agent were screened for disease activity. A cohort of those in remission according to standardized disease activity indices (DAS28<2.6, BASDAI<4) was offered a reduction in the dosing frequency of two commonly used biologic therapies (etanercept 50mg once per fortnight instead of weekly, adalimumab 40mg once per month instead of fortnightly). Patients were assessed for disease activity at 3, 6 and 12 months following reduction in dosing frequency. Cost saving was calculated as the difference between the cost of the actual amount of biologic agent used over one year compared with the cost if the dosing interval had not changed.

Results: Seventy nine patients with inflammatory arthritis in remission were recruited. Fifty seven per cent had rheumatoid arthritis (n=45), 13% psoriatic arthritis (n=10) and 30% ankylosing spondylitis (n=24). Fifty seven per cent (n=45) were taking etanercept and 43% (n=34) adalimumab. The percentage of patients in remission at 12 months was 61% (n=48). Using paired sample t-tests in SPSSv20, no significant difference in measures of disease activity or functional status (DAS28, HAQ or BASDAI scores) was identified from baseline to 12 months in those who remained in remission. This resulted in an actual saving to the state of approximately 300,000 euro over the year.

Conclusion: This small study suggests reduction in biologic dosing frequency is feasible in inflammatory arthritis. The study resulted in considerable cost savings at 1 year. The potential for major cost savings in biologic usage should be pursued further.

Disclosure: C. L. Murphy, None; **M. O'Sullivan**, None; **S. Awan**, None; **S. Chavrimootoo**, None; **C. Bannon**, None; **L. Martin**, None; **T. Duffy**, None; **E. Murphy**, None; **M. Barry**, None.

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Uptake Of The American College Of Rheumatology's Rheumatology Clinical Registry: Quality Measure Summary Data. Jinoos Yazdany[1], Salahuddin Kazi[2], Rachel Myslinski[3] and Melissa Francisco[3]. [1]University of California, San Francisco, San Francisco, CA, [2]UT Southwestern Medical Center, Dallas, TX, [3]American College of Rheumatology, Atlanta, GA.

Background/Purpose: The RCR provides ACR members with an infrastructure for quality reporting related to rheumatoid arthritis, gout, osteoarthritis, osteoporosis, and drug safety. Currently in its fourth year of operation, the RCR contains data on over 32,000 patients.

Here we report the uptake of the RCR by U.S. rheumatologists and performance on quality measures regarding functional status, disease modifying drug (DMARD) use, tuberculosis screening, prognosis, and disease activity assessment for RA patients in 2011 and 2012.

Methods: Data derive from retrospective medical records abstractions performed by providers and/or designated practice staff for a sample of patients seen by rheumatologists. Reporters submit data on quality measures via a secure, web-based registry system. Patients included in the denominator of all quality measures are >18 years of age with a diagnosis of RA who are receiving treatment by the reporting rheumatology provider. Additional details of each measure are listed in Table 1. We report the mean performance on each quality measure, defined as percentage of eligible patients receiving recommended care.

Results: Table 1 summarizes performance on RA measures reported through the RCR. From January 1, 2012 to December 31, 2012, 301 rheumatology providers in 138 practices submitted data on 9154 encounters with RA patients. Comparative data are provided for the previous reporting period. These data summarize 8096 encounters with RA patients submitted by 257 rheumatology providers in 143 practices from January 1, 2011–December 31, 2011. Reporting providers practice in sites ranging from solo offices to large academic medical centers.

Table 1. Performance on RA Measures Assessed through the RCR

	CY2011		CY2012	
	Patients (N)	QM Performance Rate	Patients (N)	QM Performance Rate
Disease activity assessed at least once within 12 months, using a standardized descriptive or numeric scale or composite index, and classified as low, moderate or high	8075	43.3%	6485	54.4%
Functional status assessment performed at least once within 12 months, and documented	8077	70.5%	6485	86.6%
using a standardized descriptive or numeric scale, standardized questionnaire, or notation of assessment of the impact of RA on patient activities of daily living				
Patient prescribed, dispensed, or administered at least one ambulatory prescription for a DMARD within 12 months	7808	97.9%	6485	86.6%
Documentation of TB screening performed and results interpreted within 6 months prior to receiving first course DMARD	1650	73.6%	1048	92.9%
Assessment and classification of disease prognosis at least once within 12 months	7771	49.5%	6441	73.4%

Conclusion: Performance rates increased on four out of five measures from CY2011 to CY2012. Based on preliminary results, the ACR plans to complete in-depth analyses of both measure and population performance.

Disclosure: J. Yazdany, None; **S. Kazi**, None; **R. Myslinski**, None; **M. Francisco**, None.

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Discordance Of Patient-Physician Assessments Of General Health In a US Hispanic Population With Rheumatoid Arthritis. Leyda Díaz-Correa[1], Mariely Nieves-Plaza[2], Yesenia C. Santiago-Casas[1], Tania González-Rivera[3], Grissel Ríos[1] and Luis M. Vilá[1]. [1]University of Puerto Rico Medical Sciences Campus, San Juan, PR, [2]University of Pittsburgh, Pittsburgh, PA, [3]University of Michigan School of Medicine, Ann Arbor, MI.

Background/Purpose: Instruments to measure rheumatoid arthritis (RA) activity such as the 28-Joint Disease Activity Score (DAS28) are used to assess response to treatment. One component of the DAS28 is the patient

global assessment of general health. This is a subjective measurement that has been shown to be influenced by multiple factors such as depression. Moreover, some studies have reported discordance between patient and physician ratings of general health; however, the factors associated with these discrepancies have not been well established. The aims of this study were to determine the level of discordance of patient-physician assessments of general health in a group of US Hispanics with RA, and to evaluate the factors associated with such discordance.

Methods: A cross-sectional study was conducted in 213 US Hispanics with RA (per 1987 ACR criteria) participating in an observational study. Demographic parameters, clinical manifestations, disease activity (per DAS28), comorbid conditions, functional status (per Health Assessment Questionnaire [HAQ]), pharmacologic profile, and patient and physician global assessments (measured on a visual analogue scale [VAS]) were determined. Positive discordance of general health was defined as a patient rating minus physician rating >25 mm on a 100-mm VAS. Differences between study groups were evaluated using multivariable logistic regression analysis. All variables with a $p \leq 0.10$ in the bivariable analysis plus age, gender and disease duration were entered into the regression model.

Results: The mean (standard deviation [SD]) age of RA patients was 56.6 (13.6) years; 88.0% were females. The mean (SD) disease duration was 11.2 (10.0) years. Positive patient-physician discordance was found in 78 (36.6%) patients. Only 2 patients exhibited negative discordance. In the multivariable analysis, patients with positive discordance were more likely to have a higher global assessment of pain (OR=1.05, 95% CI 1.03–1.07, $p<0.001$) and HAQ scores (OR=3.19, 95% CI 1.70–6.00, $p<0.001$), and were more likely to receive therapy with biologic agents (OR=3.06, 95% CI 1.40–6.71, $p=0.005$) than those without discordance. Conversely, patients with positive discordance had lower physician's assessment of function (OR=0.96, 95% CI 0.93–0.98, $p=0.002$). No association was found for comorbidities including depression and fibromyalgia syndrome.

Conclusion: In this group of patients with RA, a large number differed from their physicians in the assessment of general health. Positive discordance was associated with patients' self-report of pain and disability, and the use of biologics. The awareness of these factors may help to better assess disease activity and treatment response in this population.

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Accuracy Of International Classification Of Diseases (Ninth Revision) Coding For Rheumatoid Arthritis In The Primary Care Setting. Sheena Ogando, Karolina M. Weiss and Harry D. Fischer. Albert Einstein College of Medicine at Beth Israel Medical Center, New York, NY.

Background/Purpose: Current quality measures are diagnosis driven and focus on management. For rheumatoid arthritis (RA), the Physician Quality Reporting System requires that a disease modifying anti-rheumatic drug (DMARD) therapy be prescribed. Quality measures do not account for incorrect diagnoses. Diagnostic error can stem from a physician or from a patient report of a medical history. Prior studies have shown a discrepancy between patient report and physician diagnosis. One study reported diabetes - a well defined disease - had no variance, while arthritis - a less clearly defined disease - had a 15% variance, with patients over reporting the disease. Our objective is to determine the accuracy of RA diagnosis in our institution's primary care offices and to evaluate if quality measures are met

Methods: Adult patients with the International Classification of Diseases, Ninth Revision (ICD-9) code for Rheumatoid Arthritis (714.0) were searched from April 2011 to April 2013 using our institution's primary care electronic medical record. The medication list was reviewed for the presence of a DMARD. The paper chart of patients seen in our institution's rheumatology clinic was reviewed for a more accurate diagnostic code.

Results: 246 patients were identified by ICD-9 code using the primary care electronic medical record; 172 were used for evaluation. The average age of the patient population was 60.4 with a standard deviation of 12.7. 88.4% (152) were female. The rate of incorrect ICD-9 coding by primary care physicians was 24–38% [CI of 95%]. The top 5 rheumatologist established diagnoses in these patients were osteoarthritis (20), other inflammatory arthritis (10), undifferentiated connective tissue disease (8), osteoporosis/osteopenia (5), and systemic lupus erythematosus (5). In patients with rheumatologist confirmed RA, 12–26% [CI of 95%] did not have a DMARD in the primary care medication list.

Conclusion: The high incidence of primary care physicians erroneously utilizing the 714.0 ICD-9 code in our institution can be attributed to inaccurate reporting of the disease by the patient and its usage to rule out the disease. In 48 cases, a patient reported to their primary care physician that they suffered from rheumatoid arthritis when in fact they had another diagnosis. These patients with inaccurate ICD-9 codes will be inappropriately categorized as receiving poor levels of care by not meeting RA quality measures. In patients with true disease, a lower percentage is noted to not meet the quality measure of DMARD treatment. Interestingly, it was observed that injectible medications were not documented in the primary care medication list. This could be due to the fact that patients often bring physical bottles for medication reconciliation and not the injectables. Taking this into consideration, the percentage of RA patients not meeting quality measures is likely considerably lower. In conclusion, since quality measures do not address the issue of inaccurate diagnosis, its emphasis on management and its potentially associated penalties should be reevaluated. Further studies are needed to determine if patients with inaccurate coding are subjected to unnecessary treatment or testing.

Disclosure: S. Ogando, None; **K. M. Weiss**, None; **H. D. Fischer**, None.

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Overcoming The Barriers To Adequate Hydroxychloroquine Retinal Toxicity Screening. Cristina Arriens[1] and Elizabeth Blair Solow[2]. [1]University of Texas Southwestern Medical Center at Dallas, Dallas, TX, [2]UT Southwestern Medical Center, Dallas, TX.

Background/Purpose: Hydroxychloroquine (HCQ) is considered a minimal risk drug in the treatment arsenal for rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and other rheumatic diseases; however it has a well-documented risk of retinal toxicity in approximately 1% of patients following 5 years of use. Adequate ophthalmologic examination monitoring can limit the impact of toxicity on vision by early detection. The American College of Rheumatology's position statement regarding screening for HCQ retinopathy recommends baseline ophthalmologic examination within the first year of treatment and annual examinations after 5 years of therapy as the minimum for healthy patients. It was recognized that multiple patients in a busy county hospital system receiving treatment with HCQ lacked retinopathy screening exams. A quality improvement project to ascertain the factors that lead to failure within this system was devised with the goal of improving compliance with the accepted guidelines.

Methods: In this busy county hospital outpatient rheumatology clinic we performed a chart review to evaluate provider, patient, and system factors to determine where the level of breakdown in achieving baseline eye examinations occurred. A referral to ophthalmology clinic was required for the provider to adequately fulfill their role. A scheduled appointment with ophthalmology was required for the system to meet its responsibility. The patients' role was assessed by their appointment attendance. A physician-initiated, patient driven intervention was instituted in which rheumatology physicians provided the ophthalmology clinic phone number and asked the patient to call to schedule their appointment. Compliance with screening guidelines was re-assessed 1 year later.

Results: The average age of the 60 patients was 48 years and included 30 RA, 20 SLE, and 10 other connective tissue diseases. Prior to the intervention, 32 patients (53%) had completed a baseline retinal toxicity exam, 2 (3%) were not referred, 6 (10%) had no-showed an appointment, and 20 (33%) had a referral without an appointment scheduled. Failure occurred at the system level. Following the intervention, of the 53 patients still taking HCQ, now 36 (68%) had completed their screening visit, 0 (0%) were not referred, 1 (0.2%) had no-showed, and 16 (30%) were referred with no appointment. Pre- intervention 25 of the remaining 53 were compliant with screening examination and eleven more patients became compliant post-intervention, a statistically significant improvement determined by McNemar's test ($p=0.0026$).

Conclusion: In this quality improvement project the major barrier to patients receiving baseline eye exams for HCQ toxicity was found to be a system issue. The physician-initiated, patient driven intervention was successful in improving compliance in the 1 year time frame of study. In addition to this intervention, future efforts will be aimed at inter-departmental communication and education between ophthalmology and rheumatology regarding the necessity of timely retinal evaluations.

Disclosure: C. Arriens, None; **E. B. Solow**, None.

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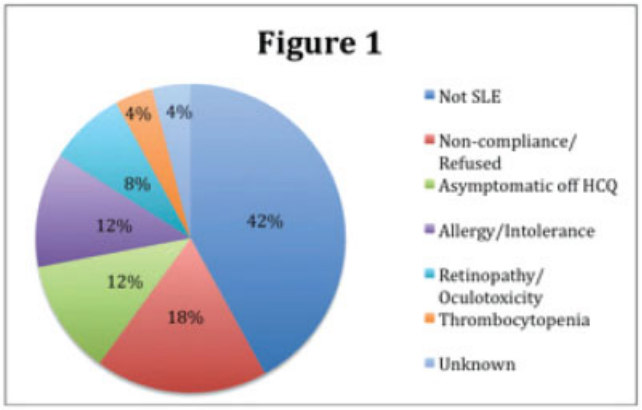
Hydroxychloroquine Use Among Systemic Lupus Erythematosus Patients In An Academic Rheumatology Practice. James G. Miceli[1] and Harry D. Fischer[2]. [1]Beth Israel Medical Center, New York, NY, [2]Albert Einstein College of Medicine at Beth Israel Medical Center, New York, NY.

Background/Purpose: Hydroxychloroquine (HCQ) is a mainstay in the current treatment of systemic lupus erythematosus (SLE). HCQ has been shown to reduce the incidence of SLE flares, reduce the risk of irreversible end-organ damage, and improve survival in SLE patients. Yet, few studies have been devoted to examining its prevalence of use. Prior papers have either examined HCQ use as a secondary endpoint (56–64%) or as a primary endpoint in a community practice (55%). Our study aims to identify the prevalence of HCQ use in an urban academic rheumatology practice and to identify the reasons for nonuse

Methods: A search of medical records with a diagnostic code for systemic lupus erythematosus (710.0) was performed for patients seen within a three-month period (September 1–December 1, 2011) at Beth Israel Medical Center's rheumatology clinic. Charts for 211 patients were reviewed for active use of HCQ; if the patient was not on HCQ, the chart was further reviewed and an explanation for nonuse was documented if present.

Results: A total of 161 out of 211 SLE subjects (76.3%) were found to be actively using hydroxychloroquine. Among nonusers, 21 (42%) did not have a definitive diagnosis of SLE; 9 (18%) were either non-compliant or refused treatment; 6 (12%) had an allergy or intolerance to HCQ; 6 (12%) were not taking HCQ for unclear reasons but were asymptomatic; 4 (8%) reported a history of HCQ-induced oculotoxicity; and 2 (4%) developed thrombocytopenia presumed secondary to HCQ (Figure 1).



Conclusion: The use of HCQ in SLE patients at our institution exceeded rates of use reported elsewhere. Nonetheless, almost ¼ of potential candidates for treatment were not prescribed HCQ. Almost half of the non-prescribed patients lacked a definitive diagnosis of SLE. The majority of the other non-takers had a documented explanation. Our results help to better define reasons for nonuse of HCQ in patients with SLE. It is hoped that recognition of these factors could help to further increase the use of HCQ in SLE patients.

Disclosure: J. G. Miceli, None; **H. D. Fischer**, None.

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Comparison To Organisational Models For EARLY Rheumatoid Arthritis Management: Routine Care Versus EARLY Arthritis Clinic. Giovanni Ciancio[1], Ilaria Farina[1], Federica Pignatti[2] and Marcello Govoni[1]. [1]Rheumatology Unit-Azienda Ospedaliera-Universitaria Sant'Anna, Ferrara, Italy, [2]Rheumatology Unit-Azienda Ospedaliera-Universitaria Sant'Anna, Ferrara, Italy, ferrara, Italy

Background/Purpose: although the Early Arthritis Clinic (EAC) institution is considered the best approach for the management of rheumatoid arthritis (RA) at an early stage, to the best of our knowledge there is no formal demostration that this organisational model is better than a conventional model in terms of public health care and of improved clinical, therapeutic and radiographic outcomes. Our purpose was to evaluate whether significant differences in clinical and therapeutic outcomes exist between two groups of patients with Rheumatoid Arthritis followed in a EAC and in a routin care (RC) model, respectively.

Methods: Two groups of RA patients fulfilling 1987/ACR criteria were retrospectively analised. In the first group, RA diagnosis was made in our centre between 2002 and 2008 and patients were followed with a RC model. In the second one, RA diagnosis was made in our centre between 2009 and 2013 and patients were followed in our EAC. Patients with a follow-up of at least 2 years were included. For each patient of the two groups, lag time from symptom onset to diagnosis and from symptom onset to the beginning of DMARDs therapy were calculated. Disease activity were compared between the two groups using DAS28 and EULAR response criteria at baseline (T0) and after 6 (T6), 12 (T12) and 24 (T24) months. The ratios (%) of patients who started a biological therapy within 24 years after diagnosis were compared between the two groups

Results: A total of 273 RA patients, divided into two groups, were evaluated: 209 (mean age 59 ± 24.04 years,165 F, 44 M) followed in RC and 64 (mean age 59 ± 13.44 years, 50 F,14 M) in EAC. Lag time from symptom onset to diagnosis resulted significally lower ($p<0,0001$) in patients assessed in EAC (5.73 ± 8.09 mesi) compared to that of the other group (20.90 ± 30.3 mesi) and treatment beginning occured before in EAC population (7.17± 8.26 mesi) respect to that followed in RC (21.98±32.39 mesi) with a significant difference ($p<0.0004$). At baseline DAS28 evaluation was similar between groups (4.76±1.24 in RC vs 4.94 ± 1.41 in EAC) and was significally reduced to 2.82 ± 1.24 (RC) and 2.46 ±1.12 (EAC) after 24 months ($p<0.036$). A significant statistical difference emerged from the comparison to the mean VES value (19.9 ±15.9 RC vs 13.6 ± 11.3 EAC, $p<0.003$) and SJ (swollwn joints) value (1 ± 1.8 RC vs 0.43 ± 1.2 EAC, $p<0.02$) at T-24. Within 24 months, biologic therapy was initiated in 29% of patients followed in RC and in 9.3% of patients followed in EAC population ($p<0,0013$).

Conclusion: In comparison with the RC model, the EAC institution has allowed in our experience a significant reduction of the time for diagnosis and for the therapeutic intervention, with an improvement in clinical outcomes, less use of biological drugs and a significant long-term savings on pharmaceutical spending

Disclosure: G. Ciancio, None; **I. Farina**, None; **F. Pignatti**, None; **M. Govoni**, None.

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Analysis Of Non-Steroidal Anti-Inflammatory Drug Burden Among Rheumatoid Arthritis Patients Using The Dougados Algorithm. E Alemao[1], L Xie[2], R Wong[1], G Lltalien[1] and O Baser[3]. [1]Bristol-Myers Squibb, Princeton, NJ, [2]SATinMED Research, Ann Arbor, MI, [3]STATinMED Research and University of Michigan, Ann Arbor, MI

Background/Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) are used to alleviate RA pain symptoms, but they may be associated with adverse events. Previous studies examining clinical and economic outcomes associated with NSAID use in RA have not implemented a systematic algorithm for NSAID use, which would more precisely define the NSAID burden. This study evaluated the correlation between the NSAID intake score developed by Dougados *et al.*[1] and other traditional measures of NSAID burden. In addition, clinical and economic outcomes in patients with high versus low NSAID scores were compared.

Methods: A retrospective analysis was performed on RA incidence populations using National Medicare claims data (01/01/2006–12/31/2010) with a 12-month baseline and 24-month follow-up period. Patients had to have at least two RA diagnoses at least 60 days apart between January 1, 2007 and December 31, 2009. The date of the first RA diagnosis was designated as the index date. High, middle and low cohorts were created based on the distribution of the NSAID intake score.[1] The correlation between NSAID score and traditional measures was determined by univariate analysis. Clinical and economic outcomes during follow-up were compared with a generalized linear model (GLM).

Results: Approximately 19% (n=10,313) of 52,973 incident patients with RA used NSAIDs during the baseline period. Dougados NSAID score correlated with percentage of days with at least one NSAID intake (0.69 [$p<0.05$]) and number of NSAID tablets (0.59 [$p<0.05$]). At baseline, 36.34% of patients had a low NSAID score (≤10% follow-up time on diclofenac 150 mg or equivalent), 58.33% had a medium NSAID score (11–90% time on diclofenac 150 mg or equivalent) and 5.32% had a high NSAID score (>90% time on diclofenac 150 mg or equivalent). Compared with the high NSAID cohort, the low NSAID cohort were older (mean age 75.9 vs 74.4 years, $p<0.05$), had higher Charlson Comorbidity Index scores (3.2 vs 2.8, $p=0.05$), and higher rates of chronic kidney disease (CKD) (11.39 vs 6.38%, $p<0.05$), chronic obstructive pulmonary disease (22.9 vs 18.94%, $p<0.05$), and respiratory disorders (57.54 vs 52.28%, $p<0.05$). Prior to

baseline adjustments, patients in the low NSAID cohort had fewer gastrointestinal perforation cases (0.53 vs 1.28%, $p<0.05$), and lower per patient per year (PPPY) total costs ($26,235 vs $30,078, $p<0.05$) and outpatient pharmacy costs ($4,347 vs $6,547, $p<0.05$) than patients in the high NSAID cohort. After adjusting for baseline differences in demographic and clinical characteristics with the GLM, patients in the high NSAID cohort had a higher risk for CKD (20.23 vs 17.31%, $p<0.05$), higher PPPY inpatient costs ($13,187 vs $10,652, $p<0.05$) and higher PPPY outpatient pharmacy costs ($4,605 vs $3,515, $p<0.05$) during the follow-up period.

Conclusion: The Dougados NSAID algorithm, developed to evaluate NSAID burden in spondyloarthritis, is also applicable to the RA patient population. Medicare patients with RA with high NSAID scores had a higher probability of CKD and higher average in/outpatient costs. Therapies that reduce NSAID burden in elderly patients may protect those with RA from CKD and help reduce cost.

Reference:

1. Dougados M, *et al. Ann Rheum Dis* 2011;**70**:249–51.

Disclosure: E. Alemao, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **L. Xie**, Baistol-Myers Squibb, 5; **R. Wong**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **G. Lltalien**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3, SimplySmiles (www.simplysmiles.org), 6; **O. Baser**, Bristol-Myers Squibb, 5.

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Belief In Self-Adjustability Of Medication Dosing Is Negatively Correlated With Medication Adherence In Patients With Rheumatoid Arthritis. Wenxin Sun[1], Dianne Carrol Tan Bautista[1], Xiaohui Xin[2], Yu Ting Saw[2], Wee Boon Tan[2], Kanchanadevi Balasubramaniam[2], Wan Pin Lee[2], Steve Thein Htay Oo[2], Yin Bun Cheung[1] and Julian Thumboo[2]. [1]Duke-NUS Graduate Medical School, Singapore, Singapore, [2]Singapore General Hospital, Singapore, Singapore.

Background/Purpose: Medication adherence in Rheumatoid Arthritis (RA) is reported to be generally low. This major problem needs to be addressed because it leads to reduced treatment benefits and greater healthcare costs. We hypothesized that specific medication beliefs would influence adherence to disease-modifying anti-rheumatic drugs (DMARDs) in RA patients, and assessed this in a cross-sectional study.

Methods: Based on focus groups and a quantitative survey, we identified 5 belief factors in patients with RA: that DMARDs harm health; that DMARDs benefit health; that DMARD dosing/regimens can be changed by patients; that DMARD side effects can be effectively managed; that DMARD side effects cannot be effectively managed. In this IRB approved study, we administered a Medication Behavior Survey (n=21, developed from focus group data) assessing these 5 belief factors and the 8-item Morisky Medication Adherence Scale (MMAS-8, score range 0–8.0) to measure non-adherence in a consecutive sample of English-speaking RA patients during routine outpatient visits from November 2012 to April 2013 at our tertiary referral center. Multiple linear regression (MLR) was used to examine the relationship between the 5 belief factors and MMAS-8, as well as MMAS-8 intentional and unintentional non-adherence subsets, adjusting for demographic factors (gender, race, age and education).

Results: Among 279 English-speaking RA patients (82% females; 56% Chinese, 15% Malays, 22% Indians; mean age (SD) 53.8 (12.7) years). MLR with MMAS-8 scores showed that a stronger belief that DMARD dosing/regimens can be changed by patients was significantly negatively correlated with MMAS-8 scores (beta=−0.53, 95% CI −0.75 to −0.37, $p<0.001$) in a model that also included the other 4 factors (none of which was significantly associated with MMAS-8 scores). Similarly, MLR with MMAS-8 subsets showed that a stronger belief that DMARD dosing/regimens can be changed by patients was negatively correlated with both intentional and unintentional non-adherence MMAS-8 subsets (beta=−0.25, 95% CI −0.39 to −0.11, $p<0.001$; beta=−0.28, 95% CI −0.42 to −0.14, $p<0.001$, respectively). Additionally, belief that DMARDs side effects cannot be effectively managed was negatively associated with intentional non-adherence MMAS-8 subset (beta = −0.18, 95% CI −0.32 to −0.03, $p=0.019$).

Conclusion: We found that stronger belief that DMARD dosing/regimens can be changed by patients was an important factor associated with non-adherence in an urban Asian population. Other beliefs do not apparently provide additional value in accounting for non-adherence. If confirmed in prospective studies, this observation may provide a simple and rapid way to identify patients who are more likely to be non-adherent with DMARD therapy.

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Evaluation Of Hospitalizations and Costs In Patients With Rheumatoid Arthritis In United States Medicare Population. E Alemao[1], L Wang[2], G Lltalien[1], O Baser[3], H Yuce[4] and M Hochberg[5]. [1]Bristol-Myers Squibb, Princeton, NJ, [2]STATinMED Research, Dallas, TX, [3]STATinMED Research and University of Michigan, Ann Arbor, MI, [4]New York City College of Technology (CUNY), Brooklyn, NJ, [5]University of Maryland, Baltimore, MD

Background/Purpose: RA-related hospitalization and surgery (e.g. total joint arthroplasty [TJA]) are important long-term outcomes in RA. While advances in treatment for RA have resulted in decreased admissions for active disease, the national rates of RA-related procedures, hospitalizations and their costs in elderly patients with RA have not been reported. We evaluated the rates of first and subsequent RA-related surgery, hospitalization and mortality in a US Medicare population, analyzed predictors of RA-related surgery and compared total costs between RA patients with and without surgery.

Methods: Data from patients enrolled in the US Medicare Claims Database from January 1999 to December 2009, who had ≥2 RA diagnoses (ICD 714.0) ≥2 months apart during the identification period were analyzed. The date of the first RA diagnosis was designated as the index date. Those with a baseline period <12 months (i.e. those diagnosed during 1999 and 2000) were considered prevalent cases. Kaplan–Meier analysis was used to estimate the cumulative incidence of orthopedic surgery following RA diagnosis. Cox proportional hazards (CPH) modeling identified factors associated with surgery (TJA, TJA-associated procedures, non-TJA) and overall mortality. Estimated healthcare costs (mean and standard deviation) for all RA patients with surgery were compared with those for RA patients without surgery.

Results: The study population comprised 360,912 patients with RA enrolled in Medicare who met the study inclusion criteria. Cumulative 4- and 10-year TJA incidence rates were 7.5 and 13.2%, respectively; mortality rates were 13.2 and 27.9%. Of all RA patients with surgical experience, 86.5% had a TJA procedure. Patient characteristics are shown (Table). Based on CPH models, predictors of surgery varied by type of procedure; positive factors often included regional demographic and co-morbid osteoarthritis (OA) at baseline, and negative predictors often included follow-up therapy and minority race. For example, for TJA, patients with OA and patients living in the Midwest had a higher hazard (hazard ratio [HR]=2.11, $p<0.01$; HR=1.38, $p<0.01$, respectively). Patients receiving combination (MTX + biologic DMARD) RA therapies during follow-up had a lower hazard (HR=0.41, $p<0.01$). RA patients with surgery had almost double the average inpatient cost at $19,382 vs $10,282 for patients without surgery ($p<0.01$). RA patients with surgery also had significantly higher outpatient, outpatient emergency room, and office costs ($p<0.01$).

	Patients with surgery	Patients without surgery	Standard deviation
Mean age, years	74	76	22.45
White	88%	82%	17.76
Mean Charlson's Comorbidity Index scores	2.27	2.60	17.04
OA	63%	46%	33.85
High RA severity score	35%	27%	17.91

Conclusion: Medicare patients with RA continue to experience high rates of RA-related surgery, hospitalization and overall mortality. However, biologic DMARD therapies appear to have a protective effect on all outcomes. Greater availability of efficacious RA therapies has the potential to reduce RA-related surgery, hospitalization and costs.

Disclosure: E. Alemao, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **L. Wang**, Bristol-Myers Squibb, 5; **G. Lltalien**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3, SimplySmiles (www.simplysmiles.org), 6; **O. Baser**, Bristol-Myers Squibb, 5; **H. Yuce**, None; **M. Hochberg**, Abbott Laboratories, Amgen Inc., BMS, Eli Lilly and Company, EMD Serono Inc., Genentech/Roche, Merck & Co., Inc., Novartis Pharma AG, Pfizer Inc, 5, Bioberica SA, IBSA, 8, NIH, 2.

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Temporal Trends In The Prescribing Of Disease Modifying Anti-Rheumatic Drugs For Rheumatoid Arthritis and The Impact Of Guidelines. Gemma L Wallace[1], C. J. Edwards[2], Nigel K. Arden[3], Daniel Prieto-Alhambra[4] and Andrew Judge[5]. [1]University of Oxford, Oxford, United Kingdom, [2]University Hospital Southampton, Southampton, United Kingdom, [3]Oxford NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, United Kingdom, [4]URFOA-IMIM, Parc de Salut Mar; Idiap Jordi Gol; University of Oxford; University of Southampton, Barcelona, Spain, [5]Oxford University, Oxford, United Kingdom

Background/Purpose: Disease modifying anti-rheumatic drugs (DMARDs) are standard initial treatments for rheumatoid arthritis (RA). Many RA treatment guidelines have been published including from the American College of Rheumatology (ACR), European League Against Rheumatism (EULAR) and British Society for Rheumatology (BSR). However, there is little evidence to demonstrate that guidelines alter prescribing practice. BSR guidelines for treatment of RA were published in 2006 and recommended initiation of DMARDs in the first 90 days after RA diagnosis. We aimed to test whether publication of these guidelines changed clinical practice.

Methods: We used the Clinical Practice Research Datalink, consisting of primary care records & prescriptions, secondary care referral details, procedures and diagnoses, for >10 million patients from a representative sample of primary care practices in the UK. DMARDs are usually initiated in the UK by a rheumatologist, with ongoing DMARD prescribing usually performed by primary care physicians with supervision by a rheumatologist. Incident diagnoses of RA in persons aged ≥18 years between 1995–2010 were identified. For each calendar year and quarter, the proportion of patients receiving any DMARD prescription within 90 days and 1 year of diagnosis was ascertained. An interrupted time-series regression model was used to assess whether trends in the proportion of patients receiving DMARDs within 90 days and 1 year changed following publication of the 2006 BSR Guidelines.

Results: Between 1995 and 2010, 25,963 incident cases of RA were identified, 69% female, average age of diagnosis 59 years. There was a progressive increase in the proportion of patients prescribed a DMARD by a primary care physician within 90 days from 16.6% in 1995 to 23.5% in 2005. The proportion receiving DMARD/s within 90 days increased more rapidly following publication of the BSR guidelines (Figure 1) to 27.9% by end 2006 and 36.0% in 2010 (p=0.01). A similar pattern was observed for the proportion of patients receiving DMARD/s within 365 days of diagnosis (p=0.002).

FIGURE: Time series of proportions of patients receiving DMARD within 90 or 365 days of rheumatoid arthritis diagnosis in UK by quarter from January 1995 to December 2010

Conclusion: The proportion of patients prescribed a DMARD in primary care in this study is lower than generally accepted estimates. This may reflect reality for patients with RA outside of specialist centres although secondary care prescribing is not captured within this database. Nevertheless, prescriptions that are captured should be representative of overall trends in prescriptions within the UK and suggests that guidelines published by a national body can improve the proportion of patients receiving DMARD treatment in the first year after diagnosis of RA.

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American College Of Rheumatology's Rheumatology Informatics System For Effectiveness Registry Pilot. Peter J. Embi[1], William Stephens[2] and Rachel Myslinski[3]. [1]The Ohio State University, Columbus, OH, [2]Ohio State University, Columbus, OH, [3]American College of Rheumatology, Atlanta, GA

Background/Purpose: There is a significant need in the rheumatology community to access and integrate data across diverse patient populations in order to aid quality improvement efforts, help rheumatologists meet quality reporting requirements, as well engage in clinical research. We report on the pilot results of the American College of Rheumatology's registry expansion initiative that links disparate clinical data resources across multiple clinical sites and systems in support of rheumatology practice and research. This effort is aimed at providing a reliable, cost-effective means of connecting data from multiple EHR systems, using these data for quality improvement, quality reporting, and research querying.

Methods: The design and execution of effective quality improvement projects and clinical studies requires access to high quality, longitudinal data. In most instances, such data are collected, formalized, stored and retrieved using project- or organization-specific disease registries or data warehouses. It is increasingly desirable to access data across multiple clinical sites for quality improvement and clinical research purposes, but disparate EHR systems remain difficult to connect for data interchange. Furthermore, in these types of settings, organizational and policy barriers often preclude the use of centralized repositories. To address this need, the ACR is piloting this system – called the Rheumatology Informatics System for Effectiveness (RISE) – to enhance registry efforts to benefit rheumatic disease research and quality reporting efforts. RISE is a federated system of interconnected clinical data repositories. The RISE architecture allows data to remain at the sites thereby allowing sites full control of their data. Data is accessed by a Federated Query Processor service that maintains no source practice data internally, but instead acts as a secure router and aggregator for information as it passes through the grid. The RISE system enables access to clinical data across multiple sites while maintaining high levels of data security.

Results: The model employed by RISE uses an approach to enable the federated query of geographically distributed data sources. This platform is being implemented at 6 sites, with several more planned. The initial sites include a variety of academic and community centers, which demonstrate feasibility for implementation in a variety of practice settings. The following table shows aggregate data from two of the initial sites:

Query	Aggregate Result
Number of patients with an RA diagnosis	6,131
Number of patients with a RAPID score ≥ 3	260*
Number of patients taking methotrexate	6,724
All patients in the registry	44,390

Conclusion: The design, deployment and initial use of the ACR RISE network addresses the need for data access across disparate sites using otherwise non-interoperable information systems and creates the opportunity for a robust source of rheumatology clinical data that can be used for multiple purposes. We believe that such an approach to distributed data sharing in rheumatology will help advance science and improve clinical practice.

Disclosure: P. J. Embi, None; **W. Stephens**, None; **R. Myslinski**, None.

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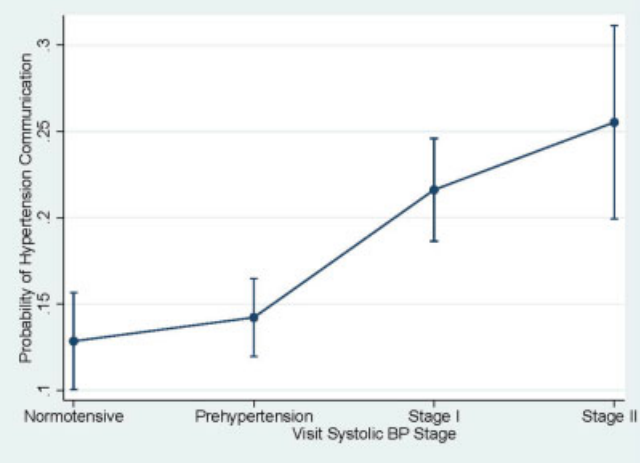
Frequency and Predictors Of Hypertension Communication In Rheumatoid Arthritis Visits. Christie M. Bartels, Heather Johnson, Elizabeth A. Jacobs, Patrick McBride and Maureen Smith. University of Wisconsin School of Medicine and Public Health, Madison, WI

Background/Purpose: Patients with rheumatoid arthritis (RA) have a 60% higher cardiovascular disease (CVD) event risk, yet previously we demonstrated they were ~30% less likely to have hypertension diagnosed. We sought to examine the frequency and predictors of documented hypertension/blood pressure (BP) communication during rheumatology visits for RA patients with undiagnosed and/or uncontrolled hypertension.

Methods: Electronic health record searches from 2004–11 identified RA patients (defined by ICD-9 algorithm) who had uncontrolled or undiagnosed

hypertension and who had encounters at 1 of 3 rheumatology clinics. Using Joint National Committee-7 criteria, undiagnosed was defined as ≥3 BPs ≥140/90 mmHg or 2 readings ≥160/100 mmHg without prior diagnosis or antihypertensive medication; BP control was ≥3 consecutive BP's <140/90 mmHg. We abstracted rheumatology clinic notes from first eligible date for hypertension diagnosis/control through date of hypertension control or end of data. We examined the frequency and predictors of any hypertension communication beyond vital sign documentation. We used multivariate logistic regression to examine the impact of systolic BP stage at a rheumatology visit on the predicted probability (PP) of hypertension communication. Covariates included patient sociodemographics, comorbidity, utilization, visit date, and rheumatologist.

Results: Among 1267 RA patients, 501 were studied who had uncontrolled hypertension, and 232 of the 501 patients met criteria and lacked a hypertension diagnosis. Mean age was 62 years, 76% were female, 11% were current and 35% former smokers, and prior CVD was noted in >20%. In 2677 abstracted visits, BP's varied with 20% Normotensive (<120 mmHg) at a given visit, 45% Prehypertensive (≥120 - <140 mmHg), 32% with Stage I (≥140 - <160 mmHg) and 11% with Stage II (≥160 mmHg) elevations. Overall 23% of RA visits contained any hypertension communication. After adjustment, even in visits with systolic BPs ≥160 mmHg, only 25% contained hypertension communication (PP 25%, CI 20,31). Compared to Stage I systolic elevations, Stage II elevations did not significantly increase the probability of communication (Figure 1), although both were higher than normotension and prehypertension. When examining other predictors, active tobacco users were least likely to have hypertension communication (PP 12%, CI 8,16).



Conclusion: Despite higher CVD risk, many RA patients had undiagnosed or uncontrolled hypertension. Even with systolic BPs≥160 mmHg only 1 in 4 rheumatology encounters documented communication about hypertension, demonstrating lost opportunities for identifying and managing modifiable CVD risks. Future research should investigate patient and provider role perceptions and other barriers and facilitators of hypertension management to systematically improve CVD prevention in RA patients.

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Three Approaches To Evaluating Step Therapy Policies For Immune Disorder Specialty Pharmaceuticals. Michael P. Ingham[1], Andrew Paris[2], Lorie A. Ellis[1] and Chris Kozma[3]. [1]Janssen Scientific Affairs, LLC, Horsham, PA, [2]Vigilytics, Victor, NY, [3]CK Consulting, Saint Helena Island, SC

Background/Purpose: Rheumatology practices are increasingly exposed to patient health care benefit plans that include "step therapy" (ST) policies which affect medication choice. Managed care companies implement ST policies for specialty pharmaceuticals to reduce utilization of infused biologics (IV) in new patients, based on an assumption that there will be cost savings. To assess whether managed care policies that limit access to infusion biologics in order to shift new patients to injection biologics (SQ) have had the desired effect.

Methods: The share of utilization of biologic products for plans identified with ST policies, were evaluated versus a comparison cohort using three separate methodologies. ST plans were first identified using data from Symphony Health Solutions Corp.'s ProMetis database. This database provides a unique opportunity for this type of analysis, as it spans multiple identifiable plans which can be cross-referenced to known ST policies. Data included payer, prescription and procedure claims with unique anonymised patient identifiers. Analyses #1 & #2 included data from plans with ST policies throughout 2010. Analysis #1 compared the percentage of patients with biologic claims for plans with ST policies to all other plans in the database during the same time period (ALL OTHER). Analysis #2 compared the percentage of patients with biologic claims for plans with ST policies to a set of plans matched roughly to the ST plans based on region and relative size (MATCHED). Analysis #3 included data from 1/1/2006 through 4/30/2011 for plans with a known ST implementation date (index date) and with available biologic claims within 365 days before and after this index date. Analysis #3 evaluated the period after ST policy implementation to the period before implementation (PRE/POST). Data for each analysis were descriptive of the number of patients with access and using any biologic in the ST and comparison cohorts. The net change in percentage of patients with infusion claims is reported.

Results: Sixteen different plans were identified with a ST policy. The only analysis to demonstrate a shift in patient utilization away from IV biologics was the ALL OTHER comparison (−5.1%). When comparison plans were MATCHED to ST plans, or when evaluating existing plans using PRE/POST methods, patient access and use of infusion biologics increased (+7.0% and +2.8% respectively).

Conclusion: These data suggest that policies designed to reduce overall patient proportions using infusion biologics may not have the intended effect, or may at most affect 5.1% of biologic users in any given year. The limited potential benefit needs to be weighed against the cost of implementing and monitoring this type of policy, as well as the provider resource implications.

Disclosure: M. P. Ingham, Janssen Scientific Affairs, LLC, 3; **A. Paris**, Janssen Scientific Affairs, LLC, 5; **L. A. Ellis**, Janssen Scientific Affairs, LLC, 3; **C. Kozma**, Janssen Scientific Affairs, LLC, 5.

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Focus on cardiovascular Risk Factor Recording In a Rheumatology Outpatient Clinic. Eirik Ikdahl[1], Silvia Rollefstad[1], Inge C. Olsen[1], Tore K. Kvien[2], Inger Johanne Widding Hansen[3], Dag Magnar Soldal[4], Glenn Haugeberg[4] and Anne Grete Semb[1] [1]Diakonhjemmet Hospital, Oslo, Norway, [2]University of Oslo, Oslo, Norway, [3]Hospital of Southern Norway Trust, Kristiansand, Norway, Kristiansand, Norway, [4]Hospital of Southern Norway Trust, Kristiansand, Norway

Background/Purpose: There is an unmet need of implementing the knowledge of cardiovascular (CV) risk in patients with rheumatoid arthritis (RA) into clinical practice. Our aim was to evaluate CV risk factor (CVRF) recording in a rheumatology outpatient clinic (ROC), where the standard was annual CVRF recording for all patients. Moreover, we evaluated how various clinical models influenced the extent of CVRF recording, comparing a regular ROC (RegROC) to an arthritis clinic (AC), a structured, team-based model.

Methods: Of the 1142 RA patients visiting ROC at the Hospital of Southern Norway during 2012, 612 attended RegROC and 530 attended the AC. Allocation to either RegROC or the AC was based on clinical judgement by the rheumatologist and did not include any inclusion criteria. For all patients, CVRFs were to be recorded in the medical journal as well as in a computerized journal program, GoTreatIT-rheuma (GTI-r). We searched both journal systems to ascertain how many patients had CVRFs recorded.

Results: Overall, 38.2% of patients had CVRFs recorded and only 26.9% had recorded all the CVRFs included in the CV risk calculator, SCORE. When comparing the AC to the RegROC, odds ratios (OR) for CVRFs being recorded in the medical journal was for: lipids: 5.0–6.0, blood pressure (BP): 12.4, glucose: 9.1, and HbA1c: 6.1 (p for all < 0.001) (Table). In the GTI-r

journal the discrepancies between the AC and RegROC were even more pronounced. OR for CVRFs being recorded was for lipids: 15.9, BP: 27.5 and for having recorded all the CVRFs included in SCORE: 21.0 (p for all < 0.001).

Table. Cardiovascular risk factors recorded in patients attending rheumatology consultations in a rheumatology outpatient clinic

Cardiovascular Risk factors	ROC (n=1142)	AC (n=530)	RegROC (n=612)	OR* (95% CI)	AC vs. RegROC P-value*
Medical journal: *n (%)*					
Brachial BP	576 (50.4)	421 (79.4)	155 (25.3)	12.36 (9.27, 16.48)	< 0.001
Total cholesterol	537 (47.0)	354 (66.8)	183 (29.9)	5.02 (3.89, 6.48)	< 0.001
LDL-cholesterol	503 (44.1)	347 (65.5)	156 (25.5)	5.87 (4.53, 7.62)	< 0.001
HDL-cholesterol	515 (45.1)	350 (66.0)	165 (27.0)	5.59 (4.31, 7.23)	< 0.001
Triglycerides	472 (41.3)	333 (62.8)	139 (22.7)	6.02 (4.63, 7.82)	< 0.001
Fasting blood glucose	351 (30.7)	281 (53.0)	70 (11.4)	9.11 (6.71, 12.35)	< 0.001
HbA1c	385 (33.7)	284 (53.6)	101 (16.5)	6.10 (4.62, 8.04)	< 0.001
GTI-r journal *n (%)*					
Brachial BP	422 (37.0)	371 (70.0)	51 (8.3)	27.46 (19.41, 38.85)	< 0.001
Lipid values	378 (33.1)	321 (60.6)	57 (9.3)	15.90 (11.45, 22.08)	< 0.001
Smoking	756 (66.2)	378 (69.3)	378 (61.8)	1.44 (1.12, 1.85)	0.05
Complete risk profile	307 (26.9)	276 (52.1)	31 (5.1)	20.97 (14.04, 31.33)	< 0.001
CV medication	251 (22.0)	198 (37.4)	53 (8.7)	6.31 (4.52, 8.82)	< 0.001
CV co-morbidities	231 (20.2)	184 (34.7)	47 (7.7)	6.43 (4.53, 9.14)	< 0.001

*Adjusted for age and gender
ROC: rheumatology outpatient clinic, RegROC: Regular rheumatology outpatient clinic, AC: Arthritis clinic, CV: Cardiovascular, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, BP: Blood pressure, HbA1c: Glycated haemoglobin, GTI-r: GoTreatIT-rheuma, Complete risk profile: Complete lipid values, smoking and blood pressure, CV medication: Anti-hypertensive and statins, CV co-morbidities: Hypertension, angina pectoris, acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, cerebrovascular accident, premature familiar cardiovascular disease

Conclusion: Despite high focus on CV disease, recording of CVRFs in the ROC was low; however it was augmented, but still not satisfactory in a structured, team-based model. There is necessity for improving systems for CVRF recording in patients with RA.

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Medication Adherence In Patients With Gout: A Systematic Review. Mary De Vera[1], Sharan Rai[1] and Vidula Bhole[2]. [1]Arthritis Research Centre of Canada, Richmond, BC, [2]EpiSolutions Consultancy Services, Thane, India

Background/Purpose: Recent data suggesting the growing problem of medication non-adherence in gout has called for the need to understand the magnitude of the problem as well as its determinants. To date, only one systematic review has summarized medication adherence across a variety rheumatic diseases, including three studies in gout. To update this data as well as better understand patterns and determinants of adherence in this population, our objective was to a conduct a systematic review of the literature examining medication adherence among patients with gout.

Methods: We conducted a systematic search of MEDLINE (1946-), EMBASE (1974-), and INTERNATIONAL PHARMACEUTICAL ABSTRACTS (1970-) databases and selected original studies that included patients with gout and measured and/or reported medication adherence in real-world settings. We extracted information on: 1) study design, 2) sample size, 3) length of follow-up, 4) data source (e.g. prescription records vs. electronic monitoring vs. self-report), and 5) adherence measures and reported estimates. We assessed quality of studies by adapting and applying published recommendations for the reporting, assessment, and evaluation of medication adherence studies.

Results: After screening 963 potential articles, 14 met inclusion criteria. We divided studies according to methods used to measure adherence including prescription records (9), electronic monitoring devices (1), and self-report (4). Studies using prescription records have the largest sample sizes and lowest reported adherence, ranging from 17% to 44%. Higher adherence rates (or scores) were reported in studies based on self-report, which may be due to social desirability bias. With respect to determinants, younger age has been shown as a predictor of poor adherence while other factors including gender and gout-related factors (e.g., flares) are less consistent across studies.

Conclusion: This is the first systematic review of medication adherence, with particular focus on gout patients. Adherence rates may vary according to methods used to measure adherence. Overall, synthesis of current evidence suggest that medication non-adherence is substantial in gout. Findings highlight the importance of discussing adherence with gout medications during health care professional encounters with gout patients.

Study	N	Follow-up	Adherence Measure	Main Result
Prescription Records				
Riedel 2004	5,597	2 yr	weighted average compliance rate	18% adherent
Sarawate 2006	2,405	2 yr	medication possession ratio >0.80	26% adherent
Briesacher 2008	9,715	1 yr	medication possession ratio >0.80	36.8% adherent
Solomon 2008	9,823	1 yr	proportion days covered >0.80	36% adherent
Halpern 2009*	10,070	1 yr	medication possession ratio >0.80	44% adherent
Harrold 2009	4,166	6 yr	medication possession ratio >0.80	44% adherent
Harrold 2010*	4,166	6 yr	therapy gap (>60 days no refill)	30% adherent (no gap)
Park 2012	352	1 yr	proportion days covered >0.80	27% adherent
Zandman 2013	7,644	6 yr	proportion days covered >0.80	17% adherent
Electronic Monitoring				
de Klerk 2003	29	1 yr	taking compliance dosing compliance	colchicine: 65% allopurinol: 84% colchicine: 44% allopurinol: 74%
Self-Report				
Silva 2010	34	1 yr	taking medication regularly	16.7% adherent
Dalbeth 2011*	142	n/a	questionnaire score (45=high)	39.8
Dalbeth 2012*	273	n/a	questionnaire score (45=high)	40.2
Martini 2012*	60	n/a	semi-structured interview	79% adherent

**medication adherence evaluated as exposure and not outcome*

Disclosure: M. De Vera, None; **S. Rai**, None; **V. Bhole**, None.

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The Economic Burden Of Gout: A Systematic Review Of Direct and Indirect Costs. Sharan Rai[1], Aliya Haji[1], Lindsay C Burns[2] and Hyon K. Choi[3]. [1]Arthritis Research Centre of Canada, Richmond, BC, [2]University of British Columbia, Vancouver, BC, [3]Boston University School of Medicine, Boston, MA

Background/Purpose: The prevalence of gout, an excruciating and disabling joint disease, has been increasing in recent decades such that it now constitutes the most common inflammatory arthritis in the US. A high rate of uncontrolled disease and high comorbidity burden suggest that the economic impact of gout could potentially be substantial. To clarify this impact, we systematically reviewed the literature on the productivity loss and healthcare costs associated with gout.

Methods: We conducted a mapped search of MEDLINE, EMBASE, IPA, and CINAHL databases for articles published between Jan 1993 to Jun 2013 that reported either direct or indirect costs of gout, encompassing healthcare utilization and productivity loss, respectively. Our search strategy employed mapped subject headings terms together with keywords for unindexed terms relating to the themes of gout and cost. Titles and abstracts were reviewed for preliminary inclusion criteria of: 1) full-text, original, published article; 2) gout patient population; 3) direct or indirect costs reported; 4) English language. Non-human studies and case-reports/series were excluded. Where possible, data were abstracted and tabulated on annual all-cause and gout-related direct and indirect costs per patient.

Results: Our search strategy yielded a total of 2,954 unique articles. Of these, 11 studies reporting direct and indirect costs for gout met our inclusion criteria and were included for review. Seven studies reported gout-specific data on direct costs (medical services + prescriptions), 5 on medical services, and 4 on indirect costs (work productivity loss). US estimates of the annual direct costs per patient ranged from $3,985–$22,562 for all-cause costs and $192–$5,924 for gout-specific costs. Annual per-patient medical services costs ranged from $3,122–$14,866 and corresponding indirect costs ranged from $915–$3,900 US. Patient characteristics associated with increased costs included: 1) ≥ 3 flares per year; 2) serum uric acid levels ≥ 6 mg/dL; 3) presence of tophi (**Table**).

DIRECT (MEDICAL SERVICES + PRESCRIPTION) COSTS

Gout Population	All-Cause Healthcare Cost	Gout-Related Healthcare Cost	Country	Cost Year	References
<3 attacks	$9,009[a]-$10,547[b]	$192[b]	USA	2011	Lynch *et al.* 2013; Saseen *et al.* 2012
≥3 attacks/year	$9,748[a]-$17,603[b]	$870[b]-$5,924[b]	USA	2008–2011	Lynch *et al.* 2013; Saseen *et al.* 2012; Wu *et al.* 2012
Employees with gout	$3,985[c]	–	USA	2001–2004	Brook *et al.* 2006
SUA < 6.0 mg/dL	$11,365[d]-$15,237[e]	$332[d]-$505[b]	USA	2002–2010	Halpern *et al.* 2009; Park *et al.* 2012; Wu *et al.* 2008;
SUA ≥6.0 and < 9.0 mg/dL	$11,551[d]-$14,935[e]	$353[d]-$696[b]	USA	2002–2010	Halpern *et al.* 2009; Park *et al.* 2012; Wu *et al.* 2008;
SUA ≥ 9.0	$14,474[d]-$18,340[e]	$663[d]-$723[e]	USA	2005–2010, NS*	Halpern *et al.* 2009; Park *et al.* 2012; Wu *et al.* 2008;
Gout patients with tophi	$22,562[b]	–	USA	2005	Wu *et al.* 2008
Gout patients without tophi	$14,574[b]	–	USA	2005	Wu *et al.* 2008
Physician diagnosed gout	$14,734[b]	$876[b]	USA	2005	Wu *et al.* 2008
≥3 attacks/year	€ 1259[f]	–	Spain	2007	Sicras-Mainar *et al.* 2013

MEDICAL SERVICES COSTS

Gout Population	All-Cause Healthcare Cost	Gout-Related Healthcare Cost	Country	Cost Year	References
<3 attacks/year	$7,332[a]-$8,209[b]	$176[b]	USA	2011	Lynch *et al.* 2013; Saseen *et al.* 2012
≥3 attacks/year	$8,505[b]-$14,866[b]	$834[b]-$5,477[b]	USA	2008–2011	Lynch *et al.* 2013; Saseen *et al.* 2012; Wu *et al.* 2012
Employee with gout	$3,122[c]	–	USA	2001–2004	Brook *et al.* 2006
≥3 attacks/year	€ 2517[f]	–	Spain	2007	Sicras-Mainar *et al.* 2013

INDIRECT (WORK PRODUCTIVITY LOSS) COSTS

Gout Population	Indirect Cost	Country	Cost Year	References
<3 attacks/year	$915[a]	USA	2011	Lynch *et al.* 2013
≥3 attacks/year	$2,021[a]	USA	2011	Lynch *et al.* 2013
Employee with gout	$2,885[c]	USA	2001–2004	Brook *et al.* 2006
SUA ≥ 6.0 mg/dL	$3,900[b]	USA	2006	Edwards *et al.* 2011
≥3 attacks/year	€ 88[f]	Spain	2007	Sicras-Mainar *et al.* 2013
1–2 attacks/year	€ 29[f]	Spain	2007	Sicras-Mainar *et al.* 2013

[a]Adjusted for age, sex, marital status, race, exempt status, full-time status, salary, tenure, region, and history of flares
[b]Unadjusted cost
[c]Adjusted for age, sex, annual salary, tenure, exempt status, race, marital status, location, and Charlson comorbidity index
[d]Adjusted for age, sex, insurance, Charlson comorbidity index, presence of hypertension, and number of all-cause prescriptions
[e]Adjusted for age, sex, index year, Charlson comorbidity index, and medication use
[f]Adjust for age, sex, resource utilization, and Charlson comorbidity index

Conclusion: Overall, the economic burden of gout was found to be substantial, with direct healthcare costs comparable to chronic rheumatic conditions such as rheumatoid arthritis. There was a paucity of data on indirect costs associated with gout, the population costs of gout (rather than patient subgroups), a lack of standardized cost reporting, and a lack of validated instruments for cost assessment in gout. Characteristics associated with increased costs generally reflected poorly controlled disease and were largely modifiable. As gout represents a metabolically-driven arthropathy that can be fully controlled with proper therapeutic approaches, substantial resources could be spared through by closing the gap between guideline recommendations and practice.

Disclosure: S. Rai, None; **A. Haji**, None; **L. C. Burns**, None; **H. K. Choi**, None.

ACR Poster Session A
Imaging of Rheumatic Diseases I: Imaging in Gout, Pediatric, Soft and Connective Tissue Diseases
Sunday, October 27, 2013, 8:30 AM–4:00 PM

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Dual-Energy Computed Tomography for Monitoring of Urate Deposition in Tophaceous Gout: A Prospective Longitudinal Study Examining Sensitivity to Change. Ashwin Rajan[1], Opetaia Aati[1], Ramanamma Kalluru[2], Gregory Gamble[1], Anne Horne[1], Anthony Doyle[1], Fiona M. McQueen[1] and Nicola Dalbeth[1] [1]University of Auckland, Auckland, New Zealand, [2]Department of Rheumatology, Auckland District Health Board, Auckland, New Zealand

Background/Purpose: Dual-energy computed tomography (DECT) is an advanced imaging method with potential for monitoring urate deposition in patients with gout. The aim of this prospective longitudinal study was to analyse the sensitivity to change of DECT urate volume measurement.

Methods: Seventy-three patients with tophaceous gout attended study visits at baseline and 12 months. All patients had a comprehensive clinical assessment including serum urate (SU) testing and DECT scanning of both feet at both visits. Two readers analysed the DECT scans for the total urate volume in both feet. Paired scans were read in chronological order. The readers were blinded to each other's measurements and all clinical measures including serum urate concentrations. Analysis included inter-reader intra-class correlation coefficients (ICCs) and limits of agreement, and calculation of the smallest detectable change (SDC).

Results: Allopurinol was prescribed in 85% patients during the study period. Mean (SD) SU concentration for both timepoints was 6.3 (1.5) mg/dL. The median (IQR) baseline DECT urate volume was 0.49 (0.16, 2.18) cm^3, and change in DECT urate volume was −0.01 (−0.40, 0.28) cm^3. Inter-reader ICCs were 1.00 for baseline DECT volumes and 0.93 for change values. Inter-reader bias (SD) for baseline volumes was −0.18 (0.63) cm^3 and for change was −0.10 (0.93) cm^3. The SDC was 0.91cm^3. There were 47 (64%) patients with baseline DECT urate volumes <0.91cm^3. Higher mean SU concentrations were observed in patients with increased DECT urate volumes above the SDC (one way ANOVA p=0.006). However, a relationship between changes in DECT urate volumes and mean SU concentrations was not observed in the entire group (Figure).

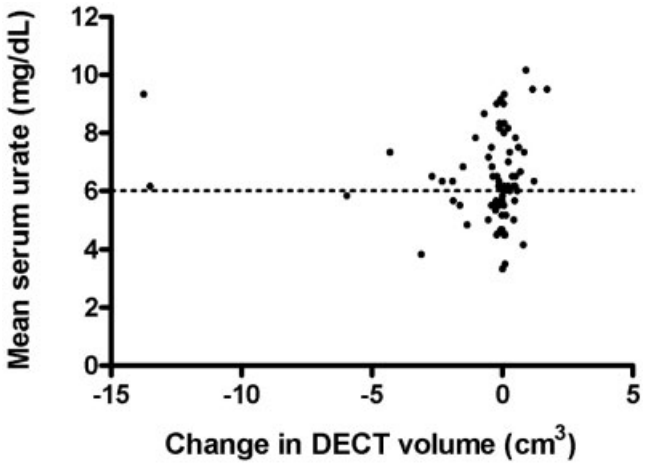

Figure. Scatter plot showing the relationship between change in DECT urate volumes and mean serum urate concentrations (baseline and Year 1).

Conclusion: DECT urate volume measurement has high inter-reader agreement but low sensitivity to change over one year in patients with tophaceous gout receiving conventional urate-lowering therapy. These data raise questions about the role of DECT as an outcome measure for clinical studies of gout.

Disclosure: A. Rajan, None; **O. Aati**, None; **R. Kalluru**, None; **G. Gamble**, None; **A. Horne**, None; **A. Doyle**, None; **F. M. McQueen**, None; **N. Dalbeth**, None.

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Digital Tomosynthesis for Measurement of Bone Erosion in Gout: Comparison With Computed Tomography. Nicola Dalbeth[1], Anthony Doyle[1], Mark Roger[2], Angela Gao[2] and Fiona M. McQueen[1]. [1]University of Auckland, Auckland, New Zealand, [2]Auckland District Health Board, Auckland, New Zealand

Background/Purpose: Digital tomosynthesis is a recently developed imaging method in which multiple projected images obtained at different angles are collected with a digital detector. These projected images are used to reconstruct multiple thin planar images of the scanned object in a plane parallel to the detector. Recent reports indicate that this technology allows low-cost, low-radiation detection of bone erosion in patients with inflammatory arthritis. The aim of this study was to determine the sensitivity and reproducibility of tomosynthesis, compared with conventional computed tomography (CT), for measurement of bone erosion in gout.

Methods: Tomosynthesis and CT scans of the dominant wrist were prospectively obtained in 37 patients with gout (mean disease duration 18 years, 86% with subcutaneous tophi) (Figure). Each scan was scored separately by two radiologists for bone erosion using semi-quantitative volume assessment (sites and 0–10 scoring as for RAMRIS erosion method).

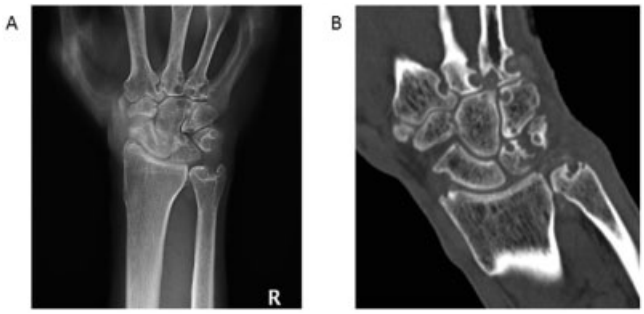

Figure. A. Tomosynthesis and B. corresponding coronal CT images of the right wrist in a participant with tophaceous gout.

Results: The mean total erosion score in the tomosynthesis scans was lower than CT scans (10.8 vs 13.2, $p=0.004$). For many individual sites (radius, scaphoid, triquetrum, trapezium, capitate, MC1 base), tomosynthesis erosion scores were significantly lower than CT scores. There were no sites where tomosynthesis scores were higher than CT. The inter-reader intraclass correlation coefficients (ICC) for the total erosion score was 0.64 (0.59–0.89) for tomosynthesis and 0.80 (0.64–0.94) for CT. At all individual sites except MC2 base, ICCs were lower for tomosynthesis than CT. We were unable to identify a combination of sites for which mean scores or ICCs for tomosynthesis approximated those of CT. There was a high correlation between tomosynthesis and CT total scores ($r=0.95$, $p<0.0001$) and at most individual sites. Total erosion scores for both tomosynthesis and CT correlated highly with hand tophus count, grip strength, and Health Assessment Questionnaire scores ($p<0.001$ for all).

Conclusion: Tomosynthesis erosion scores correlate highly with CT erosion scores and clinical measures of disease severity in patients with gout. However, tomosynthesis has lower reproducibility and detection of erosion compared with CT. These findings indicate that CT remains the gold standard for measurement of bone erosion in gout.

Disclosure: N. Dalbeth, None; **A. Doyle**, None; **M. Roger**, None; **A. Gao**, None; **F. M. McQueen**, None.

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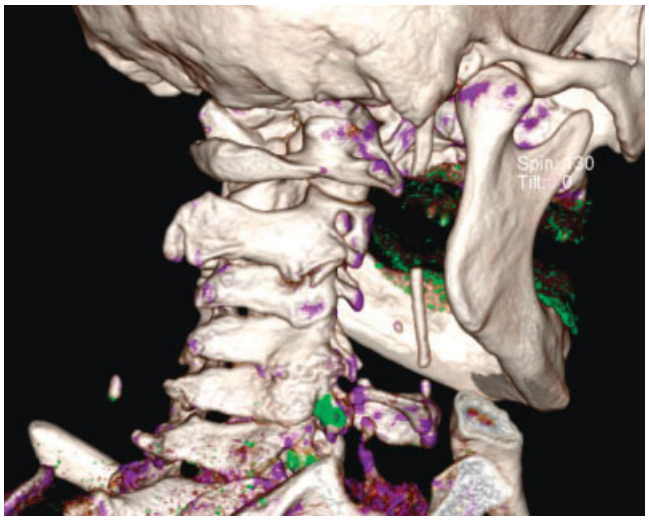
Use Of Dual-Energy Computed Tomography In Evaluation Of Axial Gout. Kristin Logee[1], Ranadeep Mandhadi[1], William Traverse[2] and Santhanam Lakshminarayanan[3]. [1]University of Connecticut, Farmington, CT, [2]Saint Francis Hospital and Medical Center, Hartford, CT, [3]University of Connecticut School of Medicine, Farmington, CT

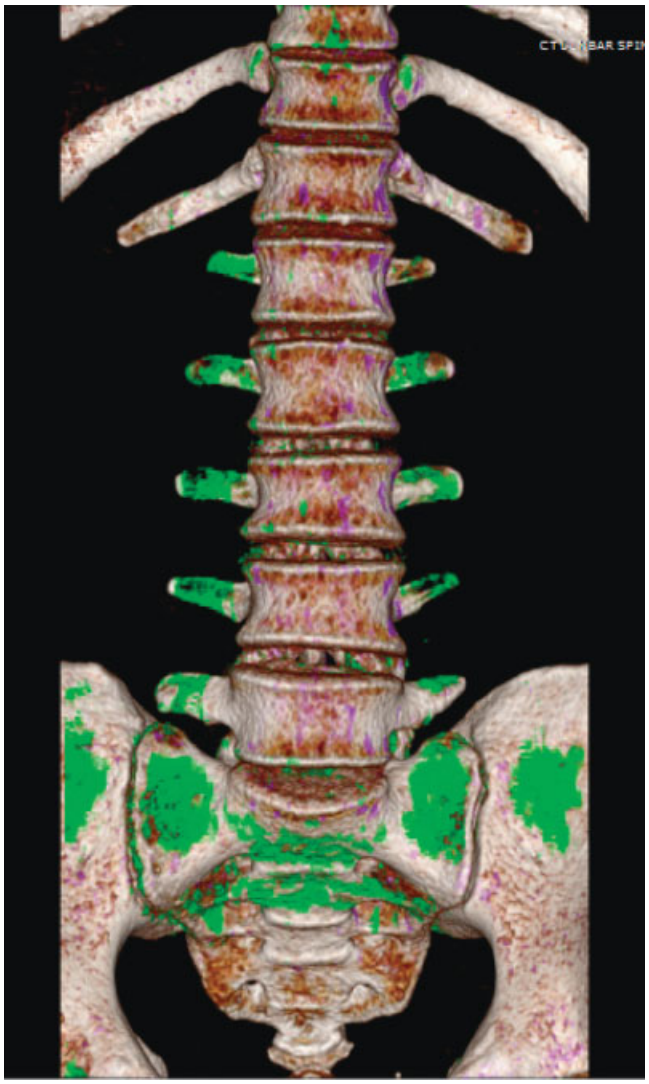
Background/Purpose: Axial (spinal) involvement has become increasingly recognized as a potential manifestation of gouty arthritis. The presentation can vary widely from mild, asymptomatic disease to severe back pain, radiculopathy or frank spinal cord compression. Axial gout is frequently a missed diagnosis for a variety of reasons: it can mimic other spine diseases, is under-recognized as a possible manifestation of gout, and current imaging techniques (X-ray, MRI and CT) often produce non-specific findings which do not distinguish gouty erosions and tophi from other pathologies.

Dual-energy CT has recently been recognized as very sensitive and specific for identifying monosodium urate (MSU) crystal deposition. By using a specific display algorithm that assigns different colors to materials of different chemical composition, MSU can be color-coded and thereby distinguished from surrounding structures. Up until now, it has been used mainly to image peripheral sites but has not been evaluated as a diagnostic tool for axial gout.

Methods: We present two cases that demonstrate the efficacy of dual-energy CT in detecting MSU deposition within the axial skeleton. Patient X was a 91 year-old male with severe neck pain, fevers and leukocytosis. MRI showed abnormal T2 signal around the C4-C5 facet joint with fluid consistent with synovitis. However, septic arthritis could not be ruled out. The patient also complained of right knee pain and swelling. Aspirate of the knee revealed intracellular MSU crystals with negative cultures, consistent with acute gout flare. This raised suspicion that the patient's presentation could be secondary to spinal involvement of gout. Patient Y was a 29 year-old male with a long-standing history of chronic tophaceous gout who presented with incapacitating mid-low back pain. Traditional CT showed extensive subchondral erosions throughout the lumbar spine and right sacroiliac joint.

Results: Dual-energy CT of the cervical spine of Patient X (Image 1) showed MSU deposition on the cervical facet joints (color-coded in green) which correlated with the MRI findings. The patient's symptoms quickly resolved with colchicine and IV methylprednisolone. Similarly, lumbar spine dual-energy CT of Patient Y (Image 2) showed extensive MSU deposition along the transverse processes and pelvic bony structures. Symptoms remitted with colchicine and oral prednisone.





Conclusion: Dual-energy CT can be used to visualize the presence of axial MSU deposition. This may lead to appropriate diagnosis and management of axial gout while avoiding invasive procedures and erroneous treatment.

Disclosure: K. Logee, None; **R. Mandhadi**, None; **W. Traverse**, None; **S. Lakshminarayanan**, None.

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Relationship Between Structural Joint Damage and Urate Deposition In Gout: A Site-By-Site Analysis Using Plain Radiography and Dual Energy Computed Tomography. Nicola Dalbeth[1], Opetaia Aati[1], Ramanamma Kalluru[2], Anne Horne[1], Anthony Doyle[1] and Fiona M. McQueen[1]. [1]University of Auckland, Auckland, New Zealand, [2]Department of Rheumatology, Auckland District Health Board, Auckland, New Zealand

Background/Purpose: Structural joint damage, including erosion, joint space narrowing (JSN) and new bone formation (NBF), is frequently observed in patients with tophaceous gout. Although imaging studies have implicated tophi in the development of these changes, the relationship between monosodium urate (MSU) crystals and structural joint damage has not been examined. The aim of this work was to examine the relationship between joint damage and MSU crystal deposition in patients with tophaceous gout.

Methods: Plain radiographs and dual energy computed tomography (DECT) scans of the feet were prospectively obtained from 92 patients with tophaceous gout. Two readers analysed the 10 metatarsophalangeal joints (MTPJs) for the presence of MSU crystals using DECT (920 total joints analysed, inter-reader agreement 94.2% and kappa 0.82). For the purposes of analysis, DECT MSU crystal deposition was considered present if recorded by both readers. A further reader, who was blinded to the DECT results, scored the same joints on plain radiography for Sharp-van der Heijde erosion score (0–10), JSN score (0–4) and presence of NBF features (spur, sclerosis and osteophyte).

Results: DECT MSU crystal deposition was more frequently observed in joints with erosion (odds ratio (OR) 11.2), JSN (OR 5.1), spur (OR 13.4), osteophyte (OR 5.3) and sclerosis (OR 9.1), $p < 0.0001$ for all. For those joints with any erosion, erosion scores were higher in joints with DECT urate deposition compared with those without MSU crystals (mean (SD) erosion scores 5.2 (2.7) and 3.3 (2.11) respectively, $p<0.0001$). A strong linear relationship was observed in the frequency of joints affected by MSU crystals with increasing radiographic erosion score ($p<0.0001$). In contrast, for those joints with any narrowing, JSN scores were no different in those with and without DECT urate deposition ($p=0.75$). DECT MSU crystal deposition and all features of joint damage were most frequently observed at the 1st MTPJ (Figure). There was a very high correlation between the number of joints at each site affected by MSU crystal deposition and all features of radiographic joint damage ($r>0.88$ for all, $p<0.05$ for all).

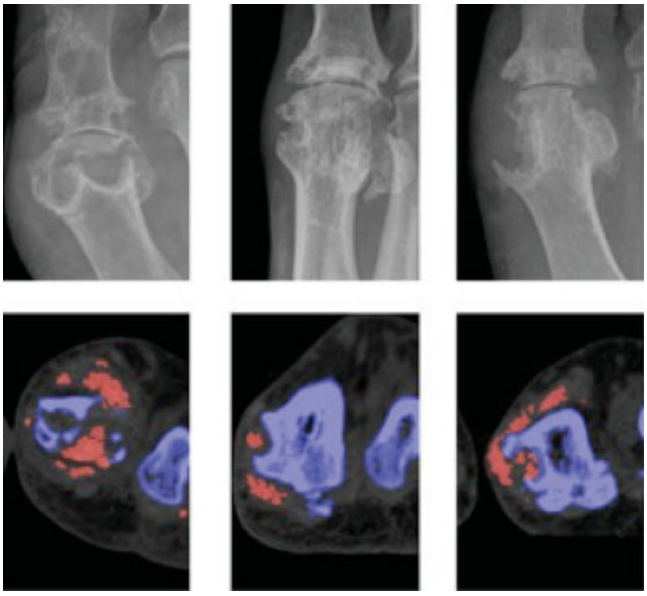

Figure. Examples of plain radiographs (upper panel) and corresponding axial DECT images (lower panel) of eroded 1st MTPJs from three separate participants. MSU crystals are shown as red on DECT images.

Conclusion: MSU crystals are frequently present in joints affected by radiographic damage in patients with gout. These findings support the concept that MSU crystals directly interact with articular tissues to influence the development of structural joint damage in this disease.

Disclosure: N. Dalbeth, None; **O. Aati**, None; **R. Kalluru**, None; **A. Horne**, None; **A. Doyle**, None; **F. M. McQueen**, None.

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Systematic Staging For Uric Acid Deposits With Dual-Energy Computed Tomography and Ultrasound In Suspected Gout. Wolfgang A. Schmidt[1] and Alexander Huppertz[2]. [1]Med Ctr Rheumatology Berlin Buch, Immanuel Krankenhaus Berlin, Berlin, Germany, [2]Imaging Science Institute Charité, Berlin, Germany

Background/Purpose: To evaluate the diagnostic accuracy of Dual-Energy Computed Tomography (DECT) and ultrasound for detecting monosodium urate crystal deposits in patients with clinically suspected gout.

Methods: In this case control study DECT and comprehensive ultrasound of feet, knees, hands, wrists, and elbows were performed bilaterally in 60 consecutive patients (49 males; 11 females; mean age, 62 years; age range, 36–82 years) of a tertiary rheumatology referral center with suspected gout and compared with pooled clinical information including polarization microscopy, maximum documented uric acid levels, presence of podagra and the final rheumatological diagnosis as standard-of-reference.

Results: Finally, 39 patients were classified as gout positive, 31 of which had been newly diagnosed. Sixteen of these patients had gout and a concomitant rheumatic disease. Although an experienced rheumatologist aimed at receiving material from tissue or joint aspirates of every patient, if necessary with ultrasound guidance, the diagnosis could be confirmed by polarization microscopy only in 46% of the gout patients.

DECT had a sensitivity of 84.6%. Ultrasound had a sensitivity of 100%. The specificity for the diagnosis of gout was 85.7% for DECT and 76.2% for ultrasound. The positive predictive value was 0.92 for DECT and 0.89 for ultrasound. The negative predictive value was 0.75 for DECT and 1 for ultrasound.

Uric acid deposits occurred most commonly in the medial and lateral aspects of the knee joint, in the quadriceps tendon and in the first MTP 1 joints. The evaluation on a joint-basis compared to ultrasound as reference revealed a sensitivity of 46.2% and a specificity of 97.6% for DECT. Ultrasound detected smaller crystal deposits than DECT. DECT failed to show crystal deposits on the cartilage, representing the "ultrasound double contour sign", but delineated larger intra-articular and extra-articular tophi.

Ultrasound was false positive in one patient with calcium pyrophosphate dihydrate disease (CPPD), hydroxyapatite deposition disease and rheumatoid arthritis, respectively, and in two patients with severe peripheral arterial occlusive disease.

DECT was false positive in 3 patients showing minimal deposits suggestive of gout tophi in the lateral menisci. One patient was finally diagnosed with CPPD, one with psoriatic arthritis and one with undifferentiated oligoarthritis. Small signals that are not representing urate deposits also appear in nails.

The DECT volumetry computed a mean uric acid deposit load of 2.0 cm^3 (SD 9.6 cm^3). A mean effective dose between 0.4 and 0.5 mSv was estimated.

Conclusion: DECT is specific for the diagnosis of gout particularly when excluding small signals in the lateral menisci and in the nails. However, it fails to detect small uric acid deposits. It is particularly useful for patients with ambivalent findings, concomitant rheumatic diseases, and for those whose joint aspiration and microscopy did not successfully detect gout crystals.

Disclosure: W. A. Schmidt, Esaote, 2, GE Healthcare, 2; **A. Huppertz**, Siemens, 3.

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Clinical Value Of ^{18}f-Fluoro-Dexoxyglucose Positron Emission Tomography In Patients With Adult-Onset Still's Disease. Hiroyuki Yamashita, Kazuo Kubota, Yuko Takahashi, Hiroshi Kaneko, Toshikazu Kano and Akio Mimori. National Center for Global Health and Medicine, Tokyo, Japan

Background/Purpose: The aim of this study was to assess the usefulness of 18F-fluoro-dexoxyglucose positron emission tomography/Computed tomo-

graphy (18F-FDG PET/CT) for the diagnosis or the evaluation of Adult-onset Still's disease (AOSD) visually.

Methods: 7 consecutive AOSD patients who had undergone PET at our department between 2007 and 2012 were included in the study. In addition, the literature review was performed about 6 previously reported AOSD patients who had undergone PET. We evaluate FDG uptake for characteristic findings in patients with AOSD.

Results: FDG accumulation was positive mainly in the bone marrow (70%), spleen (80%), lymph nodes (77.8%), and joints (50%). In addition, FDG uptake was positive in the pericardium, pleura, salivary glands, eyelids, muscle, and major blood vessels. 8 patients underwent FDG PET/CT for evaluating the efficacy of treatment. The follow-up PET showed diminished FDG accumulation in the bone marrow, spleen, lymph nodes, with SUVmax being significantly reduced from 4.03±0.95 to 2.20±0.75 (P=0.04), from 4.15±1.10 to 2.55±1.13(P=0.04), and from 5.47±5.19 to 2.10±1.91 (P=0.11), respectively. No significant correlation was found between max SUVs in each site and the laboratory data; the only significant correlation was between LDH and the spleen SUV.

Conclusion: Our study suggests that 18F-FDG PET may play a potential role in diagnosing or monitoring of disease activity marker in patients with AOSD. Additionally, we suspect that future PET/CT imaging will reveal that AOSD is a disease involving lesions with a little clinical description.

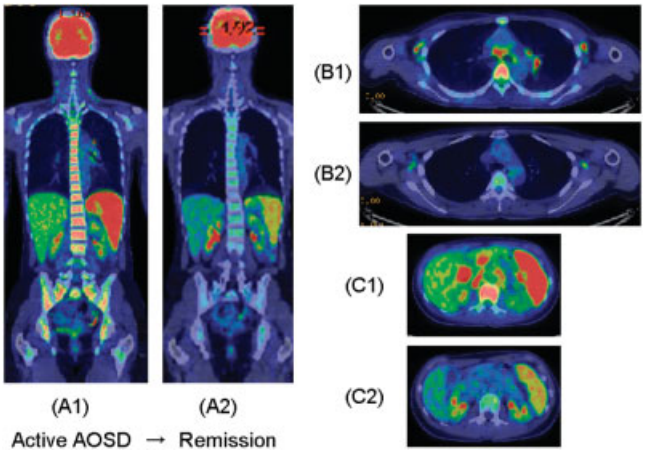

Fig. 1. FDG-PET/CT images at diagnosis (A1,B1,C1) and after steroid and Tocilizmab treatment (A2,B2,C2) in a 32-year-old woman (Patient 4) with AOSD.

Marked FDG accumulation was observed in the bone marrow, spleen and multiple lymph nodes at the time of diagnosis before treatment. After treatment, bone marrow FDG uptake improved from SUVmax 004.02 (A1) to 2.50 (A2) and spleen FDG uptake decreased from SUVmax 006.05 (A1,C1) to 4.38 (A2,C2). In addition, multiple lymph node FDG uptake observed in the axilla, mediastinum, hilar region of the lung, hilar region of the liver and para-aortic region declined or disappeared (B1/C1→B2/C2).

Disclosure: H. Yamashita, None; **K. Kubota**, None; **Y. Takahashi**, None; **H. Kaneko**, None; **T. Kano**, None; **A. Mimori**, None.

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The Role Of Salivary GLAND Ultrasound In Sjogren Syndrome: A Single Center Experience. Giuseppe Germanò[1], Niccolò Possemato[1], Olga Addimanda[1], Pierluigi Macchioni[1] and Carlo Salvarani[2]. [1]Arcispedale S Maria Nuova, IRCCS, Reggio Emilia, Italy, [2]Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy

Background/Purpose: There is increasingly scientific evidence of salivary gland ultrasonography accuracy and usefulness in diagnosing Sjogren Syndrome. [1–2]

Methods: 82 patients with suspected Sjogren Syndrome from a single center were evaluated. Demographic (age and sex), clinical (sicca syndrome, artralgia), ultrasonographic (salivary gland ultrasound following the score proposed by Ariji et al [3], serologic (anti nuclear antibodies – ANA, anti ENA, anti HCV) and histological (salivary glands biopsy with Chisholm-Mason score evaluation) features were analyzed. Patients were classified according to ACR/EULAR criteria for SS (AEC).[4]

Results: all patients with HCV infection were counted out as well as all the patients with one of the exclusion criteria present in the Primary Sjogren Syndrome classification. Male/female ratio was 1/9; 91.2 % of patients presented xerostomia, 75% xerophthalmia. Schirmer test was positive in 72% of the patients; break up time positive in 65%. The biopsy was positive (Chisholm and Mason score >1) in 61% and ultrasound was positive (score ≥2 out of 4) in 40.2%. ENA test (SSA and\or SSB) was positive in 37.4%. The diagnosis of Sjogren Syndrome has been assessed, according to AECG classification criteria, in 36 patients out of 82 (43.9%). 80.6% of patients with positive ultrasound were classified as affected by Sjogren Syndrome, 89.1% of patients with negative ultrasound didn't fill the classification criteria. The ultrasound score presented a positive likelihood ratio of 4.58 (95% *confidence interval 2.34<x>8.98) and a negative one of 0.135 (0.058<x<0.313). The test showed a sensibility of 80.6% and a specificity of 89.1%. Concordance (Cohen K) between classification criteria and US score was 0.701 (medium level), higher than that between classification criteria and biopsy Chisholm-Mason score (0.572). Surprisingly ENA screening didn't add diagnostic power to the ultrasound scan due to a wide overlapping of the two tests.*

Conclusion: in our experience salivary gland ultrasound seems to be an useful tool in the diagnostic process of Sjogren Syndrome due to its good sensibility and specificity. Moreover the exam is simple to perform, fast, incruent and well accepted by patients.

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3. Ariji Y, Ohki M, Eguchi K, *et al.* Texture analysis of sonographic features of the parotid gland in Sjögren's syndrome. *AJR Am J Roentgenol* 1996;166:935–41.

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Disclosure: G. Germanò, None; **N. Possemato**, None; **O. Addimanda**, None; **P. Macchioni**, None; **C. Salvarani**, None.

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Contrast-Enhanced Ultrasound Of The Sovraortic Arteries: The Potential Role In Monitoring Disease Activity and Response To Treatment In Large Vessel Vasculitis. Giuseppe Germanò[1], Pierluigi Macchioni[1], Niccolò Possemato[1] and Carlo Salvarani[2]. [1]Arcispedale S Maria Nuova, IRCCS, Reggio Emilia, Italy, [2]Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy

Background/Purpose: promising data has been recently published about the role of contrast-enhanced ultrasound (CEU) in the diagnosis and follow up of Takayasu arteritis (TA) −1,2-

Objective: To assess the role of CEU examination of the carotid artery in patients with large vessel vasculitis (LVV) compared to Positron Emission Tomography (PET).

Methods: 10 patients (8 TA,2 LVV, mean age 46±19y, mean disease duration 3.9±3.1y) were contemporary evaluated with total body PET and carotid arteries US gray scale and CEU (Esaote MyLab70, 13-5MH linear probe, contrast agent Sonovue). All the patients underwent complete clinical examination and laboratory determination of acute phase reactants. Imaging results were reported using a semiquantitave score ranging from 0 (no activity) to 3 (high activity). Comparison between the two tests were made using Cohen K test.

Results: At US gray scale examination 8/10 patients have high intima/media thickness (mean 1,5 mm ±0.46). In patients with positive contrast enhanced ultrasound the mean carotid intima-media thickness was 2,1mm ±0.48, while patients with negative contrast enhanced ultrasound presented a mean wall thickness of 0,9mm ±0.47; P = 0.009. There was no significant differences in clinical, demographic and laboratory data between patients with active and inactive disease. All the 4 patients with high/medium carotid activity at PET examination presented positive (activity score >1) CEU. Five of the 6 patients with low/absent PET signal have negative (activity score <2) CEU (K test = 0.800, good concordance).

Conclusion: CEU have a good concordance with PET. These results outline the potential role of CEU to be used in monitoring disease activity and response to treatment in LVV

References:

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Asymptomatic Myocardial Ischemic Disease In Takayasu's Arteritis: Detection By Magnetic Resonance Imaging. Cloé Comarmond[1], Philippe Cluzel[2], Dan Toledano[3], Nathalie Costedoat-Chalumeau[4], Richard Isnard[5], Fabien Koskas[6], Patrice Cacoub Sr.[7] and David Saadoun[8]. [1]Hôpital Pitié Salpétrière, Paris, France, [2]Pitié-Salpétrière, Paris, France, [3]Hôpital Pitié-Salpêtrière, Paris, France, [4]Hopital Cochin, Paris, France, [5]CHU Pitié-Salpêtrière, 47-83 Boulevard de l'hôpital, 75651 Paris Cedex 13, Paris, France, Paris, France, [6]Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Paris, France, [7]CHU Pitié-Salpêtrière, Paris, France, [8]Pitié-Salpêtrière Hospital, APHP, Paris, France

Background/Purpose: Takayasu's arteritis (TA) may affected myocardium and caused coronary stenosis. The aim of this study was to assess the prevalence and pattern of myocardial disease in patients with TA, using late gadolinium enhancement (LGE) of cardiac magnetic resonance imaging (CMRI).

Methods: Twenty-seven consecutive patients with TA and 80 age and sex matched controls without known cardiovascular disease underwent CMRI. The prevalence of myocardial ischemic disease, as revealed by LGE, was compared between patients with TA and controls, and factors associated with myocardial disease were identified in patients with TA.

Results: Myocardial ischemic disease, as characterized by LGE on CMRI, was present in 7 (25.9%) of 27 patients with TA, and imaging with LGE showed a typical pattern of myocardial infarction (MI) in 6 patients (22.2%). Although both patients with TA and control subjects shared a similar risk of cardiovascular events, the prevalence of myocardial ischemia was more than 5 times higher in patients with TA ($P = 0.002$ versus controls). No association was found between myocardial disease in patients with TA and cardiovascular atherosclerotic risk factors. The presence of myocardial scarring tended to be more closely associated with specific features of TA, such as renovascular hypertension, older age at the onset of TA symptoms, male gender, aneurysmal dilatation, and numano type V.

Conclusion: The finding of a significant and unexpectedly high prevalence of occult myocardial scarring in patients with TA indicates the usefulness of CMRI with LGE for the identification of occult myocardial disease in such patients.

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Detection Of Cerebral Microvascular Lesions In Patients With Acute Phase Neuropsychiatric Systemic Lupus Erythematosus By 7Tesla MRI. Nobuhito Sasaki, Okinori Murata, Yukari Ninomiya, Yuka Oikawa, Hitoshi Kobayashi, Kohei Yamauchi, Makoto Sasaki, Takashi Sawai and Yutaka Nakamura. Iwate Medical University School of Medicine, Morioka, Japan

Background/Purpose: The cerebral microvascular lesions of patients with neuropsychiatric systemic lupus erythematosus (NPSLE) have not been fully elucidated. The 7Tesla MR scanner has high image resolution and can be expected to detect cerebral microvascular lesions that have never before been visible. We examined the cerebral microvascular lesions of NPSLE using a 7Tesla MR scanner.

Methods: We studied 7 acute phase-NPSLE patient and 11 non-NPSLE. MRI was performed using a 1.5Tesla MR scanner and 7Tesla MR scanner (T1-weighted imaging, T2-weighted imaging, diffusion-weighted imaging, magnetic resonance angiography). Two radiologists performed the interpretation without clinical information. Diagnosis of was determined by a neurologist, psychiatrist and rheumatologist.

Results: Examination by the 7Tesla MRI revealed cerebral microvascular lesions(under 100 micrometer) in 6 of 7 NPSLE patient. These findings were not detected in any of the patients with non-NP SLE. These findings were not detected by 1.5 Tesla MRI. There were not findings at all in 1.5Tesla MRI, and the case that included findings was found in only 7TeslaMRI. The cerebral microvascular lesions were found around the central sulcus especially in T2-weighted image. These MRI findings disappeared after central nervous symptom improvement in two of the three NPSLE patient that reexamined three months later. However, we did not find a direct association between the MRI findings and the neuropsychology dysfunction.

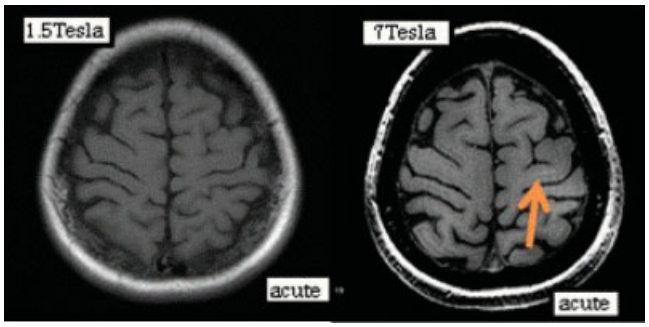

Image: 41 years old female She had both legs motor nerve disorder.

The cerebral microvascular lesions were found around the central sulcus in T2-weighted image. It could be find only by using 7TeslaMRI.

Conclusion: Cerebral microvascular lesions could be detected in patients with NPSLE by 7 Tesla MRI, suggesting that 7 Tesla MRI is a useful tool for diagnosing the cerebral lesions of NPSLE. It will be necessary to elucidate the association between cerebral microvascular lesions and neuropsychological dysfunction.

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Comparison Of Whole Body Versus Targeted Magnetic Resonance Imaging For Assessing Disease Activity and Damage In Idiopathic Inflammatory Myopathies. Adam Schiffenbauer[1], Evrim Turkbey[2], Lisa G. Rider[1], Suvimol Hill[2], Irene Z. Whitt[3], Songtao Liu[2], David A. Bluemke[2] and Frederick W. Miller[1]. [1]NIEHS, NIH, Bethesda, MD, [2]NIH, Bethesda, MD, [3]Duke, Durham, NC

Background/Purpose: In the idiopathic inflammatory myopathies (IIM) MRI imaging is traditionally focused on the proximal upper or lower extremities. Whole body MRI (WBMRI) is a technique where the entire body is scanned into one complete study. The purpose of this study was to assess what additional information is gained from WBMRI and to determine its relationship to clinical parameters.

Methods: 24 patients with a variety of IIM, including juvenile dermatomyositis (JDM, n=7), dermatomyositis (DM, n=6), polymyositis (PM, n=4), sporadic inclusion body myositis(s-IBM, n=3), and familial inclusion body myositis (f-IBM, n=4) underwent WBMRI. Using a Siemens 3 Tesla MRI scanner the patients were scanned in a head to toe manner and had T1, T2, and STIR images obtained. These images were then scored in a blinded manner across 34 muscle groups and each group was scored on a scale of 0 to 3 for T2/STIR intensity, T2/STIR area of involvement, and fatty infiltration on T1. WBMRI and thigh MRI (THMRI) scores were evaluated for correlation with a variety of measures of disease activity and damage.

Results: 3 out of 24 patients (12.5%) who were scored to have activity (at least a 1 for STIR intensity) on WBMRI had no activity present on THMRI. Similarly, 4 of 24 patients (16.67%) had fatty replacement on WBMRI, but no fatty replacement on THMRI. Patients had MRI STIR abnormalities by WBMRI in many areas that would not be scanned in a MRI of the thigh or proximal arms, including the paraspinal muscles (20% of patients) and the chest (16% of patients) as well asforearms and distal extremities (Table).

Region	Percentage positive on Right	Percentage positive on Left
Anterior forearm	7.69	7.14
Posterior forearm	30.77	21.43
Distal lower extremity anterior	20.83	45.83
Distal lower extremity posterior	37.5	37.5

Among all IIM patients, physician global disease damage on a visual analogue scale (VAS) and a Likert scale correlated with imaged fatty infiltration ($p<0.0001$). R squared for comparison of WBMRI and THMRI fatty replacement with physician global disease damage were 0.796 and 0.695 respectively. Also amongst all patients serum levels of creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) were found to correlate significantly with WBMRI STIR intensity and involvement scores, as well as with THMRI STIR intensity scores ($r^2=0.23–0.49$, $p<0.05$ for all).

In adult and juvenile DM and PM patients, the physician global activity by VAS correlated with WBMRI and THMRI intensity and involvement scores ($r^2=0.28–0.33$, $p<0.05$). WBMRI and THMRI intensity and involvement scores also correlated significantly with CK, AST, ALT, and LDH ($r^2=0.42–0.81$, $p<0.05$) in this population.

Conclusion: WBMRI was able to detect areas of muscle edema and fatty infiltration in IIM patients that would not be detected on traditional focal MRI of the thighs or arms. WBMRI also correlated well with physician assessment of disease activity and damage as well as with multiple laboratory markers of disease activity. These findings suggest utility of WBMRI in assessing patients across the IIM spectrum.

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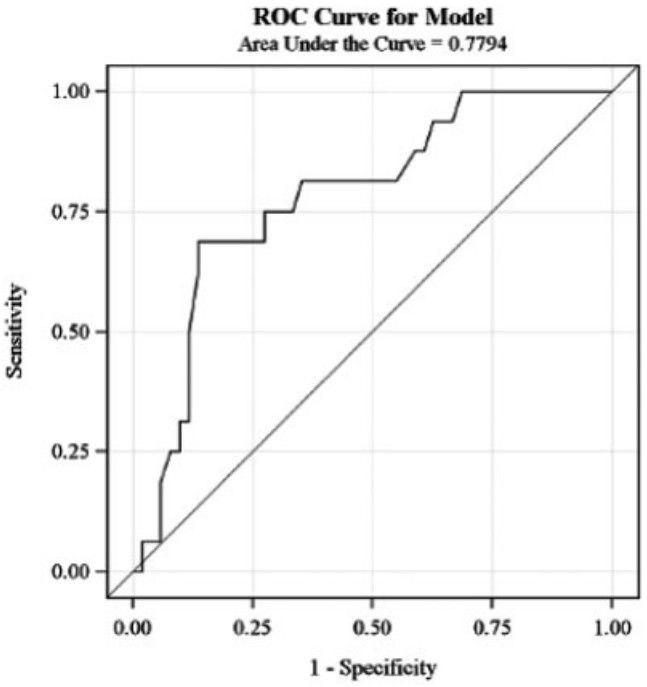
Clinical Predictors For Subcutaneous Power Doppler Signals Detected By Ultrasound in Hands Of Scleroderma Patients. Anat Scheiman-Elazary[1], Ami Ben-Artzi[2], V.K. Ranganath[2], Nabeel Borazan[1], Philip J. Clements[2], Suzanne Kafaja[2] and Daniel Furst[2]. [1]Rheumatology UCLA, Los Angeles, CA, [2]David Geffen School of Medicine, UCLA, Los Angeles, CA

Background/Purpose: Skin thickening in scleroderma was demonstrated previously in US studies, although subcutaneous tissue was not yet evaluated. We evaluated scleroderma patients for subcutaneous Power Doppler signal (SCPD) on the dorsal aspect of the MCPs of the dominant hand. Out of 74 patients, 17 (22.9%) had a positive signal. Our aim was to compare SCPD positive (N= 17, 22.9%) versus SCPD negative (N=57, 77.1%) patients and to look for clinical and laboratory predictors for SCPD.

Methods: Seventeen SCPD positive patients were compared with 57 SCPD negative patients. US exam was performed using GE logic E9 scanner with a linear array (5–16 MHz) for PD in subcutaneous tissue. SCPD was defined as a positive PD signal in the subcutaneous tissue on the dorsal aspect of either MCPs 2–5 in both longitudinal and short views that was not involving the tendon. At least one MCP had to be involved. A binary grading was used to score SCPD (0–1). Patients were divided into 2 groups, with or without SCPD. GS and PD examinations of 13 joints (wrist, MCP 2–5, PIPs 2–5) and tendons were done. A step wise linear regression model was used to identify predictors for SCPD. The following parameters were included: age, gender, disease duration, disease type (limited or diffuse), modified Rodnan skin score (MRSS), lung involvement (symptoms, pulmonary function test and high resolution CT), pulmonary hypertension (echo), ESR, CRP, ulcers, calcinosis, sclerodactaly and contractures.

Results: After univariate analysis with $P<0.2$ cut-off, MRSS, disease duration and lung involvement were included. MRSS ($OR=0.93$, $p=0.14$) and lung disease($OR=0.28$, $p=0.047$) decreased the likelihood for SCPD while longer disease duration increased its likelihood ($OR=1.117$, $p=0.036$). The final model included only lung and disease duration with a ROC curve, AUC of 0.77 (figure 1). There was no statistical difference in mean joint GS and PD between both groups (mean joint GS 0.34 and 0.31 in the negative and positive SCPD patients respectively, mean joint PD 0.08 and 0.04 in the negative and positive SCPD patients respectively). Mean ESR was 21 and 18 mm/h in the positive and negative SCPD patients respectively (P value 0.94).



Conclusion: Twenty two percent of patients with scleroderma had positive subcutaneous power doppler signal above the dorsal aspect of the MCPs. Patients with this phenomenon had longer disease duration and less lung involvement with moderately good predictive value (ROC AUC- 77). There was not increased synovitis or elevated ESR in this group. We therefore assume that this is not an inflammatory phenomenon. We speculate that SCPD may be related to increased blood flow to the skin during the resolution phase of the skin. Further studies are needed to understand the underling mechanism.

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Ultrasound Evaluation Of Joints, Tendons and Subcutaneous Tissue Of Hands In 74 Scleroderma Patients. Anat Scheiman-Elazary[1], Ami Ben-Artzi[2], Suzanne Kafaja[2], V Ranganath[2], Nabeel Borazan[1], Philip J. Clements[2] and Daniel Furst[2]. [1]Rheumatology UCLA, Los Angeles, CA, [2]David Geffen School of Medicine, UCLA, Los Angeles, CA

Background/Purpose: A previous ultrasound study of the hands in scleroderma (SSC) and rheumatoid arthritis (RA), found mild inflammatory changes in the tendons and joints of the SSC patients. Our aim was to evaluate joints, tendons and subcutaneous tissue in SSC patients compared to RA patients and healthy controls (HC).

Methods: A total of 74 SSC patients and 14 HC were examined in this cross sectional study and compared to a database of 32 RA patients. The patients underwent clinical and laboratory assessment. Blinded US exam of 13 joints (Wrist, MCPs 2–5, PIPs 2–5,DIPs 2–5) was performed, using GE logic E9 scanner with a linear array (5–16 MHz). Gray scale (GS) (0–1) and Power Doppler (PD) (0–3) scoring were used for tendons. GS and PD (0–3) scoring were used to evaluate joints. In 13 patients, we were unable to examine all 13 joints due to contractures. We therefore calculated separate GS and PD scores for joints and tendons by summing up scores for individual joints and dividing it by the number of joints examined. Subcutaneous tissue over the dorsal aspect of the MCPs was evaluated by PD (SCPD). Tuft resorption was examined by evaluating shortening of the distal second to fifth phalanges on the palmar and dorsal aspects. RA patients only had data on 5 joints (wrist, MCPs 2–3 and PIPs 2–3) and this subset was compared across the groups.

Results: Mean age was similar between all 3 groups. Percentage of females was 82, 90, and 71 for SSC, RA and HC respectively. Mean disease duration was 6.9 and 5.7 in the SSC and RA patients (Table 1). Mean DAS28

and CDAI in the RA patients was 5.07 and 22 respectively. For SSC patients 13.5% had tuft resorptions compared to none of the RA patients and HC. Mean GS and PD score for joints and tendons of the 13 joints exam were significantly higher in the SSC patients then HC (mean joint GS 0.33 and 0.08, mean join PD 0.07 and 0.01, mean tendon GS 0.08 and 0, mean tendon PD 0.09 and 0 for the SSC and HC respectively, $p<0.05$ for all). For the 5 joint exam, mean GS and PD for tendons and joints was significantly higher in the SSC versus HC as well as RA patients except PD for tendons which was not significant in the SSC compared to HC. RA patients had a higher frequency of +2 or +3 PD in joints and tendons while HC had none (Table 1). Twenty one percent of SSC patients with swollen joint count of zero, had +2 or +3 PD signals in joints or tendons. Subcutaneous PD signals were found nearly exclusively in SSC patients.

	Age	% F	Disease duration (y)	Mean ESR	5 Joint GS	5 Joint PD	5 Tendon GS	5 Tendon PD	% patients with +2 or +3 join PD	% Patients with +2 or +3 Tendon PD	% SCPD (N)
SSC (N=74)	53.46	82	6.9	18.6	0.42	0.09	0.11	0.1	16	24	22 (17)
RA (N=32)	53.75	90	5.7	39.6	1	0.52	0.33	0.41	93	62	0.03 (1)
HC (N=14)	52.2	71	NA	NA	0.08	0.004	0.01	0	0	0	0
Total	0.97	0.26	0.012	0.0013	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
P value											
SSC-RA P value	NA	NA	NA	NA	<0.01	<0.01	<0.01	<0.01	<0.01	0.0003	0.0113
SSC-HV P value	NA	NA	NA	NA	<0.01	0.0328	0.0133	0.0662	0.208	0.0642	0.0459

HC-Healthy controls, SSC-scleroderma, SCPD- subcutaneous power Doppler, PD-Power Doppler, GS-gray scale, F-females, NA-not applicable

Conclusion: Joint and tendon inflammation in scleroderma is increased compared to HC but milder then in RA. US detected synovitis more frequently than physical examination in the SSC patients. Since it is sometimes difficult to estimate synovitis on physical examination in SSC patients due to tight skin and contractures, US would be useful in the assessment of synovitis in these patients.

Ref.

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Cardiovascular Involvement In Erdheim-Chester Disease: A Magnetic Resonance Imaging Study On Seven Patients. Enrica Rossi, Lorenzo Buttarelli, Augusto Vaglio, Davide Gianfreda, Chiara Martini and Massimo De Filippo. University of Parma, Parma, Italy

Background/Purpose: Erdheim-Chester Disease (ECD) is a rare non-Langherans form of histiocytosis, characterized by xanthomatous or xanthogranulomatous infiltration of tissues by foamy histiocytes, surrounded by fibrosis. ECD is a multisystemic disease and its clinical course depends mostly on cardiovascular manifestations, that are responsible for poor prognosis and death. In order to assess the cardiovascular extent of the disease, we studied 7 consecutive cases with biopsy-proven ECD by magnetic resonance imaging (MRI).

Methods: The patients underwent cardiac and thoracic aorta MRI. Images were acquired with a 1,5T RM, using T2W with and without fat suppression, long and short axis cine B-TFE and late gadolinium enhancement sequences evaluated by dedicated software.

Results: Four patients (57%) showed abnormal heart imaging. Four patients had myocardium involvement with typical pseudo-mass aspects in the anterior and lateral walls of right atrium. In three cases it extended to the right atrioventricular sulcus, sheathing the right coronary artery; only in one case both coronary arteries were surrounded by periarterial infiltration. None of the cases showed signs of coronary stenosis. One case also presented atrial septal thickening. In three cases imaging studies recognized pericardial effusion; just in one case it was massive (50mm), even if without signs of cardiac tamponade. The pericardium facing the right ventriculum was thickened in two cases.

Imaging showed a mild cardiomegaly in one patient, but no atrial enlargement was detected. In no case we recognized cardiac insufficiency or cardiac signs of systemic hypertension. No patients had valvular defects.

The angiography assessment suggested the presence of periaortic fibrosis with "coated aspect" in two cases. In these, epiaortic vessels were surrounded by irregular, non stenosing fibrosis.

Conclusion: Our study confirms the frequent cardiovascular involvement in ECD. A systematic cardiac and aortic evaluation by MRI would be indicated in patients with ECD.

Disclosure: E. Rossi, None; **L. Buttarelli**, None; **A. Vaglio**, None; **D. Gianfreda**, None; **C. Martini**, None; **M. De Filippo**, None.

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Omeract Definitions For The Sonographic Appearance Of The Normal Pediatric Joint. Johannes Roth[1], Sandrine Jousse-Joulin[2], Silvia Magni-Manzoni[3], Ana Narrodi[4], Nikolay Tzaribachev[5], Annamaria Iagnocco[6], Esperanza Naredo[7], Maria-Antonietta D'Agostino[8] and Paz Collado[9]. [1]University of Ottawa, Ottawa, ON, [2]C.H.U. La Cavale Blanche, Brest, France, [3]Ospedale Pediatrico Bambino Gesù, Rome, Italy, [4]Rheumatology, Madrid, Spain, [5]Center for Rheumatic Diseases, Bad Bramstedt, Germany, [6]University La Sapienza, Rome, Italy, [7]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [8]Ambroise Paré Hospital, and Versailles Saint Quentin en Yvelines University, Boulogne-Billancourt, France, [9]Severo Ochoa University Hospital, Madrid, Spain

Background/Purpose: Musculoskeletal ultrasound (MSUS) has significant potential in the assessment of disease activity and early structural damage in childhood arthritides. In order to assess pathology, the ultrasonographic characteristics of the normal pediatric joint need to be defined first. The aims of this study were to develop definitions for the various components of the pediatric joint that can be evaluated by MSUS through a consensus process and to validate these definitions in their practical application.

Methods: In a first step, members of the pediatric group of the OMERACT Ultrasound Task Force developed definitions of the ultrasonographic appearance for various components of the pediatric joint through a Delphi process. In a second step, standardized scans of the knee and ankle joint were acquired on 4 healthy volunteers aged 12, 10 and 4 years old (2 volunteers) by seven members of the group on the same day. Subsequently, for each of the stored images, the applicability (validity) of each of the definitions was scored by all 7 participants on a 1–5 Likert scale. A minimum of 80 % grade 4 or 5 agreement across all images was required in order to validate the definition.

Results: Five definitions were developed through the Delphi process addressing articular bone, cartilage, joint capsule, the epiphyseal ossification centre and the synovial membrane. A total of 224 images were acquired by the seven participants. 172 of these images were selected for analysis and on each of them the five definitions were rated by all 7 participants. In the first practical application on stored images the minimum of 80 % agreement was not met for either definition. After further modification of the definitions 95%, 81%, 86%, 97% and 91% agreement were reached respectively.

Conclusion: In this study, definitions of the ultrasonographic appearance for the various components of the normal pediatric joint were successfully developed through a Delphi process and validated in a practical exercise. These results represent the essential first step in order to develop definitions for pathology and support the standardization of the ultrasonographic assessment of the pediatric joint. This carries relevant implications in defining the role of MSUS both in routine clinical assessment and as an outcome measure in research.

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Quantitative Image Analysis Of Articular Involvement In Blau Syndrome By Radiographic Calpal Length and Ultrasound Assessment. Tsuyoshi Yamatou[1], Tomohiro Kubota[1], Harumi Akaike[1], Yuichi Yamasaki[1], Yukiko Nonaka[1], Yasuhito Nerome[1], Tomoko Takezaki[1], Hiroyuki Imanaka[1], Kei Ikeda[2], Naotomo Kambe[3], Syuji Takei[1] and Tomokazu Nagakura[4]. [1]Kagoshima University, Kagoshima, Japan, [2]Chiba University Hospital, Chiba, Japan, [3]Chiba University Graduate School of Medicine, Chiba, Japan, [4]House of Meguminoseibo, Usuki, Japan

Background/Purpose: Blau syndrome (Blau) is a rare auto-inflammatory disease, and it has now been shown to be caused by *NOD2/CARD15* gene

mutations. Clinical features of Blau consist of granulomatous inflammation in the joints, eyes, and skin. However, most of the patients were initially miss-diagnosed as JIA because the symmetrical polyarthritis occurred in early phase of the disease, and "boutonniere" deformities-like fingers appeared during the disease course. However, the articular involvement in Blau has been considered as non-erosive. Therefore, we evaluate the joint damage in Blau patients by measuring calpal length (CL), an objective tool for evaluating cartilage damage in polyariticular JIA (poJIA)[1–2].

Methods: A total of 6 Blau patients were followed up their CL for mean 9.2 years. Their disease duration at the first CL measurement was 5.2 years. Since biologic agents were used in 5 of 6 of the Blau patients, changes in CL of 46 poJIA patients treated with biologics were also followed up. CL was analyzed by standard deviation (SD) calculated by Poznanski's formula established from healthy children[3)].

In addition, ultrasound examination was carried out in 4 Blau patients at the last observation. A total of 3 joints and 4 tenosynovial sites in the wrist were scanned and the ultrasound images of gray-scale (GS) or Power Doppler (PD) findings were graded from 0 (normal) to 3 (severe).

Results: Though all Blau patients had comptodactyly with "boutonniere" deformities like fingers, CL(SD) maintained normal range (within −2SD to +2SD) during the observation period regardless of biologic therapy (Figure 1). On the contrary, CL(SD) in poJIA decreased with disease course especially before initiating biologic therapy, and there were negative correlation between the CL(SD) and the disease duration in both RF positive (p=0.0018) and RF negative (p=0.008) poJIA patients.

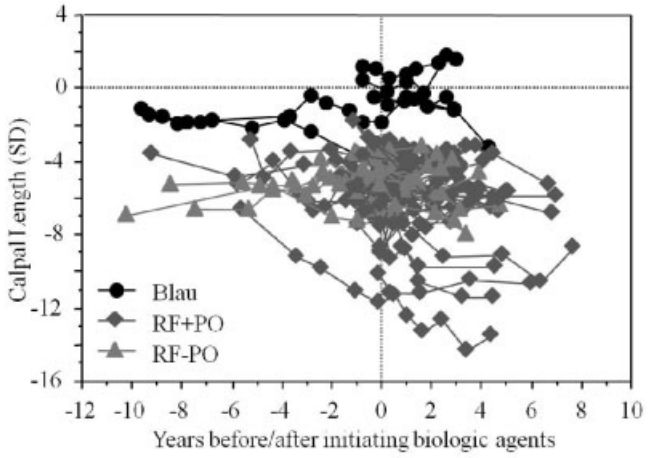

Figure 1: Changes in calpal length (SD) during treatment period
Blau: Blau syndrome, RF−PoJIA:RF positive polyarticular JIA

Ultrasound examination revealed that tenosynovitis was more frequent and severe than intra-articular synovitis in the 8 wrists of 4 Blau patients; Grade 1–3 findings were found in 62.5% by PD and 31.2% by GS in scanned tenosynovium sites, while it was 29.2% by PD and 4.2% by GS in intra-articular synovium sites (tendon vs intra-articular sites: p=0.0169 by PD, p=0.0161 by GS).

Conclusion: Comptodactyly with "boutonniere" deformities-like findings, a characteristic feature of Blau, may be caused by tenosynovitis but not by cartilage destruction in finger joints. The finding indicates the usefulness of CL and ultrasound examination in differentiating Blau from JIA, and is also suggestive that tenosynovitis may be more predominant than intra-articular synovitis in Blau syndrome.

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The Composition and Structure Of Calcifications In Juvenile Dermatomyositis Differs From Calcified Aortic Valves Removed From Adults Without JDM. Lauren M. Pachman[1], Gabrielle A. Morgan[1], Patrick M. McCarthy[2], Anna Huskin[2], S. Chris Malaisrie[2], Lyudmila Spevak[3], Stephen Doty[3] and Adele Boskey[3]. [1]Ann & Robert H. Lurie Children's Hospital of Chicago Research Center, Chicago, IL, [2]Northwestern University Feinberg School of Medicine Bluhm Cardiovascular Institute, Chicago, IL, [3]Hospital for Special Surgery, New York, NY

Background/Purpose: Juvenile Dermatomyositis (JDM) is a systemic vasculopathy, primarily involving the micro vasculature. Soft tissue calcification occurs in 15–30% of cases, and is associated with increased morbidity and mortality. The calcifications develop in conjunction with chronic inflammation, and are often located at pressure points of daily trauma (elbows, buttocks, hands). In contrast, calcifications of aortic heart valves in non-JDM patients are more common and are associated with interrelated factors such as hypertension, hyperlipidemia, obesity, smoking and diabetes. The purpose of this investigation was to compare the composition and structure of the calcific deposits obtained from children with JDM with those in removed aortic valves.

Methods: Five children (2 boys, 3 girls) previously reported (Arthritis Rheum 54:10 2006, 3345–3350) with definite JDM, had a mean age of JDM onset, 3.3 years ± 1.9 years. They had sustained persistent cutaneous inflammation for 81.3 ± 58.7 months, and donated calcium deposits, after obtaining informed consent. The calcifications, removed by surgery, were a focus of constant pain and contributed to decreased range of motion. Fresh, calcified aortic heart valves were obtained at cardiovascular surgery, after obtaining informed consent, from 5 White adult donors without JDM (age range 43–85, mean age= 69.2 years), two were women, with severe aortic stenosis. Four of the donors were hypertensive, one had diabetes and one smoked. Fourier transform infrared radiography images (FTIRI) were obtained of the calcifications, which had been fixed in 90% ethanol, embedded in polymethyl methacrylate (PMMA) and sectioned. Transmission Electron Microscopy was performed.

Results: In JDM, electron microscopy documented extensive macrophage and giant cell infiltration; the mineral definitely formed crystals, even within the cytoplasm of the affected cells, whereas in plaque the calcium appeared to be associated with large lipid deposits were not crystalline (verified by EDAX microanalysis).

Average FTIRI Parameters for the 5 Calcified Aortic Valves

	Min/Mat	CO3/min	XLR	XST
Mean	12	0.0104	4.20	1.10
SD	1.7	0.0013	0.90	0.05
Average FTIRI Parameters for the 5 JDM Deposits				
Mean	25	0.014	5.0	1.12
SD	14	0.013	1.8	0.06
Average FTIRI Parameters for 2 Pediatric Iliac Crest Biopsies Cortical Bone				
Mean	4.57	0.0065	3.17	1.25
SD	0.64	0.0004	0.02	0.02
Average FTIRI Parameters for 2 Pediatric Iliac Crest Biopsies Cancellous Bone				
Mean	4.53	0.0065	3.18	1.20
SD	0.20	0.0003	0.08	0.001

On FTIRI, the mineral/matrix ratio of the calcified aortic valves was greater than in human cortical or cancellous bone, but less than those in JDM deposits; JDM calcifications were much more punctate. The ratios of carbonate to phosphate and the carbonate/matrix ratios were not different from those of bone, nor were the values for collagen maturity and crystallinity. In JDM calcifications, but not calcified aortic valves, intracellular crystals were present.

Conclusion: The composition and structure of calcifications occurring in aortic valves differ from those that develop in the soft tissue of children with JDM, suggesting that the deposition mechanism differs as well.

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Positron Emission Tomography Assessment Of Children With Systemic-Onset Juvenile Idiopathic Arthritis. Taichi Kanetaka, Tomo Nozawa, Kenichi Nishimura, Masako Kikuchi, Tomomi Sato, Nodoka Sakurai, Ryoki Hara, Kazuko Yamazaki and Shumpei Yokota. Yokohama City University School of Medicine, Yokohama, Japan

Background/Purpose: Systemic-onset juvenile idiopathic arthritis (s-JIA) is a systemic inflammatory disorder manifesting spiking fever, rheumatoid rash, and arthritis. The onset is nonspecific, and may be triggered by infectious agents. A body of evidence indicates involvement of cells and inflammatory cytokines produced in innate immune response in the induction phase of the disease, and then augmented in an auto-inflammatory fashion, suggesting that s-JIA may be one of the auto-inflammatory diseases. However, the causative agents and the responsible organs for exaggerated innate immune responses are still to be elucidated. The ^{18}F-FDG-Positron Emission Tomography (PET) is a hybrid imaging technique displaying the sites of high metabolic turnover of both physiologic and pathologic origin and visualizes infection focus and inflammatory lesions as well as malignancy. Application of ^{18}F-FDG-PET to patients with s-JIA will possibly localize inflammatory lesions of this disease.

To examine and delineate inflammatory focus in patients with s-JIA, ^{18}F-FDG-PET was applied to patients with s-JIA and polyarticular (p)-JIA, and the images of these patients were compared.

Methods: Sixty eight children (57 with s-JIA and 11 with p-JIA) were included in this study who needed the diagnosis work-up of fever-of-unknown origin. The diagnosis of s-JIA and p-JIA was done to meet the ILAR criteria (2004). After fasting for at least 6 hours, whole body PET-scans were acquired 60 minutes after intravenous injection of 3–5 MBq/kg ^{18}F-FDG. The interpretation of ^{18}F-FDG uptake was based on visual characteristics.

Results: ^{18}F-FDG uptake in shoulder joint areas was found in 42 out of 57 patients with s-JIA (74%) and in 5 out of 11 patients with p-JIA (45%). ^{18}F-FDG uptake in knee joint areas was demonstrated in 19 patients with s-JIA (33%) and 7 patients with p-JIA (64%). Although in patients with s-JIA ^{18}F-FDG uptake was found in shoulder areas, physical examination failed to reveal inflammatory symptoms/signs around shoulders. Additionally, two types of PET images were outstanding in s-JIA; one was ^{18}F-FDG uptake in red bone marrow such as the spine, femur heads, and pelvis as well as spleen (11 cases), and other type was the uptake in the major joints such as hips, elbows, wrists, knees, and ankles (7 cases). The former findings were correlated with elevated levels of inflammatory markers (WBC, ESR, and ferritin) while the latter were with significantly increased levels of MMP-3 ($P<0.05$).

Conclusion: There was a noticeable accumulation of ^{18}F-FDG uptake in bone marrow of s-JIA patients which may indicate the inflammatory focus of this disease and play an important role in the pathogenic basis of arthritides and systemic inflammation of s-JIA.

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An Examination Of Shoulder Pain Using Magnetic Resonance Imaging In Older People. Tiffany K. Gill[1], E. Michael Shanahan[2], Dale Allison[3], Daniel Alcorn[3] and Catherine L. Hill[4]. [1]University of Adelaide, Adelaide, South Australia, Australia, [2]Flinders University, Bedford Park, South Australia, Australia, [3]Bensons Radiology, Adelaide, Australia, [4]The Queen Elizabeth Hospital, Woodville, Australia

Background/Purpose: Shoulder pain is a common problem in the general population and can cause significant difficulties with activities of daily living. Magnetic resonance imaging (MRI) is often used in the assessment of shoulder pain. This pilot study aimed to determine if the pathology demonstrated on shoulder MRI correlates with the pain reported by study participants.

Methods: Participants for this pilot study were obtained from the North West Adelaide Study (NWAHS), a longitudinal cohort study of 4056 randomly selected adults aged 18 years and over at the time of recruitment from the northern and western regions of Adelaide, Australia. Thirty participants aged 55 to 74 years were recruited from the cohort and allocated to one of three groups, those with no shoulder pain in Stage 2 and 3 of the NWAHS, those with pain in Stage 2 but not Stage 3 and those with pain in Stage 2 and Stage 3. Range of movement was assessed and the Shoulder Pain and Disability Index (SPADI) completed. An MRI and X-ray were undertaken of the affected or previously affected shoulder, or matched side (in those with no current or previous shoulder pain). The X-rays and MRIs were read independently by two radiologists blinded to the participant group and each other. All participants provided written informed consent.

Results: Overall, 30 participants took part in the study. The mean range of flexion, abduction and external rotation were all lower for the pain group compared to the other two groups. The mean SPADI percentage score for the pain group was 41.80 (SD 20.10, range 18–74) and the mean percentage function score was 31.88 (SD 20.41, range 8.75–60). On X-ray there were few differences between each group. The MRI findings are presented in Table 1. Subacromial bursitis was common (90%) in each group, 90% of participants also demonstrated a degree of acromioclavicular degeneration. There was a slightly higher number of supraspinatus tendinosis/tears and involvement of the LHB in the current pain group.

Table 1. MRI findings

	No shoulder pain		Previous shoulder pain		Current shoulder pain	
	n	%	n	%	n	%
Supraspinatus						
Normal/Equivocal	3	30.0	3	30.0	-	-
Tendinosis	1	10.0	2	20.0	2	20.0
Partial thickness tear with/without tendinosis	4	40.0	3	30.0	6	60.0
Full thickness tear with/without tendinosis	2	20.0	2	20.0	2	20.0
Infraspinatus						
Normal/Equivocal	7	70.0	4	40.0	7	70.0
Tendinosis	3	30.0	5	50.0	1	10.0
Partial thickness tear with/without tendinosis	-	-	1	10.0	2	20.0
Subscapularis						
Normal/Equivocal	4	40.0	3	30.0	5	50.0
Tendinosis	2	20.0	5	50.0	1	10.0
Partial thickness tear with/without tendinosis	4	40.0	2	20.0	4	40.0
Teres Minor						
Normal/Equivocal	10	100.0	10	100.0	10	100.0
Long head of biceps						
Normal/Equivocal	8	80.0	6	60.0	2	20.0
Tendinosis	1	10.0	3	30.0	3	30.0
Partial thickness tear with/without tendinosis	1	10.0	1	10.0	4	40.0
Full thickness tear	-	-	-	-	1	10.0
GHJ cartilage degeneration						
Normal/Equivocal	2	20.0	3	30.0	4	40.0
Mild	8	80.0	7	70.0	5	50.0
Moderate	-	-	-	-	1	10.0

Conclusion: Shoulder pathology is present on imaging in people with shoulder pain, those who have a history of shoulder pain, and those who have never had shoulder pain. Clinical symptoms do not necessarily match the radiological findings. The value of MRI as a clinically useful diagnostic investigation for shoulder pain is questionable.

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Variable Imaging Characteristics Identified By Point-Of-Care Ultrasound For Greater Trochanteric Pain Syndrome. Minna J. Kohler[1], Naina Rastalsky[1] and Liana Fraenkel[2]. [1]Massachusetts General Hospital/Harvard Medical School, Boston, MA, [2]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare System, New Haven, CT

Background/Purpose: Greater trochanteric pain syndrome (GTPS) is a common cause of musculoskeletal pain that has been typically attributed to trochanteric bursitis. It encompasses a spectrum of disorders [gluteal tendinopathy, tears, bursitis, and iliotibial band (ITB) syndrome] that are difficult to distinguish by clinical exam alone. Few modalities for the treatment of GTPS exist and are recommended without consideration of the structural etiology of pain. Better understanding of ultrasound (US) imaging characteristics in relation to clinical symptoms may be helpful in identifying those patients who would most benefit from the various treatment options available.

Methods: A prospective, observational, descriptive study was performed to describe the soft tissue and bony structural US findings identified in the lateral hip in patients presenting with GTPS to a dedicated outpatient rheumatology musculoskeletal US clinic. US imaging was obtained using a standardized protocol by 2 US-trained rheumatologists (NR, MK). Eligible subjects included ages 18 and above with lateral hip pain thought to be due to GTPS with pain for at least 1 week and a pain score of at least 2 out of 10 on an 11-point numeric rating scale at rest or with activity. For subjects with bilateral GTPS, the most symptomatic hip was considered the study hip. Most important ineligibility criteria included Body Mass Index (BMI) >40, groin pain, and symptomatic osteoarthritis of the hip. All US images were reviewed by both doctors for consensus of image interpretation.

Results: 74 eligible subjects were identified ranging in age from 25–85, with a mean BMI of 28 (±4.77); 62 (84.0%) were female. Forty-five (60.8%) had concomitant low back pain and 11 (14.9%) had chronic widespread pain. The mean duration of symptoms was 18 (±23.0) weeks. The mean level of pain at rest and activity were 4.8 (±2.87) and 6.7 (±2.36) respectively. Twenty-five (35.0%) had a prior episode of lateral hip pain. The most common location of bursal fluid was the subgluteus maximus bursa. Frequency and percentage of various imaging characteristics are summarized in the Table.

US Imaging Characteristics	N (%)
Bony changes (Grade 0)	42 (56.8)
Bony changes (Grade 1)	18 (24.3)
Bony changes (Grade 2)	13 (17.6)
Bony changes (Grade 3)	1 (1.4)
Bursal fluid collections	34 (46.0)
Calcifications of gluteus medius	29 (39.2)
Calcifications of gluteus minimus	7 (9.5)
Calcifications in other locations	4 (5.4)
Enthesophytes in gluteus medius	7 (9.5)
Enthesophytes in gluteus minimus	1 (1.4)
Gluteus medius tendinopathy	57 (77.0)
Gluteus medius partial thickness tear	11 (14.9)
Gluteus medius full thickness tear	1 (1.4)
Gluteus minimus tendinopathy	10 (13.5)
Gluteus minimus partial thickness tear	3 (4.1)
Gluteus minimus full thickness tear	0 (0.0)
Tensor fascia latae abnormality (tendinopathy, tear, fluid)	14 (18.9)
Distal ITB tendinopathy	6 (8.1)
Distal ITB peritendinous fluid	3 (4.1)

Conclusion: GTPS is commonly attributed to trochanteric bursitis, but only 46% of the subjects had US evidence of true bursitis. The addition of US evaluation to the clinical assessment of GTPS increase may diagnostic accuracy and improve medical decision making.

Disclosure: M. J. Kohler, None; **N. Rastalsky**, None; **L. Fraenkel**, None.

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Can Musculoskeletal Ultrasonography Examination (MSUS) Predict Outcome In Shoulder Impingement Syndrome (SIS)? A Prospective Blinded Study. Mumtaz Khan[1], Karen McCreesh[2], Aamir Saeed[1], Tomas Ahern[3] and Alexander D. Fraser[4]. [1]Limerick University Hospital, Limerick, Ireland, [2]University of Limerick, Limerick, Ireland, [3]St. Vincent's University Hospital, Dublin, Ireland, [4]Limerick Univeristy Hospital, Limerick, Ireland

Background/Purpose: Steroid injection and active physiotherapy are the two standard conservative therapies used to treat SIS and the outcome from these two treatments varies depending on numerous prognostic factors. Outcome predictors may identify patients suitable for specific therapies.The role of MSUS in the diagnosis of rotator cuff disease is well documented, however its utility in determining prognosis and selecting treatment pathways has not been yet assessed. This prospective investigation was designed to assess the utility of MSUS in determining which patients may respond to guided steroid injection or active physiotherapy in SIS.

Methods: Twenty consecutive patients with a new diagnosis of isolated SIS (symptoms duration less than 6 months) underwent MSUS. Participants chose to receive either ultrasound guided steroid injection or active physiotherapy. Participants were assessed at baseline, 6 weeks and 12 weeks. Assessments included shoulder pain and disability index (SPADI) and clinical assessment by an independent (blinded) rheumatologist. This clinical assessment included determination of the physician global assessment (PGA), the presence of Hawkins sign and the presence of supraspinatus tendon (SST) tenderness. Data are expressed as median (interquartile range) or as number (percentage).

Results: At baseline and at 12 weeks there were no significant differences in assessed parameters. 12 (60%) of the cohort had an abnormal initial MSUS: of these 5 (42%) received a steroid injection and 7 (58%) received active physiotherapy. After six weeks those who received a steroid injection had significantly different clinical parameter measurements than those receiving active physiotherapy:

- decrease in PGA was 80% (61–88%) vs 38% (30–43%, p=0.003);
- decrease in SPADI was 85% (37–90%) vs 14% (10–23%, p=0.01);
- resolution of SST tenderness occurred in 5 (100%) vs 0 (0%, p=0.003); and
- resolution of Hawkins sign occurred in 4 (100%) vs 1 (14%, p=0.006).

10 (50%) of the cohort received a steroid injection: of these 5 (50%) received had an abnormal MSUS. After six weeks those with an abnormal MSUS had significantly different clinical parameters measurements than those with a normal MSUS:

- decrease in PGA was 80% (61–88%) vs 20% (20–35%, p=0.008);
- decrease in SPADI was 85% (37–90%) vs 19% (10–63%, p=0.05);
- resolution of SST tenderness occurred in 5 (100%) vs 0 (0%, p=0.002); and
- resolution of Hawkins sign occurred in 4 (100%) vs 0 (0%, p=0.002).

Resolution of SST tenderness and Hawkins sign remained significantly different at 12 weeks.

Conclusion: The presence of a significant structural abnormality at baseline MSUS suggests that outcome, in the short term at least, may be superior when patients receive a guided injection rather than physiotherapy. And conversely a normal baseline scan may indicate that physiotherapy is the preferred option. Adequately powered randomized clinical trials are required to determine whether treatment decision-making based on MSUS findings is superior to standard management without use of MSUS.

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Ultrasonographic Evaluation Of Patellar Cartilage and Triangular Fibrocartilage In Patients With Familial Benign Hypercalcemia. Alberto Batticciotto[1], Diana Certan[2], Valentina Varisco[1], Marco Antivalle[1], Fabiola Atzeni[1], Maurizio Bevilacqua[2] and Piercarlo Sarzi-Puttini[1]. [1]Rheumatology Unit, L. Sacco University Hospital, Milan, Italy, [2]Endocrinology Unit, L. Sacco University Hospital, Milan, Italy

Background/Purpose: Familial benign hypercalcemia (FBH) is a rare autosomal dominant disease that is caused by a mutation in calcium sensing receptor (CaSR) genes and characterised by hypercalcemia and hypocalciuria with normal serum parathormone levels. The typical clinical symptoms are fatigue, weakness and polydipsia, but rare cases may be associated with chondrocalcinosis, pancreatitis and gallstones. One sensitive and specific means of diagnosis is an oral calcium and peptone load test.

The aim of this study was to evaluate the presence of calcium deposits in patellar cartilage and triangular fibrocartilage levels in FBH patients using the same ultrasonographic guidelines as those proposed for patients with gout and chondrocalcinosis.

Methods: Twenty-three patients with FBH (2 M, 21F; mean age 69 yrs, range 51–85; mean serum ionised calcium level 1.33 mmol/L, range 1.2–1.5) and 22 controls (1 M, 20 F; mean age 68 yrs, range 45–89; mean serum ionised calcium level 1.1 mmol/L, range 1.1–1.3), with normal serum ionised calcium levels who had negative oral calcium and peptone load test results, were evaluated be means of patellar cartilage and triangular fibrocartilage ultrasonography (ESAOTE My Lab 70, linear probe 13–18 MHz).

Results: The two groups were statistically similar in terms of age (p=0.709), serum parathormone levels (p=0.548), serum vitamin D levels (p=0.508) and calciuria levels (p=0.194), but different in terms of serum ionised calcium levels (p<0.001). Ultrasonography revealed microcrystalline deposits in at least one cartilage in 16/23 (69.6%) FBH patients and in 8/22 (36,4%) controls with a statistically significant difference (p=0.026).

Conclusion: Patients with hypercalcemia due to FBH have a higher prevalence of ultrasonographically detectable microcrystalline deposits in patellar cartilage and triangular fibrocartilage than normocalcemic controls.

	FBH	Control Group	P
Age (yrs)	69 (range 51–85)	68 (range 45–89)	0.709
Parathormone (pg/ml)	49,1 ± 11,4	46,67 ± 13,67	0.548
Ionised Calcium (mmol/L)	1.33 ± 0.6	1.18 ± 0.5	0.001
Vitamine D (ng/ml)	37.3 ± 13.6	40±13.9	0.508
Calciuria /24h (mg/dl)	216 ± 120.8	170 ± 88.3	0.194

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The Power Doppler Modalities Of 5 Ultrasound Machines Perform Very Differently, Ascertained By a Microvessel Flow Phantom. David F. Ten Cate, Jolanda J. Luime, Myrthe van der Ven, Johanna M.W. Hazes, Klazina Kooiman, Nico De Jong and Johannes G. Bosch. Erasmus University Medical Center, Rotterdam, Netherlands

Background/Purpose: In many patients with rheumatoid arthritis (RA) subclinical disease activity can be detected with ultrasound (US), especially using power Doppler US (PDUS).[1–3] However, in our experience, PDUS is highly dependent on type of machine. This is a problem when conducting multicentre trials or in clinical practice. US machines should be able to detect the blood flow velocities in capillaries as low as 0.5 mm/s. [4–5] The objective of the study was to determine the lowest detectable flow by PDUS of 5 different US machines using microvessel flow phantom.

Methods: The flow phantom, consisted of an acrylic (PMMA) container filled with tissue mimicking material(TMM)[6], with 3 microvessels (150, 1000, 2000 micron). The blood mimicking fluid was based on the recipe by Ramnarine.[7] A syringe pump generated the flows. We tested the Aloka α7, Esaote MyLab60, Philips iU22, Ultrasonix SonixTouch, and VisualSonics Vevo2100. Settings were optimised to detect the lowest flows by adjusting pulse repetition frequency, velocity range, wall filters, frequency and gain. Lowest possible flow was defined as a continuous PDUS signal. Flow velocities were calculated from pump flow setting and microvessel diameter.

Results:

Table 1. Lowest detected flow velocity (mm/s), still resulting in a continuous positive PDUS signal; N.D. = none detected.

	Flow velocity		
Vessel size (micron)	**2000**	**1000**	**150**
Machine (probe)			
Aloka α7(UST-5411)	4	2.2	11.1
Esaote MyLab 60 (LA 435)	<0.05	0.06	0.11
Philips iU22 (L9-3)	1	0.56	1.68
Ultrasonix SonixTouch (L14-5/38)	1	0.56	N.D.
Visual Sonics Vevo2100 (MS200)	0.5	0.33	N.D.

Conclusion: The performance of the PDUS modality of 5 US machines for detecting very low flows in small vessels was very different, when tested on a microvessel flow phantom. The large differences found between the machines are partly explained by different lower limits of PRF and wall filter, but also by fundamental differences in processing of the PD signal or internal settings inaccessible to users. In the 150 micron vessel, minimal detectable velocity is higher because of sensitivity issues. The actual flow velocity in the 1000 micron vessel was probably slightly higher than calculated and similar to that in the 2000 micron vessel. A reason for this could be compression by the TMM and a more parabolic flow velocity profile in the 1000 micron vessel, with a relatively high peak flow, as compared to the 2000 micron vessel. Caution should be exercised when conducting a multi-machine trial or when making treatment decisions based on PDUS. Based on the results of our study it would be advisable to standardise and validate US machines both for rheumatological clinical practice and for clinical trials. Our flow phantom could be used for this purpose.

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Meniscal Extrusion Is a Better Predictor Of Radiographic Osteoarthritis Change Over Ten Years Compared To Cartilage Volume Loss. Louisa Chou[1], Hussain Ijaz Khan[1], Andrew McBride[1], Dawn Aitken[1], Changhai Ding[1], Leigh Blizzard[1], Jean-Pierre Pelletier[2], Johanne Martel-Pelletier[2], Flavia Cicuttini[3] and Graeme Jones[1]. [1]Menzies Research Institute Tasmania, University of Tasmania, Hobart, 7000, Australia, [2]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [3]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, 3004, Australia

Background/Purpose: Change in joint space narrowing (JSN) on radiographs is currently the gold standard for monitoring disease progression of knee osteoarthritis in clinical trials and is considered a surrogate marker for cartilage volume. However, this method can be unreliable due to high measurement error and it is insensitive to early change. Furthermore, cross-sectional studies have shown that JSN not only reflects hyaline articular cartilage but also meniscal pathology. Therefore, the aim of this study was to quantitate the correlation between changes in meniscal extrusion and cartilage volume loss over two years and radiographic osteoarthritis (ROA) change over ten years.

Methods: A sample of 220 subjects (mean age 45 years at baseline; age range 26–61 years) was evaluated at baseline, two, and ten years. Approximately half were adult offspring of subjects who had a knee replacement performed for knee osteoarthritis and the remaining were randomly selected controls that were initially matched by age and sex. Knee cartilage volume and meniscal extrusion were determined using T1-weighted fat-suppression MRI techniques at baseline and two years. ROA, JSN, and osteophytes were scored using fixed flexion radiographs at baseline and ten year using standard protocols. Spearman-ranked correlation analysis was used to analyse the correlation between changes in medial meniscal extrusion (MME) and medial tibial cartilage (MTC) loss with changes in ROA, JSN, and osteophytes. All were adjusted for age, sex and BMI.

Results: The mean MTC volume was 2234mm^3 at baseline with a 2.5% loss per annum over two years. At baseline, 8% of participants had any medial meniscal extrusion and 3% had an incident meniscal extrusion over two years. An increase in MME over two years predicted a change in ROA over ten years in adjusted analysis (r=0.22, p=0.003), an increase in medial JSN (r=0.30, p=<0.001) and an increase in medial osteophytes (r=0.15, p=0.046) [Fig 1]. However, a change in MTC over two years did not correlate with a change in ROA over ten years (r=−0.12, p=0.096) or a change in medial JSN (r=−0.10, p=0.182) and weakly with change in medial osteophytes (r=−0.14, p=0.045) [Fig 1].

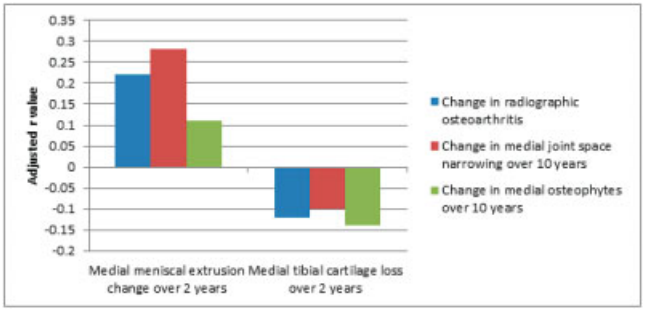

Figure 1. Correlation between changes in medial meniscal extrusion and medial tibial cartilage loss over two years with radiographic changes over ten years

Conclusion: In a midlife cohort at higher risk of osteoarthritis, a change in MME, despite being quite rare, is more strongly correlated with subsequent change in ROA than cartilage volume loss. These findings suggest ROA is a composite measure of joint pathology and does not primarily or sufficiently reflect cartilage loss.

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Hip Bone Marrow Lesions In Asymptomatic and Osteoarthritic Adults: Prevalence, Risk Factors and Significance. L Dawson[1], Yuanyuan Wang[1], Anita Wluka[1], Kim Bennell[2], Andrew Teichtahl[1] and Flavia Cicuttini[3]. [1]Monash University, Melbourne, Australia, [2]University of Melbourne, Melbourne, Australia, [3]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, 3004, Australia

Background/Purpose: Bone marrow lesions (BMLs) at the knee have an important role in the pathogenesis of osteoarthritis (OA), being associated with increased pain, accelerated cartilage loss, and increased risk of total knee replacement. However, data is limited for the role of BMLs at the hip. The aim of this study was to determine the prevalence and associations of BMLs at the hip in an asymptomatic and an osteoarthritic population.

Methods: 142 asymptomatic and 19 participants with hip OA were recruited from existing cohorts. Hip magnetic resonance imaging was performed and used to assess femoral head BMLs, cartilage volume and bone area.

Results: The demographic characteristics of the asymptomatic versus the OA population were as follows: age 66.8 +/− 7.4 vs. 59.5 +/− 7.6 years ($p<0.001$), female 55.6% vs. 57.9% ($p=0.85$), body mass index 27.6 +/− 4.8 vs. 27.2.+/−.4.8 kg/m2. ($p=0.73$). The prevalence of BMLs was 17.6% in the asymptomatic population and 63.2% in the OA population ($p<0.001$). BMLs were strongly associated with OA after adjusting for age, gender and body mass index (odds ratio 5.32, 95% CI 1.78, 15.9, $p=0.003$). BMLs were associated with lower femoral head cartilage volume in the whole population (regression coefficient −245.7 mm3, 95% CI −455.5, −36.0, $p=0.02$). In the OA population, BMLs were also associated with lower femoral head cartilage volume (regression coefficient −426.6 mm3, 95% CI −855.2, 2.14, $p=0.05$) after adjusting for age, gender, body mass index, femoral head bone area and hip OA (for analysis of the total population).

Conclusion: Femoral head BMLs are common in those with OA, but are also present in asymptomatic individuals with no clinical hip OA. They are associated with reduced hip cartilage volume. These findings suggest that BMLs at the hip may provide a novel target for the treatment and prevention of hip OA.

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The Association Of Radiographic Disease With Lesions On MRI In Lateral Compartment Knee Osteoarthritis: The Osteoathritis Initiative. Barton L. Wise[1], Jingbo Niu[2], Felix Liu[3], John A. Lynch[4], Yuqing Zhang[2], Ali Guermazi[5], David T. Felson[2], C. Kent Kwoh[6] and Nancy E. Lane[1]. [1]UC Davis School of Medicine, Sacramento, CA, [2]Boston University School of Medicine, Boston, MA, [3]University of California at San Francisco, San Francisco, CA, [4]University of California-San Francisco, San Francisco, CA, [5]Boston University, Boston, MA, [6]University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Lateral compartment knee tibio-femoral radiographic osteoarthritis (ROA) is associated with pain and disability, and the epidemiology of this form of knee OA is not well known. We examined MRI abnormalities and their association with lateral compartment ROA.

Methods: We analyzed knees from participants in the Osteoarthritis Initiative (OAI), an NIH-funded study of persons aged 45–79 at baseline with, or at high risk of knee ROA. Baseline radiographs with central readings and MRIs were used to assess knee structure lesions. We defined cases as knees with Kellgren/Lawrence (K/L) grade >=2 and with joint space narrowing (JSN) >0 in the lateral compartment but JSN = 0 in the medial compartment; controls were defined as having K/L=0 and JSN=0 in all compartments. Cases and controls were matched by sex and age in 10-year bands. MRI readings for cases and controls were obtained from two ancillary studies in the OAI and further MRI readings were generated for this analysis. MRIs were scored at each subregion for cartilage lesions, bone marrow lesions, and meniscal tear or extrusion using the MOAKS scoring system. The score for each lesion was dichotomized into "any" or "none". Lesions in medial and lateral compartments were defined separately for whether any of the subregions in each compartment exhibited that lesion. We compared cases and controls for each structural lesion separately in both lateral and medial compartments using conditional logistic regression, adjusting for age, race, body mass index (BMI), and clinic site.

Results: Included in this analyses were 200 cases (mean age: 63.8, 34.5% men, mean BMI 29.5, and 76.5% white) and 200 controls (mean age: 63.1, 34.5% men, mean BMI 27.1, and 87.5% white). Isolated lateral compartment ROA was strongly associated with lateral compartment cartilage lesions (odds ratio (OR)=89.9, 95%CI 29.7–271.9), BMLs (OR=40.0, 95% CI: 21.1–75.7) and meniscal tear or extrusion (OR= 93.8, 95% CI 43.5–202.3). Medial compartment cartilage lesions, BMLs and meniscal abnormalities were also associated with isolated lateral compartment ROA; the magnitude of association, however, was much smaller. (See table)

		Medial TF Compartment MRI damage n/N (%)		Adjusted Model for Medial Compartment		Lateral TF Compartment MRI damage n/N (%)		Adjusted Model for Lateral Compartment	
Exposure	Level	among control knees	among case knees	OR (95% CI)	p-value	among control knees	among case knees	OR (95% CI)	p-value
BML>0 in any subregion	Lesion	24/200 (12%)	63/200 (31.5%)	3.44 (1.99, 5.94)	<.0001	21/200 (10.5%)	158/200 (79%)	39.96 (21.11, 75.65)	<.0001
	No Lesion	176/200 (88%)	137/200 (68.5%)	1		179/200 (89.5%)	42/200 (21%)	1	
Cartilage lesion area>0 in any subregion	Lesion	72/200 (36%)	122/200 (61%)	2.48 (1.63, 3.79)	<.0001	89/200 (44.5%)	196/200 (98%)	89.85 (29.69, 271.90)	<.0001
	No Lesion	128/200 (64%)	78/200 (39%)	1		111/200 (55.5%)	4/200 (2%)	1	
Meniscal tear or extrusion	Lesion	55/200 (27.5%)	82/200 (41%)	1.85 (1.19, 2.89)	0.0066	28/200 (14%)	183/200 (91.5%)	93.77 (43.46, 202.32)	<.0001
	No Lesion	145/200 (72.5%)	118/200 (59%)	1		172/200 (86%)	17/200 (8.5%)	1	

Conclusion: Knees with isolated radiographic OA in the lateral compartment have more MRI abnormalities of cartilage, meniscus and BMLs in the lateral compartment than knees without radiographic OA. Isolated lateral compartment ROA is also associated with medial compartment MRI lesions, but less strongly.

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Structural Predictors Of Ten Year Knee Cartilage Volume Loss. Dawn Aitken[1], Hussain Ijaz Khan[1], Changhai Ding[1], Leigh Blizzard[1], Jean-Pierre Pelletier[2], Johanne Martel-Pelletier[2], Flavia Cicuttini[3] and Graeme Jones[1]. [1]Menzies Research Institute Tasmania, University of Tasmania, Hobart, 7000, Australia, [2]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [3]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, 3004, Australia

Background/Purpose: Cartilage volume loss is considered a key feature of knee osteoarthritis (OA) and increased loss over two years is associated with future knee replacement surgery. Previous studies have identified structural predictors of cartilage loss over 2–3 years including baseline cartilage volume, cartilage defects, bone marrow lesions (BMLs), meniscal pathology and bone area. These are now considered important risk factors for osteoarthritis progression. However no study has examined whether these features predict loss over longer timeframes. The aim of this study was to examine structural predictors of cartilage volume loss over ten years.

Methods: 220 participants [mean age 45 (26–61); 57% female] were studied at baseline, two, and ten years. Approximately half were adult offspring of subjects who had a knee replacement performed for knee OA and the remaining were randomly selected controls that were initially matched by age and sex. Cartilage volume (tibial, patella), cartilage defects (tibial, femoral), BMLs (tibial, femoral, patella), meniscal extrusion (medial, lateral) and bone area (tibial) were measured using MRI. Predictors of ten year cartilage loss were examined using linear regression and all models were adjusted for age, sex, BMI, and offspring-control status. Interactions between offspring-control status and knee structures on cartilage loss were explored.

Results: Cartilage change over ten years was −2.5% per annum (pa), −1.1% pa, and −2.1% pa for the medial and lateral tibial and patella sites respectively.

BMLs predicted tibial ($\beta = -433$ mm^3 per 1 unit increase in BML size, $P < 0.01$) but not patella cartilage loss. Meniscal extrusion predicted lateral tibial cartilage loss ($\beta = -872$ mm^3 in those with a baseline extrusion versus those without, $P < 0.01$) but not medial tibial or patella cartilage loss. Cartilage volume at baseline predicted tibial and patella ten year cartilage loss ($\beta = -0.26$ to -0.41 mm^3 per unit increase in baseline volume, $P< 0.01$).

There was interaction between offspring-control status for cartilage defects. Baseline defect score predicted lateral tibial cartilage loss in offspring (B= −242 mm^3 per unit increase in defect score, $P < 0.01$); but, surprisingly defects appeared to be protective against medial and lateral tibial cartilage loss in controls ($\beta = 276$ to 327 mm^3 per unit increase in defect score, $P<0.01$).

Both change in cartilage volume (r = −0.58 to −0.62, all $P < 0.01$) and progression of cartilage defects (r = −0.18 to −0.58, all $P < 0.01$) over two years predicted ten year tibial cartilage loss.

Bone area did not predict ten year change in cartilage.

Conclusion: Structural features which have been identified as risk factors for cartilage loss over 2–3 years appear to predict long-term cartilage changes with the most consistent data for BMLs. This was seen in a largely pre-radiographic cohort and indicates that bone marrow lesions, presence of meniscal extrusion; and to a lesser extent, cartilage volume and cartilage defects, may be used to identify individuals who will lose the most cartilage long-term. Additionally this study demonstrates that cartilage loss and cartilage defect progression over two years are reasonable predictors of long-term cartilage changes.

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A Family History Of Knee Joint Replacement Increases The Progression Of Knee Joint Radiographic Osteoarthritis and Cartilage Volume Loss Over Ten Years. Hussain Ijaz Khan[1], Dawn Aitken[1], Louisa Chou[1], Andrew McBride[1], Changhai Ding[1], Jean Pierre Pelletier[2], Johanne M. Pelletier[3], Leigh Blizzard[1], Flavia Cicuttini[4] and Graeme Jones[1]. [1]Menzies Research Institute Tasmania, University of Tasmania, Hobart, 7000, Australia, [2]Institut de Rhumatologie de Montréal, Montreal, QC, [3]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, [4]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, 3004, Australia

Background/Purpose: Osteoarthritis (OA) is a disease of multifactorial origin with a modest but significant heritable effect for disease severity in the knee joint. The aim of this study was to describe radiographic osteoarthritis (ROA) progression and cartilage loss over 10 years in a midlife cohort at higher risk of osteoarthritis and community based controls.

Methods: 220 participants [mean age 45 (26–61); 57% female] were studied at baseline and ten years. Approximately half were the adult offspring of subjects who had a knee replacement performed for knee OA and the remaining were randomly selected controls that were initially matched for age and sex. Joint space narrowing (JSN) and osteophytes on radiographs and cartilage volume (tibial, patella) on MRI were assessed using standard protocols. Negative binomial and linear regression were used to describe radiographic changes (expressed as difference in ratios (dr)) and cartilage loss (expressed as difference in means (dm)) respectively. Multivariable analyses were first adjusted for age, sex and the corresponding baseline measures (i.e. baseline cartilage volume for cartilage loss).Then the four baseline measures which were significantly different between offspring and controls (BMI, knee pain, cartilage defects and tibial bone area) were added to the model.

Results: In unadjusted analysis for radiographic changes, there was a significant difference between offspring and controls for changes in total ROA, medial JSN, total tibial, total femoral and total osteophyte scores (Table 1). The associations persisted after adjusting for age, sex, and corresponding baseline measures. However, with the exception of medial JSN, most of the other associations were markedly attenuated after adjustment for baseline pain, weight, cartilage defects and tibial bone area.

Table 1. Differences between offspring and controls

Outcome factor	Unadjusted	Adjusted*
Radiographic changes	**Difference in ratios and 95% confidence interval**	
Increase in medial JSN	**+2.0 (+1.1, +3.5)**	**+1.9 (+1.0, +3.5)**
Increase in lateral JSN	+0.8 (+0.3, +2.8)	+0.5 (+0.2, +1.9)
Increase in total JSN	+1.5 (+0.9, +2.6)	+1.4 (+0.82, +2.3)
Increase in total tibial osteophytes	**+2.1 (+1.2, +3.9)**	+1.7 (+0.9, +3.1)
Increase in total femoral osteophytes	**+2.4 (+1.1, +5.0)**	+1.6 (+0.72, +3.4)
Increase in total osteophytes	**+2.3 (+1.3, +4.0)**	+1.6 (+0.9, +2.9)
Increase in total ROA score	**+1.9 (+1.3, +3.0)**	+1.5 (+0.9, +2.3)
Cartilage loss	**Difference in means and 95% confidence interval**	
Medial tibial	**−91.5 (−181.6, +1.33)**	**−83.4 (−166.2,−0.53)**
Lateral tibial	−3.0 (−107.9, +101.8)	+32.1 (−72.9, +137.1)
Total Tibial	−89.6 (−263.0, +83.8)	−56.2 (−221.4, +109.0)
Patellar	−0.9 (−171.6, +169.8)	+77.2 (−70.1, +224.1)

Bold denotes statistical significance
*Adjusted for age, sex, corresponding baseline measure and baseline differences(BMI, knee pain, cartilage defects and tibial bone area)
JSN(Joint Space Narrowing)
ROA(Radiographic Osteoarthritis)

In unadjusted analysis for cartilage loss, offspring lost more cartilage at the medial tibial site only. This persisted after adjustment for age, sex, baseline cartilage volume and baseline differences.

Conclusion: The offspring of subjects having a total knee replacement have greater incidence of radiographic osteoarthritis (both joint space narrowing and osteophytes) and higher medial tibial cartilage loss over ten years. This is mediated, in part, by baseline differences in pain, weight, cartilage defects and tibial bone area and suggests this group could be a target for early prevention strategies.

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Longitudinal Femorotibial Cartilage Thickness Increase In Young Athletes At The End Of Adolescence. Felix Eckstein[1], Heide Boeth[2], Gerd Diederichs[3], Wolfgang Wirth[1], Martin Hudelmaier[1], Sebastian Cotofana[1] and Georg Duda[2]. [1]Paracelsus Medical University, Salzburg, Austria, [2]Julius Wolff Institute, Charité – Universitätsmedizin Berlin, Berlin, Germany, [3]Department of Radiology, Charité - Universitätsmedizin Berlin, Berlin, Germany

Background/Purpose: Anterior or posterior cruciate ligament (ACL/PCL) ruptures are thought to lead to early knee osteoarthritis (KOA) and thus considered scientifically valuable "models" of pre-radiographic change. Further, longitudinal studies can be initiated at a precise set-point, which is the time of the trauma. Quantitative measurement of cartilage thickness change with MRI provides a powerful and sensitive tool for longitudinal analysis of structural cartilage change before, during, and after the onset of radiographic KOA. Because ACL/PCL rupture frequently occurs in young athletes, the purpose of this study was to obtain reference data of normal longitudinal subregional femorotibial cartilage thickness change in such subjects, specifically at the end of adolescence.

Methods: The knees of the dominant leg (the one used for take off) of 18 young top volleyball athletes (Olympic center Berlin) were examined. One participant was retrospectively excluded because of a history of ACL rupture, and one because of an imaging artifact. The age range (n=16; 8 female, 8 male) was 15–17 y at baseline. MR images were acquired using a 3D VIBE with water excitation, at baseline and two years later. Femorotibial cartilage thickness was measured by manual segmentation, using the images and commercially available software (Chondrometrics GmbH, Ainring, Germany). Cartilage thickness data were computed in the medial (MFTC) and lateral femorotibial compartment (LFTC), in tibial and femoral cartilages, and in 16 femorotibial subregions.

Results: Of the 16 subjects, 11 displayed open epiphyses at baseline, and all showed closed epiphyses at follow-up. In the MFTC, a cartilage thickness increase of +114±126μm (mean±standard deviation) or +3.3±3.7% was observed, with a standardized response mean (SRM= mean/standard deviation of change) of +0.90. This increase was less in the LFTC (+2.3±2.5%; SRM +0.93); and was greater in the weight-bearing medial femur (+4.4±3.7%; SRM +1.19) than in the medial tibia (+2.0±4.3%; SRM +0.46). The greatest increase was observed in the internal aspect of the medial femur (+5.5±5.8%; SRM +0.94) whereas no increase was seen in the internal aspect of the medial tibia (−0.5±6.6%; SRM −0.07). Over the two years, the subchondral bone area (tAB) increased by 0.8±1.5% in the MFTC and by 1.2±1.2% in the LFTC.

Conclusion: A substantial increase in femorotibial cartilage thickness (and subchondral bone area) was observed in young athletes towards the end of adolescence, i.e. a period during which the epiphyseal line is closing. This increase should be considered when measuring longitudinal cartilage change in young athletes after ACL/PCL rupture. Further studies need to clarify whether the increase is due mainly to normal growth, or to high exercise levels. Longitudinal studies in young adults with cruciate ligament rupture should hence include healthy reference cohorts of similar age (and activity level), to adequately differentiate pathological (post traumatic) change from that occurring physiologically.

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Exploratory Factor Analysis Of a Parsimonious Medial Cartilage Damage Index Reveals One Factor Associated With Radiographic Severity and Symptoms: Data From The Osteoarthritis Initiative. Grace H. Lo[1], Lori Lyn Price[2], Ming Zhang[3], Jeffrey B. Driban[3], Daniel Harper[3] and Timothy E. McAlindon[3]. [1]Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX, [2]Tufts University, Boston, MA, [3]Tufts Medical Center, Boston, MA

Background/Purpose: The cartilage damage index (CDI) is a parsimonious method of measuring articular cartilage approximating regional cartilage volume based on 18 locations within the knee, 9 in the medial tibia and femur (figure). Understanding locations that are simultaneously pathologic may better clarify the pathophysiology of knee osteoarthritis (OA). Therefore, we conducted an exploratory factor analysis of the CDI.

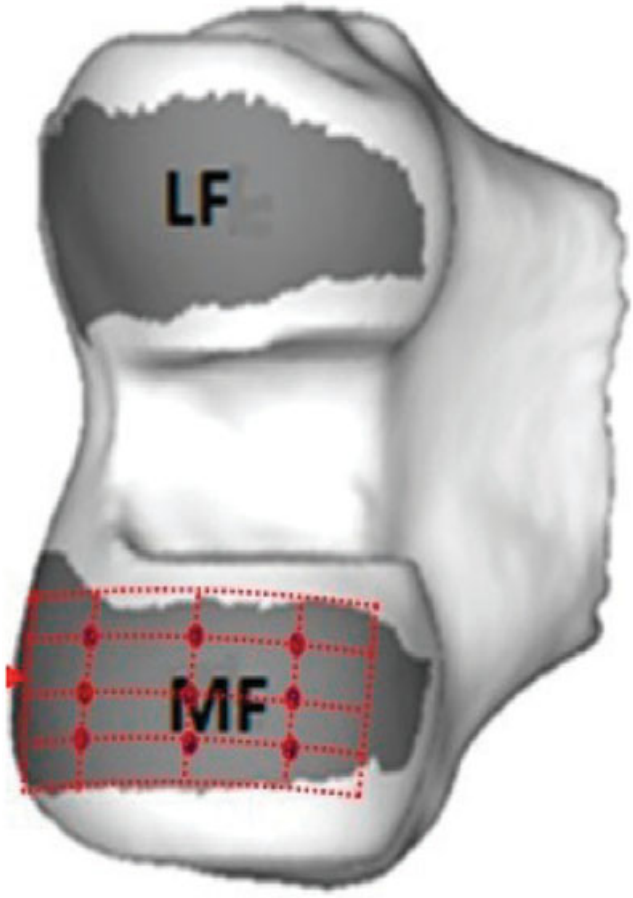

Figure. Spatial diagram of 9 of the femoral CDI points. Each red dot in the grid represents a separate location where CDI of articular cartilage is measured.

Methods: We included a convenience sample of 200 participants of the progression cohort of the Osteoarthritis Initiative (OAI) with 3T knee MRIs, PA radiographs, and WOMAC pain scores (0 – 20) at the OAI 24- month visit. Long limb films obtained at the OAI 12-, 24-, or 36- month visits were used to measure Hip-Knee-Ankle (HKA) angle using a semi-automated program (negative = varus). One assessor performed CDI measurements on MRI sagittal DESS sequences. Medial joint space narrowing (JSN) (0–3) and Kellgren-Lawrence (KL) score (0–4) were centrally assessed. An exploratory factor analysis was conducted on the 18 CDI points. To assess the characteristics of factors resulting from that analysis, we performed Spearman's correlations with the full CDI measure, the separate factors, medial JSN (construct we are trying to capture), KL score (OA severity), HKA (risk factor for medial OA), and WOMAC score (OA symptoms).

Results: Mean age was 62.5 (9.5) years, mean BMI was 30.0 (4.5) kg/m^2, 47% were female. 3 factors resulting from the factor analysis were: (1) anterior and weight bearing portions of the femur and tibia (AntWB) (2) posterior tibia (PostTib) and (3) posterior femur (PostFem), explaining 75%, 11%, and 9% of the data variation.

Table. Spearman's correlations of CDI, anterior weight-bearing (Ant WB) CDI, posterior tibia (PostTib) CDI, posterior femur (PostFem) CDI, Medial JSN, KL Score, HKA, and WOMAC scores

	CDI	AntWB CDI	PostTib CDI	PostFem CDI	Medial JSN	KL Score	HKA	WOMAC
CDI	1	0.97832	0.67338	0.68628	−0.50802	−0.28166	0.28489	−0.14135
		<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.0459
AntWB CDI		1	0.61494	0.56546	−0.57167	−0.35091	0.32417	−0.1724
			<.0001	<.0001	<.0001	<.0001	<.0001	0.0146
PostTib CDI			1	0.45342	−0.1569	−0.10798	−0.04208	−0.04712
				<.0001	0.0269	0.129	0.5581	0.5076
PostFem CDI				1	−0.1293	0.12819	0.11757	0.02053
					0.0687	0.0712	0.1008	0.7729
Medial JSN					1	0.56874	−0.52189	0.09234
						<.0001	<.0001	0.1946
KL Score						1	−0.19741	0.29629
							0.0057	<.0001
HKA							1	0.02272
								0.7519
WOMAC								1

Conclusion: These findings suggest 3 patterns of cartilage damage occur in the medial tibia and femur. While PostTib and PostFem CDI are correlated with the full CDI, they are at best weakly correlated with medial JSN and not correlated with KL score, static alignment or pain. The AntWB CDI pattern contributes most of the variation in the 18 points and shows construct validity, correlating with medial JSN, KL score, static alignment, and pain, better than the full CDI measurement. Future studies confirming these findings are warranted.

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Elevated Systemic Blood Pressure Is Associated With Increased Prevalent Knee Osteoarthritis and Knee Pain: Data From The Osteoarthritis Initiative. Grace H. Lo[1], Timothy E. McAlindon[2], Jeffrey N. Katz[3], Jeffrey B. Driban[2], Lori Lyn Price[4], Charles Eaton[5], Nancy Petersen[6], Christie Ballantyne[7] and Maria E. Suarez-Almazor[8]. [1]Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX, [2]Tufts Medical Center, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]Tufts University, Boston, MA, [5]Brown University, Providence, RI, [6]Michael E. DeBakey VA Medical Center Health Services Research and Development Center of Excellence, Houston, TX, [7]Baylor College of Medicine, Houston, TX, [8]University of Texas MD Anderson Cancer Center, Houston, TX

Background/Purpose: Epidemiologic studies have linked osteoarthritis (OA) to atheromatous vascular disease, both age-related diseases. Systemic hypertension (HTN) is an important risk factor for cardiovascular disease and may also be for OA. The objective of this study was to evaluate whether there is an association between HTN and prevalent knee OA and pain in the Osteoarthritis Initiative (OAI).

Methods: This is a longitudinal study of the OAI, a multi-center observational study of knee OA. Systolic (SBP) and extensive medication data were accumulated on participants at their OAI baseline, 12-, 24-, and 36-month visits. Bilateral PA knee radiographs were taken at the OAI 48-month visit. Central readers assessed radiographic OA severity, Kellgren and Lawrence (KL) grade (0–4). WOMAC pain scores were assessed for both knees at the 48-month visit. The greatest WOMAC score within one participant represented the maximal WOMAC score. There may be a lag between exposure to HTN and development of OA; therefore, we evaluated a 4 year interval between exposure and outcome. We performed logistic regression of quartiles of baseline SBP and 48-month status of prevalent radiographic OA (KL > 2) in either knee. We evaluated prevalent instead of incident knee OA to minimize the likelihood of right sided censorship. We performed a least square means of the maximum WOMAC score by quartile of SBP. The adjusted model included age, sex, and body mass index (BMI) as covariates. To eliminate the influence of HTN treatments, we performed subgroup analyses of those not taking anti-HTN medications at the baseline visit. To address the possibility that participants' SBPs fluctuated over time, we performed a sensitivity analysis using mean SBP over the baseline, 12-, 24-, and 36-month OAI visits as the exposure.

Results: 3644 people were included with a mean age of 61.1 (9.1), mean BMI of 28.5 (2.7), 42% were male. 61% of participants were not on anti-HTN medications. 20%, 13%, 5%, and 1% were on 1, 2, 3, and > 4 anti-HTN medications.

Table. Systolic blood pressure is associated with prevalent radiographic knee osteoarthritis and knee pain. Logistic regression of SBP quartile and prevalent knee OA. Least Squared Means of maximal WOMAC score by SBP quartiles, adjusted for age, sex, BMI, and radiographic OA status

	Outcome = Prevalent Knee OA	Outcome = Knee Pain		
N = 3644	Prevalence of Knee OA by SBP Quartile	Unadjusted Odds Ratio (95% CI)	Odds Ratio (95% CI) Adjusted for Age, Sex, BMI	LS Means of Maximal WOMAC Score, Adjusted for Age, Sex, BMI, Rad OA status
SBP Quartile 1 (76 – 112)	531/1031 (52%)	Referent	Referent	2.6 (2.4–2.8)
SBP Quartile 2 (114 – 122)	519/846 (61%)	1.5 (1.2–1.8)	1.2 (1.0–1.5)	2.8 (2.6–3.0)
SBP Quartile 3 (123 – 134)	586/865 (68%)	2.0 (1.6–2.4)	1.4 (1.2–1.7)	2.9 (2.7–3.1)
SBP Quartile 4 (135 – 210)	619/902 (69%)	2.1 (1.7–2.5)	1.3 (1.0–1.6)	3.2 (3.0–3.4)
		p-for trend < 0.0001	p-for trend = 0.006	p trend = 0.0016

Sensitivity analyses of participants who did not report anti-HTN medications showed similar results, as did using mean SBP over baseline – OAI 36 month as the exposure.

Conclusion: To our knowledge, this is the first epidemiologic study to show elevated systemic blood pressure is associated with increased prevalence of knee OA and greater levels of knee pain. The associations were weakened when adjusting for age, sex, and BMI, but were still significant. These findings suggest a new and promising avenue for research on disease modification as well as symptom control in knee OA. Future epidemiologic studies are needed to confirm these findings.

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The Association Between Metabolic Syndrome and Hand Osteoarthritis - Data From The Framingham Study. Ida K. Haugen[1], Vasan Ramachandran[2], Devyani Misra[2], Tuhina Neogi[2], Jingbo Niu[2], Yuqing Zhang[2] and David T. Felson[2]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Boston University School of Medicine, Boston, MA

Background/Purpose: Metabolic factors may have a negative effect on cartilage, and may be especially relevant in the pathogenesis of hand OA. Our aim was to investigate whether metabolic syndrome and its components were associated with prevalent and incident hand OA in a large community-based sample.

Methods: We included participants from the Framingham Offspring cohort, who were examined for OA at exam 5 (1991–95) and 7 (1998–2001). Inclusion criteria were: available data on symptomatic hand OA, clinical data, no anti-hypertensive, anti-diabetic and lipid-lowering treatment, no rheumatoid arthritis, and age 50–75 years at exam 5. Symptomatic hand OA was defined as Kellgren-Lawrence grade ≥2 and pain in the same joint(s). Metabolic syndrome was defined as central obesity (men: ≥37.0 inches, women: ≥31.5 inches waist circumference) plus two of the following: hypertension (systolic ≥130 mmHg and/or diastolic ≥85 mmHg), elevated fasting blood glucose (>100 mg/dL), elevated triglycerides (>150 mg/dL) and low HDL (men: <40 mg/dL, women: <50 mg/dL). In cross-sectional analyses, we examined whether metabolic syndrome and its components were associated with presence of symptomatic hand OA using logistic regression. In longitudinal analyses, we examined the associations between metabolic syndrome and incident symptomatic hand OA at exam 7. We adjusted for age and sex.

Results: Of the 748 participants who fulfilled the inclusion criteria, 74 (9.9%) had symptomatic hand OA. Participants with symptomatic hand OA were older than those without (mean (SD) 62.2 (5.9) vs. 57.7 (6.0) years) and more likely to be women (75.7% vs. 51.0%). There was no significant association between metabolic syndrome and symptomatic hand OA (Table). The strength of association between metabolic syndrome and symptomatic hand OA was attenuated when we adjusted for body mass index (BMI) (cross-sectional association: OR 1.19, 95% CI 0.68–2.10). When evaluating the individual components of metabolic syndrome separately, we found a significant association between central obesity and symptomatic hand OA in the adjusted cross-sectional analyses (Table). In the longitudinal analyses, we found a statistically significantly *lower* risk of incident symptomatic hand OA associated with elevated triglycerides (Table). The association remained after adjustment for lipid-lowering treatment (data not shown). Similar results were found when we included BMI in the adjusted models (data not shown).

Table. Associations between metabolic syndrome and hand OA.

	Frequency of metabolic syndrome (%)		Logistic regression OR (95% CI)	
	No hand OA	Hand OA	Crude analyses	Adjusted for age and sex
Cross-sectional analyses[1]				
Metabolic syndrome	39.0	48.6	1.48 (0.91–2.40)	1.44 (0.87–2.38)
Central obesity	64.2	79.7	2.19 (1.22–3.94)	2.24 (1.22–4.12)
Hypertension	40.2	50.0	1.49 (0.92–2.41)	1.27 (0.77–2.11)
High blood-glucose	27.5	24.3	0.85 (0.49–1.48)	0.89 (0.49–1.61)
High triglycerides	33.4	33.8	1.02 (0.61–1.69)	1.01 (0.60–1.73)
Low HDL	64.1	70.3	1.32 (0.78–2.23)	1.30 (0.75–2.23)
Longitudinal analyses (only those without hand OA at baseline were included)[2]				
Metabolic syndrome	38.6	31.5	0.73 (0.45–1.18)	0.77 (0.47–1.25)
Central obesity	63.5	59.8	0.85 (0.56–1.43)	0.90 (0.56–1.43)
Hypertension	37.4	41.3	1.18 (0.74–1.86)	1.24 (0.77–1.20)
High blood-glucose	28.0	18.7	0.59 (0.33–1.04)	0.64 (0.35–1.14)
High triglycerides	34.0	21.7	0.54 (0.32–0.92)	0.56 (0.33–0.96)
Low HDL	64.9	55.4	0.67 (0.43–1.06)	0.67 (0.42–1.05)

[1] n=674 and n=74 without and with symptomatic hand OA at exam 5, respectively,
[2] n=430 and n=92 without and with incident symptomatic hand OA at exam 7, respectively (n=152 lost to follow-up),

Conclusion: Metabolic syndrome was not associated with higher probability of presence or development of hand OA. If anything, we observed a *lower* probability of incident symptomatic hand OA in participants with high triglycerides.

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Association Between Serum Adipokine Levels and Extent Of Symptomatic Joint Involvement In Hip and Knee Osteoarthritis. Anthony V. Perruccio[1], Vinod Chandran[2], Nizar N. Mahomed[3] and Rajiv Gandhi[4]. [1]Toronto Western Hospital, Toronto Western Research Institute, and University of Toronto, Toronto, ON, [2]University of Toronto, Toronto Western Hospital, Toronto, ON, [3]University Health Network and University of Toronto, Toronto, ON, [4]University Health Network, Arthritis Program, Toronto, ON

Background/Purpose: Osteoarthritis (OA) has not traditionally been considered a systemic joint disease. However, a growing body of evidence suggests that OA cannot solely be accounted for by a single phenotype, and that systemic factors may play a contributing role in its pathogenesis. Obesity is an important risk factor for OA, but the underlying mechanisms are not fully understood (e.g. strong association between obesity and hand OA cannot be explained by mechanical stresses). Finally, the presence of multiple symptomatic joints among many with OA further suggests potentially underlying systemic mechanisms. In this pilot study, we investigated the association between serum levels of adipokines and the extent of symptomatic joint involvement among patients scheduled for hip and knee replacement surgery for OA.

Methods: Serum levels of adipokines (leptin, adiponectin, adipsin, resistin) were determined by ELISA in 78 patients (45 females, 33 males) scheduled for total hip or knee replacement surgery for OA. Individuals reporting inflammatory arthritis, cardiovascular disease or diabetes were excluded. Patients indicated on a homunculus all joints that were symptomatic on most days for at least a month in the past 12 months. A count score of symptomatic regions (neck; spine; shoulders; elbows; wrists; hands; hips; knees; ankles; feet) (not including surgical joint) was developed (range: 0 to

9). Analysis was stratified by sex, and Poisson analyses used to investigate associations.

Results: Bivariate associations suggested opposite effects of leptin, adiponectin, and adipsin between women and men. Adjusted for age, BMI, and hip/knee group membership, higher levels of leptin and adiponectin, and lower levels of adipsin (all $p<0.01$) were associated with a greater regional joint count among women (Table 1). However, among men only resistin was significantly ($p=0.03$) associated in adjusted analyses, with higher levels of resistin associated with lower regional joint counts.

Table 1. Multivariate adjusted associations between regional joint count (outcome) and adipokines.

	IRR*	Lower 95% CL	Upper 95% CL	Pr > ChiSq
Predictors		**Females**		
Age	**1.03**	1.005	1.058	**0.0204**
BMI	1.01	0.973	1.054	0.5407
Knee vs. hip	1.25	0.765	2.048	0.3725
Leptin (ng/ml)	**1.03**	1.010	1.047	**0.0021**
Adiponectin (μg/ml)	**1.03**	1.011	1.056	**0.0031**
Adipsin (mg/ml)	**0.85**	0.751	0.961	**0.0094**
Resistin (ng/ml)	1.01	0.987	1.038	0.3613
		Males		
Age	1.02	0.979	1.054	0.4017
BMI	1.03	0.933	1.143	0.5330
Knee vs. hip	0.92	0.430	1.949	0.8181
Leptin (ng/ml)	0.97	0.923	1.020	0.2485
Adiponectin (ug/ml)	0.97	0.937	1.010	0.1563
Adipsin (mg/ml)	0.96	0.790	1.176	0.7190
Resistin (ng/ml)	**0.97**	0.942	0.997	**0.0307**

*IRR: Incident rate ratio, per unit of measurement - Poisson analysis; 95% CL: 95% confidence limits.

Conclusion: This work suggests to some degree that there may be a dose-response association between OA (using extent of regional symptomatic joint involvement as an indicator) and serum levels of adipokines. However, these associations differ between women and men. This suggests the possibility of distinct OA phenotypes, and supports potential systemic effects in OA. OA as a systemic disorder entails a need to reevaluate OA treatment and management strategies, with consideration for multimodal approaches. Systemic factors in OA may also help explain high levels of comorbidity in these populations and may be a target for comorbidity prevention.

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C-Reactive Protein But Not Erythrocyte Sedimentation Rate Is Associated With Decrease In Muscle Strength In Patients With Knee Osteoarthritis: A 2 Year Follow Up Study. Diana C Sanchez-Ramirez[1], Marike van der Leeden[2], Martin van der Esch[2], Leo D. Roorda[3], Sabine Verschueren[4], Jaap van Dieen[5], Joost Dekker[6] and Willem F. Lems[6]. [1]VU university Amsterdam, Amsterdam, Netherlands, [2]Reade, Amsterdam, Netherlands, [3]Reade, centre for rehabilitation and rheumatology, Amsterdam, Netherlands, [4]KU University of Leuven, Leuven, Belgium, [5]VU University, Amsterdam, Netherlands, [6]VU University Medical Center, Amsterdam, Netherlands

Background/Purpose: In patients with knee osteoarthritis activity limitations and disease progression have been associated with muscle weakness (OA). Muscle weakness might be determined by factors such as increased pain, immobilization, disuse, avoidance of activities and aging. Additionally, recent cross-sectional studies have found an association between elevated inflammatory markers and a decrease in knee muscle strength in this group of patients (1;2). However, longitudinal studies which assess the association between inflammatory markers and muscle strength in patients with OA are still needed. Therefore, the aim of the study was to examine the associations of serum c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) with changes in muscle strength in patients with knee osteoarthritis (OA) after two years.

Methods: Data from 186 patients with knee OA part of the Amsterdam Osteoarthritis cohort (AMS-OA) were gathered at baseline and at two years follow up. CRP (mg/l) and ESR (mm/l) were measured in serum from patients' blood. Strength of quadriceps and hamstrings muscles was assessed using an isokinetic dynamometer. Univariable and multivariable linear regression analyses were used to assess the association of CRP and ESR with changes in muscle strength, adjusting for relevant confounders.

Results: Persistently elevated or increased serum CRP values ($\beta=-0.23$; $p=0.002$), but not ESR values ($\beta=-0.05$; $p=0.55$), were associated with a decrease in knee muscle strength after two years, even after adjustment for age, sex, comorbidities, NSAIDs use, BMI, pain, physical activity and baseline muscle strength.

Conclusion: Our results indicate that persistently elevated or an increase in inflammatory markers are independently related to decreased muscle strength in patients with knee OA. Although the mechanism to explain this relationship is not clear yet, targeting inflammation might have the potential to control the loss of muscle strength in this group of patients.

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Bone Mineral Density and the Risk of Knee Osteoarthritis: The Johnston County Osteoarthritis Project. Kamil E. Barbour[1], Jennifer M. Hootman[2], Charles G. Helmick[1], Louise Murphy[3], Jordan B. Renner[4] and Joanne M. Jordan[5]. [1]Centers for Disease Control and Prevention, Atlanta, GA, [2]Centers for Disease Control and Prevention, Kennesaw, GA, [3]CDC, Atlanta, GA, [4]University of North Carolina at Chapel Hill, Chapel Hill, NC, [5]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC

Background/Purpose: There is credible evidence that high bone mineral density (BMD) is associated with an increased risk of incident radiographic osteoarthritis (ROA) of the knee. However, less is known about the relationship of BMD and the outcome with greater clinical and public health relevance, incident symptomatic ROA (sROA).

Methods: Using data (N=951) from the Johnston County Osteoarthritis Project's first (1999–2004) and second follow-up (2005–2010), we examined the association between BMD and both incident knee ROA and sROA among participants aged ≥45 years. Total hip BMD at baseline was measured using dual-energy X-ray absorptiometry. Participants were grouped into sex-specific BMD quartiles because of large sex-specific differences in BMD. Incident knee ROA was defined as development of a Kellgren-Lawrence grade of ≥2 in a knee at second follow-up. Incident knee sROA was defined as onset of both ROA and symptoms in at least one knee at second follow-up. Weibull regression modeling, which accounted for interval censored data, was used to estimate hazard ratios (HR) and 95% confidence intervals (95% CIs). Multivariate models adjusted for age, BMI, sex, race, education, smoking, physical activity, and history of knee injury.

Results: Median follow-up time was 6.8 (range=4.0–10.2) years. Compared with participants in the lowest BMD quartile, the multivariable adjusted HRs (95% CIs) of sROA for participants in the second, third, and highest quartiles of total hip BMD were 1.4 (0.9 to 2.4), 1.7 (1.1 to 2.7), and 1.6 (1.02 to 2.5), respectively, p trend=0.03. Risk of sROA risk did not vary by total hip BMD quartiles, nor was the test of trend significant across BMD quartiles (p trend=0.23).

Conclusion: Although high levels of BMD may significantly increase one's risk of knee ROA, we found no evidence of an association between BMD and the more clinically relevant outcome of knee sROA. These findings suggest that adults can achieve and maintain a healthy BMD without the tradeoff of increasing their risk of the painful and potentially debilitating outcome of sROA.

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Associations Between Levels Of Urinary C-Telopeptide Fragments Of Type II Collagen and Knee Structure In Asymptomatic Middle-Aged Women. Binghui Wang[1], Hans Kurniawan Pramono[1], Flavia Cicuttini[2], Anita Wluka[1], Fahad Hanna[1], Susan Davis[1], Robin Bell[1], Andrew Teichtahl[1] and Yuanyuan Wang[1]. [1]Monash University, Melbourne, Australia, [2]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, 3004, Australia

Background/Purpose: There is evidence for an association between levels of urinary C-telopeptide fragments of type II collagen (uCTX-II) and the risk of knee osteoarthritis. The aim of this study was to examine the association between uCTX-II levels and knee cartilage and bone changes in a cohort of asymptomatic women.

Methods: 140 women, aged 40–67 years with no history of knee pain, injury or clinical knee disease, underwent knee MRI at baseline and two years later. Cartilage volume, cartilage defects, tibial plateau bone area and bone marrow lesions (BMLs) were measured using validated methods. Baseline uCTX-II concentrations were determined using enzyme-linked immunosorbent assay (ELISA).

Results: Increased uCTX-II level was associated with increased prevalence of medial tibiofemoral cartilage defects (OR 4.5, 95% CI 1.6–12.5, p = 0.004) and lateral tibiofemoral BMLs (OR 10.6, 95% CI 1.8–61.8, p = 0.01), greater medial (regression coefficient 80.2 mm^2, 95% CI 9.3–151.1, p = 0.03) and lateral (regression coefficient 86.0 mm^2, 95% CI 33.3– 138.7, p = 0.02) tibial plateau bone area. No significant association was found for tibial cartilage volume. Baseline uCTX-II levels were not associated with the changes in cartilage and bone over two years.

Conclusion: In asymptomatic women, increased uCTX-II levels were associated with adverse knee structural changes, as evidenced by increased prevalence of cartilage defects and BMLs, and bigger tibial plateau bone area. These data suggest that uCTX-II may be a sensitive biomarker for early knee cartilage changes. Longitudinal studies with larger sample size and longer follow-up are needed.

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Hand Osteoarthritis Is Associated With Increased Type II Collagen Degradation In Women: The Ofely Study. Jean-Charles Rousseau[1], Elisabeth Sornay-Rendu[1], Cindy Bertholon[1], Patrick Garnero[2] and Roland Chapurlat[3]. [1]INSERM UMR 1033, Lyon, France, [2]INSERM, UMR 1033, Lyon and Cisbio Bioassays, Bagnols/Cèze, France, [3]INSERM UMR 1033 and Université de Lyon, Hôpital Edouard Herriot, Lyon, France

Background/Purpose: Hand osteoarthritis (OA) is one of the most common sites of OA and predominantly affects women. Patients with knee, hip or spine OA exhibit increased cartilage type II collagen degradation as detected by the urinary excretion of C-terminal crosslinking telopeptide of type II collagen (CTX-II), but data on hand OA is lacking. The aim of this study was to investigate the relationship between urinary CTX-II and hand OA in women.

Methods: We investigated 590 women from the OFELY population-based study (mean age: 61.8 years ± 10.2), including 475 postmenopausal women. Clinical hand OA was defined according to the ACR criteria (Altman *et al*, 1990), slightly modified (without functional complains). At the same time of hand OA evaluation, knee and spine OA were assessed by radiographs and self-reported hip OA was recorded. Levels of urinary CTX-II measured by ELISA (Urine CartiLaps®, IDS) in the 186 women with hand OA (mean age: 67.2 years ± 8.4) were compared to those of the 404 other women without hand OA (mean age: 59.4 years ± 10.1). All analyses were adjusted for age and concomitant knee, hip or spine OA.

Results: Urinary CTX-II levels were significantly increased in women with hand OA (237 ±134 ng/mmolCr) compared to controls (165 ± 97 ng/mmolCr, p = 0.001) after adjustment for age and for prevalent knee, spine and hip OA. When urinary CTX-II concentrations were considered in quartiles, subjects with levels in the highest quartile had an increased risk of prevalent hand OA, with an odds-ratio of 2.06 (95% CI: 1.3–3.2; p = 0.002), after adjustment for OA at the other anatomical sites.

Conclusion: Hand OA is characterized by increased type II collagen degradation. Urinary CTX-II could be a useful biomarker for the clinical investigation of hand OA.

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Biomarkers Reflect Differences In Osteoarthritis Phenotypes Of The Lumbar Spine: The Johnston County Osteoarthritis Project. Adam P. Goode[1], Amanda E. Nelson[2], Virginia B. Kraus[3], Jordan B. Renner[4] and Joanne M. Jordan[2]. [1]Duke University, Durham, NC, [2]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC, [3]Duke University Medical Center, Durham, NC, [4]University of North Carolina at Chapel Hill, Chapel Hill, NC

Background/Purpose: We have previously identified differences in associations between joint metabolism biomarkers and radiographic features of the lumbar spine (disc space narrowing (DSN) and osteophytes (OST)). Due to anatomical differences, there may be distinct associations between biomarkers and different phenotypes of osteoarthritis (OA) in the spine. Therefore, our aim was to determine if differences exist in the associations between biomarkers and OA in the spine, defined as 1) facet osteoarthritis (FOA) and 2) the combination of DSN and OST at the same level; we further explored variations by gender, race and low back symptoms.

Methods: Of the 1,015 participants enrolled in the Johnston County OA Project from 2003–04, 547 participants had complete data for serum hyaluronan (sHA), serum Cartilage Oligomeric Matrix Protein (sCOMP), serum collagen neoepitope (sC2C), serum C-propeptide (sCPII), and urinary N-terminal telopeptide (uNTX-I); 529 participants had complete data for urinary cross-linked C-telopeptide of type II collagen (uCTX-II). The mean age and body mass index (BMI) were 62 (SD 10) years and 30 (SD 6) kg/m^2, respectively; 62% were female, 38% were African American (AA), 29% had knee OA, 24% hip OA, 28% hand OA and 49% low back symptoms. Each lumbar spine level was graded for OST and DSN in a semi-quantitative fashion (0–3) and FOA was graded as present or absent according to the Burnett Atlas. Spine OA was defined as the presence of DSN and OST grade 1 or more at the same lumbar level. Biomarkers were natural log (ln) transformed. Linear regression was used to determine adjusted geometric mean values of biomarkers and binary logistic regression models were used to estimate adjusted odds ratios (aOR) and 95% confidence intervals (CI) between biomarkers and spine radiographic variables. All analyses were adjusted for demographic (age, race, gender), clinical (BMI) and radiographic (knee, hip, hand and spine OA or FOA) variables. Interactions were tested with likelihood ratio tests at a p-value$<$0.05.

Results: FOA was present at least at one level of the lumbar spine in 57% of participants, while spine OA was present in 49%. Geometric mean biomarker levels of lnHA were significantly (p=0.04) greater in the presence of FOA while lnCTX-II levels were significantly (p$<$0.01) greater with in presence of spine OA. Significant associations were found between lnHA and FOA (aOR=1.26 ((95% CI 1.02, 1.55)) whereas lnCTX-II was significantly associated with spine OA (aOR=1.64 ((95% CI 1.22, 2.21)). The association between lnHA and FOA was significantly (interaction p$<$0.01) greater among Caucasians (aOR=1.56 ((95% CI 1.18, 2.05)) than with AA (aOR=0.92 ((95% CI 0.68, 1.25)). The association between lnCOMP and spine OA was significantly greater (interaction p=0.03) among those with low back symptoms (aOR=2.14 ((95% CI 1.08, 4.28)), than those without (aOR=0.76 ((95% CI 0.51, 1.68)).

Conclusion: Joint metabolism biomarkers reflect the anatomical (HA with FOA and CTX-II with spine OA), demographic (HA with race and FOA) and clinical (COMP with spine OA and symptoms) differences between FOA and a composite definition of spine OA. This may indicate a different pathophysiologic process exists for these two phenotypes of OA in the lumbar spine.

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Synovial Inflammation In Meniscal Tear Patients: CCL19 mRNA Expression Is Independently Associated With Knee Related Disability. Anjali Nair, Charles Bush-Joseph, Nikhil Verma, Matthew Tetreault, Kanta Saha, Arkady Margulis, Louis F. Fogg and Carla R. Scanzello. Rush University Medical Center, Chicago, IL

Background/Purpose: In patients with knee osteoarthritis (OA), synovitis is associated with severity of knee symptoms. Previously, we demonstrated that in patients undergoing partial meniscectomy without radiographic OA, synovitis is associated with worse preoperative knee pain and function using the Lysholm score, which measures knee-specific pain and disability on a single scale. mRNA expression levels of the chemokine CCL19 and its receptor CCR7 were associated with presence of synovitis, and strongly correlated with worse Lysholm scores. However, unlike the patients in our previous study, most patients with meniscal tears indicated for arthroscopy already have pre-existing cartilage degeneration indicative of early-stage OA. In this study we sought to validate these markers in more typical patients presenting for arthroscopy to determine their utility as markers of more symptomatic early knee disease. To measure knee specific pain and functional deficits we used the Knee Injury and Osteoarthritis Outcome score (KOOS).

Methods: Synovial biopsies were collected during surgery from 19 patients undergoing arthroscopic meniscal procedures. Relative mRNA expression levels (RE) of CCL19 and CCR7 were measured using Real Time polymerase chain reaction. The KOOS was administered preoperatively and measures knee function and disability on 5 separate domains: Pain, symptoms, activities of daily living (ADL), sport and recreation function, knee-related quality of life (QOL). Pearsons correlations were used to determine relationships between mRNA levels and KOOS scores. Multivariable linear regression models were run to test if associations were independent of age, gender, BMI, cartilage degeneration (measured using Outerbridge Classification) and radiographic OA (Kellgren-Lawrence (K/L)) scores. Post-hoc power analysis showed our study was powered at 73% to detect a moderate correlation ($\rho = 0.5$) between chemokine levels and KOOS scores.

Results: The majority of patients had grade 2–4 Outerbridge scores and median K/L scores of 2, indicative of pre-existing OA. CCL19 and CCR7 transcripts were detected in all patients. Unadjusted analysis revealed CCL19 RE was associated with KOOS ADL ($r = -0.620$, $p = 0.005$), Pain ($r=-0.547$, $p=0.015$), and QOL scores ($r=-0.479$, 0.038). Adjusted analyses showed CCL19 RE was independently associated with KOOS ADL scores ($\beta = -4.201$, 95% CI [−8.071, −0.331], $p = 0.036$). Trends were observed for associations with KOOS Pain (CCL19 $\beta = -3.252$, 95% CI [−6.748, 0.243], $p = 0.065$) and KOOS QOL CCL19 $\beta = -3.719$, 95% CI [−7.786, 0.349], $p = 0.070$).

Conclusion: CCL19 is important in lymphocyte recruitment and was identified in our previous work as a marker of synovitis. Our current work extends these findings by demonstrating a relationship between CCL19 expression and knee-related difficulty with activities of daily living in typical patients presenting for arthroscopic meniscal surgeries. These findings increase the potential for this marker to be useful in identifying patients with synovitis after a meniscal tear and with early-stage OA. Future work is needed to determine the role of this marker in development and pathogenesis of symptomatic OA after meniscal injury.

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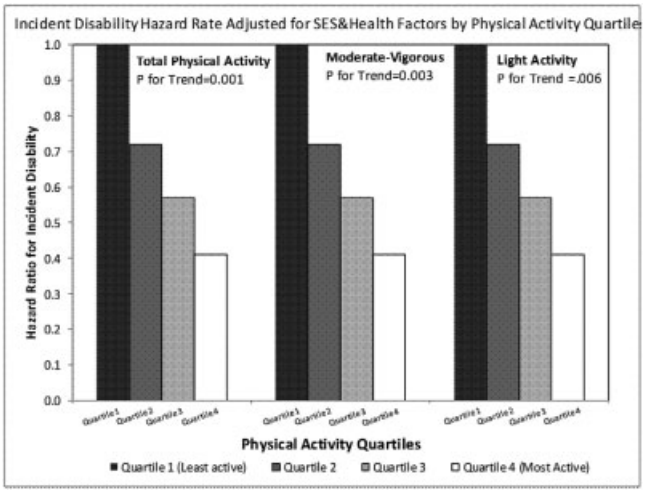
Physical Activity Is Associated With Reduced Incident Disability: Evidence From The Osteoarthritis Initiative. Dorothy D. Dunlop[1], Jing Song[1], Pamela A. Semanik[1], Leena Sharma[1], Joan M. Bathon[2], Charles Eaton[3], Marc C. Hochberg[4], Rebecca D. Jackson[5], C. Kent Kwoh[6], W, Jerry Mysiw[5], Michael C. Nevitt[7] and Rowland W. Chang[8]. [1]Northwestern University, Chicago, IL, [2]Columbia University, New York, NY, [3]Brown University, Providence, RI, [4]University of Maryland, Baltimore, MD, [5]Ohio State University, Columbus, OH, [6]University of Pittsburgh, Pittsburgh, PA, [7]University of California, San Francisco, San Francisco, CA, [8]Northwestern University Medical School, Chicago, IL

Background/Purpose: Over 56 million people in the U.S. are classified as disabled. Physical activity is a low cost, broadly applicable approach to improve cardiovascular fitness, but it is not established if improved fitness translates to reduced disability, a key to containing healthcare costs. This study evaluated whether accelerometer measured physical activity is related to incident disability.

Methods: We prospectively examined the relationship of accelerometer measured physical activity with two-year development of disability measured by instrumental and basic activity of daily living limitations (IADL/ADL). We studied 1666 participants aged 49 years or older from the Osteoarthritis Initiative observational study of adults at high risk for or having knee OA and were free of baseline IADL/ADL limitations. This sample represents a large segment of community-dwelling adults at elevated risk for disability. Hazard ratios were estimated from discrete survival methods to investigate a graded relationship between baseline physical activity quartile groups and the development of disability within two years.

Results: Higher physical activity levels had a significant inverse association with the development of disability. For higher active physical activity quartiles, hazard ratios for incident disability were 1.00, 0.67, 0.51, and 0.36, respectively (P for trend, <0.001) controlling for socioeconomic (age, gender, race/ethnicity, education, income) and health factors (comorbidity, depressive symptoms, obesity, smoking, lower extremity pain, function, and knee factors: osteoarthritis severity, pain, symptoms, prior injury). Consistent trends between greater physical activity and less incident disability were demonstrated from analyses stratified by age, gender, and presence/absence of knee osteoarthritis and analyses based on time spent in moderate-intensity or light-intensity physical activities. Sensitivity analyses applying a more stringent definition of disability based on reported IADL/ADL dependency/assistance also demonstrated a statistically significant inverse graded relationships.

Conclusion: These prospective data demonstrated an inverse relationship between higher physical activity levels and the development of disability in community-dwelling adults at elevated risk for disability. Importantly, this study demonstrated greater physical activity, regardless of intensity, was related to less incident disability. Reduced incident disability was associated with greater time spent in light intensity as well as moderate-to-vigorous intensity activities. These findings support policies that encourage adults, including persons with arthritis, to increase their physical activity of any intensity to prevent and slow disability.



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The Association Of Knee Buckling With Vibratory Perception and Muscle Strength: The Multicenter Osteoarthritis Study. Najia Shakoor[1], David T. Felson[2], Jingbo Niu[2], Neil A. Segal[3], Uyen Sa D.T. Nguyen[2], Jasvinder A. Singh[4] and Michael C. Nevitt[5]. [1]Rush University Medical Center, Chicago, IL, [2]Boston University School of Medicine, Boston, MA, [3]University of Iowa, Iowa City, IA, [4]University of Alabama, Tuscaloosa, AL, [5]University of California, San Francisco, San Francisco, CA

Background/Purpose: Knee buckling ("giving way") is a common symptom in knee osteoarthritis (OA). Yet, little is known regarding risk

factors for buckling. Knee buckling has been found to be associated with muscle weakness, a treatable cause, in one study and this finding needs to be confirmed. In addition, vibratory deficits have been shown to be present in knee OA, and may create alterations in knee position, increasing vulnerability to buckling but this has not been examined. Here, we evaluate the association of muscle strength and vibratory perception with buckling in older adults with, or at high risk for, knee OA.

Methods: MOST is a NIH-funded longitudinal study of persons with symptomatic knee OA or at increased risk of OA. At the 60-month visit, participants underwent evaluation of isokinetic muscle strength at the right leg, bilateral evaluation of vibratory perception threshold (VPT) at predetermined anatomic sites, and were asked about buckling and its frequency in the past 3 months. Knee buckling was defined in each subject as (a) any buckling and (b) repeated buckling (≥ 2 episodes). VPT was evaluated using a biothesiometer. The applicator tip of the instrument was placed on preselected anatomic bony prominences and the voltage increased by 1 volt/sec until the participant acknowledged sensation. Mean VPT between the limbs was used for analyses. Quadriceps strength was measured as the maximum torque during active isokinetic extension using a dynamometer and scaled to body size by dividing the maximum torque by BMI. VPT and strength were categorized into groups based on ±1 SD of the gender-specific mean of the sample. A person-based analyses using logistic regression to estimate adjusted odds ratios for the association of VPT and strength with buckling in the past 3 months was performed. We adjusted in analyses for age, sex, BMI, race, clinic site, and WOMAC knee pain.

Results: We evaluated 2,291 subjects (60% women, age±SD=68±8 yrs, BMI±SD=31±6 kg/m^2). 16.7% of participants reported buckling and 13.4% reported repeated buckling in the past 3 months. Results are summarized in the Table. A borderline association was found between muscle strength and any buckling episode, however, a significant association was observed with repeated buckling. High quadriceps strength was associated with a significantly decreased odd of repeated buckling (Adj OR: 0.59[0.36,0.99]. There was no significant association found between VPT and buckling.

Table

		Adjusted OR (95% CI)*	p value	Adjusted OR (95% CI)**	p value
Any buckling					
VPT at tibial tuberosity	Low	1.20 (0.88, 1.62)	0.244	1.13 (0.83, 1.54)	0.441
	Normal	1 (referent)		1 (referent)	
	High	1.15 (0.88, 1.49)	0.301	1.15 (0.88, 1.49)	0.312
Quadriceps muscle strength	Low	1.47 (1.16, 1.87)	0.002	0.97 (0.75, 1.25)	0.787
	Normal	1 (referent)		1 (referent)	
	High	0.51 (0.34, 0.75)	0.001	0.70 (0.46, 1.05)	0.087
Repeated buckling					
VPT at tibial tuberosity	Low	1.36 (0.98, 1.90)	0.067	1.24 (0.88, 1.76)	0.225
	Normal	1 (referent)		1 (referent)	
	High	1.22 (0.91, 1.64)	0.180	1.21 (0.90, 1.62)	0.204
Quadriceps muscle strength	Low	1.71 (1.31, 2.21)	<0.001	1.09 (0.82, 1.44)	0.568
	Normal	1 (referent)		1 (referent)	
	High	0.42 (0.26, 0.69)	<0.001	0.59 (0.35, 0.98)	0.041

*VPT adjusted for muscle strength and muscle strength adjusted for VPT
**adjusted for all covariates

Conclusion: In this large cohort of participants with knee OA or at high risk for knee OA, greater quadriceps strength was found to be associated with decreased odds of repeated knee buckling. There was no significant association found between vibratory perception and knee buckling. Future studies should continue to evaluate for other potential risk factors for buckling in knee OA.

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Higher Leg Extensor Muscle Power Output Is Associated With Reduced Pain and Better Quality Of Life In Patients With Symptomatic Knee Osteoarthritis. Kieran F. Reid[1], Lori Lyn Price[2], William F. Harvey[2], Jeffrey B. Driban[2], Roger A. Fielding[1] and Chenchen Wang[2]. [1]Tufts University, Boston, MA, [2]Tufts Medical Center, Boston, MA

Background/Purpose: Muscle strength, the maximal force generating capacity of skeletal muscle, has been widely characterized in patients with knee osteoarthritis. However, skeletal muscle power, defined as the product of dynamic muscular force and the velocity of muscle contraction, declines earlier and more precipitously than muscle strength across the adult life span. In older populations, peak muscle power is also a more robust predictor of functional outcomes compared to muscle strength, particularly when assessed during closed chain testing. Despite its clinical relevance as a potential determinant of disease burden in knee osteoarthritis (OA), no study to date has comprehensively evaluated lower extremity muscle power output in patients with knee OA. The purpose of this investigation was to examine the relationships between lower extremity muscle power and perceived disease severity in a large population of patients with symptomatic knee OA. We hypothesized that, compared to muscle strength, peak muscle power assessed during bilateral leg press exercise would be a more influential determinant of self-reported pain and health-related quality of life within this patient population.

Methods: We used baseline data collected as part of a 4-year randomized controlled clinical trial in 181 patients (mean age: 60.2 ± 10yrs, BMI: 32.7 ± 10 kg/m^2, 69% female, 52% Caucasian) who met the American College of Rheumatology criteria for knee OA. Pain was measured using the pain subscale of the Western Ontario and McMaster Osteoarthritis Index (WOMAC) and health-related quality of life was measured using the Medical Outcomes Study Short Form 36 physical component summary and mental component summary. One-repetition maximum (1RM) strength was measured using the bilateral leg press exercise and peak leg press muscle power was measured during 5 repetitions performed as fast as possible with resistance set to 40% of the 1RM (Keiser Pneumatic Leg Press A420, Keiser Corporation, Fresno, CA).

Results: In univariate regression analysis, greater peak muscle power output was significantly and inversely associated with lower WOMAC pain score ($r = -0.17$, $P = 0.02$). Peak muscle power was also significantly and positively associated with SF36 physical component summary score ($r = 0.15$, $P = 0.05$) but not mental component summary score ($r = -0.02$, $P = 0.8$). After adjusting for age, BMI, sex, race and depressive symptoms, peak muscle power was a significant and independent predictor of SF 36 physical component summary score ($P = 0.02$). Muscle strength was not associated with any measure of disease severity or quality of life ($P \geq 0.07$).

Conclusion: Leg press muscle power output is a significant determinant of perceived disease burden in patients with symptomatic knee OA. While the overall magnitude of these relationships are modest, peak muscle power exerts a greater influence on self reported pain and quality of life compared to muscle strength within this patient population. These data suggest that the efficacy of resistance training interventions specifically designed to improve leg extensor muscle power output should be examined in patients with knee OA.

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The Relationship Of Foot Pronation During Walking To Risk Of Incident Medial Tibiofemoral and Lateral Patellofemoral Cartilage Damage: The Multicenter Osteoarthritis Study. K. Douglas Gross[1], Howard J. Hillstrom[2], Yuqing Zhang[3], Emily K. Quinn[1], Michael C. Nevitt[4], Neil A. Segal[5], Cora E. Lewis[6] and David T. Felson[3]. [1]Boston University, Boston, MA, [2]Hospital Special Surgery (HSS), New York, NY, [3]Boston University School of Medicine, Boston, MA, [4]University of California, San Francisco, San Francisco, CA, [5]University of Iowa, Iowa City, IA, [6]University of Alabama, Birmingham, Birmingham, AL

Background/Purpose: Studies of older adults suggest an association between plantar pressure measures of foot pronation and medial tibiofemoral (med TF) cartilage damage, while studies of younger adults suggest an association with lateral patellofemoral (lat PF) pain. These were cross-sectional studies, however. We assessed the longitudinal relationship of foot pronation in walking with 2-year risk of incident med TF and lat PF cartilage damage in at-risk older adults.

Methods: The Multicenter Osteoarthritis Study (MOST) includes adults aged 50–79 years that have or are at risk of knee OA. At the 60 month exam, plantar pressure was assessed using an EmedX to quantify Center of Pressure Excursion Index (CPEI) during 5 trials of self-paced walking (14-day retest ICC > 0.82). Smaller CPEI values indicate increased pronation. From 1.0 T MRIs obtained at 60 and 84 months readers scored one knee per subject for cartilage damage in each sub-region comprising the med TF and lat PF compartments using WORMS grades (weighted kappa > 0.63). Among

sub-regions with WORMS < 2 at 60 months, incident cases had WORMS ≥ 2 at 84 months. With the highest quintile (least pronated feet) as a reference, separate logistic regression models estimated relative odds of incident med TF and lat PF damage in each case-based CPEI quintile while adjusting for age, BMI, sex, and using GEE to account for non-independent sub-regions of a compartment.

Results: 1123 participants (mean age 66.8 ± 7.5 yrs, BMI 29.7 ± 4.8 kg/m^2, 62.4% female) contributed one knee each (mean CPEI 19.8 ± 6.6) to the analysis of med TF damage, while 904 participants with similar characteristics contributed to the analysis of lat PF damage. Only 3.6% and 2.6% of sub-regions had incident med TF and lat PF damage, respectively. Although relative odds of lat PF damage were increased (OR = 2.04; 95% CI: 0.72, 5.82) among the most pronated feet (CPEI 13.7 to −7.7), pronation was not strongly associated with odds of med TF damage (see table). With few incident cases contributing, no findings achieved statistical significance ($p > 0.05$).

Table. Relative odds (OR) of incident medial tibiofemoral and lateral patellofemoral cartilage damage in quintiles of increasing foot pronation during walking.

	CPEI (high)	Center of Pressure Excursion Index (CPEI) Increasing Pronation →			CPEI (low)
	44.2, 24.9	24.8, 20.9	20.8, 17.6	17.5, 13.8	13.7, −7.7
Incident Medial Tibiofemoral Cartilage Damage					
# Knees	243	220	214	190	189
# Sub-regions	864	756	784	654	682
% Damage	3.8%	4.1%	3.8%	3.2%	3.7%
Adj OR* (95% CI)	1.00 (ref)	0.96 (0.54, 1.70)	0.93 (0.50, 1.73)	0.78 (0.42, 1.44)	0.81 (0.41, 1.58)
	CPEI (high)	Increasing Pronation →			CPEI (low)
	44.2, 25.6	25.5, 21.4	21.3, 17.9	17.8, 13.8	13.7, −7.7
Incident Lateral Patellofemoral Cartilage Damage					
# Knees	160	174	190	161	165
# Sub-regions	259	266	290	237	243
% Damage	2.3%	1.9%	1.7%	2.1%	4.1%
Adj OR* (95% CI)	1.00 (ref)	0.82 (0.25, 2.70)	0.78 (0.24, 2.58)	0.97 (0.29, 3.24)	2.04 (0.72, 5.82)

* Adjusted for age, BMI, sex, and non-independent sub-regions of a knee compartment.

Conclusion: In the first longitudinal data on foot pronation and risk of knee cartilage damage, we cannot confirm cross-sectional findings of an association between excessive pronation and med TF disease. Yet, this data does suggest a possible association between extreme foot pronation and elevated risk of lat PF damage. Studies with higher incidence rates are needed to confirm this.

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History Of Knee Injury Is Weakly Associated With Knee Structural Change In Middle Or Older Aged Adults. Hussain Ijaz Khan[1], Dawn Aitken[1], Changhai Ding[1], Leigh Blizzard[1], Jean Pierre Pelletier[2], Johanne M. Pelletier[3], Flavia Cicuttini[4] and Graeme Jones[1]. [1]Menzies Research Institute Tasmania, University of Tasmania, Hobart, 7000, Australia, [2]Institut de Rhumatologie de Montréal, Montreal, QC, [3]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, [4]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, 3004, Australia

Background/Purpose: History of knee joint injury is a strong risk factor for the development of knee osteoarthritis (OA) but it's not clear how different structures comprising the knee joint are affected by injury. The aim of this study was to describe the association between history of knee injury and knee structural changes on MRI in middle aged and older adults.

Methods: This study included two population based samples. (I)the Offspring Study comprised of middle aged adults (n=372; mean age 45.0 years, range 26–61 years; 57.5% female). Approximately half were adult offspring of subjects who had a knee replacement performed for knee OA and the remaining were randomly selected controls that were initially matched by age and sex.(II) the Tasmanian Older Adult Cohort (TASOAC) Study comprised of older adults(n=430; mean age 63.0 years, range 51 – 79 years; 51% female) which were selected from the electoral roll using sex-stratified simple random sampling without replacement. 1.5 T MRI scans of the right knee at baseline was performed in both studies to measure bone marrow lesions (BMLs), cartilage volume, tibial bone area, cartilage defects, and meniscal pathology. History of knee injury was assessed using a self-administered questionnaire. The association between knee injury and knee structures was determined using multiple linear and log binomial regression models.

Results: In middle aged adults, only BML prevalence (Prevalence Ratio (PR)=1.6 (1.2, 2.0)) was significantly higher in those with knee injury in adjusted analysis (Table 1). In older adults, cartilage defects (PR=1.3 (1.0,1.7), total tibial cartilage volume (Difference of Means (df)= −323 (−616,−32)) and BMLs (PR=1.4 (1.0,1.9)) showed significant associations with knee injury in adjusted analysis. Meniscal tears and extrusions showed no significant associations in either of the two cohorts and tears were very common.

Table 1. Association between injury and bone marrow lesions in the knee

BMLs Absent/ Present(site)	Injury	No Injury	Unadjusted PR (95% CI)	Adjusted* PR (95% CI)
OFFSPRING	**%**	**%**		
Medial Tibial	33 (13/39)	16 (25/159)	**2.1 (1.2, 3.8)**	**1.9 (1.0, 3.4)**
Lateral Tibial	31 (12/39)	25 (40/161)	1.2 (0.7, 2.1)	1.3 (0.8, 2.3)
Medial Femoral	31 (12/39)	11 (17/160)	**2.9 (1.5, 5.6)**	**2.7 (1.3, 5.3)**
Lateral Femoral	21 (8/39)	14 (23/159)	1.4 (0.7, 2.9)	1.5 (0.7, 3.2)
Total	72 (28/39)	49 (82/158)	**1.5 (1.1, 1.9)**	**1.6 (1.2, 2.0)**
TASOAC				
Medial Tibial	33 (15/46)	18 (63/346)	**1.9 (1.1, 3.1)**	**1.8 (1.1, 3.1)**
Lateral Tibial	17 (8/46)	15 (51/346)	1.5 (0.8, 3.0)	1.6 (0.8, 3.2)
Medial Femoral	17 (8/46)	12 (40/346)	**2.0 (1.0, 3.9)**	**1.9 (1.0, 3.5)**
Lateral Femoral	30 (14/46)	17 (58/346)	1.7 (0.9, 3.0)	1.7 (0.9, 3.0)
Total	52 (24/46)	41 (143/346)	**1.4 (1.1, 1.9)**	**1.4 (1.0, 1.9)**

PR-Prevalence Ratio
CI-Confidence Interval
*Adjusted for age, sex and bmi

Conclusion: In terms of specific structural abnormalities, history of knee injury is weakly and inconsistently associated with knee structural changes in either middle age or later life suggesting most structural change in the knee is atraumatic.

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Classification Of Alignment By Self-Report Versus Radiograph Results In Unexpected and Discrepant Pain and Functional Outcomes. E Megan Erickson, Jeffrey B. Driban, Lori Lyn Price, Chenchen Wang, Timothy E. McAlindon and William F. Harvey. Tufts Medical Center, Boston, MA

Background/Purpose: Malalignment is a potential risk factor for structural progression of knee osteoarthritis (OA), but data conflict as to its association with knee pain. We hypothesize that subjective alignment measures are less burdensome and yield results similar to radiographic measures. As obesity is also associated with pain in knee OA, there could be interactions between obesity and alignment when assessing pain and function. Thus, we investigated if pain and function differ between obese and non-obese individuals with and without knee malalignment using both radiographic and self-reported classification of alignment.

Methods: We used baseline data derived from two clinical trials for symptomatic knee OA. Both trials used similar definitions of knee OA (ACR radiographic criteria). We assessed pain and function at baseline with the WOMAC and Short Form 36 Health Survey (SF-36) subscales and chair stand time. Participants were asked if they perceived themselves as bow-legged, straight-legged, or knock-kneed. One reader measured anatomic axis from posteroanterior fixed-flexion weight-bearing knee radiographs using a validated standard method [ICC (3, 1) = .94]. We adjusted anatomic axis measures (female, −3.5°; male, −6.4°) to better reflect mechanical axis and categorized them using typical definitions (see table). To analyze the influence of malalignment, obesity, and their interaction, we performed a 2 (obesity) × 2 (alignment) analysis of variance for each outcome. We conducted analyses using the self-report and radiographic classifications with varus (< 178°) and valgus (> 182°) groups collapsed.

Results: Characteristics of our 201 participants, stratified by obesity and radiographic alignment, are shown in the table. Using radiographic classification, malaligned groups had better WOMAC pain and function, SF-36 body pain, and chair stand time, independent of obesity. Using self-report classi-

fication, malaligned groups had worse WOMAC pain and function, SF-36 body pain and physical function, and chair stand time, again independent of obesity, but no outcome reached statistical significance. We found no significant interactions between obesity and either alignment method. Multiple sensitivity analyses using 3 categories of alignment, restricting analyses to women, and examining the trials separately, did not change the results.

Table. Study Sample Characteristics

Outcome	Radiographic Alignment: Non-obese (≤ 30 kg/m^2) Neutrally aligned (178°–182°) (n = 21)	Non-obese (≤ 30 kg/m^2) Malaligned (<178° or >182°) (n = 65)	Obese (> 30 kg/m^2) Neutrally aligned (178°–182°) (n = 32)	Obese (> 30 kg/m^2) Malaligned (<178° or >182°) (n = 83)	*p*-value: Obesity Main Effect	*p*-value: Alignment Main Effect	*p*-value: Obesity* Alignment Interaction
Female (n, %)	18 (85.7)	24 (36.9)	27 (84.4)	53 (63.9)	0.003	< 0.0001	
Caucasian (n, %)	13 (61.9)	42 (64.6)	13 (40.6)	46 (55.4)	0.09	0.1	
K/L Grade > 2 (n, %)	6 (28.6)	35 (53.8)	8 (25.0)	59 (71.1)	0.1	< 0.0001	
Age (years)	59.7	60.1	57.8	58.3	0.1	0.7	0.99
BMI (kg/m^2)	26.3	26.6	36.1	35.3			
WOMAC pain (VAS, 0–500)*	223.7	205.3	264.8	223.5	0.05	0.02	0.4
WOMAC Function (VAS, 0–1700)*	818.4	707.8	968.6	784.8	0.02	0.001	0.4
SF-36 Body Pain (0–100)**	46.4	49.9	37.2	47.7	0.1	0.009	0.2
SF-36 Physical Functioning (0–100)**	52.6	52.0	36.1	47.0	0.02	0.09	0.1
Chair Stand Time (secs)	21.6	18.1	27.5	23.2	0.002	0.04	0.8
Outcome	**Self-Reported Alignment: Non-obese (≤ 30 kg/m^2) Neutrally aligned (178°–182°) (n = 57)**	**Non-obese (≤ 30 kg/m^2) Malaligned (<178° or >182°) (n = 29)**	**Obese (> 30 kg/m^2) Neutrally aligned (178°–182°) (n = 80)**	**Obese (> 30 kg/m^2) Malaligned (<178° or >182°) (n = 35)**	***p*-value: Obesity Main Effect**	***p*-value: Alignment Main Effect**	***p*-value: Obesity* Alignment Interaction**
Female (n, %)	26 (45.6)	16 (55.2)	57 (71.3)	23 (65.7)	0.003	< 0.0001	
Caucasian (n, %)	36 (63.2)	19 (65.5)	45 (56.3)	14 (40.0)	0.09	0.4	
K/L Grade > 2 (n, %)	27 (47.4)	14 (48.3)	42 (52.5)	25 (71.4)	0.1	0.1	
Age (years)	59.3	61.3	58.8	56.6	0.1	0.8	0.1
BMI (kg/m^2)	26.4	26.8	35.1	36.5			
WOMAC pain (VAS, 0–500)*	200.6	227.7	235.3	234.2	0.04	0.4	0.3
WOMAC Function (VAS, 0–1700)*	714.7	774.3	831.2	846.8	0.02	0.5	0.6
SF-36 Body Pain (0–100)**	52.0	43.3	44.8	44.8	0.1	0.2	0.1
SF-36 Physical Functioning (0–100)**	55.1	46.4	45.4	40.6	0.01	0.08	0.6
Chair Stand Time (secs)	19.06	18.99	23.90	25.27	0.002	0.7	0.7

*Smaller is better.
** Larger is better.

Conclusion: Conventional wisdom suggests that both obesity and malalignment should cause more pain in people with knee OA. However, our results suggest that assessing the exposure of malalignment using radiographs vs. self-report may yield different, counterintuitive, results. Because more people classified themselves as neutrally aligned, the discrepancy could not have been due to a perceived connection between malalignment and pain. Studying these classifications of exposure with longitudinal outcomes will provide further insights into their relative utilities.

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The Association Of Proximal Tibia Shape With Sex: The Osteoarthritis Initiative. Barton L. Wise[1], Felix Liu[2], Neeta Parimi[3], John A. Lynch[4], Yuqing Zhang[5], Lisa Kritikos[1] and Nancy E. Lane[1]. [1]UC Davis School of Medicine, Sacramento, CA, [2]University of California at San Francisco, San Francisco, CA, [3]California Pacific Medical Center Research Institute, San Francisco, CA, [4]University of California-San Francisco, San Francisco, CA, [5]Boston University School of Medicine, Boston, MA

Background/Purpose: Knee osteoarthritis (OA) manifests disproportionately in women and the etiology remains unclear. Bone shape has been found to be associated the development of knee OA in prior studies. To further explore this relationship, we examined the association of proximal tibia shape with sex to begin to understand these relationships.

Methods: We used information from the NIH-funded Osteoarthritis Initiative (OAI), a cohort of persons aged 45–79 at baseline who either had symptomatic knee OA or were at high risk of it. We randomly sampled knees from women and men from the OAI cohort who had Kellgren/Lawrence grade of 0 in central readings on baseline radiograph who were aged between 45 and 60 years. Using baseline radiographs we characterized proximal tibia shape using Active Shape Modeling to generate the modes of shape difference across our selected population. Given that all modes were normally distributed, we performed linear regression to examine the association of proximal tibia shape with sex, adjusting for age, race, body mass index (BMI) and clinic site. Beta estimates and 95% confidence intervals report the amount of standard deviation increase or decrease in mode shape among women compared to men.

Results: The mean age of subjects in the analysis was 52.7 years (±4.3 SD) for both men and women. There were 191 female knees and 149 male knees. 10 modes were derived for tibial shape. The 10 modes described 95.5% of the total variance in proximal tibia shape in the population sampled. Mode 2 had the highest significance for association with sex (p=0.009). (See table for beta estimates and description of first 5 modes.)

Mode	Adjusted Beta (95%CI)	P-value	Mode Description – primary alteration of shape with increased SD weighting
1	−0.2 (−0.42 to 0.02)	0.0797	Decreased concavity, elevation of lateral compartment plateau, and decreased shaft width
2	−0.29 (−0.51 to −0.07)	0.0091	Tibial head shifted laterally in relation to the shaft, and head width increased. The lateral tibial plateau is more concave
3	−0.22 (−0.43 to −0.01)	0.0376	Slightly increased tibial width, depression of medial plateau and elevation of lateral plateau
4	−0.23 (−0.45 to −0.02)	0.0324	Increased concavity of medial compartment and elevation of medial lip, with broadening of lateral plateau
5	−0.01 (−0.23 to 0.2)	0.9097	Narrowed medial plateau width and slight elevation of lateral plateau

Conclusion: Tibial knee shape may be associated with sex. Further work to understand how these shape modes are associated with knee OA, and whether they can explain differences in prevalence of OA by sex, is warranted.

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Underdiagnosis and Undertreatment Of Knee Osteoarthritis In The Obese Population: The Need For Physician Education and Advocacy. Janice Lin, Ryan Flanagan, Jay Bhatia, Manish Parikh, Christine Ren-Fielding, Renata La Rocca Vieira, Steven B. Abramson and Jonathan Samuels. NYU Langone Medical Center, New York, NY

Background/Purpose: Obesity is a modifiable risk factor of knee osteoarthritis (KOA). While medical treatments for KOA can have a limited effect, an alternative strategy would target weight loss to reduce the arthritis burden. Supportive of other literature, we recently showed in a retrospective analysis that 51% of patients who underwent LapBand surgery reported complete improvement in KOA pain after 18 months. Therefore we began a prospective study to evaluate the prevalence of knee pain and KOA in the obese population, observe how knee pain is treated, and track how bariatric weight loss affects KOA-related pain and physical function.

Methods: We screened consecutive patients prior to bariatric surgery with the LapBand, sleeve gastrectomy, or gastric bypass. We enrolled patients (age'21) with knee pain for ≥1 month and a visual analog scale (VAS) pain score ≥30mm, excluding lupus, inflammatory arthritis, or psoriasis. Treatment history for knee pain was recorded. Baseline assessments included validated questionnaires: Western Ontario McMasters Universities Osteoarthritis Index (WOMAC), Assessment of Obesity-Related Comorbidities, and Knee Injury and Osteoarthritis Outcome Score. Those with radiographic KOA by the Kellgren-Lawrence (KL) grading scale >1 will repeat questionnaires post-surgery.

Results: We evaluated 262 patients, with 136 reporting knee pain and 62 consenting for the study (88.7% female, mean BMI 44.5 kg/m^2±8.3, range: 32.0–60.4, and mean age 44 years±10.3, range:22–70). 52% were scheduled for sleeve gastrectomy (mean BMI=43.0 kg/m^2), 26% for Lapband (BMI=43.7), and 22% for gastric bypass (BMI=48.8). The mean VAS score was 65.4 (±19.1;range:30–100), WOMAC pain 265.1 (±101.8;range:13–466), WOMAC stiffness 99.1 (±59.2;range:0–187) and WOMAC physical function 917.1 (±427.9;range:0–1589). Baseline radiographs revealed that 96% had evidence of OA (70.6 % KL 2–4 and 25.4% KL1). Despite significant knee pain in this cohort, only 4.8% (3/62) had seen rheumatologists and 17.7% orthopedists – while 55% were treated by primary care and 22.5% had never discussed their knee pain treatment with a physician. Only 37% had taken x-rays previously to evaluate knee pain. Not surprisingly, the ACR OA treatment guidelines were not met in a majority of our cohort: Only 40.3% had been referred for physical therapy, 80.6% tried acetaminophen, 70.9% NSAIDs, 6.4% narcotics, 1.9% SSRI, 12.9% tramadol, 11.2% topical NSAIDs, 16.1% intra-articular steroids, and 3.2% viscosupplementation.

Conclusion: In this early phase of our prospective study of bariatric patients, we found that moderate radiographic KOA is common in obese patients with knee pain. In many cases, pain had been attributed to mechanical load from obesity without proper evaluation or treatment. Few patients were referred to rheumatologists, though would benefit from such evaluation and management. These data indicate that knee OA in obese patients is underdiagnosed and undertreated. There is a need to educate primary care and bariatric providers that knee pain from OA and other pathology in obese patients should be diagnosed and treated appropriately to maximize their function and quality of life.

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Examining Patient Reported Outcome Measurement Information System Measures In Community Dwelling Adults With Arthritis. Ana-Maria Orbai[1], Leigh F. Callahan[2], Rebecca J. Cleveland[3], Sharon R. Ghazarian[1], Susan J. Bartlett[1] and Clifton O. Bingham III[1]. [1]Johns Hopkins University, Baltimore, MD, [2]University of North Carolina, Chapel Hill, NC, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC

Background/Purpose: Arthritis is the leading cause of disability in the US and impacts on multiple aspects of health-related quality of life (HRQoL). Many multidimensional HRQoL measures used in arthritis have complex scoring algorithms and are sometimes proprietary limiting their utility in clinical care and research. The Patient Reported Outcome Measurement Information System (PROMIS) was developed by NIH using modern psychometrics to provide publicly available, population normalized measures to assess domains of physical, emotional, and social health. Assessments of PROMIS measures in arthritis have been limited to pain, function and fatigue in small numbers of patients. It was our goal to evaluate PROMIS measures in a large group of adults with self-reported arthritis.

Methods: Six PROMIS short forms for pain interference (6 items), physical function (10), fatigue (7), sleep quality (8), depression (8), and satisfaction with social roles (7) were administered to community dwelling adults with self-reported arthritis enrolled in the Walk with Ease (WWE) study. Raw scores were transformed to T scores for analysis, with the population mean 50 and standard deviation 10. Other measures included general health; pain, fatigue and stiffness VAS; and the improved HAQ (score range 0 to 100). Analyses were conducted to examine the effect of age and BMI using Stata 12.

Results: Instruments were administered to 439 adults with arthritis: 88% female, 70% White, 26% Black or African-American; general health 34% very good and excellent, 48 % good and 18 % fair; mean (SD) age 64 (12) BMI 30 (7); pain VAS 38.1 (25.3) fatigue VAS 37.3 (28.3), stiffness VAS 42.4 (26.7), IHAQ 14 (14). Mean (SD) PROMIS T scores were: pain interference 54.5 (6.9), fatigue 52.3 (8.3), physical function 42.8 (6.5), depression 49 (7.8), sleep quality 50.1 (9.66), satisfaction with social roles 48.6 (9). After adjustment for age, T scores were significantly worse for obese vs. non-obese for pain interference, fatigue, physical function, satisfaction social roles (Table).

Table. PROMIS T scores in obese versus non-obese people with self-reported arthritis

	T scores Mean (SD)		
	BMI<30 (n=254)	BMI ≥30 (n=185)	Age adjusted p-value
PROMIS Pain Interference	53.4 (7.4)	55.9 (6.3)	<0.001
PROMIS Fatigue	50.7 (8.3)	54.5 (7.8)	<0.001
PROMIS Physical Function*	43.8 (6.7)	41.4 (5.9)	<0.001
PROMIS Depression	48.4 (7.3)	49.8 (8.4)	0.1
PROMIS Sleep Quality	49.9 (9.7)	50.6 (9.4)	0.7
PROMIS Satisfaction with Social Roles	50.1 (8.8)	46.4 (9.0)	<0.001

*Lower scores represent worse physical function

Conclusion: PROMIS measures identify worse pain interference, fatigue, and physical function in people with self-reported arthritis compared to population-based norms. PROMIS social role satisfaction measures indicate arthritis impacts participation in valued life activities. Significantly worse fatigue (0.4 SD) and decreased satisfaction with social roles (0.4 SD) were seen in obese vs. non-obese, after adjustment for age. Studies are ongoing to evaluate responsiveness of PROMIS measures compared with legacy measures with an exercise intervention in the WWE study. Further studies are needed to evaluate the impact of obesity on other measures of HRQL in individuals with arthritis.

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Pain, Functional Impairment and Ultrasound Detected Changes In Patients With Erosive and Non-Erosive Hand Osteoarthritis. Olga Sleglova[1], Olga Ruzickova[2], Karel Pavelka[2] and Ladislav Senolt[3]. [1]Institute of Rheumatology, Prague, Prague, Czech Republic, [2]Institute of Rheumatology and Department of Rheumatology, 1st Medical Faculty, Charles University Prague, Prague, Czech Republic, [3]Institute of Rheumatology, Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic

Background/Purpose: Hand osteoarthritis (HOA) is a common and frequent cause of pain. HOA is a heterogeneous group of disorders with two main subsets including non-erosive disease and erosive, sometimes referred to as inflammatory, HOA. Few studies demonstrated inflammatory ultrasound changes and more severe clinical symptoms in patients with erosive compared with non-erosive disease, however the results are inconclusive. The aim of the study was to compare pain, stiffness, physical impairment and ultrasound features between patients with erosive and non-erosive HOA in a cross-sectional study.

Methods: Consecutive patients with symptomatic HOA fulfilling the American College of Rheumatology (ACR) criteria were included in this study. Joint tenderness and swelling were assessed. Patients reported joint pain on 100 mm visual analogue scale (VAS) was completed. Pain, joint stiffness and disability were assessed by the Australian/Canadian OA hand index (AUSCAN). Radiographs of both hands were examined and erosive disease was defined by at least one erosive interphalangeal joint. Effusion, synovial hypertrophy and power Doppler signal (PDS) were scored with ultrasound. Synovitis was graded on a scale of 0–3 and osteophytes were defined as cortical protrusions seen in two planes.

Results: Altogether, 81 patients (five male) with symptomatic nodal HOA were included in this study between April 2012 and April 2013. Out of these patients, 46 had erosive disease. Patient's characteristics are given in table 1. The intensity of pain assessment on VAS ($p<0.05$), duration of morning stiffness ($p<0.05$) and number of clinically swollen joints ($p<0.05$) were significantly higher in patients with erosive compared with non-erosive disease. Accordingly, functional impairments assessed by AUSCAN showed more disability in patients with erosive compared with non-erosive disease ($p<0.05$). US-detected pathologies (gray-scale synovitis, power Doppler signal and osteophytes) were common in both groups of patients. Although, synovial hypertrophy was higher in patients with erosive compared with non-erosive disease (total score: 7.7 vs. 3.8; $p<0.05$), the differences in intensity of power Doppler signal and number of osteophytes did not differ between both groups.

Table 1.

	All patients	Non-erosive HOA	Erosive HOA
Age, years (mean ± SD)	66.74 ± 8.87	64.49 ± 8.21	68.46 ± 8.97
Female, no. (%)	76 (96.30%)	33 (94.29%)	43 (93.48%)
Disease duration, years (mean ± SD)	8.78 ± 8.18	7.91 ± 8.57	9.43 ± 7.81
BMI, kg/m2 (mean ± SD)	28.36 ± 5.42	28.98 ± 6.06	27.88 ± 4.82
AUSCAN, total (mean ± SD)	22.94 ± 11.43	20.51 ± 10.51	24.78 ± 11.53
AUSCAN A, pain (mean ± SD)	8.47 ± 4.41	8.03 ± 4.45	8.80 ± 4.36
AUSCAN B, function (mean ± SD)	2.00 ± 0.89	1.83 ± 1.06	2.13 ± 0.71
AUSCAN C, stiffness (mean ± SD)	12.04 ± 6.52	10.37 ± 6.21	13.30 ± 6.46
VAS, pain (mm)	43.19 ± 24.20	39.71 ± 24.80	45.84 ± 23.40
Tender joints, no.	9.49 ± 6.58	9.26 ± 7.23	9.67 ± 6.04
Swollen joints, no.	3.49 ± 4.28	2.83 ± 3.52	4.00 ± 4.71
NSAIDs, no. (%)	37 (45.68%)	16 (45.71%)	21 (46.65%)
SYSADOA, no. (%)	55 (67.90%)	23 (65.71%)	32 (69.57%)

Conclusion: This study shows that patients with erosive HOA have more hand pain, joint stiffness and functional limitation associated with US-

detected synovial hypertrophy, but not with inflammatory signs or osteophyte formation.

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Concordance Of Hip Pain With Radiographic Hip Osteoarthritis In An Urban US Community: The Framingham Osteoarthritis Study. Kyu Chan Kim[1], David T. Felson[2], Katherine D. Linsenmeyer[1], Ali Guermazi[3], Steven C. Vlad[3], Mary M. Clancy[3] and Jingbo Niu[2]. [1]Boston Medical Center, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Boston University, Boston, MA

Background/Purpose: While it is well known that knee pain and radiographic knee osteoarthritis (OA) are often discordant, little is known of the concordance of hip pain with the presence of radiographic hip OA. From a prevalence study of hip osteoarthritis done in Framingham, Massachusetts, we examined the relationship between hip pain and radiographic hip OA.

Methods: We performed a community based study of OA among persons age 50–79 living in Framingham in 2002–2005 with recruitment by random digit dialing and subjects studied without respect to joint pain or arthritis. Anteroposterior standing long-limb radiographs of the lower extremities including the pelvis were obtained and were read for radiographic hip OA(ROA) by two trained physicians. Cases of ROA were confirmed by an experienced musculoskeletal radiologist. ROA was defined as Kellgren-Lawrence score ≥ 2. Using a homunculus in which the hip joint was depicted as a large circle in the groin, participants were asked whether they had hip pain on most days. Those who said 'yes' were defined as having hip pain. If they had hip pain, subjects then answered another question asking location of pain: groin, front of the leg (anterior), outside the leg (lateral), lower back, or buttocks. Also, many participants had a standardized hip exam during which they were asked about pain during passive internal rotation. We examined sensitivity (Sn), specificity (Sp) and positive and negative predictive values (PPV, NPV) of different constellations of hip pain and location specific pain with ROA.

Results: Radiographs from 948 participants were evaluated including 419 men and 529 women. The average age was 63.5 years (s.d. 9 yrs). One hundred sixty participants (87 men and 73 women) had ROA (16.9%). One hundred eighty-two participants (19.2%) had hip pain. Only 22% of participants with hip pain had ROA in the same hip whereas 15.7% of participants without hip pain had ROA in that hip. The Sn of hip pain for ROA was 25%, the Sp of hip pain for ROA was 82%, and the PPV for hip pain was 22% (See table). However, when we restricted analyses to those with hip pain who localized this pain to the groin, the PPV rose to 38.1%. But of those with ROA, only 6.3% had hip and groin pain. For hip pain with anterior pain, the PPV was 27.8%, and the Sn was 7%. The diagnostic test performance for other sites of pain was poorer. If a participant had hip pain and pain with passive internal rotation, 18% had ROA.

	Sensitivity	Specificity	PPV	NPV
Hip Pain	25% (40/160)	82% (646/788)	22.0% (40/182)	84.3% (646/766)
Hip Pain with Groin Pain	6.3% (8/128)	98% (646/659)	38.1% (8/21)	84.3% (646/766)
Hip Pain with Anterior Pain	7.0% (9/129)	96.4% (646/670)	27.8% (9/33)	84.3% (646/766)
Hip Pain with Lateral Pain	13% (18/138)	89.7% (646/720)	19.6% (18/92)	84.3% (646/766)
Hip Pain with Low Back Pain	10% (12/132)	90% (646/719)	14.1% (12/85)	84.3% (646/766)
Hip Pain with Buttocks Pain	5.5% (7/127)	95% (646/680)	17.1% (7/41)	84.3% (646/766)
Hip Pain with Pain on Internal Rotation	6.3% (8/128)	94.7% (646/682)	18.9% (8/44)	84.3% (646/766)

Conclusion: We found poor agreement between hip pain on most days and radiographic OA in the ipsilateral hip. Many older persons with frequent hip pain including pain in the groin or front of the thigh did not have positive x-rays in that hip, and many persons with radiographic OA did not have hip pain. Of the constellation of questions for hip pain, those with the highest PPV were hip pain with groin or anterior pain.

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Is There a Role For Non-Mendelian Inheritance In Severe Osteoarthritis Of The Knee. Allen D. Sawitzke[1], Richard Pimentel[2], Jathine Wong[2], Helena Martinez[3], Marta Herrero[4], Josep Verges[5] and Daniel O. Clegg[6]. [1]University of Utah, Salt Lake City, UT, [2]University of Utah, Salt Lake, UT, [3]BIOIBERICA, S.A:, Barcelona, Spain, [4]Bioiberica, Barcelona, Spain, [5]Pharmacological Research Unit, Scientific Medical Department, Bioibérica, S.A., Barcelona, Spain, [6]George Wahlen VA Medical Center/University of Utah, Salt Lake City, UT

Background/Purpose: Although the etiopathogenesis of osteoarthritis of the knee remains largely unknown, it is clear that genetic risks are contributory. Traditional family, twin, case control and GWAS designs have all contributed to the extensive knowledge in this area. Recently, groups have reported that mitochondrial genes are involved (1) and not-involved (2) in OA risk. The Utah Population Database (UPDB), a unique genealogic resource housed at the University of Utah has previously been used to study large founder pedigrees for evidence of many heritable diseases and we have used it to examine traditional Mendelian inheritance in OA of the knee. We hypothesized that these pedigrees could also be used to assess the potential role of non-Mendelian inheritance, specifically mitochondrial inheritance on the development of OA of the knee by comparing the statistical measures of mitochondrial models (MP) to autosomal models (AP) in these same founder families.

Methods: All OA cases who underwent TKA in Utah were selected based on billing codes in the International Classification of Diseases and data pulled from statewide hospital discharge data for a ten year period (1996–2007). Cases and controls matched for gender and age and their families were linked to the UPDB for analysis. The software kinship analysis tool (KAT) was used to analyze mitochondrial (MP) with autosomal (AP) by comparing familial standardized incidence ratio (FSIR) under each inheritance models.

Results: Over 18,000 OA patients who underwent TKA in Utah hospitals were linked to the UPDB and analysis performed for mitochondrial inheritance. The linkage resulted in 683 founder families with at least 5 affected members for analysis in comparison to randomly selected control families.

Pattern	FSIR	Extended Bayes FSIR	PAR
Autosomal Pattern	1	1.75 (1.61–1.91)	0.21 (0.18–0.24)
Mitochondrial Pattern	1.015	1.77 (1.61–1.96)	0.14 (0.12–0.15)

MP had a very low population-attributable risk, PAR value, 14, where AP has a higher value of 0.21. It suggested approximately *% of the population who have OA of the knee could be from mitochondrial inheritance, whereas 21 percent of OA of the knee resulting in TKA are familial.

Conclusion: The UPDB is a resource that has confirmed a Mendelian heritable risk for OA of the knee with a PAR of 21%. Now, it has also been used to shown non-Mendelian, in particular mitochondrial inheritance is not likely responsible for a large fraction of the heritability of OA of the knee severe enough to result in TKA as its associated PAR is 14.

1. Rego-Perez I, Fernandez-Moreno M, Fernandez-Lopez C, Arenas J, Blanco FJ. Mitochondrial DNA haplogroups: role in the prevalence and severity of knee osteoarthritis. Arthritis Rheum. 2008;58(8):2387–96.

2. Hudson G, Panoutsopoulou K, Wilson I, Southam L, Rayner NW, Arden N, et al. No evidence of an association between mitochondrial DNA variants and osteoarthritis in 7393 cases and 5122 controls. Ann Rheum Dis. 2013;72(1):136–9.

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"Generalized Osteoarthritis": A Systematic Review. Amanda E. Nelson[1], Michael W. Smith[2] and Yvonne M. Golightly[3]. [1]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC, [2]Saint Luke's Hospitals, Kansas City, MO, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC

Background/Purpose: To perform a systematic review of definitions, risk factors, and outcomes in "generalized osteoarthritis" (GOA).

Methods: We performed a systematic review of Medline literature using the terms osteoarthritis, generalized, polyarticular, multiple joint, multi-joint, and others to obtain articles related to GOA, following PRISMA guidelines.

The search was completed on 9/25/12 by a professional librarian. The initial searches produced 948 articles for title and abstract review (performed by MWS and AEN), after which 108 underwent full text review (AEN and YMG). Of these, 74, along with 24 identified through bibliographic review of included articles (total=98), were included for data extraction (AEN) based on pre-specified criteria including the requirement for a clearly stated definition of OA (clinical, radiographic, or symptomatic) assessed at more than one body site.

Results: In the 98 included articles, 24 large cohorts (n~30,000) were represented along with numerous clinical series (n~9000), across 22 countries and 60 years (1952–2012). The sites assessed, and OA definitions at each site, varied widely but most often included the hands and knees. In 30 studies where a definition of GOA was stated, no less than 15 definitions of GOA were given; at least 6 groups used a summed score of joints or radiographic grades at multiple sites (Table). While interphalangeal joints were almost always included, there was debate about the appropriateness of including other joints such as spine and hip. Estimates of the prevalence of such variably defined GOA ranged from 1–80%, although a majority were in the 5–25% range.

	Author (year)	No. joints or groups	Nodes	IP	CMC	Knee	Hip	Spine	Other specified sites	PMID
1	Kellgren (1952)			X	X	#	#	#	MTP, TMT	14896078
2	Lawrence (1969)	3+ or 5+	#	#	#	#	#	#		5356946
3	Hordon (1993)	3+		X	#	#	#	#	MTP, shoulder, ankle	8252314
4	Cooper (1996)	2+ to 5+		#	#	#	#			8923371
5	Multiple	2+		#	#	#	#	#		(1)
6	Solomon (1976)	2+	X	#	#		#	#		984909
7	Loughlin (1994)	3+	X							8000735
8	Multiple			X (3+)						(2)
9	Price (1987)	6+	X	#	#	#	#	#		3625636
10	Multiple			X	X	X	#			(3)
11	Hopkinson (1992)		X	X (3+)	#	#	#			1525625
12	Dougados (1996)			X		X		X	bilateral IP or spine + bilateral knee	8938865, 19089534
13	Huang (2000)			X (3+)		X	X			10662878
14	Carroll (2006)		X	X		X			MTP	16755236
15	Hoogeboom (2010)	3+							+ clinical signs + ADL impairment by HAQ	20594308
16	Summary scores									(4)

X=required, #=considered as a potential site.
IP=interphalangeal; CMC=carpometacarpal; MTP=metatarsophalangeal; TMT=tarsometatarsal; ADL=activities of daily living; HAQ=health assessment questionnaire.
(1) PMID: 15818669, 19575196, 18226556.
(2) PMID: 6134929, 9458216, 10402070.
(3) PMID: 8447703, 11132207, 2042984, 10070270, 10760642.
(4)PMID: 6712295, 3780105, 7840096, 9627016, 16079167, 21572158.

A variety of risk factors and outcomes were considered in the included papers. Increased risk of GOA or its progression was associated with age, female sex, and genetic/familial factors. GOA constructs were generally identified more frequently among individuals of European descent. Associations with increased BMI or other measures of body mass were not consistent across studies. A higher BMD was seen in GOA patients in some series but not others. One study estimated the heritability of GOA at 42%. Biomarker (cartilage oligomeric protein [COMP] and urinary type II collagen C-telopeptide [uCTX-II]) levels increased with greater numbers of involved joints. Increased OA burden was associated with higher mortality, poorer health and function, and increased disability.

Conclusion: While there remains no clear or widely agreed upon definition of GOA, this term is commonly used in the literature. There remains substantial debate regarding the existence of GOA as a distinct disease entity, and in what populations, although there appears to be a greater impact on health in the presence of OA in more than one joint. It may be more appropriate for individual studies to clearly define joints evaluated and involved with OA, and use alternate, more descriptive terms, such as multi-joint or polyarticular OA.

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The Proportion Of Knee Osteoarthritis Patients In Southern Sweden That Seek Medical Care. Aleksandra Turkiewicz[1], Maria Gerhardsson de Verdier[2], Gunnar Engström[3], Stefan Lohmander[1] and Martin Englund[1]. [1]Department of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, [2]Astra Zeneca R&D Molndal, Molndal, Sweden, Molndal, Sweden, [3]Dept of Cardiovascular epidemiology, Clinical Sciences, Lund University, Lund, Sweden

Background/Purpose: To provide estimates of the proportion of subjects with knee osteoarthritis (OA) that seek healthcare for knee OA or joint pain within an 8-year period.

Methods: In 2007 a random sample of 10 000 56 to 84 year old Region Skåne residents from the Malmö Diet and Cancer Study (Manjer et al 2001) were sent a mailed questionnaire about knee pain in the last 12 months; this being the first part of the Malmö Osteoarthritis Study (MOA). We classified subjects with knee pain with duration of at least 4 weeks as having *frequent knee pain*. A random sample of 1300 subjects with frequent knee pain and a random sample of 650 subjects without (out of the 7737 questionnaire responders) were invited for a clinical and radiographic examination including assessment of *clinical knee OA* according to the American College of Rheumatology (ACR) clinical criteria. Participants underwent radiography of both knees in weight-bearing and semi-flexion. An independent radiologist who was blinded to clinical data assessed all frontal and patellofemoral radiographs. Subjects who fulfilled criteria approximating Kellgren and Lawrence (KL) grade 2 or worse were considered as having *radiographic knee OA*. We considered those having radiographic knee OA and frequent knee pain to have *symptomatic knee OA*. Using the subject's personal identification number and individual linkage with the Skåne Health Care Register, covering the entire population in the county, we retrieved information on all doctor visits with a diagnosis of knee OA (ICD-10 code M17) or pain in joint (joint unspecified, ICD-10 code M25.5) for the years 2004 to 2011, i.e. the 8-year period preceding and following the MOA examination. We used weighting to adjust for different sampling probabilities depending on the knee pain status as well as for the nonresponse and volunteer bias in the MOA study. We used multiple imputation to account for missing diagnostic codes in the register.

Results: The 10 000 MOA subjects had mean (SD) age of 70 (7.6) years, mean (SD) body mass index was 27.1 (5.0) and 62% were women. The response rate in mailed questionnaire was 77.4% and 1527 invited subjects (78.3%) attended the clinical visit. Out of subjects classified as having *symptomatic knee OA*, 74.6% (95%CI: 70.0% to 79.3%) had consulted a physician during the 8-year time frame and received a diagnosis of knee OA or pain in joint (Table). Among subjects having *clinical knee OA* the corresponding percentage was 66.8% (95%CI: 59.1% to 74.6%). The ICD-10 diagnosis of knee OA was set in 62.9% (95%CI: 57.7% to 68.1%) of subjects with *symptomatic knee OA* and 49.9% (95%CI: 41.8% to 58.1%) of patients with *clinical knee OA*.

Table. The percentage of subjects with knee osteoarthritis (OA) who received a diagnosis of knee OA or pain in joint, respectively, set by a physician during the examined 8-year time frame (2004–2011).

OA definition	Diagnosis of knee OA or pain in joint % (95% CI)*	Diagnosis of knee OA % (95% CI)*	Diagnosis of pain in joint % (95% CI)*
Radiographic knee OA†	56.8(49.1–64.5)	43.4(36.5–50.4)	31.3(23.7–39.0)
Clinical knee OA†	66.8(59.1–74.6)	49.9(41.8–58.1)	39.7(31.0–48.4)
Symptomatic knee OA†	74.6(70.0–79.3)	62.9(57.7–68.1)	40.8(35.2–46.4)
Symptomatic or clinical knee OA†	68.9(63.8–74.0)	53.2(47.6–58.9)	40.1(34.3–45.9)

*- 95%CI: 95% confidence intervals.
†- Radiographic knee OA - changes on x-ray approximating Kellgren-Lawrence grade 2 or worse; Clinical knee OA - clinical OA according to the American College of Rheumatology clinical criteria, recursive positioning method; Symptomatic knee OA - knee pain of duration at least 4 weeks in the last. 12 months in combination with radiographic OA as defined above.

Conclusion: Only 2 of 3 subjects with clinical or symptomatic knee OA consult a physician for his/her knee(s) symptoms in an 8-year time frame. Self-management or coping strategies as well as over-the-counter pain treatments are plausible explanations.

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All-Cause Mortality and Incident Cardiovascular Disease In Knee Osteoarthritis: The Framingham Study. Devyani Misra[1], David T. Felson[1], Ida K. Haugen[2], Martin Englund[3] and Tuhina Neogi[1]. [1]Boston University School of Medicine, Boston, MA, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Department of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden

Background/Purpose: Studies examining the relation of osteoarthritis (OA) to mortality or cardiovascular disease (CVD) have reported conflicting results, raising the question of whether OA itself increases such risks, or rather OA may simply be a marker of these outcomes due to its relation to other factors that heighten such risks, such as obesity. We assessed the relation of knee OA to mortality and incident CVD in a population-based cohort of older adults in which knee OA status, death and CVD were comprehensively assessed in a standardized, validated manner.

Methods: We included participants aged 50–75 from the Framingham OA Study comprising the Original and Offspring cohorts with knee x-rays obtained at exam 18 (1983–85) for the Original cohort, and exam 7 (2002–2005) for the Offspring cohort. Radiographic knee OA (ROA) was defined as Kellgren and Lawrence grade ≥2, and symptomatic knee OA (SxOA) as ROA plus pain in the same knee. All-cause mortality was defined as death due to any cause. *Incident* CVD was defined as a new diagnosis of coronary heart disease, intermittent claudication, CHF, stroke or TIA in the absence of any of these diseases prior to knee OA assessment. All deaths and CVD events were adjudicated by a panel of cardiologists and neurologists using published criteria to review clinical data and hospitalization records. Follow-up started from the date of knee OA ascertainment and continued until the outcome (death/incident CVD) or last assessment in 2009. We truncated follow-up at 10 years to avoid universal occurrence of events in these older subjects. In sensitivity analyses, we evaluated outcomes beyond 10 years. For the incident CVD analysis, only those free of CVD at the time of knee OA ascertainment were eligible for inclusion. The relation of knee OA to overall mortality and incident CVD were examined in both cohorts combined as well as separately, using Cox proportional hazards models, adjusting for age and sex in the first model, and then additionally adjusted in a second model for body mass index (BMI), diabetes mellitus, hypertension, renal disease, aspirin use, lipid-lowering medications and smoking status.

Results: Among 2037 participants (mean age 66 yrs, 58% women, mean BMI 27 kg/m^2, 499 ROA, 163 SxOA), there were 873 deaths and 624 incident CVD cases. No association was found between knee OA (ROA or SxOA) and overall mortality or incident CVD (Table), with effect estimates in the adjusted models ranging from 0.93–1.27. Results were similar when the cohorts were analysed separately and in the sensitivity analyses. While OA was associated with obesity and other risk factors for CVD, additionally adjusting for these factors did not affect the risk of the outcomes.

Table. Relation of Knee Osteoarthritis to All-cause mortality and incident cardiovascular disease in Framingham Original and Offspring cohorts combined

Knee OA status	N (%)	Mean follow-up (years)	Crude HR	Adjusted HR* (95% CI)	Adjusted HR** (95% CI)
		All-cause mortality			
ROA					
Yes (N=499)	258 (52)	6.06	0.99	0.93 (0.78, 1.10)	1.04 (0.85–1.28)
No (N=1538) (referent grp)	615 (40)	5.23			
SOA					
Yes (N=163)	58 (36)	4.53	0.99	0.98 (0.71, 1.35)	1.00 (0.67, 1.50)
No (N=1852) (referent grp)	802 (43)	5.48			
		Incident Cardiovascular Events			
ROA					
Yes (N=499)	183 (42)	4.22	1.13	1.06 (0.84, 1.34)	0.97 (0.75, 1.27)
No (N=1538) (referent grp)	441 (31)	3.56			
SOA					
Yes (N=163)	50 (34)	2.28	1.23	1.23 (0.81, 1.91)	1.27 (0.77, 2.07)
No (N=1852) (referent grp)	566 (34)	3.80			

*Adjust for age and sex only.
**Additionally adjusted for BMI, diabetes mellitus, hypertension, renal disease, aspirin use, lipid-lowering medication use, smoking.

Conclusion: In this large cohort of community-dwelling older adults, there was no significant relation of knee OA to mortality or incident CVD, suggesting knee OA itself likely does not have systemic effects.

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Cardiovascular Disease In Osteoarthritis: Hip Versus Knee and The Influence Of Multiple Symptomatic Joint Involvement. Anthony V. Perruccio[1], Rita A. Kandel[2] and Aileen M. Davis[3]. [1]Toronto Western Hospital, Toronto Western Research Institute, and University of Toronto, Toronto, ON, [2]Mount Sinai Hospital and University of Toronto, Toronto, ON, [3]Health Care and Outcomes Research, Toronto Western Research Institute; Departments of Rehabilitation Science and Health Policy, Management and Evaluation, University of Toronto, Toronto, ON

Background/Purpose: The strength of association between obesity and osteoarthritis (OA) is reported to vary by joint (e.g. stronger association with knee than hip). As well, the association between obesity and non weight-bearing joints, such as the hands, suggests that systemic/metabolic factors are involved. The presence of multiple symptomatic joints among individuals with severe OA in at least one joint further suggests likely systemic factors in OA. Given known associations between systemic/metabolic factors and cardiovascular disease (CVD) risk, this study investigated the likelihood of reporting CVD between those with hip vs. knee OA, and further considered if the number of symptomatic joints influenced this likelihood.

Methods: Patients with severe OA (443 hip; 540 knee) reported CVD, diabetes, high blood pressure (HBP), symptomatic joints, height, weight, age and sex. The cross-sectional association between study measures and prevalent CVD was investigated using logistic regression, with the inclusion of an interaction term between symptomatic joint count and knee/hip group membership. Subsequently, the analysis was stratified by knee/hip.

Results: Knee: ages 41–88 years, 64% female, 4% CVD, 14% diabetes, 50% HBP. Hip: ages 40–91 years, 55% female, 5% CVD, 9% diabetes, 43% HBP. Mean joint count was 5 (±4), ranging from 1–20. Adjusted for age, sex, body mass index, and presence of diabetes or HBP, the knee cohort had odds 4 times greater than hips for reporting CVD ($p<0.01$). There was a significant interaction between joint count and knee/hip group status, such that the effect of increasing joint count was greater for the hip cohort. From stratified analyses, joint count was associated with CVD in the hip cohort only, with a 25% increased odds with each numerical increase in symptomatic joint count (odds ratio (OR): 1.25, $p<0.001$). In the knee cohort, the presence of diabetes or HBP was significantly associated with reporting CVD (OR: 3.74, $p=0.02$), whereas a similar association was not found in the hip cohort (OR: 1.23, $p=0.68$).

Conclusion: The variable association observed with CVD between hip and knee OA, alongside the differential influence of the extent of symptomatic joint involvement between joint groups suggests different OA phenotypes, with potentially varying roles for systemic factors. This has potential implications for our understanding of OA, and suggests a potential need for multimodal approaches to treatment and management.

Disclosure: A. V. Perruccio, None; **R. A. Kandel**, None; **A. M. Davis**, None.

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Risk Of Falls Increases With Additional Symptomatic Osteoarthritic Joints: The Johnston County Osteoarthritis Project. Adam Dore[1], Yvonne M. Golightly[1], Vicki Mercer[1], Jordan B. Renner[1], Xiaoyan A. Shi[2], Joanne M. Jordan[3] and Amanda E. Nelson[3]. [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]SAS Institute, Inc, Cary, NC, [3]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC

Background/Purpose: Falls, a growing problem among older adults, often lead to hospitalizations, surgeries, and death. Knee and hip osteoarthritis (OA) are known risk factors for falls, but whether they together additionally contribute to falls risk is unknown. This study utilizes a cohort of African American and Caucasian men and women with and without OA to examine the influence of body OA burden on risk for future falls.

Methods: A longitudinal analysis was performed using data from 2 time points of the Johnston County OA Project. The outcome of interest was falls at follow up (~5 years after initial visit), based on the response to the question "In the last 12 months, have you had any falls of any type?" Baseline risk factors included age, sex, race, body mass index, and prior falls, with a focus on symptomatic OA of the hip and knee (Model 1). Symptomatic OA was defined as patient reported symptoms (pain, aching, or stiffness on most days) and radiographic evidence of OA (Kellgren Lawrence grade ≥ 2 or joint replacement secondary to OA in the tibiofemoral or hip joint) in the same

joint. Additional potential contributing factors were 6 comorbid conditions, alcohol and medication use (sleep aids, narcotics, vitamin D, and bisphosphonates), and low back symptoms (Model 2). Logistic regression analyses were used to determine associations (adjusted odds ratios [aOR]) between baseline covariates and falls at follow-up in both Models 1 and 2.

Results: Participants (n=1,619) had a mean age of 62 years (SD 9.03); 72% were Caucasian, 35% male, 22% had ≥ 1 fall within 12 months of the baseline time point and 26% had ≥1 fall within 12 months of the follow up visit. Caucasians (aOR 1.37), females, older adults, those who reported a history of lung problems (aOR 1.56) and particularly those who had a fall at baseline (aOR 2.42) had greater odds of a fall at follow-up (Model 1; Table 1). When controlling for baseline characteristics (Model 1), patients who had symptomatic knee or hip OA had increased odds for falling (aOR 1.41 and 1.70, respectively). In Model 2, Caucasians (aOR 1.41), older adults, those who had a previous fall (aOR 2.38), reported a history of depression (aOR 1.02), and symptomatic hip OA (aOR 1.56) had increased odds of falls. However, the association between falls and symptomatic knee OA as well as female sex were no longer significant. The odds of falls increased with an increasing number of knee and/or hip joints with symptomatic OA: the aOR for patients with 1 involved joint was 1.56 (95% CI 1.12, 2.17), for 2 joints was 1.85 (CI 1.28, 2.68), and for 3–4 joints was 1.91 (95% CI 1.01, 3.65).

Table 1. Characteristics of the Sample (n=1619)

	Frequency	**Model 1**	**Model 2**
Characteristic	*Baseline n(%) or mean (range)*	*OR (95% CI)*	*OR (95% CI)*
Caucasian	1245 (71.6)	**1.37 (1.04 ,1.81)**	**1.41 (1.05 ,1.88)**
Male	484 (34.7)	**0.72 (0.55 ,0.93)**	0.80 (0.61 ,1.05)
Mean Age (years)	62 (45–89)	**1.03 (1.01 ,1.04)**	**1.03 (1.01 ,1.04)**
Mean BMI (kg/m^2)	30.8 (17.1–65.8)	1.01 (0.99 ,1.03)	1.01 (0.99 ,1.03)
Falls at baseline	352 (21.8)	**2.42 (1.85 ,3.17)**	**2.38 (1.80 ,3.14)**
Symptomatic Knee OA	321 (20.2)	**1.41 (1.05 ,1.91)**	1.28 (0.92 ,1.78)
Symptomatic Hip OA	196 (12.9)	**1.70 (1.22 ,2.36)**	**1.56 (1.08 ,2.25)**
Lung problems[1]	311 (19.2)	–	**1.56 (1.15 ,2.10)**
Narcotic use[2]	50 (3.1)	–	1.70 (0.88 ,3.29)
CES-D[3]	6.1 (0–53)	–	**1.02 (1.00 ,1.03)**
Low Back Symptoms[4]	776 (48.0)	–	1.00 (0.77 ,1.29)

1. Includes patient report of chronic bronchitis, emphysema or other chronic lung trouble (dichotomous).
2. Defined as self-reported narcotic use for > 2 weeks (dichotomous).
3. Center for Epidemiologic Studies Depression scale (continuous, 0–60).
4. Answer to: "On most days, do you have pain, aching, or stiffness in your low back?"

Conclusion: This study confirms that symptomatic knee and particularly hip OA are important risk factors for falls and reveals that the risk increases with additional symptomatic knee and hip joints. Future interventions aimed at enhancing fall prevention should not ignore the impact of multiple symptomatic OA joints.

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ACR Poster Session A
Pediatric Rheumatology - Clinical and Therapeutic Aspects I: Juvenile Idiopathic Arthritis
Sunday, October 27, 2013, 8:30 AM–4:00 PM

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Inflammatory Bowel Disease In Juvenile Idiopathic Arthritis Patients Upon Biologics. Deborah Barthel[1] and Gerd Horneff[2]. [1]Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany, [2]Centre of Pediatric Rheumatology, Sankt Augustin, Germany

Background/Purpose: Inflammatory bowel disease (IBD) is a matter of interest in patients with juvenile idiopathic arthritis (JIA) treated with biologics.

Methods: Baseline demografics, clinical characteristics and medication have been documented in the German BIKER JIA registry between 2001 and 2013. Exposure time of treatment was used to calculate IBD incidence. Published data of IBD incidence in the general pediatric population were used as reference.

Results: 3070 patients were followed in the BIKER registry with a total observation time of 8389 patient years (py). 13 events of IBD-flares in 12 patients (33% male), 8 with Crohn's disease (CD, 67%) and 4 with ulcerative colitis (UC, 33%). were documented.

4 patients had extended oligoarthritis (eoJIA, 33%), 3 seronegative polyarthritis (RF-JIA, 25%), 3 enthesitis-related arthritis (ERA, 25%) and 2 psoriatic JIA (PsA, 17%). HLA-B27 was positive in 3 (25%) and anti-nuclear antibodies were positive in 7 IBD patients (58%).

Thus patient with IBD as adverse event more commonly had ERA, eoJIA and PsA than expected in the total BIKER cohort, but not statistitically significant. No IBD occurred in systemic JIA, RF positive or pers-oligo JIA. IBD incidence in patients with pers-oligo JIA was significantly decreased.

IBD incidence in JIA patients was 143/100,000 py and significantly higher than IBD incidence in the general pediatric population (5.2/100,000 py, p<0.001; OR 27.50 [15.54–48.67]). Mean disease duration until IBD was 7.8 ± 4.0 years (1.8–16.8).

The total exposure time was 4575PY for NSAIDs, 1981PY for corticosteroids, 195PY for sulfasalazine (SUL), 5455PY for methotrexate (MTX), 212PY for leflunomide (LEF), 3557PY for ETA and 369PY for adalimumab (ADA). Incidence of IBD was significantly higher in patients treated with etanercept (p<0.05; OR 4.53 [1.25–16.47]), leflunomide (p<0.05; OR 7.03 [1.55–31.91]) and also sulfasalazine (p<0.001; OR [12.63 (3.45–46.24]). In patients treated with methotrexate the IBD incidence decreased significantly (p<0.05; OR 0.16 [0.04–0.59]).

At admission to the registry, JIA patients later developing IBD had been treated with MTX (100%), steroids (67%), SUL (33%), azathioprine (25%), LEF (17%) and hydroxychloroquine (8%). At time of IBD diagnosis 83% were on ETA, 33% on steroids, 25% on MTX, 25% on SUL, 17% on LEF and 1 on ADA. Thus, therapy with non-biologic agents has markedly been reduced.

Results			**IBD events no.**	**IBD-rate/ 1000PY**	**p-value**	**odds ratio (95% CI)**
Patient cohort	JIA registry		12	1,430	<0.001	27.50 (15.54–48.67)
	ref. population*		739	0,052		
Treatment group	NSAIDs	+	6	1.31	0.5442	0.71 (0.24–2.13)
		–	7	1.84		
	Steroids	+	4	2.02	0.5437	1.44 (0.44–4.68)
		–	9	1.40		
	Sulfasalazine	+	3	15.41	<0.001	12.63 (3.45–46.24)
		–	10	1.22		
	MTX	+	3	0.55	0.0015	0.16 (0.04–0.59)
		–	10	3.41		
	Leflunomide	+	2	9.45	0.0032	7.03 (1.55–31.91)
		–	11	1.35		
	Etanercept	+	10	2.81	0.0118	4.53 (1.25–16.47)
		–	3	0.62		
	Adalimumab	+	1	2.71	0.5638	1.81 (0.24–13.95)
		–	12	1.50		

* Reference population children aged <16 years (see Sawczenko et al.)

Conclusion: Incidence of IBD in JIA patients is higher than expected. Especially patients with ERA, PsA and eoJIA are at risk. IBD seems to be associated with treatment of ETA, LEF and SUL, while MTX turned out to be protective. The impact of discontinuation of MTX, AZA and corticosteroids in patients later on developing IBD has to be discussed. Unfortunately case numbers so far are too small for further statistical analyses including linear regression models.

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Marked Improvement In Patient Reported Outcomes Of Children With Active Systemic Juvenile Idiopathic Arthritis With Canakinumab Treatment – Results Of The Phase III Program. Rayfel Schneider[1], Hermine I. Brunner[1], Nicolino Ruperto[2], Nico Wulffraat[2], Pierre Quartier[3], Riva Brik[2], Liza McCann[2], Helen E. Foster[2], Michael Frosch[2], Valeria Gerloni[2], Liora Harel[2], Claudio Len[2], Kristin Houghton[1], Rik Joos[2], Ken Abrams[4], Karine Lheritier[5], Sophia Kessabi[5], Alberto Martini[2] and Daniel J. Lovell[1]. [1]Pediatric Rheumatology Collaborative Study Group (PRCSG), Cincinnati, OH, [2]Pediatric Rheumatology International Trials Organization (PRINTO)-Istituto Gaslini, Genova, Italy, [3]Necker-Enfants Malades Hospital, Paris, France, [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [5]Novartis Pharma AG, Basel, Switzerland

Background/Purpose: Efficacy and safety of canakinumab (CAN), a selective, fully human, anti-interleukin-1β monoclonal antibody, in systemic

juvenile idiopathic arthritis (SJIA) patients has been demonstrated in two phase 3 trials (1 and 2). [1]SJIA is associated with severe functional impairment and chronic pain that markedly affect the health-related quality of life (HRQoL). Here, we present the effects of CAN therapy on patient-reported outcomes (PROs) from the phase 3 studies.

Methods: In Trial 1, 84 pts were randomized to CAN (43) and PBO (41) and followed for 1 month. In Trial 2, 177 pts (including 71 from Trial 1) received open label CAN in Part 1, of which 100 CAN-responders entered part 2 and were randomized 1:1 to placebo or continued CAN. PROs considered were functional ability by the Childhood Health Assessment Questionnaire [CHAQ©], pain as measured on a visual analog scale [VAS] of 0–100 mm, and HRQoL by the Child Health Questionnaire–Parent Form (CHQ-PF50 for pts age 5–18 yrs) with rating on physical (PhS) and psychosocial (PsS) health status. Between-treatment differences were evaluated using analysis covariance models with repeated measures adjusting for treatment group, time, stratification factors and the treatment group-by-time interaction as explanatory variables.

Results: At the end of Trial 1, there was significant improvement ($p=0.0002$) in functional ability with CAN, resulting in an estimated difference (ED) in CHAQ score of -0.69 between the CAN and PBO group at Day 29 from baseline [BL]; this ED constitutes about 3.6x the minimal clinically important difference $(-0.19)^2$ in the CHAQ score. Pain intensity significantly declined (both $p<0.0001$) in the CAN group vs. PBO both at Day 15 (ED, -46.42) and Day 29 (ED, -41.86). Similarly, HRQoL significantly improved from BL for CAN vs. PBO, with an ED in CHQ-PF50 PhS scores of 12.07 and 7.28 for the CHQ-PsS (both, $p<0.005$) over 1 month with CAN, respectively. Even more pronounced improvements in functional ability, pain and HRQoL were observed in Trial 2 (Table).

Patient Reported Outcomes in Trial 2

Outcome measure, mean (SD)	Baseline CAN, N=177	End of Part 1 CAN, N=177	End of Part 2 CAN, N=50	End of Part 2 PBO*, N=50
CHAQ disability score	1.7 (0.8)	0.74 (0.9)	0.5 (0.9)	0.6 (0.8)
Pain intensity by 0–100 mm VAS	66.6 (23.3)	20.2 (25.8)	13.6 (26.9)	17.0 (24.2)
CHQ-PF50 PhS score	16.1 (14.3)	37.7 (17.2)	43.6 (17.4)	39.0 (18.1)
CHQ-PF50 PsS score	41.6 (11.1)	50.7 (11.1)	53.6 (11.3)	52.7 (9.8)

Note: Results are based on patients with both baseline and post-baseline values. n<N (177/50) for CHQ-PF50 as assessment not done in pts <5 and >18 years old. *PBO pts received CAN during Part 1 of Trial 2.

Conclusion: Treatment with CAN demonstrated rapid, marked and continued improvement in patient-reported outcome of SJIA patients, including a significant increase in functional ability, reduction of pain and HRQoL.

References:

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Disclosure: R. Schneider, Hoffmann-La Roche, Inc., 5, Novartis Pharmaceutical Corporation, 5, Innomar Strategies, 5; **H. I. Brunner**, Novartis, Genentech, Medimmune, EMD Serono, AMS, Pfizer, UCB, Jannsen, 5, Genentech, 8; **N. Ruperto**, To Gaslini Hospital: Abbott, Astrazeneca, BMS, Centocor Research & Development, Eli Lilly and Company, "Francesco Angelini", Glaxo Smith & Kline, Italfarmaco, Novartis, Pfizer Inc., Roche, Sanofi Aventis, Schwarz Biosciences GmbH, Xoma, Wyeth Pharmaceuti, 2, Astrazeneca, Bristol Myers and Squibb, Janssen Biologics B.V., Roche, Wyeth, Pfizer, 8; **N. Wulffraat**, Novartis, Pfizer, Roche, 5; **P. Quartier**, Abbvie, Chugai-Roche, Novartis, Pfizer, 2, Abbvie, BMS, Chugai-Roche, Novartis, Pfizer, Servier, Sweedish Orphan Biovitrum, 5, Chugai-Roche, Novartis, Pfizer, 8; **R. Brik**, Novartis, 2, Novartis, 5; **L. McCann**, None; **H. E. Foster**, Pfizer, BioMarin, 2, Pfizer Inc, 8; **M. Frosch**, None; **V. Gerloni**, None; **L. Harel**, None; **C. Len**, None; **K. Houghton**, None; **R. Joos**, None; **K. Abrams**, Novartis Pharmaceutical Corporation, 3, Novartis, 1; **K. Lheritier**, Novartis Pharma AG, 3, Novartis, 1; **S. Kessabi**, Novartis Pharma AG, 3; **A. Martini**, Abbott, Astrazeneca, Bristol Myers and Squibb, Janssen Biologics B.V., Ely Lilly and Company, "Francesco Angelini", Glaxo Smith & Kline, Italfarmaco, Novartis, Pfizer Inc., Roche, Sanofi Aventis, Schwarz Biosciences GmbH, Xoma, Wyeth Pharmaceuticals Inc., 2, Abbott, Astrazeneca, Bristol Myers and Squibb, Janssen Biologics B.V., Ely Lilly and Company, "Francesco Angelini", Glaxo Smith & Kline, Italfarmaco, Novartis, Pfizer Inc., Roche, Sanofi Aventis, Schwarz Biosciences GmbH, Xoma, Wyeth Pharmaceuticals Inc., 5, Astellas, Astrazeneca, Bristol Myers and Squibb, -Glaxo Smith & Kline, Italfarmaco, MedImmune, Novartis, 8; **D. J. Lovell**, NIH, 2, Astra-Zeneca, Centocor, Jansen, Wyeth, Amgen, Bristol-Meyers Squibb, Abbott, Pfizer, Regeneron, Hoffman La-Roche, Novartis, Genentech, 5, Genentech, Roche, 8.

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Canakinumab In The Treatment Of Systemic Juvenile Idiopathic Arthritis: Results From a 12-Week Pooled Post-Hoc Analysis For Efficacy. Hermine Brunner[1], Pierre Quartier[2], Tamas Constantin[3], Shai Padeh[3], Inmaculada Calvo[3], Muferet Erguven[3], Laurence Goffin[3], Michael Hofer[3], Tilmann Kallinich[3], Sheila Oliveira[3], Yosef Uziel[3], Stefania Viola[4], Kiran Nistala[3], Carine Wouters[3], Karine Lheritier[5], Josef Hruska[5], Ken Abrams[6], Alberto Martini[3], Nicolino Ruperto[3] and Daniel J. Lovell[1]. [1]Pediatric Rheumatology Collaborative Study Group (PRCSG), Cincinnati, OH, [2]Necker-Enfants Malades Hospital, Paris, France, [3]Paediatric Rheumatology International Trials Organization (PRINTO), Genova, Italy, [4]Pediatria 2, Genova, Italy, [5]Novartis Pharma AG, Basel, Switzerland, [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ

Background/Purpose: Interleukin-1β (IL-1β) plays a key role in the pathogenesis of systemic juvenile idiopathic arthritis (SJIA), a severe disabling subtype of JIA characterized by arthritis plus systemic symptoms. Canakinumab (CAN), a selective, fully human, anti-IL-1β monoclonal antibody has demonstrated efficacy and safety in 2 phase III trials in SJIA patients (pts). Here we present results of a post-hoc pooled analysis evaluating the 12-week efficacy of CAN 4 mg/kg every 4 weeks.

Methods: Pooled data from the 3 phase III trials were used. Pts aged 2–19 yrs with active SJIA were enrolled and received subcutaneous CAN 4 mg/kg or placebo every 4 weeks. The post-hoc analysis presented here focuses on response to CAN therapy in the initial treatment period for a total of 178 CAN-naïve pts. Methodological factors precluded a comparator group, so this analysis is of a descriptive nature.

Results: At baseline (BL), 94% of pts had intermittent spiking fever due to SJIA and 73% were on steroids (mean dose 0.38 mg/kg/d). By Week 2, evidence of profound SJIA improvement was observed (Table), with 20% of pts achieving inactive disease status.

Table. Percentage of patients with adapted JIA ACR (aACR) response* and inactive disease

	CAN, N=178; n (%)	
	Week 2	Week 12
aACR30	142 (80%)	125 (70%)
aACR50	125 (70%)	122 (69%)
aACR70	102 (57%)	108 (61%)
aACR90	65 (37%)	87 (49%)
aACR100	38 (21%)	54 (30%)
Inactive disease	36 (20%)	50 (28%)

*Data from missing patients not shown; aACR response = ACR response level plus absence of fever

The median CRP level of 158 mg/L at BL decreased by a median of 82% and 94% by Weeks 2 and 12, respectively. There was a rapid improvement in the median number of active joints from 10 at BL to 2.5 at Week 2 and 0 at Week 12. Similarly, for joints with limitation of motion, median values decreased from 9 at BL to 2.5 at Weeks 2 and 1 at Week 12, respectively. While 94% pts had fever due to SJIA at BL, only 13% at Week 2 and 2% at Week 12 had fever. Notably, CAN therapy resulted in marked improvements in patient-reported outcomes: parent/patient assessment of pain (0–100 mm, VAS) decreased from a mean of 67 mm at BL to 22 mm at Week 2 and 11 mm at Week 12. The median CHAQ disability score decreased from 1.8 at BL to 0.6 at Week 2 and 0.3 at Week 12. Between BL and Week 12, the median parent's/patient's assessment of overall well-being improved from 63 mm to 4.5 mm and the physician's global assessment of SJIA activity (0–100 mm, VAS) decreased from 70 mm to 3 mm.

Conclusion: Based on this post-hoc analysis, response of the SJIA patients studied in the CAN program showed rapid and clinically important improvements in patient reported outcomes and disease activity by Week 12

of therapy, with aACR 50 or higher responses reached by the majority of SJIA pts within 2 weeks of the initial CAN dose.

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Baseline Characteristics Of Patients With Active Systemic JIA On Canakinumab Therapy Successfully Discontinuing Corticosteroids: Secondary Analyses From A Pivotal PHASE 3 Study. Hermine Brunner[1], Nicolino Ruperto[2], Tamás Constantin[2], Nico Wulffraat[2], Gerd Horneff[2], Jordi Anton[2], Reinhard Berner[2], Fabrizia Corona[2], Rubén J. Cuttica[2], Marine Desjonqueres[2], Michel Fischbach[2], Maria Alessio[2], Alice Chieng[2], Wolfgang Emminger[2], Elie Haddad[1], Karine Lheritier[3], Ken Abrams[4], Josef Hruska[3], Daniel J. Lovell[1] and Alberto Martini[2]. [1]Pediatric Rheumatology Collaborative Study Group (PRCSG), Cincinnati, OH, [2]Pediatric Rheumatology International Trials Organization (PRINTO)-Istituto Gaslini, Genova, Italy, [3]Novartis Pharma AG, Basel, Switzerland, [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ

Background/Purpose: Interleukin-1β (IL-1β) is a key cytokine in the pathogenesis of systemic juvenile idiopathic arthritis (SJIA). Canakinumab (CAN), a selective fully human anti-IL-1β monoclonal antibody, is efficacious in the treatment of SJIA.[1] Limitation of use of corticosteroids (CS), a current mainstay of therapy for SJIA, is desirable given their well-known long-term side effects. The present study was aimed to determine patient characteristics that are associated with CS discontinuation with CAN therapy and provide details for the CS-reducing potential of CAN in SJIA.

Methods: As part of the phase 3 program of CAN, patients aged 2–19 years with active SJIA plus fever received CAN (4 mg/kg; max:300 mg) every 4 weeks subcutaneously.[1] During a CS-tapering phase of up to 20 weeks, CS were reduced as per pre-specified rules, provided patients achieved an adapted JIA ACR50.[1] Here, we present patient baseline features pertinent to CS tapering successes, defined as at least a 25% reduction of the baseline CS dose (primary endpoint), reaching a low-dose CS requirement, i.e. $\leq$0.2 mg/kg/day and CS-free status (secondary endpoints).

Results: At baseline, 128/177 patients used daily CS [median (range) mg/kg dose: 0.27 (0.02–1.00)] of whom 72% (92/128) entered the CS-tapering phase. Upon completion of the CS-tapering phase 57/128 patients (44.5%; $p<0.0001$; 90%CI: 37.1–52.2) qualified as CS-tapering successes (primary endpoint). Of note, the majority of the patients either discontinued CS entirely (n=42) or required only low-dose CS (n=24) (secondary endpoints). Compared to patients still on CS (n=86), the 42 patients achieving CS-free status [values are all medians (1st, 3rd quartile)] had fewer joints with active arthritis [15 (8, 29) vs. 7 (3, 13)], fewer joints with limitation on motion [14 (7, 33) vs. 5.5 (2, 12)] at baseline. The groups were no different in terms of gender, race, SJIA duration, CRP, number of flares in 6-months period preceding baseline, or specific types of systemic features (hepatosplenomegaly, lymphadenopathy or serositis). Additional associations of CS-free status, initial CAN response, and select laboratory baseline features will be provided.

Conclusion: Findings of the Phase III program of CAN in SJIA suggest that CS requirements are substantially reduced after as few as 4 injections. The CS-sparing potential of CAN appears to be great as CS were discontinued entirely in a sizeable proportion of patients with active SJIA in this study.

References:

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Predictive Markers Of Joint Damages Of Children With Systemic-Onset Juvenile Idiopathic Arthritis In Long-Term Course Of Treatment With Tocilizumab. Tomo Nozawa, Taichi Kanetaka, Kenichi Nishimura, Masako Kikuchi, Tomomi Sato, Nodoka Sakurai, Ryoki Hara, Kazuko Yamazaki and Shumpei Yokota. Yokohama City University School of Medicine, Yokohama, Japan

Background/Purpose: Systemic-onset juvenile idiopathic arthritis (s-JIA) is a subtype of chronic childhood arthritis characterized by spiking fever, rash, and arthritis. Tocilizumab (TCZ), an anti-IL-6 receptor monoclonal antibody, has dramatically improved patients' inflammatory symptoms/signs as well as their prognosis. In the long-term treatment of s-JIA patients with TCZ, however, there found joint damages in some patients on X-ray examination although their clinical inflammatory symptoms/signs and laboratory findings were well-controlled. The objective of this study was to determine predictive markers of joint damages of s-JIA patients under the TCZ treatment.

Methods: Although 62 patients have been treated with TCZ, 33 patients were excluded from the study because 17 patients were effectively treated with TCZ to be drug-off, and the duration of TCZ treatment in 16 patients was shorter than 48 months and/or progression of radiographic joint damages were not detectable. Twenty-nine patients (16 boys and 13 girls) with s-JIA were eligible in this study who have been treated with TCZ over 48 months. The following blood tests were determined before and 6, 12, 24, 36, 48 months after the TCZ administration: CBC, CRP/ESR, D-dimer, liver function tests, creatinine, and MMP-3. The radiographs were serially examined before and after TCZ treatment.

Results: The mean age of disease onset was 5.2$\pm$2.9 years old. Of the 29 patients, 12 patients (41.3%) had radiographic progression of joint damages during the long-term TCZ treatment (JD (+)), and 17 patients (58.7%) had no joint damages on X-ray examinations (JD (−)) although there were no systemic inflammatory symptoms/signs demonstrable in both groups. Before TCZ treatment there were no significant differences of laboratory data between JD (+) and JD (−). By 12 months after TCZ treatment WBC counts were apparently more increased to normal range in JD (+) group than JD (−) group ($p<0.05$). By 24 months after TCZ treatment MMP-3 levels were still higher in JD (+) group than in JD (−) group ($p<0.05$). Taken together, although TCZ completely blocked clinically the inflammatory symptoms/signs as well as laboratory changes of inflammation such as CRP and ESR, there found a part of patients who had progressive joint damages even under the TCZ treatment, suggesting some biological mechanisms which were IL-6-independent will play an important role in damaging joints. For the patients who complained of something different on their joints, the tapering of prednisolone tended to be delayed. As the results, the mean doses of prednisolone at 12 months were significantly higher in JD (+) group than JD (−) group.

Conclusion: The long-lasting elevation of MMP-3 levels and higher WBC counts in patients with s-JIA treated with TCZ will be predictive of radiographic progression of joint damages.

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Neutropenia With Tocilizumab Treatment Is Not Associated With Increased Infection Risk In Patients With Systemic Juvenile Idiopathic Arthritis. Fabrizio De Benedetti[1], Hermine I. Brunner[2], Eileen M. Baildam[3], Ruben Burgos-Vargas[3], Gerd Horneff[4], Hans-Iko Huppertz[3], Kirsten Minden[5], Barry L. Myones[2], Karen Onel[2], Jianmei Wang[6], Kamal N. Bharucha[7], Daniel J. Lovell[2], Alberto Martini[8] and Nicolino Ruperto[3]. [1]IRCCS Ospedale Pediatrico Bambino Gesú, Rome, Italy, [2]PRCSG, Cincinnati, OH, [3]PRINTO, Genoa, Italy, [4]Pediatric Rheumatology International Trials Organization (PRINTO)-Istituto Gaslini, Genova, Italy, [5]pediatric rheumatology, Berlin, Germany, [6]Roche, Welwyn Garden City, United Kingdom, [7]Genentech, South San Francisco, CA, [8]Istituto Giannina Gaslini, Genova, Italy.

Background/Purpose: In the phase 3 TENDER trial of tocilizumab (TCZ) in patients with systemic juvenile idiopathic arthritis (sJIA), decreases in neutrophil count were commonly observed. The purpose of this analysis was to determine if neutropenia was associated with increased risk of infection and to investigate variables associated with development of neutropenia in patients treated with TCZ for up to 2 years in TENDER.

Methods: One hundred twelve children with active, persistent sJIA were randomized 2:1 to receive TCZ by body weight (12 mg/kg $<$30 kg or 8 mg/kg $\geq$30 kg) or placebo IV every 2 weeks for 12 weeks and continued in an ongoing TCZ open-label extension.[1] Worst Common Toxicity Criteria (CTC) neutropenia grade (grade 1, $\geq$1.5 and $<2.0\times10^9$/L; grade 2, $\geq$1.0 and $<1.5\times10^9$/L; grade 3, $\geq$0.5 and $<1.0\times10^9$/L; grade 4, $<0.5\times10^9$/L) and lowest observed neutrophil count (10^9/L) were identified for each patient. Univariate linear regression analysis was performed to investigate association of patient characteristics with lowest observed neutrophil count. Rates of infections and serious infections (per 100 patient years [PY]) in periods $\pm$15 days around grade1–2 neutropenia (22.9 PY) and around grade 3–4 neutropenia (5.5 PY) were compared to corresponding rates in periods with normal neutrophil count (173.6 PY).

Results: Up to week 104, 64/112 patients (57.1%) had at least 1 episode of grade 1–4 neutropenia; worst grade: 1 (n=2), 2 (n=34), 3 (n=26), and 4 (n=2). Rates of infections and serious infections during period of normal neutrophil counts (276.5/100 PY [95% CI: 252.3, 302.3] and 11.5/100 PY [95% CI: 7.0, 17.8], respectively) were comparable to those observed $\pm$15 days around grade 1–2 neutropenia (226.7/100 PY [95% CI: 169.3, 297.3]; 8.7/100 PY [95% CI: 1.1, 31.5]) and grade 3–4 neutropenia (292.5/100 PY [95% CI: 167.2, 475.0]; 0/100 PY), with no trend toward increased risk with higher grade neutropenia. Methotrexate (MTX) use (Yes/No) was significantly associated with lowest observed neutrophil count (difference: –0.575 [95% CI: –1.02, –0.13], p=0.012), with 62% of 77 patients receiving MTX vs 46% of 35 patients not receiving MTX having grade 1–4 neutropenia. Younger age was borderline associated with lowest observed neutrophil count (β=0.04661, p=0.047). Concurrent use of glucocorticoids (GC) and TCZ exposure were not associated with lowest observed neutrophil count ($p>0.3$).

Conclusion: No trend for association between neutropenia and increased risk of infections was observed in the TENDER trial. Background MTX, and somewhat younger age, was associated with increased risk of neutropenia, while TCZ exposure and concurrent GC use were not. Reference: 1. De Benedetti F et al. *N Engl J Med* 2012;367:2385.

Disclosure: F. De Benedetti, Abbott, Pfizer, BMS, Roche, Novimmune, Novartis, SOBI, 2; **H. I. Brunner**, Novartis, Genentech, Medimmune, EMD Serono, AMS, Pfizer, UCB, Janssen, 5, Genentech, 8; **E. M. Baildam**, None; **R. Burgos-Vargas**, Abbott, BMS, Janssen, Pfizer, Roche, 5, Abbott, BMS, Janssen, Pfizer, Roche, 8, Abbott Immunology Pharmaceuticals, 2; **G. Horneff**, Abbott, Pfizer, 2; **H. I. Huppertz**, Abbott, Chugai, Pfizer, Roche, Swedish Orphan, 5; **K. Minden**, Pfizer, Abbvie, Roche, Chugai, Medac, 5, Pfizer, Abbvie, 2; **B. L. Myones**, None; **K. Onel**, None; **J. Wang**, Roche Pharmaceuticals, 3; **K. N. Bharucha**, Genentech and Biogen IDEC Inc., 3; **D. J. Lovell**, NIH, 2, AstraZeneca, Centocor, Janssen, Wyeth, Amgen, Bristol-Meyers Squibb, Abbott, Pfizer, Regeneron, Hoffmann-La Roche, Novartis, Genentech, 5, Roche, Genentech, 8; **A. Martini**, Abbott, AstraZeneca, BMS, Centocor, Lilly, Francesco Angelini, GSK, Italfarmaco, MerckSerono, Novartis, Pfizer, Regeneron, Roche, Sanofi Aventis, Schwarz Biosciences, Xoma, Wyeth, 2, Abbott, AstraZeneca, BMS, Centocor, Lilly, Francesco Angelini, GSK, Italfarmaco, MerckSerono, Novartis, Pfizer, Regeneron, Roche, Sanofi Aventis, Schwarz Biosciences, Xoma, Wyeth, 5, Abbott, Boehringer, BMS, Novartis, Astellas, Italfarmaco, MedImmune, Pfizer, Roche, 8; **N. Ruperto**, To Gaslini Hospital: Abbott, Astrazeneca, BMS, Centocor Research & Development, Eli Lilly and Company, "Francesco Angelini", Glaxo Smith & Kline, Italfarmaco, Novartis, Pfizer Inc., Roche, Sanofi Aventis, Schwarz Biosciences GmbH, Xoma, Wyeth Pharmaceuti, 2, Astrazeneca, Bristol Myers and Squibb, Janssen Biologics B.V., Roche, Wyeth, Pfizer, 8.

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Reported Macrophage Activation Syndrome In Patients With Systemic-Onset Juvenile Idiopathic Arthritis Treated With Tocilizumab. Shumpei Yokota, Yasuhiko Itoh, Tomohiro Morio, Naokata Sumitomo and Seiji Minota. The Safety Evaluation Committee of Actemra® for JIA, Tokyo, Japan.

Background/Purpose: Systemic-onset juvenile idiopathic arthritis (s-JIA) is a subtype of chronic childhood arthritis that is characterized by a spiking fever, rash, and arthritis. About 7% of s-JIA patients develop macrophage activation syndrome (MAS), a potentially fatal complication. Although several biologic therapies have dramatically improved the prognosis of s-JIA, the risk of developing MAS under biologic therapy seems not vanished because there are several reports of MAS associated with etanercept and canakinumab in patients with s-JIA.

To evaluate the prevalence of MAS in patients with s-JIA under the treatment of tocilizumab.

Methods: During the post-marketing surveillance of tocilizumab conducted by Chugai Pharmaceutical Co. Ltd. in Japan from 2008 to 2012, a total of 394 patients was registered. Tocilizumab, 8 mg/kg, was administered to the patients every 2 weeks, and routine investigations including CBC, CRP/ESR, D-dimer, liver function tests, creatinine, urinary beta 2-microglobulin, total cholesterol/triglyceride, and serum ferritin were determined before each infusion. Among them, 23 patients (5.8%) were diagnosed by the pediatrician in attendance with MAS, suspected MAS, or hemophagocytic syndrome; and then clinical course and laboratory data of the patients were reported as severe adverse events. Data were analyzed by the members of the Safety Evaluation Committee. Data were provided by Chugai Pharmaceutical Co. Ltd.

Results: The Committee investigated the clinical manifestations and the changes of laboratory data along with the time course of each patient reported. Three patients were defined as definitive MAS (0.76%), 2 patients as EB virus-associated hemophagocytic syndrome (0.51%). Among other 18 patients, 11 patients (2.8%) were defined as probable MAS because the patients' information including laboratory data was incomplete. Seven patients (1.8%) were judged as possible MAS or non-MAS because the treatment intervention for MAS was too early to define as MAS, or other diseases such as infectious disease, and hemolytic-uremic syndrome were suspected. Among 8 out of 14 patients defined as definitive or probable MAS, clinical manifestations were quite different from those seen in MAS on conventional therapy were. One patient died due to multi-organ failure, and none experienced sequelae.

Conclusion: The frequency of definitive MAS under the tocilizumab therapy is estimated as 0.76%, and possible MAS as 2.8% (total 3.6%). Since the development of MAS in s-JIA patients under the conventional therapy was reported to be 6.8% $\sim$ 13%, tocilizumab may have reduced the frequency of MAS developing in s-JIA. However, the clinical symptoms/signs such as fever, rash and an anguish look were not apparent in about half of the patients, and the inflammatory markers such as CRP and ESR were suppressed owing to the inhibition of IL-6 by tocilizumab. Taken together, physical examination and laboratory tests should be carefully taken at each visit in patients on tocilizumab in order to detect deadly MAS incipiently.

Disclosure: S. Yokota, Chugai, 7; **Y. Itoh**, Chugai, 5; **T. Morio**, Chugai, 5; **N. Sumitomo**, Chugai, 5; **S. Minota**, Chugai, 7.

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Changes In Serum IL-18 Level In Systemic Juvenile Idiopathic Arthritis Patients Who Attained Drug-Free Remission By Tocilizumab. Tomohiro Kubota[1], Syuji Takei[1], Yuichi Yamasaki[1], Junko Yasumura[2], Naomi Kuwada[3], Yukiko Nonaka[1], Tomoko Takezaki[1], Tsuyoshi Yamatou[1], Tomokazu Nagakura[4], Yasuhito Nerome[1], Hiroyuki Imanaka[1] and Harumi Akaike[1]. [1]Kagoshima University, Kagoshima, Japan, [2]Hiroshima University, Hiroshima City, Japan, [3]Kumamoto University, Kumamoto City, Japan, [4]House of Meguminoseibo, Usuki, Japan

Background/Purpose: Tocilizumab (TCZ), anti-human interleukin-6 receptor monoclonal antibody, was the first biologic agent used in the treatment of systemic juvenile idiopathic arthritis (sJIA) in Japan. We have previously reported that long-term TCZ therapy could induce drug-free remission in sJIA patients resistant to conventional prednisolone (PSL) therapy[1)]. On the other hand, extremely high levels of serum IL-18 ($>$10,000

pg/ml) was reported in active phase of sJIA[2]. Therefore, serum IL-18 levels were monitored in order to find the way how to taper and discontinue TCZ in sJIA patients.

Methods: sJIA patients treated with 8 mg/kg of TCZ for more than 1 year who were initially resistant to 3 times of consecutive weekly methyl-PSL pulse therapy in active phase and/or had been refractory to long-term oral steroid therapy were recruited. Our tapering protocol for patients who maintained clinical remission by TCZ was as following; decrease PSL dose gradually to less than 0.2mg/kg/day, prolongation of TCZ interval from every 2w to 3w, discontinuation of PSL, and discontinuation of TCZ, in tern. Serum levels of IL-6/IL-18 were measured by ELISA.

Results: A total of 28 sJIA patients were recruited in this study; their mean disease duration was 4.1 years, and mean PSL dose was 0.5mg/kg/day at initiating TCZ.

Twenty-seven patients (96%) attained clinical remission with combination therapy of PSL<0.2mg/kg/day and TCZ every 3w. Thereafter, 10 patients (36%) completed PSL-free remission, and 7 (25%) attained drug-free remission by discontinued TCZ (Figure 1). No significant difference was found in TCZ treatment period between the two patient groups who achieved the drug-free remission (mean 7.0 yrs) and who maintained clinical remission (mean 5.5 yrs).

Serum IL-6 decreased quickly in correlating with improvement of clinical symptoms after starting TCZ. On the contrary, serum IL-18 did not decrease in a patient who was resistant to TCZ therapy, or in patients who flared or developed to macrophage activation syndrome during the TCZ therapy. In patients who attained clinical remission by TCZ, however, IL-18 steadily decreased with treatment course (figure 2). In all patients maintained the drug-free remission for more than 2 years, serum IL-18 was < 1,000 pg/ml when the TCZ was discontinued.

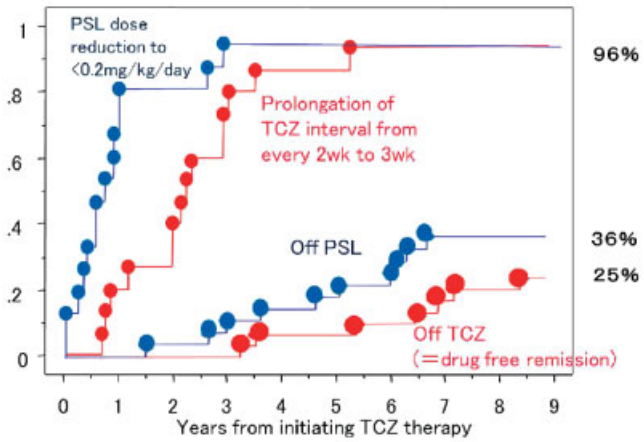
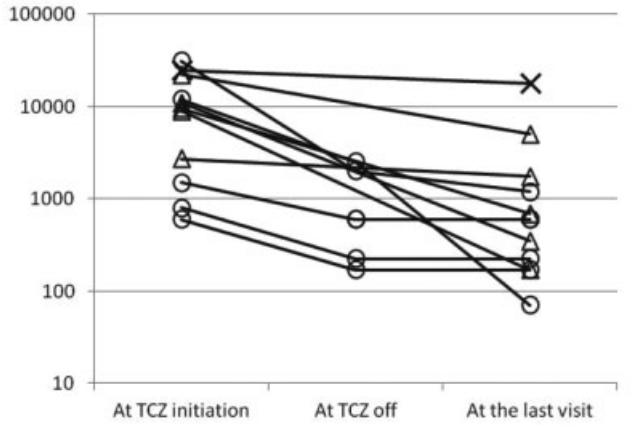


Figure1:Cumulative incidence of sJIA attained each endpoints



○ : Pts attained drug-free remission △ : Pts maintained clinical remission
× : Pts refractory to TCZ

Figure 2:Changes in serum IL-18 in sJIA treated with TCZ

Conclusion: TCZ had the potential to induce drug-free remission in 1/4 of sJIA patients who had been refractory to the conventional therapy. Serum IL-18 level could be a useful bio-marker in tapering the TCZ therapy in sJIA.

1) Kubota T, et al: #267, 2011 ACR meeting
2) Shimizu M, et al □FRheumatology 2010;49:1645–1653

Disclosure: T. Kubota, None; **S. Takei**, Chugai,Eisai, Takeda, Bristol-Myers, 2, Caugai, Eisai, Takeda, Abbvie, Astellas, Teijin, Novartis, Pfizer, Asahi Kasei, 8; **Y. Yamasaki**, None; **J. Yasumura**, None; **N. Kuwada**, None; **Y. Nonaka**, None; **T. Takezaki**, None; **T. Yamatou**, None; **T. Nagakura**, None; **Y. Nerome**, None; **H. Imanaka**, None; **H. Akaike**, None.

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Assessment Of Radiographic Progression In Patients With Systemic Juvenile Idiopathic Arthritis Treated With Tocilizumab: 2-Year Results From The Tender Trial.

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Background/Purpose: A phase 3 trial (TENDER) demonstrated the efficacy of the interleukin-6 receptor inhibitor tocilizumab (TCZ) in patients with systemic juvenile idiopathic arthritis (sJIA).[1,2] The purpose of this analysis was to investigate progression of radiographic joint damage in patients with sJIA treated with TCZ for up to 2 years in TENDER.

Methods: One hundred twelve patients 2–17 years old with active, refractory sJIA of ≥6 months' duration and an inadequate response to previous non-steroidal anti-inflammatory drugs and oral corticosteroids were enrolled in TENDER. Patients were randomized 2:1 to receive TCZ according to body weight (12 mg/kg <30 kg or 8 mg/kg ≥30 kg) or placebo IV every 2 weeks for 12 weeks. Patients then received open-label TCZ in the ongoing long-term extension. Radiographic progression was calculated as change in adapted Sharp/van der Heijde score (aSH) score and/or Poznanski score, assessed on hand and wrist radiographs, from baseline to weeks 52 and 104. Radiographic progression was indicated by a positive aSH score change or negative Poznanski score change. Clinical efficacy endpoints included American College of Rheumatology (ACR) Pediatric (Pedi) 70/90 responses.

Results: Baseline and ≥1 postbaseline aSH and Poznanski scores were available for 47 and 33 patients, respectively (reasons for missing x-rays: early withdrawal, no consent, unreadable x-rays). Baseline characteristics for patients with radiographic data were similar to the whole TCZ population.[1] Patients with assessable aSH/Poznanski scores had 5.2/4.8-year disease duration, 21.3/19.2 active joints, 20.0/18.2 joints with limitation of movement, and erythrocyte sedimentation rates of 53.9/59.2 mm/h. At weeks 52 and 104, 20 and 19 patients, respectively, had aSH progression, and 8 and 6 patients, respectively, had Poznanski score progression. Median change in aSH score from baseline to weeks 52 and 104 were 0 and 0.5, respectively (Table). Median change in Poznanski score from baseline to weeks 52 and 104 were 0.3 and 0.17, respectively (Table).

	Week 52	Week 104
aSH score (n = 47), median (IQR)	0.00 (–8.70: 4.00)	0.50 (–7.50: 12.00)
Poznanski score (n = 33), median (IQR)	0.30 (–0.02: 1.03)	0.17 (0.01: 1.04)
ACR Pedi 70 (n = 112), n/N (%)	92/106 (86.8)	57/65 (87.7)
ACR Pedi 90 (n = 112), n/N (%)	67/106 (63.2)	46/65 (70.8)

IQR, interquartile range.

Conclusion: Though changes in radiographic scores over time were seen in many patients, on average, patients with sJIA did not experience

noticeable progression of radiographic damage over 2 years of treatment with TCZ.

References:

1. De Benedetti F et al. *N Engl J Med* 2012;367:2385.
2. De Benedetti F et al. *Ann Rheum Dis* 2012;71(Suppl 3):425.

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Childhood Arthritis and Rheumatology Research Alliance (CARRA) Standardized Consensus Treatment Plans for New Onset Polyarticular Juvenile Idiopathic Arthritis. Sarah Ringold[1], Pamela F. Weiss[2], Robert A. Colbert[3], Esi Morgan DeWitt[4], Tzielan C. Lee[5], Karen Onel[6], Sampath Prahalad[7], Rayfel Schneider[8], Susan Shenoi[9], Richard K. Vehe[10] and Yukiko Kimura[11]. [1]Seattle Children's Hospital, Seattle, WA, [2]The Children's Hospital of Philadelphia, Philadelphia, PA, [3]NIAMS NIH, Bethesda, MD, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]Stanford University School of Medicine, Stanford, CA, [6]PRCSG, Cincinnati, OH, [7]Emory Children's Center, Atlanta, GA, [8]Pediatric Rheumatology Collaborative Study Group (PRCSG), Cincinnati, OH, [9]Seattle Children's Hospital, University of Washington, Seattle, WA, [10]University of Minnesota, Minneapolis, MN, [11]Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ

Background/Purpose: There is no standardized approach to the initial treatment of polyarticular juvenile idiopathic arthritis (pJIA) among North American pediatric rheumatologists. Understanding the comparative effectiveness of the diverse therapeutic options available will result in better health outcomes for children with pJIA. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) developed consensus treatment plans (CTP) for use in clinical practice to facilitate such studies.

Methods: A case-based survey was administered to CARRA members to identify the most common treatment approaches for new-onset pJIA. Two face-to-face consensus meetings employed modified nominal group technique to agree on the treatment plans, operational case definitions, endpoints and data elements to be collected. A core workgroup reviewed the literature, refined the plans and developed medication dosing and monitoring recommendations. The final CTPs were presented for approval at a face-to-face meeting in April 2013.

Results: Sixty percent of 230 members answered the survey, which identified significant variability in treatment for new onset pJIA. 72 (2011) and 58 (2012) CARRA members attended consensus meetings to develop the 3 CTPs based on treatment strategies that focus on timing of introduction of medication categories (biologic and non-biologic DMARDs) for the first 12 months of therapy. Case definitions and clinical and laboratory monitoring schedules were established. The 3 CTPs include a Step-Up CTP (non-biologic with the addition of a biologic DMARD after 3–6 mos), Early Combination CTP (non-biologic plus biologic DMARD as initial treatment), and a Biologic Only CTP. This approach was approved by 96% of the 72 CARRA JIA Committee members attending the 2013 CARRA meeting.

Conclusion: Standardized CTPs based on 3 treatment timing strategies were developed for new-onset pJIA. Coupled with data collection at defined intervals, use of these CTPs will enable studying their comparative effectiveness in an observational setting like the CARRA Registry to optimize initial management of pJIA. Based on a high level of agreement among pediatric rheumatologists during the development process, sufficient participation and enrollment in all CTPs is anticipated.

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Results Of a 24 Month Extension Study In Patients Who Participated In The Trial Of Early Aggressive Therapy In Polyarticular Juvenile Idiopathic Arthritis. Carol A. Wallace[1], John Bonsack[2], Steven J. Spalding[3], Hermine Brunner[4], Kathleen M. O'Neil[5], Diana Milojevic[6], Sarah Ringold[7], Laura E. Schanberg[8], Gloria C. Higgins[9], Beth S. Gottlieb[10], Joyce J. Hsu[11], Marilynn G. Punaro[12], Yukiko Kimura[13] and Audrey F. Hendrickson[14]. [1]Seattle Childrens Hosp & Research Institute, Seattle, WA, [2]University of Utah Health Sciences Center, Salt Lake City, UT, [3]The Cleveland Clinic, Cleveland, OH, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]Riley Hospital for Children, Indianapolis, IN, [6]University of California, San Francisco, San Francisco, CA, [7]Seattle Children's Hospital, Seattle, WA, [8]Duke University Medical Center, Durham, NC, [9]Nationwide Childrens Hosp, Columbus, OH, [10]Cohen Children's Medical Center of New York, New Hyde Park, NY, [11]Stanford University, Palo Alto, CA, [12]Texas Scottish Rite Hospital, Dallas, TX, [13]Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [14]Seattle Children's Research Institute, Seattle, WA

Background/Purpose: The Trial of Early Aggressive Therapy in Polyarticular Juvenile Idiopathic Arthritis (TREAT-JIA) was a double-blind, randomized, placebo-controlled trial in 85 patients with onset of polyarticular JIA < 12 mos to determine if clinical inactive disease (CID) could be achieved by 6 months. Two aggressive treatment arms were used; (i) (MTX arm) SQ methotrexate (MTX; 0.5 mg/kg/wk) or (ii) (M-E-P arm) etanercept (ETN 0.8 mg/kg/wk), prednisolone (0.5 mg/kg/d tapered to zero by 17 wks) and MTX at the dose above. The purpose of this investigation was to follow these children beyond the original study for 2 additional years to understand the longer-term outcomes.

Methods: Patients who completed a minimum of 6 mos in the TREAT study were eligible to enroll in this extension study, regardless of response during the original trial and whether or not they continued to receive the same medications. Patients were treated as per standard of care. Physician, patient/parent and laboratory reported measures of disease status and safety information were collected at clinic visits every 3 mos for up to 2 years. Information regarding disease status and safety during the time period between studies was collected from chart review. Adverse events grade 3 and higher as well as infections requiring systemic therapy were reported.

Results: Twelve of the 15 original TREAT study sites participated and enrolled 52 of 77 (67.5%) eligible patients, 48 of whom returned for follow-up visits. TREAT baseline demographic and disease characteristics as well as disease state at the end of the TREAT trial did not differ between those who participated in the extension and those who did not. At enrollment into the extension study, 21 (44%) were receiving ETN and MTX, 13 (27%) MTX alone, 6 (12%) ETN alone, 7 (15%) no meds or NSAIDs alone, 1 patient each on prednisone, adalimumab and abatacept. Twenty-five (52%) entered the extension study in CID, while 23 (48%) had active disease. Patients were followed for a mean of 21.4 mos (range 9 to 24) and 27 (56%) patients spent more than 50% of their follow up time in CID. Eight patients were in CID >12 months and 2 were in CID off meds for the entire study. Disease activity during periods of AD tended to be low with means of MD global of 2.4; active joint count of 3.5; parent global evaluation of 2.4; CHAQ of 0.32; ESR 19; and morning stiffness of 23 minutes. Patients who were RF(−) tended to spend more study time in CID than RF(+) patients (52% vs 43%), as did patients who were ANA (−) 58% vs 47% ANA (+). Patients who achieved CID at 6 months in the TREAT study tended to spend more time in CID (58% vs 45%) than did those who ended the TREAT study in AD (55% vs 43%). There were no serious adverse events or adverse events grade 3 or higher reported. Four patients had 6 infections requiring systemic antibiotics.

Conclusion: Early aggressive therapy in this group of polyarticular JIA patients, with high initial disease activity and proportion with RF positivity, was associated with prolonged periods of CID in the majority of patients during this 24 month extension study. Those not in CID had low levels of disease activity.

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Safety and Effectiveness Of Adalimumab In Children With Polyarticular Juvenile Idiopathic Arthritis Aged 2 To <4 Years Or ≥4 Years Weighing <15 Kg. Daniel J. Kingsbury[1], Pierre Quartier[2], Vipin Arora[3], Jasmina Kalabic[4], Hartmut Kupper[4] and Neelufar Mozaffarian[3]. [1]Legacy Emanuel Children's Hospital, Portland, OR, [2]PRINTO, Genoa, Italy, [3]AbbVie, North Chicago, IL, [4]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany

Background/Purpose: Adalimumab (ADA) is approved for use in moderate to severe juvenile idiopathic arthritis (JIA) in patients (pts) ≥4 years (yrs) old in the US, EU, and Japan. Limited data are available in pts <4 yrs old. The objective of this study was to assess the safety and effectiveness of >1 year of ADA therapy in pts aged 2 to <4 yrs old or ≥4 yrs old weighing <15 kg with moderately to severely active polyarticular JIA.

Methods: JIA pts were treated with ADA 24 mg/m^2 (maximum=20 mg/dose) every other week (wk) +/− methotrexate for 96 wks in an ongoing international, multicenter, open-label, phase 3b study until achieving the limit for age (≥4 yrs) and weight (≥15 kg). Adverse events (AEs) were summarized for all visits up to 96 wks. Clinical effectiveness endpoints included American College of Rheumatology pediatric (PedACR) 30/50/70/90 responses through wk 60, and JIA outcome parameters (PhGA, PaGA, DICHAQ, AJC73, LOM69, CRP, TJC, SJC, and POM75).

Results: 32 pts were randomized; through wk 60, two pts withdrew due to AEs (JIA worsening or flare) and 2 withdrew for other reasons. AE incidence rates included: any AEs (91%), serious AEs (16%), infectious AEs (78%), and serious infections (9%). No deaths, malignancies, or opportunistic infections were reported. 90% of pts had achieved PedACR30 at wk 60 (Table 1). High PedACR 50/70/90 response rates were achieved at wk 24 and maintained through wk 60. Statistically significant improvements in other JIA outcomes were also observed (Table 2). Growth was not adversely impacted by ADA treatment; based on CDC growth standards, at baseline, 50%/53% of pts were in the ≥33rd percentile for height and body mass index, respectively; at wk 60, this had increased to 76%/67%.

Table 1. PedACR Response Over Time (Observed Case Analysis)

	Week 24 Response Rate N=30 n (%)	Week 60 Response Rate N=20 n (%)
PedACR30	27 (90.0)	18 (90.0)
PedACR50	25 (83.3)	16 (80.0)
PedACR70	22 (73.3)	14 (70.0)
PedACR90	11 (36.7)	10 (50.0)

Table 2. JIA Outcomes at Week 60[a]

	Mean Change (SD) from Baseline N=20
PhGA of Disease Activity[b] (VAS 0–100 mm)	–42.7 (28.2)*
PaGA of Disease Activity[b] (VAS 0–100 mm)	–34.5 (33.3)*
Child Health Assessment Questionnaire[b] (DICHAQ)	–0.6 (0.7)**
Active Joint Count (AJC73)	–9.5 (7.5)*
Limitation on Passive Motion (LOM69)	–5.5 (8.3)**
CRP (mg/dL)	–0.3 (1.8)
Tender Joint count (TJC75)	–4.5 (5.9)**
Swollen Joint Count (SJC66)	–8.4 (7.2)*
Pain on Passive Motion (POM75)	–5.9 (5.3)*
PaGA of Pain[b] (VAS 0–100 mm)	–35.2 (34.4)*

[a]Observed case analysis. [b]N=21. *P<.001. **P<.05. SD, standard deviation.

Conclusion: In this very young population with polyarticular JIA, primary clinical trial data revealed that the safety profile and effectiveness of ADA were comparable to that observed in older children with JIA. No adverse effects on growth were observed; however, data did reflect improvement in growth through wk 60 of the study.

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Long-Term Safety and Efficacy Of Etanercept In Paediatric Subjects With Extended Oligoarticular Juvenile Idiopathic Arthritis, Enthesitis-Related Arthritis, Or Psoriatic Arthritis. Tamas Constantin[1], Ivan Foeldvari[2], Jelena Vojinovic[3], Gerd Horneff[4], Ruben Burgos-Vargas[5], Irina Nikishina[6], Jonathan Akikusa[7], Tadej Avcin[8], Jeffrey Chaitow[9], Elena Koskova[10], Bernard Lauwerys[11], Jack Bukowski[12], Chuanbo Zang[13], Joseph Wajdula[13], Deborah Woodworth[13], Bonnie Vlahos[13], Alberto Martini[14] and Nicolino Ruperto[15]. [1]Semmelweis University, Budapest, Hungary, [2]Hamburger Zentrum für Kinder- und Jugendrheumatologie, Klinikum Eilbek, Hamburg, Germany, [3]Dept Pediatric Rheumatology, Clinical Center, School of Medicine University of Nis, Nis, Serbia, [4]Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany, [5]Hospital General de Mexico, Mexico DF, Mexico, [6]Scientific Research Institute of Rheumatology RAMS, Moskow, Moskow, Russia, [7]Royal Childrens Hospital, Parkville, Australia, [8]The Ljubljana University Medical Centre, Pediatric Clinic, Ljubljana, Slovenia, [9]Children's Hospital Westmead, Sydney, Australia, [10]National Institute of Rheumatic Diseases, Piestany, Slovakia, [11]Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium, [12]Pfizer Inc, Collegeville, PA, [13]Pfizer Inc., Collegeville, PA, [14]Istituto Giannina Gaslini, Genova, Italy, [15]PRINTO, Genoa, Italy

Background/Purpose: Etanercept (ETN) is approved for the treatment of pediatric patients with the polyarticular subtype of juvenile idiopathic arthritis (JIA). In addition, based on the interim 12-week data from the first part of the CLIPPER study,[1] ETN was recently approved in the EU for the treatment of pediatric patients with the extended oligoarticular (eo), enthesitis-related (ERA), and psoriatic (PsA) JIA subtypes. The majority of studies performed with ETN to date have enrolled subjects with polyarticular-onset JIA and limited information is available on the eoJIA, ERA, and PsA JIA subtypes. The objective of the second part of the CLIPPER study was to assess the long-term safety and clinical benefit of ETN in pediatric subjects with these JIA subtypes.

Methods: CLIPPER was a 96-week, Phase 3b, open-label, multicenter study. Subjects with eoJIA (2–17 years old), ERA (12–17 years old), or PsA (12–17 years old) received ETN 0.8 mg/kg once weekly (maximum dose 50 mg) for 96 weeks. Safety was assessed by reporting treatment-emergent adverse events (TEAEs) and serious TEAEs throughout the study. Efficacy endpoints included the proportions of subjects achieving JIA American College of Rheumatology (ACR) 30/50/90 responses and inactive disease criteria at Week 96.

Results: 127 subjects (eoJIA n=60, ERA n=38, PsA n=29) received ≥1 dose of ETN. Mean age was 11.7 (SD, 4.5) years and disease duration was 26.8 (SD, 26.4) months. Safety results are summarized in the table. Most frequently reported TEAEs were (number of events, events per patient year [EPPY]): headache (23, 0.107), pyrexia (12, 0.056), diarrhea (10, 0.046), leukopenia (8, 0.037), increased alanine aminotransferase (8, 0.037), and arthralgia (8, 0.037). The most commonly reported treatment emergent (TE) infections were (number of events, EPPY): upper respiratory tract infection (83, 0.386), pharyngitis (50, 0.232), gastroenteritis (22, 0.102), bronchitis (19, 0.088), and rhinitis (17, 0.079). No cases of malignancy, active tuberculosis, demyelinating disorders, or deaths were reported. At Week 96, the overall proportions (95% CI) of subjects achieving JIA ACR 30/50/90/inactive disease criteria were 99.1% (94.9, 100), 98.1% (93.5, 99.8), 65.4% (55.6, 74.4), and 34.0% (25.0, 43.8), respectively. Approximately a 2-fold and 3-fold increase in the percentage of JIA ACR 90 and inactive disease responders from Week 12 to Week 96, respectively, was noted.

Table. Safety Summary at Week 96

	eoJIA n = 60 EXP = 103.603 N (EPPY)*	ERA n = 38 EXP = 61.298 N (EPPY)*	PsA n = 29 EXP = 50.185 N (EPPY)*	Total n = 127 EXP = 215.086 N (EPPY)*
TEAEs†	136 (1.313)	112 (1.827)	52 (1.036)	300 (1.395)
TE infections	219 (2.114)	60 (0.979)	76 (1.514)	355 (1.651)
TE ISRs	22 (0.212)	29 (0.473)	12 (0.239)	63 (0.293)
TEAEs causing withdrawal,† n (%)	0	3 (7.9)	0	3 (2.4)
TE infections causing withdrawal, n (%)	1 (1.7)	0	1 (3.4)	2 (1.6)
Serious TEAEs†	2 (0.019)	11 (0.179)	3 (0.060)	16 (0.074)
Serious TE infections	4 (0.039)	3 (0.049)	3 (0.060)	10 (0.046)
Opportunistic infections‡	0	1 (0.016)	0	1 (0.005)
Infections considered preventable by vaccination in subjects not previously vaccinated	5 (0.048)	1 (0.016)	1 (0.020)	7 (0.033)
Infections considered preventable by vaccination in subjects previously vaccinated	1 (0.010)§	0	0	1 (0.005)
TE autoimmune disorders#	1 (0.010)	2 (0.033)	1 (0.020)	4 (0.019)

*All values are reported as number of events (N) per patient-year (EPPY) of exposure (EXP) to ETN, unless otherwise stated. †Excluding infections and injection site reactions (ISRs); ‡one case of herpes zoster affecting two dermatomes was considered to be an opportunistic infection and one case of latent tuberculosis (purified protein derivative conversion) was not considered to be an opportunistic infection; §one case of rubella; #two cases of uveitis, one case of iridocyclitis, and one case of Crohn's disease were TE and one case of Crohn's disease was not considered TE based on missing last dose data.

Conclusion: ETN treatment for 96 weeks was well-tolerated and effective in treating subjects with the JIA subtypes, eoJIA, ERA, or PsA, as expected from the previous data from polyarticular JIA.

Reference:

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GO-Kids Imaging Substudy: MRI Treatment Response To 30 Mg/m^2 4-Weekly Subcutaneous injections Of Golimumab In Children With Polyarticular JIA–Preliminary Results Of The Open Label Portion.

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Background/Purpose: The **GO-KIDS** trial is a double blind placebo controlled Phase III trial, where patients 2–17 yrs of age with pJIA receive open label SC GLM 30 mg/m^2 every 4 weeks until week 16, followed by 1:1 randomization to placebo or GLM from Weeks 1648 for children achieving ACR Pedi 30 response at Week 16. Primary endpoint is % of children who experience flares of JIA between Weeks 16 and 48.

173 patients were enrolled.

The aim of the MRI based **GO-KIDS Imaging** substudy is to evaluate the efficacy of GLM on MRI measurements within 16 weeks of drug initiation.

Methods: Patients participating in the **GO-KIDS** trial at a single center could voluntarily participate in the **GO-KIDS Imaging** substudy after obtaining separate informed consent. Gadolinium enhanced MRI of a reference peripheral joint region and the temporomandibular joints (TMJ) were obtained at week 0 (baseline) and week 16 (before randomization). MRI was scored (grade 0 – 3) for peripheral joints/TMJ for synovitis (S), synovial hypertrophy (SH) and for peripheral joints for tenosynovitis (TS). Statistical analysis: Shapiro- Wilk-W-test (for normality of distribution); non-parametric Wilcoxon rank-sum test (changes of the MRI scoring).

The clinical response data (ACR Pedi Score) were extracted from the **GO-KIDS** trial and compared to the MRI response.

Results: 19 children (10 female) with a median age of 9 (7–17) years at study inclusion participated in the **GO-KIDS Imaging** substudy. At week 16 the number of ACR Pedi 100 responders was 11/19, ACRPedi 90–15/19, ACR Pedi 70–17/19 and 2 children were non-responders.

At week 16 the MRI was significantly improved compared to week 0 in all components of the MRI scoring: peripheral joints ($p<0.001$ for S, $p=0.001$ for SH and $p=0.002$ for TS) and TMJ ($p<0.001$ for S and SH each). Eight patients showed no inflammatory activity on MRI at week 16 and 9 patients significantly ($p<0.002$) improved. Two patients did not demonstrate significant change on MRI (same as ACR Pedi non-responders).

MRI results did not completely correlate with improvements in ACR Pedi Score: 5 children showed inactivity on MRI but did not achieve an ACR Pedi Score of 100.

Conclusion: During the open label treatment with GLM of the **GO-KIDS** trial, children with pJIA demonstrated significant improvement on MRI measurements between Weeks 0 and 16 with a large proportion of patients achieving MRI inactivity. MRI appeared to be more sensitive in detecting inflammatory inactivity than ACR Pedi scoring systems.

Disclosure: N. Tzaribachev, None; **C. Tzaribachev**, None; **B. Koos**, None.

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Rates Of Flare-Free Survival In Juvenile Idiopathic Arthritis When Tapering Individual Components Of Tumor Necrosis Factor Inhibitor and Methotrexate Combination Therapy.

Caroline Y Chang, Rika Meyer and Andreas Reiff. Children's Hospital Los Angeles, Los Angeles, CA

Background/Purpose: Combination therapy of tumor necrosis factor inhibitors (TNFi) and methotrexate (MTX) is a well-established treatment that has dramatically changed outcomes in Juvenile Idiopathic Arthritis (JIA). Given the high relapse rate of patients with JIA, it is crucial to determine the appropriate timing and method of tapering medications once disease control is achieved.

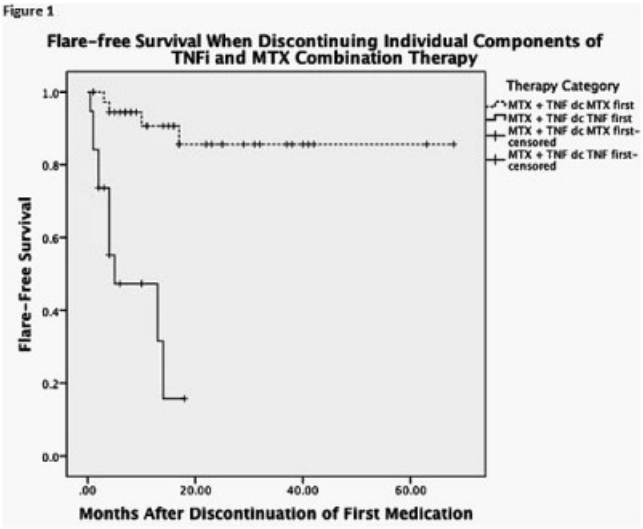
Methods: This is a retrospective single-center observational cohort study of patients with polyarticular JIA (pJIA) seen in our institution's pediatric rheumatology clinic between January 2000 and December 2011. Demographic information (Table 1), diagnosis, antibody status, medication history, and dates of achieving inactive disease and flare were extracted from patient charts. Inactive disease was defined per Wallace criteria and flare was defined as no longer fulfilling these criteria for more than 1 visit. We performed a flare-free survival analysis, looking at 4 treatment arms of patients who had achieved inactive disease and tapered medications: TNFi plus MTX, tapered off MTX first (group 1,n=45), TNFi plus MTX, tapered off TNFi first (group 2,n=19), MTX monotherapy (group 3,n=32), and TNFi monotherapy(group 4,n=6). We also evaluated outcomes based on rheumatoid factor (RF) status.

Results: We included 194 pJIA patients with a mean follow-up of 4.74 ± 2.8 years. After a mean of 23.6 months (range 5–120), 129/194 patients (66%) achieved inactive disease. Group 2 had a significantly worse outcome with only 47% of patients remaining flare-free for 12 months off TNFi despite continued MTX therapy compared to 90% of those who had weaned MTX first and continued TNFi ($p<.0005$) (Figure 1). After a mean of 21months (range 0–81) with inactive disease, 30% of patients were able to discontinue all medications. Of these, 33% flared within 3 months, 46% within 6 months, and 67% within 12 months. When comparing the 4 treatment arms, group 3 had a significantly better outcome in terms of flare-free survival off medications compared to group 1($p=0.007$). Time to flare was independent of time in remission and RF status.

Table 1

Demographic Information	N = 194 (%)
Female Sex	161 (83)
Ethnicity	
Hispanic	127 (65)
Non-Hispanic	67 (35)
Age at disease onset, mean years (range)	9.8 (1–18)
Mean follow-up, years (SD)	4.74 (2.8)
RF positive	90/187 (48)
CCP positive	56/106 (53)

Figure 1



Conclusion: This study confirms that flare rates in JIA patients are high. However, when tapering TNFi/MTX combination therapy to monotherapy, weaning TNFi first carries a significantly higher risk of flare than weaning MTX first. After discontinuation of all medications, patients on MTX

monotherapy had better flare-free survival compared to those on combination therapy, possibly due to inherently milder disease.

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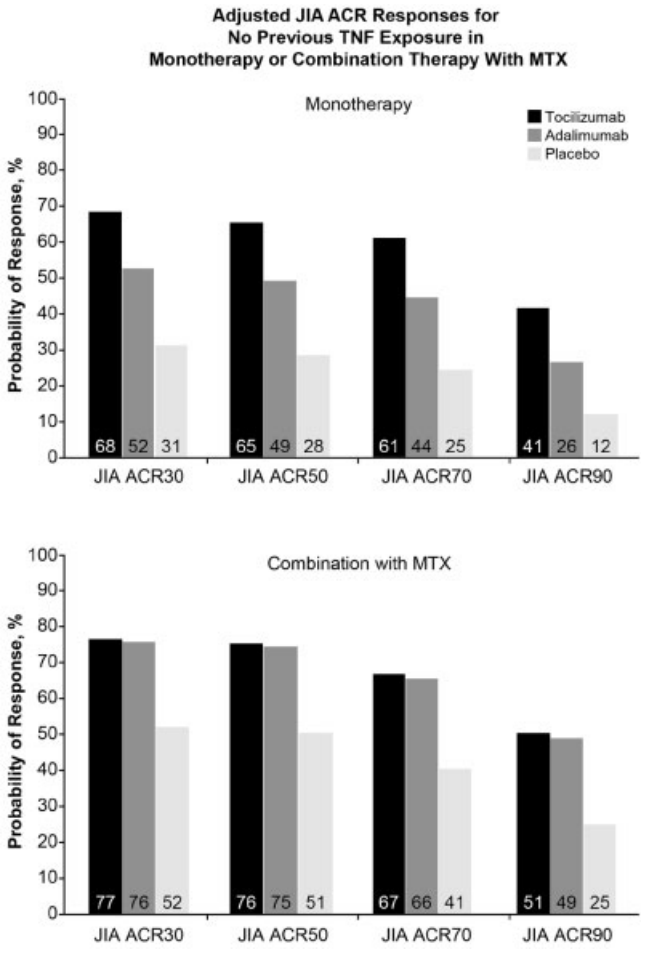
Efficacy Of Biologic Treatments In Juvenile Idiopathic Arthritis With a Polyarticular Course: An Indirect Comparison. Laura Sawyer[1], Alex Diamantopoulos[1], Hermine I. Brunner[2], Fabrizio De Benedetti[3], Nicolino Ruperto[4], Fred Dejonckheere[5] and Caroline Keane[6]. [1]Symmetron Limited, London, United Kingdom, [2]PRCSG, Cincinnati, OH, [3]IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, [4]PRINTO, Genoa, Italy, [5]F. Hoffmann-La Roche Ltd, Basel, Switzerland, [6]Roche, Welwyn Garden City, United Kingdom

Background/Purpose: To date there are no head-to-head trials comparing the efficacy of biologic treatments for polyarticular-course JIA (pcJIA). The purpose of this study was to use statistical methods to estimate the relative efficacy of biologic treatments, alone and in combination with methotrexate (MTX), in the management of pcJIA by means of indirect comparison of randomised controlled trials (RCTs).

Methods: Based on a literature review, we identified RCTs of abatacept,[1] adalimumab[2] (ADA), etanercept,[3] infliximab,[4] and tocilizumab[5] (TCZ; CHERISH) in pcJIA. Comparative effectiveness was estimated on the reported American College of Rheumatology response rates (JIA ACR30/50/70/90) measured at the end of the randomized, double-blind phase by means of a Bayesian indirect comparison using a fixed-effects ordered probit model. Probabilities of achieving different levels of JIA ACR response were calculated for biologic treatments and placebo using all observed comparisons.

Results: The 5 RCTs identified showed differences in reporting JIA ACR responses with regard to methods of nonresponder imputation during the blinded, controlled phase, allowing only for the comparison of ADA and TCZ. After correction for previous biologic use (Figure), for a JIA ACR30 placebo response of 31%, TCZ monotherapy had a higher predicted probability of achieving JIA ACR30 (68%), JIA ACR50 (65%), JIA ACR70 (61%), and JIA ACR90 (41%) vs ADA monotherapy, with 52%, 49%, 44%, and 26%, respectively. On MTX background therapy and a JIA ACR30 placebo response of 52%, TCZ had a higher expected probability of response at JIA ACR30 (77%), JIA ACR50 (76%), JIA ACR70 (67%), and JIA ACR90 (51%) vs ADA, with 76%, 75%, 66%, and 49%, respectively. In neither monotherapy nor combination therapy did differences between TCZ and ADA reach statistical significance.



Conclusion: Based on JIA ACR response rates from this analysis, the expected efficacy of ADA vs TCZ appears comparable in pcJIA. As monotherapy, however, TCZ may be better than ADA. These data should be interpreted in the context of differences in the duration of the withdrawal phase, which was shorter in the TCZ study (CHERISH) than in the ADA trial and might have resulted in a smaller difference in the number of flares observed between placebo and TCZ.

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Disclosure: L. Sawyer, Hoffmann-La Roche, Inc., 5; **A. Diamantopoulos**, Hoffmann-La Roche, Inc., 5; **H. I. Brunner**, Novartis, Genentech, MedImmune, EMD Serono, AMS, Pfizer, UCB, Janssen, 5, Genentech, 8; **F. De Benedetti**, Abbott, Pfizer, BMS, Roche, Novimmune, Novartis, SOBI, 2; **N. Ruperto**, Abbott, AstraZeneca, BMS, Centocor, Lilly, Francesco Angelini, GSK, Italfarmaco, MerckSerono, Novartis, Pfizer, Regeneron, Roche, Sanofi Aventis, Schwarz Biosciences, Xoma, Wyeth, 2, Abbott, AstraZeneca, BMS, Centocor, Lilly, Francesco Angelini, GSK, Italfarmaco, MerckSerono, Novartis, Pfizer, Regeneron, Roche, Sanofi Aventis, Schwarz Biosciences, Xoma, Wyeth, 5, Abbott, Boehringer, BMS, Novartis, Astellas, Italfarmaco, MedImmune, Pfizer, Roche, 8; **F. Dejonckheere**, F. Hoffmann-La Roche, 3; **C. Keane**, Roche Pharmaceuticals, 3.

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What Is the Relative Priority of the ACR Pediatric Core Set Measures for Youth With Juvenile Idiopathic Arthritis and Their Parents? Jaime Guzman[1], Oralia Gomez-Ramirez[2], Susanne M. Benseler[3], Roberta A. Berard[4], Rollin Brant[2], Ciaran M. Duffy[5], Roman Jurencak[6], Kiem Oen[7], Ross E. Petty[8], Natalie J. Shiff[9] and Lori B. Tucker[2]. [1]BC Children's Hospital and University of British Columbia, Vancouver, BC, [2]University of British Columbia, Vancouver, BC, [3]Hospital for Sick Children, Toronto, ON, [4]Children's Hospital of Western Ontario, London, ON, [5]Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa, ON, [6]University of Ottawa, Ottawa, ON, [7]University of Manitoba, Winnipeg, MB, [8]BCs Children Hosptial, Vancouver, BC, [9]University of Saskatchewan, Saskatoon, SK

Background/Purpose: The ACR has endorsed a core set of six measures to assess the course of JIA and the impact of treatment: active joint count, limited joint count, physician's global assessment of disease activity, functional ability, patient/parent's global assessment of well being and a laboratory measure of inflammation. We sought to determine the relative priority given by patients and their parents to the ACR pediatric core measures, in relation to other disease features.

Methods: Three separate study sessions consisting of focus group discussions and reciprocal interviews (participants interview each other), were conducted with youth with JIA, experienced parents and novice parents. Participant youth (7 female, 2 male, aged 16 to 23 years old) had JIA for 2 to 12 years (1 oligo, 2 poly, 2 systemic, 2 ERA, 1 psoriatic, 1 unclassified). Experienced parents (5 female, 5 male, 2 couples) participated 9 months to 14 years after JIA diagnosis in their child (4 oligo, 1 poly, 1 ERA, 1 psoriatic, 1 unclassified). Novice parents (5 female, 3 male, one couple) participated 2 to 6 months after JIA diagnosis in their child (2 oligo, 1 systemic, 1 ERA, 1 psoriatic, 2 unclassified). A list of 34 clinical features often used for the monitoring of JIA in cohort studies and therapeutic trials was provided to participants. The list included the core set ACR pediatric measures and lay language definitions for all the features. Participants were asked to add any other relevant features, and discuss the features' relative priority in describing the course of JIA. Focus group discussions were professionally facilitated, recorded, and transcribed. Reciprocal interview answers were reported in standard forms. Focus group transcripts and interview answers underwent content analysis by two investigators; themes and priority rankings were discussed with all co-authors.

Results: Among core set measures, the active joint count was considered to be of high priority by parents and of medium priority by youth. The parent's global assessment was considered to have medium priority by

parents and low priority by youth. The limited joint count and functional ability were considered to have low priority by the three groups. The physician global assessment was not discussed to any extent or given any priority, although the concept of disease activity was considered to be important. Laboratory measures were not discussed. By contrast, youth and parents gave high priority to pain, quality of life, medications required to control the disease and medication side-effects. Youth felt that visual analogue scales and standardized questionnaires were poor reflections of their experiences with JIA. Experienced parents were particularly interested in disease flares and flare triggers. Novice parents were still coming to terms with the emotional impact of their child's JIA diagnosis and found the prioritizing task difficult.

Conclusion: Among the six core measures, only the number of active joints has enough relevance in the eyes of youth and parents to be considered a central feature of JIA course. If more patient-relevant measures are desired, consideration should be given to include pain and quality of life indicators as core set measures.

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Juvenile Idiopathic Arthritis Patients Demonstrate Alterations In HDL Functionality Without Accelerated Subclinical Atherosclerosis. Preethi Mani[1], Kiyoko Uno[2], Katherine Wolski[2], Steven J. Spalding[3], Stephen J. Nicholls[2] and M. Elaine Husni[2]. [1]Cleveland Clinic Lerner College of Medicine, Cleveland, OH, [2]Cleveland Clinic Foundation, Cleveland, OH, [3]The Cleveland Clinic, Cleveland, OH

Background/Purpose: Previous literature supports an increase in cardiovascular (CV) morbidity and mortality in adults with inflammatory joint disease, however it is not known whether children with JIA also carry this risk. While the precise mechanism for accelerated atherosclerosis is unknown, impaired high density lipoprotein (HDL) functionality may contribute to increased CV risk in these patients. It has not been established if younger patients with JIA also have accelerated subclinical disease or alterations in HDL function.

Methods: HDL functionality, as measured by cholesterol efflux capacity and receptor expression, NMR spectroscopy, antioxidant activity, and promotion of endothelial function, were compared in JIA patients and controls. Carotid intima-media thickness (cIMT) was measured as a validated, non-invasive surrogate of subclinical atherosclerosis were also compared. Apolipoprotein B depleted serum capacity to promote cholesterol efflux via ABCA-I (J774 macrophages), ABCG-I (baby hamster kidney cells) and SR-BI (Fu5AH hepatoma cells) were measured. Change in mRNA expression of ABCA-I, ABCG-I, and SR-BI on murine bone marrow-derived macrophages upon exposure to serum was assessed. HDL particle distributions were characterized using NMR spectroscopy. Antioxidant activity by arylesterase and ability of serum to promote endothelial cell migration were compared.

Results: 29 patients with JIA and 14 healthy controls between the ages of 10–32 were studied. Patients were younger than controls (17.3±6 vs. 21.7±6 years, p= 0.05) and had lower HDL-C (47.0 (40, 56) vs. 56.0 (53, 63) mg/dL, p = 0.04). There was no difference in mean cIMT (0.5 ± 0.05 vs 0.5 ± 0.06, p = 0.27), however, alterations in HDL functionality were noted. JIA patient serum demonstrated greater cholesterol efflux via ABCA-I (17.3 (12.8, 19.7) vs. 10.0 (5.8, 16.0), p=0.05), but less efflux via ABCG-I (3.2 (2.0, 3.9) vs. 4.8 (3.5, 5.8), p=0.01) and SR-BI (6.9 (6.0, 8.4) vs. 9.2 (8.6, 10.2), p=0.002). Exposure of macrophages to patient serum resulted in less expression of ABCA-I (2±0.9 vs. 7±5.7 fold increase, p=0.01), but greater expression of ABCG-I (1.37 (0.88, 1.52) vs. 0.76 (0.71, 1.07) fold increase, p=0.04) and SR-BI (1.3± 0.47 vs. 0.65±0.25 fold increase, p=0.001). JIA patients had less large HDL (5.1 (3.7, 7.3) vs. 8.0 (6.7, 9.7) mg/dL, p=0.04) and less HDL particles (29.5 (27.9, 32.3) vs. 32.9 (31.6, 36.3) particles, p=0.05). Arylesterase activity was lower in JIA patients (128.9±27.6 vs. 152.0±45.2 umoles/min/mL, p = 0.04). Endothelial cell migration was lower upon exposure to patient serum (491.2±68.9 vs. 634.2±227.4 cells/field, p = 0.01).

Conclusion: Although JIA patients did not demonstrate increase in subclincal disease by cIMT compared to controls, they demonstrate changes in HDL functionality despite being on active treatment. These changes may lead to increased CV risk as these patients age further. While larger studies are critical to further characterize HDL functionality and subclinical disease in subsets of JIA patients, these patients warrant close monitoring of CV risk beginning at a younger age than the general population and aggressive, early implementation of CV risk management strategies.

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Cardiovascular Risk In Adults With Juvenile Idiopathic Arthritis. Elizabeth Coulson[1], Wan-Fai Ng[2], Philip N. Platt[3] and H. E. Foster[4]. [1]Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, [2]Newcastle University, Newcastle upon Tyne, United Kingdom, [3]Freeman Hospital, Newcastle upon Tyne, United Kingdom, [4]Musculoskeletal Research Group, Institute of Cellular Medicine, Newcastle University and Great North Children's Hospital, Newcastle Upon Tyne, United Kingdom

Background/Purpose: Increased cardiovascular mortality and morbidity have been observed in adults with Rheumatoid Arthritis. The long-term risk of cardiovascular disease for individuals with Juvenile Idiopathic Arthritis (JIA) remains uncertain. This study aims to determine whether adults with JIA have an increased risk of cardiovascular disease compared to the general population.

Methods: 51 patients with JIA (mean age 35.6 years, SD 13.23) were compared to 26 controls (mean age 37.3 years, SD 13.14). Data regarding traditional cardiovascular risk factors were collected including fasting blood glucose and lipid profile, blood pressure, BMI and history of hypertension, hypercholesterolaemia, diabetes mellitus, smoking history and family history of cardiovascular disease. Disease sub-type (ILAR criteria) and duration were recorded. In the patient group the sub-types were as follows: systemic 3/51 (5.9%), enthesitis-related arthritis (ERA) 5/51 (9.8%), extended oligoarticular 12/51 (23.5%), polyarticular 27/51 (52.9%), juvenile psoriatic (JPSA) 4/51 (7.8%). Median disease duration was 24 years (3–57). Many (23/51 (45%)) patients were taking biological therapy, 13 as monotherapy and 10 in combination with a DMARD; a further 17/51 (33%) patients were taking one or more DMARDs. Common carotid artery intima-media thickness (CCA IMT) was examined by B-mode ultrasound (Toshiba AplioXU and 12 MHz transducer) as a surrogate marker of cardiovascular disease. Images were analysed blinded using the M'athñ software package (Intelligence in Medical Technologies). Continuous, parametric variables were analysed using the independent samples T-test, non-parametric using the Mann Whitney U test and categorical data using the chi-squared test.

Results: The Table shows that a significantly higher proportion of patients had a pre-existing diagnosis of hypertension compared to controls (p=0.029) but no significant differences in other pre-existing traditional cardiovascular risk factors. The patient group had a significantly higher CRP (p=0.006). No significant differences were found in ESR, fasting glucose or lipid levels, BMI or systolic or diastolic blood pressures recorded in clinic. CCA IMT showed good correlation with age (Pearson's coefficient 0.76, p=0.000). The patient group had a significantly higher mean CCA IMT (0.54 vs. 0.49, p=0.037) compared to controls. Subgroup analysis revealed a significantly higher mean CCA IMT in those with polyarticular disease (0.56 vs. 0.48, p=0.01), but not for other subtypes. CCA IMT was not significantly higher in patients taking biologics (0.51 vs. 0.49 p=0.396) but was for those taking DMARDs (0.58 vs. 0.48, p=0.029) compared to controls.

	Patient n=51	**Control n=26**	***P value***
Hypertension n(%)	12 (23.5)	1 (3.9)	0.029
Hypercholesterolaemia n(%)	4 (7.8)	1 (3.9)	*0.501*
Diabetes mellitus n(%)	2 (3.9)	1 (3.9)	*0.987*
Family history of cardiovascular disease n(%)	6 (11.8)	3 (11.5)	*0.771*
Smoking history n(%)	Ever 12 (23.5) Never 39 (76.5)	Ever 3 (11.5) Never 23 (88.5)	*0.305*
Pack Years (mean)	10.4	8.5	
CRP (mg/l) mean (SD)	9.0 (9.02)	5.6 (1.97)	0.006
ESR (mm/hr) mean (SD)	12.6 (12.75)	6.4 (7.70)	*0.106*
BMI (kg/m^2) mean (SD)	25.0 (6.5)	24.9 (4.3)	*0.483*
Systolic BP (mmHg) mean (SD)	122 (15.4)	120 (14.0)	*0.684*
Diastolic BP (mmHg) mean (SD)	79 (10.1))	78 (8.6)	*0.859*
Glucose (mmol/l) mean (SD)	4.9 (1.87)	4.9 (0.34)	*0.496*
Cholesterol (mmol/l) mean (SD)	4.6 (0.97)	4.8 (1.00)	*0.417*
Triglycerides (mmol/l) mean (SD)	1.04 (0.51)	1.01 (0.61)	*0.374*
HDL (mmol/l) mean (SD)	1.5 (0.49)	1.7 (0.45)	*0.109*
LDL (mmol/l) mean (SD)	2.5 (1.04)	2.6 (1.06)	*0.954*
CCA IMT (mm) mean (SD)	0.54 (0.10)	0.49 (0.08)	0.037
Polyarticular n=27	0.56 (0.11)	0.48 (0.08)	0.010
JPSA n=4	0.48 (0.07)	0.46 (0.02)	*0.289*
Systemic n=3	0.68 (0.05)	0.51 (0.07)	*0.050*
Extended oligoarticular n=12	0.51 (0.65)	0.46 (0.42)	*0.054*
ERA n=5	0.46 (0.06)	0.47 (0.09)	*0.806*

Conclusion: Adults with JIA were found to have an increased cardiovascular risk measured using carotid IMT compared to age- and sex-matched controls. This may in part be explained by an increased prevalence of hypertension.

Disclosure: E. Coulson, None; **W. F. Ng**, None; **P. N. Platt**, None; **H. E. Foster**, None.

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Long-Term Evaluation Of Cardiac Function In Juvenile Idiopathic Arthritis Under Anti-Tumor Necrosis Factor Therapy. Alessandro C. Lianza[1], Nadia E. Aikawa[1], Julio C. B. Moraes[2], Gabriela N. Leal[1], Samira S. Morhy[1], Eloisa Bonfa[1] and Clovis A. Silva[3]. [1]University of São Paulo, Sao Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil

Background/Purpose: Subclinical cardiac involvement was previously described in juvenile idiopathic arthritis (JIA) patients, however there is no data regarding echocardiography and cardiac biomarkers evaluations in JIA under biologic therapy. Therefore, the objectives of this study were to perform a global assessment of the long-term cardiac function in JIA patients under TNF blockage therapy.

Methods: Twenty-five polyarticular-course JIA patients pre-anti-TNF (etanercept or adalimumab) and 22 healthy controls underwent conventional/tissue Doppler imaging echocardiography and cardiac biomarkers measurements [N-terminal pro-brain natriuretic peptide (NT-pro-BNP, cut-off≥125pg/mL for elevated values) and troponin T (cut-off>0.01μg/l for myocardial damage) by electrochemiluminescence immunoassay] at baseline (BL). Additionally, 21 JIA patients completed six evaluations during two consecutive years: BL, and 3, 6, 12, 18 and 24 months after anti-TNF treatment. Number of active joints, patient and physician visual analogue scales (VAS), Childhood Health Assessment Questionnaire (CHAQ), acute phase reactants [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] were evaluated before and after anti-TNF therapy.

Results: JIA patients and controls were comparable regarding current age (11.6 vs. 9.2 years, p=0.15) and female gender (47 vs. 40%, p=1.0). The median of disease duration was 2.7 (0.4–9.9) years and 24 (96%) were under non-steroidal antiinflammatory drugs, 8 (32%) prednisone, 23 (92%) methotrexate, 5 (20%) leflunomide and 7 (28%) cyclosporine. At BL, on the conventional Doppler evaluation, there was a lower isovolumetric relaxation time of left ventricle in JIA patients compared to healthy controls [76 (56–89) vs. 81.5 (71–96)m/s, p=0.03]. On the tissue Doppler, all parameters were within normal values at BL, although ventricular septum velocity (VS) E' wave (p=0.014) and VS S wave (p=0.03) were lower in JIA patients compared to healthy controls. Frequencies of elevated NT-pro-BNP levels were similar in JIA patients and controls (28 vs. 13.6%, p=0.3). Further comparison of JIA patients according to NT-pro-BNP levels at BL revealed that JIA patients with elevated levels of this cardiac biomarker had significantly more active joints (8 vs. 3, p=0.03) and higher ESR (55 vs. 29 mm/1sthour, p=0.03) compared to those with normal levels. Positive correlations were observed between NT-pro-BNP levels and number of active joints (r=0.59, p=0.002) and between NT-pro-BNP levels and ESR (r=0.51, p=0.009). Prospective evaluation of 21 JIA patients revealed that none of the participants had symptoms of heart failure and all of them remained with normal ejection fraction, and no alteration was observed in other parameters of conventional and tissue Doppler imaging echocardiography. Only one patient had mild elevated levels of troponin T at 18 and 24 months evaluations.

Conclusion: Long-term TNF blockage safety was demonstrated in JIA patients in spite of the observed mild subclinical diastolic involvement. Elevated cardiac biomarker in these patients was associated with inflammatory parameters reinforcing the need for a careful interpretation of this finding in patients with active disease.

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MRI Findings In Juvenile Spondyloarthopathy and Effects Of Treatment On Subsequent MRI. Clara Lin[1] and Diana Milojevic[2]. [1]University of California-San Francisco, San Francisco, CA, [2]University of California, San Francisco, San Francisco, CA

Background/Purpose: The aim of our study was to

- describe pelvic MRI findings of juvenile spondyloarthopathy
- describe the treatment effects on subsequent MRIs in juvenile spondyloarthropathy
- determine predictors of active sacroiliitis in children

Methods: This was a retrospective chart and imaging review of children ages 5 to 21 year old seen in the pediatric rheumatology clinic from 2009 to 2012 with a MRI of the sacroiliac joints (MRI-SI). Data collected included demographics, patient's history, physical exam, and laboratory results at each visit. The pelvic joints (sacroiliac, hip, and facet)and entheses were reviewed on MRI-SI, and the sacroiliac joints were graded on a semi-quantitative scale (0–3) for bone marrow edema (BME), synovial enhancement, erosions to create a composite score ratio.

Results: 50 subjects with 76 MRI-SI were studied, and 32 subjects had sacroiliitis on 48 MRIs. Of the subjects with sacroiliitis, mean age± standard deviation was 13.68±2.59 years, 71% were male and 41% were HLA-B27 positive. In 22.9% of subjects with sacroiliitis, history and physical exam did not reveal signs of sacroiliitis. Inflammatory markers (ESR, CRP, WBC, Platelet count) were normal in 50% of cases of (+) sacroiliitis. In 16.7% of cases of sacroiliitis (n=8) in 7 subjects, physical exam of SI joints, Modified Schober's exam, and inflammatory markers were normal. In subjects with sacroiliitis, MRI also revealed hip arthritis and pelvic enthesitis in 71.4% and 40.6% of exams, respectively. Longitudinal data was available for 13 subjects. MRI-SI composite score ratio improved in 8 subjects with the greatest improvement occurring with initiation of etanercept therapy. Improvements in composite score ratio were due to improvement of BME and SE components, but erosion scores remained stable or worsened in all but 1 subject.

Conclusion: In our group of children with sacroiliitis, male:female ratio was 2.56 and HLA-B27 was present in 41% of subjects. Predicting active sacroiliitis from history, physical exam, and laboratory findings remains a challenge. Hip arthritis and pelvic enthesitis were common findings in cases of sacroiliitis in children. Greatest improvement of sacroiliitis on MRI was seen after initiating etanercept by decreasing bone marrow edema and synovial enhancement; however, erosions did not seem to improve on therapy.

Disclosure: C. Lin, None; **D. Milojevic**, None.

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Development and Validation Of The Cutoff Values For Disease Activity States Of The Three-Item Version Of The Juvenile Arthritis Disease Activity Score. Alessandro Consolaro[1], Sara Verazza[1], Maria C. Gallo[1], Giulia Bracciolini[1], Giorgia Negro[1], Alessia Frisina[1], Nicolino Ruperto[1], Alberto Martini[2] and Angelo Ravelli[2]. [1]Istituto Giannina Gaslini, Genova, Italy, [2]University of Genova, Genova, Italy

Background/Purpose: A new approach to the measurement of disease activity in juvenile idiopathic arthritis (JIA) is based on the Juvenile Arthritis Disease Activity Score (JADAS). The feasibility of the JADAS for use in standard clinical practice may be enhanced by implementing a 3-item version, which does not include the acute phase reactant. Inflammatory markers frequently are not obtained or available at a visit. The lack of this information would hinder the potential to make immediate therapeutic decisions based on the JADAS and, thus, the potential benefit of intensifying therapy. As for the original tool, the use of the cJADAS as a guide to pursuing tight disease control requires cutoff values to identify the target disease activity states. Aim of the study was to determine cutoff values in the cJADAS that correspond to the states of inactive disease (ID), minimal disease activity (MDA) and high disease activity (HDA), and to the parent/child acceptable symptom state (PASS/CASS).

Methods: For the selection of cutoff values, data from a clinical database including 609 patients were used. Optimal cutoffs were determined against external criteria by calculating the 75th percentile of cumulative score distribution for ID, MDA, PASS and CASS and the 25th percentile cumulative score distribution for HDA, and through receiver operating characteristic curve analysis. External criteria were based on formal definitions for ID and MDA, on the subjective rating of satisfaction with illness outcome by parents and patients for PASS and CASS, and on the therapeutic decision made by the attending physician at the time of the visit for HDA. MDA and HDA cutoffs were developed separately for oligoarthritis and polyarthritis. The choice of optimal cutoffs was made on clinical and statistical grounds. Cross-validation

was performed using 5 JIA patient samples that included a total of 1,421 patients, and was based on assessment of construct, discriminant, and predictive validity.

Results: The table shows the selected cutoff values for the cJADAS10 and the sensitivity (se) and specificity (sp) of each cutoff. In cross-validation analyses, the cutoffs revealed strong ability to discriminate between different levels of ACR Pedi response in 2 clinical trials (one on methotrexate and one on abatacept) and revealed good concordance with the subjective assessment of the disease state (remission, continued activity or flare) by the physicians and the parents. Furthermore, they proved able to predict functional and radiographic outcomes.

	cJADAS10 cutoff (se/sp)
Inactive disease	**1 (84.1/87.0)**
MDA oligoarthritis	**1.5 (75.4/91.7)**
MDA polyarthritis	**3.5 (96.8/94.7)**
PASS	**4 (75.6/91.4)**
CASS	**3.5 (77.5/86.5)**
HDA oligoarthritis	**7 (74.9/93.5)**
HDA polyarthritis	**11 (76.9/93.2)**

Conclusion: The cutoff values in the cJADAS that correspond to the states of ID, MDA, PASS, CASS, and HDA in JIA were developed. In cross-validation analyses, they proved to have strong construct and discriminant validity and ability to predict disease outcome.

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Children With JIA Show Distinct Patterns Of Improvement In Their Health-Related Quality Of Life During The First Year On Treatment: Growth Mixture Modeling Of a Prospective Cohort Of Newly Diagnosed Patients. Bin Huang[1], Chen Chen[2], Stacey Niehaus[2], Hermine Brunner[1], Rina Mina[1] and Michael Seid[1]. [1]Cincinnati Children's Hospital Medical Center/University of Cincinnati School of Medicine, Cincinnati, OH, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background/Purpose: Health-related quality of life (HRQOL) is a key outcome in clinical care and research for children with JIA. Despite excellent clinical control and the availability of biologic treatment, HRQOL remains suboptimal in half of patients with JIA. The aims of the study were, for children with JIA during the first year post diagnosis with JIA, to: 1) identify distinct patterns of improvement in HRQOL; and 2) identify baseline disease, patient/parental characteristics that predict improvement in HRQOL.

Methods: Patients were enrolled within 6 months of diagnosis (N=230; 2–16 years of age), and followed up semi-annually. Patient HRQOL (Generic and Rheumatologic Core via self-report if ≥5 years and parental proxy-report) and non-medical patient/parental characteristics were obtained via survey during clinic visits; disease medical characteristics were obtained from clinical database. Primary outcome Generic PedsQL total score has mean 83 in healthy children, with <78.6 considered suboptimal. Longitudinal growth mixture model (GMM) was used to identify patterns (latent class) of improvement in HRQOL. Multivariable multinomial logistic regression with stepwise selection was used to predict GMM latent class membership using baseline measures; the model predictive ability was evaluated by the receiver operation characteristics (ROC, 1.0 being perfect).

Results: Table 1 presents study results for primary study outcome. Three distinct patterns of improvement were identified for patient self-report: 72% of patients maintained HRQOL at healthy norm (class I: 84.46+0.23×month), 21% improved (class III: 54.46+2.03×month), but 13% of patients with initial suboptimal HRQOL deteriorated over time (class II: 66.63-1.40×month). Modeling parent proxy-report, four latent classes were identified. The final logistic regression model for patient self-report found that less pain, adherence barriers, better self-efficacy managing emotion, and social support from parents are most predictive to more favorite pattern of HRQOL improvement (ROC 0.90). The final model for parental proxy-report found that parent- reports of less child pain and adherence barriers, better functional status and lower parental distress at baseline predicts more favorite pattern of improvement in child HRQOL (ROC 0.83).

Table 1. Latent Class of Pattern of Improvement (GMM Results) and their predictors (multinomial logistic regression results)

	HRQOL Self-Report (N = 180)			HRQOL Proxy-Report (N = 230)			
	Beta (SD) from GMM						
	Class I (High)	Class II (Deteriorate)	Class III (Low Improve)	Class I (High)	Class II (Stable Suboptimal)	Class III (Stable poor)	Class IV (Poor Improve)
Number Pts (%)	132 (72%)	13 (7%)	39 (21%)	129 (57%)	65 (29%)	24 (11%)	10 (4%)
Intercept	84.46*** (1.27)	66.63*** (4.08)	54.46*** (2.24)	88.22*** (1.08)	73.57*** (2.03)	53.21*** (3.73)	47.11*** (8.32)
Slop	0.23 (0.13)	−1.40* (0.58)	2.03*** (0.31)	0.54*** (0.10)	0.05 (0.16)	−0.15 (0.43)	4.02*** (0.75)
	OR (CI) from Multinomial Logistic Regression						
Age (year)	Ref	0.87 (0.41, 1.84)	1.42 (0.84, 2.41)	Ref	1.01 (0.70, 1.46)	1.14 (0.64, 2.03)	1.65 (0.75, 3.63)
Gender (Female)		8.71 (1.00, 76.15)	2.12 (0.58, 7.83)		0.57 (0.27, 1.19)	0.28 (0.08, 1.05)	0.73 (0.08, 6.54)
Age at onset (year)		1.14 (0.56, 2.33)	0.82 (0.50, 1.35)		1.01 (0.70, 1.47)	0.99 (0.54, 1.80)	0.57 (0.25, 1.30)
JIA Subtype: Oligo vs. Poly		1.61 (0.21, 12.17)	0.21 (0.03, 1.45)		0.47 (0.19, 1.12)	1.21 (0.24, 6.15)	0.05 (0.00, 3.23)
JIA Subtype: Other vs. Poly		1.27 (0.21, 7.76)	1.19 (0.33, 4.27)		1.49 (0.65, 3.41)	0.45 (0.10, 2.15)	0.48 (0.05, 4.21)
Less Pain (PedsQL Rheu. Core)		0.96 (0.93, 1.00)	0.95*** (0.92, 0.98)		0.98** (0.96, 0.99)	0.94*** (0.91, 0.97)	0.87*** (0.81, 0.94)
Less Adherence Barriers (PedsQL Rheu. Core)		0.93** (0.89, 0.97)	0.93*** (0.90, 0.97)				
Childhood Health Assessment Questionnaire (CHAQ)					1.52 (0.81, 2.84)	7.62*** (3.06, 19.01)	0.50 (0.10, 2.59)
Better Self-Efficacy Emotion (CASE)		0.44* (0.22, 0.90)	0.54* (0.33, 0.88)				
Better Parental Social Support (SSC)		0.29 (0.05, 1.81)	0.13** (0.03, 0.50)				
More Parental Distress (SCL)					3.96** (1.56, 10.04)	5.67** (1.57, 20.46)	12.68*** (2.93, 54.93)

* indicates P<.05; ** indicates P<.01; *** indicates P<.001

Conclusion: During the first year on treatment, children newly diagnosed with JIA showed distinct patterns of improvement in HRQOL. Although a majority of JIA patients maintained or reached healthy norm, 28–43% of patients remained or deteriorated below healthy norm, despite therapy, suggesting at risk factors of poor HRQOL outcomes need to be better considered in the care of children with JIA.

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Growth In Children and Adolescents With Juvenile Idiopathic Arthritis (JIA) After 2 Years Of Treatment With Etanercept: Results From The British Society For Paediatric and Adolescent Rheumatology (BSPAR) Etanercept Cohort Study. Lianne Kearsley-Fleet[1], Rebecca Davies[1], Mark Lunt[1], Kimme L. Hyrich[2], Taunton R. Southwood[3] and on Behalf Of The BSPAR Etanercept Cohort Study[1]. [1]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Sciences Centre, Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom, [3]Institute of Child Health, University of Birmingham and Birmingham Children's Hospital, Birmingham, United Kingdom

Background/Purpose: Etanercept (ETN) is licensed in Europe for use in children with Juvenile Idiopathic Arthritis (JIA) and is routinely prescribed after failure of other disease-modifying antirheumatic drugs. Children with JIA are reported to have restricted growth, with the estimated prevalence of short stature in JIA ranging from 1 to 17%. Chronic inflammation with or without corticosteroid use are thought to contribute. The objective of this study was to investigate the influence of ETN on vertical growth in patients with severe JIA over the initial 2 years of treatment.

Methods: The British Society for Paediatric and Adolescent Rheumatology (BSPAR) initiated a national ETN register in 2004. This analysis was restricted to children in the ETN cohort who had complete height data at baseline, 1 and 2 years. Patient height at each follow-up was age and sex matched with The WHO Child Growth Standards to calculate a z-score. The change in z-score from baseline to 2 years was calculated. Multiple imputation was used to account for missing data. Multivariate linear regression was used to identify factors associated with change in height z-score from baseline. Growth over 2 years was also compared in those who had and had not achieved Minimal Disease Activity (MDA; defined as polyarticular

JIA = PGA ≤ 3.4cm, PGE ≤ 2.1cm, ≤ 1 swollen joint; oligoarticular JIA = PGA≤ 2.5cm, no swollen joints) at 3 months.

Results: 191 ETN treated patients were included; median baseline age 11.0 (7.3–12.9), 65% female, and median disease duration at start of treatment 3.5 years (1.7–7.1) (Table). At baseline the mean height z-score was 0.74 (1.4) standards deviations below the reference mean. After 2 years of ETN treatment the mean height z-score increased by 0.29 (0.5) to a mean of 0.45 (1.4) standard deviations below the reference mean (p=0.041). There was a trend towards better improvement in growth over 2 years in children who achieved MDA at 3 months (42%) although this did not reach statistical significance (p=0.281) (Figure). In multivariable analysis, factors associated with an improvement in height z-score included lower baseline z-score (−0.112 per unit z-score [95% CI −0.163, −0.061] p<0.001) and no steroid use at baseline (−0.194 [95% CI −0.345, −0.043] p=0.012).

Table. Baseline Characteristics of the Cohort [N=191]:

	N (%)/median (IQR)
Female	124 (65%)
Age [years]	11.0 (7.3, 12.9)
Steroid Use	71 (38%)
Concomitant MTX	108 (58%)
Disease Duration [years]	3.5 (1.7, 7.1)
ILAR Category	
Systemic arthritis	25 (13%)
Enthesitis-related arthritis	14 (7%)
Oligoarthritis [Extended]	41 (22%)
Oligoarthritis [Peristent]	7 (4%)
Polyarthritis RF-	68 (36%)
Polyarthritis RF+	12 (6%)
Psoriatic arthritis	8 (4%)
Undifferentiated arthritis	15 (8%)
Disease Activity	
Active Joint Count	5.5 (3, 10)
Limited Joint Count	5 (2, 10)
Physician Disease Global (PGA)	4 (2, 6)
Parent Global Well-Being (PGE)	4.5 (2, 6.9)
CHAQ	1.1 (0.6, 1.9)
VAS	4.3 (2.4, 6.7)
ESR	18.5 (6, 41)
CRP	9 (5, 39)
JADAS	16.1 (10.3, 22.4)
Height z-score; mean (SD)	–0.74 (1.4)
1 year	–0.57 (1.4)
2 years	–0.45 (1.4)
BMI z-score; mean (SD)	0.67 (1.7)

Conclusion: ETN therapy was associated with a higher rate of improvement in height z-score over the first 2 years of therapy. Children who were not receiving concurrent steroids had a greater improvement, which may be a marker for less severe disease.

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Body Surface Area-Based Dosing Approach Produced Comparable Golimumab Exposure Across Different Age Ranges After Subcutaneous Administration Of Golimumab In Pediatric Patients With Juvenile Idiopathic Arthritis. Jocelyn H. Leu[1], Alan M. Mendelsohn[1], Joyce Ford[2], Hugh M. Davis[1] and Zhenhua Xu[1]. [1]Janssen Research & Development, LLC., Spring House, PA, [2]Janssen Research and Development, LLC., Spring House, PA

Background/Purpose: To evaluate the pharmacokinetics (PK) of body surface area (BSA)-adjusted dosing of SC golimumab 30 mg/m^2 every 4 weeks (q4w) + methotrexate (MTX) in pediatric patients with juvenile idiopathic arthritis (JIA) and to determine the similarity in golimumab exposure between these patients and adult rheumatoid arthritis (RA) patients following SC administration of 30 mg/m^2 or 50 mg fixed dose q4w, respectively.

Methods: A dosing regimen of SC golimumab 30 mg/m^2 (maximum 50 mg) q4w + MTX in pediatric patients with JIA was predicted to be equivalent to SC golimumab 50 mg q4w + MTX in adult RA patients. GO-KIDS is a randomized-withdrawal, double-blind, placebo-controlled, parallel-group, multicenter Phase 3 trial of SC golimumab 30 mg/m^2 (maximum 50 mg) q4w + MTX in pediatric patients aged 2 to < 18 years old with active JIA despite current MTX therapy. PK, safety, and efficacy evaluations were performed every 4 weeks. Serum golimumab trough concentrations for 119 patients were determined via a validated, specific and sensitive immunoassay at weeks 0, 4, 8, 12 and 16 and were summarized by age.

Results: Treatment with SC golimumab 30 mg/m^2 q4w resulted in median trough serum golimumab concentrations of 1.05 to 1.28 μg/mL at steady state in three different age groups of JIA patients (Table). The steady-state trough concentrations in patients with JIA were similar to that seen in adult RA patients (median: 0.93 μg/mL; mean [SD]: 1.17 [0.99] μg/mL) who received golimumab 50 mg + MTX.

	<6 Years Old	≥6 to <12 Years Old	≥12 Years Old	Combined
N	17	29	63	109
Mean (SD) (μg/mL)	1.28 (0.620)	1.05 (0.670)	1.10 (0.801)	1.12 (0.740)
Median (μg/mL)	1.34	1.12	1.09	1.15

Conclusion: The study results confirmed that serum golimumab exposure in pediatric patients with JIA following administration of 30 mg/m^2 q4w was similar to that observed with 50 mg q4w in the adult RA population and was consistent across the various age groups studied.

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The Efficacy Of Etanercept In Patients With Juvenile Idiopathic Arthritis With Inadequate Response To Infliximab As a First TNF Inhibitor. Ekaterina Alekseeva[1], Tatyana Bzarova[2], Anna Fetisova[2], Tatyana Sleptsova[2], Saniya Valieva[2], Kseniya Isayeva[2], Rina Denisova[2], Elena Mitenko[2], Evgeniya Chistyakova[2] and Nikolay Taybulatov[2]. [1]PRINTO, Genoa, Italy, [2]Scientific Center of Children's Health of RAMS, Moscow, Russia

Background/Purpose: Lack of efficacy of Methotrexate, primary and secondary resistance to biologics and their intolerance lead to juvenile idiopathic arthritis (JIA) of progression. Therefore, the problem of switching to another biologic agent is very urgent.

The objective of this work was to evaluate the efficacy and safety of Etanercept plus Methotrexate in patients with JIA in case of infliximab primary/secondary inefficacy or intolerance.

Methods: 32 children were examined, 12 of them had oligoarthritis, 20 - polyarthritis. The average age of the children was 9.6 (3.0; 17.0) years. Duration of disease was 5,0 (3,0;8).

All patients received Infliximab as a first biologic agent. It was withdrawn in 8 cases due to primary inefficacy within first 3 months of therapy, in 21 - due to secondary inefficacy, and in 3 - to intolerance. The secondary Infliximab inefficacy developed at different periods of drug administration: within 3 m in 2 children, 6 m - 3 children, 9 m - 4 children, 14 m - 2 children, 18 m - 3 children, 24 m - 5 children, 36 m - 1 child, and 48 m 1 child. All patients were switched to Etanercept. Etanercept was given in the form of ubcutaneous injections twice a week at a dose 0.4 mg/kg on the background of Methotrexate at a dose 15 mg/m^2/week. The observation period was 52 weeks. The efficacy of the therapy was assessed according to American College of Rheumatology (ACR-Pedi) criteria 50, 70, 90% improvement and remission criteria (Wallace, 2011).

Results: The perfect effect of switching to the second inhibitor was obtained both in patients with the Infliximab secondary inefficacy and intolerance and in patients with the primary inefficacy of the first TNFα inhibitor. The pain was arrested in the patients within 1 m (the number of painful joints decreased from 6 (3;10.5); to 0; g <0,001); the number of joints with active arthritis significantly decreased (6 (3,5;12); 1 (0;3,5) before and after Week 4, respectively; g <0,001); and the number of joints with limited motion also decreased (6 (13,5;3,5); 2 (1;6,2) before and after Week 4, respectively; g <0,01). Remission of arthritis was observed within 3 m. Joints function recovered completely in 30 patients within 6 m of follow up. The permanent normalization of the serum CRP level and ESR was observed in all patients within 9 and 2 m, respectively. Within 1 month improvement according to ACR pedi criteria 50, 70, 90% was achieved in 84, 66, and 55% of patients, respectively. Within 3 months improvement 50/70 was achieved in 92 and 85% of patients, respectively.

Inactive disease was registered in all patients within 6 months of follow up, the remission was observed in 85% of patients within 9 months and in 100% of patients within 12 months of observation. No withdrawals of the product due to primary, secondary inefficacy or intolerance were observed 1 year after switching. Adverse events were mild or moderate: acute bronchitis (1), local allergic reaction (2).

Conclusion: Switching of patients with JIA with inadequate response to Infliximab to Etanercept ensured the development of remission and contributed to almost complete recovery of joint function in all patients. In addition to high therapeutic efficacy, Etanercept demonstrated good tolerability.

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Physical Activity In Children With Juvenile Idiopathic Arthritis (JIA): The LEAP (Linking Exercise, Activity and Pathophysiology in Childhood Arthritis) Study. Lori B. Tucker[1], Heather A. McKay[1], Leanne M. Ward[2], Jaime Guzman[3], Adam Baxter-Jones[4], Kiem Oen[5], Alan M. Rosenberg[6], Johannes Roth[2], Elizabeth Stringer[7], Rae SM Yeung[8], Kristin M. Houghton[1], Heather Macdonald[9], Debbie Ehrmann Feldman[10], Ciaran M. Duffy[11] and LEAP Study Investigators[12]. [1]University of British Columbia, Vancouver, BC, [2]University of Ottawa, Ottawa, ON, [3]BC Children's Hospital and University of British Columbia, Vancouver, BC, [4]College of Kinesiology, University of Saskatchewan, Saskatoon, SK, [5]University of Manitoba, Winnipeg, MB, [6]Royal University Hospital, Saskatoon, SK, [7]IWK Health Centre and Dalhousie University, Halifax, NS, [8]The Hospital for Sick Children and University of Toronto, Toronto, ON, [9]The University of British Columbia, Vancouver, BC, [10]Université de Montréal, Montreal, QC, [11]Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa, ON, [12]BC Children's Hospital, Vancouver, BC

Background/Purpose: Although children with JIA have lower fitness levels than healthy peers, little is known about their level of habitual physical activity. The LEAP study is a prospective longitudinal multicentre study of children and teens with JIA, aimed at describing the trajectory of physical activity (PA) in JIA, and its relationship to disease factors, inflammation, quality of life, bone health and muscle function. Here we report PA levels of children and teens with JIA in early and late disease at study entry.

Methods: We enrolled patients with JIA (aged 8–16 y) at 12 pediatric rheumatology centres in Canada as either an inception cohort (early disease; within 6 months of diagnosis) or an established disease cohort (late disease; > 2yr after diagnosis). We assessed PA with a validated Physical Activity Questionnaire for children (PAQ-C, age 8–13 y) or teens (PAQ-A, age 14–16 y). This 7-day recall self-report tool has scores from 0 (no PA) to 5, high level ofPA. Participants record weekly PA across a wide range of activities and sports; normative data has been published. Patients completed a pain scale (VAS 0–100), the Childhood Health Assessment Questionnaire (CHAQ), and Juvenile Arthritis Quality of life Questionnaire (JAQQ). Examining physicians recorded physician global assessment of disease activity (VAS 0–100) and presence of active joints. We used descriptive statistics and two-way ANOVA to assess differences between groups. We used PAQ standard population normative values to compare to JIA patients (female 2.69, SD 0.62; male 3.0 SD 0.72).

Results: We collected complete PA data from 127 patients (85 F, 42 M, med age 9.5 y) from March 2012-April 2013. The early cohort included 49 patients (enrolled median 1.2 mo after diagnosis) and the late cohort included 78 patients (enrolled median 3.3 yr after diagnosis). Active arthritis was found in 48 patients, with a mean of 5.4 active joints (range 1–56); PGA was a mean of 12.7 (range 0–74). Overall mean PAQ score for the JIA patients was 2.6 (SD 0.73, range 1–4).Table 1 describes PAQ scores by sex, disease cohort, and presence of active arthritis. When controlled for sex, PAQ scores were significantly different between new onset and late disease. Factors significantly associated with PAQ score included patient-reported pain ($p=0.001$), CHAQ score ($p<0.0001$), JAQQ score ($p=0.0001$), number of active joints ($p=0.002$) and PGA ($p=0.001$); ESR and presence of joints with limited range of motion were not associated with PAQ score.

Table 1. PAQ scores in patients with JIA

	Total	Female (mean, SD)	Female z-score (mean, SD)	Male (mean, SD)	Male z-score (mean, SD)
Total	2.5 (O.73)	2.4 (0.66)	–0.46 (1.08)	2.71 (0.822)	–0.39(1.14)
Early disease	2.34 (0.73)	**2.31 (0.67)**	–0.60 (1.08)	**2.38 (0.85)**	–0.85 (1.18)
Late disease	2.60 (0.71)	2.45 (0.66)	–0.38 (1.07)	2.96 (0.72)	–0.05 (1.0)
Active joints present	2.27 (0.68)	**2.12 (0.6)**	–0.92 (0.97)	**2.56 (0.76)**	–0.61 (1.06)
No active joints	2.68 (0.71)	2.62 (0.63)	–0.10 (1.01)	2.81 (0.86)	–0.44 (1.14)

Conclusion: Children with JIA reported significantly lower levels of PA than healthy peers; this was especially evident in girls, patients with active arthritis, and early in disease. Disease activity, self reported quality of life and functional status may play a role in moderating PA in JIA. The longitudinal data collection of the LEAP study will provide important insight into factors associated with poor PA in JIA.

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Uveitis In The Nordic Juvenile Idiopathic Arthritis Cohort; High Incidence, Frequent Complications, and Gender Associated Risk Factors. Ellen Nordal[1], Lillemor Berntson[2], Kristiina Aalto[3], Suvi Peltoniemi[3], Susan Nielsen[4], Troels Herlin[5], Anders Fasth[6] and Marite Rygg[7]. [1]University of Tromsø, Tromsø, Norway, [2]Uppsala University Hospital, Uppsala, Sweden, [3]Helsinki University Children's Hospital, Helsinki, Finland, [4]Juliane Marie Centret, Rigshospitalet, Copenhagen, Denmark, [5]Aarhus University Hospital, Aarhus, Denmark, [6]University of Gothenburg, Gothenburg, Sweden, [7]St Olav University Hospital, Trondheim, Norway

Background/Purpose: Uveitis is the most common extra-articular manifestation of juvenile idiopathic arthritis (JIA). Both incidence and reported outcome varies, and population-based data are scarce. Early identification of asymptomatic cases is important in order to avoid complications and reduced vision. The pupose of the study was to identify incidence, risk factors and outcome of uveitis in a cohort of Nordic children with JIA followed for eight years in a population-based setting.

Methods: Consecutive cases of JIA from defined geographical areas of Denmark, Finland, Sweden and Norway with disease onset in 1997–2000 were included. The incidence of JIA in the study area in 1997–98 was 15 per 100 000. The study aimed to be as close to population-based as possible, as centers participated only if they were able to include all children diagnosed with JIA in their catchment area. Clinical and ophthalmologic data were registered at regular follow-up visits.

Results: Of 500 children included at baseline, 440 were followed for at least 7 years, and 389 (78%) had available ophtalmologic data. Uveitis developed in 89 (23%) of the 389 children; acute uveitis in 12 and chronic uveitis in 77 children. Fifty percent (6/12) of patients with acute uveitis were HLA-B27 positive. Young age at onset of JIA was a significant predictor of chronic uveitis in girls ($p=0.0001$), but not in boys ($p=0.47$). Also the presence of anti-nuclear antibodies (ANA Hep-2) ($p=0.003$) was a significant predictor in girls ($p=0.003$), but not in boys ($p=0.05$). Neither female gender nor oligoarticular onset JIA category was significantly associated with uveitis. Chronic uveitis was diagnosed at a median of 0.8 years after onset of disease, and in 88 % within the first four years after onset of disease. The longest interval between JIA onset and uveitis development was 8.6 years. Complications occurred in 39 eyes in 22 of the 89 patients with uveitis (25%), glaucoma occurred in 19 eyes and cataract in 14 eyes. At the last visit visus <0.5 in 10 eyes in 9 patients.

Conclusion: We found high incidence of uveitis among Nordic children with JIA, and the majority develop early after onset of disease. Age at onset of JIA and presence of ANA Hep-2 were associated with development of uveitis in girls, but not in boys. Complications were present seven years after onset of arthritis in 25%, showing that uveitis contributes significantly to morbidity and disability in children with JIA.

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Declines In Levels Of Disease Activity and Physical Disability In Children With Juvenile Idiopathic Arthritis Seen In Standard Clinical Care Over The Last 25 Years. Alessandro Consolaro[1], Stefano Lanni[1], Francesca Minoia[1], Sergio Davì[1], Sara Dalprà[1], Benedetta Schiappapietra[1], Rossana Pignataro[1], Cristina Ferrari[1], Alberto Martini[2] and Angelo Ravelli[1]. [1]Istituto Giannina Gaslini, Genova, Italy, [2]University of Genova, Genova, Italy

Background/Purpose: Over the last 3 decades there have been important advances in the management of juvenile idiopathic arthritis (JIA), which include the introduction of methotrexate and, later on, the tendency toward its earlier initiation, the widespread use of intra-articular corticosteroid injections, and, more recently, the availability of the biologic response modifiers. Although this therapeutic progress is likely to have led to a marked improvement in the outlook of children with JIA, the prognostic impact of the newer therapeutic modalities is still poorly documented.

Methods: The clinical information recorded during visits made in children with JIA from January 1987 to March 2012 was retrieved from the study center database. Visits were divided in the following time intervals: 1987–1995 (n=826), 1996–2000 (n=1,337), 2001–2005 (n=2,022), 2006–2012 (n=2,317). Measures of disease activity included the physician's and parent's global ratings (both made on a 0–10 cm visual analog scale, VAS), the parent's pain rating (made on a 0–10 cm VAS) and the count of joints with swelling, pain on motion/tenderness and active disease. Measures of disability included the count of joints with restricted motion and a physical function tool (the Childhood Health Assessment Questionnaire, CHAQ before March 2007 and the Juvenile Arthritis Functionality Scale, JAFS after that date). To enable comparability of functional ability evaluations, both CHAQ and JAFS scores were converted to a 0–10 scale (0=best; 10=worst). Parent's global and pain ratings as well as functional ability assessment were not available for visits made prior to 1995 because before this year these assessments were made on scales not comparable with those used afterwards.

Results: A total of 6,502 visits made in 1,079 patients were identified. The mean (SD) values of disease activity and physical disability measures recorded in visits made at the various time intervals are presented in the table.

	Physician global (0–10)	Active joints	Restricted joints	Parent global (0–10)	Parent pain (0–10)	Physical function (0–10)
1988–1996	5.4 (2.8)	8.2 (9.4)	8.0 (10.4)	–	–	–
1996–2000	5.0 (3.4)	5.7 (8.4)	5.5 (9.5)	2.8 (2.5)	2.5 (2.5)	1.7 (2.0)
2001–2005	4.0 (3.5)	3.8 (5.7)	3.1 (6.2)	2.4 (2.5)	2.4 (2.7)	1.3 (1.8)
2006–2012	2 (2.7)	2.2 (4.5)	1.9 (4.2)	2.1 (2.5)	1.9 (2.6)	0.4 (0.9)

Conclusion: We observed a progressive decline in the levels of disease activity and physical disability over time among children with JIA seen from the mid of the 1980s to the 2010s. This finding confirms the notion that the recent advances in the management of JIA have led to a substantial improvement in disease outcome.

Disclosure: A. Consolaro, None; **S. Lanni**, None; **F. Minoia**, None; **S. Davì**, None; **S. Dalprà**, None; **B. Schiappapietra**, None; **R. Pignataro**, None; **C. Ferrari**, None; **A. Martini**, None; **A. Ravelli**, None.

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Plasma Nicotinamide Phosphoribosyltransferase Correlates With Markers Of Inflammation and May Predict Early Therapeutic Response To Low-Dose Methotrexate In Juvenile Idiopathic Arthritis. Ryan S. Funk, Leon van Haandel, Marcia Chan, Lanny J. Rosenwasser, Andrew Lasky, Maria F. Ibarra, Mark F. Hoeltzel, S.Q. Ye, J.S. Leeder and Mara L. Becker. Children's Mercy Hospital, Kansas City, MO

Background/Purpose: Despite a poor understanding of its biochemical role in the inflammatory process, nicotinamide phosphoribosyltransferase (NAMPT) has been implicated in a number of autoimmune conditions, and its inhibition has resulted in the reduction of pro-inflammatory cytokines. This study evaluates pre- and post-treatment plasma levels of NAMPT and other inflammatory biomarkers in response to initiation of low-dose methotrexate (MTX) in JIA.

Methods: Plasma samples from thirty-two JIA patients between 3 and 17 years of age were evaluated. Samples were collected prior to and 3 months after the initiation of MTX therapy, with twenty-six patients providing samples for both sampling periods. Plasma levels of IL-1α, IL-1β, IL-1RA, IL-6 and TNFα were determined by multiplex analysis (Milliplex MAP, Millipore). Plasma NAMPT levels were determined by competitive EIA. Therapeutic response was determined by Peds ACR and JADAS-71 scoring at 3 months on therapy. Statistical analyses were conducted by Spearman's rank correlation, simple linear regression, Wilcoxon signed rank, and Wilcoxon rank-sum tests, as appropriate.

Results: Plasma levels of Nampt were found to correlate with IL-1α (ρ=0.45, p<0.001), IL-1β (ρ=0.31, p<0.05), IL-1ra (ρ=0.49, p<0.001), IL-6 (ρ=0.34, p<0.01) and CRP (ρ=0.28, p<0.05). At 3 months on MTX, significant reductions in IL-1α (p<0.05), IL-1β (p<0.05), IL-1RA (p<0.001) and TNFα (p<0.05) were observed, however IL-6 and NAMPT did not decrease significantly. Patients achieving Peds ACR 30 had lower plasma IL-1α levels at 3 months than non-responders (4.2±7.7 vs. 17.5±14.3 pg/mL, p < 0.05), and JADAS-71 scores were associated with 3 month IL-6 (p<0.01) and TNFα (p<0.05) concentrations.

Pre-treatment NAMPT concentrations were lower in patients achieving a Peds ACR 50 response at 3 months (11.9±2.1 vs. 16.7±4.1 ng/mL, p< 0.01). In addition, an inverse relationship was observed between pre-treatment NAMPT concentrations and the change in active joint count (p<0.01) and change in JADAS-71 (p=0.06) from baseline to 3 months on MTX therapy.

Conclusion: Plasma NAMPT correlates with several cytokines observed in inflammatory arthritis, and although NAMPT concentrations did not significantly change over the treatment period, pre-treatment NAMPT concentrations were lower in JIA responders at 3 months. Therefore, NAMPT may provide a novel predictive biomarker of early therapeutic response in JIA patients treated with low-dose MTX.

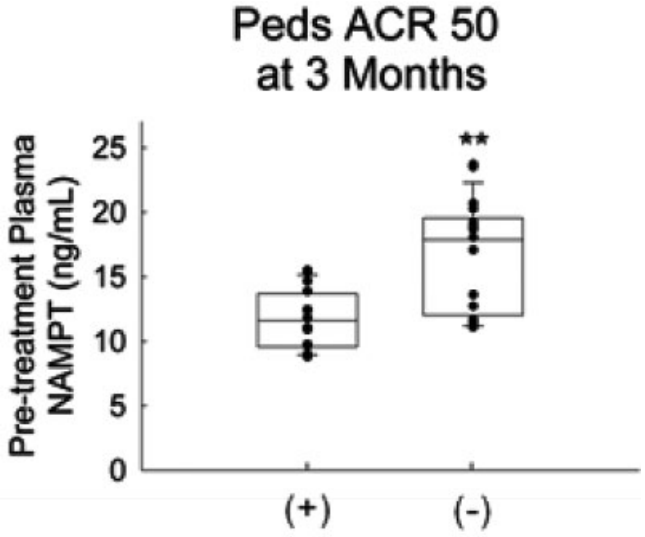

Figure. Pre-treatment plasma NAMPT levels are lower in JIA patients with a Peds ACR 50 response (+) as compared to those failing to meet the response criteria (−) after 3 months of low-dose MTX therapy (**, p-value < 0.01).

Disclosure: R. S. Funk, None; **L. van Haandel**, None; **M. Chan**, None; **L. J. Rosenwasser**, None; **A. Lasky**, None; **M. F. Ibarra**, None; **M. F. Hoeltzel**, None; **S. Q. Ye**, None; **J. S. Leeder**, None; **M. L. Becker**, None.

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Preliminary Prospective Study Of Ultrasonography In Patients With Juvenile Idiopathic Arthritis In Clinical Remission: Subclinical Synovitis May Predict Flare? Vanessa B Miotto e Silva[1], Sônia A.V. Mitraud[1], Rita NV Furtado[2], Jamil Natour[1] and Maria Teresa Terreri[2]. [1]Escola Paulista de Medicina/Universidade Federal de São Paulo (EPM/UNIFESP), São Paulo, Brazil, [2]Escola Paulista de Medicina/Universidade Federal de São Paulo (EPM/UNIFESP), Sao Paulo, Brazil

Background/Purpose: Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood and has variable prognosis, characterized by periods of activity and remission. Studies in patients with JIA in remission evaluated by ultrasonography (US) demonstrated presence of subclinical synovitis. It is unclear whether subclinical synovitis detected by

imaging techniques can predict progressive joint damage and functional deterioration in clinically asymptomatic joints. The aim of our study were: 1) to assess if the presence of subclinical synovitis detected by US in patients with JIA in remission may predict flare over a two years follow up and 2) to detect associations between disease activity and clinical, laboratory, functional and ultrasonographic features.

Methods: Inclusion criteria: oligoarticular and polyarticular JIA, clinical and laboratory remission, aged between 5 and 18 years. Clinical assessment: active/limited joint count, functional capacity by the Childhood Health Assessment Questionnaire, physician global visual analogue scale (VAS), patient global VAS, medications on use. The clinical, laboratory and ophthalmological evaluations were performed at baseline and every 6 months for up to 30 months. US assessed 17 joints bilaterally at baseline and every 12 months for up to 24 months. The US parameters evaluated were synovial hypertrophy and synovial blood flow on Power Doppler (PD). Subclinical synovitis was considered in the presence of moderate to severe degree of synovial hypertrophy and/or any positive synovial flow on PD. Flare was considered in the presence of at least one joint active until six months after each US evaluation.

Results: Thirty-five patients, 28 girls, mean age at assessment was 11.5 ± 3.7 years and mean age at disease onset was 4.4 ± 3.2 years, with a total of 1190 joints assessed. Fifiteen patients had persistent oligoarticular JIA, 11 extended oligoarticular and 9 polyarticular with negative rheumatoid factor. Regarding the type of remission, 8 were off medication and 27 were on medication, with an average time of remission of 1.9 ± 2.2 years. So far, a total of 74 evaluations were performed by US and 28 (37.8%) showed subclinical synovitis in at least one joint (28 with synovial hypertrophy and 9 with positive synovial flow on PD). There were 15 flares and in 8 of these episodes the US showed previously subclinical synovitis (p=0,166). There was also no association between positive synovial flow on PD and flares (p=0,676).

Conclusion: Subclinical synovitis was present in patients with JIA in clinical remission and may predict flare. These data are still preliminary.

Disclosure: V. B. Miotto e Silva, None; **S. A. V. Mitraud**, None; **R. N. Furtado**, None; **J. Natour**, None; **M. T. Terreri**, None.

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Phenotypic Cluster Analysis Of Juvenile Idiopathic Arthritis: Relationship To International Leagues Of Associations For Rheumatology Classification Criteria. Jay Mehta[1], Juan Lin[2], Norman T. Ilowite[3] and for The CARRA Registry Investigators[4]. [1]Children's Hospital at Montefiore/ Albert Einstein College of Medicine, Bronx, NY, [2]Albert Einstein College of Medicine, Bronx, NY, [3]The Children's Hospital at Montefiore, Bronx, NY, [4]Multiple Affiliations, Palo Alto, CA

Background/Purpose: The ILAR classification of Juvenile Idiopathic Arthritis (JIA) delineated categories of childhood chronic arthritis based on predominant clinical and laboratory features. As consensus criteria, they may not reflect clinically significant disease patterns that exist among patients. Phenotypic analysis of patient characteristics may provide a more optimal way to group patients. The aim of this study was to identify distinct clusters of JIA patients based on demographic, clinical, laboratory, and imaging features.

Methods: The source population was subjects with JIA enrolled in the CARRA Registry from May 2010 to April 2012, representing 60 centers throughout the US. Demographic, clinical, laboratory, and imaging data were gathered through patient reporting, physician assessment, and chart review. K-means clustering analysis was performed to identify distinct clusters of patients based on major features. Weighted gap statistics were used to estimate the number of clusters present in the dataset. Association between cluster assignment and physician-assigned ILAR JIA category was determined using Fisher's exact test.

Results: A total of 4810 subjects with JIA were enrolled in the CARRA registry during the enrollment period. 3872 patients had data for all items used in the cluster analysis and were therefore included. 10 distinct clusters were identified and are shown in Table 1. For each variable used in the analysis, at least one cluster was significantly different (p<0.001) from all other clusters. Fisher's exact test revealed that cluster assignment was highly correlated (p<0.001) to physician-assigned ILAR JIA category (see Table 2).

Table 1. Distribution of demographic, clinical, laboratory and imaging variables among clusters in JIA patients

Cluster #	Whole cohort	1	2	3	4	5	6	7	8	9	10
N (%)	3872	159	284	219	829	294	285	1006	328	348	120
Median Age at onset (years)	5.6	11.7	4.5	6.0	4.5	2.8	2.5	6.1	11.1	6.4	7.8
% male	28.1	16.4	47.5	26.0	25.5	19.0	20.7	23.1	55.8	20.4	47.5
% nonwhite race	9.0	27.7	15.8	5.9	7.0	4.1	7.4	7.0	12.8	11.2	5.0
% Hispanic	10.6	28.9	13.4	9.1	9.9	8.8	8.4	9.1	12.5	10.1	6.7
% FHx psoriasis	7.0	1.9	4.2	16.0	5.7	6.8	6.0	6.8	9.1	4.6	19.2
% FHx JIA	4.9	1.3	1.8	13.2	4.2	4.1	4.6	4.6	5.5	5.5	7.5
% FHx RA	6.8	7.5	3.2	100.0	0.0	0.0	0.0	0.0	3.4	0.0	11.7
Mean ACR worst ever functional class	2.2	2.5	2.9	2.1	1.9	2.0	2.1	2.2	2.1	2.2	2.2
% polyarticular course*	56.7	89.3	72.5	54.8	0.0	42.9	39.3	100.0	47.0	72.1	100.0
% ANA+	43.8	42.1	15.5	47.9	46.9	64.3	55.8	44.9	24.7	48.3	35.0
% imaging evidence joint damage (ever)	18.7	39.6	23.2	18.3	0.0	15.3	14.7	0.0	30.5	100.0	17.5
% HLAB27+	7.7	2.5	0.4	4.1	5.5	4.4	5.6	3.4	45.4	3.7	11.7
% RF+	4.2	99.4	0.0	0.5	0.0	0.0	0.0	0.0	0.3	0.0	1.7
% anti-CCP +	4.4	52.2	0.4	4.1	0.5	0.0	0.0	4.6	1.2	6.0	0.8
% history of uveitis*	10.5	1.3	0.4	9.6	0.0	100.0	15.1	0.0	8.2	0.0	14.2
% history of IBD*	1.6	0.6	1.1	1.8	0.4	0.7	2.1	0.9	6.1	0.9	9.2
% SI tenderness*	9.4	3.1	0.7	7.3	0.2	1.0	1.4	0.3	87.8	2.0	29.2
% enthesitis*	10.9	3.1	2.1	10.5	4.3	3.1	6.0	3.4	68.3	3.4	46.7
% psoriasis*	4.8	1.3	1.4	6.4	2.9	2.4	2.8	3.3	7.3	2.0	52.5
% LLD*	9.6	1.9	2.1	12.3	0.0	0.0	100.0	0.0	4.9	0.0	28.3
% dactylitis*	4.5	1.3	1.4	2.7	3.5	4.8	4.9	3.7	4.3	2.6	39.2
% nail pitting*	3.1	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.2
% serositis*	2.0	0.0	24.3	0.0	0.0	0.0	0.4	0.0	0.6	0.0	5.0
% HSM*	3.0	0.0	34.2	0.9	0.1	0.0	0.4	0.4	0.3	0.9	6.7
% LAD*	4.2	1.9	49.6	0.9	0.2	0.0	0.4	0.3	0.9	0.3	6.7
% rash*	7.6	0.6	94.4	3.2	0.0	0.0	0.0	0.6	0.3	1.1	5.0
% fever*	8.1	0.6	97.9	2.7	0.4	0.0	0.4	1.3	1.5	0.0	6.7

a: ever or in past

Table 2. Comparison of cluster assignment to physician-assigned ILAR JIA category

Cluster #	Whole cohort	1	2	3	4	5	6	7	8	9	10
N (%)	3872	159	284	219	829	294	285	1006	328	348	120
Physician-assigned JIA category											
Systemic	7.8	0.6	95.8	2.3	0.8	0.0	1.1	1.2	0.0	0.6	0.8
RF-negative polyarticular	29.7	1.9	2.5	33.8	3.3	26.9	24.2	69.1	9.1	46.0	6.7
RF-positive polyarticular	6.9	88.6	0.7	4.1	0.6	0.3	0.7	7.7	1.2	8.3	0.0
Oligoarticular - persistent	29.4	3.8	0.0	30.1	79.0	52.7	51.9	1.1	4.6	21.3	8.3
Oligoarticular - extended	7.6	0.6	0.4	8.2	2.4	13.9	13.0	12.0	2.7	12.4	2.5
Psoriatic	5.6	0.6	0.4	8.7	4.0	3.1	1.4	4.0	6.7	2.6	65.8
Enthesitis-related	10.1	0.0	0.4	6.8	6.8	2.0	4.9	3.2	70.1	6.3	12.5
Undifferentiated	1.9	1.9	0.0	3.7	2.5	0.7	2.1	1.7	1.5	1.7	3.3

Conclusion: Children with JIA have distinct phenotypical patterns of demographics, and clinical, laboratory, and imaging findings. However, patient groupings based on these patterns may not be of more utility than the currently available, consensus-driven, categorizations. Further registry data that provides patient outcome data, which is actively being collected, will be of use to determine whether phenotypic clustering has prognostic value.

Disclosure: J. Mehta, None; **J. Lin**, None; **N. T. Ilowite**, None; **F. T. CARRA Registry Investigators**, None.

ACR Poster Session A
Spondylarthropathies and Psoriatic Arthritis: Clinical Aspects and Treatment: Psoriatic Arthritis: Clinical Aspects and Treatment I
Sunday, October 27, 2013, 8:30 AM–4:00 PM

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Higher Disease Activity In Psoriatic Arthritis Is Associated With Elevated Total Cholesterol and Triglycerides. Monalyn Labitigan[1], Asha Shrestha[1], George W. Reed[2], Robert P. Magner[3], Nicole Jordan[1], Joel M. Kremer[4], Jeffrey D. Greenberg[5], Asena Bahce-Altuntas[1] and Anna R. Broder[1]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]CORRONA, Inc., Southborough, MA, [3]University of Massachusetts Medical School, Worcester, MA, [4]Center for Rheumatology, Albany Medical College, Albany, NY, [5]New York Hospital for Joint Diseases, New York, NY

Background/Purpose: Psoriatic Arthritis (PsA) is linked to both obesity and an increased cardiovascular risk. However, the relationship between PsA disease activity and lipids, a major cardiovascular risk factor, has not been well studied. We assessed the relationship between PsA disease activity and lipid profiles in the Consortium of Rheumatology Researchers of North America (CORRONA) Registry.

Methods: We performed a cross-sectional analysis of all CORRONA participants followed from 6/2008 to 10/2012 with complete data for lipids and disease activity. Longitudinal subanalysis of PsA patients with paired lipid measurements on stable statin doses was also performed. Moderate to high disease activity was defined as CDAI>10 and/or presence of enthesitis/dactylitis. Abnormal lipids were defined as: total cholesterol (TC)>200 mg/dl (5.17 mmol/L), High Density Lipoprotein (HDL)<40 mg/dl (1.0 mmol/L, men), HDL<50 mg/dl (1.3 mmol/L, women), Low Density Lipoprotein (LDL)>100 mg/dl (2.59 mmol/L), Triglycerides (TG)>150 mg/dl (1.7 mmol/L), and atherogenic ratio (TC/HDL) >5. Models were adjusted for gender, duration of PsA, mHAQ, disease-related medication use, smoking, body mass index (BMI), diabetes (DM), use of cholesterol lowering medications and fish oil.

Results: Of 5713 PsA patients, 725 had complete data for lipids and disease activity. 284/725 (39%) had moderate to high disease activity. Compared to the low disease activity group, the moderate to high disease activity group had more women (57% vs 46%, p=0.006) and smokers (12.7% vs 7.7%, p=0.029), and had shorter disease duration (mean 8.7 vs 11.2 years, p=0.001). Moderate to high disease activity patients were more likely to be prescribed prednisone (13% vs 4.5%, p<0.001) and non-biologic DMARDs (63% vs 51%, p=0.002), but were less likely to be prescribed anti-TNFs (57% vs 66%, p=0.015). Mean BMI in the moderate to high and low groups were 31.7kg/m2 and 30.6kg/m2, respectively, p=0.02. There were no differences between age, rate of DM, frequency of cholesterol lowering medications, and fish oil use.

Moderate to high disease activity was associated with higher odds of TC>200 mg/dl, OR 1.6 (1.1, 2.2 95%CI), p=0.01, and higher odds of TG>150 mg/dl, OR 1.6 (1.2, 2.3 95% CI), p=<0.01. Enthesitis/dactylitis was positively associated with TC>200 mg/dl, OR 1.6 (1.1, 2.5), p=0.02. There was no significant association found between disease activity and other lipid measures in the moderate to high disease vs low disease groups.

In the longitudinal analysis of 54 PsA patients with paired lipid measurements, higher PsA activity was associated with higher TG levels (β 3.85, p=0.02) and lower HDL levels (β −0.62, p<0.01) adjusted for duration between visits.

Conclusion: Moderate to high disease activity in PsA is associated with increased levels of TC and TG. Increasing disease activity is associated with increasing TG and decreasing HDL. This pattern of dyslipidemia in PsA is similar to the pattern observed in obesity. Our findings suggest a commonality between PsA disease mechanisms and lipid metabolism providing a possible link between obesity, PsA and cardiovascular disease.

Disclosure: M. Labitigan, None; **A. Shrestha**, None; **G. W. Reed**, Corrona, Inc, 3; **R. P. Magner**, University of Massachusetts Medical School, 3; **N. Jordan**, None; **J. M. Kremer**, Corrona, Inc, 1, Corrona Inc., 3; **J. D. Greenberg**, CORRONA, 1, AstraZeneca, CORRONA, Novartis, Pfizer, 5; **A. Bahce-Altuntas**, None; **A. R. Broder**, None.

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Arthritis and Nail Involvement In Patients With Plaque-Type Psoriasis. Odirlei Andre Monticielo[1], Karen Regina Rosso Schons[2], Cristiane Faccin Knob[2], Walter Neumaier[2], Maristela de Oliveira Beck[2] and André Avelino Costa Beber[2]. [1]Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [2]Universidade Federal de Santa Maria, Santa Maria, Brazil.

Background/Purpose: Psoriasis is a chronic disease that presents in individuals of all ages, affecting skin, nails and joints. Nail changes are estimated to be present in 10–80% of psoriatic patients at some point in their lives, with consequent aesthetic and functional repercussions and quality of life impairment. In Brazil, there are no epidemiological studies on nail psoriasis (NP) so far. The aim of this study is to evaluate the nails of a sample of psoriatic patients from the south of Brazil, determining the prevalence of nail involvement and its association with arthritis and other clinical features.

Methods: This is a cross-sectional study that evaluated 65 outpatients with plaque-type psoriasis treated at the Hospital Universitário de Santa Maria - RS, from January 2012 to March 2013. Skin severity was evaluated using the PASI method and the nail changes were assessed using the NAPSI score. Psoriatic arthritis was determined by CASPAR criteria. Demographic variables were assessed by specific questionnaire.

Results: The prevalence of NP was 46.1%. Patients with NP had an average of 8.1±5 nails affected and the main morfological sign found was onycholysis (80%). Most patients (63.3%) reported functional or aesthetic discomfort related to nails involvement. When compared to patients without nail changes, patients with NP showed lower mean age of onset of psoriasis (27,6±14,9 vs. 42,7±15,9 years, p=0.001) and longer duration of the disease (17,5±10,7 vs. 9,1±9,7 years, p=0.003). Patients with NP also had higher PASI score (11,1±8,3 vs. 6,5±6,1, p=0.024), higher frequency of family history of psoriasis (40% vs. 7,4%, p=0.011) and higher frequency of psoriatic arthritis (43,3 vs. 3,7, p=0,002).

Conclusion: The NP is still poorly studied, despite its clinical consequences such as pain, functional limitation and aesthetic disorders. Its importance as a predictor of joint involvement and more severe cutaneous disease was demonstrated by this study. Family history and early onset of disease were also associated with NP.

Disclosure: O. A. Monticielo, None; **K. R. R. Schons**, None; **C. F. Knob**, None; **W. Neumaier**, None; **M. D. O. Beck**, None; **A. A. Costa Beber**, None.

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Maintenance Of Efficacy and Safety Of Ustekinumab In Patients With Active Psoriatic Arthritis Despite Prior Conventional Nonbiologic and Anti-TNF Biologic Therapy: 1-year Results Of a Phase 3, Multicenter, Double-Blind, Placebo-Controlled Trial. Christopher T. Ritchlin[1], Iain B. McInnes[2], Arthur Kavanaugh[3], Lluis Puig[4], Proton Rahman[5], Carrie Brodmerkel[6], Shu Li[6], Yaung-Kaung Shen[6], Mittie K. Doyle[6], Alan M. Mendelsohn[6] and Alice B. Gottlieb[7]. [1]University of Rochester, Rochester, NY, [2]University of Glasgow, Glasgow, United Kingdom, [3]University of California, San Diego, La Jolla, CA, [4]Universitat Autònoma de Barcelona, Barcelona, Spain, [5]Memorial University, St. Johns, NF, [6]Janssen Research & Development, LLC., Spring House, PA, [7]Tufts Medical Center, Boston, MA.

Background/Purpose: Ustekinumab (UST) has demonstrated substantial efficacy and an acceptable safety profile, and is approved for use, in treating moderate-to-severe psoriasis. UST has also demonstrated efficacy in pts with active psoriatic arthritis (PsA) at wk24 in the Phase 3, multicenter, PBO-controlled PSUMMIT2 trial. Results through wk52 PSUMMIT 2 are presented herein.

Methods: 312 adults with active PsA were randomized to UST 45mg or 90mg at wk0, wk4, and q12w or PBO at wks0, 4, and 16 followed by crossover to UST 45mg at wk24, wk28, and wk40. Randomization was stratified by site, weight (≤100kg, >100kg) and baseline MTX use, and pts previously treated with biologic anti-TNF agents were eligible. At wk16, pts with <5% improvement in both tender/swollen joint counts entered blinded early escape (PBO→UST 45mg, 45mg→90mg, 90mg→90mg). The primary endpoint was ACR20 at wk24. Secondary endpoints were HAQ-DI, ACR50, ACR70, and ≥75% improvement in the Psoriasis Area and Severity Index (PASI75).

Results: Anti-TNF-experienced pts had more active disease at baseline than anti-TNF-naïve pts. More UST (43.8%-combined, 43.7%-45mg, 43.8%-90mg) than PBO (20.2%) treated pts had ACR20 at wk24 (all P<0.001). Significant treatment differences were also observed for ACR50 and PASI75 response at wk24 (table). Efficacy was sustained through wk52. At wk52, 51% and 44% of pts who were and were not, respectively, receiving MTX at baseline had ACR20. UST efficacy at wk52 was more robust in anti-TNF-naïve (ACR20 59–73%) than anti-TNF-experienced (37–41%) pts and pts who had previously received 1 (50–55%) vs. 2 (13–39%) or ≥3 (13–30%) anti-TNF agents. UST was generally well tolerated, with no deaths or tuberculosis and similar rates of AEs (78.6%-45mg, 77.9%-90mg), serious AEs (5.8%-45mg, 5.8%-90mg), and AEs leading to discontinuation (5.8%-45mg, 3.8%-90mg) reported across doses through wk60. Two pts, both anti-TNF-experienced, had malignancies (breast cancer-45mg, squamous cell carcinoma-90mg); 2/287 (0.7%) of UST-treated pts (both 90mg) had serious infections. Three pts (2–45mg, 1–90mg) had major adverse cardiovascular events (myocardial infarctions) through wk60, all had multiple cardiovascular risk factors and prior anti-TNF experience.

Table. Summary of efficacy among randomized PsA pts

(N)	Placebo (104)	UST 45 mg (103)	UST 90 mg (105)	Combined UST (208)
BASELINE				
Anti-TNF experienced pts				
Tender(0–68)/swollen (0–66) joints	24/11	24/15	26/13	25/14
Physician/Pt global disease (0–10 VAS)/HAQ-DI (0–3)	7.2/6.1/1.31	7.7/6.6/1.44	7.6/6.9/1.56	7.6/6.8/1.50
Anti-TNF naïve pts				
Tender/swollen joints	20/10	19/12	19/10	19/11
Physician/Patient global disease/HAQ-DI	7.0/6.1/1.13	6.4/5.7/1.25	6.6/5.5/1.06	6.6/5.6/1.13
WEEK 24 EFFICACY				
ACR20/ACR50/ACR70	20.2/6.7/2.9%	43.7***/17.5*/ 6.8%	43.8***/22.9**/ 8.6%	43.8***/20.2**/ 7.7%
PASI75[1]	5.0%	51.3%***	55.6%***	53.4%***
WEEK 52 EFFICACY (N)	**Placebo→UST 45 mg, (**77)	**UST 45 mg** (94)	**UST 90 mg** (95)	**Combined UST** (189)
ACR20/ACR50/ACR70	55.8/28.6/15.6%	46.8/27.7/12.8%	48.4/26.3/17.9%	47.6/27.0/15.3%
ACR20 by baseline MTX use (Yes/No)	51.2/61.1%	46.0/47.7%	56.5/40.8%	51.0/44.1%
ACR20 – anti-TNF-naïve/ exper	73.0/40.0%	60.0/37.0%	58.5/40.7%	59.3/38.9%
ACR20 by no. of prior anti-TNF agents (1/2/ ≥3)	54.5/12.5/30.0%	52.4/25.0/29.4%	50.0/38.9/12.5%	51.0/32.4/24.0%
% improve dactylitis/ enthesitis[1]	33.3/100.0%	36.7/95.0%	60.0/90.9%	50.0/95.0%
PASI75[2]	56.1%	56.5%	64.4%	60.6%

*, **, *** indicate p < 0.05, 0.01, 0.001, respectively, versus placebo. Data are reported as % of pts or median. [1]Among patients with dactylitis or enthesitis at baseline. [2]Among pts with ≥ 3% body surface area psoriasis involvement at baseline (mean PASI scores at baseline were 11.3 for placebo, 13.4 for UST 45 mg, and 12.1 for UST 90 mg).
ACR=American College of Rheumatology, HAQ-DI=Health Assessment Questionnaire-Disability Index, PASI=Psoriasis Area and Severity Index, TNF=tumor necrosis factor, UST=ustekinumab, VAS=visual analogue scale.

Conclusion: Both UST doses (45/90 mg q12w) yielded significant and sustained improvements in PsA signs/symptoms with favorable and comparable safety profiles. UST was effective in both anti-TNF-naïve and anti-TNF-experienced pts, with greater efficacy in anti-TNF naïve pts and anti-TNF-experienced pts previously treated with 1 or 2 anti-TNF agents.

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Risk Of Cardiovascular Events In Patients With Psoriatic Arthritis, Psoriasis, and Rheumatoid Arthritis: A General Population-Based Cohort Study.

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Background/Purpose: Psoriatic arthritis (PsA), psoriasis, and rheumatoid arthritis (RA) are associated with an increased risk for major adverse cardiovascular events (MACE; myocardial infarction (MI), cerebrovascular accidents (CVA), and cardiovascular death) but are also associated with traditional cardiovascular risk factors (TCVRFs). Little is known about the risk for MACE in patients with PsA after adjusting for TCVRFs or relative rates of MACE among these 3 diseases. We aimed to determine the risk of MACE among patients with PsA compared to psoriasis without known PsA, RA, and the general population after adjusting for TCVRFs.

Methods: Longitudinal cohort studies were conducted for the following outcomes: cardiovascular death, MI, CVA, and MACE (composite outcome). Data from 1994–2010 from The Health Improvement Network (THIN), a primary care medical record database in the United Kingdom, were included. Patients aged 18–89 were selected if they had a diagnosis of PsA, RA, or psoriasis (PsA, RA, psoriasis, MI, and CVA have been validated in THIN). Up to 10 unexposed controls matched on practice and start date within the practice were selected for each patient with PsA. Cox proportional hazards models were used to calculate the relative hazards for each of the outcomes adjusted for TCVRFs (age, sex, diabetes, smoking, hypertension, hyperlipidemia) and additional confounders which changed the main effects by >10%. *A priori* we hypothesized an interaction between disease status and disease modifying anti-rheumatic drug (DMARD) use and this was significant ($p<0.02$) for all endpoints.

Results: Patients with PsA (8,706), RA (41,752), psoriasis (138,424) and unexposed controls (81,573) were identified. After adjusting for TCVRFs, the risk of MI was increased in all disease groups although not statistically significant in patients with psoriasis without a DMARD prescription. The risk for MACE was increased in all disease groups but not significant in patients with PsA not prescribed a DMARD. These results were not affected by sensitivity analyses varying definitions of the outcomes, restricting to patients followed regularly, utilizing multiple imputation for smoking and body mass index, and imputing additional DMARD users.

Conclusion: Patients with PsA, psoriasis, and RA are at increased risk for MACE, particularly MI, compared to the general population but patients with RA and severe psoriasis have a substantially higher risk than unexposed controls.

Table. Incidence Rate and Hazard Ratios (95% CIs) for Major Adverse Cardiovascular Events

COMPOSITE OUTCOME		**Incidence per 1000 PYs**	**Age-Sex Adjusted HR**	**Fully Adjusted* HR**
Unexposed		5.03	Ref	Ref
PsA	No DMARD	6.76	1.34 (1.13–1.58)	1.24 (1.03–1.49)
	DMARD	4.61	1.15 (0.94–1.40)	1.16 (0.93–1.43)
RA	No DMARD	13.54	1.43 (1.33–1.53)	1.38 (1.28–1.50)
	DMARD	11.09	1.62 (1.51–1.74)	1.57 (1.50–1.70)
Psoriasis	No DMARD	5.41	1.17 (1.11–1.23)	1.08 (1.02–1.14)
	DMARD	6.50	1.31 (1.13–1.52)	1.31 (1.12–1.53)
MYOCARDIAL INFARCTION		**Incidence per 1000 PYs**	**Age-Sex Adjusted**	**Fully Adjusted***
Unexposed		1.96	Ref	Ref
PsA	No DMARD	3.02	1.46 (1.15–1.87)	1.36 (1.04–1.77)
	DMARD	2.28	1.33 (1.01–1.76)	1.34 (1.00–1.81)
RA	No DMARD	4.23	1.36 (1.21–1.54)	1.33 (1.17–1.51)
	DMARD	4.87	2.02 (1.82–2.24)	1.96 (1.75–2.19)
Psoriasis	No DMARD	2.20	1.18 (1.09–1.29)	1.07 (0.98–1.17)
	DMARD	2.67	1.36 (1.09–1.71)	1.31 (1.03–1.65)

*The fully adjusted model includes Age, Sex, Diabetes, Hypertension, Hyperlipidemia, Start Year in the Cohort, Smoking Status.
†DMARDs included azathioprine, leflunomide, hydroxychloroquine, chloroquine, methotrexate, sulfasalazine, mycophenolate, adalimumab, etanercept, and infliximab. Patients with psoriasis were considered to be on a "DMARD" if they had been prescribed etretinate, acitretin, hydroxyurea, PUVA or phototherapy.

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Anti-Citrullinated Protein Antibodies In Patients With Psoriatic Arthritis: Clinical Relevance. Doquyen H. Huynh[1], Carol Etzel[2], Vanessa Cox[3], J. M. Kremer[4], Jeffrey D. Greenberg[5] and Arthur Kavanaugh[6]. [1]UC San Diego School of Medicine, San Diego, CA, [2]CORRONA, Inc, Southborough, MA, [3]UT MD Anderson Cancer Center, Houston, TX, [4]Albany Medical College and The Center for Rheumatology, Albany, NY, [5]NYU Hospital for Joint Diseases, New York, NY, [6]University of California San Diego, San Diego, CA.

Background/Purpose: Anti-citrullinated protein antibodies (ACPA) have been considered a relatively specific marker for rheumatoid arthritis (RA), and may play a role in its pathogenesis. In recent years, it has been shown that ACPA can be found at a greater prevalence among psoriatic arthritis (PsA) patients (approximately 8% or more) than in the general population. Also, ACPA have been isolated from the synovial fluid of PsA patients. Several small anecdotal reports have suggested that PsA patients with positive ACPA may have greater swollen/tender joint counts with more deformities and radiologic changes than ACPA negative PsA patients; however, other studies have suggested no difference. The present study evaluated whether clinical features differ between PsA patients who are ACPA (+) from those who are ACPA (−).

Methods: A cross sectional study of patients with physician diagnosed PsA in the CORRONA database, a large national registry of patients with RA and PsA. ACPA was performed in local labs. ACPA (+) and ACPA (−) PsA patients were evaluated for differences in disease activity, disease severity and immunomodulatory medication use. Evaluations included: tender joint count, swollen joint count, HAQ, patient global assessment, physician global assessment, DAS 28, CDAI, presence of enthesitis, presence of dactylitis, skin psoriasis activity, presence of Sjogrens symptoms, and radiographic changes (defined by presence or absence of erosions, joint space narrowing and joint deformity). ACPA (+) and ACPA (−) groups were also assessed for smoking status and the presence of rheumatoid factor (RF) and repeat analysis was done to determine if RF presence contributed to any differences.

Results: Through 2012, there were 5,363 PsA patients in the CORRONA database, 17.7% of whom had test results for ACPA: 842 were ACPA (−) and 116 ACPA (+). There was no significant differences in any measures of disease activity or disease severity (including radiographic changes) or the use of immunomodulatory medications between ACPA (+) and ACPA(−) patients. Interestingly, ACPA (+) patients had a lower average tender joint count (a mean difference of −0.89; 95% CI −1.78, −0.02). Further stratification into subgroups based upon the presence of RF did not reveal any clinically important differences with the exception of ACPA (+)/RF (−) group who had a higher swollen joint count (a mean SJC of 4.57, p 0.003). There was also no difference in smoking status amongst ACPA (+) and ACPA (−) PsA patients.

Conclusion: In a large cohort of PsA patients in clinical practice, there were no differences in disease activity, disease severity (including radiographic changes) or the use of immunomodulatory medications between ACPA (+) and ACPA (−) PsA patients. The data suggest that different than for RA, the presence of ACPA(+) may represent only an epiphenomenon in PsA. The fine specifities of ACPA in PsA patients have not yet been defined.

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Incidence of Herpes Zoster in Patients with Psoriatic Arthritis. Devy Zisman[1], Haim Bitterman[2], Ilan Feldhamer[3], Doron Comanesther[3], Erez Battat[3], Sari Greenberg-Dotan[3], Sarit Cohen[4] and Arnon-Dov Cohen[3]. [1]The Ruth and Bruce Rappaport Faculty of Medicine, Haifa, Israel, [2]Chief Physician's Office, Clalit Health Services, Haifa, Israel, [3]Chief Physician's Office, Clalit Health Services, Tel Aviv, Israel, [4]Carmel Medical Center, Haifa, Israel.

Background/Purpose: To assess the incidence of Herpes Zoster (HZ) in patients with psoriatic arthritis (PsA) and its relation to treatment regimen: Traditional disease-modifying anti-rheumatic drugs (c-DMARDs) versus anti-TNF α agents.

Methods: A retrospective cohort study of patients with PsA insured by Clalit Health Services between 2006 and 2012 was conducted. The incidence of HZ events was calculated among four groups of patients with PsA: no DMARDS treatment (Group A); treatment with c-DMARDS (Group B); treatment only with anti-TNF α agents, including infliximab, adalimumab or enbrel (Group C); treatment with an anti-TNF α agent (infliximab, adalimumab or enbrel) in combination with c-DMARDS (Group D). For each group, incidence rates of HZ events were calculated as well as hazard ratios (HR) adjusted for age, sex, steroid use, comorbidities index, current and previous treatment regimens. Crude incidence rates were calculated as the number of HZ infections per 1000 follow-up patient-years (under specific treatment). Survival analysis methods (Cox regression Andersen-Gill models) were applied to identify risk factors for HZ and to estimate the contribution of anti-TNF α treatment and time-independent and time-dependent covariates at the first development of HZ reactivation.

Results: The study population consisted of 3158 patients, with a mean age of 52.31±14.74 years; 1479 (46.8%) were male. During the accumulated study period of 15763 years, 156 HZ events occurred. The incidence rate (95% Confidence Interval (95%CI)) of HZ events per 1000 treatment years among Groups A-D were 8.59 (6.72–10.97), 10.28 (8.05–13.14), 9.45 (5.53–16.11), 18.42 (11.53–29.30), respectively. In a multivariate analysis, only age (HR=1.016, 95% CI 1.003–1.03, P=0.015), treatment with steroids (HR=1.079, 95% CI 1.027–1.133, p=0.003) and a combination of anti-TNF α agents and c-DMARDS (HR =2.29, 95%CI=1.204–4.358, p=0.012) were statistically significantly associated with the time until the first HZ event. Treatment with c-DMARDS, anti-TNF α agents alone, previous treatment with biological agents, sex and the Charlson Comorbidity Index Score did not statistically significantly influence the time to the first HZ event.

Conclusion: In the study population the incidence rate of an HZ event is 9.9 per 1000 treatment years. The risk of a first HZ event increased statistically significantly with patient age, treatment with steroids, and a combination of an anti-TNF α agent and c-DMARDS, but not with c-DMARDS or anti-TNF α therapy administrated separately.

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Responsiveness To Change Of a Global Ultrasound Assessment Score In Psoriatic Arthritis Patients. Maria Laura Acosta Felquer[1], Santiago Ruta[1], Javier Rosa[1], David A. Navarta[1], Carla Saucedo[1], Ricardo Garcia-Monaco[2], Mirtha Sabelli[1] and Enrique R. Soriano[3]. [1]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Radiology and Imagenology Department, Hospital italiano de Buenos Aires, Buenos Aires, Argentina, [3]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina.

Background/Purpose: Psoriatic arthritis (PsA) manifests clinically in several ways, including arthritis, enthesitis, and dactylitis,. Assessment of disease activity in PsA should ideally record each feature. An Ultrasound (US) composite score could help in this evaluation. The objective was to analyze the responsiveness to disease activity change of a US global assessment score, including entheses tendons and joints in patients with PsA.

Methods: Consecutive PsA patients (CASPAR criteria), initiating or changing traditional DMARDs or TNF inhibitors as decided by their treating rheumatologists were included. US examination was performed by an experienced rheumatologist using both grey scale (GS) and power Doppler (PD). The following areas were assessed: 2–3 MCP joints, 2–3 proximal PIP joints, wrists, knees and second and fifth MTP joints. Knee and heel enthesis were examined. Both second and third flexor and fourth and sixth extensor tendons of the hands were examined for tenosynovitis. Synovitis, tenosynovitis and enthesitis were defined according to OMERACT definitions. Both GS and PD synovitis were graded on a semiquantitative scale from 0 to 3, and enthesis and tendons with a 0 to 1 scale. For each one of the structures examined (enthesis, tendons and synovial) an initial US score was obtained by multiplying the semiquantitative scale by the number of sites involved. Finally adding the US structure specific scores a global US score was constructed. Physical examination was performed before US examination and included swollen and tender joint counts, patient's pain and disease activity VAS, HAQ, DAS28, CDAI, SDAI, PASE, PASI, CPDAI, Leeds Enthesitis Index (LEI) and BASDAI. CRP level and ESR were obtained within 48 hours. All patients underwent both clinical and ultrasound assessment at the day entering the study and at three months follow-up.

Results: 26 patients (69% males, mean (SD) age: 51 (13), mean disease duration 3 years (95% CI: 1.45–4.66) were included. Eleven patients initiated

therapy with DMARDs, 6 changed DMARDs, 3 added second DMARDs, and finally, 6 patients started therapy with TNF inhibitors. Basal and three months follow up data are shown in the table. All features except LEI improved. Global Ultrasound assessment score and their different components also showed significant improvement after therapy change. After three months of treatment 14 (54%) patients achieved Minimal Disease Activity (MDA). The US score showed an area under the ROC curve of 0.64 (95% CI:0.43–0.87), for discrimination of non MDA and a score equal or greater than 10 showed 75% sensitivity and 64% specificity for the diagnosis of non MDA.

	Basal assessment, mean (95% CI)	Three months follow-up assessment, mean (95% CI)	P value (Wilcoxon signed Rank test)
DAS28	4.05 (3.4–4.7)	3.1 (2.3–3.8)	<0.0001
BASDAI	5.6 (4.1–7.1)	3.4 (1.9–5)	<0.0001
HAQ	0.84 (0.43–1.25)	0.55 (0.18–0.92)	0.0005
LEI	0.56 (0.01–1.1)	0.125 (0–0.3)	0.1178
Dactylitis	1.15 (0.41–1.9)	0.5 (0.01–1.01)	0.0017
ESR	21 (8.1–33.9)	15.3 (7.5–23.1)	0.0058
CRP	6.8 (2.3–11.2)	2.2 (0.87–3.5)	0.0091
PASI	2.8 (0.86–4.8)	1.8 (0.1–3.6)	0.0001
PASE	40.6 (32.9–48.2)	34.1 (25.8–42.3)	0.0003
CPDAI	4.5 (2.9–6.1)	1.9 (0.06–3.6)	<0.0001
CDAI	17.7 (11.9–23.5)	9.7 (4.5–14.9)	<0.0001
SDAI	18.8 (13–24.5)	10.2 (4.8–15.6)	0.0008
% MDA (95% CI)	3.8 (0.9–19.6)	54 (33–73)	0.0004 (chi2)
Ultrasound joint score	14.1 (6.7–21.5)	7.2 (2.6–11.9)	<0.0001
Ultrasound tendon score	1.3 (0.3–2.3)	0.3 (0.008–0.63)	0.0010
Ultrasound enthesitis score	9.75 (7.2–12.3)	5.1 (3.6–6.7)	<0.0001
Ultrasound total score	25.2 (17.1–33.2)	13.3 (8.1–18.5)	<0.0001

Conclusion: This new global ultrasound score showed responsiveness to treatment change over the short term in patients with PsA. Further validation in a larger population is needed.

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Abnormal Imaging and Increased Osteoclast Precursors In a Psoriasis Cohort Are Associated with New Onset of Psoriatic Arthritis. Ralf G. Thiele, Yahui Grace Chiu, Francisco A. Tausk, Bethany A. Marston, Gregory Dieudonne, Vaseem Chengazi, Michelle Smith, Sharon Moorehead, Rick Barrett and Christopher T. Ritchlin. University of Rochester, Rochester, NY.

Background/Purpose: Psoriasis (Ps) precedes joint inflammation by about 10 years in patients who develop psoriatic arthritis (PsA). Several studies have documented abnormal musculoskeletal imaging findings and we found elevated osteoclast precursor (OCP) frequency in Ps patients without musculoskeletal signs or symptoms. The association of imaging abnormalities and OCP frequency with arthritis onset in a prospective psoriasis cohort, however, has not been examined.

Methods: Ps patients with >5 years of psoriasis or >10% body surface area (any disease duration) were enrolled if they scored less than 36 on the Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire and showed no active arthritis or enthesitis on rheumatologic exam. All patients were imaged with a 3-phase bone scan and Power Doppler Ultrasound (PDUS) of joints and entheses. If the bone scan revealed evidence of inflammation, a gadolinium enhanced 3T MRI was performed on the joint with the highest scintigraphy signal. All imaging studies were analyzed by 2 radiologists. A diagnosis of PsA was confirmed by the CASPAR criteria on follow-up annual exams. Blood samples were drawn for OCP quantification after 8-day cell culture.

Results: 39 Ps patients (44% female) were enrolled with a mean age 45±6 years, disease duration 15±2 years, BMI 30±3 kg/m^2 and PASI score 9±2. Eleven subjects had normal studies, 8 had active joint inflammation on imaging but remained asymptomatic but 5 additional subjects with baseline imaging abnormalities subsequently developed PsA. Thirteen patients showed evidence of active or prior enthesitis (calcification at insertions) on imaging. Two patients had active tenosynovitis and 1 patient had plantar fasciitis. The patients were categorized into 4 subsets based on the imaging analysis and/or clinical features: (1) no imaging abnormality, n=11; (2) joint inflammation (imaging) without clinical symptoms, n=8; (3) development of PsA, n=5; (4) enthesitis or entheseal calcification, n=13. The OCP frequency was examined in cultured PBMC or purified monocytes isolated from these 4 patient subsets (Table 1).

Table 1. OCP frequency in 4 cohorts of Ps patients categorized by imaging results (mean+SEM).

	(1) Normal	(2) Imaging Arthritis	(3) PsA	(4) Enthesitis
PBMC	9 ± 9.3	140 ± 141	316 ± 267	64 ± 49
Monocytes	168 ± 96	1,209 ± 492	1,273 ± 549	467 ± 231

Conclusion: Among 39 Ps patients monitored for 3 months to 3 years, 8 patients showed baseline imaging abnormalities but remained asymptomatic; 5 patients with imaging abnormalities subsequently developed PsA, and 13 patients had acute or chronic entheseal signals. The OCP frequency was highest in patients with new onset PsA and inflammation on imaging studies. These results demonstrate the high prevalence of subclinical joint inflammation and entheseal changes in Ps and provide evidence that elevated OCP frequency may serve as a surrogate marker for joint inflammation and risk for arthritis in Ps patients.

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Cross-Cultural Adaptation, Validation and Reliability Of The Brazilian Version Of The Psoriatic Arthritis Screening Evaluation Tool. Roberto Ranza[1], Claudia G Schainberg[2], Sueli Carneiro[3], Gladys Martins[4], Jose Joaquim Rodrigues[5], Jamille Carneiro[6], Ricardo Romiti[7], Thiago B. M. Barros[8], Ana Luiza Sampaio[9], Amanda Pedreira[9], Carolina Z Costa[10], Rogerio MC Pinto[11], M. Elaine Husni[12] and Abrar A. Qureshi[13]. [1]Universidade Federal de Uberlandia, Uberlandia MG, Brazil, [2]Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, [3]Brazilian Registry of Spondyloarthritis, São Paulo, Brazil, [4]Dermatologia Hospital Universitario Universidade de Brasilia, Brasilia, Brazil, [5]Dermatologia, Universidade Federal de Uberlandia, Uberlandia, Brazil, [6]Reumatologia, Universidade de Brasilia, Brasilia, Brazil, [7]Dermatologia Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, [8]Reumatologia Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [9]Dermatologia Hospital Universitário e Faculdade de Medicina, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [10]Reumatologia, Universidade Federal de Uberlandia, Uberlandia, Brazil, [11]Matematica, Universidade Federal de Uberlandia, Uberlandia, Brazil, [12]Cleveland Clinic Foundation, Cleveland, OH, [13]Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Psoriatic Arthritis (PsA) remains an underdiagnosed disease among patients with psoriasis (PsO). Dermatologists are not routinely trained to detect musculoskeletal manifestations hence arthritis, enthesitis and spondylitis may be frequently missed at dermatology settings. The Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire is a patient reported outcome that may help dermatologists identify patients who may need a rheumatology referral. PASE is composed of 15 questions (2 subscales on symptoms and function), is reliable, generates a continuous score (15–75) higher in patients with PsA and is sensitive-to-change with disease severity and treatment. Purpose - to validate a Brazilian Portuguese version of the PASE (PASE-P).

Methods: PASE was translated into Portuguese with a wording adaptation of subscales titles and rating scale (disagree-agree substituted with false–true) to fit the cultural response style of Brazilian patients. A multicenter study was conducted in four university dermatology clinics, from January to March 2011. In each center, consecutive patients with a confirmed diagnosis of PsO responded to the PASE-P and were subsequently evaluated by a rheumatologist blind to the questionnaire. Based on clinical history and physical examination, patients were classified as: PsO only, PsO + osteoarthritis (OA) and/or chronic myofascial pain (CMP) syndrome, PsA (CASPAR criteria) ± OA and/or CMP. Laboratory tests and x-Ray imaging were performed as clinically indicated by the rheumatologist. PASE-P was retested in a sub-sample after a mean time of 20 days (12–30).

Results: 465 PsO patients completed the study. Mean age was 48.8±15.7 yrs, 50% were females and PsO mean duration was 15.5±11.8yrs. The PASE-P distinguished participants with PsA (158) from non-PsA (307), with mean scores of 37.8 ±17.2 vs 22.7±11.5 ($p<0.001$), ROC AUC of 0.777 (95%CI: 0.732–0.823); the best cut point was 25, giving 0.728 sensitivity (SE) and 0.735 specificity (SP). Patients with PsA not on any systemic treatment (42) had higher scores (mean 47.5±14.1) and the best cutoff from non-PsA was 38, SE 0.786, SP 0.876 (AUC 0.908, 95%CI 0.868–0.948). A subanalysis of PsA vs OA (66), showed scores of 37.8 vs 24.4±14.3 ($p<0.001$) and a cutoff of 22, 0.785 SE, 0.697 SP. (AUC 0.881, 95%CI 0.818–0.945). The internal consistency for PASE-P was high (Cronbach′s alfa 0.928) and the test-retest ICC was 0.974.

Conclusion: PASE-P is a newly translated tool that is reliable, sensitive and specific to screen for PsA in a population of Brazilian portuguese-speaking PsO patients seen in dermatology clinics.

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Diagnostic Delay Of Even More Than 6 Months Contributes To Poor Radiographic and Functional Outcome In Psoriatic Arthritis. Muhammad Haroon, Phil Gallagher and Oliver FitzGerald. Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland.

Background/Purpose: Diagnostic delay in Psoriatic Arthritis (PsA) is not uncommon with a recent study of psoriasis patients attending a dermatology clinic showing that 29% of patients had undiagnosed PsA. Delay in diagnosis in turn delays introduction of appropriate disease-modifying treatment and may contribute to poor patient outcome. The objectives of this study were: 1) to investigate the demographic and clinical characteristics contributing to the delay from symptom onset to the first visit with a rheumatologist; 2) to compare clinical and radiographic features and patient-reported outcome measures in those who saw a rheumatologist early in their disease course compared to those who were diagnosed later, in a long-term follow-up cohort of PsA patients.

Methods: All PsA patients, fulfilling CASPAR criteria, with an average disease duration of >10 years were invited for detailed clinical evaluation. The total lag time from symptom onset to their first rheumatologic encounter was studied. All patients were interviewed in order to determine the date of symptom onset, defined as onset of stiffness, pain, or joint swelling, and the subsequent first visit to a rheumatologist, dates which were further confirmed by data extracted from referral letters and medical records. Patients were classified as early consulters or late consulters depending on whether they were seen by a rheumatologist within or beyond 6 months of symptom onset. Following informed consent, patients underwent a detailed skin and rheumatologic assessment including disease activity measures.

Results: A total of 283 PsA patients [mean age 54.6±12 years; 52% female; mean PsA duration of 19±9 years] were studied. Median lag time from the disease onset to the first rheumatologic assessment of the cohort was 1.00 years (IQR 0.5–2). Thirty percent (n=86) of the cohort was seen by a rheumatologist within 6 months of the disease onset. Similarly, 53% (n=149) and 71% (n=202) of the cohort was reviewed within one and 2 years of the symptoms onset, respectively. On univariate analysis, late consulters (>6 months delay at first encounter), had significantly more erosions (OR 4.58, p=<0.001), osteolysis (OR 3.6, p=0.01), sacroiliitis (OR 2.28, p=0.01), arthritis mutilans (OR 10.6, p=0.02), deformed joints (OR 2.28, p=0.002), number of deformed joints (OR 1.06, p=0.006), more DMARDs/TNFi failures (OR 1.47, p=0.007), less patients achieving drug free remission (OR 0.42, p=0.01), and worse functional disability as reflected by the HAQ scores (OR 2.17, p=0.003). On multiple step-wise regression analysis, the model predicted significant association of late consulters with the development of peripheral joint erosions (OR 4.25, p=0.001), radiographic sacroiliitis (OR 1.47, p=0.09) and worse HAQ scores (OR 2.2, p=0.004).

Conclusion: Even a 6 month delay from symptom onset to the first visit with a rheumatologist contributes to the development of peripheral joint erosions, sacroiliitis and worse long-term physical function.

Disclosure: M. Haroon, None; **P. Gallagher**, None; **O. FitzGerald**, Pfizer, Abbott, UCB, Roche, MSD, BMS, 2, Janssen Pharmaceutica Product, Pfizer, Abbott, Roche, MSD, BMS, 5, 9, Pfizer, Abbott, UCB, Roche, Janssen, 8.

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Long-Term Safety and Tolerability Of Apremilast, An Oral Phosphodiesterase 4 Inhibitor, In Patients With Psoriatic Arthritis: Pooled Safety Analysis Of Three Phase 3, Randomized, Controlled Trials. Philip J. Mease[1], Arthur Kavanaugh[2], Dafna D. Gladman[3], Adewale O. Adebajo[4], Juan J. Gomez-Reino[5], Jürgen Wollenhaupt[6], Maurizio Cutolo[7], Georg Schett[8], Eric Lespessailles[9], Kamal Shah[10], ChiaChi Hu[10], Randall M. Stevens[10], Christopher J. Edwards[11] and Charles A. Birbara[12]. [1]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA, [2]University of California San Diego, San Diego, CA, [3]University of Toronto, Toronto Western Hospital, Toronto, ON, [4]University of Sheffield, Sheffield, United Kingdom, [5]Hospital Clinico Universitario, Santiago, Spain, [6]Schön Klinik Hamburg Eilbek, Hamburg, Germany, [7]University of Genova, Genova, Italy, [8]University of Erlangen-Nuremberg, Erlangen, Germany, [9]University of Orléans, Orléans, France, [10]Celgene Corporation, Warren, NJ, [11]University of Southampton, Southampton, United Kingdom, [12]University of Massachusetts Medical School, Worcester, MA.

Background/Purpose: Apremilast (APR), an oral phosphodiesterase 4 inhibitor, works intracellularly to modulate inflammatory mediators. PALACE 1, 2, and 3 compared the efficacy and safety of APR with placebo (PBO) in pts with active PsA despite prior DMARDs and/or biologics. The overall safety and tolerability of APR was assessed in a pooled analysis of PALACE 1, 2, and 3.

Methods: Pts were randomized 1:1:1 to PBO, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by BL DMARD use. At wk 16, pts with <20% reduction from BL in swollen/tender joint counts qualified for protocol-defined early escape; those on PBO were re-randomized to APR20 or APR30 and those on APR remained on the initial APR dose. At wk 24, all remaining PBO pts were re-randomized to APR20 or APR30 through wk 52. Pts taking concurrent DMARDs were allowed to continue stable doses (MTX, sulfasalazine, leflunomide, or a combination). The analysis comprises data from the APR-exposure periods (wks 0-≥52).

Results: 1,493 pts received study drug (PBO, 495; APR20, 501; APR30, 497) and were included in the safety population. The APR-exposure period included 720 pts treated with APR20 (766.4 pt-yrs) and 721 with APR30 (769.0 pt-yrs). No new safety findings were identified; previously identified AEs were reported at a lower rate for wks 24–52 vs 0–24 (Table). The most common AEs were diarrhea (14.3%), nausea (12.6%), headache (10.1%), URTI (10.3%), and nasopharyngitis (7.4%). Diarrhea, nausea, and headache appeared to increase in a dose-dependent manner. Most AEs were mild/moderate in severity. Discontinuations due to AEs (APR20, 7.5%; APR30, 8.3%) were low, occurring primarily in the first 24 wks of treatment. Nausea and diarrhea were predominantly mild and occurred at a reduced incidence after the first month of dosing, with the highest incidence reported in the first 2 wks of treatment. Most cases resolved within 30 days despite continued therapy. The proportion of pts with severe nausea (APR20, 0.3%; APR30, 0.4%) and diarrhea (APR20, 0.6%; APR30, 0.3%) was low. GI AEs leading to APR discontinuation with ≥52 wks of exposure were 4% over 52 wks, with nausea (1.7%) and diarrhea (1.5%) being the most common. In the 24-≥52 wk period, no new severe AEs were reported for diarrhea, nausea, URTI, and nasopharyngitis vs 0–24 wks. Serious AEs occurred in 6.8% (APR20) and 7.2% (APR30) of pts. One death occurred (APR20) due to multiorgan failure not suspected to be treatment-related. Exposure-adjusted incidence rates of major adverse cardiac events, serious infections including systemic opportunistic infection, or malignancies were comparable to PBO. There were no clinically meaningful effects on laboratory measurements.

Overall Safety Profile

	Weeks 0–24 as Initially Treated*			Long-term APR Exposure§	
Patients, n (%)	PBO (n = 495)	APR20 (n = 501)	APR30 (n = 497)	APR20 (n = 720)	APR30 (n = 721)
≥1 AE	235 (47.5)	308 (61.5)	302 (60.8)	524 (72.8)	534 (74.1)
≥1 serious AE	19 (3.8)	17 (3.4)	19 (3.8)	49 (6.8)	52 (7.2)
≥1 severe AE	19 (3.8)	16 (3.2)	32 (6.4)	48 (6.7)	60 (8.3)
AE leading to drug withdrawal	21 (4.2)	28 (5.6)	36 (7.2)	54 (7.5)	60 (8.3)
Death‡	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)

*PBO-controlled period includes all data through week 16 for patients initially assigned PBO who escaped and data through week 24 for all other patients.
§Includes all patients who received ≥1 dose of APR regardless of when randomized.
‡Multiorgan failure considered by investigator to be unrelated to study drug.

Conclusion: APR demonstrated an acceptable safety profile and was generally well tolerated for up to 52 wks with no new safety concerns identified with long-term exposure. These data do not indicate a need for laboratory monitoring.

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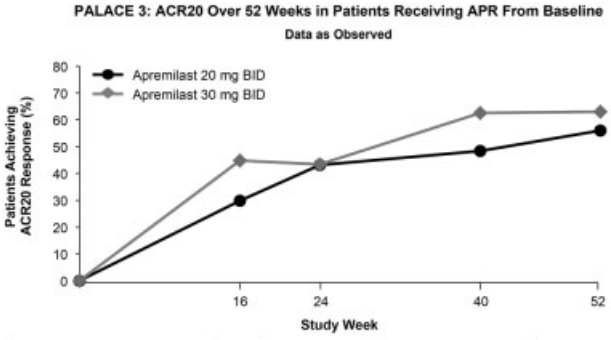
Long-Term (52-Week) Results Of a Phase 3, Randomized, Controlled Trial Of Apremilast, An Oral Phosphodiesterase 4 Inhibitor, In Patients With Psoriatic Arthritis and Current Skin Involvement (PALACE 3). Christopher J. Edwards[1], Francisco J. Blanco[2], Jeffrey Crowley[3], ChiaChi Hu[4], Randall M. Stevens[4] and Charles A. Birbara[5]. [1]University of Southampton, Southampton, United Kingdom, [2]INIBIC-Hospital Universitario A Coruña, A Coruña, Spain, [3]Bakersfield Dermatology, Bakersfield, CA, [4]Celgene Corporation, Warren, NJ, [5]University of Massachusetts Medical School, Worcester, MA.

Background/Purpose: Apremilast (APR), an oral phosphodiesterase 4 inhibitor, works intracellularly to modulate inflammatory mediators. PALACE 3 compared the efficacy/safety of APR with placebo (PBO) in pts with active PsA and at least 1 psoriatic lesion ≥2 cm at baseline (BL) despite prior DMARDs and/or biologics.

Methods: Pts were randomized 1:1:1 to PBO, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by BL DMARD use and BSA ≥3%. At wk 16, pts with <20% reduction from BL in swollen/tender joint counts qualified for protocol-defined early escape; those on PBO were re-randomized to APR20 or APR30 and those on APR remained on the initial APR dose. At wk 24, all remaining PBO pts were re-randomized to APR20 or APR30 through wk 52. Pts taking concurrent DMARDs were allowed to continue stable doses (MTX, sulfasalazine, leflunomide, or combination).

Results: 505 pts were randomized and received ≥1 dose of study drug (PBO, 169; APR20 169; APR30, 167). At wk 16 (primary endpoint), significantly more APR20 (29.4%; $P=0.0235$) and APR30 pts (42.8%; $P<0.0001$) achieved ACR20 vs PBO (18.9%). For those pts originally randomized to APR and completing 52 wks of study, improvements were maintained or increased over 52 wks for multiple endpoints, including: (1) ACR20 of 56.0% (APR20) and 63.0% (APR30) (Figure); (2) HAQ-DI mean change from BL (SD) of −0.332 (0.505) for APR20 and −0.350 (0.505) for APR30 pts, meeting the MCIDs of 0.13 and 0.30; and (3) in pts with BL BSA ≥3%, PASI-75 was achieved by 28.6% (APR20) and 39.1% (APR30) of pts; PASI-50 was achieved by 49.2% (APR20) and 54.7% (APR30). The magnitude of responses was higher for APR30 than APR20. Pts randomized to APR at wks 16 or 24 demonstrated results consistent with those originally randomized to APR. APR was generally well tolerated. AEs occurring in ≥5% of all pts exposed to APR through wk 52 were diarrhea, nausea, headache, URTI, nasopharyngitis, and vomiting. The majority of AEs were mild/moderate and predominantly did not lead to discontinuation. Gastrointestinal AEs occurred at a reduced incidence rate after the first wk of dosing. SAEs occurred in 5.4% (APR20) and 4.1% (APR30) of pts. No new safety signals were identified and the incidence of pts experiencing any AE was comparable over the 0–24 and 0–52 wk periods. No imbalance in the exposure-adjusted incidence rates of severe AEs, SAEs, major adverse cardiac events, serious infections including systemic opportunistic infection, or malignancies between APR and PBO was observed. No cases of TB (novel or reactivation) were reported in the APR treatment groups; TB screening was not required per protocol.



Apremilast 20 mg BID, n=	161	146	124	116
Apremilast 30 mg BID, n=	154	145	131	127

Conclusion: Over 52 wks, APR continued to demonstrate efficacy in the treatment of PsA and associated psoriasis, including clinically meaningful improvements in signs and symptoms and physical function. APR demonstrated an acceptable safety profile with up to 52 wks of treatment and was generally well tolerated.

Disclosure: C. J. Edwards, Pfizer, 2, Pfizer, Samsung, Roche, Celgene, 5, Roche, Pfizer, Abbott, Glaxo-SmithKline, 8; **F. J. Blanco**, Pfizer, Bioiberica, Gebro Pharma, 5; **J. Crowley**, AbbVie, Amgen, Celgene, Janssen, Merck, Pfizer, 2, AbbVie, Amgen, 5, AbbVie, 8; **C. Hu**, Celgene Corporation, 3; **R. M. Stevens**, Celgene Corporation, 3; **C. A. Birbara**, Amgen, Lilly, Pfizer, Incyte, Merck, Bristol-Myers Squibb, 2.

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Effect Of Certolizumab Pegol Over 48 Weeks On Signs and Symptoms In Patients With Psoriatic Arthritis With and Without Prior Tumor Necrosis Factor Inhibitor Exposure. Philip J. Mease[1], Roy M. Fleischmann[2], Jürgen Wollenhaupt[3], Atul Deodhar[4], Dafna Gladman[5], Christian Stach[6], Bengt Hoepken[6], Luke Peterson[7] and Désirée van der Heijde[8]. [1]Swedish Medical Center and University of Washington, Seattle, WA, [2]University of Texas Southwestern Medical Center, Dallas, TX, [3]Schön Klinik, Hamburg, Germany, [4]Oregon Health & Science University, Portland, OR, [5]Toronto Western Hospital and University of Toronto, Toronto, ON, [6]UCB Pharma, Monheim, Germany, [7]UCB Pharma, Raleigh, NC, [8]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Previous reports of RAPID-PsA demonstrated efficacy and safety of certolizumab pegol (CZP), a PEGylated Fc-free anti-TNF, over 24 weeks (wks) in psoriatic arthritis (PsA) patients (pts), including pts with prior TNF inhibitor therapy.[1] We report the clinical efficacy and safety of CZP in PsA pts to Wk48.

Methods: The ongoing RAPID-PsA trial (NCT01087788) is double-blind and placebo (PBO)-controlled to Wk24 and dose-blind to Wk48.[1] Pts had active PsA and had failed ≥1 DMARD. Pts originally randomized to CZP (200mg Q2W or 400mg Q4W, following 400mg loading dose at Wks 0, 2, 4) continued on their assigned dose in dose-blind phase; PBO pts entering dose-blind phase were re-randomized to CZP loading dose followed by CZP 200mg Q2W or CZP 400mg Q4W. We report efficacy for pts in randomized set (RS) originally randomized to CZP. Primary endpoints were ACR20 response at Wk12 and change from baseline (BL) in modified Total Sharp Score (mTSS) at Wk24.[1] Other pre-planned endpoints included PASI75/90 and ACR20/50/70 response, change from BL HAQ-DI, PsAQoL, pain (VAS) and fatigue (NRS) at Wk24 and 48, and mTSS at Wk48. Post-hoc analyses evaluated minimal disease activity (MDA) at Wk24 and 48, and compared ACR response rates to Wk48 in pts with and without prior TNF inhibitor exposure. NRI was used for categorical measures, LOCF for quantitative measures. Safety set consists of all pts treated with CZP at any stage of the 48-wk trial.

Results: 409 pts were randomized, of which 273 received CZP from Wk0. 54 (19.8%) combined CZP pts (200mg Q2W + 400mg Q4W) had prior TNF inhibitor exposure, with similar BL characteristics to pts without. Of CZP-randomized pts, 91% completed to Wk24 and 87% to Wk48. ACR20/50/70 and MDA response rates were maintained from Wk24 to Wk48 (Figure A), and similar ACR response rates to Wk48 were observed in pts with and without prior TNF inhibitor exposure (Figure B). Change from BL in HAQ-DI, PsAQoL, pain (VAS) and fatigue (NRS) were maintained to Wk48 (Figure A). In pts with ≥3% skin involvement at BL (60.8% CZP pts), PASI75 and PASI90 responses were maintained from Wk24 to Wk48 (Figure

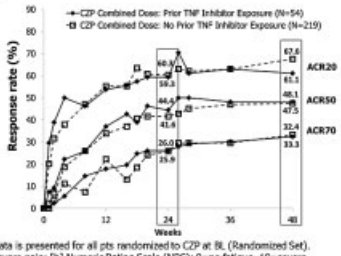
A). Radiographic progression in CZP-treated pts remained low (LS mean mTSS change from BL: Wk24, 0.00; Wk48, 0.13). In the safety set (N=393), adverse events (AEs) occurred in 304 pts (77.4%; event rate [ER] per 100 pt-yrs=394.6), serious AEs in 39 (9.9%; ER=15.3). Serious AEs included 8 infections (2.0%; ER=3.0), including 1 case of tuberculosis (0.3%; ER=0.3), and 3 deaths in the overall 48-week period (0.8%), including 1 death (0.3%) between Wk24 and 48 (breast cancer).

Figure: A) Clinical outcomes at Wk24 and Wk48 for all pts by treatment arm, B) ACR response rates for all CZP pts (200mg Q2W and 400mg Q4W) with and without prior TNF inhibitor exposure in the RAPID-PsA trial

A.

Outcome	CZP 200mg Q2W N=138		CZP 400mg Q4W N=135	
	Wk24	Wk48	Wk24	Wk48
ACR20 (%)	63.8	66.7	56.3	65.9
ACR50 (%)	44.2	49.3	40.0	45.9
ACR70 (%)	28.3	34.8	23.7	30.4
MDA (%)	33.3	37.7	34.1	34.8
CFB HAQ-DI	-0.52	-0.56	-0.43	-0.49
CFB PsAQoL	-4.4	-4.8	-3.3	-3.5
CFB Pain [a]	-28.6	-31.6	-28.4	-29.5
CFB Fatigue [b]	-2.2	-2.4	-1.9	-2.0
PASI75 [c] (%)	62.2	66.7	60.5	61.8
PASI90 [c] (%)	46.7	48.9	35.5	42.1

B.



Presented data are mean values except where otherwise stated. Data is presented for all pts randomized to CZP at BL (Randomized Set). [a] Visual Analog Scale (VAS): 0–100mm: 0=no pain, 100=most severe pain; [b] Numeric Rating Scale (NRS): 0=no fatigue, 10=severe fatigue; [c] PASI response rates reported in patients with ≥3% body surface area skin involvement at BL (CZP 200mg, N=90; CZP 400mg N=76). ACR: American College of Rheumatology; CZP: Certolizumab Pegol; MDA: Minimal Disease Activity; CFB: Change From Baseline; HAQ-DI: Health Assessment Questionnaire – Disability Index; PsAQoL: Psoriatic Arthritis Quality of Life; PASI: Psoriasis Area and Severity Index.

Conclusion: Clinical efficacy of CZP was maintained over 48 wks in pts with PsA, including pts with and without prior TNF inhibitor exposure. Low radiographic progression and improvements in PASI were maintained to Wk48. Safety profile was in line with that observed for CZP in RA.

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1. Mease P.J. Arthritis Rheum 2012;64(10):1107

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The DC-STAMP$^+$IL17A$^+$ Cell Subset Is Elevated In Psoriatic Arthritis (PsA) Patients and Declines Following Anti-TNFi Therapy. Yahui Grace Chiu, Edward M. Schwarz, Hua He, Francisco A. Tausk, Sharon Moorehead, Michelle Smith and Christopher T. Ritchlin. University of Rochester, Rochester, NY.

Background/Purpose: Approximately 25% of psoriasis (Ps) patients develop psoriatic arthritis (PsA), a potentially destructive joint disease, within 10 years of Ps onset. Although early diagnosis and therapy of PsA can prevent bone and joint damage, diagnostic and response biomarkers of psoriatic diseases are currently absent. To address this unmet need, we focused on Dendritic Cell-Specific Transmembrane protein (DC-STAMP), a valid marker of osteoclast precursors (OCP). We examined the frequency of the DC-STAMP$^+$IL-17$^+$ subset (monocytes and T cells) in the peripheral blood of healthy controls (HC), Ps and PsA patients and monitored this cell subset in PsA patients before and after the anti-Tumor Necrosis therapy (TNFi).

Methods: Ps was confirmed by a dermatologist and PsA by a rheumatologist based on the CASPAR criteria. Blood samples were collected from 61 subjects (Ps, n=19; PsA, n=17; HC, n=25). Blood samples from PsA patients were collected at baseline and 16 weeks following treatment with an anti-TNF reagent (adalimumab, infliximab or etanercept). Cell populations were analyzed by flow cytometry with an 11-color antibody cocktail and OC were enumerated by TRAP staining after 8-day cell culture in vitro.

Results: The DC-STAMP$^+$IL-17$^+$ subset was significantly increased in PsA but not in Ps or HC (Figure 1). The area under the Receiver Operating Characteristic (ROC) curve for DC-STAMP+IL17A+ cells (PsA vs. HC) was 0.769. The DC-STAMP$^+$IL17A$^+$ cell frequency decreased significantly following TNFi therapy in PsA patients considered as anti-TNFi responders (12 out of 17). Figure 2 summarizes the frequency of DC-STAMP$^+$IL17A$^+$ before and after anti-TNFi medication (8.2 ± 13.7 (prior) vs. 1.6 ± 1.5 (after), p=0.09). Intriguingly, the reduction in DC-STAMP$^+$IL17A$^+$ cell subset was associated with a decreased circulating OCP frequency (930 ± 857 (prior) vs. 142 ± 144 (after)/per 10^6 monocytes, p=0.004).

Conclusion: Our results demonstrate that the DC-STAMP$^+$IL17A$^+$ cell subset: (1) can distinguish PsA from HC and Ps subjects; (2) declines rapidly following TNFi therapy; (3) positively correlates with circulating OCPs. Collectively, these data reveal a novel susceptibility and response biomarker and underscore the importance of IL-17 expressing cells in PsA pathogenesis.

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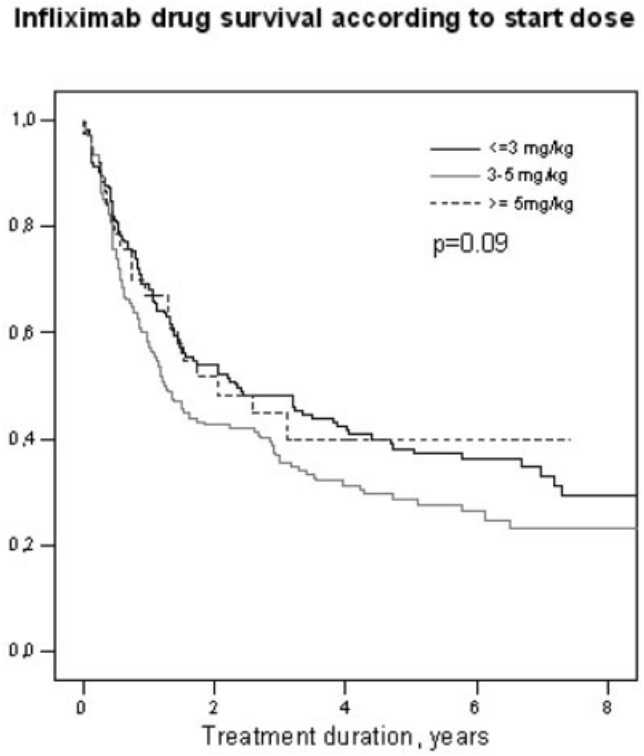
Impact Of Low Infliximab Dose Regimen On Treatment Response and Drug Survival In 462 Patients With Psoriatic Arthritis. Results From The Nationwide Registries Danbio and Icebio. Bente Glintborg[1], Bjorn Gudbjornsson[2], Niels Steen Krogh[3], Emina Omerovic[4], Natalia Manilo[5], Mette Holland-Fischer[6], Hanne M. Lindegaard[7], Anne Gitte Loft[8], Henrik Nordin[9], Laura Johnsen[10], Sussi Flejsborg Oeftiger[11], Annette Hansen[12], Claus Rasmussen[13], Gerdur Grondal[14], Árni Jón Geirsson[14] and Merete Lund Hetland[15]. [1]The Danish Rheumatologic Database (DANBIO), Glostrup Hospital, Glostrup, Denmark, [2]Faculty of Medicine, University of Iceland, Reykjavik, Iceland, [3]ZiteLab ApS, Copenhagen, Denmark, [4]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Glostrup Hospital, Glostrup, Denmark, [5]Department of Rheumatology, Frederiksberg Hospital, Copenhagen, Denmark, [6]Department of Rheumatology, Aalborg University Hospital, Aalborg, Denmark, [7]Odense University Hospital, Odense, Denmark, [8]Department of Rheumatology, Sygehus Lillebaelt, Vejle, Denmark, [9]Department of Infectious Diseases and Rheumatology, Rigshospitalet, Copenhagen, Denmark, [10]Department of Rheumatology, Helsingør and Hillerød Hospital, Hillerød, Denmark, [11]Department of Rheumatology, Køge Hospital, Køge, East Timor, [12]Department of Rheumatology, Gentofte University Hospital, Copenhagen, Denmark, [13]Vendsyssel Teaching Hospital/Aalborg University, Hjoerring, Denmark, [14]Department of Rheumatology, Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland, [15]The Danish Rheumatologic Database (DANBIO), Glostrup Hospital., Copenhagen, Denmark.

Background/Purpose: International guidelines recommend that in psoriatic arthritis infliximab should be dosed with 5 mg/kg bodyweight every 8th week. Data on the use of lower doses is however scarce. We aimed to describe dose regimens, the frequency of dose escalation and outcomes in patients with psoriatic arthritis treated with infliximab in routine care.

Methods: Observational cohort study based on the nationwide Danish DANBIO and Icelandic ICEBIO registries. Demographics and baseline characteristics among tumor-necrosis-factor-α inhibitor (TNFi) naïve patients treated with ≤3 mg infliximab/kg body weight, 3–5 mg/kg or ≥5 mg/kg with treatment scheduled at 0, 2, 6 and then every 8th week were described. Dose escalation was defined as an increase in either the dose and/or frequency. Treatment responses were evaluated by ACR20/50/70 and EULAR-good-response after 6 months' treatment and disease activity after one year's treatment. Kaplan-Meier plots and regression analyses were performed for drug survival analyses and to identify predictors of treatment response and drug survival.

Results: Among the 1589 psoriatic arthritis patients identified in the registries, 462 patients (29%, 376 Danish, 86 Icelandic) received treatment with infliximab. Start infliximab dose was ≤3 mg/kg in 174 patients (38%), 3–5 mg/kg in 174(38%), ≥5mg/kg in 38(8%) and unregistered in 76 patients (16%). After one years' treatment, corresponding percentages were 35, 53, 12 and 22%, respectively. Patients with higher body weight received lower infliximab doses per kg. The median time until first dose escalation (273 days (interquartile range, IQR 153–553) was independent of start dose (log rank 0.1, p=0.9). The ACR20/50/70 or EULAR-response rates, drug survival (Figure) and one-year disease activity were also independent of baseline dose. Icelandic patients received lower infliximab doses than Danish (2.3mg/kg (2.1–2.9) vs. 3.1mg/kg (3.0–3.8)) (median (IQR), p<0.05), they had also longer drug survival, but similar one-year response rates.



Figure

Conclusion: In clinical practice, >80% of infliximab treated patients with psoriatic arthritis received sustained treatment with doses less than the 5 mg/kg/8weeks recommended in international guidelines. Low infliximab start dose did not affect drug survival or treatment response. Low start dose with gradual dose escalation was a preferred and effective strategy.

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Long Term Outcomes In Psoriatic Arthritis 2; A Prospective Multicentre Observational Study Of Work Disability In Psoriatic Arthritis: First Report Of The Clinical and Socioeconomic Associations Of Work Disability In Psoriatic Arthritis.

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Background/Purpose: Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that is associated with joint damage, impaired quality of life and high levels of work disability (WD). However, data on the associations of WD in PsA is limited. Long Term Outcomes in Psoriatic Arthritis II is a prospective UK multicentre observational study of the impact of PsA on WD and the effect of treatment intervention. In this first analysis we set out to determine to what extent structural damage, clinical disease activity, demographic and social factors are associated with WD.

Methods: Four hundred patients fulfilling CASPAR criteria for PsA were recruited from 23 hospitals across the UK at initiation of DMARD or anti-TNF therapy. Physician assessments (DAPSA score), radiographs (PsA Ratingen score) and patient reported outcomes (HAQ, EQ5D, FACIT, DLQI, global, joint and skin specific activity VAS scores, comorbidities, demographic details, education, location, employer awareness/helpfulness) and work type were collected. WD was assessed with the WPAI which reports work disability as percentage of absenteeism (work time missed), presenteeism (impairment at work/ reduced effectiveness) and work productivity loss (overall work impairment/absenteeism plus presenteeism). All variables were considered for inclusion. Logistic and linear regressions were conducted to investigate independent associations with WD. Age demonstrated a non-linear relationship with WD and was therefore included as a quadratic term.

Results: Of the 400 participants three hundred and fifty three were of UK working age (18–65 years), mean age 46.8 years (sd 11.02), mean disease duration 5.8 years (sd 8.00), 49.9% female. Two hundred and twenty six (64%) were in work with a further 10 over retirement age, but still working. Unemployed participants were older than those in employment, 55 years (sd 14.7) versus 47 years (sd 10.9), had longer disease duration, 8 years (sd 9.8) versus 6 years (sd 7.8), had worse physical function, HAQ 1.3 (sd 0.78) versus 1.0 (sd 0.68), had worse quality of life, EQ5D 0.4 (sd 0.36) versus 0.5 (sd 0.54) and had more radiographic damage, Ratingen score 19 (sd 31.9) versus 8 (sd 16.5). Of the 236 participants in work the mean absenteeism, presenteeism and productivity loss was 14% (sd 29.0), 39% (sd 27.2) and 46% (sd 30.4) respectively. Independent associations with WD are reported in table 1.

Table 1. Regression models for work disability associations

Variable	Model 1- logistic Employed Odds Ratio (CI)	Model 2- Logistic Absenteeism (0–1) Odds Ratio (CI)	Model 3- Linear Presenteeism (0–1) Estimate (CI)	Model 4- Linear Productivity loss (0–1) Estimate (CI)
Intercept	0.01 (0.000 to 1.622) p=0.07	0.04 (0.010 to 0.127) p<0.01	−0.02 (−0.114 to 0.074) p=0.67	−0.05 (−0.143 to 0.040) p=0.27
Age years	**1.31 (1.029 to 1.672) p=0.03**			
Age (quadratic) years	**0.99 (0.994 to 0.999) p=0.02**			
Disease duration 2–5 years	**0.41 (0.180 to 0.953) p=0.03**		0.02 (−0.066 to 0.112) p=0.61	
Disease duration >5 years	1.36 (0.557 to 3.319) p=0.49		**−0.09 (−0.167 to −0.021) p=0.01**	
Global activity VAS 0–10			**0.02 (0.001 to 0.053) p=0.01**	0.03 (0.001 to 0.06) p<0.01
Joint activity VAS 0–10		**1.04 (1.018 to 1.055) p<0.01**	0.03 (0.006 to 0.055) p=0.01	0.02 (0.000 to 0.049) p=0.05
HAQ 0–3	**0.56 (0.343 to 0.926) p=0.02**		**0.63 (0.005 to 1.200) p=0.03**	0.12 (0.066 to 0.182) p<0.01
Employer very helpful	**15.10 (4.658 to 48.753) p<0.01**			
Employer helpful	**17.46 (4.395 to 69.355) p<0.01**			
No help required	**3.22 (1.264 to 8.229) p<0.01**			
Employer unhelpful	1.29 (0.325 to 5.155) p=0.72			
Employer very unhelpful	0.39 (0.039 to 3.942) p=0.42			

Conclusion: Greater global, joint specific disease activity and worse physical function exerted a negative influence on presenteeism and productivity loss suggesting disease activity is important amongst those who are in work. Greater age, recent disease onset and worse physical function exert a negative influence on remaining in employment. Patient reported employer awareness and helpfulness exerts a strongly positive influence on remaining in employment, even if patients perceive no help is required.

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Quantiferon-TB Test Can Be Usefull For Decision Of Anti-Tuberculosis Prophylaxis During Anti-TNF Treatment: Result Of Real Life. Umut Kalyoncu[1], Levent Kilic[1], Ahmet Cagkan Inkaya[2], Omer Karadag[3], Sule Apras Bilgen[2], Ali Akdogan[2], Sedat Kiraz[3] and Ihsan Ertenli[3]. [1]Hacettepe University School of Medicine, Ankara, Turkey, [2]Hacettepe University, Faculty of Medicine, Ankara, Turkey, [3]Hacettepe University Faculty of Medicine, Ankara, Turkey.

Background/Purpose: Anti-tumor necrosis factor (TNF) treatments may increase tuberculosis. Most of the national guidelines recommend tuberculin skin test (TST) for screening of latent tuberculosis. However, BCG vaccine is mandatory in some countries and TST may be positive in more than 80% of those country[1]. Thus, vast majority of those patients use isoniazid prophylaxis and this drug is not innocent. Objective of this study was to assess accuracy of QuantiFERON-TB Gold In-Tube (QFT-GIT) test for anti-tuberculosis prophylaxis during anti-TNF treatment.

Methods: TST have been used for detection of latent tuberculosis between 2003–2011 in our center. After March 2011, QFT-GIT test was replaced TST for these purpose in routine practice. All patients who started anti-TNF therapy were recorded in a database prospectively between March 2011 to June 2013 according to QFT-GIT test results. This database included name of anti-TNF drugs, switch of anti-TNF, duration of follow-up. Clinical signs of tuberculosis were examined every 3 months by physicians or experienced study nurses. Isoniazid prophylaxis started in patients with positive QFT-GIT test. In June 2013, all database screened regularly by a physician. If patients were not examined in last 3 months, patients were called by phone [112/516 (21,7%)] for drug survival and signs of tuberculosis. If patients were not reached by phone, data of tuberculosis extracted from "tuberculosis control dispensary of health ministry" [24/516 (6,2%) patients].

Results: A total of 516 (289 female, 56%) patients were started anti-TNF therapy. Mean age of patients were 40 ± 12 years. Initial diagnosis of patients were spondyloarthritis 309 (59,9%), rheumatoid arthritis 158 (30,6%), psoriatic arthritis 45 (8,7%) and juvenil idiopathic arthritis 4 (0,8%). Anti-TNF drugs were adalimumab 191 (37,0%), etanercept 177 (34,3%), infliximab 133 (25,8%) and golimumab 15 (2,9%). Anti-TNF drugs was switched in 64 (12,4%) patients. QFT-GIT test was found to be positive in 110 (21,6%) patients. Isoniazid prophylaxis started in those patients. Median follow-up duration of patients were 5 (0–24) months and 191 of 516 (37,0%) patients were followed more than 9 months. Patients were classified as follows; regularly follow-up 344 (66.7%), just started within last 3 months 60 (11,6%), never follow-up 47 (9.1%), and irregularly follow-up 65 (12,6%). None of the patients from this cohort had tuberculosis.

Conclusion: BCG vaccine is mandatory in our country. Unfortunately, BCG vaccine affects adversely on TST for detection of latent tuberculosis. Although median follow-up duration is limited in this study, QFT-GIT test may be effective and reliable alternative for detection of latent tuberculosis before commencement of anti-TNF treatment in real life.

Reference:
[1]Kalyoncu U et al. Comparison of quantiferon-TB test and TST in routine practice during anti-TNF treatment. Ann Rheum Dis 2013;72(Suppls3):231

Disclosure: U. Kalyoncu, None; **L. Kilic**, None; **A. C. Inkaya**, None; **O. Karadag**, None; **S. Apras Bilgen**, None; **A. Akdogan**, None; **S. Kiraz**, None; **I. Ertenli**, None.

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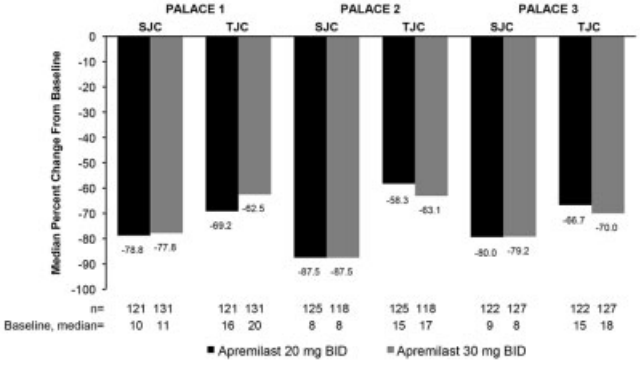
Apremilast, An Oral Phosphodiesterase 4 Inhibitor, Is Associated With Long-Term (52-Week) Improvement In Tender and Swollen Joint Counts In Patients With Psoriatic Arthritis: Results From Three Phase 3, Randomized, Controlled Trials. Maurizio Cutolo[1], Philip J. Mease[2], Dafna D. Gladman[3], Arthur Kavanaugh[4], Adewale O. Adebajo[5], Juan J. Gomez-Reino[6], Jürgen Wollenhaupt[7], Georg Schett[8], Eric Lespessailles[9], Kamal Shah[10], ChiaChi Hu[10], Randall M. Stevens[10], Christopher J. Edwards[11] and Charles A. Birbara[12]. [1]University of Genova, Genova, Italy, [2]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA, [3]University of Toronto, Toronto Western Hospital, Toronto, ON, [4]University of California San Diego, San Diego, CA, [5]University of Sheffield, Sheffield, United Kingdom, [6]Hospital Clinico Universitario, Santiago, Spain, [7]Schön Klinik Hamburg Eilbek, Hamburg, Germany, [8]University of Erlangen-Nuremberg, Erlangen, Germany, [9]University of Orléans, Orléans, France, [10]Celgene Corporation, Warren, NJ, [11]University of Southampton, Southampton, United Kingdom, [12]University of Massachusetts Medical School, Worcester, MA.

Background/Purpose: Apremilast (APR), an oral phosphodiesterase 4 inhibitor, works intracellularly to modulate pro- and anti-inflammatory mediators. The PALACE 1, 2, and 3 trials compared the efficacy and safety of APR with placebo (PBO) in pts with active PsA despite prior DMARDs and/or biologics.

Methods: Pts were randomized 1:1:1 to PBO, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by BL DMARD use. At wk 16, pts with <20% reduction from BL in swollen and tender joint counts (SJC/TJC) qualified for protocol-defined early escape; those on PBO were re-randomized to APR20 or APR30 and those on APR remained on the initial APR dose. At wk 24, all remaining PBO pts were re-randomized to APR20 or APR30 through wk 52. Pts taking concurrent DMARDs were allowed to continue stable doses (MTX, sulfasalazine, leflunomide, or a combination). Given the relative weighting of SJC/TJC in the ACR20 composite index and their clinical importance, we examined these measures across the 3 trials.

Results: APR resulted in statistically significant and clinically meaningful improvement in ACR20 response (primary endpoint) in all 3 PALACE trials. Median percent reductions (improvement) in SJC/TJC were statistically significant vs PBO at wk 16 in all 3 trials; SJC (PBO, APR20, APR30, respectively): −16.7%, −39.3% (P=0.0035), −50.0% (P<0.0001) (PALACE 1); −33.3%, −50.0% (P=0.0029), −53.9% (P=0.0009) (PALACE 2); 20.0%, −36.4% (P=0.0301), −50.0% (P=0.0014) (PALACE 3); TJC: −7.0%, −23.3% (P=0.0007), −42.9% (P<0.0001) (PALACE 1); −8.7%, −36.2% (P<0.0001), −33.3% (P=0.0015) (PALACE 2); −8.6%, −30.0% (P=0.0001), −43.7% (P<0.0001) (PALACE 3). Pts receiving APR20 and APR30 for 24 wks had median percent reductions in SJC in PALACE 1, 2, and 3, respectively, of −53.8% and −66.7%; −71.4% and −75.0%; and 61.3% and −69.2%. Median percent reductions in TJC for APR20 and APR30 were 46.2% and −59.4%; −51.0% and −47.1%; and −53.3% and −55.0%. In pts receiving APR for 52 wks, sustained improvements in SJC/TJC were observed at wk 52, with SJC improvements up to −87.5% and TJC improvements up to −70.0% (Figure). Pts randomized to APR at wks 16 and 24 demonstrated results consistent with those originally randomized to APR. No new safety findings were identified and the incidence of pts experiencing any AE was comparable over the 0–24 and 0–52 wk periods. No imbalance in the exposure-adjusted incidence rates of major adverse cardiac events, serious infections including systemic opportunistic infection, or malignancies between APR and PBO was observed. No cases of TB (novel or reactivation) were reported in the APR treatment groups; TB screening was not required per protocol.

PALACE 1, 2, and 3: SJC and TJC at Week 52 in Patients Receiving APR 20 and 30 mg BID From Baseline*



*A negative change from baseline indicates improvement.

Conclusion: Over 52 wks, APR continued to demonstrate efficacy in the treatment of PsA, including clinically meaningful improvements in SJC and TJC. APR demonstrated an acceptable safety profile and was generally well tolerated for up to 52 wks.

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Effect Of Brodalumab (AMG 827) On Pain and Physical Functioning In Patients With Psoriatic Arthritis. Mark C. Genovese[1], Philip J. Mease[2], Hema Viswanathan[3], Dina Chau[3], JingYuan Feng[3], Ngozi Erondu[3] and Ajay Nirula[3]. [1]Stanford University, Palo Alto, CA, [2]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA, [3]Amgen Inc, Thousand Oaks, CA.

Background/Purpose: Psoriatic arthritis (PsA) has a significant impact on health related quality of life (HRQoL). This analysis evaluated the efficacy of brodalumab, a human anti-IL-17 receptor A monoclonal antibody, on HRQoL with an emphasis on pain and physical functioning in patients with PsA.

Methods: Analysis of data from a phase 2 study of subjects with PsA (Classification Criteria for PsA and ≥3 tender and ≥3 swollen joints) for ≥6 months randomized to brodalumab (140 or 280 mg Q2W) or placebo for 12 weeks followed by an open-label extension (OLE) in which all subjects received 280 mg brodalumab. Patient reported outcome (PRO) measures of pain and HRQOL included subject global assessment (SGA)-joint pain, SGA-disease activity, Health Assessment Questionnaire Disability Index (HAQ-DI), 36-item Short Form Health Survey (SF-36 v2), and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Analyses included available data up to week 24 of the ongoing OLE and were based on observed data.

Results: The majority of subjects enrolled (113 brodalumab and 55 placebo) were female (64%), white (94%), and rheumatoid factor negative (92%). Mean (SD) age, weight, and duration of PsA were 52 (12) years, 91 (21) kg, and 9 (8) years, respectively. 156 subjects enrolled in the OLE. Median (IQR) percent change in SGA-joint pain from baseline to week 12 was −23% (−54, 10) in the 140-mg group (P=.06) and −28% (−49, 10; P=.04) in the 280-mg group, compared with −5% (−32, 29) in placebo. Median (IQR) percent change in HAQ-DI from baseline to week 12 was −7% (−45, 6) in the 140-mg group (P = .30) and −14% (−36, 0) in the 280-mg group (P = .12), compared with −8% (−23, 13) in placebo. Compared with placebo, SGA-disease activity was significantly lower in the 140-mg group (least squares mean difference [95% CI] −17.2 [−32.7, −1.6]; P=.031) and the 280-mg group (least squares mean difference [95% CI] −24.6 [−40.3, −8.9]; P=.002). There was a significantly greater change in BASDAI score from baseline to week 12 in the 140-mg group (least squares mean difference [95% CI] −0.7 [−1.3, −0.1]; P=.03) and 280-mg group (least squares mean difference [95% CI] −0.8 [−1.4, −0.2]; P=.01) compared with placebo. Nonsignificant trends of improvement were observed for SF-36 physical component, mental component, and some other domain scores. During the OLE, all response measures continued to improve in both brodalumab groups and responses in the prior placebo group at week 24 were similar to those of the brodalumab group at week 12.

Conclusion: Brodalumab treatment was associated with significant improvements in joint pain and physical functioning in subjects with PsA.

Disclosure: M. C. Genovese, Amgen Inc., 2, Amgen Inc., 5; **P. J. Mease**, AbbVie, Amgen, BiogenIdec, BMS, Celgene, Crescendo, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, Vertex, 2, AbbVie, Amgen, BiogenIdec, BMS, Celgene, Crescendo, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, Vertex, 5, AbbVie, Amgen, BiogenIdec, BMS, Crescendo, Genentech, Janssen, Lilly, Pfizer, UCB, 8; **H. Viswanathan**, Amgen Inc, 1, Amgen Inc, 3; **D. Chau**, Amgen Inc, 1, Amgen Inc, 3; **J. Feng**, Amgennc., 1, Amgen Inc, 3; **N. Erondu**, Amgen Inc., 1, amgen Inc., 3; **A. Nirula**, Amec, 1, Amgen Inc, 3.

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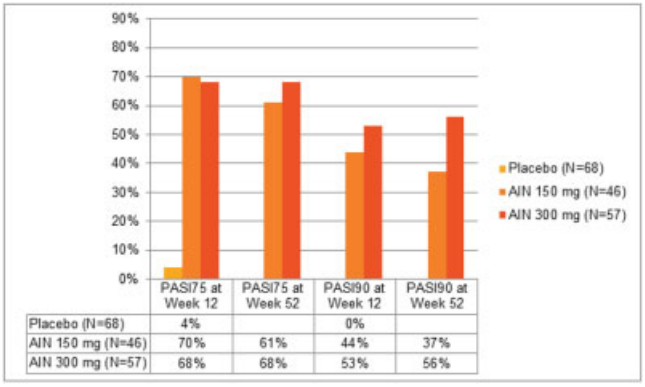
Secukinumab Shows Substantial Improvement In Both Psoriasis Symptoms and Physical Functioning In Moderate-To-Severe Plaque Psoriasis Patients With Psoriatic Arthritis: A Subanalysis Of a Phase 3, Multicenter, Double-Blind, Placebo-Controlled Study. Alice B. Gottlieb[1], Bardur Sigurgeirsson[2], Andrew Blauvelt[3], Shephard Mpfofu[4], Ruvie Martin[5] and Charis Papavassilis[4]. [1]Tufts Medical Center, Boston, MA, [2]University of Iceland, Kópavogur, Iceland, [3]Oregon Health and Sciences University, Portland, OR, [4]Novartis Pharma AG, Basel, Switzerland, [5]Novartis Pharma AG, East Hanover, Switzerland.

Background/Purpose: Since interleukin (IL)-17A has a potential role in the pathogenesis and chronic inflammation of psoriatic disease, with similar pathways impacting skin and joints, strategies aimed at blocking IL-17A may be beneficial in the treatment of psoriasis and psoriatic arthritis (PsA). Secukinumab (AIN457) is a fully human anti-IL-17A monoclonal antibody.

Methods: A total of 738 subjects aged ≥18 years with moderate-to-severe plaque psoriasis (incl. Psoriasis Area and Severity Index (PASI) score ≥12) were randomized 1:1:1 to subcutaneous secukinumab 150 mg or 300 mg or placebo given at randomization, Weeks 1, 2, and 3, followed by dosing every four weeks starting at Week 4 through Week 48. At Week 12, subjects not achieving a PASI 75 response were re-randomized 1:1 to secukinumab 150 mg or 300 mg. A pre-specified subanalysis of PASI responses and changes from baseline in the Health Assessment Questionnaire–Disability Index (HAQ-DI) up to Week 52 in subjects with concomitant PsA at baseline is reported here.

Results: Baseline PASI and HAQ-DI scores were balanced across treatments. In 171 subjects with concomitant PsA, PASI 75 responses at Week 12 were 70% in the 150 mg group and 68% in the 300 mg group (4%, placebo); PASI 90 responses were 44% and 53% in the 150 mg and 300 mg groups, respectively (0%, placebo). PASI 75 responses (61%, 150 mg; 68%, 300 mg) and PASI 90 responses (37%, 150 mg; 56%, 300 mg) were maintained up to one year (Fig 1). Physical function as measured by HAQ-DI change from baseline was significantly greater at Weeks 4 and 12 with 300 mg vs placebo (P < 0.05). HAQ –DI responses were more pronounced in patients with more disability. In patients with baseline HAQ-DI ≥0.5, reduction in HAQ-DI score was statistically significantly greater for 150 mg at Week 12 and for 300 mg at Weeks 4 and 12 vs placebo (Fig 2) and responses continued up to Week 52. Secukinumab was well tolerated with no unexpected safety findings.



	PASI75 at Week 12	PASI75 at Week 52	PASI90 at Week 12	PASI90 at Week 52
Placebo (N=68)	4%		0%	
AIN 150 mg (N=46)	70%	61%	44%	37%
AIN 300 mg (N=57)	68%	68%	53%	56%

Figure 1. PASI 75/90 Response at Weeks 12 and 52
All PsA Patients (Non-Responder Imputation)

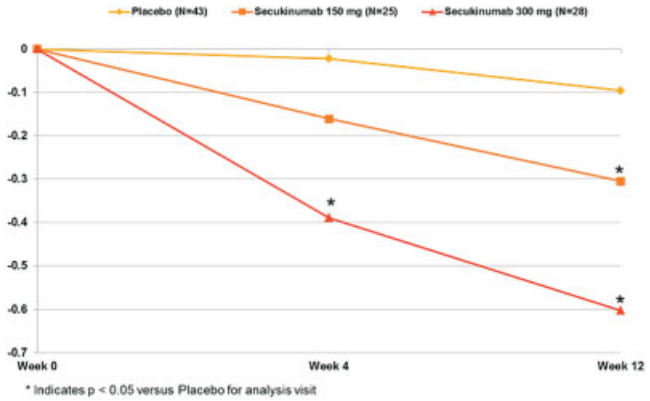


Figure 2. Change from Baseline in HAQ-DI Score to Week 12. *Placebo-comparison (LOCF) for patients with baseline HAQ-DI ≥0.5*

Conclusion: In subjects with psoriasis and concomitant PsA, secukinumab was associated with superior improvement in skin symptoms and physical functioning compared with placebo. These data strongly support continued evaluation of secukinumab in patients with PsA.

Disclosure: A. B. Gottlieb, Janssen, Amgen, Abbott (Abbvie), Novartis, Celgene, Pfizer, Lilly, Coronado, Levia, 2, Astellas, Janssen, Celgene Corp., Bristol Myers Squibb Co., Beiersdorf, Inc., Abbott Labs. (Abbvie), TEVA, Actelion, UCB, Novo Nordisk, Novartis, Dermipsor Ltd., Incyte, Pfizer, Canfite, Lilly, Coronado, Vertex, Karyopharm, CSL Behring Biotherapies for Li, 5; **B. Sigurgeirsson**, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, 5; **A. Blauvelt**, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, 5, Novartis Pharmaceutical Corporation, 8; **S. Mpfofu**, Novartis Pharmaceutical Corporation, 3; **R. Martin**, Novartis Pharmaceutical Corporation, 3; **C. Papavassilis**, Novartis Pharmaceutical Corporation, 3, Novartis Pharmaceutical Corporation, 1.

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Sustained Improvement In Health-Related Quality Of Life, Work Productivity, Employability, and Reduced Healthcare Resource Utilization Of Patients With Rheumatoid Arthritis, Psoriatic Arthritis and Ankylosing Spondylitis Treated With Golimumab: 5-Year Results From 3 Phase III Studies. Chenglong Han[1], Arthur Kavanaugh[2], Mark C. Genovese[3], Benjamin Hsu[4], Atul A. Deodhar[5] and Elizabeth C. Hsia[6]. [1]Janssen Global Services, LLC., Malvern, PA, [2]University of California, San Diego, La Jolla, CA, [3]Stanford University, Palo Alto, CA, [4]Janssen Research & Development, LLC., Spring House, PA, [5]Oregon Health & Science University, Portland, OR, [6]Janssen Research & Development, LLC./U of Penn, Spring House/Philadelphia, PA.

Background/Purpose: To summarize changes from baseline in health-related quality of life (HRQOL), impact of disease on work productivity, employability, and healthcare resource utilization among patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) treated with golimumab (GLM) through 5 years.

Methods: Patients with active RA despite MTX (GO-FORWARD), active PsA (GO-REVEAL), and active AS (GO-RAISE) were randomized to placebo (PBO) or GLM (50mg or 100mg Q4w). In GO-FORWARD, treatment also included concomitant MTX (GLM monotherapy in GO-FORWARD was not included in this analysis). Patients randomized to PBO crossed over to GLM at wk 24, with follow-up through wk256. HRQOL was measured using 36-item short-form of health survey (SF-36); impact of disease on work productivity was measured using a VAS scale (0=no impact, 10=impact very much); Employable was defined as being actively employed or to be able to work if a job was available. Healthcare resource utilization included the number of physician visits in the past 4 wks, ER visit in the past 3 months, and hospitalizations in the past 12 months. Changes from baseline through wk 256 in SF-36 PCS and MCS, work productivity, employability, and healthcare resource utilization were summarized from observed patients.

Results: At baseline, *both* mean SF-36 PCS (30.19, 32.91, and 30.00) and MCS (43.65, 45.19, and 44.03) scores in the combined GLM group for RA, PsA, and AS, respectively were below the US norm, indicating impaired HRQOL. Baseline percent of RA, PsA, and AS patients unemployable before retirement were 13.7%, 12.1%, and 14.1%, respectively. At wk24, RA, PsA, and AS GLM-treated pts had statistically significant greater improvement in *both* mean SF-36 PCS (7.65, 7.83, and 9.36, $p<0.001$) and MCS (3.07, 3.84, and 4.01, $p<0.05$) and had a statistically significant greater mean change from baseline in reduction in impact of disease on work productivity in the combined GLM-treated patients vs PBO (−1.987, −2.242, −2.805, all $p<0.001$) in RA, PsA and AS, respectively. At wk256, sustained improvement in SF-36 PCS and MCS was observed in the RA, PsA, and AS GLM-treated patients (mean change from baseline: PCS 9.3, 9.8, and 13.0 and MCS 4.5, 4.7, and 5.1, respectively), while mean change in impact of disease on work productivity for RA, PsA, and AS was −2.71, −3.0, and, −3.9, respectively. In addition, RA, PsA, and AS patients employable at baseline remained employable (all >95%), while those unemployable at baseline became more likely to be employable (RA 33.3%, PsA 64.3%, and AS 76.5%) at Wk256. A reduction in physician visits (RA −84%, PsA −89%, and AS −88%) was observed, as well as a reduction in the number of hospitalizations, ER visits, and days hospitalized, although these events were rare. Patients randomized to PBO at baseline and crossed-over to active treatment achieved similar outcomes overtime as those patients who were randomized to active treatment at baseline.

Conclusion: Golimumab-treated patients showed sustained improvement in HR QoL, reduced impact of disease on work productivity, improved employability, and less healthcare resource utilization through 5yrs.

Disclosure: C. Han, Janssen Global Services, LLC., 3; **A. Kavanaugh**, Janssen Research & Development, LLC., 9; **M. C. Genovese**, Janssen Research & Development, LLC., 2, Janssen Research & Development, LLC., 5; **B. Hsu**, Janssen Research & Development, LLC., 3; **A. A. Deodhar**, Abbvie, Amgen, Novartis, UCB, Pfizer, Janssen, 2, UCB, Merck Sharp & Dohme, Pfizer, Abbvie, Novartis, 9; **E. C. Hsia**, Janssen Research & Develpment, LLC., 3.

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Evaluation and Comparison Of Performance Of Different Classification Criteria For Reactive Arthritis. Mariana Benegas[1], Rafael Chaparro[1], Oscar L. Rillo[1], Luciana Casalla[1], Emilce Schneeberger[2], Federico Ceccatto[3], Sergio Paira[3], Federico Zazzetti[4], Juan C. Barreira[5] and Emilio Busquiazzo[6]. [1]Hospital Gral. de Agudos Dr. E. Tornú, Buenos Aires, Argentina, [2]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [3]Hospital Jose María Cullen, Santa Fé, Argentina, [4]Hospital Británico, Buenos Aires, Argentina, [5]Buenos Aires British Hospital, Buenos Aires, Argentina, [6]Hospital del Milagro, Salta, Argentina.

Background/Purpose: Reactive Arthritis (Re.A) is an inflammatory joint disease that according to different records represents from 6% to 47% of the seronegative spondyloarthropathies (SS). These differences may be due to genetic and/or environmental variations as well as the absence of an agreement on the definition of case and validated classification criteria. Objective: to assess and compare the diagnostic value of the classification criteria for Re.A in a cohort patients.

Methods: consecutive adult patients (≥18 years old) were included from 5 Argentinian centers, with Re.A diagnosed by rheumatologists with broad experience in this entity, and as a control group, patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA). Clinical data, laboratory and radiological characteristics employed by the different criteria were retro-prospectively collected and recorded. We classified each patient according to different classification criteria: Calin, Third International Workshop of ReA, American College of Rheumatology (ACR), European Spondylarthropathy Study Group (ESSG), Amor and Assessment of Spondyloarthritis international Society (ASAS) for peripheral arthritis, having registered their fulfillment. *Statistical analysis:* we described the variables under study. Sensitivity, specificity, positive and negative predictive value (PPV/NPV) and likelihood ratios (LR) for each criteria were assessed by double entry table.

Results: thirty six patients with Re.A (78% male), were included, median age (SD): 36 (12) years, median (IQR) disease duration: 22 (2–444) months. Fifty-six percent presented urethritis, 28% gastroenteritis, 8% cervicitis and 8% other infections. Forty-four, 33 and 17% had mono, oligo y polyarthritis respectively, 86% asymmetrical and 61% predominant in lower limbs. Inflammatory spinal pain and sacroiliitis were detected in 56% and 36% respectively; enthesitis 50% and dactylitis 14%. Extra-articular manifestations: uveitis 17%, conjunctivitis and balanitis 8%, keratoderma blennorrhagica and genital ulcer 3%. Radiographic features: 30% had sacroiliitis. In the control group 36 patients (16 PsA, 15 RA, 5 AS) were evaluated; they had similar demographic characteristics and typical findings of each of these entities. The following table shows the sensitivity, specificity, PPV, NPV and LR obtained by the different classification criteria:

	Calin	ACR	Amor	ESSG	ASAS	3° Workshop
Sensitivity (%)	**81**	**64**	**53**	**97**	**97**	**64**
Specificity (%)	**100**	**100**	**47**	**57**	**50**	**100**
PV (%) +	100	54	50	69	66	100
PV (%) -	84	73	50	95	95	73
LR	∞	∞	1	2.19	1.94	∞

Conclusion: the highest sensitivity was observed by applying the ESSG, ASAS and Calin criteria. The highest specificity was obtained by applying the Calin, ACR and Third International Workshop criteria. We observe, in this study, that Calin's criteria showed excellent specificity, keeping a good sensitivity and high positive predictive values and likelihood ratios.

Disclosure: M. Benegas, None; **R. Chaparro**, None; **O. L. Rillo**, None; **L. Casalla**, None; **E. Schneeberger**, None; **F. Ceccatto**, None; **S. Paira**, None; **F. Zazzetti**, None; **J. C. Barreira**, None; **E. Busquiazzo**, None.

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Ustekinumab Improves Physical Function, Quality Of Life, and Work Productivity Of Patients With Active Psoriatic Arthritis Who Were Methotrexate-naïve Or Previously Treated With Methotrexate Or Anti-Tumor Necrosis Factor Agent: Data From 2 Phase 3, Randomized, Placebo-Controlled Trials. Proton Rahman[1], Lluis Puig[2], Alice B. Gottlieb[3], Arthur Kavanaugh[4], Iain B. McInnes[5], Christopher T. Ritchlin[6], Shu Li[7], Yuhua Wang[7], Ning Zhao[8], Rita Ganguly[8], Michael Song[7], Alan M. Mendelsohn[7] and Chenglong Han[8]. [1]Memorial University, St. Johns, NF, [2]Universitat Autònoma de Barcelona, Barcelona, Spain, [3]Tufts Medical Center, Boston, MA, [4]University of California, San Diego, La Jolla, CA, [5]University of Glasgow, Glasgow, United Kingdom, [6]University of Rochester, Rochester, NY, [7]Janssen Research & Development, LLC., Spring House, PA, [8]Janssen Global Services, LLC., Malvern, PA.

Background/Purpose: To examine the impact of ustekinumab (UST) treatment on patient reported outcomes in patients with active psoriatic arthritis (PsA) using week 24 data from two Phase 3 clinical studies, PSUMMIT I and II.

Methods: Adult patients with active PsA despite DMARD and/or NSAID therapy (PSUMMIT I, n=617) or previously treated with anti-TNFα therapy (PSUMMIT II, n=312) were randomized to receive UST 45mg, 90mg, or placebo (PBO) at wks 0, 4, and q12wks, thereafter. Patient reported outcomes were measured using the Health Assessment Questionnaire (HAQ), Dermatology Quality Life Index (DLQI), SF-36 health survey questionnaire (SF-36), Visual Analogue Scales (VAS) for impact of PsA on work productivity (0–10), patient assessment of pain (0–10), and disease activity (0–10). Sub-analyses were conducted by combining both studies into 3 mutually exclusive groups based on treatment history: MTX naïve, previously treated with MTX therapy, and previously treated with anti-TNF therapy.

Results: At baseline, patients in both studies had moderate to severe physical disability and impaired health related quality of life with a mean HAQ score of ≥1.25, mean DLQI score of ≥10 and mean SF-36 PCS and MCS below 50 (normal population score). In PSUMMIT I, UST-treated patients achieved statistically significantly greater improvements in HAQ (−0.31 and −0.4 vs. −0.1), DLQI (−6.6 and −7.5 vs. −1.4), and SF-36 PCS (4.9 and 6.2 vs. 1.4), for the UST 45mg, 90mg, vs. PBO groups, respectively. When compared to PBO, greater proportions of UST-treated patients achieved clinical meaningful improvements in HAQ (≥0.3) (47.8% and 47.5% vs. 28.2%), DLQI (≥5) (58.6% and 63.1% vs. 32.9%), and SF-36 PCS (≥5) (45.5%, and 53.3% vs. 26.0%), for the UST 45mg, 90mg, vs. PBO groups, respectively. Similar results were observed in PSUMMIT II and in the sub-analyses by MTX naïve, prior MTX experienced, and prior anti-TNFα experienced patients. Similar results were also observed in SF-36 sub-scales, especially in bodily pain and physical health. In the anti-TNF naïve population, statistically significantly greater improvement in SF-36 MCS was observed in the combined UST 45mg and 90mg group vs PBO Additionally, UST-treated patients achieved statistically significantly greater improvements in patient assessment of pain, patient assessment of disease activity, and greater reduction in impact of disease on work productivity vs PBO-treated patients.

Conclusion: UST improves physical function, improves general, arthritis and skin-related quality of life, and reduces the impact of disease on work productivity in patients with active PsA regardless of current or prior MTX use or prior anti-TNF experience.

Disclosure: P. Rahman, Amgen, Abbott, BMS, Merck, Pfizer, Janssen, Hoffman-La Roche, UCB, Novartis, Sanofi-Aventis, 5, Amgen, Abbott, BMS, Merck, Pfizer, Janssen, Hoffman-La Roche, UCB, Novartis, Sanofi-Aventis, 9; **L. Puig**, Abbvie, Amgen, Janssen, Lilly, Novartis, Pfizer,VBL, 2, Celgene, Abbvie, Janssen, Novartis, MSO, Pfizer, Leo Pharma, 5; **A. B. Gottlieb**, Janssen, Amgen, Abbott (Abbvie), Novartis, Celgene, Pfizer, Lilly, Coronado, Levia, 2, Astellas, Janssen, Celgene Corp., Bristol Myers Squibb Co., Beiersdorf, Inc., Abbott Labs. (Abbvie), TEVA, Actelion, UCB, Novo Nordisk, Novartis, Dermipsor Ltd., Incyte, Pfizer, Canfite, Lilly, Coronado, Vertex, Karyopharm, CSL Behring Biotherapies for Li, 5; **A. Kavanaugh**, Janssen Research & Development, LLC., 9; **I. B. McInnes**, Novartis, Janssen Research & Development, LLC., 8, UCB, 9; **C. T. Ritchlin**, Amgen, Janssen, UCB, Abbott, Boerhinger Ingleheim, Lilly, 5; **S. Li**, Janssen Research & Development, LLC., 3; **Y. Wang**, Janssen Research & Development, LLC., 3; **N. Zhao**, Janssen Global Services, LLC., 3; **R. Ganguly**, Janssen Global Services, LLC., 3; **M. Song**, Janssen Research & Development, LLC., 3; **A. M. Mendelsohn**, Janssen Research & Development, LLC., 3; **C. Han**, Janssen Global Services, LLC., 3.

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Safety Of Ustekinumab From The Placebo-Controlled Periods Of Psoriatic Arthritis and Psoriasis Clinical Developmental Programs. Iain B. McInnes[1], Kim Papp[2], Lluis Puig[3], Kristian Reich[4], Christopher T. Ritchlin[5], Bruce Strober[6], Proton Rahman[7], Arthur Kavanaugh[8], Alan M. Mendelsohn[9], Michael Song[9], Daphne Chan[9], Yaung-Kaung Shen[9], Shu Li[9] and Alice B. Gottlieb[10]. [1]University of Glasgow, Glasgow, United Kingdom, [2]Probity Research, Waterloo, ON, [3]Universitat Autònoma de Barcelona, Barcelona, Spain, [4]Dermatologikum Hamburg, Hamburg, Germany, [5]University of Rochester, Rochester, NY, [6]University of Connecticut, Farmington, CT, [7]Memorial University, St. Johns, NF, [8]University of California, San Diego, La Jolla, CA, [9]Janssen Research & Development, LLC., Spring House, PA, [10]Tufts Medical Center, Boston, MA.

Background/Purpose: To describe the short-term safety experience of UST during the double-blind, PBO-controlled portion of the PsA & PsO clinical developmental programs.

Methods: Safety data for the PsA population were pooled from a Ph2 (n=146) & 2 Ph3 (PSUMMIT I [n=615], PSUMMIT II [n=312]) studies of UST in pts with active PsA. Safety data for the PsO population were pooled from 1 Ph2 (n=320) & 2 Ph3 (PHOENIX 1 [n=766] & PHOENIX 2 [n=1230]) studies of UST in pts with moderate-to-severe PsO, including a sub-grp of pts with documented PsA (history of or current) at baseline (BL) [n=628]. Pts were randomized to PBO, UST45mg, or UST90mg. The PBO-controlled period was 16wks for all PsA studies, 20wks for the Ph2 PsO study, & 12wks for Ph3 PsO studies. Concomitant therapy(i.e. stable doses of MTX/oral corticosteroids/NSAIDs) were permitted in PsA studies; no concurrent therapies for PsO/PsA were permitted in the PsO studies. Event rates for overall safety endpoints (overall AEs, infections, AEs leading to discontinuation, serious AEs [SAEs]) & AEs of interest (serious infections, nonmelanoma skin cancer

[NMSC], other malignancies, major adverse CV events [MACE]) were analyzed & compared between the PBO & UST grps within each population. Data for the UST dose grps were analyzed & presented as a combined grp. All pts who received ≥1 dose of tx were included in the analyses. Results were reported as number of events per 100 pt-yrs of follow-up (PY).

Results: 1071 treated pts (379 PBO, 692 UST) were included in the PsA population & 2314 treated pts (732 PBO, 1582 UST) were included in the PsO population (including 207 PBO, 421 UST in PsA sub-grp). BL demographics & medical history were generally comparable between the PsA & PsO populations with similar proportions of pts reporting relevant comorbidities, including diabetes, hyperlipidemia, hypertension & family history of coronary heart disease. In the PsA population, median duration of PsA at BL was ≥4 yrs & >75% had PsO with ≥3% BSA skin involvement. In the PsO population, median BSA involvement was 21%; median PASI score was 17 & 27% had PsA. Safety outcomes observed during the PBO-controlled period are detailed (Table). Within each population, rates of overall AEs, infections, & SAEs in pts receiving PBO or UST were generally comparable. Slightly higher rates of AEs leading to discontinuation were observed across all PBO grps & a slightly higher rate of SAEs was observed in the PBO grp in the PsA population. Event rates of AEs of interest were generally comparable, with overlapping confidence intervals, between the PBO & UST grps within the PsA & PsO populations.

Table. Overall safety during the PBO-controlled period of the PsA and PsO studies (Events per 100 PY)

	PSA studies		PSA sub-grp from PSO studies		All pts from PSO studies	
	PBO	UST	PBO	UST	PBO	UST
Treated pts (n)	379	692	207	421	732	1582
PY of follow-up	110	209	49	106	177	407
AEs	348.07	375.83	476.42	481.32	413.24	502.91
Overall infections	110.59	100.06	139.89	142.79	142.79	141.16
AEs leading to d/c	13.79	3.85	12.37	5.71	9.74	5.95
SAEs	12.69	5.75	4.05	6.62	6.78	7.62

AE of interests during the PBO-controlled period of the PsA and PsO studies (Events per 100 PY [95% CI])*

	PSA Studies		All Pts from PSO studies	
	PBO	UST	PBO	UST
Treated pts (n)	379	692	732	1582
PY of follow-up	110	209	177	407
Serious Infections	0.91 (0.02, 5.05)	0.00 (0.00, 1.43)	1.70 (0.35, 4.96)	1.23 (0.40, 2.87)
NMSC	0.00 (0.00, 2.72)	0.48 (0.01,2.67)	1.13 (0.14, 4.09)	0.74 (0.15, 2.16)
Other malignancies	0.00 (0.00, 2.72)	0.00 (0.00,1.43)	0.57 (0.01, 3.15)	0.25 (0.01, 1.37)
MACE	0.91 (0.02, 5.05)	0.00 (0.00, 1.43)	0.00 (0.00, 1.69)	1.23 (0.40, 2.87)

*Event rates for AEs of interest for the PsA sub-grp of the PsO studies are not presented separately due to low number of events observed.

Conclusion: During the PBO-controlled portion of the studies, UST was well-tolerated in pts with PsA & PsO. Overall safety observations were consistent between both populations, & safety event rates were generally comparable between pts receiving PBO & UST within each population.

Disclosure: I. B. McInnes, Novartis, Janssen Research & Development, LLC., 8, UCB, 9; **K. Papp**, Janssen, Amgen, Celgene Eli Lilly, Novartis, Pfizer, 5; **L. Puig**, Abbvie, Amgen, Janssen, Lilly, Novartis, Pfizer,VBL, 2, Celgene, Abbvie, Janssen, Novartis, MSO, Pfizer, Leo Pharma, 5; **K. Reich**, Abbvie, Amgen, Biogen-Idec, Celgene, Covagen, Forward Pharma, GSK, Janssen, Janssen-Cilag, Leo, Lilly, Medac, MSD, Novartis, Pfizer, Vertex, Takeda, 9; **C. T. Ritchlin**, Amgen, Janssen, UCB, Abbott (AbbVie), Regeneron, 5, Amgen, Janssen, UCB, 2; **B. Strober**, AbbVie, Amgen, Lilly, Merck, 9, Amgen, AbbVie,Celgene, Johnson & Johnson, Pfizer, Forward, Maruho, Medac, 5; **P. Rahman**, Amgen, Abbott, BMS, Merck, Pfizer, Janssen, Hoffman-La Roche, UCB, Novartis, Sanofi-Aventis, 5, Amgen, Abbott, BMS, Merck, Pfizer, Janssen, Hoffman-La Roche, UCB, Novartis, Sanofi-Aventis, 9; **A. Kavanaugh**, Janssen Research & Development, LLC., 9; **A. M. Mendelsohn**, Janssen Research & Development, LLC., 3; **M. Song**, Janssen Research & Development, LLC., 3; **D. Chan**, Janssen Research & Development, LLC., 3; **Y. K. Shen**, Janssen Research & Development, LLC., 3; **S. Li**, Janssen Research & Development, LLC., 3; **A. B. Gottlieb**, Janssen, Amgen, Abbott (Abbvie), Novartis, Celgene, Pfizer, Lilly, Coronado, Levia, 2, Astellas, Janssen, Celgene Corp., Bristol Myers Squibb Co., Beiersdorf, Inc., Abbott Labs. (Abbvie), TEVA, Actelion, UCB, Novo Nordisk, Novartis, Dermipsor Ltd., Incyte, Pfizer, Canfite, Lilly, Coronado, Vertex, Karyopharm, CSL Behring Biotherapies for Li, 5.

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Long-Term Safety Of Ustekinumab: 5 Years Of Follow-Up From The Psoriasis Clinical Development Program Including Patients With Psoriatic Arthritis. Kim Papp[1], Christopher E.M Griffiths[2], Kenneth B. Gordon[3], Mark Lebwohl[4], Philippe O. Szapary[5], Yasmine Wasfi[5], Daphne Chan[5], Yaung-Kaung Shen[5], Vincent Ho[6], Pierre-Dominique Ghislain[7], Bruce Strober[8] and Kristian Reich[9]. [1]Probity Research, Waterloo, ON, [2]Dermatology Centre, University of Manchester, Manchester Academic Health Science Centre, Salford Royal NHS Foundation Trust, Manchester, United Kingdom, [3]Northwestern University, Chicago, IL, [4]Mount Sinai Medical Center, New York, NY, [5]Janssen Research & Development, LLC., Spring House, PA, [6]University of British Columbia, Vancouver, BC, [7]7. Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium, [8]University of Connecticut, Farmington, CT, [9]Dermatologikum Hamburg, Hamburg, Germany.

Background/Purpose: Ustekinumab(UST) is approved for moderate-to-severe psoriasis (PsO), and is currently in Phase 3 development for psoriatic arthritis (PsA). We report the long-term safety experience of UST in the sub-group of PsO patients with a medical history of PsA (PsA Sub-group) compared with the overall PsO population (Overall Population) from the PsO development program with up to 5yrs of treatment and follow-up.

Methods: Pooled safety data across one Phase 2 and three Phase 3 [PHOENIX 1, PHOENIX 2, ACCEPT] clinical trials in pts with moderate-to-severe PsO were analyzed. Pts received UST 45mg or 90mg SC 12wkly through up to 5yrs. The presence or absence of PsA (history of or current) at baseline was reported. No concurrent treatment for PsO or PsA was permitted throughout the studies, except for low potency topical steroids for PsO during the open-label long-term extensions of PHOENIX 1 and 2. Event rates for overall safety endpoints (adverse events [AEs], infections, AEs leading to discontinuation, serious AEs [SAEs]) and AEs of interest (serious infections, nonmelanoma skin cancers [NMSC], other malignancies, major adverse CV events [MACE]) were analyzed. All patients who received ≥1 dose of UST were included in the analyses. Data from the two UST dose groups were analyzed as a combined group. Results are expressed in events per 100 pt-years of follow-up (PY) and compared between the PsA Sub-group and Overall Population.

Results: The Overall Population included 3117 pts (8998 PY) who received ≥1 dose of UST; with 1482 (47.5%) pts treated for ≥4yrs or more (including 838 [26.9%] for ≥5yrs). At baseline, the majority of pts were white (92.2%), male (68.5%), median age of 46yrs. Mean BSA involvement was 26.2%±16.7 and mean PASI score was 19.7±7.7; 27.5% of pts had concomitant PsA. Safety results for the PsA Sub-group and Overall Population are detailed in Table 1. Through Yr5, event rates for overall safety endpoints and AEs of interest were generally comparable between the groups.

Safety Through up to 5yrs Follow-up (Events per 100 pt-yrs of follow-up)

	PSA Sub-group	Overall Population
Treated pts(n)/Pt-yrs of follow-up	858/2490	3117/8998
Overall Safety:		
AEs	249.40 (243.23, 255.68)	232.59 (229.44, 235.76)
Infections	91.49 (87.77, 95.32)	86.52 (84.61, 88.47)
AEs leading to d/c	2.77 (2.16, 3.51)	2.40 (2.09, 2.74)
Serious AE	8.59 (7.48, 9.83)	7.10 (6.56, 7.67)
AEs of Interests:		
Serious infxns	1.53 (1.08, 2.09)	1.10 (0.89, 1.34)
NMSC/Other malignancies	0.48 (0.25, 0.84)/ 0.72(0.43, 1.15)	0.52 (0.39, 0.70)/ 0.60 (0.45, 0.78)
MACE	0.56 (0.31, 0.94)	0.44 (0.32, 0.61)

Conclusion: With continuous UST exposure for up to 5yrs and approximately 9000 patient-years of follow-up in the PsO development program, long-term safety in the Overall Population were consistent with previous reports at earlier follow-up and event rates were generally comparable to other currently approved biologic agents. Long-term safety in the sub-group of PsO patients with a history of PsA at baseline were generally comparable to those in the overall study population.

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Certain Class I HLA Alleles and Haplotypes Have Important Positive and Negative Associations With Psoriatic Arthritis Phenotype. Muhammad Haroon[1], Robert Winchester[2], Jon T. Giles[3] and Oliver FitzGerald[1]. [1]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [2]Columbia University, New York, NY, [3]Columbia University, College of Physicians & Surgeons, New York, NY.

Background/Purpose: Psoriatic arthritis (PsA) is strongly associated with the inheritance of several different class I alleles, suggesting separate patterns of MHC effect result in PsA. The present study was based on the hypothesis that the genetic heterogeneity also contributes to the clinical heterogeneity of PsA, and that severity of clinical features of disease may be associated to different HLA alleles or haplotypes.

Methods: A cohort of 282 PsA patients was studied. Following informed consent, HLA-B and HLA-C genotypes were determined. Patients underwent a detailed skin and rheumatologic assessments, and an extensive medical record review was performed to obtain information regarding their psoriatic disease features. We ranked PsA patients according to the number of PsA features present (enthesitis, dactylitis, sacroiliitis, joint deformity, joint fusion, erosion, and osteolysis) using a propensity score model, where the PsA patient with the smallest aggregate of these features was assigned the lowest score, and those with highest aggregate assigned the highest score.

Results: The studied cohort had following demographics and clinical characteristics: mean age 54.6±12 years; 52% female; mean PsA duration=19±9 years; 25% with sacroiliitis; 43.5% with peripheral joint erosions**.** Enthesitis was very strongly associated with the inheritance of HLA-B*270502 (OR 2.951, p=<0.0018), HLA-C*010201 (OR 3.53, p=<0.0018) and their shared haplotype B*270502.C*010201 (OR 3.71, p=<0.0018). Similarly, HLA-C*020202 was significantly associated with the presence of radiographic osteolysis (OR 3.07, p=<0.0018). Interestingly, we found relatively strong negative association of HLA-B*440301 with enthesitis, dactylitis, joint deformities and joint fusions (p=<0.05). Based on the composite severity propensity score the cohort was divided into tertiles (mild, moderate, severe). The more severe PsA phenotype was characterized by B*0801 (OR 2.42, p=0.001), C*020202 (OR 10.94, p=0.005), C*070101 (OR 2.27, p=0.002), B*0801-C*0701 (OR 2.35, p=0.002), and B*270502-C*020202 (OR 9.78, p=0.010). In contrast, B*44020101 (OR 0.35, p=0.008), any B*44 allele (OR 0.34, p=0.001) and B*44020101-C*05010101 (OR 0.36, p=0.01) were associated with milder disease.

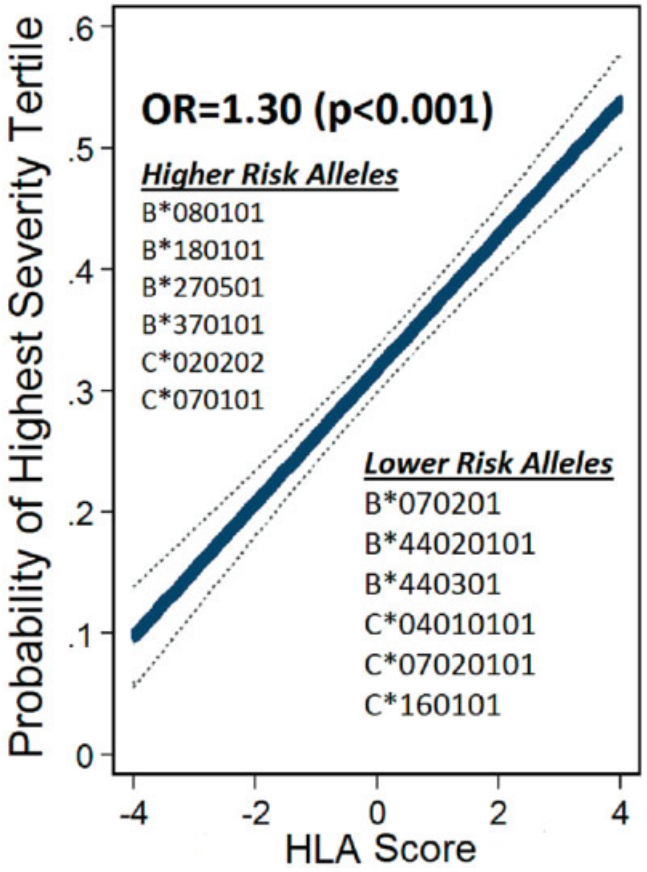

Figure. Each patient was assigned an HLA score based on their number of high and low risk alleles (from univariate modeling on the outcome of PsA Severity Propensity). A patient with 4 low risk alleles was assigned a score of -4, while one with 4 high risk alleles was assigned a score of +4. Each unit increase in the HLA score was associated with a 30% higher odds of being in the highest tertile of PsA Severity Propensity (p-value<0.001). The least squares estimator of the average probability (thick line) and 95% CI (dotted line) are depicted, with adjustment for age, current smoking, pack-years of smoking, duration of psoriasis and psoriatic arthritis, years between psoriasis and psoriatic arthritis, and TNF inhibitor use.

Conclusion: HLA genotype importantly influences the clinical phenotype, with certain alleles specifying a severe or milder disease phenotype, and that the phenotype is likely the result of cis and trans interactions of multiple individual alleles. Certain alleles, such as those of the HLA-B*0801-C*0701 haplotype, which were not strongly associated with PsA susceptibility, contributed much more importantly to disease severity.

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Reduction Of Disease Burden On Workplace and Household Productivity In Psoriatic Arthritis Over 48 Weeks Of Treatment With Certolizumab Pegol. Arthur Kavanaugh[1], Dafna Gladman[2], Désirée M. van der Heijde[3], Oana Purcaru[4] and Philip J. Mease[5]. [1]University of California San Diego, San Diego, CA, [2]University of Toronto, Toronto Western Hospital, Toronto, ON, [3]Leiden University Medical Center, Leiden, Netherlands, [4]UCB Pharma, Brussels, Belgium, [5]Swedish Medical Center and University of Washington, Seattle, WA.

Background/Purpose: Compared to the general population, patients (pts) with psoriatic arthritis (PsA) suffer greater amounts of disability and substantially lower employment rates.[1] To date there is limited data on the burden of work and household productivity among pts with PsA.[2] The results from the RAPID-PsA study indicate significant improvements in work and household productivity with certolizumab pegol (CZP) vs placebo (PBO) up to Week

(Wk) 24.[3] The purpose of this report is to estimate the economic burden of moderate to severe PsA on productivity and to examine the long-term effect of CZP on workplace and household productivity in RAPID-PsA up to Wk48.

Methods: The ongoing RAPID-PsA trial (NCT01087788) is double-blind and PBO-controlled to Wk24 and dose-blind to Wk48.[4] Pts had active PsA and had failed ≥1 DMARD. Pts originally randomized to CZP (200mg Q2W or 400mg Q4W, following 400mg loading dose at Wks 0, 2, 4) continued on their assigned dose in dose-blind phase; PBO pts entering dose-blind phase were re-randomized to CZP loading dose followed by CZP 200mg Q2W or CZP 400mg Q4W. The arthritis-specific Work Productivity Survey (WPS),[5] administered Q4W from baseline (BL), assessed the impact of PsA on workplace and household productivity in the randomized set (RS). Disease burden was evaluated at study BL. WPS responses (LOCF imputation) in both CZP groups are summarized descriptively over 48 wks.

Results: At BL, pts had a mean age of 48 years and 55% were female; 61.6% had psoriasis skin involvement ≥3% body surface area. 59.5% of pts were employed outside the home, 14.0% were work disabled due to PsA and 13.5% were retired at study BL. A high burden of PsA on workplace and household productivity was reported at study BL, with on average >1 wk of paid work affected (mean 6.7 days), ~2 wks of household duties (mean 13.3 days), and mean 3.7 days of social activities affected over previous month. In employed patients in both CZP groups, decreases in absenteeism and presenteeism reported to Wk24 were sustained up to Wk48 (Table). Additionally, the improvements in household productivity and increased participation in social activities reported in both CZP groups over 24 wks were maintained up to Wk48 (Table).

Table. Workplace and household productivity over 48 wks in the RAPID-PsA trial (RS population)

WPS responses, mean	CZP 200mg Q2W n = 138	CZP 400mg Q4W n = 135
Productivity at workplace (employed subjects)		
Work days missed due to arthritis per month [a]		
BL	2.0	1.6
Wk24	0.2	0.6
Wk48	0.1	0.6
Days with work productivity reduced by ≥50% due to arthritis per month [a,b]		
BL	5.2	5.1
Wk24	1.3	2.1
Wk48	0.8	1.9
Level of arthritis interference with work productivity (0–10 scale) [a,c]		
BL	4.4	3.8
Wk24	1.7	1.9
Wk48	1.2	1.8
Household productivity and social participation (all subjects)		
Household work days missed due to arthritis per month		
BL	5.9	5.5
Wk24	2.4	2.5
Wk48	2.0	2.7
Household work days with productivity reduced by ≥50% due to arthritis per month [b]		
BL	7.1	7.1
Wk24	2.9	3.5
Wk48	2.3	3.3
Level of arthritis interference with household productivity (0–10 scale) [c]		
BL	5.2	4.9
Wk24	2.2	2.6
Wk48	2.0	2.4
Days missed family/social/leisure activities due to arthritis per month		
BL	4.1	3.3
Wk24	1.1	1.0
Wk48	1.1	1.6

[a] Based only on employed pts at the specific visit; pts employed at BL (CZP 200 mg Q2W/ CZP 400mg Q4W): 83/83; [b] Does not include work days missed counted in the previous question; [c] 0–10 scale, 0 = no interference and 10 = complete interference.

Conclusion: PsA is associated with a high burden of disease on workplace and household productivity that could lead to large financial burden for pts and society. This analysis indicates that CZP improved workplace productivity in patients with PsA by reducing absenteeism and presenteeism and improved household productivity and increased participation in social and daily activities. The benefits of CZP were maintained up to Wk48.

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Major Differences In The Pattern Of Joint Swelling and Tenderness In a Large Psoriatic Arthritis Cohort – Results From An Exploratory Hierarchical Cluster Analysis. Burkhard Möller[1], Daniel Stekhoven[2] and Peter M. Villiger[3]. [1]Inselspital, Bern, Switzerland, [2]Swiss Clinical Quality Management in Rheumatic Diseases-SCQM Foundation, Zurich, Switzerland, [3]Inselspital-University Hospital of Bern, Bern, Switzerland.

Background/Purpose: Psoriatic arthritis (PsA) shows the largest complexity in joint involvement among all inflammatory types of arthritis. In order to improve feasibility and to reduce the number of joints to be evaluated for a global PsA disease activity assessment, we aimed to identify clusters of joint involvement in the Swiss Clinical quality management (SCQM) PsA cohort.

Methods: From inclusion visits of all 1256 patients with PsA diagnosis, manifestations in the 66 swollen/68 tender joint score were clustered according to their dissimilarities in profiles by an iterative algorithm, at each stage joining the two most similar joint profiles into one cluster. The distances between clusters were recomputed by the Lance-Williams dissimilarity update formula. Dendrograms of hierarchical clustering were performed separately on the swollen and tender joint data. Distances between clusters were reported by the number of patients with differences in their state of joint involvement.

Results: Among 1256 individuals diagnosed of PsA by board certified rheumatologists, 749 patients (60%) fulfilled the CASPAR classification criteria. Numbers [in brackets] are from CASPAR+ patients. Patients had mean age 50 [48] years, mean disease duration 5.8 [5.9] years (IQR 2–12 for both) and 48% [45%] female gender. Current skin involvement was moderate to severe in 21 [24] %, absent in 21 [14] %, and nail involvement reported in 29 [29] %. Skin involvement was reported in the patient's history in 92 [98] %, arthritis in 84 [92] %, enthesitis in 62 [65] %, dactylitis in 57 [74] %, spine involvement in 45 [44] %, and a positive family history in 38 [41] % of the cases. Treatment at inclusion were: NSAIDs 54 [57] %, synthetic DMARDs 61 [65] % or biologics 50 [52] %. Mean SJC was 2;IQR 0–6 [3;IQR 0–7], and mean TJC 4; IQR 0–10 [5; IQR 1–11]. Favourable clustering and symmetry in 9 out of ten clusters was obtained only for tender joints. The level of agreement was likewise the highest for symmetric involvement of wrist and knee joints in all and in CASPAR+ patients. Other clusters, symmetric involvement of PIP 2–5, MCP 1, MCP 2–5 [−3], MTP 1–5, shoulder joints, ankle joints, IP 1 + DIP 2–3 [−5], and a very complex pattern in the 10th cluster were the same, but varied in sequence of agreement between analyses in all or only in CASPAR+ patients. In contrast, the cluster resolution for swollen joints was far from satisfying even when applying the Ward's method, which minimizes the increase of within-cluster variance in each merging step. With exception of the wrist, knee and ankle joint clusters, all other obtained SJ clusters differed substantially from TJ clusters. An oligoarticular pattern according to Moll & Wright was seen in 42% and polyarticular in 16%. In contrast to highly prevalent dactylitis, predominant DIP involvement was seen in only 3% of cases.

Conclusion: Swollen and tender joint patterns in PsA are hardly in agreement. The enormous complexity in type and pattern of joint involvement may limit the definition of joint involvement only on basis of clinical data. With regard to the many cases with oligoarticular disease, it appears that no joint from the 66/68 joint count should be omitted for a meaningful joint count based PsA disease activity assessment.

Disclosure: B. Möller, None; **D. Stekhoven**, None; **P. M. Villiger**, None.

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Clinical Characteristics Of Patients Who Switch Biologic Therapy Within The First Two Years: Results From a Large US Registry Population. Philip J. Mease[1], Emily Edson-Heredia[2], Katherine C. Saunders[3], Catherine L. Shuler[2], Baojin Zhu[2], Monica Chaudhari[4] and Jeffrey D. Greenberg[5]. [1]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA, [2]Eli Lilly and Company, Indianapolis, IN, [3]CORRONA, Inc., Southborough, MA, [4]Axio Research LLC, Seattle, WA, [5]New York Hospital for Joint Diseases, New York, NY.

Background/Purpose: The use of biologic therapy in psoriatic arthritis (PsA) has altered the disease course and has been shown to reduce disease activity. Data comparing the clinical characteristics of PsA patients and their biologic therapy switching patterns are sparse. We sought to compare baseline characteristics at biologic initiation between patients who go on to switch biologic therapy and those who do not switch in the setting of a real-world US registry population.

Methods: Patients with a current diagnosis of PsA in the CORRONA registry, a large observational registry population in the US, who initiated a biologic were followed for two years to identify whether or not they switched to second biologic. We did not restrict this analysis to patients who were biologic-naïve at initiation. We defined non-switchers as those who either continued to use initial biologic for the entire follow-up period, or discontinued their initial biologic but did not add a second biologic. Measures of disease activity including MD and patient global assessment of disease, tender and swollen joint counts, CDAI, presence of enthesitis or dactylitis, and MD and patient global assessment of skin were evaluated at initiation and at the end of the observation period. P-values comparing non-switchers to switchers were calculated using the Mann-Whitney-Wilcoxon test to account for skewed distribution of disease activity measures.

Results: In this population, mean age at PsA onset was 42.4 years: 42.6 for non-switchers and 41.2 for switchers. Median duration of PsA was 6 years: 7 for non-switchers, and 5 for switchers. 54.6% were bio-experienced (53.7% for non-switchers and 58.3% for switchers) and the majority of the population (79.7%) did not switch to another drug (Non-switchers were 451 vs 115 switchers). Switchers had significantly higher mean MD and patient assessment of disease activity, higher mean tender and swollen joint counts, higher mean CDAI and Physician assessment of skin. Patient assessment of skin (23.7 versus 24.9) was not found to be statistically different.

Table 1. Comparison of Non-Switchers and Switchers

	Non-Switchers N=451 Mean (SD)	Switchers N=115 Mean (SD)	P-value
Physician Global Assessment	17.6 (16.6)	26.1 (20.8)	<.001
Patient Global Assessment	29.2 (24.0)	41.0 (26.8)	<.001
Tender Joint Count	2.7 (4.8)	5.3 (6.9)	<.001
Swollen Joint Count	2.6 (4.3)	4.1 (5.6)	0.002
CDAI	10.0 (9.6)	16.3 (13.1)	<.001
Physician Assessment of Skin	28.0 (30.8)	37.3 (27.6)	0.006

Conclusion: At initiation, patients who go on to switch biologic therapy had worse disease activity compared to those who did not switch. Rheumatologists appear to switch biologics based on their assessment of both arthritis and skin related disease activity.

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Health-Related Quality Of Life In Early Psoriatic Arthritis In Comparison With Early Rheumatoid Arthritis. A 5-Year Follow-Up Report From The Swedish Early Psoriatic Arthritis Registry and The Swedish Early Intervention In RA Registry. Lars Törnqvist[1], Tomas Husmark[2], Ulla R. C. Lindqvist[3], Gerd-Marie Alenius[4], Per Larsson[5], Annika Teleman[6], Mats Geijer[7], Lars Erik Kristensen[8], Ingrid Thyberg[9] and Elke Theander[10]. [1]Skåne University Hospital Malmö, Lund University, Sweden, Malmö, Sweden, [2]Department of Rheumatology, Falu Hospital, Falun, Sweden, [3]Department of Medical Sciences, Rheumatology, University Hospital, Uppsala university, Uppsala, Sweden, [4]Department of Public Health and Clinical Medicine, Rheumatology, Umeå University, Umeå, Sweden, [5]Karolinska University Hospital, Stockholm, Sweden, [6]Department of Rheumatology, Spenshult Hospital, Oskarstrom, Sweden, [7]Skåne University Hospital, Lund, Center for Medical Imaging and Physiology, Lund, Sweden, [8]Skåen University Hospital, Lund University, Lund, Sweden, [9]Linköping University Hospital, Linkoping, Sweden, [10]Lund University, Malmö, Sweden.

Background/Purpose: Studies on early psoriatic arthritis (ePsA) are still rare and data on health related quality of life (HRQoL) in ePsA are lacking completely. To assess the degree of HRQoL reduction compared to the background population in ePsA at diagnosis and during the first 5 years of follow-up in patients exposed to Swedish standard of care. To compare HRQoL in ePsA and early RA (eRA) and analyze associations and predictors at baseline.

Methods: Patients included in the Swedish early psoriatic arthritis (SwePsA) and the Swedish early Intervention in RA (TIRA 2) registries having available SF 36 assessments at baseline and 5-year follow-up, were included. Differences from expected levels were calculated for each individual patient and used for the analysis, thus making further age and gender adjustment unnecessary. Measures of physical function (HAQ), disease activity (DAS-28), delay before diagnosis, smoking (only in PsA), pain and general well-being (VAS) were used as explanatory variables. Adequate T-tests as well as uni-and multivariate linear regression analysis were performed.

Results: Both RA (n= 133, 73% women) and PsA (n=166, 52% women) patients displayed a profound statistically significant reduction of HRQoL when being diagnosed with their chronic joint disease. In general the degree of impairment at baseline was similar. However, after 5 years the eRA group had almost normalized their HRQoL, while the ePsA patients still suffered from significant decrease in several SF-36 domains. Figure. A comparison of baseline variables between RA and ePsA revealed longer symptom duration before diagnosis in PsA, a factor independently contributing to hampered improvement during follow-up. Disease activity measured as DAS-28 (and its components) and physical dysfunction measured as HAQ were more severe in TIRA 2-RA patients, possibly motivating early aggressive intervention. In ePsA high disease activity and impaired function at inclusion were associated with worse outcome. In ePsA also current smoking status contributed independently to persistent impairment of HRQoL.

Conclusion: Both newly diagnosed RA and PsA are characterized by profoundly reduced HRQoL. Normalization is seen in RA during the early phase of the disease, but not in ePsA, despite more severe disease in RA at inclusion. This paradox finding may be due to aggressive intervention provoked by the disease severity in RA and longer diagnostic delay in ePsA. Smoking contributed to HRQoL reduction in ePsA, no data were available for the RA group. Earlier detection, lifestyle intervention and more ambitious management strategies similar to those in RA may be needed for ePsA care.

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Proteomic Profiling Of Synovial Fluid For The Identification Of Psoriatic Arthritis Soluble Biomarkers. Daniela Cretu[1], Fawnda Pellett[2], Rajiv Gandhi[3], Eleftherios Diamandis[4] and Vinod Chandran[2]. [1]University of Toronto, Department of Laboratory Medicine and Pathobiology, Toronto, ON, [2]University of Toronto, Toronto Western Hospital, Toronto, ON, [3]University Health Network, Arthritis Program, Toronto, ON, [4]Mount Sinai Hospital, Department of Pathology and Lab Medicine, Toronto, ON.

Background/Purpose: There is a high prevalence of undiagnosed psoriatic arthritis (PsA) in patients seen in dermatology clinics. Identifying soluble biomarkers for PsA will help in screening psoriasis patients for appropriate

referral to a rheumatologist as well as provide further insight into disease pathogenesis. However, identification of novel protein biomarkers in peripheral blood is difficult and unreliable. Potential PsA biomarkers are likely to originate in sites of inflammation such as inflamed joints and subsequently enter systemic circulation. We hypothesize that quantitative proteomic analysis of synovial fluid (SF) obtained from PsA patients, will generate a comprehensive list of proteins specific to PsA, facilitating the identification of potential PsA screening biomarkers.

Methods: SF was obtained from swollen knee joints of PsA patients, and age/sex matched early osteoarthritis (OA) controls. Using strong cation exchange chromatography, followed by liquid chromatography and tandem mass spectroscopy, we extensively characterized the proteomes of pooled SF from ten PsA and ten controls. Extracted ion current (XIC) intensities were used to calculate protein abundance ratios, and were utilized to identify upregulated proteins (PsA/OA ratio>2). Selected reaction monitoring (SRM) assays were developed to relatively quantify potential markers in individual SF samples.

Results: We identified and quantified 443 proteins from both groups (False Discovery Rate <0.05). Only 45 proteins represented upregulated proteins in PsA SF ($p<0.05$). These were investigated using two publicly available databases (Ingenuity Pathway Analysis and DAVID Bioinformatics Resources 6.7) to identify disease relevant proteins. Gene ontology (GO) analysis classified these proteins into categories pertaining to five main biological processes: complement activation, defense response, immunoglobulin mediated response, response to wounding, and extracellular matrix remodeling, all of which are attributes of PsA. Application of subsequent filtering criteria yielded approximately 17 proteins, which served as putative PsA biomarkers. SRM validation confirmed that 13 proteins were indeed elevated in the 10 PsA SF samples, and these included positive controls, MMP3, S100A9, and CRP.

Conclusion: We have developed and utilized a high-throughput proteomics platform using LC-MS/MS to delineate the SF proteome from PsA patients and controls with early OA. Proteins that were differentially expressed were validated using targeted mass-spectrometric assays. Using these methods we have identified several candidate PsA biomarkers. In the future, these proteins must be verified using highly specific immunoassays in serum, in order to identify their clinical utility.

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Apremilast, An Oral Phosphodiesterase 4 Inhibitor, Is Associated With Long-Term (52-Week) Improvement In Physical Function In Patients With Psoriatic Arthritis: Results From Three Phase 3, Randomized, Controlled Trials. Georg Schett[1], Philip J. Mease[2], Dafna D. Gladman[3], Arthur Kavanaugh[4], Adewale O. Adebajo[5], Juan J. Gomez-Reino[6], Jürgen Wollenhaupt[7], Maurizio Cutolo[8], Eric Lespessailles[9], Kamal Shah[10], ChiaChi Hu[10], Randall M. Stevens[10], Christopher J. Edwards[11] and Charles A. Birbara[12]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA, [3]University of Toronto, Toronto Western Hospital, Toronto, ON, [4]University of California San Diego, San Diego, CA, [5]University of Sheffield, Sheffield, United Kingdom, [6]Hospital Clinico Universitario, Santiago, Spain, [7]Schön Klinik Hamburg Eilbek, Hamburg, Germany, [8]University of Genova, Genova, Italy, [9]University of Orléans, Orléans, France, [10]Celgene Corporation, Warren, NJ, [11]University of Southampton, Southampton, United Kingdom, [12]University of Massachusetts Medical School, Worcester, MA.

Background/Purpose: Apremilast (APR), an oral phosphodiesterase 4 inhibitor, works intracellularly to modulate pro- and anti-inflammatory mediators. The PALACE 1, 2, and 3 trials compared the efficacy and safety of APR with placebo (PBO) in pts with active PsA despite prior DMARDs and/or biologics.

Methods: Pts were randomized 1:1:1 to PBO, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline (BL) DMARD use. At wk 16, pts with <20% reduction from BL in swollen and tender joint counts qualified for protocol-defined early escape; those on PBO were re-randomized to APR20 or APR30 and those on APR remained on the initial APR dose. At wk 24, all remaining PBO pts were re-randomized to APR20 or APR30 through wk 52. Patients taking concurrent DMARDs were allowed to continue stable doses (MTX, sulfasalazine, leflunomide, or a combination).

Results: APR administration resulted in statistically significant and clinically meaningful improvement in ACR20 response (primary endpoint) in all 3 PALACE trials. APR30 was associated with significant improvements in Health Assessment Questionnaire-Disability Index (HAQ-DI) ($P\leq0.03$) and SF-36 Physical Functioning (PF) domain ($P\leq0.05$) vs PBO at wk 24 across all 3 trials. For those pts originally randomized to APR and completing 52 wks of study, improvements were maintained or increased over 52 wks (Table). At wk 52, mean changes in HAQ-DI were −0.369 (APR20) and −0.318 (APR30) in PALACE 1; −0.192 (APR20) and −0.330 (APR30) in PALACE 2; and −0.332 (APR20) and −0.350 (APR30) in PALACE 3. Mean changes from BL exceeded minimal clinically important differences (MCID) thresholds‡ of ≥0.13 or ≥0.3 in pts treated with APR20 and APR30 for 52 wks, and the proportion of APR20 and APR30 pts achieving MCID was maintained between wks 24 and 52. Mean changes in SF-36 PF were 6.98 (APR20) and 5.69 (APR30) in PALACE 1; 4.05 (APR20) and 4.97 (APR30) in PALACE 2; and 5.68 (APR20) and 5.87 (APR30) in PALACE 3. Mean changes from BL exceeded MCID of ≥2.5 in pts treated with APR20 and APR30 for 52 wks, and the proportion of APR20 and APR30 pts achieving MCID was maintained between wks 24 and 52. Pts randomized to APR at wks 16 and 24 demonstrated results consistent with those originally randomized to APR. No new safety findings were identified and the incidence of pts experiencing any AE was comparable over the 0–24 and 0–52 wk periods.

PALACE 1, 2, and 3: Improvements in Physical Function at Week 52 in Patients Receiving APR From Baseline

	PALACE 1		PALACE 2		PALACE 3	
	APR20 (n = 168)	APR30 (n = 168)	APR20 (n = 163)	APR30 (n = 162)	APR 20 (n = 169)	APR30 (n = 167)
Baseline, Mean						
HAQ-DI (0–3)	1.156	1.249	1.133	1.220	1.118	1.184
SF-36 PF	35.13	33.02	34.54	33.67	34.88	34.17
SF-36 PCS	35.02	33.82	34.64	33.26	35.35	34.32
Mean Change From Baseline						
HAQ-DI (0–3)*	−0.369	−0.318	−0.192	−0.330	−0.332	−0.350
SF-36 PF§	6.98	5.69	4.05	4.97	5.68	5.87
SF-36 PCS§	7.81	6.45	5.05	6.35	6.29	5.91
Patients Achieving MCID, %						
HAQ-DI ≥0.13[1]	60.0	59.8	48.0	58.1	61.5	58.3
HAQ-DI ≥0.3[2]	45.8	44.7	36.8	47.0	45.1	52.0
SF-36 PF ≥2.5	64.2	60.0	51.6	53.9	61.2	58.3
SF-36 PCS ≥2.5	71.7	66.2	66.1	69.6	72.7	68.3

The n reflects randomized patients; actual number of patients available for each endpoint may vary.
*Decrease in score indicates improvement.
§Increase in score indicates improvement.
‡Pre-specified thresholds based on literature at time of protocol and analysis.
1. Kwok T, et al. *J Rheumatol.* 2010;37:1024–1028.
2. Mease PJ, et al. *Ann Rheum Dis.* 2004;63(Suppl 1). Abstract #SAT0015.

Conclusion: Over 52 wks, APR continued to demonstrate meaningful clinical response in PsA pts, including measures of physical function. APR demonstrated an acceptable safety profile and was generally well tolerated for up to 52 wks.

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Risk Of Cardiovascular Disease Among Patients With Psoriatic Arthritis Compared To Ankylosing Spondylitis (retrospective cohort study). Zohair Abbas[1] and Marina N. Magrey[2]. [1]Case Western Reserve University at Metrohealth Medical Center, Cleveland, OH, [2]Case Western Reserve University School of Medicine at MetroHealth Medical Center, Cleveland, OH.

Background/Purpose: Both patients with psoriatic arthritis (PsA) and ankylosing spondylitis (AS) are at increased risk of cardiovascular disease (CVD). This increased risk is in part attributed to traditional cardiovascular risk factors. Patients with PsA have higher body mass index (BMI) compared to patients with AS. Based on this we hypothesized that patients with PsA are at higher risk of CVD compared to patients with AS. The purpose of the study is to compare the risk of CVD in patients with PsA to patients with AS.

Methods: Explorys is a clinical research informatics tool that uses unified medical language system ontologies to standardize, normalize and aggregate clinical data from multiple electronic heath records. The data are de-identified and presented through a secure web interface usable by researchers. At the time of this study several million patients from multiple distinct healthcare systems from year 1999 to 2012 were present in the Explorys database. Using the SNOMED hierarchy, we searched for all patients with a diagnosis of either PsA or AS using the terms "ankylosing spondylitis" and "psoriasis with arthropathy." This was further stratified by adding search term "anti tumor necrosis factor alpha drug", and only patients using anti TNF therapy were included in the analysis. Using the first Body mass index (BMI) recorded; we categorized patients into one of three categories: < 25 kg/m2 (normal weight); 25 kg/m2 to < 30 kg/m2 (overweight); and ≥ 30 kg/m2 (obese). Presence of CVD was defined by the occurrence of myocardial infarction (MI), cerebrovascular disease or peripheral vascular disease (PVD). The occurrence of CV events was searched in a temporal sequence. The comparison between the 2 cohorts was made using Fishers exact test.

Results: We identified 2360 cases of PsA and 1020 cases of AS from the database. Demographics are shown in the table 1. 52.5% patients with PsA had a BMI of more than 30 as compared to 37.8% patients with AS ($p=0.0001$). A total cholesterol > 200 was found in 41.9% patients with PsA compared to 36.6% with AS ($p=0.11$). HDL < 40 was found in 34.2% patients with PsA compared to 31% patients with AS ($p=0.34$).There was no significant difference between the PsA and AS cohorts in terms of prevalence of MI 2.1% vs 1.9% ($p= 0.79$), cerebrovascular disease 4.2% vs 2.9% (p-value 0.79) and PVD 5.9% vs 5.8% ($p=0.93$) respectively as shown in table 2.

Table 1.

		AS n=1020 (%)	PsA n=2360 (%)
Age			
	25–50	520 (50)	850 (36)
	50–65	350 (34)	1030 (43)
	>65	100 (10)	380 (16)
Gender			
	Male	673 (66)	1133 (48)
	Female	347 (34)	1227 (52)
Race			
	Caucasian	790 (77)	1900 (80)
	African American	80 (8)	80 (3)
	Asian		20 (1)

Table 2.

		AS (%)	PsA (%)	P value
BMI				
	<19.9	30/660* (4.5)	40/1580* (2.5)	0.016
	20–24.9	150/660 (22.7)	230/1580 (14.5)	0.0001
	25–29.9	230/660 (34.8)	480/1580 (30.3)	0.04
	>30	250/660 (37.8)	830/1580 (52.5)	0.0001
Metabolic Profile				
	Total Cholesterol (>200)	110/300 (36.6)	340/810 (41.9)	0.11
	HDL (<40)	90/290 (3)	260/760 (34.2)	0.34
	HbA1c (>7)	50/200	190/590	0.06
Cardiovascular Disease				
	MI	20/1020(1.9)	50/2360 (2.1)	0.79
	Cerebrovascular Disease	30/1020 (2.9)	100/2360 (4.2)	0.79
	PVD	60/1020 (5.8)	140/2360 (5.9)	0.93

Conclusion: Despite higher BMI in patients with PsA, the prevalence of acute MI, cerebrovascular disease and PVD was similar to patients with AS. The results did not support our hypothesis that increased BMI in PsA increases the risk of CVD. Hence, other risk factors need to be further investigated.

Disclosure: Z. Abbas, None; **M. N. Magrey**, None.

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Changes In Weight Associated With Tumour Necrosis Factor Inhibition In Psoriatic Arthritis. Barry J. Sheane, Arane Thavaneswaran, Dafna D. Gladman and Vinod Chandran. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with progressive joint damage and disability. In the last 15 years, tumour necrosis factor inhibitors (TNFi) have emerged as an effective treatment in reducing the incidence of joint damage.

It has been reported that TNFi are associated with weight gain in both psoriasis and PsA. If true, such an adverse effect could contribute to the increased prevalence of cardiovascular disease in PsA and its associated risk factors. In the general population, however, weight increases with age. Studies that have reported weight gain with TNFi in PsA have not accounted for this natural tendency.

In this study, the aim was to investigate whether therapy with TNFi is associated with weight gain in patients attending a large PsA clinic.

Methods: Patients were selected for inclusion in this study if they had at least 2 weight measurements prior to, and after, commencing TNFi. The relevant data were obtained from the clinic database where clinical, radiologic and laboratory data are collected prospectively on all patients satisfying the CASPAR classification criteria for PsA. Change point modelling, to model weight using a random effects analysis, was used to assess differences in weight over time using the mean of the slope before and after starting TNFi. The 'pre' and 'post' slopes were compared using a t-test. All 4 TNFi licensed for use in PsA were analysed as a single entity.

Results: One hundred seventy two patients were eligible for inclusion, of which 60% were male. At the first clinic visit, mean age was 41.7 ± 12.8 years, while mean disease duration was 6.6 ± 8.0 years. At the visit prior to initiation of TNFi, mean number of tender and/or swollen joints was 10.2 ± 10.9, while 115 patients had clinical evidence of joint damage (mean number of damaged joints: 12.9 ± 12.9). Of those taking disease modifying therapy at the time of TNFi initiation, 51% (n=87) were prescribed methotrexate, 9% (n=16) sulphasalazine and 13% (n=22) leflunomide. Mean weight for visits prior to TNF use (adjusting for repeated visits) is 83.5 ± 17.0 kg, while the mean weight after TNFi use was 84.9 ± 17.7 kg ($p=0.006$).

The means of the pre- and post-TNFi slopes were 0.26 ± 0.17 and 0.13 ± 0.13, respectively, which were not significantly different ($p=0.55$). This implies that there was no weight gain after commencement of TNFi therapy in this patient population.

Conclusion: TNF inhibitors do not cause an increase in weight in PsA, contradicting previous reports pertaining to weight gain. The statistical methods employed along with consideration of adults' natural propensity for weight gain with age may account for our findings.

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The Joint Effect Of Carotid Ultrasound and Preventive Cardiology Referral On Cardiovascular Risk Factor Modification in Psoriatic Arthritis Patients. Michael Lucke[1], Soo Hyun Kim[1] and M. Elaine Husni[2]. [1]Cleveland Clinic, Cleveland, OH, [2]Cleveland Clinic Foundation, Cleveland, OH.

Background/Purpose: Cardiovascular disease risk is elevated in psoriatic arthritis (PsA) compared to the general population. Prior studies have demonstrated suboptimal evaluation and control of modifiable cardiovascular risk factors in patients with inflammatory arthritis by both Rheumatologists and Primary Care providers. The presence of carotid plaque guides further risk stratification as it highly correlates with cardiovascular events. It is unclear if the addition of carotid plaque screening in PsA would alter medical management. This study investigates the value of screening asymptomatic PsA patients for carotid plaque on cardiovascular risk factor control.

Methods: 86 patients with PsA from the COMPASS database underwent carotid duplex ultrasound (CDU) and screened for the presence of plaque, which was defined using the Mannheim consensus criteria. Referral to preventive cardiology was automatically generated through the electronic health record upon study enrollment for all patients. Repeat US was performed at 12–24 months in 38 patients. Demographics, cardiovascular risk factors, PsA history and disease activity, and medication use were recorded. Fasting glucose, C-reactive protein, and lipid panels were assessed. Our institution has identified a primary prevention consensus algorithm regarding a minimal low density lipoprotein (LDL) goal of 100 mg/dL, initiation of antiplatlet therapy, and lifestyle counseling, as appropriate, in patients with PsA whom are deemed as high risk for cardiovascular disease.

Results: Carotid plaque was identified in 34 patients at baseline screening (39.5%). Of patients with baseline plaque, 18 had a repeat ultrasound within 12–24 months time and all had persistent plaque. Of patients without plaque at baseline, 15% (3/20) had new plaque formation on repeat ultrasound. Mean LDL was 120 and 102 mg/dL, mean HDL was 55 and 55, and mean triglycerides were 203 and 96 in the plaque and no plaque groups, respectively. Overall, 33% (12/36) of patients with repeat screening had an LDL under 100 and 27% (10/36) were on antiplatelet medication. Current statin use was 39% (7/18) by patients with plaque and none were on maximum doses. Despite automatic referral, only 12% (11/86) of patients were seen by Preventive Cardiology, and 14 other patients were seen by a cardiologist for other reasons.

Conclusion: Despite noninvasive screening and automatic referrals in a high risk population, few PsA patients completed consultations with the Preventive Cardiology service. Low utilization of preventive services was observed even in those patients with definitive evidence of atherosclerotic disease by identification of plaque. The percentage of patients with plaque is similar to other cohorts of PsA patients and is increased compared to the general population. A minority of patients met stated LDL goals and few were on antiplatelet therapy. Further characterization of lapses in the referral process is required to improve proactive modification of cardiovascular risk in PsA.

Disclosure: M. Lucke, None; **S. H. Kim**, GE Healthcare, 2, Philips Ultrasound, 5; **M. E. Husni**, National Psoriasis Foundation, 2, Arthritis National Research Foundation, 2.

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Comparing Adalimumab and Etanercept As First Line Agents In Patients With Psoriatic Arthritis. Data From The Rhumadata® Clinical Database and Registry. Sabrina Hoa[1], Denis Choquette[2], Louis Bessette[3], Diane Sauvageau[2], Boulos Haraoui[2], Jean Pierre Pelletier[2], Jean-Pierre Raynauld[2], Edith Villeneuve[2] and Louis Coupal[2]. [1]Centre hospitalier de l'université de Montréal (Hôpital Notre-Dame), Montréal, QC, [2]Institut de Rhumatologie de Montréal, Montreal, QC, [3]Centre Hospitalier Universitaire de Québec, pavillon CHUL, Sainte-Foy, QC.

Background/Purpose: No long term head-to-head comparative studies of anti-TNF agents in psoriatic arthritis have been published. Controversy exists over the selection of initial biologic therapy after DMARDs failure. We aim to assess if patients with psoriatic arthritis (PSO) treated with adalimumab or etanercept after failure to a first line agent (MTX-IR) have different drug survival rates. A secondary objective is to explore the role of MTX co-prescription.

Methods: PSO patients prescribed a first biologic agent after January 1st 2004 were included in the present analysis. The cohort use in the analysis includes patients prescribed either adalimumab (ADA) or etanercept (ETA) as a first biologic treatment. Baseline demographics for both cohorts included age, disease duration, HAQ-DI, fatigue and pain visual analog scale evaluation (VAS), TJC, SJC, DAS 28 ESR, SDAI and patient-years of treatment. Statistical analysis was performed using SAS version 9.3. RHUMADATA® is a clinical database and registry used daily in clinical practice at the IRM and the CORQ.

Results: A total of 134 patients were analysed and no significant differences in baseline characteristics were noted between treatment groups except for morning stiffness and disease duration. The 5 year retention rate of ADA and ETA were respectively 64% and 47% without a significant statistical difference (Log-Rank p=0.084). When combining biologics, the use of DMARDs did not improve drug survival over biologic monotherapy (52% for combination therapy vs. 67% for monotherapy, Log-Rank p=0.74).

Conclusion: In this analysis, adalimumab and etanercept after DMARDs failure have statistically similar 5-years retention rates. Adalimumab, however, demonstrated numerical superiority over etanercept for the entire follow-up period. More data will be required to confirm this observation. Combination with methotrexate did not demonstrate improved 5-year retention.

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Cluster Analysis Of Psoriatic Arthritis Patients At Follow-Up. Arane Thavaneswaran, Vinod Chandran and Dafna Gladman. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Our previous research showed that baseline characteristics would enable the sub-categorization of psoriatic arthritis (PsA) into the distinct phenotypic groups of axial and peripheral disease using cluster analysis (CA). We aimed to determine if demographic and disease characteristics of PsA patients with at least five years of follow-up can be clustered into distinct groups.

Methods: 527 PsA patients from an observational cohort of patients seen from 1978 to 2013. Patients had at least 5 years of follow-up and genetic information in order to be included in the analysis. CA using Ward's method was conducted to identify groups of patients based on the following characteristics at follow-up: gender, type of psoriasis (type I or II), duration of PsA, race, family history of psoriasis, ESR, severe PASI, psoriasis vulgaris, nail disease, dactylitis, swollen joint count, damaged joint count, axial disease, presence of arthritis mutilans, presence of arthritis prior to psoriasis, HLA-B*27 and HLA-C*06. 7 clusters were formed and matched to non-overlapping arthritis patterns: distal arthritis, oligoarthritis, polyarthritis, axial only, distal arthritis and axial, oligoarthritis & axial, and polyarthritis & axial. Comparisons between the clusters and arthritis patterns were conducted using t-tests and Chi-squared analysis.

Results: The baseline characteristics of the 527 patients were as follows: 306 (58.1%) males, mean age at diagnosis of PsA 28.3 (14.2) yrs, mean age at first visit 42.5 (12.3) yrs, mean duration of PsA 6.8 (8.0) years, mean active joint count 10.6 (9.2), mean PASI 5.2 (8.1), mean Steinbrocker score 12.7 (25.9), HLA-B*27 94 (18%)]. At follow-up, mean age was 57.6 (12.6) yrs, mean PASI 4.6 (6.6), mean Steinbrocker score 28.0 (37.3) with an average follow-up of 15.0 (7.6) yrs. Two main clusters of patients were identified. One consisted of distal arthritis, oligoarthritis and polyarthritis and the other of axial only, distal and axial, oligoarthritis & axial, and polyarthritis & axial, thus clearly identifying patients into peripheral and axial disease. Comparison of the two clusters showed more patients with psoriasis vulgaris among patients with peripheral disease. Patients falling into the axial disease cluster had a higher prevalence of males and HLA-B*27, higher PASI, more dactylitis, higher clinically damaged joint and swollen joint count, more axial disease, more arthritis mutilans and more patients who developed arthritis first.

Table. Comparison of two clusters

Variable	Frequency (%) or Mean (sd)		p-value
	Cluster I	Cluster II	
Age at diagnosis of Ps (>40 vs. ≤40)	63 (20.9%)	44 (19.5%)	0.68
Duration of PsA	21.3 (11.1)	22.5 (9.8)	0.16
Gender (Males)	149 (49.5%)	157 (69.5%)	<0.0001
Race (Caucasian vs. others)	267 (88.7%)	210 (92.9%)	0.10
Family history of Psoriasis	142 (47.7%)	116 (51.6%)	0.38
Nail disease	124 (44.6%)	106 (51.0%)	0.16
Dactylitis	6 (2.0%)	18 (8.3%)	0.001
Psoriasis vulgaris	236 (81.9%)	142 (66.4%)	<0.0001
Severe PASI (≥10)	18 (7.2%)	30 (19.4%)	0.0002
ESR	15.9 (15.8)	15.3 (17.2)	0.69
Swollen joint count	0.74 (1.72)	1.40 (3.4)	0.008
Clinically damaged joints	8.4 (12.2)	14.7 (16.4)	<0.0001
Axial disease	104 (34.9%)	177 (79.0%)	<0.0001
Presence of arthritis mutilans	76 (25.3%)	99 (43.8%)	<0.0001
Presence of arthritis prior to psoriasis	30 (10.0%)	15 (6.6%)	0.18
HLA-B*27	44 (14.6%)	50 (22.1%)	0.03
HLA-C*6	83 (27.6%)	64 (28.3%)	0.85

Conclusion: Based on patients' characteristics at follow-up, CA analysis separated PsA patients into two predominant arthritis patterns coinciding with the results that looked at a the same cohort at baseline with the exclusion of B27 and C6 as clustering variables. The study provides further evidence to classify patients into just two groups based on the presence or absence of axial arthritis not only at baseline but also at follow-up.

Disclosure: A. Thavaneswaran, None; **V. Chandran**, None; **D. Gladman**, None.

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Fatigue and Work Disability In Psoriatic Arthritis. Jessica Walsh[1], Molly McFadden[2], Gerald G. Krueger[1], Allen D. Sawitzke[1] and Daniel O. Clegg[3]. [1]University of Utah, Salt Lake City, UT, [2]University of Utah, SLC, UT, [3]George Wahlen VA Medical Center/University of Utah, Salt Lake City, UT

Background/Purpose: Fatigue and work disability (WD) are common in people with psoriatic arthritis (PsA). Pain and discomfort from PsA contribute to fatigue by impairing sleep quality. Inflammatory mediators implicated in the pathogenesis of PsA may also impact fatigue with direct effects on the central nervous system. It is unclear if fatigue contributes to WD, independently of musculoskeletal and cutaneous disease activity in people with PsA. The purpose of this study was to explore the relationships between fatigue, WD, and PsA activity.

Methods: Phenotype data were collected from participants in the Utah Psoriasis Initiative Arthritis registry between January 2010 and May 2013. WD was measured with the Work Limitations Questionnaire (WLQ). Two variables were used to assess fatigue, including question 1 from the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI #1), "How would you describe the overall level of fatigue/tiredness you have experienced?" and question 1 from the Psoriatic Arthritis Quality of Life Questionnaire (PsAQoL #1) "I feel tired whatever I do." PsA activity was assessed with tender joint count (TJC), swollen joint count (SJC), dactylitis count, enthesitis count, inflammatory back pain (IBP), and the product of a cutaneous physician global assessment (PGA) and body surface area (BSA) (PGAxBSA). Depressed mood was measured with PsAQoL question 4 (PsAQoL #4) "I feel there is no enjoyment in my life." Chi square, Fisher's exact test, t-test, and Wilcoxon rank sum statistics were used to compare demographics and disease characteristics. ANCOVA analyses were used to determine the adjusted mean WLQ scores for PsQOL #1 and BASDAI #1.

Results: Evaluations were completed with 107 participants. 54 (50.5%) were classified as having fatigue according to PsAQoL #1, and 64 (60.0%) were classified as high fatigue by BASDAI #1. TJC, SJC, enthesitis count, IBP, and depressed mood were highest or most frequent in fatigued participants (Table 1). After adjustments for PsA activity and depressed mood, WLQ work productivity loss was associated with fatigue, as measure by PsAQoL #1 (p=0.02) and BASDAI #1 (p= 0.002) (Table 1).

Table 1. Demographics and disease characteristics

	PsAQoL #1 Yes/No			BASDAI #1 0–10 Likert scale		
Characteristic	No fatigue n = 53	Fatigue n = 54	p	Low fatigue (BASDAI #1 <6) n = 43	High fatigue (BASDAI #1 ≥6) n = 64	p
Age	47.0 ± 11.9	48.4 ± 10.1	0.81	47.5 ± 12.4	48.0 ± 10.1	0.89
Male sex	32 (60.4)	28 (51.9)	0.37	27 (62.8)	33 (51.6)	0.25
White race	50 (94.3)	49 (90.7)	0.71	41 (95.3)	59 (92.2)	0.29
Body mass index	29.9 ± 7.8	32.7 ± 9.4	0.14	30.6 ± 10.7	31.8 ± 7.4	0.13
Duration of PsA (years)	10.4 ± 11.8	10.1 ± 10.6	0.57	10.2 ± 11.7	10.1 ± 10.8	0.48
Tender joint count (scale range 0–68)	4.1 ± 5.8	10.4 ± 10.9	0.001	4.0 ± 5.1	9.4 ± 12.4	0.003
Swollen joint count (scale range 0–66)	3.0 ± 5.3	4.7 ± 6.0	0.06	2.3 ± 3.7	4.7 ± 6.5	0.007
Dactylitis count (scale range 0–20)	0.6 ± 1.7	0.4 ± 1.0	0.76	0.4 ± 1.2	0.5 ± 1.4	0.49
Enthesitis count* (scale range 0–8)	0.4 ± 0.9	0.8 ± 1.0	0.01	0.3 ± 0.7	0.8 ± 1.1	0.004
Inflammatory back pain (yes/no)	12 (22.6)	29 (53.7)	<0.001	9 (20.9)	31 (48.4)	<0.001
PGAxBSA (scale range 0–500)	7.6 ± 16.4	3.0 ± 4.0	0.07	6.4 ± 16.1	4.5 ± 8.5	0.91
Depressed mood (yes/no)	3 (5.7)	11 (20.4)	0.03	3 (7)	11 (17.2)	<0.001

*Entheses included plantar fascia insertions, Achilles tendon insertions, lateral epicondyles, & medial femoral condyles

Table 2. Work Limitation Questionnaire scores in psoriatic arthritis participants with and without fatigue

	PsAQoL #1 Yes/No			BASDAI #1 0–10 Likert scale		
WLQ Scores	No fatigue* (Mean WLQ score)	Fatigue* (Mean WLQ score)	p	Increase in WLQ score for each 1 point increase in BASDAI #1*	SE	p
Composite WLQ Productivity Loss	7.6	10	0.02	0.87	0.18	0.002
Time management subscale	35.2	42.4	0.26	3.53	1.11	0.127
Mental-interpersonal subscale	24.2	31.6	0.09	3.29	0.71	<0.001
Output subscale	28.9	37.3	0.123	3.92	0.93	0.004
Physical subscale	33.6	49.2	0.005	2.49	0.99	0.05

*Adjusted for age, gender, tender joint count, swollen joint count, enthesitis count, inflammatory back pain, PGAxBSA, and depressed mood.

Conclusion: WD was associated with fatigue, and the associations were not entirely explained by the musculoskeletal, cutaneous, or psychiatric manifestations of PsA. Additional research is required to characterize the relationship between fatigue and WD in people with PsA.

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Tailored Approach To Early Psoriatic Arthritis Patients: Ultrasonographic Predictors For Structural Joint Damage. Yasser El Miedany[1], Maha El Gaafary[2], Sally Youssef[2] and Annie Nasr[2]. [1]Medway Hospital, Gillingham, United Kingdom, [2]Ain Shams University, Cairo, Egypt.

Background/Purpose: To evaluate the use of musculoskeletal US as a predictor for inflammatory structural progression in psoriatic patients.

Methods: Measures of association (OR) were tested, in a prospective 1-year follow up study, between structural deterioration and the presence of baseline synovitis, or its persistence. 126 psoriatic patients were prospectively evaluated both clinically and by US (both US-GS and US-PD) at time 0, 6 and 12 months, in order to collect the following variables: 1. 42 joints (2 wrists, 10 MCP, 10 PIP, 10 DIP and 10 MTP) for the presence of synovial hypertrophy and vascularisation (0–3 scale), and the number and dimension of bone erosions; 2. Enthesitis: GUESS (Glasgow Ultrasound Enthesitis Scoring System) index scores was calculated; 3. Onychopathy. X-ray was carried out at time 0 and at 12 months and lesions were graded using the Sharp/van der Heijde. Potential prognostic determinants for structural joint damage obtained at the first examination and during follow-up were entered in a conditional logistic regression analysis.

Results: Structural deterioration was observed in 47% of the 5292 evaluated joints in 126 patients. Clinical variables associated with the risk of arthritis in psoriatic patients included: higher BMI (OR 1.7, 95% CI 1:02 to 1:10), percentage of body surface area affected (OR 1.13, 95% CI 1:01 to 1:09), family history of PsA (p <0.001/OR 5.72, 95% CI 2.79– 91.62). and nail involvement (OR 2.25, 95% 1:36 to 3:41). High BMI was significantly correlated (P < 0.01) with shorter interval of time for the onset of arthritis in psoriatic patients.

Baseline synovial score > 2/PD score ≥2 increased the risk of structural progression: OR=2.61 (1.26–2.94) p<0.001 versus 1.98 (1.05–2.65) p=0.01 versus 2.66 (1.08–2.76) (P< 0.001) for the clinical versus US-GS versus US-PD evaluation, respectively. In the joints with normal baseline examination (clinical or US), an increased probability for structural progression in the presence of enthesitis was also observed (OR=2.46 (1.15–4.12) (P< 0.01) and 3.50 (1.77–6.95) p<0.001 for US-GS and US-PD and 2.79 (1.05–5.41) P<0.001) for clinical examination. The baseline GUESS scores in psoriatic patients who developed PsA later was significantly higher than those of patients who did not develop joint disease (9.86 ± 2.4 vs. 5.62 ± 2.31, respectively, P< 0.01). Onychopathy was also associated with structural joint damage (OR 2.30, 95%CI 1.17– 3.69). In multiple conditional logistic regression analysis, persistent (vs disappearance) of synovitis/enthesitis at 6 months of therapy was also predictive of subsequent structural progression.

Conclusion: Identifying predictor risk factors for the development of inflammatory arthritis in psoriatic patients are essential to clinical practice. The presence of US determined synovial thickness, enthesitis and/or onycholopathy associated with positive PD signal at baseline and the persistent PD signal over time have relevant prognostic value for the development of articular damage in psoriatic patients. These results could be an appropriate reference to dermatologists and rheumatologists, and a step forward to tailor the medical management to the patient's condition.

Disclosure: Y. El Miedany, None; **M. El Gaafary**, None; **S. Youssef**, None; **A. Nasr**, None.

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The Association Between Obesity and Radiographic Progression Of Joint Damage Among Patients With Psoriatic Arthritis. Lihi Eder[1], Arane Thavaneswaran[1], Vinod Chandran[1], Richard J. Cook[2] and Dafna D. Gladman[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Waterloo, Waterloo, ON.

Background/Purpose: The prevalence of obesity among patients with psoriatic arthritis (PsA) is increased compared to the general population. Obese patients with PsA tend to respond less favorably to TNF alpha blockers compared to patients with normal weight. We aimed to investigate whether obesity is associated with higher risk of development of radiographic damage among patients with PsA.

Methods: A retrospective cohort analysis was performed among patients who have been followed in a large PsA clinic from 1998 to 2013. Patients were followed according to a standard protocol at 6–12 month intervals. Body Mass Index (BMI) was calculated and patients were categorized accordingly into the following groups: Normal (<25), Overweight (25–30) and Obese (>30). Radiographs of the hands, feet and spine were performed at 2 years

intervals. Radiographic damage to 42 joints in the hands and feet was assessed according to a modification of the Steinbrocker method. Radiographic damage to the lumbar and cervical spine was scored using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). For each patient all available radiographic data were included. Patients who initiated treatment with TNFα blockers were censored. The outcome of interest was the annual rate of radiographic progression that was calculated as the difference in modified Steinbrocker score and mSASSS compared to the previous radiographic assessment divided by the interval of time between the assessments. Multivariate regression analysis using Generalized Estimating Equations (GEE) for repeated measures was used to compare progression in radiographic damage across the three BMI categories incorporating available information from all time points.

Results: 339 PsA patients were included in the study (28.6% with normal weight, 38.9% were overweight and 32.4% were obese). At first visit, patients who were overweight and obese had higher mean erythrocyte sedimentation rate (p=0.007) and trended for higher CRP levels (p=0.06). There was no difference in the number of tender or swollen joints, dactylitic digits or active entheseal sites. At baseline, overweight and obesity were associated with the presence of radiographic damage (61.9% in normal weight, 65.2% in overweight and 75.5% in obese, p=0.03); however, no difference was observed in modified Steinbrocker score and mSASSS across the three groups. Regression analysis did not show an association between the rate of radiographic progression of modified Steinbrocker score and BMI category (p=0.85). In multivariate regression analysis only the use of disease modifying anti rheumatic drugs was associated with an increased rate of radiographic damage progression. Similarly, BMI category was not associated with rate of progression of mSASSS (p=0.9).

Conclusion: Among patients with PsA, increased BMI was associated with the presence of radiographic damage at first assessment. However, no association was found between BMI and the rate of radiographic progression of damage in the peripheral joints and the spine.

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Baseline Characteristics and Treatment Outcomes In Psoriasis Patients With Polyarthritis Or Oligoarthritis. Philip S. Helliwell[1], Philip Mease[2], Eustratios Bananis[3], Heather Jones[3], Annette Szumski[3] and Lisa Marshall[3]. [1]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [2]University of Washington School of Medicine, Seattle, WA, [3]Pfizer Inc., Collegeville, PA.

Background/Purpose: Most randomized control trials (RCTs) for psoriatic arthritis (PsA) include patients with asymmetric oligoarthritis (AO) and polyarthritis (PA). There are limited data from RCTs on the demographic and disease characteristics of PsA patients with either AO or PA and how these different patient groups respond to treatment. Our analyses compared baseline characteristics and treatment outcomes of AO and PA patients receiving ETN 50 mg QW for 24 wks in the PRESTA trial.

Methods: PRESTA was a large, randomized, 24-wk, multicenter study to evaluate the efficacy and safety of etanercept (ETN) in patients with moderate-to-severe psoriasis (≥10% of body surface) and active PsA ≥3 months. Patients received ETN 50 mg BIW or 50 mg QW for 12 wks in a double-blind phase, and open-label ETN 50 mg QW for 12 additional wks. Patients who received ETN 50 mg QW for 24 wks were included in this analysis if they received ≥1 dose of ETN and had ≥1 post-baseline efficacy value. AO (inflammation of 2–4 joints) and PA (inflammation of ≥5 joints) was based on clinical diagnosis by rheumatologists. Standard clinical outcomes were assessed among patients with AO or PA at baseline.

Results: A total of 363 subjects (46 with baseline AO, 317 with baseline PA) were included in these analyses. At baseline, patients with PA were significantly older (47.6 vs 43.0 years, P=0.01) and had significantly higher HAQ, PGA of arthritis, PGA of psoriasis, subject assessment of joint pain and numbers of painful and swollen joints than those with AO (Table). Significant improvement at wk 24 was observed for all endpoints in both groups; mean % change and adjusted mean change from baseline were similar for PA vs AO patients at wk 24. At 24 wks, a significantly greater proportion of AO than PA patients achieved HAQ ≤0.5 (Table). The proportion of patients achieving ACR/20/50/70, PASI75, and PGA of psoriasis ≤1 was not significantly different between AO and PA groups. Similar results between the 2 groups were observed after 12 wks of treatment.

Efficacy Assessment	Oligoarthritis (N=46)	Polyarthritis (N=317)	P-value
Baseline (Mean)			
HAQ	0.76 (0.7)	0.96 (0.7)	0.060
PASI	18.5 (9.8)	19.1 (9.9)	0.695
PGA Arthritis	41.7 (20.9)	51.5 (20.5)	0.004
PGA Psoriasis	3.37 (0.5)	3.65 (0.7)	0.006
Subject assessment of joint pain (VAS)	55.0 (28.5)	63.2 (24.5)	0.039
Total painful joints 68	2.89 (0.8)	19.71 (15.3)	<0.0001
Total swollen joints 66	2.37 (1.1)	12.70 (13.3)	<0.0001
Week 24 (LOCF) (% responders)			
ACR 20/50/70	70.5/54.5/36.4	71.6/53.0/36.4	0.879/0.851/0.994
HAQ ≤0.5	82.6	63.7	0.011
PASI 75	67.4	61.6	0.449
PGA ≤1	58.7	49.2	0.230

Conclusion: ETN 50 mg QW was effective in the treatment of PsA regardless of the subtype examined. As expected, AO patients had less baseline joint disease but achievement of low level joint disease activity at 24 wks was similar in PA and AO groups, whereas functional improvement was greater in the AO group. Similar significant improvement in skin disease was observed in both patients with PA and AO.

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Impact Of Persistent Minimal Disease Activity On Long-Term Outcomes In Psoriatic Arthritis: Results From 5 Years Of The Long Term Extension Of a Randomized, Placebo-Controlled, Study. Arthur Kavanaugh[1], Iain B. McInnes[2], Philip J. Mease[3], Gerald G. Krueger[4], Dafna D. Gladman[5], Stephen Xu[6], Linda Tang[7] and Katrien van Beneden[8]. [1]University of California, San Diego, La Jolla, CA, [2]University of Glasgow, Glasgow, United Kingdom, [3]Swedish Medical Center and University of Washington, Seattle, WA, [4]University of Utah, Salt Lake City, UT, [5]University of Toronto, Toronto Western Hospital, Toronto, ON, [6]Janssen Research & Development, LLC., Spring House, PA, [7]Janssen Research & Development, LLC., Horsham, PA, [8]Janssen Biologics Europe, Leiden, Netherlands.

Background/Purpose: Although criteria for Minimal Disease Activity (MDA) in psoriatic arthritis (PsA) have been developed and validated, a paucity of data concerning the impact of reaching MDA on long-term outcomes remains. We assessed this concept using 5 yr long term extension (LTE) data from the GO-REVEAL study of PsA pts treated with golimumab (GLM).

Methods: Data were obtained from the open label LTE of GO-REVEAL, a double-blind, PBO controlled Ph3 study comparing the efficacy and safety of GLM 50 mg and 100mg q4wks to PBO in pts with active PsA (≥3 swollen, ≥3 tender joints, and psoriasis). Pts with <10% improvement in both tender and swollen joints could enter early escape at wk16; all pts received GLM from wk24 forward. Last GLM injection was at wk252. MDA was defined as the presence of ≥ 5 of the following: ≤ 1/66 swollen joints; ≤ 1/68 tender joints; PASI score ≤ 1; pt pain VAS ≤ 15 (0–100); pt global assessment of disease activity VAS ≤ 20 (0–100); HAQ-DI ≤ 0.5; ≤ 1 tender enthesis point.[1] These criteria were assessed at wks 14, 24, 52, 104, 148, 196, and 256. Pts were selected who never achieved MDA and who achieved persistent MDA (defined as MDA for at least 3 consecutive time points) through Wk 256. Comparisons between patients who achieved/did not achieve MDA and the relationship between HAQ-DI or radiographic progression measured using vdHS scores were performed. These analyses utilized observed data from randomized pts. Statistical tests used ANOVA with Van der Waerden normal score and chi-squared test.

Results: At the end of the PBO-controlled period until wk24, MDA was achieved in 7.7% and 28.1% of pts in the PBO and GLM groups, respectively. Through wk256, MDA was achieved in 44.2%-51.7% of pts (Table 1). Irrespective of treatment randomization, a better clinical meaningful HAQ improvement and less radiographic progression were observed in pts who achieved persistent MDA compared to pts who never achieved MDA (Table 2). While stratifying for treatment, pts achieving persistent MDA, who

crossed-over from PBO to GLM, experienced similar HAQ improvement and radiographic outcomes compared to pts randomized to the GLM groups (Table 2), suggesting that delayed initiation with GLM did not result in a worsening of physical function or radiographic progression. In contrast, for pts not achieving MDA, delayed start with GLM resulted in numerically less radiographic benefit.

Table 1. Proportion of pts who achieved MDA by randomized treatment and visit

	PBO	GLM combined	p-value
Week 14	1/104 (1.0%)	67/285 (23.5%)	<0.0001
Week 24	8/104 (7.7%)	80/285 (28.1%)	<0.0001
Week 52	29/96 (30.2%)	111/262 (42.4%)	0.0368
Week 104	32/87 (36.8%)	107/250 (42.8%)	0.3260
Week 148	41/84 (48.8%)	122/236 (51.7%)	0.6496
Week 196	37/82 (45.1%)	106/222 (47.7%)	0.6839
Week 256	34/77 (44.2%)	106/205 (51.7%)	0.2585

Table 2. MDA status and improvement in HAQ, SHS change after 5 yrs

Efficacy endpoints	Randomized treatment	Never achieved MDA	Achieved persistent MDA
HAQ improvement at wk 256			
No. of pts	PBO	30	27
Mean ± SD		0.25 ± 0.551	0.79 ± 0.553
p-value			<0.001
No. of pts	GLMcombined	70	94
Mean ± SD		0.28 ± 0.470	0.66 ± 0.516
p-value			<0.001
SHS change at wk 256			
No. of pts	PBO	29	25
Mean ± SD		1.29 ± 5.475	−0.78 ± 1.501
p-value			<0.05
No. of pts	GLMcombined	66	91
Mean ± SD		0.68 ± 3.993	−0.43 ± 2.392
p-value			<0.05

Combined GLM (50mg and 100mg groups).

Conclusion: The data of the current analysis show that MDA occurred in approximately 50% of pts receiving effective treatment through 5 years. Aiming for MDA may serve as an argument for a treat-to-target strategy since persistent MDA can improve long-term functional and radiographic outcomes in pts with active PsA.

[1]Coates LC et al. Arthritis Car Res 2010;62:965–9.

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TNF Blockage In Psoriatic Arthritis: Long-Term Effect On Lipid Profile.

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Background/Purpose: Psoriatic arthritis (PsA) patients have increased cardiovascular morbidity and mortality. Altered lipid profile is an important risk factor for the development of these complications. There are, however, no data regarding prospective long-term evaluation of lipid profile in PsA patients under TNF blockers. The purpose of this study is to evaluate prospectively the long-term effect of anti-TNF therapy on lipid profile in PsA patients.

Methods: Thirty-two consecutive PsA patients, who were eligible to receive anti-TNF therapy, were prospectively enrolled. All patients were treated with TNF blockers, and they were evaluated for lipid profile, atherogenic index (AI), body mass index (BMI), waist circumference and disease parameters at baseline and at 104 weeks after treatment. Lipoprotein risk level for coronary heart disease (CHD) were defined by National Cholesterol Education Program (total cholesterol > 240 mg/dL, LDL-cholesterol >160 mg/dL, HDL-cholesterol < 40mg) or patients requiring statin during study period. Patients using statin at study entry were excluded but initiation of this drug was allowed during follow-up.

Results: Prospective evaluation of lipid profile revealed a significant increase in levels of total cholesterol (177±39mg/dL vs. 195±45mg/dL, p=0.002) and LDL-cholesterol (105±34mg/dL vs. 117±40mg/dL, p=0.007), in spite of statin introduction in one fourth of these patients during the study. No changes were found in the concentration of HDL-cholesterol (48±12mg/dL vs. 50±12mg/dL, p=0.26), triglycerides [105 (69–160)mg/dL vs. 112 (92–183)mg/dL p=0.06], in AI (3.9±1.4 vs. 4.1±1.3, p=0.48), BMI (28.4±5.2kg/m2 vs. 29.1±5.7kg/m2, p=0.62) and waist circumference (92.2±15cm vs. 97.8±14.9cm, p=0.23. The frequency of patients with high risk levels for total cholesterol (6.3% vs. 28.1%, p=0.023) and high/very high LDL- (6.3% vs. 28.1%, p=0.023) significantly increased from entry to 104 weeks whereas no change in the frequency of HDL-cholesterol and triglycerides classification rate were observed. Anti-TNF treatment improved inflammation parameters: C-reactive protein (p<0.001), and erythrocyte sedimentation rate (p<0.001).

Conclusion: The novel demonstration that anti-TNF therapy has a specific pattern of long-term deleterious effect in lipid profile of PsA patients reinforces the importance of this cytokine as a potent lipid metabolism regulator and emphasizes the recommendation for a close monitoring and a more vigorous intervention in this modifiable cardiovascular risk factor.

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Conventional Dmards For Psoriatic Arthritis: Data On 1351 Treatment Courses With Methotrexate, Sulfasalazine and Leflunomide.

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Background/Purpose: Methotrexate (MTX), sulfasalazine (SSZ) and leflunomide (LEF) are recommended treatments for PsA patients with active peripheral arthritis. In the publication of a recent negative placebo-controlled randomised trial of MTX in PsA, it was suggested that the sequencing of conventional DMARDs before biologics should be re-evaluated[1]. Our objective was to assess the pattern of conventional DMARD use, and to compare the effectiveness of MTX, SSZ and LEF in a longitudinal observational study (LOS) of patients with PsA.

Methods: Data were extracted from NOR-DMARD, a LOS of arthritis patients starting a new DMARD treatment, with follow-up at 3, 6, 12 months and then yearly. Patients diagnosed with PsA and starting treatment with MTX, SSZ or LEF were identified. We studied baseline characteristics and 3- and 6-month treatment responses overall, and performed statistical comparisons between treatments. For the statistical comparisons we selected the first inclusion of those patients included sequentially with several DMARDs so that only individual patients were included. Unadjusted comparisons were done by ANOVA, Kruskall-Wallis or Chi^2 test, as appropriate, and analyses with adjustment for important baseline differences were performed by ANCOVA and logistic regression analysis. Swollen and tender joint counts included the standard 28 joints for RA and ankles and forefeet bilaterally (32-SJC and 32-TJC, respectively).

Results: A total of 1351 prescriptions of MTX (n=1000), SSZ (n=212) and LEF (n=139) in 1212 individual patients were identified – 128 patients were registered with >=2 of the drugs and 11 patients with all 3 drugs. Among MTX/SSZ/LEF patients 71% vs. 61% vs. 6.5% were

DMARD na·ve, respectively, and 47% of patients on LEF had failed both MTX and SSZ. Patients treated with LEF also had longer disease duration. Mean baseline DAS28 for MTX/SSZ/LEF was 4.2/4.0/4.3, respectively. The baseline characteristics across groups for the first inclusion per patient (MTX n=949, SSZ n=177, LEF n=86) were very similar (baseline DAS28 4.2/3.9/4.3 for MTX/SSZ/LEF, respectively). Selected 3- and 6-month outcomes are shown in the Table. Responses were numerically similar for the overall group of patients (n=1351). Two-year drug survival was superior for MTX (0.71) vs. SSZ (0.40; HR 1.96; p<0.001) and LEF (0.29; HR 2.47, p<0.001), with no significant difference between SSZ and LEF. Reasons for discontinuation were inefficacy and intolerance in roughly the same frequency (40–50%) for both SSZ and LEF. Mean dose of MTX was 15.1 mg at 6 months; for SSZ 88% used >=2000 mg daily and for LEF 86% used 20 mg daily at 6 months.

Table. 3- and 6-month responses (individual patients)

	3 months					6 months				
	MTX n=781	SSZ n=143	LEF n=73	*P**	*P***	MTX n=700	SSZ n=97	LEF n=52	*P**	*P***
ACR20¤	32.0%	29.4%	34.7%	0.72	0.39	40.5%	31.9%	29.2%	0.10	0.34
ACR50¤	17.4%	12.5%	8.3%	0.07	0.34	22.8%	17.6%	8.3%	0.04	0.25
ACR70¤	6.5%	2.2%	5.6%	0.15	0.17	11.6%	7.7%	4.4%	0.17	0.39
DAS28	−0.77	−0.77	−0.47	0.17	0.40	−1.04	−0.86	−1.03	0.52	0.62
32-SJC	−1.9	−1.4	−1.4	0.28	0.66	−2.5	−1.9	−1.4	0.08	0.80
32-TJC	−1.7	−1.3	−2.8	0.13	0.48	−2.2	−1.6	−2.3	0.55	0.46
CRP, mg/L	−5.9	−2.1	−3.7	0.07	0.02	−6.4	−1.4	−4.9	0.01	0.32
PGA	−12.6	−8.5	−6.1	0.03	0.09	−13.9	−11.9	−9.2	0.37	0.75

Values are percentages and means. *Unadjusted. **Adjusted for age, sex, number of previously used DMARDs, disease duration, and for continuous outcomes the respective baseline values. PGA=Patient Global Assessment. ¤Based on 32-joint counts.

Conclusion: MTX was the most commonly used first-line DMARD while LEF was rarely used as a first-line DMARD. Effectiveness was modest and generally similar, but MTX performed better for some measures, including drug survival.

1. Kingsley G et al, Rheumatology 2012;51:1368–77.

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Clinical Phenotype Of Patients With Arthritis Mutilans Has Important Differences Compared To Other Patients With Psoriatic Arthritis. Muhammad Haroon, Phil Gallagher and Oliver FitzGerald. Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland.

Background/Purpose: Arthritis mutilans (AM), a severe form of psoriatic arthritis (PsA), is characterised clinically by digital shortening resulting from osteolysis and/or erosions. It is still unclear whether AM is simply the end-stage of polyarticular PsA, or whether it is a unique entity with different pathogenic mechanisms. Given its rarity, there is little data regarding its clinical and laboratory associations. The objectives of our study were 1) to investigate the prevalence of AM in an ethnically homogenous consecutive cohort of established PsA, 2) to identify the clinical phenotype of AM and its effect on quality of life, functional impairment and fatigue scores compared to those PsA patients who do not have AM.

Methods: A cohort of 283 consecutive PsA patients, fulfilling CASPAR criteria, was included. Following informed consent, patients underwent detailed skin and rheumatologic assessments including disease activity measures [PASI, Body Surface Area (BSA) for psoriasis; tender and swollen joint counts, CRP, ESR] HAQ (health assessment questionnaire), Dermatology Life Quality Index (DLQI), Bristol Rheumatoid Arthritis Fatigue Numeric Rating Scale (BRAF-NRS) and SF-36. Radiographs were taken of involved joints along with hands, feet and sacroiliac joints. AM was considered present when there was one or more shortened digit accompanied on radiographs by osteolysis or erosions on both sides of the joint.

Results: A total of 283 PsA patients [mean age 55±12 years; 47% male; mean PsA duration=19±9 years; 25% with sacroiliitis; 44.5% with radiographic erosions; 34% with enthesitis; 53% with dactylitis; 79% with psoriatic nail disease, 60% of this PsA cohort requiring TNFi therapy] were studied. Among this cohort, 8% (n=23) of patients were found to have AM, with 65% female and a mean age of 56.5±11 years. On univariate analysis, longer PsA duration (OR 1.06, p=<0.001), longer diagnostic delay (OR 1.10, p=0.01), more tender joint counts (OR 1.07, p=0.009), more swollen joint counts (OR 1.09, p=0.009), PsA requiring TNFi (OR 3.37, p=0.03), oral corticosteroids usage (OR 9.2, p=<0.001), earlier PsA age of onset (OR 0.96, p=0.08), lower CRP maximum (OR 0.98, p=0.07), lower ESR maximum (OR 0.98, p=0.13) and higher HAQ score (OR 1.07, p=0.10), MCS-SF36 (OR 1.02, p=0.16) and PCS-SF36 (OR 1.00, p=0.80). Given the small number of AM patients, few models were tested on multivariate regression analysis, but it was noted that heavier alcohol intake (OR 1.08, p=0.002), lower CRP rise (0.96, p=0.007), greater oral corticosteroids usage (OR 7.6, p=0.003) and longer duration of PsA (OR 1.08, p=0.001) all remained significantly associated with the diagnosis of AM.

Conclusion: The clinical profile of patients with AM when compared to other PsA patients suggests that non-inflammatory pathogenic mechanisms, possibly related to bone turnover, may explain this unique clinical phenotype.

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Prevalence Of Peri-Articular Manifestations (Enthesitis and Dactylitis) and Disease Activity In Psoriatic Arthritis Patients: Impact Of Treatment With TNF Inhibitors In a Real-World Canadian Population. Proton Rahman[1], Denis Choquette[2], William G. Bensen[3], Majed M. Khraishi[4], Isabelle Fortin[5], Andrew Chow[6], Maqbool K. Sheriff[7], Julie Vaillancourt[8], John S. Sampalis[9], Susan M. Otawa[10], Allen J. Lehman[10] and May Shawi[10]. [1]Memorial University, St. Johns, NF, [2]Institut de Rhumatologie de Montréal, Montreal, QC, [3]St. Joseph's Hospital and McMaster University, Hamilton, ON, [4]MD, Memorial University of Newfoundland, Nexus Clinical Research, St Johns, NF, [5]Centre de Rhumatologie de l'Est du Québec, Rimouski, QC, [6]Credit Valley Rheumatology, Mississauga, ON, [7]Nanaimo Regional General Hospital, Nanaimo, BC, [8]JSS Medical Research, Montreal, QC, [9]JSS Medical Research, St-Laurent, QC, [10]Janssen Canada Inc, Toronto, ON.

Background/Purpose: To determine the point prevalence of periarticular manifestations (PAMs) in psoriatic arthritis (PsA) patients treated with anti-TNF in a real-world, Canadian, routine clinical practice setting.

Methods: BioTRAC is an ongoing, prospective, registry of patients initiating treatment for PsA, AS or RA with infliximab or golimumab as first biologics or after having been treated with a biologic for < six months. In this analysis of data collected since 2010, 91 PsA patients with available baseline information on PAMs were included: enthesitis (n=62), dactylitis of hands (n=76) or feet (n=77), nail pitting of hands (n=76) or feet (n=75).

Results: Baseline characteristics included mean (SD) age, disease duration of 48.7 (10.3), 6.5 (6.9) years, respectively, and mean (SD) DAS28-CRP score of 4.1 (1.2).

Among all patients at baseline, 50 (54.9%) had a PAM. Dactylitis (feet − 39.0%; hands – 15.8%) was the most common PAM followed by enthesitis (27.4%), and nail pitting (hands–26.3%; feet–24.0%). Patients with enthesitis had greater mean (SD) DAS28-CRP (4.7 (1.0) vs. 3.9 (1.3); P=0.042) and HAQ-DI (1.33 (0.73) vs. 0.94 (0.77); P=0.076) compared to patients without enthesitis. However, mean (SD) age (47.0 (10.0) vs. 48.8 (9.5) years; P=0.544), disease duration (6.1 (7.3) vs. 6.0 (6.2) years; P=0.937), and morning stiffness (52.6 (43.4) vs. 56.7 (45.2) min; P=0.750) were comparable between-groups. Among patients with/without dactylitis, baseline mean (SD) parameters were: age (46.8 (12.5) vs. 50.5 (8.9) years; P=0.145), disease duration (6.2 (6.8) vs. 7.0 (7.7) years; P=0.666), DAS28-CRP (4.5 (0.9) vs. 4.0 (1.4); P=0.105), HAQ-DI (1.08 (0.69 vs. 1.09 (0.69); P=0.925), and morning stiffness (73.2 (44.8 vs. 51.6 (42.0) min; P=0.033).

Upon six months of treatment, significant improvement in all disease activity parameters studied was observed. Six-month PAM data were available for 50 (54.9%) patients. Overall, the prevalence of PAMs decreased from baseline to six months post-treatment (P=0.001). Among patients with available six-month information that had a PAM at baseline (n=33), (48.5%) did not present any manifestation after six months. The incidence of new PAMs by six months was minimal.

Conclusion: In this Canadian real-world cohort of PsA patients, a high prevalence of PAMs was observed at treatment initiation. Patients with enthesitis or dactylitis had increased disease activity compared to patients without PAMs. Infliximab or golimumab treatment for six months was associated with a significant improvement in patient parameters and reduction in the prevalence of PAMs.

Disclosure: P. Rahman, Amgen, Abbott, BMS, Merck, Pfizer, Janssen, Hoffman-La Roche, UCB, Novartis, Sanofi-Aventis, 5, Amgen, Abbott, BMS, Merck, Pfizer, Janssen, Hoffman-La Roche, UCB, Novartis, Sanofi-Aventis, 9; **D. Choquette**, None; **W. G. Bensen**, None; **M. M. Khraishi**, Hoffman-La Roche Canada, Amgen and Pfizer Canada, and Abbott Canada., 2; **I. Fortin**, None; **A. Chow**, None; **M. K. Sheriff**, None; **J. Vaillancourt**, JSS, 3; **J. S. Sampalis**, None; **S. M. Otawa**, Janssen Canada, 3; **A. J. Lehman**, Janssen Canada, 3; **M. Shawi**, Janssen Canada, 3.

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Rheumatoid Arthritis, a More Severe Disease Than Psoriatic Arthritis? A Comparison Of Disease Activity In Patients With Psoriatic Arthritis and Rheumatoid Arthritis From The Swedish Early Psoriatic Arthritis Registry (SwePsA) and The Swedish Rheumatology Registry For Early Rheumatoid Arthritis (SRR). Gerd-Marie Alenius[1], Tomas Husmark[2], Elke Theander[3], Per Larsson[4], Mats Geijer[5], Annika Teleman[6] and Ulla R. C. Lindqvist[7]. [1]Department of Public Health and Clinical Medicine, Rheumatology, Umeå University, Umeå, Sweden, [2]Department of Rheumatology, Falu Hospital, Falun, Sweden, [3]Lund University, Malmö, Sweden, [4]Karolinska University Hospital, Stockholm, Sweden, [5]Skåne University Hospital, Lund, Center for Medical Imaging and Physiology, Lund, Sweden, [6]Department of Rheumatology, Spenshult Hospital, Oskarstrom, Sweden, [7]Department of Medical Sciences, Rheumatology, University Hospital, Uppsala university, Uppsala, Sweden.

Background/Purpose: In clinical practise patients with psoriatic arthritis (PsA) seem to have milder disease expression compared with patients having rheumatoid arthritis (RA). Studies have, however, shown that PsA is a more severe disease than known before. The aim of this study was to compare the disease activity and treatment between psoriatic arthritis (PsA) and rheumatoid arthritis (RA) in patients with early disease, and after five years of disease duration.

Methods: 208 patients included in SwePsA were compared to 381 patients included in SRR. The patients were matched (1:1–2) for age, gender, year of inclusion in the registries and region of residence. Inflammatory parameters such as DAS28, its components, CRP, HAQ, pain VAS and treatment (DMARDs, steroids and biologics), were measured at inclusion and at 5 year-follow up. Single and multiple regression analyses were performed and the stratified proportional hazards model has been used to model the 1–2 or 1-1 matching designs depending on the number of controls available for a case.

Results: At inclusion, patients with RA had significantly higher DAS28, ESR, CRP, tender joint counts (TJC), swollen joint counts (SJC), HAQ, pain VAS and patient global VAS (PGVAS) compared to patients with PsA (Table 1). After 5 years all parameters had decreased and ESR was slightly higher in RA-patients compared with PsA-patients (15.22 vs 12.36, p=0.046), while tender joint count now was higher in patients with PsA (3.58 vs 1.95, p=0.000). No other differences between the groups were seen (See Table). DMARDs, steroids and biologics were less common among PsA-patients than RA-patients at inclusion (40.9 % vs 84.7%, 9.1 vs 39.6 and 0.5 vs 2.8% respectively), and at 5-year-follow up (46.2% vs 80%, 8.2% vs 18.7%, and 13% vs 37.7% respectively).

Table.

	Inclusion			5-year-follow up		
	PsA Mean (±SD)	RA Mean (±SD)	P (95% CI)	PsA Mean (±SD)	RA Mean (±SD)	P (95% CI)
DAS28	3.34 (±1.34)	5.04 (±1.34)	**0.000 (0.330–0.485)**	2.62 (±1.22)	2.81 (±1.38)	0.281 (0.812–1.062)
ESR	18.72 (±20.13)	32.98 (±25.03)	**0.000 (0.954–0.976)**	12.36 (±12.47)	15.22 (±14.58)	**0.046 (0.970–1.000)**
CRP	16.67 (±25.65)	30.51 (±33.36)	**0.000 (0.970–0.987)**	7.28 (±8.71)	8.09 (±13.54)	0.540 (0.980–1.010)
TCJ	5.59 (±7.82)	7.17 (±5.65)	**0.000 (0.934–0.990)**	3.58 (±6.39)	1.95 (±3.58)	**0.000 (1.035–1.123)**
SJC	4.31 (±4.87)	8.73 (±5.76)	**0.009 (0.787–0.868)**	1.53 (±2.87)	2.03 (±3.35)	0.089 (0.894–1.008)
PGVAS	43.48 (±25.59)	49.43 (±25.60)	**0.008 (0.983–0.997)**	31.86 (±23.83)	29.49 (±23.64)	0.193 (0.998–1.012)
PainVAS	44.15 (±25.72)	50.75 (±25.07)	**0.003 (0.982–0.996)**	31.50 (±25.38)	29.20 (±23.16)	0.216 (0.997–1.012)
HAQ	0.62 (±0.53)	0.99 (±0.60)	**0.000 (0.179–0.391)**	0.48 (±0.6)	0.54 (±0.59)	0.521 (0.668–1.227)

Conclusion: In this study, the disease activity at inclusion was higher in patients with RA compared to PsA. At 5-year-follow up the disease activity had decreased in both patient groups and there were only significant differences in two of the parameters, ESR that was slightly higher in the RA-patients and TJC that was higher in the PsA-patients showing that PsA-patients suffer from joint pain. The patients in the RA-group were more often aggressively treated with steroids, DMARDs and biologics indicating that RA may be a more severe disease. However, after 5 years the PsA-patients had more tender joints which could have an effect on quality of life.

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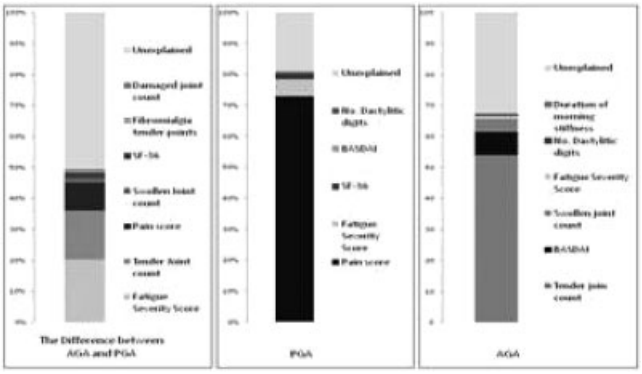
Factors Explaining The Discrepancy Between Patient and Physician Global Assessment Of Disease Activity In Psoriatic Arthritis. Lihi Eder[1], Arane Thavaneswaran[1], Vinod Chandran[1], Richard J. Cook[2] and Dafna Gladman[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Waterloo, Waterloo, ON.

Background/Purpose: Patients and physicians often perceive the extent of disease activity differently. We aimed to assess the factors contributing to the variability in scoring of patient global assessment (PGA), physician (assessor) global assessment (AGA) of disease activity and the discrepancy in scoring between PGA and AGA among patients with psoriatic arthritis (PsA).

Methods: A cross sectional study was conducted of patients attending a large PsA clinic from 2008 to 2013. Three different outcomes were studied: AGA, PGA and the difference between AGA and PGA. The scores of PGA and AGA ranged from 0 (no disease activity) to 10 (high disease activity). The difference between AGA and PGA reflected the discrepancy between the physician and patient global assessment of joint activity and could take values from −10 (worse estimation of disease activity by the patient) to 10 (worse estimation of disease activity by the physician). Predictors of these outcomes included demographics, skin and joint assessment by the physician, patient reported information about function, quality of life and fatigue. Multivariate linear regression identified variables that contributed significantly to each of the outcomes. The proportion of variability of each outcome explained by each predictor was expressed using a partial R^2.

Results: A total of 565 patients were included in the analysis. Their mean age was 51.7±13.2 years and 58.6% were males. The mean duration of psoriasis and PsA were 24±13.8 and 14.3±19.4 years, respectively. 81% of the variability in PGA and 68% of the variability in AGA were explainable. The main factors associated with PGA were pain ($R^2_{partial}$ =72.9%, Figure 1), fatigue (by Fatigue Severity Scale (FSS) $R^2_{partial}$ =5.5%) and disability scores (by Short Form (SF) −36 $R^2_{partial}$ =2.1%). The main factors associated with AGA were tender joint count ($R^2_{partial}$ =53.9%), swollen joint count ($R^2_{partial}$ =4.2%) and patient perception of joint activity (by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) $R^2_{partial}$ =7.5%). Increased fatigue by FSS accounted for 20.4% of the variation in the difference between AGA and PGA and pain ($R^2_{partial}$ =9.2%) and disability scores by SF-36 ($R^2_{partial}$ =1.6%) were also important; these led to worse patient assessments while increased tender joint count ($R^2_{partial}$ =15.9%) and swollen joint counts ($R^2_{partial}$ =1.7%) resulted in a worse physician assessment of arthritis.



Conclusion: Fatigue, pain, disability, tender and swollen joint counts were the most important factors contributing to discrepancy between patient and physician assessment of joint activity.

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Laboratory Abnormalities In Patients With Psoriatic Arthritis Receiving Apremilast, An Oral Phosphodiesterase 4 Inhibitor: Pooled Safety Analysis Of Three Phase 3, Randomized, Controlled Trials. Philip J. Mease[1], Arthur Kavanaugh[2], Adewale O. Adebajo[3], Juan J. Gomez-Reino[4], Jürgen Wollenhaupt[5], Dafna D. Gladman[6], Maurizio Cutolo[7], Georg Schett[8], Eric Lespessailles[9], Kamal Shah[10], ChiaChi Hu[10], Randall M. Stevens[10], Christopher J. Edwards[11] and Charles A. Birbara[12]. [1]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA, [2]University of California San Diego, San Diego, CA, [3]University of Sheffield, Sheffield, United Kingdom, [4]Hospital Clinico Universitario, Santiago, Spain, [5]Schön Klinik Hamburg Eilbek, Hamburg, Germany, [6]University of Toronto, Toronto Western Hospital, Toronto, ON, [7]University of Genova, Genova, Italy, [8]University of Erlangen-Nuremberg, Erlangen, Germany, [9]University of Orléans, Orléans, France, [10]Celgene Corporation, Warren, NJ, [11]NIHR Wellcome Trust Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, [12]University of Massachusetts Medical School, Worcester, MA.

Background/Purpose: Apremilast (APR), an oral phosphodiesterase 4 inhibitor, works intracellularly to modulate inflammatory mediators. The PALACE 1, 2, and 3 trials compared the efficacy and safety of APR with placebo (PBO) in pts with active PsA despite prior DMARDs and/or biologics. The impact of APR on laboratory measurements was assessed in a pooled analysis of PALACE 1, 2, and 3.

Methods: Pts were randomized 1:1:1 to PBO, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline (BL) DMARD use. At wk 16, pts with <20% reduction from BL in swollen/tender joint counts qualified for protocol-defined early escape; those on PBO were re-randomized to APR20 or APR30 and those on APR remained on the initial APR dose. At wk 24, all remaining PBO pts were re-randomized to APR20 or APR30 through wk 52. Pts taking concurrent DMARDs were allowed to continue stable doses (MTX, sulfasalazine, leflunomide, or a combination). The analysis comprises all data from the APR-exposure periods (wks 0-≥52).

Results: 1,493 patients received study drug (PBO, 495; APR20, 501; APR30, 497) and were included in the safety population. The APR-exposure period included 720 pts treated with APR20 (766.4 pt-yrs) and 721 pts treated with APR30 (769.0 pt-yrs). Over the APR-exposure period, there were no clinically meaningful effects on laboratory measurements. Marked abnormalities in hematology and chemistry laboratory variables at any time during the exposure period were infrequent, with no treatment or dose effect evident. All marked hematological abnormalities occurred in a similar percentage of PBO pts vs APR pts during the PBO-controlled phase and continued without any significant changes during the APR-exposure period (wks 24-≥52). Overall, mean changes from BL clinical chemistry parameters were small and not clinically significant; no dose relationships were noted. Median values for both hematological and chemistry labs did not change meaningfully from BL during the trials. Most of the marked abnormal laboratory changes were transient, did not recur in spite of continuation of study drug, did not lead to study discontinuation, and were not clinically significant requiring specific treatment. Most pts had ALT and AST values ≤1 × ULN; ALT and AST values ≥3 × ULN were asymptomatic and transient with increased values returning to normal or BL in most pts despite continued treatment with APR, and similar to hematology parameters, without recurrence. There were no cases of liver function test elevations meeting Hy's Law (ALT/AST ≥3 ULN along with bilirubin ≥2 ULN without relevant clinical finding may indicate potential for drug-induced liver injury) during the APR-exposure period.

Select Markedly Abnormal Laboratory Parameters Over 0–≥52 Weeks of Apremilast Exposure

	Weeks 0–24*			Weeks 0–≥52§		
EAIR/100 Patient-Years	PBO (n=495) 168.2 Patient-Years	APR20 (n=501) 212.9 Patient-Years	APR30 (n=497) 209.1 Patient-Years	APR20 (n=720) 766.4 Patient-Years	APR30 (n=721) 769.0 Patient-Years	APR Total (n=1,441) 1,535.4 Patient-Years
Hematology						
Hemoglobin <10.5 (M) or <8.5 (F) g/dL	0.6	1.4	1.0	0.7	0.8	0.7
Leukocytes <1.5 10^9/L	0.0	0.0	0.0	0.0	0.0	0.0
Lymphocytes <0.8 10^9/L	10.3	4.3	7.8	4.0	4.0	4.0
Neutrophils <1 10^9/L	1.2	0.5	0.5	0.5	0.5	0.5
Platelets <75 10^9/L	0.0	0.0	0.0	0.1	0.0	0.1
Chemistry						
ALT >3 × ULN, U/L	0.6	0.5	3.4	1.1	1.2	1.1
AST >3 × ULN, U/L	1.2	0.5	1.0	0.5	0.5	0.5
Creatinine >1.7 × ULN, μmol/L	0.6	0.0	0.5	0.1	0.1	0.1
Glucose >13.9 mmol/L	1.8	2.8	1.4	2.3	2.0	2.1
Hemoglobin A1C >9%	1.9	1.5	0.0	1.5	0.6	1.0
Cholesterol >7.8 mmol/L	6.0	8.1	8.2	4.2	3.6	3.9
Triglycerides >3.4 mmol/L	31.0	28.2	26.8	18.3	17.5	17.9

*PBO-controlled period includes all data through week 16 for patients initially assigned PBO who escaped and data through week 24 for all other patients.
§Includes all APR-exposure data up to ≥52 weeks. EAIR = exposure-adjusted incidence rate; M = male; F = female; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Conclusion: APR demonstrated an acceptable safety profile and was generally well tolerated for up to 52 wks. No clinically meaningful effects on laboratory parameters were noted. These data do not indicate a need for laboratory monitoring.

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Serum CTX-I Predicts Systemic Bone Loss At The Hip Over 1 Year In Patients With Early Psoriatic Arthritis. Agnes Szentpetery, Mark Kilbane, Myra P. O'Keane, Muhammad Haroon, Phil Gallagher, Susan van der Kamp, Malachi McMenna and Oliver FitzGerald. Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland.

Background/Purpose: There is a growing interest in bone and cartilage biomarkers that could be used predicting and assessing changes in structural damage in inflammatory arthritis. Disease-related bone loss assessed by dual-energy X-ray absorptiometry (DXA) is a well known feature in RA and PsA, however data on bone loss during the first year of treatment in early disease are limited.

The aim of this study was (1) to study changes in serum levels of bone biomarkers and bone mineral density (BMD) measurements in early PsA and RA prior to and 12 months after introducing an anti-rheumatic drug; (2) to explore associations between disease-related variables, serum bone biomarkers and BMD measurements; (3) to investigate if serum bone biomarkers prior to treatment predict systemic bone loss over 1 year in patients with PsA and RA.

Methods: Recent-onset (<12 months), active, treatment naive PsA and RA patients were recruited. We measured serum bone-specific alkaline phosphatase (bone ALP), a marker of bone formation, and C-terminal cross-linking telopeptide (CTX-I), a degradation marker of type-I collagen reflecting systemic bone resorption at baseline, 3 and 12 months by immunoassay. We assessed bone remodelling balance by calculating bone ALP/CTX-1 ratios. BMD measurements were obtained at left total hip and lumbar spine at baseline and 12 month by DXA. Clinical parameters were correlated with bone biomarkers and BMD measurements.

Results: 64 patients (32 PsA, 32 RA) were included with median age 43 years. 95% of the patients were commenced on a DMARD therapy at baseline and 11.7 % (12.5% RA; 10.7% PsA) were also started on a TNF inhibitor. At 12 months 94.8% of the patients were on a DMARD and 34.5% on TNF inhibitor (33.3 % RA; 35.7% PsA).

Bone ALP levels did not change significantly in either cohort during the study. CTX-I levels decreased after 3 months of treatment in RA ($p=0.013$) and in the entire group ($p=0.043$) remaining lower at 12 months ($p=0.042$; $p=0.012$ respectively) compared to baseline. Bone ALP/CTX-I ratio was higher ($p=0.05$) at 1 year compared to baseline in the entire group reflecting improvement in bone remodelling balance.

Hip BMD decreased in both diseases, significantly in RA ($p=0.021$), whilst spine BMD decreased in RA ($p=0.056$) but increased in PsA ($p=0.017$).

CTX-I levels were correlated inversely with hip BMD in PsA at both baseline and 12 months ($r = -0.38$, $p=0.04$; $r = -0.51$, $p=0.007$) and similarly in the entire group ($r = -0.29$, $p=0.03$; $r = -0.3$, $p=0.02$). Baseline CTX-I levels correlated with the change in hip BMD over 12 month in the whole group ($r = 0.31$, $p=0.03$).

Stepwise multiple logistic regression analysis revealed significant associations of baseline CTX-I levels with change in BMD of the hip over 12 months in PsA (OR 2.8, $p=0.009$) and in the entire cohort (OR 2.5, $p=0.014$) with the model also including bone ALP, ESR, CRP, DAS28 CRP and HAQ.

Conclusion: The improvement in bone remodelling balance seen in early PsA and RA patients is most likely due to decrease in bone resorption after 1 year of appropriate anti-rheumatic therapy. High baseline levels of serum CTX-I may predict systemic bone loss at the hip over 1 year in patients with PsA.

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Cortical Bone Density As Measured By Digital X-Ray Radiogrammetry Correlates with Radiographic Joint Damage In The Hands Within 1 Year In Psoriatic Arthritis. Agnes Szentpetery, Muhammad Haroon, Phil Gallagher, Eric J. Heffernan and Oliver FitzGerald. Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland.

Background/Purpose: Structural destruction in peripheral joints may occur over time in both PsA and RA. We previously reported that 47% of early PsA patients treated with DMARD developed erosions within 24 months of disease onset. Digital X-ray radiogrammetry (DXR) is a sensitive method for quantifying changes in cortical bone mineral density (DXR-BMD) in the early phase of the disease. Radiological assessment using conventional X-rays is essential as an outcome measure to evaluate treatment efficacy.

The aim of this study was (1) to investigate radiographic changes in early PsA and RA prior to and 3, 12 months after introducing an anti-rheumatic drug; (2) to explore associations between radiographic assessment and DXR-BMD; and (3) to study if DXR-BMD measurements are predictive for radiographic progression over 12 months in patients treated with a DMARD or in combination with a TNFi.

Methods: Recent-onset (<12 months), active, treatment naïve PsA and RA patients were selected. Hand X-rays were obtained at 0, 3 and 12 months and read by a radiologist blinded for the study. Sharp-van der Heijde modified scoring method for PsA was used. Erosion (ES) and joint space narrowing scores (JSNS) were calculated. X-rays from PsA patients were also scored for proliferation (PS) according to the Ratigen Score. DXR-BMD was measured on the same X-rays scored for joint damage. Mean DXR-BMD (mg/cm^2) values of both hands and changes in DXR-BMD (mg/cm^2/month) were calculated. Regression analysis was used to assess predictors for radiographic progression from baseline to 12 months.

Results: 64 patients (32 PsA, 32 RA) were included. 95% were commenced on DMARD at baseline and 11.7 % (12.5% RA; 10.7% PsA) were also started on a TNFi. At 12 months 94.8% of the patients were on DMARD and 34.5% on TNFi (33.3 % RA; 35.7% PsA).

53% of RA and 66% of PsA patients had normal X-rays at baseline; 53% and 61% at 12 months respectively. Erosions were present in 41% of RA and 22% of PsA patients at baseline; 40% and 25% at 12 months.

There was no significant difference in mTSS between RA and PsA, but mTSS was higher in PsA at 12 months compared to baseline and 3 months ($p=0.05$). There was little radiographic progression over 1 year in both groups (2 RA and 4 PsA patients). ES and mTSS were higher, JSNS was lower in RA compared to PsA at all time points.

Inverse correlations were observed approaching significance between mTSS and DXR-BMD at all time points in PsA and in the entire cohort at 3 and 12 months. Changes in DXR-BMD from 3 to 12 months correlated significantly with baseline mTSS in both groups (RA $r=-0.37$, $p=0.04$; PsA $r=-0.45$, $p=0.02$) and in the entire cohort ($r=-0.34$, $p=0.01$).

Linear regression analyses indicated that high DXR-BMD at baseline associated with lower mTSS ($\beta=18.26$, $p=0.03$) in PsA and with JSNS and mTSS ($\beta=5.68$, $p=0.04$; $\beta=9.17$, $p=0.04$) in the entire group at 12 months. Change in DXR-BMD over 12 months associated significantly with ES, JSNS and mTSS at 3 and 12 months in the entire group.

Conclusion: To our knowledge this is the first prospective study showing correlations between DXR-BMD and radiographic damage in PsA in the early phase of the disease. Hand DXR-BMD correlated with subsequent radiographic damage in patients with PsA.

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Psoriatic Arthritis Mutilans: Clinical and Radiographic Definitions. A Systematic Review. Amir Haddad[1], Mansour Somaily[1], Sindhu R. Johnson[2], Rouhi Fazelzad[3], Amie T. Kron[4], Cathy Chau[5] and Vinod Chandran[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]Toronto Western Hospital, Toronto General Hospital, Mount Sinai Hospital, and University of Toronto, Toronto, ON, [3]University Health Network, Toronto, ON, [4]Toronto Scleroderma Research Program, Toronto Western Hospital, Mount Sinai Hospital, and University of Toronto, Toronto, ON, [5]Toronto Scleroderma Research Program, Toronto Western Hospital, Mount Sinai Hospital, University of Toronto, Toronto, ON.

Background/Purpose: Psoriatic Arthritis Mutilans (PAM) is the most severe form of psoriatic arthritis. Research on PAM has been impeded by the lack of an accepted definition. We performed a systematic review of the literature to identify clinical and radiographic features associated with the definition and manifestations of PAM.

Methods: Medline, Embase, Cochrane Central Register for Controlled trials, Cochrane databases of Systematic Reviews and CINAHL databases from 1946 until March 2013, were searched without language restriction but limited to humans studies. Two investigators independently screened titles and abstracts and included studies that reported information on patients with PAM with clinical or radiographic information. The selected articles were retrieved for extraction of the data. Machine translation software was used to translate articles to English. Two investigators independently used a standardized form to collect items mentioned in the definition of PAM including the presence of shortening of digits, digital telescoping, flail joints, number and type of joints affected, time to joint destruction, the presence of total erosions at both sides of the joint, bone resorption, pencil-in-cup change, ankylosis, and subluxation. Patients demographics, disease characteristics, clinical and radiographic outcomes were also recorded.

Results: 8145 citations were identified of whom 7080 were excluded as they were not related to the topic, 68 were on patients with other rheumatic diseases, 82 had missing or different outcomes and 866 were duplicates. Of the 103 articles selected for full review, 49 were eligible for data abstraction and included 17 review articles, 13 case studies, 12 cohort studies, 6 case series, 2 case-control and 2 cross sectional studies. The most commonly used definition was that by Moll and Wright[i] (78%). The clinical features that were mentioned in the definitions included shortening of digits (38%), presence of digital telescoping (36%) and flail joints (15%). Only 21% of the articles specified the type of joints affected and few commented on time to joint destruction. The radiographic items that were mentioned in the definition included the presence of bone resorption (45%), pencil-in-cup change (17%), ankylosis (21%), total joint erosion (13%) and subluxation (9%). The studies reported a total of 244 patients. Based on data availability, 49% were males and had a mean age of 44.7 $\pm$ 14.7 years, most of the cases had psoriasis before the diagnosis of arthritis with a mean age of psoriasis diagnosis at 25.6 $\pm$ 6 years and psoriatic arthritis at 30.9 $\pm$ 6.7 years. They had invariably one or more of the aforementioned clinical and radiographic features that affected one or more of the small joints in hands and feet within different time intervals.

Conclusion: The systematic review has shown a lack of consensus on the clinical and radiographic items used to define and characterize patients with PAM and advocates a formal definition of PAM.

[i] Semin Arth Rheum 1973;3:55–78

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Efficacy and Safety Of Vaccination Against seasonal 2012 Influenza Virus Among Patients With Psoriatic Arthritis and Psoriasis. Arik Polackek[1], Yuri Korobko[1], Noa Madar-Balakirski[1], Uri Arad[2], David Levartovsky[3], Ilana Kaufman[4], Marina Anouk[5], Irena Litinsky[6], Ella Mendelson[7], Daphna Paran[8], Hagit Matz[9], Dan Caspi[9], Michal Mandelbaum[10] and Ori Elkayam[2]. [1]Tel Aviv Medical Center, Tel Aviv, Israel, [2]Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [3]Tel Aviv Medical Ctr, Tel Aviv, Israel, [4]Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel-aviv, Israel, [5]Tel Aviv Sourasky Medical Ctr, Tel-Aviv University, Tel Aviv, Israel, [6]Department of Rheumatology, Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine Tel Aviv University, Tel Aviv, Israel, [7]Sheba Medical Center, Ramat Gan, Israel, [8]Tel Aviv Sourasky Medical Ctr, Tel-Aviv university, Tel Aviv, Israel, [9]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [10]Sheba Medical Center, Tel Aviv, Israel.

Background/Purpose: Patients with psoriatic arthritis (PsA) and psoriasis (Pso) are considered to be immunosuppressed and are therefore recommended to receive vaccination against seasonal influenza. However, in this population of patients, data on the efficacy and safety of vaccination

against influenza is scarce.The purpose of this study was to assess the efficacy and safety of vaccination against seasonal influenza in psoriatic arthritis and psoriasis patients.

Methods: Patients with PsA, Pso and healthy controls were vaccinated using the Sanofi Pasteur vaccine recommended by the WHO in 2012 which included 3 serotypes (A/California/7/2009, A/Victoria/361/2011 and aB/Wisconsin/1/2010 influenza virus i.eH1N1, H2N3 and B). Clinical and laboratory assessment were performed on the day of the vaccination and 4–6 weeks later. The immunogenicity of the vaccine was evaluated by hemagglutination inhibition assay. Geometric mean titers and the rate of seroconversion was analyzed in each group. The effect of the vaccine on disease activity was evaluated using 68 tender and 66 joint counts, number of dactylitis, psoriasis area severity index (PASI), patient visual analogue scale (VAS) for pain, physician VAS for pain, c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Results: 67 patients (63 PsA, 4 Pso, mean age 50.1, 37 female, 30 male, 55.2% treated with TNF α blockers, 31.3% on disease-modifying anti rheumatic drugs (DMARDs)) and 30 healthy controls participated in this study. Immunogenicity: The geometric mean titers increased significantly in both the patients and control group for each of the subtypes tested. A substantial and similar proportion of patients in both groups responded to the vaccine. The response rate was not affected by parameters such as age, gender, disease activity or the use of TNF α blockers or DMARDs. Effect of the vaccine on parameters of disease activity: no significant changes were observed in the tender and swollen joint counts, dactylitis, PASI, global evaluation of the patient and physician and ESR, while a raise in CRP was noticed. The most common side effect was transient local inflammation at the site of vaccination, the rate being similar in both groups.

Conclusion: Vaccination against seasonal influenza is safe and induces an appropriate response in patients with psoriatic arthritis and psoriasis, similar to healthy controls.

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Time Interval Between The Onset Of Psoriasis and The Onset Of Psoriatic Arthritis May Define Disease Subsets. Arane Thavaneswaran, Vinod Chandran and Dafna Gladman. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Psoriatic Arthritis (PsA) is a heterogeneous disease with widely varying clinical features and outcomes. Phenotypic heterogeneity may reflect genetic heterogeneity. We aimed to investigate whether the interval between the onset of psoriasis and PsA could be used to define more homogeneous subsets of PsA.

Methods: Data on the age at onset of psoriasis and PsA, clinical and radiographic features at baseline as well as HLA B*27 and C*06 status was obtained from a large well-phenotyped PsA cohort. Patients were divided into 4 quartiles based on the time interval between the onset of psoriasis and the onset of PsA. The distribution of the above HLA alleles between the 4 quartiles was investigated. Subsequently, the patients were divided into 2 groups by combing the first two and the last two quartiles. Differences between the clinical and radiographic features at baseline (t-tests, chi-squared test, logistic regression) between the two groups were then investigated.

Results: 1202 patients [56.7% males, mean (s.d.) age at first visit 47.4 (13.3) years, duration of psoriasis 18.2 (13.3) years, duration of PsA 10.1 (9.0) years] were distributed into the following 4 quartiles based on the time interval between onset of psoriasis and PsA- quartile 1: <0 years (n=318 patients, 26.5%), quartile 2: 0–5 years (n=291 patients, 24.2%), quartile 3: 5–13 years (n=262 patients, 21.8%) and quartile 4: >=13 years (n=331 patients, 27.5%). The distribution of HLA C*06 by quartile was 15.5%, 23.0%, 29.7% and 36.3% (trend test p-value <0.0001), while that of HLA B*27 was 21.2%, 18.1%, 15.6%, and 13.1% (trend test p-value =0.01), respectively.

At baseline, compared to group 1 (quartile 3 and 4), group 0 (quartile 1 and 2) had a significantly higher proportion of males, older age at onset of psoriasis but lower age at onset of PsA, lower PASI scores, higher prevalence of dactylitis, radiographic joint damage and patients treated with NSAIDs. There was no significant difference in the tender and swollen joint counts, ESR and the proportion of patients treated with DMARDs and biologics (Table 1). Since the proportion of patients positive for HLA B*27 and C*06 were different between the two groups, we examined whether the differences remained after adjusting for HLA status. After adjusting for HLA B*27 positivity there were no significant differences in the proportion of males, age at onset of PsA, and PASI score. When adjusting for HLA C*06 there was no difference in the proportion of males. When adjusting for HLA B*27 and C*06 differences between the two groups in age at onset of psoriasis, age at onset of PsA, PASI score, dactylitis and radiographic damage remained significant ($p<0.05$).

Table 1.

	Group 0 (N=609)	Group 1 (N=593)	P value
Age at first visit	43.38 (13.38)	44.57 (12.75)	0.1147
Males	370 (60.76%)	311 (52.45%)	0.0037
Age at psoriasis onset	35.01 (14.12)	21.92 (12.18)	<0.0001
Age at onset of PsA	35.38 (13.69)	38.93 (12.85)	<0.0001
Tender joint count	9.42 (9.10)	8.40 (8.20)	0.0664
Swollen joint count	5.08 (4.77)	5.18 (5.95)	0.7859
PASI	4.56 (6.86)	7.24 (9.17)	<0.0001
Dactylitis	217 (35.75%)	162 (27.41%)	0.0019
ESR	24.30 (19.83)	23.11 (21.31)	0.3464
Patients with erosions	296 (57.14%)	253 (48.28%)	0.0042
Modified Steinbrocker score	14.44 (34.37)	9.40 (26.45)	0.0082
Patients with at least unilateral sacroiliitis	182 (35.14%)	159 (30.34%)	0.0993
Patients satisfying NY criteria	137 (26.45%)	117 (22.33%)	0.1215
Treatment with NSAIDs	478 (82.84%)	423 (76.35%)	0.0067
Treatment with DMARDs	306 (53.31%)	269 (48.47%)	0.1038
Treatment with biologics	34 (6.19%)	38 (7.22%)	0.499
HLA B*27	93 (19.75%)	63 (14.16%)	0.0245
HLA C*06	90 (19.11%)	149 (33.56%)	<0.0001

*Mean (standard deviation) or proportion.

Conclusion: There are differences in the clinical phenotype of PsA when taking the interval between the onset of psoriasis and PsA into account. These differences are not fully explained by the differences in the HLA -B*27 and –C*06 status between the two groups.

Disclosure: A. Thavaneswaran, None; **V. Chandran**, None; **D. Gladman**, None.

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Disease Burden Among Patients With Psoriatic Arthritis Who Have Experienced First Line Tumor Necrosis Factor Inhibitor Regimen Failure In The European Union. Siva Narayanan[1], Yao Lu[2], Richard Hutchings[2] and Amanda Baskett[2]. [1]Ipsos Healthcare, Columbia, MD, [2]Ipsos Healthcare, London, United Kingdom.

Background/Purpose: Data on second line biologic patients who have experienced 1st line tumor necrosis factor inhibitor (TNF) failure and associated disease burden among patients (pts) with Psoriatic Arthritis (PsA) in the European Union (EU) is lacking. We assessed the clinical characteristics of pts with PsA on 2nd line biologics after 1st line anti-TNF failure.

Methods: A multi-country medical chart-review study of PsA pts was conducted among physicians (rheumatologists: 96%) in hospitals/private practices to collect de-identified data on pts recently treated with a biologic as part of usual care. Physicians from UK/Germany/France/Italy/Spain (5EU) were screened for practice duration and pt volume and recruited from a large panel to be geographically representative in each country. Eligible pt charts (>2) were randomly selected from a sample of prospective pts visiting each center/practice during the screening period. Physicians abstracted pt diagnosis, treatment patterns/dynamics and pt symptomatology/disease status. EU sites did not require local ethics reviews owing to de-identified retrospective data collection methodology.

Results: Between Jan2011 and Dec2012, 454 PsA pts (mean age:48.8yrs; female:49.6%) on 2nd line biologic after 1st line anti-TNF failure were identified. Mean time-to-1st line anti-TNF from diagnosis was 51.6 months; mean time on 1st line anti-TNF was 18.3months (pts <6:/7–12/13–24>/24months: 33%/21%/19%/27%). Top-3 1st line anti-TNFs observed were: etanercept (38%), adalimumab (32%), and infliximab (27%). The top-5 reasons for 1st line anti-TNF discontinuation were 'long-term efficacy failure', 'disease worsened', 'side-effects not tolerated', 'insufficient improvement', and 'short-term efficacy failure'. Mean time on current 2nd line biologic was 18.5months (pts <6/7–12/13–24>/24months: 28%/21%/25%/27%). Current 2nd line biologics (top-5) included: adalimumab (39%), etanercept (31%), infliximab (14%), golimumab (11%), abatacept (2%).

Top-5 reasons for choice of 2nd line biologic were 'mechanism of action', 'prevention of structural damage', 'improve signs/symptoms', 'disease worsened', 'positive personal experience'. Key lab measures documented were: ESR-21.7mm/h and CRP-8.3mg/dl. Among pts with available data, current HAQ was 1.1, Swollen Joint Count was 1.9 and Tender Joint Count was 3.4. Current disease severity per physician judgment (mild:moderate:severe) were: 48%:47%:5%. Current disease severity (mild:moderate:severe) by time on 1st line anti-TNF biologic (<6/7–12/13–24>/24months) were 47%:48%:5%/55%:42%:3%/49%:48%:4%/44%:49%:7% respectively.

Conclusion: Among PsA pts on their 2nd biologic who have experienced prior anti-TNF failure, 54% discontinued their 1st line anti-TNF regimen within 12months of initiation. There was considerable disease burden despite current 2nd line biologic. Further research is warranted to assess the effectiveness of switching in PsA pts and optimize the treatment strategies to alleviate disease burden among 1st line anti-TNF failures.

Disclosure: S. Narayanan, Ipsos Healthcare, 3; **Y. Lu**, Ipsos Healthcare, 3; **R. Hutchings**, Ipsos Healthcare, 3; **A. Baskett**, Ipsos Healthcare, 3.

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Response To Etanercept With Or Without Methotrexate Combination Therapy In Patients With Psoriatic Arthritis. Bernard Combe[1], Urs Kerkmann[2], Fiona Brock[3] and Gaia Gallo[2]. [1]Hôpital Lapeyronie-Service d'Immuno-rhumatologie, Montpellier, France, [2]Pfizer Europe, Rome, Italy, [3]Quanticate, Hitchin, Hertfordshire, United Kingdom.

Background/Purpose: Randomized controlled trials in psoriatic arthrtitis (PsA) have allowed treatment with TNF inhibitors (TNFi) as monotherapy as well as co-medication with methotrexate (MTX), but no trials have indicated any difference in response to TNFi in subgroups with and without concomitant MTX.[1] Current PsA treatment guidelines do not provide clear recommendations on the use of TNFi as monotherapy or combined with MTX.[2–4] Recent real-life data found no additional benefit in response but a trend towards better drug survival in patients receiving TNFi and concomitant MTX.[5,6] We pooled data (post-hoc) from two clinical trials[7,8] to evaluate clinical and functional outcomes in PsA patients receiving etanercept (ETN) with and without MTX.

Methods: Data from PsA patients with active disease receiving ETN (25 mg twice weekly[7] or 50 mg once weekly[8]) with (ETN+MTX arm) and without MTX (ETN arm) were included in descriptive summaries. Demographic and disease activity characteristics at baseline, PsARC and ACR20, 50, and 70 responses at 24 weeks, and change from baseline to week 24 in DAS28-CRP, HAQ-DI, and PASI were summarized for patients in the ETN arm and in ETN+MTX arm across both studies.

Results: At baseline, patients in the ETN (n=322) and ETN+MTX (n=153) arms had a mean age (SD) of 47.0 (11.7) and 47.3 (11.1) years, respectively; weight of 84.7 kg (18.7) and 87.1 (20.6); 38% and 42% were female. The duration of psoriasis was 18.4 (12.0) and 17.5 (11.0) years, respectively; duration of PsA, 8.2 (7.8) and 8.9 (7.0) years; DAS28-CRP, 4.7 (1.2) and 4.7 (1.1); HAQ-DI, 0.9 (0.7) and 1.1 (0.7); and PASI, 18.3 (10.2) and 16.1 (9.6). Other demographic and baseline disease characteristics were also similar for patients in the ETN arm and ETN+MTX arms. Similar proportions of patients in both arms achieved PsARC and ACR20 responses; numerically, a higher proportion of patients in the ETN arm achieved ACR50 and ACR70 responses than in the combination therapy arm. Little difference between groups was observed in DAS28-CRP, HAQ-DI, and PASI improvement from baseline (Table).

Table. Clinical and functional outcomes in patients in the ETN and ETN + MTX arms across studies[7,8]

	ETN Arm	ETN+MTX Arm
% patients achieving endpoint at week 24 (n/N)		
PsARC	80.3 (240/299)	82.6 (119/144)
ACR20	70.5 (203/288)	69.9 (100/143)
ACR50	54.9 (158/288)	48.3 (69/143)
ACR70	34.7 (100/288)	26.6 (38/143)
Change from baseline to week 24, mean (SD)		
DAS28-CRP	−1.9 (1.3)	−1.8 (1.1)
HAQ-DI	−0.5 (0.6)	−0.6 (0.6)
PASI	−13.6 (9.6)	−12.2 (9.5)

PsARC, Psoriatic Arthritis Response Criteria; ACR20/50/70, American College of Rheumatology 20%, 50%,and 70% improvement; DAS28, Disease Activity Score based on 28-joint count using C-reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index; PASI, Psoriasis Area and Severity Index.

Conclusion: Etanercept with or without MTX combination therapy provided similar benefit across clinical and functional outcomes in patients with active PsA at 24 weeks of treatment. Further research is warranted to investigate the effect of concomitant MTX on responses and drug survival in patients with PsA starting their first TNFi.

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ACR Poster Session A
Rheumatoid Arthritis - Clinical Aspects I: Comorbidities in Rheumatoid Arthritis
Sunday, October 27, 2013, 8:30 AM–4:00 PM

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Outcomes Of Patients With Rheumatoid Arthritis and Comorbid Hyperlipidemia. L Rosenblatt[1], JR Curtis[2], G Yang[1] and T Hebden[3]. [1]Bristol-Myers Squibb, Plainsboro, NJ, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Formerly of Bristol-Myers Squibb, Plainsboro, NJ.

Background/Purpose: Patients (pts) with RA have an increased prevalence of cardiovascular disease (CVD). Whether due to comorbidity or related to RA medications, many pts with RA have hyperlipidemia, a risk factor for CVD. Using data from a real-world setting we determined the overall and sex-specific risk of cardiovascular (CV) events in pts with RA, with or without comorbid hyperlipidemia, relative to those in a non-RA cohort.

Methods: This retrospective cohort study using claims data from a US commercial health plan (2005–2011) included pts with ≥2 physician diagnoses of RA (ICD-9: 714.0, 714.2) and a non-RA cohort, matched 3:1 with the RA cohort on demographics (age, gender, region, index year). Follow-up began at the index date, 1 year after initiation of full coverage with medical and pharmacy benefits, and lasted until the first CV event, end of enrollment, or end of data availability. Incidence of the first hospitalized CV event (composite of myocardial infarction and ischemic stroke) or *percutaneous coronary intervention*/coronary artery bypass graft in the post-index period was determined for each cohort and stratified by sex and the presence of hyperlipidemia (defined by the presence of a ICD-9. 272.xx diagnosis claim or antihyperlipidemic agent drug claim during the pre-index period). Cox proportional hazards regression model determined the hazard ratio (HR) for CV events, using the presence of RA as the independent variable, controlling for other baseline covariates (age, sex, hyperlipidemia, diabetes, and hypertension).

Results: The RA cohort consisted of 51,130 pts who were matched with 154,292 non-RA pts (37.9% and 38.7% with hyperlipidemia during baseline, respectively). The incidence of CV events per 1000 person-years was 10.19 for the RA cohort and 6.41 for the non-RA cohort (crude rate ratio [RR]=1.59). Within the RA cohort, incidence was 15.54 for pts with hyperlipidemia and 7.05 for pts without hyperlipidemia (crude RR=2.21); in the non-RA cohort, incidence was 10.55 and 3.82 for those with and without hyperlipidemia, respectively (crude RR=2.76). When controlling for covariates, the HR of CV events for pts with RA was 1.68 (95% CI: 1.50, 1.87) relative to non-RA pts. Among covariates, presence of hyperlipidemia conferred a significant risk of CV events ($p<0.0001$); the interaction between RA and hyperlipidemia was not significant ($p=0.13$). Sex-specific RRs and risk differences are shown.

Cohort	Hyperlipidemia (Yes/No)	Sex	CVD incidence rate (/1000 person-years)	Crude RR (with/without hyperlipidemia)	Crude rate difference (with – without hyperlipidemia)
RA	Yes	M	23.25	1.81	10.4
	No	M	12.85		
	Yes	F	12.32	2.21	6.74
	No	F	5.58		
Non-RA	Yes	M	14.74	2.23	8.13
	No	M	6.61		
	Yes	F	8.66	2.76	5.52
	No	F	3.14		

Conclusion: This real-world analysis demonstrates that pts with RA have an increased risk of CV events and, as seen with the non-RA cohort, CV event rates are incrementally higher for those pts with hyperlipidemia. Therefore, mitigating the increased CV risk associated with hyperlipidemia and optimizing lipid levels are key treatment strategies for pts with RA.

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Predictive Value Of Anti Cyclic Citrullinated Peptide and Rheumatoid Factor To The Development Of Rheumatoid Arthritis In a Cohort Of Healthy Relatives Of Patients With Rheumatoid Arthritis. Jose Dionisio Castillo-Ortiz[1] and Cesar Ramos-Remus[2]. [1]Maastricht University Medical Center, Maastricht, Netherlands, [2]Unidad de Investigacion en Enfermedades Cronico-Degenerativas, Guadalajara, Mexico.

Background/Purpose: Consanguineous relatives of patients with RA are at a higher risk to develop RA. It is also known that specific antibodies including CCP and RF may occur years prior to the disease onset. To assess the predictive value of serum IgM-RF and anti-CCP to the development of RA in a 5-year prospective cohort of healthy consanguineous relatives of RA patients.

Methods: RA patients (ACR criteria) attending one tertiary- and two secondary-care outpatient rheumatology clinics were asked to invite their consanguineous relatives to participate in the study. All patients and relatives underwent medical history; serum IgM-RF (nephelometry) and anti-CCP antibodies (ELISA II) were determined in patients and healthy relatives at baseline. Thereafter participant relatives were contacted by phone every four months using a structured interview (COPCORD questionnaire). When COPCORD was positive subjects had an in-office rheumatology assessment including physical examination, *erythrocyte sedimentation rate*, and plain x-Ray. The outcome was defined as fulfillment of ACR-EULAR criteria of RA. The Kaplan Meier curve was done to assess the time to the outcome and Cox analysis was used to determine baseline predictors (age, sex, anti-CCP, IgM-RF).

Results: A total of 771 consanguineous relatives from 257 RA patients were included. At baseline, all had COPCORD negative and the mean age was 35 (±12), 69% were females and 33% siblings. Thirteen (2%) subjects were positive to both CCP and RF: 9 (1 %) only to CCP and 16 (2 %) only to RF. Sixteen of 771 subjects (2%) developed rheumatoid arthritis during the 5-yrs follow up (3348 person-years), with an annual rate of 0.5% (Kaplan-Meier). The positive predictive value when CCP and RF are positive was 54% and 56% when only CCP was positive. RF per se had no predictive value (table 1). Cox analysis showed that age at baseline, CCP, RF, and siblings were significant predictors for developing RA over follow-up.

Conclusion: The positivity of CCP may be useful to detect preclinical disease in healthy relatives of RA patients.

Disclosure: J. D. Castillo-Ortiz, None; **C. Ramos-Remus**, None.

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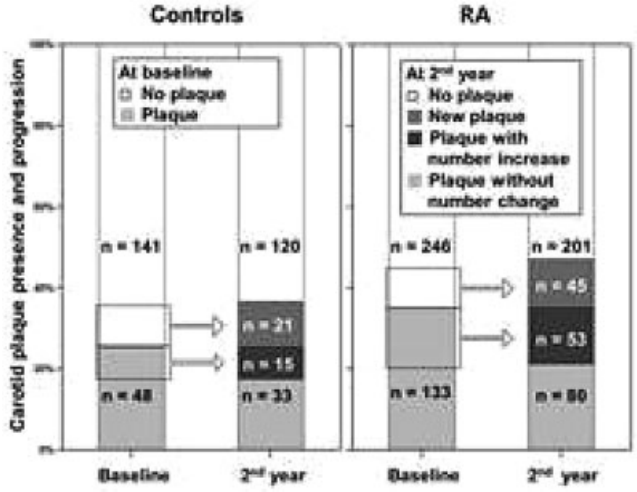
Inflammatory Burden Predicts Carotid Plaque Progression and Subsequent Cardiovascular Events In Rheumatoid Arthritis: The 2-Year Prospective Cohort Study. Churl Hyun Im, Sang Hoon Kwon, Jeong Soo Eun, Na Ri Kim, Eon Jeong Nam and Young Mo Kang. Kyungpook National University School of Medicine, Daegu, South Korea.

Background/Purpose: Rheumatoid arthritis (RA) patients have increased prevalence of carotid atherosclerosis, especially plaque formation, which has been associated with inflammatory burden in a previous study. We sought to investigate the risk factors of carotid atherosclerosis progression and cardiovascular events (CVE) in RA patients in a prospective cohort study.

Methods: Progression of carotid atherosclerosis, determined by carotid ultrasound and the incidence of CVE were investigated in a prospective KARRA cohort. All patients and healthy controls were prospectively followed up for 5 y ears or until deaths. Conventional CV risk factors, RA disease activity and severity markers, medication histories, and calculated areas under the curve of erythrocyte sedimentation rate (ESR-AUC) for 2 years follow-up were analyzed.

Results: Mean age and female frequency of RA patients were not different compared with those of healthy controls (54 ± 12 vs. 55 ± 12, 81.6 vs. 78.8%, respectively). The number of carotid plaques increased more rapidly in RA patients compared with controls during 2 years of follow-up (0.3 ± 0.7 and 0.2 ± 0.6, respectively, $P = 0.030$). Frequencies of new carotid plaques among subjects without plaque at baseline were not different between RA patients and controls. However, subjects with increased number of plaques who had plaques at baseline were more frequent in RA patients compared with controls (OR 3.086 [95% CI 1.518–6.276; $P = 0.002$]). RA patients with increased number of plaques who had plaques at baseline were significantly associated with modified health assessment questionnaire, tender and swollen joint counts, DAS28, methotrexate (MTX) dose, and ESR-AUC for 2-year period. In a multivariate analysis, tender joint count 68 (OR 1.129 [95% CI 1.025–1.243; $P = 0.014$]), ESR-AUC (OR 1.001 [95% CI 1.000–1.002; $P = 0.022$]), and MTX dose (OR 1.424 [95% CI 1.103–1.839; $P = 0.007$]) were independently associated with these patients. During the 2-year period, CVE occurred in seven (1.7%) among RA patients compared with one (0.5%) among controls. In RA patients, higher number of carotid plaques was significantly associated with CVE ($P = 0.001$). Furthermore, the incidence of CVE was 4.1% among patients with plaque, compared with 0.4 % among patients without plaque (RR 10.859 [95% CI 1.294–91.095; $P = 0.011$]). In a Cox regression model, two or more carotid plaque presence predicted CVE in RA patients during 2-year period (hazard ratio 27.463 [95% CI 3.306–228.124; $P = 0.002$]).

Conclusion: These prospective data suggest that the incidence of CVE depends on by baseline carotid plaques, the progression of which is strongly associated with time-integrated inflammatory burden in RA patients.



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Tocilizumab Treatment Increases Left Ventricular Ejection Fraction and Decreases Left Ventricular Mass Index In Rheumatoid Arthritis Patients Without Cardiac Symptoms: Assessment By Cardiac Magnetic Resonance Imaging At 3.0 Tesla. Hitomi Kobayashi[1], Isamu Yokoe[2], Hiroshi Sato[2], Yasuyuki Kobayashi[3], Kihei Yoneyama[3], Masaharu Hirano[4] and Masami Takei[1]. [1]NIhon University School of Medicine, Tokyo, Japan, [2]Itabashi Chuo Medical Center, Tokyo, Japan, [3]St.Marianna University School of Medicine, Kawasaki, Japan, [4]Tokyo Medical Colleage, Tokyo, Japan.

Background/Purpose: Left ventricular (LV) dysfunction in rheumatoid arthritis (RA) may result, at least in part, from inflammation that may be regional and global. Therefore, therapies that reduce inflammation (anti-IL-6 therapy) may delay onset and/or slow progression of LV dysfunction. Cardiac magnetic resonance imaging (CMR) is a sensitive technique for assessing subclinical LV dysfunction. The overall goal of this pilot study was to prospectively evaluate the effect of inhibition of IL-6 on LV function and structure in patients with RA without cardiac symptoms as assessed by using CMR at 3.0 T.

Methods: Consecutive RA patients (pts) with active disease and healthy controls were enrolled. All subjects had no history or clinical findings of hypertension, cardiovascular disease, diabetes mellitus, or dyslipidemia. The

RA pts who each had inadequate clinical response to methotrexate were prescribed tocilizumab (TCZ; 8 mg/kg IV every 4 wks). All subjects underwent baseline evaluation of LV function and structure, as measured by non-contrast CMR at 3.0 T. The following parameters were measured: global LV function (LV ejection fraction, end-systolic volume, end-diastolic volume, stroke volume, and cardiac output); and LV hypertrophy (absolute LV mass, LV mass index [mass/BSA]). After the baseline (BL) CMR, treatment with TCZ was initiated and pts were followed for 52 wks. Pts underwent follow-up CMR evaluation at 52 wks of treatment with TCZ. We examined differences in LV structure and function between control subjects and RA pts. We compared RA pts at BL and at 52 wks, and determined the association of LV structure and function with disease activity and severity measures.

Results: All RA pts received TCZ treatment for 52 wks. We compared 20 RA pts (100% female; mean age 53.4±10.2 y) at BL and at 52 wks, with 20 non-RA controls (100% female; mean age 54.0±4.6 y). DAS28-ESR, SDAI and swollen joint count were significantly lower in RA pts at 52 wks than at BL ($p<0.0001$, $p<0.0001$, $p<0.0001$, respectively). In RA pts at BL, ejection fraction (EF) was significantly lower than in controls ($p=0.04$), and LV mass Index was also significantly higher than in controls ($p=0.05$). Median EF at BL was 60.5% (25th and 75th percentiles 56.1% and 63.4%, respectively), and TCZ treatment resulted in a significant increase of EF at 52 wks (median value 64.3%; 25th and 75th percentiles 61.6% and 69.0%; $p<0.0001$). Median LV mass index at BL was 59.4 gm/m^2 (25th and 75th percentiles 54.3 gm/m^2 and 63.0 gm/m^2, respectively), and TCZ treatment also resulted in a significant decrease in mass index at 52 wks (median value 48.0 gm/m^2; 25th and 75th percentiles 44.1 gm/m^2 and 52.1 gm/m^2; $p=0.0013$). Percentage change in LV mass index in RA pts was significantly associated with percentage change in SDAI ($r=-0.63$, $p=0.0028$).

Conclusion: TCZ treatment contributed significantly to increasing LVEF and decreasing LV mass. Furthermore, we found a significant relationship between disease activity and measures of LV structure and function. TCZ may reduce progression of LV dysfunction and improve LV structure in association with reduced disease activity. These findings suggest that RA itself may be an important contributor to functional and structural abnormalities of LV.

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Visit-To-Visit Variability In Blood Pressure In Patients With Rheumatoid Arthritis (RA) Vs General Population, and Its Impact On Cardiovascular Events and All-Cause Mortality In Rheumatoid Arthritis. Elena Myasoedova, Cynthia S. Crowson, Abigail B. Green, Eric L. Matteson and Sherine E. Gabriel. Mayo Clinic, Rochester, MN.

Background/Purpose: Blood pressure (BP) variability has been associated with increased risk of cardiovascular (CV) disease and death in the general population. The impact of BP variability on CV events and mortality in RA is uncertain. We aimed to examine long-term visit-to-visit BP variability in RA vs non-RA subjects and to assess the impact of BP variability on CV events and all-cause mortality in RA.

Methods: The study included a population-based incident cohort of RA patients (1987 ACR criteria first met between 1980 and 2007) and a cohort of non-RA subjects of similar age and sex. All available clinic BP measures were collected from the medical records. BP variability was defined as within-subject standard deviation (SD) in systolic and diastolic BP. Cox models were used to examine the effect of BP variability on CV events (i.e. hospitalized/silent myocardial infarction, CV mortality, heart failure, ischemic heart disease, angina, or revascularization procedures) and all-cause mortality in RA.

Results: The study included 452 RA patients (mean age 55.5 years, 31% males) and 436 non-RA subjects (mean age 55.7 years, 31% males). During the mean follow-up of 7.1±2.7 years in RA and 7.2±2.6 years in the non-RA cohort there were 13,470 BP measures in RA and 9,476 in the non-RA subjects; median time between the measurements: 30 days in RA vs 27 in the non-RA cohort (p=0.93). The mean systolic BP at RA incidence/index date was higher in RA vs non-RA cohort (131.2±18.7 mmHg vs 128.2±19.3 mm Hg, p=0.018); the mean diastolic BP was similar in RA (75.1±10.9 mm Hg) vs non-RA cohort (75.6±11.0 mm Hg, p=0.53). There were 290 (64%) patients with hypertension in RA vs 241 (55%) in the non-RA cohort at index date. The proportion of hypertensive subjects on antihypertensive drugs was similar in RA and non-RA cohort at index date (35% vs 33%, respectively, p=0.59) and during the follow-up (36% vs 31% at 10 years, respectively, p=0.30). Patients with RA had higher visit-to-visit variability in systolic BP (13.8±4.7 mm Hg), but not diastolic BP, than the non-RA subjects (13.0±5.2 mm Hg, p=0.004). There was a significant decline in systolic BP variability in RA (p<0.001) after RA incidence/index date, adjusting for age, sex and calendar year of RA; no such trend was noted in the non-RA cohort (p=0.73). Diastolic BP variability remained unchanged in RA (p=0.56) and non-RA (p=0.15) cohort. During the follow-up, 33 CV events and 57 deaths occurred in the RA cohort. Adjusting for systolic and diastolic BP, body mass index, smoking, diabetes, dyslipidemia and use of antihypertensives, higher systolic BP variability was associated with increased risk of CV events in RA (hazard ratio [HR] 1.15, 95% confidence interval [CI] 1.02–1.3); higher diastolic BP variability was associated with all-cause mortality (HR 1.14, 95%CI 1.03–1.27).

Conclusion: Patients with RA had higher long-term visit-to-visit variability of systolic BP than non-RA subjects. Systolic BP variability declined significantly after the index date in RA patients, but not in the non-RA subjects. Higher visit-to-visit variability in systolic and diastolic BP was associated with adverse CV outcomes and all-cause mortality in RA.

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Risk Of Venous Thromboembolism and Use Of Disease-Modifying Antirheumatic Drugs For Rheumatoid Arthritis. Seoyoung C. Kim[1], Daniel H. Solomon[2], Jun Liu[3], Jessica M. Franklin[4], Robert J. Glynn[1] and Sebastian Schneeweiss[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Harvard Medical School, Brigham and Women's Hospital, Division of Rheumatology, Division of Pharmacoepidemiology, Boston, MA, [3]Brigham and Women's Hospital, Harvard Medical School, Boston, Boston, MA, [4]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Recent research suggests that rheumatoid arthritis (RA), an autoimmune systemic inflammatory disease, increases the risk of venous thromboembolism (VTE) including pulmonary embolism and deep vein thrombosis. We compared the risk of VTE in RA patients initiating treatment with biologic disease-modifying antirheumatic drugs (bDMARD), methotrexate (MTX) or non-biologic DMARD (nbDMARD).

Methods: We conducted a population-based cohort study combining three U.S. commercial insurance claims databases (2001–2012). Adult patients with a new diagnosis of RA were identified based on ≥2 RA diagnoses that were ≥7 days apart with a baseline period free of RA diagnosis or DMARD use for ≥1 year. Among these patients, initiators (starting or switching) of various DMARDs were identified. Patients with a history of VTE, malignancy and use of anticoagulants at baseline were excluded. Drug regimens were categorized into three mutually exclusive hierarchical groups: (1) a biologic DMARD with or without nbDMARDs, (2) MTX without a biologic DMARD, or (3) nbDMARDs without a biologic DMARD or MTX. We calculated incidence rates (IR) with 95% confidence intervals (CI) of VTE identified by a previously validated algorithm with inpatient diagnosis codes (PPV 75–90%). Cox proportional hazards models stratified by propensity score (PS) deciles after asymmetric trimming were used for 3 pairwise comparisons, controlling for baseline demographic factors, comorbidities, medications, and health care utilization. Sensitivity analysis limited to 180 days of follow-up and PS-matched analyses were also performed.

Results: A total of 29,481 RA patients with 39,647 treatment episodes were identified. Mean (SD) age was 49 (12) years for bDMARD and nbDMARD groups and 51 (12) for MTX. The crude IR of VTE per 1,000 person-years was higher in the bDMARDs group (5.53, 95% CI 3.67–8.32) compared to nbDMARDs and MTX (**Table**). In the PS decile-stratified Cox regression, the hazard ratio (HR) of VTE associated with initiation of bDMARDs was 1.83 (95% CI 0.92–3.63) compared to nbDMARDs and 1.39 (95% CI 0.73–2.64) compared to MTX. The HR of VTE associated with initiation of MTX versus nbDMARDs was 0.78 (95% CI 0.50–1.21). In a sensitivity analysis limiting the follow-up up to 180 days, bDMARDs was associated with a significantly increased risk (HR 2.48, 95% CI 1.14–5.40). In the PS-matched analyses, the HR was 1.34 (95% CI 0.65–2.75) in bDMARDs vs. nbDMARDs and 1.73 (95% CI 0.90–3.32) in bDMARDs vs. MTX.

Table. Risk of venous thromboembolism associated with initiation of DMARDs: PS decile-stratified 'as treated' analysis

Exposure	Treatment episodes	VTE	Person-years (PY)	IR (95% CI) per 1,000 PY	HR (95% CI)	HR (95% CI) 0-180d only
bDMARDs	4488	23	4157.90	5.53 (3.67–8.32)	1.83 (0.92–3.63)	**2.48 (1.14–5.40)**
nbDMARDs	12859	32	7220.08	4.43 (3.13–6.26)	Ref	Ref
bDMARDs	4597	21	4368.17	4.81 (3.14–7.38)	1.39 (0.73–2.64)	1.80 (0.84–3.85)
MTX	13912	32	9258.12	3.46 (2.45–4.89)	Ref	Ref
MTX	16352	42	11075.60	3.79 (2.80–5.13)	0.78 (0.50–1.21)	0.86 (0.50–1.48)
nbDMARDs	14618	41	8249.97	4.97 (3.66–6.75)	Ref	Ref

Conclusion: Among newly diagnosed RA patients, initiating a bDMARD was associated with a likely increase, but not statistically significant, in the risk of incident VTE compared to those initiating MTX or nbDMARDs, albeit low absolute risks of VTE. Initiation of bDMARDs was significantly associated with a 2.5-times elevated risk of VTE in the first 180 days.

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Management Of Hyperlipidemia In Patients With RA: Results From The Corrona Certain Study. Dimitrios A. Pappas[1], Ani John[2], Joel M. Kremer[3], George W. Reed[4], Tanya Sommers[4], Jeffrey D. Greenberg[5], Ashwini Shewade[2] and Jeffrey R. Curtis[6]. [1]Columbia University, New York, NY, [2]Genentech Inc., South San Francisco, CA, [3]Albany Medical College and The Center for Rheumatology, Albany, NY, [4]CORRONA, Inc., Southborough, MA, [5]NYU Hospital for Joint Diseases, New York, NY, [6]7University of Alabama at Birmingham Division of Clinical Immunology and Rheumatology, Birmingham, AL.

Background/Purpose: RA is associated with an increased risk for cardiovascular disease (CVD).[1] Patients (pts) with RA share similar risk for CVD with non-RA pts who are 10 years older and with diabetics and may benefit from lipid-lowering therapies such as statins[2]; however, information on management of hyperlipidemia in pts with RA is not well characterized. This study evaluated adequacy of lipid-lowering therapy in a cohort of 779 ptswith RA participating in the CORRONA registry.

Methods: Pts with at least moderate disease activity (CDAI $>$ 10) initiating a biologic DMARD participated in an ongoing comparative effectiveness study (CERTAIN) nested within CORRONA. Lipid levels and information about statin or other lipid-lowering use was obtained at baseline. Clinical and demographic characteristics of pts receiving antihyperlipidemic therapy at baseline were compared with pts with increased lipid levels (LDL $\geq$ 100 mg/dL and LDL $\geq$ 130 mg/dL) who were not receiving lipid-lowering agents.

Results: A total of 779 CERTAIN enrollments were evaluated between November 20, 2010, and July 2, 2012. At baseline, 485 (62.3%) pts had LDL $\geq$ 100 mg/dL (223 [28.6%] with LDL $\geq$ 130 mg/dL), 84 (10.8%) had HDL $<$ 40 mg/dL, 311 (39.9%) had TC $\geq$ 200 mg/dL, 298 (38.3%) had TG $\geq$ 150 mg/dL and 69 (8.9%) had a TC/HDL ratio $>$ 5. Of 779 pts, 191 (24.5%) were already using statins and/or other lipid-lowering therapies at baseline. A total of 408 (52.4%) pts with an LDL $\geq$ 100 mg/dL and 192 (24.6%) pts with LDL $\geq$ 130 mg/dL were not on statin therapy. Pts receiving statins were older (62.1 $\pm$ 11.0 vs 54.1 $\pm$ 12.8 years), less frequently female (66.5% vs 78.4%) and had more frequent history of CVD (22.5 vs 3.4%) and diabetes mellitus (9.4 vs1.7%) compared with pts having LDL $\geq$ 100 mg/dL who were not receiving statins. Similar differences were seen comparing pts on statins with pts with LDL $\geq$ 130 but not on statins.

Conclusion: Consistent with previous reports,[3,4] a considerable proportion of hyperlipidemic RA pts at risk for CVD were not receiving lipid-lowering therapy. Practicing rheumatologists need to be aware of the prevalence of hyperlipidemia and appropriate management to reduce risk for CVD.

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Comparing Myocardial Infarction Risks Associated With Biologics Of Varying Mechanisms Of Action Among Older Rheumatoid Arthritis Patients. Jeffrey R. Curtis[1], Huifeng Yun[2], Jie Zhang[2], Fenglong Xie[2], Lang Chen[2], Emily Levitan[2], James Lewis[3], Timothy Beukelman[2], Kenneth G. Saag[2] and Iris Navarro-Millan[2]. [1]University of Alabama at Birmingham, Division of Clinical Immunology and Rheumatology, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Anti-TNF biologics have been associated with a reduced risk for acute myocardial infarction (AMI) in some rheumatoid arthritis (RA) populations. The comparative risks for AMI associated with newer biologics with alternative mechanisms of action other than TNF blockade have not been well characterized.

Methods: Using Medicare data from 2006–2011 for patients with RA, we identified new users of abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab. New users were defined specific to each drug using a 12 month 'baseline' period. To increase homogeneity of patients' characteristics to allow comparison with biologics typically not used as first line agents, patients were required to have used another biologic during baseline.

Eligible subjects must have been continuously enrolled in Medicare Parts A, B and D in baseline and throughout follow up and could not have had a hospitalized AMI during baseline. Follow up started from the drug initiation date and ended at the earliest of: AMI (primary position or non-primary), a 30 day gap in current exposure, death, loss of Medicare coverage or Dec 31, 2011. Confounding was controlled through a person-specific risk score. We calculated the incidence rate of AMI for each biologic and risks during follow-up using Cox regression adjusting for risk score decile, disability, baseline glucocorticoid use, methotrexate use, and dual eligible status, and accounting for clustering of biologic exposure treatment episodes within patients.

Results: Of 27,082 new biologic users, 11.3% initiated etanercept, 15.8% adalimumab, 6.1% certolizumab, 4.4% golimumab, 12.6% infliximab, 29.0% abatacept, 14.6% rituximab and 6.3% tocilizumab. Among 24,237 eligible RA patients, we identified 181 hospitalized AMIs, yielding an overall crude incidence rate of 0.88/1000py. After adjustment for potential cofounders and compared to abatacept users, the adjusted hazard ratios of various biologics were not significantly different (Table). Ongoing work is confirming the robustness of the results across a range of sensitivity analyses.

Table. Events, absolute incidence rate and adjusted hazard ratio of hospitalized MI

Biologic Exposures	Events	Crude incidence rate per 100 py	Adjusted Hazard Ratio* (95% CI)
Abatacept	71	0.96	1.0 (referent)
Anti-TNF	70	0.78	0.87 (0.55, 1.36)
Rituximab	34	1.00	0.98 (0.57, 1.68)
Tocilizumab	$<$11	0.374	0.43 (0.13, 1.42)

* Adjusted for age, sex, risk score decile, steroid use during baseline, specific biologic use during baseline, original reason for Medicare coverage and dual eligible status.

Conclusion: Among patients with RA, the risk for hospitalized myocardial infarction was similar between anti-TNF therapies and biologics with other mechanisms of action. The protective effect previously observed with anti-TNF therapies may apply more broadly to newer biologics and may be a consequence of reduction in inflammation rather than a drug-specific effect.

Disclosure: J. R. Curtis, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, Abb Vie, 2, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, Abb Vie, 5; **H. Yun**, None; **J. Zhang**, Roche/Genentech, 2; **F. Xie**, None; **L. Chen**, None; **E. Levitan**, Amgen, 2; **J. Lewis**, Pfizer, Prometheus, Lilly, Shire, Nestle, Janssen, AstraZeneca, Amgen, 5, Centocor, Shire, Takeda, 2; **T. Beukelman**, Genentech and Biogen IDEC Inc., 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 2; **K. G. Saag**, Ardea; Regeneron; Savient; Takeda, 5, Ardea; Regeneron; Savient; Takeda, 5; **I. Navarro-Millan**, None.

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Hyperuricemia As a Risk Factor for Cardiovascular Disease in Patients With Rheumatoid Arthritis. Daniel Kuo, Cynthia S. Crowson, Sherine E. Gabriel and Eric L. Matteson. Mayo Clinic, Rochester, MN.

Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk of developing cardiovascular disease (CVD). There is growing evidence that serum uric acid plays an important role in CVD in the general population. The purpose of this study was to evaluate whether hyperuricemia is a risk factor for CVD in patients with RA.

Methods: A population-based inception cohort of patients diagnosed between 1980 and 2007 with adult-onset RA according to 1987 ACR guidelines was assembled. A comparison cohort of subjects without RA (non-RA) but with similar age and sex was also assembled. All subjects were followed from inception/index until death, migration, or December 31, 2008. All clinically obtained uric acid values were collected. Per reference ranges, hyperuricemia was defined as serum uric acid >8.0 mg/dl for males and >6.1 mg/dl for females. CVD recorded for each patient included angina, coronary heart disease, revascularization procedures, myocardial infarction (MI) and heart failure (HF). Noncardiac vascular diseases included stroke, thromboembolism, and peripheral arterial disease (PAD). Cox proportional hazards models were used to assess the impact of hyperuricemia on the development of CVD and mortality among RA and non-RA subjects as well as noncardiac vascular disease in RA patients.

Results: The study included 813 patients with RA and 813 subjects without RA (mean age 55.9 years; 68% female in both cohorts). There was no significant difference in the presence of hyperuricemia between the cohorts at baseline (10% in RA vs. 13% in non-RA; p=0.15). Cumulative incidence of hyperuricemia was higher in RA patients (19.1% ± 1.8% at 10 years in RA vs. 12.4% ± 1.5% in non-RA; p=0.005). In patients without RA, after adjusting for traditional cardiovascular risk factors, hyperuricemia was associated with HF (HR: 1.87; 95% CI: 1.08, 3.25) and CVD (HR: 1.79; 95% CI: 1.13, 2.84). In patients with RA, hyperuricemia was not significantly associated with the assessed cardiac outcomes. However, hyperuricemia appeared to be more strongly associated with mortality among RA patients (HR: 1.93; 95% CI: 1.43, 2.60) than among the non-RA subjects (HR: 1.51; 95% CI: 1.06, 2.16). After adjusting for vascular risk factors, in patients with RA, hyperuricemia was significantly associated with PAD (HR: 2.74; 95% CI: 1.28, 5.86).

Conclusion: Patients with RA were more likely to develop hyperuricemia than patients without RA. In patients with RA, hyperuricemia was a significant predictor of increased mortality and PAD but not CVD. Further studies are needed to improve our understanding of the effects of hyperuricemia in RA.

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Oral Calcium Supplementation Is Associated With Subclinical Atherosclerosis In Rheumatoid Arthritis. Shanthi Dhaduvai[1], Laura Geraldino-Pardilla[1], Jon T. Giles[2] and Joan M. Bathon[3]. [1]Columbia University Medical Center, New York, NY, [2]Columbia University, College of Physicians & Surgeons, New York, NY, [3]Columbia University, New York, NY.

Background/Purpose: Recent studies in the general population highlight possible adverse cardiovascular effects with calcium supplementation; however, the association between calcium intake and subclinical markers of atherosclerosis has not been explored in patients with rheumatoid arthritis, a group with increased risk for coronary artery disease and cardiovascular mortality.

Methods: Among RA patients participating in a cohort study of subclinical cardiovascular disease (CVD), daily supplemental calcium dose was assessed from prescription and over the counter medications at baseline and at the first follow-up visit (median time from baseline 20 months). Participants underwent 64-slice cardiac multidetector row CT scanning at baseline and at visit 3 (median time 39 months from baseline) to assess coronary artery calcium (CAC), a measure of coronary atherosclerosis. The relationship of average daily intake of calcium (mg/day) with CAC was assessed by multivariable ordinary logistic regression with CAC score dichotomized at 100 units (a level predictive of subsequent CVD events), and adjusting for relevant confounders.

Results: A total of 145 RA patients [38% male, mean age 59±8 years, median RA duration 9 years, mean DAS28 3.6±1.0] had complete longitudinal data. At baseline, 42 (28%) were taking ≥1000mg/d of calcium while the remainder took <1000mg/d. A CAC score ≥100 units was observed in 44 (30%) at baseline and 51 (35%) at follow-up. Age, gender, body mass index (BMI), and use of anti-hypertensives were associated with both CAC and calcium intake, and were considered as relevant confounders in subsequent analyses. At baseline, CAC scores of ≥100 were significantly less frequent in the higher vs. lower dose calcium supplementation groups [OR 0.30 (95% CI 0.12–0.78) (Fig 1a)], and this difference remained significant after adjustment for relevant confounders [OR 0.31 (95% CI 0.97-0.95) (Fig 1a)]. Similarly, at follow-up, CAC scores of ≥100 were also significantly less frequent in the group taking an average calcium supplement dose of ≥1000mg/d vs. those taking <1000mg/d (Fig 1b); however, when adjusted for relevant confounders, there was only a trend to significance [OR 0.40 (95% CI 0.14–1.15) (Fig 1b)]. There was no gender heterogeneity in the association of calcium intake with CAC score. Change in CAC score over time between baseline and follow-up was not statistically significantly different between the two calcium groups.

Conclusion: Calcium supplementation was not associated with a higher risk of coronary atherosclerosis in this RA population, and may have even been protective, a finding with relevant therapeutic implications in the daily treatment of RA patients.

Disclosure: S. Dhaduvai, None; **L. Geraldino-Pardilla**, None; **J. T. Giles**, None; **J. M. Bathon**, None.

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Traditional Cardiac Risk Factors Predict Significant Coronary Plaque Burden In Asymptomatic Patients With Rheumatoid Arthritis. George A. Karpouzas, Jennifer Malpeso, Tae-Young Choi, Youngju Pak and Matthew Budoff. Harbor-UCLA Medical Center, Torrance, CA.

Background/Purpose: Computed tomography angiography (CTA) provides prognostic information in patients with suspected but unknown coronary artery disease (CAD); subjects without plaque had no incident major cardiovascular events (MACE) at 52 months. In those with obstructive plaque (>50% stenosis) or significant plaque burden [segment involvement score (SIS)>5, or segment stenosis score (SSS)>5] incident MACE was noted in 69%, 75%, and 80% respectively at 52 months. We evaluated the contributions of demographic, traditional cardiac risk factors (CRF) and rheumatoid arthritis (RA)-associated variables on the risk of having obstructive plaque, SIS>5, or SSS>5 in 150 subjects with RA and no symptoms or diagnosis of CAD compared to 150 age and gender-matched controls.

Methods: Patients and controls underwent CTA; qualitative and quantitative plaque evaluation was carried out using a standard 15-coronary segment American Heart Association Model. Subjects with either obstructive plaque, or SIS>5, or SSS>5 where considered high-risk; the remainder were considered low-risk. Chi-square or Fisher's exact tests evaluated the associations between binary variables and high-risk outcomes while simple logistic regression model was used for continuous variables. The Breslow-Day test assessed homogeneity of OR between two groups.

Results: A higher proportion of RA subjects were classified in the high-risk group: 23 (15.3%) vs. 8 (5.3%) in controls, OR (95%CI)=3.2 (1.4–7.4), p=0.004. Age was a significant determinant of high risk for the entire cohort (n=300) [OR=1.08 (1.04–1.13), p=0.0004], as well as for the RA group [OR=1.09 (1.04–1.15), p=0.001], but not the controls [OR=1.06 (0.98–1.15), p=0.14]. In RA patients, age>55 years was the best predictor of high-risk outcome, followed by male gender, diabetes, and hypertension (table 1); none of the RA-associated parameters predicted such outcome. No demographic or CRF predicted high-risk outcomes in controls. Significant interactions were observed between male gender and hypertension for high-risk outcomes in RA patients (p=0.024, and p=0.04 respectively).

Table 1. Outcome= presence of obstructive plaque (>50% stenosis), or SSS>5, or SIS>5 (High-risk) vs. not (low-risk)

	RA-univariate		Controls-univariate		RA vs. controls-differences in OR (Breslow-Day test)
parameters	OR	p	OR	p	p
Age>(55)	5.93 (2.1–17)	***0.0003***	2.27 (0.5–9.9)	0.3	0.29
Male	5.62 (1.9–16.2)	***0.002***	N/A*	0.6	***0.026***
HTN	2.9 (1.1–7.5)	***0.02***	0.4 (0.09–2.3)	0.47	***0.04***
DM	4.2 (1.56–11.1)	***0.005***	1.56 (0.3–8.2)	0.6	0.3
Dyslipidemia	0.4 (0.09–1.9)	0.37	1.3 (0.3–5.5)	0.7	0.25
smoking	1.0 (0.2–4.86)	1	N/A*	0.6	0.27
FHx	1.1 (0.12–9.95)	1	0.4 (0.1–1.9)	0.3	0.48
RA>5 years	2.35 (0.75–7.3)	0.14	–	–	–
RF (+) & a-CCP (+)	1 (0.2–4.8)	1	–	–	–
DAS28-3v>3.2	1.37 (0.56–3.3)	0.5	–	–	–
Erosions	1.55 (0.57–4.2)	0.47	–	–	–
JRS	1.43 (0.37–5.5)	0.7	–	–	–

*N/A: OR not applicable due to presence of 0 cell value.

Conclusion: Demographic and traditional CRF such as age, male gender, diabetes, and hypertension in decreasing significance predict obstructive or high burden coronary plaque by CTA in patients with RA and no symptoms or diagnosis of CAD. Male gender and hypertension differentially predict such outcomes in RA compared to controls.

Disclosure: G. A. Karpouzas, None; **J. Malpeso**, None; **T. Y. Choi**, None; **Y. Pak**, None; **M. Budoff**, None.

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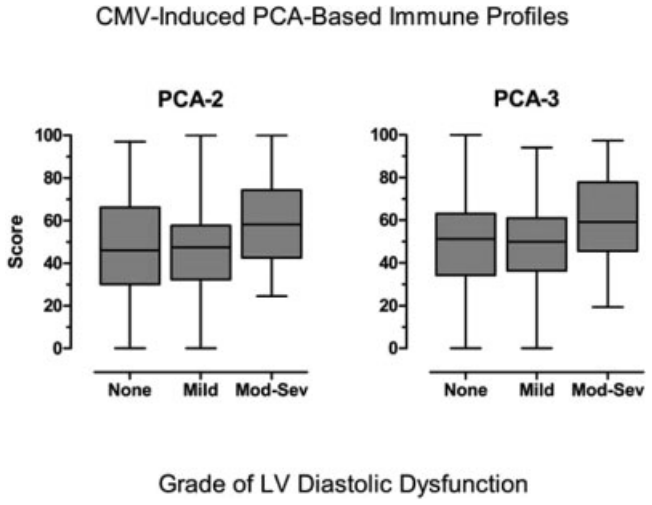
Cytomegalovirus-Related Immunity Correlates With Myocardial Disease In Rheumatoid Arthritis. John M. Davis III, Cynthia S. Crowson, Michael A. Strausbauch, Terry M. Therneau, Eric L. Matteson, Keith L. Knutson and Sherine E. Gabriel. Mayo Clinic, Rochester, MN.

Background/Purpose: We recently discovered correlations between a profile of cytokines produced in response to human cytomegalovirus (CMV), poor treatment outcome, and erosive joint damage. The objective of this study was to determine if a similar CMV-induced cytokine profile would also correlate with myocardial disease in patients with RA.

Methods: A correlative study of 324 patients with RA in our population-based inception cohort was performed. Diastolic function was evaluated using transthoracic 2D/Doppler echocardiography and categorized as normal, mild LVDD, moderate-to-severe LVDD or heart failure, or indeterminate. Immunological profiles of 17 cytokines (IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17A, MCP-1, MIP-1β, G-CSF, GM-CSF, TNF-α) produced by peripheral blood mononuclear cells (PBMCs) in response to stimulation with combined cytomegalovirus or Epstein-Barr virus lysates (CMV/EBV) were assessed using multiplex assays. Principal components analysis (PCA) was used to derive robust and informative cytokine profiles based on the 1st, 2nd and 3rd principal components. Mixed effects models were used to normalize the data and test for associations between the CMV/EBV PCA scores and moderate-to-severe LVDD/HF, adjusting for age, sex, cardiovascular risk factors, and RA disease characteristics. Among a separate sample of 64 patients with early RA having available viral serologies, the PCA scores were correlated with CMV or EBV IgG.

Results: The mean age of the subjects was 60.4 years, 74% were female, and the mean RA duration was 9.9 years. 151 (47%) had normal diastolic function, 64 (20%) had mild LVDD, 35 (11%) had moderate-to-severe LVDD or HF, and 74 (23%) were indeterminate. The PCA scores for the 2nd and 3rd principal components (PCA-2 and PCA-3, respectively) were associated with moderate-to-severe LVDD or HF compared to patients with normal diastolic function (odds ratio = 1.28 per 10-unit increase in the 100 point score, p = 0.022 and odds ratio = 1.24, p = 0.067, respectively). The five most informative cytokines in PCA-2 (from highest to lowest importance) were G-CSF, IL-6, IL-8, IL-1β, and GM-CSF and in PCA-3 were TNF-α, MIP-1β, IL-8, IL-1β, and IFN-γ. Among patients with early RA, both PCA-2 (r = 0.25, p = 0.06) and PCA-3 (r = 0.38, p = 0.003) were shown to correlate with CMV IgG whereas neither of the PCA scores were found to correlate with EBV IgG (r < 0.1 for all). A signature incorporating PCA-2 was developed with very good accuracy in predicting advanced myocardial disease (C-statistic = 0.834).



Conclusion: A profile of CMV-related immunity is associated with moderate-to-severe LVDD in persons with RA. The findings are relevant to developing myocardial risk assessment tools and to understanding how perturbations in innate and adaptive immunity in relation to latent CMV infection impact the pathophysiology of myocardial disease in RA.

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Detrimental Impact Of Long-Term Cumulative Burden Of Rheumatoid Arthritis (RA) Disease Severity On Cardiovascular Outcomes In RA. Elena Myasoedova[1], Birkan Ilhan[2], Helen Khun[1], Eric L. Matteson[1] and Cynthia S. Crowson[1]. [1]Mayo Clinic, Rochester, MN, [2]Marmara University, School of Medicine, Istanbul, Turkey.

Background/Purpose: Several studies have shown the associations of various measures of rheumatoid arthritis (RA) disease severity with unfavorable cardiovascular (CV) outcomes in RA. The association of cumulative RA severity burden on CV disease has not been investigated in longitudinal population-based studies. We aimed to examine the impact of long-term cumulative burden of RA disease severity on CV outcomes in RA.

Methods: A previously validated Claims-based Index of RA Severity (CIRAS; Ting et al. Arth Res Ther. 2008;10:R95) was used to estimate RA severity in a population-based incident cohort of patients with RA who were >/= 30 years old, fulfilled 1987 ACR criteria between 1/1/1988 and 1/1/2008, and had no history of CV disease. Claims-based data were used to calculate the CIRAS score: number of inflammatory marker tests, platelet counts, and chemistry panels; number of rheumatology visits, rehabilitation visits, assessment of rheumatoid factor, and the presence of Felty's syndrome. CIRAS score was calculated at RA incidence and monthly during the follow-up using 12 months of prior information for each estimate. Data on antirheumatic medications (i.e. methotrexate, hydroxychloroquine, other disease-modifying antirheumatic drugs, biologics and corticosteroids), CV risk factors (i.e. hypertension, diabetes, smoking and dyslipidemia), incident CV events (myocardial infarction, CV death, angina, stroke, intermittent claudication, and heart failure) were collected from the medical records. Cox models with time-dependent covariates were used to assess the association of CIRAS score with the risk of CV events, adjusting for age, sex, calendar year of RA, CV risk factors and antirheumatic medication use.

Results: The study included 526 patients with RA (mean age at RA incidence 54.6 years, 71% female). The mean CIRAS score at RA incidence was 4.5 (standard deviation [SD] 1.9; min 0.6; max 9.5). During the mean follow-up of 7.3 years 103 CV events occurred. There was no apparent association of baseline CIRAS with the occurrence of CV events (hazard ratio [HR] 1.08 per 1 unit increase, 95% confidence interval [CI] 0.96, 1.22, p=0.20). The associations of the highest CIRAS value in the first year (HR 1.14 per 1 unit increase, 95%CI 0.99, 1.31, p=0.063) and monthly CIRAS (HR 1.13 per 1 unit increase, 95%CI 0.98, 1.31, p=0.096) with CV events approached statistical significance. Increase in cumulative moving average of monthly CIRAS was associated with significantly increased risk of CV events (HR 1.34 per 1 unit increase, 95%CI 1.09, 1.66). By cumulative moving percentage of time, patients who spent more time in medium and high CIRAS tertiles were more likely to have an increased risk of CV events vs those who spent more time in the lower tertile (HR 1.07, 95%CI 0.97, 1.17 and HR 1.14, 95%CI 1.03, 1.25, respectively, per 10 unit increase in the amount of time in the tertile).

Conclusion: Higher long-term burden of RA severity as expressed by cumulative moving average of monthly CIRAS and cumulative moving percentage of time in medium and high CIRAS tertiles was associated with significantly increased risk of CV events in RA suggesting accrued detrimental impact of RA severity over time.

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Prolongation Of QT Interval In Patients With Rheumatoid Arthritis and Its Impact On Mortality: Results From a Population-Based Study. Krati Chauhan[1], Michael Ackerman[2], Cynthia S. Crowson[1], Eric L. Matteson[1] and Sherine E. Gabriel[1]. [1]Mayo Clinic, Rochester, MN, [2]Mayo Clinic, Rochester Minnesota, Rochester, MN.

Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk of cardiovascular morbidity and mortality. This risk persists even when RA disease characteristics are taken into account. Heart rate corrected QT interval (QTc) obtained on standard electrocardiogram (EKG) represents ventricular repolarization. QTc prolongation is related to increased cardiovascular mortality. The primary purpose our study is to determine the impact of QTc prolongation on mortality in patients with RA.

Methods: A population based inception cohort of patients with RA fulfilling 1987 ACR criteria in 1988–2007 was identified, along with an age and sex matched comparison cohort and followed until death, migration or 12–31-2008. Data were collected on EKG variables (heart rate, QRS interval, QT interval, QT interval corrected for heart rate calculated using the Bazett's formula(QTc), atrial fibrillation, atrial flutter, supraventricular tachycardia, bundle branch block, paced rhythm, and ST-T wave changes), medications known to prolong QT interval, electrolytes, cardiovascular risk factors and disease status (hypertension, DM, lipids, BMI, smoking status, myocardial infarction, cardiovascular death, sudden death, heart failure), RA disease characteristics (erythrocyte sedimentation rate [ESR], rheumatoid factor, large joint swelling, joint erosions, destructive changes on radiographs, extraarticular manifestations of RA). Cox proportional hazards models were used as to examine QTc prolongation as predictor of mortality.

Results: Among 650 RA and 650 non RA patients, QTc prolongation prior to RA incidence/index date was similar in RA (15%) and non RA (18%). During follow-up, the cumulative incidence of QTc prolongation was higher among RA (48% at 20 years after RA incidence) than non-RA (38% at 20 years after index date; p= 0.004). This difference remained significant (RA: 22%, non RA: 17% at 20 years, p = .025) after excluding QTc prolongation in the presence of EKG variables, electrolytes and QT prolonging medications. Elevated ESR at RA diagnosis was associated with developing prolonged QTc (Hazard ratio [HR}: 1.14 per 10 mm/hr increase; 95% confidence interval [CI]: 1.03–1.27). QTc prolongation was not significantly associated with all-cause mortality in RA patients (HR: 1.28; 95% CI: −.91-1.81, p=0.16) or coronary heart disease mortality (HR: 1.10; 95% CI:0.43–2.86, p= 0.83) adjusted for age, sex and calendar year of RA incidence/index.

Conclusion: RA patients have a significantly elevated risk of developing prolonged QTc interval. Prolonged QTc was not associated with all cause and coronary heart disease mortality in RA patients. The clinical implications of these findings and their relationship to sudden cardiac death in RA require further study.

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Shift In Cardiovascular Risk and Lipid Levels In Rheumatoid Arthritis Patients Using ATP-3 Guidelines: Corrona Certain Study. Dimitrios A. Pappas[1], Ani John[2], Jeffrey R. Curtis[3], George W. Reed[4], Tanya Sommers[4], Jeffrey D. Greenberg[5], Ashwini Shewade[2] and Joel M. Kremer[6]. [1]Columbia University, New York, NY, [2]Genentech Inc., South San Francisco, CA, [3]University of Alabama at Birmingham, Division of Clinical Immunology and Rheumatology, Birmingham, AL, [4]CORRONA, Inc., Southborough, MA, [5]New York Hospital for Joint Diseases, New York, NY, [6]Albany Medical College and The Center for Rheumatology, Albany, NY.

Background/Purpose: RA is associated with an increased risk for cardiovascular (CV) disease. Hyperlipidemia is a recognized risk factor for CVD. This study followed the changes in lipid levels after 3 months of therapy with biologic agents.

Methods: Patients (pts) with at least moderate disease activity (CDAI >10) initiating a biologic DMARD participated in an ongoing comparative effectiveness study (CERTAIN) nested within CORRONA. Characteristics, including lipid values in pts initiating a TNF-α inhibitor (TNFi) or non-TNFi (rituximab [RTX], abatacept [ABA] or tocilizumab [TCZ]), were measured at baseline and 3 months. Adult Treatment Panel III (ATP-3) guideline lipid categories were used to evaluate lipid levels: LDL (optimal < 100), HDL (low < 40), total cholesterol (TC) (desirable < 200) and triglycerides (TG) (normal < 150). TC/HDL ratio (desirable ≤ 5) thresholds were determined by American Heart Association (AHA) recommendations and were used to categorize pts into low/normal risk and elevated risk for CV disease. We describe the proportion of pts who shifted lipid level categories from baseline to 3 months of therapy for each biologic. Pts who started or stopped lipid-lowering therapy between baseline and 3 month follow up visit were excluded from this analysis.

Results: 715 initiations of a biologic were analyzed. Baseline characteristics: age 55.6 ± 13.3, female 76.1%, and baseline CDAI 28.7 ± 12.7. History of prior CVD was present in 7.0% of pts; 3.1% had diabetes mellitus and 39.4% were obese (BMI>30). 55.9% of pts received TNFi, 5.9% RTX, 20.14% ABA and 18.0% TCZ. Changes in lipid levels after three months of therapy and shifts between lipid categories are listed in Table 1. Of all pts with an optimal LDL at baseline, 24.2% had LDL shifted to an above optimal level at 3 months and of those pts with an above optimal LDL at baseline, 12.4% shifted to an optimal level at 3 months; for TC, of pts at a desirable level at baseline, 18.3% shifted to a higher than desirable level at 3 months and of pts at a higher than desirable level at baseline, 20.4% shifted to a desirable level at 3 months. For TC/HDL ratio, of pts at a desirable level at baseline, 41.4% shifted to a higher than desirable level at 3 months whereas of pts with a higher than desirable level at baseline, 4.4% shifted to a desirable level at 3 months. Similar bi-directional changes were noted for all biologics.

LDL	LDL increase from <100 mg/dL at baseline to ≥100 mg/dL at 3 months (% of patients at optimal level)	LDL decrease from ≥100 mg/dL at baseline to <100 mg/dL at 3 months (% of patients above optimal level)
Overall N=715	64/265 (24.2%)	56/450 (12.4%)
TNFi N=400	39/144 (27.1%)	34/256 (13.3%)
Rituximab N=42	5/21 (23.8%)	3/21 (14.3%)
Abatacept N=144	8/58 (13.8%)	10/86 (11.6%)
Tocilizumab N=129	12/42 (28.6%)	9/87 (10.3%)
Total cholesterol (TC)	**TC increase from <200 mg/dL at baseline to ≥ 200 mg/dL at 3 months (% of patients at desirable level)**	**TC decrease from ≥ 200 mg/dL at baseline to <200 mg/dL at 3 months (% of patients above desirable level)**
Overall N=715	79/431 (18.3%)	58/284 (20.4%)
TNFi N=400	36/234 (15.4%)	39/166 (23.5%)
Rituximab N=42	3/24 (12.5%)	4/18 (22.2%)
Abatacept N=144	12/94 (12.8%)	6/50 (12.0%)
Tocilizumab N=129	28/79 (35.4%)	9/50 (18.0%)
TC/HDL ratio	**TC/HDL ratio increase from ≤ 5 at baseline to >5 at 3 months (% of patients at desirable level)**	**TC/HDL ratio decrease from >5 at baseline to ≤ 5 at 3 months (% of patients above desirable level)**
Overall N=715	29/657 (4.4%)	24/58 (41.4%)
TNFi N=400	13/369 (3.5%)	11/31 (35.5%)
Rituximab N=42	2/39 (5.1%)	3/3 (100%)
Abatacept N=144	4/132 (3.0%)	5/12 (41.7%)
Tocilizumab N=129	10/117 (8.6%)	5/12 (41.7%)

Conclusion: In this study, lipid level alterations were noted after three months of therapy with biologic agents. Notably for some pts, lipid levels increased while in others levels decreased over three months. Further studies with long-term follow-up would be needed to determine the clinical significance of lipids and systemic inflammation for CVD risk.

Disclosure: D. A. Pappas, CORRONA, 3, Novartis, 5; **A. John**, Genentech Inc., 3; **J. R. Curtis**, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, Abb Vie, 2, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, Abb Vie, 5; **G. W. Reed**, CORRONA, 3; **T. Sommers**, CORRONA, 3; **J. D. Greenberg**, CORRONA, 1, AstraZeneca, CORRONA, Novartis, Pfizer, 5; **A. Shewade**, Genentech, Inc., 3; **J. M. Kremer**, CORRONA, 1, CORRONA, 3.

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Inflammatory Cell Infiltrates In The Heart Of Patients With Coronary Artery Disease With and Without Inflammatory Rheumatic Disease: A Biopsy Study. Jacqueline Kirsti Andersen[1], Ingvild Oma[2], Ingjerd Lien Kveldstad[2], Knut Mikkelsen[3], Terje Veel[4], Sven M. Almdahl[5], Matthew H. Liang[6], Øystein T. Førre[7], Morten Fagerland[7] and Ivana Hollan[3]. [1]Gjøvik University College, Gjøvik, Norway, [2]Innlandet Hospital Trust, Lillehammer, Norway, [3]Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway, [4]Feiringklinikken, Feiring, Norway, [5]University Hospital of North Norway, Tromsø, Norway, [6]Harvard Medical School, Boston, MA, [7]Oslo University Hospital, Oslo, Norway.

Background/Purpose: Systemic rheumatic diseases (SRDs) are associated with increased cardiovascular (CV) morbidity due to accelerated atherosclerosis. However, SRDs are associated also with cardiac vasculitis that may contribute to the increased CV risk (1). The objective is to examine the occurrence and extent of inflammatory cell infiltrates (ICI) and small vessel

vasculitis in all layers of the right atrium (epicardium, myocardium and endocardium) in patients with coronary artery disease (CAD) with and without SRDs.

Methods: We examined biopsies from the right atrium taken in a standardized way during coronary artery bypass grafting from the edge of the openings for cannulation due to extracorporeal circulation from patients with and without SRD (matched for age, sex and acute coronary syndrome) included in Feiring Heart Biopsy Study (2). The specimens were fixed with paraffin and stained by hematoxylin and eosin, and one 3-mm thick section from each specimen was examined by light microscopy in a blinded manner. The number and extent of ICIs in the three layers of the heart wall were semi-quantified.

Results:

	IRD (n = 40)	Non-IRD (n = 48)	Fisher mid-p test
Age, mean ± SD (years)	66,83 ± 10,5	66,42 ± 10,2	0.85
Male (%)	27 (67,5)	28 (58,3)	0.39
ICIs of epicardium (%)	24 (60%)	27 (56,2)	0.75
ICIs of myocardium (%)	0 (0%)	3 (6,2%)	0.17
ICIs of endocardium (%)	0 (0%)	1 (2,1%)	0.73
Vasculitis (%)	0 (0%)	0 (0%)	1.00

The infiltrates consisted predominantly of lymphocytes. Perivascular infiltrates occurred in all patients except for one. All the infiltrates in the myocardium were perivascular. There was no significant difference in the scores for the size and number of ICIs in the epicardium between the groups.

Conclusion: In patients with CAD, vasculitis was not observed, but the occurrence of ICIs in the right atrium was high, mostly localized around small vessels. The ICIs were found predominantly in the epicardium, and the occurrence and extent of epicardial ICIs was similar in SRD and non-SRD patients. In the myocardium and endocardium, the ICIs occurred in a low frequency, and in the non-SRD group only (but the difference was not statistically significant). In theory, the observed ICIs might be secondary to or independent of cardiovascular disease (CVD), but the inflammation might also contribute to CAD by compromising of the function of epicardial coronary arteries. Interestingly, abnormalities in epicardium (increased mass of epiicardial adipose tissue) are related to CV prognosis, and we propose that inflammation in the epicardium might be of particular importance. Our findings do not support the hypothesis that inflammation in the heart including small vessel cardiac vasculitis is more common in SRD than non-SRD patients. However, this possibility cannot be completely ruled out as the number of examined specimens were small, taken from apparently healthy tissue, and the right atrium was the only site sampled.

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(2) Hollan I *et al.* Arthritis Rheum 2007; 56: 20072-9

Disclosure: J. K. Andersen, None; **I. Oma**, None; **I. Lien Kveldstad**, None; **K. Mikkelsen**, None; **T. Veel**, None; **S. M. Almdahl**, None; **M. H. Liang**, None; **T. Førre**, None; **M. Fagerland**, None; **I. Hollan**, None.

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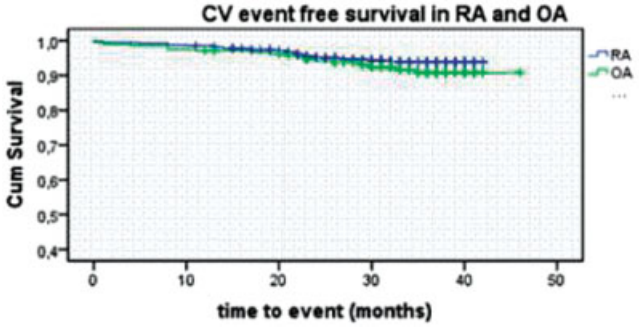
Cardiovascular Risk In Intensively Treated Rheumatoid Arthritis: Comparison To An Osteoarthritis Population. First Prospective Analysis Of The ACT-CVD Cohort. Inger L. Meek[1], Harald E. Vonkeman[2] and Mart A.F.J. van de Laar[2]. [1]Rheumatology Center Twente, Medisch Spectrum Twente & Twente University, Enschede, Netherlands, [2]Medisch Spectrum Twente & University of Twente, Enschede, Netherlands.

Background/Purpose: Rheumatoid arthritis (RA) is associated with increased cardiovascular (CV) morbidity and mortality. This association is thought to be due to the chronic inflammatory disease process, clustering of lifestyle associated CV risk factors, as well as the use of medication such as non steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids in patients with RA. Most studies on CV risk in patients with RA were performed before the introduction of modern powerful anti-inflammatory therapies and intensive treatment strategies aiming at remission. It is important to obtain more information on CV risk in intensively treated RA.

The objective of this study was to evaluate CV event risk and its predictors in intensively treated RA in comparison with an OA population.

Methods: first prospective analysis of occurrence of CV events (myocardial infarction, acute coronary syndrome, coronary intervention, acute heart failure, acute cardiac death) in a cohort of consecutive patients attending the Arthritis Centre Twente (ACT-CVD). All patients with a diagnosis of RA (n=495) or OA (n=208) without previous CV events were included in this study. Inclusion took place between February 2009 and November 2011, follow up data for this analysis were collected onto November 2012. Incidence of CV events in RA and OA groups was compared by Kaplan Meier survival analysis, potential CV event risk factors (traditional CV risk factors and RA severity markers) within groups were evaluated by COX-regression.

Results: At baseline RA and OA groups did not differ in sex (% female; RA=72, OA=78), age (mean years; RA=59, OA=59) and estimated 10-year risk of CV death (mean %; RA=5.7, OA=5.5). The RA group (mean disease duration 7.5 years, 50 % RF positive) was characterized by low disease activity (mean DAS28 2.5, 72% remission). After a median follow up of 36 months 46 events had occurred (RA=29, OA=17, p=0.25, figure 1). Age, systolic blood pressure and non-use of methotrexate significantly contributed to CV event risk in RA, age and current smoking in OA.



Conclusion: Preliminary data suggest that CV event risk in intensively treated RA equals CV event risk in OA. Use of methotrexate is independently associated with lower CV event incidence in RA.

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Menopause Occurs Earlier and Is An Independent Risk Factor For Osteoporosis In Women With Rheumatoid Arthritis. Michael Cocker[1], Alexander Oldroyd[2] and Marwan Bukhari[1]. [1]Royal Lancaster Infirmary, Lancaster, United Kingdom, [2]Lancaster University, Lancaster, United Kingdom.

Background/Purpose: Rheumatoid arthritis (RA) and early menopause (<45 years) are recognised risk factors for the development of osteoporosis and form part of the World Health Organisation "FRAX" 10-year fracture risk-stratification tool[1]. It is not known whether age of menopause is an independent risk factor for osteoporosis in women with RA. Evidence exists linking connective tissue diseases to earlier menopause[2]however whether this also occurs in RA is unknown.

This paper aims to establish whether RA is associated with earlier menopause and whether age of menopause is an independent risk factor for osteoporosis in RA.

Methods: Data from female patients with RA attending for dual-energy X-ray absorptiometry (DXA) assessment between 2004 and 2011 was analysed using a nested case-control approach. Control subjects with no pre-defined indication for DEXA assessment were age-matched with RA subjects. Osteoporosis was defined as any hip or lumbar spine (L1-L4) T-score <−2.5. Student's t-test was used to compare age of menopause in the RA and control group. Subjects were divided into 3 tertiles according to age of menopause and logistic regression performed to assess for relationships with osteoporosis. All statistical analysis was performed using STATA v11.2, with results expressed as odds ratios (OR) with 95% confidence intervals (95%CI). P values <0.05 were considered significant.

Results: 397 subjects (median age 69.5 years, interquartile range 62.1,76.5) were matched for age with 397 controls. Mean age of menopause was lower in RA subjects (48.1 years vs. 49.7 years, mean difference 1.6 years) and was significant (p<0.001). After adjusting for age the earliest menopause tertile (median age of menopause 43.9 years) was associated with the highest odds of osteoporosis (OR 1.65 95%CI 1.13,2.41 p=0.01). Odds were increased to a lesser degree in the second-earliest tertile (median menopause age 50.2 years, OR 1.48 95%CI 1.00,2.17 p=0.048). No such associations were seen in controls.

Conclusion: This case-control study has demonstrated for the first time that women with RA experience the menopause earlier, and that earlier age of menopause is an independent risk factor for the development of osteoporosis in this population.

References:

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2. Ekblom-Kullberg S. et al "Reproductive health in women with systemic lupus erythematosus compared to population controls." Scandinavian Journal of Rheumatology. 2009;38(5): 375–380

Disclosure: M. Cocker, None; **A. Oldroyd**, None; **M. Bukhari**, None.

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Effect Of Age At Menopause In Women With Early Rheumatoid Arthritis. Lauren Wong[1], Wei-Ti Huang[1], Juan Xiong[2], Gilles Boire[3], Boulos Haraoui[4], Janet E. Pope[5], J. Carter Thorne[6], Carol A. Hitchon[7], Diane Tin[6], Edward Keystone[8] and Vivian P. Bykerk[1]. [1]Hospital for Special Surgery, New York, NY, [2]Mount Sinai Hospital, University of Toronto, Toronto, ON, [3]Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, [4]Institut de Rhumatologie de Montréal, Montreal, QC, [5]St. Joseph's Health Care, University of Western Ontario, London, ON, [6]Southlake Regional Health Centre, Newmarket, ON, [7]University of Manitoba, Winnipeg, MB, [8]Mount Sinai Hospital, Toronto, ON.

Background/Purpose: Rheumatoid arthritis (RA) preferentially affects women and studies suggest that various hormonal and reproductive factors may affect disease onset and severity. This study assessed how age at menopause affects disease presentation in post-menopausal women with early RA and explored the effects of hormone use.

Methods: Post-menopausal women from the Canadian early ArThritis CoHort (CATCH) under age 65 at time of enrollment were included. Early age at menopause (EM) was defined as age at menopause < 45; usual age at menopause (UM) was defined as age at menopause >/=45. The Wilcoxon rank sum test was applied to continuous variables and Chi-square test to categorical variables. Multivariate logistic regression analysis was used to adjust for age, smoking, education, and use of exogenous hormones.

Results: 534 women met inclusion criteria (see Table 1). The EM group was more likely to report current use of hormone replacement therapy (HRT) and had higher mean patient global scores and pain scores. The EM group was more likely to meet 1987 criteria for RA and have positive serologies for RF and ACPA. There was a non-significant trend for women to have more erosions in the EM group. There was no difference in DAS28. Multivariate logistic regression analysis showed that the EM group was more likely to be RF positive (OR 2.1, CI 1.2–3.6, p=0.01) and current HRT users were less likely to be RF positive (OR 0.5, CI 0.2–0.8, p=0.01). Current smokers were more likely to be RF positive (OR 1.6, CI 1.0–2.6, p=0.03) and ACPA positive (OR 2.5, CI 1.5–4.3, p=0.001). At the time of analysis, 35% of subjects did not have ACPA data available. After confirming that missing data had occurred at random, multiple imputation analysis was used and showed that the EM group was also more likely to be ACPA positive (OR 1.8, CI 1.1–2.9, p=0.03). Sensitivity analysis removing current hormone therapy users did not change these findings.

Table 1: Baseline Characteristics

	All Post-Menopausal Women (n=534)	Age at Menopause <45 (N=93)	Age at Menopause ≥45 (N=441)	P-value
Age at Study Entry	55.5 ± 5.3	55.3 ± 6.0	55.5 ± 5.2	0.98
Age at Menopause	49.4 ± 6.5	38.5 ± 6.5	51.7 ± 3.5	0.001
CRP, mg/l	1.3 ± 1.6	1.3 ± 1.6	1.3 ± 1.6	0.95
DAS28	5.0 ± 1.5	5.0 ± 1.5	5.0 ± 1.5	0.76
ESR, mm/h	28.5 ± 24.6	27.6 ± 24.0	28.7 ± 24.7	0.74
Patient global	5.9 ± 2.8	6.6 ± 2.9	5.8 ± 2.8	0.01
Pain	5.8 ± 2.6	6.5 ± 2.7	5.6 ± 2.6	0.002
Education ≥ High school	264 (49.4%)	31 (33.3%)	233 (52.8%)	0.001
Currently Employed	340 (63.7%)	57 (61.3%)	283 (64.2%)	0.599
Current Smoking	123 (23.0%)	31 (33.3%)	92 (20.9%)	0.01
Current Use of HRT	55 (10.6%)	19 (21.1%)	36 (8.4%)	<0.0001
Current Use of OCP	4 (0.8%)	1 (1.1%)	3 (0.7%)	<0.0001
Meeting 1987 ACR	337 (65.1%)	66 (75.0%)	271 (63.0%)	0.032
Meeting 2010 ACR	428 (80.2%)	77 (82.8%)	351 (79.6%)	0.481
Erosion positive	106 (24.8%)	22/71 (31.0%)	84/356 (23.6%)	0.188
RF positive	284 (57.7%)	58 (71.6%)	226 (55.0%)	0.01
ACPA positive	175 (48.8%)	34/56 (60.7%)	141/303 (46.5%)	0.05

Conclusion: These data suggest that EM compared to UM is associated with different features at disease presentation in early RA, most notably in RF and ACPA positivity. Further research is needed to better understand how changes in hormonal states and exposure to exogenous hormone influence disease in women with rheumatoid arthritis.

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Systemic Inflammation Contributes To Depression In Patients With Rheumatoid Arthritis. Mary Margaretten, Laura Trupin, Patricia P. Katz, Gabriela Schmajuk, Jinoos Yazdany, Chris Tonner, Jennifer Barton and Edward H. Yelin. University of California, San Francisco, San Francisco, CA.

Background/Purpose: Prior research suggests that systemic inflammation contributes to the pathogenesis of depression, but longitudinal studies in patients with rheumatoid arthritis (RA) are lacking. Comorbid depression is common in patients with RA and traditional risk factors such as disability, fatigue, and pain explain only a portion of the increased prevalence of depression in RA. We prospectively examined the association between serum C-reactive protein (CRP) and depression to determine whether an increase in CRP precedes an increase in depressive symptoms in adults with RA.

Methods: Participants were patients from a multi-site observational RA cohort. Inclusion criteria for this analysis included age ≥ 18 years of age, meeting the American College of Rheumatology classification criteria for RA, and at least two clinical visits that included a measure of depression, the Patient Health Questionnaire-9 (PHQ-9), and two measurements of serum high-sensitivity CRP**.** In order to calculate a change in CRP that occurred prior to the change in depression score, the first CRP was collected up to 6 weeks prior to the first PHQ-9 score, and the second CRP was collected up to 6 weeks prior to the second PHQ-9 score. Given the non-linear relationship between predictor and outcome, odds ratios were estimated using a restricted cubic spline regression analysis. Post-estimation Wald test confirmed there was a non-linear relationship between changes in CRP and successive PHQ-9 scores.

Results: There were 362 observations for 212 patients with a pair of clinical visits with two serum CRP measurements and a subsequent change in PHQ-9 score measured. The mean ± SD of the 1st CRP and change in CRP were 8.6 ±13 and 0.14 ±12, respectively. With regard to the prevalence of depressive symptoms, 41% of patients scored ≤ 10 on the PHQ-9 during at least one clinic visit, which corresponds to a symptom severity of at least moderate depression. The mean ± SD of the 1st PHQ-9 and change in PHQ-9 was 6 ±5 and −0.2 ±4, respectively corresponding to an initial symptom severity of mild depression. A significant non-linear relationship existed ($p<.001$) between change in CRP and change in depression score in patients with RA (Figure). Adjustment for age, gender, race/ethnicity, body mass index, and socioeconomic status did not significantly alter results.

Conclusion: An increase in systemic inflammation as measured by CRP contributes to an increase in depressive symptoms in a subset of patients with RA. For these patients, further investigation is warranted as to whether treating RA with additional anti-inflammatories may have the extra benefit of decreasing depression.

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The Risk Of Pneumococcal Infections After Immunisation With Pneumococcal Conjugate Vaccine Compared To Non-Vaccinated Inflammatory Arthritis Patients. Johanna Bengtsson[1], Pierre Geborek[2], Tore Saxne[2], Martin Englund[3], Ingemar F. Petersson[2], Jan-Åke Nilsson[4], Göran Jönsson[5] and Meliha C. Kapetanovic[6]. [1]Section of Rheumatology, Lund University and Skåne University Hospital, Lund, Sweden, Lund, Sweden, [2]Lund University, Lund, Sweden, [3]Department of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, [4]Lund University, Malmö, Sweden, [5]Dept of Clinical Sciences Lund, Section of Infectious Diseases, Lund, Sweden, [6]Dept of Clinical Sciences Lund, Section of Rheumatology, Lund University, Lund, Sweden.

Background/Purpose: The purpose was to examine the risk of putative pneumococcal infections between adult arthritis patients on different anti-rheumatic drugs immunised with heptavalent pneumococcal conjugate vaccine (Prevenar7; PCV7) and non-vaccinated individually matched arthritis patients.

Methods: A consecutive cohort of 505 patients with rheumatoid arthritis (RA) and spondylarthropathy (SpA) including psoriatic arthritis, regularly followed at the outpatient Department of Rheumatology Skåne University Hospital in Lund and Malmö, was immunised with a single dose of PCV7 (exposed group). Of these, 497 patients (RA=248; SpA=249) were included. At vaccination, RA patients were treated with methotrexate (MTX) (n=84), anti-TNF+MTX (n=87) or anti-TNF as monotherapy (n=77). SpA patients were treated with anti-TNF as monotherapy (n=81), anti-TNF+MTX (n=82) or NSAIDs/analgesics (n=86). For each vaccinated patient, we identified four reference subjects (n=1988) from the same geographic area (Skåne county, Sweden), individually matched for age, gender, diagnosis and date. These were considered unexposed to conjugate pneumococcal vaccination. The Skåne Health Care Register containing all data on inpatient and outpatient health care was searched for all individuals seeking health care for putative pneumococcal infections using ICD-10 diagnostic codes. All events occurring 4 years before vaccination and up to 4.5 years after vaccination were divided into serious infections; (pneumonia, other lower respiratory infections, meningitis, sepsis, septic arthritis) and non-serious infections; (upper respiratory infections, otitis media and sinusitis). Relative risks (RR) of infections were calculated as events after/events before vaccination. Ratios of relative risk (RRR) were calculated between exposed and unexposed groups of patients. Generalized Estimating Equation was used to handle correlated data for several events in the same individual, PROC GENMOD in the SAS System 9.3.

Results: Although non-significant, the point estimate of RRR suggested a reduced risk of serious infections in vaccinated patients compared to the unexposed group (Table). However, time to first event of all infections before and after vaccination did not differ between the groups. Mean time (CI 95%) to first serious infection was significantly longer for immunised patients compared to the unexposed group [48.5 months (47.9–49.0) and 47.0 (46.7–47.3)], respectively.

RA+SpA	All exposed (vaccinated) (N=497)	All unexposed (non-vaccinated) (N=1988)	RRR (95% CI) (exposed/unexposed)	Risk reduction (%)
Serious infection (event Nr after/before); RR (95% CI)	27/18 1.52 (0.74–3.15)	132/49 2.76 (1.97–3.85)	0.55 (0.25–1.22)	45%
Non-serious infections (event Nr after/before); RR (95% CI)	45/26 1.78 (1.00–3.18)	165/101 1.64 (1.22–2.21)	1.09 (0.57–2.08)	9 % increased risk
All infections (event Nr after/before); RR (95% CI)	72/44 1.69 (1.07–2.69)	297/150 2.06 (1.63–2.60)	0.82 (0.49–1.38)	18%
RA	**RA exposed (vaccinated) (N=248)**	**RA unexposed (non-vaccinated) (N=992)**	**RRR (95% CI) (exposed/unexposed)**	**Risk reduction (%)**
Serious infections (event Nr after/before) RR (95% CI)	23/13 1.84 (0.76–4.46)	91/33 2.84 (1.88–4.28)	0.65 (0.24–1.72)	35%
Non-serious infections (event Nr after/before); RR (95% CI)	28/11 2.60 (1.26–5.38)	100/62 1.63 (1.13–2.36)	1.60 (0.71–3.60)	60% increased risk
All infections (event Nr after/before); RR (95% CI)	51/24 2.25 (1.21–4.20)	191/95 2.13 (1.59–2.86)	1.06 (0.53–2.10)	6% increased risk
SpA	**SpA exposed (vaccinated) (N=249)**	**SpA unexposed (non-vaccinated) (N=996)**	**RRR (95% CI) (exposed/unexposed)**	**Risk reduction (%)**
Serious infection (event Nr after/before); RR (95% CI)	4/5 0.80 (0.21–3.04)	41/16 2.62 (1.47–4.67)	0.31 (0.07–1.31)	69%
Non-serious infections (event Nr after/before); RR (95% CI)	17/15 1.16 (0.47–2.85)	65/39 1.68 (1.02–2.76)	0.69 (0.25–1.93)	31%
All infections (event Nr after/before); RR (95% CI)	21/20 1.08 (0.54–2.16)	106/55 1.98 (1.33–2.93)	0.64 (0.31–1.34)	36%

Conclusion: Vaccination with heptavalent pneumococcal conjugate vaccine tended to reduce the risk of putative serious pneumococcal infections with about 45% compared to unvaccinated patients in this observational cohort study.

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Risk Factors For Stroke In Patients With Rheumatoid Arthritis. Anja Strangfeld[1], Yvette Meißner[2], Adrian Richter[1], Matthias Schneider[3], Hans Peter Tony[4], Kerstin Gerhold[1], Angela Zink[5] and Joachim Listing[6]. [1]German Rheumatism Research Center, a Leipniz Institute, Berlin, Germany, [2]German Rheumatism Research Center Berlin, Berlin, Germany, [3]University of Duesseldorf, Duesseldorf, Germany, [4]University of Würzburg, Würzburg, Germany, [5]German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany, [6]German Rheumatism Research Center, Berlin, Germany.

Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk of stroke. This event is associated with considerable sequelae and might result in death or major physical and neurological disability. Despite its clinical relevance data regarding stroke are rare. Our objective was to analyse the impact of different risk factors on the development of stroke within our German biologics register RABBIT.

Methods: RABBIT is an ongoing prospective cohort study. Since 2001 patients have been enrolled at start of an approved biological therapy or a new synthetic DMARD treatment after at least one DMARD failure. At fixed time points at follow-up rheumatologists assess the clinical status, report treatment details and adverse events according to ICH guidelines. We analysed all patients enrolled in the register until 31.08.2012 with at least 3 months of follow-up. All reports of stroke were included, transient ischemic attacks were not. Diagnoses of stroke were re-validated at on-site visits. Medical records as well as hospital reports were analysed. To assess the impact of different risk factors for stroke we performed a multivariate Cox regression analysis. Patients treated with biologics were considered to be exposed to these drugs up to 6 (rituximab: 12) months after the last dose.

Results: 10,159 patients were included. 77% of them were female, the mean age at enrollment was 56 years, mean disease duration 10.4 years, and mean disease activity score (DAS28) 5.5. The mean observation time was 3.5 years. 109 patients experienced a stroke. Older age and male sex were significant risk factors for the development of stroke, as well as hypertension, DAS28 and smoking (see Table). Factors not significantly associated were functional capacity and treatment with antiTNF or other biologics and use of glucocorticoids. As relevant comorbidities we investigated diabetes (db), coronary heart disease (chd), heart failure (hf) and atrial fibrillation (af). All of those were more prevalent in patients who developed a stroke (db 19 vs 10%, chd 17 vs 6%, hf 7 vs 2%, af 3 vs 0.5%). These portions were significantly different in univariate comparisons but did not achieve statistical significance in the multivariate model. DAS28 was a better predictor than erythrocyte sedimentation rate.

Table. Results of the multivariate Cox regression analysis.

	HR	95% CI
Age (by 10 years)	1.7	[1.4; 2.1]
Males vs. females	1.6	[1.0; 2.4]
Hypertension (yes/no)	1.7	[1.1; 2.5]
Atrial fibrillation (yes/no)	2.8	[0.9; 9.1]
DAS28 at follow-up per unit increase	1.6	[1.4; 1.9]
Smoking ever vs. no	1.2	[1.0; 1.4]
antiTNF vs. DMARDs	1.1	[0.8; 1.7]
Other biologics vs. DMARDs	1.3	[0.8; 2.1]

Conclusion: Biologic treatments and glucocorticoids did not have an influence on the risk of stroke. Among traditional risk factors for stroke such as age, male gender, smoking and hypertension, a higher disease activity and atrial fibrillation seem to increase the risk for stroke. This could have implications for the cardiovascular risk assessment in patients with RA.

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HBV Reactivation and Consequent Hepatitis In Rheumatoid Arthritis Patients With Different HBV Carring State: A Clinical Observation Follow-Up. Lie Dai, An Qi Liang, Ying Qian Mo, Jian Da Ma, Le Feng Chen, Dong Hui Zheng and Lang Jing Zhu. Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China.

Background/Purpose: Approximate 7.2% Chinese were infected with hepatitis B virus (HBV), and the prevalence of concurrent HBV carriers in Chinese rheumatoid arthritis (RA) patients was 9.4% (Lie D, et al. Clin Rheumatol, 2013). Antiviral prophylaxis is recommmended for HBV carriers with RA during DMARDs treatment except hydroxychloroquine by ACR 2008, similar to the professional guideline of Asian Pacific Association for the Study of the Liver. However, antiviral prophylaxis is not commonly used in China due to high economic burden, poor patient compliance and the efficacy/safety of antiviral drugs. This study was to explore the risk of DMARDs associated HBV reactivation and consequent hepatitis in different HBV carriers with RA and the efficacy of antiviral prophylaxis.

Methods: HBV carriers with RA (HBsAg+ and normal transaminases) were enrolled from July 2007 to December 2012 and patients with ≥6-month's follow-up were qualified for analysis. HBV carriers were divided into inactive group (either HBeAg or HBV-DNA negative) and chronic group (HBeAg and/or HBV-DNA positive). HBV reactivation was defined as a 10-fold rise in HBV-DNA compared to baseline or switch from undetectable to detectable.

Results: (1) 36 HBV carriers with RA were enrolled and 6 of them failed to complete the ≥6-month's follow-up due to home migration or conversion to Chinese herbal therapy. Among the qualified 30 patients, 77% were female, mean age was 48 years (range, 17~80), median disease duration was 19 months (range, 1~360) and mean DAS28 was 4.6 (range, 1.7~7.6). There were no significant differences between inactive group (n=15) and chronic group (n=15) in age, gender, disease duration, disease activity (all P>0.05). (2) During a median follow-up period of 12 months (range, 6–69months), 87% patients received low-dose corticosteriods, 100% received MTX, 17% received leflunomide, 50% received sulfasalazine and 67% received hydroxychloroquine. All patients were treated with combination DMARDs therapy with or without low-dose corticosteriods. (3) The outcome of different HBV carriers with RA was shown in figure 1. 33% developed HBV reactivation and 17% developed the consequent hepatitis. Survival curves showed patients in chronic group tend to develop HBV reactivation and consequent hepatitis earlier than in inactive group (figure not shown). (4) Multivariate logistic regression analyses showed the risk factors of HBV reactivation were leflunomide (OR: 6.376, 95% CI: 1.063–38.227) and poor patient compliance of antiviral drugs (OR: 21.140, 95% CI: 1.309–341.467), the risk factor of the consequent hepatitis was past history of acute hepatitis (OR: 17.334; 95% CI: 1.225–245.267).

Conclusion: Our preliminary results suggest that HBV carriers with RA should avoid leflunomide and antiviral prophylaxis should be prescribed for either chronic or inactive HBV carriers during DMARDs treatment, especially for patients with past history of acute hepatitis.

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Osteoporotic Fracture and Post-Operative Clinical and Cost Outcomes In Rheumatoid Arthritis: Results From Two UK Inception Cohorts. Elena Nikiphorou[1], Lewis Carpenter[2], Josh Dixey[3], Peter Williams[4], Patrick D. Kiely[5], David Walsh[6], Richard Williams[7] and Adam Young[8]. [1]ERAS, St Albans City Hospital & University College London (UCL), London, United Kingdom, [2]University of Hertfordshire, Hatfield, United Kingdom, [3]New Cross Hospital, Wolverhampton, United Kingdom, [4]Medway Maritime Hospital, Gillingham, United Kingdom, [5]St George's Hospital, London, United Kingdom, [6]University of Nottingham, Nottingham, United Kingdom, [7]County Hospital, Hereford, United Kingdom, [8]St Albans City Hospital, St Albans, United Kingdom.

Background/Purpose: The risk of osteoporotic fracture is known to be high in RA. Yet less is known about RA related predictive factors for this complication & its associated economic burden.

Methods: The Early RA Study (ERAS, 9 centres) recruited 1465 DMARD naïve patients between 1986–1998 & the Early RA Network (ERAN, 23) 1236 patients, 2002–2012. Standard clinical, radiological & laboratory measures were performed yearly for 25 & 10yrs (median 10 & 3yrs respectively). Major comorbidities & in-patient hospital episodes were recorded yearly, including fracture sites & orthopaedic surgery. Clinical databases were supplemented & validated with national databases: National Joint Registry (data available 2003–2011), Hospital Episode Statistics (1997–2011) & National Death Register (1986–2011). Treatment regimens followed guidelines of the era, mainly conventional DMARD therapies, +/− steroids, & latterly biologics.

Results: A total of 178 (6.6%) patients had 182 fractures, the majority hip (42%), wrist fractures (17.5%), & vertebrae (12%). Other fractures (28.5%) included the distal forearm, foot & ankle. 13 hip fractures resulted in total hip replacements & 57 in dynamic hip screw surgery. None of the procedures were complicated by death in the postoperative period, although hip & vertebral fractures were recorded as contributory causes of death in 12 & 2 respectively. The average length of stay (LoS) varied across procedures, with hip fractures incurring the longest LoS (median 15days in the first decade of the study, 8days in the last). The LoS appeared to drive costs (graphs to demonstrate this). Compared to national data, both LoS & consequently costs were higher in RA patients sustaining osteoporotic fractures, compared to other RA-related intervention or other orthopaedic surgery undertaken nationally by non-RA patients (figure 1). The median time from baseline to hip fracture was 8yrs (IQR 5–15). In hip fracture patients, the mean number of all & major comorbid conditions was increased (3.7 & 1.4) compared to non-fracture (1.8 & 0.9, p <0.001), & survival reduced (48% vs 20%, p<0.0001). Aside from traditional risk factors (age, gender), baseline & 1yr disease activity measures were identified as potential predictors: erosions (OR 2.4, 95%CI 1.4–4.0), high rheumatoid factor (OR 1.7, 95%CI 1.1–2.9), high HAQ (OR 1.7, 95%CI 1.1–2.9), high ESR (OR 1.9, 95%CI 1.1–3.1), low haemoglobin (OR 1.99, 95%CI 1.2–3.1). Steroid use predicted higher risk for fracture: OR 2.7, 95% CI 1.1–6.5.

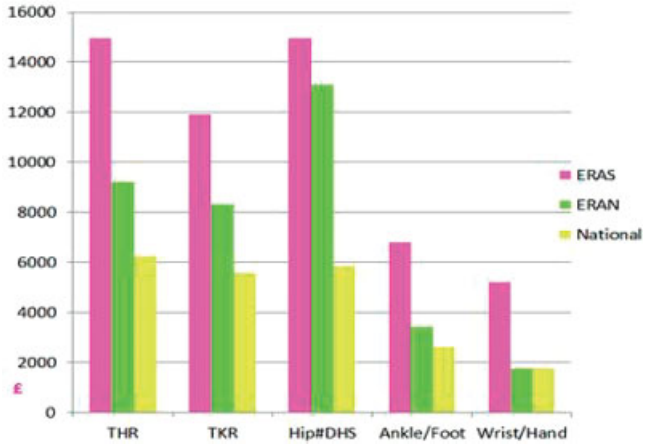

Figure 1.

Conclusion: RA over 25yrs was complicated by osteoporotic fracture in 6.6% patients, mainly hip fractures, which were not a late complication of RA. Most required major orthopaedic surgery, & were associated with comorbidity & reduced survival, as well as high costs. Markers of active disease were associated with a higher risk of fracture, highlighting the need for more active therapies for RA control & bone protection.

Disclosure: E. Nikiphorou, None; **L. Carpenter**, None; **J. Dixey**, None; **P. Williams**, None; **P. D. Kiely**, None; **D. Walsh**, None; **R. Williams**, None; **A. Young**, None.

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Active Rheumatoid Arthritis Is An Independent Risk Factor Of Chronic Kidney Disease. Ryosuke Hanaoka[1], Kazuhiro Kurasawa[2], Ayae Tanaka[3] and Harutsugu Okada[4]. [1]Kamitsuga General Hospital, Kanuma, Tochigi, Japan, [2]Dokkyo Medical University, Mibu-machi, Shimotsuga-gun, Tochigi-ken, Japan, [3]Dokkyo Medical University, Mibu, Tochigi, Japan, [4]Dokkyo Medical University, Mibu-machi, Tochigi-ken, Japan.

Background/Purpose: Rheumatoid arthritis (RA) is a systemic inflammatory disease that affects not only joints but also many organs. RA causes vascular damages to contribute to progression of atherosclerosis. RA itself is a risk factor for cardiovascular diseases as well as hypertension and/or hyperlipidemia that could be induced by medication for RA. However, it has not been determined whether RA itself is a risk factor for chronic kidney disease (CKD). The aim of this study is to determine whether RA is an

independent risk factor for CKD. And if so, to determine whether the disease activity contributes to renal function in RA patients.

Methods: A prospective cohort study was performed. The study included 134 RA patients who met ACR criteria 1987 and were treated at our hospital, and 1156 non-RA individuals who received annual medical screening at the same hospital. Demographic data, general risk factors for CKD, laboratory data, medications and data for RA activity were collected. Estimated glomerular filtration rate (eGFR) was calculated as follows; eGFR = $1.94 \times \text{Cr (mg/dl)}^{-1.094} \times \text{age (year)}^{-0.287} \times$ (1.0 if male/0.739 if female). When patients showed eGFR less than 60 ml/min/1.73m^2 or positive for urinary protein test, they were judged as having CKD. To identify risk factors, univariate and multivariate analysis were conducted.

Results: RA patients were 38 male, and 96 female, mean age; 65.3 year, mean disease duration; 100.1 months, and DAS28 CRP; 2.41. Control individual were 768 male and 388 female and mean age; 53.4 year. At baseline, eGFR were 71.5 ml/min/1.73m^2 in RA and 77.7 ml/min/1.73m^2 in controls, and CKD was found in 33.6 % of RA patients, while 12.6 % of controls had CKD. Annual decline of eGFR was greater in RA group compared with control (−5.81 %, 95%CI. −7.82 to −3.79 vs. 0.71 %, 95%CI. 0.22 to 1.20). Annual incidence of CKD was significantly higher in RA group compared with control (15.7 % vs. 4.6 %, relative risk 1.210, 95%CI. 1.051 to 1.393). Univariate analysis for identification of risk factors for CKD development revealed RA is a risk factor for CKD ($p<0.001$) as well as hypertension, hypercholesterolemia, and anemia. Multivariate analysis using logistic regression analysis showed RA is an independent risk factor of incident of CKD (P = 0.005, relative risk = 2.968, 95%CI. =1.393 to 6.327) as well as hypertension.

Among RA patients, active RA patients showed greater annual decline of eGFR compared to those in remission (−8.89 %, 95%CI. −10.38 to−7.40 in active disease vs. −3.52 %, 95%CI. −4.86 to 2.18 in remision). Significant correlation was found between DAS28CRP at baseline and annual decline of eGFR (correlation coefficient −0.238, P = 0.006). Active group had significantly greater annual decline of eGFR compared to remission group (−8.89 %, 95%CI. −10.38 to −7.40 vs. −3.52 %, 95%CI. −4.86 to 2.18). Multiple regression analysis showed that high DAS28 CRP is correlated with annual decline of eGFR in the patients with RA (coefficients −2.026, 95%CI. −3.909 to −0.142).

Conclusion: RA is an independent risk factors of CKD incident. RA activity is correlated with annual decline of eGFR in patients with RA, suggesting that RA activity, presumably systemic inflammation, could contribute to development of CKD.

Disclosure: R. Hanaoka, None; **K. Kurasawa**, None; **A. Tanaka**, None; **H. Okada**, None.

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Coronary Endothelial Dysfunction Directly Measured By N13 Positron Emission Tomography (PET) Is Detected In Established Rheumatoid Arthritis (RA), But Not Early RA. OM Troum[1], OL Pimienta[1], B Hidalgo[2] and WA Hsueh[3]. [1]Keck School of Medicine, University of Southern California, Los Angeles, CA, [2]University of Alabama, Birmingham, AL, [3]Weill Cornell Medical College, Houston, TX.

Background/Purpose: Rheumatoid arthritis (RA) is associated with increased risk of cardiovascular (CV) disease. The endothelium is a key regulator of vascular function. Subclinical CV disease and its progression are intimately related to endothelial dysfunction (ED), a preclinical marker of atherosclerosis. Endothelial function has been measured indirectly as the response to hyperemic flow in the peripheral vasculature to identify and monitor CV risk in RA. Positron Emission Tomography (PET/CT) with Cold Pressor Test (CPT) *directly* measures coronary artery endothelial cell function during sympathetic stimulation. This non-invasive index of coronary function predicts atherosclerosis. We evaluated the differences in large and small vessel coronary endothelial reactivity in early RA (< 2 years), established RA (> 2 years) and healthy subjects by PET/CT with CPT.

Methods: Delta percent Myocardial Blood Flow (Delta % MBF) was assessed by cardiac N-13 ammonia PET/CT scan. Myocardial perfusion (MP) was evaluated at baseline (BL) following intravenous (IV) administration of N-13 ammonia. After acquiring BL perfusion images with PET, cold pressor stress was assessed by immersing one hand in ice water while a second dose of N-13 ammonia was injected. MP and blood flow were determined from serially acquired images and left ventricular function was assessed from gated images. 15 non-smoking subjects (87% female) were studied: 5 early RA (mean age 60.8 y, mean disease duration 5.0 months), 5 established RA Methotrexate [MTX] inadequate responders (mean age 46.2 y, mean disease duration 153.6 months), and 5 healthy subjects (mean age 53.8 y). Means were calculated for demographic and physiologic characteristics, with one-way Anova and Kruskall-Wallis to compare differences across groups. Univariate correlations of Delta % MBF were also performed in the RA groups. Studies were controlled for age, body mass index (BMI), gender, and mean arterial blood pressure (MAP).

Results: Characteristics between groups were similar, except for sedimentation rate (P=0.003), and age (P=0.002). Low-density lipoprotein cholesterol (LDLC), and MAP positively correlated with Delta % MBF ($P<0.05$). Delta %MBF was similar in normal and early RA subjects. However, RA > 2 years compared to RA <2years demonstrated markedly decreased endothelial reactivity (mean 34.0 (9.7) vs 61.6 (26.7); P=0.0001) when clinical disease activity index (CDAI) and vascular cell adhesion molecule (VCAM-1) were added to the model.

Conclusion: Premature coronary endothelial dysfunction is present in patients with established RA. CDAI and VCAM-1 impact the difference in endothelial function between established RA and early RA. These results raise the question of whether further disease modifying therapy beyond MTX will be useful to improve endothelial function in established RA patients.

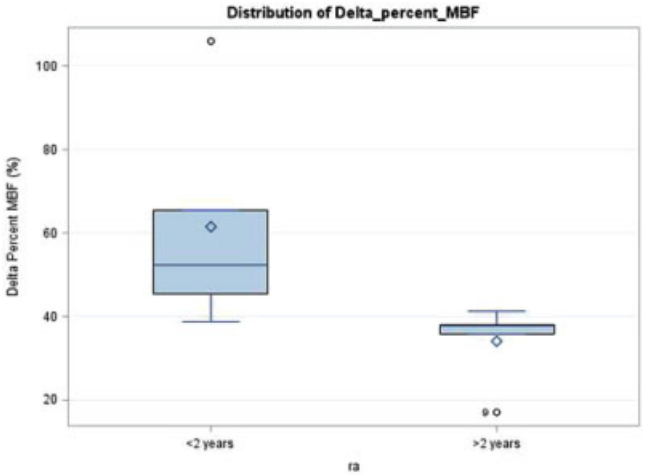

Figure 1. Distribution of Delta % MBF across groups, adjusting for Age, Gender, BMI, MAP and CDAI

Disclosure: O. Troum, Bristol Myers Squibb, 2; **O. Pimienta**, None; **B. Hidalgo**, None; **W. Hsueh**, Bristol Myers Squibb, 2.

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Effect Of Biologic Disease Modifiers On Cardiovascular Risk Of Patients With Rheumatoid Arthritis – 2 Years Prospective Cohort Study. Majed M. Khraishi[1] and Rana Aslanov[2]. [1]MD, Memorial University of Newfoundland, Nexus Clinical Research, St Johns, NF, [2]MD, MSc, Memorial University of Newfoundland, St.John's, NF.

Background/Purpose: People with RA have a higher risk for developing cardiovascular diseases than the general population. The pathogenic mechanisms in RA appear to be complex and multifactorial.

1. To assess the effect of Biologic Disease Modifier Anti-Rheumatic Drugs (BDMARDs) on a 10-year CV event risk in patients with RA after 2 years of follow-up

2. To evaluate the impact of BDMARDs on the incidence of CV events in patients with RA

Methods: Patients with RA receiving biologic therapy were prospectively followed-up. The FRS was used for the assessment of 10-year CVD risk. The presence of CV risk factors was ascertained at the baseline and at every six months of observation up to 24 months. Analyses of the relationships between lipids and inflammatory indices before and after treatment with biologics were performed. Ten-year CVD event risk was assessed by gender and age.

Results: From 228 patients, 2 patients passed away and 6 patients dropped out of the study. Total 220 patients (73% females) with the mean (SD) age of 56.2 (11.6) years were prospectively followed up to 24 months. The mean (SD) age at RA diagnosis was 41.6 (12.9) years with the mean (SD) duration of RA symptoms 14.5 (8.5) years. Nine patients with documented MI and 5 patients with TIA/Stroke had CV events prior to the study. Two male patients had MI during the observation period. Forty-two patients (62% females) smoked at the baseline. Sixty-five patients were on Lipid-lowering treatment, of them 48% started it after the initiation of the treatment with biologics.

TJC and SJC were significantly reduced after 24 months of treatment. TC did not change significantly after 1 year but was significantly reduced after 2 years. HDL increased significantly at 12-month and then significantly reduced at 24-month period. Comparison of LDL measurements at 12 and 24-month periods showed significant improvement from 1.8±1.6 to 1.3±1.5 with p<0.001. The AI was significantly reduced during the two follow-up periods. CRP, ESR and DAS28 were also significantly reduced from the baseline levels (Table).

RA Characteristics	Baseline, mean (SD)	12-month F-Up, mean (SD)	P	24-month F-Up, mean (SD)	P
Total Joint Count (TJC)	12.3 (8.1)	5.3 (4.7)	<0.001	5.1 (5.6)	<0.001
Swollen Joint Count (SJC)	4.3 (3.7)	2.1 (2.6)	<0.001	1.1 (1.9)	<0.001
C-Reactive Protein (CRP), mg/l	15.5 (29.0)	10.1 (15.5)	0.004	4.7 (8.3)	<0.001
ESR, mm/h	29.7 (22.8)	22.9 (20.1)	<0.001	16.4 (17.7)	<0.001
DAS28 score	4.1 (1.2)	3.6 (1.2)	<0.001	3.0 (1.1)	<0.001
CDAI score	18.2 (9.6)	14.2 (9.8)	<0.001	10.7 (7.2)	<0.001
HAQ score	1.2 (0.7)	1.1 (0.7)	0.030	0.9 (0.7)	<0.001
Total Cholesterol, mmol/l	3.0 (2.8)	3.3 (2.7)	0.038	2.0 (2.5)	<0.001
HDL Cholesterol, mmol/l	0.7 (0.7)	0.8 (0.7)	0.001	0.6 (0.7)	0.025
Atherogenic Index (TC/HDL)	4.6 (1.7)	4.1 (1.2)	<0.001	3.8 (0.8)	<0.001
Overall 10-year CV Event Risk (%)	12.5 (9.3)	12.1 (9.0)	0.019	11.9 (8.9)	<0.001

The overall risk of cardiovascular event significantly reduced in 12 months (p=0.019, 95%CI 0.1–0.7) and 24 months of the study (p<0.001; 95%CI 0.3–0.9). Thirty seven patients switched biologics during their treatment course. The analysis of the impact of individual biologic DMARD on 10-year CV event risk showed significant improvement at 24-month period in Tocilizumab (p=0.002) and Abatacept (p=0.042) groups.

Conclusion: Our results showed a trend in reducing a 10-year CV event risk in RA patients treated with BDMARDs. This improvement was influenced by many factors. The study results demonstrated a possible favorable effect of biologic DMARDs on the serum levels of TC, LDL and AI. Good control of the inflammation by BDMARDs effectively decreased inflammation and possibly played a pivotal role in reducing the risk for cardiovascular event in patients with RA.

Disclosure: M. M. Khraishi, Hoffman-La Roche Canada, Amgen and Pfizer Canada, and Abbott Canada., 2; **R. Aslanov**, None.

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Increased Incidence Of Low-Energy Fractures In Rheumatoid Arthritis Patients. Kristina Wiberg[1], Marie-Louise Öhman[1], Ulrika Bergström[1] and Solbritt M. Rantapaa-Dahlqvist[2]. [1]Umeå University, Umeå, Sweden, [2]Institution of Public health and clinical medicine/Rheumatology, University of Umeå, Umeå, Sweden, Umea, Sweden.

Background/Purpose: Patients with rheumatoid arthritis (RA) have increased development of osteoporosis. The fracture indicence is not well explored. The aim of this study was to estimate the incidence of low-energy fractures in RA patients identified with a population based register of fractures in northern Sweden.

Methods: The register of patients with RA (ACR criteria) consecutively included since 1995 (n=1178) was coanalysed with the register of Umeå injury data base, Umeå, Sweden of low-energy fractures. This data base was constituted in 1993 and covers six communities with a population at risk of 118000 adults. All individuals admitted to the emergency ward are included. The individuals in this study were followed until fracture or to Jan 1st2011. The standard incidence ratio (SIR) was calculated.

Results: Among the RA patients, 329 individuals (246 females and 83 males) were identified with a fracture. The corresponding figures among controls were 14102 females and 13313 males with fractures. The SIR for a fracture in the RA patients was overall in females OR=1.35 (1.19–1.53) and in males OR=1.70 (1.36–2.11). Stratification for age showed increased SIR in the year group over 65 years of age; females OR=1.39 (1.19–1.62) and males OR=1.88 (1.44–2.42). The highest SIR was for hip fracture; females OR=2.51 (1.21–4.61) and males OR=4.75 (1.74–10.35) with a similar mean age for cases and controls; 72–75 years. The duration of time from diagnosis of RA to the first fracture was during the follow up in females mean (SD) 16.9 (12.4) years and in males 11.7 (9.9) years. The RA patients had similar frequence of fractures in- as out-doors as compared with controls who had significantly higher frequency of fractures outdoors.

Conclusion: RA is associated with a higher incidence for fractures among individuals seeking emergency care. In this study the highest SIR was for hip fractures both in females and males.

Disclosure: K. Wiberg, None; **M. L. Öhman**, None; **U. Bergström**, None; **S. M. Rantapaa-Dahlqvist**, None.

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Carotid Artery Plaques Are Associated With Coronary Atherosclerosis In Patients With Inflammatory Joint Diseases Independent Of Several Cardiovascular Risk Calculators. Silvia Rollefstad[1], Eirik Ikdahl[1], Inge C. Olsen[1], Tore K. Kvien[2], Anne S. Eirheim[1], Terje R. Pedersen[2] and Anne G. Semb[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]University of Oslo, Oslo, Norway.

Background/Purpose: Patients with rheumatoid arthritis (RA) and carotid plaque (CP) have been shown to have increased risk of future acute coronary syndrome. We have established a cardiovascular (CV) preventive clinic and in a CV risk evaluation it is of clinical value to know if CP is associated with coronary atherosclerosis (CA) in addition to the CV risk algorithms in patients with inflammatory joint diseases (IJD). Our objective was to evaluate if CP was associated with CA in patients with IJD.

Methods: In a preventive cardio-rheuma clinic 157 patients with IJD (98 with rheumatoid arthritis, 42 with ankylosing spondylitis, 17 with psoriatic arthritis) were referred for CV risk evaluation. Traditional CV risk factors were recorded. All patients underwent B-Mode ultrasound of the carotid arteries for evaluation of CP and multidetector computer tomography (MDCT) coronary angiography for evaluation of CA.

Results: In a cross sectional analysis all patient characteristics as age, traditional CV risk factors and CRP/ESR were comparable across the various IJD, apart from gender (p<0.01) and disease duration (p<0.01). The presence of CP was also comparable across the various IJD [RA, n= 76 (77.6%), ankylosing spondylitis: 36 (85.7), psoriatic arthritis 15 (88.2), p=0.38]. A total of 98 (62) had CA, while 59 (37.6) did not have CA and there was no difference between the 3 IJD groups. In logistic regression analyses CP was significantly associated with CA (Table, model 1a, 2a and 3a respectively) independent of the 3 CV risk calculators: SCORE, Framingham and Reynolds. When number of CP was added in the models (Table, model 1b, 2b, 3b), it increased the associations of CP with CA.

Table. Association of carotid plaque (CP) to coronary atherosclerosis

		a	b
Model 1	SCORE	1.17 (1.06, 1.30) p=0.002	
	CP	2.92 (1.18, 7.22) p=0.02	
	SCORE		1.16 (1.05, 1.29) p=0.003
	Number of CP		1.78 (1.25, 2.54) p=0.001
Model 2	Framingham	1.09 (1.04, 1.14) p<0.001	
	CP	2.76 (1.06, 7.19) p=0.04	
	Framingham		1.001 (1.03, 1.13) p=0.001
	Number of CP		1.67 (1.15, 2.40) p=0.04
Model 3	Reynolds	1.08 (1.03, 1.14) p<0.001	
	CP	3.02 (1.20, 7.58) p=0.02	
	Reynolds		1.08 (1.03, 1.14) 0.004
	Number of CP		1.73 (1.21, 2.47) p=0.003

Cardiovascular risk algorithms:
SCORE (Systematic coronary risk evalution), Framingham and Reynolds

Conclusion: CP was independently associated with coronary atherosclerosis. CP can therefore be regarded as CV disease in patients with IJD and has direct clinical implications in CV risk evaluation and prevention.

Disclosure: S. Rollefstad, None; **E. Ikdahl**, None; **I. C. Olsen**, None; **T. K. Kvien**, None; **A. S. Eirheim**, None; **T. R. Pedersen**, Pfizer, Merck-Schering Plough, AstraZeneca, 5; **A. G. Semb**, Merck/Schering-Plough, Abbott, BMS, Pfizer/Wyeth, Genentech and Roche, 5.

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Systemic Inflammation In Patients With Inflammatory Joint Disease Does Not Influence Statin Dose Needed To Obtain Low Density Lipoprotein Cholesterol Goal In Cardiovascular Prevention. Silvia Rollefstad[1], Eirik Ikdahl[1], Tore K. Kvien[2], Terje R. Pedersen[2], Ingar Holme[3] and Anne G. Semb[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]University of Oslo, Oslo, Norway, [3]Oslo University Hospital-Ullevaal, Oslo, Norway.

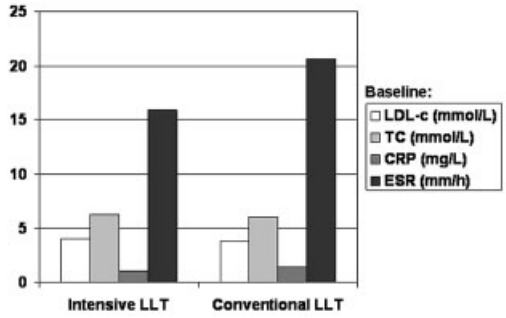
Background/Purpose: There is a lipid paradox in rheumatoid arthritis (RA): despite low lipids influenced by systemic inflammation, there is an increased risk of cardiovascular (CV) disease. Our aim was to describe doses of statins needed to obtain recommended lipid goals in patients with inflammatory joint disease (IJD), including RA, ankylosing spondylitis (AS)

and psoriatic arthritis (PsA). Further, to evaluate if baseline systemic inflammation and lipid levels were associated with statin dose (conventional vs. intensive) needed to obtain guideline recommended low density lipoprotein cholesterol (LDL-c) goal in patients with IJD.

Methods: CV risk stratification was performed at the first consultation in a preventive cardio-rheuma clinic in 202 patients (RA: n=124, AS: n=52, PsA: n=26). The patients were classified to either primary or secondary CV prevention with lipid lowering (LL) treatment, or to have low risk with no indication for medical intervention. LL treatment was initiated with statins and adjusted until at least two lipid targets were achieved. Any side effects/intolerance was recorded. Intensive LL treatment was defined as rosuvastatin ≥ 20 mg, atorvastatin and simvastatin ≥ 80 mg, and conventional LL treatment was defined as all lower doses.

Results: Type or dosage of statins and number of dose adjustments to obtain lipid goals were similar in patients with RA, AS and PsA. There was equal need for change of statin medication across the 3 IJD's due to intolerance/adverse event(s). In a univariate analysis neither systemic inflammation (CRP/ESR: p-value 0.10 and 0.11, respectively) nor lipid levels (LDL-c/total cholesterol (TC): p-value 0.17 and 0.34, respectively) at baseline were associated with the dose of statin needed to achieve LDL-c targets (Figure).

Figure: Doses of lipid lowering treatment (LLT) needed to achieve LDL-c goals



Conclusion: Systemic inflammation or lipid levels did not influence statin dose (conventional or intensive) needed to obtain guideline recommended lipid targets in CV prevention. Whether the background inflammation in IJD patients over time influences the CV risk reduction related to statins is yet unknown.

Disclosure: S. Rollefstad, None; **E. Ikdahl**, None; **T. K. Kvien**, None; **T. R. Pedersen**, Pfizer, Merck-Schering Plough, AstraZeneca, 5; **I. Holme**, Pfizer, Merck/Schering Plough, AstraZeneca, Roche, 5; **A. G. Semb**, Merck/Schering-Plough, Abbott, BMS, Pfizer/Wyeth, Genentech and Roche, 5.

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Rheumatoid Arthritis Is Associated With Systemic Inflammation In Coronary Vessels. Inge A.M. van den Oever[1], Alper M. van Sijl[1], Umit Baylan[1], Michael. T. Nurmohamed[1], Alexandre E. Voskuyl[1], Hans W. Niessen[1] and Suat Simsek[2]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Medical Center Alkmaar (MCA), Alkmaar, Netherlands.

Background/Purpose: Patients with a chronic inflammatory disease (CID), particularly rheumatoid arthritis (RA), have an increased risk of fatal myocardial infarction (MI), as compared to the general population. This risk might be explained, in part, by an increased systemic inflammatory burden in CID causing coronary plaque instability. With tissue specimens of epicardial coronary arteries, we studied whether individuals with CID who died of a fatal MI have an increased influx of inflammatory cells, as compared to individuals without CID but with fatal MI.

Methods: All epicardial coronary artery tissue was collected from 11 individuals with CID (including RA) who had a fatal MI and controls without CID who also had a fatal MI. Controls were matched for age, gender and maximum stenosis of coronaries. Coronary arteries were immunohistochemically stained with specific antibodies against myeloperoxidase (neutrophilic granulocytes), CD45 (lymphocytes), CD68 (macrophages) and tryptase (mast-cells). Intramyocardial coronaries were stained with N-epsilon-(Carboxymethyl)lysine (CML), an advanced glycation end product, visualizing a pro-inflammatory status. Inflammatory cell density (cells/mm2) was calculated for each section of the coronary artery (intima, media and adventitia) for each stain. Subsequently, grade of coronary stenosis (0–100%) was measured. Correlations of grade of coronary stenosis and inflammatory cell density within each of these groups was calculated using the non-parametric Spearman's Rank correlation.

Results: In RA patients, there was a significant correlation between grade of stenosis and inflammatory cell density of macrophages and lymphocytes in the intima of coronaries, with correlation coefficients of 0.313 ($p < 0.05$) and 0.205 ($p < 0.05$), respectively. This was also noted in granulocyte and mast-cell staining, but less strongly. These correlations were not observed in the control group and were also not observed in the media or adventitia of coronaries. Also, in patients with RA, a pro-inflammatory status of intramyocardial coronaries was shown, not only around the infarcted areas, but also in areas of the myocardium distant from MI.

Conclusion: Patients with RA who developed a fatal MI had a significant association between increasing grade of coronary stenosis and influx of inflammatory cells into the intima of all coronary arteries, irrespective of their relationship with the coronary implicated in MI. In particular, an increased influx of macrophages and lymphocytes was noted in the intima of all epicardial coronaries, as well as an increased endothelial activation of intramyocardial coronary vessels. The underlying inflammatory process in RA might drive a more inflammatory form of atherosclerosis, resulting in plaque vulnerability.

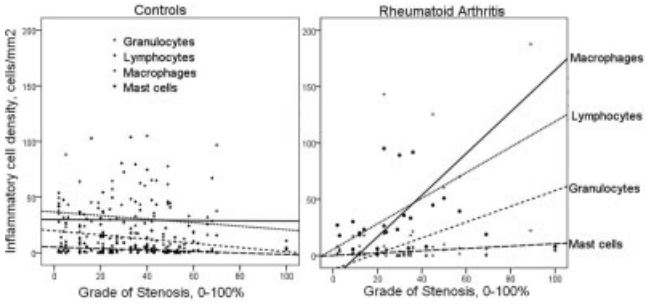

Figure 1. Scatter-plot depicting the correlation between inflammatory cell density of the intima and grade of stenosis of the epicardial coronary

Disclosure: I. A. M. van den Oever, None; **A. M. van Sijl**, None; **U. Baylan**, None; **M. T. Nurmohamed**, None; **A. E. Voskuyl**, Actelion Pharmaceuticals, 5; **H. W. Niessen**, None; **S. Simsek**, None.

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Left Ventricular Myocardial Tissue In Rheumatoid Arthritis Shows Systemic Inflammation After Fatal Myocardial Infarction. Inge A.M. van Den Oever[1], Alper M. van Sijl[1], Umit Baylan[1], Michael. T. Nurmohamed[1], Alexandre E. Voskuyl[1], Hans W. Niessen[1] and Suat Simsek[2]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Medical Center Alkmaar (MCA), Alkmaar, Netherlands.

Background/Purpose: Patients with a chronic inflammatory disease (CID), particularly rheumatoid arthritis (RA), have an increased risk of fatal myocardial infarction (MI) and a diminished survival rate as compared to the general population. This risk might be explained, in part, by the systemic inflammatory process in CID. We investigated whether individuals with CID who developed a fatal myocardial infarction (MI) had an increased influx of inflammatory cells in different areas of myocardial tissue, as compared to individuals without CID.

Methods: Myocardial tissue of 11 individuals with CID (5 with RA, 4 with psoriasis, 2 with an inflammatory bowel disease) who died of a fatal MI were used. Controls were matched for age, gender and time elapsed between myocardial infarction and death. Myocardial tissue was immunohistochemically stained with specific antibodies against myeloperoxidase (neutrophilic granulocytes), CD45 (lymphocytes), CD68 (macrophages) and tryptase (mast-cells). Cell density (cells/mm2) was calculated for the right ventricular (RV) myocardium (internal control; remote area), left ventricular (LV-) myocardium free from MI (internal control) and left ventricular (LV+) myocardium of the MI for each stain. Differences in cell densities between the CID group and controls, and within these groups; between LV+, LV- and RV, were analysed using the non-parametric Mann-Whitney U test.

Results: The CID group and controls showed a similar propensity towards inflammatory cell influx in infarcted myocardium. However, in patients with RA, an increased influx of lymphocytes and macrophages was noted in LV+ as well as LV-, as compared to RV, lymphocyte density: 16.5 ($p < 0.05$) and 14.8 ($p < 0.05$) vs. 7.9, macrophage density: 17.1 ($p < 0.05$)

and 20.3 ($p < 0.05$) vs. 9.9 ($p < 0.05$). These findings were not found in the control group. There was no significant influx of granulocytes or mast-cells in ventricular tissue of patients with RA.

Conclusion: Left ventricular myocardial tissue of patients with RA, showed an increased propensity towards systemic inflammation outside the regions of myocardial infarction. In particular, an increased influx of macrophages and lymphocytes was noted. This underlying inflammatory process in RA might enhance more cytokine release, thereby causing more cardiac depression and tissue damage after myocardial infarction.

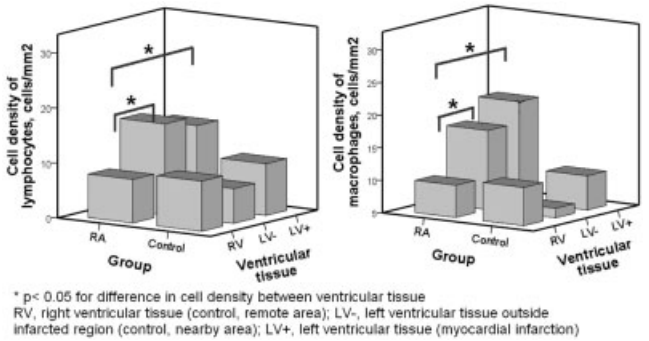

Figure 1. Bar chart depicting the difference in inflammatory cell density of several types of myocardial tissue and the presence of rheumatoid arthritis

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Vitamin D Levels and Inflammation In The Aortic Wall Of Patients With Inflammatory Rheumatic Disease and Coronary Artery Disease. Ingvild Oma[1], Jacqueline Kirsti Andersen[2], Torstein Lyberg[3], Øyvind Molberg[4], Jon Elling Whist[1], Ingjerd Lien Kvelstad[1], Terje Veel[5], Morten Fagerland[3], Sven M. Almdahl[6], Knut Mikkelsen[7] and Ivana Hollan[7]. [1]Innlandet Hospital Trust, Lillehammer, Norway, [2]Gjøvik University College, Gjøvik, Norway, [3]Oslo University Hospital, Oslo, Norway, [4]University of Oslo, Oslo, Norway, [5]Feiringklinikken, Feiring, Norway, [6]University Hospital of North Norway, Tromsø, Norway, [7]Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway.

Background/Purpose: Vitamin D is involved in immune reactions, and vitamin D deficiency is associated with autoimmune diseases and with cardiovascular diseases. In Feiring Heart Biopsy Study (FHBS), we previously demonstrated a high occurrence of mononuclear cell infiltrates (MCIs) in subintimal layers of the aorta, related to inflammatory rheumatic disease (IRD). In theory, vitamin D deficiency might contribute to vascular inflammation involved in the pathogenesis of cardiovascular disease (CVD) along with the premature and accelerated CVD in IRD.

We looked for differences in plasma levels of $25(OH)D_3$ and $1,25(OH)_2D_3$ in patients with coronary arterial disease (CAD) and CAD+IRD, and examined if the levels of $25(OH)D_3$ and $1,25(OH)_2D_3$ were related to inflammation in subintimal aortic layers in terms of MCIs.

Methods: Plasma levels of $25(OH)D_3$ were examined by radioimmunoassay and $1,25(OH)_2D_3$ by immunoassay in 53 patients with CAD and 68 patients with CAD and IRD from FHBS. The D vitamin levels were then correlated to the number of MCI previously identified in the subintimal aortic layers of these patients (I. Hollan *et.al*., *Arthritis Rheum*, 56 (2007), 2072–9).

Results: From our univariate analysis, we observed no differences in $25(OH)D_3$ and $1,25(OH)_2D_3$ levels between patients with CAD+IRD and patients with CAD only (see Table). Nor did we observe any relationships between vitamin D levels and occurrence of MCIs in the subintimal aortic layers. However, after adjustment for variables with $p<0,20$ (CRP, glucocorticosteroids, daily vitamin and mineral supplementation, group, MCI) and age and sex, there was a significant inverse relationship between $1,25(OH)_2D_3$and the occurrence of MCIs in the subintimal aortic layers (B=−17, p=0.019, CI= −31.3, −2.8).

Table.

	CAD-IRD (n=68)	CAD-nonIRD (n=53)	*P* value
Age – years	67 ± 10	68 ± 10	0.601
Women – no. (%)	26 (38)	19 (36)	0.851
$25(OH)D_3$ – nmol/l	59 ± 20	59 ± 14	0.930
$1,25(OH)_2D_3$ – pmol/l	108 ± 46	96 ± 23	0.055
MCI in aortic adventitia–no. (%)	30 (48)	10 (20)	0.002

Conclusion: Our study does not support the hypothesis that vitamin D deficiency contributes to the premature and accelerated CVD in IRD. However, based on multivariate analyses, low $1,25(OH)_2D_3$ might be related to the presence inflammation in the subintimal layers of the aorta. This fact needs more exploration in future studies. If there is a causal relationship, vitamin d supplementation might represent a simple and cheap treatment for vascular inflammation.

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Small Intestine Enteropathy In Patients With Rheumatoid Arthritis and Osteoarthritis, Taking Regularly Non-Steroidal Antirheumatic Drugs. Has The Basic Disease Effect On Incidence and Degree Of Damage? Petr Bradna[1], Ilja Tachecí[2], Drahomira Bastecka[2], Stanislav Rejchrt[2], Jan Bures[3] and Marcela Kopacova[4]. [1]Charles University Prague Faculty of Medicine Hradec Kralove and University Hospital, Hradec Králové, Czech Republic, [2]Charles University Prague Faculty of Medicine Hradec Kralove and University Hospital, Hradec Kralove, Czech Republic, [3]Charles University Prague,Medical Faculty Hradec Kralove and University Hospital, Hradec Kralove, Hradec Kralove, Czech Republic, [4]Charles University Prague, Medical Faculty Hradec Kralove and University Hospital, Hradec Kralove, Czech Republic.

Background/Purpose: The involvement of small intestine is demonstrable up to 72% of patients, using non-steroidal antirheumatic drugs (NSAIDs). Quite a few is known about the influence of the principal diagnosis on incidence and severity of enteropathy. The aim of our study was to compare small bowel enteropathy in rheumatoid arthritis and osteoarthritis patients, which are regularly use NSAIDs.

Methods: Capsule endoscopy is currently the leading method for non-invasive diagnostics of small bowel lesions. This method is safe, reproducible, with high diagnostic yield, discriminating extend localization, severity and character of lesions.

We examined 37 rheumatoid arthritis (RA) patients and 14 patients, using NSAIDs on a regular basis for osteoarthritis (OA). Group of 13 healthy persons, who are not using NSAIDs served as a control group. We excluded people with comorbidities potentially involving the bowel or leading to a blood loss.

We evaluated extend, severity and localizations of lesions. Qualitative data were evaluated by Fisher′s exact test, Armitage test or chi2 test, quantitative data were evaluated by Student′s T-test or Mann Whitney test in case of nonparametric distribution.

Results: We demonstrated enteropathy in 67.5% of rheumatoid arthritis patients, moderate or severe lesions in 20% of RA patients. In osteoarthritis group there were 42.9% patients with enteropathy, severe in 7% of them. In control group there were demonstrated only mild changes in 15% people. Moderate or severe lesions were not demonstrated in NSAIDs non-users. Lesions were equally frequent in ileum and jejunum, duodenum was involved rarely. The same distribution was demonstrated also in moderate and severe lesions.

Conclusion: Rheumatoid arthritis patients, using non-steroidal antirheumatic drugs, have significantly more frequent and more severe lesions of small bowel, then osteoarthritis NSAIDs users.

Jejunum and ileum were involved with equal frequency and severity, duodenal involvement was rare. Next studies should reply, if differences are caused by genetic predisposition, co-medication, or they are caused by direct impact of rheumatoid arthritis.

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Autonomic Dysfunction In Rheumatoid Arthritis Improves With Disease Modifying Anti Rheumatic Drugs. Ashit Syngle[1], Inderjeet Verma[2], Pawan Krishan[3] and Nidhi Garg[3]. [1]Healing Touch City Clinic, Fortis Multispeciality Hospital, Chandigarh, India, [2]Punjabi University Patiala, India, Chandigarh, India, [3]Punjabi University Patiala, India, Patiala, India.

Background/Purpose: Autonomic (AN) function is impaired in rheumatoid arthritis (RA) and is a significant risk predictor of sudden cardiac death. However, even half a century after the description of AN dysfunction in rheumatic diseases, we do not know the impact of disease modifying anti-rheumatic diseases (DMARDs). There is need to study the effect of different DMARDs which are routinely employed in the treatment of RA, So we examined the clinical efficacy of DMARDs on AN function in patients with RA.

Methods: We evaluated total 30 RA patients of which 20 were DMARDs naïve; 9 Rheumatoid Factor (RF) RF +ve and 11 RF –ve; mean age 40.5± 7.1 years; disease duration 5.37±6.8; 11/9 (F/M) and 10 biologics naïve; 6 RF +ve and 4 RF -ve; mean age 49.28±6.62; disease duration 9.5±5.1; 4/8 (F/M). 20 aged matched healthy subjects aged 26–57 years were also enrolled as control group. AN function was assessed by applying a battery of 5 non invasive cardiovascular reflex tests according to Ewing and peripheral sympathetic AN function was assessed by Sudoscan. CAN is considered to exist if at 2 two of 5 cardiovascular reflex tests were positive.

Results: Patients with RA had significantly impaired AN function tests compared with healthy controls. After 12 weeks treatment with combination synthetic DMARDs, heart rate (HR) response to standing in RA patients significantly improved. After treatment with different biologic DMARDs there was significant improvement in HR responses to the deep breathing ($p<0.05$), standing up ($p<0.05$) and sustained handgrip (($p<0.05$)) and sudomotor function ($p<0.05$). DMARDs naïve RF +ve patients had more CAN [77% (7/9)] as compared to the RF -ve patients [45.4% (5/11)]. 83 % (5/6) biologics naïve RF +ve and 75% (2/3) RF –ve patients had CAN. 44% (4/9) DMARDs naïve RF +ve patients and 18 % (2/11) RF –ve had sudomotor dysfunction. 66.6% (4/6) biologics naïve RF +ve patients had sudomotor dysfunction while there was no sudomotor dysfunction in RF –ve patients. After 12 weeks treatment with csDMARDs 28% (2/7) RF +ve patients and 20% (1/5) RF–ve patients improved CAN. After treatment with biologic DMARDs, 100% (5/5) RF +ve patients and 66.6% (2/3) RF –ve patients had significantly improved CAN. 75 % (3/4) of the biologics naïve RF +ve patients who had sudomotor dysfunction improved significantly with biologics. There was no significant improvement in sudomotor function in RF +ve and RF−ve DMARDs naïve RA patients. Patients with normal AN function had no change in their autonomic function after treatment with synthetic or biologic DMARDs.

Conclusion: Synthetic DMARDs significantly improved HR response to standing. Biologics DMARDs significantly improved HR response to deep breath, HR response to standing, BP response to handgrip and sudomotor function in RA biologics naïve patients. RF +ve RA patients have more AN dysfunction than RF –ve patients. In this study biologics and csDMARDs improve CAN & sudomotor function but RF +ve biologics naïve RA patients achieved significantly greater reductions in AN dysfunction compared to RF –ve biologics naïve patients.

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Insulin Resistance As A Risk Factor For Subclinical Atherosclerosis In Rheumatoid Arthritis. Adel M. Elsayed[1], Samah A. El Bakry[1], S. A. M. Hassan[1], Rehab A. Rahman[1], Rania A. Abo-Shady[1] and Nouran Abaza[2]. [1]Ain Shams University, Cairo, Egypt, [2]Lecturer of Physical medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Background/Purpose: Insulin resistance (IR) is a state in which a high insulin concentration is associated with an inadequate response to glucose with normal or high levels of glycaemia. It is strongly associated with systemic inflammation. IR is known to be increased in patients with established rheumatoid arthritis (RA) and has been shown to be a risk factor for both clinical CVD and subclinical atherosclerosis. The aim of this study is to estimate the prevalence of IR among RA patients and its relation to disease activity and disease duration.

Methods: Forty RA patients and 10 age and sex matched healthy individuals as controls were included. RA patients were fulfilling the 2010 ACR/EULAR diagnostic criteria for RA. Patients with Diabetes mellitus, Obesity and Hypertension were excluded. For all, detailed medical history and thorough examinations were performed. Fasting plasma sugar and fasting serum insulin were done, RA disease activity assessed using DAS28-ESR score and IR was evaluated by the homeostasis model assessment (HOMA2). Carotid artery intima media thickness (IMT) was evaluated using ultrasound.

Results: RA patients had significantly higher ESR, CRP positivity, fasting plasma sugar and fasting serum insulin, HOMA2-IR levels than the controls. Insulin resistance as defined by HOMA2-IR>1 was seen in 33(82.5%) RA patients while it was present in only one (10%) of the controls ($p=0.001$). RA patients with insulin resistance have significantly longer disease duration ($p=0.003$), higher disease activity ($p=0.000$), greater carotid IMT ($p=0.000$), and have more carotid plaques ($p=0.043$) than those without insulin resistance. Dividing the RA patients according to the cut-off IMT value (0.72 mm), a significant difference was detected in disease duration ($p=0.002$), DAS28 score ($p=0.000$) and HOMA2-IR ($p=0.000$) being higher in RA patients with increased IMT(>0.72).

Conclusion: In patients with RA, IR was significantly higher than that of healthy controls. A significant positive correlation was found between IR with both disease activity and disease duration in RA patients. Our study pointed out a significant association between IR and subclinical atherosclerosis in RA.

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Prevalence Of Cardiovascular Risk Factors and Cardiovascular Disease In Rheumatoid Arthritis Patients Across International Regions: A Comparison Of The Corrona International and Corrona United States Registries. Dimitrios A. Pappas[1], Kathy Lampl[2], Joel M. Kremer[3], Sebastião C. Radominski[4], Janos Gal[5], Fredrik Nyberg[6], Anand N. Malaviya[7], Aimée Whitworth[8], Oscar Luis Rillo[9], Allan Gibofsky[10], Tatiana Popkova[11], Meilien Ho[12], Ieda Laurindo[13], George W. Reed[8], Eduardo Mario Kerzberg[14], Laura Horne[2], Roman Záhora[15], Katherine C. Saunders[8], Bernado Pons-Estel[16], Alina U. Onofrei[17] and Jeffrey D. Greenberg[18]. [1]Columbia University, New York, NY, [2]AstraZeneca R&D Wilmington, Wilmington, DE, [3]Center for Rheumatology, Albany Medical College, Albany, NY, [4]Universidade Federal do Paraná, Curitiba, Brazil, [5]County Hospital, Kecskemet, Hungary, [6]AstraZeneca R&D, Mölndal, Sweden, [7]Consultant Rheumatologist, ISIC Superspeciality Hospital, New Delhi-11007-, India, [8]CORRONA, Inc., Southborough, MA, [9]CONAART - Hospital Tornú, Buenos Aires, Argentina, [10]Hospital for Special Surgery, New York, NY, [11]Research Institute of Rheumatology -Russian Academy of Medical Science, Moscow, Russia, [12]AstraZeneca R&D Alderley Park, Macclesfield, United Kingdom, [13]Universidade de São Paulo, São Paulo, Brazil, [14]J. M. Ramos Mejía Hospital, School of Medicine, University of Buenos Aires, Buenos Aires, Argentina, [15]Revmatologická ambulance, Terezin, Czech Republic, [16]Hospital Provincial de Rosario, Rosario, Argentina, [17]University of Massachusetts Medical School, Worcester, MA, [18]NYU Hospital for Joint Diseases, New York, NY.

Background/Purpose: Cardiovascular disease (CVD) is a major comorbidity in patients (pts) with rheumatoid arthritis (RA). We explored variations in the prevalence of cardiovascular (CV) risk factors and CVD among patients (pts) in different international regions using data in CORRONA International (C.Intl) and CORRONA US (C.USA) registries.

Methods: The C.Intl registry, launched in September 2011, is a multicenter, observational registry. Adult RA pts have been enrolled from 83 rheumatology practices in 10 countries in 3 regions [Latin America: Mexico, Brazil, Argentina; Eastern Europe: Poland, Czech Republic, Hungary, Romania, Russia, Ukraine; Asia: India]. The only exclusion criteria are functional class IV and age >85 years old.

The C.USA registry was launched in 2001 and enrolls pts from 111 rheumatology practices across the United States. There are no exclusion criteria.

Both registries collect data in a similar manner on demographics, lifestyle characteristics, anthropometry, medication exposures, adverse events and comorbidities from rheumatologists and RA pts at regular clinical encounters.

We present cross-sectional baseline descriptive data for demographic and disease characteristics for the C.Intl regions. We compare this information with cross-sectional data from the most recent visit of C.USA-enrolled pts excluding those with functional class IV and >85 years of age. Prevalence for CV risk factors and CVD are presented crude for C.USA and age/gender-

standardized to the C.USA age/gender distribution (age categories <50, 50-<60, 60-<70, ≥70 years) for C.Intl regions. No formal statistical testing was conducted.

Results: As of March 4 2013, 5696 pts had been enrolled in C.Intl and 20291 pts with functional class <IV and age ≤85 were actively followed in C.USA.

While there are cross-sectional differences across all regions, in general, the greatest differences are between the US and C.Intl overall. There is a higher percentage of male pts in C.USA, disease duration is longer, and pts tend to have lower disease activity, yet are more likely to receive a biologic (Table 1).

After adjusting for age and gender differences by standardization, enrolled pts in India have the lowest BMI, are more rarely smokers and have a low prevalence of hyperlipidemia and CVD compared to other C.Intl regions and C.USA (Table 1). C.USA participants have the highest BMI. Participants from Eastern Europe suffer more frequently from hypertension and hyperlipidemia and have the highest prevalence of all manifestations of CVD (Table 1).

Table 1. *Demographic and disease characteristics, CV risk factors and CVD in RA patients from international regions and from the US

	CORRONA International - regions			
	Latin America	Eastern Europe	Asia	CORRONA US
NUMBER OF PATIENTS (N)	2030	2517	1149	20291
Demographic and disease characteristics				
Females (n,%)	1759 (86.7%)	2099 (83.4%)	982 (85.5%)	15358 (76.6%)
Age/years (mean, SD)	54.2 (12.9)	57.1 (12.2)	47.6 (11.9)	60.3 (12.6)
Disease duration/years (mean, SD)	9.9 (8.7)	9.1 (8.6)	6.3 (5.8)	12 (10.1)
Anti-CCP or RF positive (%)	1695 (83.5%)	1922 (76.4%)	750 (65.4%)	9867 (76%)
CDAI (mean, SD)	14.6 (13.3)	19.1 (14.3)	15.3 (11.8)	10.4 (11.2)
Current RA medications				
On biologic (n,%)	400 (19.7%)	323 (12.8%)	6 (0.5%)	10516 (51.8%)
On DMARD(s) but not on biologics (n,%)	1374 (67.7%)	1782 (70.8%)	1026 (89.3%)	8430 (41.5%)
Corticosteroids (n,%)	842 (41.5%)	690 (27.4%)	304 (26.5%)	4635 (22.8%)
Prevalence of CV risk factors (age/gender standardized)				
Family history of early AMI (<60 years) (n,%)	255 (12.5%)	270 (10.2%)	84 (6.8%)	677 (3.3%)
Family history of early stroke (<60 years) (n,%)	115 (5.4%)	194 (7.2%)	21 (2.1%)	259 (1.3%)
BMI (mean, SD)	27.3 (7.6)	27.4 (6)	24.2 (5.3)	29.4 (7)
Current smoker (n,%)	327 (15.9%)	339 (12.9%)	23 (2.7%)	3015 (15%)
Hypertension (n,%)	655 (39.4%)	1378 (58.1%)	186 (31.7%)	6359 (31.4%)
Hyperlipidemia (n,%)	317 (18.6%)	677 (28%)	33 (5.3%)	1463 (7.2%)
Prevalence of CVD (age/ gender standardized)				
Congestive Heart Failure (n,%)	19 (1.3%)	48 (2.1%)	0 (0%)	44 (1.1%)
Coronary artery disease (n,%)	21 (1.9%)	282 (12.9%)	12 (1.8%)	920 (4.5%)
AMI (n,%)	20 (1.6%)	69 (3.6%)	6 (2.2%)	560 (2.8%)
Unstable angina (n,%)	1 (0.1%)	20 (0.8%)	2 (0.1%)	78 (0.4%)
Peripheral arterial disease (n,%)	4 (0.3%)	26 (1.2%)	0 (0%)	50 (0.2%)
Stroke (n,%)	15 (0.9%)	44 (2.2%)	1 (0.9%)	407 (2%)
TIA (n,%)	9 (0.8%)	38 (1.5%)	2 (0.4%)	175 (0.9%)

* all data are from baseline visits for CORRONA International, and cross-sectional data from the most recent visit of pts enrolled in CORRONA US.
ABBREVIATIONS CCP: Cyclic Citrullinated Peptide; CDAI: Clinical Disease Activity Index; DMARDs: Disease Modifying Anti-Rheumatic Drugs; AMI: Acute Myocardial Infarction; BMI: Body Mass Index; TIA: Transient Ischemic Attack

Conclusion: Data from the C.Intl and C.USA registries reveal variations in disease characteristics, as well as prevalence of CV risk factors and CVD across different regions. Observed differences may be influenced by differences in the composition and treatment of pts populations and should be considered in analyses and evaluation of pts from different geographic origins.

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Survival In Rheumatoid Arthritis Associated Pulmonary Arterial Hypertension Is Comparable To Idiopathic Pulmonary Arterial Hypertension. Saghar Sadeghi[1], John T. Granton[2], Pooneh Akhavan[3] and Sindhu R. Johnson[4]. [1]Toronto Scleroderma Research Program, Toronto Western Hospital, Mount Sinai Hospital, and University of Toronto, Toronto, ON, [2]Toronto Pulmonary Hypertension Programme, Toronto General Hospital and University of Toronto, Toronto, ON, [3]Early Rheumatoid Arthritis Program, Mount Sinai Hospital and University of Toronto, Toronto, ON, [4]Toronto Western Hospital, Toronto General Hospital, Mount Sinai Hospital, and University of Toronto, Toronto, ON

Background/Purpose: To evaluate survival in rheumatoid arthritis associated pulmonary arterial hypertension (RA-PAH) compared to idiopathic PAH (IPAH) patients. Secondary outcomes included evaluation of differences in sex predisposition, age of diagnosis, disease severity, co-morbid diseases and pulmonary hypertension treatment.

Methods: A retrospective cohort study of RA-PAH and IPAH seen at the University Health Network Pulmonary Hypertension Programme, Toronto, Canada was conducted. The primary outcome was time to all cause mortality. Unadjusted survival was evaluated using Kaplan-Meier survival curves. Propensity score models were used to adjust for differences in baseline covariates, and to assemble a matched cohort. Cox proportional hazards models were used to estimate survival in the matched cohort.

Results: Screening of 1385 patients identified 18 RA-PAH and 155 IPAH patients. RA-PAH patients had a lower proportion of males (17% versus 30%), and had an older median age of onset (64.0 years versus 53.7 years). RA-PAH patients more frequently had coronary artery disease (33% versus 16%), lower baseline mPAP (43 mmHg versus 51 mmHg), lower proportion of WHO functional class III or IV (39% versus 52%), lower median baseline BNP (58.4 pg/mL versus 95.0 pg/mL), longer 6-minute walk distance (478 m versus 381 m), less calcium channel blocker (22% versus 29%), phophodiesterase-5 inhibitor (11% versus 19%) and prostaglandin analogues (6% versus 15%) use. There were 35 deaths, 2/18 (11%) RA-PAH patients and 33/155 (21%) IPAH patients. The unadjusted 1-year survival for RA-PAH patients was 93% and for IPAH was 94%. The unadjusted hazard ratio comparing RA-PAH to IPAH survival was 1.52 (95% CI 0.16, 2.76). In the matched cohort there were 7 deaths, 2/18 (11%) RA-PAH patients and 5/18 (28%) IPAH patients, with a hazard ratio of 1.53 (95% CI 0.15, 2.84).

Conclusion: PAH is a serious manifestation of RA. Despite milder disease at presentation, survival is comparable to IPAH.

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Vitamin D Deficiency In Patients With Early Inflammatory Arthritis. Seung-Geun Lee[1], Guen-Tae Kim[2], Joung-Wook Lee[3], Seong-Ho Kim[4] and Seung-Hoon Baek[5]. [1]Divsion of Rheumatology, Department of Internal Medicine, Pusan National University School of Medicine, Pusan National University Hospital, Busan, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Kosin University College of Medicine, Busan, South Korea, [3]Divsion of Rheumatology, Department of Internal Medicine, Busan St. Mary's Medical Center, Busan, South Korea, [4]Division of Rheumatology, Inje University College of Medicine, Haeundae Paik Hospital, Busan, South Korea, [5]Divsion of Rheumatology, Department of Internal Medicine, Ilsin Christian Hospital, Busan, South Korea.

Background/Purpose: To investigate the status of vitamin D in patients with early inflammatory arthritis (EIA) compared with healthy controls.

Methods: The study included 101 patients with EIA (≥ 1 swollen joint, symptom duration of ≤ 6 months, not explained by another disease) and 101 healthy controls matched for age, gender and the month of serum vitamin D measurements, not receiving vitamin D supplementation, at a university-affiliated rheumatology center in South Korea from March 2012 to February 2013. Serum 25(OH) vitamin D levels were assessed by radioimmunoassay. EIA patients were subdivided into rheumatoid arthritis (RA) and non-RA

according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria.

Results: No significant difference in serum 25(OH) vitamin D levels between EIA and controls was observed (median 14.2 vs 16.3, p=0.229, Table 1). Among 101 EIA patients, 38 subjects (37.1%) were categorized as RA. In subgroup analyses of EIA patients, RA patients had significantly higher swollen joint count (SJC), tender joint count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, anti-citrullinated protein antibody (ACPA) and lower serum 25(OH) vitamin D levels than in non-RA subjects. Serum 25(OH) vitamin D levels in EIA patients were inversely correlated with the titer of ACPA ($\rho=-0.214$, p=0.031), SJC ($\rho=-0.196$, p=0.049) and patient's visual analogue scale ($\rho=-0.202$, p=0.043). Low serum 25(OH) vitamin D levels in EIA patients tended to be related to a greater likelihood of fulfilling the 2010 ACR/EULAR criteria after adjusting age, sex, Health Assessment Questionnaire score and season (OR=0.952, 95% CI=0.905–1.001, p=0.054, Table 2). In particular, multivariable logistic regression analysis showed that severe vitamin D deficiency (25(OH) vitamin D < 10ng/mL) was significantly associated with the diagnosis of RA (OR=3.259, 95% CI=1.137–9.342, p=0.028, Table 2).

Table 1. Demographics and disease characteristics of patients with early inflammatory arthritis and healthy controls

Variables	EIA (n=101)	Controls (n=101)
Age, years	56.5 ± 12.2	56.6 ± 12.1
Female, n (%)	86 (85.1)	86 (85.1)
Serum (OH) vitamin D, ng/mL	14.2 (5.5–67.9)	16.3 (4.6–23.3)
Severe vitamin D deficiency (<10 ng/mL), n (%)	18 (17.8)	15 (14.9)
Diagnosis		
RA, n (%)[1]	38 (37.6)	
Non–RA, n (%)	63 (62.4)	
OA, n (%)	37 (36.7)	
UIA, n (%)	24 (23.1)	
Other, n (%)	2 (2.0)	

EIA, inflammatory early arthritis; RA, rheumatoid arthritis; OA, osteoarthritis; UIA, undifferentiated arthritis.
[1] RA was classified as 2010 ACR/EULAR criteria.

Table 2. Association between serum 25 (OH) vitamin D and the presence of rheumatoid arthritis in early inflammatory arthritis

Variables	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Serum 25 (OH) vitamin D, ng/mL,	0.95 (0.91 – 1.00)	0.054	0.95 (0.91 – 1.00)[1]	0.054
Severe vitamin D deficiency (<10 ng/mL)	3.26 (1.14 – 9.34)	0.028	3.26 (1.14 – 9.34)[1]	0.028
Age, years	1.00 (0.98 – 1.04)	0.612		
Female vs male	0.89 (0.29 – 2.73)	0.837		
HAQ	1.85 (0.96 – 3.53)	0.064		
Season				
Spring	1.0			
Summer	0.37 (0.12 – 1.12)	0.078		
Autumn	0.37 (0.12 – 1.12)	0.078		
Winter	0.31 (0.10 – 1.00)	0.050		

[1] Estimated using multivariable logistic regression analyses with backward selection, adjusted for age, sex, HAQ and season.

Conclusion: Although serum vitamin D levels in EIA patients were similar to those of controls, vitamin D deficiency contributed to the presence of RA in EIA patients.

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Sex Differences In Lean Mass Deficits In Rheumatoid Arthritis. Joshua Baker[1], David I. Daikh[2] and Patricia P. Katz[2]. [1]University of Pennsylvania, Philadelphia, PA, [2]University of California, San Francisco, San Francisco, CA.

Background/Purpose: Significant differences in adiposity between men and women with RA have been observed (1). Another alteration of body composition, rheumatoid cachexia, characterized by low lean mass, is also clinically important because it has been linked to increased risk of disability and mortality (2). Our objective was to identify the extent of lean mass deficits in men and women with RA compared to age- and sex-specific national reference data.

Methods: Subjects were recruited from a university-based cohort of patients with RA. Exclusion criteria were non–English speaking, age >18 years, current daily oral prednisone dose >50 mg/day, pregnancy, and joint replacement within 1 year. Body composition and regional fat and lean mass distribution were assessed with whole body dual energy X-ray absorptiometry (DXA) using a Lunar Prodigy DXA system. Precision error (1 SD) was 1.0 kg for fat mass, and 0.8 kg for lean mass. Appendicular lean mass and overall lean body mass were adjusted for height to create indices (ALMI and LBMI, respectively). Indices for each subject were compared to previously published NHANES reference ranges to generate age- and sex-specific Z-scores according to the guidelines defined by Kelly et al (3). Sarcopenia was defined as an ALMI Z-score <-1 (corresponding to the16th percentile) (4).

Results: DXA was performed for 141 individuals (56 men, 85 women). There were no significant differences in self-reported disease activity, functioning (by Health Assessment Questionnaire), prednisone use, or disease duration. Men had significantly lower ALMI and LBMI Z-scores compared to women (Table). On average among men, ALMI and LBMI were at the 8th and 7th percentiles, respectively. In contrast, average ALMI and LBMI among women were at the 37th and 32st percentiles, respectively. Sarcopenia was present among 55% of men and 25% of women, with the odds of sarcopenia significantly greater for men ([OR 3.78 [1.84–7.78], p<0.001).

Table. Mean lean mass Z-Scores (SD) and percentiles for men and women with RA based on NHANES reference ranges

	Men (n = 56)	Women (n = 85)	p*
Appendicular lean mass index (ALMI) z-score	−1.39 (1.34)	−0.34 (0.92)	< .0001
ALMI percentile	8th	37th	
Overal lean body mass index (LBMI) Z-score	−1.44 (1.36)	−0.47 (0.86)	< .0001
LBMI percentile	7th	32nd	

* p-value from t-tests comparing men and women

Conclusion: Among subjects with RA, men had significantly greater lean mass deficits than women. Combined with previous observations of greater obesity among men with RA, it appears that men with RA may experience greater alterations in body composition than women when compared to normal sex-specific ranges. Further study may help confirm these findings and to clarify the factors leading to these differences.

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The Dosage Of Prednisolone Is a Risk Factor For Falls In Rheumatoid Arthritis Patients—The Third Year Results Of The Tomorrow Study. Yuko Sugioka, Tatsuya Koike, Kenji Mamoto, Tadashi Okano, Masahiro Tada, Kentaro Inui and Hiroaki Nakamura. Osaka City University Graduate School of Medicine, Osaka, Japan.

Background/Purpose: Population-based studies suggest an association between musculoskeletal problems and an increased risk of falls. Patients with rheumatoid arthritis (RA) who have muscle weakness and stiff or painful joints might be at an increased risk of falling. But, no prospective cohort study concerning fall incidence in RA has been performed. This study used a prospective cohort design to determine the incidence of falls and to elucidate their risk factors in patients with RA who participated in the TOMORROW study (UMIN000003876) that was started in 2010.

Methods: We have started the TOMORROW study examining several risk factors affecting RA. The participants in the study consist of 202 RA patients (109 patients receiving biological agents) and 202 age-and sex-matched healthy volunteers were collected through mass media as controls.

As a baseline, all participants completed a self-administered questionnaire on general health status. Laboratory data and anthropometric parameters were also collected. Body composition was determined by whole body dual X-ray absorptiometry. Vertebral fractures using thoracolumbar spine X-rays were evaluated. In addition, incidence of falls was tracked with a "fall calendar" for 3 years and we collected the calendar yearly.

Results: The incidence of having at least one fall during the 3-year period did not significantly differ between the patients and controls (37.1% vs. 30.2%, NS). However, the patients fell significantly more often than controls (2.48 vs.1.74 falls; $p = 0.03$) and had a higher prevalence of vertebral fractures (46% vs. 30%) and semiquantitative (SQ) grade ≥2 (15% vs. 5%) than the controls. After adjusting for risk factors of falls such as age, gender, smoking and BMI, multiple logistic regression analysis identified that a history of falls was the most significant parameter associated with the incidence of falls (odds ratios: all, 2.49, $p < 0.001$; patients, 1.98, $p = 0.047$; controls, 3.60, $p = 0.017$). Existing vertebral fractures and SQ grade ≥2 did not correlate with the incidence of falls. Multiple regression analysis revealed that the number of falls experienced by patients with RA was associated with the dosage of prednisolone (PSL; $\beta = 0.214$, $P = 0.027$,) and matrix metalloproteinase-3 (MMP-3; $\beta = 0.141$, $P = 0.046$) (Table 1.).

Table 1. Association between number of falls and parameters adjusted for potential confounders for falls

Multivariate number of falls	RA patients β	P value
mHAQ	0.071	0.347
Prednisolone (PSL: mg/day)	0.214	0.027
MMP-3	0.141	0.046
Whole BMD (mg/cm^2)	−0.020	0.843
Body fat (kg)	0.181	0.201
Walking period (min/day)	0.044	0.535

Conclusion: We evaluated the associated risk factors for falls in RA patients. Multiple falls in RA patients were significantly higher than in controls over the past three years. In RA patients, history of fall and a prednisolone use were associated with falls. The patients who fell at least once tend to fall again. To prevent falls, various interventions are necessary for the patients.

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Does Elevated Disease Activity Or Medication Use Influence The Bone Density Of The Prepubertal Offspring In Pregnant Women With Rheumatoid Arthritis? Florentien D.O. de Steenwinkel[1], Anita C.S. Hokken-Koelega[2], Johanna Hazes[1] and Radboud J.E.M. Dolhain[1]. [1]Erasmus Medical Center, Rotterdam, Netherlands, [2]Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, Netherlands.

Background/Purpose: Elevated rheumatoid arthritis disease activity and prednisone use during pregnancy are both associated with a lower bone mineral density (BMD) of the patients, but both can be inevitable in pregnant women with RA. It is unknown if these variables influence the BMD of their offspring. Our purpose was to investigate whether medication or disease activity during pregnancy in patients with RA, influence the BMD of their prepubertal offspring

Methods: Children were included if their mother participated in a prospective cohort study on RA and pregnancy. In 108 children, approximately 7-years-old, the BMD was assessed by dual-energy X-ray absorptiometry. The bone mineral density was expressed in standard deviation score (SDS) for total body and lumbar spine. Variables of the child known to influence the BMD were taken into account: calcium intake, physical activity, serum 25-hydroxyvitamin D, gender, length and weight. Pre- and postnatal variables known to influence the BMD are gestational age, maternal smoking, birth weight, postnatal tempo of growth and type of feeding. The independent variables were prednisone, sulfasalazine and RA disease activity during pregnancy.

Results: The mean BMD total body SDS was −0.11 (0.10) and the mean BMD lumbar spine SDS was −0.20 (0.99). Both variables were comparable to zero, thus the mean of aged and sexed matched healthy controls. No association was found between prednisone or RA disease activity during pregnancy and BMD of 7-years-old offspring, even after correcting for all known associated variables. Sulfasalazine had a positive effect on the whole body BMD (difference in SDS=0.53; p=0.005).

Conclusion: Neither elevated RA disease activity nor medication use during pregnancy is associated with a lower BMD of the 7-year-old offspring. The results of this study may be a help in balancing the risk and benefits of prescribing medication during pregnancy versus accepting active disease.

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Does Elevated Disease Activity Or Medication Use Influence The Body Composition Of The Prepubertal Offspring In Pregnant Women With Rheumatoid Arthritis? Florentien D.O. de Steenwinkel[1], Radboud J.E.M. Dolhain[1], Johanna M.W. Hazes[2] and Anita C.S. Hokken-Koelega[3]. [1]Erasmus Medical Center, Rotterdam, Netherlands, [2]Erasmus University Medical Center, Rotterdam, Netherlands, [3]Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, Netherlands.

Background/Purpose: Elevated rheumatoid arthritis (RA) disease activity during pregnancy is associated with lower birth weight and rapid post-natal growth. Lower birth weight and rapid post-natal growth can negatively influence the body composition later in life, creating a negative health profile and hence contribute to cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) in adulthood. Glucocorticoids are one of the few medications that can be given safely during pregnancy, but animal studies have shown a negatively influence on the metabolic profile of the offspring. Whether the same holds true for humans is not known. The purpose of the study was to investigate if RA disease activity or medication during pregnancy influences the body composition, or increases the presence of early risk on CVD or T2DM determinants, in the prepubertal offspring.

Methods: Children were included if mother participated in a prospective cohort study on RA and pregnancy. In 108 children, approximately 7-years-old, the body compositions were assessed by dual-energy X-ray absorptiometry. The body compositions was expressed in standard deviation score (SDS) for lean body mass (LBM) and fat mass (FM).The presence of the early risk on CVD or T2DM determinants was determined by assessing the individual components (abdominal obesity, high triglyceride, low high-density lipoprotein, high systolic or diastolic pressure and high fasting glucose) of the metabolic syndrome (MetS) adapted for children Independent variables were prednisone, sulfasalazine and RA disease activity during pregnancy.

Results: The mean LBM SDS was −0.65 (0.70) and FM SDS was, 0.21 (0.94). Both variables were significantly different from 0 SDS, the mean of healthy controls, LBM SDS ($p<0.001$) and FM SDS ($p=0.02$). In multivariate analysis a significant association of gender, birth weight, height and weight was found ($p<0.001$) in LBM and only on height and weight ($p<0.001$) in FM. No association was found between elevated RA disease activity or the presence of medication use during pregnancy. RA disease activity or medication use were also not associated with the individual components of the MetS and only 1 child could be diagnosed with MetS.

Conclusion: The elevated fat mass compared to the low lean body mass points to a relative higher fat distribution in the prepubertal children born from mothers with RA. Since this was not associated with disease activity or medication use during pregnancy, this could implicate that RA during pregnancy has an impact on the body composition of children through other mechanisms. In addition, prednisone use during pregnancy was not associated with the individual components of the MetS. This underscores that in humans, in contrast to animal studies, corticosteroids do not influence the metabolic profile of the offspring and can hence be prescribed safely.

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Nausea and Vomiting During Pregnancy and Spontaneous Abortion In Women With Rheumatoid Arthritis. Balambal Bharti[1], Diana L. Johnson[2] and Christina D. Chambers[2]. [1]University of California San Diego, La Jolla, CA, [2]University of California, San Diego, La Jolla, CA.

Background/Purpose: Nausea and Vomiting during Pregnancy (NVP) has been associated with a decreased risk for spontaneous abortion (SAB). However, the Th1/Th2 imbalance that occurs in pregnancy and is accentuated

in women with NVP has not been studied in women with autoimmune diseases (AI) with respect to risk for SAB.

Methods: As part of the ongoing Organization of Teratology Information Specialists Autoimmune Diseases in Pregnancy Project, pregnant women were surveyed regarding 1st trimester vomiting using the Pregnancy Unique Quantification of Emesis (PUQE) questionnaire. Other characteristics assessed included maternal demographics, lifestyle factors and health status, AI status, current pregnancy related characteristics, pregnancy planning, previous pregnancy loss, and outcome of the current pregnancy. The severity of NVP was compared using the mean PUQE scores as well as categories of NVP. Cox proportional hazards regression models were constructed to estimate the adjusted hazard ratios for SAB in those with and without NVP. Separate models were constructed for women with and without AI.

Results: Data were available for 182 women with AI (n = 92) and without AI (n = 90). The mean age of the women at delivery was 33±5 years, with enrollment in the study taking place at an average gestational age of 9±3 weeks. The prevalence of NVP in the entire sample was 65%, with a mean PUQE score of 4.91±1.96. The overall crude rate of SAB was 11%; the rate in women with AI was 13% compared to 9% in those without AI. Women with AI had lower PUQE scores as compared to those without AI, although the difference was not statistically significant (4.7 vs. 5.1; p=0.14). The crude rate of SAB among those with NVP was 9% compared to 16% among those without NVP. The adjusted hazard ratio for SAB among women who had NVP compared to those who did not was 0.61 (95% CI, 0.23–1.62). The adjusted hazard ratios for SAB in women with NVP compared to those without were similar and close to 1 both in women with and without AI (95% CIs, 0.19–2.02 and 0.08–1.47, respectively).

Conclusion: The prevalence of NVP in this cohort of pregnant women with and without AI is comparable to the general population (65% compared to 60–90% in the general population). Women with NVP had a lower risk of SAB compared to those without NVP. The association between NVP and SAB did not differ appreciably between women with and without AI.

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Parotid Ultrasound Abnormalities Among Rheumatoid Arthritis Patients: Prevalence and Clinical Correlates. Hong Yang[1], Doquyen H. Huynh[2], Arnold Ceponis[3] and Arthur Kavanaugh[4]. [1]UCSD, San Diego, CA, [2]UC San Diego School of Medicine, San Diego, CA, [3]University of California San Diego, La Jolla, CA, [4]University of California San Diego, San Diego, CA.

Background/Purpose: Sjögren's syndrome (SS) occurs commonly among rheumatoid arthritis (RA) patients. It may be an indicator of, and even a contributor to, increased RA disease activity and severity. Thus, secondary SS may impact outcome assessment in RA. Diagnosis of SS has traditionally depended on signs and symptoms and serologic test, but also invasive procedures such as minor salivary gland biopsy. Work from several independent groups has shown common, consistent and characteristic findings on parotid and minor salivary gland ultrasound (US) among patients with SS. We used US to assess the parotid and submandibular glands of RA patients, and correlated these findings with clinical characteristics.

Methods: Patients with an established diagnosis of RA attending UCSD Arthritis clinics were randomly recruited. Parotid and submandibular glands US were performed using a standardized protocol; a total US score was calculated according to an validated system (1,2). This system assesses gland texture (echogenicity), posterior border appearance, and parenchymal homogeneity. The US score was calculated as summation of the grades of 5 parameters for all four glands (range 0 to 48). From the literature, the optimal cut-off score for diagnosing SS was 17. Demographic and clinical information were collected, including the sicca syndrome questionnaire, standard RA patient demographics, functional status (using HAQ), RA disease activity (using RAPID3), dental health assessment (using the oral health impact profile [OHIP] short form; range of scores 0 to 56), and cigarette smoking status. Serologic testing included RF, ACPA, SS-A, SS-B. Schirmer's test was performed.

Results: Among the initial 20 patients, half had SS related symptoms per sicca questionairre. Also, 45% patients showed significant ultrasonographic changes (score ≥ 17) in their major salivary glands. Among patients with ultrasonographic salivary changes, 78% had sicca symptoms. The mean dental health assessment score from OHIP short form of patient with US changes was 18.2 compared to 3.2 among patients without US changes. The mean HAQ score was 1.2 among patients with US changes and 0.9 among those without. The mean RAPID3 score of patient with and without US changes was 16.3, and 15.1 respectively. Although ~ 66% patients had abnormal results for Schirmer's test, there was not a strong correlation with US changes.

Conclusion: SS related symptoms are common among unselected RA patients, as are abnormalities on parotid and submandibular gland US. Sonographic salivary gland findings correlate with SS related symptoms, and also with overall dental health. Further study to assess the potential correlation between sonographic salivary gland findings and RA disease activity and severity is needed.

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Chest Pain Is Not Associated With Coronary Atherosclerosis In Patients With Rheumatoid Arthritis and Ankylosing Spondylitis. Silvia Rollefstad[1], Eirik Ikdahl[1], Inge C. Olsen[1], Jonny Hisdal[2], Tore K. Kvien[3], Anne S. Eirheim[1], Terje R. Pedersen[3] and Anne G. Semb[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Uslo University Hospital-Aker, Oslo, Norway, [3]University of Oslo, Oslo, Norway.

Background/Purpose: During cardiovascular (CV) risk stratification in patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS), it can be difficult to distinguish between chest pain related to coronary atherosclerosis (CA), or to the rheumatic disease itself. The aim was to evaluate associations between chest pain, CV risk factors and CA in RA and AS patients without established CV disease.

Methods: Detailed information concerning chest pain and CV risk factors was obtained in 335 patients with RA and AS. In addition, 119 patients (RA n=86 and AS n=33) underwent multi detector computer tomography (MDCT) coronary angiography.

Results: Thirty-one percent (104/335) reported chest pain. Only 6 patients (1.8%) had atypical angina pectoris (pricking pain at rest). In 50 patients with chest pain, 26 (52.0%) had CA, while in 69 patients without chest pain, 51 (73.9%) did have CA (Fig. 1). In a logistic regression analysis with CA (by CT coronary angiography) as the dependent variable, chest pain was not associated with CA (p=0.28). About 30 % of CA was explained by any of the three following CV risk calculators: SCORE, Framingham and Reynolds in these models (Fig. 2).

Conclusion: Chest pain was surprisingly infrequently reported considering the underlying rheumatic joint disease, but when present, chest pain was of limited value in CV risk evaluation.

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Can Modulators Of Inflammation Serve As Biomarkers For Subclinical Atherosclerosis In Rheumatoid Arthritis? Kimberly P. Liang, Douglas P. Landsittel, Suresh R. Mulukutla, Steven E. Reis, Marc C. Levesque, Donald M. Jones, Rachel Gartland, Ali Shoushtari, Flordeliza S. Villanueva, Hunter C. Champion and Larry W. Moreland. University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Rheumatoid arthritis (RA) is independently associated with a higher risk of cardiovascular disease (CVD) and premature atherosclerosis. Mechanisms of atherosclerosis include (1) Endothelial dysfunction/activation mediated by intercellular adhesion molecules (e.g., ICAM-1, VCAM-1, E-selectin) and oxidative stress (e.g., through MPO

activity); (2) Inflammation mediated by cytokines (e.g., IL-6); (3) Plaque stability mediated by CD40-CD40L interactions; and (4) Proteolysis/Plaque rupture mediated by proteolytic enzymes (e.g. MMP-9). This study evaluates whether these serum biomarkers are higher in RA subjects, and/or associated with subclinical carotid atherosclerosis.

Methods: Carotid ultrasounds were performed with measurement of intima-media thickness (cIMT, using maximum of both sides) and plaque presence (of either side), and serum biomarkers (ICAM-1, VCAM-1, E-selectin, MPO, IL-6, CD40L, and MMP-9) were measured by ELISA in all subjects (46 RA cases and 70 controls). Each of the biomarkers, cIMT, plaque presence, and demographic data, were tested for differences between cases and controls, using the Wilcoxon rank-sum test (for continuous data) or chi-square test. The relationship between each serum biomarker and cIMT or plaque presence was tested by Spearman correlations or rank-sum test (for IL-6 only, which was categorized as above detection limit [for 21%] or not).

Results: Mean age, BMI, and gender frequency were similar ($p \geq 0.19$) between RA (59.3 years, 28.9, 72% female) and controls (54.7 years, 28.7, 67% female); race was significantly different (4.4% African-American or other in RA vs. 28.6% in controls; $p=0.001$). Mean cIMT and detectable IL-6 presence were higher in RA (0.88 and 31.8%) than controls (0.79 and 14.3%; $p=0.02$ and 0.03). Mean (+/−SD) MPO was lower in RA (594.9+/−670.9) than controls (727.4+/−464.6) ($p=0.01$). Plaque presence was found in 47.8% of RA cases vs. 37.7% of controls ($p=0.28$). None of the other serum biomarkers were significantly different between RA vs. controls.

ICAM-1 ($r=0.36$, $p<0.001$), VCAM-1 ($r=0.28$, $p=0.002$), and E-selectin ($r=0.32$, $p<0.001$) were positively associated with cIMT in the overall group. Mean cIMT was higher in those with IL-6 above detection limit (0.91 vs. 0.80; $p=0.05$). Mean CD40L and MPO were lower in those with plaque presence (8385 for CD40L and 554 for MPO) compared to plaque absence (9433 for CD40L and 754 for MPO). Results were similar when examined in the RA and control groups separately, though the magnitude of the correlations with cIMT was slightly higher in the control group for ICAM-1, VCAM-1, and E-selectin. In the RA group only, mean ICAM-1 was higher (292) in those with plaque than in those without plaque (234) ($p=0.05$).

Conclusion: This study confirms previous observations that cIMT is higher in RA than non-RA subjects. Markers of endothelial dysfunction (ICAM-1, VCAM-1, E-selectin) are significantly associated with higher cIMT in both RA and non-RA subjects. This suggests possible common pathways of atherosclerotic progression as evidenced by cIMT and biomarker elevation. Further studies are needed to determine the predictive ability of these and other serum biomarkers in CVD risk stratification algorithms in RA patients.

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Peripheral Blood Biomarkers Of Rheumatoid Arthritis-Associated Interstitial Lung Disease. Juan Chen[1] and Dana P. Ascherman[2]. [1]The First Afflicted Hospital of Xiamen University, Xiamen, China, [2]University of Miami, Miami, FL.

Background/Purpose: Interstitial lung disease (ILD) is a common extra-articular manifestation of rheumatoid arthritis (RA) and a significant cause of morbidity and mortality. Asymptomatic, subclinical RA-associated ILD (RA-ILD) may represent a more treatable precursor to end stage fibrotic lung disease. The objective of this study was therefore to define peripheral blood protein signatures capable of identifying subclinical RA-ILD.

Methods: We analyzed the serum concentration of 37 cytokines, chemokines, and remodeling proteins in 55 RA patients and 24 healthy controls recruited through the First Hospital of Xiamen University. RA patients were independently classified as RA-ILD or RA−no ILD based on the presence/absence of high resolution chest CT (HRCT) abnormalities consisting of ground glass opacification, septal thickening, traction bronchiectasis, and/or honeycombing. Levels of specific serum proteins were then correlated with disease subset as well as pulmonary function tests (percent predicted forced vital capacity (%FVC), total lung capacity (%TLC), and carbon monoxide diffusion capacity (%DLCO)) using non-parametric rank sum analysis and Spearman's correlation coefficients, respectively.

Results: Among the 55 RA patients who generally lacked symptoms of dyspnea or cough (2/55 patients presented with these pulmonary manifestations) at the time of serum assessment, 38 (69%)had HRCT evidence of ILD (RA-ILD), while 17 (31%) had no clinical or radiographic evidence of ILD (RA-no ILD). Within the RA-ILD subgroup, the predominant HRCT abnormality was ground glass opacification (55%) suggestive of nonspecific interstitial pneumonia (NSIP).

Multiplex ELISA demonstrated that concentrations of MMP7, IFNg, IP-10, and IL-2Ra were statistically higher in the sera of RA-ILD relative to RA-no ILD patients (respective means ± SEM: 1739 ± 292.3 vs. 761.5 ± 83.85 pg/ml ($p=0.0317$); 9.084 ± 1.502 vs. 4.419 ± 0.6553 pg/ml ($p=0.0474$); 204.6 ± 34.83 vs. 95.49 ± 13.75 pg/ml ($p=0.0449$); and 157.0 ± 25.16 vs. 71.55 ± 11.04 pg/ml ($p=0.0307$)). By ROC analysis, levels of MMP7, IFNg, and IL-2Ra distinguished RA-ILD from RA-no ILD with optimal sensitivities and specificities of 0.87/0.71/0.95 and 0.71/0.65/0.47, respectively. A composite index based on levels of MMP7, IFNg, IL-2Ra, IP-10, and TNFa further discriminated these subgroups with a sensitivity of 0.76 and a specificity of 0.94. Individual concentrations of MMP7, IFNg, IL-2Ra, and IP-10 correlated significantly with overall disease activity, effectively distinguishing individuals with RA-ILD and RA-no ILD. At the same time, MMP7, IFNg, IL-2Ra, and IP-10 concentrations were negatively correlated with %FVC, %TLC, and %DLCO.

Conclusion: In a cohort of RA patients lacking overt clinical features of pulmonary involvement, MMP7, IFNg, IL-2Ra, and IP10 emerged as serum biomarkers of radiographically defined ILD. Supporting a relationship to underlying pulmonary disease activity, serum levels of these proteins were inversely correlated with various measures of pulmonary function. However, future longitudinal studies will be required to fully assess the capacity of these serum biomarkers to predict disease progression.

Disclosure: J. Chen, None; **D. P. Ascherman**, None.

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Arterial Stiffness Is Associated With Abnormal Left Ventricular Geometry In Patients With Rheumatoid Arthritis. Helga Midtbø[1], Eva Gerdts[2], Inge C. Olsen[3], Tore K. Kvien[3], Einar Davidsen[1] and Anne Grete Semb[3]. [1]Haukeland University Hospital, Bergen, Norway, [2]University of Bergen, Bergen, Norway, [3]Diakonhjemmet Hospital, Oslo, Norway.

Background/Purpose: Rheumatoid arthritis (RA) predisposes for increased arterial stiffness(1). In hypertension, arterial stiffness is a powerful modulator of left ventricular (LV) geometry(2). Whether this is true in patients with RA is unknown.

Methods: Echocardiography, clinical and laboratory assessment were performed in 134 RA patients without prior myocardial infarction or cardiac surgery and 102 healthy controls. Arterial stiffness was determined by echocardiography as pulse pressure/stroke volume indexed to height$^{2.04}$ (PPSVi). LV geometry was evaluated by relative wall thickness (RWT) and LV mass, and considered concentric if RWT≥0.43.

Results: The RA patients were older, more often female, had higher blood pressure (BP) and PPSVi compared to controls (all $p<0.05$). In univariate analyses, higher PPSVi was associated with having RA, LV concentric remodeling, older age, and higher systolic BP (all $p<0.001$).In multivariate linear regression analysis, having RA was not directly associated with increased arterial stiffness, when adjusted for other variables (Table).

Table. Covariates of arterial stiffness in total study population (n = 236).

	Dependent variable: Arterial stiffness Multiple $R^2=0.50$	
Independent variable	**Beta**	**p-value**
Systolic BP (mmHg)	0.51	<0.001
Concentric remodeling	0.36	<0.001
Age (years)	0.07	0.234
Female gender	−0.03	0.609
RA	0.01	0.909

Multivariate linear regression analysis. Results reported as multiple R^2 for model and standardised beta coefficients for individual variables.

Conclusion: In RA patients without established cardiovascular disease, increased arterial stiffness is mainly associated with higher systolic BP and concentric remodeling of the LV, pointing to the importance of BP control in RA patients.

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Gout and RA: Not Such a Rare Coexistence After All. Christina Petsch, Elizabeth Araujo, Matthias Englbrecht, Axel J. Hueber, Georg Schett, Bernhard Manger and Juergen Rech. University of Erlangen-Nuremberg, Erlangen, Germany.

Background/Purpose: According to the current rheumatology literature, the simultaneous occurrence of rheumatoid arthritis (RA) and gout is rare and only a few cases have been reported to date (1). However, clinical practice suggests otherwise. The goal of this study was to investigate the coexistence of RA and gout in patients with known RA and identify prognostic factors that could lead to the development of gout in these patients.

Methods: Patients who fulfilled ACR criteria for RA and had a serum uric acid (SUA) level above 6 mg/dl were included. The presence of uric acid deposits in joints was confirmed by means of a dual energy computed tomography (DECT). DECT is a new imaging tool which uses x-ray beams of two different energies to differentiate monosodium urate (MSU) deposits from connective tissues and from calcium containing structures by their absorption properties (2). The following baseline parameters were assessed: gender, age, BMI, duration of disease, DAS 28, current RA therapy, use of medications that interfere with SUA, ESR, CRP, SUA and presence of metabolic syndrome. DECT of patients' feet was performed.

Results: 100 patients (45 females, 55 males) were recruited. 55 patients were seropositive and 45 seronegative. Mean ± SD age was 63.05 ±11.15 years, mean ± SD duration of disease was 8.76 ± 11.15 years, mean ± SD DAS 28 was 3,28 ±1,58. DECT was positive in 16.3% of all scanned patients (9% in seropositive and 24% in seronegative patients). Regarding those, the mean ± SD SUA level was 7,82 ±2,18 mg/dl, mean ± SD age was 63.44 ± 11.71 years, and mean ±SD BMI was 28.06 ±3.45. 88% were male, 20% had a metabolic syndrome and 69% were taking medications that could elevate SUA. According to a logistic regression model analysis, the following parameters showed significance for the presence of uric acid deposits: male gender (Wald x^2 = 3.897, Exp B = 5.678, 95% CI = 1.013–31.844, p=0.048) and seronegativity (Wald x^2 = 4.973, Exp B = 0.171, 95% CI = 0.036–0.807, p=0.026). Interestingly, SUA was not statistically significant.

Conclusion: Our study showed that a considerable number of patients with a diagnosis of RA and elevated SUA level present MSU deposits in typical locations. Male gender and seronegative status are independent variables related to positive findings. Based on this study it is always necessary to think of gout as an additional diagnosis in patients with RA and hyperuricemia.

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Disclosure: C. Petsch, None; **E. Araujo**, None; **M. Englbrecht**, None; **A. J. Hueber**, None; **G. Schett**, None; **B. Manger**, None; **J. Rech**, None.

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Cardiovascular Case Fatality In Rheumatoid Arthritis Is Decreasing; Results From a Current Low Disease Activity Rheumatoid Arthritis Cohort and Review Of The Literature. Inger L. Meek[1], Harald E. Vonkeman[2] and Mart A.F.J. van de Laar[2]. [1]Rheumatology Center Twente, Medisch Spectrum Twente & Twente University, Enschede, Netherlands, [2]Medisch Spectrum Twente & University of Twente, Enschede, Netherlands.

Background/Purpose: Rheumatoid arthritis (RA) is associated with increased cardiovascular (CV) morbidity and mortality. Previous studies, found increased case fatality after myocardial infarction and more frequent sudden death in RA patients compared to non-RA subjects. Trends in case fatality rate in RA after the introduction of potent anti-inflammatory biologic therapies and treat-to-target treatment strategies aiming at remission are not known. The objective of this study was to examine the case fatality rate in current low disease activity RA associated cardiovascular (CV) disease, and to evaluate trends in RA associated CV case fatality over time.

Methods: Prospective study to determine the incidence of fatal and nonfatal CV events in 480 RA patients included in the ACT-CVD cohort between February 2009 and December 2011. Patients with prior CV disease were excluded. Cox regression analysis was performed to determine CV event risk and contributing risk factors over time. The results of the cohort analysis were put into the context of a review of the literature to evaluate trends in RA associated CV fatality rate over time.

Results: The study included 480 RA patients, 72.3% female with a median disease duration of 4.2 years, 72.1% being in clinical remission (Disease Activity Score in 28 joints). During a mean follow up of 2.9 years 29 patients (6%, 21/1000 person years) experienced a first CV event, 2 fatal and 27 non-fatal, corresponding to a 6.9 % case fatality rate. Comparison with previous studies in cohorts with successive enrolment periods showed stable high CV event rates in RA cohorts with enrollment between 1955 and 2011, however CV case fatality in these RA cohorts decreased from 52.9% in 1998 to 6.9% in our study.

Conclusion: CV case fatality in current low disease activity RA is importantly lower than in previous studies. Composite CV event rates remain high, but a trend towards decreasing CV fatality in RA is observed.

Disclosure: I. L. Meek, None; **H. E. Vonkeman**, None; **M. A. F. J. van de Laar**, None.

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Association Between Anti-Cyclic Citrullinated Peptide Antibodies Titres and The Presence and Severity Of Diffuse Interstitial Lung Disease Secondary To Rheumatoid Arthritis. Juan Manuel Ponce-Guarneros[1], Alberto Daniel Rocha Muñoz[2], Jorge Ivan Gámez Nava[3], Soraya Amalí Zavaleta Muñíz[4], Miriam Lizette Díaz Toscano[5], Mario Salazar Paramo[6], Liliana Faviola De La Cerda Trujillo[7], Norma Guadalupe González Montoya[3], Ernesto German Cardona Muñoz[8], Monica Vazquez del Mercado[9] and Laura González López[2]. [1]Hospital General Regional 110, Instituto Mexicano del Seguro Social. Guadalajara., Guadalajara, Jalisco, Mexico, [2]Departamento de Medicina Interna-Reumatología, Hospital General Regional 110, Instituto Mexicano del Seguro Social., Guadalajara, Jalisco, Mexico, [3]Unidad de Investigación en Epidemiología Clínica, Hospital de Especialidades Centro Médico Nacional de Occidente., Guadalajara, Jalisco, Mexico, [4]Universidad de Guadalajara, Guadalajara, Jalisco, México, Mexico, [5]Doctorado en Farmacología, Centro Universitario de Ciencias de la Salud, Guadalajara, Jalisco, Mexico, [6]Instituto Mexicano Del SS, Guadalajara, Mexico, [7]Unidad de Investigación en Epidemiología Clínica del Hospital de Especialidades Centro Médico Nacional de Occidente, IMSS, Guadalajara, Jalisco, Mexico, [8]Departamento de Fisiología, Universidad de Guadalajara, Guadalajara, México, Guadalajara, Jalisco, Mexico, [9]Universidad de Guadalajara, Guadalajara, Mexico.

Background/Purpose: To evaluate the association between anti-cyclic citrullinated peptide antibody titres (anti-CCP) and other clinical factors with the presence and severity of Interstitial Lung Disease in patients with Rheumatoid Arthritis (ILD-RA).

Methods: A total of 81 RA patients were included in a cross-sectional study. Forty-one patients with ILD-RA were compared with 40 Rheumatoid Arthritis without pulmonary involvement (RA w/out). ILD was screened with pulmonary function tests (PFT) and diagnosed by definite findings in the high-resolution computed tomography (HRCT). Clinical impact of ILD was evaluated with PFP, six-minute walk test (6MWT); Borg scale, Saint George's respiratory scale (SGRQ), and severity of ILD according to the HRCT score. Serum anti-CCP levels were measured by ELISA. Multivariate logistic regression was conducted to identify independent risk factors for ILD-RA.

Results: There was no difference in the frequency of smoking history between the group ILD-RA compared with the group of RA w/out (23.1% vs. 31.0% respectively, p = 0.46). The group of ILD-RA has higher score of DAS28 compared with RA w/out (3.59 ± 1.09 vs. 2.77 ± 0.84 respectively, p <0.001), HAQ-Di, (0.90 ± 0.52 vs. 0.58 ± 0.45 respectively, p < 0.05) and higher frequency of positive anti-CCP (100% vs. 64.3%, p < 0.001). Anti-CCP titres correlated with severity of dyspnea (r=0.535, p <0.001), SGRQ symptoms (r = 0.547, p <0.001), SGRQ activity (r = 0.616, p <0.001), SGRQ impact (r = 0.523, p <0.001), HCRT alveolar score (r =

0.695, p <0.001), HCRT interstitial score (r = 0.547, p <0.001) and HCRT total score (r = 0.549, p <0.001). In the multivariate analysis, after adjusting by age, disease duration, smoking status and disease activity anti-CCP titres remained as a risk factor (OR, 1.06; 95%CI, 1.02–1.10; p= 0.001) as well as duration of treatment with methotrexate (OR, 2.82; 95%CI, 1.51–5.29 p = 0.001).

Conclusion: High anti-CCP titers are associated with the severity of the ILD secondary to RA. Follow-up studies are required to identify if patients with higher titers of this antibody are associated with a poor outcome in patients suffering ILD-RA.

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Comorbidity In Early Rheumatoid Arthritis.Does Inflammation Matter? Lena Innala[1], Clara Sjöberg[1], Ewa H. Berglin[1], Anna Södergren[1], Bozena Möller[2], Solbritt M. Rantapaa-Dahlqvist[3] and Solveig Wållberg-Jonsson[1]. [1]Institution of Public health and clinical medicine/Rheumatology, University of Umeå, Umeå, Sweden, [2]Department of Rheumatology, Sunderby Hospital, Luleå, Sweden, [3]Institution of Public health and clinical medicine/Rheumatology, University of Umeå, Umeå, Sweden, Umea, Sweden.

Background/Purpose: Patients with rheumatoid arthritis (RA) suffer from comorbidities that contribute to a shortened lifespan. The degree of inflammation is of importance for the development of cardiovascular disease, but little is known on its relationship with other comorbidities in RA. In the present prospective study we examined the prevalence of comorbidities in early RA and the role of inflammation in this context.

Methods: All patients with early RA (symptom duration <12 months) in Northern Sweden are since 1995 included in a study on co-morbidities. By now 950 patients have been included. At the time of this compilation, 715 patients were followed-up of whom 498 had been ill for ≥ 5 years. Data on comorbidities, disease activity, x-ray (hands, feet) and laboratory samples (autoantibodies, inflammatory variables) and pharmacological therapy were collected in record studies and validated using a survey at RA onset (T0) and after 5 years of disease (T5).

Results: 56% had one or more comorbidities at RA onset. After 5 years, 44% developed at least one new comorbidity. At T0, the most common comorbidities were: hypertension (26.7%), obstructive pulmonary disease (13.4%), diabetes (7.1%), hypothyroidism (7.0%) and malignancy (5.2%). At T5, the most common new comorbidities during the first five years of RA were: hypertension (14.3%), malignancy (7.6%), stroke/TIA (5.0%), myocardial infarction (4.8%) and osteoporosis (4.4%). Univariate regression analyses showed that age (p< 0.001), ESR (p< 0.01), extra-articular RA, Larsen score and corticosteroids (p<0.05 for all) were associated with a new comorbidity during 5 years. Female gender and biologics reduced the risk of comorbidity (p<0, 05 for both). In a regression model adjusted for sex, age, corticosteroid treatment and smoking, extra- articular RA was associated with new endocrine disease during 5 years. In another model, adjusted for age, sex and smoking, AUC for DAS28 (24 months) was associated with lung disease ever.

Conclusion: There is substantial comorbidity among RA patients already at disease onset and considerable new comorbidity during the first five years of disease. Measures of disease activity were associated with occurrence of comorbidity.

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Rheumatoid Arthritis-Associated Interstitial Lung Disease: Lung Inflammation Evaluated With High Resolution Computed Tomography Scan Is Correlated To Rheumatoid Arthritis Disease Activity. Jorge Rojas-Serrano[1], Renzo Perez-Dorame[2], Heidegger Mateos-Toledo[2] and Mayra Mejia[3]. [1]Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico, [2]Instituto Nacional de Enfermedades Respiratorias, Mexico, Mexico, [3]Instituto Nacional de Enfermedades Respiratorias Dr. Ismael Cosío Villegas. México DF., México, D.F., Mexico.

Background/Purpose: To describe the association between rheumatoid arthritis disease activity (RA) and interstitial lung damage (inflammation and fibrosis), in a cohort of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) patients.

Methods: A retrospective study of RA patients with interstitial lung disease (restrictive pattern in lung function tests and evidence of interstitial lung disease in high resolution computed tomography (HRCT)). Patients had a complete evaluation to exclude other causes of pulmonary disease. RA disease activity was measured with the CDAI index. Interstitial lung inflammation and fibrosis were determined by Kazerooni scale. We compared Kazerooni ground-glass score with the nearest CDAI score to HRCT date scan. In 18 patients, a bronchoalveolar lavage (BAL) cell profile (lymphocytes cell count, neutrophils cell count and macrophages cell count) was available and was correlated with the nearest CDAI index. In nine patients, we compared the first ground-glass score with a second one after treatment with DMARs and corticosteroids. Spearman's rank correlation coefficient was used to evaluate the association between RA disease activity with the Kazerooni ground-glass and fibrosis scores, and with the BAL cell profiles.

Results: Thirty-four patients were included. A positive correlation between CDAI and ground-glass scores was found (r_s= 0.3767 (P < 0.028). Fibrosis and CDAI scores were not associated (r_s= −0.0747, p < 0.6745). In the 18 patients with BAL lavage, lymphocytes cell count correlated strongly with the CDAI index (r_s= 0.58, p < 0.011). After treatment, a tendency to lowering in ground-glass score was observed (median [IQR]): (2.33 [2–3] vs. 2 [1.33–2.16]), p<0.056, along with lowering in CDAI score (27 [8–43] vs. 9 [5–12]), p<0.063.

Conclusion: there is a correlation between RA disease activity and ground glass in HRCT in RA-ILD patients. Lymphocytic BAL in RA seems to correlate with disease activity. Ground glass may respond to treatment.

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Correlation of Carotid Intima Media Thickness With Interleukin-6, Tumor Necrosis Factor-α and Anti-Cyclic Citrullinated Peptides In Rheumatoid Arthritis. Lourdes Nuñez Atahualpa[1], Mauricio Figuroa Sanchez[1], Daniel Alberto Rocha Muñoz[2], Raul Vargas Ramirez[3], Beatriz Teresita Martin Marquez[4], Jorge Ivan Gamez Nava[5], Laura González López[6], Erika Martínez García[3], Esther Sanchez Corona[3], Marcelo Petri[4], Rosa Navarro Hernandez[3], Veronica Gonzalez Diaz[1], Jorge Aguilar Arreola[7], Ana Guisllaine Bernard Medina[1], Alejandra Nuñez Atahualpa[8], Javier Andrade Garduño[8], Eduardo Gomez Bañuelos[3] and Monica Vazquez Del Mercado[7]. [1]Hospital Civil Fray Antonio Alcalde, Guadalajara, Mexico, [2]Unidad de Investigación en Epidemiología Clínica del Hospital de Especialidades Centro Médico Nacional de Occidente, IMSS, Guadalajara, Jalisco, Mexico, [3]Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético, Guadalajara, Mexico, [4]Universidad de Guadalajara, Guadalajara, Mexico, [5]Unidad de Investigación en Epidemiología Clínica, Hospital de Especialidades Centro Médico Nacional de Occidente., Guadalajara, Jalisco, Mexico, [6]Departamento de Medicina Interna-Reumatología, Hospital General Regional 110, Instituto Mexicano del Seguro Social., Guadalajara, Jalisco, Mexico, [7]Hospital Civil Dr Juan I Menchaca, Guadalajara, Mexico, [8]Universidad Autónoma de Guadalajara, Guadalajara, Mexico.

Background/Purpose: The main cause of death in rheumatoid arthritis patients are cardiovascular events which cannot be entirely explained by traditional risk factors, suggesting, that systemic inflammation may accelerate them.Anti-cyclic citrullinated peptides (Anti-CCP) antibodies are well known as predictors and markers of clinical activity in RA. Cytokines play an important role in RA. It has been shown that carotid intima media thickness (IMT) values are higher in patients positive for anti-CCP positive.

The aim of this work is to evaluate the relationship of interleukin-6 (IL-6), Tumor Necrosis Factor α (TNF-α), anti-CCP titers and carotid IMT in patients with RA evaluated by bilateral carotid ultrasound.

Methods: Cross-sectional study. The study population was recruited from 2010 to 2012 and included patients with RA of 18 years or older who met the ACR criteria (1987). For the controls we included blood donators matched by gender and by age range. The exclusion criteria for both groups were history of ischemic cardiovascular disease (CVD), hypertension, diabetes mellitus type II, thyroid disease, liver disease, renal impairment, malignancy, dyslipidemia and premature menopause. We also excluded patients treated with high doses of steroids (>10 mg/day). RA disease activity was measured by the Disease Activity Score 28 (DAS28). Carotid IMT was measured using a high-resolution B-mode ultrasound with a 12-MHz transducer. Both left and right carotid arteries were examined. All measurements were performed by a single operator. Anti-CCP and other laboratory measurements: ESR, mm/h was measured using the Winthrobe method; hs-CRP levels were calculated by the nephelometric method and expressed as milligrams per liter. Triglycerides, HDL-cholesterol and LDL-cholesterol were measured and expressed as milligrams per deciliter. Serum was obtained and stored at −70°C for determination of anti-CCP antibodies, IL-6 and TNFα by ELISA. Statistical analysis. Variables were tested for normality using the Kolmogorov-Smirnov test. Student's t-test or Mann–Whitney U-test was applied for comparison between continuous variables, as well as chi-square or Fisher's exact test for categorical variables. Multiple regression analysis was performed to assess independent associations between carotid IMT and various clinical and laboratory factors that had $p<0.2$. All data were analyzed using SPSS 8.0 software, considering a two-tailed level of $p<0.05$ statistically significant for univariate and multivariate analysis.

Results: Correlation coefficients between carotid IMT and characteristics of the evaluated groups showed a *r* and p values of 0.319 and 0.02 for age, TNF-α 0.791 and <0.001, IL-6 0.794 and <0.001, anti-CCP 0.539 and <0.001. It was also found an increased carotid IMT between blood donors and RA patients of 61.3 vs 90% (<0.001). The patients were classified as negative or positive for anti-CCP antibodies and we found an association of increased carotid IMT with higher anti-CCP titers ($p<0.001$).

Conclusion: Pro-inflammatory cytokines are highly correlated with the presence of anti-CCP antibodies and carotid IMT in RA patients.

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Differential Effects of biologics On The Removal Of Amyloid Deposition Between The Kidney and Gastric Tract Of Amyloid A Amyloidosis Patients With Rheumatoid Arthritis. Hiroshi Uda, Tamaki Harada, Ayumi Matsumoto, Aya Mizumoto, Toshirou Takama and Osamu Saiki. Higashiosaka City General Hospital, Higashiosaka, Japan.

Background/Purpose: Several biologics therapy reportedly regress gastric amyloid deposition in amyloid A (AA) amyloidosis patients with rheumatoid arthritis (RA), but it is uncertain whether the biologics therapy can also reduce renal amyloid deposition or not, because it is difficult to repeat a renal biopsy in these patients. We classified renal amyloidosis into two groups, glomerular and vascular types (J. Rheumatology, 2006, 1). In patients with vascular type disease, renal involvements are limited, which enabled us to carry out a follow-up histological study. The main focus of the present study is to compare the regression of amyloid deposition in kidney before and after biologics treatment in patients with vascular type disease.

Methods: The diagnosis of AA amyloidosis was determined by Congo-red stain and anti-AA antibody of gastric biopsy specimen. At first, the RA patients with AA amyloidosis were treated with methotrexate and 5mg of prednisolone, but they did not achieve adequate responses. Subsequently, they were treated with tocilizumab or etanercept for more than three years. Gastric and renal biopsies were performed before and after biologics treatment at least three years' interval. Renal biopsies were examined only in patients with AA amyloidosis of vascular type disease because renal function does not significantly deteriorate (1).

Results: The vascular type of AA amyloid patients with RA received either etanercept or tocilizumab and the clinical symptoms and laboratory data were significantly improved and sustained for more than 3 years during treating with the biologics. Before biologics treatment, renal biopsy specimens showed amyloid deposition around the blood vessels selectively (Figure A). After biologics treatment (mean 4.5 years), however, amyloid deposition did not significantly regress, similar to those observed in the initial study (Figure B). Renal function of the patients was not also changed significantly. The results of AA deposition in kidney were also confirmed by anti-AA antibody. In the gastrointestinal tract, after treatment (mean 4.5 years) with etanercept or tocilizumab, amyloid deposition was markedly regressed (Figure D) compared to the initial study (Figure C) as reported.

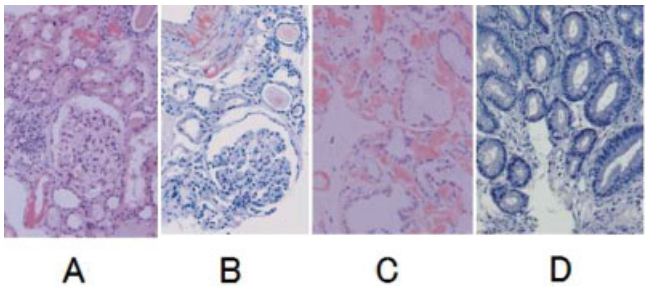

Figure. Results of renal biopsy (**A**, **B**) and gastrointestinal biopsy (**C**, **D**) before therapy (**A, C**) and after therapy (**B, D**) by etanercept. (Congo red stained; original magnification × 200.)

Conclusion: Amyloid deposition of the kidney, unlikely to the gastric tract, does not significantly regress in AA amyloidosis patients with RA by biologics therapy, suggesting that regression of amyloid deposition is differently regulated between the kidney and the gastric tract.

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1. Two distinct clinical courses of renal involvement in rheumatoid patients with AA amyloidosis. J Rheumatol. 2006;33:1482–7.

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Clinical Characterization Of Extensive Interstitial Lung Disease In Rheumatoid Arthritis Patients. Masaomi Yamasaki. Shin-Yokohama Yamasaki Clinic, Yokohama, Japan.

Background/Purpose: To investigate clinical characteristics of interstitial lung disease (ILD) in rheumatoid arthritis (RA) patients, and to analyze whether high resolutional CT (HRCT) can predict the outcome of ILD in RA.

Methods: 365 patients with RA were treated at our hospital and followed up at least one year. All patients were performed chest radiological examinations at the initial presentation. The HRCT findings which include (1) ground glass opacity, (2) air-space consolidation, linear opacity including (3) septal line and (4) non-septal line, (5) honeycomb lung, (6) traction bronchiectasis, (7)pleural irregularity, and (8)pleural effusion were scored as the CT scoring system. The extent of involvement of each abnormality was assessed independently for each of the three zones of each lung. The HRCT extent score was represented the sum of the score of each lung. HRCT parameters which include the extension score and the clinical features at the initial presentation were retrospectively analyzed.

Results: 177 out of 355 patients had abnormal chest radiological findings which included bronchiectasis, bronchitis and ILD (49.8%). 91 (26 male(39.3%), 65 female(22.4%)) out of 355 patients showed ILD at initial presentation (25.6%). 5 out of 91 patients had shortness of breath and showed a rapidly progressive ILD (5.5%). In HRCT findings, ILD in these 5 cases were widely spread at the initial presentation. The rest of 86 patients showed no progression of ILD and asymptomatic. However there were no difference in the HRCT findings which include nonseptal linear attenuation, ground-glass attenuation and air space consolidation between rapidly progressive ILD group and asymptomatic group, rapidly progressive ILD group showed more higher degree in honeycombing ($p=0.0002$) and extensive ILD ($p=0.007$). Prognosis of the rapidly progressive ILD was variable. The rapidly progressive ILD are treated with immunosuppressive agent which include high dose steroid, cyclophosphamide, azathioprine, cyclosporineA (CsA) and Mycophenolate Mofetil(MMF) for IP. 2 patients treated with CsA and one patient treated with MMF shows improving of ILD on HRCT. But in other 2 patients were resistant to these immunosuppressive agents.

Conclusion: HRCT findings focused on the extension score at the initial presentation is a useful predictor of the outcome of ILD in RA. And this study suggests that RA patients with preexisting honeycombing lung must be aware of rapidly progressive ILD.

Disclosure: M. Yamasaki, None;

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A Multiple Cause-Of-Death Study In Rheumatoid Arthritis. Frederico A. G. Pinheiro[1], Deborah C. C. Souza[1] and Emilia I. Sato[2]. [1]Universidade Federal de São Paulo, São Paulo, Brazil, [2]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil.

Background/Purpose: Rheumatoid arthritis (RA) is the most common chronic inflammatory arthritis and has a high standardized mortality ratio when compared to general population. One of the possible ways to assessing mortality is to use the death certificate (DC) that is nationally available and has a broad coverage and further continuity. The evaluation of multiple cause-of-deaths provides beyond the underlying cause of death, the understanding of whole context of death, by the recognition of non-underlying causes of death, which are very important in chronic diseases. The aim of study was to evaluate the mortality profile of RA using the multiple cause-of-death method.

Methods: The DC is established according to World Health Organization recommendation and is composed by two parts: the first presents the sequence of events leading to death, with underlying cause of death stated at last line, and the second part is composed by contributing causes of death.

Death information was provided by the state public center responsible to receive the data from civil registry office. The data about the whole population were obtained from the site of public health care system. Were chosen DC which has had RA (ICD-10: all group M05, M06.1, M06.8 and M06.9) on any line of the medical certification. All DC (N=3938) age above 19 years, for the period of 1996 to 2010 on which RA was listed as an underlying (N=1091) or non-underlying (N=2847) cause of death were analyzed. The variables gender, age and cause of death were analyzed, as well as comparisons between the two sub-periods (1996 –2000 and 2006–2010). To compare the proportional mention of causes of death between the sub-periods, we used chi-square test, performed at SPSS version 20.0. We set the level of significance at $p < 0.05$.

Results: For RA as an underlying cause of death, 251 were males (M) and 840 females (F), with a ratio M/F of 1/3.3. The mean age of death was 67.12 (SD 13.32) years and the main non-underlying causes of death associated with RA were pneumonia (38.86%), septicemia (29.7%), interstitial lung disease (10.91%) and heart failure (9.17%). Comparing the sub-periods, there was an increase of infectious causes (pneumonia and septicemia) and a reduction of heart failure, while interstitial lung disease remained stable.

For RA as a non-underlying cause of death, the mean age of death was 67.92 (SD 13.03) years, with 672 males and 2175 females and a sex ratio of 1/3.2. The most common underlying causes of death were circulatory (35.16%) and respiratory system diseases (21.81%). Comparing the two sub-periods, there was a decrease in respiratory system (all group), pneumonia and cerebral infarction, but an increase in interstitial lung disease in more recent period.

There were 19 cases of tuberculosis (3 as non-underlying and 16 as underlying cause-of-death), but without any type of predominance.

Conclusion: The cardiovascular (CV) disease remains as an important cause of death in RA, justifying a judicious follow-up and treatment of CV risk factors. The infectious diseases are an increasing cause of death in RA patients, bringing the question if infection is related with the vigorous immunosuppressive treatment.

Disclosure: F. A. G. Pinheiro, None; **D. C. C. Souza**, None; **E. I. Sato**, None.

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High Prevalence Of Obesity Among Early and Established Rheumatoid Arthritis. Ines Colmegna[1], Maria Celia Bazan Bardales[2], Susan J. Bartlett[2] and Carol A. Hitchon[3]. [1]McGill University Health Centre, Montreal, QC, [2]McGill University, Montreal, QC, [3]University of Manitoba, Winnipeg, MB.

Background/Purpose: Rheumatoid arthritis (RA) is characterized by early, accelerated atherosclerosis leading to increased disability, morbidity and mortality. Inflammation and traditional cardiovascular (CVD) risk factors contribute to poor outcomes, and obesity further increases risks of CVD, diabetes and disability. New sex-specific RA cutpoints for obesity have been proposed. We estimated the prevalence of obesity among Canadian RA patients using the existing and new thresholds.

Methods: Patients receiving care during 2011–13 at two university centers were included. Height and weight were measured and selected demographic (age, sex, tobacco use), RA (duration, RF+, CCP+, ESR, CRP, tender + swollen joints) and patient reported outcomes (patient global, HAQ, morning stiffness) were obtained at the visit. Patients were classified according to WHO criteria and proposed new RA cutpoints, and results were compared with 2008 StatsCan data.

Results: Participants were 200 RA patients (106 from Winnipeg, 94 from Montreal) who were mostly female (76%) with a mean ± SD age of 56.9 ± 15.3 yr, median [IQR] RA duration of 5 [6] yr (29% < 2 yrs) and HAQ of .7 [IQR 1]. 83% were RF+ and 63% anti-CCP+. Groups did not differ between sites by age, sex or BMI, however, patients in Montreal were more likely to have early RA (38 vs 20%; p =.001) and less likely to have smoked (31% vs. 66%, p <.001). Women were significantly younger than men (56 ± 16 vs 61 ± 14; p=.025) and less likely to report tobacco use (47 vs. 68%; p=.023). RA duration, HAQ and BMI was similar between sexes. Using WHO, 34% of the RA patients were obese; women with RA had higher rates of obesity than men (see table). Using the proposed RA cutpoints, 55% were classified as obese, and men with RA had higher rates of obesity than women. Demographic and RA characteristics were not significantly (p>.05) different between obese and non-obese patients. Although HAQ was only weakly associated with BMI (r=.311 p< .001), obese patients had more than twice the odds of HAQ scores ≥ 1 (OR 2.3 95% CI 1.2, 4.2).

	All	Men	Women
Canadian Population (2008)	24.1%	24.3%	23.9%
Rheumatoid Arthritis			
BMI ≥ 30	34%	29%	36%
Risk Ratio (95% Confidence Interval)	1.4 (0.9–2.2)	1.2 (0.8, 1.9)	1.5 (1.0, 2.3)
Proposed RA Cutpoints			
BMI ≥ 24.7 men; 26.1 women	55%	67%	53%
Risk Ratio	2.3 (1.5, 3.4)	2.8 (1.9, 4.1)	2.2 (1.5, 3.3)

Conclusion: Our results suggest that Canadian RA patients are more likely to be obese than their peers and men appear to be at particular risk. Obesity in RA is associated with greater rates of self-reported disability. Identifying and addressing obesity among newly and established RA patients may be relevant to reduce the excess CVD-associated morbidity and mortality associated with this disease.

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Stability Of Carotid Intima Media Thickness and No Plaque Formation In Inflammatory Arthritis Patients On Biologics Over One Year. Stephanie O. Keeling[1], Asvina Bissonauth[1], Jeff Odenbach[1], Quazi Ibrahim[2] and Michael Sean McMurtry[1]. [1]University of Alberta, Edmonton, AB, [2]EPICORE, Edmonton, AB.

Background/Purpose: Carotid intima media (cIMT) measurement is a validated surrogate measure of cardiovascular (CV) disease. Our aim was to evaluate baseline and follow-up cIMTs in a cohort of northern Alberta inflammatory arthritis (IA) biologic patients to determine if CIMT correlates with traditional CV factors, arthritis activity measures or risk scores.

Methods: CIMT's were performed on 83 IA patients at the Mazankowski Heart Institute as part of their evaluation in the "Cardiovascular Risk Reduction Clinic for Inflammatory Rheumatic Diseases" (CRRC). Univariate and multivariate logistic regression analyses evaluated associations between CV and IA risk factors and the composite outcomes (cIMT > 0.9 mm, presence of plaque or both). Change in cIMT or new plaques were evaluated with repeat cIMT at > 1 year in 13 patients.

Results: CIMTs were performed on 83 IA patients, mean age 60 (SD 12) years, female:male = 58:28. Baseline characteristics included: disease duration 18 (SD 13) years, ESR 16 (SD 16) mm/hr, CRP 6 (SD 8) mg/L, 48 RF/anti-CCP + patients, DAS28 2.92 (SD 1.46). All patients had been on at least one biologic and 59 with past prednisone. Traditional CV risk factors included: 13 current smokers, 6 diabetics, 33 patients with systolic hypertension, 31 patients with dyslipidemia (mean values (mmol/L): total cholesterol 4.80 (SD 1.01), LDL 2.69 (SD 0.78), HDL 1.50 (SD 0.49), total cholesterol/HDL 3.38 (SD 0.91), triglycerides 1.41 (SD 0.76) mmol/L. Twenty-nine patients had family history of premature CVD, 14 patients with personal history of CVD, mean Framingham 12.5% (SD 8.1), mean Framingham with

EULAR adjustment 22.0% (SD 13.4). Mean cIMT was 0.69 (SD 0.15) and 15 patients had one or more plaques. Age > 65 years old was associated with worse cIMT (> 0.9 mm) at baseline (OR 4.58 (95% CI 1.26–16.57). No significant change in cIMT or new plaque formation was seen in 13 patients with repeat cIMT at 1 year or longer. The composite score of cIMT > 0.9 & presence of plaque was associated with moderate Framingham risk score (with EULAR adjustment) (OR 18 (95% CI 1.65–196.35).

Conclusion: Stability of cIMT over time is demonstrated, suggesting possible modification of the increased cardiovascular risk in this small sample of IA patients on biologics. Associations of cIMT with the EULAR-adjusted Framingham risk score requires further study.

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Changes In Body Composition On Two Different Glucocorticoid Regimens In Early RA: Experience From The Cobra-Light Trial. Nicole P.C. Konijn[1], Karin Britsemmer[2], Marieke M. ter Wee[1], Debby den Uyl[1], Birgit S. Blomjous[1], Maarten Boers[2], Dirkjan van Schaardenburg[2], Willem F. Lems[2] and Michael T Nurmohamed[2]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Jan van Breemen Research Institute/Reade, Amsterdam, Netherlands.

Background/Purpose: Prednisolone improves joint inflammation and disease severity in rheumatoid arthritis (RA), but is associated with multiple cardiovascular, metabolic and endocrine side effects and may negatively influence body composition (BC) [1,2]. Rheumatoid cachexia (i.e. loss of lean mass [LM] and gain in fat mass [FM]) is often observed among RA patients, with deleterious effects on morbidity and functional capacity [2]. The net effect of prednisolone on BC in active RA is unknown. The aim of this study was to determine if different dosages of prednisolone have different effects on BC in early RA patients.

Methods: In total, 164 patients with early, active RA were randomised to either COBRA therapy (prednisolone starting at 60 mg/day tapered to 7.5 mg/day in 6 weeks, methotrexate 7.5 mg/week and sulfasalazine 2 g/day; cumulative prednisolone dose at 26 weeks 2.3 g, mean dose: 12.5 mg/day; n = 81) or COBRA light therapy (prednisolone starting at 30 mg/day tapered to 7.5 mg/day in 9 weeks and methotrexate escalated to 25 mg/week in 9 weeks; cumulative prednisolone dose 1.8 g, mean dose: 9.6 mg/day) (n = 83) [3]. Of these, 40 resp. 42 had BC assessments by whole body DXA scans at baseline (BL) and after 26 weeks of treatment. These patients were similar to the other patients with respect to demographics and baseline disease severity (data not shown). Main outcomes of the trial included disease activity (DAS_{44}) and physical functioning (HAQ).

Results: Mean age was 51 years, 67 % were female, median symptom duration was 16 weeks. At baseline, median BMI was above the upper limit of normal in both groups (Table 1); 48% (COBRA) vs. 36% (COBRA light) were classified as overweight, and 15% vs. 19% as obese.

Table 1. Changes in disease activity, physical functioning and body composition parameters after 26 weeks prednisolone treatment

	COBRA group (n=40) (mean pred 12,5 mg/d)		COBRA light group (n=42) (mean pred 9,6 mg/d)	
	Week 0	*Δ after 26 weeks*	*Week 0*	*Δ after 26 weeks*
Disease Activity Score (DAS_{44})	3.87 (0.75)	−2.37 (1.17)*	3.95 (0.91)	−2.22 (1.11)*
Health Assessment Questionnaire (HAQ)	1.25 [0.75]	−0.94 [1.03]*	1.13 [1.12]	−0.57 [0.90]*
Body Weight (Total Body Mass, kg)	76.4 [15.1]	2.4 [2.8]*	72.6 [22.8]	1.3 [4.5]*
Body Mass Index (kg/m^2)	25.7 [4.5]	0.7 [1.2]*	25.1 [7.1]	0.4 [1.8]*
Fat Mass (kg)	23.4 [12.4]	1.5 [2.6]*	23.3 [15.2]	1.8 [3.3]*
- on trunk (kg)	13.0 [8.4]	1.0 [1.8]*	11.3 [10.8]	0.5 [2.4]*
- on arms & legs (kg)	10.0 [4.9]	0.7 [1.3]*	10.5 [4.8]	0.4 [1.1]*
- trunk/arms & legs (truncal distribution) FM (kg)	1.19 [0.70]	0.01 [0.13]	1.10 [0.53]	−0.01 [0.16]
- Fat Mass/Total Mass (% Body Fat)	32% [14%]	1% [3%]*	35% [13%]	1% [3%]*
Lean Mass (kg)	45.4 [10.2]	0.3 [1.6]*	43.7 [15.4]	0.1 [1.3]
- on arms & legs (kg)	20.5 [6.4]	0.2 [1.2]*	19.0 [8.7]	0.1 [0.8]

*Data are presented as mean (SD) for normally distributed variables and as median [IQR] for non-parametric variables;*significant difference between week 0 and 26 within treatment group (p<0.05);*

In both groups, DAS_{44} and HAQ decreased significantly after 26 weeks of treatment. In the COBRA group the effect on HAQ was more prominent at week 13 (data not shown). Both groups gained weight (median 1–2 kg) with slight but significant deterioration in BC parameters: increases in BMI, total FM, truncal FM, FM of arms and legs and BF%, without significant differences between treatment groups. Interestingly, in the COBRA treatment group, total LM and LM of arms and legs increased significantly, with a trend for significant difference between both groups (p=0.058 and p=0.070, resp.).

Conclusion: This study suggests a potentially negative effect of intermediate dose prednisolone treatment on body composition in RA patients, as multiple fat mass parameters indicated a more unfavourable body composition after 26 weeks. The increase of lean mass in the COBRA treatment group also suggests positive effects, possibly explained by a rapid improvement in physical functioning. Results have to be interpreted with caution as most patients were overweight, and body composition before the onset of RA was not recorded.

References:
1: Townsend & Saag, Clin Exp Rheumatology 2004
2: Engvall et al, Scand J Rheumatology 2011
3: den Uyl et al, ARD 2013

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Consensus Statement On The Diagnosis and Management Of Comorbidity In Rheumatoid Arthritis. Cristina Lajas[1], José Luis Andreu[2], Alejandro Balsa[3], Manuel Crespo[4], Carlos M. Gonzalez[5], Oscar Illera[6], Juan A. Jover[1], Isabel Mateo[7], Javier Orte[8], Javier Rivera[9], Jose M Rodriguez-Heredia[10], Fredeswinda I. Romero[11], Juan A Martínez-López[11], Ana M. Ortiz[12], Esther Toledano[1], Virginia Villaverde[13], Estibaliz Loza[14], Loreto Carmona[14] and Santos Castañeda[15]. [1]Hospital Clínico San Carlos, Madrid, Spain, [2]HU Puerta de Hierro Majadahonda, Madrid, Spain, [3]La Paz University Hospital, Rheumatology, Madrid, Spain, [4]Hospital universitario Severo Ochoa, Madrid, Spain, [5]Gregorio Marañon Hospital, Madrid, Spain, [6]Hospital Infanta Sofía, Madrid, Spain, [7]Servicio De Reumatología, Hospital 12 De Octubre, Madrid, Spain, [8]Hospital Universitario Ramón y Cajal, Madrid, Spain, [9]Instituto Provincial de Rehabilitación, Madrid, Spain, [10]Hospital Universitario de Getafe, Getafe, Spain, [11]Jiménez Díaz Foundation University Hospital, Madrid, Spain, [12]Hospital Universitario de La Princesa. IIS Princesa, Madrid, Spain, [13]Hospital Universitario de Móstoles, Mostoles, Spain, [14]Institute for Musculoskeletal Health, Madrid, Spain, [15]Hospital Universitario de La Princesa, IIS Princesa, Madrid, Spain.

Background/Purpose: comorbidity in rheumatoid arthritis (RA) is very important because it might delay diagnosis and influence treatment decisions. It is usually related to complications, alters survival, outcomes and confounds analysis. Moreover, managing care for patients with several chronic conditions currently represents one of the greatest challenges to health care systems. The aim of this study was to to develop evidence based recommendations for the diagnosis and management of comorbidity in RA in daily practice

Methods: four systematic literature reviews, following the guidelines of the Cochrane Collaboration were performed by 4 evidence reviewers, a librarian and two methodologists, to identify comorbidity indexes or scales and to assess the prevalence, mortality, impact on quality of life and costs of comorbidity in RA. Evidence from other consensus, relevant publications and available clinical guidelines was also revised. Comorbidity included co-existent diseases as well as complications of RA or RA therapies. This evidence was discussed in two different meetings, summarized and recommendations were finally formulated by a task force comprising 16 expert rheumatologists and 2 methodologists. The level of evidence and strength of recommendation were classified according to the Center for Evidence Based Medicine of Oxford. The level of agreement was established through Delphi technique.

Results: the consensus covers: 1) which comorbidities and how they should be identified in clinical practice in the first and following visits (including treatments, risk factors and/or patient′s features that might interfere with RA management); 2) specific recommendations on comorbidities related and not to RA, including major adverse events of RA treatment; 3) disease prevention and health promotion (general and musculoskeletal health); 4)

when comorbidities management should be referred and/or shared with other specialities and who with: primary care, other specialists, etc.; 5) specific recommendations to assure an integral care approach for RA patients with any comorbidity: health care models for chronic inflammatory patients, early arthritis units, primary care relationships, specialized nursing care, self-management.

Conclusion:these recommendations are intended to provide rheumatologists, patients and other stakeholders with a consensus on the diagnosis and management of comorbidity in RA, in order to improve the final disease outcomes.

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Assessment Of Treatment Effect Over Insulin Resistance and Adipokines In Patients With Early Rheumatoid Arthritis: A 6 Months Longitudinal Observational Study. Sara Manrique-Arija[1], José Rioja[2], Pedro Valdivielso[2], María América López-Lasanta[3], Pilar Espiño[4], Inmaculada Ureña[4], Francisco G. Jiménez-Núñez[4], Carmen M. Romero-Barco[4] and Antonio Fernández-Nebro[1]. [1]Hospital Carlos Haya. University of Malaga. IBIMA, Malaga, Spain, [2]Department of Medicine. University of Malaga, Malaga, Spain, [3]Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [4]Hospital Carlos Haya. University of Malaga, Malaga, Spain.

Background/Purpose: To analyze treatment effects over insulin resistance (IR), adipokines, inflammatory cytokines and clinical and laboratory characteristics in patients with early rheumatoid arthritis (RA).

Methods: A 6 month prospective longitudinal observational cohort study. Patients with early untreated RA (disease duration <1 year) according to 2010 ACR/EULAR criteria, in follow-up by Rheumatology service of HRU Carlos Haya of Málaga(Spain) were included. After a baseline blood test, treatment for RA was initiated. At six months, another blood test was done. Exclusion criteria: Patients with Diabetes (2010 ADA Criteria) or patients in treatment with glucocorticoids or DMARDs were excluded. All subjects provided written informed consent. Outcome 1°: changes in Insulin Resistance (IR),after starting treatment for RA,estimated by the Homeostasis Model Aassesment for insulin resistance (HOMA-IR), by HOMA β, McAuley and by QUICKI index. Secondary Variables:Changes in the follow variables:Glucose, lipid profile,blood pressure, RF, antiCCP and ESR were measured. Insulin,CRP, IL6, TNFα,resistin, adiponectin, and leptin were determined in frozen serum stored at −80°C. Measurement of waist and hip circumference was performed. *Statistical analysis:* Baseline comparisons between groups were performed using Chi-square, T-test or Mann Whitney test. To analyse the changes Mc Nemar, paired sample T-Test and Wilcoxon tests were used. Multiple linear regression was carried out.

Results: A total of 103 subjects were investigated.12 were excluded (6 other types of arthritis,6 Diabetics) and finally, 91 subjects were included in the study; 46 RA and 45 healthy controls. Most of them were women (76.1% in RA). Cases and controls were similar in age, sex and BMI. Regarding baseline characteristics of patients with RA, the mean time duration of RA was 5.9 (SD± 3.5) months, and more than 70% of patients had positive RF and/or AntiCCP. CRP and ESR were higher in RA patients than in controls ($p<0,001$). In baseline evaluation no differences were found in IR estimated by different index. In multiple linear regression noted a positive correlation between HOMA IR and AR evolution time to diagnosis.After baseline evaluation, all patients were treated with DMARDs. After 6 month of follow–up, a non-significant increase in BMI was observed. The blood pressure and the metabolic characteristics, including lipid profile, fasting glucose, fasting insulin, HOMA-IR, HOMA-B, and QUICKI, remained steady. However, an improvement was observed in all variables related with activity index: hsCRP(12.3 Vs5.6), ESR(32.9(21.4)Vs 18.7(12.0), joint counts, patient's assessment of disease, DAS28(5.5(1.3)Vs3.2(1.4)), and HAQ(1.3(0.7)Vs 0.548(0.567)) with ($p<0.001$). Both cytokines and adipokines decreased after the treatment.

Conclusion: The patients with untreated early RA still do not show insulin resistant observed in patients with established RA despite having high levels of activity index a inflammatory cytokines. Lack of association in baseline evaluation between AR and IR indexes might be due to the short course of the disease but after six months of follow up, we do not find IR which could be due to inflammatory activity is controlled in most of them.

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A Long Term Observation Of Rheumatoid Arthritis Who Developed Methotrexate Related Lymphoproliferative Disorders. Yukiko Kamogawa, Kyohei Nakamura, Ryu Watanabe, Tsuyoshi Shirai, Yoko Fujita, Yuko Shirota, Noriko Fukuhara, Hiroshi Fujii, Shinichiro Saito, Tomonori Ishii and Hideo Harigae. Tohoku University, Sendai, Japan.

Background/Purpose: Methotrexate (MTX) has been increasingly administered by patients with rheumatoid arthritis (RA). In rare cases, we experience development of malignant lymphoma in patients treated with MTX, resulting as methotrexate-associated lymphoproliferative disorders (MTX-LPDs). However, there are few reports about analyzing relation between lymphoma chemotherapy and RA prognosis. We tried to show how anti-tumor therapies affect the activity of RA.

Methods: We retrospectively enrolled 14 RA patients (4 males and 10 females) who had taken MTX and developed lymphoproliferative disorders in Tohoku University Hospital between 2008 and 2013. Then we analyzed the RA disease duration, period of MTX administration, histology of lymphoma including EBER-1 in situ hybridization for Epstein-Barr virus (EBV), chemotherapies, prognosis of RA and how RA was treated thereafter.

Results: The median age of patients at the time of lymphoma diagnosis was 69 years (57–83). The average period of MTX administration was 6.4 years. 7 of 13 patients were diagnosed as diffuse large B-cell lymphoma (DLBCL), 3 as MALT lymphoma (MALT), 1 as peripheral T-cell lymphoma (PTCL), 2 as Hodgkin lymphoma (HL), 1 as Follicular lymphoma (FL). EBER-1 in situ hybridization for EBV showed positive signals in tumor cells in 4 of 11 cases. After withdrawal of MTX, 2 cases of DLBCL, 1 case of PTCL, and 1 case of MALT showed spontaneous regression of tumors. The 10 patients with LPD persisted after MTX withdrawal treated with R-CHOP (n=4), R-VP+R-COP (n=1), Rituximab (n=3) or ABVD (n=2). 7 out of 14 patients presented RA relapse and treated with prednisolone (PSL), Tacrolimus, Iguratimod, Etanercept, or Tocilizumab. 6 out of 8 patients treated with Rituximab kept remission and other 2 relapsed patients showed weak RA activity, required only small amount of PSL but no DMARDs or Biologics.

Conclusion: Administration of Rituximab toward MTX-LPDs thought to have assisted to keep the RA activity low unexpectedly by suppressing auto-reactive B cells "and "non-remission" in both treatment arms. Autoantibody profiles measured before treatment were then correlated with the status "remission" and "non-remission".

Results: A previously identified diagnostic panel of six novel antigens allowed to distinguish ERA HITHARD samples from age and sex-matched healthy controls with an AUC=0.94. Comparing pre- and post-treatment samples, a small, but significant reduction (−1.3 fold) of autoantibody reactivities towards two antigens was detected in both treatment arms, even though levels were not normalized compared to healthy controls. A specific autoantibody signature was identified in a subgroup of ERA patients who achieved clinical remission after 24 weeks under ADA/MTX combination therapy. A classification biomarker panel of 5–10 autoantigens appears to be sufficient to identify RA patients who will achieve clinical remission upon ADA/MTX therapy. This panel was independent of anti-citrullinated protein antibody (ACPA) positivity. A different set of up to nine antigens was identified that could predict remission in RA patients upon PLACEBO/MTX therapy.

Conclusion: We identified autoantibody patterns in ERA patients associated with clinical response to an induction therapy and identified two independent marker panels that, if further developed into a screening test, could help to guide future treatment selection for MTX alone or a combined use of MTX/ADA.

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Lean Body Mass (LBM) Distribution Negatively Impacts On Health Related Quality Of Life (HRQoL) In Patients With Rheumatoid Arthritis (RA). Rocio V. Gamboa-Cardenas[1], Manuel F. Ugarte-Gil[1], Erika Noriega[1], Mariela Medina-Chinchon[1], Francisco Zevallos-Miranda[1], J. Mariano Cucho-Venegas[1], Jose L. Alfaro-Lozano[1], Zoila Rodriguez-Bellido[2], Risto A. Perich-Campos[2], Karim E. Diaz-Deza[1] and Cesar A. Pastor-Asurza[2]. [1]Hospital Almenara, Lima, Peru, [2]Universidad Nacional Mayor de San Marcos, Lima, Peru.

Background/Purpose: Sarcopenia is more frequent in RA patients than in general population, probably due to persistent inflammatory state. The impact of inflammatory burden seem to be higher in appendicular lean mass than in trunk lean mass, and it could be evaluated using the trunk-to-appendicular lean mass ratio. The aim of this study was to determine whether LBM distribution, in particular trunk-to-appendicular lean mass ratio, is associated with HRQoL in RA patients.

Methods: This cross-sectional study was conducted in consecutive RA patients seen in our Rheumatology Department from January 2012 to June 2013. An interview, chart review, physical examination, laboratory tests and dual energy X-ray absorptiometry (DXA) were performed. RA was defined using the ACR criteria; LBM was determined by DXA and it was analyzed as subtotal LBM (whole body excluding the head), trunk LBM, appendicular LBM and trunk to appendicular lean mass ratio. Socioeconomic status was evaluated according to Graffar′s scale. HRQoL was ascertained using the SF-36. Disease activity was ascertained using the DAS28CRP and disease damage with the Sharp van der Heidje score. Use of prednisone was recorded as current dose of prednisone. The association between HRQoL and LBM was evaluated using Pearson's correlation. Subsequently, a linear regression model was performed to evaluate the association between the SF-36 subcategories and LBM, adjusted for age, socioeconomic status, rheumatoid factor, disease duration, disease damage, disease activity and use of prednisone.

Results: Two-hundred and thirty six patients were evaluated; their average (SD) age was 57.4 (12.8) years. Disease duration was 14.0 (10.4) years; almost all patients were mestizo. 204 (87.9%) were rheumatoid factor positive. DAS28CRP was 4.0 (1.2), the Sharp van der Heidje total score was 99.5 (80.9), the current dose of prednisone was 4.7 (3.2) mg/d. Percentage of subtotal LBM was 58.2 (5.9), percentage of trunk LBM was 60.7 (6.8) and of appendicular LBM was 53.4 (6.3); trunk to appendicular lean mass ratio was 1.4 (0.1). Physical component summary (PCS) was 38.5 (16.9) and mental component summary (MCS) was 45.3 (16.6). In the univariate analysis, trunk to appendicular lean mass ratio was associated with lower PCS (Rho: −0.18); MCS (Rho: −0.21), physical function (Rho: −0.12), general health (Rho: −0.14), vitality (Rho: −0.18), social functioning (Rho: −0.17), role emotional (Rho: −0.15) and mental health (Rho: −0.15). In the adjusted model trunk to appendicular lean mass ratio was associated with PCS (standardized β: −0.17), MCS (β: −0.18), physical function (β: −0.19), general health (β: −0.17), vitality (β: −0.19), social functioning and mental health (β: −0.16); $p<0.05$ in all analyses.

Conclusion: There was a negative association between trunk to appendicular lean mass ratio and the components of HRQoL independent of age, socioeconomic status, rheumatoid factor, disease activity, joint damage, disease duration and use of steroids in our RA patients. The preservation of LBM should be part of the overall goals in the management of RA patients.

Disclosure: R. V. Gamboa-Cardenas, None; **M. F. Ugarte-Gil**, None; **E. Noriega**, None; **M. Medina-Chinchon**, None; **F. Zevallos-Miranda**, None; **J. M. Cucho-Venegas**, None; **J. L. Alfaro-Lozano**, None; **Z. Rodriguez-Bellido**, None; **R. A. Perich-Campos**, None; **K. E. Diaz-Deza**, None; **C. A. Pastor-Asurza**, None.

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Enhanced Cardiovascular Risk Factor Screening In Rheumatoid Arthritis: Does This Have a Sustained Impact? Mark J Ponsford[1], Jennifer K. Cooney[2], Bethany Anthony[2], Fflur A. Huws[2], Lauren Evans[1], Jeanette Thom[2] and Yasmeen Ahmad[1]. [1]Peter Maddison Research Centre, Llandudno, United Kingdom, [2]School of Sport, Health and Exercise Sciences, Bangor University, George Building, Bangor, Gwynedd, LL57 2PZ, UK., Bangor, United Kingdom.

Background/Purpose: Rheumatoid Arthritis (RA) patients face a burden of cardiovascular disease (CVD) twice that of the general population. RA patients have reduced physical fitness, a risk factor for CVD not routinely measured or addressed. Enhanced risk profiling was performed in 100 RA patients between October 2010 and March 2011 combining traditional risk factors with a novel assessment of physical fitness. Patients were given written feedback on lifestyle modification, smoking cessation, where appropriate offered statin or antihypertensive medications, and invited to an 8-week aerobic training research programme. Here we examine the impact on CVD risk and fitness 2 years on.

Methods: All 100 RA patients (69 female, 31 male) were invited for reassessment between February and June 2013. Of these, 58 did not participate (3 died, 28 opted-out, 23 unable to attend, 4 not eligible). Forty-two patients returned for assessment of RA activity scores (DAS-28), CVD risk factors, anthropometric measures, 10-year Framingham and QRISK2–2013 risk score, and physical fitness using the Siconolfi Step Test. Assessments using the Health Assessment (HAQ), International Physical Activity (IPAQ) and study specific questionnaires were completed. Statistical analysis was performed in SPSS v21 and GraphPad.

Results: During the follow-up period (median 2.2 years) there were no cardiovascular events. Results are outlined in table 1. Patients found feedback on CVD risk and fitness useful in 76% cases, citing it prompted an increase in exercise for 48% and to pursue a low fat diet in 63%. Lifestyle modification occurred with smoking cessation in 4 of 7 active smokers and greater engagement with lipid-lowering and antihypertensive agents. A significant rise in physical activity was reported, however observed physical fitness decreased ($p = 0.026$) and body mass index rose ($p = 0.014$).

The QRISK2 10-year CVD risk estimate rose slightly, whereas Framingham risk scores did not significantly change. Ageing increases CVD risk, and Framingham 10-year risk at reassessment (15%) was significantly lower than that predicted by age-adjusted initial CVD risk factor data (18%). Diastolic pressures fell, and a similar trend in systolic blood pressure was seen.

Table 1. Two-Year Follow-up Data: Changes in CVD Risk, Physical Fitness and RA Status

	Initial Assessment	Reassessment	Probability (2-tailed)
Number	42	42	–
Age	62.3 ± 9.3	64.6 ± 9.3	–
Sex (F: M)	29:14	29:14	–
Rheumatoid Arthritis Factors			
Disease duration/years	13.3 ± 10.2	15.4 ± 10.2	–
DAS28 CRP	2.64 ± 1.2	2.45 ± 0.77	0.355
Health Assessment Questionnaire (HAQ)	0.74 ± 0.64	0.97 ± 0.80	0.009**
Physical Fitness			
Step test VO2 (ml/kg/min)	21.6 ± 5.5	20.4 ± 5.1	0.026*
Observed vs. Predicted V02 (ml/kg/min)	21.6 ± 5.3	21.2 ± 5.3	0.491
Able to step (%)	76	79	1.000 †
IPAQ Activity Category (low/moderate/vigorous)	21/17/4	12/11/19	0.0001 ** ††
Anthropometry			
Body mass index (kg/m^2)	26 ± 4.9	27 ± 5.5	0.014**
Body fat (%)	36 ± 14	35 ± 13	0.353
Waist: hip ratio	0.89 ± 0.7	0.88 ± 0.9	0.388
Cardiovascular Risk Factors			
Systolic Blood Pressure (mmHg)	141 ± 20	134 ± 21.8	0.081
Diastolic Blood Pressure (mmHg)	80 ± 11	73 ± 16	0.012*
Hypertensive or on anti-hypertensive (%)	60	64	0.823 †
Hypertensive not on medication (%)	29	19	0.443 †
Total Cholesterol (mmol/L)	5.4 ± 1.1	5.2 ± 1.1	0.112
Triglyceride (mmol/L)	1.4 ± 0.7	1.6 ± 1.1	0.284
Low density lipoprotein (mmol/L)	3.2 ± 1.0	3.0 ± 0.9	0.132
High density lipoprotein (mmol/L)	1.6 ± 0.5	1.6 ± 0.5	0.778
Dyslipidaemia not on medication (%)	40	37	0.791 †
Current Smoking (%)	17	7	0.313 †
Cardiovascular Risk Score			
10 year Framingham risk (%)	16 ± 8.6	15 ± 9.2	0.454
Predicted vs. Observed Framingham risk (%)	18 ± 9.1	15 ± 9.2	0.026*
10 year QRISK2 (%)	19 ± 11	21 ± 12	0.020*
Predicted vs. Observed QRISK2 (%)	22 ± 12	21 ± 12	0.272

Paired T-Test unless otherwise stated. †- Fisher's Exact Test, ††- Chi Squared
* - Significant at 5%, **- Significant at 1%

Conclusion: Our study showed providing patients with an assessment of CVD risk factors and physical fitness had a positive impact on smoking, uptake of risk modifying medications, and perceived physical activity and healthy diet. CVD risk increased but less than that expected with ageing. Disappointingly this was not reflected in body composition or physical fitness, and uptake of a training programme was low (19%) - even in this returning cohort. Behavioural modification such as improving physical activity is fundamental to improving cardiac risk and functional status. Further work is needed in how these changes can be introduced and maintained as pharmacological and prescriptive interventions alone are inadequate.

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Disease Activity In Rheumatoid Arthritis Is Associated With Abnormal Left Ventricular Geometry. Helga Midtbø[1], Eva Gerdts[2], Inge C. Olsen[3], Tore K. Kvien[3], Einar Davidsen[1] and Anne Grete Semb[3]. [1]Haukeland University Hospital, Bergen, Norway, [2]University of Bergen, Bergen, Norway, [3]Diakonhjemmet Hospital, Oslo, Norway.

Background/Purpose: Disease activity is related to risk of cardiovascular (CV) disease in rheumatoid arthritis (RA) patients[1,2]. Left ventricular (LV) geometry strongly predicts CV mortality and morbidity. Less is known about the relation between LV geometry and RA disease activity. Our objective was to study if RA or RA disease activity was associated with abnormal LV geometry measured as increased LV relative wall thickness (RWT) or LV mass.

Methods: Echocardiography, clinical and laboratory assessments were performed in 129 RA patients without prior myocardial infarction or valvular disease and 102 healthy controls. Age-adjusted RWT (LV posterior wall thickness to internal LV radius ratio) and LV mass were calculated by validated equations.

Results: The RA group was older, had higher blood pressure (BP) and included more women compared to controls (all $p<0.05$).

Among RA patients, higher RWT correlated with higher systolic BP, wall stress, and RA disease activity measured by Modified Health Assessment Questionnaire (MHAQ), Clinical Disease Activity Index (CDAI), Simple DAI (SDAI) and Disease Activity Score in 28 Joints (DAS28) in univariate analyses (all $p<0.05$). Wall stress and systolic BP were the main covariates of higher RWT in multivariate analyses both among RA patients and controls (both $p<0.001$) (Table). However, the analyses showed that among RA patients, RWT was associated with higher RA disease activity independent of gender, systolic BP and wall stress (Table). Higher LV mass was independently associated with higher systolic BP, age and body weight, male gender and lower LV ejection fraction (all $p<0.05$), but was not associated with any marker of RA disease activity (data not shown).

Table. Covariates of RWT for RA patients and controls. Multivariate linear regression analyses, results are reported as standardised beta coefficients for individual variables and multiple R^2 for models.

	RA group n=129								RA and control group n=231	
	Model with CDAI		Model with SDAI		Model with DAS 28		Model with MHAQ			
Multiple R^2 for model	0.32	<0.001	0.32	<0.001	0.30	<0.001	0.32	<0.001	0.24	<0.001
Variable	**Beta**	**P**	**Beta**	**P**	**Beta**	**P**	**Beta**	**P**	**Beta**	**P**
CDAI score	0.19	0.01								
SDAI score		0.19	0.01							
DAS 28 score					0.16	0.04				
MHAQ score							0.19	0.01		
Systolic BP (mmHg)	0.43	<0.001	0.43	<0.001	0.44	<0.001	0.44	<0.001	0.32	<0.001
Wall stress (dynes/cm^2)	−0.55	<0.001	−0.54	<0.001	−0.54	<0.001	−0.54	<0.001	−0.44	<0.001
Female gender	0.00	0.99	0.01	0.88	0.02	0.78	0.04	0.64	−0.04	0.55
Anti-hypertensive medication									0.20	<0.01
RA									−0.09	0.21

Conclusion: Abnormal LV geometry was independently associated with markers of increased disease activity in RA, pointing to the importance of disease activity control in RA patients.

References:

1. Provan S *et al* Remission is the mission in cardiovascular disease prevention: A cross-sectional controlled study of CVD risk markers in Rheumatoid Arthritis. Ann Rheum Dis. 2011 May;70(5):812–7.

2. Semb AG *et al.* TK Kvien. Carotid plaque characteristics and disease activity in rheumatoid arthritis. J Rheumatol 2013;40;359–368

Disclosure: H. Midtbø, None; **E. Gerdts**, None; **I. C. Olsen**, None; **T. K. Kvien**, None; **E. Davidsen**, None; **A. G. Semb**, None.

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Serological Biomarkers For The Development Of Rheumatoid Arthritis Related Interstitial Lung Disease. Elena Nikiphorou[1], Esther Chan[2], Vadivelu Saravanan[2], Julie Dawson[3], Navtej Sathi[4], Felix Woodhead[5], Mohamed Nisar[6], Subhashini Arthanari[6], Yasmeen Ahmad[7], Adam Young[8] and Clive Kelly[2]. [1]ERAS, St Albans City Hospital & University College London (UCL), London, United Kingdom, [2]Queen Elizabeth Hospital, Gateshead, United Kingdom, [3]St Helens Hospital, St Helens, United Kingdom, [4]Wrightington Hospital, Wigan, United Kingdom, [5]University Hospitals Coventry and Warwickshire, Coventry, United Kingdom, [6]Burton Hospital, Burton-on-Trent, United Kingdom, [7]Peter Maddison Research Centre, Bangor, United Kingdom, [8]St Albans City Hospital, St Albans, United Kingdom.

Background/Purpose: Interstitial Lung Disease (ILD) is the commonest manifestation of lung disease in Rheumatoid Arthritis (RA) and the only complication reported to be increasing in prevalence, accounting for 6% of all RA deaths. High resolution computed tomography (HRCT) confirmed 25% of RA patients had radiological evidence of ILD. This study examines predictive factors for RA-ILD in a large multi centre UK cohort.

Methods: Data from 14 UK centres was collected using a standard form for patients with both RA and ILD diagnosed over a 25 year period (1987–2012). Analysis included gender, age, duration of both RA and ILD, smoking history, rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) antibody status. Results were compared to age and gender matched RA patients with neither clinical nor radiological evidence of lung disease.

Results: A total of 230 patients with proven RA-ILD were identified: 110 male patients (48%), median (range) age at diagnosis of RA-ILD was 64 (42–83) years, no significant difference between males and females. Articular disease predated ILD in 191 patients (82%), lung disease predated RA in 22 (10%) and synchronous in 17 (7%). The median (range) duration of RA at the time of diagnosis of ILD was 9 (0–31) years. Median age at diagnosis of RA was 56 (23–76) years. 154 patients (67%) were past (121) or present (33) smokers, with a median (range) of 26 (5–88) pack years. Smoking was significantly more frequent among males (75%) than females (60%), odds ratio 1.95 (95%CI 1.11–3.43).The median number of pack years was greater in males (35) than females (20) [p=0.01]. Smoking was less prevalent among RA controls (60%) and median pack year consumption was lower at 21 (5–60) [p=0.03].Although CCP was only available in a subset of RA-ILD patients (n=100), CCP antibody titres were significantly higher in patients with RA-ILD. The table shows univariate analysis (odds ratios & 95% confidence intervals) and multivariate logistic regression (LR) with & without anti-CCP.

	Univariate Analysis		LR without CCP		LR model with CCP	
	OR	95% CI	OR	sig	OR	sig
Sex	1.67	1.2–2.2	.63	.006	.75	.284
Age	2.14	1.4–3.1	.61	.031	.49	.062
RF	2.81	1.8–4.1	.27	.000	.36	.008
Smoker	1.91	1.3–2.7	.62	.011	.72	.279
ACCP	4.00	2.0–7.8			.33	.003

Conclusion: This is the largest and longest multicentre study of factors associated with RA-ILD in the UK. RF and anti-CCP antibodies were both strongly associated with RA-ILD, and may predate articular disease, especially in smokers, with anti-CCP an important and easily measured risk factor for RA-ILD. As smoking is both more prevalent and heavier in males, it may contribute to the increased frequency of RA-ILD in men. As lung abnormalities may also develop before articular symptoms occur, tobacco smoking may precipitate site specific citrullination in the lungs leading to the generation of anti CCP antibodies in early RA. This may alter enzyme expression in the lungs and trigger an abnormal response in genetically susceptible individuals. This suggests a causal role for B cell activation, possibly induced by smoking, in the development of RA-ILD in some patients. A detailed smoking history and titres of anti-CCP antibody should therefore be documented in all RA patients.

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ACR Poster Session A
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy I
Sunday, October 27, 2013, 8:30 AM–4:00 PM

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2-Year Results From The Ample (Abatacept versus Adalimumab Comparison in Biologic-Naïve RA Patients with Background Methotrexate) Trial: Changes In Patient-Reported Outcomes In Response To Subcutaneous Abatacept Or Adalimumab In Rheumatoid Arthritis. R Fleischmann[1], ME Weinblatt[2], M Schiff[3], D Khanna[4], MA Maldonado[5], A Nadkarni[5] and D E Furst[6]. [1]University of Texas Southwestern Medical Center, Dallas, TX, [2]Rheumatology & Immunology, Brigham & Women's Hospital, Boston, MA, [3]University of Colorado, Denver, CO, [4]University of Michigan, Ann Arbor, MI, [5]Bristol-Myers Squibb, Princeton, NJ, [6]University of California at Los Angeles, Los Angeles, CA.

Background/Purpose: RA is a debilitating disease that can impact health-related quality of life (HRQoL) through impairment of activity, loss of independence and reduced work productivity. Year 1 data from the 2-year head-to-head AMPLE study showed comparable improvements in HRQoL and similar onset of response with subcutaneous abatacept and adalimumab on background MTX for multiple patient-reported outcomes (PROs).[1] Longer term data are important to assess maintenance of response over time. Here, we present PRO data from 2 years of the AMPLE study.

Methods: AMPLE is a Phase IIIb, randomized, investigator-blinded study. Biologic-naïve patients with RA and an inadequate response to MTX were randomized to 125 mg abatacept weekly or 40 mg adalimumab bi-weekly, with background MTX. Pain, fatigue, and patient global assessment (PtGA) were measured by 100 mm visual analog scales. Physical function was evaluated using the Health Assessment Questionnaire-Disability Index (HAQ-DI). HRQoL was assessed using the Short Form-36 (SF-36; including Physical and Mental Component Summary subscores [PCS and MCS]). The Activity Limitation Questionnaire (ALQ) measured the number of days patients were unable to perform usual activities during the past 30 days. Psychosocial independence was assessed using the ALQ plus the Role Emotional, Social Functioning and Role Physical subscale items from the SF-36 survey. Physical independence was evaluated using 15 items from the HAQ-DI. The Work Productivity and Activity Impairment questionnaire assessed work productivity. Data are mean (SE) improvements from baseline, unless stated otherwise.

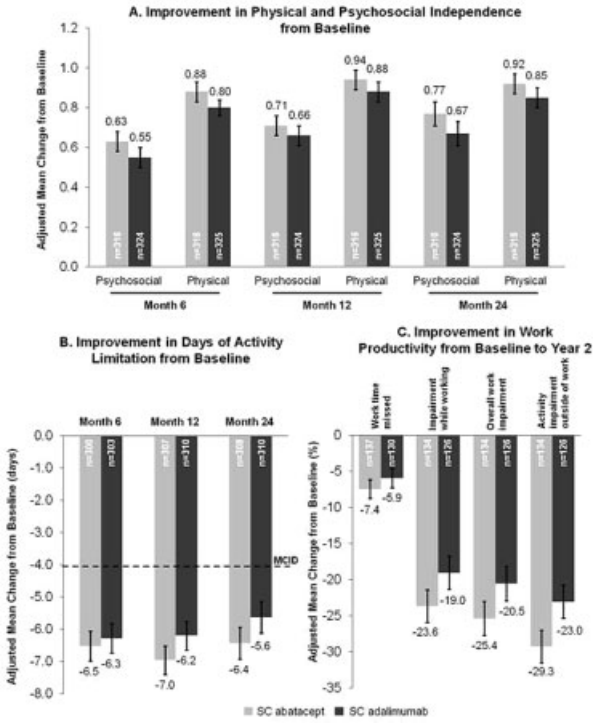

Figure. Mean change in independence, activity limitation, and work productivity over 2 years. Error bars=SE. MCID=minimal clinically important difference.

Results: 646 patients were randomized and treated with abatacept (n=318) or adalimumab (n=328) on background MTX. Baseline characteristics were balanced between the two treatment arms. A similar proportion of abatacept- and adalimumab-treated patients (54.1% and 48.8%, respectively) achieved a HAQ-DI response (improvement of ≥0.3 units from baseline) at 2 years. Improvements [% (SD)] in PtGA at 2 years were 43.5 (3.7) vs 40.6 (3.6)% for abatacept and adalimumab, respectively. Improvements in all domains of the SF-36 observed at 1 year were maintained at 2 years (PCS: 9.3 [0.6] vs 8.6 [0.6]%; MCS: 4.1 [0.6] vs 3.3 [0.6]%, abatacept vs adalimumab at Year 2). Comparable improvements in activity limitation, independence, and work productivity were observed between the two treatments (Figure).

Conclusion: Year 2 data from this head-to-head study show that the improvements in PROs, including productivity and independence, with both SC abatacept plus MTX and adalimumab plus MTX observed at Year 1 are maintained up to Year 2, with similar onset and durability of response.

Reference:
1. Fleischmann, et al. *Arthritis Rheum* 2012;**64**(Suppl 10):S577.

Disclosure: R. Fleischmann, Bristol-Myers Squibb, Abbvie, 5, Bristol-Myers Squibb, Abbvie, 2; **M. Weinblatt**, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, Roche/Genentech, UCB, Janseen, 5; **M. Schiff**, Bristol-Myers Squibb, Abbvie, 5; **D. Khanna**, Bristol-Myers Squibb, 5; **M. Maldonado**, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1; **A. Nadkarni**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **D. E. Furst**, Bristol-Myers Squibb, AbbVie, Actelion, Amgen, Gilead, GSK, NIH, Novartis, Pfizer, Roche/Genentech, UCB, 2, Bristol-Myers Squibb, AbbVie, Actelion, Amgen, Janssen, Gilead, GSK, NIH, Novartis, Pfizer, Roche/Genentech, UCB, 5, AbbVie, Actelion, UCB, 8.

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Efficacy, Pharmacokinetics, and Safety of Different Doses of Methotrexate in Combination With Adalimumab: Results From the Concerto Trial. Gerd R. Burmester[1], Alan J. Kivitz[2], Hartmut Kupper[3], Udayasankar Arulmani[4], Stefan Florentinus[5], Sandra Goss[4], Suchitrita S. Rathmann[4] and Roy Fleischmann[6]. [1]Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]Altoona Center for Clinical Research, Duncansville, PA, [3]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany, [4]AbbVie Inc., North Chicago, IL, [5]AbbVie, Rungis, France, [6]University of Texas Southwestern Medical Center, Dallas, TX.

Background/Purpose: Anti-TNF plus methotrexate (MTX) is more effective than either as monotherapy. Thus far, no controlled data are available on the benefit:risk of different doses of MTX in combination with anti-TNF. The purpose of this study was to determine the effect of MTX dose in combination with adalimumab (ADA) on efficacy, pharmacokinetics, and safety in patients (pts) with early rheumatoid arthritis (RA).

Methods: CONCERTO was a 26-week (wk), double-blind, parallel-arm trial in MTX and biologic-naive pts with active RA [DAS28(CRP) ≥3.2; CRP ≥1.5 mg/dL or ESR ≥28 mm/hr; ≥1 erosion or RF+ or ACPA+] of <1 year duration. Pts were randomized 1:1:1:1 to wkly oral MTX (2.5, 5, 10, or 20 mg) and received open-label (OL) ADA 40 mg every other wk (eow). Pts in the 20 mg arm began 10 mg and escalated 2.5 mg eow to 20 mg. The primary endpoint was the achievement of low disease activity [LDA, defined as DAS28(CRP) <3.2] at wk 26. Secondary endpoints included DAS28(CRP) (<2.6), ACR50/70/90, SDAI (≤3.3)/CDAI (≤2.8) remission, radiographic nonprogression (ΔmTSS ≤0.5), and ΔHAQ-DI ≤-0.22 at wk 26. Dose-response was assessed via Cochran-Armitage linear trend test. Non-responder imputation was used for missing data. Serum samples for pharmacokinetics were collected prior to baseline and at all study visits. Safety was assessed in terms of adverse events (AEs) for all pts who received ≥1 dose of study drug.

Results: Of the 395 randomized pts, 358 (83, 93, 93, and 89 from the 2.5, 5, 10, and 20 mg arms, respectively) completed 26 wks. At wk 26, there was a statistically significant trend in the proportion of pts achieving DAS28(CRP) <3.2 with increasing dose of MTX in combination with OL ADA (**Table**). Significant trends were noted as early as wk 12 and sustained through wk 26. Similar results were observed for ACR50/70/90 and DAS28(CRP) < 2.6, SDAI/CDAI remission. Numerically increasing trends were also apparent in the proportions achieving radiographic nonprogression and ΔHAQ-DI ≤-0.22 at wk 26. Clinical and radiographic outcomes generally appeared comparable between the 10 and 20 mg arms. ADA serum concentrations were similar in the 10 and 20 mg MTX arms, with slightly lower mean ADA serum concentrations in the 2.5 and 5 mg arms. AEs were consistent with the known profile of anti-TNF and were generally consistent between arms, occurring most frequently in the 20 mg arm.

Parameter[a]	2.5 mg MTX + OL ADA	5 mg MTX + OL ADA	10 mg MTX + OL ADA	20 mg MTX + OL ADA	*P* value
DAS28(CRP) <3.2, n/N (%)	42/98 (43)	44/100 (44)	56/99 (57)	59/98 (60)	.005
DAS28(CRP) <2.6, n/N (%)	27/98 (28)	32/100 (32)	37/99 (37)	44/98 (45)	.008
SDAI ≤3.3, n/N (%)N (%)	11/98 (11)	22/100 (22)	28/99 (28)	29/98 (30)	.005
CDAI ≤2.8, n/N (%)	12/98 (12)	22/100 (22)	29/99 (29)	27/98 (28)	.02
ACR50/70/90, %	46/24/7	51/34/10	54/41/17	62/46/16	.02/.003/.04
ΔmTSS ≤0.5, n/N (%)	63/98 (64)	72/100 (72)	76/99 (77)	76/98 (78)	.06
ΔHAQ-DI ≤-0.22, n/N (%)	67/98 (68)	70/100 (70)	73/99 (74)	76/98 (78)	.12

[a]Non-responder imputation.

Conclusion: MTX and biologic-naïve pts with early RA demonstrated robust and dose-dependent clinical responses with increasing doses of MTX in combination with OL ADA through 26 wks. Interestingly, clinical responses and ADA serum concentrations generally appeared similar between the 10 and 20 mg MTX arms.

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Characteristics of Protocol-Specified Responders/Non-Responders Treated With Etanercept Plus Methotrexate in Period 1 of the Prize Study. Paul Emery[1], Annette Szumski[2], Jack Bukowski[3], Eustratios Bananis[2] and Lisa Marshall[2]. [1]Institute Rheumatic and Musculoskeletal Medicine University of Leeds, Leeds, United Kingdom, [2]Pfizer Inc., Collegeville, PA, [3]Pfizer Inc, Collegeville, PA.

Background/Purpose: Although frequently effective, treatment with synthetic or biologic disease-modifying antirheumatic drugs (DMARDs) does not adequately control disease activity in all patients. Prompt identification of patients unlikely to achieve long-term therapeutic targets is a clinically relevant strategy that may allow for timely alterations in treatment and optimal outcomes. The objective of this subanalysis was to determine disease characteristics of responders and non-responders to treatment with etanercept (ETN) plus methotrexate (MTX) in patients with early, active moderate-to-severe RA participating in Period 1 of the PRIZE study.

Methods: MTX- and biologic-naïve RA patients (DAS28 >3.2; symptom onset ≤12 months from enrollment) received ETN 50 mg QW and MTX (ETN50/MTX) for 52 wk. At the investigator's discretion, the initial 10 mg/wk MTX dose was titrated to a maximum 25 mg/wk; corticosteroid boosts were administered to patients not achieving low disease activity (LDA; DAS28 ≤3.2) at week 13 and/or 26. Prior DMARD, NSAID, and corticosteroid use and disease characteristics were analyzed in responders at week 39 and 52 (defined as patients with DAS28 ≤3.2 and DAS28 <2.6, respectively) and non-responders at week 39 and 52 (defined as patients with DAS28 >3.2 and DAS28 ≥2.6, respectively, or unsatisfactory response due to efficacy [based on investigators' judgment]), as specified by the study protocol and using a last observation carried forward approach.

Results: Of 306 patients receiving ETN50/MTX in Period 1, 30 (9.8%) and 24 (7.8%) were non-responders at wk 39 and 52, respectively; 7 (2.3%) had an unsatisfactory response. Among responders (n=194) and non-responders (n=61), 33 (17.0%) and 3 (4.9%) received prior DMARDs, respectively (P=0.018); 80 (41.2%) and 22 (36.1%), prior corticosteroids (P=0.472); and 129 (66.5%) and 31 (50.8%), prior NSAIDs (P=0.027). A lower proportion of responders received corticosteroid boosts than non-responders at week 13 (29.0% v 63.9%) and week 26 (17.0% v 61.7%). DAS28, SDAI, and HAQ values were significantly higher in non-responders at baseline (P<0.01) and from weeks 2–52 (P<0.0001; Table). Significantly lower proportions of non-responders had normal HAQ (≤0.5) vs responders from week 2–52 (P<0.0001). Both responders and non-responders had improved disease activity and function with treatment over time, but non-responders had slower rates of response. Both groups appeared to achieve a steady state by week 39.

Table. Differences in disease characteristics at baseline (BL) and weeks 39 and 52 in protocol-specified responders and non-responders to ETN50/MTX at week 52 (LOCF)

Characteristic	Mean (SD)/Adjusted Mean Change (SE) Responders	Non-Responder	Mean Difference (95% CI)	P Value
DAS28 at BL	5.9 (1.1)	6.3 (1.1)		0.004
Week 39	2.0 (0.7)/−4.0 (0.06)	3.8 (1.5)/−2.3 (0.12)	−1.6 (−2.0, −1.4)	<0.0001
Week 52	1.8 (0.6)/−4.1 (0.06)	4.1 (1.4)/−2.0 (0.11)*	−2.1 (−2.3, −1.8)	<0.0001
SDAI at BL	36.4 (13.5)	41.8 (14.7)		0.008
Week 39	2.8 (2.8)/−34.5 (0.6)	15.8 (15.8)/−23.0 (1.0)	−11.5 (−13.9, −9.2)	<0.0001
Week 52	2.0 (1.9)/−35.4 (0.6)	16.6 (15.8)/−22.3 (1.0)*	−13.1 (−15.4, −10.8)	<0.0001
HAQ at BL	1.2 (0.6)	1.5 (0.7)		0.0007
Week 39	0.3 (0.4)/−0.9 (0.0)	0.9 (0.7)/−0.5 (0.1)	−0.5 (−0.6, −0.3)	<0.0001
Week 52	0.3 (0.4)/−1.0 (0.0)	0.9 (0.7)/−0.5 (0.1)*	−0.5 (−0.6, −0.4)	<0.0001
	% of Patients (95% CI)			P Value
Normal HAQ (≤0.5)				
Week 39	77.8 (16.5, 28.7)	34.4 (52.3, 77.3)		<0.0001
Week 52	81.4 (75.2, 86.7)	36.1 (50.6, 75.8)*		<0.0001

* ≥50% of patients were discontinued at week 39 and were carried forward to week 52.

Conclusion: In Period 1 of the PRIZE trial, patients with early, moderate-to-severe RA who did not meet protocol-specified response criteria after treatment with etanercept plus methotrexate showed higher levels of disease activity and greater functional disability at baseline and throughout the period, and were more likely to require corticosteroid boosts, compared with patients who satisfied response criteria.

Disclosure: P. Emery, Abbott, Bristol-Myers Squibb, Merck, Novartis, Pfizer Inc, Roche-Chugai, UCB Pharma Ltd, 5; **A. Szumski**, Pfizer Inc, 5; **J. Bukowski**, Pfizer Inc, 1, Pfizer Inc, 3; **E. Bananis**, Pfizer Inc, 1, Pfizer Inc, 3; **L. Marshall**, Pfizer Inc, 1, Pfizer Inc, 3.

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US Veterans With Rheumatoid Arthritis Who Switch Among Tumor Necrosis Factor Blocking Agents Have No Additional Clinical Benefit With The Change In Therapy and Incur Higher Costs. Grant W. Cannon[1], Scott L. DuVall[2], Candace L. Hayden[2], Liron Caplan[3], Jeffrey R. Curtis[4], Kaleb Michaud[5], Ted R. Mikuls[6], Andreas M. Reimold[7], David H. Collier[8], George Joseph[8], David J. Harrison[8] and Brian C. Sauer[9]. [1]Salt Lake City VA and University of Utah, Salt Lake City, UT, [2]VA Salt Lake City Health Care System and University of Utah School of Medicine, Salt Lake City, UT, [3]Denver Veterans Affairs Medical Center, Denver, CO, [4]University of Alabama at Birmingham, Birmingham, AL, [5]National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE, [6]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [7]Dallas VA and University of Texas Southwestern, Dallas, TX, [8]Amgen Inc., Thousand Oaks, CA, [9]George E. Wahlen Veteran Affairs Medical Center, Salt Lake City, UT.

Background/Purpose: While tumor necrosis factor (TNF) blockers can be effective in treating rheumatoid arthritis (RA), the benefit of switching among TNF blockers is not clear. The objective of this study was to compare clinical outcomes and costs in US veterans who switch between adalimumab (ADA), etanercept (ETN), and infliximab (INF) to patients treated with the same TNF blocker.

Methods: The Veterans Affairs Rheumatoid Arthritis (VARA) registry is a longitudinal, observational, cohort study of US veterans with RA. It links to VA pharmacy and administrative data and documents longitudinal assessments of RA disease activity and outcomes. VARA patients initiating ADA, ETN, or INF from March 2003 (the date after which all agents were available within VA) to Sept 2010 were identified and followed until Sept 2011. A treatment course was defined as continuous TNF blocker use without a ≥90-day gap in treatment. The cost of TNF blockers with associated drug administration costs was determined for the first course initiated within the VA and compared to the second course with the same or a different TNF blocker.

Results: Data from 563 RA patients (204 ADA, 290 ETN, 69 INF) initiating TNF-blocker therapy were analyzed. All groups had a similar decrease in DAS28 during their first TNF-blocker course; however, baseline DAS28 prior to treatment and during treatment was higher during the first course for patients who eventually switched TNF blocker therapy. In the 61 patients who had 2 courses of therapy with DAS28 measurements available during both courses of treatment, there were no significant differences

between mean DAS28 during the first and second TNF-blocker courses. Thus, patients who switched TNF-blocker therapies had higher DAS28 prior to and during TNF-blocker treatment compared with patients with a single TNF-blocker course or patients who had 2 courses with the same therapy interrupted by a ≥90-day gap; however, the relative change in DAS28 was the same in all groups during TNF-blocker treatment. While annualized costs were similar in all groups during the first course of therapy, these costs were significantly higher during the second course in patients who switched than for patients who restarted their initial TNF blocker ($P<0.05$).

Conclusion: In VARA patients receiving 2 courses of TNF-blocker therapy, improvements in DAS28 scores were not significantly different in patients treated with a different second agent than re-starting the initial agent. Patients who switched TNF blockers had higher DAS28 scores during the initial course and higher costs overall than patients who remained on the same TNF-blocker therapy. Because of potential confounding factors inherent in observational studies, more research is needed to understand reasons for switching and the effects of switching TNF blockers on overall outcomes in RA.

Table. Comparison of patients with a single vs a second course with and without switching

	Single course (N=264)		Second course, same TNF blocker (N=143)		Second course, different TNF blocker (N=156)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Age at start of Rx (yrs)	63.1	61.9, 64.3	57.7	55.6, 59.8	59.0	57.5, 60.5
RA disease duration at Rx (yrs)	10.6	9.3, 11.9	10.9	9.1, 12.7	9.9	8.4, 11.3
Male sex, n (%)	234 (89)	(85, 92)	131 (92)	(88, 97)	142 (91)	(87, 96)
First TNF-Blocker Course						
Course duration (mos)	34.1	30.7, 37.5	18.1	15.4, 20.9	18.0	14.9, 21.1
Annual drug and admin costs (US $ × 1000)	13.8	13.4, 14.2	13.2	12.1, 14.3	14.2	13.4, 14.8
DAS28 before Rx	4.5	4.3, 4.7	4.6	4.3, 4.9	5.3	5.0, 5.6
DAS28 after ≥90 days on Rx	3.5	3.3, 3.7	3.5	3.3, 3.8	4.3	4.0, 4.6
Change in DAS28 on Rx	−0.9	−1.2, −0.7	−1.1	−1.5, −0.6	−0.8	−1.3, −0.4
Second TNF-Blocker Course						
Course duration (mos)	N/A	N/A	15.6	12.8, 18.5	17.7	14.9, 20.5
Annual drug and admin costs (US $ × 1000)	N/A	N/A	12.9	12.1, 13.6	15.1	13.6, 16.5
DAS28 after ≥90 days on Rx	N/A	N/A	3.4	3.1, 3.8	4.2	3.9, 4.5
Change in DAS28 1st to 2nd course	N/A	N/A	−0.2	−0.6, 0.1	−0.2	−0.6, 0.1

CI, confidence interval; Rx, treatment; DAS28, disease activity score based on 28 joints

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Correlation Between Objective and Patient Self-Reported Clinical Improvement After Multiple Courses of Rituximab in Rheumatoid Arthritis Patients With Inadequate Response to Tumour Necrosis Factor Inhibitors: Data From Repeat Study. Ioan Ancuta[1], Catalin Codreanu[2], Ruxandra Ionescu[3], Magda Parvu[4], Dan Nemes[5], Rodica Chirieac[6], Paulina Ciurea[7], Maria Suta[8], Andra Balanescu[9], Eugenia Mociran[10] and Elena Rezus[11]. [1]"Dr. I. Cantacuzino" Hospital, Bucharest, Romania, [2]"Dr. I. Stoia" Center for Rheumatic Diseases, Bucharest, Romania, [3]Clinic Hospital Sf. Maria, Bucharest, Romania, [4]"N.Gh. Lupu" Clinical Hospital, Bucharest, Romania, [5]"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania, [6]C.M.I. Rodica Chirieac, Iasi, Romania, [7]Emergency County Hospital, Craiova, Romania, [8]Emergency County Hospital, Constanta, Romania, [9]University of Medicine and Pharmacy, Bucharest, Romania, [10]Emergency County Hospital Dr Constantin Opis, Maramures, Romania, [11]Recovering Clinical Hospital, Iasi, Romania.

Background/Purpose: Rituximab (RTX) has been evaluated in many clinical trials and objective assessment of rheumatoid arthritis (RA) activity must comply with Treat to Target principles. Little is known about the relationship between objective clinical outcomes and self-reported health status in RA patients treated with repeated courses of biologics over extended periods of time.

We wanted to compare evolution of clinical outcome measures and self-perceived health status in patients with severe active RA treated with multiple courses of RTX in Romania.

Methods: In this open-label, multicentre, prospective observational study, patients were treated with initial (2×1000 mg IV, at 2 weeks apart) and subsequent RTX courses. Clinical assessments including 28-joint disease activity score (DAS-28) were performed at baseline (before treatment initiation), and after each retreatment course at 6, 12, 18 and 24 months. A visual analogue scale (VAS; 0=best, 100=worst) allowed patients to report health status at each clinical assessment. Delta DAS-28 and delta VAS were calculated as difference between values found at two consecutive evaluations and tested with unpaired t-tests and Pearson correlation coefficients R^2. Linear regression models were estimated at baseline, 6, 12, 18, and 24 months with the DAS-28 as the outcome variable and the VAS as a predictor. Statistical analyses were performed with STATA SE 11.0 software.

Results: A total of 943 adult (>18 years) patients with active RA and inadequate response to at least one TNF inhibitor received initial RTX treatment. In our study, 805 (85.37%) patients had only one anti-TNF treatment and 138 (14.63%) had more than one, with a median duration of anti-TNF treatment of 21 and 47 months, respectively. Median DAS-28 and VAS scores steadily decreased after each retreatment:

Evaluation	DAS-28	VAS
1st (baseline)	5.67	50
2nd (6 months)	3.87	20
3rd (12 months)	3.38	12
4th (18 months)	2.96	10
5th (24 months)	2.80	10

Sustained, statistically significant delta DAS-28 changes ($p<0.00001$, $p<0.0005$ and $p<0.0128$) and delta VAS changes ($p<0.00001$, $p<0.0026$ and $p<0.0005$) were found at 12, 18 and 24 months, respectively. Linear regression analysis showed DAS-28 and VAS scores significantly correlated in all evaluations, with R^2Pearson correlation coefficients of 0.7291, 0.5651 (n=877), 0.3951 (n=580), 0.3169 (n=302), and 0.2754 (n=112), at baseline, 6, 12, 18, and 24 months, respectively ($p<0.0001$ in all). Taken together, our results indicate that VAS score can have predictive value for clinical outcome.

Conclusion: We found strong correlation between objective clinical outcomes and self-reported health status, with clinical response maintained or improved after each fixed interval retreatment with Rituximab, even in patients with a long history of inadequate response to TNF inhibitors. Major improvements occurred early in our study, at 6 months, and were appreciated by patients. This synergy is important for doctor-patient relationship, increased patient confidence and treatment compliance, key factors for a successful therapy.

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Sustained Clinical Efficacy After Multiple Courses of Rituximab in Rheumatoid Arthritis Patients With Inadequate Response to Tumour Necrosis Factor Inhibitors: 2-Year Data From the Repeat (Repeated Courses in Routine Clinical Practice) Study. Catalin Codreanu[1], Ioan Ancuta[2] and Ruxandra Ionescu[3]. [1]"Dr. I. Stoia" Center for Rheumatic Diseases, Bucharest, Romania, [2]"Dr. I. Cantacuzino" Hospital, Bucharest, Romania, [3]Clinic Hospital Sf. Maria, Bucharest, Romania.

Background/Purpose: In the last decade, biologic therapy changed dramatically treatment options for rheumatoid arthritis (RA). However, a significant number of patients failed to maintain the initial response to a TNF blocker. More information is needed regarding efficacy and safety of multiple courses of biologics administered over extended periods of time.

We tried to assess clinical efficacy of subsequent courses with Rituximab (RTX) in patients with moderate-severe active RA despite treatment with a TNF inhibitor in routine clinical practice in Romania.

Methods: In this open-label, multicentre, prospective observational study started in 2010, patients were treated with RTX at each 6 months. Clinical efficacy was assessed at baseline and after each retreatment course at 6, 12, 18 and 24 months. Clinical assessments included DAS-28, SDAI and CDAI. Δ DAS-28, Δ SDAI and Δ CDAI were calculated based on two consecutive evaluations. Statistical analyses: STATA SE

11.0 software, unpaired t-tests and Pearson correlation coefficients R2 in regression analysis (for Δ DAS-28, Δ SDAI and Δ CDAI) and Cuzick non-parametric trend tests across ordered groups (for disease activity state).

Results: 943 adult (>18 years) patients with active RA and inadequate response to at least one TNF inhibitor received initial RTX treatment. Median clinical disease activity scores steadily decreased after each retreatment indicating improvement in clinical response:

Evaluation	DAS-28	SDAI	CDAI
Baseline	5.67 (n=943)*	27.68 (n=935)**	26 (n=943)
6 months	3.87 (n= 877)	10.98 (n=862)	10 (n=877)
12 months	3.38 (n=580)	7.40 (n=564)	6 (n=580)
18 months	2.96 (n=302)	4.70 (n=299)	3.80 (n=302)
24 months	2.80 (n=118)	4.44 (n=116)	3 (n=118)

* Patient's number (n) decreases in time because of the enrolment timeframe and represents the number of patients who reached each evaluation (data cut-off 1st of December 2012)
** SDAI patient's number is lower as CRP was not dosed to all patients analysed

Remission rate progressively increased after each retreatment course: 10.95%, 18.79%, 35.1% and 39.83%, whereas initial percentage of patients showing high disease activity (HDA) (63.94%) steadily decreased to 16.65%, 3.62%, 1.66% and 0.85% at 6, 12, 18 and 24 months, respectively. Similar trends were observed in SDAI and CDAI scores. In SDAI, remission rate increased from 4.28% to 11.02%, 18.79%, 31.44% and 35.34%, whereas initial proportion of patients with HDA (53.48%) decreased to 9.63%, 1.67%, 1.42% and 0%. Similarly, in CDAI, remission rate increased from 4.24% to 11.4%, 20.17%, 36.75% and 37.29%, with steadily decreased HDA after each retreatment, from 58.43% to 14.25%, 2.59%, 2.32% and 0%, respectively. All Δ DAS-28, Δ SDAI and Δ CDAI changes, as well as DAS-28 vs. SDAI and DAS- 28 vs. CDAI comparisons were statistically significant ($p<0.0001$).

Conclusion: Our study showed a sustained improvement of clinical response after each retreatment course with RTX (at 6 months interval), regardless of assessment tool used (DAS28, SDAI or CDAI). Each RTX course led to an increased and cumulative clinical response versus the previous one with respect to Treat to Target principles and EULAR/ACR recommendations.

Disclosure: C. Codreanu, None; **I. Ancuta**, None; **R. Ionescu**, None.

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Comparing abatacept to Adalimumab, Etanercept and Infliximab As First Or Second Line Agents in Patients With Rheumatoid arthritis: Experience From the rhumadata® Clinical Database and Registry. Denis Choquette[1], Diane Sauvageau[1], Louis Bessette[2], Boulos Haraoui[1], Jean Pierre Pelletier[1], Jean-Pierre Raynauld[1], Edith Villeneuve[1] and Louis Coupal[1]. [1]Institut de Rhumatologie de Montréal, Montreal, QC, [2]Centre Hospitalier Universitaire de Québec, pavillon CHUL, Sainte-Foy, QC.

Background/Purpose: The order of use of biologic agents is still a question for debate. Phase III trial data in MTX-IR patients show comparable efficacy results across biologic agents and limited head-to-head studies have been published. Prospective registries offer a unique opportunity to observe the effectiveness of these agents in a clinical setting. Our objectives are to evaluate if patients with rheumatoid arthritis (RA) treated with abatacept after failure to either a first line agent (MTX-IR) or a second line anti-TNF agents (TNF-IR) have a different drug survival rate than patients similarly treated with adalimumab, etanercept or infliximab. A secondary objective is to explore the role of MTX co-prescription.

Methods: RA patients prescribed a first biologic agent after January 1st 2007 were included in the present analysis. Two cohorts were extracted, the first included all patients prescribed their first biologic agent, abatacept (ABA), adalimumab (ADA), etanercept (ETA) or infliximab (INF); the second included all patients failing their first biologic agent and switching to a second one. Baseline demographics for both cohorts included age, disease duration, HAQ-DI, fatigue and pain visual analog scale evaluation (VAS), TJC, SJC, DAS 28 ESR and SDAI. Person-years of treatment were also compared across biologic agents. Statistical analysis was performed using SAS version 9.3. RHUMADATA® is a clinical database and registry used daily in clinical practice at the IRM and the CORQ.

Results: A total of 493 patients were analysed, 339 were included in the first cohort and 154 composed the second cohort. No significant differences in baseline characteristics were noted between treatment groups. The 5 year retention rate of ABA, ADA, ETA and INF post MTX failure were 66%, 44%, 47% and 50% without significant statistical differences (Log-Rank $p=0.35$). When combining all biologics, the use of DMARDs did exhibit better drug survival than biologic monotherapy, 50% (combination therapy) vs. 33% (monotherapy). This difference however did not reach statistical significance (Log-Rank $p=0.09$). However, patients having failed a first anti-TNF agent had a better 5 years drug survival rate if treated with ABA than those treated with ADA, ETA or INF as demonstrated by rates of 47% (ABA), 28%(ADA), 27% (ETA) and 13% (INF) (Log-Rank $p=0.01$).

Conclusion: Abatacept, adalimumab, etanercept and infliximab after MTX failure have similar 5-years retention rates. Combination with methotrexate did not, however, demonstrate statistically significant improved 5-year retention. Prescribing abatacept after a previous TNF agent failure seems to offer a more favorable outcome.

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Prediction Of Week 52 Treatment Response Based On A Week 12 Assessment In Rheumatoid Arthritis Patients Receiving Certolizumab Pegol: Comparison Of A Patient-Reported Instrument Versus Physician-Based Disease Activity Assessment. Jeffrey R. Curtis[1], Willem Koetse[2], Jeymi Tambiah[3], Lucian Ionescu[4] and Yusuf Yazici[5]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]UCB Pharma, Raleigh, NC, [3]UCB Pharma, Smyrna, GA, [4]UCB Pharma, Brussels, Belgium, [5]New York University Hospital for Joint Diseases, New York, NY.

Background/Purpose: Guidelines support early intervention in rheumatoid arthritis (RA).[1,2] The aim was to prospectively test whether outcome assessment at 12 weeks (wks) using a patient-reported tool (RAPID3) was comparable with investigator-based assessment (CDAI) in RA patients (pts) treated with certolizumab pegol (CZP) for predicting attainment of low disease activity (LDA) or better at Wk 52. Both scoring tools are used as clinical measures of disease activity in the absence of inflammatory laboratory markers.

Methods: In this 52-wk study (PREDICT; NCT01255761) pts received CZP standard dosing regimen (400mg at Wks 0, 2, 4 [loading dose] then 200mg Q2W). Pts were ≥18 yrs with adult onset active RA, unsatisfactory response to ≥1 DMARD and ≤2 prior TNF inhibitors. Pts were randomized 1:1 to RAPID3 or CDAI for classification as responder/non-responder at Wk12. Treatment decision at Wk12 was based upon randomization arm (RAPID3 responder, ≤6 or 20% improvement from baseline [BL]; CDAI responder, ≤10 or 20% improvement from BL). Pts who showed no improvement by Wk12 (<1 point improvement in CDAI or no improvement in RAPID3) were classified as failures and withdrawn. All other pts continued CZP 200mg Q2W unless they reached high disease activity (HDA; CDAI>22 or RAPID3>12) at 2 consecutive visits, at which point they escaped. Pts were permitted concomitant DMARDs if their regimen was unmodified between Wks 0 and 12. Long-term treatment success was defined as DAS28(ESR) ≤3.2 (LDA or better) at Wk52. Safety was monitored. The results are presented for the full analysis set (FAS; all pts who had valid BL and post-BL measurements) and both arms were adjusted for baseline DAS28(ESR) scores. Non-responder imputation (NRI) was applied.

Results: Enrolled pts (FAS; N=733) had longstanding disease (mean±SD 8.9±9.1 years), HDA (mean±SD DAS28[ESR] 6.3±1.1, RAPID3 16.1±5.6, CDAI 40.2±13) and over half (55.5%) were prior TNF inhibitor failures.

At Wk12, 64.7% (238/368) and 76.4% (279/365) of pts randomized to RAPID3 and CDAI, respectively, were classed as responders (Table 1). At

Wk52, 31.5% (75/238) of Wk12 RAPID3 responders, and 32.3% (90/279) of Wk12 CDAI responders, achieved DAS28(ESR) LDA or better (Table 1) demonstrating similar positive predictive values of these measures. No new safety signals were observed.

Table 1. Response at Wkl2, proportion of Wkl2 responders with DAS28 (ESR) LDA at Wk52, and DAS28(ESR) remission/LDA at Wk 12 and Wk52 (FAS, NRI)

Response at Wkl2	**RAPID3**	**CDAI**
N	368	365
Yes, n (%)	238 (64.7)	279 (76.4)
Difference in proportion of Wk12 responders [a]		
RAPID3 − CDAI	−0.12	
(95% CI)	(−0.18, −0.05)	
Wkl2 responders who achieved DAS28(ESR) LDA at Wk52 [b]	**RAPID3**	**CDAI**
N	238	279
Yes, n (%)	75 (31.5)	90 (32.3)
Difference in proportion of Wk12 responders [a]		
RAPID3 − CDAI	−0.01	
(95% CI)	(−0.09, 0.07)	
DAS28(ESR) Remission [c]	**RAPID3**	**CDAI**
% pts DAS28(ESR) Remission at Wk 12 (n/N)	12.8% (47/368)	15.6% (57/365)
% pts DAS28(ESR) Remission at Wk 52 (n/N)	14.9% (55/368)	17.8% (65/365)
DAS28(ESR) LDA [d]	**RAPID3**	**CDAI**
% pts DAS28(ESR) LDA at Wk 12 (n/N)	25.0% (92/368)	28.2% (103/365)
% pts DAS28(ESR) LDA at Wk 52 (n/N)	21.5% (79/368)	24.9% (91/365)

[a] The difference in proportion (RAPID3 − CDAI) was analyzed using non-parametric ANCOVA with assessment tool as factor and baseline DAS28(ESR), gender, age, prior TNF inhibitor use and duration of RA (<2 or ≥2 years) as covariates; [b] = positive predictive value; [c] DAS28(ESR) <2.6; [d] DAS28(ESR) ≤3.2.

Conclusion: In pts with chronic, severe RA the physician-based assessment detected greater CZP response at Wk12 compared with the patient-reported tool. Although the two outcome measures were not statistically comparable at Wk12, the positive predictive value for LDA at Wk52 for both assessments was similar. Further analysis is needed to evaluate the sensitivity and specificity of these measures for clinical disease activity assessments and treatment decisions in RA.

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Use Of Rituximab As Second Line Biologic Agent Compared With Adalimumab, Etanercept and Infliximab In Patients With Rheumatoid Arthritis. A Report From The Rhumadata® Clinical Database and Registry. Louis Bessette[1], Denis Choquette[2], Diane Sauvageau[2], Boulos Haraoui[2], Jean Pierre Pelletier[2], Jean-Pierre Raynauld[2], Edith Villeneuve[2] and Louis Coupal[2]. [1]Centre Hospitalier Universitaire de Québec, pavillon CHUL, Sainte-Foy, QC, [2]Institut de Rhumatologie de Montréal, Montreal, QC.

Background/Purpose: The order of use of biologic agents after failing a TNF inhibitor is still a question for debate. Phase III trial data in TNF-IR patients show comparable efficacy results across biologic agents and limited head-to-head studies have been published. Prospective registries offer a unique opportunity to observe the effectiveness (combined evaluation of efficacy and safety profile over time) of these agents in a clinical setting. Our objectives is to evaluate if patients with rheumatoid arthritis (RA) treated with rituximab after failing a first anti-TNF agents (TNF-IR) have a different drug retention rate than patients similarly prescribed adalimumab, etanercept or infliximab.

Methods: Data from TNF-IR RA patients prescribed adalimumab (ADA), etanercept (ETA), infliximab (INF) or rituximab (RIT) as a second biologic agent on or after January 1st 2007 was extracted. Baseline demographics included age, disease duration, HAQ-DI, fatigue and pain visual analog scale evaluations (VAS), TJC, SJC, DAS 28 ESR and SDAI. Person-years of treatment were also compared across biologic agents. Five-year drug retention rates were estimated and compared using Kaplan-Meier survival estimates. Statistical analysis was performed using SAS version 9.3. RHUMADATA® is a clinical database and registry used in daily clinical practice at the IRM and CORQ.

Results: The data from 126 RA patients were extracted. No significant differences in baseline variables were observed between treatment groups. The 5 year retention rates of ADA, ETA, INF and RIT after failing second line anti-TNF agent were 28%, 27%, 13% and 66% with significant statistical differences (Log-rank $p<0.001$).

Conclusion: As a second line agent in TNF-IR patients rituximab demonstrate a better 5 year retention rate than the comparator agents.

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Retrospective Analysis Of Certolizumab Pegol Use During Pregnancy: Update Of Impact On Birth Outcomes. Megan E. B. Clowse[1], Douglas C. Wolf[2], Frauke Förger[3], John J. Cush[4], Christian Stach[5], Gordana Kosutic[6], Susan Williams[6], Chidi Maduka[6] and Uma Mahadevan[7]. [1]Duke University Medical Center, Durham, NC, [2]Atlanta Gastroenterology Associates, Atlanta, GA, [3]University of Bern, Bern, Switzerland, [4]Baylor Research Institute and Baylor University Medical Center, Dallas, TX, [5]UCB Pharma, Monheim, Germany, [6]UCB Pharma, Raleigh, NC, [7]UCSF Medical Center, San Francisco, CA.

Background/Purpose: Certolizumab pegol (CZP) is a PEGylated Fc-free anti-TNF approved in 45 countries for the treatment of rheumatoid arthritis (RA) and/or Crohn's disease (CD). An earlier analysis of pregnancies reported to the UCB Pharma global safety database[1] suggested pregnancy outcomes after maternal CZP exposure are similar to those reported for the US general population (65% live births, 17% fetal losses and 18% elective terminations; data from 6,578,000 pregnancies, 1990–2008).[2] The aim was to provide an updated analysis of pregnancy outcomes after CZP exposure by including new reports and ongoing pregnancies since the last retrospective analysis.[1]

Methods: The UCB Pharma global safety database was searched retrospectively for all medically confirmed cases of pregnancy, including both clinical trial (incidental exposures as all trial protocols exclude pregnant women and those not receiving reliable contraception) and post-marketing reports, through March 28 2013. The number of live births, spontaneous miscarriages and elective terminations for neonates exposed to CZP (maternal and paternal exposure) before and during pregnancy was examined. Congenital abnormalities, neonatal deaths and maternal demographics were also investigated.

Results: As of March 28 2013, 337 pregnancies were reported: 17/337 (5.0%) occurred following paternal exposure and 320/337 (95.0%) occurred following maternal exposure to CZP. Within the 320 maternal exposure pregnancies, 234 were reported from the US and 86 from the rest of the world. The underlying maternal conditions were CD (219/320) and RA (52/320), and the majority of mothers were <35 years old (192/320). For pregnancies following maternal CZP exposure (Table 1), outcomes were unreported for 67/320 (20.9%) and known outcomes were available for 253/320 (79.1%): 191/253 (75.5%) resulted in live births, 37/253 (14.6%) in spontaneous miscarriages and 25/253 (9.9%) women had elective terminations. Within the 191 live births after maternal CZP exposure there were 3 reported cases of congenital disorder: one infant had vesicoureteric reflux, one infant was born with congenital morbus hirschsprung and club feet, and one infant had a high aortic arch with aberrant left subclavian. None of the treating physicians considered these events related to CZP administration. A single neonatal death was reported after maternal exposure in one of a set of twins delivered before 26 weeks gestation.

Table 1. Maternal demographics and pregnancy outcomes for pregnancies after maternal exposure to CZP (N=320)

	Live birth [a]	Miscarriage [a]	Elective termination [a]	Outcome unreported
All pregnancies, n (%) [b]	191 (75.5%)	37 (14.6%)	25 (9.9%)	67
Clinical trial pregnancies (n=104), n (%) [b]	56 (57.1%)	21 (21.4%)	21 (21.4%)	6
Maternal medical condition (n where known)				
Crohn's disease				
All pregnancies (n=219)	133	28	8	50
Clinical trial pregnancies (n=64)	40	14	7	3
Rheumatoid arthritis				
All pregnancies (n=52)	30	7	9	6
Clinical trial pregnancies (n=29)	12	6	8	3
Other [c]				
All pregnancies (n=14)	7	1	5	1
Clinical trial pregnancies (n=7)	1	1	5	0
Mean age of mother at conception, [d] years (SD)[e]	29.3 (5.7)	33.0 (6.5)	30.9 (7.0)	30.0 (5.6)
n (where age reported)	151	34	22	48

[a] Reported outcomes were categorized based on MedDRA 15.1 preferred terms followed by manual validation; [b] Expressed as % of pregnancies with known outcomes (N = 253); [c] Other category includes, but is not limited to, psoriatic arthritis, axial spondyloarthritis, juvenile idiopathic arthritis, unspecified colitis and psoriasis; [d] Conception date was estimated based on a combination of various available data, such as estimated delivery date and date of last menstruation, using an algorithm-based calculation; [e] Age, as reported in global drug safety database, was only reported for 255 pregnancies.

Conclusion: Updated analysis of pregnancy outcomes after exposure to CZP supported previous reports[1] suggesting no obvious/apparent impact of maternal CZP exposure on pregnancy outcomes. Additional data from large numbers of pregnant women are required to fully evaluate the safety and tolerability of CZP in pregnancy.

References:

1. Clowse M. Arthritis Rheum 2012;64(Suppl10):S702; 2. Ventura S.J. Natl Vital Stat Rep 2012;60:1–21

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Results Of 64 Weeks Of Treatment With An Anti-IL-17 Antibody, Ixekizumab, In Patients With Rheumatoid Arthritis In a Phase 2 Study.

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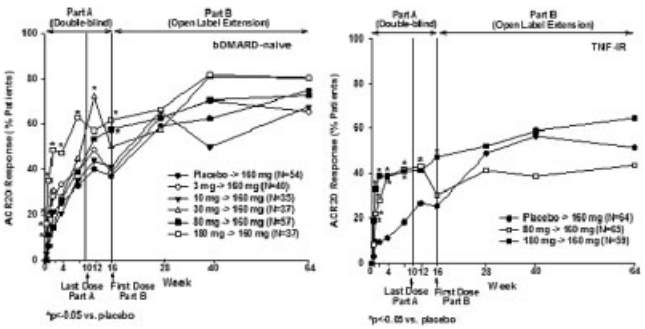
Background/Purpose: Ixekizumab, a monoclonal antibody that neutralizes IL-17A with high affinity and specificity, has been evaluated in patients (pts) with moderate to severe rheumatoid arthritis (RA) who were naïve to biologic therapy (bDMARD-naïve) or were inadequate responders to TNF inhibitors (TNF-IR) in a Phase 2 study. The primary endpoint at 12 weeks was achieved, and significant improvements versus placebo (PB) were observed in both populations[1]. The long-term safety and efficacy after 64 weeks of ixekizumab treatment in the two populations were evaluated in an optional open-label extension (OLE) of the study.

Methods: In this randomized, double-blind study, PB or ixekizumab was administered subcutaneously (SC) to 260 bDMARD-naïve pts (ixekizumab 3, 10, 30, 80, or 180 mg) and 188 TNF-IR pts (ixekizumab 80 or 180 mg) at Weeks 0, 1, 2, 4, 6, 8, and 10 receiving concomitant conventional DMARD therapy (Part A). After a treatment hiatus between Weeks 10 to 16, 232 bDMARD-naïve and 158 TNF-IR pts elected to participate in the OLE period, receiving ixekizumab 160 mg SC at Weeks 16, 18 and 20 and then every 4 weeks (Q4W) through Week 64 (Part B).

Results: A total of 202 bDMARD-naïve (87%) and 99 TNF-IR (62%) pts completed the OLE period. ACR20 response rates observed at Week 16 were maintained or improved after switching to 160 mg Q4W through Week 64 (Figure). Similar maintenance or improvement was observed for ACR50 and ACR70 responses as well as for DAS28-CRP in both populations. Among bDMARD-naïve pts with an ACR20 (n=107), ACR50 (n=39), or ACR70 (n=13) response at Week 16, this response was maintained in 89%, 77%, and 69% pts, respectively. Among TNF-IR pts with an ACR20 (n=41), ACR50 (n=18) or ACR70 (n=11) response at Week 16, this response was maintained in 76%, 67%, and 44% pts, respectively. Similar maintenance of response was observed for EULAR responses. For pts on PB in Part A, disease activity decreased in Part B to levels comparable with pts originally assigned to ixekizumab groups in Part A. DAS28<2.6 was achieved in 23% bDMARD-naive (n=46) and 22% TNF-IR pts (n=23) after 64 weeks of ixekizumab treatment. Adverse events (AEs) occurred in 73% (n=283) pts during Part B. Most AEs were mild to moderate in severity and did not lead to study discontinuation. Serious AEs were reported in 9% (n=35) pts including 2% (n=9) cases of serious infections. No mycobacterial or systemic fungal infections were reported.



Conclusion: Clinical improvements observed with ixekizumab treatment in the double-blind phase were maintained or improved in the pts that participated in the open label extension period through Week 64. Ixekizumab was well-tolerated, and there were no unexpected safety findings observed in Part B relative to Part A.

1. Genovese et al. (2012) *Ann Rheum Dis* 71(Suppl3):59

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Final 5-Year Safety and Efficacy Results Of a Phase 3, Randomized, Placebo-Controlled Trial Of Golimumab In Methotrexate-naïve Patients With Rheumatoid Arthritis.

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Background/Purpose: Final 5yr safety and efficacy results of subcutaneous golimumab (GLM)+/−MTX evaluated in a phase 3 trial (GO-BEFORE) of MTX-naïve pts with rheumatoid arthritis (RA) are reported.

Methods: Pts in GO-BEFORE were randomized to placebo (PBO)+MTX, GLM 100mg+PBO, GLM 50mg+MTX, or GLM 100mg+MTX q4w. PBO+MTX pts crossed over to GLM+MTX at wks 28 (blinded early escape)

or 52 (pts with ≥1 swollen/tender joint). Pts continued treatment at wk52 (start of long-term extension). After the last pt completed wk52 and unblinding occurred, PBO+MTX pts could switch to GLM 50mg+MTX, MTX and corticosteroid use could be adjusted, and a one-time GLM dose change (50–100mg or 100–50mg) was permitted at investigator's discretion. The last GLM injection was at wk252. Observed efficacy results (ACR20/50/70, DAS28-CRP, HAQ-DI, radiographic) by randomized treatment group and cumulative safety data are reported through wks 256 and 268, respectively.

Results: Of 637 randomized pts, 3 were never treated; 419 continued treatment through wk252, and 215 pts withdrew (111 for AE, 23 for lack of efficacy, 20 lost to follow-up, 53 for other reasons, 8 deaths). 402 pts completed the safety follow-up through wk268. Efficacy results are presented in the table. At wk 256, 84.3% of all pts had an ACR20, 93.9% had DAS28-CRP EULAR response, and 80.6% had improvement in HAQ-DI ≥0.25. Mean changes from baseline in total vdH-S score were small and 64% of pts randomized to GLM+MTX had no radiographic progression (DvdH-S≤0). The most common AEs were upper respiratory tract infection(29.4%), nausea(19.6%), bronchitis(16.6%), and increased alanine aminotransferase (16.1%); 11.9% of pts had an injection-site reaction. Through wk268, 204/616 (33.1%) pts had an SAE; 17.5% of pts discontinued study agent due to AEs. Overall rates of serious infections, malignancies, and death were 12.2%, 3.4%, and 1.9%, respectively. Of 595 pts with available samples, 58 (9.7%) were positive for antibodies to GLM.

Efficacy results at wk256	PBO+MTX[a,b]	GLM 100mg+PBO[b]	GLM 50mg+MTX[b]	GLM 100mg+MTX[b]	Total
ACR20	87/110 (79.1%)	89/105 (84.8%)	92/108 (85.2%)	87/98 (88.8%)	355/421 (84.3%)
ACR50	68/110 (61.8%)	68/105 (64.8%)	72/108 (66.7%)	73/98 (74.5%)	281/421 (66.7%)
ACR70	53/110 (48.2%)	47/105 (44.8%)	47/108 (43.5%)	52/98 (53.1%)	199/421 (47.3%)
DAS28-CRP EULAR Response	96/106 (90.6%)	98/103 (95.1%)	99/106 (93.4%)	94/97 (96.9%)	387/412 (93.9%)
DAS28-CRP <2.6	56/106 (52.8%)	50/103 (48.5%)	59/106 (55.7%)	60/97 (61.9%)	225/412 (54.6%)
SDAI ≤3.3	42/106(39.6%)	33/103(32.0%)	35/106(33.0%)	38/98(38.8%)	148/413(35.8%)
HAQ-DI improvement ≥0.25	90/109 (82.6%)	86/104 (82.7%)	78/106 (73.6%)	83/99 (83.8%)	337/418 (80.6%)
Radiographic results at wk256					
Estimated annual progression rate at baseline[c]	8.8 ± 20.2	8.8 ± 29.0	10.1 ± 26.2	6.8 ± 14.9	8.6 ± 23.2
Mean ± SD annual rate of progression through 5yrs[d]	0.5±1.5	0.3 ± 1.3	0.2 ± 0.8	0.1 ± 0.6	0.3 ± 1.1
Mean ± SD change in vdH-S score	2.3 ± 6.7	1.8 ± 6.8	0.7 ± 3.7	0.6 ± 2.9	1.4 ± 5.3
Change in vdH-S score ≤0	65/120 (54.2%)	64/113 (56.6%)	75/120 (62.5%)	73/112 (65.2%)	277/465 (59.6%)

[a]Pts randomized to PBO who switched to GLM at wk28 or 52.
[b]After wk52 pts could receive GLM50 mg or 100mg, and MTX could be added/adjusted.
[c]Estimated as vdH-S score divided by the disease duration per pt.
[d]Estimated as change in vdH-S score divided by GLM treatment duration per pt.

Conclusion: The retention rate was high (66.1%) through 5yrs. GLM+MTX therapy resulted in maintained improvements in signs/symptoms of RA and in physical function, and inhibited structural damage progression long-term. No new safety signals were detected through 5 years in MTX-naïve RA pts.

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Efficacy and Safety Study Of a Sequential Therapy Of Tocilizumab and, If Initially Inadequately Responded To Tocilizumab, Followed By Rituximab In Patients With Rheumatoid Arthritis and Inadequate Response To Traditional Disease Modifying Anti-Rheumatic Drugs (MIRAI)-Interim Analysis 2.

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Background/Purpose: The MIRAI study evaluates a sequential exposure to two defined biologics under rigorous study conditions within a homogeneous population of patients (pts) who inadequately responded to traditional disease modifying anti-rheumatic drugs (DMARD-IR). This study investigates the early response to the IL-6 inhibitor tocilizumab (TCZ) in rheumatoid arthritis (RA) patients; non-responders to TCZ will subsequently receive 1 cycle of rituximab (RTX; anti-CD20 therapy).

Methods: We report the results of a 2nd interim analysis (first-pat-in: MAR-2011; last-pat-in: FEB-2013) of MIRAI (NCT01332994), an ongoing, German, multicenter, two-arm, open-label, phase-III-study in DMARD-IR pts with moderate to severe active RA, DAS28>3.2, biological naïve and on ≥1 concomitant traditional DMARD. All pts received 4 TCZ infusions (8 mg/kg, q4w; 1st treatment period) until week 16. Partial responders (ΔDAS28<1.2 or DAS28≥2.6 and ≤3.2) received further 4 TCZ infusions (8 mg/kg, q4w); non-responders (ΔDAS28<1.2 and DAS28>3.2) received a subsequent biological treatment with RTX (1g each at weeks 16 and 18). All pts with a 2nd treatment period (TCZ or RTX) will complete study at week 32. Primary endpoint: patients in remission (DAS28<2.6) at week 16. Secondary endpoints include: DAS28<2.6 at week 32, ACR response, adverse events (AE).

Results: 510 pts (ITT-Main; mean age: 56 years, females 68.2%) entered the first treatment period and received TCZ. All pts had previously received DMARDs (mostly methotrexate, 412 pts). 432 pts (85%) completed week 16, 155 pts (30%) completed week 32. At week 16, 186 pts (36%) initiated a second TCZ treatment period (ITT-TCZ2) and 24 pts (4.7%) received a subsequent RTX therapy (ITT-RTX). At week 16, efficacy parameters had improved considerably in the ITT-Main population. At week 32, further improvement was seen in all efficacy parameters under continued TCZ therapy (ITT-TCZ2); up to now, the few pts who received a subsequent RTX therapy showed slight improvements (ITT-RTX).

Parameter	Baseline	Week 16	Week 32
ITT-Main			
DAS28, mean ± SD	5.7 ± 1.0 (N=507)	2.6 ± 1.3 (N=423)	2.7 ± 1.4 (N=150)
VAS DA pat, mean ± SD	63.3 ± 20.6 (N=509)	26.3 ± 22.5 (N=429)	28.9 ± 25.3 (N=155)
SJC28, mean ± SD	8.3 ± 4.9 (N=509)	3.2 ± 3.6 (N=425)	3.0 ± 3.9 (N=152)
VAS pain, mean ± SD	63.5 ± 21.1 (N=509)	27.2 ± 22.9 (N=429)	29.1 ± 24.6 (N=155)
HAQ-DI, mean ± SD	1.25 ± 0.66 (N=428)	0.73 ± 0.67 (N=292)	0.83 ± 0.70 (N=101)
ITT-TCZ2			
DAS28, mean ± SD	6.0 ± 0.9 (N=186)	3.2 ± 0.7 (N=184)	2.5 ± 1.3 (N=131)
VAS DA pat, mean ± SD	66.9 ± 19.2 (N=186)	30.3 ± 20.5 (N=186)	26.8 ± 24.0 (N=136)
SJC28, mean ± SD	9.4 ± 4.8 (N=186)	4.1 ± 3.2 (N=185)	2.7 ±3.5 (N=133)
VAS pain, mean ± SD	66.2 ± 19.2 (N=186)	31.2 ± 20.6 (N=186)	27.0 ± 23.4 (N=136)
HAQ-DI, mean ± SD	1.27 ± 0.66 (N=174)	0.81 ± 0.66 (N=124)	0.77 ± 0.69 (N=88)
ITT-RTX			
DAS28, mean ± SD	5.7 ± 1.0 (N=24)	5.2 ± 1.2 (N=24)	4.2 ± 1.6 (N=18)
VAS DA pat, mean ± SD	64.6 ± 18.3 (N=24)	58.5 ± 22.6 (N=24)	43.8 ± 31.0 (N=18)
SJC28, mean ± SD	9.5 ± 6.4 (N=24)	9.0 ± 6.1 (N=24)	4.7 ± 5.7 (N=18)
VAS pain, mean ± SD	67.6 ± 17.2 (N=24)	57.6 ± 22.7 (N=24)	45.1 ± 28.9 (N=18)
HAQ-DI, mean ± SD	1.31 ± 0.64 (N=20)	1.49 ± 0.75 (N=17)	1.26 ± 0.70 (N=12)

Data are presented "as-observed".
DAS = Disease Activity Score; HAQ-DI = Health Assessment Questionnaire-Disability Index; SD = Standard Deviation; SJC28 = Swollen Joint Count (28 joints); VAS = Visual Analogue Scale.

The total incidence of AEs/serious AEs with a suspected causal relationship to treatment is 30.4%/4.1%. SAEs suspected to be causally related to TCZ include 2 cases each of diverticulitis, pneumonia and elevated liver enzymes; 1 case each of atrial fibrillation; neutropenia plus leucopenia; thrombopenia. One death with a suspected causal relationship to TCZ was reported (fall plus craniocerebral injury). Up to now, no SAEs suspected to be causally related to RTX have been reported.

Conclusion: Early response to TCZ was demonstrated by a substantial improvement in all efficacy parameters within the first 16 weeks of treatment. Initially partial responders to TCZ benefited from a continued TCZ therapy. Notably, the proportion of TCZ non-responders who received a subsequent RTX-treatment was low.

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Patterns Of Use Of Oral and Subcutaneous Methotrexate Use In Rheumatoid Arthritis Patients Enrolled In The U.S. Medicare Program.

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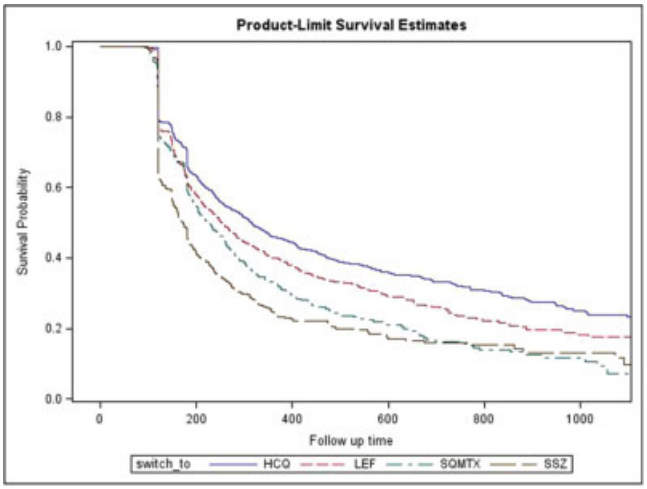
Background/Purpose: Although methotrexate (MTX) is the cornerstone of RA treatment, use of oral and subcutaneous (SC) preparations in real-world settings is not well characterized.

Methods: Using national data from the U.S. Medicare program 2006–2010, we identified RA patients (pts) on the basis of 2 physician diagnosis codes initiating oral MTX (no prior use ever, minimum of 6m clean period) who had no use of hydroxychloroquine (HCQ), sulfasalazine (SSZ), or leflunomide (LEF) in the previous 6 mo with no prior biologic use. During follow-up (>=1 year required), dose escalation of oral MTX and switch to SC MTX, HCQ, SSZ, and LEF were characterized. Persistence with each was examined and defined as a gap > 90 days after the end of the days' supply. Subsequent use and timing of addition of biologics was examined among those who had at least one switch, adjusting for multiple potential confounders using Cox proportional hazards models, using the switch date as the time axis.

Results: New oral MTX users (n=20406) were 76.9% women, had mean +- SD age of 69.7 + −11.7 years and contributed a median (IQR) follow-up of 2.6 (1.7, 3.5) years; 32.1% never changed dose of oral MTX and remained at their starting dose (most common dose: 7.5mg, 22%; and 10.0mg, 23%). Of all patients, only 39.4% used oral doses of >= 20mg/week at any time. At 1 year and beyond, 75.8% stayed on oral MTX (with or without dose increase) and did not add or switch to HCQ, SSZ, LEF, or SC MTX. The remainder switched or added HCQ (11.9%), SSZ (5.0%), LEF (9.3%) or switched to SC MTX (3.9%). The median (IQR) dose of oral MTX prior to switch to SC was 15.0 (12.5, 20.0) mg/wk and occurred at a median (IQR) of 292 (133,557) days. Persistence with SC MTZ, HCQ, SSZ, and LEF was similar (figure) and was lower than with oral MTX.



Overall, 19.1% of the cohort starting oral MTX initiated a biologic, mostly (84.7%) anti-TNF therapy. Of these individuals, 55.5% had never used MTX at a dose of >= 20mg prior to biologic use; 32.8% never used MTX at a dose of >= 15mg. Among pts who used biologics after a switch to SC MTX, the median (IQR) interval of time between switching to SC MTX and initiation of a biologic was 165 (66, 336) days. Among patients who increased oral MTX dose or switched to SC MTX or other nbDMARDs (n=12,652) and after multivariable adjustment, there were no significant differences in use of biologics between patients who switched to SC MTX vs. added or switched to SSZ or LEF. Pts who added HCQ were less likely to require biologics (hazard ratio 0.53, 95% CI 0.37–0.77), with some evidence suggesting that HCQ use was a proxy for less severe RA (not shown).

Conclusion: Titration to higher doses of oral MTX and use of SC MTX preparations among Medicare pts with RA is infrequent and may be underutilized. Further work to optimize MTX dosing before pts are switched to a biologic may be warranted.

Disclosure: J. R. Curtis, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescnedo, AbbVie, 5; **F. Xie**, None; **J. Zhang**, Roche/Genentech, 2; **L. Chen**, None; **H. Yun**, None; **M. H. Schiff**, Antares biopharma, Abbvie, BMS, Pfizer, Amgen, Roche, UCB, 5; **D. Mackey**, None; **S. Ginsberg**, None.

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Tofacitinib, An Oral Janus Kinase Inhibitor, In A Rheumatoid Arthritis Open-Label Extension Study Following Adalimumab Therapy In A Phase 3 Randomised Clinical Trial.

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Background/Purpose: Tofacitinib is a novel, oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. Here, we describe the efficacy and safety for adalimumab (ADA) patients (pts) transitioning to tofacitinib open-label extension (OLE) without washout. These data were presented previously.[1]

Methods: In the Phase 3 randomized controlled trial (RCT, NCT00853385) ORAL Standard, pts on background methotrexate received tofacitinib 5 mg twice daily (BID), tofacitinib 10 mg BID, ADA 40 mg subcutaneous injections (every other week [Q2 Wk]), placebo (PBO) advanced to tofacitinib 5 mg BID, or PBO advanced to tofacitinib 10 mg BID (4:4:4:1:1). Primary results were reported.[2] Eligible pts from the RCT were permitted to enroll in an OLE receiving tofacitinib 10 mg BID without washout (last RCT ADA dose to first OLE tofacitinib dose ≤1 Wk). In this post-hoc analysis, results are described for ADA pts 4.5 months (Mo) before and at end of the RCT, and 4.5 Mo after transition to tofacitinib in OLE. Data for tofacitinib 10 mg BID during RCT and OLE are shown at the same time points.

Results: 145/204 pts randomized to ADA were eligible and enrolled in OLE; 125 started tofacitinib without washout. There were 8 (6.4%) discontinuations during the first 4.5 Mo of OLE (3 drug-related adverse event [AE], 1 unrelated AE, 1 pregnancy, 1 death, 2 other reasons). 148/201 pts randomized to tofacitinib 10 mg BID were eligible and enrolled in OLE; 124 took their first dose of tofacitinib in the OLE ≤1 Wk after their last dose of tofacitinib in the RCT. There were 9 discontinuations in the first 4.5 Mo of OLE (1 drug-related AE, 2 unrelated AE, 6 other reasons). American College of Rheumatology (ACR)20 response rate in ADA to tofacitinib pts (N=124) was 74.2% at 4.5 Mo before end of RCT, 76.6% at end of RCT, and 90.5% at 4.5 Mo after transition to tofacitinib. ACR50 response rates (44.4%, 50.8%, 65.5%) and ACR70 response rates (16.1%, 21.0%, 36.2%) at the same time points showed a similar pattern. Mean change from baseline in health assessment questionnaire-disability index (HAQ-DI) was −0.55, −0.60, and −0.70 at the same time points. Results in tofacitinib to tofacitinib pts were similar at the same time points and showed a similar pattern of increases from RCT to OLE.

	ADA to Tofacitinib (N=125)		Tofacitinib to Tofacitinib (N=124)	
	Last 4.5 Mo, RCT	First 4.5 Mo, OLE	Last 4.5 Mo, RCT	First 4.5 Mo, OLE
Discontinuations due to AEs, pts (%)	Not applicable	4 (3.2)	Not applicable	3 (2.4)
Serious AEs, pts (%)	1 (0.8)	9 (7.2)	4 (3.2)	9 (7.3)
Serious infection, pts (%)	0 (0)	3 (2.4)	1 (0.8)	3 (2.4)

ADA, adalimumab; AE, adverse event; Mo, month; OLE, open label extension; RCT, randomized controlled trial

Conclusion: Changing directly from ADA in RCT to tofacitinib in OLE resulted in sustained clinical response, with numerical improvements in ACR 20, 50, and 70 response rates and mean change in HAQ-DI from baseline. Safety-related events appeared to increase post-transition from

ADA to tofacitinib; however, similar increases were seen in tofacitinib-treated pts in the RCT after they transitioned to OLE tofacitinib. The increase in safety-related events in both groups suggests that the increase was not simply the result of overlapping immunomodulatory effects of ADA and tofacitinib.

References:
1. Genovese et al. Ann Rheum Dis 2013; 72: 65.
2. van Vollenhoven et al. N Engl J Med 2012; 367: 508–519.

Disclosure: M. C. Genovese, Pfizer Inc, 2, Pfizer Inc, 5; **R. F. van Vollenhoven**, Pfizer Inc, 2, Pfizer Inc, 5; **B. Wilkinson**, Pfizer Inc, 1, Pfizer Inc, 3; **L. Wang**, Pfizer Inc, 1, Pfizer Inc, 3; **S. H. Zwillich**, Pfizer Inc, 1, Pfizer Inc, 3; **D. Gruben**, Pfizer Inc, 1, Pfizer Inc, 3; **B. Benda**, Pfizer Inc, 1, Pfizer Inc, 3; **T. V. Jones**, Pfizer Inc, 1, Pfizer Inc, 3.

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Tofacitinib, An Oral Janus Kinase Inhibitor: Analysis Of Gastrointestinal Adverse Events Across The Rheumatoid Arthritis Clinical Program.

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Background/Purpose: Tofacitinib is a novel, oral Janus kinase inhibitor being investigated as a targeted immunomodulator in rheumatoid arthritis (RA). This analysis aimed to describe and report the incidence of gastrointestinal (GI) adverse events (AEs) that occurred in the tofacitinib RA program up to 29 March 2011. These data were presented previously.[1]

Methods: Data from 5 randomised Phase 3 (P3) studies or 2 open-label long-term extension (LTE) studies were pooled. Patients (pts) were treated with tofacitinib 5 mg twice daily (BID), tofacitinib 10 mg BID, placebo (PBO; P3 only), or adalimumab (ADA; P3 only). Analyses of integrated safety data were from 3315 (P3; 2480 pt-y) and 3227 pts (LTE; 3118 pt-y) (LTE pts rolled over from P2 and P3). GI perforation data were analyzed from P2 (1608 pts), P3, and LTE studies.

Results: In P3 studies, exposure-adjusted event rates (EAER) (per 100 pt-y) of AEs (regardless of causality) coding to the GI System Organ Class and MedDRA preferred term, Month (Mo) 0–12, was numerically lower in pts receiving tofacitinib 5 mg BID (33.48), 10 mg BID (31.03) and ADA (21.23) vs PBO (49.87). In LTE, EAERs of GI AEs were 17.52 and 25.26 in the 5 and 10 mg BID groups, respectively. GI AEs included gastritis, constipation, diarrhea, abdominal pain, dyspepsia, nausea and vomiting; diarrhea (3.4%) and nausea (2.3%) were the most frequently reported with tofacitinib. EAERs for discontinuations (DCs) due to GI AEs in P3 (Mo 0–3, PBO-controlled period) were similar for tofacitinib (doses combined) (1.52) and PBO (1.93); EAER for ADA was 4.26. EAERs for DCs due to GI AEs for Mo 3–6 and > Mo 6 were similar to Mo 0–3. EAERs for DCs due to GI AEs in LTE were numerically lower vs P3: 0.72 (5 mg) and 0.34 (10 mg). Abdominal pain was the most common GI cause leading to DC (0.1%) with tofacitinib. Serious adverse events (SAEs) (all causality) due to GI disorders were uncommon in P3 and LTE. In P3, no GI SAE occurred in more than one pt in any dose group during Mo 0–3, 3–6 and >6. In LTE the most common abdominal SAEs were pancreatitis (4 pts, 0.12%) and cholecystitis (5 pts, 0.15%). To assess the occurrence of GI perforations, potential cases were retrospectively reviewed by Pfizer gastroenterologists based on pre-specified criteria. Ten cases of probable or definite perforation occurred in tofacitinib-treated pts; one resulted in death associated with appendicitis and sepsis. The overall GI perforation incidence rate was 0.18 (95% CI 0.095, 0.329) events per 100 pt-y. GI perforations primarily involved the lower GI tract (9 pts), and generally occurred in pts with other underlying risk factors, eg non-steroidal anti-inflammatory drugs (7 pts), glucocorticoid use (8 pts), or comorbidity of diverticulitis (3 pts).

Conclusion: GI AEs occurred commonly in all treatment groups including PBO, but were uncommon causes for DCs. Serious GI AEs were uncommon. The rate of GI perforation falls between the rates reported for pts treated with tocilizumab (0.19) and TNF inhibitors (0.13).[2]

1. Lee et al. Annals of the Rheumatic Diseases. 2012; 71 (Suppl. 3): 202.
2. Gout T et al. Clin Rheumatol 2011; 30:1471–1474.

Disclosure: E. B. Lee, Pfizer Inc, 5; **J. R. Curtis**, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **R. Riese**, Pfizer Inc, 1, Pfizer Inc, 3; **C. A. Connell**, Pfizer Inc, 1, Pfizer Inc, 3; **R. Chew**, Pfizer Inc, 1, Pfizer Inc, 3; **M. G. Boy**, Pfizer Inc, 1, Pfizer Inc, 3; **E. Maller**, Pfizer Inc, 1, Pfizer Inc, 3; **C. Su**, Pfizer Inc, 1, Pfizer Inc, 3; **L. Wang**, Pfizer Inc, 1, Pfizer Inc, 3.

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Cardiovascular Safety Findings In Rheumatoid Arthritis Patients Treated With Tofacitinib, A Novel, Oral Janus Kinase Inhibitor.

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Background/Purpose: Tofacitinib is a novel, oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Here we evaluated the cardiovascular (CV) event rates and changes in blood pressure (BP) in the tofacitinib Phase 3 (P3) and long-term open-label extension (LTE) studies up to March 29, 2011. These data were presented previously.[1]

Methods: Five P3 studies in patients (pts) with inadequate response to nonbiologic/biologic disease-modifying anti-rheumatic drugs (DMARDs) and 2 LTE studies were included. Tofacitinib was administered as monotherapy or with background nonbiologic DMARDs, predominantly methotrexate. One P3 study included adalimumab (ADA) as active control. An independent CV Safety Endpoint Adjudication Committee performed blinded adjudication of deaths, potential major adverse CV events (MACE), and events of congestive heart failure (CHF). MACE was defined as CV death and non-fatal CV events.

Results:

		All P3 Studies (0–12 Months)			LTE Studies
		PBO (N=681)	*All Dose tofacitinib (5 and 10 mg BID) (N=3030)	ADA 40 mg SC q2w (N=204)	All Dose tofacitinib (5 and 10 mg BID) (N=3227)
Exposure		202.6 pt-y	2098.2 pt-y	178.9 pt-y	2622.2 pt-y
MACE	Events (n)	2	14	3	5
	IR per 100 pt-y (95% CI)	0.99 (0.25, 3.95)	0.57 (0.33, 1.01)	1.68 (0.54, 5.20)	0.19 (0.08, 0.46)
CV Mortality	Events (n)	0	2	1	**1**
	IR per 100 pt-y (95% CI)	0	0.10 (0.02, 0.38)	0.56 (0.08, 3.97)	0.04 (0.01, 0.27)
Non-fatal myocardial infarction	Events (n)	0	4	2	**1**
	IR per 100 pt-y (95% CI)	0	0.19 (0.07, 0.51)	1.12 (0.28, 4.47)	0.04 (0.01, 0.27)
Non-fatal cerebrovascular accidents	Events (n)	2	8	0	3
	IR per 100 pt-y (95% CI)	0.99 (0.25, 3.95)	0.33 (0.16, 0.70)	0	0.11 (0.04, 0.36)
CHF	Events (n)	0	7	0	3
	IR per 100 pt-y (95% CI)	0	0.29 (0.13, 0.64)	0	0.08 (0.02, 0.31)

* Pts advanced from PBO to tofacitinib are 'PBO' until advanced and only in 'All Dose' post-advancement

MACE IRs (per 100 pt-y) in placebo (PBO) and tofacitinib groups in P3 were low. IR in the LTE studies in the tofacitinib All Dose group (0.19) was lower than in P3 (0.57). IRs of CHF in tofacitinib groups were low. In P3, mean changes from baseline at Month 3 for systolic and diastolic BP, respectively, were 0.1 mmHg and −0.8 mmHg for PBO and −0.2 and 0.3 mmHg for tofacitinib. Mean BP changes at Months 6 and 12 and in the LTE studies remained stable.

Conclusion: Incidence rates of MACE were similar across groups in P3 with lower rates in LTE, suggesting no increased risk over 3 years of follow up. Tofacitinib was not associated with clinically meaningful increases in BP. Although the number of events has been few and longer observation periods are warranted, CV risk does not appear to be increased with tofacitinib treatment, and rates of CV events are consistent with those observed among patients with RA of similar disease severity.[2–4]

1. Charles-Schoeman et al. Ann Rheum Dis 2012; 71(Suppl. 3): 201.
2. Solomon DH et al. Circulation 2003; 107: 1303–1307.
3. Solomon DH et al. Ann Rheum Dis 2006; 65: 1608–1612.
4. Nicola PJ et al. Arthritis Rheum 2006; 54: 60–67.

Disclosure: C. Charles-Schoeman, Pfizer Inc, 9; **P. Wicker**, Pfizer Inc, 1; **M. A. Gonzalez-Gay**, Abbott, MSD, Roche, 2, Abbott, MSD, Roche, Pfizer, 5, Abbott, MSD, Roche, Pfizer, 8; **S. P. Wood**, Pfizer Inc, 1, Pfizer Inc, 3; **M. G. Boy**, Pfizer Inc, 1, Pfizer Inc, 3; **J. Geier**, Pfizer Inc, 1, Pfizer Inc, 3; **D. Gruben**, Pfizer Inc, 1, Pfizer Inc, 3; **K. Soma**, Pfizer Inc, 1, Pfizer Inc, 3; **R. Riese**, Pfizer Inc, 1, Pfizer Inc, 3.

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Tofacitinib, An Oral Janus Kinase Inhibitor: Safety Comparison In Patients With Rheumatoid Arthritis and An Inadequate Response To Nonbiologic Or Biologic Disease-Modifying Anti-Rheumatic Drugs.

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Background/Purpose: Tofacitinib is a novel, oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). This analysis provides comparative safety data on the incidence of safety events for patients (pts) with an inadequate response (IR) to a nonbiologic disease-modifying antirheumatic drug (DMARD-IR) versus pts with an IR to a biologic DMARD (bDMARD-IR). These data were presented previously.[1]

Methods: The primary comparison was performed on pooled data from 5 randomized, controlled Phase 3 (P3) studies in RA pts treated with tofacitinib 5 mg or 10 mg BID for 6 to 12 months. Supportive analyses were conducted on 2 pooled open-label long-term extension (LTE) studies. All pts enrolled were nonbiologic or biologic DMARD-IR.

Results: In the pooled P3 studies, 2389 tofacitinib-treated pts with 1783 pt-years (pt-yrs) of exposure were analyzed in the DMARD-IR population and 641 pts with 315 pt-yrs of exposure in the bDMARD-IR group. Baseline demographics were generally similar, albeit the bDMARD-IR group was generally older, heavier and had fewer Asian pts. Compared with the DMARD-IR, the bDMARD-IR population exhibited increases in the rate (events/100 pt-yrs) of serious adverse events (SAEs) (12.3 [95% confidence interval (CI) 9.0, 16.9] vs 9.9 [8.6, 11.5]) and discontinuations due to adverse events (AE DC) (15.0 [95% CI 11.3, 20.0] vs 9.6 [7.7, 12.1]) in both tofacitinib treatment arms and in placebo. There were four adalimumab pts (and 0 events) that were bDMARD-IR. The rates of deaths, serious infections (SI), malignancies and major adverse cardiovascular events were similar across the populations (Table). LTE studies included 2715 pts with 3588 pt-yrs of exposure in the DMARD-IR population and 566 pts with 514 pt-yrs of exposure in the bDMARD-IR group. As compared with the DMARD-IR, the bDMARD-IR population showed increases in rates (events/100 pt-yrs) of SAEs (14.6 [95% CI 11.6, 18.4] vs 10.2 [9.2, 11.3]), AE DC (10.0 [95% CI 7.6, 13.1] vs 6.8 [6.0, 7.7]) and SIs (4.7 [95% CI 3.1, 7.0] vs 2.7 [2.2, 3.3]). The rates of the other safety events were similar.

	DMARD-IR Incidence Rate (95% CI) [number of pts with event]				bDMARD-IR Incidence Rate (95% CI) [number of pts with event]				
	Tofacitinib					Tofacitinib			Placebo n=181
Parameter	5 mg BID n=969	10 mg BID n=973	All* n=2389	Placebo n=500	Adalimumab n=200	5 mg BID n=247	10 mg BID n=241	All* n=641	
Mortality (deaths within 30 days of last dose)	0.52 (0.20, 1.40) [4]	0.51 (0.19, 1.37) [4]	0.45 (0.22, 0.90) [8]	0.63 (0.09, 4.44) [1]	0.57 (0.08, 4.04) [1]	0.71 (0.10, 5.05) [1]	0	0.64 (0.16, 2.54) [2]	0
Serious Infections	3.29 (2.22, 4.86) [25]	3.08 (2.07, 4.60) [24]	2.92 (2.23, 3.84) [52]	1.88 (0.61, 5.82) [3]	1.71 (0.55, 5.31) [3]	2.85 (1.07, 7.58) [4]	2.30 (0.74, 7.13) [3]	2.86 (1.49, 5.49) [9]	0
Malignancies (excl. NMSC†)	0.52 (0.20, 1.40) [4]	0.77 (0.35, 1.71) [6]	0.56 (0.30, 1.04) [10]	0	0.57 (0.08, 4.05) [1]	0.71 (0.10, 5.05) [1]	1.53 (0.38, 6.13) [2]	0.95 (0.31, 2.95) [3]	0
Composite MACE$^{\Psi}$ (adjudicated)	0.39 (0.13, 1.22) [3]	0.64 (0.27, 1.54) [5]	0.45 (0.22, 0.90) [8]	1.25 (0.31, 5.00) [2]	1.71 (0.55, 5.30) [3]	0.71 (0.10, 5.06) [1]	0.77 (0.11, 5.45) [1]	1.27 (0.48, 3.39) [4]	0

*Tofacitinib All group comprises pts randomized to tofacitinib 5 or 10 mg BID at study start plus placebo pts advanced to tofacitinib treatment per protocol design. Placebo pts advanced to tofacitinib are counted in placebo until advancement and in the "Tofacitinib All" group after advancement.
†NMSC, nonmelanoma skin cancer.
$^{\Psi}$MACE, major adverse cardiovascular events. All data as of 29 Sep 2011

Conclusion: Event rates for important safety events for both DMARD-IR and bDMARD-IR pts are within the ranges observed with biologic therapies approved for treatment of RA with some differences noted in SI (LTE only), SAE and AE DC favoring the DMARD-IR population.

Reference:

1. Burmester G et al. Ann Rheum Dis 2013; 72: 245–245.

Disclosure: G. R. Burmester, Abbott, BMS, MSD, Pfizer, Roche, UCB, 2, Abbott, BMS, MSD, Pfizer, Roche, UCB, 5, Abbott, BMS, MSD, Pfizer, Roche, UCB, 8; **C. Charles-Schoeman**, Pfizer Inc, 2; **J. D. Isaacs**, Pfizer Inc, 2, Pfizer Inc, 5, Pfizer Inc, 8; **T. Hendrikx**, Pfizer Inc, 1, Pfizer Inc, 3; **K. Kwok**, Pfizer Inc, 1, Pfizer Inc, 3; **S. H. Zwillich**, Pfizer Inc, 1, Pfizer Inc, 3; **R. Riese**, Pfizer Inc, 1, Pfizer Inc, 3.

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Tolerability and Non-Serious Adverse Events In Rheumatoid Arthritis Patients Treated With Tofacitinib As Monotherapy Or In Combination Therapy.

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Background/Purpose: Tofacitinib is a novel, oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). Tolerability remains an ill-defined construct in clinical trials. Most commonly the term is used to refer to non-serious adverse events (AEs) that despite being non-serious may still impact the patient's experience taking a drug, potentially affecting satisfaction and adherence. The objective of this analysis is to describe occurrence of the most common non-serious AEs (excluding infections and laboratory test abnormalities) in patients treated with tofacitinib as monotherapy or in combination with nonbiologic DMARDs.

Methods: The most common non-serious investigator-reported AEs (those with an incidence rate (IR) ≥5 per 100 patient-years and IR exceeding that for patients taking PBO for both doses of tofacitinib combined) were evaluated in a post-hoc pooled analysis of five DMARD inadequate responder Phase 3 studies. IRs were computed for patients taking placebo (PBO) or tofacitinib 5 or 10 mg twice daily (BID) using the data from all five Phase 3 studies. Additionally, the proportion of patients experiencing an AE were computed for each group within the first three months of exposure for the monotherapy study and for the combined four studies in which tofacitinib was taken with nonbiologic DMARDs.

Results: The most commonly reported non-serious AEs (excluding infections and laboratory test abnormalities) were headache, diarrhea, hypertension, dyspepsia, back pain, upper abdominal pain, and constipation. Incidence rates per 100 patient-years for tofacitinib 5 mg BID, 10 mg BID and PBO, respectively, from the pooled Phase 3 data were: headache: 21, 15 and 11; diarrhea: 16, 12, and 10; hypertension: 7, 9, and 4; dyspepsia: 7, 9, and 7; back pain: 6, 7, and 3; upper abdominal pain: 8, 5, and 3; constipation: 6, 6, and 4. The proportion of patients with one or more events in the first three months was <5% for all AEs except headache in patients taking tofacitinib 5 mg BID (see Table).

Table. Non-serious, non-infectious treatment-emergent AEs (excluding infections and laboratory test abnormalities) in Phase 3 studies (Months 0–3)

	Monotherapy			Combination therapy		
AE	5 mg BID N=243	10 mg BID N=245	PBO N=122	5 mg BID N=973	10 mg BID N=969	PBO N=559
Headache, %	5.3	4.5	2.5	4.2	2.8	2.1
Diarrhea, %	4.5	3,7	2.5	3.5	2–6	3.0
Hypertension. %	0.8	2.9	1.6	1.7	2.0	0.9
Dyspepsia, %	2.1	2.4	3.3	1.4	2.0	1–3
Back pain. %	2.1	2.0	1.6	1.1	1.3	0,5
Upper abdominal pain. %	2.5	1.6	0.0	1.7	0.9	0.9
Constipation, %	2.1	2.0	2.5	1.1	1.1	0.5

Conclusion: The most common non-serious AEs (excluding infections and laboratory test abnormalities) were headache, hypertension, back pain and abdominal pain, and selected gastrointestinal events. A rate of 10 or more events per 100 patient-years for at least one dose of tofacitinib was observed for headache and diarrhea. Overall, the proportions of patients experiencing non-serious, non-infectious AEs were similar for patients receiving tofacitinib as monotherapy or in combination with nonbiologic DMARDs.

Disclosure: A. Dikranian, Pfizer Inc, Amgen, AbbVie, UCB, Genentech, BMS, 8; **K. Soma**, Pfizer Inc, 1, Pfizer Inc, 3; **R. Riese**, Pfizer Inc, 1, Pfizer Inc, 3; **D. Gruben**, Pfizer Inc, 1, Pfizer Inc, 3; **T. V. Jones**, Pfizer Inc, 1, Pfizer Inc, 3.

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Efficacy and Safety Analyses Of Tofacitinib From Pooled Phase 2, Phase 3 and Long-Term Extension Rheumatoid Arthritis Studies: US Compared With Non-US Populations.

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor approved in the US for the treatment of rheumatoid arthritis at 5 mg BID.

Phase (P) 3 studies demonstrated efficacy of tofacitinib and elucidated its safety profile at 5 and 10 mg twice daily (BID). These post-hoc analyses of pooled P2, P3 and long-term extension (LTE) data assessed whether there were differences in efficacy and/or safety between the patient (pt) populations in the United States (US) and the Rest of World (ROW, non-US).

Methods: Data from DMARD-inadequate responder pts receiving tofacitinib 5 or 10 mg BID ± background nonbiologic DMARDs were pooled from six P2 and five P3 randomized studies and two open-label LTE studies for safety analyses: comparisons evaluated the incidence rates (IRs) (events/100 pt-years) for all tofacitinib groups combined for events of special interest. Pooled P3 data were assessed for efficacy comparisons of tofacitinib 5 and 10 mg BID and placebo (PBO) at Month 3 (PBO could be rescued at Month 3); descriptive statistics are presented.

Results: Data from 664 (US) and 2447 (ROW) pts were included in the efficacy analyses; 974 (US) and 3815 (ROW) pts were included in the safety analyses. Pts in the US and ROW had similar demographics other than a greater proportion of Caucasians seen in the US (PBO, 83.1%; 5 mg BID, 81.1%; 10 mg BID, 82.0%) compared with ROW (PBO, 58.7%; 5 mg BID, 55.3%; 10 mg BID, 55.5%). At Month 3, there were slight differences in the efficacy of tofacitinib between the US and ROW by ACR criteria with the PBO-adjusted response rate very similar for ACR20/50/70 (Table). DAS28-defined remission (DAS28-4(ESR)<2.6) at Month 3 was achieved in numerically more (5 mg) and fewer (10 mg) pts treated with tofacitinib in the US compared with ROW. The HAQ-DI score achieved similar improvement from baseline in the US and ROW. The IRs for safety events in the US and ROW demonstrated numerical differences with higher rates for tuberculosis, herpes zoster (HZ) and lymphoma in ROW compared with the US but higher rates of serious infection events, malignancies and deaths in the US (Table); 95% confidence intervals were largely overlapping. There were no cases of lymphoma or serious HZ in the US.

Table. Efficacy and Safety in the US and ROW patient populations (observed data)

	PBO		Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		PBO-adjusted 5 mg		PBO-adjusted 10 mg	
POOLED P3 DATA	US N=160	ROW N=521	US N=249	ROW N=967	US N=255	ROW N=959	US N=249	ROW N=967	US N=255	ROW N=959
Efficacy, Month 3										
ACR20, %	24.0	30.2	53.3	60.9	63.4	67.5	29.3	30.8	39.4	37.4
ACR50, %	9.6	9.9	30.6	31.2	38.4	34.7	21.0	21.3	28.8	24.8
ACR70, %	3.4	2.7	15.3	11.5	18.1	16.2	11.9	8.7	14.7	13.5
DAS28-4(ESR)<2.6, %	<1.0	2.6	9.0	6.4	7.5	11.0	8.3	3.8	6.7	8.4
△HAQ-DI, mean	−0.16	−0.16	−0.43	−0.46	−0.50	−0.55	−0.27	−0.30	−0.34	−0.39

POOLED P2, P3 and LTE†† DATA	All patients receiving tofacitinib† US N=974 (1642.9 pt-years of exposure)	ROW N=3815 (6817.5 pt-years of exposure)
Safety		
IR per 100 pt-years (95% Cl) [n]		
Serious infection events TB	3.50 (2.70, 4.54) [57]	2.99 (2.60, 3.43) [202]
TB	0.06 (0.01, 0.43) [1]†	0.22 (0.13, 0.37) [15]
Opportunistic infections, including TB	0.06 (0.01, 0.43) [1]	0.59 (0.43, 0.80) [40]
All HZ	3 37 (2.57, 4.41) [53]	4.49 (4.01, 5.04) [293]
Serious HZ	0	031 (0.20, 0.47) [21]
All-cause mortality (30-day rule)§	0.43 (020, 0.89) [7]	026 (0.17, 0.42) [18]
Malignancies (excluding non-melanoma skin cancer)	1.22 (0.79, 1.89) [20]	0.81(0.62, 1.05) [55]
Lymphoma	0	0.06 (0.02, 0.16) [4]

†Includespts receiving 5 and 10 mg BID; ††Data as of April 19 2012; ‡the one case of TB and the one OI were the same event; §includes those events occurring within 30 days of Last Dose of study drug
ACR, American College of Rheumatology; DAS. disease activity score; HAQ-DI, Health Assessment Questionnaire - Disability Index; TB. tuberculosis

Conclusion: US study pts achieved similar delta change in ACR responses at both tofacitinib 5 and 10 mg BID in P3 at Month 3 compared with ROW study pts; there was a difference in achieving DAS-defined remission. There were differences seen with respect to safety events of interest, particularly with fewer selected infections of significance in the US. Conclusions are limited by the difference in population sizes.

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Reversibility Of Pharmacodynamic Effects After Short- and Long-Term Treatment With Tofacitinib In Patients With Rheumatoid Arthritis.

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Background/Purpose: Tofacitinib is a novel oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). It has a short pharmacokinetic (PK) half-life of 3 hours, with systemic concentrations falling below pharmacologically active levels within 24 hours after cessation of therapy. This analysis investigated the reversibility of the pharmacodynamic (PD) effects of tofacitinib over a range of biomarkers. Phosphorylation of signal transducer and activator of transcription (STAT)5 was measured as a direct read-out of JAK1/3 dependent signaling. In addition, changes reflecting downstream events such as interferon-inducible protein-10 (IP-10), lymphocyte subsets (natural killer (NK) and B cells), neutrophils, C-reactive protein (CRP), and clinical efficacy were monitored.

Methods: Data following discontinuation (dc) of tofacitinib from 2 randomized Phase 2 (P2) studies of 4–6 weeks' treatment duration, and temporary withdrawal from 1 long-term extension (LTE), were assessed. In P2 study A (NCT00976599), tofacitinib 10 mg twice daily (BID) or placebo were administered to 29 RA patients (pts) on stable methotrexate for 4 weeks and blood samples were collected during therapy and ≤1 week post-dc. In P2 study B (NCT00147498), tofacitinib 5, 15, or 30 mg BID or placebo were administered to 264 RA pts as monotherapy for 6 weeks and blood samples were collected during therapy and 2 and 6 weeks after dc. In the LTE study (NCT00413699), after a median of approximately 22 months of exposure, CRP, disease activity score defined using 28 joint counts (DAS28) and Health Assessment Questionnaire Disability Index (HAQ-DI) were assessed in pts in whom tofacitinib was administered continuously throughout the study or in whom tofacitinib was withdrawn for a 2-week period.

Results: After short-term tofacitinib treatment (4–6 weeks), mean and median pSTAT5 levels fully reversed to baseline within 24 hours after dc, while serum IP-10 levels and NK and B cell counts completely reversed to baseline levels 1–2 weeks after dc; mean CRP and neutrophil counts partially reversed over 2–4 weeks after dc. After temporary withdrawal from longer-term tofacitinib treatment, B cell counts decreased and CRP, DAS28 and HAQ-DI values increased after 1–2 weeks (Table).

Table. Reversibility of Pharmacodynamic Endpoints After Tofacitinib Treatment is Discontinued

	Biomarker	Change during treatment	Time to reversal (weeks)
Phase 2 RCT	pSTAT5[a]	↓	<1
	IP-10[a]	↓	1
	CRP[b]	↓	2
	B cells[b]	↑	2
	NK cells[b]	↓	2
	Neutrophils[b]	↑	4
LTE*	B cells	↑	1
	CRP	↓	1
	DAS28-4(ESR)	↓	1
	HAQ-DI	↓	2

RCT, randomized controlled trial; [a]P2 study A (4 weeks); [b]P2 study B (6 weeks); *LTE, long-term extension study (median 22 months)

Conclusion: The PD effects of short- or long-term tofacitinib treatment are reversible, after approximately 2 weeks of dc. These data provide a scientific basis for a 2-week dc of tofacitinib to reverse many of the pharmacologic effects of the agent.

Disclosure: M. C. Genovese, Pfizer Inc, 2, Pfizer Inc, 5; **T. Kawabata**, Pfizer Inc., 1, Pfizer Inc., 3; **K. Soma**, Pfizer Inc, 1, Pfizer Inc, 3; **S. Menon**, Pfizer Inc., 1, Pfizer Inc., 3; **J. D. Clark**, Pfizer Inc, 1, Pfizer Inc, 3; **J. Hodge**, Pfizer Inc., 1, Pfizer Inc., 3; **L. Takiya**, Pfizer Inc., 1, Pfizer Inc., 3; **R. Riese**, Pfizer Inc, 1, Pfizer Inc, 3; **S. Krishnaswami**, Pfizer Inc., 1, Pfizer Inc., 3.

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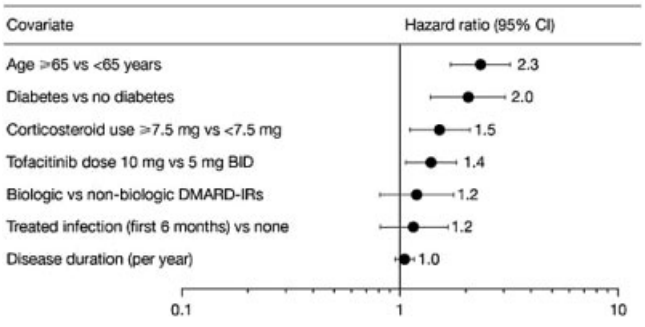
Post-Hoc Analysis Of Serious Infection Events and Selected Clinical Factors In Rheumatoid Arthritis Patients Treated With Tofacitinib. J. J. Gomez-Reino[1], A. Hazra[2], C. Fosser[2], S. Menon[2], S. H. Zwillich[2], R. Riese[2] and S. Krishnaswami[2]. [1]Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain, [2]Pfizer Inc, Groton, CT.

Background/Purpose: Tofacitinib is a novel oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). Serious infections (requiring hospitalization or parenteral antibiotics; SIEs) have been reported at an incidence of approximately 3 events per 100 patient-years (pt-y) in tofacitinib-treated RA patients (pts). This retrospective analysis incorporating Phase (P) 2, 3 and long-term extension (LTE) safety data assessed the relationship between selected clinical factors and SIE occurrence.

Methods: Data from pts receiving tofacitinib were pooled from five randomized P2, five randomized P3 and two open-label LTE studies. Clinical factors in the analysis were a) age (≥65 years vs <65 years), b) diabetes status (yes/no), c) concomitant baseline glucocorticoid use (≥7.5 mg vs <7.5 mg), d) tofacitinib dose (as a continuous variable incorporating dose changes over time), e) prior treatment (inadequate responders; IR) with biologic vs non-biologic disease modifying anti-rheumatic drugs (DMARDs), f) pts experiencing a treated infection (i.e. infection requiring antimicrobial therapy) within the first 6 months of treatment vs none, and g) duration of disease (RA) at baseline (as a continuous variable). SIE data were analyzed using a Cox Proportional Hazards model with time dependent covariates (dose), with simultaneous inclusion of the above covariates. Separate interaction tests between tofacitinib dose and age, diabetes or glucocorticoid dose were performed. Results were expressed as hazard ratios with 95% confidence intervals (CIs).

Results: Based upon the exclusion of 1 for 95% CI of hazard ratios, age (elderly), corticosteroid dose ≥7.5 mg, diabetes and tofacitinib dose were identified as independent factors associated with the risk of SIE (Figure). Elderly pts had an estimated 2.3 times increased risk of SIE. Pts with diabetes had 2 times increased risk of SIE, while a separate infections analysis irrespective of severity did not show noticeable differences (data on file). There was a 50% increase in SIE risk in pts receiving corticosteroid doses ≥7.5 mg and 40% increased risk of SIE with 10 mg vs 5 mg tofacitinib. Interaction tests did not show an increase in tofacitinib risk in the above sub-populations. Relative to non-biologic DMARD IRs, biologic DMARD IRs showed a hazard ratio of 1.2, with CIs including 1.

Figure: Hazard Ratios for Serious Infections, Cox Proportional Hazards Model



Data as of 29 Sept 2011; Post-hoc anaylsis of tofacitinib-treated patients

Conclusion: Identification of age, diabetes and corticosteroid dose as independent risk factors is consistent with reports from multiple RA pt databases (Listing et al., 2013; Strangfeld A, et al. 2011) of biologic DMARDs. Tofacitinib dose was an independent risk factor for SIEs. However, interaction tests suggest that the identified risk factors are reflective of underlying characteristics of the RA population, particularly DMARD-treated pts, rather than tofacitinib.

Disclosure: J. J. Gomez-Reino, Roche, UCB, MSD, 8, Abbott, BMS, MSD, Pfizer Inc, Roche, 5, Abbott, BMS, MSD, Pfizer Inc, Roche, 8; **A. Hazra**, Pfizer Inc., 1, Pfizer Inc., 3; **C. Fosser**, Pfizer Inc., 1, Pfizer Inc., 3; **S. Menon**, Pfizer Inc., 1, Pfizer Inc., 3; **S. H. Zwillich**, Pfizer Inc, 1, Pfizer Inc, 3; **R. Riese**, Pfizer Inc, 1, Pfizer Inc, 3; **S. Krishnaswami**, Pfizer Inc., 1, Pfizer Inc., 3.

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Remission Rates During Golimumab Treatment For Rheumatoid Arthritis Are Associated With Differences In Baseline Disease States Across Geographic Regions. P Durez[1], K Pavelka[2], M Lazaro[3], A Garcia Kutzbach[4], R Moots[5], H Amital[6], R Yao[7], M Govoni[8], N Vastesaeger[9] and HH Weng[7]. [1]Université Catholique de Louvain and Cliniques Universitaires Saint-Luc, Brussels, Belgium, [2]Revmatologicky Ustav, Praha, Czech Republic, [3]Instituto de Asistencia Reumatológica Integral, San Fernando, San Fernando, Argentina, [4]Universidad Francisco Marroquin Guatemala School of Medicine, Guatemala City, Guatemala, [5]University Hospital Aintree, Liverpool, United Kingdom, [6]Sheba Medical Center, Tel-Hashomer, Israel, [7]Merck Sharp & Dohme, Kenilworth, NJ, [8]Merck Sharp & Dohme, Rome, Italy, [9]Merck Sharp & Dohme, Brussels, Belgium.

Background/Purpose: Regional differences in practice patterns and access to biologic treatment for rheumatoid arthritis (RA) may lead to regional differences in baseline disease characteristics, which could influence response to biologic treatments. The purpose of this analysis of the GO-MORE study was to compare across geographic regions the baseline disease levels and remission rates among biologic-naïve RA patients during 6 months of add-on golimumab (GLM) treatment.

Methods: GO-MORE was an open-label, multinational, prospective study in biologic-naïve patients with active RA (DAS28-ESR ≥3.2) despite nonbiologic disease-modifying antirheumatic drug treatment. Patients received 50-mg SC GLM once monthly for 6 months. In planned and post hoc analyses, baseline disease activity, disease duration, and DAS28-ESR remission rates were evaluated across geographic regions.

Results: Baseline disease activity varied across regions (table), with high EULAR disease activity most prevalent in South Africa, Asia, and Latin America. Disease duration was longest in Latin America and South Africa. Overall, after 6 months of GLM treatment, DAS28-ESR remission rate was approximately 25%. Remission rates varied substantially by region, with lower remission rates generally found in the regions with the greatest initial disease activity and disease duration, with the exception of South Africa. Within the European region, the largest population in the study, the countries with the lowest remission rates were Russia and Romania (6.8% and 7.8% at month 6, respectively), also had high rates of baseline disease activity (96.6% and 86.3% of patients had high disease activity, respectively; mean DAS28-ESR 6.4 and 6.2, respectively). In the European countries with the highest remission rates, Belgium and Austria (43.1% and 40.2% at month 6, respectively), much lower baseline disease activity was observed (40.2% and 59.8% of patients had high disease activity, respectively; mean DAS28-ESR 5.0 and 5.2, respectively). Regardless of geographic region, patients with moderate baseline disease activity were more likely to achieve remission than those with high baseline disease activity (43.4% and 18.5%, respectively, $P<.0001$).

Geographic Region	Baseline EULAR Disease Activity[a] n (%)		Baseline Disease Duration, y Mean (SD)	Baseline DAS28-ESR Mean (SD)	Month 6 DAS28-ESR Remission[b] n (%)
	Moderate	High			
South Africa, N=117	10 (8.5)	107 (91.5)	7.6 (7.9)	6.7 (1.1)	34 (29.1)
Asia, N=133	10 (7.5)	123 (92.5)	5.4 (4.8)	6.2 (0.8)	20 (15.0)
Europe, N=1818	525 (29.0)	1286 (71.0)	7.4 (7.8)	5.7 (1.0)	507 (27.9)
Latin America, N=906	84 (9.3)	821 (90.7)	8.6 (8.2)	6.4 (1.0)	156 (17.2)
Middle East, N=88	19 (21.8)	68 (78.2)	6.9 (7.0)	6.0 (1.0)	24 (27.3)
Canada, N=218	50 (23.0)	167 (77.0)	6.6 (8.4)	5.9 (1.1)	43 (19.7)

[a]Moderate disease activity: DAS28-ESR 3.2–5.1; high disease activity: DAS28-ESR >5.1. [b]Remission: DAS28-ESR <2.6.

Conclusion: After 6 months of GLM treatment, patients in South Africa, Europe, and the Middle East had higher remission rates than those in Latin America and Asia. This pattern may be due to differences in baseline disease activity and duration, which may reflect differences in practice patterns and access to biologic treatments. Overall, patients with moderate baseline disease activity were more likely to achieve remission than those with high baseline disease activity.

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High Levels Of Memory B CELLS ARE Associated With Response To A First ANTI-TNF Drug In Patients With Rheumatoid Arthritis. Claire I. Daien[1], Sarah Gailhac[2], Thibault Mura[3], Bernard Combe[1], Michael Hahne[4] and Jacques Morel[1]. [1]Lapeyronie Hospital, Montpellier, France, [2]CNRS, Montpellier, France, [3]Hopital Gui De Chauliac, Montpellier, France, [4]IGMM, CNRS UMR5535, Montpellier, Montpellier, France.

Background/Purpose: Tumor necrosis factor (TNF) inhibitors (TNFi) are effective treatments for rheumatoid arthritis (RA). Some reports suggested that TNFi affect B cell homeostasis. We studied the effect of TNFi on peripheral B cells and elucidated B cell related biomarkers to predict TNFi response.

Methods: Peripheral B cells were analyzed for expression of CD19, CD27, CD38, IgD in 31 healthy donors and 96 RA patients, including 21 patients who were followed 3 months after TNFi introduction. We compared B cell subsets between patients with RA and controls; TNFi and non TNFi users as well as before and after TNFi introduction in RA patients. We also aimed to identify phenotypes associated with EULAR response.

Results: B cell subsets in blood were influenced by age and glucocorticoids doses. After adjustment on age, gender and glucocorticoid doses, patients with RA were found to have similar B cell subset frequencies as controls. No significant effect of TNFi on B cell repartition was found when comparing TNFi and non TNFi users at baseline or patients before and after TNFi introduction. TNFi responders at 3 months had significantly higher percentage of $CD27^+$ memory B cells at baseline and those with $CD27^+$ above 26% at inclusion were 4.9 (1.3–18.6) more likely to respond TNFi treatment. $CD27^+$ cells produced 3 times more TNF alpha than naïve B cells which was correlated with IFN gamma-producing $CD4^+$ in patients free of TNFi.

Conclusion: High levels of memory B cells at baseline were associated with response to TNFi which may be related to the activation of the Th1 pathway in a TNFa depending manner.

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Effectiveness Of Tocilizumab In Monotherapy and In Combination With Different Synthetic Dmards: A Registry-Based Comparison Study. Cem Gabay[1], Myriam Riek[2], Merete L. Hetland[3], Ulrik Tarp[4], K. Pavelka[5], Matija Tomsic[6], Helena Canhao[7], Katerina Chatzidionysiou[8], R.F. van Vollenhoven[9], Galina Lukina[10], E. Nasonov[11], Dan C. Nordström[12], Elisabeth Lie[13], Ioan Ancuta[14], Estibaliz Loza Santamaria[15], Piet Van Riel[16] and Tore K. Kvien[13]. [1]Geneva University Hospitals, Geneva, Switzerland, [2]SCQM Registry, Zurich, Switzerland, [3]DANBIO, Center for Rheumatology and Spine Diseases, Glostrup Univ Hospital, Glostrup, Denmark, [4]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [5]Department of Clinical and Experimental Rheumatology, Charles University, Prague, Czech Republic, [6]University Medical Centre Ljubjana, Ljubljana, Slovenia, [7]Instituto de Medicina Molecular, Rheumatology Research Unit, Rheumatology Research Unit, on behalf of the Rheumatic Diseases Portuguese Register, Lisbon, Portugal, [8]Unit for Clinical Research Therapy. Inflammatory Diseases (ClinTrid), Karolinska Institute, Stockholm, Sweden, [9]Karolinska Institute, Stockholm, Sweden, [10]ARBITER, Institute of Rheumatology, Moscow, Russia, [11]Institute of Rheumatology, Moscow, Russia, [12]ROB-FIN, Helsinki University Central Hospital, Helsinki, Finland, [13]Diakonhjemmet Hospital, Oslo, Norway, [14]"Dr. I. Cantacuzino" Hospital, Bucharest, Romania, [15]Instituto de salud Musculoesqueletica, Madrid, Spain, [16]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.

Background/Purpose: Tocilizumab (TCZ) is efficacious in monotherapy and in combination with methotrexate (MTX) or other DMARDs. However, longitudinal data from large registry populations are missing. To examine the effectiveness of TCZ administered alone or in combination with DMARDs in the TOcilizumab Collaboration of European Registries in RA (TOCERRA).

Methods: All RA patients treated with TCZ having a baseline (BL) visit were considered. Patients were assigned to groups: TCZ monotherapy (TCZ), TCZ+MTX, TCZ+MTX+other DMARDs (TCZ+MTX+other), and TCZ+other DMARDs based on BL information. Effectiveness was measured in terms of percentages of patients achieving DAS28 and CDAI remission and according to changes in DAS28 and CDAI at around 6 and 24 months post TCZ start. Groups were compared by time point using Fisher's exact test or a Kruskal-Wallis test. A covariate-adjusted non-linear mixed effects model with an exponential decrease over time was fitted to the longitudinal DAS28 and CDAI data for patients with complete covariate information, including country, sex, age, disease duration, number of prior biologics, corticosteroid use, seropositivity and use of co-DMARDs.

Results: 1515 RA patients with 1537 treatment courses (TCs) were retrieved. 26% were treated with TCZ, 52% with TCZ+MTX, 9% with TCZ+MTX+other, and 13% with TCZ+other. Group frequencies varied significantly among countries (P=0.0005). For 78% of TCs DMARD co-therapy did not change over time. Median TCZ treatment duration was 0.75 years (IQR: 0.31 – 1.60 years, max: 4.25 years). BL characteristics of patients are described in Table 1. Number of TCs with a value for DAS28 and CDAI were 631 and 470 at 6 and 170 and 148 at 24 months. DAS28 and CDAI remission at 6 and 24 months in the different groups ranged from 47 to 52% and from 62 to 73% for DAS28 and from13 to 21% and from 18 to 30% for CDAI, respectively. Differences were not significant (all P>0.05). In all groups mean DAS28 and CDAI had decreased rapidly (to 2.7–3.0 and 9.8–14.1, respectively) by 6 months and leveled off thereafter, at 2.4–2.5 and 8.2–10.0 by 24 months, respectively (all P>0.05). There was no indication for an effect of DMARD use on the decrease of DAS28 and CDAI from the mixed effects analysis including 7096 and 6050 observations from 1251 and 985 TCs (with comparable percentages of groups as above), respectively (both P>0.05). However, country as well as use of prior biologics (in terms of none, 1, or ≥ 2) were found to significantly affect DAS28 and CDAI decrease (all P<0.001).

Table 1. Baseline demographic and disease characteristics

Variable	All (N=1537)	TCZ (N=393)	TCZ+MTX (N=787)	TCZ+MTX+ other (N=143)	TCZ+other (N=193)	*P*
Age (yrs), mean ± sd (N)	54.7 ± 13.3 (1531)	57.7 ± 13.8 (391)	53.9 ± 12.9 (783)	51.7 ± 13.3 (143)	55.6 ± 12.2 (193)	< 0.0001 *
Disease duration (yrs), mean ± sd (N)	11.4 ± 9.7 (1453)	12.9 ± 10.8 (353)	11.3 ± 9.5 (755)	8.4 ± 7.5 (136)	12.3 ± 9.1 (188)	< 0.0001 *
Female, n/N (%)	1200/1532 (78.3)	314/391 (80.3)	601/784 (76.7)	112/143 (78.3)	156/193 (80.8)	= 0.41 ¤
Prior bDMARDs use, n (%)						
0	329 (21.5)	87 (22.2)	143 (18.2)	45 (31.5)	34 (17.6)	= 0.01 ¤
1	355 (23.2)	84(21.5)	191 (24.3)	35 (24.5)	45 (23.3)	
≥ 2	849 (55.4)	220 (56.3)	451 (57.5)	63 (44.1)	114 (59.1)	
RF positive, n/N (%)	1035/1340 (77.2)	270/330 (81.8)	537/687 (78.2)	98/129 (76)	130/173 (75.1)	= 0.26 ¤
Anti-CCP positive, n/N (%)	420/619 (67.8)	82/120 (68.3)	242/362 (66.8)	48/68 (70.6)	48/69 (69.6)	= 0.93 ¤
RF or anti-CPP positive, n/N (%)	1094/1357 (80.6)	274/334 (82)	576/697 (82.6)	108/130 (83.1)	136/175 (77.7)	= 0.49 ¤
Corticosteroid use, n/N (%)	649/1501 (43.2)	141/386 (36.5)	347/781 (44.4)	70/142 (49.3)	91/192 (47.4)	= 0.009 ¤
DAS28, mean ± sd (N)	5.0 ± 1.3 (1441)	4.8 ± 1.3 (363)	5.1 ± 1.4 (744)	5.0 ± 1.3 (134)	5.0 ± 1.4 (179)	= 0.0075 *
DAS28-CRP, mean ± sd (N)	4.8 ± 1.2 (1415)	4.6 ± 1.2 (355)	4.9 ± 1.2 (732)	4.8 ± 1.1 (133)	4.7 ± 1.4 (174)	= 0.03 *
CDAI, mean ± sd (N)	29.7 ± 14.4 (980)	27.2 ± 12.5 (228)	31.4 ± 15.4 (528)	27.4 ± 12.4 (104)	28.7 ± 14.0 (120)	= 0.0016 *
HAQ, mean ± sd (N)	1.4 ± 0.7 (1273)	1.5 ± 0.7 (299)	1.4 ± 0.7 (674)	1.3 ± 0.7 (132)	1.6 ± 0.8 (168)	= 0.02 *

Numbers shown represent numbers of treatment courses (TCs). P-values are from Kruskal-Wallis test (*) or Fisher's exact test (¤)
bDMARDs, biological DMARDs; sd, standard deviation; yrs, years

Conclusion: The results from a large cohort of patients followed longitudinally indicate that TCZ has similar effectiveness when used in monotherapy or in combination with different synthetic DMARDs.

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Work Instability In Early Rheumatoid Arthritis With Elevated Risk Of Employment Loss: Effects Of Adalimumab/Methotrexate Combination Therapy Versus Methotrexate In a Randomized Clinical Trial. Arthur Kavanaugh[1], Josef S. Smolen[2], Arijit Ganguli[3], Hartmut Kupper[3], Mary Cifaldi[3], Naijun Chen[3] and Dennis Revicki[4]. [1]University of California, San Diego, La Jolla, CA, [2]Medical University of Vienna, Vienna, Austria, [3]AbbVie Inc., North Chicago, IL, [4]United BioSource, Bethesda, MD.

Background/Purpose: Intensive treatment of early rheumatoid arthritis (RA) has been shown to reduce functional disability over time and to positively impact employment outcomes. Adalimumab (ADA) is approved

for the treatment of RA and has demonstrated improvements in clinical, patient-reported, and work productivity outcomes.[1,2] We aimed to evaluate the effects of combination therapy with ADA plus methotrexeate (MTX) compared with MTX monotherapy on work instability outcome, a significant predictor of employment loss, among patients at elevated risk for job loss.

Methods: A secondary analysis was conducted using data from the 26 week, randomized, double-blind period of OPTIMA, a study designed to compare the safety and efficacy of ADA plus MTX to placebo plus MTX in subjects with early (<1 year duration), active RA. Work instability was assessed using the Rheumatoid Arthritis-Work Instability Scale (RA-WIS) (range 0–23), where scores of ≥17, ≥10 to <17, and <10 represent high-, medium-, or low-risk for job loss. To meet study objectives, only employed patients with baseline RA-WIS score ≥10 (moderate to high risk) were included in this analysis. Improvements of 5 points in RA-WIS has been determined to be clinically meaningful. Chi-square tests were used to assess treatment group differences in the percentage of patients who: a) demonstrated improvement by at least 1 risk category; and b) achieved improvements of ≥5, ≥7 or ≥9 points, at Weeks 4, 12 and 26 from baseline. Missing values were imputed using NRI method. As sensitivity analysis, responders were defined as patients with both improvement by at least 1 category and a ≥5 point change.

Results: A total of 320 patients (146 ADA plus MTX; 174 PBO plus MTX) were included in the analysis sample (mean age: 46; females: 69%). The mean baseline RA-WIS score was 16.7(±3.8). Significant differences favoring ADA were observed among patients who improved by at least 1 risk category at Weeks 4, 12, and 26 (50% vs 33%; P=.0025, 62% vs 44%; P=.0019, and 58% vs 47%; P=.048, respectively). A significantly greater percentage of ADA treated patients also improved by 5 points (42% vs 23%; P=.0003, 58% vs 43%; P=.010, and 56% vs 43%, P<.027 at Weeks 4, 12, and 26, respectively), 7 points (29% vs 16%; P=.004, 45% vs 33%; P=.031, and 47% vs 36%; P=.035 at Weeks 4, 12, and 26, respectively), or 9 points (23% vs 9%; P=.0008, 34% vs 23%; P=.036, and 42% vs 26%, P=.004 at Weeks 4, 12, and 26, respectively) compared to patients receiving MTX monotherapy. Sensitivity analysis also showed significant differences favoring patients treated with ADA at Weeks 4, 12 and 26 (38% vs 21%; P<.001, 53% vs 38%; P<.001, and 53% vs 41%; P=.031, respectively).

Conclusion: Among early RA patients with elevated risk of employment loss, combination therapy with ADA plus MTX was associated with clinically meaningful greater improvements in RA-WIS compared with MTX monotherapy.

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Disclosure: A. Kavanaugh, AbbVie, 5, AbbVie, 2; **J. S. Smolen**, AbbVie, 5, AbbVie, 2; **A. Ganguli**, AbbVie, 3, AbbVe, 1; **H. Kupper**, AbbVie, 3, AbbVie, 1; **M. Cifaldi**, AbbVie, 3, AbbVie, 1; **N. Chen**, AbbVie, 3, AbbVie, 1; **D. Revicki**, AbbVie, 5.

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Tocilizumab Monotherapy Compared With Adalimumab Monotherapy In Patients With Rheumatoid Arthritis: An Evaluation Of High-Density Lipoprotein Composition. Cem Gabay[1], Katie Tuckwell[2], Jennifer Green[2], Micki Klearman[3] and Arthur Kavanaugh[4]. [1]SCQM registry, University Hospitals of Geneva, Geneva, Switzerland, [2]Roche, Welwyn Garden City, United Kingdom, [3]Roche, South San Francisco, CA, [4]University of California, San Diego, La Jolla, CA.

Background/Purpose: Rheumatoid arthritis (RA) patients (pts) are at increased risk for cardiovascular (CV) disease. Although analysis of lipids such as LDL-C and HDL-C is useful in the general population to estimate CV risk, disease-associated inflammation also contributes to CV risk among RA pts. Chronic inflammation in RA is associated with low HDL-C and altered HDL composition. HDL particles may become atherogenic due to association with acute-phase reactants (ie, serum amyloid A [SAA] and secretory phospholipase A_2 [sPLA2]), thereby losing their ability to protect LDL from oxidation. Elevated serum HDL-associated SAA (HDL-SAA) and sPLA2 have been identified as markers of increased CV risk.[1] We conducted a post hoc analysis of HDL-SAA and sPLA2 to investigate changes in HDL composition in RA pts after initiation of 2 biological therapies with different mechanisms of action.

Methods: ADACTA was a phase 4, randomized, double-blind study in RA pts (tocilizumab [TCZ], n=163; adalimumab [ADA], n=163).[2] Pts received TCZ 8 mg/kg IV Q4W or ADA 40 mg SC Q2W for 24 wks, both as monotherapy. Available serum samples were analyzed at baseline (BL) and wk 8 for HDL-C, HDL-SAA, and sPLA2. Change from BL to wk 8 was analyzed by ACR20 response (responders [R]/nonresponders [NR]) at wk 24. Change from BL to wk 8 in median HDL-SAA and sPLA2 was compared using nonparametric Kruskal-Wallis analyses. Spearman rank correlation coefficients were used to determine associations between changes in these parameters and C-reactive protein (CRP) and apolipoprotein A-1 (apoA-1) collected during the trial.

Results: A greater increase in HDL-C was observed after treatment with TCZ vs ADA (TCZ, 0.14 mmol/L, n=129; ADA, 0.07 mmol/L, n=137). Reductions in HDL-SAA and sPLA2 were seen in both arms, with a greater response with TCZ (Table). Larger reductions in sPLA2 were seen with TCZ for ACR20-R. For ACR20-NR, smaller reductions were seen in both arms, also in favor of TCZ. There were similar reductions in HDL-SAA for ACR20-R and -NR, but again reductions were greater with TCZ (Table); the same effect was seen for EULAR good responders (data not shown). In both arms, a moderate positive correlation was seen between HDL-SAA and sPLA2 (TCZ, r=0.57, p<0.0001; ADA, r=0.54, p<0.0001). A stronger correlation was observed between HDL-SAA and CRP (TCZ, r=0.58, p<0.0001; ADA, r=0.69, p<0.0001) and sPLA2 and CRP (TCZ, r=0.66, p<0.0001; ADA, r=0.74, p<0.0001). There was a weak negative correlation between HDL-SAA or sPLA2 and apoA-1 with TCZ (HDL-SAA, r=–0.27, p=0.05; sPLA2, r=–0.25, p=0.04) and a weaker correlation with ADA (HDL-SAA, r=–0.19, p=0.13; sPLA2, r=–0.16, p=0.14).

Table. Change From Baseline to Week 8 in HDL-SAA and sPLA2

		HDL-SAA mg/L		SPLA2 ng/mL	
Subgroup	**Statistic**	**ADA 40 mg**	**TCZ 8 mg/kg**	**ADA 40 mg**	**TCZ 8 mg/kg**
Allpatients	n	62	55	86	73
	Mean (SD)	−4.4 (12.3)	−9.3 (18.3)	−1.8 (9.2)	−7.8 (12.8)
	Median	−1.1	−3.2	−1.3	−4.1
	Quartiles (25%, 75%)	−7.1, 0.6	−11, −1.0	−2.9, 0.8	−7.8, −1.1
	P^a	0.0077		<0.0001	
ACR20 responders	n	32	39	47	52
	Median	−1.0	−3.3	−1.3	−4.8
	Quartiles (25%, 75%)	−6.8, 0.6	−10, 1.0	−3.2, 0.7	−9.5, −1.3
	P^a	0.0475		<0.0001	
ACR20 nonresponders	n	30	16	39	21
	Median	−1.1	−3.1	−0.6	−3.1
	Quartiles (25%, 75%)	−8.7, 1.2	−13, −1.2	−2.8, 1.9	−4.9, −1.0
	P^a	0.0816		0.0012	

The table includes patients for whom samples and valid results were available for HDL-SAA and SPLA2.
[a] Analysis was performed using the Kruskal-Wallis test. The descriptive p value is presented, and no adjustment was made for multiple testing.

Conclusion: TCZ had a greater effect than ADA on reducing HDL-SAA and sPLA2 levels, suggesting a greater positive impact of TCZ on the antiatherogenic properties of HDL.

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Disclosure: C. Gabay, Roche Pharmaceuticals, 2, Roche, Abbvie, Pfizer, UCB, BMS, MSD, 5; **K. Tuckwell**, Roche Pharmaceuticals, 3; **J. Green**, Roche Pharmaceuticals, 3; **M. Klearman**, Genentech and Biogen IDEC Inc., 3; **A. Kavanaugh**, Roche, Abbott, Amgen, UCB, BMS, Pfizer, Janssen, 2.

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Evaluation Of Disease Activity By The Routine Assessment Of Patient Index Data 3 In Patients With Rheumatoid Arthritis Receiving Tocilizumab. Yu F. Asanuma, Takashi Maruyama, Maiko Yanagisawa, Kazuhiro Yokota, Yoshihiro Yoshida, Hiroshi Kajiyama, Kojiro Sato, Yuji Akiyama and Toshihide Mimura. Saitama Medical University, Saitama, Japan.

Background/Purpose: Interleukin-6 (IL-6) has been demonstrated to play a pathological role in rheumatoid arthritis (RA). IL-6 strongly induces production of C-reactive protein (CRP) and fibrinogen in hepatocytes. Marked decrease of serum CRP level and erythrocyte sedimentation rate (ESR) has been shown soon after administration of IL-6 antagonist, tocilizumab (TCZ). Therefore, usual disease activity scores using clinical data including CRP or ESR may not reflect real clinical response to the treatment with TCZ in patients with RA. RAPID3 includes the 3 patient-reported RA core data set measures: physical function, pain, and patient global estimate without formal joint counts and laboratory test, ESR or CRP. We investigated the usefulness of RAPID3 to evaluate disease activity and functional disability in RA patients receiving TCZ.

Methods: Twenty four patients with RA were enrolled in this prospective, IRB proven study. The patients were started on TCZ therapy at Saitama Medical University Hospital from 2010 to 2012. TCZ was infused every 4 weeks at a dose of 8 mg/kg. All patients were followed up to week 52. RAPID3 was calculated from a multidimensional health assessment questionnaire, pain and patient global estimate. The primary outcomes were the DAS28-ESR, CDAI, SDAI, HAQ and RAPID3 at week 52 of TCZ treatment. Secondary outcomes included proportion of patients in remission of RAPID3 or other indices to assess patients with RA. The association between RAPID 3 and other indices at week 52 was also examined.

Results: Mean age of patients was 53 years, 71 percent of patients were female, the mean duration of disease was 10 years and 75 percent of patients had received prior treatment of other biologics. Seventy one percent of patients were methotrexate users and 67 percent were corticosteroid users. Significant reduction of DAS28-ESR, CDAI, SDAI and RAPID3 were observed at week 52 compared to baseline ($P<0.05$). Remission rate of RAPID3 (29%) was not significantly different with that of CDAI (17%), SDAI (25%), ACR/EULAR Boolean (17%) and HAQ (38%) in patients receiving TCZ for 52 weeks, although the remission rate of RAPID3 was lower than that of DAS28-ESR (54%) ($p=0.07$). RAPID3 scores were correlated significantly with those of DAS28-ESR (rho = 0.66), CDAI (rho = 0.79), SDAI (rho = 0.78) and HAQ (rho = 0.85) (all $P<0.001$) at week 52.

Conclusion: RAPID3 may be useful for evaluating disease activity and functional disability without formal joint counts and laboratory tests in RA patients receiving TCZ.

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What Are The Implications Of Concomitant and Pre-Medication On Infusion Reactions To Infliximab: Results From "RemiTRAC Infusion", a Prospective Real-World Community Registry. Denis Choquette[1], Rafat Y. Faraawi[2], Merlin Njoya[3], Andrew Chow[4], William G. Bensen[5] and Francois Nantel[6]. [1]Institut de Rhumatologie de Montréal, Montreal, QC, [2]Rheumatologist, KW Musculoskeletal Research Inc., Kitchener, ON, [3]McKesson Canada, Toronto, ON, [4]Credit Valley Rheumatology, Mississauga, ON, [5]St. Joseph's Hospital and McMaster University, Hamilton, ON, [6]Janssen Canada Inc, Toronto, ON.

Background/Purpose: Infliximab (IFX) is a therapeutic monoclonal antibody targeting TNFa indicated in the treatment of a number of chronic inflammatory diseases. IFX is administered by intravenous infusion and may be associated with infusion reactions (IRs).

Methods: RemiTRAC Infusion is a prospective observational registry conducted in 12 Canadian sites from 2005–2012. IFX infusions were followed to document IRs and their management, pre-medication use and adverse events. An IR was defined as any AE occurring during the infusion or within 1 hour post-infusion. The effects of concomitant medication and pre-medication prior to infusions on the incidence of IRs were evaluated by propensity score adjusted analysis using a Multilevel logistic regression model with the following variables as predictors: Patient age, weight and gender; prior enrolment use of IFX, any prior biologic use; indication; season and year of infusion; patient eligibility; dose; time since the last infusion and number of previous IRs.

Results: 1632 patients were enrolled and 24,852 infusions were recorded. The majority (63%) of patients in this cohort are treated with IFX for rheumatologic conditions such as RA (40%), AS (18%) and PsA (6%). 201/1632 (12.3%) patients reported at least one IR. Of 24,852 infusions, 322 resulted in an IR (1.3%) and most IRs were mild to moderate in severity (95%). The most common IR was pruritus, occurring in 19.9% of infusion reactions. Flushing (9.9%) and dyspnoea (6.2%) are the only other infusion AEs occurring in ≥5% of IRs. Four serious IRs (fever, itching/flushing, chest pain, chest pain/flushing) and no serious anaphylactic reactions occurred.

The effects of concomitant medications and pre-medication are shown in table 1. Neither immunosuppressive agent overall, nor do MTX or corticosteroids have any effect in reducing the incidence of IRs. In contrast, pre-medication with anti-histamines and/or steroids were associated with a significant increase in the incidence of IRs. Only the use of acetaminophen monotherapy was associated with a significant reduction in the incidence of IRs.

Table 1. Effect of concomitant medication and pre-medication on the incidence of IRs (Propensity scores adjusted effect).

Treatment	*N*	*% of all infusions*	*Infusions with reactions*	*% with reaction*	*Odds Ratio*	*95% Confidence Interval*	*p-value vs None group*
Concomitant Medication							
None	4163	16.75%	59	1.42%			.
Any immunosuppressive	12414	49.95%	180	1.45%	0.83	(0.44, 1.55)	0.5487
MTX	9364	37.68%	142	1.52%	0.82	(0.43, 1.58)	0.5473
Corticosteroids	4461	17.95%	65	1.46%	0.71	(0.36, 1.40)	0.3106
Pre-Medication							
None	12996	52.29%	148	1.14%			.
Any Pre-medication	11856	47.71%	174	1.47%	1.19	(0.94, 1.49)	0.1491
Includes Acetaminophen (AA)	8424	33.90%	93	1.10%	0.97	(0.74, 1.27)	0.8151
Includes Antihistamines (AH)	5672	22.82%	127	2.24%	1.58	(1.22, 2.07)	0.0007
Includes Steroids (S)	5588	22.49%	105	1.88%	1.50	(1.13, 2.01)	0.0057
AA alone	3508	14.12%	20	0.57%	0.61	(0.38, 0.98)	0.0426
AH alone	1059	4.26%	31	2.93%	1.79	(1.13, 2.82)	0.0129
S alone	1243	5.00%	14	1.13%	1.00	(0.53, 1.92)	0.9900
S + AH	859	3.46%	33	3.84%	3.34	(2.05, 5.43)	<.0001
S + AA	1162	4.68%	12	1.03%	0.91	(0.49, 1.66)	0.7447
AH + AA	1387	5.58%	13	0.94%	1.13	(0.61, 2.09)	0.6956
S + AH + AA	2101	8.45%	37	1.76%	1.44	(0.97, 2.15)	0.0701

Conclusion: This registry shows that in community-based infusion clinics, IR to IFX are uncommon and largely mild to moderate in nature. Anti-histamines, intravenous steroids and acetaminophen have been widely used to decrease the odds of IRs. However, the results of this registry demonstrate that anti-histamines[1] and steroids[2]are ineffective as prophylactic pre-medication. The effectiveness of acetaminophen as pre-medication suggests that most IRs are of a non-immunological mechanism.

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Impact Of Inadequate Adherence On Clinical Outcomes: Results From The Biologics In Rheumatoid Arthritis Genetics and Genomics Study Syndicate Cohort. James Bluett[1], Catharine Morgan[1], Layla Thurston[2], Darren Plant[1], Ann W. Morgan[3], Anthony G. Wilson[4], John Isaacs[5], Kimme L. Hyrich[1], Lis Cordingley[1] and Anne Barton[1]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]Manchester Medical School, The University of Manchester, Manchester, United Kingdom, [3]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [4]Department of Infection and Immunity, University of Sheffield, Sheffield, United Kingdom, [5]National Institute for Health Research, Newcastle Biomedical Research Centre, Newcastle Hospitals Foundation Trust and Newcastle University, Newcastle Upon Tyne, United Kingdom.

Background/Purpose: Biologic therapy has revolutionised patient prognosis in rheumatoid arthritis (RA). In the UK, continuing biologic therapy requires a sustained response as determined by the 28 joint-count disease activity score (DAS28). Adherence to DMARDs is low but little is known about adherence to biologic therapies and its relationship to treatment response.

The purpose of this study is to investigate the association of adherence to subcutaneous (SC) biologics and EULAR response criteria in subjects with RA.

Methods: Participants were recruited to the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGSS), a large UK multicentre prospective observational cohort study. Demographic

information for patients receiving SC biologic therapy and disease characteristics were assessed at baseline. Self-reported adherence was recorded at 3 and 6 months if the biologic was taken on the day agreed with the healthcare professional. Non-adherence was defined as 'ever non-adherent' for these periods. DAS28 was recorded at baseline and following 3 and 6 months of therapy and categorised according to the EULAR response criteria. Descriptive statistics, Student's t-test, chi-squared test and Mann-Whitney U test statistics were used to analyse the data.

Results: Data were collected for 390 patients with median disease duration of 7 years (IQR 3–15). Adherence data were collected in 286 patients. 27% reported non-adherence with biologic therapy according to our criteria. There were significantly smaller changes in DAS28, ESR and poorer EULAR response in patients reporting non-adherence as shown in table 1. There were no differences between the adherent and the non-adherent group in terms of other DAS components; tender or swollen joint counts nor patient visual analogue scale. Age, disease duration and baseline DAS28 were not significantly associated with adherence status in this cohort; however it was associated with gender with self-reported adherence lower in women.

	Total sample	Adherent group	Non-adherent group	*P*-value
Age in years: mean (SD)	57.2 (11.5)	57.7 (11.4)	56.1 (12.0)	0.205
Gender F: n (%)	291 (74.6)	146 (69.9)	64 (83.1)	**0.024**
Change in DAS28 at 6 months: median (IQR)	−2.9 (−1.7 to −3.8)	−3.1 (−2.0 to −3.8)	−2.35 (−1.1 to −3.7)	**0.025**
Change in ESR at 6 months: median (IQR)	−8.5 (0 to −20)	−10 (−1 to −25)	−3.5 (4 to −14)	**0.004**
EULAR non response: n (%)	26 (11.0)	13 (7.6)	13 (20.3)	
EULAR moderate response: n (%)	91 (38.6)	66 (38.4)	25 (39.1)	
EULAR good response: n (%)	119 (50.4)	93 (54.1)	26 (40.6)	**0.014**

Conclusion: RA patients who reported not taking their biologic on the day agreed with their healthcare professional showed poorer clinical outcomes than their counterparts, emphasising the need for strict adherence to biologics in patients with RA. Female gender was a baseline predictor of patient reported non-adherence.

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Antibody Response To Pneumococcal and Influenza Vaccination In Patients With Rheumatoid Arthritis Receiving Subcutaneous Abatacept. MC Genovese[1], CO Bingham 3rd[2], S Cohen[3], L Calabrese[4], JR Curtis[5], A Block[6], J Fay[6], S Kelly[6], A Luo[6], D Wong[6] and R Alten[7]. [1]Stanford University, Palo Alto, CA, [2]Johns Hopkins University, Baltimore, MD, [3]Metroplex Clinical Research Center, Dallas, TX, [4]Cleveland Clinic, Cleveland, OH, [5]University of Alabama at Birmingham, Birmingham, AL, [6]Bristol-Myers Squibb, Princeton, NJ, [7]Schlosspark-Klinik, University Medicine Berlin, Berlin, Germany.

Background/Purpose: Previous small studies have suggested that responses to some immunizations may be attenuated by intravenous abatacept but remain clinically meaningful.[1,2] We investigated the magnitude of antibody response to the standard 23-valent pneumococcal polysaccharide vaccine (PPV23) and the 2011–2012 seasonal influenza trivalent vaccine in a large number of adult patients (pts) with RA receiving subcutaneous (SC) abatacept and background DMARDs.

Methods: Two multicenter, open-label sub-studies of PPV23 and seasonal influenza vaccine enrolled pts in the ACQUIRE (pneumococcal and influenza) or ATTUNE (pneumococcal) studies. Pts were enrolled at any point during their SC abatacept treatment cycle after completion of ≥3 months' abatacept treatment. All pts received fixed-dose SC abatacept 125 mg/week with background DMARDs. A pre-vaccination blood sample was collected and vaccines administered, while continuing background SC abatacept and DMARDs. After 28 ± 3 days, a final post-vaccination blood sample was collected. For PPV23, the primary endpoint was the proportion of pts achieving an immunologic response, defined as a ≥2-fold increase in post-vaccination titers to ≥3 of 5 evaluated pneumococcal antigens (9V, 14, 18C, 19F, and 23F) in the vaccine at Day 28 in the subgroup of pts without a protective antibody level (titer ≥1.6 μg/mL to ≥3 of 5 pneumococcal antigens) to these antigens at baseline. For influenza vaccination, the primary endpoint was the proportion of the subgroup of pts achieving an immunologic response, defined as a ≥4-fold increase in post-vaccination titers to ≥2 of 3 evaluated 2011–2012 influenza antigens (H1N1, H3N2, and Brisbane) at Day 28 in pts without a protective antibody level (titer ≥1:40 to ≥2 of 3 influenza antigens) to these antigens at baseline. Safety and tolerability were assessed throughout the studies.

Results: Pre- and post-vaccination titers were available for 113/125 and 186/191 enrolled pts receiving the pneumococcal and influenza vaccines, respectively. Among vaccinated pts, 47/113 pneumococcal and 121/186 influenza pts were without protective antibody levels at baseline. Of these pts, 73.9% (34/46) and 61.3% (73/119) met the primary endpoint and demonstrated an immunologic response to PPV23 or influenza vaccine, respectively. In all pts who received the vaccine and had pre- and post-vaccination antibody titers available at 4 weeks post-vaccination, 83.9% (94/112) demonstrated protective antibody levels with PPV23 (titer ≥1.6 μg/mL to ≥3 of 5 pneumococcal antigens), and 82.1% (151/184) in the influenza study demonstrated protective antibody levels (titer ≥1:40 to ≥2 of 3 influenza antigens). Vaccination during SC abatacept administration was well tolerated, with no new safety signals identified.

Conclusion: In this group of pts with RA on SC abatacept and background DMARDs, most pts without protective antibody levels at baseline were able to mount an immune response to the PPV23 and influenza virus vaccines, and vaccination was well tolerated. These data are consistent with previous smaller studies.

1. Tay L, et al. *Arthritis Res Ther* 2007;**9**:R38 2. Schiff M, et al. *Arthritis Rheum* 2007;**56**:S392

Disclosure: M. Genovese, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5; **C. Bingham 3rd**, Bristol-Myers Squibb, 5, Bristol-Myers Squibb, 2; **S. Cohen**, Amgen, Biogen Idec, Bristol-Myers Squibb, Centocor, Genentech, Johnson Johnson, Pfizer, Merck, Roche, 2; **L. Calabrese**, None; **J. Curtis**, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **A. Block**, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1; **J. Fay**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **S. Kelly**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **A. Luo**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **D. Wong**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **R. Alten**, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 9.

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Oskira-2: A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Parallel-Group Study Of 2 Dosing Regimens Of Fostamatinib In Rheumatoid Arthritis Patients With An Inadequate Response To Disease-Modifying Antirheumatic Drugs. Peter Dawes[1], Aleksandar Dimic[2], Mark C. Genovese[3], Désiréé van der Heijde[4], Martin Jenkins[5], Chris O'Brien[6], Barry Oemar[7], Jiri Vencovsky[8] and Michael Weinblatt[9]. [1]University of North Staffordshire NHS Trust, Stoke-on-Trent, United Kingdom, [2]Rheumatology Institute, Niška Banja, Serbia, [3]Stanford University, Palo Alto, CA, [4]Leiden University Medical Center, Leiden, Netherlands, [5]AstraZeneca R&D Alderley Park, Macclesfield, United Kingdom, [6]AstraZeneca R&D Wilmington, Wilmington, DE, [7]AstraZeneca R&D Boston, Boston, MA, [8]Institute of Rheumatology, Prague, Czech Republic, [9]Division of Rheumatology, Brigham & Women's Hospital, Boston, MA.

Background/Purpose: Fostamatinib (Fosta) is a novel spleen tyrosine kinase (SYK) inhibitor. The Phase II TASKi studies showed benefit in patients (pts) with active rheumatoid arthritis (RA). A formal, prospective, international, phase III research program (OSKIRA) was initiated in 2010. This 52-wk study, (OSKIRA-2) evaluated Fosta in pts with active RA who had an inadequate response to DMARDs.

Methods: 908 pts who fulfilled 1987 ACR criteria were randomly allocated to 1 of 3 groups: Fosta 100 mg bid (Group A, n = 308); Fosta 100 mg bid for 4 wks then Fosta 150 mg qd (Group B, n = 298); or placebo (PBO) for 24 wks then Fosta 100 mg bid (Group C, n = 302). All

treatment regimens were taken in combination with DMARDs. Non-responders at Wk 12 could leave the study and enter an active extension. The primary endpoint was the proportion of pts achieving ACR20 at Wk 24. Secondary endpoints evaluated efficacy, safety and tolerability up to 52 wks.

Results: There were no notable imbalances in demographics, disease duration and activity/disability/erosions or concomitant medications at baseline between the 3 groups (mean age: 53 yrs; 82% female; mean disease duration: 7.5 yrs; RF seropositive: 78%; erosive score ≥ 3: 80%; mean DAS28-CRP score: 5.6). Background medications included methotrexate (83% of pts) and sulfasalazine, hydroxychloroquine or chloroquine (17% of pts). There were statistically significant improvements in ACR20 at Wk 24 for both Fosta groups vs PBO ($p < 0.001$ for both groups; Table). For all the key secondary endpoints evaluating RA signs and symptoms up to Wk 24, Fosta Group A achieved statistically significant differences vs PBO ($p < 0.001$ for all; Table) and there were statistical differences from PBO for these endpoints for Group B ($p < 0.001$), except ACR70 (Table). Changes in ACR20 were seen as early as Wk 1. Change in mTSS at Wk 24 did not show a significant difference compared with PBO for either Fosta group ($p = 0.904$; $p = 0.342$, respectively).

Table. Patient discontinuations, primary endpoint and key secondary endpoints at or up to Wk 24

Endpoint*	Group A	Group B	Group C
	Fosta 100 mg bid (n = 308)	Fosta 100 mg bid for first 4 wks then 150 mg qd (n = 298)	Placebo for 24 wks then Fosta 100 mg bid (n = 302)
Patients discontinuing treatment up to Wk 24	100 (32.5%)	105 (35.0%)	155 (50.8%)
ACR20 at Wk 24 (primary endpoint)	122 (39.6%)	118 (39.6%)	74 (24.5%)
ACR50 at Wk 24	64 (20.8%)	54 (18.1%)	25 (8.3%)
ACR70 at Wk 24	28 (9.1%)	18 (6.0%)	8 (2.6%)
ACR20 at Wk 1	97 (16.0%)		25 (8.3%)
DAS28-CRP < 2.6 at Wk 12	53 (17.2%)	32 (10.7%)	9 (3.0%)
DAS28-CRP < 2.6 at Wk 24	44 (14.3%)	3S (12.8%)	7 (2.3%)
HAQ-DI reduction ≥ 0.22 at Wk 24	142 (46.1%)	126 (42.3%)	80 (26.5%)
	(n = 266)	(n = 260)	(n = 260)
Change from baseline in mTSS score at Wk 24	0.64	0.37	1.16

* Patients who withdrew for any reason, including non-response at Wk 12, or had an increased dose of their background DMARD or any DMARD initiated were considered non-responders at all subsequent visits. Non-responders at Wk 12 could be transferred to an extension study to receive Fosta 100 mg bid; however, the treatment arm to which they were initially randomized remained blinded for the duration of the study. Patients who successfully completed the scheduled treatment period could also enter the extension study.

The most frequently reported AEs in Fosta-treated pts included hypertension, nasopharyngitis, diarrhea and hepatic enzyme increases. No major differences in serious AEs were encountered between the 3 groups (6.8%, 4.7% and 3.3% of pts, respectively). As expected, patients developed elevated blood pressure with Fosta, with elevated BP (≥ 140/90 mmHg) observed in 49.8% and 48.1% (Groups A and B), vs. 29.5% of pts (PBO) at ≥ 1 visit during the first 24 wks.

Conclusion: Fosta had an early beneficial effect on signs and symptoms, disease activity and physical function in RA vs. PBO. The overall level of response with Fosta was not as large as observed in the phase ll (TASKi) program. Treatment at the higher dose (100 mg bid) generally showed a more consistent improvement in signs and symptoms. However, Fosta failed to show benefit in mTSS. Safety and tolerability findings were consistent with the profile observed in earlier Fosta studies.

Disclosure: P. Dawes, Haywood Foundation, 2, AstraZeneca, 5; **A. Dimic**, AstraZeneca, 9; **M. C. Genovese**, Rigel Pharma, 2, Rigel Pharma, 5, AstraZeneca, 2, AstraZeneca, 5; **D. van der Heijde**, AstraZeneca, 5, AbbVie, 5, Amgen, 5, Augurex, 5, Bristol-Myers Squibb, 5, Celgene, 5, Centocor, Inc., 5, Chugai, 5, Covagen, 5, Daiichi Pharmaceutical Corporation, 5, Eli Lilly and Company, 5, GlaxoSmithKline, 5, Janssen Biologics, 5, Merck Pharmaceuticals, 5, Novartis Pharmaceutical Corporation, 5, Novo-Nordisk, 5, Otsuka, 5, Pfizer Inc, 5, Roche Pharmaceuticals, 5, Sanofi-Aventis Pharmaceutical, 5, Schering-Plough, 5, UCB, 5, Vertex, 5, Imaging Rheumatology BV, 9; **M. Jenkins**, AstraZeneca, 1, AstraZeneca, 3; **C. O'Brien**, AstraZeneca, 1, AstraZeneca, 3; **B. Oemar**, AstraZeneca, 3; **J. Vencovsky**, None; **M. Weinblatt**, Rigel Pharma, 5, AstraZeneca, 5.

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Oskira-3: A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Parallel-Group Study Of 2 Dosing Regimens Of Fostamatinib In Rheumatoid Arthritis Patients With An Inadequate Response To a Tumor Necrosis Factor-α Antagonist.

Mark Genovese[1], Désiréé van der Heijde[2], Edward Keystone[3], Alberto Spindler[4], Claude-Laurent Benhamou[5], Arthur Kavanaugh[6], Edward Fudman[7], Kathy Lampl[8], Chris O'Brien[8], Emma Duffield[9], Jeffrey Poiley[10] and Michael Weinblatt[11]. [1]Stanford University, Palo Alto, CA, [2]Leiden University Medical Center, Leiden, Netherlands, [3]University of Toronto, Toronto, ON, [4]Centro Medico Privado de Reumatologia, Tucuman, Argentina, [5]Centre Hospitalier Régional d'Orléans, Orleans, France, [6]University of California San Diego, San Diego, CA, [7]Austin Rheumatology Research PA, Austin, TX, [8]AstraZeneca R&D Wilmington, Wilmington, DE, [9]AstraZeneca R&D Alderley Park, Macclesfield, United Kingdom, [10]Arthritis Associates, Orlando, FL, [11]Division of Rheumatology, Brigham & Women's Hospital, Boston, MA.

Background/Purpose: Fostamatinib (Fosta) is an oral SYK inhibitor. This 24-wk study (NCT01197755) compared Fosta vs placebo (PBO) on methotrexate (MTX) treatment in patients (pts) with active RA and an inadequate response to a single TNF-α antagonist.

Methods: Adult pts on MTX were randomized (1:1:1) to Fosta (100 mg bid for 24 wks [n = 105; Group (Gp) A] or 100 mg bid for 4 wks then 150 mg qd [n = 108; Gp B]) or to PBO (n = 109; Gp C) for 24 wks. Non-responders at Wk 12 could leave the study and enter an active extension study. The primary endpoint was the proportion of pts achieving ACR20 response at Wk 24. Secondary endpoints evaluated efficacy, safety and tolerability up to 24 wks.

Results: Baseline characteristics were well balanced across gps. Fosta Gp A, but not Gp B had significantly more pts achieving ACR20 at Wk 24 vs PBO (Table, p=0.004; p=0.168 respectively). At Wk 24, 36.2% of pts in Gp A, 27.8% of pts in Gp B, and 21.1% of pts on PBO achieved ACR20 (Table). Improvement was seen as early as Wk 1 (Table). Secondary endpoints were not tested statistically for Gp B due to failure of the primary endpoint. Fosta Gp A did not show a difference in radiographic outcomes at Wk 24 vs PBO. Frequently reported adverse events (AEs) in Gps A, B and PBO were diarrhea (20.0%, 26.9%, 6.4%), hypertension (13.3%, 13.9%, 8.3%) and headache (7.6%, 8.3%, 10.1%). Serious AEs occurred in 6.7%, 6.5% and 5.5% of pts. AEs leading to discontinuation (DAE) occurred in 9.5%, 10.2% and 8.3% of pts, the most frequent being diarrhea, abdominal pain, and vomiting. Elevated BP (≥ 140/90 mmHg) was observed in 46.7%, 51.9%, and 26.6% of pts at ≥ 1 visit.

Table. Patient discontinuations and secondary endpoints at or up to Wk 24

Endpoint*	Group A	Group 8	Group C
	Fosta 100 mg bid + MTX (n = 105)	Fosta 100 mg bid + MTX for the first 4 wks then 150 mg qd + MTX (n = 108)	PBO + MTX (ns 109)
Patients discontinuing treatment up to Wk 24	38 (36.2%)	43 (39.8%)	54 (49.1%)
ACR20 at WK 24	38 (36.2%)	30 (27.8%)	23 (21.1%)
ACR50 at Wk 24	19 (18.1%)	14 (13.0%)	9 (8.3%)
ACR70 at Wk 24	15 (14.3%)	3 (2.8%)	3 (2.8%)
HAQ-DI reduction ≥ 0.22 at Wk 24	44 (41.9%)	34 (31.5%)	26 (23.9%)
ACR20 at Wk 1	54 (25.4%)		4 (3.7)
DAS ≤ 3.2 at Wk 12	19 (18.1%)	22 (20.4%)	6 (5.5%)
DAS < 2.6 **at** Wk 24	12 (11.4%)	8 (7.4%)	4 (3.7%)
	(n = 81)	**(n = 87)**	**(n = 88)**
Mean change from baseline in mTSS score at Wk 24	0.80	**0.18**	0.84
Patients with mTSS change ≤ 0.5 **from** baseline at Wk 24	**56 (69.1%)**	**72 (82.8%)**	**63 (71.6%)**

*Pts who withdrew for any reason, or had an increased MTX dose or had any DMARD initiated were considered non-responders at all subsequent vi sits. Non-responders at WK 12 could be transferred to an extension study to receive Fosta 100 mg bid, however, the treatment arm to which they were initially randomized remained blinded for the duration of the study. Overall exposure up to 24 wks was 35.60 patient-years (PY) for PBO and 79.36 PY for Fosta.

The majority of pts' hypertension could be managed per protocol. 30/187 pts without baseline hypertension started antihypertensives during

the study (10, 15, and 5 in Gps A, B and C, respectively). In pts on baseline antihypertensives, 50/135 pts had an increase in baseline medication and/or a new therapy (21, 18, and 11 in Gps A, B and C, respectively). Three pts (2 Gp A; and 1 in Gp B) had a DAE due to hypertension.

There were 3 adjudicated CV events in Fosta Gp B (cardiopulmonary arrest with fatal myocardial infarction [2.4/100 PY]; heart failure; syncope). One event in PBO was adjudicated as indeterminate (2.7/100 PY; sudden death, unknown etiology). These were the only two deaths in the trial. There was 1 malignancy (2.4/100 PY; renal cell carcinoma) in Fosta Gp B.

Conclusion: In this phase III study in pts with an inadequate response to a single TNF-α antagonist, Fosta 100 mg bid but not Fosta 100 mg bid for 4 wks then 150 mg qd achieved statistical improvements in ACR20 response rate at 24 wks vs PBO. The overall level of response was not as large as had been anticipated based on evaluation of Phase 2 results (eg the TASKi program). Safety and tolerability findings were consistent with the profile observed in earlier Fosta studies.

Disclosure: M. Genovese, Rigel Pharma, 2, Rigel Pharma, 5, AstraZeneca, 2, AstraZeneca, 5; **D. van der Heijde**, AbbVie, 5, Amgen, 5, AstraZeneca, 5, Augurex, 5, Bristol-Myers Squibb, 5, Celgene, 5, Centocor, Inc., 5, Chugai, 5, Covagen, 5, Daiichi Pharmaceutical Corporation, 5, Eli Lilly and Company, 5, GlaxoSmithKline, 5, Janssen Biologics, 5, Merck Pharmaceuticals, 5, Novartis Pharmaceutical Corporation, 5, Novo-Nordisk, 5, Otsuka, 5, Pfizer Inc, 5, Roche Pharmaceuticals, 5, Sanofi-Aventis Pharmaceutical, 5, Schering-Plough, 5, UCB, 5, Vertex, 5, Imaging Rheumatology BV, 9; **E. Keystone**, AstraZeneca, 2, Abbott Laboratories, 2, Amgen, 2, Baylis Medical, 2, Bristol-Myers Squibb, 2, Hoffmann-La Roche, Inc., 2, Janssen Pharmaceutica Product, L.P., 2, Lilly Pharmaceuticals, 2, Novartis Pharmaceutical Corporation, 2, Pfizer Inc, 2, Sanofi-Aventis Pharmaceutical, 2, UCB, 2, Abbott Laboratories, 5, AstraZeneca, 5, Biotest, 5, Bristol-Myers Squibb, 5, Hoffmann-La Roche, Inc., 5, Genentech and Biogen IDEC Inc., 5, Jannsen Inc,, 5, Lilly Pharmaceuticals, 5, Merck Pharmaceuticals, 5, Nycomed, 5, Pfizer Inc, 5, UCB, 5, Abbott Laboratories, 8, AstraZeneca, 8, Bristol-Myers Squibb, 8, Hoffmann-La Roche, Inc., 8, Janssen Inc, 8, Pfizer Inc, 8, UCB, 8, Amgen, 8; **A. Spindler**, AstraZeneca, 9; **C. L. Benhamou**, Servier, 2, Amgen, 2, Rotta Pharmaceuticals Inc., 5, Novartis Pharmaceutical Corporation, 6, Roche Pharmaceuticals, 6; **A. Kavanaugh**, None; **E. Fudman**, AstraZeneca, 2, Astellas, 2, Bristol-Myers Squibb, 2, Genentech and Biogen IDEC Inc., 2, Pfizer Inc, 2, Sanofi-Aventis Pharmaceutical, 2; **K. Lampl**, AstraZeneca, 1, AstraZeneca, 3; **C. O'Brien**, AstraZeneca, 1, AstraZeneca, 3; **E. Duffield**, AstraZeneca, 3; **J. Poiley**, AstraZeneca, 2; **M. Weinblatt**, Rigel Pharma, 5, AstraZeneca, 5.

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Pharmacodynamic Effect Of Intravenous Golimumab By Messenger Ribonucleic Acid Expression Profiling. Yauheniya Cherkas, Carrie Brodmerkel, Mark Curran and Sarah Lamberth. Janssen Research & Development, LLC., Spring House, PA.

Background/Purpose: RA is a chronic systemic autoimmune disease resulting in joint inflammation and damage. Despite the current therapies available, only a small percentage of RA pts achieve remission. To improve care and treatment for RA pts, a deeper understanding of the mechanisms that drive disease and response to therapy are desirable. The molecular understanding of disease and treatment mechanisms of RA continues to evolve. To explore the utility of peripheral blood expression profiling for informing disease and treatment mechanisms, samples derived from the GO-FURTHER golimumab study in RA were evaluated. This study examines if whole blood (WB) gene expression profiles can be utilized to: identify a baseline disease profile (DP) for pts with moderate-to-severe RA elucidate the pharmacodynamic (PD) and response profile of golimumab IV treatment, and delineate the peripheral biological processes dysregulated in RA and modulated by golimumab IV.

Methods: mRNA from 487 WB samples collected in a Phase III study of golimumab IV (GO-FURTHER) in pts with active RA despite methotrexate (MTX) therapy was isolated and profiled using the Affymetrix HT HG-U133+ PM Array (Santa Clara, CA). Samples were collected at Wks 0 and 14 from pts treated with IV placebo + MTX (PBO; n= 161) or IV golimumab 2mg/kg + MTX (GLM; n=326) administered at Wks 0, 4, and every 8 wks thereafter. Non-RA WB samples (healthy controls; n=22) were obtained from Bioreclamation (Hicksville, NY).

Results: A disease profile comparing baseline gene expression profiles of RA to healthy controls yielded about 2000 differentially expressed genes (DEGs), while comparison of post-treatment to pretreatment samples generated a PD profile of about 3000 DEGs. Over 70% of genes in the DP are downregulated as well as humoral immune response and B and T cell receptor signaling pathways. Pathways upregulated in the DP include innate immune response, Toll-like receptor (TLR), and cell activation. Treatment with golimumab modulates more than 30% of the disease profile, while just over 25% of PD effect is shared with the DP. The above mentioned pathways are common between the DP and PD profiles and are reversed, in part, through changes in peripheral cell populations post-golimumab treatment. A significant decrease in neutrophils and increase in lymphocytes was observed in the periphery at Wk 12 and in gene expression profiles representative of these cells at Wk 14 post-treatment. In addition, response to golimumab at Wk 14 was associated with more gene changes in B and T cell receptor signaling pathways in comparison to nonresponders.

Conclusion: Gene expression from the periphery of RA pts can be used for identification of a DP as well as the PD effect and response profile to golimumab IV. The most significant biological pathways and functions associated with the DP or PD effect are related to immune response and function. At baseline, RA pts had an increased innate and decreased adaptive immune profile in the periphery and majority of these processes were reversed by treatment with golimumab IV. Defining the pathways dysregulated in RA and modified by effective treatment as well as those that remain dysregulated aids in defining novel areas for potential therapeutic intervention.

Disclosure: Y. Cherkas, Janssen Research & Development, LLC., 3; **C. Brodmerkel**, Janssen Research & Development, LLC., 3; **M. Curran**, Janssen Research & Development, LLC., 3; **S. Lamberth**, Janssen Research & Development, LLC., 3.

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High Levels Of Natural Killer CELLS ARE Associated With Response To Tocilizumab In Patients With Severe Rheumatoid Arthritis. Claire I. Daien[1], Sarah Gailhac[2], Rachel Audo[3], Thibault Mura[4], Michael Hahne[3], Bernard Combe[1] and Jacques Morel[1]. [1]Lapeyronie Hospital, Montpellier, France, [2]CNRS, Montpellier, France, [3]IGMM, CNRS UMR5535, Montpellier, Montpellier, France, [4]Hopital Gui De Chauliac, Montpellier, France.

Background/Purpose: Inhibition of interleukin 6 (IL-6) receptor with tocilizumab (TCZ) is effective for rheumatoid arthritis (RA). However, the effect of TCZ on lymphocytes remains poorly studied. We analyzed the effect of TCZ on proportion of B, T, natural killer (NK) and NK T (NKT) cells in patients with RA and healthy controls and cell type predictors of disease activity response (disease activity in 28 joints [DAS28]). Secondary objectives were association of NK cells and disease activity in patients with RA, effect of TCZ on NK-cell cytotoxicity and effect of anti-tumor necrosis factor (anti-TNF) therapy on NK-cells.

Methods: Included patients had to meet 2010 ACR/EULAR criteria, be receiving steroids with stable doses $<$ 10 mg per day and not have received rituximab in the previous year. Healthy subjects were recruited. Patients with TCZ introduced at baseline were followed at 3 and 6 months. Different B and T cell subsets, NK and NKT were assessed by flow cytometer as well as perforin A and granzyme B to estimate NK-cell cytotoxicity.

Results: We included 25 controls and 92 RA patients, including 20 requiring TCZ treatment and 15 requiring anti-TNF drugs. At baseline, patients with RA had significantly lower proportion of regulatory T cells (Tregs), as defined by $CD4^+CD25^{hi}CD127^{lo}$, than controls ($p=0.003$), and the proportion of $CD56^{dim}CD16^+CD3^-$ NK cells was inversely correlated with DAS28. The proportion of Tregs was increased at 3 months but not 6 months. Baseline proportion of $CD3^-CD56^+$ NK cells was inversely correlated with change in DAS28 score at 3 months, and the proportion was three-fold greater for patients with DAS28 $<$ 2.6 (disease remission) at 3 months than other patients. Change in proportion of $CD56^{bri}CD16^-$ NK cells was linearly correlated with change in DAS28 at 3 months. The baseline proportion of NK cells did not predict change in disease activity at 3 months with anti-TNF therapy. Perforin content in NK cells was increased with TCZ treatment.

Conclusion: This study supports NK cell involvement in RA. TCZ transiently increased the proportion of Tregs and increased perforin content in NK cells. NK cells at baseline could be a predictive factor of TCZ response if results are confirmed.

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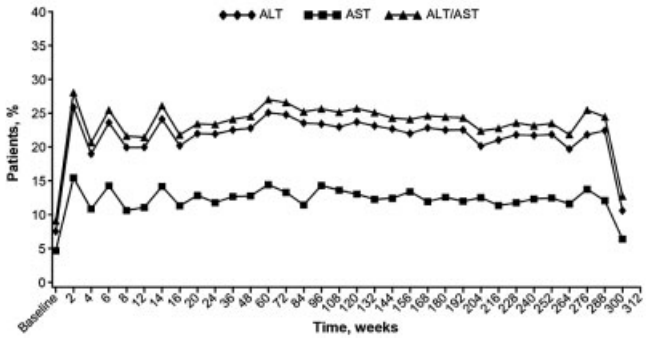
Transaminase Levels and Hepatic Events Observed During Tocilizumab Treatment: Pooled Analysis Of Long-Term Clinical Trial Safety Data In Patients With Rheumatoid Arthritis. Mark C. Genovese[1], Joel M. Kremer[2], Ronald F. van Vollenhoven[3], Rieke Alten[4], Juan José Scali[5], Ariella Kelman[6], Lucy Rowell[7] and Laura Pitts[7]. [1]Stanford University Medical Center, Palo Alto, CA, [2]Center for Rheumatology, Albany Medical College, Albany, NY, [3]Karolinska Institute, Stockholm, Sweden, [4]University of Berlin, Berlin, Germany, [5]Durand University Hospital, Buenos Aires, Argentina, [6]Genentech, South San Francisco, CA, [7]Roche, Welwyn Garden City, United Kingdom.

Background/Purpose: The interleukin-6 receptor inhibitor tocilizumab (TCZ) has demonstrated efficacy in improving signs/symptoms, reducing joint damage, and improving function and is well tolerated in patients (pts) with rheumatoid arthritis (RA). Elevated transaminase levels can occur, and, therefore, routine monitoring is recommended with TCZ treatment. This analysis examined the effect of TCZ on transaminase levels and evaluated hepatic serious adverse events (SAEs) observed in the clinical trial program.

Methods: Analyses were performed in all pts who received ≥1 dose of TCZ in 1 of 5 phase 3 placebo-controlled studies (OPTION, TOWARD, RADIATE, AMBITION, LITHE), a clinical pharmacology study, a phase 4 TCZ monotherapy study (ADACTA), or long-term extension studies. Pts with ALT/AST >1.5×ULN were excluded from the studies. Per protocol and consistent with recommendations in the USPI, DMARDs and TCZ dose were modified for ALT/AST elevations. Data were pooled and analyzed from initial TCZ exposure to May 2, 2012.

Results: In total, 4171 pts were included. Mean (median [range]) duration was 3.9 y (5.1 [0.0–6.8]); observation time was 16204.8 pt-y (PY). At baseline, 92.2%/95.2% of pts had ALT/AST levels within the normal range. Most pts were taking concomitant methotrexate at baseline or during the studies. Mean and median ALT/AST levels increased within the normal range after initiation of TCZ and remained stable at the higher level thereafter. ALT/AST levels increased from normal at baseline to >ULN at least once in 70.6% (2712/3839) and 59.4% (2357/3965) of pts, respectively, during the study period. In most of these pts, the highest postbaseline value was >1-≤3×ULN; elevations to >5×ULN occurred in 2.9% and 0.9% of pts, respectively. There was no trend for increased risk of transaminase level elevations over time (Figure). Analysis of ALT/AST increases >3×ULN over time showed that the elevations were single occurrences in most pts; at most, 0.2% of pts sustained elevations in ALT/AST during any 12-month study period. Elevated transaminase levels led to withdrawal in 2.5% of pts (105/4171); most withdrawals occurred during the first 12 months of treatment. There were 7 cases of hepatic SAEs (overall rate: 0.04/100 PY [95% CI: 0.02, 0.09]). Events were variable in nature with no pattern over time, and the rate was consistent with the background rate of hepatic SAEs estimated for RA pts treated with other biologic and conventional DMARDs.[1, 2]

Figure. Rate of ALT and AST Elevations >ULN to 3×ULN (All Exposure Population).



Conclusion: Mean transaminase levels increased early in TCZ treatment, and the proportion of pts with elevations did not increase with continued TCZ exposure. In most pts, the elevations were single occurrences ≤3×ULN. To date, there is no evidence of increased rate of hepatic SAEs in pts treated with TCZ.

References:

1. Suissa S et al. *Am J Med.* 2004;117:87; 2. US MarketScan healthcare claims database analysis (Genentech, data on file; manuscript in prep).

Disclosure: M. C. Genovese, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5; **J. M. Kremer**, Pfizer, Lilly, 2, Pfizer, Lilly, Vertex, 5; **R. F. van Vollenhoven**, Abbott Immunology Pharmaceuticals, 2, BMS, 2, GSK, 2, MSD, 2, Pfizer Inc, 2, Roche Pharmaceuticals, 2, UCB, 2, Abbott Immunology Pharmaceuticals, 5, BMS, 5, GSK, 5, MSD, 5, Pfizer Inc, 5, Roche Pharmaceuticals, 5, UCB, 5; **R. Alten**, Horizon Pharma, Inc, 5; **J. J. Scali**, GSK, BMS, GADOR, Janssen, UCB-Montpellier, Roche, 8; **A. Kelman**, Genentech and Biogen IDEC Inc., 3; **L. Rowell**, Roche Pharmaceuticals, 3; **L. Pitts**, Roche Pharmaceuticals, 3.

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Comparative Efficacy Of Novel Disease-Modifying Antirheumatic Drugs As Monotherapy and In Combination With Methotrexate In Rheumatoid Arthritis Patients With An Inadequate Response To Traditional Disease-Modifying Antirheumatic Drugs: A Network Meta-Analysis. Felicity Buckley[1], Axel Finckh[2], Thomas W.J. Huizinga[3], Fred Dejonckheere[4] and Jeroen P. Jansen[1]. [1]MAPI Consultancy, Boston, MA, [2]University of Geneva, Geneva, Switzerland, [3]Leiden University Medical Center, Leiden, Netherlands, [4]F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Background/Purpose: To compare ACR responses of novel DMARDs as monotherapy or in combination with methotrexate (MTX), including subcutaneous (SC) abatacept and SC tocilizumab (TCZ), in RA patients with an inadequate response to conventional DMARDs (DMARD-IR).

Methods: A systematic literature review identified randomized clinical trials (RCTs) that evaluated abatacept (intravenous [IV] and SC), anakinra, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, tofacitinib, and TCZ (IV and SC). Thirty RCTs were identified. Reported treatment effects in terms of ACR responses at 24 weeks were synthesized by means of Bayesian network meta-analyses to allow comparisons of the different treatments as monotherapy and combination therapy. Based on previous reviews[1,2] an assumption was made that the effects of anti-tumor necrosis factor (aTNF) therapy were exchangeable. Given this, and the limited data identified for these therapies in monotherapy, aTNF data were pooled.

Results: aTNFs + MTX, tofacitinib + MTX, abatacept IV/SC + MTX, and TCZ IV/SC + MTX demonstrated comparable ACR responses while anakinra + MTX was less efficacious. Among biologic monotherapies, greater ACR20/50/70 responses were observed with TCZ IV than with aTNFs and tofacitinib (Figure 1). When comparing biologics + MTX with biologic monotherapies, ACR20, ACR50, and ACR70 responses with TCZ + MTX were similar to TCZ as monotherapy (OR=1.04, 95% CI, 0.39–2.80; OR=1.28, 95% CI, 0.46–3.51; OR=0.97, 95% CI, 0.38–2.49, respectively), whereas with aTNF + MTX greater ACR20/50/70 responses were observed than with aTNF monotherapy (OR=2.22; 95% CI, 0.46–10.83, probability better=84%; OR=3.12, 95% CI, 0.60–16.32, probability better=92%; OR=1.39, 95% CI, 0.26–6.78, probability better=68%, respectively). For tofacitinib, sensitivity analyses showed conflicting results for the indirect comparison of tofacitinib + MTX versus tofacitinib.

Conclusion: Results of this meta-analysis suggest that most available novel DMARDs, in combination with MTX, have similar levels of efficacy in DMARD-IR patients. As monotherapy, TCZ is likely to have a greater response than aTNFs and tofacitinib. TCZ monotherapy also shows comparable efficacy compared to TCZ + MTX, whereas aTNFs in combination with MTX showed greater ACR responses compared with aTNF monotherapy at 24 weeks.

References:

1. Nixon R *Rheumatology.* 2007;46:1140; 2. Salliot *Ann Rheum Dis*. 2011;70: 266.

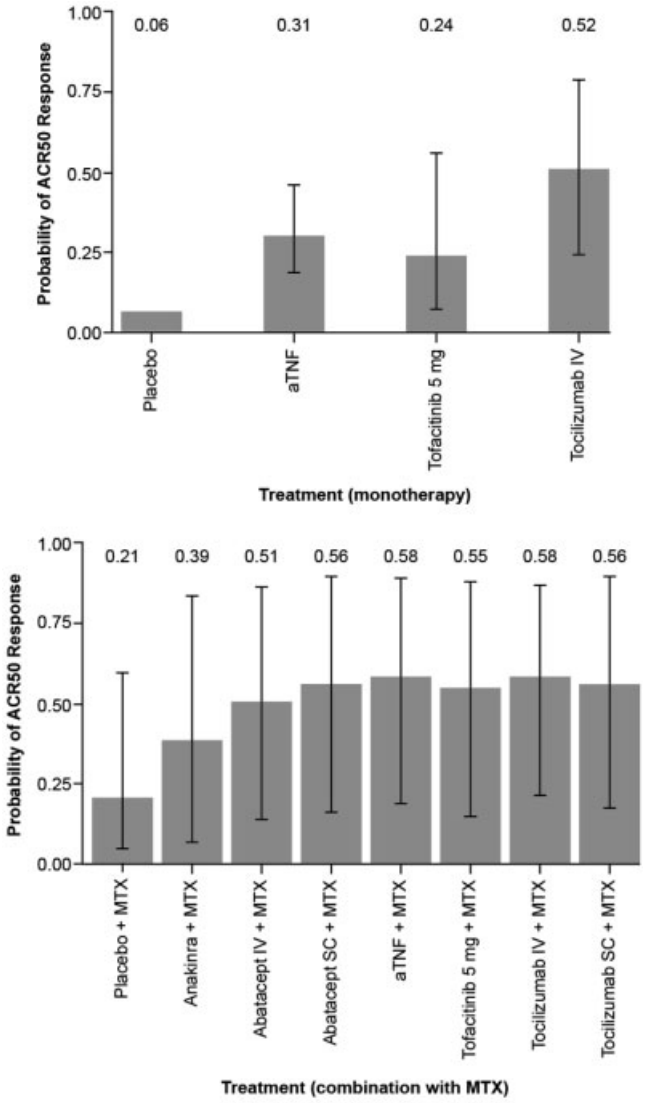

Figure. Expected ACR50 response at 24 weeks with monotherapy (**top**) or combination therapy (**bottom**) (random effects network meta-analysis)

Disclosure: F. Buckley, Roche Pharmaceuticals, 5; **A. Finckh**, BMS, Pfizer;, 2, BMS, Abbott, Roche, Pfizer, 5, Roche Pharmaceuticals, 8; **T. W. J. Huizinga**, Abbott, Axis Shield Diagnostics, Biotest AG, BMS, Crescendo Bioscience, Roche, Novartis, Schering-Plough, UCB, Wyeth, Pfizer, 5; **F. Dejonckheere**, F. Hoffmann-La Roche, 3; **J. P. Jansen**, Roche Pharmaceuticals, 5.

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Higher TNFi Dosing Is Not Associated With More Serious Infectious Events (SIE), Elevated AST/ALT Or WBC. Daniel Furst[1], Mei Liu[2], Jeffrey D. Greenberg[3] and Joel M. Kremer[4]. [1]David Geffen School of Medicine, UCLA, Los Angeles, CA, [2]CORRONA, Inc, Southborough, MA, [3]NYU Hospital for Joint Diseases, New York, NY, [4]Albany Medical College and The Center for Rheumatology, Albany, NY.

Background/Purpose: There is a perception that higher TNFi doses result in increased adverse events (AEs) in selected AEs such as SIE, increased ALT/AST or WBC<1.5. We examined this perception in the USA CORRONA database.

Hypothesis: Higher doses of TNFi are associated with an increased incidence of SIE, increased ALT/AST and/or WBC<1.5.

Methods: We examined the US CORRONA registry between Oct 1, 2001 and Feb 15, 2013. This registry is an independent, prospective, observational cohort of rheumatic disease patients (in this case rheumatoid arthritis (RA) patients (pts)) among 159 sites in the United States.

Inclusions Patients with a diagnosis of RA who started their first TNFi without prior biological use, with TNFi doses recorded and followed for ≥ 3 months.

High-dose TNFi was defined as: ≥ 5 mg/kg infliximab q8wks, > 50 mg etanercept wkly, 40 mg adalimumab wkly, >400 mg certolizumab q4wk or > 50 mg golim. q4wk for at least 3 months.

Adverse Events (AEs) were defined as: SIE (infection requiring hospitalization or IV antibiotic), AST+/−ALT > upper limit of normal or WBC<1.5.

Analysis Descriptive statistics were done. A Cox proportional hazards model assessed the association of TNFi AEs of interest; if P≤0.2 in the univariate model, the variables were included in the multivariable model. For WBC, hazard ratio (HR) from the univariate Cox regression was used because there were too few instances for multivariate analysis.

Results: Of 4195 TNFi-starter RA patients naïve to other biologics, 2688 met inclusion criteria and constituted the test set. There were 388 high dose (14.4%), versus 2300 low dose (85.6%) pts.

The High dose group was older and generally had more active, severe disease (High versus Low P value): Age: 60 vs. 56 yrs; CDAI: 17.2 versus 14.5; erosion: 41.1 versus 18.8%; RF/CCP pos.: 80.1 versus 74.6%-all P <0.05–0.001. Shorter F/U for the High dose group (35.8±27.9 vs. 39.7±30.0 mos; P= 0.02) was not clinically significant (10%). The incidence rates and dose effects for SIEs, ALT/AST and WBC<1.5 are shown in table 1.

		SIE	ALT/AST	WBC < 1.5
% event (High + Low)		3.3	26.7	0.6
Incidence/100 pt-yrs	High*	0.7	9.8	0.20
	Low**	1.1	11.8	0.23
Person yrs f/u × 100	High	11.6	8.6	10.0
	Low	76.1	53.8	69.5
Dose comparison HR (95% CI)		0.52 (0.24, 1.12)	0.77 (0.59, 1.02)	0.91 (0.21, 3.95)

*High dose n= 388
**Low dose n= 2300

Discussion: In this real-life cohort of RA pts, higher dose users had more active, severe disease. Since the high-dose group had lower BMI (P< 0.05), the High dose users were especially likely to be using higher milligrams/m2 doses, supporting the credibility of the results. As in all registries, however, some selection bias may have contributed to the lack of differences found in High vs. Low dose TNFi users.

Conclusion: High dose TNFi users with RA did not seem to be subject to more SIE, AST/ALT elevations or WBC<1.5 than Low dose users, within the limits of TNFi doses used within usual clinical practice in this real-life cohort of patients in the USA.

Disclosure: D. Furst, AbbVie, 2, Actelion Pharmaceuticals US, 2, Amgen, 2, BMS, 2, Gilead, 2, GSK, 2, NIH, 2, Novartis Pharmaceutical Corporation, 2, Pfizer Inc, 2, Roche/Genentech, 2, UCB, 2, Janssen Pharmaceutica Product, L.P., 5; **M. Liu**, CORRONA, 3; **J. D. Greenberg**, Corrona Inc., 1, Corrona, Inc, 5, AstraZeneca, 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5; **J. M. Kremer**, CORRONA, 1, CORRONA, 3.

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Reduced Response To Biologic Treatments in Rheumatoid Arthritis Patients Affected By Arterial Hypertension. Marco Antivalle[1], Michel Chevallard[2], Michele Battellino[2], Alberto Batticciotto[1], Maria Chiara Ditto[2], Alessandra Mutti[2], Federica Rigamonti[2], Valentina Varisco[2], Sara Bongiovanni[2], Fabiola Atzeni[3] and Piercarlo Sarzi-Puttini[1]. [1]Rheumatology Unit, L. Sacco University Hospital, Milan, Italy, [2]Rheumatology Unit, L. Sacco University Hospital, Milano, Italy, [3]Rheumatology Unit, L. Sacco University Hospital, MiIano, Italy.

Background/Purpose: Several reports show that the presence of comorbidities negatively influences both functional status (1) and quality of life (2) in rheumatoid arthritis (RA). No published study, however, has addressed the impact of comorbidities on the response to biologic treatments. Aim of the present study was to assess whether the presence of arterial hypertension influences the clinical response to biologics in RA.

Methods: The study population consisted of 526 patients affected by RA (416 F 110 M, mean age 53.8±14.27 yrs) treated with first-line biologic treatments. 349 (66.3%) patients were normotensive (NT), and 177 (33.7%) hypertensive (AH). Disease activity was evaluated by DAS28. The 6-month response to biologic treatments was evaluated by EULAR response criteria, and by the percentage of patients in low disease activity (DAS28 <3.2) and in remission (DAS28<2.6). The differences in the percentage of responders between the 2 groups were analyzed by generalized linear models, correcting data for confounder variables (age, sex, baseline disease activity, disease duration), and for the presence of other comorbidities (diabetes, dyslipidemia, ischemic heart disease, osteoporosis, fibromyalgia, thyroid disease and COPD). In the following test, the observed percentages are reported, while statistical significance (p values) refers to corrected values. All statistical analyses were performed with the IBM SPSS 20.0 software.

Results: The vast majority of patients were treated with anti-TNF biologics in both groups (AH 94.5%, NT 90.6%, p=0.177). The percentage of females (AH 82% NT F 78%, p=0.586) was not significantly different in the 2 groups, while mean age was significantly higher in AH patients (59.85±12.53 vs 51.29±14.29 yrs, p=0.000), and disease duration in NT patients (4.4±6.4 vs 2.5±5.1 yrs, p=0.001). Among the other comorbidities, only the prevalence of dyslipidemia, osteoporosis, and COPD was significantly higher in AH group (p<0.05). Biologic treatment was stopped or switched in 192/526 (36.5%) patients before the 6th month, without a significant difference between the 2 groups (AH: 75/177 (42.4%); NT 117/349 (33.5%), p=0.361). Baseline DAS28 was higher in AH patients (5.73±1.11 vs 5.18±1.34, p=0.000). EULAR response at 6 months (Fig. 1), and the percentage of patients in low disease activity (14/102 (13.7)% vs 71/232 (30.6%), p=0.000) and in remission (8/102 (7.8%) vs 48/232 (20.7%), p=0.001) (Fig. 2) were significantly lower in AH patients.

Fig 1. EULAR response after 6 months of treatment with biologics in normotensive and hypertensive RA patients

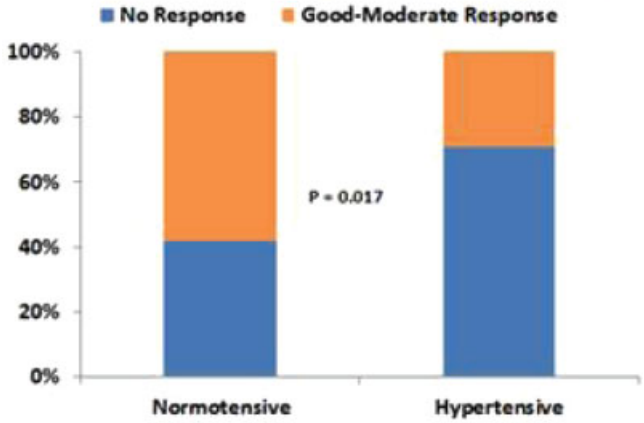
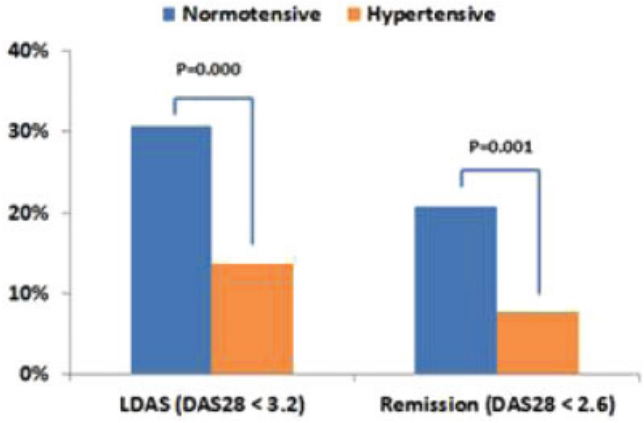


Fig 2. Percentage of patients in low disease activity and remission after 6 months of treatment with biologics



Conclusion: Concomitant arterial hypertension influences negatively the response to biologic treatments in rheumatoid arthritis. The presence of comorbidities should be taken into account in the evaluation of the clinical response to biologic treatments.

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1) van den Hoek J, et al. Arthritis Care Res (Hoboken). 2013 Jan 17. [Epub ahead of print]

2) Radner H, et al. Rheumatology 2011;50:381–388.

Disclosure: M. Antivalle, None; **M. Chevallard**, None; **M. Battellino**, None; **A. Batticciotto**, None; **M. C. Ditto**, None; **A. Mutti**, None; **F. Rigamonti**, None; **V. Varisco**, None; **S. Bongiovanni**, None; **F. Atzeni**, None; **P. Sarzi-Puttini**, None.

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An Indirect Comparisons Analysis Between Biologic Disease Modifiers in The Treatment Of Rheumatoid Arthritis To Evaluate For Efficacy and Safety. Aaron C. Garza Romero, Elie Donath, Hernan Osorno and Suresh Kumar. University of Miami Miller School of Medicine Palm Beach Regional Campus, Atlantis, FL.

Background/Purpose: There are primarily six groups of biologic disease modifiers (BDM) for treatment of rheumatoid arthritis (RA): tumor necrosis factor inhibitors (infliximab (IFX), etanercept (ETN), adalimumab (ADM), certolizumab pegol (CZP) and golimumab (GLM), B-Cell depleting anti CD20 antibodies (rituximab), selective coestimulator blocker (abatacept (ABT), interleukin 6 inhibitor (tocilizumab (TCZ), interleukin 1 receptor antagonist (anakinra) and Janus associated kinase inhibitor (tofacitinib). BMD are known to interfere in the immune system leading to concerns on their safety. In general, patient/physician preference is what mandates the choice of drug. This is partially due to lack of evidence comparing these drugs to one another (the majority of evidence is based on randomized controlled trials (RCT's) that are compared to methotrexate (MTX). The objective of this research is to perform a network meta-analysis among these drugs, using the MTX group as a common comparator, to determine their efficacy and safety.

Methods: Studies were extracted from a computerized literature search of MEDLINE and EMBASE of all relevant RCT's. 41 RCT's, including 12,487 patients, were identified. There were three outcomes of interest for efficacy: ACR20, ACR50 and ACR70 response. There were several outcomes of interest for safety, primarily serious infections requiring intravenous antibiotics or hospitalization: pneumonia, cellulitis, skin abscess, sepsis, septic arthritis, urinary tract infection, TB and opportunistic infections, sudden cardiac death and death. For each outcome, a fixed-effects meta-analysis was employed to compare each drug to MTX. A mixed-treatment comparisons analysis was then used to compare each of these drugs to one another indirectly. Calculation of the probability that each treatment is best was implemented using the Bayesian Markov chain Monte Carlo method.

Results: In terms of ACR20 response, patients taking IFX (10mg/kg) had a highly statistically significant likelihood of achieving response compared to ADM (RR 0.33, 95% CI 0.11 – 1.00) and a similar benefit was seen in patients taking CZP compared to ADM (RR 0.21, 95% CI 0.06 – 0.69). In terms of ACR50 response, patients taking CZP had a statistically significant increased likelihood of achieving response compared to ABT (RR 0.32, 95% CI 0.11 – 1.04). In terms of ACR70 response, patients taking IFX (10 mg/kg) had a statistically significant higher likelihood of response compared to ABT (RR 0.31, 95% CI 0.09 – 0.90), ADM (RR 0.30, 95% CI 0.09 – 0.82), ETN (RR 0.22, 95% CI 0.06 – 0.70) and GLM (RR 0.29, 95% CI 0.07 – 0.98) and a similar benefit was seen in patients taking TCZ compared to ABT (RR 0.30, 95% CI 0.10 – 0.99), ADM (RR 0.29, 95% CI 0.09 – 0.87) and ETN (RR 0.21, 95% CI 0.06 – 0.80). Patients taking IFX (3mg/kg) had a statistically significant decreased risk of death compared to ADM (RR 0.09, 95% CI 0.01 – 0.97. The degree of incoherence (measuring how closely the network fits together) was low for all outcomes.

Conclusion: This was the first attempt to include all BDM used in the treatment of RA in a network meta-analysis. Important results on safety and efficacy outcomes were discovered, future research is required to better elucidate these findings.

Disclosure: A. C. Garza Romero, None; **E. Donath**, None; **H. Osorno**, None; **S. Kumar**, None.

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The Efficacy and Safety Of Tocilizumab Subcutaneous Versus Tocilizumab Intravenous, In Combination With Traditional Dmards In Patients With RA At 49 Weeks (SUMMACTA). Gerd R. Burmester[1], Andrea Rubbert-Roth[2], Alain G. Cantagrel[3], Stephen Hall[4], Piotr Leszczynski[5], Daniel Feldman[6], Madura J. Rangaraj[7], Georgia Roane[8], Charles L. Ludivico[9], Eduardo F. Mysler[10], Chris Wells[11], Melanie Bennett[12] and Ivana Vranic[12]. [1]Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]Klinikum der Universität zu Köln, Köln, Germany, [3]Centre Hospitalier Universitaire de Toulouse, Toulouse, France, [4]Cabrini Medical Centre, Malvern, Australia, [5]J. Strus Poznan Municipal Hospital, Poznan University of Medical Sciences, Poznan, Poland, [6]Universidade Federal de São Paulo, Sao Paulo, Brazil, [7]Arthritis & Diabetes Clinic, Inc., Monroe, LA, [8]Rheumatology Associates of South Carolina, Charleston, SC, [9]East Penn Rheumatology Associates, PC, Bethleham, PA, [10]Organización Médica de Investigación, Buenos Aires, Argentina, [11]Roche, Welwyn Garden City, United Kingdom, [12]Roche Products Ltd., Welwyn Garden City, United Kingdom.

Background/Purpose: The efficacy and safety of subcutaneous tocilizumab (TCZ SC) were demonstrated in a 24 week (wk) randomized clinical trial (SUMMACTA). The cumulative safety, immunogenicity and continued efficacy in patients (pts) with RA who were rerandomized to receive either TCZ SC or TCZ IV in the open label (OL) period was evaluated at 49 wks.

Methods: SUMMACTA is a 2-year, Phase 3 trial, which is a randomized, active controlled, parallel group study that includes a 24 wk double-blind (DB) period, followed by a 72 wk OL phase. During the DB period, pts were

randomized 1:1 to receive TCZ SC weekly (qw) or TCZ IV every 4 wks (q4w) in combination with traditional DMARDs. After the DB period, pts who initially received TCZ SC 162 mg qw were re-randomized 11:1 to receive TCZ SC 162 mg qw or TCZ IV 8mg/kg q4w and pts who initially received TCZ IV 8mg/kg q4w were re-randomized 2:1 to receive TCZ IV 8mg/kg q4w or TCZ SC 162 mg qw.

Results: A total of 1262 pts were initially enrolled (TCZ SC, n = 631; TCZ IV, n = 631). At Wk 25, 521 pts continued TCZ SC and 372 pts continued TCZ IV; 48 pts switched from TCZ SC to TCZ IV and 186 pts switched from TCZ IV to TCZ SC. 61 (12%) pts in the TCZ SC group and 43 (12%) pts in the TCZ IV group withdrew from the study in the OL period; most commonly due to safety. The percentage of pts who continued TCZ SC and TCZ IV who achieved ACR20/50/70 responses, DAS28 remission and an improvement from baseline in HAQ-DI ≥ 0.3 were sustained up to 49 wks and were comparable between the groups (Table). Efficacy in pts after switching from TCZ IV to TCZ SC or TCZ SC to TCZ IV was comparable to pts who received continuous TCZ SC or TCZ IV. Rates of adverse events (AE), serious AEs, serious infections and malignancies for TCZ SC and TCZ IV were comparable between 24 and 49 wks (Table). The rate of injection site reactions (ISRs) decreased over time, but remained higher for pts receiving TCZ SC compared with pts receiving TCZ IV, as previously reported for wk 24. There were 3 deaths each in the TCZ SC and TCZ IV groups that occurred between wks 24 to 49. AntiTCZ antibody development remained low to wk 48 and no anaphylaxis occurred. The safety profile of pts who switched from TCZ IV to TCZ SC and vice versa were similar to pts who received continuous TCZ SC or TCZ IV.

	TCZ SC qw Week 24	TCZ SC qw Week 49	TCZ IV q4w Week 24	TCZ IV q4w Week 49	TCZ IV to SC Week 49	TCZ SC to IV Week 49
Efficacy (ITT population[a,b])						
N	**631**	**521**	**631**	**372**	**186**	**48**
ACR20, %	67.7	76.2	70.2	74.7	80.6	66.7
ACR50, %	45.5	53.4	46.6	55.4	55.9	45.8
ACR70, %	23.6	33.2	26.5	34.9	35.5	27.1
DAS28<2.6, %	37.9	43.6	36.3	44.3	48.3	37.8
Decrease from BL in HAQ-DI ≥ 0.3, %	66.3	69.5	66.8	69.8	70.1	63.6
Safety (safety population), Rate/100 PY (95% CI) [no. events]						
N	**631**	**631**	**631**	**631**	**186**	**48**
Patient years	289.8	817.4	288.4	663.8	185.7	46.8
	602.8	450.2	588.4	447.4	453.0	290.9
AEs	(574.9, 631.7)	(435.8, 465.0)	(560.8, 617.1)	(431.5, 463.8)	(422.9, 484.7)	(244.1, 344.1)
	[1747]	[3680]	[1697]	[2970]	[841]	[136]
	11.7	16.0	14.9	15.5	18.3	10.7
SAEs	(8.1, 16.4)	(13.4, 19.0)	(10.8, 20.1)	(12.7, 18.8)	(12.7, 25.6)	(3.5, 25.0)
	[34]	[131]	[43]	[103]	[34]	[5]
	120.1	112.06	124.8	109.2	102.3	89.8
Infections	(107.8, 133.4)	(104.9, 119.6)	(112.3, 138.4)	(101.4, 117.5)	(88.3, 118.0)	(64.8, 121.4)
	[348]	[916]	[360]	[725]	[190]	[42]
	3.1	4.3	3.5	3.8	7.0	2.1
Serious infections	(1.4, 5.9)	(3.0, 6.0)	(1.7, 6.4)	(2.5, 5.6)	(3.7, 12.0)	(0.1, 11.9)
	[9]	[35]	[10]	[25]	[13]	[1]
	0.4	0.4	0	0.3	1.1	0
Opportunistic infections[c]	(0.01, 1.9)	(0.08, 1.1)		(0.04, 1.1)	(0.1, 3.9)	
	[1]	[3]	[0]	[2]	[2]	[0]
	1.4	1.2	0.7	0.9	0	2.1
Malignancies[d]	(0.4, 3.5)	(0.6, 2.3)	(0.1, 2.5)	(0.3, 2.0)		(0.0, 11.9)
	[4]	[10]	[2]	[6]	[0]	[1]
	58.0	32.1	32.6	13.7	128.7	0
ISRs	(49.5, 67.4)	(28.3, 36.2)	(26.3, 39.9)	(11.0, 16.8)	(112.9, 146.1)	
	[168]	[262]	[94]	[91]	[239]	[0]
	0.7	0.6	1.0	0.3	0	0
Serious hypersensitivity events[e]	(0.1, 2.5)	(0.2, 1.4)	(0.2, 3.0)	(0.0, 1.1)		
	[2]	[5]	[3]	[2]	[0]	[0]
	0	0.4	0.4	0.6	1.1	0
Deaths		(0.01, 1.1)	(0.01, 1.9)	(0.2, 1.5)	(0.1, 3.9)	
	[0]	[3]	[1]	[4]	[2]	[0]

[a] The Week 24 ITT population contained all patients who received a dose of TCZ, and groups are presented according to the treatment randomized at baseline. The Week 49 ITT Population contained all patients who received a dose of TCZ post week 24 and groups contain patients who were re-randomized to the same treatment they were allocated at baseline.
[b] The per protocol population is the primary efficacy analysis for week 24.
[c] Excludes tuberculosis (TB). Up to Week 49 data cut, there was 1 case of latent TB in the TCZ SC arm and none in other treatment groups.
[d] All malignant and unspecified tumors were included.
[e] SAEs occuring during or within 24 hours of the injection/infusion, excluding ISRs, and that were not deemed to be unrelated to treatment by the investigator.

Conclusion: These data demonstrate that efficacy rates for pts continuing on TCZ SC over 49 wks are maintained and remain comparable to TCZ IV, as shown at Wk 24. The wk 49 cumulative safety profiles of pts on TCZ SC were consistent with Wk 24 data and to TCZ IV, with the exception of ISRs, which were lower in the TCZ IV group. The efficacy and safety profile of pts who switched from TCZ IV to TCZ SC and vice versa was similar to pts who remained on TCZ SC or TCZ IV. AntiTCZ antibody (including IgE isotype) development did not correlate with AEs or loss of efficacy with prolonged TCZ SC exposure. TCZ SC formulation could provide an additional, more convenient administration route for pts with RA.

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Higher Titer Of Anti-Citrullinated Protein Antibodies In Biologic-Naïve Rheumatoid Arthritis Patients Are Candidate Biomarkers To Predict Sensitivity Leading To Clinical Remission With Abatacept; Data From The Abroad Study.

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Background/Purpose: Biomarkers to predict each rheumatoid arthritis (RA) patient's sensitivity for biologic disease modifying anti-rheumatic diseases, especially for the only T cell modulator abatacept (ABT), is of high interest from the points of view of medication and medical economy. The purpose of this study is to determine the predicting factors of clinical remission by ABT in biologic-naïve RA patients.

Methods: Efficacy and safety of ABT are being investigated with Japanese biologic-naïve RA patients (N=155) in the ABROAD study (ABatacept Research Outcomes as a first-line biological Agent in the real worlD, an ongoing, prospective, multicenter cohort study in the west side of Japan, female = 83.2%, mean age at the ABT initiation = 61.3 years old, and disease duration = 8.1 years). In this study, simplified disease activity index (SDAI) remission (μ3.3) rate at 24 wks is defined as a goal of treatment and a merkmal of patient's sensitivity to ABT. Correlation between the SDAI remission rate and other clinical indexes before ABT treatment were analyzed by the univariate analysis method. During the analysis, anti-citrullinated protein antibodies (ACPA) titer values before treatment were classified into 4 groups; negative (less than the upper limit of normal [ULN], <4.5 U/mL), low-positive (less than 3 times of the ULN, 4.5–13.5 U/mL), high-positive (less than 22 times of the ULN, 13.6–99 U/mL), and very high-positive (equal or more than 22 times of the ULN, μ99 U/mL), and each group was studied independently.

Results: SDAI remission at 24 wks was achieved in 16% of the patients. Very high-positive ACPA (Odds ratio [OR] = 4.44, 95% confidence interval [CI] = 1.28–15.38, p = 0.019) were significantly associated with the SDAI remission. High-positive group was slightly inclinable but insignificant. Low-positive and negative groups had no correlations. As the reference, short disease duration (<1 year) (OR =2.79, 95% CI = 1.02–7.61, p = 0.045 vs. μ1 year) and moderate disease activity at baseline defined by DAS28-CRP (OR = 4.39, 95% CI = 1.55–12.5, p = 0.005 vs. high disease activity) were also significantly associated with the SDAI remission at 24 wks, and male gender (OR = 2.76, 95% CI = 0.91– 8.40, p = 0.072 vs. female) appeared to be linked. While age at ABT initiation, concomitant use of methotrexate, CRP level at baseline, and the 1987 ACR criteria fulfillment were not statistically associated with the SDAI remission. ACPA positivity association with a better response to ABT observed in this study sustained French report of the ORA registry (Gottenberg JE, *et al, ARD* 2012;71:1815).

Conclusion: Higher titer of ACPA in biologic-naïve RA patients, in whom T and B lymphocytes are possibly activated, could be a candidate biomarker to predict sensitivity for ABT.

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Biologic Monotherapy in French Rheumatoid Arthritis (RA) Patients From a Real-Life Clinical Practice Compared To Patients Treated with a Combination Therapy (Biologic + DMARD). Philippe Dieude[1], Chantal Deslandre[2], Emilie Desfleurs[3], Jeanne Antheaume[3] and Jean-Charles Balblanc[4]. [1]Rheumatology departement & INSERM U699, Paris Diderot university, APHP, Bichat hospital, Paris, France, [2]Cochin Hospital, Paris, France, [3]Roche SAS, Boulogne-Billancourt, France, [4]Centre Hospitalier Général de Belfort, Belfort, France.

Background/Purpose: Combination therapy (Biologic+non-biologic (nb)DMARDs) is the recommended therapeutic strategy in biologic-based RA treatment. However, biologics in montherapy represent around 30% of the biologic-treated patients (1–3).

Objectives: Evaluate in a real life setting the rate of patients treated with biologics as monotherapy (Mono) vs in combination with a nbDMARD (Combo) and compare the characteristics of these two populations.

Methods: 15-week prospective survey among 121 French representative rheumatologists (region and activity) treating RA patients with biologics in Mono or in Combo. Each physician completed a short record-sheet for biologic-treated RA patients seen in Q4 2012 (CENSUS). A more detailed record sheet was filled-in for the 5 next Mono patients and the 5 next Combo patients (FOCUS). Reported data were patients' and disease characteristics, current and previous treatment and therapeutic strategy.

Results: 1949 patients were included in the CENSUS. Patients characteristics were as followed: mean age 54,2 years, 72% female, mean disease duration 12,5 years, 81% ACPA positive and 68% erosive RA. Regarding disease activity, 40% were in DAS28 remission (<2,6) and 36% presented a low disease activity (DAS<3,2).The survey showed that 34% (n=662) of these patients were on biologic Mono. Patients treated by an office-based rheumatologist (n=404) were more often on a biologic in Mono (43% vs 32%, $p<0.01$) than patients treated at hospital. No differences in terms of patients characteristics were observed between Mono and Combo patients except for a negative ACPA serology (22% Mono patients vs 14% Combo, $p<0.01$) and corticosteroids which were more frequently used in Mono patients (64% vs 58%, $p=0.02$). The main biologics prescribed in Combo were Etanercept (ETN, 35%) and Adalimumab (ADA, 24%) and in Mono ETN (34%), ADA (23%) and Tocilizumab (TCZ, 19%). Compared to the other biologics, TCZ appeared to be more frequently used in Mono than in Combo with 54% of TCZ-patients treated in Mono vs 33% for both ETN- and ADA-patients. The survey also showed that among patients treated with a biologic without Mono label, approximately 1/3 received it in Mono. The majority (86%) of Combo patients were on MTX at a median dosage of 15mg/week. The FOCUS included 445 patients on Combo and 369 patients on Mono, who were representative of the CENSUS patients (no difference observed between both parts). For patients treated currently with a biologic in Mono, main reasons for stopping DMARDs were: intolerance 43%, lack of efficacy 31%, remission 18%, and patients' refusal 12%.

Conclusion: This survey showed that in a French real life clinical practice, 34% of RA patients treated with a biologic received it in Mono. This result is concordant with French and European registries (1–3) data. Surprisingly, no relevant difference was observed in terms of characteristics between patients treated in Mono and patients treated in Combo, except for ACPA status.

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Disclosure: P. Dieude, Roche, Pfizer, BMS, 2, Roche, Pfizer, BMS, 5; **C. Deslandre**, Pfizer, Roche, 5; **E. Desfleurs**, Roche SAS, 3; **J. Antheaume**, Roche SAS, 3; **J. C. Balblanc**, Roche, 5, Cryonic, 5, Pfizer, 9.

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Adherence To Conventional Disease Modifying Anti-Rheumatic Drugs (cDMARDs) In Rheumatoid Arthritis (RA) Patients Treated In Association With a Biologic: A French Cross-Sectional Survey. Jean-Charles Balblanc[1], Philippe Dieude[2], Emilie Desfleurs[3], Jeanne Antheaume[3] and Chantal Deslandre[4]. [1]Centre Hospitalier Général de Belfort, Belfort, France, [2]Rheumatology departement & INSERM U699, Paris Diderot university, APHP, Bichat hospital, Paris, France, [3]Roche SAS, Boulogne-Billancourt, France, [4]Cochin Hospital, Paris, France.

Background/Purpose: A recent meta-analysis of aTNF and abatacept clinical trials established in those drugs that the efficacy of combination therapy with biologic is superior to methotrexate for remission (1). Therefore, non-adherence to cDMARDs prescribed in combination with a biologic may reduce the benefit obtained with these agents.

Objectives: To evaluate the adherence to cDMARDs and biologics in RA patients from both a rheumatologist's and patient's perspective.

Methods: A panel of French representative rheumatologists (rheums) were questioned on their perception of their patient's adherence to cDMARDs and were asked to collect data (age, gender, disease duration, disease activity, treatment characteristics) on their five next patients treated with biologic in combination with cDMARDs and in monotherapy and seen between Nov. 12, 2012 –Feb. 21, 2013. Each included RA patient was invited to complete a self-administered questionnaire (SAQ) on treatment adherence. Adherence to cDMARDs and BT was assessed by the Morisky Medication Adherence Scale (MMAS-4)(2).

Results: This survey included 121 physicians, who collected data on 814 biologic-treated RA patients of whom 445 were treated in combination with cDMARDs. SAQ was returned by 82% (n=365) of these 445 patients. Regarding non-adherence to cDMARDS, 21% of rheums estimated this situation as frequent. In concordance with that, rheums considered that, among their RA patient pool, the mean proportion of patients non-adherent to cDMARDs was 17%. In contrast, the MMAS-4 showed that 35% of patients presented a medium/low adherence (2) to cDMARD. No differences in terms of age, gender, disease duration and disease activity were observed between high adherent and medium/low adherent patients. Patients highly adherent to cDMARD were significantly more often highly adherent to their biologic (90% vs 61%) compared to medium/ low adherent patients. Additionally, the main reasons for cDMARD dose reduction or dose spacing from a patient's perspective were adverse events (27%), on physician's advice (24%), forgotten (24%), convenience (23%) and lassitude (17%). Reasons given by rheums were intolerance (72%), lassitude (48%) and disease remission (36%). Over 90% of interviewed rheums evaluated their patients' adherence, mainly by questioning the patient; 61% did it systematically and 31% frequently. While 23% of patients declared informing their treating rheums of their lack of adherence to cDMARDs, rheums declared being informed only by 17% of their patients.

Conclusion: Adherence to cDMARD in RA patients treated in combination with a biologic should be taken into consideration in patient management as this survey showed that it concerns around 35% of these patients, which is a more frequent situation than expected by their treating rheums. Tools to evaluate patients' adherence should be developed to help physicians to detect this situation.

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Disclosure: J. C. Balblanc, Roche, 5, Cryonic, 5, Pfizer, 9; **P. Dieude**, Roche, Pfizer, BMS, 2, Roche, Pfizer, BMS, 5; **E. Desfleurs**, Roche SAS, 3; **J. Antheaume**, Roche SAS, 3; **C. Deslandre**, Pfizer, Roche, 5.

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The Differential Role Of T Helper Cells In The Pathogenesis and Responsiveness To Abatacept Therapy In Rheumatoid Arthritis. Shunsuke Fukuyo[1], Shingo Nakayamada[1], Kunihiro Yamaoka[1], Satoshi Kubo[1], Shigeru Iwata[2], Kazuyoshi Saito[1] and Yoshiya Tanaka[1]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]University of Occupational and Environmental Health, Kitakyushu, Japan, Kitakyushu, Japan.

Background/Purpose: Abatacept (ABT) works through a different mechanism of action from TNF inhibitors in the treatment of rheumatoid arthritis (RA). ABT decreases T cell responses by limiting CD28 mediated signaling that is required for T cell activation and differentiation. However,

little is known about T cell populations targeted by ABT. We investigated the relevance of the phenotype of $CD4^+$ helper T cells to disease activity in patients with RA and responsiveness to treatment, elucidating targets to ABT.

Methods: Heparinized whole blood samples were obtained from 19 patients with RA and 15 healthy donors (HD). All patients were treated with ABT at baseline, week 2 and every 4 weeks, and blood samples were taken at baseline and week 24 after treatment. The phenotype of T cells was determined by flow cytometry and the results were correlated with the clinical disease activity with simplified disease activity index (SDAI), disease activity score based on 28 joints and Erythrocyte Sedimentation Rate (DAS28 (ESR)), anti-cyclic citrullinated peptide (CCP) antibody and rheumatoid factor (RF).

Results: The proportion of $CD28^-$ cells among $CD4^+$ cells increased in RA, compared to HD ($p=0.04$). Baseline levels of CD28 on $CD4^+$ cells have positively correlated with DAS28 ($p=0.00$) and SDAI ($p=0.03$) at baseline as well as‡™DAS28 ($p=0.0115$) and ‡™SDAI ($p=0.0574$) in response to ABT for 24 weeks. By contrast, baseline proportion of $CD4^+CD28^-$ cells was higher in patients who failed to achieve a remission at 24 week after treatment. The proportion of $CD4^+$ $CXCR5^+$ Tfh ($p=0.00$) and $CD4^+CXCR3^+$ Th1 ($p=0.08$) cells increased in RA compared to HD. Those cells also expressed active surface markers such as CD38. $CD4^+CD28^+$ cells consisted of activated Tfh and Th1 in naïve and central memory phase: the proportion of Tfh cells increased in anti-CCP antibody-positive patients ($p=0.05$), whereas that of Th1 cells tended to be correlated with disease activity ($p=0.07$). $CD4^+CD28^-$ cells consisted of Th1 in effector memory phase, showing no correlation to disease activity and antibody production. Finally, the proportion of Tfh cells was significantly decreased after ABT treatment ($p=0.03$), but those of Th1 cells was not changed ($p=0.26$).

Conclusion: These results imply that $CD4^+CD28^+$ cells, which consist of Tfh cells in central memory phase associated with production of anti-CCP, are target of ABT, whereas $CD4^+CD28^-$ cells, which consist of terminally differentiated Th1 cells, might be associated with refractoriness to ABT therapy. The evaluation of T cell phenotype may serve to predict to the response to ABT therapy in advance in patients with RA.

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Anti-TNF Therapy Induces Positive Changes In The Lipoprotein Profile Of RA Patientes. Results Of a Prospective Study. Jaime Calvo-Alén[1], Carmela Baamonde[1], Ignacio Villa[1], Víctor Martínez-Taboada[2], Mario Agudo[3] and Juan Gómez-Gerique[2]. [1]Hospital Universitario Sierrallana, Torrelavega, Spain, [2]Hospital Universitario Marqués de Valdecilla, Santander, Spain, [3]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain.

Background/Purpose: Anti-TNF therapy induces elevations in total cholesterol levels although does not seem to modify the atherogenic index. Otherwise, it appears to have a cardiovascular protective effect. We have tried to study in depth the effect of this therapy in the lipidic metabolism through a comprehensive analysis of the lipid and lipoprotein induced modifications.

Methods: RA patients naive to any type of biologic therapy starting anti-TNF therapy, were evaluated at two points (first, just before the first dose of the anti-TNF agent and second, at six months of stable anti-TNF therapy) according to a pre-established protocol including the following assessments of lipidic metabolism: Lipoprotein, and apolipoprotein A1 (ApoA1) and B (ApoB) levels (total and lipoprotein specific), levels of paroxonase 1 (PON1), HDL, LDL, VLDL and total cholesterol, triglycerides and phospholipids levels, as well as number of molecules of these lipids (mc, mt and mf respectively) in each lipoprotein, total mass (M) and number of particles (np) of the afore mentioned lipoproteins and levels of PCSK9 receptor. Inflammatory markers (ESR, hsCRP, Pentraxina 3 and SAA) and disease activity by joints counts and DAS28 index were also performed. Standard statistical tests were used for comparing both assessments.

Results: Nineteen RA (mean age±SD: 60.7±13.2 years; disease duration±SD: 124.3±296.8 months; 68% women; 47% seropositive and mean±SD DAS28 at first evaluation: 5.5±1.2) patients were evaluated. As expected patients showed a decrease in disease activity (4.6±1.4; p=0.08)). Regarding to the lipidic determinations, although the total cholesterol increased (191 mg/dl ±25 vs 208 mg/dl ±24; p=0.07) without modifying the atherogenic index, anti-TNF induced several biochemical and structural lipoprotein changes with a final positive balance including the following: increase levels of total and HDL ApoA1 (p=0.05 and 0.04), decrease of LDL ApoB (p=0.08) with increase of ApoB VLDL (p=0.08) increase of MHDL (p=0.003) and HDL triglyceride (p=0.035) and protein (p=0.0003) content, decrease in np LDL (p=0.08) and increase of np VLDL which are less atherogenic.

Conclusion: Anti-TNF therapy induces global positive lipoprotein balance with increases of ApoA1 levels and a metabolic shift towards HDL and VLDL molecules instead of LDL. Future studies with larger samples and times of follow up will help us to better define this modifications.

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Sarilumab, a Subcutaneously Administered, Fully Human Monoclonal Antibody Inhibitor Of The IL-6 Receptor Alpha: Relationship Between Inflammation Suppression and Changes In Cholesterol Levels. Christina Charles-Schoeman[1], Steven P. Weinstein[2], Janet van Adelsberg[3], Tanya Momtahen[4], Richard Wu[5], Neil Graham[5] and Stefano Fiore[4]. [1]UCLA David Geffen School of Medicine, Los Angeles, CA, [2]Regeneron Pharmaceuticals Inc, Tarrytown, NY, [3]Regeneron Pharmaceutials, Inc., Tarrytown, NY, [4]Sanofi, Bridgewater, NJ, [5]Regeneron Pharmaceuticals, Inc., Tarrytown, NY.

Background/Purpose: Sarilumab (SAR) is a fully human monoclonal antibody directed against the alpha subunit of the IL-6 receptor (IL-6Rα) which is currently being evaluated for treatment of rheumatoid arthritis (RA). Patients with active RA have increased CV risk despite lower levels of total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) as well as high density lipoprotein cholesterol (HDL-C) associated with active inflammation. The current work explores further the acute phase relationship of cholesterol levels in relation to measures of inflammation in RA. In particular we evaluated the changes in cholesterol levels following SAR treatment as well as their relationship to decreases in inflammation using data from a 12-wk phase 2 study (MOBILITY Part A [NCT01061736]) of SAR + methotrexate in patients with RA.

Methods: Patients with RA (n=306) were randomized to one of the following 6 treatment groups: Placebo (PBO), SAR 100, 150, 200 mg every other week (q2w) or 100, 150 mg weekly (qw). Changes from baseline to wk 12 in TC, LDL-C, and HDL-C were assessed in the intent-to-treat (ITT) population (n= 306 patients). These changes, and changes in C-reactive protein (CRP) and serum amyloid A (SAA) levels, were assessed according to tertiles of baseline CRP and SAA levels in the 2 SAR dose groups whose dose regimens were subsequently chosen for study in phase 3 trials (150 mg and 200 mg q2w).

Results: At wk 12, changes in TC and LDL-C but not HDL-C were statistically significantly greater in the SAR group compared with PBO (TABLE). Patients with the highest baseline levels of inflammation as assessed by the top tertiles of CRP and SAA, showed the largest decreases in inflammation and the largest increases in TC with SAR treatment. Similar trends were observed for LDL-C (TABLE).

Mean SAA, hsCRP, TC, LDL-C, and HDL-C changes from baseline to 12 weeks grouped by tertiles of baseline SAA and CRP, ITT population, MOBILITY Part A, placebo vs. pooled SAR 150mg and 200 mg q2weeks

Mean Change from Baseline to 12 weeks in Biomarker	Placebo (n=52)	Pooled SAR (n=103)	Pooled SAR: Tertile of Baseline ≤12.7 (n=29)	>12.7–≤45.9 (n=32)	>45.9 (n=29)	P-trend
hsCRP (mg/L)	−2.5	−24.2*	−5.1	−15.6	−27.9	<0.0001
SAA (mg/L)	−0.7	−59.1*	6.8	−18.5	−99.1	<0.0001
TC (mmol/L)	0.07	0.61*	0.31	0.53	0.82	0.0679
LDL-C (mmol/L)	0.06	0.42*	0.19	0.43	0.57	0.0489
HDL-C (mmol/L)	0.06	0.10	0.09	0.03	0.14	0.2175
			Pooled SAR: Tertile of Baseline CRP (mg/L)			
	Placebo (n=52)	Pooled SAR (n=103)	≤14.2 (n=33)	>14.2–≤27.5 (n=34)	>27.5 (n=33)	P-trend
hsCRP (mg/L)	−2.5	−24.2*	−3.3	−16.6	−54.0	<0.0001
SAA (mg/L)	−0.7	−59.1*	−8.3	−34.8	−142.3	<0.0001
TC (mmol/L)	0.07	0.61*	0.36	0.61	0.84	0.0247
LDL-C (mmol/L)	0.06	0.42*	0.23	0.52	0.49	0.0338
HDL-C (mmol/L)	0.06	0.10	0.04	0.08	0.17	0.4505

P-trend is value for nonparametric signed-rank test across the SAR tertiles; * P value ≤0.05 vs. placebo

Conclusion: Treatment with sarilumab at either 150 mg or 200 mg every other week in the phase 2 study MOBILITY Part A was associated with increases in TC and LDL-C compared to placebo. These increases in TC and LDL-C observed with sarilumab were associated with both the baseline burden of inflammation assessed by SAA and CRP, as well as the degree of suppression of inflammation by sarilumab. Further investigation of additional CV biomarkers which are less sensitive to the acute phase response and adequately assess CV risk in the setting of high levels of systemic inflammation from active RA may be warranted. The effect of sarilumab on markers of inflammation and lipid parameters will be further evaluated in the Phase 3 program.

Disclosure: C. Charles-Schoeman, Pfizer Inc, 2, Bristol-Myers Squibb, 2, Pfizer Inc, 5, Regeneron, 5, Pfizer Inc, 8; **S. P. Weinstein**, Regeneron, 3, Regeneron, 1; **J. van Adelsberg**, Regeneron, 3, Regeneron, 1; **T. Momtahen**, Sanofi-Aventis Pharmaceutical, 3, Sanofi-Aventis Pharmaceutical, 1; **R. Wu**, Regeneron, 3, Regeneron, 1; **N. Graham**, Regeneron, 3, Regeneron, 1; **S. Fiore**, Sanofi-Aventis Pharmaceutical, 3.

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Etanercept 25 Mg Once Weekly Program For Rheumatoid Arthritis, Psoriatic Arthropathy and Ankylosing Spondylitis Patients In Sustained Clinical and Radiological Remission. Joaquín Borrás-Blasco[1], Antonio Gracia-Pérez[1], Dolores-Elvira Casterá[1], J. Dolores Rosique-Robles[1], Javier Abad[1] and Alejandro González Álvarez[2]. [1]Hospital de Sagunto, Sagunto, Spain, [2]Hospital Obispo Polanco, Teruel, Spain.

Background/Purpose: Etanercept 50mg/week (ETN50) has demonstrated efficacy in patients with rheumatoid arthritis (RA), psoriatic arthropathy (PA) and ankylosing spondylitis (AS). In certain patients in sustained clinical remission with ETN 50, a dose reduction to etanercept 25 mg/week (ETN25) could be done. This strategy of dose reduction could have advantages in terms of safety and costs. The aim of the study is determine the clinical and economic impact of the use of ETN25 in RA, PA and AS patients in sustained clinical remission.

Methods: Observational, retrospective cohort of patients in an off-label program receiving ETN25 for at least 6 months between January 2006 and June 2013. Inclusion Criteria: patients treated with ETN50 that achieve and maintain clinical remission (DAS28<2.6 or BASDAI<2) during 1 year and slow worsening of structural changes were selected to change their standard dose of ETN50 to ETN25. We collected age, sex, indication, duration (in years) of ETN25 during the study period. In these patients, we simulated the cost of treatment with etanercept as if they had received ETN50 during their ETN25 respective periods. Economic impact was assessed using Enbrel® Spanish official prices.

Results: From Jan 2006 to 1st Jun 2013, 39 patients (18 women; age 53±7 years; 24 RA, 7 PA, 8 AS) received ETN25 for at least 0.5 years (2.6±2.0 years; range 0.5–7.3 years). At 1st Jun 2013, 29 (74%) patients continued on ETN25 (17 RA, 4 PA and 8 AS). Table 1 shows associated clinical data of these patients. 10 (26%) patients discontinued due to: RA patients: 5 patients due to reactivation of RA (4 switched to ETN50 and 1 switched to adalimumab, all patients achieved clinical remission) and 2 patients due to adverse reactions; PA patients: 2 patients due to reactivation of PA (switched to ETN50 and achieved clinical remission) and 1 patient due to adverse reactions. All AS patients continued on ETN25 (Table 1). Total associated costs of this low dose strategy throughout the observation period were 622.073€. If these patients had been treated with ETN 50, the total cost of therapy would have been 1.224.146€. The implementation of the once-weekly ETN25 in these patients saved 622.073€ during 7 years. This cost savings achieved with an ETN25 regimen could lead to treat approximately 52 additional patients with RA, PA or AS for a year without increasing the total cost of etanercept therapy.

Conclusion: ETN25 produces important cost savings when used in patients with slow worsening of structural changes who maintain clinical remission for at least 1 year with ETN50. Reducing the dosage in selected patients could make treatment more cost-effective and allow physicians to treat more patients with a fixed budget.

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Clinical Efficacy Rate Of The Non-Specific Effect (the placebo effect) In The Tumour Necrosis Factor Inhibitors For Rheumatoid Arthritis Treatment After Methotrexate Failure: Meta-Analysis. Julie Azaïs[1], Thomas Barnetche[2], Pascale Vergne-Salle[3], Christine Bonnet[1], Carine Dufauret-Lombard[1], Richard Treves[1] and Philippe Bertin[1]. [1]CHU Dupuytren Limoges, Limoges, France, [2]CHU Bordeaux Pellegrin, Bordeaux, France, [3]CHU Dupuytren Limoges, limoges, France.

Background/Purpose: Therapeutics generate non-specific effects (the placebo effect), and specific ones, like the 5 tumor necrosis factor (TNF) inhibitors used in the treatment of Rheumatoid Arthritis (RA). Few abstracts deal with the placebo effect. Its role in clinical responses to treatments has not been clearly accounted for. A systematic review must henceforth be conducted to appraise its rate in TNF-blockers treatments. This rate seems quite important in the first 3 months of treatment. The aim of this study was to estimate the placebo effect in ACR 20, 50 and 70 responders in patients suffering from RA and being treated by TNF-blockers after MTX failure.

Methods: A systematic literature review was conducted using PubMed, Embase and Cochrane library databases. The articles selected till March 2013 reported on double-blind RCTs of TNF-blockers versus placebo with patients receiving concomitant MTX. These patients, suffering from RA according to ACR 1987 criteria, were naive of biotherapies. MTX therapy with a minimum dosage of 10 mg/week had proved unsuccessful for at least 6 months. The data collected dealt with RA patients and the rates of ACR 20, 50 and 70 responders in each group at week 24. A meta-analysis was conducted using Methodomics for global responders, each molecule and injection method.

Results: Twenty-two RCTs out of 1,386 were included in the systematic review and meta-analysis: 6 studied infliximab, 5 etanercept, 4 adalimumab, 3 certolizumab, and 4 golimumab. ACR 20 responses at W24 were available in 13 RCTs. The placebo effect was 24.70% on the whole (IC95% [0.192; 0.301] p=0) with significant statistical results for adalimumab: 26.70% (IC95% [0.161;0.373] p=0.001), certolizumab: 16.40% (IC95% [0.068;0.26] p=0), infliximab: 31.90% (IC95% [0.154;0.485] p=0.001). The subgroup analysis concerning the injection method showed 31.90% vs. 23.30% for the IV route (IC95% [0.154;0.485] p=0.001). The ACR 50 non-specific response at W24 was 10.90% (IC95% [0.074;0.144] p=0) for the 14 RCTs. It was only significant for adalimumab, estimated at 15.40% (IC95% [0.026; 0.281] p=0). It was not increased by the IV relative to the SC routes. The ACR 70 placebo effect response at W24 was estimated at 3.40% (IC95% [0.019;0.049] p=0) in 13 studies. No result was statistically significant. The more the ACR criteria were stringent, the more the placebo effect decreased. Heterogeneity was important due to both MTX and TNF-blockers different dosages and administration frequencies. The rates were analysed by the random model.

Conclusion: Even if RCTs showed that TNF-blockers were more efficient than MTX alone, this meta-analysis shows that the non-specific effect must be taken into account. It is estimated at about 20% even if patients are in failure with the treatment. Adalimumab, certolizumab and infliximab rose above others in placebo effect responses, as well as for the IV route. This placebo effect seems to decrease with strict evaluation criteria. It would be interesting to better consider its role in clinical responses aspects and to take into account the cost margin.

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Real-World Effectiveness and Safety Of Infliximab In The Treatment Of Rheumatoid Arthritis Over 5 Years: The Canadian Experience. Denis Choquette[1], William Bensen[2], Andrew Chow[3], John T. Kelsall[4], Maqbool K. Sheriff[5], Jude F. Rodrigues[6], Emmanouil Rampakakis[7], John S. Sampalis[7], May Shawi[8], Francois Nantel[8], Susan M. Otawa[8] and Allen J. Lehman[8]. [1]Institut de Rhumatologie de Montréal, Montreal, QC, [2]St. Joseph's Hospital and McMaster University, Hamilton, ON, [3]Credit Valley Rheumatology, Mississauga, ON, [4]Mary Pack Arthritis Centre, Vancouver, Vancouver, BC, [5]Nanaimo Regional General Hospital, Nanaimo, BC, [6]Rheumatology, Windsor, ON, [7]JSS Medical Research, St-Laurent, QC, [8]Janssen Canada Inc, Toronto, ON.

Background/Purpose: Efficacy and safety of anti-TNF in rheumatoid arthritis (RA) management has been demonstrated in numerous controlled clinical trials. Longitudinal observational studies assessing the real-world effectiveness and safety of anti-TNF agents are essential to demonstrate the true population-based benefit-risk ratio. The purpose of this study was to assess in Canadian routine clinical practice the long-term effectiveness and safety profile of infliximab (INF) in RA patients.

Methods: Biologic Treatment Registry Across Canada (BioTRAC) is an ongoing, prospective registry of rheumatology patients initiating INF or golimumab treatment as first biologics or after having been treated with a biologic < 6 mos. RA patients treated with INF who enrolled between 2002 and 2011 and had at least one follow-up assessment were included in the

effectiveness analysis (N=628), while the safety population comprised all patients treated with INF during that period (N=838). Adverse events (AEs) were classified as per the Medical Dictionary for Regulatory Activities and were counted once per System Organ Class and Preferred Term.

Results: Mean (SD) age and disease duration among the effectiveness population were 55.8 (13.6) yrs and 10.2 (10.0) yrs, respectively. At the time of the analysis, 96 (15.3%) had completed 5 yrs of followup. At treatment initiation, 90.9% were treated with DMARDs, 56.1% with NSAIDs, and 40.0% with steroids. Mean (SD) patient parameters at baseline: C-reactive protein (CRP) = 19.5 (24.9) mg/L, erythrocyte sedimentation rate (ESR) = 32.2 (24.0) mm/hr, morning stiffness = 70.4 (43.6) min, tender joint count (TJC28) = 12.5 (7.9), swollen joint count (SJC28) = 10.6 (7.1), health assessment questionnaire (HAQ) = 1.7 (0.7), patient global assessment of disease activity (PtGA) = 6.0 (2.4) cm, physician global assessment of disease activity (MDGA) = 6.6 (2.1) cm, and DAS28-CRP = 5.4 (1.3). Upon 6 mos of treatment, statistically significant ($P<0.05$) and clinical meaningful improvements were observed in all parameters analyzed, which were sustained over 60 mos of treatment.

A total of 1,740 AEs were reported for 43.3% patients in the safety population (110.24 events / 100 patient yrs (PYs)), the majority of which (92.3%) were non-serious as per the judgment of the treating physician. Most frequently reported AEs included arthralgia (5.3% of patients), headache (3.8%), and upper respiratory tract infections (3.8%). There were 134 serious AEs reported for 84 (10.0%) patients (8.49 events/100 PYs). The incidence of serious infections and neoplasms was 1.96 and 0.70 events per 100 PYs, respectively. Five deaths (pulmonary fibrosis, miliary tuberculosis, severe arteriosclerotic heart disease, intestinal gangrene, and atrial fibrillation with hypotension and interstitial lung disease) were reported during the study, of which three (pulmonary fibrosis, intestinal gangrene, atrial fibrillation with hypotension and interstitial lung disease) were judged by the treating physician as unlikely related to INF.

Conclusion: The results of this Canadian longitudinal observational study have shown that INF is well tolerated and effective in reducing symptom severity and improving outcomes in RA patients over a 5-yr period.

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HM-0523, a Novel Syk Inhibitor Significantly Ameliorates The Severity Of Arthritis In Rodents. Yu Cai, Zhong Cui Sun, Ping Ren, Lei Fang, Xiaoming Dai, Zhipeng Wu, Qianqian Dong, Xinrong Wang, Jian Wang, Yang Sai, Xiong Li and Weiguo Su. Hutchison Medipharma Limited, Shanghai, China.

Background/Purpose: Spleen tyrosine kinase (SYK) is a key mediator of signaling events downstream of a wide array of receptors important for immune function, including the B cell antigen receptor, immunoglobulin receptors bearing the Fcg or Fce chain, and other ITAM-containing C-type lectin and integrin receptors. Therefore, Syk inhibition has attracted considerable interest for treatment of autoimmune and allergic diseases. In this report, we present a highly potent and selective, orally available Syk inhibitor and its efficacies in rodent models of rheumatoid arthritis.

Methods: Utilizing a series in vitro biochemical and cellular assays and in vivo pharmacological models of rheumatoid arthritis, Syk inhibitors were designed and evaluated to identify a drug candidate with excellent potency, selectivity, and drug-like properties.

Results: HM-0523 demonstrated high potency against Syk enzyme activity (IC_{50}=20 nM) in vitro. The compound also exhibited its high kinome selectivity, although it cross-inhibited several kinases such as Flt3 with IC_{50}=63 nM. HM-0523 also displayed functional activities in multiple cellular assays in various human cell types. It blocked FceR crosslinking-induced degranulation in mast cells (IC_{50}=30 nM), FceR engagement-mediated TNF-a and IL-6 production in BMMC (IC_{50}=52 and 78 nM, respectively), FcgR engagement-mediated TNF-a production in monocytes (IC50=54 nM). In human whole blood, HM-0523 potently inhibited BCR mediated B cell activation (IC_{50}=120 nM) and FcεR1 mediated basophil degranulation (IC_{50}=145 nM). HM-0523 was further evaluated in the models of rheumatoid arthritis. In mice collagen-induced arthritis model, treatment with HM-0523 after disease onset significantly reduced disease severity in a dose dependent manner with estimated ED_{50}=4~5 mg/kg QD. Consistent with its efficacy in mice, HM-0523 also suppressed paw swelling with ED_{50}=1.4 mg/kg QD in rat collagen-induced arthritis model. Furthermore, HM-0523 inhibited synovial proinflammatory cytokine production and inflammatory markers in the blood, suggesting its mechanism of action correlated with its clinical benefits in those models of rheumatoid arthritis. In addition, HM-0523 has demonstrated its superior in vitro potency, selectivity, in vivo efficacy and PK profile in preclinical animal models to current clinical lead fostamatinib that is under evaluation in Phase III clinical trials for Rheumatoid Arthritis.

Conclusion: Our data demonstrated that HM-0523, acting through selective inhibition of Syk activation, exhibited significantly beneficial effects in rodent models of rheumatoid arthritis. These results strongly support further development of HM-0523 as a promising new agent for the treatment of rheumatoid arthritis.

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Alteration Of Aortic Distensibility Within 6 Months Of Treatment In RA Patients: An Observational Comparison Of Infliximab and Synthetic Dmards. Birgul Ay[1], Dilek Keskin[1], Goksal Keskin[1] and Ayhan Dinc[2]. [1]DYB Research and Training Hospital, Ankara, Turkey, [2]Patio Clinic, Ankara, Turkey.

Background/Purpose: The proximal aorta accounts for most of the global arterial stiffening and subsequent complications. Aortic stiffness can be demonstrated by changes in aortic dimensions such as strain (proportional change of aortic area to the minimum area) and, when combined with pressure, distensibility (relative dimensional change related to changes in local pressure). We report aortic size and stiffness changes over 6 months after treatment with infliximab or synthetic DMARDs in a group of RA patients.

Methods: The study comprised thirty-eight female patients with RA and 30 otherwise healthy female individuals. Those with stable co-morbidities were allowed, but not with a documented cardiovascular disease. According to the clinical decision of attending physicians (blinded to study protocol), 20 patients received infliximab, while 18 patients received single or combined synthetic DMARDs during the study period.

At baseline and six months later (prior to first and last infusions), all subjects underwent, complete 2-dimensional transthoracic echocardiography, and systolic and diastolic ascending aortic diameters (SD and DD) were recorded in M-mode 3 cm above the aortic valve from a parasternal long-axis view. Aortic elastic properties were calculated using aortic data and forearm blood pressure values.

Results: Regarding baseline demographic features and comorbid conditions, all patients and healthy controls, were comparable. Baseline treatment profiles and disease activity scores were also similar between two RA groups. Echocardiographic parameters were normal in all subjects, none having significant valvular heart disease, segmental wall motion abnormalities or myocardial hypertrophy.

All groups had similar aortic diameters, but RA groups had significantly reduced aortic strain and distensibility, compared with healthy controls. In both treatment arms, a significant and comparable DAS28 response was achieved at six months.

At the end of study, infliximab-treated group showed significant improvement in either aortic strain (4,3±3,2 vs. 9,2±5,7, %, $p<0,01$) or aortic distensibility (0,18±0,14 vs. 0,44±0,28, cm^2/dynes/103, $p<0,01$), whereas synthetic DMARD-treated group did not show a significant change. Correlation analysis revealed that, this achievement, significantly associated with changes in DAS28 and hs-CRP values.

Conclusion: RA patients have impaired aortic elasticity, which could be improved with infliximab, but not with synthetic DMARDs, over six months.

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Two-Year Results From The Ample Trial: Low Disease Activity and Association Between Remission and Changes In Physical Function and Radiographic Outcomes With Subcutaneous Abatacept Or Adalimumab. R Fleischmann[1], M Schiff[2], M E Weinblatt[3], M Maldonado[4], E Massarotti[5] and Y Yazici[6]. [1]University of Texas Southwestern Medical Center, Dallas, TX, [2]University of Colorado, Denver, CO, [3]Brigham & Women's Hospital, Boston, MA, [4]Bristol-Myers Squibb, Princeton, NJ, [5]Brigham and Women's Hospital, Boston, MA, [6]New York University Hospital for Joint Diseases, New York, NY.

Background/Purpose: Remission and low disease activity (LDA) are now more achievable goals in RA. Year 1 data from the head-to-head AMPLE (Abatacept vs Adalimumab Comparison in Biologic-Naive RA Patients with Background MTX) study showed comparable rates of remission and LDA for patients treated with subcutaneous (SC) abatacept or adalimumab.[1] To assess whether these responses are maintained over time and to evaluate the relationship with functional and radiographic outcomes, we report Year 2 data from AMPLE.

Methods: AMPLE is a 2-year, Phase IIIb, randomized, investigator-blinded study. Biologic-naïve patients with RA and an inadequate response to MTX were randomized to 125 mg SC abatacept weekly or 40 mg SC adalimumab bi-weekly, with background MTX.[1] The proportions of patients achieving remission (defined as Disease Activity Score [DAS]28 [C-reactive protein; CRP] <2.6, Clinical Disease Activity Index [CDAI] ≤2.8, Simplified Disease Activity Index [SDAI] ≤3.3, Routine Assessment of Patient Index Data [RAPID]3 <3, Boolean score ≤1) or LDA (defined as DAS28 [CRP] ≤3.2, CDAI ≤10, SDAI ≤11, RAPID3 ≤6) are presented. Physical function (assessed with the Health Assessment Questionnaire-Disability Index [HAQ-D]I; responders defined as an improvement of ≥0.3) and radiographic non-progression (defined as change in modified total Sharp score of ≤ smallest detectable change) were analyzed in patients achieving remission at 2 years.

Results: A total of 646 patients were randomized and treated with abatacept (n=318) or adalimumab (n=328) on background MTX. Baseline clinical characteristics were balanced between treatments. The proportions of patients in remission or LDA at Year 2 were comparable for both treatments (Table), and were higher than those reported at Year 1.[1,2] More patients achieved DAS28 (CRP) remission compared with CDAI, SDAI, and RAPID3 remission, with the smallest proportion achieving Boolean remission. Depending on the criteria used to assess remission, 65.9–80.2% of adalimumab-treated patients and 72.7–81.2% of abatacept-treated patients who were in remission at Year 1 were maintained in a state of remission at Year 2. Across all criteria, >70% of patients in remission at Year 2 were also HAQ-DI responders, and >85% were radiographic non-progressors at Year 2. Improvement in physical function and radiographic outcomes at Year 2 were consistent between the two treatments.

	SC abatacept + MTX n/N (%)	**SC adalimumab + MTX** n/N (%)
Remission criteria		
DAS28 (CRP) <2.6	127/251 (50.6)	130/244 (53.3)
CDAI ≤2.8	80/250 (32.0)	74/244 (30.3)
SDAI ≤3.3	78/250 (31.2)	79/243 (32.5)
RAPID3 (0–30) ≤3	77/248 (31.0)	61/233 (26.2)
Boolean	52/251 (20.7)	50/244 (20.5)
Low disease activity criteria		
DAS28 (CRP) ≤3.2	164/251 (65.3)	166/244 (68.0)
CDAI ≤10	164/250 (65.6)	165/244 (67.6)
SDAI ≤11	163/250 (65.2)	168/243 (69.1)
RAPID3 (0–30) ≤6	123/248 (49.6)	116/233 (49.8)

Conclusion: Over 2 years of the AMPLE study, rates of remission and LDA increased over time across all criteria and remained comparable for SC abatacept and adalimumab. All remission criteria demonstrated high correlation with physical function and radiographic outcomes, with similar improvements in each treatment group at Year 2. **References:** 1. Weinblatt M, et al. *Arthritis Rheum* 2013;**65**:28–38. 2. Fleischmann R, et al. *Ann Rheum Dis* 2013;**72**(Suppl. 3):626.

Disclosure: R. Fleischmann, Bristol-Myers Squibb, Abbvie, 5, Bristol-Myers Squibb, Abbvie, 2; **M. Schiff**, Bristol-Myers Squibb, Abbvie, 5; **M. E. Weinblatt**, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, Roche/Genentech, UCB, Janseen, 5; **M. Maldonado**, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1; **E. Massarotti**, Bristol-Myers Squibb, 2, UCB, 5; **Y. Yazici**, Abbvie, Bristol-Myers Squibb, Celgene, Genentech, UCB, 5, Bristol-Myers Squibb, Genentech, 2.

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Golimumab Improves Patient-Reported Outcomes In Patients With Active Rheumatoid Arthritis. B Dasgupta[1], P Bertin[2], L Settas[3], JE Fonseca[4], V Wolff[5], R Yao[6], M Govoni[7], N Vastesaeger[8] and HH Weng[6]. [1]Southend University Hospital, Westcliff-on-Sea, United Kingdom, [2]Hôpital Dupuytren, Limoges, France, [3]AHEPA University Hospital of Thessaloniki, Thessaloniki, Greece, [4]Lisbon Academic Medical Centre, Lisboa, Portugal, [5]Hospital del Salvador, Santiago, Chile, [6]Merck Sharp & Dohme, Kenilworth, NJ, [7]Merck Sharp & Dohme, Rome, Italy, [8]Merck Sharp & Dohme, Brussels, Belgium.

Background/Purpose: Rheumatoid arthritis (RA) has a substantial impact on patient quality of life (QOL), physical functioning, and other outcomes important to patients. This subanalysis of the GO-MORE study aimed to evaluate patient-reported outcomes (PROs) and their associations with disease characteristics in RA patients receiving add-on subcutaneous (SC) golimumab (GLM).

Methods: GO-MORE was a large, open-label, multinational, prospective study in biologic-naïve patients with active RA (DAS28-ESR ≥3.2) despite non-biologic disease-modifying antirheumatic drug (DMARD) treatment. Patients received 50-mg SC GLM once monthly for 6 months in addition to their current DMARD treatments. Clinical responses and PROs were assessed, including Health Assessment Questionnaire-Disability Index (HAQ-DI); patient's global assessment (PGA) of disease activity; patient assessments of pain, disease state, and fatigue; EuroQol 5-dimension (EQ-5D) index and health state; and patient acceptable symptom state (PASS). Associations between PROs and several baseline disease and treatment history characteristics were tested with chi-square tests.

Results: After 6 months of add-on GLM therapy, 82.1% of 3280 efficacy-evaluable patients attained a good or moderate EULAR response. Substantial improvement occurred in pain/discomfort, disease activity, fatigue, and QOL at month 6 (table). 37.4% of patients achieved minimal or no functional impairment (HAQ-DI ≤0.5), and the percentage of patients with PASS improved from 13.9% at baseline to 66.0% at month 6. Patients in the upper 2 tertiles of baseline rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) had greater improvements in PASS and EQ-5D health state than patients in the lowest tertile. Most of these effects met the predefined $P<.001$ criterion early in treatment, but not at month 6. Early in treatment, the PASS rate was highest in patients with the longest disease duration (>10 years).

	Baseline, Mean (SD)	**Month 6, Mean (SD)**
HAQ-DI	1.44 (0.672)	0.88 (0.690)
PGA Disease Activity (0–100 mm VAS)	65.5 (19.50)	35.4 (25.37)
Pain/Discomfort (0–100 mm VAS)	64.5 (20.55)	34.9 (26.54)
Fatigue (1–4 scale)	2.9 (0.86)	2.2 (0.89)
Disease State (1–5 scale)	4.1 (0.90)	2.7 (1.14)
EQ-5D QOL Index (index range –0.59 to 1.0)	0.42 (0.33)	0.67 (0.262)
EQ-5D Health State (0–100 mm VAS)	46.6 (21.12)	68.7 (22.20)

Note: Lower scores indicate better outcomes, except for the EQ-5D. VAS, visual analog scale.

Conclusion: In patients with active RA despite DMARD treatment, 6 months of add-on GLM treatment led to substantial improvement in PROs, including QOL, pain, fatigue, PASS, and functioning. Higher baseline levels of RF and anti-CCP may be associated with better early response to GLM as assessed by PROs.

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Analysis Of The JAK1 Selectivity Of GLPG0634 and Its Main Metabolite In Different Species, Healthy Volunteers and Rheumatoid Arthritis Patients. René Galien[1], Béatrice Vayssière[1], Steve de Vos[2], Marielle Auberval[1], Nick Vandeghinste[2], Sonia Dupont[1], Philippe Clément-Lacroix[1], Philippe Delerive[1], Frédéric Vanhoutte[2], Reginald Brys[2], Annegret Van der Aa[2], Luc Van Rompaey[2] and Gerben van 't Klooster[2]. [1]Galapagos SASU, Romainville, France, [2]Galapagos NV, Mechelen, Belgium.

Background/Purpose: The 4 Janus kinases (JAK1, JAK2, JAK3 and TYK2) are cytoplasmic tyrosine kinases that transduce intracellular signaling for cytokines including interleukins and interferons, and for growth factors

such as erythropoietin. GLPG0634 is a JAK inhibitor that has been shown to be selective for JAK1 over JAK2 in human whole blood and over JAK3 and TYK 2 in biochemical assays. GLPG0634 showed a favorable safety and efficacy profile in two 4-week Phase 2A studies in patients with rheumatoid arthritis (RA). Its activity is supported by an active metabolite that shows a high plasma exposure in humans. Here, we have evaluated the JAK1 selectivity of GLPG0634 and its main metabolite in animals, healthy volunteers and RA patients.

Methods: JAK selectivity of GLPG0634 and its metabolite was evaluated by measuring STAT phosphorylation (pSTAT) in whole blood from humans, dogs and monkeys incubated with triggers that activate JAK-dependent pathways by flow cytometry. STAT phosphorylation measurement in cells transfected with JAK siRNA was performed using SureFire technology. Effects on JAK–dependent gene signatures in blood incubated with or without triggers were assessed by QRT-PCR. Sources of blood were from healthy volunteers (untreated or following 10 days of GLPG0634), RA patients (4-week GLPG0634 treatment), untreated animals and mice subjected to CIA (2-week treatment with GLPG0634).

Results: An approximately 30-fold selective inhibition of JAK1 over JAK2 by parent GLPG0634 using the IL6/pSTAT1 assay for JAK1 and GM-CSF/pSTAT5 for JAK2 was similarly found with its metabolite. However, the metabolite displayed an >10 fold lower JAK inhibition potency. In cellular knock-down experiments with siRNA we confirmed IL-6-induced pSTAT1 to be an exclusive JAK1-driven event. The JAK1 selective inhibition by GLPG0634 and its metabolite was confirmed in complementary whole blood assays for alternative pathways: IL-2/pSTAT5 (JAK1/JAK3) and IFNα/pSTAT1 (JAK1/TYK2). In these pathways, where JAK1 partners with other JAKs, a 10-fold selectivity over the inhibition of JAK2-driven signalling was found in human, dog and monkey blood. Transcriptional profiling was applied to assess selectivity of GLPG0634 using genes such as MX1, MX2 and GBP1 (IFNα-induced) and HRH4 (GM-CSF-induced) in human whole blood. In samples from human healthy volunteers exposed to GLPG0634 (and its metabolite as formed), gene expression analysis showed that selectivity was conserved up to the highest dose (450 mg QD). In addition, JAK1 selectivity over JAK2 was confirmed in blood from mice with collagen-induced arthritis (CIA) treated with GLPG0634, as well as from RA patients administered GLPG0634 at the doses of 100 mg BID and 200 mg QD.

Conclusion: These data demonstrate that GLPG0634 and its metabolite are highly selective JAK1 inhibitors in humans and animal species, using various technologies. The disease status did not alter selectivity, as a similar JAK inhibition profile was observed in blood from either healthy subjects or RA patients. Longer-term clinical studies are ongoing to confirm a favorable risk-benefit by selective inhibition of JAK1 and avoiding effects related to JAK2, such as anemia.

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Attainment Of Remission, Functional, and Quality Of Life Improvements With Golimumab Treatment In Rheumatoid Arthritis Are Associated With Patient Expectations. B Dasgupta[1], B Combe[2], I Louw[3], J Wollenhaupt[4], C Zerbini[5], A Beaulieu[6], H Schulze-Koops[7], P Durez[8], V Wolff[9], R Yao[10], HH Weng[10], M Govoni[11] and N Vastesaeger[12]. [1]Southend University Hospital, Westcliff-on-Sea, United Kingdom, [2]Hôpital Lapeyronie, Montpellier, France, [3]Panorama Medical Centre, Cape Town, South Africa, [4]Schön-Klinik, Hamburg, Germany, [5]Hospital Heliópolis, Serviço de Reumatologia, São Paulo, Brazil, [6]Centre de Rhumatologie, St-Louis, QC, [7]University of Munich, Munich, Germany, [8]Université Catholique de Louvain and Cliniques Universitaires Saint-Luc, Brussels, Belgium, [9]Hospital del Salvador, Santiago, Chile, [10]Merck Sharp & Dohme, Kenilworth, NJ, [11]Merck Sharp & Dohme, Rome, Italy, [12]Merck Sharp & Dohme, Brussels, Belgium.

Background/Purpose: Golimumab (GLM) and other tumor necrosis factor antagonists are used as add-on therapy for patients with rheumatoid arthritis (RA) who have not responded to disease-modifying antirheumatic drugs (DMARDs). Comprehensive management of RA involves clinical goals such as remission and outcomes important to patients such as daily functioning and improvement in quality of life (QoL). After DMARD failure, patients may have low treatment expectations, which could affect outcomes. This subanalysis of the GO-MORE study investigated relationships between patient expectations and GLM treatment outcomes.

Methods: GO-MORE was an open-label, multinational, prospective study in biologic-naïve patients with active RA despite DMARD treatment. Patients received 50-mg subcutaneous GLM once monthly for 6 months. At baseline and month 3, patients rated their expectation of how well their treatment would control RA symptoms and improve QoL 3 months later using 5-point Likert scales (1=good outcome, 5=poor outcome). Patients were divided into tertiles of expectation scores: most positive ($\leq$1.5), intermediate (>1.5 to <1.86), or least positive ($\geq$1.86). Efficacy outcomes were compared among tertiles using ANCOVA; *P* values were calculated for pairwise differences from the comparator group.

Results: At baseline, 3280 efficacy-evaluable patients had moderate (21.3%) or high disease activity (78.7%), mean age 52.3 (SD=12.8) years, mean disease duration 7.6 (SD=7.9) years, mean Health Assessment Questionnaire Disability Index (HAQ-DI) 1.44 (SD=0.67), and mean EQ-5D 0.42 (SD=0.33). Overall, patients had high expectations, with a mean expectation score of 1.4 (1=good expectation, 5=poor expectation) at baseline. Higher expectations were observed in patients who had failed fewer DMARDs (1 vs 2 failures, $P=.0039$; 1 vs $\geq$3 failures, $P<.0001$) and patients who had high baseline disease activity (moderate vs high disease activity, $P=.0014$). Patients expected improvement in physical (pain, joint swelling, fatigue) and functional (ability to participate in activities) outcomes. After 6 months of GLM, patients with the most positive expectations had higher remission rates ($P<.0001$). More positive expectations were also associated with greater improvements in functional impairment and EuroQoL Questionnaire (EQ-5D) scores (table).

Table. Relationship Between Patient Expectations and GLM Treatment Outcomes

	Patient Expectations at Baseline		
Treatment Outcome at Month 6	**Most Positive n=1212**	**Intermediate n=1009**	**Least Positive n=1054**
Remission 28-joint Disease Activity Score (DAS28-ESR)<2.6, n (%)	339 (28.0)	236 (23.4)	209 (19.8) $P<.0001$[a]
Minimal Functional Impairment HAQ-DI ≤0.5, n (%)	562 (46.4)	368 (36.5) $P<.0001$[a]	294 (27.9) $P<.0001$[a]
Change in EQ-5D Score Mean (SD)	0.28 (0.35)	0.25 (0.33)	0.21 (0.34) $P<.0001$[a]

[a]*P* values for comparison with most positive expectation group. *P* values >.001 not reported.

Conclusion: Patients had high expectations for add-on GLM treatment despite previous treatment failures. Patients with more positive expectations had better outcomes and better comprehensive control of their RA than those with less positive expectations, as evidenced by higher DAS28 remission rates and improvement in patient-reported measures, such as physical function and QoL.

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Levels Of Circulating Mirnas Before and After 12 Months Therapy With Dmards In Patients With Early Rheumatoid Arthritis. Mária Filková[1], Borbala Aradi[2], Ladislav Senolt[3], Klara Prajzlerova[4], Serena Vettori[2], Herman F. Mann[5], Jiri Vencovsky[4], K. Pavelka[6], Beat A. Michel[7], Renate E Gay[2], Steffen Gay[2] and Astrid Jüngel[2]. [1]Institute of Rheumatology and Department of Rheumatology of the First Faculty of Medicine, Charles University in Prague, Czech Republic, Prague, Czech Republic, [2]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [3]Institute of Rheumatology, Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [4]Institute of Rheumatology, Department of Clinical and Experimental Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [5]Institute of Rheumatology, Prague, Prague, Czech Republic, [6]Department of Clinical and Experimental Rheumatology, Charles University, Prague, Czech Republic, [7]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland.

Background/Purpose: The altered expression of cellular miRNAs in the immune and resident cells involved in the pathogenesis of rheumatoid arthritis (RA) has been shown to contribute to the maintenance of pathognomic features typical of RA. Differential levels of circulating miRNAs in plasma were reported between patients with RA and osteoarthritis. Our aim was to analyze the effect of therapy on levels of circulating miRNAs in sera of patients with early RA (ERA).

Methods: Sera were obtained from patients with ERA (n=34, disease duration <8 months, fulfilling 2010 EULAR/ACR criteria) at baseline and correspondingly after 3 (M3) and 12 (M12) months therapy with disease modifying antirheumatic drugs (DMARDs, methotrexate n=28, sulphasalazine n=4, leflunomide n=1) and glucocorticoids (n=30). In addition, sera were obtained also from patients with established RA (estRA, n=28, disease duration 9.28±6.52 years, fulfilling 1987 revised ACR criteria) treated with DMARDs (methotrexate n=14, sulphasalazine n=2, leflunomide n=8), glucocorticoids (n=6) or biologics (n=19). Total RNA was isolated using phenol-chloroform extraction and the levels of RA-associated miR-155, 223, 16, 146a, 132, 203 and 124a were analyzed using specific primers by TaqMan Real-Time PCR. dCt method was used for relative quantification using let-7a as a normalization control (with a detection limit at Ct= 40).

Results: MiR-155 in sera of treatment naïve ERA patients showed significantly lower levels than in patients with estRA (dCt −6.31±1.05 v.s. −4.68±1.86, $p<0.001$). Treatment in ERA did not change the levels of miR-155 at M3 (dCt −6.13±1.62) or M12 (dCt −6.99±1.54). Interestingly, levels of miR-155 dropped below the detection limit in 14 ERA patients at M12. Levels of miR-223 were comparable between treatment naïve ERA and estRA (dCt 5.67±1.04 vs. 6.23±1.45) and did not change after M3 following treatment initiation in ERA (dCt 5.12±0.91). Most impressively, miR-223 in ERA showed significantly lower levels at M12 (dCt 4.34±0.78) in comparison with baseline ($p<0.001$) as well as M3 ($p<0.01$). MiR-16 was found at significantly lower levels in treatment naïve ERA patients compared with estRA (dCt 4.93±0.91 v.s. 6.10±1.22, $p<0.001$). During treatment levels of miR-16 in ERA did not change after 3 months (M3: dCt 5.71±1.27) but they significantly decreased after 12 months (M12: dCt 3.85±1.37 in comparison with baseline ($p<0.05$) and M3 ($p<0.001$). The levels of miR-146a were significantly lower in ERA sera in comparison with estRA (dCt 0.44±0.93 v.s. 1.20±1.00, $p<0.01$) but were not changed upon treatment in ERA (dCt 0.50±0.64 at M3, 0.02±1.97 at M12 respectively). The levels of miR-132 in ERA before treatment were comparable with estRA (dCt −4.31±0.90 v.s. −3.76±1.07) and were not affected by therapy over time (dCt −4.47±0.0.91 at M3, −4.94±1.83 at M12, 4 were undetectable). MiR-124a and miR-203 in sera were present in negligible amounts close to the detection limit and were therefore excluded from further analysis.

Conclusion: We show here that the levels of circulating miRNA-16 and −223 are changed upon therapy such as MTX combined with glucocorticoids in patients with ERA after 12 months suggesting miRNAs as potential biomarkers in ERA.

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Down-Titration of Biological Therapies In Rheumatoid Arthritis In Daily Clinical Practice. Miguel Arredondo, Iciar Cañamares, Esther Ramírez-Herráiz, Isidoro Gonzalez-Alvaro, Alberto Garcia-Vadillo, Alberto Morell, Rosario Garcia-Vicuña and Jose María Alvaro-Gracia. Hospital Universitario de La Princesa, Madrid, Spain.

Background/Purpose: One of the limiting factors for the use of biological therapies (BT) is cost. For this reason, the development of cost optimization strategies without compromising effectiveness is becoming increasingly frequent in clinical practice. Herein, we report our experience with titration of biological therapies in rheumatoid arthritis (RA) in daily clinical practice, and a comparison between two different periods of time.

Methods: An observational transversal study was performed including all patients with RA under BT (except anakinra and rituximab) in a University Hospital setting. First three months of 2011 and 2013 were included for comparison. Analyzed parameters included: dose, intervals and cost. Data were extrapolated to one year. Patients were considered as down-titrated when the quarterly dose of BT was ≤ 83% of approved dose. Effectiveness was measured by DAS28. Statistical comparison of both periods was performed by T-test and Chi-squared test.

Results: 211 and 265 patients were studied in 2011 and 2013 respectively. Percent of patients down-titrated, total mean dose and mean dose in the titrated group are shown in Table. Our data show an average decrease in total cost of 16.19% in 2013, in comparison with 9.44% in 2011. These data ranged from 0 to 34.75% with the different BT. Paired analysis of DAS28 revealed no significant differences between both time periods, 2.94 (2.05–3.84) vs 2.88 (1.80–3.96) ($p=0.742$).

	2011				2013			
	n	% pdt*	Total mean dose (%)	Mean dose in down-titrated (%)	n	% pdt*	Total mean dose (%)	Mean dose in down-titrated (%)
TOTAL	211	32.54†	88.87†	58.82††	265	41.06	83.90	59.01
Adalimumab	86	39.53	86.01	64.61	91	47.20	83.10	64.30
Etanercept	58	39.66	80.01	52.85	80	53.70	74.20	52.06
Certolizumab	14	0	100	-	35	17.10	93.40	61.48
Infliximab	23	21.73	115.64	65.07	18	5.16	107.39	82.35
Golimumab	1	0	100	-	3	0	100	-
Tocilizumab	19	31.57	85.74	54.20	20	55.00	77.28	56.70
Abatacept	10	20.00	93.33	66.67	18	11.1	96.30	66.67

* % pdt = percentage of patients down-titrated.
† $p<0.05$ compared to 2013.
†† $p>0.05$ compared to 2013.

Conclusion: Down-titration of BT in RA is feasible and occurs with increasingly frequency in daily clinical practice. This results in cost containment and contributes to rational use of these therapies.

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Methotrexate Use At Infliximab Initiation and Impact On Treatment Outcomes: An Analysis From A Canadian Registry. Denis Choquette[1], J. Carter Thorne[2], John T. Kelsall[3], Michel Zummer[4], Michael Starr[5], Maqbool K. Sheriff[6], William G. Bensen[7], Andrew Chow[8], Philip Baer[9], Emmanouil Rampakakis[10], John S. Sampalis[10], Francois Nantel[11], Allen J. Lehman[11], Susan M. Otawa[11] and May Shawi[11]. [1]Institut de Rhumatologie de Montréal, Montreal, QC, [2]Southlake Regional Health Centre, Newmarket, ON, [3]Mary Pack Arthritis Centre, Vancouver, Vancouver, BC, [4]Ch Maisonneuve-Rosemont, Montreal, QC, [5]Montreal General Hospital, Montreal, QC, [6]Nanaimo Regional General Hospital, Nanaimo, BC, [7]St. Joseph's Hospital and McMaster University, Hamilton, ON, [8]Credit Valley Rheumatology, Mississauga, ON, [9]Rheumatology, Scarborough, ON, [10]JSS Medical Research, St-Laurent, QC, [11]Janssen Canada Inc, Toronto, ON.

Background/Purpose: Clinical trials of anti-TNF therapies have shown that concurrent methotrexate (MTX) therapy enhances the efficacy of infliximab (IFX)[1]. Data on the benefits of combination therapy with MTX and IFX in a real-life clinical setting are scarce. The objective of this analysis is to describe changes in the use of MTX at IFX initiation in patients enrolled in routine clinical practice and assess the impact of the MTX dose on the real-life effectiveness of IFX.

Methods: BioTRAC is an ongoing, prospective registry of RA, AS or PSA patients initiating treatment with IFX or golimumab as first biologics or after having been treated with a biologic <6 mos. Data from RA patients treated with IFX between Jan 2002 and Jun 2011 were analysed. Patients were stratified based on the use of MTX (0mg of MTX,≤10mg/week, 10.1–24.9mg/week, ≥25mg/week) or by the 3-yr period of enrolment (01/2002–06/2005,07/2005–06/2008,07/2008–06/2011). Cox regression was used to examine time-dependent association between the attainment of disease remission as per the DAS28, CDAI and SDAI criteria and MTX dose.

Results: 790 RA patients were included with a mean (SD) age of 55.75 (13.46) yrs, mean (SD) disease duration of 10.15 (10.08) yrs. The concomitant use of MTX at infliximab initiation increased across enrolment periods (66.5% vs. 73.3% vs. 77.6%; P=0.022) which was also associated with decreased disease activity at baseline. Concomitant use of azathioprine (5.2% vs. 0.2%; P<0.001) and leflunomide (46.1% vs. 14.5%; P<0.001) at baseline, and prior past use of MTX (77.8% vs. 65.7%; P=0.001) was more frequent in patients not treated with MTX at infliximab initiation than those treated with MTX. Among patients treated with MTX at baseline the most common MTX dose category was 10–25mg/week (66.3% of patients). A trend towards higher MTX doses was observed over time with more patients treated with >25mg/week of MTX in recent yrs. Survival analysis shows that, upon adjusting for baseline disease activity, use of MTX over time was associated with an increased hazard ratio [HR (95%CI)] of attaining disease DAS28-CRP [1.35 (1.06–1.71)], CDAI [1.33 (1.02–1.72)], and SDAI [1.62 (1.14–2.32)] remission. This effect was observed across all MTX dose categories except for DAS28-CRP and CDAI in the >25mg/week dose category.

Conclusion: Clinical practice has changed over time with physicians using concomitant MTX at IFX initiation more frequently in recent years despite lower disease activity in patients today. The data support improved outcomes among patients treated with IFX in routine clinical care when receiving concomitant MTX. This is consistent with the current label and recent recommendations of the Canadian Rheumatology Association.

References:
1-Arthritis Rheum 1998;41:1552–63

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Adalimumab and Methotrexate Pharmacokinetics Following Combination Therapy With Different Methotrexate Doses in Methotrexate and Biologic-Naïve Rheumatoid Arthritis Patients: Concerto Study. Sandra L Goss[1], Cheri E Klein[1], Hartmut Kupper[2], Gerd R Burmester[3] and Walid Awni[1]. [1]AbbVie Inc., North Chicago, IL, [2]AbbVie Deutschland GmbH & Co KG, Ludwigshafen, Germany, [3]Charité-Universitätsmedizin Berlin, Free University and Humboldt University of Berlin, Berlin, Germany.

Background/Purpose: Higher exposure and lower immunogenicity rates have been observed for adalimumab when co-administered with methotrexate (MTX) compared to adalimumab monotherapy. The CONCERTO study was designed to evaluate the effect of fixed MTX doses on adalimumab exposure and to assess the pharmacokinetics of MTX polyglutamates 1, 2, 3, 4 and 5 (PG1–5) in red blood cells in MTX and biologic-naïve RA patients. The efficacy and safety from the CONCERTO study was previously reported.

Methods: CONCERTO was a Phase 4, 26-wk, double-blind, and parallel-arm trial in MTX and biologic-naive patients with active RA. Subjects were randomized 1:1:1:1 to blinded weekly oral MTX doses (2.5, 5, 10, or 20 mg). MTX dose remained constant throughout the entire study for the 2.5, 5 and 10 mg per wk MTX groups. Subjects in the 20 mg MTX group started on 10 mg MTX per wk which increased every two wks by 2.5 mg until reaching 20 mg per wk at Wk 8-Wk 26. All subjects received open-label adalimumab 40 mg sc every other wk and took 5 mg weekly supplement of oral folate. Blood samples were collected at baseline and prior to dosing at Wks 2, 4, 8, 12, 16, 20 and 26 for analysis of adalimumab and anti-adalimumab antibodies (AAA) in serum and analysis of MTX PG1–5 in red blood cell (RBC). Adalimumab and AAA were determined using validated ELISA methods. MTX PG1–5 concentrations were measured using a validated LC-MS method. A patient was considered AAA+ if at least one sample had measured AAA greater than 20 ng/mL and was confirmed by the confirmatory assay within 30 days after an adalimumab dose.

Results: Adalimumab trough concentrations appeared to reach steady state by Wk 16. At Week 26, mean adalimumab concentration in the 2.5 and 5 mg per week MTX dose groups was 4.4 μg/mL (N=98) and 5.7 μg/mL (N=100), respectively. Mean adalimumab concentration at higher MTX doses (10 to 20 mg weekly) was approximately 6.5 μg/mL (N=98 for each group) at Wk 26. Forty six patients (46/394, 12%) were classified as AAA+ during the study. The percents of subjects with at least one AAA+ sample for the 2.5, 5, 10 and 20 mg MTX per week dose group were 21%, 13%, 6%, and 6% respectively. At Week 26, mean MTX PG1–5 concentrations in RBC were 19.4, 34.2, 62.8, and 119 nM for the 2.5, 5, 10 and 20 mg MTX dose groups, respectively. Time to achieve steady state PG concentration was shorter for short chain PG1–2 (4 weeks) compared to longer chain PG3–5 (20- >26 weeks), leading to longer times to reach steady state as MTX dose increased. Higher MTX doses resulted in higher percentages of longer chain PG3–5. Short-chain PG1–2 were less than dose proportional and longer chain PG3–5 were greater than dose proportional.

Conclusion: In MTX and biologic-naive patients with active RA who received a fixed dose of MTX, the mean adalimumab exposure increased with increasing MTX dose from 2.5 to 10 mg MTX; adalimumab exposure was similar following 10 or 20 mg MTX. The percent of subjects with at least one AAA positive sample decreased with increasing MTX dose up to 10 mg MTX. Time to MTX steady state is dependent on MTX dose and is longer for higher MTX doses. As MTX dose increases, the percentage of PG1–2 increases less than dose proportionally while the percentage of PG3–5 increases more than dose proportionally.

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Response To Biologic Disease-Modifying Anti-Rheumatic Drugs After Discontinuation Of Anti-Tumor Necrosis Factor Alpha Agents In Rheumatoid Arthritis Patients. Eric Elkin[1], Max I. Hamburger[2], Tripthi Kamath[3], Sarika Ogale[3], Adam Turpcu[3], Jae Oh[4], Kristin King[4], Monarch Shah[1] and Martin J. Bergman[5]. [1]ICON Clinical Research, San Francisco, CA, [2]Rheumatology Associates, Melville, NY, [3]Genentech, South San Francisco, CA, [4]ICON Late Phase and Outcomes Research, San Francisco, CA, [5]Taylor Hospital, Ridley Park, PA.

Background/Purpose: Rheumatoid arthritis (RA) patients who have failed an anti-TNF agent as their first biologic agent have the option of switching to a second aTNF agent or a biologic with other mechanism of action (oMOA), either abatacept, tocilizumab, or rituximab. An exploratory analysis was undertaken to compare the routine assessment of patient index data 3 (RAPID3) response of aTNFs vs. biologics with oMOA used as a second biologic in RA patients with a history of aTNF treatment as their first biologic DMARD.

Methods: An observational, non-interventional, retrospective chart review study was conducted in 8 community-based rheumatology practices in the United States from February to September 2012. Patient charts were eligible if the patient's first biologic DMARD was an aTNF; they were 18 years or older at time of the second DMARD; they were prescribed a second biologic DMARD during the period July 1, 2006 and October 1, 2011. Patients were also required to have a RAPID3 score at baseline (up to 6 weeks prior to the second DMARD start) and at 6 months on therapy (+/−8 weeks). The RAPID3 score ranges from 0 to 30 with higher scores indicating more severe disease. A poor response was defined as a decrease of <1.8 points and/or a follow-up score >12. In addition, if a patient discontinued therapy prior to 6 months they were classified as having a poor response. A good response was a decrease in RAPID3 score >3.6 points and a follow-up score <6. The remainder of the patients had a moderate response. The percent of patients with a good response and a poor response was compared between treatment groups using the chi-square test and mean change in RAPID3 by t-test.

Results: A total of 144 charts were available for this analysis (mean age = 59.9 years, 76% female). The second biologic DMARD was an aTNF for 101 patients and oMOA for 43 patients. At baseline, mean scores were similar (14.8±6.2 for aTNF and 15.2±6.0 for oMOA, p=0.74). A good RAPID3 response was achieved for 9.9% of aTNF patients and 18.6% of other MOA patients (p=0.15). In addition, aTNF patients had a greater percent with a poor response (69.3% vs. 46.5%, p=.01). The mean change from baseline to 6 months was also different between the two treatment

groups: −1.1±5.9 for aTNF vs. −4.6±5.2 for oMOA (p<.01). These results were similar for the third biologic DMARD.

Conclusion: In this exploratory analysis of RA patients who had discontinued their first aTNF agent, those receiving a second biologic DMARD with another MOA were more likely to have a good or moderate RAPID3 response and had a greater decrease in RAPID3 scores, compared with patients receiving a second aTNF. We did not examine RAPID3 response to individual treatments due to small numbers. In patients who have already failed an aTNF agent, physicians should consider using a biologic agent with a different mechanism of action.

Disclosure: E. Elkin, Genentech Inc., 9; **M. I. Hamburger**, Genentech, Inc., 5; **T. Kamath**, Genentech Inc., 3; **S. Ogale**, Genentech Inc., 3; **A. Turpcu**, Genentech Inc., 3; **J. Oh**, Genentech Inc., 9; **K. King**, Genentech Inc., 9; **M. Shah**, Genentech Inc., 9; **M. J. Bergman**, Genentech Inc., 5.

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Safety Of Biologic Therapy In Veterans With Rheumatoid Arthritis and Chronic Hepatitis B Infection. Jeffrey R. Curtis[1], Mary J. Burton[2], Shuo Yang[3], Lang Chen[3], Ted R. Mikuls[4], Kevin L. Winthrop[5] and John Baddley[3]. [1]University of Alabama at Birmingham, Division of Clinical Immunology and Rheumatology, Birmingham, AL, [2]VA Hospital, Jackson, MS, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [5]Oregon Health & Science University, Portland, OR.

Background/Purpose: Among patients with rheumatoid arthritis and hepatitis B infection, the impact of biologic therapy on hepatotoxicity has received limited study.

Methods: Using 1997–2011 national data from the U.S. Veteran's Health Administration, we identified a cohort of 38,453 rheumatologist-diagnosed RA patients. Patients who had hepatitis B infection (defined by detectable hepatitis B surface antigen, hepatitis B core antibody or hepatitis B DNA), initiated a new biologic (anti-TNF: infliximab, adalimumab, etanercept; vs. rituximab) that they had never been on previously and had a baseline ALT < 1.5× the upper limit of laboratory normal within 90 days prior to starting biologic therapy were eligible for analysis. Patients could contribute more than one biologic treatment episode provided they switched to a new biologic they had not previously used, or switched to a previously used biologic they had not used in the past year. The main outcome of interest was hepatotoxicity, defined as ALT elevation > 100 IU/L (corresponding to 3× ULN for women and 2.5 ULN for men). Hepatotoxicity was examined within the first year of biologic use. Current exposure was defined as-treated based on day supply (injection biologics) or usual dosing intervals (infused biologics). Results were reported as the cumulative incidence of patients achieving pre-defined hepatotoxicity at 3, 6 and 12-months post biologic exposure.

Results: 248 RA patients with hepatitis B were identified and contributed 322 new biologic treatment episodes. Mean age was 60.2 years and 91.7% were male. Overall, ALT elevations were uncommon, with 10 hepatotoxicity events (ALT > 100 IU/L) occurring among 322 episodes (3.1%) within 12-months. Most hepatotoxicity events (7/10, 70%) occurred within 90 days of initiation of biologic. The highest proportion of hepatotoxicity occurred in patients receiving rituximab (4/35, 11.4%) (p = 0.013 vs. anti-TNF).

Drug	Pts	Episodes	3-month Failures	6-month Failures	12-month Failures
ADA	122	126	1 (0.8%)	2 (1.6%)	2 (1.6%)
ETA	126	128	3 (2.3%)	4 (3.1%)	4 (3.1%)
INF	30	33	0 (0.0%)	0 (0.0%)	0 (0.0%)
RIT	25	35	3 (8.6%)	3 (8.6%)	4 (11.4%)
Total	248	322	7 (2.2%)	9 (2.8%)	10 (3.1%)

ABA=abatacept; ADA=adalimumab; ETA=etanercept; INF=infliximab; RIT=rituximab

Conclusion: In US Veterans with hepatitis B receiving biologic therapy for RA, the proportion of episodes of hepatotoxicity (ALT >100 IU/L after initiation of biologic) was low, with the highest incidence occurring in patients receiving rituximab. Among those who failed, most failures occurred early (<91 days) after biologic initiation.

Disclosure: J. R. Curtis, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, Abb Vie, 2, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, Abb Vie, 5; **M. J. Burton**, None; **S. Yang**, None; **L. Chen**, None; **T. R. Mikuls**, Roche/Genentech and Biogen IDEC Inc., 2; **K. L. Winthrop**, Pfizer Inc, 2, Genentech Inc., Pfizer, UCB, Regeneron, 5; **J. Baddley**, BMS, 2, Pfizer Inc, 2.

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The Cost Savings Associated With a Departmental Etanercept Dose Reduction Pathway For Patients With Rheumatic Diseases and Maintained Low Disease Activity. Richard CJ Campbell, Emma Sanders, Francesca Leone, Emma Gilgeours, Margaret Sibley and Patrick D. Kiely. St George's Hospital, London, United Kingdom.

Background/Purpose: Clinical trials have previously demonstrated that it is safe and effective for some rheumatoid arthritis (RA) patients with low disease activity on full dose Etanercept to switch to half dose Etanercept (25mg per week)[1]. We decided to test the feasibility of this in clinical practice by developing a departmental Etanercept dose reduction algorithm. We also considered the associated cost savings.

Methods: Patients with inflammatory rheumatic diseases were eligible to enter the treatment pathway provided they had been on full dose Etanercept for more than one year and had low disease activity according to two assessments at least one month apart (DAS 28 <3.2 for rheumatoid arthritis (RA), Bath Ankylosing Spondylitits Disease Activity Index (BASDAI) <4 for ankylosing spondylitis (AS) and zero tender/swollen joint for psoriatic arthritis (PSA)). After switching to half dose Etanercept, patients attended for clinical assessments at 1, 3 and 6 months. Patients were switched back to full dose Etanercept if they no longer met criteria for low disease activity (termed 'flare'). Patients could choose to switch back to full dose Etanercept at any point without giving a reason.

Results: 31 patients (15 RA, 4 AS, 10 PSA, 1 adult JIA and 1 reactive arthritis) were switched to half dose Etanercept. Patient and disease criteria are shown in the table. 16 patients left the pathway early and had their dose increased for the following reasons: flare of disease (13), patient choice without objective evidence of flare (2) and device preference (1). After 6 months, 15 of the patients (48%) (9 RA, 3 AS, 2 PSA and 1 adult JIA) maintained low disease activity (see table) and so met criteria to continue on reduced dose Etanercept. A much smaller proportion of the patients with psoriatic arthritis (20%) maintained low disease activity compared with those with RA (60%). The total cost savings for the patients that completed 6 months on the pathway (90 patient-months) was $49,562 (£32,175).

Table. Patient Characteristics and Summary Data

	RA	*AS*	*PSA*	*Other*
Number of Patients	15	4	10	2
Gender (female)	11	0	2	1
Mean Age Yrs (SD)	56 (15)	50 (16)	48 (15)	32 and 22
Disease Duration Yrs (SD)	11 (6)	18 (19)	8 (5)	6.5
Concomitant DMARDS	MTX 9, HCQ 2, SSZ 1	None	3 MTX, 2 LFD, 1 ciclosporin	None
Duration Etanercept Yrs (SD) Pre Reduction	3.3 (2.0)	4.1 (1.8)	3 (0.9)	5.5
Mean Baseline Disease Activity (SD)	*DAS 28:* 2.5 (0.6)	*BASDAI:* 2.0 (0.4); *Spinal VAS:* 1.1 (0.6)	*All meeting criteria*	*Clinician remission*
Mean Disease Activity (SD) at 6 months (of those remaining	DAS 28: 2.1 (1.2)	*BASDAI: 0.9 (1.3) Spinal VAS: 0.0 (0.0)*	*All meeting criteria*	*Clinical Remission*
Mean Time (months) to Exit Pathway (For Those Exiting)	1.8 (1.3)	1	1.8	2
Number Completing 6 months	9	3	2	1

Conclusion: We were able to reduce Etanercept dose for a large proportion of our patients with low disease activity and maintain low disease activity without flares of disease. This represented significant cost savings. When developing future guidance, national prescribing bodies could take this into account when determining the relative positioning for different biologic therapies.

Reference:

1) Smolen, Josef S. "L1-Low Disease Activity or Remission Induction with Etanercept 50 Mg and Methotrexate in Moderately Active Rheumatoid Arthritis: Maintenance of Response and Safety of Etanercept 50 Mg, 25 Mg, or Placebo in Combination with Methotrexate in a Randomized Double-Blind Study." (2011). ACR conference abstract.

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The Effect Of Methotrexate On Adalimumab Pharmacokinetics: Pooled Analysis Of Adalimumab Pharmacokinetics In Patients With Rheumatoid Arthritis After Subcutaneous Administration. Walid Awni[1], Sabine Pilari[2], Ghada Ahmed[3] and Peter Noertersheuser[2]. [1]AbbVie Inc., North Chicago, IL, [2]AbbVie Deutschland GmbH & Co KG, Ludwigshafen, Germany, [3]AbbVie, North Chicago, IL.

Background/Purpose: Co-administration of methotrexate (MTX) has a significant effect on the pharmacokinetics (PK) of adalimumab (ADAL). MTX may impact the PK of other drugs by multiple mechanisms including immunosuppressant and anti- inflammatory effects. This pooled analysis was conducted to examine the effect of MTX and other factors on ADAL PK.

Methods: Individual subjects' PK and demographics data from 9 ADAL Phase II and III studies in patients with Rheumatoid Arthritis (RA; n=1991) after SC administration of different ADAL dosing regimens were pooled. 642 patients were on 40 mg ADAL every other week dosing regimen. Serum samples were collected prior to dosing and at several time points for up to 1 year for measurement of ADAL and anti-ADAL antibodies (AAA) using ELISA methods. All patients with at least one measurable ADAL were included. A patient was considered AAA+ if at least one sample had AAA > 20 ng/mL within 30 days after an ADAL dose. Analyses were conducted utilizing measured ADAL concentrations and population PK (PopPK) modeling.

Results: The median (range) age and weight of patients (77% F, 23%M) were 54 (4–87) yrs and 69.7 (13–186) kg. 48.8% were on a stable dose of concomitant MTX (10 to 30 mg/wk) and 51.2% received ADAL as monotherapy. 91.4% were adults and 8.6% were children (4 to 17 yrs). Patients on a stable dose of MTX at study start had lower baseline C-Reactive Protein (CRP) and Rheumatoid Factor (RF) compared to patients who were not on MTX. Median baseline CRP was 11.0 and 33.5 mg/L with and without MTX. Median baseline RF was 68 and 148 IU/mL with and without MTX. Overall, 8.8% of patients across all 9 studies, with 3.3% of patients on MTX co-medication and 14.7% of patients on ADAL monotherapy, had at least one AAA+ sample. PopPK indicated that MTX had the most significant impact on ADAL apparent clearance (CL) in all patients (AAA+ and AAA-), and even when patients with AAA+ were excluded from the analysis. ADAL clearance (CL) was 10.6 and 20.6 mL/hr with and without MTX in all patients and was 10.1 and 17.5 mL/hr with and without MTX in AAA- patients. Median ADAL CL was similar in patients receiving MTX doses of 10 mg/wk and up to 30 mg/wk. After accounting for MTX effect, body weight, baseline CRP and baseline RF were also factors that influence the variability in ADAL PK. ADAL CL increased with increase in body weight, and higher baseline levels of CRP or RF. After accounting for the differences in body weight, ADAL CL, with and without MTX, were similar in males and females, across races, and from 4 to 87 yrs of age.

Conclusion: Pooled analyses of data from nine ADAL Phase II and III studies in patients with RA after SC administration indicate that MTX has significant effects on ADAL PK in all patients and in AAA- patients. MTX effects on ADAL PK may potentially be by multiple mechanisms including an anti-inflammatory effect in addition to the immunosuppressant effect by reducing the development of AAA. After accounting for MTX effect and AAA+ status, body weight, baseline CRP and RF are additional factors that influence the variability in ADAL PK. ADAL PK were similar regardless of patient sex, race and age.

Disclosure: W. Awni, AbbVie, 1, AbbVie, 3; **S. Pilari**, AbbVie, 1, AbbVie, 3; **G. Ahmed**, AbbVie, 1, AbbVie, 3; **P. Noertersheuser**, AbbVie, 1, AbbVie, 3.

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Combining Methotrexate To Etanercept Does Not Improve Its Retention Rate In Rheumatoid Arthritis Patients When Compared To Etanercept Monotherapy. A Report From The Rhumadata® Clinical Data Base and Registry. Denis Choquette[1], Louis Bessette[2], Boulos Haraoui[1], Diane Sauvageau[1], Jean Pierre Pelletier[1], Jean-Pierre Raynauld[1], Edith Villeneuve[1] and Louis Coupal[1]. [1]Institut de Rhumatologie de Montréal, Montreal, QC, [2]Centre Hospitalier Universitaire de Québec, pavillon CHUL, Sainte-Foy, QC.

Background/Purpose: Etanercept (ETA) has demonstrated good retention in both mono and combination therapy in clinical trials of rheumatoid arthritis patients followed over short observation periods (less than 2 years). Studies evaluating the efficacy of anti-TNF have provided better results when it is used with methotrexate compared to monotherapy. Data from registries have also demonstrated that methotrexate significantly influence the retention on anti-TNF. The rationale of this analysis is to explore the impact of combining methotrexate with etanercept on retention vs. monotherapy usage over a prolonged observation period in the Rhumadata® clinical database and registry.

Methods: RA patients prescribed ETA as a first biologic agent after January 1st 2004 were included in the present analysis. Baseline demographics for both cohorts included age, disease duration, HAQ-DI, fatigue and pain visual analog scale evaluation (VAS), TJC, SJC, DAS 28 ESR and SDAI. The drug retention rate of subjects on ETA monotherapy (n=45) were estimated and compared to the retention rate of subjects also receiving a DMARD (n=211) using Kaplan-Meier survival estimates. Six month and yearly estimates (up to 5 years) were obtained. Statistical analysis was performed using SAS version 9.3. RHUMADATA® is a clinical database and registry used in daily clinical practice at the IRM and CORQ.

Results: At six months, drug retention for ETA monotherapy and combination therapy was estimated at 87%. Yearly drug retention rates for subjects on monotherapy ranged from 64% at year 1 to 36% at year 6. Estimates for subjects on combination therapy ranged from 78% to 53%.

Therapy	6 months	Year 1	Year 2	Year 3	Year 4	Year 5
Monotherapy (n=45)						
Mean retention time in days (StdD)	166.9 (6.9)	301.2 (16.1)	520.6 (39.8)	713.6 (65.1)	897.6 (91.2)	1053.55 (115.0)
% retention (StdE)[1]	87% (5%)	64% (7%)	55% (8%)	52% (8%)	49% (8%)	36% (6%)
Combination therapy (n=211)						
Mean retention time in days (StdD)	170.7 (2.3)	322.0 (6.5)	591.2 (16.5)	832.8 (27.3)	1057.6 (38.8)	1260.4 (50.32)
% retention (StdE)	87% (2%)	78% (3%)	71% (3%)	64% (3%)	58% (4%)	53% (4%)
Log-rank p-value	0.10	0.34	0.13	0.36	0.43	0.06

[1] Product-limit survival estimates

Conclusion: Etanercept with and without methotrexate discloses statistically similar retention rates from 6 months up to 5 years. It is worth noting that combination therapy remains numerically superior to the monotherapy over the 5 year observation period.

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Does Low Disease Activity At Six Months Predict Remission At 12 Months In Rheumatoid Arthritis Patients Treated With Biologics In a Real–World Setting? Philip Baer[1], William G. Bensen[2], Andrew Chow[3], Rafat Y. Faraawi[4], Denis Choquette[5], Isabelle Fortin[6], John T. Kelsall[7], Dalton E. Sholter[8], Emmanouil Rampakakis[9], John S. Sampalis[9], Francois Nantel[10], Allen J. Lehman[10], May Shawi[10] and Susan M. Otawa[10]. [1]Rheumatology, Scarborough, ON, [2]St. Joseph's Hospital and McMaster University, Hamilton, ON, [3]Credit Valley Rheumatology, Mississauga, ON, [4]Rheumatologist, KW Musculoskeletal Research Inc., Kitchener, ON, [5]Institut de Rhumatologie de Montréal, Montreal, QC, [6]Centre de Rhumatologie de l'Est du Québec, Rimouski, QC, [7]Mary Pack Arthritis Centre, Vancouver, Vancouver, BC, [8]Rheumatology Associates, Edmonton, AB, [9]JSS Medical Research, St-Laurent, QC, [10]Janssen Canada Inc, Toronto, ON.

Background/Purpose: Remission is considered the treatment goal in the management of patients with rheumatoid arthritis (RA). The objective of this analysis was to determine if low disease activity (LDA) at 6 months is a predictor of remission at 12 months in patients with RA treated with infliximab or golimumab in a Canadian real–world setting.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis (RA), ankylosing spondylitis (AS), or psoriatic arthritis (PsA) with infliximab or golimumab as first biologics or after having been treated with a biologic for less than six months. Patients with RA treated with infliximab or golimumab who were enrolled between 2002 and 2012 and had 12 months of follow-up were included in this analysis.

Results: A total of 436 patients with a mean (SD) age of 56.1 (13.1) years and disease duration of 10.4 (9.9) years were included in the analyses. Mean (SD) DAS-ESR, DAS-CRP, CDAI, and SDAI at baseline were 5.7 (1.5), 5.3 (1.3), 34.3 (16.0), and 36.9 (16.7), respectively. At 12 months 25.3%, 32.5%, 15.9% and 16.5% had DAS-ESR, DAS-CRP, CDAI and SDAI remission, respectively. Significant predictors of DAS-ESR remission at 12 months were LDA at 6 months [OR (95%CI) = 7.9 (4.5, 14.1)], change in SJC [OR (95%CI) = 1.1 (1.0, 1.1)] and DAS-ESR [OR (95%CI) = 0.8 (0.7, 1.0)] at 6 months. For DAS-CRP remission at

12 months, significant predictors were LDA at 6 months [OR (95%CI) = 8.0 (4.3, 14.9)] and change in DAS-CRP [OR (95%CI) = 0.7 (0.6, 0.9)] at 6 months. For CDAI remission at 12 months, significant predictor was LDA at 6 months [OR (95%CI) = 9.4 (4.6, 19.4)]. For SDAI remission at 12 months, significant predictor was LDA at 6 months [OR (95%CI) = 9.9 (4.3, 22.8)]. See Figure 1. Changes in CDAI, SDAI, TJC and SJC from baseline to 6 months were not associated with CDAI and SDAI remission at 12 months.

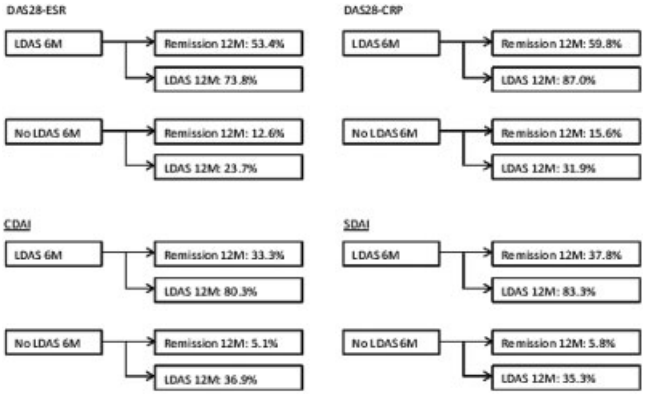

Figure 1. Proportion of LDA Patients at 6 Months in LDA and Remission at 12 Months

Conclusion: The results of this Canadian longitudinal observational study have shown that LDA at six months is a significant predictor of remission at 12 months. For patients achieving a low disease activity state at 6 months, there is a 7.9 to 9.9 odds ratio of achieving remission at 12 months. Data from this real-world registry suggest that a significant proportion of patients with LDA who had not achieved a therapeutic target of remission at 6 months do so at 12 months while maintained on the same biologic treatment.

Disclosure: P. Baer, Janssen Pharmaceutica Product, L.P., 5; **W. G. Bensen**, None; **A. Chow**, JNJ, Amgen, Pfizer, Abbvie, UCB, Eli Lilly, Celgene, Takeda, Astra Zeneca, BMS, Roche, 5; **R. Y. Faraawi**, None; **D. Choquette**, None; **I. Fortin**, None; **J. T. Kelsall**, None; **D. E. Sholter**, None; **E. Rampakakis**, None; **J. S. Sampalis**, None; **F. Nantel**, None; **A. J. Lehman**, Janssen Canada, 3; **M. Shawi**, Janssen Canada, 3; **S. M. Otawa**, Janssen Canada, 3.

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Infection Risk Among Patients Receiving Concurrent Denosumab and Biologic Or Non-Biologic DMARD Therapy: An Analysis Of The Consortium Of Rheumatology Researchers Of North America (CORRONA) Registry.

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Background/Purpose: RANKL is a cytokine member of the tumor necrosis family that mediates osteoclastic bone resorption. Denosumab prevents RANKL from activating RANK on the cell surface of osteoclasts, resulting in decreased bone resorption. RANK/RANKL also plays a role in the immune system, with RANK receptors found on macrophages and dendritic cells; as such, denosumab may interfere with normal immune pathways. Infections (including serious events such as endocarditis) have been reported in clinical trials of denosumab. Data on the potential infectious complications of denosumab in patients with autoimmune disease is lacking, despite higher baseline rates of infection among this group. We sought to identify the rate of infection among patients with autoimmune disease and recent initiation of denosumab.

Methods: We utilized the CORRONA registry to calculate the infection rate among patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) following initiation of denosumab. Eligible patients had visit data ≥ 6 months prior to the start of denosumab and at least 1 follow-up visit post drug initiation. Data between 8/2009 and 2/2013 were included. Age, sex, disease activity, prior infection history, comorbid disease, and disease specific medication use (biologic DMARD: bDMARD, non-biologic DMARD: nbDMARD and prednisone) were recorded. Overall incident and serious infections (requiring hospitalization or IV antibiotics) were recorded. Rates of incident and serious infections per 100 person-years were calculated. Cox proportional hazard analysis was performed to identify factors associated with infection risk.

Results: 33,288 patients had ≥ 2 study visits (28,852 RA + 4436 PsA); 96 were eligible for this analysis. Demographic data is presented in Table 1. Data regarding incident and serious infections are presented in Table 2. Prednisone use was associated with an increased incidence of infection (HR 3.73; [1.29–10.77]) in univariate analysis. No other variable demonstrated a significant association.

Table 1. Baseline characteristics among RA and PsA patients on denosumab

	All Patients N=96	RA Patients N=90 (93.8)	PsA Patients N=6 (6.3)
Age (years, SD)	73.3 ± 10.7	73.3 ± 10.7	73.2 ± 10.5
Female (%)	94 (97.9)	88 (97.8)	6 (100.0)
Caucasian (%)	88 (91.7)	82 (91.1)	6 (100.0)
Disease Duration (years, SD)	17.0 ± 12.8	16.7 ± 12.3	21.5 ± 20.0
Disease Activity	7.7 ± 8.4	7.8 ± 8.5	6.7 ± 7.5
CDAI (mean, SD)	71 (74.0)	67 (74.0)	4 (66.7)
Low Disease activity[1] (%)			
Drug Therapy	7 (7.3)	7 (7.8)	0 (0.0)
Denosumab alone (%)	46 (47.9)	42 (46.7)	4 (66.7)
nbDMARD[2] (%)	43 (44.8)	41 (45.5)	2 (33.3)
bDMARD[3] ± nbDMARD (%)			
Prednisone Use	30 (31.3)	28 (31.1)	2 (33.3)
Current (%)	56 (58.3)	51 (56.7)	5 (83.3)
Prior (%)			
Prior Serious Infections (%)	10 (10.4)	10 (11.1)	0 (0.0)

Abbreviations: SE: standard error. CDAI: clinical disease activity index
[1] Low disease activity defined as CDAI ≤ 10
[2] nbDMARD: leflunomide, methotrexate, cyclosporine, azathioprine
[3] bDMARD: certolizumab, anakinra, etanercept, adalimumab, golimumab, infliximab, abatacept, rituximab, or tocilizumab

Table 2. Infection Rates among Patients on Denosumab*

	Events (%)	Person-Years At Risk	Infection Rate per 100 Person-Years** (95% CI)
Incident Infections+ (N=96)	14 (14.6)	58.9	24.0 (14–40)
Denosumab alone (N=7)	0 (0)		NC
nbDMARD (N=46)	6 (13.0)		NC
bDMARD (N=10)	1 (10.0)		NC
bDMARD **and** nbDMARD (N=33)	7 (21.2)		NC
Serious Infections++ (N=96)	3 (3.1)	58.9	5 (2–16)

Incident infections: septic arthritis/bursitis, cellulitis, sinusitis, diverticulitis, sepsis, pneumonia bronchitis, gastroenteritis, meningitis, UTI, URI or other specified site
*Table includes 90 patients with RA and 6 with PsA. Among the PsA cohort, 2 total infections (1 serious) were recorded
Historical rates of infection among RA patients in CORRONA (Au et. al; *Ann Rheum Dis* 2011;70:785–791): **31.2 outpatient infections per 100 person-yrs; 0.8 hospitalized infections per 100 person-yrs
+ Kaplan-Meier estimate of incident infection 3 months post denosumab start: 2.5% (95% CI 0.6–9.3); at 6 months: 12.0% (95% CI 6.4–22)
++ Kaplan-Meier estimate of serious infection 3 months post denosumab start: 1.2% (95% CI 0.1–8.3); at 6 months 2.5% (95% CI 0.6–9.7)

Conclusion: The infection rate appears to be low among patients on denosumab and concurrent DMARD therapy. Compared to historical incidence rates for infection within the larger CORRONA database (and other historical cohorts), the rates observed herein appear comparable. Univariate analysis was limited by cohort size, but did not identify an association with nbDMARD or bDMARD use and subsequent infection. Additional study will be necessary to further delineate the risk for infection in patients exposed to denosumab.

Disclosure: V. J. Bray, Amgen, 8; **A. W. Bagley**, None; **S. G. West**, None; **C. J. Etzel**, Corrona Inc., 3; **J. M. Kremer**, CORRONA, 1, CORRONA, 3; **J. R. Kolfenbach**, None.

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Distinction Between Glucocorticoid-Responders and Non-Responders In Rheumatoid Arthritis: A New Role For Endoplasmic Reticulum Aminopeptidase 2. Ruth Fritsch-Stork, Sandra Cardoso, Jasper Broen, Marian Groot-Koerkamp, Arno Concepcion, Floris Lafeber and Johannes W.J. Bijlsma. University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: Glucocorticoids (GC) have been a cornerstone of Rheumatoid arthritis (RA)-therapy for the last decades. However, about a third of RA-patients do not respond adequately. As monocytes and T-cells play an important role in RA-pathogenesis, the differential gene expression of these cells before and 24 hours after start of pulse therapy with methylprednisolone was evaluated in order to find potential predictors of GC-response.

Methods: CD14-positive and CD4-positive cells were isolated by MACS sorting from five GC-Responders meeting the European League against Rheumatism (EULAR) response criteria and five Non-Responders. The clinical response was measured by disease activity score (DAS28) at the end of pulse therapy (3× 1000mg Methylprednisolone) at day 5. Labeled cRNA was hybridized to Agilent 4×44K microarrays and differentially expressed genes were determined by MAANOVA. False discovery rate was used as multiple testing correction and set at 5%. Genes were validated by quantitative real-time PCR (qPCR).

Results: We found eight known genes differentially expressed in CD14-cells and 4 in CD4-T-cells of GC-Responders compared to Non-Responders before start of therapy using microarrays. After 24 hours, 13 known genes were seen differentially expressed in CD14-cells and CD4-T-cells each. Higher expression of ERAP2 in monocytes and CD4-cells (fold change (FC) Responders vs. Non-Responders: 6.6 and 4.9; $p<0.007$ and $p<0.02$) and LST1 and FAM26F in CD4-Tcells of GC-Responders (FC: 2.54 and 4.4; $p<0.06$ and $p<0.009$) before start of therapy was verified by qPCR and correlated with DAS28 at day 5. In both cell types ERAP2 (CD14-cells: FC: 4.9; $p<0.01$; CD4-cells: FC: 7.5; $p<0.003$) and FAM26F (CD14-cells: FC: 4.2; $p<0.007$; CD4-cells: FC: 8.0; $p=0.058$) were also significantly higher after 24 hours in GC-Responders measured by qPCR. Additionally, CCNB2 (FC: 0.49; $p<0.008$) was significantly and TMP4 (FC: 0.62; $p=0.058$) marginally lower in CD4-Tcells and CEP350 and DICER were marginally higher (FC: 1.8; $p=0.054$ and FC: 1.55; $p=0.063$) in CD14-cells of GC-Responders compared to GC-Non-Responders.

Conclusion: We found several differentially expressed genes in GC-Responders versus GC-Non-Responders before and 24 hours after start of pulse therapy. The most striking difference is the significantly higher expression of ERAP2 in T-cells and monocytes of GC-Responders. ERAP2 constitutes a susceptibility locus in autoimmune disease, and functions as proteolytic enzyme implicated in antigen presentation. Its homologue is also known to cleave cell surface receptors (TNFR1, IL1R2, IL6Ra). The increased expression in GC-Responders compared to GC-Non-Responders may thus constitute not only a potential predictor of the clinical response to GC in RA, but also warrants further investigation to elucidate the possible role in the inflammatory process of RA.

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A Real-World Risk Analysis Of Biological Treatment (Adalimumab and Etanercep) In Country With High Prevalence Of Tuberculosis and Hepatitis B/C. Ying-Ming Chiu[1], Chao-Hsiung Tang[2], Sheng-Tzu Hung[3], Ya-Wen Yang[4], Chi-Hui Fang[4] and Hsiao-Yi Lin[5]. [1]Changhua Christian Hospital, Changhua City, Taiwan, [2]Taipei Medical University, Taipei, Taiwan, [3]Formosa Biomedical Technology Corp., Taipei, Taiwan, [4]Pfizer Limited, Taipei, Taiwan, [5]Taipei Veterans General Hospital, Taipei, Taiwan.

Background/Purpose: Biologics have been widely utilized in many rheumatic diseases. Risks associated with the use of biological treatments are revealed in many published studies. Nevertheless, it was lacking investigations in countries with high prevalence of tuberculosis (TB) and hepatitis B/C (HBC). This research aimed to analyze the difference of risk for adalimumab and etanercept in endemic areas.

Methods: National Health Insurance (NHI) Research Database was applied, which consists of administrative and claims records; covers over 99% of entire population in Taiwan. Patients who had used adalimumab or etanercept in between 2003 and 2011 were eligible for this analysis. Exposure of adalimumab or etanercept was quantified in treatment episode. Each patient could have multiple treatment episodes with different biologics. With same biologic, a new treatment episode was initiated when 6 months apart. The incidence rates of TB, HBC, acute myocardial infarction/heart failure (AMI/HF), infection hospitalization (IHP), herpes zoster (HZ) and lymphoma (Lym) were calculated in person year. All events were defined by corresponding ICD codes, medications related to events and diagnosis during hospitalization. Event was captured within 30 days posterior to the end of each treatment episode. Time to event was summarized by Kaplan-Meier curves. The Cox proportional model was conducted to estimate the hazard ratio (HR) with 95% confidence interval (CI) by adjusted covariates.

Results: From 2003 to 2011, there were 3,844 patients (4,049 episodes) treated with adalimumab and 5,933 patients (7,056 episodes) treated with etanercept. The average age of adalimumab and etanercept users were 50.8 (SD 14.58) and 51.5 (SD 15.29); about 61.4% and 73.1% were female respectively. In adalimumab group, incidence rates of TB, HBC, AMI/HF, IHP, HZ and Lym were 1.62, 0.75, 0.38, 3.05, 0.62 and 0.11 per 100 person-years. Conversely, incidence rates of TB, HBC, AMI/HF, IHP, HZ and Lym were 0.68, 0.4, 0.23, 2.16, 0.64 and 0.11 in etanercept group. Comparing adalimumab to etanercept, the crude HR of TB, HBC, AMI/HF, IHP, HZ and Lym were 2.03 ($P<0.0001$), 1.61 (0.03), 1.56 (0.14), 1.32 (0.01), 0.94 (0.78), 0.96 (0.94). The adjusted HR of TB, HBC, AMI/HF, IHP, HZ and Lym were 1.53 ($P=0.01$), 1.31, 1.27 (0.43), 1.12 (0.27), 0.90 (0.62), 0.76 (0.58).

Table 1. Incidence rates and Hazard ratios

	Adalimumab			Etanercept		
	# person-year	# event	Incidence Rate	# person-year	# event	Incidence Rate
TB	5,317	86	1.62	13,143	89	0.68
HBC	5,311	40	0.75	13,148	53	0.4
AMI/HF	5,315	20	0.38	13,134	30	0.23
IHP	5,244	160	3.05	12,924	279	2.16
HZ	5,299	33	0.62	13,042	83	0.64
Lym	5,324	6	0.11	13,146	14	0.11

	COX Proportion Hazard Model					
	Before Adjusted			After Adjusted		
	cHR[3]	95% CI	P value	aHR[4]	95% CI	P value
TB	2.03	1.50 ~ 2.74	<.0001	1.53	1.13 ~ 2.06	0.0058
HBC	1.61	1.06 ~ 2.44	0.0262	1.31	0.86 ~ 1.99	0.2076
AMI/HF	1.56	0.87 ~ 2.79	0.1362	1.27	0.71 ~ 2.28	0.4273
IHP	1.32	1.09 ~ 1.62	0.0058	1.12	0.92 ~ 1.37	0.2688
HZ	0.94	0.62 ~ 1.42	0.7783	0.9	0.59 ~ 1.37	0.6185
Lym	0.96	0.37 ~ 2.54	0.9404	0.76	0.29 ~ 2.00	0.5781

Note: 1. Per 100 person year
2. Hazard ratios were calculated for adalimumab versus etanercept (reference)
3. cHR: crude hazard ratio
4. aHR: adjusted hazed ratio; demography, disease severity, disease history/duration were used for adjustment.

Conclusion: Across different events, patients with adalimumab treatment tended to have an adverse event in a shorter time period relative to etanercept. Patients had a significant higher risk of TB if used adalimumab.

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Autoantibody Profiles Predict Responsiveness To Methotrexate and Anti-TNF Therapy In Early Rheumatoid Arthritis. Petra Budde[1], Angelika Lueking[1], Carmen Theek[1], Peter Schulz-Knappe[1], Jacqueline Detert[2], Gerd R Burmester[3] and Matthias Schneider[4]. [1]Protagen AG, Dortmund, Germany, [2]Charité - Universitätsmedizin Berlin, Berlin, Germany, [3]Charité-Universitätsmedizin Berlin, Free University and Humboldt University of Berlin, Berlin, Germany, [4]Heinrich-Heine-University, Duesseldorf, Germany.

Background/Purpose: Novel therapeutic concepts in early rheumatoid arthritis (ERA) are aiming for an early intervention and effective control of disease activity reaching remission. Most current guidelines recommend methotrexate (MTX) as the first DMARD even though at least for half of these patients MTX alone is not sufficient to achieve this goal. Currently, the clinical response to the first and probably second DMARD is used to decide

further therapeutic approaches. Here we evaluated the autoantigen repertoire as a prospective predictive tool in ERA patients treated with MTX alone or combined with Adalimumab (ADA) in an induction trial (HITHARD study, Detert et al. ARD 2012).

Methods: Luminex-based SeroTag technology was applied to perform large-scale studies in order to define the most prevalent autoantibodies in RA and other connective tissue diseases. 6,000 different human proteins from our huPROT library were incubated with patient sera to screen for autoantibody reactivities and disease or treatment induced alterations using univariate and multivariate statistical algorithms. The DAS28 score was defined as the clinical endpoint, and patients were grouped into those achieving DAS28<2.6 "remission" and "non-remission" in both treatment arms. Autoantibody profiles measured before treatment were then correlated with the status "remission" and "non-remission".

Results: A previously identified diagnostic panel of six novel antigens allowed to distinguish ERA HITHARD samples from age and sex-matched healthy controls with an AUC=0.94. Comparing pre- and post-treatment samples, a small, but significant reduction (−1.3 fold) of autoantibody reactivities towards two antigens was detected in both treatment arms, even though levels were not normalized compared to healthy controls. A specific autoantibody signature was identified in a subgroup of ERA patients who achieved clinical remission after 24 weeks under ADA/MTX combination therapy. A classification biomarker panel of 5–10 autoantigens appears to be sufficient to identify RA patients who will achieve clinical remission upon ADA/MTX therapy. This panel was independent of anti-citrullinated protein antibody (ACPA) positivity. A different set of up to nine antigens was identified that could predict remission in RA patients upon PLACEBO/MTX therapy.

Conclusion: We identified autoantibody patterns in ERA patients associated with clinical response to an induction therapy and identified two independent marker panels that, if further developed into a screening test, could help to guide future treatment selection for MTX alone or a combined use of MTX/ADA.

Disclosure: P. Budde, Protagen AG, 3; **A. Lueking**, Protagen AG, 3; **C. Theek**, Protagen AG, 3; **P. Schulz-Knappe**, Protagen AG, 6; **J. Detert**, Abbott Immunology Pharmaceuticals, 2; **G. R. Burmester**, AbbVie, Essex/Schering-Plough, Novartis, Roche, Wyeth, 2, AbbVie, Essex/Schering-Plough, 5; **M. Schneider**, None.

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The Impact Of Inadequate Response To Prior Biologic Agents On Abatacept Drug Retention In Rheumatoid Arthritis Patients. A Pan-European Analysis Of RA Registries. Axel Finckh[1], Florenzo Iannone[2], Juan Gomez Reino[3], David Neto[1], Elisabeth Lie[4], Piet van Riel[5], Merete Lund Hetland[6], Karel Pavelka[7], Carl Turesson[8], Xavier Mariette[9] and Jacques-Eric Gottenberg[10]. [1]University of Geneva, Geneva, Switzerland, [2]D.I.M.I.M.P, Rheumatology Unit - University of Bari, Bari, Italy, [3]Hospital Clínico de Santiago, Santiago de Compostela, Spain, [4]Diakonhjemmet Hospital, Oslo, Norway, [5]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [6]The Danish Rheumatologic Database (DANBIO), Glostrup Hospital., Copenhagen, Denmark, [7]Department of Clinical and Experimental Rheumatology, Charles University, Prague, Czech Republic, [8]Lund University, Malmö, Sweden, [9]Bicêtre University Hospital, Le Kremlin Bicetre, France, [10]Strasbourg University Hospital, Strasbourg, France.

Background/Purpose: In rheumatoid arthritis (RA), abatacept (ABA) may be used in biologic naïve patients (pts) or after failure to an anti-TNF or other biologic agents (BIO-IR). Drug retention is a useful overall measure of effectiveness, integrating both clinical response and tolerance. For several biologic antirheumatic agents (BIO), it has been demonstrated that a history of BIO-IR strongly decreases subsequent drug retention. The impact of BIO-IR has been less studied with ABA.

The objective of this study was to compare drug retention of ABA in BIO-IR pts.

Methods: This is an observational cohort analysis of 8 prospective, longitudinal, European cohorts of RA pts (ARTIS (Sweden), ATTRA (Czech Republic), BIOBADASER (Spain), DANBIO (Denmark), GISEA (Italy), NORDMARDS (Norway), ORA (France), SCQM (Switzerland)). We included all RA pts treated with ABA in real life settings. The primary end point was drug retention of ABA. Secondary endpoint was ABA discontinuation for ineffectiveness. Time to discontinuation was defined as the time between drug initiation and last administration plus one dispensation interval. Drug discontinuation was analyzed using a Cox proportional hazards model, adjusting for potential confounders, such as calendar year of treatment initiation, patient demographics and disease characteristics.

Results: We identified 3783 pts initiating ABA contributing 5980 patient-years of follow-up. Of these, 1159 pts were BIO-naïve, 883 pts had 1 prior BIO-IR, 861 pts had 2, 555 pts had 3 and 325 pts had 4 or more prior BIO-IRs. 85% of pts in the BIO-IR group had failed an anti-TNF agent as last biotherapy. Pts were mostly female (81%), with a mean age of 57 yrs, long disease durations (mean 12.1 yrs), and active, severe disease at baseline (mean values for DAS28: 5.1, ESR: 33 mm/hr, HAQ: 1.3).

In the 1977 ABA discontinuations, 72% were motivated by ineffectiveness, 24% by adverse events, 2% by remission and 2% by other reasons, when the reason for discontinuation was indicated. Drug retention differed significantly by prior BIO-IRs ($p<0.001$, logrank test). BIO-naïve pts had the highest drug retention (reference Hazard Ratio (HR): 1), pts with 1–3 prior BIO-IRs had lower retention (HR: 1.2–1.3, $p<0.01$), and pts with 4 or more BIO-IRs had the lowest retention (HR: 1.4, $p < 0.001$). A similar trend was observed when examining treatment discontinuation for ABA ineffectiveness ($p< 0.001$, logrank test). Drug discontinuation for ineffectiveness was uncommon in BIO-naïve pts (reference HR: 1), higher in pts with 1–2 prior BIO-IRs (HR: 1.2, $p<0.05$) and highest in pts with 3 or more BIO-IRs (HR: 1.5–1.6, $p<0.01$). Other strong predictors of drug retention were calendar year of ABA initiation, with significantly shorter drug retention in recent years (≤2007: HR=1; 2008–9: HR=1.2; ≥2010: HR: 2.2) and country of origin.

Conclusion: Drug retention of ABA is strongly influenced by a history of prior BIO-IR, with higher discontinuation rates in pts having experienced more BIO-IRs, which suggests a progressive selection of pts with more resistant disease. However, some pts with a history of several BIO-IRs remained on ABA for an extensive time, suggesting some benefit of switching modes of action after anti-TNF-IR.

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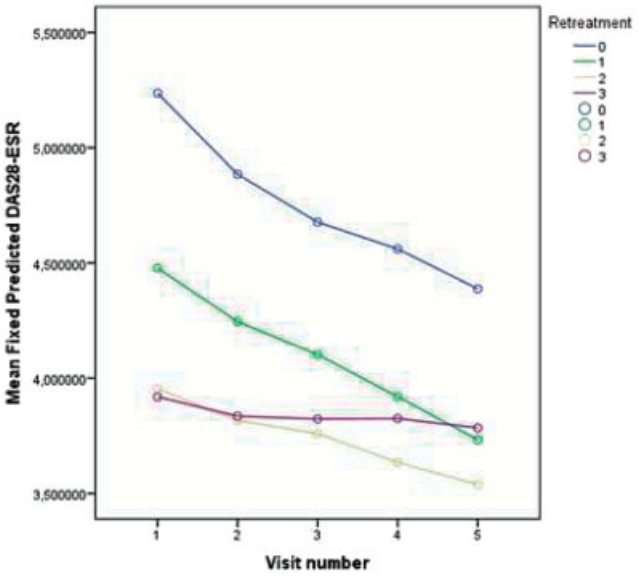
Effectiveness Of Repeated Courses Of Rituximab In RA – Results From The Cererra Collaboration. Katerina Chatzidionysiou[1], Elisabeth Lie[2], Evgeny Nasonov[3], Galina Lukina[3], Merete Hetland[4], Ulrik Tarp[5], Karel Pavelka[6], Cem Gabay[7], Dan Nordström[8], Helena Canhao[9], Matija Tomsic[10], Piet van Riel[11], Juan Gomez-Reino[12], Ioan Ancuta[13], Tore Kvien[2] and Ronald van Vollenhoven[1]. [1]Unit for Clinical Research Therapy. Inflammatory Diseases (ClinTrid), Karolinska Institute, Stockholm, Sweden, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]ARBITER, Institute of Rheumatology, Moscow, Russia, [4]DANBIO, Department of Rheumatology, Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [5]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [6]Department of Clinical and Experimental Rheumatology, Charles University, Prague, Czech Republic, [7]SCQM registry, University Hospitals of Geneva, Geneva, Switzerland, [8]ROB-FIN, Helsinki University Central Hospital, Helsinki, Finland, [9]Instituto de Medicina Molecular, Rheumatology Research Unit, Rheumatology Research Unit, on behalf of the Rheumatic Diseases Portuguese Register, Lisbon, Portugal, [10]BioRx.si, University Medical Centre Ljubjana, Ljubljana, Slovenia, [11]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [12]Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain, [13]Cantacuzino Hospital, Bucharest, Romania.

Background/Purpose: Retreatment with rituximab (RTX) is common clinical practice, although several aspects regarding retreatment, such as frequency, need to be further elucidated. The aim of this study was to describe the effectiveness of repeated courses of RTX in a large observational cohort of real-life patients with RA.

Methods: Pooled data from the Collaborating European Registries for Rituximab in RA (CERERRA) project were used. Patients with RA who received at least 4 cycles with RTX were identified and included in the analysis. A covariate-adjusted mixed effects model was fitted to the longitudinal DAS28 for patients with complete covariate information, including country, sex, age, anti-CCP status, number of prior biologics and concomitant DMARD treatment.

Results: 340 patients met the eligibility criteria for these analyses. At baseline (start of RTX) the mean (SD) age was 53.5 (12.6) years and the mean (SD) disease duration was 12.1 (8.2) years. Patients were 83% females, 79%

RF positive and 74% anti-CCP positive. 60% were treated with corticosteroids and 84% with concomitant DMARD. Patients had failed 2.7 (1.5) prior DMARDs and 1.1 (1.0) prior biologic agents. The baseline DAS28 was 6.0 (1.4). In figure 1 the mean fixed predicted decrease of DAS28 after the first cycle and after each retreatment (1st, 2nd and 3rd) is shown. Significant improvement in DAS28 ($p<0.001$) was observed for each course of RTX. Comparison between curves (based on estimated marginal means) revealed significant difference between the first cycle (0) and the fourth (3rd retreatment), $p<0.0001$, and borderline significant difference between first cycle and 2nd retreatment ($p=0.05$).



Conclusion: Repeated retreatment with RTX can lead to further clinical improvement after the first course of RTX.

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Development Of a Novel Bispecific Therapeutic For Arthritic Diseases. Mathieu Ferrari[1], Shimobi Onuoha[1], Tahereh Kamalati[2], Daniele Sblattero[3] and Costantino Pitzalis[4]. [1]William Harvey Research Institute, Barts and the London School of Medicine and Dentistry Queen Mary University of London, London, United Kingdom, [2]University College of London, London, United Kingdom, [3]University of Eastern Piedmont, Novara, Italy, [4]William Harvey Research Institute, QMUL, London, United Kingdom.

Background/Purpose: Despite the obvious success of current biological agents for treatment of rheumatoid arthritis (RA), achievement of broader efficacy and improved safety profile remains an unmet need in RA therapy. There is significant evidence demonstrating molecular heterogeneity within the endothelium of different tissues, conferring organ tropism to migrating lymphocytes subsets by direct interaction with specific homing receptors. We have previously reported the isolation of a single chain Fv (scFv A7) antibody with specificity for synovial arthritic microvasculature, following an in vivo phage display selection on SCID mice grafted with human arthritic synovium[1]. The aim of the present study was to develop the scFv A7 as a tissue specific therapeutic in arthritic disease conditions.

Methods: In order to obtain a bivalent molecule with increased avidity and serum half-life, the scFvA7 was subcloned in fusion with the CH2-CH3 domain of the human IgG (scFv A7-Fc). In addition, scFv A7-Fc was coupled with the scFv-Fc of the Adalimumab anti-TNF antibody, via a monocistronic RNA approach, to form a bispecifc antibody (BsAb) using the Knobs-into-Holes technology[2] (A7/Adalimumab). The reactivity in frozen and paraffin embedded tissue sections was investigated using immunohistochemistry and immunofluorescence analysis. *In vitro* functionality and biological activity was assessed in TNF-ELISA and TNF cytotoxicity assay on L-929 cell line.

Results: The scFv-Fc fusion protein of Adalimumab showed analogous anti-TNF properties with the parent antibody, EC50 0.008nM (Adalimumab 0.006nM), proving the validity of the scFv format. The BsAb A7/Adalimumab achieved a high degree of efficient heterodimerisation showing only 3% Adalimumab homodimer and was able to selectively bind TNFα *in vitro* with similar efficacy to the TNF blocker with a 0.01nM EC50. Despite the monovalency for the anti-TNF activity, the BsAb showed a dose dependent rescue of TNF induced cytotoxicity in L-929 cell line comparable to Adalimumab with a 0.4nM IC50 (Adalimumab 0.16nM), demonstrating the biological functionality of the construct. In addition, the A7/Adalimumab antibody proved to efficiently and specifically target the stromal compartment of human arthritic synovial microvasculature, maintaining unaltered the organ tropism of the original scFv A7.

Conclusion: Our results demonstrate that the reactivity of scFv A7 is specific to the microvasculature of human arthritic synovium. This specific reactivity suggests that the target molecule for scFv A7 may have potential as a biomarker in arthritis and also have applications as an immunotherapeutic target. The bispecific antibody format developed showed unaltered TNF blocking capacity and synovial specificity, that may allow reduction in the dosage and/or administration frequency, with the ultimate goal to reduce the systemic exposure and achieve a better therapeutic index and decreasing health care costs.

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A Systematic Review and Meta-Analysis Comparing Low- Versus High-Dose Rituximab For Rheumatoid Arthritis. Markus Bredemeier, Fernando K. de Oliveira and Claúdia M. Rocha. Hospital Nossa Senhora da Conceição - Grupo Hospitalar Conceição, Porto Alegre, Brazil.

Background/Purpose: The approved dose of rituximab (RTX) for rheumatoid arthritis (RA) is 2×1000 mg infusions given 2 weeks apart. There is contradictory evidence regarding the effectiveness of a lower dose regimen (2×500 mg) of RTX. Our aim was to compare the efficacy and safety of low- and high-dose RTX and to test the non-inferiority of the low-dose scheme.

Methods: A systematic literature review searching for randomized controlled trials (RCTs) was conducted using Embase, PubMed, Cochrane and Web of Science databases. Additional studies were hand searched in ClinicalTrials.gov, Clinicaltrialsregister.eu, and Roche-trials.com websites. The meta-analysis was conducted according to the recommendations of the PRISMA statement. The primary endpoints were ACR20, ACR50, and ACR70 responses and DAS28 score at 24 and 48 weeks. Secondary endpoints were patient reported outcomes (PRO; HAQ, SF-36, and FACIT-F scores) and adverse events. For the primary dichotomous efficacy outcomes, non-inferiority of low-dose RTX was confirmed present when the lower boundary of the 95% CI of the risk ratio (RR) was ≥ 0.80. For DAS28 and PRO, non-inferiority was confirmed when the upper boundary of the 95% CI of the standardized mean difference between low- and high-dose RTX was ≤ 0.25 (i.e., within the margin of a small effect size).

Results: Six RCTs were identified (1–6). Four RCTs (1–4) were included in the meta-analysis of efficacy outcomes, which showed no significant differences in the primary outcomes between low- and high-dose RXT (Table). Non-inferiority criteria of low-dose RTX were met for ACR20, ACR50, DAS28, and PRO (at weeks 24 and 48) (Table). The results of the efficacy outcomes of the Score trial (5), a double-blind RCT, were not extractable, but there were similar improvements in ACR20 and ACR50 responses in both RTX groups at week 52. The DAS28 and the HAQ scores at 24 and 52 weeks showed statistically significant improvements (comparing to placebo) only in the low-dose RTX group. The Results of the Smart study (6), an open-label RCT that included only anti-TNF experienced patients, demonstrated non-inferiority of low-dose RTX for DAS28-CRP in patients that initially responded to standard-dose RTX. Serious adverse events did not differ significantly, but first infusion reactions were less frequent with low-dose RTX (Table).

Table. Comparison of the efficacy and safety outcomes between low- and high-dose rituximab (RTX).

CATEGORICAL OUTCOMES

	24 weeks	48 weeks
	Risk ratio of low- versus high-dose RTX (95% CI), I^2 statistic, statistical model, P value	Risk ratio of low- versus high-dose RTX (95% CI), I^2 statistic, statistical model, P value
ACR20*	0.99 (0.92, 1.08), I^2=36%, FE, P=0.90	0.95 (0.87, 1.02), I^2=0%, FE, P= 0.17
ACR50*	0.94 (0.82, 1.09), I^2=0%, FE, P=0.40	0.90 (0.80, 1.02), I^2=0%, FE, P=0.10
ACR70*	0.81 (0.64, 1.01), I^2=0%, FE, P=0.06	0.90 (0.76, 1.08), I^2=0%, FE, P=0.26

	At 24 or 48 weeks (depending on study duration)
Serious adverse events †	0.84 (0.61, 1.16), I^2=0%, FE, P=0.29
Serious infections †	0.77 (0.37, 1.58), I^2=0%, FE, P=0.47
Early withdrawal (all causes) †	0.98 (0.70, 1.37), I^2=33%, FE, P=0.92
First infusion reactions †	0.83 (0.69, 1.00), I^2=0%, FE, P=0.05

CONTINUOUS OUTCOMES

	24 weeks	48 weeks		
	Mean difference (95% CI), I^2 statistic, statistical model, P value	Standardized mean difference (95% CI)	Mean difference (95% CI), I^2 statistic, statistical model, P value	Standardized mean difference (95% CI)
Mean change in DAS28‡	0.08 (−0.08, 0.23), I^2=17%, FE, P=0.33	0.06 (−0.05, 0.16)	0.17 (−0.01, 0.35), I^2=0%, FE, P=0.06	0.11 (−0.01, 0.23)
Mean change in HAQ‡	0.02 (−0.06, 0.10), I^2=0%, FE, P=0.65	0.03 (−0.09, 0.15)	0.03 (−0.05, 0.12), I^2=0%, FE, P=0.45	0.04 (−0.08, 0.16)
Mean change in physical component summary (SF−36)£	−0.03 (−1.47, 1.42), I^2=0%, FE, P=0.97	−0.00 (−0.17, 0.17)	−0.84 (−1.94, 0.26), I^2=0%, FE, P=0.14	−0.10 (−0.22, 0.03)
Mean change in mental component summary (SF−36) £	−0.12 (−2.22, 1.97), I^2=37%, FE, P=0.91	−0.01 (−0.18, 0.16)	0.19 (−1.33, 1.70), I^2=0%, FE, P=0.81	0.01 (−0.11, 0.14)
Mean change in FACIT−F £	−0.84 (−2.53, 0.85), I^2=0%, FE, P=0.33	−0.08 (−0.25, 0.08)	−0.78 (−2.02, 0.46), I^2=0%, FE, P=0.22	−0.08 (−0.20, 0.05)

* Values lower than 1.0 favor high-dose RTX. †Values lower than 1.0 favor low-dose RTX. ‡ Positive values favor high-dose RTX. £ Positive values favor low-dose RTX. CI: confidence interval, FE: fixed effects model.

Conclusion: Low-dose RTX has similar effectiveness and met non-inferiority criteria for most primary outcomes. Considering the lower cost, it should be the standard RTX regimen for rheumatoid arthritis.

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Efficacy and Safety Of Infliximab Or Adalimumab Vs Abatacept In Patients With Rheumatoid Arthritis and An Inadequate Response To Methotrexate: Attest-Ample Network Randomized Trial. Robin Christensen[1], Simon Tarp[1], Daniel E. Furst[2], Lars E. Kristensen[3] and Henning Bliddal[1]. [1]Musculoskeletal Statistics Unit, The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, [2]David Geffen School of Medicine, University of California, Los Angeles, CA, [3]Department of Clinical Sciences, Lund, Section of Rheumatology, Lund University, Lund, Sweden.

Background/Purpose: Using combined data from the ATTEST [1] and AMPLE [2] study comparing infliximab and adalimumab with abatacept in patients with rheumatoid arthritis (RA), we sought to assess the relative effectiveness of infliximab, adalimumab, and abatacept in patients with RA and an inadequate response to methotrexate.

Methods: The meta-dataset included results from the ATTEST (NCT00095147) and AMPLE (NCT00929864) studies. Both trials included patients who met the American College of Rheumatology (ACR) criteria for RA, were at least 18 years of age, and had an inadequate response to MTX. Major outcomes concerned the benefits and harm after 1 year on therapy, American College of Rheumatology 50% (ACR50) criterion extracted from the papers and the number of withdrawals related to adverse events (AEs), respectively. All analyses were performed using the modified intention to treat population: all patients who were randomized and received at least one dose of study drug. Patients who discontinued the study prematurely were considered non-responders subsequent to the time of discontinuation. Statistical analyses were based on mixed-effects logistic regression using an arm-based, random-effects model respecting randomization within each study [3].

Results: Compared with infliximab (IV), abatacept (IV/SC) and adalimumab SC were associated with a statistical significantly higher likelihood of achieving an ACR50 response (abatacept: OR 1.49, 95% CI: 1.03 to 2.15; P = .032; Adalimumab: OR 1.49, 95% CI: 1.02 to 2.19; P = .041). In contrast,the ACR50 responses for abatacept and adalimumab were comparable (OR 1.00, 95% CI: 0.75 to 1.32; P = .99). Abatacept was less likely than infliximab to result in discontinuation due to adverse events (OR 0.45, 95% CI: 0.21 to 0.96; P = .040) while infliximab and adalimumab were similar in this respect (OR 0.83, 95% CI: 0.39 to 1.74; P = .62)

Table. Summary of the findings of ATTEST-AMPLE network trial of selected biologics for rheumatoid arthritis

	Abatacept vs. Adalimumab			Abatacept vs. Infliximab			Adalimumab vs. Infliximab		
Comparison:	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**
Outcome: Benefit									
ACR20	1.10	(0.81to1.51)	0.54	1.91	(1.24to 2.93)	0.0032	1.73	(1.04to 2.87)	0.034
ACR50	1.00	(0.75to1.32)	0.99	1.49	(1.03to 2.15)	0.032	1.49	(1.02to 2.19)	0.041
ACR70	1.11	(0.81to1.52)	0.52	1.52	(0.99to 2.33)	0.055	1.37	(0.87to 2.15)	0.17
LDAS (DAS28)	0.91	(0.67to1.25)	0.57	1.94	(1.19to 3.16)	0.0079	2.12	(1.19to 3.78)	0.011
Remission (DAS28)	1.06	(0.77to1.44)	0.72	1.71	(0.93to 3.16)	0.084	1.62	(0.82to 3.21)	0.17
Outcome: Harm									
Deaths	n.e.	n.e. n.e.	n.e.	n.e.	n.e. n.e.	n.e.	n.e.	n.e. n.e.	n.e.
SAEs	1.09	(0.68to1.77)	0.72	0.50	(0.30to 0.81)	0.0056	0.45	(0.26to 0.78)	0.0044
Related SAEs	0.81	(0.36to1.84)	0.62	0.30	(0.14to 0.66)	0.0027	0.37	(0.17to 0.84)	0.018
Discontinuation d/t SAEs	0.54	(0.21to1.44)	0.22	0.46	(0.15to 1.41)	0.17	0.85	(0.28to 2.53)	0.77
AEs	1.21	(0.79to1.85)	0.37	0.54	(0.28to 1.07)	0.077	0.45	(0.23to 0.89)	0.023
Related AEs	0.83	(0.60to1.15)	0.27	0.58	(0.38to 0.90)	0.015	0.70	(0.41to 1.19)	0.19
Discontinuation d/t AEs	0.54	(0.27to1.05)	0.07	0.45	(0.21to 0.96)	0.040	0.83	(0.39to 1.74)	0.62
Serious Infections	0.76	(0.31to1.90)	0.56	0.23	(0.10to 0.53)	0.0006	0.30	(0.13to 0.72)	0.0067
Autoimmune events	2.30	(0.72to7.35)	0.16	3.44	(0.41to28.88)	0.25	1.50	(0.14to15.45)	0.74

OR = Odds Ratio; 95% CI = 95% Confidence Interval; n.e. = Not estimable.
ACR = % improvement in patient- and physician-reported criteria of the American College of Rheumatology (ACR20, ACR50, ACR70)
LDAS (DAS28) = Low disease activity (i.e., DAS28 score of ≤ 3.2); Remission (DAS28) = Clinical remission (i.e., DAS28 score of ≤ 2.6)

Conclusion: The network analysis allowed indirect comparisons across all three groups. We conclude that infliximab, at the recommended dose, is less efficacious than either adalimumab or abatacept and that adalimumab and abatacept are approximately equivalent both in terms of benefit and short-term harm (up to 1 year).

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[3] Singh JA, CMAJ. 2009;181(11):787–96.

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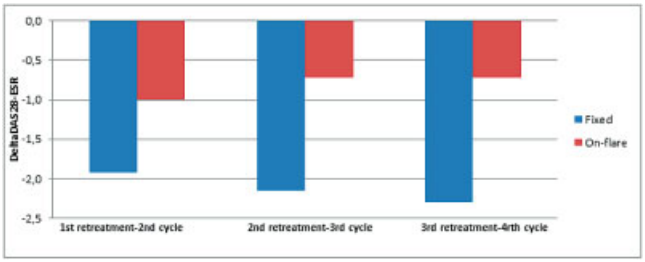
Fixed Versus On-Flare Retreatment With Rituximab In RA—Results From The Cererra Collaboration. Katerina Chatzidionysiou[1], Elisabeth Lie[2], Evgeny Nasonov[3], Galina Lukina[3], Merete Hetland[4], Ulrik Tarp[5], Karel Pavelka[6], Cem Gabay[7], Dan Nordström[8], Helena Canhao[9], Matija Tomsic[10], Piet van Riel[11], Juan Gomez-Reino[12], Ioan Ancuta[13], Tore Kvien[2] and Ronald van Vollenhoven[1]. [1]Unit for Clinical Research Therapy. Inflammatory Diseases (ClinTrid), Karolinska Institute, Stockholm, Sweden, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]ARBITER, Institute of Rheumatology, Moscow, Russia, [4]DANBIO, Department of Rheumatology, Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [5]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [6]Department of Clinical and Experimental Rheumatology, Charles University, Prague, Czech Republic, [7]SCQM registry, University Hospitals of Geneva, Geneva, Switzerland, [8]ROB-FIN, Helsinki University Central Hospital, Helsinki, Finland, [9]Instituto de Medicina Molecular, Rheumatology Research Unit, Rheumatology Research Unit, on behalf of the Rheumatic Diseases Portuguese Register, Lisbon, Portugal, [10]BioRx.si, University Medical Centre Ljubjana, Ljubljana, Slovenia, [11]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [12]Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain, [13]Cantacuzino Hospital, Bucharest, Romania.

Background/Purpose: The data on how to optimally retreat patients with RA with rituximab (RTX) have been limited so far. The aim of this analysis was to compare two common retreatment strategies: A fixed retreatment approach (before flare) and retreatment when a flare occurs.

Methods: Pooled data from the Collaborating European Registries for Rituximab in RA (CERERRA) project were used. RA patients who received at least 2 retreatments (3 courses) with RTX and for whom information about the strategy for retreatment was available (according to the physician's opinion) were identified. The two retreatment strategies were compared by applying an adjusted mixed model analysis with DAS28 improvement as the dependent variable.

Results: A total of 800 patients were retreated at least 2 times: 616 retreated because of a flare (442 at 1st and 174 at 2nd retreatment) and 184 receiving fixed retreatment (128 at 1st and 56 at 2nd retreatment). Baseline characteristics (incl. age, sex, seropositivity, disease duration, number of prior DMARDs and biologics) at first course of RTX did not differ significantly between the two groups. However, patients retreated on flare had a significantly higher DAS28-ESR at the time of 1st retreatment (5.1±1.3 vs. 4.1±1.4, p<0.0001), and a higher HAQ (1.5±0.7 vs. 1.3±0.8, p=0.001), as expected. They had also a higher baseline (at the time of RTX start) DAS28 (6.3±1.0 vs. 6.1±1.2, p=0.03). Those retreated on flare were also more likely to be treated with corticosteroids (58% vs. 46%, p=0.01) but less likely to receive concomitant DMARDs (82% vs. 92%, p=0.005).

In figure 1 the baseline (=start of each cycle) DeltaDAS28 (compared to the DAS28 at the time of RTX start) for the two groups is shown. Patients receiving fixed retreatment had a significantly higher (in absolute number) DeltaDAS28 (p<0.0001) at the start of each cycle, compared to those retreated on-flare. In the adjusted mixed model analysis, we compared the two retreatment groups for the 1st and the 2nd retreatment separately using estimated marginal means. For the 1st retreatment a fixed retreatment yielded significantly better results than the "on-flare": mean DeltaDAS28=−2.4 (95% CI: −3.0; −1.7) vs. −1.8 (95% CI: −3.6; −0.03), p<0.0001. Similar results were found for the 2nd retreatment: mean DeltaDAS28=−2.6 (95% CI: −3.1; −2.2) vs. −1.6 (95% CI: −1.8; −1.4), p<0.0001.



Conclusion: A fixed retreatment strategy with RTX in RA seems to be more effective than the retreat 'on-flare' strategy.

Disclosure: K. Chatzidionysiou, None; **E. Lie**, Pfizer Inc, 5, Roche Pharmaceuticals, 5, Abbott Immunology Pharmaceuticals, 5, Bristol-Myers Squibb, 5; **E. Nasonov**, None; **G. Lukina**, None; **M. Hetland**, Pfizer, ROche og MSD., 5; **U. Tarp**, None; **K. Pavelka**, Roche, BMS, Pfizer, MSD, AbbVie, 8; **C. Gabay**, Roche Pharmaceuticals, 2, Roche, Abbvie, Pfizer, UCB, BMS, MSD, 5; **D. Nordström**, None; **H. Canhao**, None; **M. Tomsic**, None; **P. van Riel**, None; **J. Gomez-Reino**, None; **I. Ancuta**, None; **T. Kvien**, None; **R. van Vollenhoven**, None.

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A Randomized Placebo-Controlled Phase 2 Study To Evaluate Efficacy, Safety and Tolerability Of Two Secukinumab Loading Dose Regimens In Subjects With Active Rheumatoid Arthritis Despite Treatment With Methotrexate.

Silvano Adami[1], André Beaulieu[2], Proton Rahman[3], Bruno Seriolo[4], Janet S. Lee[5], Gerhard Krammer[6], Brian Porter[6], Anuradha Thulasiraman[6] and Hanno B. Richards[6]. [1]Rheumatology Clinic, University of Verona, Verona, Italy, [2]Faculty of Medicine, Laval University, Quebec, QC, [3]Memorial University, St. Johns, NF, [4]Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, [5]Novartis Pharma AG, East Hanover, NJ, [6]Novartis Pharma AG, Basel, Switzerland.

Background/Purpose: To evaluate the efficacy, safety and tolerability at week 12 of two loading regimens of secukinumab (AIN457), a fully human anti-interleukin-17A monoclonal antibody, compared to placebo and to determine whether i.v. and s.c. loading doses of secukinumab offer comparable results for patients with active RA despite treatment with methotrexate.

Methods: This was a randomized, double-blind, 12-week, phase 2 study in subjects with active RA despite stable methotrexate treatment. Subjects were randomized (2:2:1) to receive secukinumab i.v. loading (10 mg/kg week 0, 2 and 4, followed by 150 mg s.c. week 8), secukinumab s.c. loading (150 mg week 0, 1, 2, 3, 4 and 8) or placebo. The primary objective was to demonstrate the superior efficacy of pooled secukinumab compared to placebo using ACR20 criteria at week 12. Secondary efficacy objectives included ACR20/50/70, ACR components and DAS28 for pooled and individual secukinumab treatment arms.

Results: A total of 221 subjects were randomized: 88 to i.v. loading, 89 to s.c. loading and 44 to placebo. All subjects were included in efficacy and safety analyses. Subjects were mainly from Eastern Europe (78%) and had a median of 12 swollen and 20 tender joints at baseline. All were positive for either anti-CCP or RF, with a CRP ≥ 10 mg/L or ESR ≥ 28 mm/1st hr. ACR20 response rate at week 12 was numerically but not statistically significantly greater with pooled secukinumab (49.2%) compared to placebo (40.9%). Reductions of DAS28-CRP were significantly greater for both secukinumab arms compared to placebo at all visits (except i.v. loading week 8) (Figure). No statistically significant differences in ACR20, DAS28-CRP or other efficacy outcomes were observed between the i.v. and s.c. loading regimens. The safety profile was similar to that in previous secukinumab RA trials. The proportion of pooled secukinumab-treated subjects vs. placebo-treated subjects was 41.2% vs. 38.6% for any AE, 2.8% vs. 2.3% for serious AEs, and 1.7% vs. 0% for AEs leading to discontinuation.

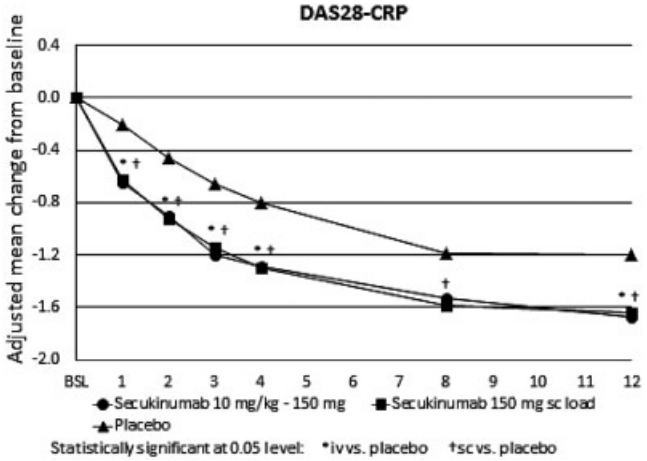

Figure. DAS28-CRP response rates by treatment arm through week 12

Conclusion: Secukinumab demonstrated improved efficacy in reducing disease activity over placebo as measured by DAS28-CRP, but not ACR20 at week 12 (primary endpoint). Reductions in disease activity were very similar for the i.v. and s.c. secukinumab loading regimens. The AE profile of secukinumab was comparable to placebo. Phase 3 studies in RA patients with inadequate response to anti-TNF treatments are ongoing.

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Early Introduction Of Biologic Treatment Is An Important Predictor Of Sustained Favorable Outcome Including Clinical Remission In Early Arthritis But Not Of Sustained Favorable Outcome On Structure and Function Only: Results From The Espoir Cohort.

Cécile Gaujoux-Viala[1], Laure Gossec[2], Maxime Dougados[3], Francis Guillemin[4] and Bruno Fautrel[2]. [1]EA 2415, Montpellier I University, Nîmes University Hospital, Rheumatology Department, Nîmes, France, [2]Paris 6–Pierre et Marie Curie University; AP-HP, Rheumatology, Pitié-Salpêtrière Hospital, -GRC-UPMC 08–EEMOIS, Paris, France, [3]Paris-Descartes University, APHP, Cochin Hospital, Paris, France, [4]CHU Nancy, Clinical Epidemiology and Evaluation, Université de Lorraine, Paris Descartes University, APEMAC, EA 4360, Nancy, France.

Background/Purpose: The relevant elements to evaluate health states in RA should include remission, good functional ability and structural stability [1]. The concept of favorable outcome could then be defined by the association of these 3 elements. An alternative definition of favorable outcome keeps only the last 2 criteria: function + structure.

Objective: To assess which variables at baseline are associated with sustained favorable outcome over 3 years in early arthritis (EA) in daily clinical practice.

Methods:- *Patients*: from the French cohort of EA ESPOIR (at least 2 swollen joints for less than 6 months and suspicion of RA) fulfilling the new ACR-EULAR criteria for RA at baseline.

Outcome: favorable outcome was defined by a criterion representing good functional ability (HAQ ≤0.5 and HAQ deterioration ≤0.25) and a criterion representing structural damage (absence of progression of the Sharp score over 1 year) with or without remission according to the new criteria of ACR/EULAR. Patients with sustained favorable outcome (according to the two definitions, ie using 2 and 3 criteria) over 3 years were analyzed.

Analysis: multinomial and ordinal logistic regression were used to determine which variables at baseline were independently associated with sustained favorable outcome. Sensitivity analyses on different definition of 'sustained' favorable outcome (sum, continuity rewarded score [2]) and on the timing of the treatment's introduction were performed.

Results: 643 patients were analyzed (mean age of patients 48±12 years; 78% were women; mean DAS28 5.4±1.2). In all, 97 patients presented sustained favorable outcome using 2 criteria (function+structure) at least at 2 time-points and 29, sustained favorable outcome using 3 criteria. (function+structure+remission). In the logistic regression models, only low HAQ and morning stiffness were always associated with sustained favorable outcome whatever the definition used (3 or 2 criteria). Being younger, living with a partner (being married/in a common-law relationship) and biological treatment during the first 6 months were associated with sustained favorable outcome using the 3 criteria (including remission). Being male, low Sharp score and no synthetic DMARD during the first year were associated with sustained favorable outcome using the 2 criteria (function+structure) (Table). To note the introduction of biological treatment after 6 months was not associated with sustained favorable outcome.

Variable at J0	OR [95%CI] Sustained favorable outcome structure+function+remission	OR [95%CI] Sustained favorable outcome structure+function
Low age	1.17 [1.07; 1.28]	NS
Low TJC	1.24 [1.01; 1.54]	NS
Living with a partner	16.67 [1.04; 250]	NS
Biological treatment during the first 6 months	28.6 [1.92; 500]	NS
Low HAQ	31.25 [3.08; 333.3]	2.38 [1.45; 3.93]
Morning stiffness >1h	6.80 [1.46; 31.2]	3.09 [1.99; 4.78]
Low Sharp score	NS	1.03 [1.005; 1.06]
Male	NS	1.70 [1.05; 2.77]
No synthetic DMARD during the first year	NS	1.70 [1.06; 2.72]

Conclusion: Early initiation of biological treatment is an important predictor of sustained favorable outcome (function+structure+remission) but not of sustained favorable outcome on structure and function only.

Reference:
1. Felson DT et al. Ann Rheum Dis 2011; 70(3):404–13
2. Boers M, et al. J Clin Epidemiol. 2010 Jun;63:633–7

Disclosure: C. Gaujoux-Viala, None; **L. Gossec**, None; **M. Dougados**, None; **F. Guillemin**, None; **B. Fautrel**, None.

ACR Poster Session A
Sjögren's Syndrome: Clinical Aspects
Sunday, October 27, 2013, 8:30 AM–4:00 PM

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Sjögren's Syndrome In American Ethnic and Racial Minorities. Ann Igoe[1], Christopher J. Lessard[1], Juan-Manuel Anaya[2], Astrid Rasmussen[1], Kiely Grundahl[3], Biji T. Kurien[4], Jacen S Maier-Moore[5], Lida Radfar[6], John A. Ice[1], Glen D. Houston[6], David M. Lewis[6], Donald U. Stone[6], Kimberly S. Hefner[7], Kathy L. Sivils[1] and R. Hal Scofield[8]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia, [3]Oklahoma Medical Research Foundation, oklahoma CIty, OK, [4]U.S. Department of Veterans Affairs Medical Center, Oklahoma City, OK, [5]University of Oklahoma Health Sciences Center, Oklahoma Medical Research Foundation, Department of Veterans Affairs, Oklahoma City, OK 73104, Oklahoma City, OK, [6]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [7]Hefner Eye Care and Optical Center, Oklahoma City, OK, [8]US Department of Veterans Affairs Medical Center, Oklahoma City, OK.

Background/Purpose: Examine the racial and ethnic make-up of a large cohort of Sjögren's syndrome (SS) gathered in the USA compared to the make-up found among SLE patients, as well as the clinical manifestations of SS in Black- and Hispanic-Americans.

Methods: Consecutive subjects, all of whom had dry eyes and mouth, attending a comprehensive sicca evaluation clinic underwent dental, ophthalmological and medical examinations. Subjects were classified according to the American-European Consensus Group Criteria (AECG) as well as the SICCA/ACR criteria. Furthermore, race and ethnicity were recorded based on self-report as well as NIH-defined race and ethnicity. Laboratory and serological studies included determination of anti-Ro/La by multiple methods.

Results: Among 256 subjects classified as primary Sjögren's syndrome, 9 (3.5%) were African-Americans and 9 (3.5%) were Hispanic-Americans. This was substantially below the representation of these minorities in the general population of the region (about 10% each), but was no different than that found among 273 subjects not classified as SS who had no anti-Ro/La and a focus score of 0.0. Compared to 152 non-Hispanic white Americans classified as SS, the blacks Americans with SS were less likely to have an abnormal Schirmer's test (1 of 9 versus 79 of 152, Fisher's p=0.03). Other clinical manifestations were similar between non-Hispanic whites and Blacks- or Hispanic Americans. Both Hispanic and black SS subjects were more likely to have anti-Ro (or SSA) than non-Hispanic white SS, and black SS were also more likely to have anti-La (or SSB) (6 of 9 versus 44 of 152, Fisher's p=0.026). We also compared the race and ethnicity of the SS cohort to a cohort of SLE patients collected in the same geographic area. Of 477 SLE patients, 106 were black. This was statistically different compared to SS (9 of 152 versus 106 of 447, $\chi 2=42.7$, p>0.001, odds ratio=7.8 (95% CI=3.9–15.8)). There were 32 Hispanics among the SLE group, and this difference almost reached statistical significance ($\chi 2=3.27$, p=0.07, OR=0.99–4.6).

Conclusion: Neither Black-Americans nor Hispanic-Americans were commonly found among a cohort with Sjögren's syndrome. Further, SS was not more severe in either Blacks or Hispanics. This is in contrast to SLE, where both these minority groups were over-represented among SLE, and disease is more severe. These findings may well represent a biological difference between Sjögren's and SLE, but socioeconomic factors impacting upon access to care and referral could be important.

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Raynaud's Phenomenon and African American Race Are Independently Associated With Non-Hodgkin's Lymphoma In Sjogrens Syndrome Patients: Findings From a United States National Study. Bella Mehta[1], Neville Jadeja[2], Marjan Mujib[3] and Petros V. Efthimiou[4]. [1]Westchester Medical Center at New York Medical College, Valhalla, NY, [2]Jacobi Medical Center, New York, NY, [3]New York Medical College, Valhalla, NY, [4]LM&MHC/Weill Cornell MC, New York, NY.

Background/Purpose: Higher incidence of lymphoma in sjogrens syndrome has been reported since more than 5 decades now. Non Hodgkin's Lymphoma (NHL) ranks as the seventh leading cause of cancer diagnosis in United States. There are numerous reports of Raynaud's syndrome being an early paraneoplastic manifestation of occult malignancies.

Objectives: To investigate the associations of rheumatologic and immunologic conditions with NHL in hospitalized patients with Sjogrens disease from a large nationwide hospital registry database.

Methods: All hospitalized patients included in the nationwide inpatient sample (NIS) 2010 database with a confirmed discharge diagnosis of Sjogrens disease, as per the ICD-9-CM code 710.2 were identified. NIS is the largest all-payer inpatient care database in the United States. Multivariable logistic regression models were used to determine the associations of rheumatic diseases and demographics of the population with Non-Hodgkin's lymphoma among these patients. Discharge weight was used to measure national estimates.

Results: From 7,800,441 hospitalizations in NIS 2010 database, 7,734 Sjogrens syndrome patients were identified. Patients had a mean age of 63.47 (±16.03) years, 91.14% (7,049) were women. We used weighted analysis to estimate the national values. 38677 sjogrens syndrome patients were thus analyzed. 34923(90.29%) had no NHL or Raynaud's, 758 (1.96%) had no Raynaud's but had NHL. 2843 (7.35%) had Raynaud's present but no NHL. 153(0.4%) had both NHL and Raynaud's. Models were adjusted for Age, Sex, Vasculitis, Systemic Lupus Erythematosus, HIV, Rheumatoid Arthritis, Dermatmyosisits, Polymyositis, Connective tissue disease, Polymyalgia Rheumatica, Systemic sclerosis, Celiac Disease, Hypthyroidism, Autoimmune hepatitis, Hepatitis C virus infection, Smoking history and African American race. African american race was independently associated with presence of NHL(adjusted odds ratio, 2.217; 95% confidence interval, 1.791–2.745; p<0.005) Raynaud's syndrome was found to be independently associated with NHL (adjusted odds ratio, 2.854; 95% confidence interval, 2.357–3.456; p<0.005) (Table 1).

CHARACTERISTICS	Adjusted Odds Ratio	95% C.I.for OR Lower	Upper	P Value
AGE	1.010	1.006	1.015	.000
SEX(FEMALE)	1.330	1.080	1.638	.007
AFRICAN AMERICAN	2.217	1.791	2.745	.000
SLE	.716	.588	.873	.001
RHEUMATIOD ARTHRITIS	0.335	0.265	0.423	.000
RAYNAUD'S	2.854	2.357	3.456	.000
VASCULITIS	1.684	1.139	2.490	.009
POLYMYOSITIS	3.606	2.172	5.987	.000
CONNECTIVE TISSUE DISEASE	1.274	.671	2.418	.458
SYSTEMIC SCLEROSIS	0.866	0.618	1.214	.405
CELIAC DISEASE	2.203	1.313	3.695	.003
HYPOTYROIDISM	.753	.636	0.893	.001
AUTOIMMUNE HEPATITIS	0.999	.516	1.935	.997
HEPATITIS C VIRUS	1.402	.573	3.430	.459
SMOKING HISTORY	0.227	0.124	0.416	.000

Conclusion: In this large national database, African american race and Raynaud's syndrome was independently associated with non-hodgkins lymphoma among hospitalized Sjogrens patients. The presence of Raynaud's syndrome in patients with Sjogren's should arouse clinical suspicion for this feared complication. Further prospective studies and are needed to understand this relationship in this high-risk population.

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Damage Accrual In a Single Centre Cohort Of Patients With Primary Sjögren's Syndrome Followed Up For Over 10 Years. Chiara Baldini[1], Francesco Ferro[1], Pasquale Pepe[2], Nicoletta Luciano[1], Francesca Sernissi[1], Carlotta Cacciatore[1], Daniela Martini[1], Antonio Tavoni[3], Marta Mosca[4] and Stefano Bombardieri[1]. [1]Rheumatology Unit, Pisa, Italy, [2]Institute of Clinical Physiology, National Research Council, Pisa, Italy, [3]Immunoallergology unit, Pisa, Italy, [4]Rheumatology Unit, University of Pisa, Pisa, Italy.

Background/Purpose: 1) To describe the progression and cumulative prevalence of damage accrued over the time in a single center cohort of patients with primary Sjögren's Syndrome (pSS) 2) to explore the influence of the patients' clinical and serologic profile on damage accrual.

Methods: Consecutive unselected pSS patients (AECG criteria) were enrolled in this study between September 2012 and April 2013. Demographic, clinical, serologic, histological and therapeutic data of the patients enrolled were collected. Damage scores were assessed at 1, 3, 5 and 10 years post-diagnosis of pSS using both the Sjogren's Syndrome Damage Index (SSDI) and the Sjögren's Syndrome Disease Damage Index (SSDDI). The category/item of damage was also noted. Friedman test and Wilcoxon signed-rank test were used to evaluate damage progression over the follow-up.

Results: The study cohort consisted of 155 pSS patients (7M:148F; median age at diagnosis= 49 years, IQR 40–58 years; median follow-up=5 years, IQR 3–10 years). The total increase of patients with damage was 28% after 1 year, 44% after 3 years, 74% after 5 years and 83% at the end of ourstudy. Median SSDI and SSDDI total damage scores steadily increased over the 10 years from 0 (IQR 0–1) to 2 (IQR 1–4) and from 0 (IQR 0–1) to 2 (IQR 1–3), respectively, with a significant correlation between SSDI and SSDDI scores (p=0.000). The domains mainly contributing to the total damage were the oral and the ocular items. More specifically, over the follow-up, 77/155 (49.5%) patients presented teeth loss and/or caries and 53/155 (34%) showed salivary flow impairment. Persistent salivary gland swelling was detected in 22/155 patients (14%) and was associated with a lower age at pSS diagnosis (p=0.002), anti-Ro/SSA (p=0.03), cryoglobulinemia (p=0.05), low C4 (p=0.04), hypergammaglobulinemia (p=0.000) and lymphocytopenia (p=0.000). Ocular damage was observed in 35/155 patients (22.6%) with corneal ulcers in 17/155 (11%) and tear flow impairment in 31/155 subjects (20%). Systemic damage manifestations were observed in 21/155 patients (13.5%) and correlated with the ESSDAI scores at the baseline (p=0.000), low C4 levels (p=0.005) and lymphocytopenia (p=0.01). Lymphoproliferative disorders were detected in 7/155 patients (4.5%) and malignancy in 14/155 (9%) cases.

Conclusion: This study demonstrated that the vast majority of pSS patients developed damage within 10 years. Damage accrued mostly in the oral and ocular domains, however systemic damage manifestations and malignancy might be observed in the 10–15% of the patients.

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Hospitalization In Patients With Primary Sjögren's Syndrome. Yemil Atisha-Fregoso, Yahaira Rivera and Gabriela Hernandez-Molina. Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubirán, Mexico City, Mexico.

Background/Purpose: There is scant information on the frequency, main causes and associated risk factors of hospitalization in patients with primary Sjögren syndrome (PSS).We aimed to identify the causes and risk factors for hospitalization of PSS patients who attended a tertiary referral center.

Methods: We identified all PSS patients who regularly attend our Rheumatology clinic from Jan 2000 to Apr 2013 and retrospectively collected demographic, clinical (parotid enlargement and extraglandular features) and serological (anti-Ro/SSA, anti-La/SSB, RF, low C3 or C4 ever and maximum globulin levels) data from medical records. Patients who required at least one hospital admission were compared with those who never were hospitalized. The Disease Damage Index (SSDDI) (excluding the oral and ocular items) and the Charlson comorbidity Index were also assessed. We used a logistic regression analysis.

Results: We included a total of 170 patients (162 females, 95%). Fifty five (32%) patients were hospitalized, representing a total number of 111 hospitalizations (28 patients had more than one hospital admission). The hospitalization incidence density rate was 6.49/100 patient years. The median length of hospital stay was 9 days (IQR 6–15). There were 7 ICU admissions and 6 deaths. The main causes of admissions were disease activity in 37 cases (33.3%), infections in 36 patients (32.4%) and miscellaneous causes in 42 patients (34.3%). When compared to patients seen during the same time period and not admitted to hospital, those admitted had a shorter disease duration (6.3 [IQR 1.6–12.1] vs. 8.2 [IQR 4.6–14-1], p=0.015), similar age (55.97 ± 16.6 vs. 56.1 ± 14.2, p=0.96), a higher median SSDDI score (2 [IQR 0–2] vs. 0 [IQR 0–2], p=0.001) and higher proportion of patients with a Charlson comorbidity index ≥ 2 (36.4% vs. 15.6%, p=0.003).

The variables associated with hospitalization at the univariate analysis were vasculitis (20% vs. 7%, p=0.01), glomerulonephritis (9.1% vs. 0%, p=0.03), neurologic manifestations (polyneuropathy, mononeuritis or myelitis) (43.6% vs. 25.2%, p=0.02), hepatic involvement (primary biliary cirrhosis, autoimmune hepatitis and overlap syndrome) (21.8 vs. 5.2%, p=0.002) and hyperviscosity syndrome (7.2% vs. 1%,

p=0.038). Hospitalized patients had higher median levels of globulins (4.2 [IQR 3.4–5.7] vs. 3.8 [IQR 3.4–44], p=0.03), a higher prevalence of low C4 (16/41, 39% vs. 13/86, 15.1%, p=0.006) and less use of antimalarials (9.1% vs. 56.5%, p<0.001) and methotrexate (5.5% vs. 17.4%, p=0.03). At the multivariate analysis we identified the hepatic involvement (OR=5.01, 95% CI 1.02–24.39, p=0.046), globulin levels (OR=1.51, 95% CI 1.06–2.13; p=0.02) and low C4 (OR=4.85, 95% CI 1.54–15.30, p=0.007) as risk factors for hospitalization, whereas the use of antimalarials (OR= 0.08; 95% CI 0.02–0.27, p<0.001) was protective.

Conclusion: Major causes for admission were disease activity and infection. The presence of serologic activity parameters such as higher levels of globulins, low C4 as well as the presence of hepatic involvement were risk factors associated with hospitalization; while the use of antimalarial seemed to protect.

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Level Of Agreement Of The AECG 2002 and ACR 2012 Classification Criteria For Sjögren's Syndrome In The Brittany Cohort: Clues To Understand Discrepancies. Divi Cornec[1], Alain Saraux[2], Jacques-Olivier Pers[1], Sandrine Jousse-Joulin[3], Yves Renaudineau[1], Beatrice Cochener[1], Thierry Marhadour[4] and Valerie Devauchelle-Pensec[5]. [1]Brest Occidentale University, Brest, France, [2]CHU Brest et Université Bretagne Occidentale, Brest, France, [3]Brest university medical school, EA 2216, UBO and CHU de la Cavale Blanche,, Brest, France, [4]CHU de la Cavale Blanche, Brest, France, [5]Brest Occidentale university, Brest, France.

Background/Purpose: New classification criteria for primary Sjögren's syndrome (pSS) have been proposed in 2012 and approved by the ACR. They differ substantially from the currently used AECG criteria in that 1) they do not include subjective ocular and buccal symptoms nor functionnal or morphological tests for salivary glands, 2) they use a new Ocular Staining Score (OSS) as the sole evaluation for ocular involvement, and 3) they consider the association of antinuclear antibody (ANA) titer ≥1:320 and rheumatoid factor (RF) positivity as equivalent to anti-SSA/SSB positivity. The aim of this work was to evaluate the agreement between the two sets of criteria, and to determinate the factors leading to an eventual discrepancy.

Methods: This study was conducted in the Brittany monocentric cohort of patients with suspected pSS, included between November 2006 and March 2013. All patients were evaluated by an ophtalmologist who used fluorescein and Lissamine green to evaluate the presence of keratoconjunctivitis sicca, allowing the subsequent calculation of the OSS. All cases were reviewed by a panel of 3 experts, who determined a clinical diagnosis of pSS or other cause of sicca symptoms. The agreement between the different criteria or tests was studied using Cohen's κ coefficient.

Results: 105 patients have been included in the study. 47 (44.8%) patients had a clinical diagnosis of pSS, 42 (40.0%) fulfilled AECG criteria and 35 (33.3%) ACR criteria. 27 patients fulfilled both classification criteria, 15 patients only AECG, 8 patients only ACR, and 55 none of them. The agreement between the two criteria was moderate (κ = 0.53). Xerophtalmia and xerostomia were noted respectively in 92.4% and 94.3% of the patients, suggesting no discriminating capacity between pSS and non-pSS patients. Only 3 patients had ANA≥1:320 and RF but no anti-SSA, but all of them fulfilled both AECG and ACR criteria. The agreement between OSS ≥3 and Schirmer's test ≤5mm/5min was very low (κ = 0.14). The agreement with SGB was lower for OSS than for Schirmer's test (κ = 0.14 and 0.35 respectively); they both displayed poor agreement with SSA/SSB positivity (κ = 0.21 and 0.27 respectively).

Conclusion: ACR 2012 and AECG criteria have a moderate agreement, suggesting that cohorts of pSS patients selected using different classification criteria would not be comparable. The main part of this discrepancy is caused by the differences between OSS and Schirmer's test. More precise evaluation of the diagnostic value of these ocular tests has to be performed.

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Is Ultrasonography Of Salivary Gland a Validate Tool In Sjögren Syndrome? Study 1: Interobserver Reliability Between International Group Of Experts. Sandrine Jousse-Joulin[1], Vera Milic[2], Elke Theander[3], Malin V. Jonsson[4], Wan-Fai Ng[5], Chiara Baldini[6], Marina Carotti[7], Alan N. Baer[8], Joel Fradin[9], Pascale Rachele[10], Hendrika Bootsma[11], Jacqueline Brown[12], Nicoletta Luciano[6], S Bombardieri[13], Roland Jonsson[4], Salvatore De Vita[14], Alojzija Hocevar[15], Matija Tomsic[16], Alain Saraux[17], Emmanuel Nowak[18], Alessandro Ciapetti Sr.[19], Arjan Vissink[11], John Rout[20], Thomas Mandl[21], Simon J. Bowman[22] and Valerie Devauchelle-Pensec[23]. [1]Brest university medical school, EA 2216, UBO and CHU de la Cavale Blanche, Brest, France, [2]Belgrade University, belgrade, Serbia, [3]Lund University, Malmö, Sweden, [4]University of Bergen, Bergen, Norway, [5]Departement of rheumatology, New-Castle University Hospital, UK, Newcastle, England, [6]Rheumatology Unit, Pisa, Italy, [7]Ospedali Riuniti, Ancona, Italy, [8]Johns Hopkins University, Baltimore, MD, [9]John Hopkins Universirty, Baltimore, MD, [10]University of Pisa, Pisa, Italy, [11]University Medical Center Groningen, Groningen, Netherlands, [12]Tower Wing Guy's hospital, london, United Kingdom, [13]Department of Rheumatology, University of Pisa, Pisa, Pisa, Italy, [14]Rheumatology Clinic, DSMB, University of Udine, Udine, Italy, [15]University Medical Centre Ljubljana, Ljubljana, Slovenia, [16]BioRx.si, University Medical Centre Ljubjana, Ljubljana, Slovenia, [17]CHU Brest et Université Bretagne Occidentale, Brest, France, [18]CHU Brest, Brest, France, [19]Department of Rheumatology, Politechnic University of the Marche, Ancona, Ancona, Italy, [20]Birmingham Dental Hospital, Birmingham, United Kingdom, [21]Skåne University Hospital Malmo, Lund University, Sweden, Malmö, Sweden, [22]Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom, [23]Brest Occidentale university, Brest, France.

Background/Purpose: Ultrasonography (US) of salivary glands is a relatively new test to diagnose primary Sjögren syndrome (pSS)[1–6]. In 2012, an international group of interest was formed to address the metric qualities of US as a potential outcome measure. A preliminary systematic review highlighted the deficiencies in the literature, particularly with regard to the reliability of interpreting and acquiring images and to delineate which abnormalities should be scored. The purpose of this study group is to improve reliability and to evaluate several US abnormalities in salivary gland according to the diagnosis or not of primary Sjögren syndrome (pSS).

Methods: We report here the first part of the study by the group that was conducted between November 2012 and june 2013 with an international group of 12 experts in ultrasonography of the salivary gland in pSS and aims were 2-fold: first to assess the interobserver reliability among experts and second to better define salivary gland abnormalities. 28 scanned imaged of parotid gland in longitudinal and transverse plans were scoredwithout preliminary training but based on experts experienced concerning salivary gland in pSS. US-GS scoring was evaluated using a 4-grade scale derived from De Vita, with the following subjective definitions for each category of homogenicity of the parenchyma: grade 0 = normal gland; grade 1:small hypoechogenic areas without echogenic bands; grade 2: multiple hypoechogenic areas measuring <2 mm with echogenic bands; grade 3, multiple hypoechogenic areas measuring 2–6 mm with hyperechogenic bands; and grade 4, multiple hypoechogenic areas measuring >6 mm. And for two grades concerning echogenicity of the parenchyma: normal or decreased. PD was not yet used for this first step. Interobserver agreement was estimated using the kappa index.

Results: Concerning hypoechogenicity the mean kappa was low: 0.3 (0.12–0.8). For homogenicity the mean kappa were respectively:0.6 (range: 0.4–0.8); 0.4 (range: −0.1–0.7) and 0.6 (range: 0.5–0.9) for grade 1, 2 and 3. The low agreement for homogenicity could be due to the absence of reference to normal parenchyma scanned image of the thyroid gland used as reference or to the absence of well defined consensus. In the absence of previous training session a relative good agreement was found between ultrasonographers. Grade 3 is related to the diagnosis of pSS. New definition of each abnormality was elaborated by the experts.

Conclusion: In the absence of well defined consensus, ultrasonography has an acceptable agreement for homogenicity of the parenchyma but not for echogenicity. Diagnosis based on grade 3 is reliable between observers. Training sessions are required and further studies will assess the scoring system and the value of US in clinical trials fro pSS.

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A Novel Screening Tool Indicative Of Primary Sjogren's Syndrome Versus Sicca Symptoms. Gerard Dumancas[1], Michael Brown[1], Indra Adrianto[1], Christopher J. Lessard[1], Jennifer A. Kelly[1], Kiely Grundahl[2], Astrid Rasmussen[1], R. Hal Scofield[3], Courtney Montgomery[1] and Kathy L. Sivils[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, oklahoma CIty, OK, [3]US Department of Veterans Affairs Medical Center, Oklahoma City, OK.

Background/Purpose: Sjogren's syndrome (SS) is a chronic, progressive disease characterized by dry eyes and dry mouth resulting from lymphocytic infiltration of the lacrimal and salivary glands, respectively. Although SS is defined by keratoconjunctivitis sicca and xerostomia (dry eyes and mouth), the full spectrum of disease can involve a complex myriad of systemic symptoms similar to other rheumatic diseases. The American-European Consensus Group (AECG) classification criteria for SS require serologic and hematologic tests as well as the expertise of at least two clinical specialties for diagnosis. As such, proper diagnosis of SS is often challenging.

Methods: In order to develop a model to better predict SS, we first assessed the predictive value of a commonly used screening tool, the AECG six-question phone interview, in 379 European American (EA) individuals with dry eyes and mouth using structural equation modeling (SEM) and logistic regression (LR). Then, using responses to 440 general health and medical history questions in addition to the six-question phone interview from the same participants, we developed a novel predictive model using genetic algorithm (GA), k-nearest neighbor and forward selection model.

Results: The six-question phone interview, which in our experience results in ~36% classification of SS, yielded an ill-fitting model with low prediction accuracy (~56% under violated assumptions) *in silico.* Our novel model generated from the general health, medical history questionnaire, and six-question phone interview data obtains an accuracy of ~61% in the test set and ~64% in the unknown set. The generated model considered clinically substantive consisted of 9 questions relating to autoimmunity, difficulty swallowing, mouth/tongue dryness, aching, and disorientation.

Conclusion: The six-question phone interview, which in our experience results in ~36% classification of SS, yielded an ill-fitting model with low prediction accuracy (~56% under violated assumptions) *in silico.* Our novel model generated from the general health, medical history questionnaire, and six-question phone interview data obtains an accuracy of ~61% in the test set and ~64% in the unknown set. The generated model considered clinically substantive consisted of 9 questions relating to autoimmunity, difficulty swallowing, mouth/tongue dryness, aching, and disorientation.

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Multicentric Analysis Of Inter and Intra Observer Reliabilities For Histopathological Abnormalities In Salivary Gland Biopsy In Primary Sjögren Syndrome. Sebastian Costa[1], Isabelle Quintin Roue[2], Agnes Lesourd[2], Sandrine Jousse-Joulin[3], Pascale Marcorelles[4], Eric Hachulla[5], Vincent Goeb[6], Marie-Christine Copin[7], Jean-Marie Berthelot[8], Jacques-Olivier Pers[9], Olivier Vittecoq[10], Emmanuel Nowak[11], Alain Saraux[12] and Valerie Devauchelle-Pensec[13] [1]Brest university hospital, Brest, France, [2]Morvan hospital, Brest, France, [3]Brest university medical school, EA 2216, UBO and CHU de la Cavale Blanche,, Brest, France, [4]Brest university hospital, CHU Morvan, Brest, France, [5]Internal Medicine, Lille CEDEX, France, [6]Amiens University Hospital, Amiens, France, [7]Lille university, Lille, France, [8]Nantes University Hospital, Nantes, France, [9]Brest Occidentale University, Brest, France, [10]Rouen University Hospital & Inserm905, University of Rouen, Rouen Cedex, France, [11]CHU Brest, Brest, France, [12]Université Brest Occidentale, Brest, France, [13]Brest Occidentale university, Brest, France.

Background/Purpose: Histopathologic evaluation of minor labial salivary gland (MLSG) is a major goal for the classification of patients with a primary Sjögren syndrome (pSS) [1,2]. The standard focus score has been described by Daniels et al [3] but several other histopathological abnormalities have been described. However, their intra and inter reliabilities have been poorly investigated.

Our objective was to examine associations between MLSG histopathology and their reliabilities in the TEARS (Tolerance and efficacy of Rituximab in primary Sjogren Syndrome) study, a randomised multicenter study evaluating efficacy of rituximab in pSS. We studied inter and intra-observer agreement concerning the focus score and other histopathological items. We also tested agreement in the estimation of B and T cells lymphocytes ratio using doubled staining immunohistochemistry.

Methods: All MLSG biopsies available from the TEARS study were reviewed and scored by an independent pathologist (SC) at two different times, after a training session (SC, IQR). All patients fulfilled the American-European Consensus Group criteria for pSS, and had an active disease. We compared with the baseline focus score, established at the patient's inclusion. We used Daniels et al's protocol to re-evaluate the MLSG. As previously described, the agreement rate was calculated for the dichotomized focus score (separating focus <1 from $\geq 1/4mm^2$) and for each following item: focal lymphocytic sialadenitis, non-specific chronic inflammation, presence of confluent foci, presence of germinal centers, acinar depletion, duct dilatation, fibrosis, and adiposis. B and T lymphocytes cells ratio was also measured after double staining in immunohistochemistry. Inter and intra-observer agreements were estimated using the kappa index.

Results: Inter observer reliabilities were evaluated in 77 MLSG biopsies and intra observer in 89 independant MLSG biopsies. MLSG specimens included 50% with focal lymphocytic sialadenitis and 41 % with non-specific or sclerosing chronic sialadenitis. For the dichotomized focus score, the inter-observer agreement was good $k = 0.70$ (95% CI 0.62–0.78). 66/77(86%) MLSG biopsies had concordant focus scores. For focal lymphocytic sialadenitis, non-specific chronic inflammation and fibrosis, reliabilities were moderate, respectively, $k = 0.63$ (95% CI 0.54–0.72); 0.42(95% CI 0.33–0.51) and 0.22 (95% CI 0.13–0.33). Intra observer reliabilities for focus score was good with a $k = 0.77$ (95% CI 0.71–0.84). Reliability for fibrosis was moderate, $k= 0.44$ (95% CI 0.34–0.53). The agreement for B/T lymphocyte ratio was excellent $k = 0.87$ (95% CI 0.82–0.92).

Conclusion: Although focus score reliability seems good, there is disparity in the way to determine the focus score. Daniels et al' s protocol fails to be systematically applied. This could result in an over estimation of the focus score. Evaluation of B and T cells infiltrate is accurate.

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Salivary Gland Lymphocyte Pattern Associated With Response To Belimumab In Primary sjogren'ssyndrome: Results Of The Beliss Study. Raphaèle Seror[1], Thierry Lazure[2], Frederic Desmoulins[3], Stephan Pavy[4], Corinne Miceli-Richard[5], Gabriel Baron[6], Philippe Ravaud[7] and Xavier Mariette[8]. [1]Université Paris Sud, Le Kremlin Bicêtre, France, [2]INSERM U1012 - Université Paris XI, Le Kremlin Bicêtre, France, [3]Université Paris-Sud, Le Kremlin Bicêtre, Le Kremlin Bicetre, France, [4]Hopital Bicetre, Paris, France, [5]Université Paris-Sud 11, Bicêtre Hospital,, Kremlin Bicêtre, France, [6]Epidemiology, Paris, France, [7]Hopital Hotel Dieu, Paris Descartes University, Paris, France, [8]Bicêtre University Hospital, Le Kremlin Bicetre, France.

Background/Purpose: To address the change in labial salivary gland (LSG) inflammation after Belimumab (biological treatment inhibiting soluble BAFF/BLyS) therapy in pSS patients and identify predictor of response to treatment.

Methods: Patients were included in 2 parallel and identical studies in 2 European centers. Patients had to fulfill AECGcriteria, to be anti-SSA/SSB positive and had to have at the time of inclusion either systemic complications or early disease (<5 yrs of symptoms), or the presence of biomarker of B-cell activation. The patients were treated with belimumab 10 mg/kg W0, W2, W4 and then every four weeks until W24. Minor labial salivary gland (LSG) biopsies of the 15 patients (all female, mean age=50 yrs, mean disease duration= 5 yrs)from the French center, performed at W0 and W28, were analyzed for estimating the focus score, the B-cell/T-cell ratio, BAFF expression and NK infiltrate.

Response to treatment was defined according to a composite primary end-point and systemic response according to a decrease of the ESSDAI≥3 points.

Results: Before treatment, significant lymphocytic sialadenitis (focus score >1) was observed in 11 (78.6%) patients, five of whom became negative at w28 ($p=0.07$). The median focus score decreased from 1.6 to 0.5 ($p=0.39$) and Chisholm score from 4 to 2 ($p=0.01$). Median B-cell/T cell ratio decreased decreased from 0.58 to 0.50, $p=0.055$. Before treatment, a

BAFF staining was detected in 11/14 (78.6%) patients, and in only 7/14 (50.0%) after belimumab (p=0.07). The median percentage of BAFF positive cells in foci significantly decreased from 27.5% to 5% after belimumab therapy (p=0.03).NKp46 staining revealed that NK cells infiltrate was predominantly located in interstitium rather than in foci (p=0.0003), and did not change after belimumab.

8/15 patients (53%) achieved the primary end-point, and 6 (40%) patients had a significant systemic improvement. The only histological parameter associated with response to belimumab was the NK infiltrate in periphery of the foci which was lower in responders than in non-responders (median number of NK cells 21.4 vs 29.4; p=0.028) Also, there was a trend to observe lower focus score in responders than in non responders (median number of foci 1.37 vs. 3.0; p=0.08). Likewise, low NK infiltrate was also associated with improvement of systemic activity (p=0.019). The rate of salivary BAFF-positive cells was not associated with the response. Dosage of serum BAFF levels and their association to response to belimumab will be presented at the meeting.

Conclusion: After belimumab therapy, there was a clear tendency in favour of a decrease of lymphocytic infiltration BAFF-expressing cells and of B-cell/T-cell ratio within LSG. Also the percentage of BAFF positive cells significantly decreased, that could be interpreted as a decrease of the BAFF expressing cells, but also as a decrease in B cells expressing BAFF receptors linked to soluble BAFF passively stained by the anti-BAFF antibody.

The patients with a higher number of foci and a higher number of NK cells at the periphery of the foci had a poor response to Belimumab, suggesting that these forms of the disease may be more linked to the IL-12/IFNg TH1/NK axis and less linked to BAFF/B-cell axis than others

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The Significance Of Ectopic Germinal Center In Minor Salivary Gland Of Patients With Sjögren's Syndrome. Kyung-Eun Lee[1], Dong-Jin Park[1], Jeong-Won Lee[1], Ji-Hyoun Kang[1], Lihui Wen[1], Tae-Jong Kim[2], Yong-Wook Park[1] and Shin-Seok Lee[1] [1]Chonnam National University Medical School, Gwangju, South Korea, [2]Chonnam National University Medical School and Hospital, Gwangju, South Korea.

Background/Purpose: To investigate whether the presence of germinal center (GC) in minor salivary glands of patients with Sjögren's syndrome (SS) is associated with different clinical and laboratory features.

Methods: Minor salivary gland tissue biopsies from 93 SS patients were used to identify GC-like structures and germinal center was confirmed by CD21-positive follicular dendritic cell networks. Sociodemographic, glandular, and extraglandular manifestations, and laboratory findings including autoantibodies, complement, and immunoglobulin levels, were analyzed. EULAR SS disease activity index (ESSDAI) and SS disease damage index (SSDDI) were also measured.

Results: GC-like structures were observed in 28 of 93 SS patients (30.1%). Mean focus score was significantly higher in GC-positive patients than in GC-negative patients. GC-positive patients had higher CRP levels and had higher prevalence of rheumatoid factor, anti-CCP antibody, and anti-SSA/Ro antibody compared to GC-negative patients. However, glandular and extra-glandular manifestations were not different between the two groups.

Conclusion: Our findings showed that SS patients who had GC-like structures in minor salivary glands had different laboratory profiles compared to those patients who didn't have. Long-term follow-up of these patients will be necessary to see whether these laboratory abnormalities translate into changes in clinical features.

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Diagnostic Value Of Labial Minor Salivary Gland Biopsy For Primary Sjögren's Syndrome. Raquel Altoe[1], Valeria Valim[1], Maria Carmem S. Santos[2], Erica V. Serrano[1] and Samira T. Miyamoto[3]. [1]Universidade Federal do Espírito Santo, Vitória, Brazil, [2]Universidade de Vila Velha, Vitória, Brazil, [3]Universidade Federal do Espírito Santo, Vitoria, Brazil.

Background/Purpose: The presence of lymphocytic infiltrate with ≥ 1 focus score/4mm^2 in minor salivary gland is a useful tool for the diagnosis of Sjögren's syndrome (SS) and was included in the American–European Consensus Criteria (AECC) (2002) and the criteria proposed by the American College of Rheumatology (ACR) in 2012. The purpose of this study is to evaluate the sensitivity and specificity of the histological analysis of minor salivary gland and the clinical profile of patients undergoing labial salivary biopsy for investigation of glandular SS.

Methods: Retrospective chart review was performed of all patients underwent labial salivary biopsy in Rheumatology Outpatient Clinic of Hospital Universitário Cassiano Antônio de Moraes/Universidade Federal do Espírito Santo (UFES) from March 2008 to March 2011. Biopsy indication, dryness symptons (AECC), unstimulated salivary flow (USF), Schirmer test (ST), presence of autoantibodies, number of foci score were obtained. The sensitivity and specificity of biopsy were calculated considering the expert opinion as the gold standard.

Results: Two-hundred forty-three patients underwent to labial salivary biopsies, 95.9% (233) were female, mean of age was 48.49 ±12.4, 95.88% (233) had dryness symptoms and 4.11% (10) systemic manifestation without dryness (parotid hypertrophy (3), pancytopenia (1), lymphopenia (1), arthritis and positive ANA (4), anemia + arthralgia and positive ANA (1)). The frequency of ≥ 1 focus score/4mm^2 was 35.8% (87), USF ≤ 1.5ml/15min was positive in 56.8% (138) and ST in 45.7% (111). For analysis of sensitivity and specificity, patients were excluded due to insufficient clinical data (N = 40), presence of another autoimmune rheumatic disease (N = 19), hepatitis C (N = 1), diagnosis by the rheumatologist expert opinion that was not described (N = 31).Of the 183 patients analyzed, 32.78% (60 patients) were classified as primary SS by AECC. In these, the frequency of positive biopsy SS, oral and ocular subjective criteria were 88.7% (53), 91.7% (55) and 93.3% (56) respectively. Only 1 patient with SS (with objective criteria, biopsy and anti-Ro positives) showed no dry mouth and eye, 81.7% (49) showed USF ≤ 1.5, 66.7% (40) ST ≤5mm/5min and 33.33% (20) positive anti-SSA and/or anti-SSB antibodies, 66.7% (40) positive ANA, 25% (15) positive rheumatoid factor. Among the systemic manifestations presented there were 1.65% (1) increase of the parotid glands, 1.65% (1) lymphoma, 20% (12) peripheral arthritis, 8.3% (5) cutaneous involvement, 6.7% (4) respiratory involvement, 6.7% (4) renal involvement, 13.3% (8) peripheral neuropathy. For 65% (39) biopsy was necessary to confirm the diagnosis of SS. Of patients with fibromyalgia and dry syndrome (87), 58.3% (35) were diagnosed with SS. The sensitivity and specificity of the biopsy found were 86.57% and 98.23% respectively.

Conclusion: The frequency of Sjögren's syndrome in suspected patients referred to be biopsy submission was 32.78%. The sensitivity and specificity of the salivary biopsy presented high values consistent with other data from the literature. The frequency of SS confirmed by biopsy in patients with fibromyalgia syndrome is high and SS should be investigated in patients with dryness.

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EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) Is Increased In Sjögren's Syndrome Patient With Fibromyalgia. Valeria Valim[1], Samira T. Miyamoto[2], Mauricio Paganotti[3], Erica V. Serrano[1] and Raquel Altoe[1]. [1]Universidade Federal do Espírito Santo, Vitória, Brazil, [2]Universidade Federal do Espírito Santo, Vitoria, Brazil, [3]Universidade de Vila Velha, Vitória, Brazil.

Background/Purpose: The *EULAR Sjögren's Syndrome Patient Reported Index* (ESSPRI) is a patient-reported index designed to assess the severity of patients' symptoms such as dryness, pain and fatigue in primary Sjögren Syndrome (pSS). Considering these symptoms are also very common in fibromyalgia (FM), the association between pSS and FM could contribute to higher scores of ESSPRI. The purpose of this study was to determine if score of ESSPRI differed between pSS patients with and without FM.

Methods: Sixty two women with pSS fulfilling the American–European Consensus Criteria (AECC) were recruited from the Rheumatology Outpatient Clinic of Hospital Universitário Cassiano Antônio de Moraes/Universidade Federal do Espírito Santo (UFES). All were submitted to American College of Rheumatology 1990 Criteria (ACR) for Fibromyalgia and submitted to ESSPRI and *EULAR Sjogren's syndrome Disease Activity Index* (ESSDAI). Student's t-test and Mann-Whitney were used to compare scores of ESSPRI between pSS patients with and without FM ($p<0.05$) and Pearson's Correlation was used to correlate score of ESSPRI and ESSDAI ($p<0.05$).

Results: The mean of age was 49.4 ± 11.6, beginning of symptoms was 7.2 ± 5.4 years and diagnostic time was 3.0 ± 3.3 years. Sixty eight percent were non-Caucasian and 32% Caucasian. ESSPRI mean was 6.87 ± 1.97 and ESSDAI mean was 4.95 ± 6.73, indicating low activity. There was no correlation between ESSDAI score and ESSPRI score ($r=0.051$; $p<0.696$). The frequency of fibromyalgia in pSS patients was 43.5%. Stratified analysis showed that pSS patients with FM have higher score of ESSPRI than those without FM (7.35 ± 1.69 vs. 6.17 ± 2.34, $p=0.028$) (Table 1).

Table 1. Descriptive statistics and score of ESSPRI between primary Sjögren Syndrome patients with and without Fibromyalgia

ESSPRI	Fibromyalgia	Median	Mean	Standard deviation	p-value
Dryness**	Yes	7.00	7.00	2.62	0.251
	No	6.00	6.15	2.92	
Fatigue**	Yes	8.00	7.00	3.32	0.067
	No	6.00	5.03	4,07	
Pain**	Yes	8.00	8.04	2.05	0.441
	No	8.00	7.33	2.89	
Total score*	Yes	7.67	7.35	1.69	0.028***
	No	6.00	6.17	2.34	

* Student's t-test; ** Mann-Whitney test; ***p<0,05

Conclusion: Fibromyalgia is a common comorbidity in pSS patients and it could raise the ESSPRI score and also could explain part of no correlation between ESSPRI and ESSDAI.

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Does Multiplex Flow Immunoassay Underdetect SSA and SSB Antibodies? An Evaluation Of The Sjogren's International Collaborative Clinical Alliance (SICCA) Cohort. Alan N. Baer[1], Laura Gutierrez[1], Mara McAdams DeMarco[2], Mi Y. Lam[3], Livia Casciola-Rosen[1], Stephen Shiboski[4], Caroline Shiboski[3] and Lindsey A. Criswell[5]. [1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [3]University of California San Francisco, San Francisco, CA, [4]University of California, San Francisco, San Francisco, CA, [5]University of California, San Francisco, Rosalind Russell Medical Research Center for Arthritis, San Francisco, CA.

Background/Purpose: Multiplex flow immunoassays (MFIA) are used by clinical laboratories to test for antibodies to extractable nuclear antigens. The use of blended Ro52 and Ro60 antigens in an MFIA can mask their reactivities, otherwise detectable with single antigen assays (Autoimmun Rev. 2009;8:632). We tested the hypothesis that single antigen solid-phase assays are more sensitive than MFIA for the detection of SSA and SSB antibodies.

Methods: We studied 162 consecutively enrolled SICCA registrants selected independently of their serologic results, including 120 with Sjogren's syndrome (SS) defined by the ACR criteria, and 42 without SS (controls). SSA and SSB antibody testing was performed by a Bio-Rad Bioplex 2200 MFIA (Quest Laboratories) and positive results were expressed in "antibody index" (AI) units and provided as continuous variable measures up to a prespecified upper limit. Levels >6 AI were stratified as strong positive, >3 to ≤6 AI moderate positive, >1 to ≤3 AI weak positive, and ≤1 AI negative. We independently tested the same samples using individual assays for Ro52 and SSB (Quantalite ELISA) and Ro60 (immunoprecipitation using in vitro transcription/translated protein: IVTT-IP). Ro52 and SSB results were stratified as negative (<20 U), weak positive (20–39 U), moderate positive (40–80 U), and strong positive (>80 U). The concordance rate was determined from individuals positive for both plus those negative for both divided by the total.

Results: SSA antibodies were detected in 92 (56.8%) subjects by MFIA and in 87 (53.7%) by ELISA/IVTT-IP. SSB antibodies were detected in 66 (40.7%) by MFIA and in 63 (38.9%) by ELISA. The concordance rate for SSA antibody testing was 93.2% and for SSB 90.7%. MFIA detected SSA antibodies in 8 subjects who tested negative for Ro52 and Ro60; 5/8 had weak SSA reactivity. Conversely, 3 subjects had Ro52 (weak reactivity) without Ro60 antibodies, but tested negative for SSA by MFIA. SSB antibodies were detected by MFIA in 9 subjects (weakly in 4) who tested negative by ELISA. Conversely, SSB antibodies were detected in 6 subjects by ELISA (weak reactivity in 3) who tested negative by MFIA. The 26 discordant (positive/negative) results were distributed evenly among the SS and control groups and the positive reactivity was weak in 15, moderate in 7 and strong in 4.

Conclusion: MFIA and single antigen solid phase immunoassays had a concordance rate of over 90% in this sample of the SICCA cohort, and there was no evidence that MFIA underperformed relative to the single antigen assays.

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Prevalence Of Seronegative Sjogren's Syndrome: A Comparative Study From The Sjogren's International Collaborative Clinical Alliance (SICCA) Cohort. Alan N. Baer[1], Laura Gutierrez[1], Mara McAdams DeMarco[2], Mi Y. Lam[3], Livia Casciola-Rosen[1], Stephen Shiboski[4], Caroline Shiboski[3] and Lindsey A. Criswell[5]. [1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [3]University of California San Francisco, San Francisco, CA, [4]University of California, San Francisco, San Francisco, CA, [5]University of California, San Francisco, Rosalind Russell Medical Research Center for Arthritis, San Francisco, CA.

Background/Purpose: Individuals with primary Sjogren's syndrome (SS) may lack systemic autoantibodies. When defined by the absence of anti-SSA and –SSB antibodies, the reported range is 26–67%(J Autoimmun 2012;39:15). We sought to: 1) determine the prevalence of seronegativity, defined more broadly by the absence of antibodies to SSA fine specificities (Ro52 and Ro60, assayed individually) and to other relevant antigens, including cyclic citrullinated peptide (CCP), centromere (CENT), and rheumatoid factor (RF) and 2) compare these antibody profiles with non-SS controls.

Methods: We studied 149 consecutively enrolled SICCA registrants who had SS, defined by focal lymphocytic sialadenitis with a focus score ≥1 (FLS) and ocular surface staining score (OSS) ≥3, irrespective of serologic test results. Control subjects were 50 consecutive registrants lacking FLS, OSS ≥3, or whole unstimulated sialometry ≤0.1 ml/min. Subjects with known rheumatoid arthritis (RA) or systemic lupus (SLE) were eligible for SICCA, while those with systemic sclerosis (SSc) were excluded. Antibodies were assayed by ELISA (Ro52, SSB, and CCP), immunoprecipitation using in vitro transcription/translated protein (Ro60), or immunofluorescent staining (CENT).

Results: 137 subjects had 1° and 12 had 2° SS (4 SLE, 8 RA). In 1°SS, anti-SSA and/or SSB were detected in 102 (74%, [66,82 CI]), including 32 with only anti-SSA and 2 with only anti-SSB; anti-CCP in 7 (5%); and anti-CENT in 8 (6%). The 50 control subjects included 1 with anti-SSA and -SSB, 4 with anti-SSB without -SSA, 6 with anti-CCP, and 1 with anti-CENT. One or more of these specificities were present in 109 (80%) of 1°SS and in 10 (20%) of control subjects. Of the 8 1°SS subjects with anti-CENT, 3 (38%) were judged to have limited SSc, and 4 (50%) had anti-SSA and/or -SSB. Inclusion of [ANA≥1:320 + RF] increased the autoantibody prevalence among 1°SS to 122 (82%), but not among the control subjects.

Conclusion: The prevalence of anti-SSA and –SSB seronegativity in this 1° SS sample was substantially less than in other cohorts. Anti-CCP and -CENT were present in an additional 6% of these seronegative patients, indicating the importance of other autoantibodies in the definition of 1° SS autoimmune subsets, particularly those with SSc overlap. The combination of ANA≥1:320 and RF, an alternative ACR classification criterion, only identified 2 (1.3%) additional 1°SS patients and thus has limited SS diagnostic utility. The 8–14% prevalence of anti-SSB, anti-CCP, RF, and ANA≥1:320 in the control population limited the diagnostic specificity of these autoantibodies.

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Antibody Responses To Oral Bacteria In Patients With Primary Sjögren's Syndrome and Comparison With Rheumatoid Arthritis and Periodontitis. Bozo Lugonja[1], Michael Milward[1], Diana Pearson[2], Thomas Dietrich[1], Iain Chapple[1], John Hamburger[1], Francesca Barone[1], Saaeha Rauz[1], Lorraine Yeo[1], Ana Povedo-Gallego[2], Geraint Williams[1], Paola de Pablo[1], Andrea Richards[2], Christopher D. Buckley[1], Dagmar Scheel-Toellner[1] and Simon J. Bowman[3]. [1]University of Birmingham, Birmingham, United Kingdom, [2]Birmingham Dental Hospital, Birmingham, United Kingdom, [3]Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom.

Background/Purpose: We set out to examine peripheral blood antibody ELISA responses to common oral bacteria in primary Sjögren's syndrome (pSS) to identify potential bacterial triggers linked to HLA-DR3 and anti-Ro/La antibodies. We also assessed the prevalence of periodontitis in relation to these antibody responses and in comparison to other patient groups.

Methods: Following Research Ethics Committee approval, 65 patients (64,female) with pSS according to American-European Criteria (mean age = 61 years; 59/65 with anti-Ro/La antibodies; 2 smokers, 22 ex-smokers), 47 female patients with rheumatoid arthritis (RA) (mean age = 59; 46 anti-CCP positive; 8 smokers, 16 ex-smokers), 35 patients with osteoarthritis (OA) (mean age = 58 years; 2 smokers, 17 ex-smokers) and 41 people (28 female, mean age = 53) previously recruited to a therapeutic study in non-smokers with periodontitis (1), participated in this study. Sonicated whole bacteria lysates from 10 common oral bacteria were used as substrates for an in-house ELISA of anti-bacterial responses. Oral periodontal status was assessed using standard approaches according to the American Academy of Periodontology/ Centres for Disease Control criteria.

Results: Periodontitis was identified in 20/42 patients with pSS who took part in this component of the study, 22/35 patients with RA and 17/30 patients with OA (not significant). RA patients were more likely than pSS to be current smokers (p=0.01). ELISA responses to *P. gingivalis*, *P. denticola*, *P. intermedia* and *S. sanguis* were significantly higher in patients with RA and periodontitis than in OA controls. *P. denticola* and *S. mutans* had greater responses in pSS patients than in OA controls. *C. showae*, *E. faecalis* and *A. actinomycetemcomitans* were particularly associated with the periodontitis group and *F. nucleatum* and *C. gingivalis*had no apparent associations with any groups.

Conclusion: Previous studies of the frequency of periodontitis in pSS have yielded conflicting results. This study did not identify an increased overall frequency of periodontitis in pSS although additional data analyses are planned. Periodontitis has been linked to active RA and *Porphyromonas gingivalis* has been proposed to play a central role in relation to anti-CCP antibody responses (2). *Prevotella intermedia* has also been identified by microbiome analysis (3) to be of potential interest in RA. Our data in RA patients supports these findings. Furthermore we have identified bacterial responses of potential interest in pSS such as to *P. denticola* and *S. mutans*. Oral microbiome analysis in pSS is now indicated to identify further bacteria of interest to direct research in this area.

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Vitamin D In Sjogren's Syndrome. Suneet Grewal[1], Judith A. James[2], R. Hal Scofield[2], Kathy L. Sivils[2], Michael H. Weisman[1] and Swamy Venuturupalli[1]. [1]Cedars-Sinai Medical Center, Los Angeles, CA, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: Unlike other autoimmune diseases in which an association with vitamin D deficiency has been established, the role of vitamin D in Sjogren's syndrome has been much less studied and data are conflicting. Vitamin D deficiency may contribute to B cell hyperactivity and autoantibody production in SLE. Given some autoantibody, genetic, and clinical similarities between Sjogren's syndrome and SLE, we hypothesized that vitamin D levels would be lower in patients with primary Sjogren's syndrome (SS) compared to patients with sicca symptoms who do not meet SS criteria and healthy controls. We studied a well characterized cohort of primary SS patients for prevalence of vitamin D deficiency as well as for the relationship between vitamin D levels and autoantibody positivity.

Methods: Samples from 70 patients who met the 2002 American-European Consensus Group classification criteria for primary SS, 78 patients with sicca symptoms who did not meet SS criteria, and 148 healthy controls matched for age, gender and race were studied. Participants were enrolled and evaluated as part of the multidisciplinary Oklahoma Sjogren's Syndrome Cohort. Clinical and laboratory data, including 25(OH)D levels, presence of sicca symptoms, anti-nuclear antibody (ANA) status, anti-SSA/Ro status, and anti-SSB/La status were utilized in the study.

Results: Mean age for primary SS patients and patients with sicca symptoms who did not meet SS criteria was 51.8 years and mean age for controls was 51.9 years. Eighty-nine percent of the population studied was Caucasian. The prevalence of Vitamin D deficiency (as defined by recommendations put forth by the Institute of Medicine) in patients with primary SS and patients with sicca symptoms who did not meet SS criteria was 16.9% whereas prevalence of Vitamin D deficiency in matched healthy controls was 52.7%. Patients with primary SS had higher 25(OH)D levels when compared to matched healthy controls (28.1 ng/mL vs. 19.1 ng/mL; p <0.0001). Patient with sicca symptoms who did not meet SS criteria also had higher vitamin D levels when compared to matched healthy controls (30.1 ng/mL vs. 22.5 ng/mL; p <0.0001). No difference in 25(OH)D levels between patients with primary SS and patients with sicca symptoms who did not meet SS criteria (p=0.78) was detected. No difference in the 25(OH)D levels of anti-SSA/Ro positive vs. anti-SSA/Ro negative patients (p=0.22) nor in the 25(OH)D levels of anti-SSB/La positive vs. anti-SSB/La negative patients (p=0.42) were detected. We also detected no difference in the 25(OH)D levels of ANA positive vs. ANA negative patients (p=0.96).

Conclusion: In our well characterized cohort, patients with either primary SS or sicca symptoms who did not meet SS criteria had significantly higher vitamin D levels than matched healthy controls. These findings are similar to those of the few studies conducted in the past, which did not show a lower vitamin D level in patients with primary SS as compared to controls, and suggest that vitamin D deficiency does not contribute to the pathogenesis of Sjogren's syndrome. Furthermore, these results also suggest that vitamin D deficiency does not contribute to autoantibody production as it may in SLE.

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Identification Of IgG4-Related Disease and Analysis Of IgG4 Serum Levels In Different Subgroups Of Patients With Sjögren's Syndrome. Antónia Szántó[1], Gábor Nagy[1], Csaba Molnár[2] and Margit Zeher[1]. [1]University of Debrecen, Medical and Health Science Center, Institute for Medicine, Debrecen, Hungary, [2]University of Debrecen, Medical and Health Science Center, Institute for Pathology, Debrecen, Hungary.

Background/Purpose: In the clinical diagnostic criteria of IgG4-related disease (IgG4-RD), Sjögren's syndrome (SS) appears as one of the exclusion criteria. However, in Europe, where Mikulicz's disease and SS were merged into one syndrome, some of the IgG4-RD patients might be hidden as a subset of SS.

There are special symptoms during the disease course of SS that raise the possibility of IgG4-RD whereas other symptoms identify certain SS patients as having high risk for developing malignant lymphoma (lymphoma high risk - LHR).

The aim of this study was to identify patients with IgG4-RD among patients followed up because of SS and to compare the aforementioned two subsets, with special attention on their IgG4 levels.

Methods: Data of 65 SS patients were analysed. Patients are followed up in the University o Debrecen, Hungary. Patients were divided into 4 subgroups:

- IgG4-RDsusp (n=15): patients at whom IgG4-RD can be raised (male gender, negative anti-Ro/SS-A and anti-La/SS-B, autoimmune pancreatitis, autoimmune hepatitis or sclerotizing cholangitis, persisting salivary gland swelling (SGS), lymphadenopathy)

- LHR (n=16): patients with high risk of malignant lymphoma: persisting leukopenia, low complement levels, polyneuropathy, vasculitis, gammopathy, cryoglobulinemia, persisting SGS or lymphadenopathy

- IgG4-RDsusp+LHR (n=20): patients eligible for both IgG4-RD and LHR group

- Control (n=14): patients with SS who are not eligible for any of the aforementioned groups.

Clinical course, total IgG and IgG4 levels, IgG4/IgG ratios and EULAR SSDAIs were compared.

Statistical analyses were performed with SPSS 19.0 software. $P<0.05$ was considered statistically significant.

Results: Four patients fulfilled the diagnostic criteria for IgG4-RD.

Total IgG level of the LHR group was significantly higher than that of IgG4-RDsusp patients (18.7 g/l vs. 11.6 g/l, p=0.0033). IgG4 concentrations were significantly higher at the IgG4-RDsusp patients than in the LHR group (0.46 g/l vs. 0.12 g/l, p=0.032).

IgG4/IgG ratio was significantly higher both in the IgG4-susp and in the IgG4-susp+LHR group compared to the other two groups.

The two common features of the IgG4-RDsusp and the LHR group, namely SGS and lymphadenopathy, were analysed separately, too.

Among patients with SGS (n=35), IgG4/IgG ratio was significantly higher (p=0.036). Neither total IgG, nor IgG4 levels differed significantly. Lymphadenopathic patients (n=10) had significantly higher IgG4 levels than those without lymphadenopathy (p=0.042).

ESSDAI median was higher in patients with elevated IgG4 concentrations (2 vs. 6, p=0.026). Average ESSDAI score was elevated in the LHR group (4.0 vs. 1.3, p=<0.001).

Conclusion: Our results support the hypothesis that some patients may be "hidden" under the diagnosis of SS unless their serum IgG4 level is measured. Measurement of IgG4 serum level is recommended before the introduction of any immunosuppressive treatment.

Based on our findings, although patients with LHR and patients with possible IgG4-RD share some clinical symptoms (SGS and lymphadenopathy), they differ significantly regarding their IgG and IgG4 levels such as IgG4/IgG ratio.

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Chronic Obstructive Pulmonary Disease Is Very Common in Primary Sjögren's Syndrome. Anna M. Nilsson[1], Elke Theander[2], Roger Hesselstrand[3], Eeva Piitulainen[4], Sandra Diaz[5], Olle Ekberg[5], Per Wollmer[6] and Thomas Mandl[7]. [1]Skane University Hospital Malmo, Lund University, Malmo, Sweden, [2]Lund University, Malmö, Sweden, [3]Skane University Hospital Lund, Lund University, Lund, Sweden, [4]Lund University & Skåne University Hospital, Malmö, Sweden, [5]Skåne University Hospital Malmo, Lund University, Malmö, Sweden, [6]Skane University Hospital Malmo, Lund University, Malmö, Sweden, [7]Skåne University Hospital Malmo, Lund University, Sweden, Malmö, Sweden.

Background/Purpose: To study the prevalence of chronic obstructive pulmonary disease (COPD) in patients with primary Sjögren's syndrome (pSS) and its association with respiratory symptoms, pulmonary radiographic findings and clinical features of pSS.

Methods: Fifty-one consecutive pSS patients, diagnosed according to the American-European Classification Criteria (AECC), were recruited from the open clinic at the Dept of Rheumatology, Malmö, Sweden and included in the study. The patients were studied by pulmonary function tests (PFT), CT scan of the lungs, the St George's Respiratory Questionnaire (SGRQ), The EULAR Sjögren's syndrome disease activity (ESSDAI) and patient reported indices (ESSPRI) and by laboratory and serological tests. The results were compared with 270 male and 186 female population-based PFT controls standardizing the variables with regard to gender, age, height, weight and tobacco consumption.

Results: pSS patients displayed a significantly decreased vital capacity (VC), forced expiratory volume in 1 second (FEV_1), FEV_1/VC, and diffusion capacity for carbon monoxide whilst the residual volume was significantly increased (Table 1). COPD, according to the GOLD criteria, was diagnosed in 41% of pSS patients (30% in never-smoking and 54% in ever-smoking pSS patients) (Table 2). The SGRQ and ESSDAI total scores were inversely correlated with the VC, TLC and D_{LCO}. However, radiographic abnormalities, IgG, C3, C4, anti-SS-A and anti-SS-B antibodies, ANA, RF and disease duration were poorly associated with PFT variables.

Table 1. Comparison of Pulmonary Function Test (PFT) results in patients with primary Sjögren's syndrome (pSS). PFT results are presented as % of predicted and in absolute numbers (mean ± SD) and COPD diagnosis in %. In comparisons between measured and predicted PFT values, the paired samples t-test was used.

	pSS patients	Predicted values	p-value
VC (L)	3.33 ± 0.82	3.60 ± 0.86	0.001
VC (% of predicted)	93.3 ± 14.2		
TLC (L)	5.61 ± 1.01	5.64 ± 0.72	0.938
TLC (% of predicted)	99.5 ± 12.8		
RV (L)	2.27 ± 0.49	2.03 ± 0.37	< 0.001
RV (% of predicted)	114.1 ± 22.5		
FEV_1 (L/s)	2.31 ± 0.64	2.70 ± 0.66	< 0.001
FEV_1 (% of predicted)	85.9±14.7		
FEV_1/VC	69.4 ± 8.2	74.8 ± 3.0	< 0.001
FEV_1/VC (% of predicted)	92.8 ± 9.8		
D_{LCO} (mmol/min kPa)	6.49 ± 1.86	7.03 ± 1.61	0.003
D_{LCO} (% of predicted)	92.4±17.6		
COPD (%)	41	–	–

VC = vital capacity, TLC = total lung capacity, RV = residual volume, FEV_1 = forced expiratory volume in one second, FEV_1/VC = ratio of FEV_1 to VC, D_{LCO} = diffusing capacity for carbon monoxide, COPD=Chronic Obstructive Pulmonary Disease.

Table 2. Prevalence of chronic obstructive pulmonary disease (COPD) in ever-smoking and never-smoking patients with primary Sjögren's syndrome (pSS).

	COPD	Not COPD
Ever-smokers	13 (54% in ever-smokers)	11
Never-smokers	8 (30% in never-smokers)	19

Conclusion: pSS patients showed signs of both obstructive and restrictive pulmonary disease and 41% fulfilled GOLD criteria for COPD. Respiratory symptoms and disease activity was associated with PFT, whilst radiographic abnormalities, laboratory and serological features of the disease were generally poorly associated with PFT in pSS patients.

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Respiratory Compromise In Patients With Primary Sjögren Syndrome. Evangelina Maria Miretti[1], Maria Haye Salinas[1], Francisco Caeiro[1], Anastasia Secco[2], Antonio Catalan Pellet[3], Paula Pucci[4], Cecilia Asnal[5], Catherine Crow[6], Cristina Amitrano[7], Alejandro Nitsche[7], Silvia Papassidero[8], Oscar L. Rillo[9], Federico Zazzetti[10], Juan C. Barreira[11], Mariano Rivero[11], Damián Duartes Noé[11], Hugo A. Laborde[11], Natalia Tamborenea[12], Eduardo Albiero[13], Maria Renata Seisdedos[14], Carla Gobbi[15], Paula Alba[16], Pablo Astesana[17], Gabriela Salvatierra[18] and Veronica Saurit[1]. [1]Hospital Privado Centro Médico de Córdoba, Córdoba, Argentina, [2]Rivadavia Hospital, Buenos Aires, Argentina, [3]Hospital Rivadavia, Buenos Aires, Argentina, [4]Aleman Hospital, Argentina, buenos Aires, Argentina, [5]Argerich, Buenos Aires, Argentina, [6]Hospital Alemán, Buenos aires, Argentina, [7]Hospital Alemán, Buenos Aires, Argentina, [8]Hospital Tornú, Buenos Aires, Argentina, [9]Hospital Gral. de Agudos Dr. E. Tornú, Buenos Aires, Argentina, [10]Hospital Británico, Buenos Aires, Argentina, [11]Buenos Aires British Hospital, Buenos Aires, Argentina, [12]OMI, Buenos Aires, Argentina, [13]Sanatorio Allende de Córdoba, Córdoba, Argentina, [14]Rivadavia Hospital, Buenos Aires, Argentina, [15]Sanatorio Allende de Córdoba, Cordoba, Argentina, [16]Hospital Córdoba, Córdoba, Argentina, [17]Sanatorio Allende, cordoba, Argentina, [18]Centro de enfermedades Reumaticas, Santiago Del Estero, Argentina.

Background/Purpose: Sjögren's syndrome (SS) is an autoimmune inflammatory disease that affects exocrine glands and may have extraglandular involvement. The respiratory compromise (RC) occurs in 19%–65% of the patients with SS and the most common type is nonspecific interstitial pneumonia (NSIP) (30–60%).

Objectives: To determine the frequency, time of occurrence and type of RC in patients with primary SS. To establish the relationship between RC and antibody profile, complement levels, leukopenia, and other extraglandular manifestations.

Methods: Observational, transversal and analytical study. We included patients who met ACR-EULAR criteria for primary Sjögren's syndrome, over 18 years old from the GESSAR (argentine SS study group) database from Jan/2011 to Jul/2011 inclusive. We evaluated demographic data, time of evolution, the presence of extraglandular manifestations and laboratory parameters. Categorical variables were compared with X2 test or Fisher test and continuous variables with the Mann-Whitney test, The p was considered significant when ≤ 0.05. We performed multivariate logistic regression analysis.

Results: Total N: 285. 95.9% female, age 55.8 ± 14.8 y. Time of evolution of SS until the RC developed: 4 years (IQR 2–6 a). 75 patients (26.3%) had RC, of which the most frequent were xerotrachea (58,6%), recurrent infections (24%), NSIP (13,3%) and pulmonary fibrosis (12.5) (Box 1). RC was more common in patients with Raynaud syndrome (22.2% vs 12.3%, p = 0.04), fibromyalgia (26.8% vs 14.3%, p: 0.01) and tinnitus (5.9% vs 1.2%, p: 0.050). There were no significant differences in laboratory parameters. In the multivariate logistic regression analysis there was an independent association of with Raynaud's (OR = 2.32, 95% CI 1.08 to 4.96, P = 0.03) and fibromyalgia (OR = 2.50, 95% CI 1.21 to 5.13, p = 0, 01) with RC.

Table 1. Distribution of the Types of Respiratory Compromise

Xerotrachea **n (%)**	44 (58,6)
Recurrent infections **n (%)**	18 (24)
Nonspecific interstitial pneumonia (NSIP) **n (%)**	10 (13,3)
Pulmonary fibrosis (UIP) **n (%)**	9 (12,5)
Lymphocytic interstitial pneumonia **n (%)**	3 (4)
Pulmonary **hipertensión n (%)**	2 (2,6)
Pulmonary thromboembolism **n (%)**	2 (2,6)
Bronchiectasis **n (%)**	2 (2,6)
Bronchiolitis obliterans **n (%)**	2 (2,6)
Pleural effusion **n (%)**	1 (1,3)
Nonspecific interstitial pneumonia **n (%)**	1 (1,3)
Solitary nodule **n (%)**	1 (1,3)

Conclusion: A quarter of patients with SS had RC of which the most frequent were xerotraquea, recurrent infections, NSIP and pulmonary fibrosis. There was no association with laboratory parameters. RC was independently associated with the presence of lung disease raynaud and fibromyalgia.

The authors declare no conflicts of interest.

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Abatacept Reduces Disease Activity In Early Primary Sjögren's Syndrome:One Year Results From a Phase II Open-Label Study. PM Meiners, A Vissink, Fkl Spijkervet, EA Haacke, WH Abdulahad, E Brouwer, MG Huitema, N Sillevis Smitt-Kamminga, FGM Kroese, S Arends and H Bootsma. University Medical Center Groningen, Groningen, Netherlands.

Background/Purpose: Traditional DMARDs have limited effects in primary Sjögren's (pSS) patients. B cell depletion therapy with rituximab showed efficacy, but had some side-effects. T and B cells are known to play a critical role in the pathophysiology of pSS. Abatacept, a selective co-stimulation modulator of T lymphocytes, could be an alternative treatment option for pSS. In this study the efficacy and safety of abatacept in early pSS patients was assessed.

Methods: All patients (12 female, 3 male) included in the open-label Active Sjögren Abatacept Pilot (ASAP) study met the revised American-European Consensus Group criteria. Disease duration was <5 years. Traditional DMARDs, hydroxychloroquine or corticosteroids were discontinued ≤ 1 month before baseline. Patients were biological DMARD naïve, and were treated with 8 abatacept infusions (≈10 mg/kg of body weight) administered intravenously on days 1, 15, and 29 and then every 4 weeks thereafter (total treatment period 24 weeks). Follow-up was conducted at 4, 12, 24 (on treatment), 36 and 48 weeks (off treatment). Disease activity was assessed with EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) and Patient Reported Index (ESSPRI). Several other functional, laboratory and subjective variables were analysed. Parotid gland biopsies were taken at baseline and week 24. Generalized estimating equations were used to analyse parameters over time.

Results: Median age and disease duration were 43 years and 11 months, respectively. Median ESSDAI decreased significantly from 11 (range 2–21) before abatacept to 2 (range 0–9) 24 weeks after abatacept (p<0.000) (Figure 1). ESSDAI increased significantly post-treatment (p<0.000). Median ESSPRI decreased significantly from 7.7 (range 3.7–8.7) to 5.8 (range 2.3–9.7) during treatment (p=0.015), followed by a trend towards increased ESSPRI post-treatment. Similar patterns were found for rheumatoid factor and IgG levels. Salivary and lacrimal gland function remained stable during treatment. Absolute numbers of T and B cells changed slightly (<12%). Fatigue and health-related quality of life improved significantly during treatment. No serious side effects or infections were seen. Histological findings are currently analysed and will be presented at the ACR meeting.

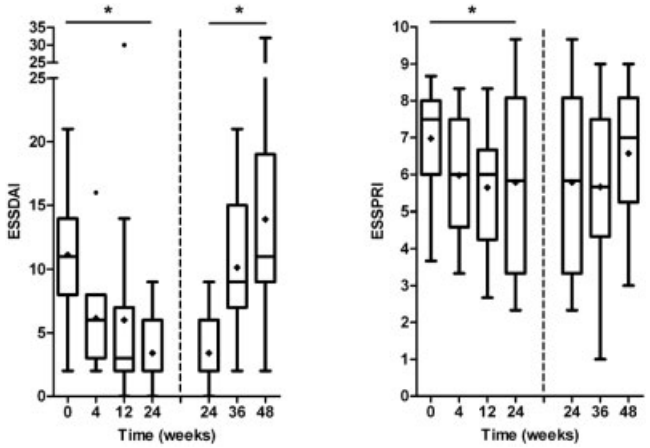

Figure 1. Change in disease activity over time, on treatment (0–24 weeks) and off treatment (24–48 weeks). Box-and-whisker plots (Tukey); boxes=medians with interquartile ranges; +=means; whiskers=1.5 times the interquartile distances; ●=outliers. *=p<0.05 over time.

Conclusion: This open label pilot study indicates that abatacept is well tolerated, safe and results in reduced disease activity, laboratory and subjective parameters in pSS patients. Most patients experienced a clinically relevant improvement in their well-being. These very promising results warrant confirmation in a randomized, double-blind, placebo-controlled clinical trial.

Disclosure: P. Meiners, BMS, 2; **A. Vissink**, BMS, 2; **F. Spijkervet**, BMS, 2; **E. Haacke**, BMS, 2; **W. Abdulahad**, BMS, 2; **E. Brouwer**, BMS, 2; **M. Huitema**, BMS, 2; **N. Sillevis Smitt-Kamminga**, BMS, 2; **F. Kroese**, BMS, 2; **S. Arends**, BMS, 2; **H. Bootsma**, BMS, 2.

ACR Poster Session A
Spondyloarthropathies and Psoriatic Arthritis: Pathogenesis, Etiology, Animal Models I
Sunday, October 27, 2013, 8:30 AM–4:00 PM

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Association Between The Presence Of Amyloidosis In Patients With Ankylosing Spondylitis and Polymorphisms In Type 1/Type 2 Serum Amyloid A Protein Genes, Mediterranean Fever Genes. Gozde Yildirim Cetin[1], Eda Ganiyusufoglu[2], Dilek Solmaz[3], Yonca Cagatay[4], Sibel Yilmaz Oner[5], Burak Erer[6], Hasan Sabit Sagliker[7], Ali Berkant Avci[8], Servet Akar[3], Omer Nuri Pamuk[9], Metin Kilinc[2], Timucin Kasifoglu[10], Haner Direskeneli[5] and Mehmet Sayarlioglu[11]. [1]Sutcu Imam University, School of Medicine, Department of Internal Medicine, Division of Rheumatology, Kahramanmaras, Turkey, [2]Sutcu Imam University, School of Medicine, Department of Biochemistry Research Laboratory, Kahramanmaras, Turkey, [3]Dokuz Eylul University School of Medicine, Izmir, Turkey, [4]Bilim University, Faculty of Medicine, Rheumatology Department, Istanbul, Turkey, [5]Marmara University, School of Medicine, Istanbul, Turkey, [6]Istanbul University, Istanbul Faculty of Medicine,, Istanbul, Turkey, [7]Sutcu Imam University, School of Medicine, Department of Internal Medicine, Kahramanmaras, Turkey, [8]Antalya University, School of Medicine, Department of Internal Medicine, Division of Rheumatology, Antalya, Turkey, [9]Trakya University Medical Faculty, Edirne, Turkey, [10]Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkey, [11]Ondokuz Mayis University School of Medicine, Samsun, Turkey.

Background/Purpose: Ankylosing spondylitis (AS) is a chronic autoinflammatory disease. The most severe complication of this disease is development of

renal amyloidosis. The etiology of AS remains largely unknown but both genetic and environmental factors are in play. This article explores the existence of a possible association between polymorphisms of the the type 1 and type 2 serum amyloid A protein (*SAA1/2)* genes and development of amyloidosis in AS patients, and also explores the Mediterranean fever (*MEFV*) genotype of AS patients.

Methods: The numbers of AS patients with amyloidosis are limited and a multicenter study was thus performed. *MEFV* mutations in exons 2 and 10 were screened and *SAA1/2* polymorphisms and HLA-B27 status evaluated in 23 AS patients with amyloidosis (M/F:18/5) and 49 AS patients without amyloidosis (M/F: 43/6).

Results: The single-nucleotide rs12218 polymorphism of *SAA1* was significantly more prevelant in AS patients with amyloidosis ($p=0.006$) than in AS patients without the complication. The prevelance of the *SAA2* rs2445174 and rs2468844 polymorphisms did not differ signicificantly between the two groups ($p=0.17$ and $p=0.65$, respectively)

HLA-B27 positivity was evident in 63 of 72 patients with AS (87.5%).

MEFV mutations were found in 47 of 72 (study and control) AS patients (65.2%) and in 53 of their 144 alleles (36.8%). Genotyping of *MEFV*exon 10 failed for one AS patient with amyloidosis and one without. Twelve M694V mutations were found (5 in the amyloidosis group and 7 in controls). Thirty-two R202Q mutations were found (9 in the amyloidosis group and 23 in controls). Ten E148Q mutations were found, the number was significantly higher in the amyloidosis group (7) than in controls (3) ($p=0.007$)

Conclusion: A relationship between the presence of amyloidosis and *SAA1* genotype has been shown in recent studies of (principally) FMF patients. To date, no study has explored *SAA1/2* polymorphisms in AS patients. We found that, as in FMF patients, the *SAA1* rs12218 polymorphism was significantly more prevelant in amyloidosis patients.

The allelic frequency of M694V among AS patients was 8.3% in our present study. Two uncontrolled studies conducted in central Turkey estimated the allelic frequency of M694V among AS patients at 6.3% and 12.3%. The corresponding figure in the general population of the same region was about 1.1%. These studies and our work suggest a role for M694V in AS pathogenesis in the Turkish population.In our study, the E148Q mutation was significantly higher in AS patients with amyloidosis than in those with AS alone. FMF patients who are compound E148Q-V726A heterozygotes appear to be more likely than other FMF patients to have severe renal amyloidosis. In a recent study in which few patients were evaluated, E148Q mutation was found in 3 of 9 patients with secondary amyloidosis due to different inflammatory diseases.

In our work, the R202Q mutation was the most prevelent *MEFV* mutation.The significance of this observation is uncertain. Earlier, it was found that the R202Q mutation occurred at a significantly higher level in FMF patients than in healthy controls. The R202Q mutation may thus contribute to the etiology of FMF. Our work shows that this may also be true of AS. Further large-scale screening is required.

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Expansion Of DC-STAMP$^+$ IL-17$^+$ Cells In Bone Marrow From Psoriasis and Psoriatic Arthritis Patients. Yahui Grace Chiu[1], Edward M. Schwarz[1], Jamie Biear[1], Debbie Campbell[2], Jennifer Hossler[1], Jennifer H. Anolik[3], R. John Looney[1] and Christopher T. Ritchlin[1]. [1]University of Rochester, Rochester, NY, [2]Univerity of Rochester, Rochester, NY, [3]University of Rochester Medical Center, Rochester, NY.

Background/Purpose: Focal erosions in inflammatory arthritis are mediated by bone marrow (BM) derived osteoclasts (OC) that enter the joint as OC precursors (OCP) from peripheral blood. We have previously shown that DC-STAMP (Dendritic Cell-Specific Transmembrane protein), a 7-pass transmembrane protein essential for cell-to-cell fusion during OC differentiation, is a valid biomarker of circulating OCPs. In bone marrow (BM), naive lymphocytes encounter self-antigens to establish immune tolerance and interact with OC and osteoblast progenitors. Herein, we dissected T cell, B cell and monocyte populations, compared the percentage of these cell populations between patients and healthy individuals, examined the potential of these cells in lineage differentiation, and searched for cell subsets uniquely present in BM.

Methods: BM and PBMC collected from 2 psoriatic arthritis (PsA), 2 psoriasis (Ps) patients and 4 healthy controls (HC) were processed and purified by Ficoll gradient, stained by antibodies, and analyzed by flow cytometry. To assess differentiation potential, cells were cultured in dendritic cell (DC)-promoting, Th17-promoting, and OC-promoting media. Phagocytic activity was assessed by FITC-dextran beads.

Results: The OCP frequency of BM and PBMC was 3,423±306 and 1,340±120 per 10e6 monocytes, respectively. Monocytes in BM differentiated into functional DC with phagocytic activity as evidenced by the intake of FITC-dextran beads. T cells in BM differentiated into Th17-like T cells (IL17A+ IL23R+DC-STAMP+CCR6+) after in vitro culture in Th-17-promoting media. Patients with both Ps and PsA had a higher percentage of DC-STAMP$^+$ IL17A$^+$ cells in the BM (patients:11.4%, HC:2.6%) and a higher percentage of IgD+CD27+CXCR3+ memory B cells in both BM and PBMC than HC (HC/patients=3/60 for BM and 24/69 for PBMC). Intriguingly, a novel DC-STAMP-expressing monocyte subset (DC-STAMP$^+$CD14$^+$CD11b$^+$CD16-CD34$^-$CD45 (intermediate)), composing of approximately 18% of rosette monocytes, was only present in BM but absent in PBMC.

Conclusion: In this study, we (1) identified a novel subset of DC-STAMP$^+$ monocytes which is uniquely present in BM but absent in PBMC; (2) showed that BM has 3-fold more OCPs than peripheral blood; (3) found that monocytes and T cells in BM can differentiate into OC/DC and Th17 cells with full effector functions; (4) identified variations in T, B, monocyte populations between PBMC and BM; (5) found that patients with Ps and PsA had a higher % of 1A2+IL17A+CD3+ T cells and IgD+CD27+CXCR3+ B cells in BM than controls.

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Evidence For Enhanced Induction Of Unfolded Protein Response Target Genes In Peripheral Blood Mononuclear Cells From Spondyloarthritis Patients. Grace Kwon, Eva Yang, Keith A. Sikora, Hemalatha Srinivasalu, Gerlinde Layh-Schmitt and Robert A. Colbert. NIAMS NIH, Bethesda, MD.

Background/Purpose: Spondyloarthritis (SpA) is an immune-mediated inflammatory disease strongly associated with HLA-B27 (B27). In a transgenic rat model where B27 causes SpA-like disease, CD8 T cells that recognize B27 peptides are not required. B27 has a tendency to misfold, and when upregulated in rat cells can cause endoplasmic reticulum (ER) stress resulting in an unfolded protein response (UPR). The UPR can promote cytokine production and activate autophagy, and may be important in SpA pathogenesis. Since B27 transgenic rats carry multiple transgene copies, an important question is whether B27 upregulation in human cells is sufficient to cause ER stress. We sought to determine whether B27 upregulation in peripheral blood mononuclear cells (PBMC) activates the UPR.

Methods: PBMC from 25 healthy controls (HCs) and 32 adult or pediatric SpA patients (27 B27 positive) meeting age-appropriate classification criteria for SpA were cultured for 20 hours without or with IFNγ, TNFα, or both (IT). Total RNA was isolated and expression of HLA-B and UPR-target genes (BiP, XBP1) was quantitated by real-time PCR. Relative gene expression was determined by normalizing to 3 housekeeping genes, and fold change calculated by comparing treated and untreated samples with statistical assessment by Mann-Whitney U test. Correlations were assessed by Spearman's. XBP1 mRNA splicing was determined on agarose gels.

Results: HLA-B expression increased 1.9-fold with IFNγ in SpA PBMC and 1.6-fold in HCs ($p<0.05$ SpA vs. HCs). When treated with TNFα or IT, HLA-B expression in SpA patients increased 1.3-fold and 2.1-fold, respectively, compared to 1.1-fold and 1.9-fold in healthy controls (NS SpA vs. HCs). BiP expression in TNFα-treated PBMC increased 1.3-fold in SpA patients vs. 1.1-fold in HCs ($p=0.05$) while no significant difference between SpA patients and HCs was seen with IFNγ (1.3-fold and 1.2 fold) or IT (1.3-fold and 1.3-fold). We also asked whether individual fold changes in BiP correlated with HLA-B upregulation. With IFNγ and/or TNFα treatment, fold change in BiP and XBP1 positively correlated with fold change in HLA-B in SpA patients ($p<0.005$), while in HCs significant correlation was only observed in TNFa-treated PBMC ($p<0.05$, $p<0.005$, respectively). More importantly, the slopes of the correlation plots between HLA-B and BiP or XBP1 were 1.3–2.3 times greater for SpA patients than HCs. In addition, XBP1 splicing was significantly increased by cytokine treatments in patient samples but not in HCs ($p<0.05$). Subanalyses of B27-positive and negative SpA patients is inconclusive due to the low number of B27-negative patients.

Conclusion: Our results reveal greater upregulation of the UPR-target gene BiP as well as increased XBP1 mRNA splicing in response to cytokines in SpA patients compared to HCs. These preliminary results support the idea that low-level HLA-B27 upregulation may be sufficient to generate ER stress in certain cell types. Further exploration of cell types affected by this response, and additional conditions that may enhance B27 heavy chain accumulation, is necessary to better understand the potential role of ER stress in SpA pathogenesis.

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Endochondral Bone Formation and Advanced Enthesitis Are Key Features Of Proteoglycan Induced Spondylitis Mouse Model Of Ankylosing Spondylitis. Gethin P Thomas[1], Hsu-Wen Tseng[1], Allison Pettit[2], Tibor T. Glant[3], Allan McRae[1] and Matthew A. Brown[4]. [1]University of Queensland Diamantina Institute, Woolloongabba, Australia, [2]University of Queensland Centre for Clinical Research, Herston, Australia, [3]Rush University Medical Center, Chicago, IL, [4]University of Queensland Diamantina Institute, Brisbane, Australia.

Background/Purpose: Transition from an initial inflammatory phase to the disabling osteoproliferative phase in ankylosing spondylitis (AS) is very poorly understood. Elucidation of the mechanisms underlying this disease progression would identify new therapeutic targets and strategies.

The proteoglycan induced spondylitis (PGISp) mouse mirrors human AS disease progression with an initial inflammatory insult resulting in excessive osteoproliferation and frequently joint fusion. We therefore sought to model human AS progression by extensively characterizing the morphological, cellular and molecular changes over a time course of disease in the PGISp mouse.

Methods: Spine and spleen cells from PGISp and control mice were analysed over a 6 month timecourse. The histological features were described using a novel scoring regime including many features seen in human AS, such as inflammation, disc destruction, bone erosion, excess tissue formation (mesenchymal tissue expansion or fibrocartilage formation) around IVDs as well as ectopic tissue formation in the longitudinal ligament. Immunohistochemistry for collagens type I, II and X was used to delineate the nature of the excessive tissue formation seen in this model. Key factors involved both at the joint and systemic levels were analyzed using FACS and qPCR.

Results: Initial inflammation at the periphery of the discs was seen from week 6 which corresponded with an upregulation in expression of inflammatory markers such as TNFa, MMP3 and MMP13. Inflammation progressed over the next 4 weeks with massive inflammatory cell infiltration, disc destruction and erosion of bone and growth plate cartilage. A switch to an "anabolic" phase was then evident with upregulation of collagen II and X, and a corresponding decrease in inflammatory/catabolic genes. An extensive fibrocartilaginous matrix is laid down (excessive tissue formation) by large numbers of chondrocytes. One key feature of severely affected vertebrae is the appearance of ectopic chondrocytes laying down a cartilaginous matrix between the vertebral joints possibly corresponding to entheseal junctions. Such a feature potentially supports a role for endochondral ossification in the disease progression in this model.

Conclusion: The PGISp mouse model displays many features of AS. Of key interest is the initial inflammation giving way to extensive tissue formation. The presence of ectopic chondrocytes indicative of endochondral ossification at the entheses is a key insight into the disease process that can be translated to the human condition.

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Presence Of Gastrointestinal Symptoms and Autoantibodies In Patients With Spondyloarthritis In A Colombian Population. Consuelo Romero-Sanchez[1], Wilson Bautista-Molano[2], Diana M Munoz C[2], Viviana Parra I[2], Alejandro Escobar[2], Carlos Martínez[3], Ferney Garcia[3], Daniel Herrera[4], Sebastían Segura[2], Juliette De Ávila[1], Ana MAría Mesa[2], Haroldo Juliao[5], John Londono[2] and Rafael Valle-Oñate[2]. [1]UIBO Institute (Oral Basic Research Unit), School of Dentistry, Universidad El Bosque, Bogotá, Colombia, [2]Spondyloarthropathy Group, Rheumatology Department, Hospital Militar Central/ Universidad de La Sabana, Bogotá, Colombia, [3]Coloproctology Deparment, Hospital Militar Central, Bogotá, Colombia, [4]Instituto de Genética Humana, Facultad de Medicina, Pontificia Universidad Javeriana, Bogotá, Colombia, [5]Gastroenterology Deparment, Hospital Militar Central, Bogotá, Colombia.

Background/Purpose: The frequency of gastrointestinal (GI) involvement in spondyloarthritis (SpA) ranges from 21% to 30% and 5% to 10% are associated with inflammatory bowel disease (IBD). The percentage of patients with SpA having subclinical intestinal inflammation documented by endoscopy and histology is significative. Due to the persistent joint inflammation in these patients, as well as the established association between SpA and GI inflammation, not only endoscopic evaluation, but also measure of auto-antibodies related to IBD is recommended. To investigate whether there is an association between clinical variables and IBD autoantibodies in SpA patients receiving treatment.

Methods: A transversal observation study was designed to compare three groups of patients. Eighty one patients with SpA according to ESSG classification criteria, 14 patients with IBD (ulcerative colitis (UC) (n=8), Chron′s disease (CD) (n=1) and undifferentiated colitis (n=5) and 80 healthy subjects (HS). Anti-*Saccharomyces cerevisiae* IgG/IgA (ASCA), anti polymorphonuclear neutrophil P (ANCA-P), anti transglutaminase (tTG) IgG/IgA, anti deaminated gliadin peptide (DGP) IgG/IgA autoantibodies, ANAS and IgA were measured in all patients. A specific questionary was applied asking for GI symptoms in the SpA group. The association between clinical variables and auto-antibodies were evaluated using the chi square test.

Results: 81 SpA patients were included with mean age of 43 ± 13.4 years, BASFI mean 4,78 ± 1,8, and BASDAI mean 4,58 ± 1,8. 64% were men, 49,4% receiving anti-TNF, and 34.6% were HLA B27(+). In the HS, 47% were men, mean age 37,7± 13,6, IgG/IgA (tTG) was negative in 98.8%, ASCA IgG/IgA was positive in 8.8%, and 6.3% were positive for p-ANCAS.

The patients with SpA in the IgG/IgA ASCA were positive with 30.9%, pANCAS were positive by 11.1%, and the IgG/IgA (tTG) were positive by 2.5%. There was a significant difference in the frequency of autoantibodies IgG/IgA ASCA's (p=0.008) and p-ANCAS (p= 0.001) between SpA and HS. When the questionary for GI symptoms was applied in the SpA patients, abdominal pain and discomfort were reported in 53% of patients, abdominal inflammation (51%) and diarrhea (33%). ANAS test was positive in 54.3%. A significative association was found between the presence of abdominal pain and BASDAI>4 (p=0,017), as well as between abdominal inflammation and BASDAI > 4 (p=0,008). SpA patients have higher titers of total IgA in patients with BASDAI >4 (p=0,012).

Conclusion: Our results shows that SpA patients have a higher presence of IgG/IgA ASCAS and p-ANCAS compared to healthy controls and IBD patients. The report of GI symptoms was associated with high disease activity; however there was not association with the presence of auto-antibodies. Therefore, it may suggest that the active search of auto-antibodies as well as the presence of gastrointestinal symptoms should be performed in Colombian SpA patients. In Colombia there is not information about this association.

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Upregulated Th17 and Innate Pathways Are More Characteristic Of The Skin Than The Synovium In Psoriatic Arthritis. Jennifer Belasco[1], Hiroshi Mitsui[1], Mayte Suarez-Farinas[1], James S. Louie[2], N. Wei[3], Nicholas Gulati[1] and James G. Krueger[1]. [1]The Rockefeller University, New York, NY, [2]UCLA School of Medicine, Los Angeles, CA, [3]Arthritis Treatment Center, Frederick, MD.

Background/Purpose: Psoriatic arthritis (PsA) is an inflammatory joint disease associated with psoriasis. There is little understanding of the relative levels of cytokines and chemokines between the skin and synovium in PsA. The purpose of this study was to better define inflammatory pathways in paired lesional skin and affected synovial tissue in patients with psoriatic arthritis. We conducted a comprehensive cytokine profile in psoriatic skin and joint disease.

Methods: RT-PCR was performed using coupled directed pre-amplification technique.

Results: Of all the cytokines evaluated, only Th17- associated cytokines (IL17A, IL17F) and IL1a were significantly increased in psoriatic skin when compared to affected synovium. IL6 was significantly increased in synovium. Th1- (IFNg) and Th2- (IL4, IL13) associated cytokines were not significantly different. Th9-(IL9), Th22- (IL22), and Treg- (FOXP3) associated cytokines, as well as IL1b, IL2, IL2RA, TNFa and IL8, were also not significantly different. There was no correlation of gene expression levels between pairs of skin and synovium from the same subject.

Conclusion: This is the first comprehensive molecular comparison of paired lesional psoriatic skin and affected synovium in psoriatic arthritis. This is also the first study to investigate IL9 in psoriatic arthritis tissue. These results demonstrate that there are many shared cytokines and chemokines between matched pairs of lesional psoriatic skin and synovium from inflamed joints in patients with PsA. However, IL1a, IL6, IL17A and IL17F were significantly different. No correlation between gene products was noted between paired samples of synovium and skin, suggesting that there are distinct immunological phenotypes for synovium and skin within the same person. Therefore, the pathomechanisms of these two symptomatic organs may be at least partially independent from one another. This could have implications for the direction of future therapies.

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Ankylosing Spondylitis and Dysfunctional Dkk. Rajbir Gulati[1], Maripat Corr[2], Michael H. Weisman[3] and David Hallegua[4]. [1]Cedars Sinai Medical Center, Los Angeles, CA, [2]Univ of California-San Diego, La Jolla, CA, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]Cedars-Sinai/UCLA, Beverly Hills, CA.

Background/Purpose: Ankylosing Spondylitis (AS) is characterized by inflammation of the spine and entheses followed by formation of syndesmophytes.

Wnt pathway is a regulator of bone and cartilage remodeling; modulated by several biomarkers like Dickkopf (DKK-types 1, 2, 3 & 4), sclerostin, etc.

DKK1 is an inhibitor of Wnt. TNF-alpha inhibits bone formation by inducing Dkk-1.

AS patients display either low levels of functional DKK1 (DKK1 that binds to LRP5/6- Low-density lipoprotein receptor related protein) or high levels of total DKK1 indicating that it is dysfunctional.

Maksymowych et al, showed that new syndesmophytes developed more frequently in vertebral corners with inflammation on baseline MRI; and more so where inflammation had resolved after 2 years of anti-TNF therapy.

We examined the relationship between inflammation, bone formation and bone biomarkers in AS patients not on anti-TNF therapy. The anthrax toxin binding protein (CMG2) is a decoy receptor for DKK; which has been found to be associated with AS; we examined its association with DKK.

Methods: We recruited 35 patients with spondyloarthritis, (34 fulfilling New York criteria & 1 fulfilling ASAS criteria for axial spondyloarthritis) from a preexisting cohort, Prospective Study on Ankylosing spondylitis Severity (PSOAS) and from the office of the principal investigator.

During the study visit, metrology measurements were done and BASMI calculated. Bath AS Disease Activity and Functional Indices (BASDAI, BASFI) were also obtained. Blood samples were examined for the following: ESR, CRP, Vitamin D, PTH, DKK, LRPDKK, OPG (Osteoprotegrin), sclerostin, antiDKK, SFRP 3, CMG2DKK, and CMG2LRP. X-rays of the pelvis and the entire spine that were available for 35 and 28 patients respectively were scored for the sacroilitis grade (SI grade) and the modified Stokes Ankylosing Spondylitis Spine Score (mSASSS). Statistical analysis was performed using Spearman correlation coefficient and Student t-test.

Results:

1. Significant correlation between DKK, LRPDKK& CMGDKK as well as between mSASSS, SI grade and BASMI. (Table 1).

2. LRPDKK increases with inflammation in AS. Bone formation as indicated by mSASSS trended higher in patients with higher levels of inflammation.

3. Patients with low CRP when separated based on high or low mSASSS, showed that high mSASSS correlated negatively with DKK and LRPDKK.

Variable	N	Mean	Std. Dev	Median	Minimum	Maximum	Correlation	P-value
Markers of inflammation and function								
CRP	32	1.99	4.64	0.57	0.03	22.9	ESR 0.83 BASDAI 0.43	< .0001 0.0119
ESR	33	23.42	23.42	14.00	1.00	98.00		
BASDAI	34	4.10	4.49	3.08	0.00	24.9	BASFI 0.55	0.0008
BASFI	34	23.70	25.52	14.95	0.00	99.00		
Bone biomarkers associated with bone formation								
DKK	35	4.03	2.93	3.47	0.39	15.52	LRPDKK 0.87 CMG2DKK 0.51	< .0001 0.0035
LRPDKK	30	2.92	1.52	2.91	0.22	6.39	CMG2DKK 0.55	0.0015
CMG2DKK	30	0.70	0.57	0.39	0.39	2.15		
Radiologic and Mobility measurements								
mSASSS	28	18.54	22.47	6.5	0.00	72.00	SIJ 0.75 BASMI 0.80	< 0.0001 <0.0001
SIJ Grade	34	3.29	1.00	4.00	0.00	4.00	BASMI 0.52	0.009
BASMI	25	3.75	1.64	4.00	0.6	6.8		
Low versus High CRP groups								
LRPDKK(low CRP)	15	–	–	1.98	0.23	4.9	–	0.0009
LRPDKK(high CRP)	12	–	–	4.04	1.38	6.39	–	
mSASSS(low CRP)	16	–	–	5.5	0	62	–	0.082
mSASSS(high CRP)	11	–	–	24	0	72	–	
DKK and LRPDKK levels influencing mSASSS in low CRP group								
DKK(low CRP,low mSASSS)	12	–	–	3.36	2	7.41	–	0.013
DKK(Low CRP, high mSASSS)	4	–	–	0.78	0.39	3.09	–	
LRPDKK(low CRP, low mSASSS)	10	–	–	2.32	1.56	4.91	–	0.008
LRPDkk(low CRP,high mSASSS)	4	–	–	1.01	0.23	1.85	–	

Conclusion: Our pilot study suggests that inflammation and low levels of functional DKK are associated with increased bone formation in anti-TNF naïve AS patients. Functional DKK levels increases with active inflammation. However, with low levels of inflammation, functional DKK correlated negatively with AS x-ray changes. A positive correlation exists between the binding of LRPDKK to a decoy receptor CMG2 and LRPDKK levels in these patients.

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Pattern Recognition Receptor Stimulated Cytokine Expression By Spondyloarthritis Patient Macrophages. Yi-Ping Liu, Ashley Bomkamp, Jens Eickhoff, Jack Schneck, Mike Khan and Judith Smith. University of Wisconsin-Madison, Madison, WI.

Background/Purpose: Spondyloarthritis (SpA) encompasses a group of chronic inflammatory conditions involving axial arthritis that includes ankylosing spondylitis (AS). GWAS studies in AS have implicated multiple genes regulating the development and activity of Th17 cells. IL23, a cytokine required for driving the pathogenicity of Th17 cells, is sufficient to cause spondylitis-like pathology in mice. Thus, excessive production of IL-23 in response to environmental stimuli might predispose towards the development of SpA. The aim of this study was to determine if macrophages from SpA patients produce excess inflammatory cytokines (including IL-23) in response to different pattern-recognition receptor (PRR) agonists.

Methods: Monocytes isolated by CD14 magnetic beads from 12 AS, 12 non-AS SpA, and 12 control subjects were differentiated into macrophages with M-CSF. Macrophages were stimulated with LPS (TLR4), CL097 (TLR7/8), PGN (TLR2), and Curdlan (Dectin-1) and IL6, IL8, IL10, IL23, and TNF-α quantitated by Luminex Multiplex assay or ELISA. Comparisons between groups were conducted using analysis of variance with adjustment for multiple comparisons. Subgroup analyses were conducted for sex, current TNF-blocker, presence of axial disease, and HLA-B27.

Results: Subjects: AS and SpA patients differed in HLA-B27 positivity (92% vs. 42% respectively, $p=0.027$), current biologic therapy (25% vs. 67%, $p=0.041$) and axial disease (100% vs. 50%, $p=0.014$). Cytokine results: No differences were observed for IL-10. AS macrophages produced more IL-8 than controls in response to PGN ($p=0.017$). LPS stimulated comparably elevated IL-6 by both AS and SpA macrophages ($p\geq0.029$). AS and SpA cells produced comparably increased TNF-α in response to LPS and PGN ($p\geq0.042$), but only SpA macrophages produced increased TNF-α in response to CL097 ($p=0.029$). IL-23 production differed in AS and SpA macrophages: Only non-AS SpA cells produced increased IL-23 in response to all agonists as compared to control ($p\geq0.042$). Subgroup analysis: Axial disease and sex were not significant. HLA-B27 presence was only significant in unstimulated SpA IL-23 ($p=0.006$). Current biologic therapy only affected AS TNF-α and IL-6 responses to PGN and LPS, respectively ($p=0.016$). Response patterns: No one patient produced the maximum amount of every cytokine analyzed. Also, different patients were maximal producers for individual agonists. Groups of 2–5 subjects displayed nearly identical patterns of response to the different agonists. For example, paired subjects showed a correlation in IL-23 production $R\geq0.92$ ($p\leq0.028$).

Conclusion: Both AS and SpA patients produced excess IL-6 and TNF-α in response to PRR agonists, but only non-AS patients produced excess IL-23 in this study. Potential issues were sample size, positive selection of monocytes, less biologic use and more female subjects compared to previous studies. Although numbers are small, the different results (e.g. effects of biologic use) in AS and non-AS SpA puts into question the extent of shared pathogenesis. Finally, the emergence of distinct patterns of PRR response may reflect shared variations at individual immunomodulatory gene loci.

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Influenza Infection Of MHC-I Transgenic Mice Reveals That Erap Is Necessary and Sufficient For Generation Of The B27-Specific Immunodominant Epitope. Ali Akram[1] and Robert Inman[2]. [1]University of Toronto and University Health Network (UHN), Toronto, ON, [2]University of Toronto and Toronto Western Hospital, Toronto, ON.

Background/Purpose: Although HLA-B27 and ERAP are known to confer susceptibility to spondyloarthritis (SpA), the role of these elements in modulating host response to infection is undefined. Despite co-dominant expression of class I MHC alleles, immune response to viral infections is characterized by immunodominance (ImDc). The exact mechanisms underlying ImDc are not clear. Defining factors contributing to ImDc has proved difficult due to multiple MHC-I allele co-expression in humans and normal mice.

Methods: To overcome this limitation, we generated human MHC-I transgenic (Tg) mice deficient for endogenous mouse MHC-I molecules and expressing only one human MHC-I allele (e.g. HLA-B7, HLA-B27, HLA-A2). To assess whether co-expression of additional MHC-I alleles in the presence or absence of ERAP influences the pattern of anti-flu CTL epitope recognition and ImDc, novel Tg mice in the context of ERAP deficiency were established.

Results: In flu-infected, double Tg A2/B7 or A2/B27 mice, IFN-γ ELISpot assays with the flu epitopes A2/M1.58–66 and B7/NP418–426 or B27/NP383–391 showed specific recognition of both peptides by both alleles respectively. In contrast, flu-infected B7/B27 Tg mice demonstrated a significantly reduced B27-restricted CTL response to NP383 while there was no change in the response of B7-restricted CTL response to NP418. Profiling the T cell response revealed that co-expression of B7 and B27 is associated with i) a partial deletion of $V\beta8.1^+$ B27-restricted/NP383 $CD8^+$ T cells and ii) a failure of $V\beta12^+$ $CD8^+$ T cell expansion following flu infection in B7/B27 Tg mice. Studies in flu infection of ERAP-deficient Tg B27 and Tg B7/B27 mice revealed complete abrogation of the B27-restricted response to NP383–391, indicating the importance of ERAP in generation of this peptide.

Conclusion: The HLA-B27 immundominant response to infection is critically dependent on ERAP. This provides a possible mechanistic basis for the findings in genetic studies of the interdependence of B27 and ERAP in conferring susceptibility to SpA.

Disclosure: A. Akram, None; **R. Inman**, None.

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Role Of Baseline C-Reactive Protein In Response To Infliximab Plus Naproxen Vs Naproxen Alone In Patients With Axial Spondyloarthritis. J Sieper[1], M Rudwaleit[1], J Lenaerts[2], J Wollenhaupt[3], L Myasoutova[4], S Park[5], Y Song[6], R Yao[7], M Govoni[8], D Chitkara[7] and N Vastesaeger[9] [1]University Clinic Benjamin Franklin, Berlin, Germany, [2]Practice Rheumatology, Hasselt, Belgium, [3]Schön-Klinik, Hamburg, Germany, [4]Kazan State Medical University, Kazan, Russia, [5]Catholic University of Korea, Seoul, South Korea, [6]Seoul National University, Seoul, South Korea, [7]Merck Sharp & Dohme, Kenilworth, NJ, [8]Merck Sharp & Dohme, Rome, Italy, [9]Merck Sharp & Dohme, Brussels, Belgium.

Background/Purpose: Baseline inflammation has been shown to influence response to tumor necrosis factor alpha antagonist treatment in patients with axial spondyloarthritis (SpA). This study evaluated the role of C-reactive protein (CRP) in the response to treatment with infliximab (IFX)+nonsteroidal anti-inflammatory drugs (NSAIDs) vs NSAIDs alone in patients with axial SpA who had early, active disease.

Methods: Part 1 of the INFAST trial was a double-blind, randomized controlled trial of IFX in biologic-naïve patients 18–48 years of age with early, active axial SpA (Assessment of SpondyloArthritis international Society [ASAS] criteria, disease duration ≤3 years, chronic back pain, and active inflammation of the sacroiliac [SI] joints on magnetic resonance imaging [MRI]). Patients naïve to NSAIDs or treated with a submaximal dose of NSAIDs were randomized (2:1) to receive 28 weeks of treatment with either intravenous (IV) IFX 5 mg/kg (weeks 0, 2, 6, 12, 18, and 24)+naproxen (NPX) 1000 mg/d or IV placebo (PBO)+NPX 1000 mg/d. ASAS partial remission was evaluated in patients with high CRP (>upper limit of normal [ULN], per local laboratory limits) or low CRP (≤ULN). Response was also evaluated in patients who met the New York modified criteria for ankylosing spondylitis (AS) by SI X-ray (bilateral ≥grade 2 or unilateral ≥grade 3, based on local rheumatologist judgement) and were not naïve to NSAIDs (AS group) versus patients with nonradiographic axial SpA (nr-axSpA group). Data were analyzed descriptively.

Results: 156 patients were included in efficacy analyses. Overall, ASAS partial remission rate was greater for the IFX+NPX group (n=105) than the PBO+NPX group (n=51) (61.9% vs 35.3%, $P=0.0021$). For patients treated with IFX+NPX, partial remission rate was greater in the 49 patients with high CRP than in the 44 with low CRP (71.4% vs 59.1%). However, for patients treated with NPX alone, partial remission rates were similar whether CRP was high or low (40.7% [n=27] vs 38.5% [n=13]). In analysis of the AS and nr-axSpA groups, partial remission was greater in the AS group than the nr-axSpA group after treatment with IFX+NPX (72.2% [n=54] vs 56.4% [n=39]); after treatment with NPX alone, partial remission was greater in the nr-axSpA than the AS group (46.7% [n=25] vs 36.0% [n=15]). This pattern might be explained by the higher baseline mean CRP values in the AS group (n=83) than the nr-axSpA group (n=63) (CRP 2.59 vs 0.92 mg/dL). Within the AS group, the difference between the 2 treatments was clear in patients with high baseline CRP (IFX+NPX, 75.8% [n=33] vs NPX, 30% [n=20]); but not with low baseline CRP (IFX+NPX, 66.7% [n=21] vs NPX, 60% [n=5]). This pattern was not observed in the nr-axSpA group, perhaps because of low baseline CRP or because of the small number of subjects available for analysis.

Conclusion: In this population of axial SpA patients with early disease and established MRI inflammation at baseline, elevated baseline CRP was associated with a better response to IFX therapy.

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Peripheral Blood Gene Expression Profiling Of Psoriatic Arthritis Patient. Bidisha Dasgupta, Yauheniya Cherkas, Sarah Lamberth and Carrie Brodmerkel. Janssen Research & Development, LLC., Spring House, PA.

Background/Purpose: Although PsA is heterogeneous and shows signs of rheumatoid arthritis (RA) and psoriasis (PsO), genetic studies indicate that PsA is a distinct disease with a strong heritable component. PsA is categorized into 5 overlapping clinical patterns: polyarthritis (POLY), arthritis of distal interphalangeal joints (DIP), spondylitis (SPON), and asymmetric peripheral arthritis (ASYM). This study examines if whole blood (WB) gene expression profiles can be utilized to: identify a baseline disease profile (DP) for pts with PsA, differentiate among the clinical subtypes, and compare/contrast the disease mechanisms of PsA, RA and PsO.

Methods: mRNA from 270 WB samples collected at wk0 in a Ph3 study of ustekinumab(PSUMMIT I) from pts with active PsA were isolated and profiled using the Affymetrix HT HG-U133+ PM Array (Santa Clara, CA). 36 healthy control WB samples were obtained from Bioreclamation (Hicksville, NY). Baseline gene expression profiling data comparing disease to healthy control (mRNA isolated from WB and run on Affymetrix HT HG-U133+ PM Array) from 487 RA patients in a Ph3 study of golimumab (GO-FURTHER) and 186 PsO patients in a Ph4 study of ustekinumab (TRANSIT) were used to compare the PsA disease profile to RA and PsO. All data were analyzed by iReport® and Ingenuity Pathway Analysis® (Ingenuity Systems).

Results: We identified a disease profile for PsA (PsA vs Healthy); the majority of the differentially expressed genes are upregulated and fall into diverse categories, such as cellular proliferation, inflammation and immune response. There were no differentially expressed genes that separated PsA subtypes. PsA showed a distinct gene expression profile from RA and PsO with moderate overlap at the gene level. The genes common to all 3 diseases are largely upregulated and the biology represented by these shared genes comprise immune/inflammatory processes and connective tissue disorders. Although PsA shows greater similarity to RA than PsO at the functional pathway level, the PsA disease profile is significantly different in that a majority of the genes are upregulated in PsA. Pathways related to cell proliferation, inflammation, B and T cell signaling are increased in PsA (these pathways are largely downregulated or not significant in RA and PsO). The differentially expressed genes unique to PsA were enriched for the Protein Kinase A and Ephrin signaling pathways. There is emerging evidence that the Ephrin signaling pathway is implicated in bone remodeling and homeostasis and these data may suggest evidence for differential pathways related to structural damage in PsA than RA.

Conclusion: PsA has a distinct gene expression profile, although the PsA clinical subtypes could not be differentiated at a molecular level. Disease profile is best represented by activated pathways related to immune function and immune response; data showed a novel association of PsA with the Ephrin signaling pathway. Majority of the differentially expressed genes are unique to PsA and provide molecular support for PsA as a distinct disease entity. WB gene expression profile of PsA pts may help in the diagnosis of PsA, provide insight into disease pathogenesis, and identification of novel disease markers and therapeutic targets.

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Death Receptor 3 Increases Region-Specific, Osteoblast-Dependent Aberrant New Bone Formation In The Axial Skeleton Of Mice In a Spontaneous Model Of Ankylosing Enthesopathy. Fraser L. Collins[1], Jessica O Williams[1], Anja C. Bloom[1], Michael D. Stone[2], Ernest Choy[1], Edward C. Wang[1] and Anwen S. Williams[1]. [1]Cardiff University, Institute of Infection and Immunity, Cardiff, United Kingdom, [2]University Hospital Llandough, Cardiff & Vale University Health Board, Cardiff, United Kingdom.

Background/Purpose: Clinical management of localised bone formation and joint ankylosis constitute major challenges in patients with seronegative inflammatory spondyloarthropathies (SpAs). Whether TNF receptor superfamily members, such as Death Receptor 3 (DR3) and their ligands modulate bone pathology in SpAs is not characterised. For the first time we evaluated DR3's role in controlling osteoblast(OB)-dependent new bone formation using the spontaneous ankylosing enthesopathy model in aging DBA/1 mice.

Methods: Osteoprogenitor cells (OPCs) cultured from the bone marrow of male DR3-deficient ($DR3^{ko}$) and age-matched wild-type (WT) DBA/1 mice were differentiated into OB using β-glycerophosphate, ascorbic acid and dexamethasone. DR3 and RANKL expression were tested by flow cytometry (fold change over isotype reported). Functional analyses; OB differentiation (by alkaline phosphatase (ALP) staining) and mineralisation (by alizarin red staining) were performed. Cellular (TNF-like protein 1A (TL1A) mRNA) and soluble cytokines (osteopontin (OPN), osteoprotegerin (OPG) and soluble RANKL) were measured by RT-PCR and ELISA respectively. Finally, a fluorescent optical probe (BoneTag™) was used to visualise and measure *in vivo* mineralization in 10-month old WT and $DR3^{ko}$mice. Mean$\pm$SEM values reported; statistical significance tested by One or 2-way ANOVA as appropriate.

Results: DR3 was expressed on both OPC (1.8 ± 0.2) and OB (1.4 ± 0.8) from WT mice. In $DR3^{ko}$ levels (1.2 ± 0.1, $P<0.05$) were comparable in both OPC and OB but significantly lower than WT. For the first time, we showed that TL1A (DR3's ligand) was constitutively expressed by OPC and OB from WT and $DR3^{ko}$. Thus autocrine signalling via the DR3/TL1A pathway functionally translated into a significant elevation in ALP ($P<0.05$), expression of the Ca2+ binding osteoid protein OPN ($P=<0.0001$) and mineral apposition ($P<0.0001$) over the 26 day OB differentiation timecourse (WT versus $DR3^{ko}$ cultures). OB derived cytokines (RANKL and OPG) control bone formation by regulating osteoclastogenesis. Pro-osteoclastogenic RANKL expression on OPCs and OB was comparable in WT versus $DR3^{ko}$ whilst soluble RANKL was not detectable in any of the culture supernatants. However, OPG, a soluble inhibitor of osteoclast formation, was significantly elevated across the timecourse in WT versus $DR3^{ko}$ ($P<0.05$). When compared against $DR3^{ko}$, *in vivo* incorporation of a fluorescent calcium-chelating probe was striking and significantly higher ($P<0.01$) in the thoracic vertebrae of WT mice 24 hours after injection. In contrast, the efficiency of probe uptake in WT knee joints and tails was low and comparable with $DR3^{ko}$levels in the spine.

Conclusion: These data identify new OB-dependent homeostatic roles for DR3 in bone and potentially explain the atypical pattern of new bone formation in the axial skeleton of mice that spontaneously develop ankylosing enthesopathy. Further studies in human disease are justified to explore the clinical implications of our findings.

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Membrane-Bound TNF Drives Axial and Peripheral Inflammation and Pathologic New Bone Formation. Leonie M. van Duivenvoorde[1], Melissa N. van Tok[1] and Dominique L. Baeten[2]. [1]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands.

Background/Purpose: The morbidity of spondyloarthritis (SpA) is determined not only by inflammation but also by structural damage, in particular osteoproliferation leading to joint ankylosis. The failure of TNF blockers to halt osteoproliferation raised the concept that inflammation and osteoproliferation are uncoupled processes in SpA. The observation that inflammation and osteoproliferation are linked in experimental and human SpA and that NSAID treatment can retard new bone formation, suggest an alternative hypothesis: inflammatory mediators distinct from soluble TNF (sTNF) are responsible for pathologic new bone formation in SpA. Here, we tested this hypothesis by studying inflammation and new bone formation in mice selectively overexpressing membrane-bound TNF (mTNF).

Methods: mTNF mice have normal levels of sTNF and increased levels of mTNF[1]. mTNF mice and non-transgenic littermates were clinically studied over time for arthritis and spondylitis development. At 3, 6 and 8 months peripheral and axial joints were collected and analyzed for inflammation and bone- and cartilage destruction by staining with HE and Saffranin-O. Additionally, X-ray images were obtained from 8 months old mice.

Results: All mTNF mice (100%; n>50) spontaneously developed arthritis, visualized by deformation of joints and loss of grip strength, and spondylitis as evidenced by crinkled tails and hunchback formation, starting at 4 weeks of age and progressing over time. Compared to hTNF and $TNF^{\Delta ARE}$ mice the severity of this arthritic disease was mild; moreover mTNF mice did not lose weight due to disease and can survive for more than 8 months.

Analysis of 3 months old mice revealed that arthritis was characterized by inflammation of synovial and entheseal tissue, which also invaded cartilage and bone in some animals. The inflammation was dominated by polymorphonuclear cells (PMNs). Interestingly, multinucleated giant cells, or osteoclasts, were not increased in affected compared to healthy joints. Hypertrophic chondrocytes, as marker for osteoproliferation, were observed outside the bone in the connective tissue next to the inflammatory infiltration. In spondylitis, inflammation was found in connective tissue located at the junction of the annulus fibrosus with the vertebral bone. More severe inflammatory infiltrate could also erode the vertebrae. Also, axial inflammation/destruction was predominantly characterized by PMNs and lack of increased numbers of osteoclasts. Hypertrophic chondrocytes were observed at the edge of the vertebral body, in conjunction with the ongoing inflammation. X-ray images from 8 months old mice also revealed bridging of the tail vertebra. These typical SpA-like features were not observed in any of the non-transgenic littermates analyzed.

Conclusion: Mice selectively overexpressing mTNF develop a SpA-phenotype with axial and peripheral joint involvement. Radiographic and histologic analysis confirmed new bone formation in this model. Based on these results, we conclude that mTNF, as inflammatory mediator, can drive osteoproliferation in experimental SpA.

Reference:

Alexopoulou L, et al. Eur J Immunol 1997; 27(10):2588–92.

Disclosure: L. M. van Duivenvoorde, None; **M. N. van Tok**, None; **D. L. Baeten**, AbbVie, BMS, Boehringer Ingelheim, Centocor, Janssen, MSD, Novartis, Pfizer, and UCB, 2, AbbVie, BMS, Boehringer Ingelheim, Centocor, Janssen, MSD, Novartis, Pfizer, and UCB, 5, AbbVie, BMS, Boehringer Ingelheim, Centocor, Janssen, MSD, Novartis, Pfizer, and UCB, 8.

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Investigating a Novel Locus For Psoriatic Arthritis. Ashley Budu-Aggrey[1], John Bowes[2], Pauline Ho[1], James Bluett[2], Harry Hébert[3], Helena Marzo-Ortega[4], Ann W. Morgan[4], Matthew A. Brown[5], Ross McManus[6], Neil McHugh[7], Oliver M. FitzGerald[8], Ian N. Bruce[1] and Anne Barton[2]. [1]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academy of Health Sciences, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, Centre for Musculoskeletal Research, Institute of Inflammation and repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [3]The Dermatology Centre, Salford Royal NHS Foundation Trust, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, [4]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [5]The University of Queensland Diamantina Insititute, Brisbane, Australia, [6]Department of Clinical Medicine, Institute of Molecular Medicine, Trinity College Dublin, Ireland, Dublin, Ireland, [7]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [8]St.Vincent's University Hospital, Dublin, Ireland.

Background/Purpose: Psoriatic arthritis (PsA) is a complex genetic disorder with a prevalence of up to 1% in the general population. The association of PsA with psoriasis has been demonstrated in the overlap of clinical features as well as the susceptibility loci identified from genetic studies. However, there are very few specific PsA risk loci that have been found. The strong heritability of this disease in comparison to psoriasis suggests that there are more specific PsA susceptibility loci that remain to be discovered.

Methods: Dense genotyping of known autoimmune susceptibility loci was carried out with a custom Illumina array (Immunochip) in a total of 1,960 Caucasian PsA patients and 8923 Caucasian healthy controls. Expression quantitative trait loci (eQTL) analysis of the 5q31 region was performed using publically available data. The regulatory role of the region was characterised and potential functional variants were identified with data sourced from the encyclopaedia of DNA elements (ENCODE) project.

Results: A significant association was detected to the SNP rs715285 on chromosome 5q31 ($P = 3.06\times10^{-10}$, OR = 1.25). This peak of association encompasses the genes *P4HA2, PDLIM4* and *SLC22A4*, and is independent from an association signal previously identified in the region with variants of the *IL13* gene. Bioinformatic analysis of the region identified potential eQTLs that influence the expression of *P4HA2, SLC22A4* and *SLC22A5*. Differential expression of *P4HA2* was found in lymphoblastoid cell lines, while *SLC22A4* and *SLC22A5* were differentially expressed in monocytes indicating the potential for cell specific effects. Functional variants that could affect the regulatory role of the region were identified, including rs10065787, rs721121, rs708455 and rs27437. These SNPs lie within gene enhancers, regions of open chromatin and transcription factor binding sites, including that of BATF. This transcription factor regulates the function of interleukin 17 – a pro-inflammatory cytokine involved in the pathogenesis of PsA.

Conclusion: We have identified a novel association on chromosome 5q31 in a region previously suggested to be specific for PsA. A number of interesting candidate genes in the region have been implicated which encode proteins involved in collagen synthesis and bone development - processes which are affected in PsA. Bioinformatics analysis supports evidence for functional SNPs in the region which now need to be validated in the laboratory. These findings can aid in further understanding of the underlying pathogenic pathways that are specific to PsA. This in turn could potentially enable the identification of a novel therapeutic target to provide more effective treatment therapies to patients.

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Ankylosing Spondylitis Associated Endoplasmic Reticulum Aminopeptidase 1 Variants Alter The Unfolded Protein Response. Nigil Haroon and Zhenbo Zhang. Toronto Western Research Institute, Toronto, ON.

Background/Purpose: Endoplasmic reticulum aminopeptidase 1 (ERAP1) has recently been identified to be strongly associated with HLA-B27 positive AS. We have shown that ERAP1 variants cause changes in free heavy chain (FHC) expression on peripheral blood mononuclear cells from HLA-B27 positive patients as well as on B27-expressing C1R cells by *in vitro* assays. Unfolding of HLA-B27 and the formation of FHC can cause the release of inflammatory cytokines by triggering the unfolded protein response (UPR). We tested if ERAP1 variants can affect the UPR.

Methods: Endogenous ERAP1 was silenced in C1R-HLA-B27 cells with ERAP1-shRNA ($C1R^{ERAP1sh}$). C1R cells with stable ERAP1-shRNA expression were identified by GFP expression and were selected with puromycin. Scrambled sequence shRNA was used as control. Western blot (WB) for ERAP1 suppression was done using ERAP1 antibody.

We then transfected either the common variant ERAP1 ($ERAP1^{WT}$) or one of the two AS-associated ERAP1 variants, K528R or Q730E into the $C1R^{ERAP1sh}$ cells. Lentivirus expression vector alone was used as control and exogenous ERAP1 expression was tracked with HA-tag. Stable cells expressing $ERAP1^{WT}$ or ERAP1-variants were selected by hygromycin. UPR was measured using PCR for spliced variants of XBP-1 and by qRT-PCR and western blot for BiP, CHOP and ATF-6.

Results: Almost all C1R cells that were selected by antibiotics were GFP positive indicating stable ERAP1-shRNA expresion. Using WB we noted more than 90% suppression of ERAP1 and more than 75% suppression by qRT-PCR in $C1R^{ERAP1sh}$, compared to the cells with scrambled-sequence shRNA. Anti-HA WB showed uniform strong expression of $ERAP1^{WT}$ and variant forms of ERAP1 in the respective cell lines.

Spliced XBP1, a marker of UPR, was upregulated in the $C1R^{ERAP1sh}$ cells. Re-introduction of ERAP1 (C1R-$ERAP1^{WT}$ cells) reduces the UPR response while C1R-$ERAP1^{K528R}$ and C1R-$ERAP1^{Q730E}$ cells expressing the ERAP1 variants had higher UPR activation compared to C1R-$ERAP1^{WT}$ cells. Other UPR markers including BiP, CHOP and ATF6 expression followed the same pattern with AS-associated variants leading to higher UPR.

Conclusion: ERAP1 suppression leads to increased UPR. AS-associated ERAP1-variants, which are known to have reduced function, leads to more UPR compared to the common variant of ERAP1.

Disclosure: N. Haroon, None; **Z. Zhang**, None.

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Effects Of ERAP1 Knockdown On HLA Class I and HLA-B27 Expression In Human Monocytic U937 Cells. Tri M. Tran[1], Sohee Hong[1] and Robert A. Colbert[2]. [1]NIAMS/NIH, Bethesda, MD, [2]NIAMS NIH, Bethesda, MD.

Background/Purpose: Polymorphisms in endoplasmic reticulum (ER) aminopeptidase 1 (ERAP1) are associated with susceptibility to ankylosing spondylitis in HLA-B27 (B27) positive individuals, implying a functional interaction between the gene products. A principle function of ERAP1 is to trim peptides that bind to HLA class I molecules such as B27. Since the quantity and quality of peptides is critical for the efficient folding and assembly of class I molecules, we developed a system to examine how reduced ERAP1 activity affects properties of HLA-B27 in cells expressing other HLA class I molecules. Our immediate objective was to determine how ERAP1 knockdown affects HLA class I and specifically B27 expression in U937 cells (U937.B27).

Methods: Lentiviral shRNA was used to knock down (KD) ERAP1 expression in U937.B27 cells (65% reduction), which were compared to U937.B27 cells expressing scrambled shRNA as a control. Total class I heavy chain expression was examined by immunoblotting whole cell lysates. Total folded and unfolded forms of HLA class I were assessed by immunoprecipation with conformation-specific monoclonal antibodies (mAb) W6/32 (anti-HLA-A,B,C) and HC10 (anti-HLA-B,C), respectively, followed by quantitative immunoblotting. Cell surface expression of folded and unfolded forms of class I were assessed by flow cytometry, and HLA-ABC.m3 was used to measure expression of folded B27.

Results: ERAP1 KD resulted in a ~20% increase in total HLA class I heavy chain in whole cell lysates by immunoblotting. Similarly, total folded and unfolded forms of immunoprecipitable HLA class I heavy chain were slightly increased, with folded forms predominating. In contrast, total folded and unfolded HLA class I heavy chain on the cell surface detected by flow was unchanged by ERAP1 KD. For HLA-B27, folded forms on the cell surface were increased by ~40%. Interestingly, treatment with IFNg resulted in more total folded heavy chain in ERAP1 KD cells, whereas the increase in total unfolded heavy chain was limited. Although IFNg induces ERAP1, the ERAP1 KD cells maintained a 50% reduction in ERAP1 expression compared to scrambled shRNA controls. Surprisingly, ERAP1 KD limited the increase in cell surface folded B27 by approximately ~15%. ERAP1 KD also resulted in greater accumulation of disulfide-linked heavy chain oligomers both without and with IFNg treatment.

Conclusion: These data demonstrate that folded and unfolded forms of HLA class I are clearly affected by reduced ERAP1 expression. Loss of ERAP1 function through KD results in a small increase in the accumulation of total cellular HLA class I heavy chain, with more folded compared to unfolded forms, but this difference is not readily apparent on the cell surface, suggesting that it may be intracellular. Differences are further increased with IFNg. Interestingly, while diminished ERAP1 function results in more folded B27 on the cell surface at steady state, upregulation of folded forms can be limited by ERAP1 KD. Our studies highlight the importance of ERAP1 in modulating folded and misfolded forms of B27, and provide a system to probe additional biological effects of these two gene products.

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ACR Poster Session A
Systemic Lupus Erythematosus - Animal Models
Sunday, October 27, 2013, 8:30 AM–4:00 PM

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Exploration Of a Novel Therapeutic Target In a Murine Model Of Systemic Lupus Erythematosus: Targeting Sphingosine-1-Phosphate (S1P) Receptors. Christopher Tracy[1], Jess Edison[1], S. Frattalone[1] and C. Moratz[2]. [1]Walter Reed National Military Medical Center, Bethesda, MD, [2]Uniformed Services University of Health Sciences, Bethesda, MD.

Background/Purpose: Systemic lupus erythematous (SLE) is an autoimmune disease characterized by symptomatic flares that often result in terminal organ failure. The pathogenesis is characterized by complex immune dysfunction, including aberrant T-cell responses. FTY720, an FDA approved therapy for multiple sclerosis (MS), is a compound with the ability to modulate T-cell proliferation through S1P receptors. The aim of this study is to attenuate tissue injury and define a subset of S1P receptors and expression patterns that may be altered in the autoimmune prone ischemic reperfusion injury (IRI) mouse model.

Methods: Immune competent (C57BL/6) and autoimmune prone (B6.MRL/*lpr*) mice were exposed to FTY720 or Pertussis toxin followed by superior mesenteric artery ischemic reperfusion injury. Histological analysis of tissue samples was performed to assess tissue injury and the extent of inflammatory cell infiltration into the injured tissues. Multiplex array based cytokine analysis and immunohistochemistry analysis of isolated tissue lysates established and confirmed the extent of induction of inflammatory cytokine production. Immunofluorescence staining of tissue samples defined specific S1P receptor expression patterns.

Results: Targeting S1P receptors with FTY720 attenuates tissue injury in the autoimmune prone mice (B6.MRL/lpr) compared to the immune competent controls (C57BL/6). Multi-ligand targeting the S1P receptors decreased T-cell infiltration, IL-6 and IL1B levels in the autoimmune prone mice compared to the immune competent controls. Immunofluorescence staining of specific S1P receptors showed increased S1P1, S1P2 and S1P3 expression patterns in the autoimmune prone mice compared to the immune competent controls after ischemic reperfusion injury.

Conclusion: These findings support the hypothesis that S1P receptor interaction is a key regulator of T-cell mediated tissue injury and represents a novel therapeutic target in SLE. The role of specific S1P receptors in the pathophysiology of tissue injury is highlighted by the increased expression patterns of targeted S1P receptors after ischemic reperfusion injury in autoimmune prone mice. Defining S1P receptor expression in human lupus and how this expression influences the cell responsiveness during states of inflammation warrants further investigation.

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An Essential Role For Caspase-1 In The Induction Of Murine Lupus and Its Associated Vascular Damage. J. Michelle Kahlenberg[1], Srilakshmi Yalavarthi[2], Wenpu Zhao[2], Jeffrey Hodgin[1], Tamra J. Reed[1], Noriko M. Tsuji[3] and Mariana J. Kaplan[2]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan Rheumatology, Ann Arbor, MI, [3]3Biomedical Research Institute, National Institute of Advanced Industrial Science and Technology, Tsukuba, Japan.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a systemic autoimmune syndrome associated with organ damage and an elevated risk of cardiovascular disease (CVD) resulting from activation of both innate and adaptive immune pathways. Recently, increased activation of the inflammasome machinery in SLE has been described. This study explores if caspase-1, the central enzyme of the inflammasome, plays a role in the development of SLE and its associated vascular dysfunction, using the pristane model of lupus.

Methods: Eight-week old wild-type or caspase-1−/− mice were exposed to PBS or pristane via intraperitoneal injection. Six months post injection, mice were euthanized and the development of a lupus phenotype and vascular dysfunction was assessed.

Results: Both wild-type and caspase-1 KO mice develop a vigorous inflammatory response to pristane; however, cell death following pristane exposure is decreased in caspase-1−/− mice. While wild-type mice exposed to pristane develop autoantibodies and a strong type I IFN response, mice lacking caspase-1 are significantly protected from these features, including pristane-induced vascular dysfunction. Further, the development of immune-complex glomerulonephritis, prominent after pristane exposure in wild-type mice, is significantly abrogated in caspase-1−/− mice.

Conclusion: These results indicate that caspase-1 is an essential component in the development of lupus and its associated vascular dysfunction following exposure to pristane. Importantly, caspase-1 may modulate autoantigen generation through regulation of cell death. Thus, caspase-1 may play an important role in the cross-talk between environmental exposures and autoimmunity development, providing a novel pathway for therapeutic targeting.

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Evidence For Involvement Of C5a Receptor in Human and Murine Lupus Nephritis. Constanze Hess[1], Ditte Tornehave[2], Peter Helding Kvist[2], Yvonne Sundström[3], Louise Berg[3], Iva Gunnarsson[4], Søren Jacobsen[5], Claus Haase[1] and Lars Hornum[1]. [1]Department of Immunopharmacology, Novo Nordisk A/S, Måløv, Denmark, [2]Department of Histology, Novo Nordisk A/S, Måløv, Denmark, [3]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [4]Karolinska Institutet, Stockholm, Sweden, [5]Department of Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.

Background/Purpose: The complement system plays an important role in the pathogenesis of systemic lupus erythematosus (SLE). Apart from the activation of the early components of the classical complement cascade, C5a levels are elevated in SLE patient plasma and C5a receptor (C5aR)-positive cells are detected in kidneys from lupus nephritis (LN) patients. We compared the expression of C5a and C5aR in samples of LN patients to healthy control samples. Moreover, we investigated the efficacy of blocking C5aR by prophylactic treatment with an anti-C5aR monoclonal antibody (mAb) in the inducible nephrotoxic nephritis (NTN) mouse model, which can be viewed as a mechanistic disease model of kidney damage downstream of immune complex (IC) deposition in the glomeruli leading to glomerulonephritis (GN).

Methods: C5a was measured in urine samples of 20 LN patients and in 10 healthy controls by ELISA at 3 visits. The expression of C5aR, CD3 and CD68 was investigated by immunohistochemistry in kidney biopsies from 9 LN patients and from 3 non-inflamed controls. GN was induced by transferring nephrotoxic serum containing sheep anti-rat GBM IgG antibodies into C57BL/6 mice pre-immunized with sheep IgG in CFA. Prophylactic administration of 5 or 25 mg/kg anti-C5aR mAb, 25 mg/kg isotype control or PBS was performed 3x weekly (n=12 per group). Sheep IgG specific antibody titers were determined by ELISA and GN development was monitored by proteinuria measurements (Uristix). Pathological changes of the kidney were analysed by periodic acid-Schiff stain. Mouse C5a was measured in renal tissue and in urine samples by ELISA.

Results: In 17 out of 20 LN patients, C5a was detectable in the urine, but not in any of the healthy controls. In kidney biopsies, C5aR was expressed by infiltrating cells located in T cell (CD3+) and macrophage (CD68+) rich lymphoid aggregates in the tubulointerstitium in 7 out of 9 LN patients. No C5aR expression was observed in normal renal tissue. In the murine NTN model, both doses of anti-C5aR mAb inhibited development of proteinuria and reduced the frequency of glomeruli showing basal membrane (BM) thickening. The prevalence of affected glomeruli correlated with the development of proteinuria. C5a was detected in renal tissue and urine samples upon NTN induction. No changes in C5a or in anti-sheep IgG Ab titers were

detected following C5aR blockade, suggesting that anti-C5aR mAb treatment targets effector functions downstream of IC deposition.

Conclusion: Preventive treatment with anti-C5aR mAb diminishes the development of proteinuria and attenuates glomerular BM thickening. This demonstrates that blockade of C5aR abrogates the development of GN in the NTN mouse model. These data combined with the detection of C5a in LN patient urine and C5aR-positive infiltrating cells in renal samples from LN patients suggest that blocking C5aR with antagonistic mAbs might be a promising future therapy of patients with LN.

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Inhibiting TWEAK (TNF-like weak inducer of apoptosis) Signaling Improves Blood Brain Barrier Integrity and Protects From Neuronal Damage In Murine Neuropsychiatric Lupus. Jing Wen[1], Jessica Doerner[1], Ariel Stock[1], Jennifer Michaelson[2], Linda Burkly[2], Maria Gulinello[1] and Chaim Putterman[1]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]Biogen Idec, Cambridge, MA.

Background/Purpose: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by involvement of multiple organs, including the central nervous system. While neuropsychiatric involvement in systemic lupus erythematosus (NPSLE) is relatively common and appears early, the underlying mechanisms are not fully understood. TWEAK is a cytokine member of the TNF superfamily; the TWEAK receptor, Fn14, is expressed in brain endothelial cells, astrocytes, microglia and neurons. TWEAK/Fn14 interactions can lead to cytokine production, neuron degeneration, and an increase in blood brain barrier (BBB) permeability. The disruption of the BBB is believed to be a key pathological feature in NPSLE, allowing the passage of neurotoxic autoantibodies into the brain. We recently found that lupus prone MRL/lpr Fn14 knockout (KO) mice display a markedly attenuated neuropsychiatric phenotype, as revealed by a significant reduction in depressive-like behavior and improved cognitive function. Similarly, NPSLE patients demonstrate high levels of TWEAK in the cerebrospinal fluid. We undertook the current studies to further investigate the mechanisms by which TWEAK signaling is involved in the pathogenesis of NPSLE.

Methods: Comprehensive neurobehavioral assessment including forced swim, anhedonia, open field, object recognition, object placement, and social preference were employed to quantify neuropsychiatric manifestations in MRL/lpr Fn14WT and MRL/lpr Fn14KO mice at 20 weeks of age. Mice were sacrificed after behavior profiling, and the brains prepared for qRT-PCR, Western blot and immunohistochemistry (IHC). To assess blood brain barrier (BBB) integrity, Western blot was performed to evaluate extravascular fibronectin and IgG deposition (which both increase with BBB permeability). Additionally, cellular infiltrates were quantified on hematoyxlin and eosin staining. Fluoro Jade B and TUNEL staining were used to analyze neuronal damage and apoptosis in the brain. Furthermore, gliosis, neuron loss and neurogenesis were assessed by immunostaining with GFAP, NeuN and Ki-67, respectively.

Results: We found that Fn14KO mice had improved BBB integrity, as shown by decreased fibronectin and IgG deposition in the brain. However, no clear differences in the magnitude of cellular infiltrates were observed in the choroid plexus. Additionally, neuronal damage, another important pathological change that can be seen in experimental NPSLE, was also ameliorated by Fn14 deficiency. Fn14KO mice displayed reduced apoptosis in the cortex, as well as less neuron loss and less gliosis in the hippocampus. Interestingly, there were no differences in neurogenesis and in microglia activation between Fn14KO and Fn14WT mice. Studies to compare cytokine expression in brain and cerebrospinal fluid of Fn14KO and Fn14WT mice are in progress.

Conclusion: Our studies indicate that TWEAK/Fn14 interactions can play a central role in the pathogenesis of NPSLE by improving BBB integrity and reducing neuronal damage, suggesting this pathway as a novel target for therapeutic intervention in this challenging disease manifestation.

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Ultraviolet-B Induced Plasmacytoid Dendritic Cell Migration and Type 1 Interferon Signaling In The Skin. Clayton Sontheimer, Thomas H. Teal, Nalini Agrawal, Denny Liggitt and Keith B. Elkon. University of Washington, Seattle, WA.

Background/Purpose: Plasmacytoid dendritic cells (pDCs) are highly specialized cells of the innate immune system that secrete very high levels of interferon alpha (IFN-a) following nucleic acid ligand mediated activation of the Toll-like receptors (TLRs) 7 and 9. Although the presence of large numbers of pDC in the skin of patients with cutaneous lupus and exacerbation of cutaneous lupus by UVB exposure suggests a causal relationship, a direct link is difficult to prove. In mice, pDC have been observed in the skin following virus infections as well as following injury by tape stripping but studies of UVB are very limited. Here, we asked whether, and under what conditions, UVB-induced inflammation could recruit pDC and type 1 IFN to the skin.

Methods: Shaved C57BL/6 (B6) mice were irradiated with UVB with either a single dose of 500 mJ/cm^2 (acute profile) or with 100 mJ/cm^2/day for 5 consecutive days (subacute profile). Serial punch biopsies (6 mm) were obtained at 3, 24, and 72 hrs following UVB exposure. Skin samples were examined for mRNA expression by quantitative PCR of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and Type 1 stimulated genes (MX1, ISG15, ISG20). mRNA fold change was calculated against non-irradiated control mice. Skin samples were also evaluated by histology with H&E staining and for the presence of pDCs by staining for the pDC-specific marker Siglec H by immunohistochemistry. The skin was also scored visually in a blinded manner based on degree of erythema and ulceration.

Results: While producing similar levels of IL-1β, TNF-α and IL-6, subacute UVB exposure of B6 mice preferentially induced expression of Type 1 IFN genes when compared to both acute UVB and non-irradiated controls. IFN-response genes were elevated at each time point with the greatest increase occurring at 72 hours post-UVB. Subacute UVB exposure also induced transient pDCs infiltration into the dermis and hypodermis that corresponded with Type 1 IFN response genes. To examine the role of UVB-induced Type 1 IFN, subacute UVB-mediated effects in B6 mice were compared to age matched IFNAR KO mice (also on a B6 background). IFNAR KO mice had increased levels of the pro-inflammatory cytokines, IL-1β and IL-6 at 3 and 24 hrs following UVB compared to B6 mice. Interestingly, TNF-α levels were similar between B6 and IFNAR KO mice. Skin scoring for erythema and ulceration showed increased levels of skin damage at 3 and 24 hrs.

Conclusion: Repeated moderate dose of UVB preferentially induced pDC recruitment and Type 1 interferon signature in the skin. Based on the findings that skin damage and inflammatory cytokines were higher in IFNAR KO compared to control mice following subacute UVB exposure, we conclude that Type 1 IFN plays a protective role in attenuating the acute inflammatory response following repeated UVB exposure. It is likely that repetitive UVB exposure as well as other genetic factors leading to hyperresponsiveness to nucleic acid debris, predispose to lupus.

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Preferential Infiltration Of Double-Negative (DN) T Cells Into The Glomeruli Of NZM 2328 Lupus Mice. Ning Yu, Shunhua Guo, William Stohl and Chaim O. Jacob. University of Southern California Keck School of Medicine, Los Angeles, CA.

Background/Purpose: Lupus nephritis affects at least 50% of patients with SLE and is a major cause of morbidity. The pathologic picture of lupus nephritis is complex and the precise mechanisms that underlie the development of lupus nephritis remain unclear. The present study was undertaken to delineate the differential localization of lymphocytes infiltrating the glomeruli versus the tubulo-interstitium in NZM 2328 mice, a murine model that closely mimics human lupus nephritis.

Methods: Kidneys were evaluated by in situ histology and immunohistochemistry. Cells infiltrating the glomeruli were separated from those infiltrating the tubulo-interstitium through enzymatic, magnetic, and mechanical procedures and were characterized by flow cytometry.

Results: B cells and macrophages each represent ~5% of the cells infiltrating both the glomeruli and tubulo-interstitium, whereas CD3$^+$ T cells represent 40–60% and 70–80% of the infiltrating cells, respectively. In the

tubulo-interstitium, 50–60% of $CD3^+$ T cells are $CD4^+$, 15–25% are $CD8^+$, and 20–30% are DN. In contrast, the T cells infiltrating the glomeruli are only 1–5% $CD4^+$ cells and <1% $CD8^+$ cells, whereas 95–98% are DN. Furthermore, most of the T cells infiltrating the glomeruli display an activated memory phenotype ($CD62L^{neg}$, $CD44^{high}$, $CD69^+$). About 20–25% of these activated T cells are also CD1d tetramer positive, indicative of an iNKT cell phenotype. A significant difference in the abundance of $NK1.1^+$ cells was also observed. Among cells infiltrating the glomeruli, 20–35% are $NK1.1^+$, whereas only 3–10% of the cells infiltrating the tubulo-interstitium are $NK1.1^+$. These data are highly relevant in comparison with the composition of T cells in the spleen of NZM 2328 mice. The activated memory T cell subset serves as a major biological surrogate marker of clinical disease progression. As determined by gene-array analysis, these activated memory T cells display neither a Th1 nor Th2 profile but rather express a Th17 profile and produce IL-17. Most importantly, these activated memory cells progressively increase in numbers during disease development, not only in the spleen, but in the kidney as well. However, during migration of these cells from the periphery to the kidney and especially into the glomeruli, they lose their $CD4^+$ expression and become mostly DN.

Conclusion: The present study is, to our knowledge, the first direct and detailed analysis of the immune infiltrates in the glomeruli and the tubulo-interstitium in lupus kidneys. The identification of DN T cells bearing an activated memory phenotype as the major cell population in the glomeruli of clinically nephritic mice is likely highly relevant to the pathogenesis of human lupus nephritis. Given that DN T cells are found in kidney biopsies of patients with lupus nephritis and these cells are capable of producing IL-17, our results further support this subset of cells as contributory to development of kidney damage.

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The Survival Of $Gr1^+CD11b^+$ cells Is Differentially Regulated In Male and Female Lupus-Prone Mice. Elena Gonzalez, Trine Jorgensen and Abhishek Trigunaite. Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, OH.

Background/Purpose: Systemic Lupus Erythematosis (SLE) is a multi-system autoimmune disease that develops far more frequently in females than in males (9:1 ratio). The (NZBxNZW)F1 lupus-prone mouse model shares a female predominance of disease. Our recently published studies have shown decreased numbers of $Gr1^+CD11b^+$ cells in the spleens of female (NZBxNZW)F1 lupus-prone mice compared to males and that the level of these cells is modulated by testosterone. These cells have been found by our lab and others to suppress both T and B cell function *in vitro*. Depletion of this cell subset in male (NZBxNZW)F1 mice resulted in increased anti-nuclear antibody production. We suggest that the difference in cell numbers has a role to play in the gender differences in lupus-like disease development. We aimed to investigate the mechanism driving the difference in numbers of $Gr1^+CD11b^+$ cells in male and female mice. We hypothesized that the comparatively decreased levels of $Gr1^+CD11b^+$ cells in the female (NZBxNZW)F1 mice is due to either their decreased proliferative capacity or to their decreased survival.

Methods: Levels of proliferation and cell death of $Gr1^+CD11b^+$ cells from male and female (NZBxNZW)F1 mice were determined *ex vivo*using anti-Ki67 and Annexin V antibodies, respectively. The effect of hormonal manipulation on proliferation and cell death was assessed through pre-pubertal castration of male mice followed by DHT or placebo supplementation for 5 weeks. Total spleen and bone marrow cells from male and female mice were cultured in various conditions to determine the effect of cytokines and components of the male and female microenvironments on proliferation and cell death.

Results: Proliferation levels were not different in $Gr1^+CD11b^+$ cells from male and female mice, and these levels were unaffected by castration and DHT supplementation. Apoptosis levels were significantly higher in $Gr1^+CD11b^+$ splenocytes from female mice compared to male mice. There was no defect in clearance of apoptotic material in female (NZBxNZW)F1 mice compared to males. The level of cell death was elevated by castration of male mice, but not statistically significantly. Components of the male and female microenvironments were examined for their ability to alter levels of cell death *in vitro*, and we found that male bone marrow supernatants can significantly increase the survival of $Gr1^+CD11b^+$ cells when compared to female supernatants. We found higher levels of IL-1β in the male bone marrow supernatants and the level of IL-1β was modulated by castration and hormonal reconstitution. Culture of bone marrow cells from male and female (NZBxNZW)F1 mice with IL-1β significantly increased the survival of $Gr1^+CD11b^+$cells.

Conclusion: Increased apoptosis of female $Gr1^+CD11b^+$ cells may represent one of several mechanisms by which these cells are decreased in female mice compared to males, allowing autoimmunity to develop. The death of $Gr1^+CD11b^+$ cells was significantly decreased by exposure to male bone marrow supernatants *in vitro*, suggesting that the male microenvironment may support the survival of these cells. Additionally, our data implies that differences in IL-1β may be the factor in the male system that supports the survival of $Gr1^+CD11b^+$ cells.

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Anti Ribosomal P Antibodies Accelerate Lupus Glomerulonephritis and Induce Lupus Nephritis In Naive Mice. Dana Ben-Ami Shor[1], Miri Blank[2], Sandra Reuter[3], Torsten Matthias[4], Alexander Volkov[5], Iris Barshack[6] and Yehuda Shoenfeld[7]. [1]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Tel-Aviv, Israel, [2]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, affiliated to Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Tel-Aviv, Israel, [3]AIRA e.V., AESKU.KIPP Institute, Wendelsheim, Germany, [4]AESKU.Diagnostics GmbH & Co. KG, Wendelsheim, Germany, [5]Institute of Pathology, Sheba Medical Center, affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Tel-Aviv, Israel, [6]Institute of Pathology, Sheba Medical Center, affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Tel-Aviv, Israel, [7]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Tel-Aviv, Israel.

Background/Purpose: Circulating anti-phosphoribosomal protein antibodies (anti-Ribos.P) were found to be associated with lupus nephritis. We have assessed the direct role of anti-Ribos.P in the development of glomerulonephritis in-vitro and in animal models.

Methods: NZBxW/F1 lupus prone mice were immunized with recombinant Ribos.P0 (rRibos.P). The following lupus parameters were analyzed: autoantibodies screen directed to Ribos.P, dsDNA and Sm by ELISA. Proteinuria was determined by protein-sticks, kidney pathology by H&E staining and immunoglobulin deposits by immunofluorescence. Anti-Ribos.P deposited in the glomerular mesangium were eluted from the kidney. Anti-Ribos.P monoclonal Ab was prepared from the rRibos.P immunized NZBxW/F1 mice by hybridoma technology. MAPKs expression was analyzed by MAPKs protein-array and confirmed by real-time PCR. To elucidate whether anti-Ribos.P induce glomerulonephritis, naïve C3H mice were immunized with recombinant Ribos.P0 (rRibos.P) and the glomerulonephritis was followed up as described above.

Results: Our data demonstrate that rRibos.P0 immunized NZBxW/F1 mice developed accelerated glomerulonephritis characterized by anti-Ribos.P deposition in the glomerular mesangium. Primary mesangial cells exposed to mouse anti-Ribos.P mAb originated from the immunized lupus mice and to human anti-Ribos.P Abs, induced p38a MAPK expression. Moreover, naïve C3H/Hen mice immunized with rRibos.P0 developed experimental lupus nephritis manifested by circulating autoantibodies directed to Ribos.P, dsDNA, Sm and glomerulonephritis with anti-Ribos.P depositions. In conclusion, Our data show for the first time that anti-Ribos.P are nephritogenic autoantibodies, as illustrated by *in-vitro* and *in-vivo* experiments: a) They accelerate the development of glomerulonephritis in lupus prone mice; b) They induce nephritis in naïve mice. c) Anti-Ribos.P Abs trigger MAPKs expression in primary mesangial cells.

Conclusion: These data contribute a direct mechanistic link between anti-Ribos.P and nephritis in lupus mice.

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Characterizing The Role Of The Granulocyte Colony Stimulating Factor Pathway In a Mouse Model Of Systemic Lupus Erythematosus. Laurence Morel and Ramya Sivakumar. University of Florida, Gainesville, FL.

Background/Purpose: Originally considered primarily a B cell disorder, lupus pathogenicity has recently been linked to enhanced functions of neutrophils. The genetic analysis of the lupus prone NZM2410 mouse has

identified a suppressor locus, *Sle2c2,* which confers resistance to spontaneous lupus in combination with NZM2410 susceptibility loci or in the chronic graft-vs.-host disease (cGVHD) induced model of SLE. We have shown that *Sle2c2* resistance is mediated by bone-marrow derived non-lymphoid cells. We hypothesize that a non-synonymous polymorphism in the granulocyte colony stimulating factor (G-CSF) receptor 3 (*Csf3r)* gene existing within *Sle2c2* is responsible for providing protection. G-CSF is required for neutrophil granulopoiesis, mobilization and activation. We hypothesize that the defective G-CSF receptor is associated with lupus resistance by controlling the homeostasis of pro-inflammatory neutrophils.

Methods: We have investigated the role of G-CSF pathway in both cGVHD induced lupus in B6.*Sle2c2* mice and spontaneous lupus in B6.*Sle1*.*Sle2*.*Sle3* triple congenic (TC) strain (also carrying the Sle2c2 locus) as compared to B6 mice. The ability of G-CSFR to bind mouse biotinylated G-CSF was compared between B6.Sle2c2 and B6 splenocytes and analyzed by flow cytometry. Treatments with varying doses of rh-GCSF (Neulesta) were tested in reversing or enhancing the course of disease in cGVHD induced SLE (B6.Sle2c2), and spontaneous lupus (TC). The effects of Neulesta on immune cell activation markers were assessed by flow cytometry and by ELISA's for antibodies against dsDNA and chromatin. Gene expression analyses by real time PCR for neutrophil and G-CSF specific genes were also employed as an alternative mechanism for studying the downstream effects of GCSF-GCSFR pathway.

Results: Neulesta treatments reversed cGVHD resistance in B6.Sle2c2 mice and increased anti-dsDNA IgG production in TC mice. Dose-dependent effects were however observed with high doses of Neulasta having a protective effect in B6.TC mice. In vitro and in vivo experiments have shown a reduced binding of G-CSF on myeloid cells and a decreased mobilization of neutrophils in response to Neulesta treatment in B6.*Sle2c2* mice compared to B6. Gene expression analyses have revealed a differential expression of G-CSFR-target genes between B6.Sle2c2 and B6 bone marrow cells and splenocytes in response to Neulesta. This included a lower expression of BAFF in B6.*Sle2c2* splenocytes than in B6, suggesting that BAFF production by neutrophils may represent a mechanism by which G-CSF regulates systemic autoimmunity.

Conclusion: Our results support the hypothesis that a G-CSF receptor with a defective binding for its ligand confers resistance to lupus. Future experiments aimed at elucidating the role of neutrophils as downstream effectors of the GCSF-GCSFR pathway will help in dissecting their pathogenic contribution to lupus. We predict that understanding the contribution of GCSFR axis towards SLE pathogenesis in mouse models of lupus will help us in identifying and designing potential and novel therapeutic targets for the disease.

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Augmented Megakaryopoiesis Supports Accumulation Of Plasma Cells In Lupus-Prone Mice. Oliver Winter[1], Niels-Peter Becker[1], Stephanie Musiol[1], Katrin Moser[2], Falk Hiepe[3] and Rudolf A. Manz[4]. [1]Charité - University Medicine Berlin, Berlin, Germany, [2]German Arthritis Research Center (DRFZ Berlin), Berlin, Germany, [3]Charité University Hospital Berlin, Berlin, Germany, [4]University of Lübeck, Lübeck, Germany.

Background/Purpose: Autoantibodies - secreted by short- and long-lived plasma cells in bone marrow and spleen - trigger the immune response, and immune complex deposits in the kidneys can lead to the development of a severe nephritis. As such, autoreactive plasma cells contribute to the pathogenesis of the autoimmune disease Systemic Lupus Erythematosus (SLE). In NZB/W mice - a mouse model for SLE - both parental strains New Zealand Black (NZB) and New Zealand White (NZW) add different *sle-loci* to the formation of SLE. The NZB strain passes the *sle2c locus* that contains the gene for the Thrombopoietin (TPO)-receptor (*c-mpl*). According to the relevance of megakaryocytes for the plasma cell niche and the correlation between plasma cell and megakaryocyte numbers, we wanted to elucidate whether megakaryopoiesis, c-Mpl or c-Mpl signaling is altered in autoimmune mice.

Methods: We assessed the amount, and cellular environment of megakaryocytes and plasma cells in spleen and bone marrow of wildtype, NZB, NZW and NZB/W mice via flow-cytometry and confocal microscopy. We also investigated the intensity of megakaryopoiesis upon TPO stimulation, the occurrence of genetic variations for *c-mpl* and the activation of signaling pathways downstream of c-Mpl by *in vitro* studies, and by gene and protein analysis.

Results: We found the 10-fold amount of long-lived plasma cells and megakaryocytes in the spleens of NZB mice compared to wildtype, in NZW mice equal numbers, and in NZB/W mice numbers between those for NZB and NZW or wildtype. Furthermore, in the spleen a fraction of plasma cells clustered around megakaryocytes and *in vitro* megakaryocytes support plasma cell survival. Upon TPO stimulation of splenocyte and bone marrow cultures, NZB megakaryocytes proliferated significantly stronger resulting in the double amount of megakaryocytes compared to NZW cultures. Via sequence analysis we detected a missense mutation in the *c-mpl* gene of NZB mice leading to an amino acid replacement within the essential TPO-binding site. However, *in vitro* experiments with wildtype and mutant *c-mpl* BaF3-clones revealed that this mutation is actually hampering the proliferation upon TPO stimulation and hyperactivation of downstream signals is overcompensating.

Conclusion: In summary, our data indicate that augmented megakaryopoiesis enables the accumulation of a greater number of autoreactive plasma cells in lupus prone NZB/W mice. Thus, we propose that enhanced megakaryopoiesis and greater megakaryocyte numbers are contributing to the development and/or pathogenesis of SLE.

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Neutrophil Gelatinase Associated Lipocalin (NGAL/Lipocalin-2) Regulates the Onset Of Serum Autoantibodies In Pristane Induced Lupus. Rahul Pawar[1], Beatrice Goilav[2], Yumin Xia[1], Haoyang Zuang[3], Leal Herlitz[4], Westley H. Reeves[3] and Chaim Putterman[1]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]Children's Hospital at Montefiore, Bronx, NY, [3]University of Florida, Gainesville, FL, [4]Columbia University Medical Center, New York, NY.

Background/Purpose: NGAL (lipocalin-2), a member of the lipocalin superfamily, is expressed by a variety of cells including neutrophils, hepatocytes, alveolar epithelial cells and renal resident cells. NGAL is a sensitive marker for tissue injury, and is upregulated following ischemia, inflammatory conditions, metabolic diseases and neoplastic disorders. Furthermore, several studies have demonstrated the use of NGAL as a biomarker in lupus nephritis. Previously, NGAL was reported to be involved in innate immune responses during bacterial infection, and was found to worsen renal disease in nephrotoxic serum nephritis. However, the role of NGAL in adaptive immunity is still largely unknown.

Methods: To investigate a possible role for NGAL in adaptive immune responses in an experimental lupus model, we injected pristane (tetramethylpentadecane) (0.5 ml/mouse intraperitoneally) into wild type B6 (n=10) and NGAL-deficient (LCN2−/−) (n=10) mice. Wild type (WT) B6 and LCN−/− mice receiving PBS injections served as controls. Serum autoantibodies were analyzed by ELISA, Hep-2 immunostaining, and immunoprecipitation. Autoantibody producing cells were quantitated by ELISPOT. Expression of mRNA in spleen was performed by real-time qPCR.

Results: Analyzing the levels of serum autoantibodies 4 months post pristane injection, we found that pristane challenged LCN2−/− mice had significant increases in IgG_{2b} anti-single and anti-double stranded DNA as well as IgG anti-histone antibodies as compared to pristane injected B6 mice. Furthermore, elevated levels of serum anti-ribonucleoprotein antibodies were observed in pristane injected LCN2−/− mice by immunoprecipitation. Confirming these results, analysis of serum anti-nuclear antibodies (ANA) on Hep-2 cells revealed significantly increased homogenous and speckled staining in pristane challenged LCN2−/− mice as compared to WT B6 mice, while ELISPOT revealed increased numbers of autoantibody producing cells to DNA, histone and RNP in the spleen. Moreover, we found significant upregulation of interferon regulatory factor-5 (IRF5), IP-10, CXCL13, CXCR5, CXCR3, and activation induced cytidine deaminase (AID) in spleens of LCN2−/− mice compared to B6 mice post pristane challenge. Pristane promoted NGAL secretion by splenocytes *in vitro*, while pristane challenge *in vivo* induced significant upregulation of NGAL expression in the spleen and serum of B6 mice.

Conclusion: NGAL/LCN2 deficiency accelerates the onset of antinuclear antibodies in pristane induced lupus, via increased levels of inflammatory mediators and autoantibody producing cells.

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Different Cell Death Programs Contribute To Severity Of Lupus Glomerulonephritis In Males and Females. Neelakshi Jog[1] and Roberto Caricchio[2]. [1]Temple University, Philadelphia, PA, [2]Temple Univ Med Office Bldg, Philadelphia, PA.

Background/Purpose: Lupus glomerulonephritis (GN) is a leading cause of long-term disability in SLE. Although lupus is more common in females, GN occurs earlier and in a more accelerated manner in males. We propose that the severity of renal damage is defined by differences in cell death program during GN. Necrosis, a pro-inflammatory form of cell death can be regulated by two mediators: 1) Poly (ADP-Ribose) Polymerase-1 (PARP-1) and 2) Receptor Interacting Protein kinase 1/3 (RIP1/3). We demonstrated previously that the protection conferred by the absence or inhibition of PARP-1 from immune-mediated nephritis shows a sex-bias, with only male mice being protected. Several studies have shown that the response of males and females to stress differs. We therefore hypothesized that these differences might be due to cell death programs in the two sexes.

Methods: We used an established model of immune complex mediated nephritis to investigate cell death in vivo and an in vitro system where bone marrow cells were allowed to differentiate in vitro into macrophages in presence or absence of estrogens. The cells were stimulated by hydrogen peroxide or toll-like receptor ligand (TLR), lipopolysaccharide (LPS). Cell death was measured by flow cytometry and morphology; cytokine were measured by quantitative PCR.

Results: We demonstrate that during nephritis, females show increased apoptotic cell death in the kidney compared to males. We also show that estrogen treatment in males induced similar levels of apoptosis as in females and importantly inhibited necrosis. Although PARP-1 was activated in both males and females, PARP-1 inhibition decreased necrosis only in males. Interestingly inhibition of RIP1 with Necrostatin-1 did not show sex bias. To understand whether male and female cells show a differential cytokine expression pattern that may further contribute to the differences in cell death, we determined cytokine gene expression by bone marrow derived macrophages from male and female cells in response to TLR ligation in presence or absence of estrogens. We found that the expression of pro-inflammatory cytokines TNF alpha and MCP-1 were higher in male cells in absence of estrogens compared to females, suggesting that these cytokines may contribute to increased necrosis observed in males. We also observed that estrogens increased IL10 production in male cells upon TLR ligation. Interestingly IL10 has been previously shown to inhibit necrosis. Finally we found that estrogens reduced the levels of pro-inflammatory cytokines TNF alpha and MCP1.

Conclusion: Taken together our data suggest that males and females differ in their susceptibility to pro-inflammatory cell death, i.e. propensity toward necrosis in males and apoptosis in females. The contributing factors to this dichotomy are the effective activation of necrotic cell death, hormones and pro-inflammatory cytokines. Our results might help understanding the increased severity of lupus nephritis in males and develop novel therapeutic strategies based on sex.

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Inhibitor Of Differentiation 3, A Transcription Factor Regulates Susceptibility To Kidney Disease. Dominika Nackiewicz, Ani Manichaikul, Barbara Szczerba, Paromita Dey, Stephen Rich, Coleen McNamara, Umesh Deshmukh and Harini Bagavant. University of Virginia, Charlottesville, VA.

Background/Purpose: Responses of renal cells to pathogenic stimuli play an important role in dictating susceptibility to kidney disease. Inhibitor of differentiation 3, ID3, is a member of the basic helix loop helix transcription factor family and is expressed in multiple cell types including glomerular mesangial cells. We have previously reported that a genetic deficiency of ID3, leads to mesangio-proliferative glomerulonephritis in spontaneously hyperlipidemic Apolipoprotein E knockout ($Apoe^{-/-}$) mice. In the present study, we investigated the mechanisms of ID3 related glomerular disease in hyperlipidemia and studied its relevance in humans. Influence of ID3 on immune mediated glomerulonephritis was also studied.

Methods: To study whether ID3 deficiency was sufficient for hyperlipidemic glomerulonephritis, C57BL/6 mice that were either ID3 sufficient wild type (WT) or ID3 deficient ($Id3^{-/-}$) mice were fed a high fat western diet and evaluated for different parameters of kidney disease. To investigate the potential mechanism of action, primary mesangial cell lines were generated from both mouse strains and stimulated with oxidized phospholipids. Cytokines and chemokines produced were measured by multiplex assays, ELISA, and QPCR. To study the relevance of ID3 in human disease, the association between *ID3* single nucleotide polymorphisms (SNPs) and kidney disease was studied in participants in the Multi-Ethnic Study of Atherosclerosis (MESA) and the influence of dyslipidemia on this association was investigated. As an additional model of kidney disease, WT and $Id3^{-/-}$ mice were injected with sheep anti-mouse glomerular basement membrane serum to induce immune mediated glomerular injury, and development of proteinuria was studied.

Results: $Id3^{-/-}$ mice on a western diet developed accelerated proteinuria and mesangio-proliferative glomerulonephritis. In vitro, $Id3^{-/-}$ glomerular mesangial cell lines produced higher levels of the monocyte chemoattractant, CXCL1 in response to oxidized phospholipids compared to WT controls. This was consistent with the rapid increase in glomerular CXCL1 expression followed by glomerular macrophage infiltration in $Id3^{-/-}$ mice fed a western diet. In humans, an analysis of MESA participants across three ethnic groups showed that of six tagging *ID3* SNPs, the T allele of a non-synonymous, functional SNP rs11574 showed a significant association with decreased urinary albumin creatinine ratios in Caucasians ($P=0.012$). This association was even stronger in participants carrying small low density lipoprotein particles ($p=0.0024$). This suggests the hypothesis that in the presence of lipid abnormalities, a change in ID3 influences kidney disease. The significance of functional ID3 in other forms of glomerular injury of kidney disease was further demonstrated in immune mediated nephrotoxic nephritis where $Id3^{-/-}$ mice developed severe and sustained proteinuria compared to WT mice.

Conclusion: A functional ID3 may regulate susceptibility to kidney disease and prevent glomerular injury by regulating local chemokine production and inflammatory cell recruitment.

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Estrogen Receptor Alpha Deficiency Protects Against Development Of Cognitive Impairment In Murine Lupus. Melissa A. Cunningham[1], Jena Wirth[1], Heather A. Boger[2], Ann-Charlotte Granholm-Bentley[1] and Gary S. Gilkeson[3]. [1]MUSC, Charleston, SC, [2]Medical University of SC, Charleston, SC, [3]Medical University of South Carolina, Charleston, SC.

Background/Purpose: Up to 80% of SLE patients have cognitive defects or affective disorders. The mechanism of CNS injury responsible for cognitive impairment is unknown. Anti-dsDNA antibodies cross-reacting with NMDA receptors in the brain mediate excitotoxic cell death, causing behavioral changes in lupus–prone mice. A breach in the blood-brain barrier (BBB) is required for these effects. Data suggest that BBB breakdown, pathogenic autoantibodies, and subsequent neuronal damage in key areas are involved in the development of neuropsychiatric SLE. Since estrogen receptor alpha (ERα) deficiency significantly reduced renal disease and increased survival in murine lupus, we hypothesized that ERα deficiency would be similarly protective in the brain. In a pilot cohort, we previously showed that ERα deficiency reduces errors made in a water maze by lupus prone mice. We hypothesized that ERα plays a role in modulating BBB integrity and/or neuroinflammation leading to CNS dysfunction in lupus prone MRL/lpr mice.

Methods: MRL/lpr lupus mice (n=46) were ovariectomized at 4wks, received 90d-release estradiol pellets at 6wks, and underwent behavioral testing beginning at 8wks with radial arm water maze (RAWM) and novel object recognition (NOR). Mice were sacrificed at 12wks. Hippocampus, pre-frontal cortex and parietal cortex were dissected. Western blotting and IHC were used to evaluate tight junction proteins, BBB and inflammatory endpoints.

Results: MRL/lpr ER$\alpha-/-$ mice (n=21) performed significantly better in RAWM testing than WT MRL/lpr mice (n=25). There was a significant reduction in reference memory errors ($p<0.02$) and start arm errors ($p=0.02$) in ER$\alpha-/-$ mice at 8–10wks. There was a trend toward reduction in working memory errors ($p<.07$). There were significant differences in NOR testing: latency discrimination ratio ($p=.05$), time with objects ($p=.009$) and contact ratio ($p<.04$), with ERα deficiency normalizing behavior. There were no significant differences in serum estradiol or dsDNA. Eighteen of 43 brains were processed and analyzed to date, with no significant differences seen in tight junction proteins (Zo-1 or occludin), GFAP (astrogliosis marker), or Iba1 (microgliosis marker) in hippocampus. There is a trend toward decreased Zo-1 and Iba-1 in cortex of ER$\alpha-/-$ mice. There were no significant differences in Glut-1 or Evan's blue staining in sections analyzed to date.

There are CA1 lesions (utilizing MAP2 and NeuN staining) seen in a subset of animals, but these do not correlate with genotype or behavior in the animals analyzed to date.

Conclusion: ERα deficiency provides significant protection against cognitive deficits in MRL/lpr mice as early as 8 wks of age. Preliminary data suggest reduced microgliosis (marker of inflammation/insult) in cortex of ERα−/− mice. BBB proteins such as Zo-1 may also be involved.

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Identification Of Stage Specific Genes Associated With Lupus Nephritis and Response To Remission induction In NZB/W Mice. Ramalingam Bethunaickan[1], Celine C. Berthier[2], Hong-dong Li[2], Weijia Zhang[3], Yuanfang Guan[2], Matthias Kretzler[2] and Anne Davidson[1]. [1]Feinstein Institute for Medical Research, Manhasset, NY, [2]University of Michigan, Ann Arbor, MI, [3]Mount Sinai School of Medicine, New York, NY.

Background/Purpose: Our goal was to use transcriptome analysis to elucidate the molecular mechanisms involved in the immunopathogenesis of renal inflammation during the onset, remission and impending relapse of nephritis in the NZB/W murine lupus model.

Methods: Targeted microarray analysis was performed on perfused kidneys obtained from NZB/W F1 mice at intervals during their disease course or after remission induction by cyclophosphamide combined with six doses of CTLA4Ig and anti-CD154 or by a combination CTLA4Ig and TACI-Ig. Validation of the differentially expressed genes was performed using real time PCR analysis. Comparisons between groups using SAM, and unbiased analysis of the entire dataset using Kohonen Networks were performed.

Results: Few changes in the renal molecular profile were detected prior to the onset of proteinuria but a significant shift in gene expression occurred at proteinuria onset. This profile reflected dendritic cell/macrophage and lymphoid cell infiltration and complement activation. As disease progressed, subsequent changes in gene expression predominantly reflected mitochondrial dysfunction and metabolic stress. Remission induction resulted in reversal of much of the inflammatory gene expression pattern however there was incomplete reversal of genes associated with early renal fibrosis, endothelial injury and hypoxia. Progression towards relapse was associated with increasing mitochondrial dysfunction and metabolic stress that preceded the onset of proteinuria. Using an unbiased approach we identified a major pattern of gene expression that was associated with proteinuria onset, nephritis progression and relapse. The top biological process identified for these genes was mitochondrial dysfunction. Finally, using Kohonen Networks we identified two major patterns of gene expression associated with progressive disease. The first, that associated with proteinuria onset and reversed with remission, involved multiple inflammatory pathways whereas the second, that associated with nephritis progression and relapse, involved multiple metabolic pathways. Using qRT-PCR we examined informative genes in a second murine lupus model NZM2410, in which remission of nephritis was induced with BAFF inhibition. While progression towards relapse was associated with recruitment of pro-inflammatory genes, the expression pattern that distinguished kidneys of mice harvested >30 weeks after remission induction from kidneys of mice with proteinuria and renal damage indicated that renal hypoxia, endothelial cell activation, tissue remodeling and tubular damage were the major mediators of renal loss.

Conclusion: Our findings show that immune cell infiltration and activation is associated with proteinuria onset and reverses with immunosuppressive therapy but that disease progression and impending relapse is associated with increasing renal hypoxia and metabolic stress. These findings suggest that that as nephritis progresses or during nephritis flares, therapeutic targeting only of inflammation becomes less likely to prevent eventual renal decline. Optimal therapy of SLE nephritis should target both immune and non-immune disease mechanisms.

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Therapeutic Inhibition Of Anti-Apoptotic BCL-2 Family Proteins In a Murine Model Of Lupus Nephritis. Li Chun Wang[1], Stuart Perper[1], Danise Perron[1], Edit Tarcsa[2], Philip Bardwell[1], Neelufar Mozaffarian[3], Andrew Souers[3], Steven Elmore[3], Tariq Ghayur[1] and Lisa Olson[1]. [1]AbbVie Bioresearch Center, Inc, Worcester, MA, [2]AbbVie Bioresearch Center, Worcester, MA, [3]AbbVie, North Chicago, IL.

Background/Purpose: Apoptosis is both a conserved and highly regulated process that is essential for normal development and tissue homeostasis. This process, also known as programmed cell death, is tightly regulated by the BCL-2 family proteins. Dysregulation of these proteins has been linked to survival of autoreactive lymphocytes and to Systemic Lupus Erythematosus (SLE). Inhibition of BCL-2 proteins may therefore ameliorate autoimmunity.

This study evaluated the effects of inhibition of BCL-2 survival proteins in a murine model of lupus nephritis, as well as the effect on human leukocytes ex vivo.

Methods: We have established previously that adenovirus vector-mediated delivery of murine IFN-α in lupus-prone (NZB × NZW)F1 mice induces a rapid and severe disease with many characteristics of SLE, including death due to severe glomerulonephritis. These mice were treated daily with vehicle or 3, 10, 30 mg/kg of navitoclax, a BH3 mimetic that binds with high affinity to BCL-2, BCL-XL, and BCL-W. Mycophenolate (100 mg/kg) was used as a clinical benchmark and positive treatment control. Proteinuria and survival data were presented as Kaplan-Meyer survival curves using Prism. For ex vivo human lymphocyte studies, B and T cells from healthy donors were cultured and treated with navitoclax overnight, prior to flow cytometric analysis. Some cultures were incubated with anti-CD40L/IgM or anti-CD3/CD28 to stimulate B or T cells, respectively. IC50 calculations were performed using GraphPad. Results were considered significant at the level of $p < 0.05$.

Results: BCL-2 family inhibition by navitoclax in the IFNƒÑ-induced (NZB × NZW) F1 lupus model significantly reduced both the incidence of severe proteinuria (> 300mg/dL) and mortality as compared to vehicle controls ($p < 0.05$). In addition, chronic administration of navitoclax at 30 mg/kg demonstrated 95% survival rate and 50% of animals without proteinuria as compared to 80% and 20%, respectively, in mycophenolate-treated animals. Consistent with its mechanism of action, navitoclax caused a dose-dependent reduction in murine lymphocyte counts, which correlated with long-term efficacy. In ex vivo human cell cultures, navitoclax treatment led to a rapid reduction in the numbers of both stimulated and unstimulated human lymphocytes, with B cells showing a higher sensitivity to navitoclax compared to T cells.

Conclusion: Treatment of lupus nephritis-prone mice with the BCL-2 family inhibitor navitoclax resulted in preservation of renal function and overall survival. Furthermore, BCL-2 inhibition in ex vivo human lymphocyte cultures led to a rapid and selective reduction of B and T cells via apoptosis. Taken together, these data support a role for BCL-2 inhibition in the treatment of autoimmune diseases such as SLE.

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Depletion Of The Gut Microbiota Prevents β_2-Glycoprotein I Antibody Production and Mortality In a Model Of Antiphospholipid Syndrome. Silvio M. Vieira, Andrew Yu, Odelya E. Pagovich, Eleni Tiniakou, John Sterpka and Martin A. Kriegel. Yale University School of Medicine, New Haven, CT.

Background/Purpose: Infectious triggers have been implicated in transient antiphospholipid antibody production in both mice and humans. The cause of persistent anti-β_2-glycoprotein I (β_2GPI) antibody production in the lupus-related antiphospholipid syndrome (APS) is unknown. We hypothesize that pathogenic antiphospholipid antibodies in the spontaneous (NZWx-BXSB)F_1 model of APS/SLE are induced and sustained by the gut microbiota that chronically colonizes its host. We therefore generated commensal-ablated animals in order to test if depletion of the microbiota with broad-spectrum antibiotics leads to attenuation of the APS phenotype characterized by multiple non-atherogenic, immune-mediated myocardial infarctions culminating in sudden deaths.

Methods: Broad-spectrum antibiotic- and control water-treated (NZWx-BXSB)F_1 hybrid males were followed until death from autoimmunity. DNA was isolated from fecal pellets (MoBio) and tested for eubacterial load by 16S ribosomal DNA real-time PCR (Bio-Rad). Urine and sera were collected longitudinally and analysed for proteinuria from lupus-related glomerulonephritis and anti-β_2-GPI titers by ELISA (Alpha Diagnostic), respectively. Hematoxylin and eosin-stained slides were prepared from myocardial tissues. Kaplan-Meier survival curves were generated comparing antibiotic- and control water-treated mice.

Results: 16S ribosomal DNA load was profoundly suppressed after treatment with a cocktail of vancomycin, metronidazole, neomycin and ampicillin that was initiated at 6 wks of age. Antibiotic-treated mice had significantly lower titers of anti-β_2GPI antibodies at 4 months of age ($p=0.014$) and were protected from APS-related deaths ($p=0.005$). Ceca were markedly enlarged on necropsy as typical also for germ-free animals. Surprisingly, SLE-related proteinuria, known to be driven by an endogenous retroviral protein, was also suppressed in antibiotic-treated mice compared to controls ($n=7–8$ mice; $p=0.026$).

Conclusion: Depletion of the gut microbiota with a regimen that approximates a germ-free state in the gastrointestinal tract leads to lower anti-β_2GPI titers and protection from APS-induced myocardial infarctions. These results suggest that gut commensals are fundamentally involved in the pathogenesis of APS. Intriguingly, endogenous retroviral-driven proteinuria secondary to lupus nephritis in the $(NZWxBXSB)F_1$ hybrid was also suppressed by this regimen, pointing towards a possible interaction between the gut microbiota and retroviruses in systemic autoimmunity. These findings support an unexpected role of commensals in both APS and SLE. Future work is aimed at identifying the causal triggers within the gut microbiome and dissecting the immunologic mechanisms behind the protective effects in this model.

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Inhibition of Calcium/Calmodulin-Dependent Protein Kinase 4 Ameliorates Th17 Related Autoimmune Disorder. Tomohiro Koga, Christian Hedrich, Masayuki Mizui, Nobuya Yoshida, Linda Lieberman, José C. Crispin and George C. Tsokos. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

Background/Purpose: IL-17-producing T helper (Th17) cells have been causally linked to tissue inflammation in several autoimmune diseases including lupus and multiple sclerosis. Blockade of Th17 action or differentiation could therefore represent a useful therapeutic strategy in these settings.

Methods: We immunized C57B/6 mice or *Camk4* deficient C57B/6 (B6 *Camk4*$^{-/-}$) mice with MOG 35–55 emulsified in complete Freund's adjuvant (CFA) containing Mycobacterium tuberculosis and evaluated the disease activity. MRL/lpr mice were treated with KN-93, an antagonist of calcium/calmodulin-dependent protein kinase IV (CaMK4), and examined IL-17 producing T cell in the spleen and lymph node *in vivo* and *in vitro*. We also tested the number of infiltrated T cell and IL-17 related genes in lungs and kidneys. Furthermore, We compared the methylation status in *Il2* or *Il17A* promoter and the binding capacity of cAMP response element modulator (CREM)-α to these promoters in *Camk4* sufficient or deficetnt conditions. To determine the relevance of our findings to human SLE, we analyzed the effect of CaMK4 inhibition on Th17 cells function in T cells from patients.

Results: Here, we show that KN-93 inhibits Th17 cell differentiation both *in vivo* and *in vitro*. The relevance of this is reflected by the fact that B6 *Camk4*$^{-/-}$ mice suffer less experimental autoimmune encephalomyelitis (EAE) and MRL/*lpr* *Camk4*$^{-/-}$ have decreased autoimmunity and organ damage. Treatment of MRL/*lpr* mice with KN-93 decreases Th17 cell differentiation, prevents double negative T cells from infiltrating lungs and kidneys, and protects against organ damage. In *in vitro* experiments, KN-93 diminishes IL-17 production and reciprocally improves IL-2 production by CD4 T cells cultured under Th17-polarizing conditions. These effects are mediated through the activity of CREM-α that controls epigenetic remodeling of the *Il2* and *Il17a* loci. Analogously, silencing of *CaMK4* in T cells from patients with SLE and healthy controls decreases the expression of *IL17A* upon stimulation in the presence of TGF-β and IL-6.

Conclusion: Collectively, our results suggest that CaMK4 inhibition might be a promising therapeutic agent for autoimmune diseases mediated by Th17 cells.

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Fli-1 Regulates Immune Cell Infiltration Through Affecting Local Chemokine Expression and IL-6 Expression In The Kidney Of Lupus Prone Mice. Shuzo Sato[1], Sarah Williams[2], Eva Karam[1] and Xian Zhang[3]. [1]Medical University of South Carolina, Charleston, SC, [2]Ralph H. Johnson VA Medical Center, Charleston, SC, [3]Medical University of South Carolina and Ralph H. Johnson VA Medical Center, Charleston, SC.

Background/Purpose: Fli-1 expression level, a member of the Ets family of transcription factors, is a mitigating factor in the development of nephritis in murine models of systemic lupus erythematosus. We have reported that reduced expression of Fli-1 in MRL/lpr mice, a murine model of lupus, resulted in significantly prolonged survival and reduced glomerulonephritis. Inflammatory cell infiltration into the kidney plays a critical role in lupus nephritis progression. In kidney, Fli-1 is mainly expressed in endothelial cells in the interstitial capillaries and glomerulus. The role of Fli-1 regarding immune cell infiltration into the kidney is still unclear. We hypothesized that reduced Fli-1 expression affects local chemokine expression, cytokine production and influences immune cell infiltration into the kidney. To investigate this hypothesis, we performed following experiments.

Methods: We generated MRL/lpr transgenic mice expressing green fluorescent protein (GFP), and isolated spleen cells from these mice (6 to 8 months old). One million cells were injected into 9 Fli-1 heterozygous (+/−) and 13 wild-type (WT) MRL/lpr mice (4 to 8-month-old). Mice were sacrificed 18 hours after injection, after that kidneys were removed and frozen sections were made. Inflammatory cells with GFP were counted by immunofluorescence studies. The expression of chemokines (CCL2, CCL3, CCL4, and CCL5) and IL-6 in the recipient kidney was analyzed by real-time PCR. To investigate whether the Fli-1 disruption actually reduces cytokine production *in vitro*, we transfected Fli-1 specific siRNA to the MS1 cells (murine endothelial cell line) and analyzed the supernatant IL-6 concentration after LPS stimulation. In addition, whether Fli-1 directly regulates IL-6 expression by binding IL-6 promoter region, we performed chromatin immunoprecipitation (ChIP) assay using anti-Fli-1 antibody in MS1 cells. Isolated ChIP DNA was amplified by real-time PCR using IL-6 promoter primers.

Results: The infiltrated GFP positive inflammatory cells were significantly decreased in kidneys of Fli-1+/− MRL/lpr mice. The number of infiltrated T cells, B cells and macrophages were also significantly decreased. The relative mRNA expression of chemokines (CCL2, 3 and 4) and IL-6 in the kidney (WT vs Fli-1+/−) showed significantly lower in Fli-1+/− MRL/lpr mice. CCL5 expression was also showed lower trends ($P=0.079$). Fli-1 disruption of MS1 cells using siRNA showed reduced production of IL-6 after LPS stimulation. Furthermore, ChIP assay using IL-6 promoter primers indicated that Fli-1 directly binds to IL-6 promoter regions in murine endothelial cells.

Conclusion: Fli-1 regulates lupus nephritis development by modulating expression of inflammatory chemokines, IL-6 and immune cell infiltration into the kidney.

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Effects Of In Vivo Treatment With Hydroxychloroquine On Endothelial Function In a Murine Model Of Systemic Lupus Erythematosus. Marta Mosca[1], Chiara Tani[1], Sabrina Vagnani[1], Linda Carli[2], Rosaria Talarico[3], Chiara Baldini[3], Stefano Bombardieri[1] and Agostino Virdis[4]. [1]Rheumatology Unit, University of Pisa, Pisa, Italy, [2]GenOMeC PhD, University of Siena, Siena, Italy, [3]Rheumatology Unit, Pisa, Italy, [4]Hypertension Unit, University of Pisa, Pisa, Italy.

Background/Purpose: Antimalarial drugs are a cornerstone of treatment of systemic lupus erythematosus (SLE). It has been suggested that antimalarial drugs may have a protective effect on thrombosis, may be beneficial on lipid profile, may reduce atherosclerosis accrual.

In the present study we aimed at assessing the endothelial function on mesenteric resistance arteries in a mouse model of SLE (NZB/W F1) treated with hydroxychloroquine (HCQ).

Methods: Sixty 12 weeks old female NZB/W F1 mice (mSLE) were divided in 3 groups: group A no therapy, Group B treated with HCQ 3 mg/Kg body weight/day (corresponding to 200 mg/day in humans), group C C56BL/6J (mC) mice as controls. Animals were monitored for 24-hours proteinuria, anti-dsDNA antibodies titers as disease progression parameters and were sacrificed at 18, 24, 30 and 42 weeks of age.

Endothelium-dependent relaxation of small arteries (pressurized myograph), was assessed by infusion of acetylcholine (Ach), while NO availability was assessed by repeating Ach under the nitric oxide synthase (NOS) inhibitor L-NAME.

Results: In Group A, a decline in relaxation to Ach emerged at 18 weeks of age, with a further worsening at 30 and 42. The inhibitory effect of L-NMMA on Ach was reduced at 18 and progressively blunted up to 30 and 42 weeks; interestingly, endothelial dysfunction (ED) appeared simultaneously to a significant increase in 24-hours proteinuria. In group B, HCQ treatment was associated with a significant delay in the appearance of

anti-dsDNA and proteinuria and concomitantly, HCQ prevented the decline of Ach-induced relaxation up to 30 weeks. Starting from this age, the protective effect of HCQ, although still present, was less evident. In group C, relaxation to Ach significantly started to decline at 30 weeks of age with a concomitant reduction of the inhibitory effect of L-NMMA on Ach. The response to sodium nitroprusside (SNP) started to decline at 30 weeks of age in Group A, while was preserved in group C (table 1).

Table 1. ED relaxation

Age (weeks)	18			24			30			42		
	Group A	Group B	Group C	Group A	Group B	Group C	Group A	Group B	Group C	Group A	Group B	Group C
Maximal vasodilation to Ach (%)	90 ± 2	98 ± 2	98 ± 2	81 ± 2	95 ± 1	98 ± 1	69 ± 2	87 ± 1	93 ± 1	63 ± 2	71 ± 1	83 ± 1
Inhibitory effect of L -NMMA on Ach (%)	42 ± 1	*Not done*	52 ± 3	30 ± 2	*Not done*	54 ± 3	10 ± 1	*Not done*	44 ± 1	7 ± 4	*Not done*	35 ± 2
Maximal vasodilation to SNP (%)	99 ± 2	*Not done*	97 ± 3	97 ± 2	*Not done*	98 ± 2	85 ± 3	*Not done*	94 ± 2	76 ± 1	*Not done*	83 ± 2

Conclusion: Treatment with HCQ seems to prevent the occurrence of ED in treated animals, suggesting an early vascular protective effect of this drug. Additional studies are underway to understand whether this observation has to be correlated with disease activity control or reflects an additional independent effect of HCQ.

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Purified IgG From Patients With Systemic Lupus Erythematosus Enhances Apoptosis In Neonatal Rat Cardiomyocytes Exposed To Simulated Myocardial Ischaemic/Reperfusion Injury. Lauren Bourke[1], James McCormick[1], Vera Ripoll[1], Charis Pericleous[1], Anna Radziszewska[2], Anastasis Stephanou[1] and Yiannis Ioannou[2]. [1]University College London, London, United Kingdom, [2]Arthritis Research UK Centre for Adolescent Rheumatology at University College London, Great Ormond Street Hospital and UCLH, University College London, London, United Kingdom.

Background/Purpose: A significant amount of myocardial damage during a myocardial infarction (MI) occurs during the reperfusion stage which is known as ischaemic reperfusion (I/R) injury and can account for up to 50% of cell death. Systemic Lupus Erythematosus (SLE) is a condition associated with a high burden of cardiovascular morbidity and mortality, when compared to the matched healthy population. Patients with SLE have circulating autoantibodies which have been linked to an increased risk of suffering an MI. Studies performed by other groups have shown accelerated I/R injury in other systems such as mesenteric I/R injury in a lupus mouse model, however to date there has been no research focusing on the heart. The purpose of this study is to assess I/R injury in the presence of polyclonal IgG from patients with SLE in an *in vitro* model of simulated myocardial I/R injury in neonatal rat cardiomyocytes.

Methods: Polyclonal IgG was isolated by protein G purification from serum of patients with SLE (n=23) and healthy controls (n=11) which were age and gender matched. Endotoxin was removed using Detoxi-Gel columns to a level below 0.225 endotoxin U/mL. It was observed that cells treated with LPS at this level did not have altered caspase-3 cleavage. Fetal calf serum used in the buffers was also heat inactivated to remove complement mediated mechanisms. We utilised an established *in vitro* model of anoxia/reoxygenation to I/R injury. Cardiomyocytes were isolated from 1–2 day old rat pups and when beating synchronously were treated with 500 μg/ml polyclonal IgG from each group and the following day exposed to simulated I/R injury for 4hr in a hypoxic chamber (argon, 5% CO_2) followed by 4hr of reoxygenation. Apoptosis was measured by assessment of caspase-3 cleavage using immunoblot.

Results: In cells exposed to simulated I/R injury caspase-3 cleavage was not significantly increased in the presence of IgG from healthy volunteers (mean increase in caspase-3 cleavage of cells treated with healthy control IgG above untreated cell baseline − 12.28% ± SD 26.01, n=11). However, in the presence of IgG from patients with SLE, caspase-3 cleavage was increased by 54.79% (±SD 28.9, n=23) above untreated cell baseline and therefore significantly increased in comparison to healthy controls (p=0.0016). The effect observed with IgG from SLE patients was not altered when serum used in the buffers was heat inactivated suggesting a non-complement mediated mechanism.

Conclusion: In this *in vitro* simulated I/R injury model IgG purified from patients with SLE enhanced I/R injury as assessed by caspase-3 cleavage. This novel pathogenic role of these antibodies will now be tested *in vivo* to validate this finding and explore potential mechanisms of action.

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Acyl-CoA Synthetase 1 Expression Is Increased In Murine Models Of Lupus As Well As In Human Systemic Lupus Erythematosus. Eyal Kedar[1], Shelley Barnhart[1], Keith B. Elkon[2] and Karin Bornfeldt[1] [1]University of Washington, Seattle, WA, [2]Division of Rheumatology, Department of Medicine, University of Washington, Seattle, WA.

Background/Purpose: The enzyme acyl-CoA synthetase 1 (ACSL1) converts free fatty acids into their biologically active acyl-CoA derivatives. It is induced by lipopolysaccharide and cytokines (including IFN-gamma and TNF-alpha) and is detected in macrophages in type 1 diabetes mellitus. Increased expression is associated with the inflammatory activation of these cells. ACSL1 promotes membrane phospholipid turnover in activated macrophages, which might contribute to its inflammatory effects. This study was conducted to investigate whether ACSL1 is upregulated in myeloid cells in both human and mouse lupus.

Methods: *Acsl1* mRNA levels were measured in human peripheral blood mononuclear cells of patients with lupus and controls, and in splenocytes of TLR7 transgenic mice. Bone marrow-derived macrophages and thioglycollate-elicited peritoneal macrophages from C57/B6 mice were also stimulated with universal type 1 interferon (5, 50 and 500 U/mL), and *Acsl1* mRNA and protein levels were measured. Finally, C57/B6 mice were injected i.p. with 0.5 mL of pristane, and blood monocytes and bone marrow monocytes were isolated by negative magnetic bead selection two weeks later. Messenger RNA levels of *Acsl1* as well as three lupus interferon signature genes (*Isg15, Irf7* and *Cxcl10*) were determined by real-time PCR.

Results: *ACSL1* mRNA expression was increased in peripheral blood mononuclear cells of patients with lupus (p=0.004) as compared to matched controls. Expression was also increased in splenocytes obtained from the TLR7 transgenic mouse model of lupus (p<0.05). Since *Acsl1* expression was increased in both mouse and human lupus, we asked whether *Acsl1* could be an interferon-stimulated gene (ISG). We observed that *Acsl1* mRNA was induced 3–4 fold by type 1 IFN in thioglycollate-elicited macrophages (p<0.05) and was induced 6–7 fold in bone marrow-derived macrophages (p=0.005), concomitant with an increase in the well-known ISG *Cxcl10*. Acsl1 protein was also increased following interferon stimulation. We observed that *Acsl1* was induced by pristane in bone marrow monocytes (p=0.03), and was positively associated with the rise of the three lupus interferon signature genes in blood monocytes (p<0.05).

Conclusion: This is the first demonstration of increased expression of *Acsl1* in human lupus as well as in mouse models of this disease. These findings demonstrate that ACSL1 is an ISG. The functional significance of these observations are that type 1 IFN's may drive expression of *Acsl1* in lupus, which in turn, given ACSL1's ability to promote membrane phospholipid turnover, may modulate the inflammatory potential of monocytes or macrophages in this disease. The direct variation of *Acsl1* with the three lupus interferon signature genes we studied further suggests a potential signaling role of ACSL1 and/or its downstream metabolites in either the TLR7 or IFN receptor (IFNAR) signaling pathways in lupus.

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The Knock-Out Of TWEAK Receptor/Fn14 Ameliorates Lupus Nephritis In MRL/Lpr Mice. Yumin Xia[1], Leal Herlitz[2], Simona Gindea[1], Jing Wen[1], Rahul Pawar[1], Alexander Misharin[3], Harris R. Perlman[3], Ping Wu[4], Jennifer Michaelson[4], Linda Burkly[4] and Chaim Putterman[1]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]Columbia University Medical Center, New York, NY, [3]Northwestern University, Chicago, IL, [4]Biogen Idec, Cambridge, MA.

Background/Purpose: Renal mesangial cells, podocytes, and tubular cells express Fn14, the sole confirmed receptor for the tumor necrosis factor (TNF)-family member cytokine TWEAK (TNF-like weak inducer of apoptosis). The activation of the TWEAK/Fn14 pathway induces kidney resident

cells to produce multiple proinflammatory mediators as well as promotes their proliferation or death. In the chronic graft-versus-host and nephrotoxic serum models of antibody-mediated renal disease, we had previously found that genetic deficiency of Fn14, or treatment with an anti-TWEAK monoclonal antibody, decreases kidney inflammation and proteinuria without affecting systemic autoantibody titers. These studies suggest that inhibition of TWEAK/Fn14 interactions might be efficacious in the treatment of immune-mediated renal diseases. The purpose of this study was to evaluate the effect of Fn14 deficiency in spontaneous murine lupus nephritis (LN).

Methods: Fn14-knock out (KO) 129 mice were backcrossed for eight generations onto MRL-lpr/lpr (wild type, WT) mice to generate MRL/lpr, Fn14 KO mice. Age and sex-matched MRL/lpr Fn14 WT littermates and MRL/MpJ mice were used as control strains. The severity of renal damage was evaluated by measuring proteinuria and renal function, and immunohistochemical staining of kidney tissues. Immunofluorescent microscopy and transmission electron microscopy (TEM) were performed on frozen kidney sections. The systemic effect of Fn14 KO was assessed by determining the levels of autoantibodies in sera, assessing lymphadenopathy, and analyzing splenocytes numbers and subsets.

Results: We found that at 26 to 38 weeks of age, female MRL/lpr Fn14-WT mice had significantly higher levels of proteinuria, BUN, and serum creatinine as compared to female Fn14-KO mice. Moreover, MRL/lpr Fn14 KO mice had significantly improved renal histopathology, with less glomerular immune deposition, endocapillary hypercellularity, mesangial proliferation, and perivascular inflammation. TEM revealed less electron-dense deposits and fusion of podocyte foot processes along the glomerular basement membrane of Fn14 KO mice. Furthermore, scoring of renal injury markers revealed diminished expression of Ki-67 and TIM-1 in the Fn14-KO mice, while immunofluorescence staining revealed reduced glomerular nephrin expression in the Fn14-WT mice. While the lymphadenopathy score was significantly improved in Fn14-KO mice, there were no differences between the strains in both autoantibody titers (anti-dsDNA, chromatin, ribosomal P, or cardiolipin IgG) at any time point between 26–38 weeks, or in splenocyte subsets at 38 weeks of age, suggesting that TWEAK likely acts by modulating events locally in the kidney.

Conclusion: Our results demonstrate that the inhibition of TWEAK signaling by genetically deleting the Fn14 receptor significantly improved renal damage in spontaneous LN in MRL-lpr mice, suggesting that the TWEAK/Fn14 axis may be a novel therapeutic target for LN.

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Hold The Rituximab: Neuropsychiatric Disease In Murine Lupus Is Not B-Cell Dependent. Jing Wen[1], Ariel Stock[1], Haowei Wang[2], Mark Shlomchik[2], Maria Gulinello[1] and Chaim Putterman[1]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]Yale University School of Medicine, New Haven, CT.

Background/Purpose: Neuropsychiatric disease is one of the earliest clinical manifestations in systemic lupus erythematosus (SLE). However, the mechanisms leading to neuropsychiatric SLE (NPSLE) are not fully understood, and the optimal treatment yet to be defined. In lupus, a compromised blood brain barrier may allow for the passage of circulating autoantibodies into the brain, where they can then induce neuropsychiatric abnormalities. Previous studies have reported that autoantibody titers correlate with the severity of depressive-like behavior, and that injection of anti-ribsomal P and anti-NMDA receptor antibodies into the brain induces neuronal damage and memory deficits. Since antibodies play an important role in lupus pathogenesis, B-cell depletion has been proposed as a targeted treatment approach. To determine if indeed B-cells and/or autoantibodies are instrumental in the pathogenesis of murine NPSLE, we evaluated neuropsychiatric disease in B-cell depleted (JhD/MRL/lpr) and wild type MRL/lpr lupus mice, the latter which are known to develop several cardinal features of human NPSLE.

Methods: Blood and cerebrospinal fluid (CSF) were collected from female JhD/MRL/lpr and MRL/lpr mice at 20 weeks of age. To confirm B cell depletion in JhD/MRL/lpr mice, PBMC were stained with CD19 and analyzed by FACS. Total IgG and IgG anti-DNA antibody concentrations in the serum and CSF were measured by ELISA. Comprehensive neurobehavioral testing including forced swim, anhedonia, open field, object recognition, object placement, and social preference were employed to evaluate the neuropsychiatric manifestations in JhD/MRL/lpr as compared to MRL/lpr mice.

Results: We confirmed that peripheral B-cells were substantially depleted in JhD/MRL/lpr mice, and that autoantibody levels were negligible in the serum and CSF. Nevertheless, we found that in the forced swim test, JhD/MRL/lpr mice showed dramatic depressive-like behavior (as indicated by increased floating time), which was no different than MRL/lpr mice (JhD/MRL/lpr: 56.2%+1.2%, n=7; MRL/lpr: 61.8%+6.9%, n=5; MRL/+: 19.9%+4.7%, n=5). Additionally, JhD/MRL/lpr mice displayed cognitive dysfunction in the object placement (OP) test, as demonstrated by the OP preference score (JhD/MRL/lpr: 40.8%+8%, n=5; MRL/lpr: 50.9%+12.5%, n=5; MRL/+: 66.0%+3.8%, n=5). Furthermore, there were no differences in object recognition and social preference between these two mice strains. However, in the open field test, an increased number of rears were observed in JhD/MRL/lpr mice.

Conclusion: B-cell depleted MRL/lpr mice surprisingly had no attenuation of key features of neuropsychiatric disease, including depressive-like behavior and cognitive dysfunction, despite negligible serum and CSF IgG concentrations. However, an increased number of rears were observed in JhD/MRL/lpr mice, indicating higher motor activity. Thus, constitutive depletion of B-cells was not sufficient to ameliorate lupus-associated neuropsychiatric disease, at least in the MRL/lpr strain. Whether conditional B-cell ablation later on in life will have the same effect remains to be determined.

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Role of TLR3 and dsRNA Hyper-Responsiveness in the Generation of the Lupus-Like Phenotype of New Zealand Black Congenic Mice. Gillian Minty[1], Nan-Hua Chang[2], Kieran Manion[1], Yuriy Baglaenko[1], Evelyn Pau[1] and Joan E. Wither[3]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]Toronto Western Hospital, Toronto, ON, [3]Toronto Western Research Institute, Toronto Western Hospital, University of Toronto, Toronto, ON.

Background/Purpose: New Zealand Black (NZB) mice develop a spontaneous lupus-like autoimmune disease, similar to human systemic lupus erythematosus. Genetic mapping studies have linked loci on NZB chromosome 13 to the generation of the autoimmune phenotype. Consistent with this, congenic mice with a homozygous NZB chromosome 13 interval introgressed onto the C57BL/6 (B6) background (B6.NZBc13 (c13)) develop an autoimmune phenotype that includes: anti-chromatin, anti-ssDNA, anti-dsDNA, and anti-SmRNP autoantibody production, increased B cell activation, marginal zone B cell expansion, increased T cell activation, and dendritic cell expansion. In previous experiments these mice were found to have an apoptosis clearance defect and hyper-responsiveness to the dsRNA TLR3 ligand poly (I:C) that mapped to different areas of the interval. To examine the role of the TLR3 and poly (I:C) hyper-responsiveness in the generation of the c13 autoimmune phenotype, a TLR3 knockout was backcrossed onto the c13 genetic background.

Methods: B6.TLR3$^{-/-}$ and c13.TLR3$^{-/-}$mice were aged to six months and their cellular phenotypes assessed by flow cytometry. B cell responses to TLR agonists were assessed by culturing cells for 2 days and then measuring B cell activation and TLR3 expression by flow cytometry. ELISA assays were used to quantify serum autoantibody production.

Results: Loss of TLR3 on both B6 and c13 genetic backgrounds rendered their splenocytes unresponsive to stimulation with poly (I:C), proving these mice to be true functional knockouts. De-novo B cell activation was attenuated in 6 month old c13.TLR3$^{-/-}$ mice. The expanded marginal zone B cell compartment of c13 mice was also lost in knockout mice. T cell activation was unaffected in c13.TCR3$^{-/-}$ mice, while there was a trend to decreased expansion of the dendritic cell population. Despite impaired B cell activation, autoantibody production was not completely abrogated in c13.TLR3$^{-/-}$ mice: IgG and IgM anti-chromatin antibodies were still produced, while anti-dsDNA and -ssDNA antibody production was attenuated.

Conclusion: Relieving the dsRNA hyper-responsive sensing defect by knocking out TLR3 led to a loss of many of the altered B cell phenotypes in c13 mice but had modest effects on autoantibody production, dendritic cell expansion, and T cell activation. These findings further support the presence

of at least two susceptibility loci within the c13 interval; one responsible for the dsRNA hyper-responsiveness and many of the characteristic B cell abnormalities, and the other which drives the other altered cellular phenotypes as well as chromatin autoantibody production.

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Differential Efficacy Of Human Mesenchymal Stem Cells On Disease In Murine Lupus Based On Source Of Origin. Erin Collins[1], Fei Gu[2], Osama S. Naga[1], Phil Ruiz[3] and Gary S. Gilkeson[1]. [1]Medical University of South Carolina, Charleston, SC, [2]Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston, SC, [3]University of Miami, Miami, FL.

Background/Purpose: Systemic lupus erythematosus (SLE) is a devastating autoimmune disease that targets multiple organ systems. Current treatment options for SLE often cause non-specific immune suppression, which can lead to undesirable side effects. Therefore a new treatment approach with limited harmful side effects, is of particular interest. A population of non-hematopoetic stem cells, mesenchymal stem cells (MSC), are of increasing interest as a therapeutic option for autoimmune diseases such as SLE. MSCs can be derived from various sources such as bone marrow or umbilical cords, and have proven successful at suppressing various immune cells. In this study we examine the efficacy of human MSCs with varying origin on disease in murine based lupus.

Methods: To define the efficacy of human MSCs on murine lupus we harvested MSCs from umbilical cords, healthy donor bone marrow, and lupus patient bone marrow (n=3–4 of each). At disease onset, 15–17 weeks of age, MRL/*lpr* mice were intravenously injected with 1×10^6 MSCs from one of the three MSC origins or PBS. Urine and blood were collected at 2,4,6 and 8 weeks post transfer to examine urine albumin excretion and anti-dsDNA antibody levels. Mice were euthanized at 8 weeks post transfer. Kidneys were collected for pathology and immunohistochemistry. Spleen and bone marrow were harvested to detect presence of plasma cells, B cells, T cells, and Tregs via flow cytometry.

Results: All mice receiving MSCs from the various sources showed improved survival, increased body weight, and decreased proteinuria compared to untreated controls. At 8 weeks post MSC transplant, glomerular IgG, but not C3, deposition was significantly decreased in mice receiving umbilical cord and healthy bone marrow MSCs. However, MSC from lupus patients caused an increase in glomerular C3 and IgG. Additionally, while the glomerular pathology score was significantly reduced in the umbilical cord and healthy bone marrow mouse groups, there was no change in pathology of the lupus MSC group when compared to PBS control mice. Although no differences were seen in the percentage of CD4+ or CD8+ T cells between treatment groups, the lupus MSC group experienced a 2-fold increase in the percentage of Foxp3+ cells in the spleen. These mice also experienced this percentage increase in TCRβ+, B220+, and CD138+ cells in the bone marrow.

Conclusion: Our results indicate that human MSC from various origins all made an impact on the disease severity of lupus prone mice. However, the inability of the lupus patient MSCs to prevent kidney damage suggests that umbilical cord or healthy donor bone marrow MSCs are more effective as disease modulators in vivo. These data indicate that MSCs derived from lupus patients are not a strong candidate for therapeutic intervention in lupus.

Disclosure: E. Collins, None; **F. Gu**, None; **O. S. Naga**, None; **P. Ruiz**, None; **G. S. Gilkeson**, None.

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A Human Monoclonal Antibody Against Domain I Of β2-Glycoprotein I prevents Clotting and Fetal Loss Induced By Polyclonal Anti-Phospholipid Antibodies In Animal Models. Chiara Agostinis[1], Paolo Durigutto[2], Daniele Sblattero[2], Maria Orietta Borghi[3], Claudia Grossi[4], Roberta Bulla[2], Paolo Macor[2], Pier Luigi Meroni[5] and Francesco Tedesco[2]. [1]Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy, [2]Department of Life Sciences, University of Trieste, Trieste, Italy, [3]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, [4]Laboratory of Immuno-rheumatology, IRCCS Istituto Auxologico Italiano, Milan, Italy, [5]Division of Rheumatology, Istituto G. Pini, Milan, Italy.

Background/Purpose: Anticoagulant, antiplatelet or immunosuppressive therapy are currently used to treat the clinical manifestations of the anti-phospholipid syndrome (APS). Side effects or recurrences in spite of the therapy suggest to develop new therapeutic tools.

Methods: We have developed a human minibody containing a single chain fragment variable fused to IgG1 CH2-CH3 domain that recognizes domain I of β2GPI from humans and other animal species.

Results: The minibody is pathogenic inducing clot formation and fetal loss in naive mice. Its biologic effect is complement-mediated as suggested by its ability to promote in-vitro and in-vivo complement deposition and its failure to induce thrombosis in C6 deficient rats and fetal loss in C5 depleted mice. We have further developed a CH2-domain-deleted minibody with the same antigen specificity but that does not activate complement. The minibody variant does not cause vessel occlusion and pregnancy loss and fails to promote complement deposition in mice. The CH2-deleted minibody is able to displace patients' antibodies bound to β2GPI and its passive infusion prevents fetal loss and clot formation induced by the anti-β2GPI antibodies from APS patients.

Conclusion: Our finding pave the way for the use of non pathogenic monoclonal antibody able to compete with the pathogenic polyclonal anti-β2GPI antibodies supporting its potential therapeutic use in patients with APS.

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Contribution Of Marginal Zone B Cells To Autoimmunity In The B6.Sle1.Sle2.Sle3 Lupus Prone Mouse. Ying Yi Zheng and Laurence Morel. University of Florida, Gainesville, FL.

Background/Purpose: We used the B6.Sle1.Sle2.Sle3 triple congenic (TC) mouse, which expresses three lupus susceptibility loci derived from NZM2410 onto the C57BL/6 (B6) background, to investigate how marginal zone B (MZB) cells, a B cell subset enriched with autoreactive clones, contribute to autoimmune pathogenesis. Early B cells entering the spleen are transitional B cells which can differentiate into MZB cells in the presence of Notch2 signaling. Notch2 signaling is initiated when Notch2 receptor (Notch2R) on B cells engage delta like 1 (DL1) ligand on myeloid or stromal cells, and this leads to the transcription of Notch2 target genes, such as Deltex 1 (Dtx1). Previous results indicated that contrary to non-autoimmune B6 mice, a large number of MZB cells in TC mice enter the follicle (FO). This breach of follicular exclusion by TC MZB cells corresponds to a breach of tolerance associated with lupus pathology. We predict that TC MZB cells contribute to autoimmunity by either becoming anti-DNA IgM secreting plasma cells, and/or entering the FO and contributing to germinal centers, either directly as GC B cells or indirectly by shuttling autoantigen, or by activating autoreactive $CD4^+$ T cells which then proceed to activate autoreactive FOB cells that contribute to the anti-DNA antibody (Ab) production.

Methods: Age matched B6 and TC mice from pre- to post-disease onset are used for FACS analysis of MZB and FOB cells, and ELISA detection of autoreactive IgM. Notch2R and DL1 expression were assessed by FACS on B cell subsets and myeloid cells, respectively, in young B6 and TC spleens. Dtx1 expression was measured by quantitative RT-PCR in FACS-sorted MZB and FOB cells. In order to determine whether MZB cell depletion from TC mice will correlate with decrease in autoreactive IgM, old B6 and TC mice were subjected to anti-DL1 monoclonal Ab mediated MZB cell depletion. One week following treatment, the anti-DL1 treated and untreated mice were sacrificed for flow analysis of B cell subsets, immunofluorescence staining of spleen sections, and ELISA detection of autoreactive IgM.

Results: TC mice displayed a preferential expansion of MZB cells and an increased production of autoreactive IgM with progression of disease. TC MZB cells expressed a significantly higher level of Notch2R protein and Dtx1 mRNA than B6 MZB cells. A same trend was observed for TC FOB cells, which express a much lower level of Notch2R than MZB cells. Although DL1 was expressed at a lower level on TC than B6 myeloid cells; there were significantly more $DL1^+$ neutrophils and macrophages in TC than B6 spleens. As previously reported, anti-DL1 treatment depleted B6 MZB cells. The same treatment, however, only partially depleted TC MZB cells, and did not reduce the level of serum anti-DNA IgM.

Conclusion: The preferential expansion of MZB cells with disease progression in TC mice corresponds to an enhanced Notch2 signaling provided by increased expression of Notch2R on MZB cells and a large number of $DL1^+$ myeloid cells. Unlike B6 mice, TC mice are resistant to anti-DL1 mediated MZB cell depletion, which is consistent with a stronger Notch2 signaling. Additional studies are ongoing to determine the role of the Notch2 pathway in the B cells of lupus mice.

Disclosure: Y. Y. Zheng, None; **L. Morel**, None.

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Pneumococcal Polysaccharide Vaccination Regulates T and B Lymphocyte Cytokine Responses and Decreases Kidney Stat1 Levels In MRL/Lpr Mice *In Vivo.* Victor Gazivoda, Shikha Mehta, Luhan Wang, Julia Ash, Kirk E. Sperber and Ioannis Tassiulas. New York Medical College, Valhalla, NY.

Background/Purpose: Zwitterionic polysaccharides can activate CD4+ T cells after processing and presentation by antigen-presenting cells. The 23-valent capsular polysaccharide pneumococcal vaccine, PneumoVax, protects against invasive pneumococcal pneumonia and is indicated for patients with chronic autoimmune diseases and/or on chronic immunosuppressive treatment. The effect of polysaccharide vaccines on the function of cellular immunity and the inflammatory response are not well defined. We studied the immunological effects of pneumococcal polysaccharide vaccination in the MRL/lpr mouse model of lupus, by analyzing the cytokine profile of activated T and B lymphocytes. We also analyzed the effect of polysaccharide vaccination on the expression of Stat1 in the kidney and brain, target organs of inflammation in this mouse model of lupus.

Methods: Eight week old MRL/lpr mice were purchased from Jackson Laboratories. The first group of mice (n=5) vaccinated with PneumoVax (0.5ml of a 23-valent unconjugated pneumococcal polysaccharide vaccine), the second group (n=5) received Mycophenolate mofetil (MMF) (100mg/kgr of body weight) in standard mouse chow, and the third group (n=5) was left untreated. Eight weeks after treatment the mice were sacrificed. T and B lymphocytes were isolated from the spleens. T cells were stimulated with soluble CD3/CD28 beads, PHA and plate bound polysaccharides. B lymphocytes were stimulated with plate bound IgM, plate bound polysaccharide, LPS and a R848. The culture supernatants of the stimulated lymphocytes were analyzed by specific ELISAs for cytokine production of IL-4, IFN-g, IL-17, IL-10, TNF-a and IL-6. Protein extracts were isolated from perfused kidneys. Stat1 and Stat3 protein levels from the extracts were analyzed with Western blotting.

Results: T lymphocytes from PneumoVax vaccinated mice showed differential regulation of cytokine production after CD3/CD28 stimulation, with complete block in IFN-g and IL-17 production compared with the non-vaccinated mice. CD3/CD28-induced IL-4 and TNF production by T cells did not differ in the two groups; however, IL-10 production was significantly increased in the vaccinated group. Interestingly, the decrease in T cell IFN-g and IL-17 production was comparable to the MMF treated group. B lymphocytes from PneumoVax vaccinated mice produced significantly decreased IL-6, IL-10 and TNF in response to plate bound IgM, LPS and R848 stimulation compared to the control group. Analysis of Stat1 protein levels in the kidneys, showed that PneumoVax vaccinated mice had significantly decreased expression compared with the control group, whereas Stat3 levels were not affected.

Conclusion: Pneumococcal polysaccharide vaccination preferentially modulates T and B lymphocyte cytokine responses, after antigen and pattern recognition receptor stimulation in the MRL/lpr mouse model of lupus. Moreover, the expression of Stat1 in the kidneys, a major target organ of inflammation in this model, was significantly decreased in the polysaccharide vaccinated animals. These results suggest that zwitterionic polysaccharides may have a role in re-establishing the immune and inflammatory homeostasis in chronic autoimmune/inflammatory conditions.

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Hydroxycholorquine Is Cardioprotective In Neonatal Rat Cardiomyocytes Exposed To Simulated Myocardial Ischaemic/Reperfusion Injury.-An Effect Mediated Through ERK Phosphorylation. Lauren Bourke[1], James McCormick[1], Anastasis Stephanou[1] and Yiannis Ioannou[2]. [1]University College London, London, United Kingdom, [2]Arthritis Research UK Centre for Adolescent Rheumatology at University College London, Great Ormond Street Hospital and UCLH, University College London, London, United Kingdom.

Background/Purpose: A significant amount of myocardial damage during a myocardial infarction (MI) occurs during the reperfusion stage which is known as ischaemic reperfusion (I/R) injury and can account for up to 50% of cell death. Systemic Lupus Erythematosus (SLE) is a condition associated with a high burden of cardiovascular morbidity and mortality, when compared to the matched healthy population. A large proportion of these patients are treated with the anti-malarial drug Hydroxycholoroquine (HCQ) and whilst retrospective studies have suggested that SLE patients prescribed HCQ have a reduced risk of suffering an MI, inevitably there are patients who still do. Therefore the purpose of this study is to determine whether HCQ has an effect on the injury occurring during the reperfusion stage.

Methods: We utilised an established *in vitro* model of anoxia/reoxygenation to simulate ischaemic reperfusion (I/R) injury. Cardiomyocytes were isolated from 1–2 day old rat pups and when beating synchronously were treated with 1–2 μg/ml HCQ and the following day exposed to simulated I/R injury for 4hr in a hypoxic chamber (argon, 5% CO_2) followed by a time-course of reoxygenation. Total cell death was measured using a colorimetric cell proliferation assay (CellTiter96 Aqueous Cell Proliferation Assay) and apoptosis assessed using a TUNEL kit and assessment of caspase-3 cleavage by immunoblot. The activation of ERK, p-38, JNK and Akt were also assessed by immunoblot.

Results: Treatment of neonatal rat cardiomyocytes with HCQ prior to simulated I/R injury was protective and reduced cell death, specifically apoptosis. This was observed using TUNEL which showed that cells exposed to hypoxia alone saw a 20.7% ($\pm$SD 7.4) increase in TUNEL positivity when compared with cells in optimal conditions. This was further increased to 30.1 % ($\pm$SD 7.0)(p value $<$ 0.001) after reoxygenation and in the presence of HCQ was abrogated back down to16.93 % ($\pm$SD 3.0)(p value $<$0.0001). This was confirmed by an increase in cleaved caspase-3 (0.24 relative to GAPDH ($\pm$SD 0.10) (p value $<$ 0.0001)) in cells exposed to simulated I/R injury when compared to cells in optimal conditions (0.03 relative to GAPDH ($\pm$SD 0.03)). In the presence of HCQ this increase in caspase-3 cleavage was reduced by 54% (0.11 relative to GAPDH ($\pm$ SD 0.06) (p value $<$ 0.01)). The colorimetric cell proliferation assay confirmed that HCQ caused a reduction in total cell death in cells exposed to simulated I/R injury of 57.89%. Correlating with decreased cell death, enhanced ERK phosphorylation in HCQ treated cells was observed in a dose-dependent manner and no significant differences in p38, JNK and Akt were observed. Cells treated with HCQ and exposed to simulated I/R injury were incubated with the ERK inhibitor U1026 and protective effects of HCQ as assessed via caspase-3 cleavage was completely reversed.

Conclusion: HCQ is cardioprotective in this *in vitro* I/R injury model and results suggest this protection is dependent upon up-regulation of ERK phosphorylation. Experiments are now being performed to confirm this observation using an *in vivo* I/R injury animal model.

Disclosure: L. Bourke, None; **J. McCormick**, None; **A. Stephanou**, None; **Y. Ioannou**, None.

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In Vivo Therapeutic Success Of Microrna-155 (miR-155) Antagomir In a Mouse Model Of Lupus Pulmonary Hemorrhage. Shiyu Zhou[1], Dong Liang[2], Xinfang Huang[3], Chunyuan Xiao[3], Yuanjia Tang[1], Qian Jia[3], John B. Harley[2] and Nan Shen[1]. [1]Shanghai Institutes for Biological Sciences Chinese Academy of Sciences & Shanghai Jiao Tong University School of Medicine, Shanghai, China, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Shanghai Institute of Rheumatology, Renji Hospital, Shanghai Jiao-Tong University School of Medicine, Shanghai, China.

Background/Purpose: MiR-155 is a typical pleiotropic miRNA that participates in various aspects of immunity. Previous in vitro studies indicated that it is both a pro-inflammatory and an anti-inflammatory regulator.

Furthermore, studies in multiple mouse models (LPS shock, EAE, and CIA) revealed a pathogenic role of this miRNA in the development of tissue damage. Also, miR-155 is abnormally overexpressed among different lupus mouse models. However, aspects of the role of miR-155 in lupus acute tissue damage remain unclear. In this study, we systemically examined the role of miR-155 in the development of pulmonary hemorrhage (PH) in Pristane-induced lupus, by assessing the effect of the administration of chemically modified complementary oligonucleotides of miR-155, called the miR-155 antagomir.

Methods: Pristane-induced PH mouse model was established as previously reported. Briefly, miR-155 knockout (KO) and wild type (WT) control mice received a single i.p injection of 0.5 ml pristane. After 14 days, lung tissues were collected for pathologic assessment. The dynamic expression of miR-155 was evaluated 1, 3, 7, 14 days post Pristane injection. In intervention experiments, the mice were divided into two groups, receiving respectively three consecutive i.v injections of miR-155 antagomir (miRNA inhibitor) (n=5) or random sequence antagomir negative control (n=5) 3 days before Pristane injection. Two weeks later, the prevalence of PH was evaluated by H&E staining. Total lung RNAs were assayed by qPCR or subjected to gene profiling. Gene profiling data was analyzed by IPA software. Serum cytokines were messured by Bio-plex Pro™ Assays.

Results: We showed that miR-155 was elevated in lung tissues in the process of PH induced by Pristane. MiR-155 KO mice appeared to develop attenuated PH, with reduced levels of pro-inflammatory cytokines (TNF-a, IL-6, IL-1β) in sera and target tissues. IPA analysis of gene profiling data indicated that IL-6 signaling pathway was dramatically activated in WT mice but not in miR-155 KO mice 7 day post pristane injection. By integrating the gene expression profiling data from miR-155 KO mice with microRNA target predication, our data suggest that PPARα, an anti-inflammatory transcription factor, is a novel functional target of miR-155. Furthermore, we showed that in vivo silencing of miR-155 by a synthetic miRNA inhibitor—miR-155 antagomir significantly ameliorated PH induced by Pristane (miR-155 antagomir: 20% PH; random sequence antagomir negative control: 80% PH). Consistently, the pro-inflammatory cytokines (TNF-a, IL-6, IL-1β) were reduced upon miR-155 silencing.

Conclusion: Overall, our study shows that knockdown of miR-155 by miR-155 antagomir inhibits Pristane induced PH through reducing the production of pro-inflammatory cytokines. This finding suggests a promising therapeutic potential of miR-155 antagonist in the treatment of acute lung inflammation in lupus and reinforces the conclusion that antagomir may prove to be a very effective general therapeutic strategy for human disease.

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Protective Effect Of Inducible Adeno-Associated Virus Mediated IL-2 Gene Therapy On Tissue Damages In Lupus-Prone Mice. Masayuki Mizui[1], Tomohiro Koga[1], Linda Lieberman[1], Jessica Beltran[1], Mark C. Johnson[2], José C. Crispin[1], Roland Tisch[2] and George C. Tsokos[1]. [1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC.

Background/Purpose: IL-2 plays critical roles not only in immune responses but also in peripheral tolerance. Impairment of IL-2 production has been linked to the development and progression of autoimmune diseases such as type 1 diabetes and systemic lupus erythematosus (SLE).

Methods: We investigated the effect of IL-2 on lupus disease development using tetracyclin-inducible recombinant adeno-associated virus (rAAV) encoding IL-2 in MRLFas$^{lpr/lpr}$ (MRL/lpr) mice.

Results: IL-2 treatment significantly decreased the levels of CD3+CD4-CD8- double-negative (DN) T cells and increased the numbers of CD4+CD25+Foxp3+ Treg cells in the spleen and lymph nodes. Autoantibody production was not changed by rAAV treatment. Notably, IL-2 supplementation ameliorated inflammatory damage in several tissues including skin, lungs and kidneys. This effect was associated to decreased infiltration of mononuclear cells into kidneys and lungs and reduced expression of inflammatory cytokines and chemokines. DNT cells preferentially produced IL-17 in aged MRL/lpr mice, therefore, reduction of DNT cells by IL-2 could be associated with the attenuation of tissue inflammation. To further examine the specificity of the IL-2 effect on T cell subsets, we used an IL-2/anti-IL-2 monoclonal antibody (mAb) complex-mediated targeting delivery system. Delivery of IL-2 to non-Treg cells rather than Treg cells effectively reduced DNT cells. However, IL-2 to both non-Treg and Treg cells attenuated inflammatory cell infiltration into kidneys.

Conclusion: These results suggest that IL-2 therapy can regulate T cell populations in the periphery and normalize the aberrant T cell activation programs leading to inhibition of organ damage in lupus-prone mice.

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Immunization With Hepatitis B Vaccine Accelerates SLE-Like Disease In An Animal Model. Nancy Agmon-Levin[1], María Teresa Arango[2], Shaye Kivity[3], Aviva Katzav[4], Boris Gilburd[5], Miri Blank[6], Juan-Manuel Anaya[7], Gisele Zandman-Goddard[8], Joab Chapman[9] and Yehuda Shoenfeld[10]. [1]The Zabludowicz Center for Autoimmune Diseases, Tel-Hashomer, Israel, [2]Doctoral Program in Biomedical Sciences Universidad del Rosario, Bogota, Colombia;Center for Autimmune Diseases Research – CREA, Universidad del Rosario,, Bogota, Colombia, [3]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, affliated to Sackler Faculty of Medicine, Tel-Aviv University Israel, Tel-Aviv, Israel, [4]Department of. Neurology and Sagol Neuroscience Center, Sheba Medical Center,Tel-Hashomer, Ramat Gan, Israel, [5]The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel, [6]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, affiliated to Sackler Faculty of Medicine,Tel Aviv University, Tel-Aviv, Tel-Aviv, Israel, [7]School of Medicine and Health Sciences, Universidad del Rosario. Center for Autoimmune Diseases Research (CREA), Bogotá, Colombia, [8]Wolfson Medical Center; Sackler Faculty of Medicine, Tel-Aviv University, Holon, Israel, [9]Department of. Neurology and Sagol Neuroscience Center, Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel, [10]Sheba Medical Center, Ramat Gan, Israel.

Background/Purpose: Hepatitis-B vaccine (HBVv) was proven to be successful and cost effective in preventing HBV infection and associated liver disease. However, in recent years concerns were raised regarding its safety, particularly among patients with autoimmune diseases (i.e. SLE)[#]. Additionally, the Aluminum adjuvant included in HBVv has been related to immune mediated adverse events. Thus, in the current study we set to evaluate the effects of immunization with HBVv or Alum in an animal model of SLE.

Methods: Three groups of 20 NZB/W F_1 mice (Jackson Laboratory, Bar Harbor, ME), were immunized with HBVv (Engerix), Aluminum hydroxide (Alum) or phosphate buffered saline (PBS) at 8 and 12 weeks of age. Mice were followed for weight, autoantibodies titers, blood cell accounts, urine protein, kidney histology and neurocognitive functions (i.e. novel object recognition, staircase, Y-maze and the forced swimming tests).

Results: Mice immunized with HBVv had significantly higher titers of anti-dsDNA antibodies ($p<0.01$), accelerated proteinuria ($p<0.05$) and advanced kidney damage on biopsy compared to those immunized with PBS or Alum. Mice immunized with HBVv or Alum had decreased cells counts and hemoglobin levels ($p<0.001$) compare with mice immunized with PBS. Similarly, long and short term memory were significantly decreased following immunization with HBVv or Alum ($p<0.01$). Mice immunized with alum displayed anxiety-like behavior.

Conclusion: Herein we have found that immunization with the HBVv accelerates kidney disease in an animal model of SLE-like disease. Both Alum and HBVv, which contains alum as an adjuvant, affected blood counts and neurocognitive functions. Further studies are required to elucidate the mechanisms by which different ingredient of HBVv affect SLE-like disease in animal models.

[#] *Agmon-Levin N, et al. Ten cases of systemic lupus erythematosus related to hepatitis B vaccine. Lupus. 2009;18:1192-7.; Bassi N, et al. Induction of the* 'ASIA' *syndrome in NZB/NZWF1 mice after injection of complete Freund's adjuvant (CFA). Lupus. 2012;21:203-9.*

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Absence Of Estrogen Receptor Alpha Reduces The Number and Function Of Bone Marrow Derived Plasmacytoid Dendritic Cells In Lupus Prone Mice. Jennifer Scott[1], Osama S. Naga[1], Melissa A. Cunningham[2], Jena Wirth[2], Jackie G. Eudaly[1] and Gary S. Gilkeson[1]. [1]Medical University of South Carolina, Charleston, SC, [2]MUSC, Charleston, SC.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that affects women at a 9:1 ratio compared to men. Previous work in our laboratory showed that estrogen receptor alpha (ERα) deficient lupus prone mice have increased survival and less renal disease compared to wild type lupus prone mice. ERα deficient mice are protected from disease despite unaltered autoantibody levels and kidney IgG and C3 deposition. We hypothesize that ERα deficiency improves SLE by reducing the innate immune system's ability to respond to immune activation. To study the innate immune response this research focuses on the role of ERa in plasmacytoid dendritic cells (pDC) and their Toll-like receptor (TLR) mediated production of type I interferon (IFN).

Methods: Bone marrow was harvested from WT and ERα deficient B6 and NZM2410 lupus prone mice. The bone marrow was cultured with IL-4 and GM-CSF or Flt3 ligand under estrogen free conditions to enrich for conventional DCs or pDCs respectively. After 8 days of culture, cells were stimulated with TLR 7 and 9 agonists or PBS control for 24 hours. The cells were stained for flow cytometry or RNA was extracted. pDCs were defined as $CD11c^+$, $PDCA1^+$, or $SiglecH^+$ and an intracellular IFNα stain was used to identify IFNα producing cells. qRT-PCR was used to measure the expression of the interferon signature genes ISG-15, CXCL-10, IRF7, MX-1, and IFNβ. Ex vivo experiments were preformed on bone marrow and spleens. Bone marrow and spleen single cell suspensions were stained for flow cytometry. pDCs were identified as $B220^+$, $SiglecH^+$, $PDCA1^+$, and $CD11c^{int}$.

Results: ERα deficiency significantly reduces TLR 7 and 9 ligand mediated expression of type I IFN signature genes in bone marrow derived DCs from lupus prone mice. Since pDCs produce large amounts of type I IFN, we investigated the impact of ERα on pDC development and IFNα production. When total bone marrow from healthy mice was cultured with Flt3L under estrogen free conditions, ERα deficiency significantly reduced the number of IFNα producing cells in response to TLR 7 and 9 ligands. ERα deficiency also significantly reduced the percent of pDCs obtained from estrogen free Flt3L cultures of bone marrow. Wild-type bone marrow yielded 25% (±1.3%) pDCs and ERα deficient bone marrow yielded 8% (±.63%) pDCs. Using the same culture conditions, a similar trend was seen in NZM 2410 and SLE1,3 mouse models. To determine if ERα deficiency alters pDC numbers in vivo, bone marrow and spleen pDC numbers are being investigated ex vivo. Preliminary data suggests ERα deficiency reduces the percent of pDCs in bone marrow while the percent and number of spleen pDCs remain unchanged.

Conclusion: ERα deficiency reduces the TLR mediated type I IFN response in bone marrow derived dendritic cells from lupus prone mice under estrogen free conditions. The absence of ERα also reduces the percentage of IFNα producing cells and pDCs yielded in estrogen free bone marrow cultures. These findings suggest that the in vivo disease modulating effect of ERα is mediated via impacts on the development and response of pDCs.

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ACR Poster Session A
Systemic Lupus Erythematosus - Clinical Aspects I - Renal, Malignancy, Cardiovascular Disease
Sunday, October 27, 2013, 8:30 AM–4:00 PM

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Oral Candidiasis in Systemic Lupus Erythematosus. Monthida Fangtham, Hong Fang and Michelle Petri. Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: *Candida* is the most common opportunistic fungal infection identified in SLE. In a previous autopsy study, 14 percent of deaths in SLE patients were associated with *Candida* infection. We assessed the frequency of oral candidiasis and the association between demographic variables, disease-related variables, corticosteroid treatment, other treatments and the occurrence of oral candidiasis in the Hopkins Lupus Cohort.

Methods: In a prospective cohort study of 2,209 SLE patients, there were 92% female, 56% Caucasian, and 37% African-American patients. There were 318 (14.4%) patients with oral candidiasis. Among these 318 patients, 124 (39.0%) patients had more than 1 episode of oral candidiasis. The demographic, clinical and treatment associates of oral candidiasis were determined by univariate and multivariate analyses.

Results:

Variable	Odds Ratio (95% CI)	p-value*
African-American ethnicity (vs Caucasian)	2.6 (1.8, 3.7)	< .0001
Smoking	1.1 (0.7, 1.5)	0.79
Depression	1.1 (0.8, 1.5)	0.69
Prednisone dose (mg/day)	1.02 (1.01, 1.03)	0.0004
Hydroxychloroquine use	0.8 (0.6, 1.1)	0.11
Immunosuppressive use	1.4 (1.0, 2.0)	0.046
White blood count (per 1,000)	1.04 (0.99, 1.10)	0.10
Low C3	1.0 (0.6, 1.6)	0.99
Serum creatinine (mg/dl)	1.1 (0.9, 1.3)	0.26
Urine protein/creatinine ratio	1.1 (1.0, 1.2)	0.0048
Bacterial infection	1.6 (1.1, 2.3)	0.024

* Generalized estimating equations were used to account for multiple observations on the same patient

In the multivariable model, African-American ethnicity, prednisone, prednisone dose (in mg), immunosuppressive use, a history of bacterial infection and the urine protein to creatinine ratio remained significant. The use of hydroxychloroquine lowered the risk of oral thrush, but was not statistically significant.

Conclusion: This study identified multiple risk factors for oral candidiasis in SLE. African-American ethnicity, one of the strongest predictors, has never been recognized in previous studies. Prednisone use, prednisone dose (in mg), immunosuppressive use, and a history of bacterial infection were expected risk factors. Secondary Sjogren's syndrome, which we had hypothesized would be a risk factor, was not. Proteinuria had an independent association beyond the effect of prednisone and immunosuppressive use. Treatment with hydroxychloroquine reduced the risk, but was not statistically significant in the multivariate models.

Disclosure: M. Fangtham, None; **H. Fang**, None; **M. Petri**, None.

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Association Of Psoriasis and Psoriatic Arthritis With Systemic Lupus Erythematosus. Ashwini Shadakshari, Jianghong Yu and Andras Perl. SUNY Upstate Medical University, Syracuse, NY.

Background/Purpose: There is a paucity of literature on the prevalence of psoriasis (Ps) and psoriatic arthritis (PsA) in patients with systemic lupus erythematosus (SLE). To determine whether there are overlaps among these autoimmune diseases, we investigated the prevalence of Ps and PsA in patients with SLE.

Methods: We examined the prevalence of Ps and PsA in 445 patients with SLE based on history, physical examination, laboratory and radiological studies performed between 01/01/1990 and 07/31/12. A diagnosis of psoriasis was made by a dermatologist or rheumatologist while the diagnosis of PsA was made on the basis of CASPER criteria (Arth Rheum 2006; 54: 2665). The diagnosis of SLE was based on ACR criteria (Arth Rheum. 1997; 40: 1725). Prevalence of SLE diagnostic criteria were compared between SLE patients with and without Ps (SLE/Ps+ and Ps-) and with and without PsA (SLE/PsA+ and PsA-). Statistical analyses were performed with chi-square test using Graphpad Prism software with $p<0.05$ considered significant.

Results: Among 445 patients with SLE, 23 (5.1%) had Ps, out of which 20, (4.5%) patients had PsA. In the general population, the prevalence of Ps and PsA are estimated to be 2% (Rev Bras Reumatol. 2012; 52: 630) and 0.25% (Rev Bras Reumatol. 2012;52:98), respectively. Therefore, the prevalence of PsA, but not Ps, was increased in SLE patients ($p < 0.0001$). The prevalence of malar rash, discoid rash, photosensitivity, and arthritis were increased while antiphospholipid antibodies were less common in SLE patient with concurrent Ps and PsA (Table 1). There was no significant association of Ps or PsA with seizures, psychosis, oral ulcers, serositis, proteinuria, anemia, leucopenia, thrombocytopenia, hemolytic anemia, anti-Sm, or anti-DNA.

Table 1. Prevalence of SLE diagnostic criteria in patients with (SLE/Ps+) and without psoriasis (SLE/Ps+) as well as in patients with (SLE/PsA+) and without psoriatic arthritis (SLE/PsA+) in a cohort of 445 SLE subjects. The data were analyzed with chi-square test.

		Malar Rash	Discoid Rash	Photosensitivity	Arthritis	APLA
SLE/Ps+	Present	11	4	13	21	1
	Absent	12	19	10	2	22
SLE/Ps-	Present	118	21	142	211	108
	Absent	304	401	280	211	314
p value		0.0409	0.0118	0.025	0.0001	0.021
SLE/PsA+	Present	10	4	12	20	1
	Absent	10	16	8	0	19
SLE/PsA−	Present	119	21	143	213	108
	Absent	306	404	282	212	317
p value		0.0341	0.0043	0.0156	< 0.0001	0.038

Conclusion: PsA has increased prevalence in patients with SLE. Subjects with overlapping Ps and PsA may represent a distinct clinical entity within SLE.

Disclosure: A. Shadakshari, None; **J. Yu**, None; **A. Perl**, None.

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Monitoring Of Opportunistic Virus Infections In Systemic Lupus Erythematosus. Lorenzo Cavagna[1], Sandra Calarota[2], Eva Scorletti[1], Roberto Caporali[3], Francesca Rovida[4], Carlomaurizio Montecucco[5] and Fausto Baldanti[4]. [1]University and IRCCS Foundation Policlinico S. Matteo, Pavia, Italy, [2]IRCCS Foundation Policlinico S. Matteo, Pavia, Italy, [3]Division of Rheumatology, IRCCS Policlinico San Matteo Foundation and University of Pavia, Pavia, Italy, [4]IRCCS Foundation Policlinico S. Matteo,, Pavia, Italy, [5]University and IRCCS Policlinico S. Matteo Foundation, Pavia, Italy.

Background/Purpose: due to disease characteristics and treatment approaches, systemic lupus erythematosus (SLE) patients are at high risk of opportunistic virus infections, as for example Epstein Barr virus (EBV) and human cytomegalovirus (hCMV). These viruses may complicate disease course, mimic SLE manifestations and have also been involved in SLE pathogenesis. An integrated clinical, virological and immunological monitoring may allow early diagnosis, characterization and right treatment of SLE patients. Aim of our study is to analyze the prevalence of both EBV and hCMV opportunistic infections in SLE and their relationship with disease characteristics/activity.

Methods: from 2/15/2013, after ethical committee approval and informed consent collection, adults SLE patients (1997 ACR classification criteria) referring consecutively to our Lupus Unit have been enrolled in this study. Quantification of EBV DNA and CMV DNA in blood was performed by real-time PCR. Detailed information regarding demographic characteristics and clinical data (disease duration, SLEDAI 2k score, occurrence of kidney involvement, etc) were obtained from the patients' medical records. Patients were stratified according to the degree of pharmacological immunosuppression (Group 1= hydroxychloroquine and/or prednisone≤5 mg/day; group 2= methotrexate/azathioprine/cyclosporine and/or prednisone>5 and <12.5 mg/day; group 3= mycophenolate mofetil/rituximab and/or prednisone≥12.5 mg/day).

Results: a total of 64 SLE patients (59 females/5 males) have been analyzed (table 1). Group 1 consisted of 20 patients, group 2 of 19 patients and group 3 of 25 patients. Although no patients were suspected for viral infection, 27 (42.2%) patients had detectable DNA either of EBV (n=24) or hCMV (n=1) or both (n=2). Viral load was generally low. Patients' age, disease duration, SLEDAI 2k score and kidney involvement did not significantly influenced viral DNA load. In group 2, detection of viral DNA was significantly higher than group 3 (p=0.0136), while no differences were observed between group 1 and 2 (p=0.3406) and group 1 and 3 (p=0.2047). Group 2 patients with detectable virus DNA (n=12) were mainly on methotrexate (n=8) and cyclosporine (n=3).

Conclusion: in our patients a high prevalence of EBV DNA and, to a lesser extent, hCMV DNA in blood has been observed. Detection of viral DNA is not related to disease and patients characteristics. However, patients treated with methotrexate and cyclosporine (group 2), were more prone to have viral DNA load with respect to patients treated with mycophenolate mofetil, rituximab or high dose corticosteroids. Our results suggest suggested the need of a careful monitoring of SLE patients for the increased risk of EBV and hCMV infections. Analyses to better understand how virus-specific immune responses relate to opportunistic viral infections in SLE patients are ongoing.

Table 1. main characteristics of patients up to now enrolled,

	Virus DNA +ve (blood)	Virus DNA –ve (blood)	p
Patients number	27	37	\
EBV DNA +	24	\	\
hCMV DNA +	1	\	\
EBV and hCMV DNA +	2	\	\
EBV DNA (copies/ml; median-IQR)	196 (115–478)	\	\
CMV DNA (copies/ml; median-IQR)	200 (150–600)	\	\
Age (years; mediana-IQR)	56 (41.5–59.5)	44 (33–52)	0.0666*
Disease duration (months; median-IQR)	118 (75–152)	84 (6–154)	0.5278*
SLEDAI-2K score (median –IQR)	2 (2–4)	2 (2–4)	0.9967*
Kidney involvement (history)	6	15	0.1893μ
Group 1 (low level immunosuppression)	9	11	0.3406 (vs group 2)μ
Group 2 (medium level immunosuppression)	12	7	0.0136 (vs group 3)μ
Group 3 (high level immunosuppression)	6	19	0.2047 (vs group 1)μ

* independent sample T test, μ Fisher's exact test.

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Is An Excess Risk Of Attention Deficit Hyperactivity Disorder In Children Born To Women With SLE Mediated By In Utero Drug Exposures? Preliminary Data From The O S L E R Cohort. Evelyne Vinet[1], Susan Scott[2], Christian A. Pineau[1], Lawrence Joseph[3], Ann E. Clarke[1], Eric Fombonne[4], Robert W. Platt[3] and Sasha Bernatsky[5]. [1]McGill University Health Center, Montreal, QC, [2]McGill University Health Centre, Montreal, QC, [3]McGill University, Montreal, QC, [4]Oregon Health and Sciences University, Portland, OR, [5]Research Institute of the McGill University Health Ctre, Montreal, QC.

Background/Purpose: Women with SLE display autoantibodies (e.g. anti-N-methyl-D-aspartate receptor antibodies) and cytokines (e.g. interleukin-6), which, in animal models, alter fetal brain development and induce behavioural anomalies in offspring. To date, no one has specifically assessed the risk of attention deficit hyperactivity disorder (ADHD) in children of SLE mothers. Using the "Offspring of Systemic Lupus Erythematosus mothers Registry (OSLER)", we aimed to determine if children born to SLE mothers have an increased risk of ADHD compared to children born to mothers without SLE.

Methods: OSLER is a large population-based cohort, which includes all women who had ≥1 hospitalization for delivery after SLE diagnosis, identified through Quebec's universal healthcare databases (1989–2009). OSLER also includes a randomly selected control group of women, matched at least 4:1 for age and year of delivery, who did not have a diagnosis of SLE prior to or at the time of delivery. We identified children born live to SLE mothers and their matched controls, and ascertained ADHD based on ≥1 hospitalization or physician visit with a relevant diagnostic code, through to end of database follow-up.

We performed multivariate analyses to adjust for maternal demographics, sex and birth order of child, and obstetrical complications. In a subsample analysis of children with maternal public drug coverage throughout pregnancy, we further adjusted for relevant maternal medications.

Results: 509 women with SLE had 719 children, while 5824 matched controls had 8493 children. Mean maternal age and follow-up were respectively 30.3 [standard deviation (SD) 5.0] and 9.1 (SD 5.8) years. Children born to women with SLE had more records of ADHD diagnoses [9.9% (95% CI 7.9, 12.3) vs 6.1% (95% CI 5.6, 6.6)]. Mean age at ADHD diagnosis was older in offspring of SLE mothers (12.5 years, 95% CI 11.7, 13.3) as opposed to controls (7.8 years, 95% CI 7.5, 8.1).

In multivariate analysis (Table 1), children born to women with SLE had substantially increased risk of ADHD (HR 1.73, 95% CI 1.25, 2.40) versus controls. Interestingly, in the subsample analysis further adjusting for in utero drug exposures (n=1925), there was no longer a clear association of SLE with

an increased risk of ADHD (HR 0.97, 95% CI 0.41, 2.28). However, in utero exposure to antidepressants appeared to be associated with a substantially increased risk of ADHD (HR 3.70, 95% CI 1.38, 9.94).

Conclusion: Compared to children from the general population, children born to women with SLE appear to have an increased risk of ADHD. Our evidence suggests that the excess risk of ADHD in SLE offspring might be mediated by in utero drug exposures.

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Ultrasonographic Findings and Inter-Observer Reliability In Danish Patients With Systemic Lupus Erythematosus - a Comparison With Clinical Examination Of Wrist and Hand Joints. Lene Dreyer[1], Søren Jacobsen[2], Lars Juul[3] and Lene Terslev[4]. [1]Copenhagen University Hospital at Gentofte, Copenhagen, Denmark, [2]Department of Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [3]Copenhagen University Hospital at Gentofte, Copenhagen, Denmark, [4]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark.

Background/Purpose: Patients with systemic lupus erythematosus (SLE) frequently encounter problems of musculoskeletal origin including arthralgia, tenosynovitis and arthritis in varying degrees of severity. Some patients develop hand deformities probably because of undetected inflammation in joints and tendons. Data on the sensitivity of clinical joint examination and inter-observer reliability of the Ultrasound (US) findings in SLE patients are limited. We aimed to determine 1) US findings in patients with SLE with and without clinical symptoms of arthritis in the hand and to compare findings with clinical evaluation 2) to determine the inter-observer reliability of the US findings.

Methods: Thirty-three female SLE patients with or without hand arthralgia (HA) at time of examination were included. They were examined twice by US by 3 trained examiners. B-mode and Doppler examination was performed of the wrist and MCP joints for synovitis and erosions and the extensor and flexor tendons at the wrist level for signs of tenosynovitis using a GE Logiq 9 US machine with Doppler settings for slow flow. All patients underwent clinical joint evaluation and were compared to 11 healthy controls (CTRLs).

Results: Among the 33 SLE patients 16(48%) had wrist synovitis +/−Doppler activity on US which was only observed in 1 CTRL (9%) ($p=0.03$). Corresponding figures for any mcp joint were 12(36%) and 0(0%) ($p=0.02$). In 21% of the SLE patients tenosynovitis was found and in 6% bone erosions in hands. Wrist synovitis +/−Doppler activity was observed significantly more in SLE patients (81%) with arthralgia in hands at time of US examination compared to patients with no symptoms (18%) ($p=0.0005$), for MCP joints this was 63% and 12% ($p=0.0071$), respectively. US findings were observed in 44% of 25 wrists of SLE patients with no tenderness at clinical examination and in 46% of 26 wrists with no swelling. Corresponding figures for 2mcp joints were 27% and 21%. The inter-observer reliability was good to excellent for MCP joints, wrists and tendons.

Conclusion: A majority of SLE patients with arthralgia in hands have US signs of synovitis, erosions and tenosynovitis indicating subclinical disease. Clinical joint examination underestimates synovitis in SLE patients compared to US examination. Good to excellent agreement for inter-observer reliability was found in US evaluation of hand joints in SLE patients. These results indicate that US examination of hand is a clinically reliable and sensitive diagnostic modality in SLE.

Disclosure: L. Dreyer, None; **S. Jacobsen**, None; **L. Juul**, None; **L. Terslev**, None.

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Switching Treatment Between Mycophenolate Mofetil and Azathioprine In Lupus Patients The Reasons and The Effect. Hesham Al Maimouni, Dafna Gladman, Dominique Ibanez and Murray B. Urowitz. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Disease activity in systemic lupus erythematosus is an important predictor of subsequent organ damage and mortality from lupus. However, the optimal agent for chronic immunosuppression of SLE is unknown. Our aim was to determine the reasons for changing treatment from MMF to AZA or vice versa in lupus patients and to evaluate the effect of the change.

Methods: Medical records of 92 lupus patients in whom treatment were changed from MMF to AZA or vice versa were reviewed. Global disease activity in the 6 months prior to the change in therapy and 6 months after the change was calculated using the Adjusted Mean SLEDAI (AMS) a validated measure of disease activity over time. The AMS was then calculated for both its clinical and laboratory parameters individually. The reasons for changing therapy were identified. AMS was compared in the 6 months prior to and after the switch using GEE adjusting for repeated measures.

Results: We identified 92 lupus patients in whom treatment was switched once in 80, twice in 8 and three times in 4 with total of 108 times between MMF and AZA. There were 89 switches from AZA to MMF: 76 (85.4%) for drug failure; 11 (12.4%) for side effects; 2 (2.2%) for renal transplant. There were 19 switches from MMF to AZA: 7 (36.8%) for pregnancy; 8 (42.1%) for side effects; 3 (15.8%) for drug failure and 1 (5.3%) for financial issues. There was a statistically significant improvement in AMS in the 6 months after drug switching compared to the 6 months prior to the switch when the reason was a drug failure, (11.2 ± 6.1) vs. (9.1 ± 5.7 $p<0.0001$).The improvement in the laboratory component was most significant ($p=0.0006$) and clinical component showed only a trend ($p=0.08$). There was no statistically significant deterioration in AMS or its clinical and laboratory components in 6 months after drug switching when the reason for the switch was a side effect, pregnancy, financial or other, AMS (6.7 ± 4.6)vs. (5.9 ± 4.6 $p<0.33$). Side effects occurred in 15 of 19 of the total group who switched (78.9%) and persisted in 4(21.1%) after drug switching. Modeling to adjust for repeated measures confirmed the results.

Conclusion: Switching from azathioprine to MMF is most often due to azathioprine failure and in that case a statistically significant improvement in disease activity occurs. When AZA is used to replace MMF, often due to pregnancy, there is no statistically significant deterioration in AMS. Switching between MMF and AZA for side effects usually resulted in elimination of the side effect.

Disclosure: H. Al Maimouni, None; **D. Gladman**, None; **D. Ibanez**, None; **M. B. Urowitz**, None.

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Lupus Nephritis Flares Precipitated By Switching From Mycophenolate Mofetil to Azathioprine in Pre-Pregnancy Planning. Natasha Jordan and David D'Cruz. Louise Coote Lupus Unit, St Thomas' Hospital, London, United Kingdom.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease that affects women of childbearing age. Lupus nephritis is a major cause of morbidity and mortality in SLE and is characterized by unpredictable exacerbations and remissions. Following induction therapy of lupus nephritis, patients are generally maintained in remission by either mycophenolate mofetil or azathioprine. Pre-pregnancy planning is an important aspect of the clinical management of lupus nephritis. Due to potential teratogenicity, the use of mycophenolate mofetil is contraindicated during pregnancy. The aim of this research was to determine the rate of flare of lupus nephritis precipitated by switching from mycophenolate mofetil to azathioprine in pre-pregnancy planning and factors associated with or predictive of flare.

Methods: We retrospectively reviewed the clinical data and obstetric outcomes of eight female lupus nephritis patients in the maintenance phase of therapy who were switched from mycophenolate mofetil to azathioprine in pre-pregnancy planning.

Results: 62% ($n=5$) of patients did not experience a flare of nephritis when their medication was switched and of these 80% ($n=4$) had uneventful pregnancies. 38% ($n=3$) patients developed significant lupus nephritis flares when switched from mycophenolate mofetil to azathioprine. Two of these patients achieved pregnancy; one was delivered at 35 weeks by Caesarean section and the other by induction at 37 weeks, both due to pre-eclampsia. Both experienced post partum flare of nephritis, one requiring cyclophosphamide and the other was controlled with an increased corticosteroid dose and reintroduction of an angiotensin-converting-enzyme inhibitor.

Urinary protein creatinine ratio was significantly higher at time of medication switching in those who experienced renal flare ($p=0.027$). Serum creatinine, haemoglobin and serum albumin levels did not significantly differ between the two groups. Age at diagnosis, duration of disease, age at medication switch and duration since renal biopsy were not significantly different between the two groups. C3 levels, anti-dsDNA antibody % binding titres and ESR were significantly higher at time of medication switching in those who experienced renal flare ($p=0.03$, 0.024 and 0.049 respectively). C4 levels did not significantly differ between the two groups.

Conclusion: When switching apparently stable patients from mycophenolate mofetil to azathioprine it is important that adequate time and consideration is given to ensure the patient is stable on their new medication regimen before proceeding to pregnancy. Current recommendations advise that stable remission of renal disease is achieved for at least 6 months before conception. This study has found that urinary protein creatinine ratio, anti-dsDNA antibody titres and C3 levels are important predictors of flare in this subset of patients.

Disclosure: N. Jordan, None; **D. D'Cruz**, None.

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Predictive Value Of The Autoantibody Triad Of Anti-Ro, Anti-Sm and Anti-RNP For The Future Development Of Lupus Nephritis. Natasha Jordan and David D'Cruz. Louise Coote Lupus Unit, St Thomas' Hospital, London, United Kingdom.

Background/Purpose: Autoantibody production against nuclear components is a characteristic feature of SLE. Autoantibody clustering may provide a valuable tool to differentiate between clinical subsets and to predict lupus disease severity. There is increasing evidence to support the role played by RNA components of Ro and Sm/RNP small ribonucleoproteins as endogenous adjuvants in the pathogenesis of autoimmunity.

The objectives of this study were to determine the frequency of positivity of the RNA-containing antibody triad of anti-Ro/anti- Sm/anti-RNP in lupus nephritis versus SLE non-nephritis patients. In addition, we examined whether patients with this antibody combination had earlier onset disease, worse renal outcomes or more rapid progression to end-stage renal disease.

Methods: A retrospective case-control study was undertaken of 180 patients with biopsy-proven lupus nephritis and a control group of 179 ethnically matched SLE patients without nephritis. Data collected included age at disease onset, degree of renal impairment and progression of renal impairment over time based on the KDOQI guidelines (kidney disease outcomes quality initiative) and autoantibody profiles of individual patients.

Results: SLE patients with nephritis were significantly more likely to have the autoantibody triad of anti-Ro/anti-Sm/anti-RNP than SLE non-nephritis controls (12% versus 6%, $p=0.03$). There was a trend towards a higher rate of progression to end-stage renal disease in nephritis patients who were antibody triad positive (19% versus 8%, $p=0.052$). Mean renal survival was significantly shorter in nephritis patients who were antibody triad positive (14 years versus 21 years, $p=0.05$). Presence of the antibody triad was not associated with earlier onset disease (24.63 years $\pm$ 2.55 versus 26.23 years $\pm$ 1.08, $p=0.60$). 75% of SLE patients with this antibody profile were of African ancestry, 19% were Caucasian and 6% were of South Asian descent.

Conclusion: This study has shown that the RNA-containing autoantibody combination of anti-Ro/Sm/RNP was significantly more common in lupus nephritis than SLE non-nephritis patients. Progression to advanced renal disease was more common in antibody triad positive patients. Renal survival was significantly shorter in nephritis patients with this autoantibody profile. Based on these findings, we recommend particular vigilance for the detection of nephritis in newly diagnosed SLE patients with this antibody triad. SLE patients with known nephritis and this antibody profile may represent a more aggressive disease subset and thus warrant more intensive clinical monitoring.

Disclosure: N. Jordan, None; **D. D'Cruz**, None.

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A Real-World Survey Of Clinical Practice Among Rheumatologists and Nephrologists In The United States Reveals Differences In Care Of Non-Nephritis Systemic Lupus Erythematosus and Lupus Nephritis As Compared With American College Of Rheumatology Treatment Guidelines. Neelufar Mozaffarian[1], Steve Lobosco[2] and Adam Roughley[2]. [1]AbbVie, North Chicago, IL, [2]Adelphi Real World Ltd., Macclesfield, United Kingdom.

Background/Purpose: Current pharmacotherapy for systemic lupus erythematosus (SLE) and lupus nephritis (LN) includes combinations of nonsteroidal anti–inflammatory drugs (NSAIDs), antimalarials (AMs), glucocorticoids (GCs), and cytotoxic immune modulators (IMs). The objective of this analysis was to evaluate the use of therapies for SLE and LN in the United States and to compare these with current treatment recommendations for non–nephritis SLE (NNSLE) and LN issued by the American College of Rheumatology (ACR).

Methods: Data were extracted from the Adelphi Real World Lupus Disease–Specific Programme®, a cross–sectional survey of 50 rheumatologists and 25 nephrologists conducted (December 2009–May 2010) in the United States. Each physician completed a comprehensive form regarding his or her 5 most recent consulting lupus patients. Treatment history, current therapy, and other data were summarized and compared with the ACR treatment guidelines.

Results: Physicians reported data for 375 patients: 168 with NNSLE (164 treated by rheumatologists), and 207 with LN (121 treated by nephrologists). The 1999 ACR guidelines recommend the use of NSAIDs for milder NNSLE, AMs for skin and joint manifestations, corticosteroids for moderate to severe disease, and cytotoxic IMs for severe NNSLE. Survey results revealed that the proportion of all NNSLE patients (n=168) receiving NSAIDs, AMs, GCs, or IMs was 29%, 69%, 54%, and 39%, respectively. The predominant induction treatments prescribed by rheumatologists for NNSLE patients (n=164) were AMs alone (27%) or the following $\pm$ AMs: GCs (27%), IMs (15%), or IMs plus GCs (16%). In 2012, the ACR published their first set of guidelines for treating LN, recommending AM treatment for all patients, and IM plus GC induction therapy for LN classes III, IV, and V (categorized based on renal biopsy). Survey results did not include patients' renal pathology classifications; however, the data revealed that the proportion of all LN patients (n=204) receiving AMs, GCs, NSAIDs, and IMs was 42%, 76%, 17%, and 67%, respectively. However, only 20% of LN patients (n=121) treated by nephrologists began therapy with IMs plus GCs during the survey; more LN patients began IMs without GCs (28%), or GCs without IMs (27%). The proportion of LN patients receiving IMs plus GCs increased with second and third therapies to 42% and 33%, respectively. The ACR guidelines suggest that rituximab may be used in some LN patients after 6 months of treatment with IM plus GCs if nephritis worsens or does not improve. Within the overall LN patient group (n=204), 1.5% received biologic therapy at some point.

Conclusion: Real–world surveys of NNSLE and LN treatment by rheumatologists and nephrologists revealed some differences between current ACR treatment guidelines and real–world clinical practice in the United States. Differences from guidelines were minor for NNSLE and more pronounced for LN, possibly due to publication of LN guidelines (2012) after the survey period (2009–2010). However, the guidelines summarized current expert recommendations rather than proposing radical changes in therapy, and therefore the potential gaps in both NNSLE and LN treatment warrant further investigation.

Disclosure: N. Mozaffarian, AbbVie, 9, AbbVie, 1; **S. Lobosco**, Adelphi Real World Ltd., 3; **A. Roughley**, Adelphi Real World Ltd., 3.

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Prognostic Significance Of Visit-To-Visit Variability, Maximum Systolic Blood Pressure, and Episodic Hypertension In Sytemic Lupus Erythematosus. George Stojan[1], Hong Fang[1], Laurence S. Magder[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD.

Background/Purpose: SLE is considered a coronary heart disease equivalent and aggressive management of all traditional risk factors is recommended. Hypertension is a major problem in SLE. Seventy-five percent of patients in our cohort are hypertensive. The presence of hypertension in SLE increases the risk of cardiovascular events 2.66-fold, as well as the risk of stroke and poor renal outcomes. Guidelines for diagnosis and treatment of hypertension focus only on mean systolic blood pressure (SBP). Our objective was to evaluate the prognostic significance of visit-to-visit variability in blood pressure, maximum blood pressure reached, and episodic hypertension on cardiovascular events in SLE.

Methods: The analysis was based on 1340 different patients with an average duration of follow-up of 74 months. For each month of follow-up for a patient in the cohort, the previous 8 blood pressure measurements were included in the analysis. The following variables were calculated: mean prior SBP and diastolic blood pressure (DBP), standard deviation of prior SBP and DBP, coefficient of variation of prior SBP and DBP, maximum prior SBP and DBP, and minimum prior SBP and DBP. Based on the maximum and minimum blood pressure values, the following categories were created: stable normotension (maximum always <= 140mmHg), episodic moderate hypertension (minimum <= 140mmHg, maximum 140–179mmHg) episodic severe hypertension (minimum <=140, maximum 180+) and stable hypertension (minimum > 140). This information was then linked with whether the patient had a cardiovascular event (CVE) in that month. Person-months were aggregated, and the risks of a CVE by monthly characteristics were calcu-

lated. Person-months after a previous CVE were excluded. CV events were defined as either stroke, myocardial infarction, incident angina, a coronary procedure (CABG or PCI), or claudication.

Results: There were 105 CV events with a rate of 12.6 per thousand person-years. Visit-to-visit SBP variability of ≥14mmHg (RR=1.9 (1.0, 3.3), p<0.05) and DBP variability of ≥9mmHg (RR=2.5 (1.3, 4.9), p<0.01) was predictive of future CVE. A single, maximum value of SBP≥150mmHg or DBP ≥ 92mmHg were strong predictors of CVE (RR=3.7 (1.7, 8.0), p<0.01). Episodic moderate (RR=2.0 (1.3, 3.2), p<0.01) and episodic severe hypertension (RR=3.1 (1.5, 6.5), p<0.01) were both highly associated with future CVE. Mean systolic blood pressure of >130mmHg was a strong, independent predictor of CVE (rate ratio 3.3 (0.6, 6.8), p<0.01). When data were controlled for mean systolic blood pressure, no other variable was statistically associated with CVE.

Conclusion: Mean systolic blood pressure is the dominant predictor of cardiovascular events in our cohort. However, visit-to-visit variability in SBP ≥14mmHg and DBP ≥9mmHg, episodic hypertension, and single, isolated maximum values of SBP≥150mmHg and DBP ≥ 92mmHg were all highly associated with cardiovascular events, drawing attention to the false reassurance of a few normal blood-pressure readings and the need for aggressive blood pressure management in SLE patients.

Disclosure: G. Stojan, None; **H. Fang**, None; **L. S. Magder**, None; **M. Petri**, None.

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The Effect Of Ramipril On Endothelial Function and Endothelial Progenitor Cells In Patients With Systemic Lupus Erythematosus. Emilia I. Sato[1], Luiz Samuel G. Machado[2] and Ana Cecilia Machado[2]. [1]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil, [2]Universidade Federal de São Paulo, São Paulo, Brazil.

Background/Purpose: Cardiovascular diseases (CVD) are one of major causes of morbidity and mortality in SLE patients. Traditional cardiovascular risk factors and disease intrinsic factors contribute to this pathogenesis. Endothelial progenitors cells (EPCs) are involved in the re-endothelialization of damaged vessels and contribute to endothelial dysfunction. SLE patients have endothelial dysfunction and have fewer EPCs than healthy controls. Angiotensin converting enzyme (ACE) inhibitors such as ramipril in patients with coronary heart disease improve endothelial function and reduced CV morbidity and mortality. The Objective of the study was to evaluate the effect of ramipril on endothelial function as well on the number and function of EPCs in SLE patients

Methods: Prospective, randomized, controlled trial. Female patients with SLE (ACR criteria) over 18 years of age, with stable medications were invited to participate. Risk factors for CVD were exclusion criteria. SLE patients who signed consent form were randomized into two groups: intervention group (IG) and control group (CG). The IG used ramipril 10mg/day for 12 weeks. All patients were assessed at baseline and after 12 weeks, with a physical exam and also collected blood sample. Disease activity was assessed by SLEDAI score and EPCs were evaluated by culture using Endocult (Stemcell Technologies, USA), according appropriate protocol and by flow cytometry using anti-KDR-APC (R&D Systems, USA), anti-CD34-FITC (Southern Biotech Assoc Inc, USA), anti-CD133-PE (Miltenyi Biotec, USA) and 7AAD (Southern Biotech Assoc. Inc, USA). The assessment of endothelial function was done through an ultrasonography of the brachial artery and flow mediated dilation (FMD), according the established protocol. Student t test was used for normally distributed variables, Fisher exact test for categorical variables and ANOVA for repeated measures. Intent to treat analysis was done. $P < 0.05$ was considered significant.

Results: 37 SLE patients were evaluated, 18 in IG and 19 in CG.

At baseline, there was no difference between IG and CG regarding the average of age, disease duration, arterial pressure, LDL cholesterol, BMI, FMD, use of immunosuppressive drug and SLEDAI score. We found a significant increase on FMD in IG (6.17±4.18% vs 11.14±5.4%, p<0.001), without difference in CG (5.37±3.91% vs 5, 02±3.62%, p=0.630), comparing first (baseline) and final (12 weeks) assessment. We also found a increase in the number of colony forming units (CFU) of EPCs in IG (21.3±10.4 vs 31.6±8.5, p<0.001), without difference in CG (24.8±13.5 vs 25.8±11.6, p=0.714). There was no difference concerning EPCs number evaluated by cytometry in IG (0.013 %±0.025 vs 0.02%±0.03 p=0.734) either in CG (0.0175±0.024 vs 0.012%±0.016%, p=0.734).

Conclusion: Ramipril improved endothelial function in patients with SLE and also increased the number of EPCs evaluated in cell culture, suggesting that the improvement of endothelial function can be due to the increase in EPCs function. ACE inhibitors should be used as a preferential drug to treat hypertension in SLE patients and may be could reduce CVD in these patients

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Breast Cancer In Systemic Lupus (SLE): Do Demographic and Clinical Factors, Including DNA serology, Influence Risk? Sasha Bernatsky[1], Rosalind Ramsey-Goldman[2], Michelle Petri[3], Murray B. Urowitz[4], Dafna D. Gladman[5], Christine Peschken[6], William Foulkes[1], Yvan St. Pierre[7], Patrice Chrétien Raymer[7], Basile Tessier Cloutier[1], Guillermo Ruiz-Irastorza[8], Ann E. Clarke[1] and Systemic Lupus International Collaborating Clinics (SLICC)[9]. [1]McGill University, Montreal, QC, [2]Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Johns Hopkins University School of Medicine, Baltimore, MD, [4]University of Toronto, Toronto Western Hospital, Toronto, ON, [5]Toronto Western Hospital and University of Toronto, Toronto, ON, [6]University of Manitoba, Winnipeg, MB, [7]McGill University Health Centre, Montreal, QC, [8]Hospital de Cruces, UPV/EHU, Barakaldo, Spain, Bizkaia, Spain, [9]Toronto Western Hospital, Toronto, ON.

Background/Purpose: There is an increase in cancer in SLE over-all, but decrease in other cancers, such as breast cancer. Of particular interest are autoantibodies targeting DNA, which may penetrate cells and interfere with DNA repair; these may be lethal to cancer cells and hence protect against breast cancer. Our primary objective was to assess breast cancer risk in females with SLE, comparing patients who test positive for anti-double stranded (ds) DNA antibodies, versus those who do not. We also assessed other demographic and clinical factors.

Methods: We used data from a very large multi-site international SLE cohort. The data presented in this preliminary analysis are from four centres: Toronto, Montreal, Winnipeg, and Baltimore. We used Cox proportional hazards regression to calculate the hazard ratio (HR) for breast cancer risk in female SLE patients, relative to their exposure in terms of anti-dsDNA positivity over time, in models that controlled for time-dependent medication exposures, demographics (age, race/ethnicity), and calendar year. Anti-dsDNA positivity was assessed on the basis of annual SLE Disease Activity Index, SLEDAI scores, assessed at baseline and annually. A weighted average of the number of times patients were anti-dsDNA positive was generated, and we included in our regression model, a time-dependent variable capturing this weighted average. We also included time-dependent measures of cumulative disease activity (adjusted mean SLEDAI scores, modified by removal of the item for anti-dsDNA). Time zero for the observation interval was SLE diagnosis, so that our analyses adjusted for SLE duration. We included cancers occurring after entry into the lupus cohort and up to the time of cohort exit (defined by death or date of last visit).

Results: These analyses include 34 SLE breast cancers cases and 3,391 female SLE patients without any cancer. Compared to controls without cancer, breast cancer cases tended to be white (78% versus 61% in controls), with a trend towards being older at cohort entry (mean 42.8 years, median 43.6; versus mean 38.4, median 36.8 in controls). The same proportion (20.6%) of cases and cancer-free controls were anti-dsDNA positive at cohort entry, and DNA positivity through the observation interval was also similar. Breast cancer cases were similar to cancer-free controls in terms of baseline disease activity and the profile of cumulative drug exposures over time. In both univariate and multivariate models, the principal factors associated with breast cancer risk were older age at cohort entry and calendar year. Of note, anti-malarial use was not demonstrated as a protective factor in these analyses, modelled either as a categorical or continuous (years exposed) variable.

Conclusion: In these preliminary data, we saw no difference in breast cancer risk in females with SLE, comparing patients who are positive for anti-ds DNA serology, versus those who are not. However, our analyses are based on only 34 cases (and 3,391 controls); as well, we have so far only assessed serology and not specifically cell-penetrating autoantibodies (which may be more important). Our analyses also did not establish anti-malarial agents as protective for breast cancer, but here further analyses are also needed.

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Blood Pressure Variability and Age-Related Blood Pressure Patterns In Systemic Lupus Erythematosus. George Stojan[1], Laurence S. Magder[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD.

Background/Purpose: Increased visit-to-visit blood pressure (BP) variability has been associated with an increased risk of all-cause mortality, stroke, left ventricular diastolic dysfunction, and cognitive impairment among diverse populations. Despite the high prevalence of cardiovascular disease among patients with systemic lupus erythematosus (SLE), BP variability and the relationship between age, BP and BP variability has not been described in this population.

Methods: The means and variances of systolic and diastolic pressures in the general population using data from the National Health Statistics Reports (19,921 adults aged 18 and over with BP estimates calculated using the mean of up to three measurements) were compared with those in a cohort of SLE patients (1340 different patients, seen quarterly, with an average duration of follow-up of 74 months). The following variables were calculated: mean systolic blood pressure (SBP), mean diastolic blood pressure (DBP), and within-person standard deviation of SBP and DBP.

Results: The systolic BP in SLE follows the trend of increase with age seen in the general population, but was statistically significantly higher in young adults 18–39 years of age ($p<0.001$) regardless of sex and race. Surprisingly, with age this trend decreased and in females older than 60 years of age it reversed, with SLE patients having a statistically significantly lower SBP compared to the general population ($p<0.001$). Diastolic BP was statistically significantly ($p<0.001$) elevated among female SLE patients across all age groups with the exception of Caucasian women 40–59 years of age. Among males, we observed higher DBP in our SLE males compared to the general population in all age/ethnic groups, however, the differences were not all statistically significant, due to the low number of males in the cohort. BP variability in SLE is elevated across all age groups. Within person standard deviation (SD) of SBP increased with age and ranged between 12.2 mmHg among 20 year olds and 16.7 mmHg among 80 year olds, while DBP variability remained stable through all age groups and ranged between 8.7 mmHg and 8.9 mmHg. These values are substantially higher than the within-person BP variability reported by NHANES which is 7.7 mmHg for SBP and 5.8 mmHg for DBP, but is comparable to previously published data in stroke cohorts (UK-TIA, Dutch TIA, ESPS-1 trials).

Conclusion: The relationship of BP to age in SLE differs from that in the general population with significantly higher mean SBP among young adults and lower mean SBP among elderly females. BP variability in SLE is elevated across all age groups compared to the general population and is comparable to the variability seen in stroke cohorts. Consistent available data obtained in a wide spectrum of non-SLE populations (from a general population to high-risk patients) show an association between increased visit-to-visit BP variability and worse cardiovascular outcomes and target organ damage. Further studies are needed to determine the causes of visit-to-visit BP variability in SLE, its association with cardiovascular outcomes, and whether treatments that reduce BP variability may improve cardiovascular outcomes.

Disclosure: G. Stojan, None; **L. S. Magder**, None; **M. Petri**, None.

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Low-Dose Aspirin Has An Anti-Platelet Effect In Systemic Lupus Erythematosus. Michelle Petri[1], Laurence S. Magder[2] and Thomas Kickler[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD.

Background/Purpose: Thrombosis is increased in SLE patients, with and without antiphospholipid antibodies. Aspirin and hydroxychloroquine are thought to have anti-platelet effects. We determined whether these drugs had an anti-platelet effect using formal platelet function studies in SLE patients.

Methods: SLE patients about to start aspirin (81 mg #51) or hydroxychloroquine (400 mg #56) had platelet function tests before and at least 1 month after starting the medication. The changes were assessed statistically using paired t-tests for quantitative variables and McNemar's test for binary variables.

Results: Aspirin led to a very significant reduction in urine thromboxane, and a borderline reduction in ADP. SLE patients also appeared to be very sensitive to aspirin in terms of reduction in epinephrine. Hydroxychloroquine also led to a reduction in urine thromboxane.

Variable	Mean change after treatment	StdError	P-value
Aspirin Treatment			
Arachidonic Acid Aggregation	−59.5200000	7.8713243	< 0.0001
ADP Agonist	−7.6938776	3.8310631	0.0503
Collagen ATP release (nm)	−0.0225208	0.1725624	0.8967
Collagen Agonist	−7.1020408	3.1146249	0.0271
Epinephrine Aggregation 10 μM	−32.5714286	6.4571089	< 0.0001
Aggregation ADP 10 μM	1.9285714	5.3738364	0.7225
Thromboxane	−1377.05	438.3165675	0.0049
Hydroxychloroquine Treatment			
Arachidonic Acid Aggregation	3.9454545	5.3208451	0.4616
ADP Agonist	−2.3454545	3.6381090	0.5219
Collagen ATP release (nm)	0.0629091	0.1104904	0.5715
Collagen Agonist	−1.4909091	3.3678888	0.6598
Epinephrine Aggregation 10 μM	−1.7297297	3.9517831	0.6642
Aggregation ADP 10 μM	−0.3947368	4.9373802	0.9367
Thromboxane	−612.3913043	191.7715594	0.0042

We next dichotomized urine thromboxane to < 1500 and > 1500.

Table 2. Pre-post results based on various treatments.

Treatment	Number (%) with low Thromboxane at both time points	Number (%) with low at baseline and high at follow-up	Number (%) with high at baseline and low at follow-up	Number (%) with high Thromboxane at both time points	P-value for difference in rates of High thromboxane pre vs. post[1]
Aspirin (all)	4 (11%)	2 (5%)	22 (59%)	9 (24%)	< 0.0001
Aspirin (no history of lupus anticoagulant)	4 (14%)	1 (4%)	17 (61%)	6 (21%)	0.0002
Aspirin (history of lupus anticoagulant)	0 (0%)	1 (11%)	5 (56%)	3 (33%)	0.21
Hydroxychloroquine	11 (22%)	1 (2%)	7 (14%)	31 (62%)	0.070

Conclusion: Aspirin led to a marked and significant change in urine thromboxane and epinephrine. Hydroxychloroquine also appeared to lead to a reduction in urine thromboxane. Because a major source of thromboxane is inflamed monocytes, this could represent an anti-inflammatory mechanism of hydroxychloroquine. Although not statistically significant (likely due to loss of power with only 9 patients with a history of the lupus anticoagulant), aspirin (81 mg) led to a reduction in urine thromboxane in the majority. About 25% of SLE patients appear to be aspirin resistent. Aspirin, in SLE patients at risk for, or who have had, arterial thrombosis, is a viable option.

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Efficacy Of Rituximab In Patients With Refractory Lupus Nephritis, a Post-Hoc Analysis From Phase II Trial In Japan. Yoshiya Tanaka[1], Kazuhiko Yamamoto[2], Tsutomu Takeuchi[3], Nobuyuki Miyasaka[4], Takayuki Sumida[5], Tsuneyo Mimori[6], Takao Koike[7] and Kazuhiro Endo[8]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [3]Keio University School of Medicine, Tokyo, Japan, [4]Tokyo Medical and Dental University, Tokyo, Japan, [5]University of Tsukuba, Tsukuba, Japan, [6]Graduate School of Medicine, Kyoto University, Kyoto, Japan, [7]NTT Sapporo Medical Center, Sapporo, Japan, [8]Zenyaku Kogyo Co., Ltd., Tokyo, Japan.

Background/Purpose: B-cell depletion therapy by rituximab has been reported to be useful for treatment of lupus nephritis (LN) in many observational uncontrolled studies, however, placebo-controlled phase III study, LUNAR has failed to find clinical benefit of rituximab over placebo[1)]. The interpretation of the study is controversial because of intense background MMF. Then, rituximab is still gaining attention as a treatment option for LN and recent ACR guideline recommends rituximab as an alternative treatment option for refractory LN with class III/IV[2)]. In order to examine efficacy and safety of rituximab in LN who responded inadequately to conventional therapy, a post-hoc analysis was done for subset of LN patients who entered into Japanese phase II clinical study in refractory SLE.

Methods: Patients (pts) with proteinuria, Upr/Ucr >1.0 and active urine sediment were eligible to the study. The treatment protocol was the same as EXPLORER and LUNAR and rituximab was administrated at a dose of 1,000mg/body on days 1, 15, 169 and 183. After the first dose of rituximab, background steroid was tapered by 20% every two weeks. Pts were followed for 53 weeks and renal response was examined by the criteria used in LUNAR[1)] and ACR[3)].

Results: A total of 34 pts were enrolled into the study and 17 pts had renal involvement with Upr/Ucr >1.0 (median:2.2, range:1.0–10.0). 10 out of 17 pts were biopsy-verified class III/IV, and 9 pts had a treatment history with steroid pulse and/or IVCY. Median predonisolone dose before rituximab therapy was 50 mg/day (range:15–100 mg/day). In all 17 pts, peripheral blood of B-cells depleted after the first rituximab and kept low throughout the study. 2 pts discontinued the study prematurely because of renal flare and were classified as non-responder. Overall response rate by ACR criteria were 58.8%; complete renal response (CR) 35.3%, partial renal response (PR) 23.5%, 95%CI:32.9–81.6%. Response rate with LUNAR were 52.9% (CR 29.4%, PR 23.5%, 95%CI:27.8–77.0%). As far as the response was evaluated in 10 pts with histologically confirmed class III/IV, overall response rate by ACR or LUNAR were 70.0% (CR 40.0%, PR 30.0%, 95%CI:34.8–93.3%) and 60.0% (CR 40.0%, PR 20.0%, 95%CI:26.2–87.8%), respectively. Successful steroid tapering achieved in all 15 pts who completed the study and median predonisolone dose at Week 53 was 5 mg/day (4–12 mg/day). As for the safety, rituximab was well tolerated and 6 infusion-associated reactions were observed in 3 pts, which were all grade 1–2 in severity. Three grade 3/4 adverse events were observed in 2 pts for which causal relationship with rituximab was not completely excluded: herpes simplex (G3), neuralgia (G3) and leukocytopenia (G4).

Conclusion: 1. Rituximab is effective for treatment of LN who were poorly controlled by conventional therapy and recent ACR guideline for LN is also applicable to Japanese patient. 2. Further studies will be needed to clarify and maximize the benefit of rituximab for treatment of LN. 3. International cooperative study such as RING (Rituximab for Lupus Nephritis in Remission as a Goal) is expected to provide new insight in rituximab in LN.

Reference:
[1)]Arthritis Rheum 2012;64:1215–1226.
[2)]Arthritis Care Res 2012;64:797–808.
[3)]Arthritis Rheum 2006;54:421–432.

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A Survey Of Physician and Patient Satisfaction With Control Of Systemic Lupus Erythematosus and Lupus Nephritis. Neelufar Mozaffarian[1], Steve Lobosco[2] and Adam Roughley[2]. [1]AbbVie, North Chicago, IL, [2]Adelphi Real World Ltd., Macclesfield, United Kingdom.

Background/Purpose: Patient satisfaction with disease control is an important component of overall health and well-being. Current treatment options for systemic lupus erythematosus (SLE) ±lupus nephritis (LN) include antimalarials, glucocorticoids, and immune modulators, but unmet treatment needs remain. The objectives of this analysis were to evaluate (1) patient and physician satisfaction with treatment–mediated disease control and (2) degree of physician–patient agreement with respect to treatment satisfaction.

Methods: Data were extracted from the Adelphi Real World Lupus Disease–Specific Programme®, a cross–sectional US survey of 50 rheumatologists, 25 nephrologists, and their consulting patients, conducted December 2009–May 2010. Each physician completed a comprehensive form regarding his or her 5 most recent lupus patients (N=375); data collected included disease severity, treatment history, and current therapy(ies). Physician– and patient–reported satisfaction with the level of disease control was assessed using a 3–point scale.

Results: Physician–reported data were obtained regarding 168 patients with non–nephritis SLE (NNSLE), 164 of whom were treated by rheumatologists, and 206 LN–patients, 120 of whom were treated by nephrologists; patient–reported data were obtained from 212 of these patients (NNSLE, 99; LN, 113). Physicians were satisfied with disease control in 79% (132/168) of NNSLE–patients; 76% (75/99) of NNSLE–patients were satisfied. However, agreement (71%) on the level of satisfaction with disease control among NNSLE–patients and their rheumatologists was "slight" (kappa=.1445). Notably, agreement on the level of satisfaction with disease control declined significantly with NNSLE severity (p=.0062); the greatest agreement was observed for mild NNSLE (59/75; 79%), with less agreement for moderate NNSLE (9/21; 43%) or severe NNSLE (2/3; 67%). As the number of drugs taken by NNSLE–patients increased, agreement on the level of satisfaction decreased (nonsignificant trend, p=.2035): 1 drug, 22/27 (81%); 2 drugs, 22/30 (73%); ≥3 drugs, 26/42 (62%).

Physicians were satisfied with disease control in 74% (152/206) of LN–patients; 65% (74/113) of LN–patients were satisfied. Agreement (71%) on the level of satisfaction among LN–patients (112) and their nephrologists was "fair" (kappa=.3695). Agreement tended to be higher (nonsignificant trend [p=.0740]) in patients with mild (42/56; 75%) or moderate LN (31/41; 76%), compared with severe LN (7/15; 47%). As the number of drugs taken by LN–patients increased, agreement on the level of satisfaction decreased (nonsignificant trend, p=.0764): 1 drug, 17/20 (85%); 2 drugs, 30/39 (77%); ≥3 drugs, 31/51 (61%).

Conclusion: For NNSLE, 21% of rheumatologists and 24% of patients were not satisfied with the level of disease control. For LN, 26% of nephrologists and 35% of patients were not satisfied with the level of disease control. Patients with more severe disease and those taking a higher number of anti–lupus drugs were less likely to agree with their physicians' level of satisfaction. These disease–control disparities highlight the need for more effective treatment options for both NNSLE and LN.

Disclosure: N. Mozaffarian, AbbVie, 9, AbbVie, 1; **S. Lobosco**, Adelphi Real World Ltd., 3; **A. Roughley**, Adelphi Real World Ltd., 3.

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Candidate Urinary Biomarkers May Predict The Future Development Of Renal Functional Loss With Lupus Nephritis In Children and Adults. Khalid Abulaban[1], Brad H. Rovin[2], Shannen Nelson[3], Huijuan Song[2], Paul Kimmel[4], John Kusek[4], Harold Feldman[5], Vasan Ramachandran[6], Michael Bennett[1], Jun Ying[7] and Hermine Brunner[8]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Ohio State University Medical Center, Columbus, OH, [3]Cincinnati Children's Hospital, Cincinnati, OH, [4]NIDDK, National Institutes of Health, Bethesda, MD, [5]The University of Pennsylvania, Philadelphia, PA, [6]Boston University School of Medicine, Boston, MA, [7]University of Cincinnati, Cincinnati, OH, [8]Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Background/Purpose: Lupus nephritis(LN) is frequently associated with a poor long-term prognosis. Current non-invasive blood and urine tests do not reliably predict the course of LN. The objective of this study was to evaluate the performance of candidate urine biomarkers in predicting future kidney function in adults and children with LN. The biomarker candidates studies were liver-type fatty acid binding protein (L-FABP), albumin (Alb), and monocyte chemoattractant protein 1 (MCP-1).

Methods: L-FABP, Alb and MCP-1 were measured by ELISA in urine from 70 adults and 29 children collected at the time of enrollment into prospective observational LN cohorts. Urine analytes were normalized to urine creatinine and logarithmically transformed. The association of each analyte to renal function loss (RFL), defined as a sustained increase of ≥ 25% in serum creatinine (SCr; adults) or a decrease in eGFR of ≥ 20% (children), was determined using a fixed effect model after adjusting for the age group (adult vs. child). Logistical models were used to predict the presence of RFL using each biomarker or a combination of all three biomarkers. Biomarker performance in predicting RFL was assessed as the area under reciever operating characteristic curve (AUC) corresponding to the logistical model.

Results: 8 children and 22 adults had RFL during the mean follow-up period of 6.1 months and 60 months, respectively. Overall patients with RFL showed significantly higher levels of L-FABP, ALB and MCP-1 than those without RFL (Table). The AUC using the combination of urine L-FABP, Alb and MCP-1 was 0.73, higher than those using any single biomarker as the predictor (all about 0.64).

Patient type	*Biomarker/ Cr$*	*Renal function loss$*	*Preserved renal function$*	*p-value*
All patients with LN	*N*	*30*	*69*	–
	LFABP	**1.96 ± 1.45**	**1.23 ± 1.62**	**0.038**
	Albumin	**5.82 ± 2.31**	**4.54 ± 2.23**	**0.012**
	MCP-1	**6.05 ± 1.14**	**4.77 ± 2.58**	**0.014**
Adults with LN	*N*	*22*	*48*	–
	LFABP	1.69 ± 1.26	1.28 ± 1.69	0.326
	Albumin	5.90 ± 2.14	5.01 ± 2.01	0.100
	MCP-1	**5.98 ± 1.16**	**4.80 ± 2.70**	**0.061**
Children with LN	*N*	*8*	*21*	–
	LFABP	**2.67 ± 1.75**	**1.09 ± 1.48**	**0.022**
	Albumin	**5.59 ± 2.86**	**3.41 ± 2.36**	**0.047**
	MCP-1	6.25 ± 1.16	4.70 ± 2.34	0.108

$ Values are mean + standard deviation

Conclusion: Urine L-FABP, Alb and MCP-1 are associated with RFL. The combination of these biomarkers was a better predictor of RFL than any individual biomarker.

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Elevated Level Of cfDNA Mainly Derive From Netosis Of Common Neutrophils As Well As Low-Density Granulocytes In Systemic Lupus Erythematosus and Is Associated With Lupus Nephritis Severity. Sigong Zhang, Guochun Wang and Xin Lu. China-Japan Friendship Hospital, Beijing, China, Beijing, China.

Background/Purpose: Insufficient clearance of neutrophil extracellular traps (NETs) has been involved in lupus nephritis and can cause the increase of residual NETs in vivo, which is considered to be one main source of circulating cell-free DNA (cfDNA). However, whether elevated level of cfDNA could be attributed to excessive formation and insufficient clearance of NETs is still unknown in SLE. This study focused on it and explored whether cfDNA could be a biomarker for organ involvement related to abnormal formation and degradation of NETs in SLE.

Methods: Fifty four patients with SLE and 43 age- and sex-matched healthy controls were included in the study. cfDNA concentration was measured with Picogreen Kit, percentage of low-density granulocytes (LDGs) in peripheral blood mononuclear cells (PBMCs) was tested by flow cytometer and DNase I activity was measured by radial enzyme-diffusion method. Linear correlation analysis were performed between these three, SLE disease activity index (SLEDAI) and other serological parameters. Multiple linear regression was performed to identify the influencing factor of cfDNA.

Results: cfDNA in SLE group was 239.76±57.15 ng/ml, significantly higher than that in healthy control group (187.96±40.55 ng/ml, P<0.0001). DNase I activity in SLE group was 0.26±0.17 U/ml, significantly lower than that in healthy control group (0.43±0.26 U/ml, P<0.0001). Percentage of LDGs in PBMCs of SLE group was 8.29%±12.86%, significantly higher than that in healthy controls group (1.15%±0.71%, P=0.0036). In SLE group, cfDNA positively correlated with percentage of LDGs in PBMCs (r=0.651, P=0.002), neutrophils (r=0.584, P<0.0001), ESR (r=0.364, P=0.007), CRP (r=0.291, P=0.032) and urine protein (r=0.350, P=0.013) and reversely correlated with albumin (r=−0.500, P<0.0001) and Ccr (r=−0.354, P=0.044). Multiple linear regression indicated that plasma albumin and neutrophils can explain 38.2% of elevated cfDNA in SLE patients.

Conclusion: The elevated level of cfDNA may mainly derive from NETosis of common neutrophils as well as LDGs and is associated with lupus nephritis severity.

Disclosure: S. Zhang, None; **G. Wang**, None; **X. Lu**, None.

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Analysis Of Relationship Between Clinical Manifestations and Autoantibody Profile In ISN/RPS Class V Lupus Nephritis. Masanori Hanaoka[1], Takahisa Gono[1], Yasushi Kawaguchi[1], Hisashi Yamanaka[2], Yasuhiro Katsumata[1], Kae Takagi[1], Hirotaka Kaneko[1], Hisae Ichida[1], Yuko Ota[1], Hidenaga Kawasumi[1], Sayumi Baba[1], Yuko Okamoto[1] and Sayuri Kataoka[1]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Clinical manifestations, pathohistology and treatment strategy are different between International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III/IV and class V Lupus Nephritis (LN). However, it has remained unknown what factors contribute to differences of pathophysiology between ISN/RPS class III/IV LN and class V LN. Moreover, in some patients with class V LN, responses to treatment such as corticosteroid or immunosuppressive agents are refractory. Predictors for treatment response have remained unknown in class V LN. The aim of this study is to clarify the differences of autoantibody profile between ISN/RPS class III/IV LN and class V LN. We also investigate associations between clinical manifestations and each autoantibody in class V LN.

Methods: 55 LN patients were consecutively enrolled and underwent renal biopsy in this study. These patients were divided into two subsets, 31 patients with ISN/RPS class III/IV LN subset and 22 patients with class V LN subset. Combined class III/IV+ V LN cases were excluded in this study. Clinical manifestations, autoantibodies positivity (anti-dsDNA, anti-SS-A, anti-U1-snRNP, Anti-Sm and anti-ribosomal P) were compared between two subsets. In addition, we analyzed the relationship between clinical manifestation and each autoantibody in class V LN subset.

Results: Disease duration was significantly longer in class III/IV LN than class V LN (P = 0.01). Anti-dsDNA titer was significantly higher in class III/IV LN than class V LN (P < 0.01). The frequency of anti-Sm and anti-ribosomal P positivity was higher in class V LN than class III/IV LN (43% vs 20% and 50% vs 25%, respectively), although there were no significant differences. The frequency of both anti-dsDNA positive and anti-U1snRNP negative was significantly higher in class III/IV LN than class V LN (54.1% vs 19.1%, P = 0.03). In contrary, the frequency of both anti-dsDNA negative and anti-U1snRNP positive was significantly higher in class V LN than class III/IV LN (33% vs 0%, P < 0.01).

Among class V LN subset, complement levels were lower and renal remission rate was higher in anti-dsDNA-positive class V LN subset than anti-dsDNA-negative class V LN subset. SLEDAI score was significantly higher (P = 0.02) and 24hr proteinuria was higher in anti-Sm-positive class V LN subset than anti-Sm-negative class V LN subset. Rash and arthritis was higher in anti-ribosomal P-positive class V LN subset than anti-ribosomal P-negative class V LN subset.

Conclusion: Anti-U1snRNP is associated with complication of class V LN. Lower complement level and anti-dsDNA positivity are the predictive markers for renal remission in class V LN.

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Urinary Prostaglandin D Synthetase As a Biomarker Of Lupus Nephritis Activity: One Year Longitudinal Study. Ranjan Gupta, Akhilesh Yadav, Ramnath Misra and Amita Aggarwal. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background/Purpose: Proteomic analysis of urine samples, from patients with active lupus nephritis (LN)[1–2] and from animal model of LN[3] has led to identification of Prostaglandin D synthetase (PGDS) as a potential biomarker in LN. The levels were increased in patients with active LN as compared to inactive LN[1].There is no longitudinal study available in patients with active LN to see its relationship with renal activity.

Methods: Patients fulfilling ACR criteria for diagnosis of SLE were included and categorized into active LN (ALN), active non renal disease (ANR) and inactive disease (ID). Urine was collected in the morning and stored after centrifugation. Patients with pregnancy or infection were excluded. Urine samples from 19 healthy young females were included as control. 25 patients with active lupus nephritis were followed up 3 monthly and urine samples were analyzed at 6, 9 and 12 months. Patients who had worsening renal disease at 3 months had sample analyzed at 3 months also. Urinary PGDS (uPGDS) was measured by ELISA using commercial kit. All values were normalized to urinary creatinine excretion.

Results: A total of 28 patients with ALN, 15 patients with ANR, 6 patients with ID and 19 healthy controls were included in cross-sectional study. Among the 49 patients, there were 46 females. Mean age was 27.8 (SD 9.5) years. The median SLEDAI in ALN was 20(6–32), in ANR was 9(4–18) and in ID was 3(0–4). In patients with ALN, the median renal SLEDAI was 10(4–16). The class of LN was II in 4, III in 11, IV in 6, V in 3 and in 4 patients biopsy could not be done.

In cross-sectional study, the median uPGDS excretion was higher in patients with ALN (61.85 ng) as compared to healthy controls (14.17ng; p<0.001), ANR (21.31ng; p=ns) and ID (5.62 ng; p<0.005). uPGDS had good correlation with renal SLEDAI (r=0.403; p=0.006) and total SLEDAI (r=0.406; p=0.007).

In longitudinal study of 28 patients with ALN, 25 patients had completed 6 months, 20 patients 9 months and 13 patients 12 months follow-up. uPDGS had excellent correlation with SLEDAI, rSLEDAI and urinary protein creatinine ratio over time. The median values are shown in the line diagram below at 0, 6, 9 and 12 months.

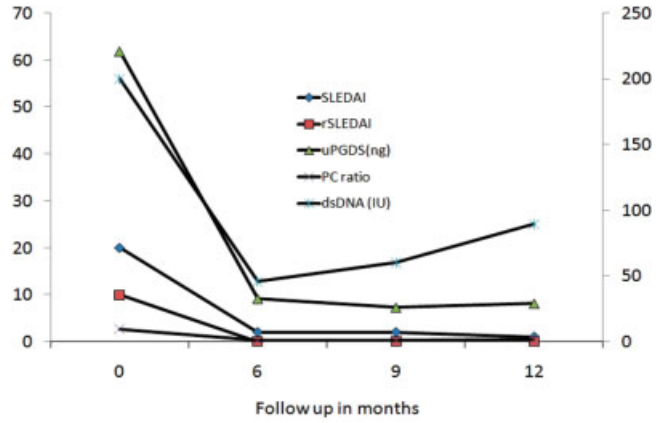

Figure.

One patient with class IV nephritis had no response at 3 months with rise in serum creatinine. Her urine sample at 3 months showed a marked rise in uPGDS (41.89 to 390.85ng). She was treated with Rituximab but developed ESRD at 6 months.

The only patient who showed a significant rise in uPGDS at 9 months (baseline: 13.9: 6 months: 10.9: 9 months 47.96 ng) relapsed at 11 months.

Conclusion: uPGDS is a good marker of lupus activity. uPGDS is partly serum derived[3] as its levels are higher in patients with ANR disease than ID. Its levels are higher in nephritis and can be used to monitor renal activity. It may be a potential marker to predict relapse.

References:

[1]*J Prot 2012;75:3240-7.*

[2]*Ped Res 2009;65:530-6.*

[3]*J Immunol2010;184;2183–93.*

Disclosure: R. Gupta, None; **A. Yadav**, None; **R. Misra**, None; **A. Aggarwal**, None.

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Renal Biopsy Findings In Lupus Patient With Insignificant Proteinuria: Relation To Disease Activity and Clinical Manifestations. Abdel Azeim M. Al-Hefny[1], Samah El-bakry[2], Sameh A. Mobasher[3], Ola H. Nada[4] and Nouran Abaza[5]. [1]Professor of Internal Medicine and Rheumatology, Faculty of Medicine, Ain Shams University, Cairo, Egypt, Cairo, Egypt, [2]Assistant professor of Internal Medicine and Rheumatology, Faculty of Medicine, Ain Shams University, Cairo, Egypt, [3]Lecturer of Internal Medicine and Rheumatology, Faculty of Medicine, Ain Shams University, Cairo, Egypt, [4]Lecturer of Pathology, Faculty of Medicine, Ain Shams University, Cairo, Egypt, [5]Lecturer of Physical medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Background/Purpose: Lupus nephritis (LN) remains one of the most serious manifestations of systemic lupus erythematosus (SLE) and is associated with significant morbidity and mortality. Early and accurate detection of kidney involvement in SLE improves outcomes. Although renal biopsy is required for proper diagnosis of the histopathological subtype of LN and direction of proper treatment, the decision to recommend renal biopsy can be complex. We aimed to investigate whether SLE patients with insignificant proteinuria have significant renal involvement and need to be biopsied. We also studied the relation between severity of nephritis and the overall disease activity and other lupus manifestations.

Methods: Forty SLE patients with proteinuria <500 mg/24 hrs were recruited from Ain Shams University Hospitals. Disease activity was assessed according to SLE disease activity index (SLEDAI). Renal biopsy was done to all patients and assessed by light, immunofluorescent and electron microscopy for identification of different pathological classes according to WHO classification. Patients were classified into two groups: Group A: with mild renal affection [class I or II according to WHO-histopathological classification of renal biopsy] and Group B: with moderate to severe renal affection [class III, or more according to WHO classification].

Results: All patients (100%) had lupus nephritis by histo-pathological examination according to the WHO classification. About 32.5% of SLE patients with insignificant proteinuria had mild lupus nephritis and 67.5% had moderate to severe nephritis. In Group A: 2 patients (5 %) had class I LN and 11 patients (27.5 %) had class II LN, while in Group B: 13 patients (32.5%) had class III LN, 10 patients (25 %) with class IV LN and 4 patients (10%) with class V LN. Comparing clinical characteristics of both groups; patients with severe LN (Group B) had higher SLEDAI scores (P= 0.049), higher ESR levels, higher Anti-dsDNA titer (P= 0.020) and lower C3 and C4 levels (P= 0.028 and <0.001 respectively). As well, they were more anemic, leucopenic, lymphopenic and thrombocytopenic than patients with mild LN (group A) (P= 0.020, P= 0.005, P= <0.001and P= 0.050 respectively).

Urinary abnormalities; especially proteinuria and hematuria were significantly higher in patients with severe LN than those with milder LN (P= 0.009 and 0.047 respectively). Furthermore, patients with severe LN had significant polyarthralgia and history of recurrent thrombosis than those with mild LN (P =0.011 and 0.035 respectively).

Conclusion: We found significant renal involvement (Class III, IV, or V LN) in SLE patients with insignificant proteinuria. Our data suggest that for better outcome; renal biopsy should be justified in SLE patients with low proteinuria and without clinical signs of renal affection, especially if they have any of the following: polyarthlralgia, recurrent thrombosis, high Anti-dsDNA titer, consumed C3 &/or C4, rising ESR, high SLEDAI scores, anemia, leukopenia, lymphopenia, thrombocytopenia, and finally active urinary sediment; especially hematuria.

Disclosure: A. A. M. Al-Hefny, None; **S. El-bakry**, None; **S. A. Mobasher**, None; **O. H. Nada**, None; **N. Abaza**, None.

595 WITHDRAWN

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Extended Follow-Up Of a Investigator-Initiated trial Comparing Two Sequential Induction and Maintenance Treatment Regimens For Proliferative Lupus Nephritis Based Either On Cyclophosphamide Or Cyclosporine A. Jakub Zavada[1], Satu Pesickova[2], Romana Rysava[2], Pavel Horak[3], Zbynek Hrncir[4], Jozef Rovensky[5], Jozef Lukac[5], Jirina Vitova[6], Jana Böhmova[7], Marta Olejarova[1], Dana Tegzova[8] and Vladimir Tesar[2]. [1]Institute of Rheumatology, Prague, Prague, Czech Republic, [2]General University Hospital and First Faculty of Medicine, Charles University, Prague, Czech Republic, [3]3rd Department of Internal Medicine University Hospital Olomouc, Olomouc, Czech Republic, [4]Faculty of Medicine and University Hospital, Hradec Kralove, Czech Republic, [5]National Institute of Rheumatology, Piestany, Slovakia, [6]Hospital, Ceske Budejovice, Czech Republic, [7]Faculty Hospital St. Anna, Brno, Czech Republic, [8]Institute of Rheumatology, Prague, Czech Republic.

Background/Purpose: In the investigator-initiated CYLOFA-LUNE trial we tested the hypothesis that immunosuppressive regimen based on Cyclosporine A (CYA) may have similar efficacy but greater safety than that based on cyclophosphamide (CPH).

CYCLOFA-LUNE TRIAL a multicenter, randomized, open-label, controlled trial conducted from January 2002 through December 2006 in 7 centers in Czech Republic and one center in Slovakia

Eligibility criteria:

• The diagnosis of systemic lupus erythematosus (by meeting 4 criteria of the American College of Rheumatology)

• Renal biopsy documenting proliferative glomerulonephritis class III or IV according to WHO/ISN-RPS

• Clinical activity as defined by presence of at least two of the following: abnormal proteinuria (> 500mg/24-hours), active urinary sediment, and/or C3 hypocomplementemia

Treatment:

The duration of the controlled study protocol was 18 months Cyclophosphamide (CPH) arm: 8 boluses of intravenous cyclophosphamide (10mg/kg) given within 9 months in subsequently prolonged intervals (2×3weeks, 4×4 weeks, 2×6 weeks) followed by 4–5 oral cyclophosphamide boluses (10mg/d in 6–8 week intervals). Cyclosporine arm: oral cyclosporine A (CyA) 4–5mg/kg/day (given in two divided doses) for 9 months followed by gradually decreasing dose of cyclosporine (3.75-1.25 mg/kg/day) within the next 9 months Glucocorticoids: prescribed according to a unified protocol

The main purpose of the current analysis was to ascertain the long-term renal outcome of patients randomised in the CYCLOFA-LUNE trial.

Methods: Data for kidney function, and adverse events (death, cardiovascular event, tumor, premature menopause) were collected by a cross-

sectional suvey for 38 of 40 patients initially randomised in the CYCLOFALUNE trial.

Results: The median follow-up time was 7.7 years (range 5.0–10.3). Rates of renal impairment and end-stage renal disease, adverse events (death, cardiovascular event, tumor, premature menopause) did not differ between the CPH and CyA group, nor did mean serum creatinine, 24 h proteinuria and SLICC damage score at last follow-up. Most patients in both groups were still treated with glucocorticoids, other immunosuppressant agents, and blood pressure lowering drugs.

	All (n=38)	CPH (n=19)	CyA (n=19)
Age (years), mean (SD)	39 (10)	37 (5)	38 (8)
Female, n	27 (71)	13 (68)	14 (74)
Follow-up (years), median (range)	7.7 (5.0–10.3)	7.4 (5.0–9.7)	5.3–10.3
50% increase in creatinine concentration	5 (13)	3 (16)	2 (11)
Non-sustained doubling of the creatinine concentration	2 (5)	1 (5)	1 (5)
Sustained doubling of serum creatinine	2 (5)	1 (5)	1 (5)
End-stage renal disease	2 (5)	1 (5)	1 (5)
Current serum creatinine (μmol/l)	67 (19)	71 (23)	63 (15)
Current 24 h proteinuria (g)	0.4 (0.6)	0.5 (0.5)	0.4 (0.7)
Additional IS drugs ever received	1 (1)	1 (2)	1 (1)
Deaths	0 (0)	0 (0)	0 (0)
Malignancy	2 (5)	0 (0)	2 (11)
Cumulative cardiovascular events	1 (3)	1 (5)	0 (0)
Premature menopause*	1 (4)	1 (8)	0 (0)
Pregnant*	9 (33)	6 (46)	3 (21)
Current SLICC DI (median, IQR)	0.0 (1.0)	0.0 (1.0)	0.5 (1.0)

2 patients included in the ESRD group are counted within the other groups with less severe renal impairment), Figures are numbers (%) of patients, or median (IQR) * since the end of the CYCLOFA-LUNE protocol treatment.

Conclusion: Both regimens based either on CPH or CyA achieved good and similar clinical results in the very long term

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Low Complement (C3), Male Gender and Methotrexate Use Are Associated With Noncalcified Plaque In Systemic Lupus Erythematosus.

Adnan Kiani[1], Armin Zadeh[2], Jens Vogel-Claussen[1], Joao Lima[2], Laurence S. Magder[3] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, [3]University of Maryland, Baltimore, MD.

Background/Purpose: New technology (CTA) can measure noncalcified coronary plaque (NCP), which is highly unstable and prone to rupture. We quantified NCP in SLE and determined the association with SLE manifestations.

Methods: 64 (n=106) or 320 (n=156) slice coronary multidetector computed tomography (MDCT) was performed in 262 SLE patients (90% female, 64% Caucasian, 30% African-American, mean age 50 years). The MDCT scans were evaluated quantitatively by a radiologist, using dedicated software. NCP score was a sum of plaque severity multiplied by the plaque composition divided by the number of vessels examined.

Results: Table 1 shows the mean NCP score, by demographics, traditional cardiovascular risk factors, history of lupus serologies and current medications. In the univariate analysis age, male gender, weight and hypertension were the major variables associated with NCP. A history of low complement (C3,C4) and anti-dsDNA (but not current) was associated with NCP. Prednisone and hydroxychloroquine therapy had no effect, but methotrexate use was associated with NCP. Table 2 shows the multivariate regression model, in which age, male gender, history of low C3 and methotrexate use remained independent predictors.

Table 1. Mean NCP Score, by Demographics, Traditional CVRF, History of Lupus Serologies and Current Medications

	Group	Mean NCP Score	p-value	p-value when age is controlled
Age	< 45 (n=110)	0.13 (0.20)	< 0.0001	–
	45–55 (n=81)	0.26 (0.29)		
	55+ (n=70)	0.42 (0.32)		
Race	White (n=167)	0.26 (0.30)	0.29	0.88
	Black (n=76)	0.26 (0.26)		
Gender	F (n=236)	0.23 (0.26)	0.015	0.031
	M (n=26)	0.38 (0.44)		
History of Smoking	No (n=168)	0.25 (0.29)	0.88	0.20
	Yes (n=94)	0.24 (0.28)		
Menopause	No (n=120)	0.20 (0.25)	0.0060	0.030
	Yes (n=104)	0.29 (0.28)		
Weight	< 150 (n=93)	0.18 (0.25)	0.0061[1]	0.030[2]
	150–199 (n=113)	0.27 (0.30)		
	200+ (n=49)	0.33 (0.31)		
Body Mass Index	< 25 (n=97)	0.18 (0.28)	0.0094[3]	0.072[4]
	25–29 (n=78)	0.27 (0.31)		
	30+ (n=80)	0.31 (0.27)		
Hypertension	No (n=98)	0.17 (0.22)	0.0009	0.0091
	Yes (n=164)	0.29 (0.30)		
Anti-ds DNA	No (n=100)	0.24 (0.26)	0.61	0.049
	Yes (n=162)	0.26 (0.30)		
Anticardiolipin	No (n=91)	0.23 (0.28)	0.38	0.60
	Yes (n=169)	0.26 (0.29)		
Low C3	No (n=116)	0.20 (0.27)	0.15	0.0038
	Yes (n=146)	0.27 (0.30)		
Low C4	No (n=137)	0.24 (0.30)	0.83	0.024
	Yes (n=125)	0.25 (0.27)		
Current Prednisone	No (n=155)	0.26 (0.30)	0.36	0.91
	Yes (n=79)	0.22 (0.28)		
Current Hydroxychloroquine	No (n=42)	0.31 (0.29)	0.13	0.18
	Yes (n=219)	0.24 (0.29)		
Current Azathioprine	No (n=242)	0.25 (0.29)	0.87	0.92
	Yes (n=20)	0.24 (0.21)		
Current Methotrexate	No (n=250)	0.23 (0.27)	0.0002	0.0026
	Yes (n=12)	0.54 (0.45)		
Current MMF	No (n=209)	0.25 (0.29)	0.70	0.13
	Yes (n=53)	0.23 (0.29)		
Current NSAIDS	No (n=185)	0.25 (0.30)	0.97	0.32
	Yes (n=76)	0.25 (0.26)		

[1] P<.0001 for trend with weight as a continuous predictor
[2] P=.0014 for trend with weight as a continuous predictor, controlling for age
[3] P=.0072 for trend with BMI as a continuous predictor
[4] P=.036 for trend with BMI as a continuous predictor, controlling for age.

Table 2. Multivariable Regression Model for Mean NCP

Variable	Effect on mean NCP score (95% Confidence Interval)	P-value
Age (per 10 years)	0.094 (0.068, 0.120)	< 0.0001
Low BMI (vs. normal)	−0.059 (−0.134, 0.015)	0.12
High BMI (vs. normal)	0.001 (−0.078, 0.081)	0.98
Hypertension	0.062 (−0.005, 0.130)	0.070
History of Low C3	0.091 (0.023, 0.159)	0.0090
History of anti-dsDNA	0.017 (−0.053, 0.086)	0.64
Male sex	0.112 (0.011, 0.214)	0.030
Methotrexate	0.248 (0.100, 0.395)	0.0011

Conclusion: NCP is a measure of immediate risk of a cardiovascular event and contributes to overall atherosclerotic burden. Male gender, history of low C3 and hypertension associate with semi-quantified noncalcified plaque in SLE. The association with methotrexate is unexpected, as in rheumatoid arthritis methotrexate reduces cardiovascular risk. Methotrexate can increase homocysteine, a known risk factor for atherosclerosis, in SLE. However, methotrexate is also preferentially used to treat lupus arthritis. Because causality cannot be proven, we cannot recommend stopping the use of methotrexate in SLE at this time.

Disclosure: A. Kiani, None; **A. Zadeh**, None; **J. Vogel-Claussen**, None; **J. Lima**, None; **L. S. Magder**, None; **M. Petri**, None.

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Gender Influence On Lupus Nephritis Outcomes In An Urban, Multi-ethnic Population. Cindy Johnston, Catarina Vila-Inda and Irene Blanco. Albert Einstein College of Medicine, Bronx, NY.

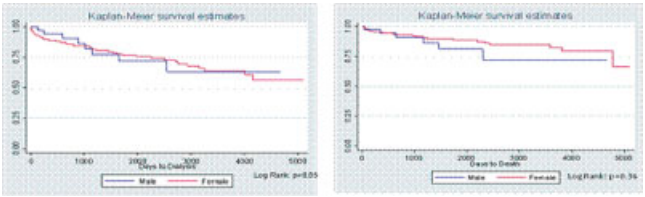
Background/Purpose: Systemic lupus erythematosus (SLE) is a disease predominately of young women that disproportionately affects minorities. Lupus Nephritis (LN) causes major morbidity and mortality in this population. It is suggested that men with SLE have worse disease outcomes with high rates of LN. This study was undertaken to identify major clinical differences and outcomes by gender in LN in an urban ethnic population.

Methods: All LN biopsies at Montefiore Medical Center, Bronx, NY were analyzed from Jan 1997- Jan 2012. All patients met ≥ 4/11 ACR SLE criteria. We collected demographics, clinical and serologic data and treatment regimens over a 1yr period post biopsy. The primary endpoints were gender differences in time to end stage renal disease (ESRD) as defined by the initiation of dialysis and inclusion in the US Renal Data System and all-cause mortality as reported to the Social Security Administration.

Results: 207 patients were included: 37 male (M) 170 female (F). Men trended to be diagnosed with SLE earlier (24.6y±14.4 v 28.2y±14.2, p=0.2) and have a shorter disease duration at the time of biopsy (median 1y v 2y, p=0.11). There were no differences with regards to ethnicity: African American 55.6% M v 55.1% F and Hispanic 36.1% M and 37.7% F (p=0.93). Both genders had similar rates of hypertension (p=0.91), diabetes (p=0.80), and cardiovascular disease (p=0.40). At biopsy, men had higher levels of dsDNA antibodies (median 263.9 v 126.3, p=0.007) but there were no difference in median C3 (p=0.74) and C4 levels (p=0.71), mean systolic BP (p=0.71), median serum creatinine (1.1 M v 1.0 F, p=0.23) or median protein to creatinine ratio (2.1 M v 2.2 F, p=0.53). The distribution of LN classes between the genders were similar: class III/IV - 59.5% M v 58.2% F; class V - 27.0% M v 25.3% F; mixed class - 8.1 %M v 12.4% F(p=0.88).

There was no difference in ACEi/ARB (p=0.54), hydroxychloroquine (p=0.72) or steroid use (p=0.14) between the genders. While men tended to get cyclophosphamide induction at higher rates than women (60.0% M v 48.8%F) both genders were mostly maintained on mycophenolate (64.0% M v 65.5% F).

Regardless of subtle, though not statistically significant, differences in treatment there was no difference between rates of ESRD (log rank, p=0.85) or all-cause mortality (log rank p=0.36) between the genders.



Conclusion: Our study suggests that there are few clinical differences between men and women lupus nephritis in this population. Race/ethnicity/socioeconomic status may play a greater role than gender when looking at disease severity and outcomes.

Disclosure: C. Johnston, None; **C. Vila-Inda**, None; **I. Blanco**, None.

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Association Between Serum Leptin and Adiponectin Levels With The Severity Of Proteinuria In Lupus Nephritis. Valeria Diaz-Rizo[1], Nicte Selene Fajardo-Robledo[2], Alan Joel Ruiz-Padilla[2], Dalia Sanchez-Mosco[3], Tania Marlene Rodriguez-Hernandez[4], Xochitl Trujillo[5], Miguel Huerta[5], Monica Vazquez del Mercado[6], Laura Gonzalez-Lopez[4] and Jorge Ivan Gamez-Nava[7]. [1]Doctorado en Ciencias Médicas, Centro Universitario de Investigación Biomédica, Universidad de Colima; UMAE, Hospital de Especialidades, Centro Médico Nacional de Occidente, IMSS, Guadalajara, Jalisco, Mexico, [2]Doctorado en Farmacología, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Jalisco, Mexico, [3]Centro Universitario de Investigación Biomédica, Universidad de Colima; Hospital General Regional 110 IMSS, Guadalajara, Jalisco, Mexico, [4]Hospital General Regional 110, Instituto Mexicano del Seguro Social (IMSS), Guadalajara, Jalisco, Mexico, [5]Centro Universitario de Investigación Biomédica, Universidad de Colima, Colima, Mexico, [6]Universidad de Guadalajara, Guadalajara, Mexico, [7]UMAE, Centro Médico Nacional de Occidente, IMSS; Doctorado en Farmacología, Universidad de Guadalajara, Jalisco, Mexico.

Background/Purpose: To identify the association between serum leptin and adiponectin levels and proteinuria secondary to lupus nephritis in women with systemic lupus erythematosus (SLE).

Methods: One-hundred and four women with SLE were included in the study. All of them were assessed in order to identify the presence of lupus nephritis; proteinuria levels in 24 hours were identified, patients were classified in two groups: SLE with proteinuria ≥0.5 g in 24 h secondary to lupus nephritis (SLE + proteinuria n=30) and SLE without nephritis (n=74). Patients with proteinuria secondary to causes different to nephritis were excluded. Other assessments included modified-SLEDAI (m-SLEDAI) for disease activity, SLICC/ACR and Body Mass Index (BMI). Serum levels of leptin, and adiponectin were measured by ELISA. Leptin was adjusted by BMI. Statistical analysis included a comparison of means between groups using Student t-test for independent samples, Pearson correlation test to identify strength of association between serum leptin and adiponectin levels with proteinuria and other quantitative variables. A multiple regression analysis was used to adjust for confounders.

Results: In the comparison between groups there were no statistically significant differences in age, weight or BMI between SLE + proteinuria versus SLE without nephritis. The group with SLE + proteinuria had higher serum adiponectin levels compared with SLE without nephritis (20.11±10.58 μg/mL vs. 15.36±7.83 μg/mL respectively; p=0.032). Serum leptin levels were not statistically different between the group with SLE + proteinuria compared with SLE without nephritis (28.68±25.79 ng/mL vs. 23.43±29.15 ng/mL respectively; p=0.39). Serum leptin levels had a positive correlation with weigh (r=0.306, p=0.002), BMI (r=0.327, p=0.001), serum creatinine in mg/dL (r=0.283, p=0.004), chloroquine (r=0.262, p=0.009) and prednisone doses (mg/day) (r=0.207, p=0.035) but did not correlated with proteinuria (r=−0.014, p=0.893) neither with m-SLEDAI (r=0.092, p=0.357) and SLICC/ACR (r=0.083, p=0.408). Serum adiponectin levels correlated with serum creatinine (r=0.255, p=0.010) and proteinuria (r=0.305, p=0.002), m-SLEDAI (r=0.299, p=0.002), chloroquine (r=0.203, p=0.046) and prednisone doses (r=0.343, p=<0.001), but there was no correlation between adiponectin and SLICC/ACR (r=0.085, p=0.394). A negative correlation was observed between adiponectin and weigh (r=−0.204, p=0.038), BMI (r=−0.203, p=0.039) and fast glucose serum levels (r=−0.347, p=<0.001). In the multivariate analysis, after adjusting by age, disease duration, BMI and leptin, serum adiponectin levels remained associated with severity of proteinuria (p=0.005).

Conclusion: Serum adiponectin levels were higher in women with SLE + proteinuria compared to SLE without nephritis. Longitudinal studies should be performed in order to identify if patients with proteinuria and high serum adiponectin levels have differences in the development of response to therapies directed against of nephritis.

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Factors Associated With Long-Term Renal Function Deterioration In Lupus Nephritis Treated Initially With Combined Prednisolone and Mycophenolate Mofetil (MMF) Or Tacrolimus (Tac). Chi Chiu Mok[1], Chi Hung To[1], King Yee Ying[2], Cheuk-Wan Yim[3] and Woon Leung Ng[3]. [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Princess Margaret Hospital, Hong Kong, Hong Kong, [3]United Christian Hospital, Hong Kong, Hong Kong.

Background/Purpose: To study the risk factors for renal function decline in patients with lupus nephritis treated initially with combined steroid and MMF or Tac.

Methods: Data were extracted from a randomized controlled trial of the efficacy of MMF vs Tac for induction treatment of lupus nephritis. All patients recruited were treated with high-dose prednisolone (0.6mg/kg/day for 6–8 weeks and tapered) with either MMF (2–3g/day) or Tac (0.1-0.06mg/kg/day) for 6 months. Patients with good clinical response were shifted to azathioprine (AZA) (2mg/kg/day) and continued on low dose prednisolone (<10mg/day) for maintenance. Rescue therapies were given to patients who did not have response to treatment at the discretion of the attending physicians. Factors associated with renal function decline at 5 years were studied by Cox regression analyses.

Results: 150 patients (92% women) with biopsy confirmed active lupus nephritis were studied (ISN/RPS class III 17%; IVG 31%; IVS 12%; III/IV+V 21%; pure V 20%). The mean age was 35.5±12.8 years and SLE duration was 50.2±62 months at the time of renal biopsy. 102 (68%) patients had first time glomerulonephritis while the others had relapsed disease. The mean histological activity and chronicity score was 8.2±3.4 and 2.6±1.6, respectively. 59(39%) patients were hypertensive, 62(41%) had active urinary casts and 112(75%) had microscopic hematuria at presentation. The mean creatinine clearance (CrCl) was 79.0±30.8 ml/min and 67% patients had CrCl less than 90ml/min. At 6 months, 61% patients achieved good clinical response, 25% had partial response but 15% patients had no response (NR) (urine P/Cr improvement <50% or >3.0 or deterioration in CrCl (>20%) ± persistently active urinary sediments and lupus serology). Rescue regimens for NR patients included: oral or intravenous pulse cyclophosphamide (68%), Tac or MMF (14%) and MMF + Tac combination (18%). 128(85%) patients received AZA (83.1±23mg/day) for maintenance therapy. After a mean follow-up of 56±28 months, 27(18%) patients had loss of CrCl by >=30% and 17 (11%) patients developed stage 4/5 chronic kidney disease (CKD) (CrCl <30ml/min). The cumulative risk of loss of CrCl by ³30% or stage 4/5 CKD was 3% at 12 months, 7.7% at 24 months, 8.4% at 36 months, 13.6% at 48 months and 17.3% at 60 months. Cox regression revealed histological activity score (HR 0.78[0.65–0.94]; p=0.007), chronicity score (1.46[1.06–2.01]; p=0.02), non-response at 6 months (HR 3.87[1.34–11.2]; p=0.01), class V histology (HR 0.35[0.16–0.74]; p=0.006) and number of renal flares (HR 1.59[1.01–2.49; p=0.04] were independent risk factors for CrCl loss by 30% of stage 4/5 CKD, after adjustment for age, sex, SLE duration, first-time renal disease, proteinuria and CrCl at presentation and the treatment arm during induction phase (MMF or Tac).

Conclusion: Combined prednisolone with MMF or Tac is equally effective for the initial treatment of active lupus nephritis. No response at 6 months, proliferative types of lupus nephritis, lower activity but higher chronicity score on renal biopsy and the number of renal flares are predictive of renal function decline at 5 years.

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Hypovitaminosis D and The Metabolic Syndrome In Patients With Systemic Lupus Erythematosus (SLE). Chi Chiu Mok[1], Ling Yin Ho[1] and Daniel Birmingham[2]. [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Ohio State University Medical Center, Columbus, OH.

Background/Purpose: Low vitamin D level has been linked to cardiovascular diseases and mortality in the general population. Hypovitaminosis D is associated with certain traditional vascular risk factors in patients with SLE. This study aims to evaluate the relationship between the metabolic syndrome (MetS) and serum 25-hydroxyvitamin D level in patients with SLE.

Methods: Consecutive patients who fulfilled >=4 ACR criteria for SLE in a two-month period were recruited from our out-patient lupus clinics. Blood was taken in the morning for the assay of 25-hydroxyvitamin D3 (enzyme immunoassay; Immunodiagnostic Systems Inc, Fountain Hills, AZ, USA) and high sensitivity C-reactive protein (hsCRP) (solid phase chemilluminescence immunometric assay; Siemens Healthcare Diagnostics, Deerfield, Il., USA). Clinical assessments (waist circumference, fasting glucose and lipid level, blood pressure) were made for each patient who was stratified for the MetS according to the 2009 International joint consensus criteria, using the Asian criteria for abdominal obesity (ref 1). The relationship between 25-hydroxyvitamin D level and the MetS was studied by linear regression, with adjustment for other confounding covariates.

Results: 257 SLE patients (94% women) were studied. All were ethnic Chinese. The mean age was 39.6±13.1 years and SLE duration was 8.3±6.9 years. Vitamin D insufficiency (25-hydroxyvitamin D3 <30ng/mL), deficiency (25-hydroxyvitamin D3 <15ng/mL, and severe deficiency (level<10ng/mL) was present in 95%, 25% and 3.5% of patients, respectively. The prevalence of the MetS was 8.3%, 11% and 22.2% in patients with vitamin D insufficiency, deficiency and severe deficiency, respectively. None of the patients with 25-hydroxyvitamin D3 levels >30ng/mL fulfilled the criteria for the MetS. Linear regression analysis revealed that levels of 25(OH)vitamin D3 were independently associated with age (Beta 0.19; p=0.002), the presence of the MetS (Beta −0.14; p=0.049) and hsCRP level (Beta −0.14; p=0.04) after adjustment for gender, SLE duration, duration of sunshine in the month of venepuncture, SLE damage scores (SDI), smoking ³3 years, renal insufficiency (estimated CrCl < 50ml/min), photosensitivity and ever use of glucocorticoids.

Conclusion: Vitamin D deficiency is prevalent in patients with SLE. Hypovitaminosis D is independently associated with the MetS and hsCRP, suggesting that it is a novel risk factor for vascular thrombosis in patients with SLE.

Reference:

1. Alberti KG et al. Circulation 2009;120:1640–5.

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Repeat Biopsy In Lupus Nephritis: A Single-Center Experience. Josefina Marin[1], Marina Scolnik[1], Eliana Lancioni[1], Gustavo Greloni[2], Cristian Quiroz[1], Johana Zacariaz[1], Carla Saucedo[1], Luis J. Catoggio[3] and Enrique R. Soriano[3]. [1]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Nephrology Service, Buenos Aires, Argentina, [3]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina.

Background/Purpose: Renal involvement in systemic lupus erythematosus (SLE) is an important cause of morbidity and even mortality. Lupus nephritis has diverse morphologic manifestations with varying clinical presentations and consequences.Treatment and prognosis accordingly range from excellent even with only observation with minimal mesangial deposits, to kidney failure despite aggressive immunosuppression in patients with severe proliferative disease. Renal biopsy plays a crucial role in the diagnosis of the specific form of lupus nephritis, and rebiopsy is often necessary during follow up in order to assess renal activity and guide treatment. The objective of our study was to describe characteristics of second biopsies in SLE patients and try to identify variables useful for prediction of histological form of lupus nephritis in second biopsies.

Methods: SLE patients (ACR criteria) who had a diagnosis of lupus nephritis and two or more renal biopsies after year 2001 were included. Electronic medical records were reviewed and clinical, laboratory and treatment data were obtained from each patient. Renal biopsy was classified according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of lupus nephritis.

Results: We identified 45 lupus patients (40 females) with at least two renal biopsies. These patients had a total of 116 biopsies. Class IV (51,8%) and V (17,2%) were the most frequent findings. Treatments received are shown in table 1. Laboratory findings at the moment of biopsy are shown in table 2 and showed no significant differences between different histology patterns. In multivariable analysis no variable was significantly associated with any histology class at time of the second biopsy. 27 patients (64%) changed histology class between successive biopsies. Those who did not change were mostly class IV (68.8%). 55 rebiopsies (82%) generated a treatment modification and 12 (18%) did not (insufficient data from 6).

Table 1. Treatment received after renal biopsies.

Induction treatment	Maintenance treatment
IV Cyclophosphamide >= 6 pulses (33%)	Mycophenolate (45,7%)
Mycophenolate (22,4%)	Azathioprine (17%)
IV cyclophosphamide < 6 pulses (13%)	Cyclophosphamide (9.5%)
Rituximab (8%)	Others (8,6%)
Others (21%)	

Table 2. Laboratory features at time of second biopsy.

	Class II	Class III	Class IV	Class V	Combination b/ III or IV + V
Mean proteinuria (g/24 hs)	0.92	1.24	2.29	3.57	5.92
Mean creatinine (mg/dl)	0.98	1.14	1.27	1.16	1
Patients with hematuria, (>4 RBC), %	88.9%	60%	69%	50%	50%
Mean Albumin (g/dl)	3.05	3.39	2.8	2.93	2.4
Low C3, %	57.1%	33%	76.7%	50%	67%
DNA +, %	66.7%	44.5%	81.8%	26.7%	50%

Conclusion: In this lupus nephritis cohort, 64 % of patients with a repeated biopsy showed change in the histological class. We were unable to identify variables capable of predicting histological class in second biopsies. In 82% of patients second biopsy was associated with treatment change.

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Factors Associated With a Double Increase In Serum Creatinine In Biopsy Proven Lupus Nephritis From a Single Center In Spain. Raúl Menor Almagro[1], M. H. Cardiel[2], Javier Rubio Garrido[1], J. Luis de la Iglesia[1], José Javier Perez Venegas[1], María Mar Ruiz Tudela[1], José Javier Salaberri[1] and Manuel Paez-Camino[1]. [1]Hospital de Jerez, Jerez de la Frontera, Spain, [2]Centro de Investigacion Clinica de Morelia, Morelia, Mexico.

Background/Purpose: Lupus nephritis is a common and feared complication in systemic lupus erythematosus (SLE). Clinicians have relied on different variables to help to predict those subjects who will eventually develop a kidney function deterioration. Our objective was to identify those variables associated with a double increase in serum creatinine in biopsy proven lupus nephritis (LN).

Methods: All patients fulfilled ACR criteria for SLE. We identified 49 cases with biopsy proven lupus nephritis. Clinical charts were reviewed by a single trained rheumatologist following predefined criteria for different variables recorded when the biopsy was performed including clinical, laboratory, immunologic and histological information. All biopsies were evaluated by a single qualified and experienced pathologist who scored activity and chronicity indices. Forty nine patients were identified. Ten of them doubled their creatinine in their follow-up. These subjects were compared with the other thirty nine patients using chi square or Mann Whitney U test. In all cases significance was set at 0.05 alfa level. Odds ratio and 95% confidence intervals were also calculated.

Results: Mean age of onset of SLE was 30.1 +/−12 years, and mean age onset of LN was 32.5 +/−12 months. Main reasons for a first renal biopsy were persistent urine abnormalities (27 patients), proteinuria (17), nephritic syndrome (4) and acute renal failure (1). Histologic diagnosis (WHO criteria) were type IV (22/44%), II (14/28%), III (10/20%), V (2/10), VI (1/2%). Our study did not found significant relationship between double increase in serum creatinine and type of biopsies, but activity and chronicity index showed a clear trend almost reaching statistical significance. Other variables are presented in table 1.

Table 1.

Variable	Doubled creatinine (n:10)	Not doubled creatinine (n:39)	OR 95% CI	p value
Age (Mean/SD)	24/9	31/11		0.06
HBP*	10	24	7 (0.8–59)	0.02
Serositis	7	11	5.9 (1.2–27)	0.02
Edema	10	24	7 (0.8–59)	0.02
Lymphopenia	10	23	7.7 (0.9–66)	0.01
APLA (+)**	6	8	5.8 (1.3–25)	0.02
Activity Index	9.8/5.9	6/4.9		0.06
Chronicity Index	2.7/2.4	1.4/1.7		0.06

* HBP: High blood pressure
** Positive anticardiolipin antibodies

Conclusion: A subgroup of clinical, laboratory and histologic variables were identified as predictors to double creatinine in biopsy proven lupus nephritis. However increasing anti-double-stranded DNA antibody and hypocomplementemia no showed statistical significance as in previous studies. These can be useful to increase clinical surveillance in these patients.

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Mycophenolate Mofetil Is Not Associated With Reduced Cardiovascular Or Lupus Damage Accumulation In a Cross-Sectional Lupus Cohort Study. Maureen A. McMahon[1], Maria Dall'era[2], Eliza Chakravarty[3], Joseph E. Craft[4], Gary S. Gilkeson[5], Kenneth C. Kalunian[6], R. John Looney[7], Gerald McGwin Jr.[8] and Meggan Mackay[9]. [1]UCLA David Geffen School of Medicine, Los Angeles, CA, [2]University of California, San Francisco, San Francisco, CA, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]Yale University School of Medicine, Internal Medicine, Section of Rheumatology, New Haven, CT, [5]Medical University of South Carolina, Charleston, SC, [6]UCSD School of Medicine, La Jolla, CA, [7]University of Rochester, Rochester, NY, [8]University of Alabama at Birmingham, Birmingham, AL, [9]Feinstein Institute for Medical Research, Manhasset, NY.

Background/Purpose: Mycophenolate mofetil (MMF) is frequently used for the treatment of lupus. The immune-modulating effects of MMF extend beyond effects on lymphocyte proliferation, and include inhibition of adhesion molecule expression, suppression of NO production, and reduction in cardiovascular morbidity and progression of atherosclerosis in cardiac and renal transplant patients. We examined the association between cardiovascular and non-cardiovascular damage among patients taking MMF, mycophenolic acid (MPA), AZA or methotrexate (MTX) in lupus centers participating in a North American patient registry of the Lupus Clinical Trials Consortium, Inc. (LCTC). We hypothesized that the use of MMF or MPA is protective against both overall and cardiovascular damage in patients with lupus, compared to azathioprine (AZA).

Methods: The LCTC registry consists of consecutively enrolled adults with SLE from 16 North American centers, each contributing approximately 100 patients. Patients who were taking MMF or MPA, AZA, or MTX at the time of enrollment into the registry were included in the current analysis. Patients taking MMF/MPA and AZA were compared as were patients taking MTX vs. AZA with respect to: a.) the prevalence of any damage on American College of Rheumatology/SLICC Damage Index at baseline (ACR/SDI), defined as SDI ≥1, and b.) the prevalence of cardiovascular damage at baseline, defined as myocardial infarction, angina/coronary artery bypass graft, claudication, and/or stroke on ACR/SDI. Patients were excluded from the analysis if they were taking more than one DMARD.

Results: Among 1507 patients enrolled, 430 patients were taking MMF or MPA, 183 were taking AZA, and 79 were taking MTX at baseline. Among treated patients, mean age was 48.1 ±13.5 in MTX group, 38.9 ±12.4 in the MMF group, and 39.4 ± 13.2 in the AZA group. A baseline history of renal disease was present in 10.1% of MTX subjects, 66.7% of MMF/MPA subjects, and 43.7% of AZA patients.

Any cardiovascular damage on the baseline SDI was seen in 9.2% of subjects. Any baseline damage on SDI (exclusive of cardiovascular damage) was present in 54.6% of subjects. The prevalence ratio (PR) for baseline cardiovascular damage present on the ACR/SDI in the MMF vs. AZA group was 0.83 (95% confidence interval [CI] 0.45 – 1.5, p=ns), while the PR for MTX vs. AZA was 1.17 (95% CI 0.5 – 2.7, p=ns). The PR for the presence of ANY non-cardiovascular damage on ACR/SDI at baseline for MMF/MPA vs. AZA was 0.96 (95% CI 0.75 – 1.2, p=ns), while the PR for MTX vs. AZA was 0.94 (95% CI 0.65 – 1.4, p=ns).

Conclusion: In this cross-sectional analysis, there was no difference in the baseline prevalence of either cardiovascular or total damage on SDI based on the use of MMF/MPA or MTX in comparison to AZA. Limitations of this study include the cross-sectional nature of the data, lack of information regarding the length of time of exposure to the medications of interest prior to study entry, and confounding by medication indication (e.g., nephritis).

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Childhood Lupus Nephritis: Long Term Outcome Of 91biopsy Proven Cases From India. Puja Srivastava, Bonnie Abujam, Ramnath Misra, Able Lawrence, Vikas Agarwal and Amita Aggarwal. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background/Purpose: Childhood SLE has a higher prevalence of lupus nephritis (LN) as well as proliferative LN than adults. There is ethnic variation in response to treatment as well as outcome of LN. There is limited data on long-term outcome of Childhood LN from Indian subcontinent.

Methods: Retrospective analysis of case records of patients of SLE over last 24 years was done. The inclusion criteria were: fulfillment of ACR 1987 criteria for diagnosis, age of onset less than 18 years, biopsy proven lupus nephritis. Data on clinical features, treatment, outcome, complications and mortality was collected.

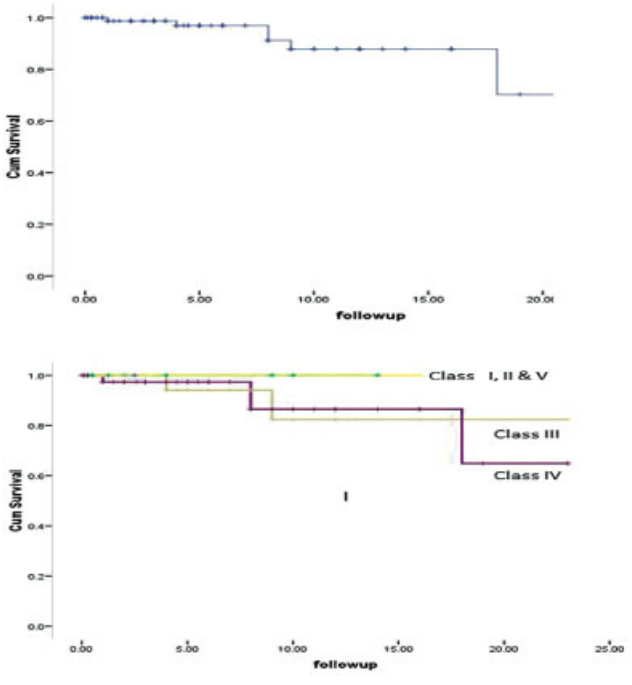
Results: Among 1015 patients with SLE there were 206 patients with childhood onset SLE. Among these 206 patients 145 had some evidence of renal disease of which 93 underwent biopsy (2 were inadequate) thus data on 91 patients was analyzed.

Among these 91 children (82 girls), the mean age at onset was 13.7± 3.5 years and the median duration of disease at presentation was 1 year. LN was present at onset in 76 patients.

Proteinuria was present in 92% (18% nephrotic range), hematuria in 75%, leucocyturia in 75% and 11% had cellular casts. 19 patients had raised serum creatinine at presentation. The distribution of histological classes was (class I: 1, class II:13, Class III: 24, Class IV: 41, Class V: 12 patients). Eight patients had associated membranous nephropathy along with proliferative GN. Out of these 63 received Cyclophosphamide and 5 received MMF as induction therapy.

The median follow up was 8 (0.1–23) years. Only 12 had less than 1 year follow up and 22 patients had more than 10 year follow up. At the last follow up 58 were in complete renal remission, 19 had partial remission, 5 had active renal disease, 3 had ESRD and 6 had died (one each due to staph sepsis, pancreatitis, disseminated TB, stroke, ESRD, unknown). 31 patients had infection of which 14 required hospitalization. 44 patients had major disease flare and 15 had minor flare.

The 5 year actuarial survival was 95% and the 10 year survival was 88%. Histological class had no effect on survival even though all deaths occurred in patients with proliferative LN. There was no effect of gender or age of onset.



Conclusion: Proliferative GN is the most common renal pathology. Almost two third patients are in complete remission at a median follow up of 7 years. 10% of children either died or had ESRD. The outcome is comparable to the Western data however the infection rate is higher.

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Characteristics Of Lupus Nephritis: Data From a Large Multicenter Registry Of Patients With Systemic Lupus Erythematosus. Diane L. Kamen[1], Graciela S. Alarcon[2], Jill P. Buyon[3], Mary Anne Dooley[4], Richard A. Furie[5], David S. Pisetsky[6] and Tammy O. Utset[7]. [1]Medical University of South Carolina, Charleston, SC, [2]University of Alabama at Birmingham, Birmingham, AL, [3]NYU School of Medicine, New York, NY, [4]University of North Carolina at Chapel Hill, Chapel Hill, NC, [5]The Feinstein Institute for Medical Research and North Shore-Long Island Jewish Health System, Lake Success, NY, [6]Duke University Medical Center, Durham, NC, [7]University of Chicago Department of Medicine, Chicago, IL.

Background/Purpose: Renal disease is strongly associated with morbidity and mortality among SLE patients. We utilized the Lupus Clinical Trials Consortium, Inc. longitudinal registry of SLE patients from 16 academic lupus centers to estimate prevalence and incidence of renal disease and associated differences in demographics, comorbidities, biopsy rates, and therapeutic exposures.

Methods: Patients were consecutively enrolled and followed at outpatient visits by participating rheumatologists. Lupus nephritis (LN) was defined by ACR Classification Criteria. Damage (end-stage renal disease (ESRD), proteinuria (≥3.5 gm/d), low GFR) was determined by SLICC Damage Index (SDI). Descriptive statistics, chi square, Fisher's exact, and ANOVA was used as appropriate to compare disease characteristics. Multivariate regression modeling was used to adjust for disease duration and race. $P < 0.05$ was considered statistically significant.

Results: Of 1507 patients, 639 (42.4%) had LN at registry enrollment. Mean age was 41.3 yrs, disease duration 9.4 yrs, 5.5 ACR Criteria, 2.6 SLEDAI score, and 1.1 SLICC-DI score. LN patients were younger at SLE diagnosis (26.2 vs 32.1 yrs, $p<0.01$) and 11.9% LN vs 6.0% non-LN patients were male ($p<0.01$). LN prevalence in non-Hispanic Blacks (49%) and Asians (53%) was higher than non-Hispanic Whites (32%, $p<0.01$).

LN and non-LN patients had similar prevalence of cardiovascular disease (7.4 vs. 8.0%, $p=0.67$), though LN patients had higher prevalence of hypertension (57.0% vs. 29.5%, $p<0.01$), hyperlipidemia (23.2% vs. 11.4%, $p<0.01$), and pre-eclampsia (10.0 vs. 5.7%, $p<0.01$). Asians with LN had a lower renal biopsy rate of 66.2% compared to non-Hispanic Blacks (79.3%, $p=0.02$). LN patients with a confirmatory renal biopsy were more likely to have received cyclophosphamide (CTX, 51.4% vs 34.4%, $p=0.0002$), mycophenolate (MMF, 75.0% vs 56.9%, $p<0.0001$), or both CTX and MMF in the past (38.4 vs 21.3%, $p<0.0001$) compared to non-biopsied LN patients.

Of 868 non-LN patients at enrollment, 10 (1.2%) developed LN over an average of 1.8 yrs follow-up. Of the 1348 with no renal damage at enrollment, 28 (2.1%) developed renal damage over an average of 1.8 yrs follow-up. Patients without renal damage at enrollment taking hydroxychloroquine (72.0% overall) had subsequently lower renal damage incidence (1.3% vs 4.0%, $p=0.0023$). Patients on MMF (26.3% overall) had higher incidence of renal damage (3.7% vs 1.5%, $p=0.014$) but no difference seen with CTX or azathioprine.

At enrollment, 55 patients had ESRD with an additional 14 incident cases over 2.5 yrs follow-up. Eight patients (12%) with low GFR vs 0.04% without low GFR by SDI at enrollment progressed to ESRD over an average of 1.8 yrs follow-up. Seven patients (15%) with proteinuria vs 0.5% without proteinuria by SDI at enrollment progressed to ESRD over an average of 1.8 yrs follow-up.

Conclusion: This study describes prevalent and incident characteristics of LN and renal damage among a large cohort of patients with SLE. Consistent with other cohorts, LN rates vary by race and hydroxychloroquine use appears to help protect from renal damage. Prior renal damage associated with progression to ESRD emphasizes the importance of early identification of high-risk SLE patients.

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Venous Thromboembolic Disease Is Associated With Increased Length Of Stay and In-Hospital Mortality In Hospitalized SLE Patients: A Multi-State, Population-Based Study. Matthew Cascino[1], Laura Trupin[2], Sara Murray[1], Mary Margaretten[1], Edward H. Yelin[1] and Jinoos Yazdany[1]. [1]University of California, San Francisco, San Francisco, CA, [2]UC San Francisco, San Francisco, CA.

Background/Purpose: Individuals with systemic lupus erythematosus (SLE) are at increased risk for venous thromboembolism (VTE). However, there is limited population-based data on outcomes associated with VTE in patients with SLE. The aims of our study were to determine 1) the prevalence of VTE among hospitalizations for SLE, and 2) the independent effect of VTE on hospital outcomes in SLE, including length of stay and in-hospital mortality.

Methods: Using data from the Health Care Cost and Utilization Project State Inpatient Databases, we performed a retrospective study of hospitalizations among adult patients with a diagnosis of SLE in five geographically dispersed states in 2009. Individuals with VTE were identified using validated administrative definitions of deep vein thrombosis (DVT) and pulmonary embolism (PE). We used multivariable regression analyses to examine the effect of VTE on length of stay and in-hospital mortality, the primary outcomes in our analysis. We adjusted for sociodemographic characteristics (age, sex, race/ethnicity), median household income based on zip code, modified Charlson comorbidity index, and a SLE-specific risk adjustment index for in-hospital mortality developed by Ward. In additional analyses, we examined the effect of DVT and PE separately.

Results: A total of 41,806 hospitalizations for patients with SLE were identified. 1,543 of these hospitalizations (3.7%) were associated with VTE; 1,063 patients had DVT (2.5%), 352 patients had PE (0.84%), and 128 (0.31%) had both. VTE patients were younger (48.1 years vs. 51.0 years, $p<0.001$), more likely to be black race (31.9% vs. 24.2%, $p>0.001$), more likely to have Medicaid as the primary payer (24.0% vs. 20.1%, $p<0.001$), had higher SLE-specific risk adjustment index (2.64 vs. 2.44, $p=0.005$), and were more likely to have nephritis (25.4% vs. 19.2%, $p<0.001$), hemolytic anemia (1.75% vs. 0.78%, $p<0.001$), thrombocytopenia (5.06% vs. 3.69%, $p<0.001$), and pleuritis (5.38% vs. 3.43%, $p<0.001$). In unadjusted analysis, VTE was associated with longer length of stay (9.8 vs. 5.8 days, $p<0.001$) and increased in-hospital mortality (4.0% vs. 2.0%, $p<0.001$). Results of adjusted analyses are depicted in the Table and demonstrate that VTE, DVT, and PE are independently associated with increased length of stay and in-hospital mortality.

Table. Adjusted regression analyses of VTE, DVT, and PE with length of stay and in-hospital mortality.

		Length of stay		Mortality	
	N (%)	B coeff. (95% C.I.)	p-value	OR (95% C.I.)	p-value
VTE	1,543 (3.69%)	3.84 (3.43–4.25)	< 0.001	2.00 (1.50–2.65)	< 0.001
PE	480 (1.15%)	2.95 (2.23–3.67)	< 0.001	2.42 (1.52–3.85)	< 0.001
DVT	1,063 (2.54%)	4.24 (3.75–4.73)	< 0.001	1.81 (1.28–2.58)	0.001

Adjusted for age, gender, race/ethnicity, median household income by zip code, primary payer, Charlson comorbidity index, and a SLE-specific risk adjustment index developed by Ward.
Separate analyses were performed to identify the individual effects of PE and DVT. Patients with both PE and DVT were classified as having PE for this analysis.

Conclusion: The development of VTE was associated with a significant increase in length of stay and in-hospital mortality among a representative population of hospitalized SLE patients.

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Effect Of Renal Damage On Extra-Renal Organ Damage and Mortality In Patients With Systemic Lupus Erythematosus (SLE): A Longitudinal Cohort Study Of 756 Patients. Chi Chiu Mok, Ling Yin Ho, Kar Li Chan and Chi Hung To. Tuen Mun Hospital, Hong Kong, Hong Kong.

Background/Purpose: To study the effect of renal damage on extra-renal organ damage and mortality in patients with SLE.

Methods: Patients who fulfilled >=4 ACR criteria for SLE between 1995 and 2011 were longitudinally followed. Organ damage in 12 systems was assessed by the ACR SLICC damage scores (SDI). The cumulative rate of survival was studied by Kaplan-Meier's plot. For those who died during the disease course, data were censored at the time of death. For those who were lost follow-up, data were censored at the time of last clinic visits. Comparison of extra-renal organ damage and survival rate was made between patients with and without renal damage during the course of SLE.

Results: 756 SLE patients were studied (696 women, 92%). All were ethnic Chinese. The mean age of onset of SLE was 32.7±13.6 years and the mean follow-up time of the entire cohort of patients was 9.4±7.4 years. 76 (10%) patients died during the course of illness and 34 (4.5%) patients were lost to follow-up. 26 (3.4%) patients developed end stage renal failure (ESRF). The main contributing causes of death in those 76 patients were: infection (49%), cardiovascular events (12%), cerebrovascular events (13%), cancer (11%), suicide (3%) and others (13%). Overall, renal damage occurred in 84 (11%) patients (64% with impaired glomerular filtration rate; 6% persistently heavy proteinuria; 30% ESRF). Compared with patients without renal damage (renal SDI=0), those with renal damage had significantly higher incidence of damage in the eyes, central nervous system, pulmonary system, cardiovascular system, musculoskeletal system, gonads and the endocrine system ($P<0.001$ in all). The corresponding mean SDI scores in these systems were also significantly higher in patients with renal damage than those without. The cumulative survival rates of our patients were 94% at 5 years, 90% at 10 years and 86% at 15 years. Patients with renal damage had significantly higher mortality than those without (log rank test; $p<0.001$). The age and sex adjusted hazard ratio for mortality in patients with renal damage relative to those without renal damage was 3.55 (95% CI 2.22–5.66; <0.001).

Conclusion: In patients with SLE, renal damage significantly and adversely affects survival. The presence of renal damage significantly increases the incidence of extra-renal organ damage, particularly in the cardiovascular, pulmonary, neuropsychiatric, ophthalmological, musculoskeletal, gonadal and endocrine systems.

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Increased Arterial Stiffness In Systemic Lupus Erythematosus (SLE) Patients At Low Risk For Cardiovascular Disease: A Cross-Sectional Controlled Study. Karim Sacre[1], Brigitte Escoubet[2], Maria Chauchard[3], Antoine Dossier[3], Marie-Paule Chauveheid[3] and Thomas Papo[1]. [1]University Paris-7, INSERM U699, APHP, Bichat Hospital, Paris, France, [2]University Paris-7, INSERM U872, APHP, Bichat Hospital, Paris, France, [3]University Paris-7, APHP, Bichat Hospital, Paris, France.

Background/Purpose: Accelerated atherosclerosis accounts for significant premature mortality rates among systemic lupus erythematosus (SLE) patients. Arterial stiffness reflects changes in mechanical properties of vascular wall that occurs early with onset of vascular disease. We aimed to characterize 1- the role for traditional and non-traditional CVD risk factors on carotid-femoral pulse wave velocity (PWV) as a measure of arterial stiffness, in this population and conversely, 2- if and how arterial stiffness impact on SLE-associated feature such as renal function.

Methods: Carotid-femoral pulse wave velocity (PWV) was prospectively in 42 SLE patients and 36 age- and sex-matched controls. Association between PWV and traditional and non-traditional risk factors for CVD, SLE disease history, steroid treatment, and renal function were analyzed.

Results: The mean age of SLE subjects was 40 ± 10 years and 34 (81%) were female. Five patients (11.9%) had antiphospholipid syndrome. All SLE patients were receiving hydroxychloroquine. All received long-term glucocorticoids and 28 (66.7%) were still under prednisone at a mean daily dose of 9 ± 3.2 mg (range: 5–17) at study time.

SLE patients were asymptomatic regarding cardiovascular diseases. Classical cardiovascular risks distribution did not differ between controls and SLE patients (Table 1).

PWV was higher in SLE patients than controls (7.1 ±1.6 m/s vs 6.4 ± 1 m/s; $p=0.03$). Among traditional and non-traditional CVD risk factors, PWV was associated with older age ($r^2=0.21$, $p=0.002$), higher systolic blood pressure (SBP) ($r^2=0.44$, $p<0.0001$) and higher cumulative glucocorticoid therapy ($r^2=0.14$, $p=0.01$). The impact of SBP on PWV was higher in SLE patients than controls ($p=0.0004$). Eventually, impaired renal function assessed by the reduction of glomerular rate filtration correlated with PWV in SLE ($r=-0.52$, $p=0.0004$). No statistical relationship was found between PWV and Framingham score, BMI, SELENA SLEDAI score, duration of SLE disease, and blood levels of LDL-cholesterol, glycated hemoglobin, homocystein and, 25(OH)-D3 vitamin.

Table 1. Characteristics of Subjects

	SLE patients (n=41)	Controls (n=35)	p
Female Sex, n (%)	34 (82.9)	28 (80)	0.77
Age, years	39.1 (± 10)	37 (±8)	0.21
Familial History of CAD, n (%)	1 (2.4)		
Smoking, n (%)	14 (34.1)	12 (34.3)	1
Hypertension, n (%)	12 (29.2)	8 (22.9)	0.61
Diabetes, n (%)	1 (2.4)	1 (2.8)	1
BMI, kg/m^2	25.5 (±5.4)	26.7 (±6.6)	0.69
Waist circumference, cm	93.4 (±15)	94.9 (±15.5)	0.63
LDL-Cholesterol, g/l	0.92 (±0.3)	1.2 (±0.3)	0.001
HbA1c, %	5.4 (±0.5)	5.4 (±0.4)	0.39
10-year risk of heart attack, %	1.8 (±3.6)	1.6 (±2.8)	0.53
Homocysteine/creatinine ratio	0.18 (±0.07)		
25 (OH)-D3 vitamin, ng/ml	23.4 (±11.5)		
GFR, ml/mn/1.73 m^2	84.9 (±34.6)	102 (±21)	0.002
Proteinuria/Creatininuria, mg/mmol	85.4 (±215)		
Duration of SLE disease, y	13 (±7.3)		
SELENA SLEDAI score	2.1 (±2.8)		
Lupus nephritis, n (%)	27 (65.8)		
APS, n (%)	5 (12.2)		
Cumulative years of steroid	10.5 (±7)		
Cumulative dose of steroid, g	42.3 (±29.2)		
Antiplatelet treatment, n (%)	7 (17.1)		
Anticoagulant treatment, n (%)	6 (14.6)		
Hormonal contraception, n (%)	12/34 (35.3)		
Statin, n (%)	10 (24.4)		
Hydroxychloroquine, n (%)	41 (100)		
Other therapy, n (%)	28 (68.3)		

Conclusion: Despite a low risk for CVD according to traditional factors, PWV was higher in SLE patients as compared to controls. Age, SBP and glucocorticoid therapy contribute to increased arterial stiffness. Conversely, arterial stiffness may contribute to alter renal function in SLE patients.

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Disease Specific Quality Of Life Domains Are Impaired In Patients With Lupus Nephritis? Meenakshi Jolly[1], Zineb Aouhab[2], Sergio Toloza[3], Ana M. Bertoli[4], Ivana Blazevik[5], Luis M. Vila[6], Ioana Moldovan[7], Karina Marianne D. Torralba[8], Arif Kaya[9], Berna Goker[10], Mehmet E. Tezcan[11], Seminur Haznedaroglu[9], Josiane Bourré-Tessier[12], Ann E. Clarke[13], D.J. Wallace[14], Michael H. Weisman[14] and Graciela S. Alarcon[15]. [1]Rush University Medical Center, Chicago, IL, [2]John H Stroger Hospital, Chicago, IL, [3]Hospital San Juan Bautista, Catamarca, Argentina, [4]Instituto Reumatológico Strusberg, Cordoba, Cordoba, Argentina, [5]University of Buenos Aires, Buenos Aries, Argentina, [6]University of Puerto Rico Medical Sciences Campus, San Juan, PR, [7]Loma Linda Univ Medical Center, Loma Linda, CA, [8]USC Keck Schl of Medicine, Los Angeles, CA, [9]Gazi University Medical School, Ankara, Turkey, [10]Gazi University, Ankara, Turkey, [11]Dr. Lutfi Kirdar Kartal EA Hastanesi, Istanbul, Turkey, [12]McGill University, Montréal, QC, [13]McGill University Health Center, Montreal, QC, [14]Cedars-Sinai Medical Center, Los Angeles, CA, [15]University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Often systemic Lupus Erythematosus (SLE) patients with Lupus Nephritis (LN) require frequent visits with their health care providers, follow up, and exposure to immunosuppressive medications with potential for significant side effects (e.g. fertility). Thus far, studies have not examined the adverse effects of LN using a disease specific patient reported outcome tool, which can address these concerns. Herein, we compare quality of life (QOL) in patients with and without history of LN using a disease specific quality of life (QOL) questionnaire-LupusPRO.

Methods: 791 SLE patients from North and South America, the Philippines and Turkey completed LupusPRO, which has 12 domains involving health-related quality of life (HRQOL) and non-health related quality of life (N-HRQOL) construct in 33 questions (Domain scores range 0–100; Hi=Better QOL). Health outcomes including Physician Global Assessment (PGA), Systemic Lupus Erythematous Disease Activity Index (SELENA-SLEDAI) and the SLICC Damage Index were physician-assessed cross-sectionally. Rheumatologists indicated on the ACR criteria if patients had a history of LN (irrespective of current activity). These patient and physician outcomes were compared using Chi square and non parametric statistical tests; p value of ≤ 0.05 was considered significant.

Results: 304/791 SLE patients had LN. Renal biopsy results were available on 184/304 LN patients: 7 LN-WHO Class I; 25-LN Class II; 120 LN Class III or IV or combinations; 29 LN-Class V; 3 LN-Class VI. Demographic, physician assessed and patient reported outcomes are shown in Table 1.

Table 1: Comparison of health outcomes by Lupus Nephritis Status

	Lupus Nephritis (+) n = 304	Lupus Nephritis (−) n = 487	P value
Age (Mean ± SD) years	39 ± 12.7	42.81 ± 13.7	≤0.001
Female n (%)	89.7	95.4	0.003
Ethnicity n (%)			
African American	13.8	16.5	≤0.001
Caucasian	25.3	43.6	
Asian	26.6	12.8	
Hispanic	30.9	25.1	
Others	3.4	2	
Disease Activity/Damage (Mean ± SD)			
PGA	1.0 ± 1.0	0.7 ± 0.7	0.004
Total SLEDAI	5.2 ± 6.1	3.3 ± 3.7	≤0.001
Total SDI	1.4 ± 2.0	0.8 ± 1.3	≤0.001
Current medications n (%)			
Steroids	72.6	50.1	≤0.001
Prednisone dose (mg/d) (M)	10.9 ± 15.4	4.9 ± 8.1	≤0.001
Hydroxychloroquine	67.9	79.8	0.002
Methotrexate	10.9	17.9	0.26
Mycophenolate Mofetil	22.3	7.4	≤0.001
Azathioprine	11.6	11.7	0.98
Cydophosphamide	0	0	N/A
Lupus PRO-HRQOL (Mean ± SD)			
Lupus Symptoms	76.6 ± 22.7	75.9 ± 21.7	0.43
Cognition	75.0 ± 24.8	71.5 ± 27.2	0.13
Lupus Medication	73.1 ± 27.4	79.2 ± 27.0	≤0.001
Procreation	82.4 ± 27.2	89.6 ± 21.4	≤0.001
Pain-Vitality	69.4 ± 25.2	66.5 ± 27.1	0.23
Physical Health	81.5 ± 24.7	83.0 ± 22.7	0.67
Emotional Health	61.3 ± 27.3	65.3 ± 27.7	0.03
Body Image	772. ± 25.3	78.1 ± 26.4	0.29
Lupus PRO Non-HRQOL (Mean ± SD)			
Desires and Goals	69.1 ± 27.64	73.1 ± 26.2	0.04
Cope	72.5 ± 25.6	69.7 ± 27.0	0.09
Social Support	70.5 ± 34.0	67.3 ± 34.0	0.18
Satisfaction with Care	76.7 ± 29.8	73.1 ± 33.7	0.47

PGA: Physician Global Assessment. SLEDAI: Systgemic Lupus Erythematous Disease Activity Index Score. SLICC/SDI Score: Systemic Lupus International Collaborating.

LN patients were younger, had greater disease activity and damage, were more often and on greater dose of prednisone, more often on mycophenolate-mofetil, and reported poorer health outcomes than SLE patients without LN, in both the HRQOL (Lupus medications, procreation, and emotional health) and the NHRQOL (Desires-Goals) constructs.

Conclusion: LN patients have worse physician and patient reported health outcomes than those without LN. They voiced concerns on several areas (concerns about lupus medications side effects, procreation, emotional health and effects on their personal goals and aspirations), which can be easily assessed with LupusPro.

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Efficacy and Safety Of Transjugular Renal Biopsy In Systemic Lupus Erythematosus and Antiphospholipid Syndrome: A Retrospective Monocentric Study Of 91 Procedures. Alexis Mathian[1], Maud Cazenave[2], Laurent Arnaud[3], Nathalie Costedoat-Chalumeau[4], Du Boutin-LE Thi Huong[3], Ahlem Chaib[3], Fleur Cohen-Aubart[5], Julien Haroche[3], Miguel Hié[3], Makoto Miyara[3], Philippe Rouvier[6], Jean-Charles Piette[7], Philippe Cluzel[8] and Zahir Amoura[7]. [1]Hôpital Pitié-Salpêtrière, AP-HP, UPMC Univ Paris 06 & French National Reference Center For Systemic Lupus and Antiphospholipid Syndrome, Internal Medicine, Paris, France, [2]Service de médecine interne 2, Centre de référence National pour le Lupus et le Syndrome des antiphospholipides, CHU Pitié-Salpêtrière, APHP, Paris, France, Paris, France, [3]Hôpital Pitié-Salpêtrière, AP-HP, UPMC Univ Paris 06 & French National Reference Center For Systemic Lupus and Antiphospholipid Syndrome, Paris, France, [4]Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Paris, France, [5]Pitié-Salpêtrière Hospital, APHP, Paris, France, [6]Service d'anatomie pathologie, CHU Pitié-Salpêtrière, APHP, Paris, France, Paris, France, [7]CHU Pitié-Salpêtrière, Paris, France, [8]Pitié-Salpétrière, Paris, France.

Background/Purpose: Percutaneous renal biopsy requires a long duration discontinuation of antithrombotic treatment which can increase the risk of thrombosis in patient with Systemic Lupus Erythematosus (SLE) or antiphospholipid syndrome (APS). *Transjugular kidney biopsy* has been used successfully to obtain renal tissue in patients with high risk of bleeding. The aim of this study was to describe the efficacy and safety of transjugular renal biopsy in SLE and APS.

Methods: We conducted a monocentric single-center and retrospective study of transjugular renal biopsies performed between January 2004 and September 2013 for patients with SLE or APS. Number of glomeruli per tissue core, histopathologic diagnosis, and rate and severity of complications were analyzed.

Results: Ninety-one consecutive procedures were analyzed: 56 patients with SLE without APS, 30 patients with SLE and APLS and 5 patients with APLS without SLE. The main indication to perform the kidney biopsy using the transjugular instead of the percutaneous way was a risk of excessive bleeding (antithrombotic treatment in 65 patients and thrombopenia in 3 patients). Renal tissue was obtained in 89 (97.8%) of 91 procedures. The median [range] numbers of intact glomeruli per tissue core were 14 [4–61] with optical microscopy and 7 [0–28] with immunofluorescent microscopy. Twenty-three (25.3%) biopsies for optical microscopy contained less than 10 glomeruli but only 3 (3.3%) less than 5 glomeruli. Tissue cores were adequate for histopathologic diagnosis in 89 procedures (97.8%). Symptomatic perirenal hematoma occurred in 7 patients with a good outcome without treatment. One patient had a major complication.

Conclusion: Use of transjugular renal biopsy provides a good diagnostic yield and safety for the diagnosis of kidney disease in SLE or APLS. It can be recommended in patients with percutaneous renal biopsy contraindication or failure.

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Increased Expression Of Membrane Endothelial Protein C Receptor Associates With Poor Response In Lupus Nephritis Independent Of Chronicity Index. Barbara Mendez[1], Ming Wu[1], Dominick Santoriello[1], Laura Barisoni[2], Peter M. Izmirly[1], Jill P. Buyon[1] and Robert M. Clancy[1]. [1]New York University School of Medicine, New York, NY, [2]University of Miami Hospital, Miami, FL.

Background/Purpose: While a consensus is that a high chronicity index (CI) is associated with a greater risk for progression to renal failure in lupus nephritis (LN), it does not explain why patients with a low index can still have a poor response to conventional therapy. The need to identify novel biomarkers of poor response has never been more pressing as new biologics enter clinical trials. A focus on the endothelium surfaced when membrane endothelial protein C receptor (mEPCR), an integral membrane protein with both anti-inflammatory and anti-thrombotic properties expressed on endothelial cells was found to predict poor outcome. In accord with this provocative finding suggesting that changes in the renal microvasculature may be important determinants of prognosis and response to therapy, mEPCR was further evaluated.

Methods: A retrospective study of 34 patients with LN was performed. Clinical data were collected at biopsy and 1 year following biopsy. Response to therapy was defined as a 50% improvement of creatinine if abnormal and/or proteinuria without worsening of either measure. Histological analyses included ISN/RPS classification, Activity Index (AI), CI and Tubulo-interstitial Damage (TID) scores. mEPCR expression was evaluated by immunohistochemistry by two pathologists independently and blinded to the clinical outcome of the patients.

Results: The average age at the time of biopsy was 37. The cohort was comprised largely of females (74%) and minorities (82.4%). Mean baseline creatinine was 1.62 mg/dl, 24% had a GFR <60 and 38% had nephrotic range proteinuria. Proliferative nephritis was diagnosed in 77% and 53% were responders to standard of care therapy at 1 year. Positive mEPCR staining of >25% of the peritubular capillaries (PTCs) was observed in 12 renal biopsies. One year after biopsy, 75% (9/12) of patients with staining for mEPCR in >25% of the PTCs did not respond to therapy (1 progressing to end-stage renal disease) compared with 7/22 (32%) with mEPCR staining in ≤25% of the PTCs $P=0.029$. There was no association between response and baseline age, gender, creatinine, abnormal GFR, nephrotic range proteinuria, microthrombi on biopsy, ISN/RPS classification, AI, CI, or treatment regimen. The only other variables measured that associated with an absence of response included minorities (P=0.019) and TID (p=.018). However, mEPCR was clearly observed in areas of non-atrophic cortex. Thus, the extent of mEPCR was not solely accounted for by TID. After excluding patients with high TID scores, mEPCR remained strongly associated with a poor response to therapy, $P=0.028$. A subset of patients with LN who presented with a normal creatinine at biopsy were analyzed separately. At 1 year, 100% (16/16) of these patients with mEPCR staining ≤25% of the PTC maintained a normal creatinine and GFR compared with 2/4 (50%) with positive staining >25% of the PTC, $P=0.03$.

Conclusion: These data suggest that mEPCR staining be added to the evaluation to aid in the overall prognosis of LN. While the biology is perplexing given the function of mEPCR as generally protective, a high stain may suggest negative feedback reflecting a state of tissue unresponsiveness to be considered in clinical trial design.

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The Influence Of Cumulative Dose Of Corticosteroids On The Presence Of Carotid Atherosclerosis In Patients With Longstanding Systemic Lupus Erythematosus. Maria Rubino[1], Ellie Aghdassi[2], Sun Makosso-Kallyth[3], Stacey Morrison[4], Lihi Eder[5] and Paul R. Fortin[6]. [1]Université Laval, Quebéc, QC, [2]University Health Network Research Institute and Department of Public Health, University of Toronto, Toronto, ON, [3]Centre de Recherche CHU de Québec, Québec, QC, [4]The Toronto Western Hospital, Toronto, ON, [5]University of Toronto, Toronto Western Hospital, Toronto, ON, [6]Division of Rheumatology, Université Laval, Québec, QC.

Background/Purpose: The purpose of this study is to determine the relationship between cumulative corticosteroid dose (CCD) with presence of carotid plaques (CP), total plaque area (TPA) and carotid intima media thickness (CIMT) in a population of women with longstanding systemic lupus erythematosus (SLE).

Methods: A retrospective cohort study, in which women with SLE followed by the University of Toronto Lupus Clinic and whom had undergone a carotid Doppler were included. Outcome variables looked at were CP, TPA and CIMT. Measured variables included were disease related factors, CCD and traditional atherosclerotic risk factors. Statistical analyses were performed using the SAS software, version 9.3. Depending on the nature of the variable, the appropriate statistical models were used to perform univariate, bivariate (Student's T-test or Chi-Square or Wilcoxon) and multivariate (logistic or linear regression) analyses. The Baron and Kenny's procedure was used to assess the mediating effect of CCD and the restricted cubic spline model was used to investigate the possible U-shaped relationship of CCD.

Results: One hundred and twelve participants were included in this study. All participants were female, their disease duration was 19 (SD=12) years and their baseline characteristics are presented in Table 1. CP was found in 37 % of the participants and the mean CIMT was of 0.611 mm (± SD 0.1). In the univariate regression models CCD significantly predicted presence of CP (P = 0.0106), as well as TPA (P = 0.0062) and CIMT (P = 0.0169). In the multivariate models (Table 2) CCD was not a significant determinant of

carotid atherosclerosis. Age, was the most influential variable in all our multivariable regression models. Other predictors were hypertension in the CP model, hypertension and diabetes in the TPA model. CCD was found to mediate the relationship between diabetes and CP as well as between diabetes and TPA. Non-linear relationships were not found between CCD and each of the outcome variables.

Table 1. Baseline Characteristics

Characteristic	Total Population (N = 112) Median (IQR)	Presence of Carotid Plaque (N = 42) Median (IQR)	Absence of Carotid Plaque (N = 70) Median (IQR)
Age (years)* **	50.6 (38.9–59.8)	57.8 (53.0–65.3)	44.2 (30.7–54.0)
Disease Duration (years) **	16.1 (9.1–26.4)	21.6 (12.2–34.8)	14.2 (7.9–23.4)
SLICC/ACR SDI *	1 (0–3)	2 (1–4)	1 (0–2)
Cumulative Corticosteroid Dose (g)*	28.73 (5.04–64.20)	45.91 (15.90–80.87)	22.41 (2.77–45.08)
BMI (kg/m^2)	23.63 (20.85–27.77)	23.57 (20.72–29.05)	23.74 (20.9–27.12)
Total Cholesterol (mmol/L)*	4.32 (3.87–4.79)	4.42 (4.02–4.81)	4.12 (3.59–4.71)
	Percentage (%)	**Percentage (%)**	**Percentage (%)**
Diabetes*	5.4	11.9	1.4
Hypertension **	30.4	47.6	20.0
Family History	55.4	63.4	51.4
Post-Menopause* **	63.4	97.6	42.9
Smoking **	32.1	50.0	24.1

Comparing between groups with and without plaques: *p=0.05 – 0.01, **p=0.01 – 0.0001, ***p<0.0001

Table 2. Multiple Logistic and Linear Regression Models for Carotid Plaques, Total Plaque Area and Carotid Intima Media Thickness

	CP (logistic regression)	TPA (linear regression)	CIMT (linear regression)
Risk Factor	Odds Ratio (95 % CI)	Parameter Estimate	Parameter Estimate
Age (years)	1.099 (1.010–1.196)*	0.0046**	4.1456***
SLICC/ACR SDI	1.257 (0.915–1.726)	0.0103	n/a
Disease Duration (years)	n/a	−0.0023	−1.4795
Cumulative Corticosteroid Dose (g)	1.0 (1.0–1.0)	0.0000004	0.0001274
BMI (kg/m^2)	0.941 (0.844–1.048)	n/a	0.01847
Total Cholesterol (mmol/L)	2.230 (0.882–5.640)	0.0183	n/a
Diabetes	<0.001 (□0.001–□999.999)	−0.2147**	n/a
Hypertension	0.177 (0.047–0.672)*	−0.0657*	−24.7054
Post-Menopause	0.136 (0.009–2.070)	0.0133	−28.2580
Smoking	0.318 (0.094–1.077)	−0.0260	n/a

Only the variables that were significant in the bivariate analysis were included in the final models. *p=0.05 – 0.01, **p=0.01 – 0.0001, ***p<0.0001

Conclusion: Cumulative corticosteroid dose was not a statistically significant determinant of carotid atherosclerosis in this cohort of SLE patients after adjusting for other relevant clinical variables.

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Causes Of Mortality In Lupus Patients Followed Prospectively At a Large Single-Centre Lupus Clinic. Barry J. Sheane, Dominique Ibanez, Dafna D. Gladman and Murray B. Urowitz. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Survival rates of patients with systemic lupus erythematosus (SLE) have improved significantly over the last four decades. Mortality rates remain high, however, and are almost 4 times that of the general population. A bi-modal pattern of mortality in SLE has been described whereby death within the first year after diagnosis was associated with active lupus and infection, while death in later years was associated with atherosclerosis and corticosteroid use.

The aim of this study was to re-examine the causes of mortality in lupus patients followed prospectively at a large lupus clinic between 1970 and 2013.

Methods: Causes of death were recorded and acquired from autopsy reports (n=48), discharge summaries (n=64), hospital notes (n=23), and death certificates (n=20). Causes were divided into 5 categories: active lupus, atherosclerosis-related, infection, malignancy and 'other', and designated as either a 'primary' or 'secondary' cause. Atherosclerosis-related (AS) deaths were those attributable to acute myocardial infarction, congestive cardiac failure (as a direct result of coronary artery disease), or stroke, all in the absence of active SLE. 'Other' causes referred to those that were not attributable to active SLE, atherosclerosis, infection or malignancy.

Results: Out of 264 patients known to have died, causes of death were established in 206 cases. Mean disease duration at time of death was 14.6 ± 11.8 years, with 47 (23%) dying within 5 years and 62 (30%) dying 20 or more years after diagnosis. Mean age at death was 52.6 ± 17.5 years, with 56 (27%) dying before the age of 40. Infection was responsible for the majority of deaths (n=71 (34.5%)), followed by active SLE (n=38 (18.4%)), AS (n=38 (18.4%)), malignancy (n=24 (11.7%)) and 'other' (n=60 (29.1%)). Renal failure in inactive SLE (n=6) and bowel perforation (n=5) were among 'other' causes.

There was a significant decline in the number of deaths attributable to infection and active SLE with increasing disease duration: 49% (n=23) and 34%(n=16) of deaths in those with SLE for less than 5 years were due to infection and active lupus, respectively, compared with 26% (n=16) and 15% (n=9) of deaths in those with SLE for 20 or more years (p=0.01). Atherosclerosis was increasingly responsible for death with increasing disease duration: 13% (n=5) with less than 5 years disease duration, compared with 23% (n=14) after 20 years of SLE (p=0.11). Malignancy also increased in prevalence as a cause of death with greater disease duration (p=0.13).

Conclusion: Within the first 5 years of disease onset, infection and active SLE account for over 80% of deaths in lupus. Despite a significant reduction as a cause of death over time, infection remains the single biggest killer in those with disease over 20 years. The importance of atherosclerosis as a cause of death increases over time and replaces active SLE as the next most important cause of death in lupus patients with increasing disease duration.

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Relationship Between 25-Hydroxyvitamin D [25(OH)D] and Risk For Cardiovascular Events In Systemic Lupus Erythematosus Over 11 Years In An Inception Cohort. Apinya Lertratanakul[1], Peggy Wu[2], Alan Dyer[1], Dafna D. Gladman[3], Murray B. Urowitz[3], Paul R. Fortin[4], Dominique Ibanez[3], Rosalind Ramsey-Goldman[2] and for the Systemic Lupus International Collaborating Clinics (SLICC)[5]. [1]Northwestern University, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL, [3]University of Toronto, Toronto Western Hospital, Toronto, ON, [4]Centre de Recherche du Chu de Québec et Université Laval, Quebec City, QC, [5]University of Toronto, Toronto Western Hospital (Coordinating Center), Toronto, ON.

Background/Purpose: 25(OH)D deficiency has been associated with increased cardiovascular disease (CVD) in the general population. We investigated the relationship between 25(OH)D and CVD events in a large international inception cohort of women and men with Systemic Lupus Erythematosus (SLE).

Methods: Baseline data were collected from 890 patients enrolled in the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort. Those with previous CVD events (N=2) or who were pregnant (N=13) were excluded. CVD events and dates were recorded between 2000–2011. The intraassay and interassay coefficients of variation for the 25(OH)D testing were 10.8% and 9.4%, respectively. Linear regression models of 25(OHD) in quartiles with risk factors were examined. These models were then adjusted for age, sex, race, season, and country, all with and without body mass index. Cox proportional hazards models were used to investigate the relationship between 25(OH)D levels and CVD events (stroke, congestive heart failure, myocardial infarction, transient ischemic attack, angina, peripheral vascular disease).

Results: Of the 875 included patients, 786 (89.2%) were female and 89 were male with a mean ± SD age of 38.9 ± 13.1 and 42.9 ± 16.4 years, respectively, and mean ± SD 25(OH)D level of 23.8 ± 13.4 ng/ml. The quartile ranges were: 1st quartile (Q1) 3.6 – <13.4 ng/ml, 2nd quartile (Q2) 13.4 – <21.6 ng/ml, 3rd quartile (Q3) 21.6 – <30.8 ng/ml, 4th quartile (Q4) 30.8 – <91.3 ng/ml. Corticosteroids were used in 67% at baseline with a mean dose of 23.3 ± 15.9 mg daily. Renal disease by ACR criteria was present in 26%, 32% were taking calcium and 25% vitamin D supplementation. Hypertension (HTN) and hyperlipidemia (HL) were present in 34% and 15.7%, respectively. Diabetes was present in 6.5%.

Compared with Q1, those in the higher quartiles of 25(OH)D were less likely to have HTN or HL (Table 1). Those in the highest quartile of 25(OH)D were more likely to have lower C-reactive protein levels when compared with Q1. Each successively higher quartile was more likely to have lower Systemic

Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) compared with Q1.

Table 1. 25(OH)D quartiles and cardiovas cular risk factors at enrollment

	Unadjusted Model		Adjusted model 1		Adjusted Model 1	
CV risk factor	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Hypertension						
Q2	0.84	0.58, 1.24	0.81	0.55, 1.21	0.83	0.55, 1.25
Q3	0.60	0.41, 0.89	0.66	0.43, 1.00	0.69	0.44, 1.06
Q4	0.43	0.29, 0.65	0.44	0.28, 0.68	0.49	0.31, 0.77
Diabetes						
Q2	1.14	0.56, 2.31	0.98	0.47, 2.03	0.93	0.43, 1.99
Q3	0.54	0.22, 1.22	0.52	0.21, 1.21	0.57	0.22, 1.35
Q4	0.81	0.37, 1.73	0.66	0.29, 1.45	0.71	0.31, 1.63
Hyperipidemia						
Q2	0.87	0.55, 1.88	0.76	0.47, 1.22	0.80	0.49, 1.29
Q3	0.31	0.17, 0.54	0.28	0.15, 0.51	0.30	0.16, 0.55
Q4	0.48	0.28, 0.79	0.43	0.24, 0.74	0.50	0.28, 0.87
CV risk factor	**β coeff**	**95% CI**	**β coeff**	**95% CI**	**β coeff**	**95% CI**
CRP						
Q2	−0.12	−0.48, 0.24	−0.11	−0.47, 0.25	−0.10	−0.47, 0.26
Q3	−0.30	−0.66, 0.06	−0.30	−0.68, 0.08	−0.30	−0.69, 0.08
Q4	−0.38	−0.76, −0.01	−0.44	−0.84, −0.04	−0.44	−0.85, −0.03
Homocysteine						
Q2	0.10	−0.04, 0.25	0.077	−0.07, 0.23	0.08	−0.08, 0.23
Q3	−0.02	−0.16, 0.13	−0.04	−0.20, 0.12	−0.03	−0.20, 0.13
Q4	−0.01	−0.16, 0.14	−04	−0.21, 0.12	−0.03	−0.21, 0.14
Creatinine						
Q2	0.14	−0.09, 0.38	0.12	−0.12, 0.36	0.13	−0.11, 0.37
Q3	0.13	−0.10, 0.36	0.09	−0.15, 0.32	0.10	−0.15, 0.34
Q4	0.06	−0.16, 0.28	0.02	−0.22, 0.25	0.03	−0.21, 0.27
SLEDA						
Q2	−1.22	−2.24, −0.20	−1.44	−2.43, −0.46	−1.38	−2.37, −0.38
Q3	−1.88	−2.90, −0.86	−2.15	−3.17, −1.12	−2.16	−3.19, −1.12
Q4	−2.27	−3.30, −1.25	−2.22	−3.26, −1.18	−2.37	−3.25, −1.31

Adjusted model 1: controls for age, season, white race, gender country (Korean, UK, US, other) except for diabetes - controls for age, white race, gender, season only.
Adjusted model 2: controls for same as model 1 plusbody mass index.
Q = 25(OH)D quartile
Q1 is the referent quartile.

25(OH)D levels were not associated with occurrence of CVD events (Table 2). The hazard ratios for CV occurrence in Q3 and Q4 were lower when compared with Q1.

Table 2. 25(OH)D Quartiles and cardiovascular disease events at follow-up

Events	**N**	**HR**	**95% CI**
A	32		
Q2	13	1.15	0.46, 2.84
Q3	5	0.68	0.21, 2.13
Q4	5	0.63	0.20, 1.97

Q1 is the referent quartile.

Conclusion: While higher levels of 25(OH)D are associated with lower likelihood of HTN and HL and less disease activity at baseline as measured by the SLEDAI-2K, 25(OH)D levels are not independently associated with likelihood of CVD events in patients with SLE. There may be a trend towards a lower likelihood of CVD events in those in the highest 25(OH)D quartiles.

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Trends Of Mortality Associated To Systemic Lupus Erythematosus At The Nation Level: A Multiple Cause-Of-Death Analysis In France. Laurent Chiche Sr.[1], Guillemette Thomas[2], Albetine Aouba[3], Julien Mancini[2], Gabrielle Sarlon[4], Noémie Jourde[2], Eric Jougla[3] and Jean-Robert Harle[2]. [1]Internal Medicine, CHU Marseille, Marseille, France, [2]APHM, Marseille, France, [3]inserm CépiDc, paris, France, [4]APHM, marseille, France.

Background/Purpose: The overall mortality rate of Systemic Lupus Erythematosus (SLE) has improved significantly over the past 50 years but is still high as compared with the general population. A better knowledge of the causes of death and the related comorbidities is pivotal to improve strategies to prevent death in SLE patients. The aim of the MORTALUP study was to analyze the mortality profile related to SLE in France using a multiple cause-of-death analysis.

Methods: For the 2000–2009 period, data collected in the French Epidemiological Center for the Medical Causes of Death (CepiDc, Inserm) database and corresponding to death certificates (DC) of adults on which SLE was listed as an underlying or non-underlying cause of death were analyzed. All the DC were collected in a dedicated database after declaration to the Informatics and Liberty National Commission (CNIL). Gender, age, sex-ratio, standardized mortality rates as well as the respective weight and frequency of the various causes of death were assessed. The age-and sex-adjusted observed/expected death ratio (O/E ratio) was calculated for the main causes of death based on the proportional mortality in the general population between 2000 and 2009 by the same cause provided by the French National Institute for Statistics and Economic Studies (INSEE).

Results: Overall, 1593 adult SLE patients died during the study period. Sex-ratio was 3.5 (1238 female and 355 male) and mean age at death was 63.5 ± 17.3 years without significant difference between gender. The mean standardized mortality rate was 3.2 per 10^6 people. For SLE as an underlying cause (n=637, 40%), mean age at death was 61.3 ± 19.3 years and the main non-underlying causes of death were cardiovascular diseases (79.3%), infectious diseases (32.7%) and renal failure (24.8%). Among cardiovascular diseases, heart failure (20.2%) and cerebrovascular diseases (14.7%) were the most frequent.

For SLE as a non-underlying cause of death (n=956, 60%), mean age at death was 65 ± 17.5 years and was significantly higher than in the group where SLE is the underlying cause of death (61.3 ± 19.3 years, $p<0.001$) years and the most common underlying causes of death were cardiovascular diseases (35.7%), neoplasms (13.9%) and infectious diseases (10.3%). The overall death O/E ratio was > 1 for infectious, cardiovascular diseases and renal failure in both gender, but was <1 for neoplams.

No differences between the Mediterranean area and the rest of France were observed concerning the causes of death. In overseas departments, the standardized mortality rate was higher (10.8 per 10^6 people) and the mean age of death was earlier (50 years, $p< 0.001$), but there was no difference regarding the proportion of SLE as underlying/non-underlying cause of death, sex-ratio or causes of death.

Conclusion: To our knowledge, this is the first mortality study using a multiple cause-of-death analysis in SLE in a developed country. At the nation level, cardiovascular diseases are the most important cause of death associated to SLE in France with a significant excess of mortality compared to general population. Cardiovascular interventions should be prioritized in developed country in order to improve SLE survival.

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The Potentiality Of Multi-Target Therapy With Cyclophosphamide and Tacrolimus For Lupus Nephritis. Ryota Sakai, Akiko Shibata, Kentaro Chino, Tsuneo Kondo, Ayumi Okuyama, Eiko Nishi, Hirofumi Takei, Hayato Nagasawa and Koichi Amano. Saitama Medical Center, Saitama Medical University, Kawagoe, Japan.

Background/Purpose: Multi-target therapy for lupus nephritis (LN) had first reported by Bao et al. 2008 regarding the treatment of mixed diffuse proliferative and membranous LN using a combination of corticosteroids, mycophenolate mofetil and tacrolimus (Tac). Following this, several studies had suggested the efficacy of combination therapies utilizing two or more immunosuppressive agents with different mechanisms of action. The objective of this retrospective study is to assess the effectiveness of multi-target therapy with cyclophosphamide (CY) and Tac for class III and IV LN as a remission induction therapy in our single center experience and to discuss the potentiality of this multi-target therapy with renal pathological findings.

Methods: We evaluated 43 patients with active LN who performed renal biopsies at Saitama Medical Center between January 2007 and August 2012. The complete renal remission was defined as spot urine protein: creatinine ratio <0.5g/gCr or under plus and minus values in urinalysis and normal GFR or improvement of GFR according to the EULAR/ERA-EDTA recommendation. Renal pathological findings were assessed according to the 2003 ISN/RPS classification for LN. Crescents, fibrinoid necrosis, interstitial cell infiltration and chronicity were evaluated as well.

Results: The number of patients in each class was as follows; II: 9, III: 4, IV: 28, V: 2. In 32 cases with class III/IV, crescents: 15 (46.9%), fibrinoid necrosis: 8 (25.0%), interstitial cell infiltration: 15 (46.9%) and chronicity: 18 (56.3%). Four cases (12.5%) had membranous nephropathy (Class IV + V). CY was initiated in 24 cases with class III/IV. Eleven out of 24 (45.8%) cases received multi-target therapy with Tac (CY + Tac group) as a remission induction therapy. In the other 13 (54.2%) cases various immunosuppressants (Tac, azathioprine, cyclosporine, mizoribine pulse) were prescribed as a maintenance therapy after CY (CY-IS group). The complete remission rate at 12 months was 45.5% in CY + Tac group and 69.2% in CY-IS group (p=0.41). However patients' background of each group was quite different. Although chronicity was observed more commonly in CY + Tac group (p=0.047), the remission rate in patients with chronicity was 44.4% in CY + Tac group and 20.0% in CY-IS group (p=0.58).

Conclusion: Multi-target therapy such as CY + Tac may be effective for refractory LN with chronicity in renal pathological findings.

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Active Renal Disease Is Associated With The Presence Of The Metabolic Syndrome (MetS) In Peruvian Patients With Systemic Lupus Erythematosus (SLE). Manuel F. Ugarte-Gil[1], Rocio V. Gamboa-Cardenas[1], Mariela Medina-Chinchon[1], Francisco Zevallos-Miranda[1], Karim E. Diaz-Deza[1], J. Mariano Cucho-Venegas[1], Zoila Rodriguez-Bellido[2], Jose L. Alfaro-Lozano[1], Risto A. Perich-Campos[2], Erika Noriega[1], Hugo Torrealva[1] and Cesar A. Pastor-Asurza[2]. [1]Hospital Almenara, Lima, Peru, [2]Universidad Nacional Mayor de San Marcos, Lima, Peru.

Background/Purpose: The MetS prevalence is increased in SLE patients, in particular in those of Hispanic origin and it is associated with a higher risk for cardiovascular disease and early mortality. Renal lupus seems to increase the risk for MetS. The aim of the study was to determine whether active renal disease is associated with the presence of the MetS in SLE patients after considering other possible risk factors.

Methods: This cross-sectional study was conducted in consecutive SLE patients seen in our Rheumatology Department from January 2012 to June 2013. An interview, medical records review, physical examination and laboratory tests were performed. SLE was defined using the ACR criteria; MetS was defined according to the 2009 consensus statement of the International Diabetes Foundation. Disease activity was ascertained using the SLEDAI and disease damage with the SLICC/ACR damage index (SDI). Active renal disease was defined as haematuria greater than five red blood cells/high power field, excluding other causes; pyuria greater than five white blood cells/ high power field, excluding infections; cast including granular o red blood cells; and/or new/recent increase of more than 500 mg/24h protein. Use of prednisone was recorded as current dose and total time of exposure. Antimalarials use was recorded as current, past or never. Traditional cardiovascular risk factors like uric acid and C-reactive protein levels and tobacco use were evaluated. The association of MetS and active renal disease and variables from the different domains was examined by Chi-square or Students' t tests, as appropriate. This was followed by multivariable analysis with a stepwise backward selection procedure. All analyses were performed using SPSS 16.0.

Results: Two-hundred and six patients were evaluated; their average (SD) age was 42.0 (12.6) years, 192 (93.2%) were female; almost all patients were mestizo (mixed Caucasian and Amerindian ancestral backgrounds). Three (1.5%) and 38 patients (18.4%) were current or past smokers, respectively. Disease duration was 7.2 (6.3) years. The SLEDAI was 5.8 (4.8) and the SDI 0.9 (1.3). The current dose of prednisone was 8.2 (5.7) mg/d and the total time of exposure to prednisone was 7.2 (6.1) years; 159 (77.2%) and 31 (15.0%) were current and former users of antimalarials, wheareas 16 (7.8%) were never users. Active renal disease was present in 27 (13.1%) patients. C-reactive protein and uric acid levels were 5.2 (10.0) mg/l and 4.6 (1.5) mg/dl, respectively. Eighty five or 41.3% patients presented the MetS. In the univariable analysis, active renal disease but not disease activity was associated with the MetS as were older age, higher SDI and higher uric acid levels; active renal disease (OR 3.41, 95% CI 1.09 to 10.61) remained associated in the multivariable analysis and so were; older age (OR 1.05, 95% CI 1.02 to 1.08) and higher uric acid levels (OR 1.34, 95% CI 1.00 to 1.80).

Conclusion: The prevalence of the MetS was high in our population, and it was associated with active renal disease. A better control of renal disease activity is desirable to reduce the increased cardiovascular risk these SLE patients have.

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Survival and Prognostic Factors In Patients With Connective Tissue Disease Associated Pulmonary Arterial Hypertension: Results From Korean Nationwide Registry. Kwi Young Kang[1], Chan Hong Jeon[2], Sung Jae Choi[3], Seung-Ki Kwok[4], Seong-Kyu Kim[5], Hyoun-Ah Kim[6], Eon Jeong Nam[7], Yong-Beom Park[8], Kichul Shin[9], Jaejoon Lee[10], Chang-Hoon Lee[11], Chan-Bum Choi[12], Shin-Seok Lee[13] and Dae-Hyun Yoo[14]. [1]Catholic University of Korea, Incheon St. Mary's Hospital, Seoul, South Korea, [2]Soonchunhyang University College of Medicine, Bucheon, South Korea, [3]Korea University Medical Center, Seoul, South Korea, [4]The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea, [5]Catholic University of Daegu School of Medicine, Daegu, South Korea, [6]Ajou University School of Medicine, Suwon, South Korea, [7]Kyungpook National University School of Medicine, Daegu, South Korea, [8]Yonsei University College of Medicine, Seoul, South Korea, [9]College of Medicine, Seoul National University, Seoul, South Korea, [10]Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea, [11]Department of Internal Medicine, School of Medicine, Wonkwang University, Iksan, Chonbuk, South Korea, [12]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [13]Chonnam National University Medical School, Gwangju, South Korea, [14]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea.

Background/Purpose: Pulmonary arterial hypertension (PAH) is a major cause of mortality in connective tissue disease (CTD). We sought to quantify survival and determine factors predictive of mortality in a registry of Korean patients with CTD-associated PAH (CTD-PAH), Registry of Pulmonary Hypertension Associated with Rheumatic Disease (REOPARD).

Methods: Patients with CTD-PAH were enrolled between April 2008 and December 2012. Hemodynamic parameters and clinical data such as demographics, WHO functional class, underlying disease, organ involvement, laboratory tests and current treatment were investigated. Follow-up data of enrolled patients were recorded at the 5 year. Survival rate was calculated by the Kaplan–Meier method and the log-rank test. Factors associated with survival were examined by Cox proportional hazards regression analysis.

Results: One hundred seventy four incident cases were diagnosed by a right heart catheterization or a doppler echocardiograpy. Among 174 patients (61 (35%) with SLE, 50 (29%) with systemic sclerosis, 10 (6%) with MCTD, 22 (13%) with RA), during 3.8 ± 2.7 (mean ± SD) years of follow-up from PAH diagnosis, there were 25 (14%) deaths. One- and 3-year survival rates were 90.7 and 87.3%. Survival was worse for patients with RA-PAH (3-yr survival, 56%; p=0.022). In multiple regression analysis, Low DLCO (p=0.008), pleural effusion (p=0.04), and DM (p=0.009) were poor prognostic factors and anti-UI RNP antibody was a protective factor of mortality (p=0.022). In patients with WHO-FC III/IV, the survival rates were significantly better in patients were received with vasodilators than in patients were not (p=0.038).

Conclusion: In this study among Korean CTD-PAH patients, three –year survival was 87%. Low DLCO, pleural effusion, and DM were independent poor prognostic factors. Anti-UI RNP antibody was a protective factor of mortality. The prompt PAH specific vasodilator therapy may improve survival in patients with severe CTD-PAH.

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Human Papillomavirus and Precancerous Lesions In Patients With Systemic Lupus Erythematosus. Eleonora Lucero[1], Laura Juarez[1], Veronica Bellomio[1], Francisco Colombres[1], Maximiliano Machado Escobar[1], Raúl Nicolás Martínez[1], Teresita Alvarellos[2], Agustina Lacaze[2], Ariel Sanchez[2], Pablo Agustín Apas Perez de Nucci[1], Guillermo Cohen Imach[1], Sonia Marcela Ortiz Mayor[1], Iris Aybar Odstrcil[1], Ana Cerón[1], Ricardo V. Juárez[3], Mirta Santana[1] and Alberto Berman[1]. [1]Padilla Hospital, Tucumán, Argentina, [2]Córdoba Private Hospital, Córdoba, Argentina, [3]Hospital Señor del Milagro, Salta, Argentina.

Background/Purpose: To evaluate the presence of Precancerous Lesions (PL) in uterine cervix in patients with Systemic Lupus Erythematosus (SLE) and its relationship with Human Papillomavirus (HPV). To determine the association between immunosuppressive therapy and the development of PL, and to compare with patients whith Rheumatoid Artrhritis (RA).

Methods: A cross sectional study was conducted. Since May 2011 to July 2012 women sexually active with RA (ACR-EULAR 2010) and SLE (ACR 1992), over 18 years old, were included in the study. They attended consecutively the Rheumatology Unit and they were matched by age with a control group without any rheumatic disease. Gynecological examination included: Papanicolaou test (PAP), Colposcopy (CP) and Polymerase Chain Reaction for HPV (PCR) for 13 genotypes (AMPLICOR Human Papillomavirus test, ROCHE). Pathology and laboratory Units were blind to both determinations.Clinical (DAS 28, HAQ, SLEDAI, SLICC) and therapeutic variables (drug, doses, cumulative doses, period of treatment) were studied.

Results: 172 women were included: 86 patients (48 SLE and 38 RA), mean age 41.4 + 12.1 years and 86 control, mean 38.3 + 11 years. Seventy one (82.5%) patients had normal PAP, while 55 (64%) of the controls had inflammatory PAP; Atypical Squamous Cellls of Undetermined Significance (ASCUS) was found in 5 patients (2 SLE, 3 RA) vs 8 controls, Low Grade Squamous Intraepitelial Lesion (LSIL) in 6 patients (5 LES, 1 AR) vs 10 controls and 6 High Grade Squamous Intraepitelial Lesion (HSIL) only in the control subjects (<0.0001). PCR for HPV was positive in 38.4% (33) patients and in 55% (47) of the control group ($p=0.046$). Discriminating by disease, the controls persisted with increasing frequency of HPV (12 RA vs 21 SLE vs 47 controls), $p<0.0001$. Estimating the prevalence of HPV adjusted to age, we found that RA group was significantly less prevalent, were in SLE and controls was similar. The logistic regression model showed that RA younger patients, had less chance of PCR+. In patients with SLE, LSIL was significantly associated with HPV, whereas in the controls was associated with ASCUS and HSIL ($p <0.0001$). In RA patients, no association was found between PAP and PCR. The use and accumulated doses of glucocorticoids and immunosuppressive therapy were not associated with HPV ($p=NS$).

Conclusion: We found no increased frequency of HPV or PL in patients with SLE compared to the control population. Immunosuppressive therapy was not associated with the presence of HPV.

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Baseline Characteristics That Predict a Short-Term Response To Immunosuppressive Treatment In Patients With Pulmonary Arterial Hypertension Associated With Connective Tissue Disease. Hidekata Yasuoka[1], Yuichiro Shirai[1], Yuichi Tamura[1], Toru Satoh[2], Tsutomu Takeuchi[1] and Masataka Kuwana[1]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Kyorin University School of Medicine, Tokyo, Japan.

Background/Purpose: Pulmonary arterial hypertension (PAH) is one of devastating organ involvements in patients with connective tissue diseases (CTDs). Recent introduction of molecular-targeting PAH drugs, such as prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, has prolonged time to clinical worsening and survival in patients with PAH-CTD. On the other hand, several reports suggest potential efficacy of immunosuppressive treatment for PAH-CTD, but positioning of immunosuppressive treatment in the PAH treatment algorithm still remains uncertain. In this study, we determined baseline characteristics that predict short-term efficacy of immunosuppressive treatment in patients with PAH-CTD, using our single-center cohort, including those in the pre- and post-PAH drug era.

Methods: This is a retrospective study involving 28 consecutive patients with PAH-CTD, consisting of 13 historical cases (diagnosis made between 1970 and 1990) and 15 recent cases (diagnosis made after 2000). These patients were selected from our PAH-CTD database, based on (i) diagnosis of PAH associated with systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), or primary Sjögren syndrome (pSS), (ii) those who received corticosteroids ($\geq$0.5 mg/kg/day prednisolone equivalent) with or without PAH drugs as an initial therapy, and (iii) observation period $>$ 3 months. The short-term treatment response was regarded as improvement of WHO functional class (FC) at 3 months. Baseline clinical characteristics, including age at diagnosis of PAH and underlying CTD, WHO-FC, hemodynamic parameters, and immunologic and autoantibody profiles, and initial treatment regimen were obtained from prospectively collected database.

Results: PAH-CTD patients treated initially with immunosuppressive treatment consisted of 11 with SLE, 14 with MCTD, and 3 with pSS. Of these, 15 (54%), including 6 historical and 9 recent cases, were short-term responders. Simultaneous diagnosis of PAH and underlying CTD was more frequent in responders than in non-responders (80% versus 15%, $P = 0.002$), but there was no difference in distribution underlying CTD, WHO-FC, hemodynamic parameters, or immunologic and autoantibody profiles between responders and non-responders. In terms of the initial treatment regimen, use of cyclophosphamide (CY) was associated with a therapeutic response, while corticosteroids without any immunosuppressant was associated with no response ($P = 0.003$ and 0.0002, respectively). Interestingly, use of any PAH drugs was not associated with the short-term response.

Conclusion: Patients with SLE, MCTD, and pSS who were diagnosed as having underlying CTD and PAH simultaneously are likely to achieve a short-term response to immunosuppressive treatment. These patients should be treated with an intensive immunosuppressive regimen containing cyclophosphamide.

Disclosure: H. Yasuoka, None; **Y. Shirai**, None; **Y. Tamura**, None; **T. Satoh**, None; **T. Takeuchi**, None; **M. Kuwana**, None.

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Serum Anti-Apolipoprotein 1 Antibodies Are Present In a Quarter Of Patients With Systemic Lupus Erythematosus At The Time Of Diagnosis and Are Associated With Earlier Mortality. Sara Croca, Maria Davari, D.A. Isenberg and Anisur Rahman. University College London, London, United Kingdom.

Background/Purpose: A large number of different autoantibodies have been reported in patients with systemic lupus erythematosus but not all have been related to clinical outcomes. Apolipoprotein A1 (ApoA1) is the main structural component of HDL, and its atheroprotective role has been firmly established. The presence of anti-ApoA1 antibodies has been reported in SLE and other non-autoimmune conditions associated with cardiovascular disease (CVD). Anti-apoA1 antibodies are higher in patients with current or persistent SLE disease activity, but it is not known whether measuring anti-apoA1 at the time of diagnosis of SLE would have clinical utility. This abstract describes the results of a cross sectional study of anti-apoA1 levels in a cohort of samples taken at the time of SLE diagnosis and correlates them with disease course, particularly CVD-related events and mortality.

Methods: Stored frozen serum samples obtained shortly after SLE diagnosis from a cohort of 499 patients with SLE and serum from 100 healthy controls (HC) were tested. Anti-apoA1 levels were measured using a direct ELISA and recorded as absorbance units (AU). Data on the initial immunological profile, mortality and CVD-related events were obtained from clinical records. SLE-associated cumulative damage was determined using the SLICC SLE damage index score.

Results: Mean anti-apoA1 levels were significantly higher in SLE than HC samples (50.5AU vs. 10.8AU, $P<0.05$). Defining a cut-off for anti-apoA1 positivity as 55AU (mean + 3SD of HC), 23.4% of SLE samples and 2% of HC samples were positive. No associations between anti-apoA1 level and gender, ethnicity or age at diagnosis were found. Patients who were positive for anti-dsDNA had higher mean anti-apoA1 levels than those who were negative (60.6AU vs 34.1 AU, $P<0.05$). Similarly, anti-cardiolipin-positive patients had higher mean anti-apoA1 levels than anti-cardiolipin-negative ones (80.1AU vs 41.6 AU $P<0.05$).

No further associations were found with other auto-antibodies or complement levels. We found no associations between anti-apoA1 levels and either CVD-related morbidity or damage score at 1,5,10,15,20 or 25 years. Mortality was 17.1% in anti-apoA1 positive patients and 12.4% in anti-apoA1 negative patients (P=0.11). When patients were divided into quartiles of anti-apoA1 activity, the top quartile had more deaths (39 vs 27 P=0.07), and significantly more early deaths - 21 vs 11 before the age of 50 (P=0.049) and 31 vs 17 before the age of 60 (p=0.023) than the lowest.

Conclusion: Anti-apoA1 levels are higher in patients with SLE compared with HC. Although no associations were found between anti-apoA1 levels and CVD-related events or overall mortality, a statistically significant association between high anti-apoA1 levels and early mortality emerged. These results suggest that the presence of anti-apoA1 antibodies early in the course of SLE may have prognostic implications. The mechanism through which anti-apoA1 may impact the course of SLE is not yet fully understood, therefore further studies to clarify this are required.

Disclosure: S. Croca, None; **M. Davari**, None; **D. A. Isenberg**, None; **A. Rahman**, None.

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Lupus Patients Have a High Prevalence Of Abnormalities On Resting Electrocardiogram That Are Associated With Increased Risk For Cardiovascular Events. Zahi Touma[1], Paula Harvey[2], Dafna Gladman[1], Arthy Sabapathy[1] and Murray B. Urowitz[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]Women's College Hospital, Toronto, ON.

Background/Purpose: Patients with lupus are at increased risk for cardiovascular disease (CVD). Abnormalities detected on resting electrocardiography (ECG) that may be associated with an increased risk for subsequent cardiovascular (CV) events include ST-segment abnormalities, T-wave abnormalities, left ventricular hypertrophy (LVH), left-axis deviation, and bundle branch block.

We aimed to describe all abnormalities on resting ECG in a cohort of lupus patients and determine the prevalence of specific abnormalities associated with increased risk for CV events.

Methods: Resting ECG was performed on all consecutive patients attending The Lupus Clinic between October 2012-May 2013. Participants underwent a standard digitally recorded 12-lead ECG at supine rest. Coded ECGs were reviewed and interpreted by a cardiologist using the Minnesota code classification system.

ECGs were grouped as normal and abnormal. Abnormalities included: pathological Q waves, ST-segment and/or T-wave abnormalities, LVH, left or right bundle branch block, left-axis deviation, arrhythmia and atrial enlargement.

We further determined the prevalence of at least one or more of the ECG findings that may be associated with subsequent CV events: ST-segment and/or T-wave abnormalities, LVH, left-axis deviation, or bundle branch block. We also determined the number of patients who had at least one or more of these variables.

Results: 274 patients were studied. 88.7% of the patients were female with mean age of 47.7 +/− 14.0 and lupus duration of 17.0 +/− 11.5 years.

Of 274 resting ECGs 40.5% were abnormal (Figure 1). 21 patients had axis deviation of which 13 had left, 5 had right l and 3 fulfilled criteria for left anterior fascicular block. 7 patients had atrial enlargement (3 right and 4 left). 32 patients with arrhythmia were identified (3 1st degree atrioventricular block, 10 sinus bradycardia, 4 sinus tachycardia, 3 ectopic atrial rhythm, 3 long QTc, 2 isolated premature atrial and 1 isolated premature ventricular contractions, 2 ventricular bigeminy, and 2 short PR interval).

ST-segment abnormalities and/or T-wave abnormalities in 54 (19.7%) LVH in 27 (9.9%), left-axis deviation in 16 (5.8%) and bundle branch block in 13 (4.7%). LBBB were present in 1 patient (0.4%) and in RBBB12 (4.4%). 17 (6.2%) patients had pathological Q waves (which may indicate previous infarct).

115 (41.9%) patients had at least one of the 4 ECG findings that may be associated with subsequent CV events. 23 (8.4%) patients had 2 more ECG abnormalities and 6 (2.2%) were observed to have at least 3 ECG abnormalities.

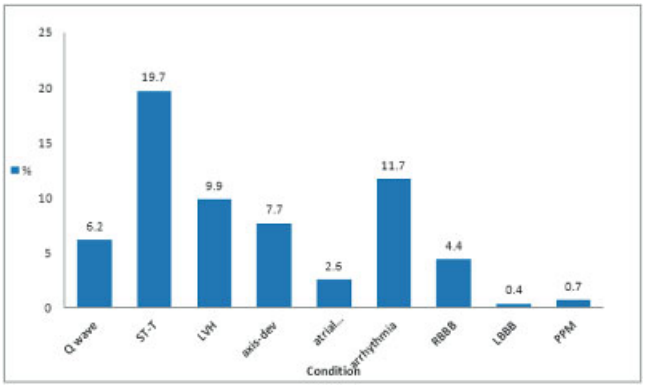

Figure 1. Percentage of abnormalities in resting ECG in lupus patients

Conclusion: 40.5% of the ECG had abnormal findings. All of the abnormal ECGs demonstrated at least one ECG finding associated with an increased risk for subsequent CV events. Further studies will determine whether ECG can serve as risk stratification factor for CVD in SLE patients.

Disclosure: Z. Touma, None; **P. Harvey**, None; **D. Gladman**, None; **A. Sabapathy**, None; **M. B. Urowitz**, None.

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Extremely High Coronary Artery Calcium Scores Among Patients With Systemic Lupus Erythematosus. Susan Due Kay[1], Anne Voss[2], Axel Cosmus Pyndt Diederichsen[3] and Mikael Kjær Poulsen[4]. [1]University of Southern Denmark, Odense - 5000, Denmark, [2]Odense University Hospital, Odense C, Denmark, [3]Odense University Hospital, Odens-5000, Denmark, [4]Odense University Hospital, Odense - 5000, Denmark.

Background/Purpose: Investigations of major lupus-cohorts have demonstrated cardiovascular disease to have major impact on morbidity and mortality (Am J Epidemiol 1997;145:408–15). The aim of this study was to determine the prevalence of coronary artery calcium and pattern of coronary artery calcium scores (CAC) among Danish patients with systemic lupus erythematosus (SLE).

Methods: In a population-based predominantly Caucasian cohort we recruited 84 SLE patients. To assess CAC a Toshiba 64-slice CT-scanner (Aquilion, Toshiba Medical Systems) with the following technical settings was used: gantry rotation time 450 msec, 3 mm collimation, 120 kV tube voltage and prospective gating at 75% of the R-R interval. Scan data were acquired during an inspiratory breathhold. CAC was expressed as Agatston score, that was calculated by summing-up the scores from each foci in the coronary arteries.

Results: Among the patients 91% were females, 98 % Caucasian, 2% Arabian, and mean age was 50,8 ± 14,2 yrs. In 43% coronary calcium was detected (CAC range 1 to 9725). Sixteen percent had a high CAC (>400), and 9% had an extremely high CAC (>1000). As shown in Table 1 patients with extremely high CAC had elevated BMI and were current smokers or previous smokers. Nephropathy and high SLICC scores were found in this group.

Table 1.

	Coronary calciumscore >1000	Coronary calcium score 0–1000
No.	8	76
Age, yrs, mean, SD	64,8 ± 13,3	53,25 ± 10,6
Female, no. (%)	5 (62)	73 (96)
Male, no. (%)	3 (37)	4 (5)
BMI, kg/m2, mean, SD	29,5 ± 5,3	25,44 ± 5,1
Ever smoker, no. (%)	7 (87)	47 (61)
Hypertension, no. (%)	7 (87)	41 (53)
Hypercholesterolemia	5 (62)	41 (53)
Hyperglycemia, no. (%)	2 (25)	8 (10)
Nephropathy, no. (%)	3 (37)	3 (3)
Disease duration, yrs, mean, SD	4 ± 1,4	12,8 ± 7,4
SLICC, mean, SD	5,6 ± 3,8	1,7 ± 1,6

Conclusion: In a population-based cohort 9% had extremely high CAC. Traditional as well as SLE related CVD risk factor predominated among these patients.

Disclosure: S. D. Kay, None; **A. Voss**, None; **A. C. P. Diederichsen**, None; **M. K. Poulsen**, None.

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Smoking and Secondhand Smoke Exposure Among Patients With Systemic Lupus Erythematosus and Controls: Associations With Disease and Disease Damage. Samantha J. Minkin, Stephanie N. Slan, Gary S. Gilkeson and Diane L. Kamen. Medical University of South Carolina, Charleston, SC.

Background/Purpose: Previous reports suggest smoking may be a risk factor for developing systemic lupus erythematosus (SLE), however the significance of this relationship varies among studies. This study explores the impact of smoking and exposure to secondhand tobacco smoke on SLE compared to controls and on disease characteristics among patients.

Methods: Data from a longitudinal cohort of SLE patients, related controls and unrelated controls was utilized. All controls were African American (AA), therefore all comparisons between patients and controls excluded non-AA patients. Medical history, smoking and secondhand smoke exposure history, SLE Disease Activity Index (SLEDAI) and SLICC-Damage Index (SDI) scores were collected at an in-person enrollment visit and confirmed by chart review. Active disease was defined as a SLEDAI ≥ 6 and disease damage was defined as SDI >0. Statistical analysis used chi square testing for proportions and multivariate logistic regression to compare groups while adjusting for covariates.

Results: There were 545 SLE patients and 386 controls with data available for analysis (**Table**). At enrollment, the mean age was 37.6 +/− 14.7 years for patients and 42.0 +/− 15.4 years for controls. Mean disease duration at enrollment was 7.0 +/− 7.5 years for patients. Patients were 91.6% female, related controls (n=222) were 76.6% female and unrelated controls (n=164) were 86.0% female. Differences between current and never smokers (p=0.51) and ever and never smokers (p=0.70) were not significantly different between patients and controls. Compared to unrelated controls, AA patients were significantly more likely to be exposed in the home to secondhand smoke before the age of 18, adjusting for age, education level, and gender (OR 1.81, 95% CI 1.13–2.89).

	Never Smokers n (%)	Ever Smokers n (%)	Current Smokers n (%)	Secondhand Smoke < 18 yo n (%)	Secondhand Smoke Ever n (%)
All Patients N = 545	407 (74.7%)	138 (25.3%)	72 (15.1%)	132 of 372 (35.5%)	158 of 376 (42.0%)
African American Patients n=416	328 (78.9%)	88 (21.2%)	49 (11.8%)	111 of 313 (35.5%)	127 of 315 (40.3%)
Caucasian Patients n = 109	63 (57.8%)	46 (42.2%)	21 (19.3%)	19 of 47 (40.4%)	26 of 47 (55.3%)
Other Patients n = 20	16 (80%)	4 (20.0%)	2 (10%)	2 of 12 (16.7%)	5 of 14 (35.7%)
All Controls (African American) **N = 386**	284 (73.6%)	102 (26.4%)	57 (14.8%)	92 of 354 (25.6%)	120 of 357 (33.6%)
Related Controls n = 222	155 (69.8%)	67 (30.2%)	36 (16.2%)	51 of 205 (24.9%)	67 of 207 (32.4%)
Unrelated Controls n = 164	129 (78.7%)	35 (21.3%)	21 (12.8%)	41 of 149 (27.5%)	53 of 150 (35.3%)

SDI scores were available for 423 of the patients. Damage by SDI was significantly associated with ever smoking (OR 3.08, 95% CI 1.4–6.6), current smoking (OR 3.17, 95% CI 1.1–9.1), and secondhand smoke exposure in childhood (OR 1.91, 95% CI 1.0–3.6), adjusting for disease duration, ethnicity, baseline age, SLEDAI, hydroxychloroquine use, education level and gender. No significant relationship was found between smoking status and either active disease at enrollment or presence of dsDNA autoantibodies. A history of discoid rash was significantly associated with ever smoking (OR 2.74, 95% CI 1.5–5.1) and current smoking (OR 4.85, 95% CI 2.2–10.5), but not with secondhand smoke exposure, adjusting for disease duration, ethnicity, baseline age, hydroxychloroquine use, education level and gender.

Conclusion: Our study suggests that secondhand smoke during childhood may be an important risk factor for SLE. Secondhand smoke during childhood, in addition to current smoking and past smoking, contributes significantly to disease damage among patients with established SLE.

Disclosure: S. J. Minkin, None; **S. N. Slan**, None; **G. S. Gilkeson**, None; **D. L. Kamen**, None.

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Ultrasound Assessment Of Both Carotid and Femoral Arteries In Patients With Systemic Lupus Erythematosus Increases Sensitivity For Detecting Asymptomatic Atherosclerosis. Sara Croca, D.A. Isenberg and Anisur Rahman. University College London, London, United Kingdom.

Background/Purpose: SLE is an independent risk factor for cardiovascular disease (CVD). Traditional risk assessment tools underestimate the actual CVD risk of these patients limiting the possibility of establishing primary prevention strategies. Vascular ultrasound (US) is an accurate, non-invasive, non-irradiating method to assess asymptomatic patients thus providing valuable insight into their real CVD risk. To our knowledge, to date only carotid US studies have been performed to assess atherosclerotic burden in patients with SLE. We propose that 4-point vascular assessment including both the carotid and femoral territories increases the sensitivity of the method and would be beneficial in assessing CVD risk in patients with SLE.

Methods: We performed US of carotid and femoral territories in 100 patients who fulfilled ACR classification criteria for SLE and had no prior diagnosis or symptoms of CVD. Intima-media thickness (IMT) of the common carotid artery (CCA) and carotid bulb were measured. Plaque and thickened IMT (>0.1cm) were defined according to the Mannheim Carotid IMT Consensus. Data on auto-antibody profile, lipids, treatment and smoking status were obtained through clinical records and patient interviews. The 10-year risk for myocardial infarction (MI) using the Framingham risk score was calculated

Results: Of the 100 asymptomatic patients, 95% were women and the overall mean age was 45.2 years (SD 12.4; range 20–66). 56 patients were Caucasian, 25 were of Afro-Caribbean-origin, 11 were Asian and 8 patients had other ethnic backgrounds (Chinese or mixed race).Only 2 had thickened IMT in the CCA but 37 had plaque. This included 14 with only carotid plaque, 7 with only femoral plaque and 16 with both. 15 had plaque in at least 3 sites. Patients with plaque were significantly older than patients without plaque at diagnosis (mean age 33 vs 27 yrs, P=0.006) and at time of scan (54 vs 40 yrs, P<0.0001) and had longer disease duration (21 vs 14 yrs, P=0.002). There were no differences in auto-antibody profile, lipids, smoking status and treatment between patients with or without plaque. The mean Framingham 10 year risk for MI for all 100 patients was <1% and there were no differences between patients with or without plaque. Interestingly, patients who had plaque on the femorals had significantly thicker carotid IMT compared to those who didn't even in the absence of carotid plaque (p=0.015).

Conclusion: Our results confirm a high prevalence of asymptomatic atherosclerotic plaque in patients with SLE even where Framingham risk scores are low and show that femoral as well as carotid ultrasound may well be valuable. In particular, almost a fifth of patients with plaque had femoral lesions only.

Disclosure: S. Croca, None; **D. A. Isenberg**, None; **A. Rahman**, None.

ACR Poster Session A
Systemic Lupus Erythematosus - Human Etiology and Pathogenesis: Mechanisms and Biomarkers
Sunday, October 27, 2013, 8:30 AM–4:00 PM

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Estrogen Modulates The Expression Of Endosome-Associated Toll-Like Receptor 8 Through Estrogen Receptor-α Which May Contribute To Sex-Bias In Systemic Lupus Erythematosus. Nicholas A. Young[1], Lai-Chu Wu[1], Craig Burd[1], Alexandra Friedman[1], Benjamin Kaffenberger[1], Murugesan Rajaram[1], Larry S. Schlesinger[1], Hayley James[2], Margaret Shupnik[2] and Wael N. Jarjour[1]. [1]The Ohio State University Wexner Medical Center, Columbus, OH, [2]University of Virginia School of Medicine, Charlottesville, VA.

Background/Purpose: Epidemiological data suggests that females of child-bearing age are more resistant to infectious disease. The sex hormone estrogen (E2) is present at elevated levels in this population and has been shown to influence immune cell function by regulating the expression of multiple genes through binding of estrogen receptors (ER) α and β. Systemic lupus erythematosus (SLE) is a multi-organ auto-inflammatory disease

predominantly affecting child-bearing age females. We hypothesize that estrogenic effects could establish a heightened immune-activation state, which would have a survival advantage in the defense against infection, but may have deleterious effects when it comes to autoimmune development.

Methods: Human peripheral blood mononuclear cells (PBMCs) were stimulated with β-estradiol (E2) and/or BOOSTRIX® immunogen to measure cellular proliferation and cytokine expression. RNA was isolated from whole blood of healthy individuals and SLE patients. PBMCs, human hematopoietic cell lines, and primary monocyte derived macrophages (MDMs) were treated with a physiological dose of testosterone, E2, and/or toll-like receptor (TLR) agonists to look at gene expression by Western blotting and real time-RT-PCR. Furthermore, E2 was injected subcutaneously into wild-type mice and lymphoid tissue was collected for real time-RT-PCR analysis to measure TLR8 expression. Additionally, siRNA was used to target ERα or IFNα. EMSAs were performed with putative ERα-binding sites defined by ChIP-seq analysis and nuclear extracts or recombinant ERα protein.

Results: Cellular proliferation and cytokine production were most significantly enhanced with E2 treatment in female PBMCs challenged with immunogen. TLR8 was identified to be over-expressed in whole blood of SLE patients and its *ex vivo* expression was induced in PBMCs by estrogen, but not by testosterone. E2-induced TLR8 expression was also observed in mouse lymphoid tissue *in vivo*. Furthermore, both estrogen and TLR agonist stimulated the expression of endosomal TLRs, but not TLR4, which is cell membrane-associated. Female sex-biased expression of TLR8 was demonstrated in human PBMCs when stimulated with both agonist and estrogen simultaneously. Moreover, siRNA targeting ERα blocked E2-mediated TLR8 expression, while siRNA against IFNα had no effect. EMSA analysis suggested that E2 enhanced ERα binding to an ER response element 25 kb downstream from the 3' end of the TLR8 gene.

Conclusion: We find that the expression of TLR8 is positively regulated by estrogen and that TLR8 is over-expressed in SLE patients. We propose that estrogen-induced up-regulation of TLR8 expression is mediated directly through ERα, but not IFNα. In conjunction with the TLR8 autocrine feedback loop, estrogen lowers the inflammation threshold, which could promote an inflammatory state contributing to higher SLE incidence among women.

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Altered ER Stress-Induced Autophagic Reactions Are Associated With Increased Apoptosis of T Lymphocytes in Systemic Lupus Erythematosus. Won Seok Lee[1], Myung-Soon Sung[1], Eun-Gyeong Lee[1], Chang-Hoon Lee[2], Myeung Su Lee[3], Yun-Hong Cheon[4], Sang-il Lee[4], Yun Kyoung Hong[5] and Wan-Hee Yoo[1]. [1]Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, [2]Department of Internal Medicine, School of medicine, Wonkwang university, Iksan, Chonbuk, South Korea, [3]Department of Internal Medicine, School of Medicine, Wonkwang University, Iksan, Chonbuk, South Korea, [4]Gyeongsang National University School of Medicine, Jinju, South Korea, [5]Department of internal medicine, Presbyterian medical center, Jeonju, South Korea.

Background/Purpose: The autophagic responses to ER stress are involved in the regulation of the maintenance of lymphocyte homeostasis and has been implicated in the pathogenesis of autoimmunity. However, there were no studies about the roles of autophagic responses and its relations with apoptosis of T lymphocytes in systemic lupus erythematosus (SLE). Thus, we investigated to study about the pathogenetic roles of ER stress-mediated pathways, autophagic and apoptotic reactions in the T lymphocyte survival and death in SLE.

Methods: We investigated the spontaneous and induced autophagic and apoptotic behavior of T lymphocytes from patients with SLE compared with that of T lymphocytes from healthy donors by measuring the autophagy marker microtubule-associated protein 1 light chain 3 (LC3) II and autophagosome by scanning electron microscope. The molecular mechanism of the altered autophagic and apoptotic responses and their relations were investigated in T lymphocyte transfected with siRNA for beclin 1, CHOP and T lymphocyte with overexpression of GRP78 by transfection. The apoptosis, autophagy and ER stress signaling molecules were examined by immunoblotting.

Results: There were increased apoptosis and decreased autophagic responses to Thapsigargin (TG) in T lymphocytes from healthy controls compared with these cells from patients with SLE. The activation of ER stress signaling molecules, including PERK, p-eIF2a, IRE1 and ATF6 to TG were decreased in lupus T cells. The expression of anti-apoptotic molecules, Bcl-2, Bcl-XL were decrease and proapoptotic molecules, Bax, caspase-6 were increased in lupus T cells. Our results also revealed that CHOP expression was increased and GRP78 was decreased in lupus T cells. GRP78 overexpression and CHOP siRNA knockdown in T cells from healthy donors were associated with altered apoptotic cell death.

Conclusion: The autophagic and apoptotic responses to TG-induced, ER stress are altered and contribute to the abnormal T cell homeostasis with increased apoptotic T cell death. We hypothesize that aberrant autophagic and apoptotic reactions of T lymphocytes to ER stress are involved in the pathogenesis of SLE and might be an important target of treatment.

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Galectin-3-Binding Protein Is Highly Increased On Circulating Microparticles In SLE Patients and Co-Localizes With IgG In Glomerular Deposits In Human Lupus Nephritis. Christoffer T. Nielsen[1], Ole Østergaard[2], Ole Petter Rekvig[3], Gunnar K. Sturfelt[4], Søren Jacobsen[5] and Niels H. H. Heegaard[6]. [1]University Hospital Rigshospitalet, Copenhagen, Denmark, [2]Statens Serum Institute, Copenhagen S, Denmark, [3]University Hospital, Tromsø, Norway, [4]Lund University, Lund, Sweden, [5]Department of Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [6]Statens Serum Institut, Copenhagen, Denmark.

Background/Purpose: The origin of autoantigens in glomerular immune complex (IC) deposits in lupus nephritis patients is unknown. They may derive from the circulation (microparticle (MP)-ICs or soluble ICs) or from apoptotic glomerular cells. Galectin-3-binding protein (G3BP) may be a specific marker of SLE cell-derived MPs. Here, we characterize G3BP-positive MPs in plasma from SLE patients compared to healthy controls (HCs), explore clinical correlates, and use G3BP to identify MP-components in IC deposits in kidney biopsies from patients with lupus nephritis.

Methods: Plasma MPs were analyzed in 56 SLE patients and 36 healthy controls. MPs were enumerated by flow cytometry for G3BP exposure and annexin V (AnxV) binding. MP-quantitation of G3BP, IgG, and C1q were obtained by tandem mass spectrometry (LC-MS/MS). Co-localization of anti-G3BP antibodies with *in vivo*-bound IgG was examined in kidney biopsies from SLE patients with class IV (diffuse proliferative, n=2) and class IV (membranous, n=1) and in one control using co-localization immune electron microscopy.

Results: LC-MS/MS quantities of MP-G3BP, -IgG and -C1q were significantly increased in SLE patients ($p<0.05$ in all cases). Three different G3BP-positive MP-populations could be identified by flow cytometry. Two of these were significantly increased in SLE patients compared to HCs ($p=0.008$ and $p=0.001$, respectively). No significant clinical associations were observed. G3BP co-localized with *in vivo*-bound IgG in all three lupus nephritis biopsies while absent from control tissue. The G3BP was confined to the IC deposits and detected diffusely throughout the sections.

Conclusion: G3BP overexpression is a key feature of SLE-MPs irrespective of clinical manifestations or disease activity. The distinct overlap of glomerular G3BP and IC deposits strongly suggests MPs to be an important source of autoantigens in lupus nephritis.

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Type I IFN Regulation Of IL-10 Is Detrimental To Endothelial Cell Differentiation and May Enhance Cardiovascular Risk In Systemic Lupus Erythematosus. J. Michelle Kahlenberg[1], Alyssa Cates[1], Victoria Holden[1], Carolyne K. Smith[1] and Mariana J. Kaplan[2]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan Rheumatology, Ann Arbor, MI.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a heterogeneous disease resulting in organ damage and an elevated risk of cardiovascular disease (CVD). Previous reports have suggested that type-I interferon (IFN)-mediated repression of IL-1β and activation of IL-18 are important pathways leading to endothelial dysfunction and CVD in lupus patients.

While typically viewed as anti-inflammatory, Interleukin-10 (IL-10) levels are elevated in SLE patients, where they may play pathogenic roles related to immune activation of B cell responses. Furthermore, IL-10 induces transcriptional repression of IL-1β synthesis. This study explores whether IL-10 has a detrimental effect on endothelial progenitor cell (EPC) differentiation and function and whether it may play a role in type I IFN-mediated repression of IL-1β in SLE with secondary detrimental effects on neoangiogenesis.

Methods: Human and murine control and lupus EPCs were induced to differentiate into mature endothelial cells (ECs) in the presence or absence of graded concentrations of recombinant IL-10 or a neutralizing Ab to this cytokine. IL-10 deficient mice were used to assess the role of this cytokine in type I IFN-mediated inhibition of neoangiogenesis using an in vivo Matrigel plug assay.

Results: In murine EPC/CAC cultures, the inhibitory effects of IFN-α on EPC/CAC differentiation were abrogated using an anti-IL-10 neutralizing antibody or cultures from IL-10 $-/-$ mice. Further, the inhibitory effects of IFN-α on neoangiogensis in vivo were abrogated in IL-10 $-/-$ mice. In human EPC cultures, anti-IL-10 neutralizing antibodies did not significantly impact the differentiation of control cells, but improved the differentiation of SLE EPCs into mature ECs. Conversely, addition of recombinant IL-10 was detrimental to EPC growth and differentiation and this was enhanced by type I IFNs in both control and SLE cultures. Upregulation of IL-10 was detected following type I IFN treatment of early EPC cultures, while both recombinant IL-10 and IFN-α resulted in enhanced repression of IL-1β in these cells.

Conclusion: These results indicate that IL-10 is detrimental to vasculogenesis and is an important intermediary in the IFN-α-mediated repression of proangiogenic IL-1β previously observed in these cells. As type I IFNs induce IL-10 synthesis, these results indicate that elevated levels of IL-10 in SLE patients may be associated with cardiovascular risk.

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Anti-Ribosomal-Phosphoprotein Autoantibodies Penetrate Into Neuronal Cells *Via* Neuron Growth Associated Protein (GAP43). Shaye Kivity[1], Yehuda Shoenfeld[2], Margalit Zusev[3], Inna Slutsky[4], Dolores J Cahill[5], Sara Louise O'Kane[6], Michal Harel-Meir[7], María Teresa Arango[8], Juan-Manuel Anaya[9], Joab Chapman[10] and Miri Blank[11]. [1]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, affliated to Sackler Faculty of Medicine, Tel-Aviv University Israel, Tel-Aviv, Israel, [2]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Affiliated to Sackler Faculty of Medicine, Tel-Aviv University,Tel-Aviv, Tel-Aviv, Israel, [3]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Israel, Ramat Gan, Israel, [4]Department of Physiology and Pharmacology, Sackler Faculty of Medicine, Tel-Aviv, Israel, [5]School of Medicine and Medical Sciences, Conway Institute of Biomolecular & Biomedical Research, University College, Dublin, Ireland, [6]School of Medicine and Medical Sciences, Conway Institute of Biomolecular & Biomedical Research, University College, Dublin, Ireland, [7]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Tel-Aviv, Israel, [8]Doctoral Program in Biomedical Sciences Universidad del Rosario, Bogota, Colombia;Center for Autimmune Diseases Research – CREA, Universidad del Rosario,, Bogota, Colombia, [9]School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia, [10]Department of. Neurology and Sagol Neuroscience Center, Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel, [11]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, affiliated to Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Tel-Aviv, Israel.

Background/Purpose: Autoantibodies targeting ribosomal phosphoproteins (anti-Ribos.P) are detected in the sera of 10–45% patients with neuropsychiatric-systemice-lupus-erythemathosus-(NPSLE) and correlate with disease-activity. Intracerebroventricular administration of anti-Ribos.P induce depression like behavior in naïve mice. We assessed the capability of anti-Ribos.P to penetrate neuronal cells and affect the cellular function.

Methods: The penetration of human affinity purified anti-Ribos.P Abs into cultured neuronal cells, was shown by confocal microscopy. Endothelial Cells (HUVEC) were used as control Identification of the molecule targeted by anti-Ribos.P Abs was performed by screening a high content human cDNA-library The cross-reactivity between ribosomal-P0 and the identified neuron-growth-associated-protein-GAP43 was done by ELISA. Inhibition of neuronal cell proliferation was carried out by Bromodeoxyuridine-(BrdU).

Results: We show herein the penetration of human anti-Ribos.P Abs into human neuronal cells and rat hippocampal cells cultures, *in-vitro*. These Abs bind mouse brain sections of hippocampus, dentate and amygdala. Moreover, anti-Ribos.P Abs target neuronal cells through GAP43 binding. The anti-Ribos.P binding to mouse hippocampus, dentate and amygdala was prevented by GAP43 protein. Interestingly, GAP43 inhibited in a dose-dependent manner the anti-Ribos.P binding to ribosomal-P0 recombinant protein, indicating a cross-reactivity between the ribosomal-P0 protein and GAP43. Furthermore, anti-Ribos.P Abs reduced neuronal cells proliferation activity, *in-vitro* $p<0.001$) whereas GAP43 prevented this inhibitory activity by 7.6 times.

Conclusion: Anti-Ribos.P Abs penetrate neuronal cells *in-vitro* by targeting GAP43. Ribos.P0 cross-react with GAP43. Anti-Ribos.P Abs inhibit neuronal-cell proliferation. Our data contribute to deciphering the mechanism for anti-Ribos.P Abs pathogenic activity in NPSLE.

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Reduced PD-1 Signaling Promotes Suppressive Function Of $CD4^+$ Regulatory T Cells In Patients With Systemic Lupus Erythematosus. Maida Wong, Jennifer M. Grossman, Antonio La Cava and Bevra H. Hahn. UCLA David Geffen School of Medicine, Los Angeles, CA.

Background/Purpose: Programmed death-1 (PD-1) has been regarded as a negative regulatory signal in T cells. Our laboratory has shown that PD-1 is important in T cell regulation of autoimmunity, as treatment with neutralizing anti-PD1 in the $NZB/NZWF_1$ mouse model of lupus increased regulatory T cell (T_{reg}) function and dramatically delayed SLE onset in young mice.

We hypothesized that SLE patients have increased PD-1 expression compared to healthy individuals, which may contribute to the compromised $CD4^+T_{reg}$ function in these patients.

Methods: Forty-five female SLE patients and twenty healthy female controls have been enrolled to date. Medical chart review was done to assess SLE disease activity index (Selena SLEDAI) score. PD-1 expression on $CD4^+T_{reg}$ (defined as $CD4^+CD25^{hi}Foxp3^+$) from the PBMC collected on the same day of the chart note was analyzed by flow cytometry, as were samples from healthy donors. Statistical analysis was performed to assess the relationship between PD-1 expression and SLEDAI. $CD4^+T_{reg}$ from patients were treated with neutralizing anti-PD-1 *in vitro* to test for their ability to induce B cell apoptosis, and $CD4^+CD25^-$ helper T cell (T_h) proliferation.

Results: SLE patients had fewer $CD4^+CD25^{hi}Foxp3^+$ T_{reg} in their PBMC compared to healthy controls ($p<0.03$), but these cells had significantly increased PD-1 expression ($p<0.02$). $CD4^+T_{reg}$ from patients with SLEDAI ≥ 4 tended to express more PD-1 than those from patients with SLEDAI <4 ($p<0.07$). Increased PD-1 expression was associated with vasculitis, thrombocytopenia and leukopenia ($p<0.05$). With *in vitro* PD-1 blockade, $CD4^+T_{reg}$ from the SLE patients were more resistant to apoptosis, and had increased ability to induce B cell apoptosis and to suppress T_h proliferation when compared to $CD4^+T_{reg}$ treated with IgG isotype.

Conclusion: SLE patients have aberrant, increased PD-1 expression on their circulating $CD4^+T_{reg}$ that may reduce the regulatory function of $CD4^+CD25^{hi}Foxp3^+$ T cells, which are important in the suppression of autoimmunity. One mechanism by which PD-1 sustains these T_{reg} is by reducing their susceptibility to apoptosis.

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IL-21/IL-21R Interaction On Lymphocyte Subsets From Lupus Patients. Vinh Nguyen[1], Horea Rus[2], Cosmin Tegla[2] and Violeta Rus[2]. [1]University of Maryland School of Medicine, Baltimore, MD, [2]University of Maryland School of Medicine and Veteran Affairs Medical Center, Baltimore, MD.

Background/Purpose: We have previously shown that IL-21 promotes autoimmunity in a mouse model of lupus through both CD4 and B cell intrinsic mechanisms. Recent studies have shown increased expression of IL-21 in CD4 cells from lupus patients and a strong association between genetic polymorphisms in IL-21 and IL-21R and systemic lupus erythema-

tosus. While these data suggest that IL-21 blockade may be an attractive therapeutic option in SLE, factors responsible for IL-21 upregulation and the effects of IL-21/IL-21R interaction on T and B cell subsets in lupus patients have not been fully characterized. To this end we assessed the expression of IL-21 in response to cytokines, the expression of IL-21R on CD4 cells and B cells from lupus patients compared to controls and the effect of IL-21/IL-21R interaction on these cells.

Methods: IL-21, IL-17, IFNg levels and IL-21R expression were determined in CD4, CD8 T cells and B cells by immunostaining. The proliferative response of purified CD4 cells and B cells to IL-21 was determined by [^{3}H] -Thymidine incorporation. IL-21R binding ability using biotinylated IL-21, IL-21 induced STAT-3 phosphorylation, plasma cell differentiation, IgG and IL-10 production by lupus and control B cells were determined by immunostaining and ELISA, respectively.

Results: IL-21 expression was significantly increased in PMA/ionomycin stimulated CD4 and CD8 T cells from lupus patients compared to controls. Functionally, supernatants of TCR stimulated CD4 cells from lupus patients induced higher levels of STAT-3 phosphorylation (which was inhibited by IL-21R:Fc) in normal B cells compared to supernatants from controls. The expression of IL-21 in TCR stimulated lupus CD4 T cells was upregulated by agonistic ICOS ligation and IL-12 but not by IFNa, IL-6, IL-10, IL-27 or TNFa. Consistent with IL-12 mediated upregulation, a higher proportion of IL-21 positive CD4 cells coexpressed IFNg (20±4%) compared to IL-17 (7±3%). IL-21 expression correlated with IL-17 expression in unstimulated and TCR stimulated CD4 T cells from lupus patients and IL-21 increased the proportion of IL-17+ CD4 T cells. IL-21R was detected at low levels on unstimulated naïve and memory CD4 T cells from both lupus patients and controls and was upregulated to a similar degree by T cell stimulation. However, CD4 T cells from patients and controls displayed decreased susceptibility to IL-21 proliferative effects. B cells from lupus patients expressed significantly higher IL-21R expression at baseline compared to controls. Among B cells CD27+CD38+plasmablasts and CD27+CD38- memory B cells from lupus patients but not CD27-CD38- naïve cells had higher binding ability for IL-21 compared to normal controls. IL-21 induced significantly higher STAT-3 phosphorylation and proliferation but not IgG and IL-10 production in lupus B cells.

Conclusion: IL-12 and ICOS ligation upregulate the expression of IL-21 in CD4 T cells from lupus patients. IL-21R expression and responsiveness to IL-21 is higher in B cells than CD4 cells from lupus patients, especially in plasmablasts and memory B cells. Therefore IL-21 blockade may attenuate IL-21 dependent aspects of B cell hyperactivity to a larger extent than CD4 T cell abnormalities such as expansion of Th17 cells.

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Multiple Altered Soluble Inflammatory Mediators Correlate With Disease Activity and Mark Impending Disease Flare In European-American Lupus Patients. Melissa E. Munroe[1], Jourdan R. Anderson[1], Krista M. Bean[1], Joan T. Merrill[1], Joel M. Guthridge[1], Virginia C. Roberts[1], Linda F. Thompson[2] and Judith A. James[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]University of Oklahoma Health Sciences Center, Oklahoma City, OK.

Background/Purpose: SLE is a waxing and waning disease characterized by immune dysregulation, major organ involvement, and disease flares. Identifying mechanistic mediators of altered disease activity would help prevent damage and improve disease management. This study seeks to identify markers that correlate with disease activity and distinguish SLE patients with impending flare.

Methods: As part of the SLE Influenza Vaccination Cohort, 28 European-American SLE patients who exhibited SELENA-SLEDAI defined flare at 6 (n=13) or 12 (n=15) weeks post-vaccination had pre-vaccination (BL) and post-vaccination disease flare (FU) plasma samples assessed for 52 soluble analytes using a multiplex bead-based assay or sandwich ELISA (BLyS and APRIL). Each SLE patient was matched by race, gender, age (± 5 years), and time of sample procurement to a unique SLE patient who did not exhibit disease flare (NF). Samples from a subset of 13 SLE patients with flare were compared to samples from the same SLE patients from another year where disease flare did not occur (self nonflare, SNF). Soluble mediator concentrations were compared between flare and NF/SNF groups and correlated with SELENA-SLEDAI disease activity scores. As a gauge of impending disease flare, a soluble mediator score was adapted from the Studies of the Aetiology of Rheumatoid Arthritis (SERA) study: BL soluble mediator values from flare and NF/SNF samples were log transformed, standardized, and weighted by their respective disease activity Spearman coefficients, with the resulting values summed for a total score.

Results: Pre-vaccination concentrations of 22 out of 52 analytes significantly correlated ($p<0.04$) with post-vaccination SELENA-SLEDAI disease activity scores, including multiple innate (IL-1α, IL-β, IFNβ) and adaptive (Th1, Th2, and Th17) cytokines, chemokines (IP-10, MCP-3), adhesion molecule (ICAM-1) and TNF superfamily members (TNF-α, Fas, FasL, TNFRI, and TNFRII). Utilizing all 52 assessed analytes weighted by their correlation with disease activity, patients with impending disease flare had a median soluble mediator score of 4.14 (± 4.40) and were 13.8 times more likely to have a positive score ($p < 0.0001$, Fisher's exact test) compared to NF SLE patients (−1.70 ± 4.64). In the subset of flare vs SNF samples, SLE patients with impending flare had a median score of 4.36 (± 7.41) and were 11.1 times more likely to have a positive score ($p=0.0469$) compared to SNF samples (−3.09 ± 8.47). Additionally, significantly higher levels ($p< 0.04$) of regulatory mediators TGF-β and IL-1RA were observed in NF/SNF samples compared to periods of impending flare.

Conclusion: Multiple innate, adaptive, and shed TNF members are altered and correlate with disease activity. A soluble analyte score created to reflect overall inflammation in SLE patients is not affected by influenza vaccine responses and serves as a promising approach for future prospective studies.

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Neutrophil-Mediated Interferon Activation In Systemic Lupus Erythematosus Bone Marrow. Anna Bird[1], Nida Meednu[1], Javier Rangel-Moreno[1], Srilakshmi Yalavarthi[2], Jennifer Barnard[1], Teresa Owen[1], Jason S. Knight[2], Alfred Rabinovich[1], Arumugam Palanichamy[1], Jane Liesveld[1], Jason W Bauer[3], Emily Baechler[3], Mariana J. Kaplan[2] and Jennifer H. Anolik[1]. [1]University of Rochester Medical Center, Rochester, NY, [2]University of Michigan Rheumatology, Ann Arbor, MI, [3]University of Minnesota, Minneapolis, MN.

Background/Purpose: Although SLE is known to be associated with a type I interferon signature in the peripheral blood, the precise site and mechanism of IFN pathway activation in SLE remain unclear. Given that IFN can impair B cell development in murine bone marrow (BM), we asked whether IFN activation is present in SLE BM and its potential consequences for disease pathogenesis.

Methods: The IFN signature was assessed in BM of SLE patients (n=28) and normal controls (NC, n=20) by examining the relative expression of 3 IFN inducible genes IFIT1, IRF7, and G1P2 by qPCR. Neutrophils were isolated using Percoll density gradient and phenotype confirmed by flow cytometry. Type I IFN, BAFF, and APRIL expression in total aspirates and purified neutrophils was measured by qPCR normalized to GAPDH. Neutrophil expression of BAFF and APRIL was confirmed by immunofluorescence. NZM2328 lupus prone female mice (pre-disease 12 wk) were compared to Balb/c (n=7 per group) for Type I IFN activation and production and secretion of cytokines that may alter B cell development. B cells were defined by flow cytometry using standard markers.

Results: The majority of SLE patients (57%) had an IFN signature in the BM that was more pronounced than the paired peripheral blood (PB) and associated with both higher autoantibodies and disease activity (BM vs. PB for IFN high group compared to NC: 45.7-fold vs. 18.5-fold, p=0.0009 for G1P2; 108.5-fold vs. 54-fold, p=0.005 for IFIT1). There was also a significantly higher expression of BAFF and APRIL in the IFN high SLE BM aspirates (BAFF: 2.45+/−0.66 fold compared to NC; APRIL: 6.04+/−2.5, p=0.01). BM neutrophils in SLE showed a significantly higher expression of APRIL and IFNα when compared to NC BM (p=0.04) and also a correlation between IFNα expression and APRIL (p=0.0004) and BAFF expression (p=0.0001), suggesting that IFNa may be driving APRIL and BAFF. SLE IFN high patients had profound alterations in the BM B cell compartment with significant reductions in precursor B cells (p=0.02) but increases in transitional B cells (27%, 4.6%, and 7.5% T1/T2 in IFN high SLE, IFN low SLE and NC, respectively; p=0.013). Lupus prone mice had similar alterations in B cell development. Notably, BM neutrophils from lupus mice displayed significant up-regulation of Mx-1 (10-fold, p=0.01), as well as increases in IFNα, IFNb, and BAFF (p=0.03, 0.03, 0.04). In bone sections, we also

detected numerous Gr-1+MPO+ neutrophils in NZM mice expressing APRIL and BAFF in close contact with B220+ B cells.

Conclusion: Overall, our results highlight the importance of the BM as a target organ in SLE and provide a previously unappreciated connection between IFN activation, neutrophils, and B cell selection.

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Proteomic Approach and Validation Of Urinary Biomarkers In Lupus Nephritis. Joo Youn Lee[1], Sung Hae Chang[2], Hye Jin Oh[3], Yong Yook Lee[1], Min Jueng Kang[1], Eun Young Lee[4], Eun Bong Lee[4], Eugene C. Yi[1] and Young Wook Song[1]. [1]Department of Molecular Medicine and Biopharmaceutical Sciences, Seoul National University, Seoul, South Korea, [2]Seoul National University Bundang Hospital, Seongnam-si, South Korea, [3]Seoul National University, Seoul, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, Seoul National University, Seoul, South Korea.

Background/Purpose: Renal involvement occurs in about half of systemic lupus erythematosus (SLE) patients. A number of biochemical markers are currently used to clinically assess lupus nephritis (LN) activity. Nevertheless, the correlation between these markers and LN is not satisfactory. We screened urinary biomarkers of LN using LTQ-Velos hybrid mass spectrometer and validated the biomarkers in a cohort of SLE patients.

Methods: Urine samples from SLE patients with nephritis (n=5) and without nephritis (n=5) were obtained from Seoul National University Hospital. We employed a nanospray interfaced LTQ-Velos hybrid mass spectrometer. Data were processed using Sorcerer™–SEQUEST. The searched data entered into Scaffold software (Proteome Software) for compilation, and the datasets were imported into the R to generate Power Law Global Error Model (PLGEM, www.bioconductor.org) values for each protein identified (FDR $< 1\%$). The spectral count was used for Gene Ontology, and pathway analysis using Ingenuity Pathway Analysis.

In 124 SLE patients (20 LN, 104 non-LN), 21 healthy controls, and 31 disease controls (IgA nephropathy and membraneous glomerulonephritis), urinary levels of retinol binding protein 4 (RBP4), vitamin D binding protein (VDBP), complement factor H (CFH), transthyretin (TTR), and prostaglandin D synthase, lipocalin type (PGDS) were measured by ELISA. Urinary levels of biomarkers were normalized against urine creatinine. Patient global assessment (PtGA), physician global assessment (PhGA) and SLE disease activity index 2K (SLEDAI 2K) were measured at the time of urine sampling.

Results: 487 unique proteins and 3550 unique peptides were identified in urine of SLE patients by MS spectroscopy. We selected five biomarker candidates with high confident level. SLE patients with LN showed significantly higher urinary levels of RBP4, VDBP, CFH, TTR, and PGDS compared with those without LN ($p = 0.0003$, $p < 0.0001$, $p = 0.0001$, $p = 0.0015$ and $p = 0.0001$, respectively) or healthy controls. Urinary level of PGDS was significantly higher in LN than disease controls (mean±SE, 7190.7 ± 2621.0 vs 1001.2 ± 126.3 ng/mgCr, $p = 0.0181$). Other biomarkers tended to be higher in LN compare to disease controls (RBP4, 22820.0 ± 17650.0 vs 2534.2 ± 983.8, $P = 0.2591$; VDBP, 413.5 ± 216.8 vs 186.6 ± 49.33, $p = 0.7589$; CFH, 100.4 ± 51.8 vs 55.5 ± 16.0, $p = 0.9923$; TTR, 267.0 ± 142.5 vs 126.3 ± 50.7, $p = 0.4813$).

Urinary levels of VDBP, CFH, TTR, and PGDS were significantly correlated with Ph GA in LN ($p = 0.0322$, $p = 0.0233$, $p = 0.0318$ and $p = 0.0009$, respectively). Urinary levels of TTR and PGDS were significantly correlated with SLEDAI 2K in LN ($p = 0.0042$ and $p = 0.0016$, respectively).

Conclusion: Urinary PGDS may serve as a biomarker for LN. It was significantly correlated with physician global assessment and SLEDAI 2K in LN.

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Estrogen-Induced STAT1 and STAT4 Expression Is Estrogen Receptor α Dependent and IFNα Independent: A Novel Mechanism For Sex-Bias In Systemic Lupus Erythematosus Pathogenesis? Nicholas A. Young[1], Giancarlo R. Valiente[2], Lai-Chu Wu[1], Michael Bruss[1], Craig Burd[1] and Wael N. Jarjour[1]. [1]The Ohio State University Wexner Medical Center, Columbus, OH, [2]The Ohio State University College of Medicine, Columbus, OH.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a devastating multi-organ autoimmune disease displaying an overwhelming female predilection. Estrogen (E2) influences gene expression by binding to estrogen receptors (ERα and ERβ) and a role for E2 has been proposed in SLE pathogenesis. Further, E2 has been shown to regulate Signal Transducer and Activator of Transcription (STAT) 1 and STAT4 function. Toll-Like Receptor 8 (TLR8) has also been implicated in SLE and is a potent inflammatory mediator. The results of this study demonstrate the E2-mediated induction of STAT1 and STAT4 for the first time in primary human peripheral blood mononuclear cells (PBMCs) and mechanistically characterize the pathway that is operative in this induction.

Methods: PBMCs isolated from SLE patients and healthy controls were treated with a physiological dose of E2. Putative estrogen response elements (EREs) in the human genome were identified from ChIP-seq data of MCF-7 cells stimulated with E2 for one hour. Radio-labeled probes corresponding to STAT1 DNA binding regions were used in EMSA analysis to examine DNA-protein complex formation in a human monocytic cell line (THP-1). In the presence of E2, siRNA was used to block ERα or STAT1 expression in THP-1 cells lacking detectable IFNα expression.

Results: Expression of STAT1 and STAT4 was elevated in PBMCs of SLE patients relative to age and sex-matched healthy controls. Moreover, E2 stimulation of freshly isolated human PBMCs significantly induced STAT1 and STAT4 expression. Given that we have previously observed that TLR8 expression is higher in SLE and induced with E2 treatment, a *bona fide* STAT1 binding region located 24 kb from the 3' end of the TRL8 gene was used in EMSA analysis to show that enhanced DNA-protein complex formation was induced by E2 stimulation. Interestingly, STAT1 is located next to STAT4 and ChIP-seq data of cells stimulated with E2 revealed an intragenic ERE binding peak within the STAT1 locus, which suggests that E2 may be promoting the expression of both genes through this response element. Using siRNA to explore E2 induction of STAT1 mechanistically, we demonstrate that this response is mediated through ERα. Furthermore, siRNA blocking STAT1 significantly reduced TLR8 induction with E2 stimulation.

Conclusion: E2 can stimulate the expression of STAT1 and STAT4 in PBMCs and potentially contribute to the pathogenesis observed in SLE due to their potent signal transducing effects over the immune system. STAT1 promotes TLR8 expression after E2 stimulation and an ERE near both STAT1 and STAT4 has been identified through ChIP analysis. The identification of molecular targets to inhibit the TLR8 inflammatory pathway presents a significant therapeutic opportunity. Collectively, our results indicate that STAT1 and STAT4 may contribute to the E2-mediated sex-bias observed in autoimmunity through ERα signaling and may potentially be ideal targets in future therapy to treat SLE.

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Examination Of The Cytokine Profile Of The Cerebrospinal Fluid In Neuropsychiatric Systemic Lupus Erythematosus. Kunihiro Ichinose[1], Takeshi Ushigusa[2], Yoshikazu Nakashima[1], Takahisa Suzuki[1], Yoshiro Horai[2], Shin-ya Kawashiri[2], Naoki Iwamoto[2], Mami Tamai[1], Kazuhiko Arima[2], Hideki Nakamura[2], Tomoki Origuchi[2] and Atsushi Kawakami[2]. [1]Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

Background/Purpose: Neuropsychiatric systemic lupus erythematosus (NPSLE) is a serious complication in systemic lupus erythematosus (SLE). NPSLE syndromes involve both the central and peripheral nervous systems. Despite advances in the understanding of the immunopathogenic and clinical aspects of SLE, NPSLE remains a diagnostic and therapeutic challenge.

Methods: We examined the cytokine profile in the cerebrospinal fluid (CSF) of NPSLE patients admitted to our hospital in a 7-year period from 2006 through 2012 and searched for markers that may be useful for the

diagnosis of NPSLE. We used the CSF of patients with multiple sclerosis (MS) or neuromyelitis optica (NMO) as a disease control group. We examined 27 types of cytokine, chemokines, and growth factors in the NPSLE group (n=27), MS group (n=10) and NMO group (n=10) using Bio-Plex Pro assays.

Results: All of the NPSLE patients were women. The mean ± SD disease duration of NPSLE was 10.6±9.56 years. The NPSLE patients' Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score was 13.3±5.86, and their anti-ds-DNA antibody level was 23.3±58.6 U/mL. The percentages of anti-phospholipid antibody syndrome, anti-ribosomal P antibody positivity, and abnormality of brain MRI were 4/27 (14.8%), 5/27 (18.5%) and 9/27 (33.3%), respectively. Aside from the cytokines that are known to be related to NPSLE such as interleukin (IL)-6, the concentrations of basic FGF, and IL-1ra, -5, -7, -9, -15 and -17 were significantly higher in the NPSLE group compared to the other two groups. A multivariate analysis revealed that the protein levels of IL-5 ($p<0.036$), IL-9 ($p<0.0005$), IL-15 (<p0.0065) and IL-17 ($p<0.0336$) were significantly correlated with IL-6.

Conclusion: In NPSLE patients who do not show IL-6 elevation, it might be advisable to examine other cytokines. The determination of various types of CSF cytokine profiles may contribute to the diagnosis of NPSLE and may help elucidate the mechanisms underlying this disease.

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Systemic Lupus Erythematosus Patients With Atherosclerosis Are Characterised By a Distinct *Invariant* Natural Killer T Cell Phenotype and Altered CD1d-Mediated Lipid Antigen Presentation. Edward Smith, Sara Croca, Andrew Pitcher, D.A. Isenberg, Anisur Rahman and Elizabeth C. Jury. University College London, London, United Kingdom.

Background/Purpose: It is widely reported that systemic lupus erythematosus (SLE) patients have an increased risk of atherosclerosis compared to the general population, irrespective of traditional risk factors. We investigated whether this was attributable to differences in the phenotype and function of *invariant* Natural Killer T cells (*i*NKT), which promote atherosclerosis by recognising and responding to lipid antigens presented by CD1d, yet have been shown to be deficient in SLE patients.

Methods: Peripheral blood was obtained from 20 healthy donors and 50 SLE patients assessed for carotid and femoral atherosclerotic plaque by ultrasound scan. Phenotyping of *i*NKT cells and $CD1d^+$antigen presenting cells was performed by flow cytomerty, confocal microscopy and ImageStream cytometry.

Results: The frequency of *i*NKT cells in SLE patients with plaque (n=20) was maintained at healthy levels compared to a significant deficiency in non-plaque SLE patients (n=30). Following adjustment for disease activity, *i*NKT cells from plaque-positive patients had a distinct phenotype compared to healthy and plaque-negative patients, characterised by an increased expression of activation markers CD25 and CD69, chemokine receptor CCR6 and elevated IL-4 and IL-10 production. Furthermore patients with more lipid rich plaque showed enhanced IL-4, IL-8 and IL-10 production compared to those with stable calcified plaque.

The distinct *i*NKT cell phenotype of plaque-positive patients could be driven by differences in their activation by $CD1d^+$ lipid-antigen presenting cells. CD1d expression was significantly reduced on B cells and pro-inflammatory $CD14^{low}$ monocytes in all SLE patients compared to healthy donors. However, a significant increased association of CD1d to membrane lipid rafts was detected only in B cells and $CD14^{low}$ monocytes from SLE patients with plaque. The defective *i*NKT cell phenotype and pattern of CD1d distribution identified in plaque-positive patients was recapitulated in cells from healthy donors by culture with serum isolated from plaque-positive SLE patients but not plaque-negative patients. Finally, we detected that altered activation of healthy *i*NKT cells could be driven *in vitro* by lipids isolated from $CD1d^+$antigen presenting cells from SLE patients but not from healthy donors.

Conclusion: These findings support a differential role for *i*NKT cells in the immunopathogenesis of SLE in patients with and without atherosclerosis that could be maintained by dylipidaemia. *i*NKT cell phenotype could represent a novel biomarker to predict atherosclerosis in SLE and could lead to improved treatment options for patients.

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Vitamin D Increases The Number and Function Of Myeloid Angiogenic Cells In Systemic Lupus Erythematosus. John A. Reynolds[1], David W. Ray[2], Terence O'Neill[1], M. Yvonne Alexander[3] and Ian N. Bruce[1]. [1]Arthritis Research UK Epidemiology Unit and NIHR Manchester Musculoskeletal Biomedical Research Unit, The University of Manchester, Manchester, United Kingdom, [2]Institute of Human Development, The University of Manchester, Manchester, United Kingdom, [3]Healthcare Science Research Institute, Manchester Metropolitan University, Manchester, United Kingdom.

Background/Purpose: Patients with Systemic Lupus Erythematosus (SLE) have an increased prevalence of cardiovascular disease (CVD). Vitamin D deficiency is common in SLE and an independent risk factor for CVD in the general population. We have previously shown that low vitamin D is associated with arterial stiffness in SLE patients.

Myeloid angiogenic cells (MACs) have an important role in endothelial repair in animal models. Preliminary studies have demonstrated impaired function of these cells in lupus. Myeloid cells are able to respond to vitamin D *in vitro* and express functional vitamin D receptors. We propose that vitamin D may have beneficial effects on MAC function and thus endothelial repair.

Methods: Peripheral blood mononuclear cells (PBMCs) from vitamin D deficient (<20ng/ml) SLE patients, or vitamin D-replete (>20ng/ml) healthy controls, were cultured for 7 days on fibronectin in endothelial growth media +/− $1,25(OH)_2D_3$ (0.1–100nM). For survival studies, the number of cells able to uptake LDL was enumerated in random fields. Surface CD marker expression (CD14, CD68, CD86, CCR7, CD206) in MACs was determined using real-time quantitative PCR. Angiogenic factor secretion was measured using a Bio-Plex®Human Angiogenesis Suspension Array. Angiogenic function of MACs was determined using human aortic endothelial cells in a Matrigel model. Data were analysed using linear regression, paired t tests and one-way ANOVA where appropriate.

Results: MACs expressed high levels of CD206, and low CCR7 compared to PBMCs consistent with an M2 macrophage phenotype. Phagocytosis was demonstrated by MAC uptake of FITC-labelled beads. MAC secreted IL-8 (mean [sd] 13.9 [20.1] ug/ml), VEGF (37.2 [26.1] pg/ml), HGF (1414 [568] pg/ml), leptin (209 [144] pg/ml), and PDGF (564 [365] pg/ml) but not GCSF or angiopoetin.

Vitamin D (0.1–100nM) increased the number of lupus MAC on day 8 in those with a low number (<150/field) at baseline ($p=0.037$) in a dose-dependent manner. This effect was replicated in healthy MACs treated with 0.1ng/ml interferon-α2b ($p=<0.001$). Expression of all macrophage markers was reduced by vitamin D (10nM) but the M2 marker CD206 was preferentially reduced compared to M1 markers CCR7 ($p=0.008$) and CD86 ($p=0.043$).

Conditioned media from vitamin D (10nM) treated SLE MACs further increased endothelial tubule network density in the angiogenesis model (mean [sd] relative density 1.43 [0.12] vs 1.66 [0.15], $p=0.012$) compared to untreated SLE MACS. Vitamin D alone, however, did not increase tubule density (0.96 [0.10], $p=0.582$). In the Bio-Plex array, secretion of any of the angiogenic factors by MACs was not directly affected by vitamin D.

Conclusion: MACs are population of M2 macrophages with angiogenic capacity *in vitro*. Vitamin D increases the number of lupus MACs and changes the surface maker profile. The angiogenic capacity of MACs was increased by vitamin D *ex vivo*, but this was not due to changes in expression of common angiogenic factors. Further work will identify the mechanism by which vitamin D may augment endothelial repair in patients with SLE.

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Serum Concentrations Of Type I Interferon-Regulated Chemokines Are Associated With Disease Activity In Systemic Lupus Erythematosus. Eric F. Morand, Kathryn Connelly and Alberta Y. Hoi. Monash University, Melbourne, Australia.

Background/Purpose: Expression array studies suggest the activity of Type I interferon (IFN), as reflected in IFN-induced genes, is associated

with phenotypic subsets in SLE. Three chemokines (CK) CCL2, CCL19, and CXCL10 induced by IFN are measurable in serum, and these have been correlated with IFN-induced gene expression and with SLE disease activity. Previous studies of clinical associations of IFN-induced CK were in patients with mild disease, were of short duration (<1y), and did not include Asian patients or analyse for the effects of glucocorticoids. We explored disease associations of IFN-CK in an SLE cohort followed for longer time periods and which included patients with more severe disease and Asians.

Methods: SLE patients (ACR criteria) attending a single centre between 2007–2012 had prospective recording of disease activity (SLEDAI-2k) at each visit and annual recording of organ damage (SLICC SDI). CCL2, CCL19, and CXCL10 were measured in matching serum samples by ELISA, and an integrated score (IFN-CK) (Bauer et al 2009) calculated.

Results: 1002 serum samples from 151 patients were analysed over a median (range) followup of 5 (1–27) visits over 2.75 (0–4.6) years. Patients were 84% female, 40% Asian ethnicity, median age 42y and disease duration 8.6y, median (range) SLEDAI 4 (0–22)) and time-adjusted mean SLEDAI (AMS) 4 (0–15). The individual chemokines CCL2, CCL19, and CXCL10 were highly correlated (P<0.0001). IFN-CK score exhibited a significant positive correlation with ESR and anti-dsDNA, and a significant negative correlation with C3 and C4. IFN-CK was significantly higher in active disease (SLEDAI>4) (P<0.0001), and accordingly SLEDAI was significantly higher in patients with high IFN-CK (P<0.001). Changes in IFN-CK and SLEDAI over time were also correlated (P=0.013), as were AMS and time-adjusted mean IFN-CK (P=0.008). Moreover, IFN-CK at baseline was correlated with subsequent disease activity as measured by AMS (P=0.04), and episodes of persistent active disease were 2-fold more likely during the period of observation in patients with high time-adjusted mean IFN-CK (RR = 2.05 (95% CI 1.06 – 3.99), P=0.0192). Patients who experienced an increase in SDI over the study period had significantly higher time-adjusted mean IFN-CK than those with no change in SDI. High IFN-CK was not associated with the presence of renal or CNS disease, but was associated with anti-ENA and dsDNA positivity (both P=0.02). Clinical associations of IFN-CK were more robust in the subset of patients of Asian ethnicity, but were less robust in patients on glucocorticoid therapy.

Conclusion: In a longitudinal cohort of SLE patients with severe disease, serum IFN-CK was strongly associated with indices of current and subsequent disease activity and damage. The associations between IFN-CK and disease activity were stronger in Asian SLE patients but were negatively influenced by glucocorticoids. Serum IFN-CK measurements appear to be a robust marker of disease activity in SLE.

Disclosure: E. F. Morand, None; **K. Connelly**, None; **A. Y. Hoi**, None.

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Potential Immunopathological Roles Of The Novel Anti-Inflammatory Cytokine Interleukin-35 In Patients With Systemic Lupus Erythematous. Zhe Cai[1], Chun-Kwok Wong[2] and Lai Shan Tam[1]. [1]The Chinese University of Hong Kong, Hong Kong, Hong Kong, [2]The Chinese University of Hong Kong, Hong Kong, China.

Background/Purpose: IL-35, a dimeric protein with two subunits, IL-12A (p35) and Epstein-Barr virus induced 3, is a novel IL-12 cytokine family regulatory T-cells (Treg)-specific immunosuppressive/anti-inflammatory cytokine. IL-35 is expressed by resting and activated regulatory T cells (Tregs/Tr35) by converting conventional T cells (Tconv) into IL-35-dependent induced Tregs (iTr35), but not effector T (Teff) cells. Similar to that of transforming growth factor-b and IL-10, IL-35 is the major component of the suppressive repertoire, but temporally different from them in the inhibition of inflammation. We hypothesize that IL-35 may play an important immunoregulatory roles in autoimmune diseases such as systemic lupus erythematous (SLE).

Methods: Plasma concentrations of IL-35 and soluble gp130 were measured using ELISA. Cell surface expression of IL-35 receptor components IL-12Rb2 and gp130 on the $CD4^+$ helper (Th) cells and $CD19^+$ B cells, and the number of $CD4^+CD25^{high}CD127^{low}$Treg cells were quantitated by flow cytometry.

Results: Plasma IL-35 levels were significantly higher in active SLE patients than healthy controls (HC). Percentages of Treg in active and inactive SLE patients were significantly higher than HC. The percentage of Treg in active SLE patient was significantly higher than in inactive SLE patients (all $p < 0.05$). Moreover, the percentage of Treg cells was positively correlated with the SLE disease activity index (SLEDAI), but it did not correlate with the expression of IL-12Rb2 and gp130 on Th and B cells. However, the expression of IL-12Rb2 on the Th cells and B cells of inactive and active SLE patients, respectively, was significantly higher than HC.

Conclusion: The above results may imply the potential immunological roles of anti-inflammatory cytokine IL-35 receptors. Since IL-35 receptor components IL-12Rb2 played the key role in the signaling transduction of the immunosuppressive mechanisms of the IL-35 in SLE immunopathogenesis, results of this cross-sectional clinical study may also furnish a biochemical basis for the development of potential therapeutic target of IL-35 for the treatment of autoimmune inflammation.

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Expansion Of $CD4^+CXCR3^+$ T Cells In Patients With Systemic Lupus Erythematosus (SLE) Correlates With Subclinical Atherosclerosis. Karim Sacre[1], Brigitte Escoubet[2], Nicolas Charles[3], Antoine Dossier[4], Marie-Paule Chauveheid[4] and Thomas Papo[1]. [1]University Paris-7, INSERM U699, APHP, Bichat Hospital, Paris, France, [2]University Paris-7, INSERM U872, APHP, Bichat Hospital, Paris, France, [3]INSERM U699, Paris, France, [4]University Paris-7, APHP, Bichat Hospital, Paris, France.

Background/Purpose: The mechanisms for accelerated atherosclerosis in SLE remain unclear. As atherosclerosis is itself immune-mediated, features of SLE-associated immunity might explain accelerated cardiovascular disease beside traditional cardiovascular risk factors.We studied the relationship between T cells expressing CXCR3, a chemokine receptors involved in transendothelial migration, and subclinical vascular disease as assessed by common carotid intima-media thickness, internal carotid wall thickness, pulse wave velocity and pulse pressure measurements in SLE patients.

Methods: The expression of CXCR3 on PBMCs was measured by flow cytometry in 33 SLE subjects asymptomatic for cardiovascular diseases (CVD) and 18 controls. Patients with SLE were assessed for vascular disease with common carotid artery intima-media thickness (IMT), internal carotid artery wall thickness (ICWT), pulse wave velocity (PWV), and pulse pressure (PP) as well as for SLE disease history, corticoid exposure and classical risk factors for cardiovascular disease.

Results: All SLE subjects had received long-term glucocorticoid and 24 (73%) were still under prednisone at a mean daily dose of 8.7 ± 2.6 mg/day. All were receiving hydroxychloroquine. Twenty-four had been treated with immunosuppressive or immunomodulatory drugs during follow-up. Four patients also had APS. Classical cardiovascular risks distribution did not differ between controls and SLE patients (Table 1).

Table 1. Characteristics of Subjects

	SLE patients (n=33)	Controls (n=18)	p
Female Sex, n (%)	26 (78.8)	9 (50)	0.06
Age, years	40 (± 10)	41.3 (±11.6)	0.97
Smoking, n (%)	11 (33.3)	7 (38.9)	0.76
High blood pressure, n (%)	11 (33.3)	6 (33.3)	0.76
Diabetes, n (%)	1 (3)	0 (0)	1
BMI, kg/m2	26.1 (±5.1)	26 (±2.7)	0.77
Cholesterol level, g/l	1.77 (±0.43)	1.93 (±0.39)	0.43
10-year risk of heart attack, %	1.9 (±3.9)	3.6 (±3.9)	0.13
Duration of SLE disease, years	13.3 (±7.8)		
SELENA SLEDAI score	2.3 (±3.3)		
Lupus nephritis, n (%)	22 (66.7)		
APS, n (%)	4 (12.1)		
Cumulative years of steroid treatment	11.8 (±7)		
Cumulative dose of steroid treatment (g)	46.9 (±29.5)		
Oral contraceptive, n (%)	11/26 (42.3)		
Statin, n (%)	10 (30.3)		
Hydroxychloroquine, n (%)	33 (100)		
Other therapy, n (%)	24 (72.7)		
HbA1c, %	5.5 (±0.5)		
Homocysteinemia/ creatininemia, ratio	0.19 (±0.07)		
25(OH)D3 vitamin (ng/ml)	24.4 (±12.3)		
Creatininemia (μmol/l)	86.2 (±51)		
Proteinuria/Creatininuria (mg/mmol)	63.7 (±130)		
Lymphocytes (G/l)	1.5 (±0.7)		

SLE-subjects displayed a higher frequency of circulating $CD4^+$ T cells (35.1±17.7 vs 23.6±8.4%; $p<0.05$), $CD8^+$ T cells (72.4±19.5 vs 44.9±14.9%; $p<0.005$), NKT cells (56.9±19.1 vs 31.3±18.8%; $p<0.001$) and B cells (24.5±16.1 vs 12.4±5.9%; $p<0.05$) that expressed the chemokine receptor CXCR3, as compared to controls.

The mean IMT was 0.54 (±0.12) mm in SLE subjects. The mean internal carotid artery wall thickness (ICWT), pulse wave velocity (PWV), and pulse pressure (PP) was 1.34 (±0.74) mm, 7.1 (±1.65) m/s and 54.7 (± 13.3) mmHg, respectively.

In SLE subjects, infraclinical vascular disease -assessed with IMT ($r^2=0.15$, $p=0.02$), ICWT ($r^2=0.12$, $p=0.04$), PWV ($r^2=0.12$, $p=0.04$), and PP ($r^2=0.23$, $p=0.004$)- correlated with expression of $CD4^+CXCR3^+$ on T cells. $CD4^+CXCR3^+$ T cells were shown to be antigen-primed $CD45RA^-CD27^{+/-}$ and to produce high levels of TNF-α upon polyclonal TCR activation..

No significant association was found between peripheral expansion of $CD4^+CXCR3^+$ T cells and traditional (Framingham score, LDL-cholesterol), non-traditional (HbA1c, homocystein, 25(OH)-D3 vitamin; creatinine blood levels) cardiovascular risk factors or SLE-related risk factors (duration of disease, glucocorticoid therapy, SLEDAI score, renal function).

Conclusion: Our study suggests that $CD4^+CXCR3^+$ T cells are instrumental in SLE-associated atherosclerosis.

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Transcript Profiling Of Blood and Kidney Biopsies From Chinese Patients With Lupus Nephritis Reveals Concordant Activation Of Type I IFN Signaling In The Blood and Kidney, Reduced B Cell Presence In The Blood, and Increased Macrophages In The Kidney. Zheng Liu[1], Chris, A. Morehouse[1], Xinfang Huang[2], Philip Brohawn[1], Nan Shen[2], Yihong Yao[1] and Brandon W. Higgs[1]. [1]MedImmune, LLC, Gaithersburg, MD, [2]Shanghai Ren Ji Hospital, Shanghai, China.

Background/Purpose: Up-regulated expression of type I interferon-regulated genes has consistently been observed within the peripheral blood in a large proportion of patients with active systemic lupus erythematosus (SLE). The activation of this pathway in inflamed tissues (e.g, the kidneys of patients with lupus nephritis [LN]) has been less studied. We investigated pathways most altered in the blood and kidney of LN to better understand the molecular and cellular mediators, and elucidate the concordance of type I IFN activation between the disease site and periphery.

Methods: Blood specimens were procured from 32 healthy and 94 LN Chinese subjects and kidney biopsies from 6 healthy and 80 LN Chinese subjects (75 matched). Among these patients, the distribution of the International Society of Nephrology and the Renal Pathology Services (ISN/RPS) classifications included: 1 Class-I, 2 Class-II, 16 proliferative LN (Class-III or -IV), 13 membranous LN (Class-V) and 21 mixed LN (Class-IV and -V or Class-V and -III), with SLEDAI scores ranging from 4–25. The Affymetrix U133+ array was used to transcript profile specimens. In the blood, 389 genes were significantly over-expressed in LN subjects (fold change (FC)≥2; $p< 0.01$) and 704 genes were under-expressed (FC′-2; $p< 0.01$). In the kidney, 166 genes were over-expressed in LN subjects (FC≥2; $p< 0.05$) and 66 genes were under-expressed (FC≤ -2; $p< 0.05$). Gene signatures were identified from ex vivo stimulation experiments with whole blood and pathway enrichment analysis was conducted.

Results: Within the blood specimens, type I IFN signaling was the most activated pathway, while complement system activation ranked first in kidney specimens. To further investigate the molecular landscape between blood and kidney in LN subjects, we surveyed a panel of different well characterized gene signatures. In both blood and kidney, a type I IFN signature was elevated in LN patients (73% and 43% patients with FC≥2, $p< 0.0001$ and $p=0.001$, respectively); the 75 matched specimens were well correlated ($r=0.82$; $p<0.0001$). A plasma cell gene signature showed no difference between LN patients and healthy controls in either blood or kidney tissues. However, in blood, a B cell gene signature was significantly lower in LN patients compared to healthy controls (59% patients with FC≤−2, $p< 0.0001$); the difference in kidney tissues was not observed. A macrophage gene signature was elevated in kidney tissue of LN patients compared to controls (54% patients with FC≥2, $p= 0.0005$).

Conclusion: Transcript profiling was used to better understand the molecular differences between the blood and disease site of patients with LN. The significantly decreased B cell gene signature in the blood, and not kidney of LN patients may reflect the migration of B cells from the periphery to local tissues, as well as the phenotype of lymphopenia in SLE patients. An elevated macrophage gene signature in the kidney may indicate the increased macrophage infiltration in diseased tissue from the blood. Type I IFN signaling was concordantly activated in both the blood and kidney tissue of LN subjects, suggesting a potential patient subgroup to target for anti-type I IFN therapies.

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Expression Of Interferon-Inducible Gene (Lymphocyte Antigen 6 Complex Locus E) In Systemic Lupus Erythematosus Patients and Its Association With Disease Activity. Eman Omran[1], Tayseer M Khidre[2], Eman Alkady[3], Eman Mosaad[4] and Mona Hussein Abd Elsamea[3]. [1]Assiut University- Faulty of Medicne, Assiut, Egypt, [2]Assiut University, Faculty of Medicine, Assiut, Egypt, [3]Assiut University-Faculty of Medicine, Assiut, Egypt, [4]AssiutUniversity- Faculty of Medicine, Assiut, Egypt.

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by immune dysregulation resulting in the production of antinuclear and other autoantibodies, generation of circulating immune complexes, and activation of the complement system. The disease course of SLE is heterogeneous, affecting different individuals with a wide range of manifestations.

Recent genetic studies identified a group of type I Interferon-inducible genes (IFIGs) that are significantly upregulated in peripheral blood cells from SLE patients. IFIGs show expression of 5 types [Myxovirus resistance 1 (Mx1), Oligoadenylate synthetase (OAS)1, and Lymphocyte antigen 6 complex, locus E (Ly6e), Oligoadenylate synthetase–like (OASL), and Interferon-inducible protein (clone IFI-15K) (ISG15)] in peripheral blood sample from SLE patients.

The aim of the study was to assess the expression of type I IFIGs (LY6E) in patients with SLE. In addition, we evaluated the association of its levels with disease activity and/or severity, and laboratory markers.

Methods: Peripheral blood sample were obtained from 40 SLE patients and 25 healthy donors and total RNA was extracted and reverse transcribed into complementary DNA. Level of expression of type I IFIGs (LY6E) was measured by real time polymerase chain reaction (PCR-RT), after which comparisons were performed between SLE patients and control individuals. Disease status was assessed according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index.

Results: Type I IFIGs (LY6E) was highly expressed in SLE patients compared with normal controls ($P<0.000$).

Type I IFIGs (LY6E) was positively associated with the SLEDAI score ($p<0.02$). Elevated type I IFIGs (LY6E) was also associated with the presence of cumulative organ damage SLICC/ACR-Damage Index ($P<0.01$). Type I IFIGs (LY6E) was positively correlated with anti–double-stranded DNA (anti-dsDNA) antibodies ($P<0.01$) and negatively correlated with C3 ($P<0.03$). LY6E expression levels was positively associated with proteinuria ($P <0.009$).

Conclusion: Type I IFIGs (LY6E) was highly expressed in SLE patients, and higher expression of LY6E gene in SLE patients is closely correlated with disease activity, degree of organ damage, proteinuria, anti-dsDNA antibody and hypocomplementemia. Besides, its elevated level may predict SLE flares.

The data suggest that type I IFIGs (LY6E) may contribute to SLE pathogenesis and the finding of this study will shed new light on dysregulation of the immune system and the involvement of inflammation in the initiation and perpetuation of autoimmunity.

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Enhanced Expression of CCR Receptors in Healthy AA and SSc ILD Monocytes. Rebecca Lee, Charles Reese, Beth Perry, Jonathan Heywood, Michael Bonner, Richard P. Visconti, Richard M. Silver, Stanley Hoffman and Elena Tourkina. Medical University of SC, Charleston, SC.

Background/Purpose: Scleroderma-associated Interstitial Lung Disease (SSc ILD) is more prevalent and more severe in African Americans (AA) than in Caucasian (C) patients, but little is known of the factors underlying this health disparity. We reported recently that healthy AA monocytes share abnormalities with SSc ILD monocytes including low caveolin-1 levels and hypermigration towards chemokine SDF-1 due to upregulation of its receptor CXCR4. In the current study we have investigated other chemokine receptors that are involved in SSc ILD, namely CCR1, CCR2, and CCR3. The aim of this study was to determine whether these receptors are also overexpressed in SSc ILD and healthy AA monocytes and the functional consequences of their overexpression.

Methods: The study was approved by the university's IRB for Human Subject Research. Monocytes were isolated from the blood of SSc ILD patients and healthy donors by negative selection. SSc ILD patients fulfilled the ACR criteria for the classification of systemic sclerosis. Monocyte migration was assayed in Multiwell Chemotaxis Chambers using cells treated with the caveolin-1 scaffolding domain (CSD) peptide or control peptide. CCR1, CCR2, CCR3, ERK, pERK, Src, pSrc, Lyn, pLyn, and caveolin-1 levels were determined by Western blotting and immunostaining.

Results: In the current study, we observed that the expression of CCR1, CCR2, and CCR3 is enhanced in SSc ILD monocytes and healthy AA monocytes compared to healthy C monocytes. In accord with these findings, compared to healthy C monocytes, the migration of healthy AA monocytes toward the CCR2 ligand MCP-1 was enhanced two-fold ($p < 0.05$) and toward the common CCR1,2,3 ligand MCP-3 was also enhanced two-fold ($p < 0.05$). SSc ILD monocyte migration (compared to C monocyte migration) toward MCP-1 was enhanced 10-fold ($p < 0.001$) and toward MCP-3 was enhanced 5-fold ($p < 0.001$). In all cases, treatment with CSD inhibited migration > 50 %, demonstrating that the enhanced migration of SSc ILD and healthy AA monocytes is due to their relative lack of caveolin-1. To study signaling downstream from CCR1, CCR2, and CCR3; healthy C, healthy AA, and SSc ILD patient monocytes were treated with MCP-1. Baseline activation of ERK and Src was two-fold increased in AA compared to C while Lyn activation was similar in C and AA. All three kinases were greatly enhanced in SSc ILD. MCP-1 activated ERK in both C and AA monocytes, but had no effect on Src and Lyn. MCP-1 did not increase the already high level of ERK activation in SSc ILD monocytes, but did further increase the already high levels of Src and Lyn activation. In contrast, MCP-3 appears to inhibit ERK, Src, and Lyn in all three groups; suggesting that MCP-1 and MCP-3 signaling during cell migration occur through distinct mechanism. The relevance of these observations to human disease was demonstrated in immunostaining experiments showing that CCR1, CCR2, CCR3, MCP-1, and MCP-3 are all overexpressed in SSc ILD lung tissue compared to control healthy lung tissue.

Conclusion: Low caveolin-1 levels may play a role in the predisposition of the AA population to SSc ILD via the regulation of the expression of chemokine receptors CCR1, CCR2, and CCR3 in monocytes and through the activation of ERK, Src, and Lyn.

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A Possible Contribution of Inducible Costimulator to the Development of Skin Sclerosis and Interstitial Lung Disease in Systemic Sclerosis. Koichi Yanaba[1], Yoshihide Asano[2] and Shinichi Sato[2]. [1]The University of Tokyo, Tokyo, Japan, [2]University of Tokyo Graduate School of Medicine, Tokyo, Japan.

Background/Purpose: Systemic sclerosis (SSc) is a heterogeneous disorder characterized by excessive fibrosis and microvascular damage of the skin and various internal organs. Cutaneous mononuclear cell infiltrates in early SSc skin lesions are mostly activated T cells which are also increased in lung interstitium and bronchoalveolar fluid from patients with SSc and active interstitial lung disease. Furthermore, cytokines or growth factors regulate SSc induction by stimulating the synthesis of extracellular matrix components, which may injure endothelial cells and modulate leukocyte function. These infiltrating activated T cells are likely to release cytokines, chemokines, or growth factors, which play a crucial part in the initiation and development of fibrosis in SSc.

Inducible costimulator (ICOS), a member of the CD28 family of costimulatory molecules, is expressed in activated T cells, but not in naïve T cells. ICOS specifically binds to ICOS ligand (ICOSL), which is constitutively expressed on antigen-presenting cells such as B cells and macrophages. ICOS-mediated costimulation is crucial for T cell proliferation, production of various cytokines, and T cell-dependent B cell responses. ICOS–ICOSL interaction is likely to contribute to the development of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. Therefore, we suggest that ICOS plays a role in the pathogenesis of SSc and, in this study, examined serum soluble ICOS (sICOS) levels in SSc patients, and evaluated the results with respect to clinical features.

Methods: Serum sICOS levels were examined by enzyme-linked immunosorbent assay in 38 patients with SSc, and 24 healthy individuals. In addition, the expression of ICOS and ICOSL in skin was examined immunohistochemically.

Results: Patients with diffuse cutaneous SSc had higher levels of sICOS than those with limited cutaneous SSc or healthy individuals. Serum sICOS levels correlated positively with the severity of skin sclerosis. Patients with SSc and elevated sICOS levels more often had interstitial lung disease and decreased vital capacity than those with normal sICOS levels. The serum sICOS levels were significantly greater in patients with early phase SSc than those with late-phase SSc. ICOS and ICOSL immunostaining was observed on infiltrating dermal mononuclear cells in lesional skin tissue.

Conclusion: The current study suggests that ICOS may contribute to the development of SSc. Given that no therapy has proven effective in suppressing or improving skin sclerosis and interstitial lung disease in SSc to date, our findings suggest that ICOS inhibition could be a potential treatment for patients with SSc who have severe skin sclerosis and interstitial lung disease. In addition, measurement of serum sICOS levels in patients with early SSc may offer an important means for further evaluation of SSc disease severity.

Disclosure: K. Yanaba, None; **Y. Asano**, None; **S. Sato**, None.

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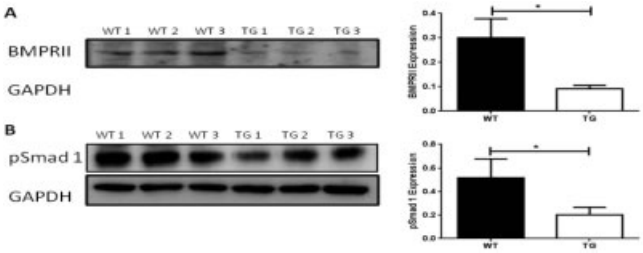
Altered BMP Signalling In a TGFβ Dependent Murine Model Of Scleroderma May Contribute To Development Of Pulmonary Arterial Hypertension. Adrian J Gilbane[1], Emma C. Derrett-Smith[1], Sarah Trinder[1], Andrew Pearce[2], Christopher P. Denton[1] and Alan M. Holmes[1]. [1]UCL Medical School, London, United Kingdom, [2]Novartis, London, United Kingdom.

Background/Purpose: Pulmonary arterial hypertension associated is an important complication of scleroderma (PAH-SSc) and has a poor prognosis compared to idiopathic (iPAH) or heritable (hPAH) forms of the disease. BMPRII mutations with concomitant effects on BMP signalling are an established cause of hPAH and some iPAH but these are not present in PAH-SSc. Furthermore, alterations in signalling through other TGFβ superfamily pathways have reciprocal effects on the BMP pathway.

Methods: We investigated BMP signalling in the lung in a mouse model of SSc in which TGFβ signalling is upregulated. Experiments were performed on whole lung isolates and explant cultured fibroblasts ($n=6$) from the TβRIIΔk-fib mouse and compared with wild type (WT) controls. Structural and biochemical analysis of components of the TGFβ superfamily and downstream signalling pathway was investigated by Western blot, immunohistochemistry and confirmed using qPCR measurement. Migration assays investigated the effects of PDGF-BB on lung fibroblasts from TβRIIΔk-fib and WT controls ($n=3$). Confirmatory biochemical and functional studies on scleroderma fibroblasts were also performed.

Results: The TβRIIΔk-fib model has increased levels of pSmad 2/3, indicative of enhanced TGFβ signalling. Consistent with an imbalance in the TGFβ/BMP axis we observed a significant reduction in BMPRII protein expression in the TβRIIΔk-fib model, both in whole lung isolates (1.43, 0.38) ($p<0.05$), and explant cultured fibroblasts (0.2985, 0.09) ($p<0.05$) (figure1). Explant cultured fibroblasts exhibited a blunted induction of phospho-Smad1 in response to BMP ligands ($p<0.05$) (figure1). TβRIIΔk-fib lung fibroblasts also exhibited enhanced migratory response compared to wild type controls ($p<0.05$). These findings were confirmed in scleroderma fibroblast studies, highlighting a reduction in BMPRII levels and an increased migratory response compared to healthy controls ($p<0.05$).



Conclusion: Association of altered BMPRII expression with PAH is well established in hPAH. Here we demonstrate the TβRIIΔk-fib model of SSc that develops a constitutive pulmonary vasculopathy, exhibits reduced expression of BMPRII as a reciprocal response to increased TGFβ signalling, with associated downstream signalling alterations independent of mutations in the BMPRII. Collectively our data suggests loss of BMPRII expression by non-genetic means may contribute to the development of PH in the TβRIIΔk-fib model of SSc.

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Parental Influence On Systemic Sclerosis. Tracy M. Frech[1], Richard Pimentel[2], Allen D. Sawitzke[3], Gopi Penmetsa[4] and Jathine Wong[2]. [1]Salt Lake City VAMC, Salt Lake, UT, [2]University of Utah, Salt Lake, UT, [3]University of Utah Medical Ctr, Salt Lake City, UT, [4]University Of Utah Hospital, Salt lake City, UT.

Background/Purpose: A genealogic resource, the Utah Population Database (UPDB) has successfully identified systemic sclerosis (SSc) pedigrees and hereditable risk for this disease (1). We hypothesized that these pedigrees could be used to assess parental influence on a SSc proband by (a) examination of mitochondrial inheritance; (b) birth order (a possible surrogate marker for microchimerism); and (c) paternal age at conception (a possible surrogate marker for telomere erosion).

Methods: SSc was defined by ICD-9 710.1 and ICD-10 34.0, 34.1, and 34.9, and identified from statewide discharge data, the University of Utah Health Science Center Enterprise Data Warehouse, and death certificates and were linked to the UPDB for analysis. Mitochondrial inheritance was evaluated by familial standardized incidence ratio (FSIR). Chi squared test and logistic regression was used to evaluate birth order and maternal/paternal age at conception of the SSc proband.

Results: A software kinship analysis tool (KAT) was used to analyze 1949 unique SSc patients and 5 controls per case (9115), which were matched by birth year. Comparing the result of using mitochondrial pedigrees (MP) with autosomal pedigrees (AP), both pedigrees yield similar result in Cox proportional hazard regression model to predict relative risk as a function of fsir, lfsir log of (1+fsir), llfsir, log of (1+ log(1+ lfsir)), and *eb* empirical Bayes adjustment to llfsir (2). Both MP and AP have a RR of 1.00 for fsir. MP has a RR of 1.43 for *eb*, and AP has a similar RR of 1.37 for *eb*. MP has a very low population-attributable risk, PAR value, 0.03, where AP has a higher value of 0.11 to 0.13. It suggested approximately 3% of the population who has SSc could be from mitochondrial inheritance, whereas 13% of the population who has SSc are familial. Thus, there is no indication of SSc is caused by mitochondrial inheritance.

We compared the affected and the unaffected individuals in each birth order group, and the distribution showed from birth order group 1 to 9, they were almost evenly distributed, affected was approximately 16 to 17%, and the unaffected was approximately 83 to 84% of each of these birth order groups. Chi Square test result shows an insignificant p value of 0.738. Since some of the table cell expected values are below 5, we re-examined the dataset using a logistic regression generalized linear model which confirmed there were no differences in the birth order of the groups in the study.

A multivariate logistic regression model with 3 covariates, birth order, father's age at conception, and mother's age at conception indicate all 3 covariates do not increase the odds for having the disease.

Covariate	RR	Lower Level CI	Upper Level CI	P-value
Birth Order	1.03	0.98	1.08	0.246
Father's age of conceived	0.998	0.951	1.05	0.939
Mother's age of conceived	0.997	0.945	1.05	0.913

Conclusion: The UPDB is a resource that allows for meaningful inheritance analysis. These data suggest that while increased inheritance of SSc is seen, patterns suggesting mitochondrial inheritance, birth order (microchimerism), and parental age at conception of a SSc proband are not likely responsible for pathogenesis.

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Growth Differentation Factor-15, a Marker Of lung disease In Systemic Sclerosis, Is Involved In Fibrosis Development But Does Not Impair Fibrosis Development. Stijn Lambrecht[1], Vanessa Smith[2], Katelijne De wilde[3], Julie Coudenys[3], Filip De Keyser[2] and Dirk Elewaut[4]. [1]Laboratory for Molecular Immunology and Inflammation, Ghent University, Ghent, Belgium, [2]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium, [3]Ghent University, Ghent, Belgium, [4]Department of Rheumatology Ghent University Hospital, Ghent, Belgium.

Background/Purpose: It is generally known that members of the TGF-β superfamily are involved in the regulation of connective tissue biology in systemic sclerosis (SSc). Growth differentiation factor 15 is a distant member of this TGF-β family. We aimed to evaluate the role of GDF15 in SSc-pathogenesis.

Methods: A longitudinal prospective cohort of SSc patients was screened for GDF15 serum levels by ELISA and associations with disease activity and tissue damage were analyzed. Moreover, in vitro stimulation experiments were performed in lung fibroblasts. The role of GDF15 in fibrosis development *in vivo* was evaluated by performing the bleomycin lung fibrosis model in GDF15 deficient mice.

Results: Baseline serum samples from a prospective cohort of 119 patients were screened for GDF15 levels. An increase in GDF15 levels was observed in patients classified as limited SSc, limited cutaneous SSc and diffuse SSc. Moreover, baseline GDF15 serum levels highly correlated with disease activity, extent of organ involvement, particularly clinical symptoms of lung fibrosis including impact on lung function in prospective follow up. This was also mimicked in the bleomycin mouse model of SSc. Here, bleomycin exposed animals displayed elevated expression levels of GDF15 in lung tissue. Isolated lung fibroblast of GDF15 deficient mice showed reduced induction of IL6 and CCL2 upon bleomycin stimulation compared to wild-type littermates. Surprisingly, no differences in fibrosis development were observed between wild-type and GDF15 deficient animals.

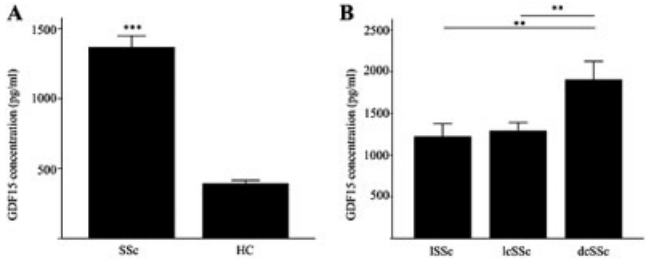

Figure 1. GDF15 serum levels are elevated in SSc patients. **Panel A:** An elevated level of GDF15 was detected in SSc patients (1367 pg/ml; n=119) compared to healthy controls (390,9 pg/ml; n=29), p<0,001. **Panel B:** An increase is observed in GDF15 serum levels of patients suffering from dcSSc (p=0,008, ANOVA).

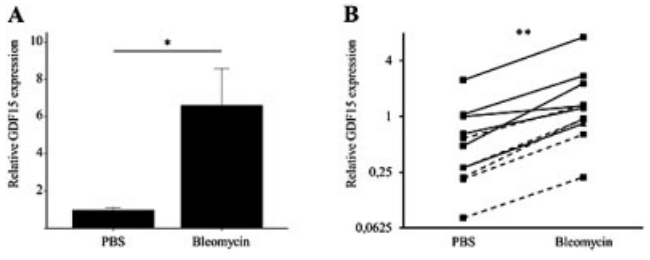

Figure 2. In vitro and in vivo experimental induction of fibrosis results in elevated GDF15 gene expression. **Panel A:** Bleomycin treated animals show elevated expression of GDF15 in lung tissue **Panel B:** Stimulation of lung fibroblasts from WT (solid line) and HZ (dashed line) with bleomycin resulted in an increased GDF15 expression compared to non-stimulated controls.

Conclusion: An intriguing profile of GDF15 serum levels was found in SSc patients. GDF15 expression is induced during fibrosis development and markedly correlates with lung function impairment in this disease. The protein may participate in fibrosis initiation, but is not indispensable in the course of fibrosis development *in vivo*.

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Pirfenidone and BIBF1120 Suppress Collagen Synthesis In Skin Fibroblast From Patients With Systemic Sclerosis. Yuko Ota, Yasushi Kawaguchi, Kae Takagi, Hisae Ichida, Yasuhiro Katsumata, Takahisa Gono, Yuko Okamoto, Tomoaki Higuchi, Hidenaga Kawasumi and Hisashi Yamanaka. Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Pirfenidone (5-methyle-1-phenyl-2-[1H]-pyridone) and BIBF1120 (Nintedanib) are currently evaluated in clinical trials as a potential idiopathic pulmonary fibrosis (IPF). Pirfenidone was approved as the first antifibrotic therapy for IPF based on demonstrated sustained clinical efficacy. BIBF1120 is a triple tyrosine kinase inhibitor and potent antagonist of growth factors such as platelet-drived growth factor (PDGF), vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF). The aim of the present study was to investigate the antifibrotic effects of pirfenidone and BIBF1120 on skin fibroblasts from patients with systemic sclerosis (SSc). We also examined signal transductions of these drugs.

Methods: Skin fibroblasts from six patients with diffuse cutaneous SSc were cultured with increasing concentrations of pirfenidone or BIBF1120 for various times. The resulting supernatants were collected and stored at −80°C. Procollagen type I C-peptide level was then measured using commercial ELISA kits. As we also evaluated the effects of pirfenidone or BIBF1120 for TGF-β1 induced skin fibrosis, skin fibroblasts stimulated with TGF-β1 were treated with pirfenidone or BIBF1120 and procollagen type I C-peptide level was measured using commercial ELISA kits. In addition, mRNA levels of collagen1α (I), collagen1a (II), TGF-β1, CTGF, IL-6 were estimated using real-time PCR.

Results: In the supernatants of fibroblasts cultured with 500 μg/ml of pirfenidone for 48 and 72 hours, the levels of procollagen type I C-peptide were significantly suppressed ($p = 0.034$ and $p = 0.009$, respectively) as compared with those in supernatants obtained from cultures lacking pirfenidone. Procollagen type I C peptide production was suppressed by 1 μM of BIBF1120 in cultured SSc fibroblasts ($p = 0.011$) compared to no stimulation. Both pirfenidone and BIBF1120 significantly down-regulated the collagen sysnthesis in TGF-b1-induced skin fibroblasts ($p < 0.05$, Figure 1). RT-PCR analysis revealed that *COL1A1, COL1A2, CTGF and TGFB1* mRNAs were suppressed by pirfenidone or BIBF1120 in cultured skin fibroblasts from patients with SSc. Inerestingly, pirfenidone inhibited IL-6 mRNA, but BIBF1120 promoted it adversely.

Conclusion: Our results showed that both pirfenidone and BIBF1120 attenuate collagen production via TGF-β1 and CTGF pathway in skin fibroblasts from patients with SSc. Pirfenidone and BIBF1120 may represent a novel therapy for skin fibrosis in patients with SSc.

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Norepinephrine-Induced IL-6 Regulates Fibrosis In Systemic Sclerosis. Sei-ichiro Motegi, Akihito Uehara, Kazuya Yamada, Akihiko Uchiyama, Sachiko Ogino, Yoko Yokoyama, Yuko Takeuchi and Osamu Ishikawa. Gunma University Graduate School of Medicine, Gunma, Japan.

Background/Purpose: Raynaud phenomenon is freaquently observed in patients of systemic sclerosis (SSc) and characterized by episodic vasospasm and ischemia of extremities in response to cold or emotional stress. It has been recogized that cold- or stress-induced norepinephrine (NE) stimulates adrenoreceptor (AR) on pericytes or vascular smooth muscle cells, resulting in vasoconstriction. However, the roles of NE in fibrosis of SSc are not well understood. The aim of this study was to elucidate the role of NE in fibrosis in SSc.

Methods: Protein and mRNA levels of IL-6 and AR expression in normal and SSc fibroblasts treated with or without NE or ARα/β antagonists were measured by ELISA and real-time PCR. The effect of ARβ blocker and ERK inhibitor on NE-induced IL-6 production was analyzed by real-time PCR. The amount of phosphorylation of ERK and total ERK in normal and SSc fibroblasts were measured by Western blot analysis. Proliferation of fibroblasts was determined using the MTS assay.

Results: The serum levels of IL-6 was elevated in patients with early SSc, and correlated with the extent of skin fibrosis. Protein and mRNA levels of IL-6 expression in normal and SSc fibroblasts was increased by NE stimulation in a dose-dependent manner. In addition, NE-induced IL-6 production in SSc fibroblasts was significantly higher than that in normal fibroblasts. The production of IL-6 in fibroblasts was induced by ARβ antagonist, isoproterenol, but not by ARα antagonist, oxymetazoline. ARβ blocker, proplanolol, inhibited NE-induced IL-6 production in normal and SSc fibroblasts, suggesting that NE may induce IL-6 production via ARβ on fibroblasts. There was no change in ARβ expression in normal and SSc fibroblasts treated with or without NE. In addition, proplanolol enhanced NE-induced phosphorylation of ERK, and ERK inhibitor, PD98059, enhanced NE-induced IL-6 production in in normal and SSc fibroblasts, suggesting that NE-induced phosphorylation of ERK via ARα may inhibit NE-induced IL-6 production. Next, we assessed the effect of the treatment with NE and endothelin-1 (ET-1), which is supposed to contribute to the pathogenesis of fibrosis in SSc. Combined treatment with NE and ET-1 resulted in an additive increase in production of IL-6 in SSc fibroblasts. Finally, we identified that NE enhanced proliferation of SSc fibroblasts compared with that of normal fibroblasts.

Conclusion: We conclude that NE enhances IL-6 production and proliferation in SSc fibroblasts via ARβ more than those in normal fibroblasts. Our results indicate that avoidance of cold exposure or emotional stress may attribute to the suppression of fibrosis as well as Raynaud phenomenon in SSc.

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Effects Of Macitentan and Its Active Metabolite In Modulating Extracellular Matrix Synthesis In Cultured Human Systemic Sclerosis and Normal Skin Fibroblasts. Maurizio Cutolo[1], Paola Montagna[2], Renata Brizzolara[2], Elisa Alessandri[3], Pietro Paolo Tavilla[4], Aurora Parodi[4], Alberto Sulli[3] and Stefano Soldano[2]. [1]University of Genova, Genova, Italy, [2]Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy, [3]Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, [4]Department of Endocrinologial and Medical Science, Unit of Dermatology, University of Genova, Genova, Italy.

Background/Purpose: Endothelin-1 (ET-1) has been shown to activate myofibroblasts and to enhance the synthesis of extracellular matrix proteins (ECM), such as collagen type I (COL-1) and fibronectin (FN), leading to tissue fibrosis in systemic sclerosis (SSc) progression (1, 2). Macitentan is a new molecule able to antagonize ET receptors. in plasma, besides macitentan, a circulating pharmacologically active metabolite (ACT-132577) has been identifyed (3, 4). We investigated the effects of macitentan and ACT-132577 on myofibroblast activation, by evaluating α-smooth musce actin (α-SMA) expression, and COL-1 and FN synthesis together with their gene expression, induced by ET-1 in cultured SSc and normal skin fibroblasts (Fbs). A comparison between the *in vitro* effects of macitentan, or ACT-132577 or bosentan was carried out.

Methods: Cultured human skin Fbs were obtained from biopsies of clinically involved skin of 6 SSc patients (4 females and 2 males, mean age 64.8±6.9 years) and 4 age-matched healthy subjects (3 females, 1 male) during diagnostic procedures (Dermatological Clinic, University of Genoa) and after signing informed consent. Following serum starvation (18 hrs), cultured human skin Fbs at 3rd culture passage were treated for 48 hrs with ET-1 (100nM), macitentan (concentration range from 1nM to 10μM), or ACT-132577 (concentration range from 10nM to 100μM), or bosentan (10μM) (Actelion Pharmaceuticals) in RPMI 1640 medium at 5% of fetal bovine serum. Cells were also pre-treated (1 hr) with macitentan, or ACT-132577 or bosentan, respectively, before treatment with ET-1 for 48 hrs. Untreated SSc and normal skin Fbs were used as controls. α-SMA expression was investigated by immunofluorescence (IF). COL-1 and FN synthesis and gene expressions were investigated by immunocytochemistry (ICC) and quantitative real time-polymerase chain reaction (qRT-PCR). Statistical analysis was performed by Mann-Whitney non-parametric t test.

Results: Macitentan and ACT-132577, at the concentration of 10μM, contrasted the increase in α-SMA expression induced by ET-1 in cultured human SSc skin Fbs, displaying same effects already showed by bosentan. Macitentan and ACT-132577 significantly antagonized the increase in COL-1 and FN synthesis induced by ET-1 ($p<0.01$; $p<0.01$ for macitentan; $p<0.05$; $p<0.05$ for ACT-132577 vs. only ET-1-treated cells). Bosentan significantly antagonized the ET-1 mediated increase in COL-1 and FN synthesis in SSc skin Fbs vs. only ET-1-treated cells ($p<0.01$; $p<0.05$). Data were confirmed by qRT-PCR. Same results were obtained in normal skin Fbs. Not significant differences were observed between macitentan, ACT-132577 and bosentan effects.

Conclusion: Macitentan and its active metabolite might down regulate the myofibroblast activation and the increased ECM protein synthesis induced by ET-1 in cultured human SSc skin Fbs at the same concentrations of bosentan.

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DNA Methylation and Systemic Sclerosis. Gloria Salazar[1], Khurshida Begum[2], Xinjian Guo[3], Minghua Wu[1], Shervin Assassi[1], Maureen D. Mayes[1], John D. Reveille[1] and Xiaodong Zhou[1]. [1]University of Texas Health Science Center at Houston, Houston, TX, [2]Baylor College of Medicine, Houston, TX, [3]The University of Texas Medical School at Houston, Houston, TX.

Background/Purpose: Epigenetic modifications are stable and heritable alterations in gene expression and cellular function that do not involve changes to the original DNA sequence. They are now known to be essential regulators of multiple key biological processes. Epigenetic mechanisms are also vital for the development and function of the immune system.

DNA methylation is one of them and is mostly achieved by methylation of CpG dinucleotides of the mammalian genome. When methylated they cause a stable, heritable repression of transcription of the affected gene. DNA methylation was shown to play a role in the pathophysiology of systemic lupus erythematosus (SLE). A few studies have also shown important DNA methylation changes in systemic sclerosis (SSc).

The objective of this study was to establish the DNA methylation pattern differences between systemic sclerosis (SSc) and control fibroblasts as well as differences based on antibody profile.

Methods: DNA methylation profiling of fibroblasts from 16 SSc patients compared to 10 healthy controls was performed. Seven patients were anti-topoisomerase I (topo-1) positive and 9 were anti-centromere antibody (ACA) positive.

Roche NimbleGen 385K RefSeq promoter array was used. Candidate genes that were significantly hypomethylated in SSc fibroblasts compared to controls and are part of fibrotic or inflammatory pathways were selected for confirmation studies. Bisulfite conversion and sequencing methods for methylation detection was performed. We designed two sets of PCR primers (one for DNA without bisulfite conversion, and one for post-conversion). Bisulfite conversion of sample DNA was performed using EZ DNA methylation kit (Zymo Research, Irvine, CA). The samples were PCR-sequenced and examined for methylation using QUAMA software.

Results: Methylation changes of CpG islands of multiple genes showed significant difference between SSc and control fibroblasts by initial global profiling.

Ten candidate genes that were significantly hypomethylated in SSc fibroblasts compared to controls were chosen for confirmation studies (table 1).

Table 1. Hypomethylated genes selected for confirmatory studies

Chromosome	Pick start	Pick end	Gene Symbol	Gene name
16	65157526	65158226	CDH11	Cadherin 11
10	71562420	71563120	COL13A1	Collagen, type XIII, alpha 1 (COL13A1)
2	228045310	228045718	COL4A3	Collagen, type 4, alpha 3 (COL4A3)
5	74668878	74669278	COL4A3BP	Collagen type IV alpha-3-binding protein
3	185514988	185516194	IGF2BP2	Insulin-like growth factor 2 mRNA-binding protein 2
1	154430446	154430946	IL6R	Interleukin-6 Receptor
15	67009542	67010342	SMAD6	SMAD family member 6
20	39680072	39680672	TOP1	(DNA) topoisomerase 1
8	144420006	144420706	TOP1MT	(DNA) topoisomerase 1 mitochondrial
1	92373559	92351559	TGFBR3	Transforming growth factor-beta receptor 3

Bisulfite sequencing analyses showed hypomethylation of DNA topoisomerase I (TOP1) and mitochondrial DNA topoisomerase I (TOP1-MT) genes in ACA positive SSc patients compared to controls with a statistically significant difference in percentage methylation of these genes ($p=0.02$ for TOP1-MT and $p=0.005$ for TOP1). No difference was found for any of the studied genes between topo-1 positive patients and controls.

Conclusion: DNA methylation is an important epigenetic mechanism implicated in the pathophysiology of SSc. There are several candidate hypomethylated genes involved in collagen production and inflammatory pathways. Bisulfite sequencing showed significant hypomethylation of TOP1 and TOP1-MT in ACA positive SSc patient fibroblasts.

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Gene Expression Variation and The Role Of Interferon In Patients With Morphea From The Morphea In Adults and Children Cohort. Daniel Grabell[1], Andrew Kim[2], Virginia Pascual[3], Shervin Assassi[4] and Heidi Jacobe[1]. [1]UT Southwestern Medical Center at Dallas, Dallas, TX, [2]Lenox Hill Hospital, New York, NY, [3]Baylor University, Dallas, TX, [4]University of Texas Health Science Center at Houston, Houston, TX.

Background/Purpose: Localized scleroderma (morphea) is characterized by inflammation and sclerosis of the dermis and underlying tissue and may be associated with significant morbidity. Overproduction of type I and III collagen by fibroblasts is thought to be a factor in the pathogenesis of morphea but, little is known about the mechanism by which these fibroblasts are activated. Endothelial cell injury, immunologic and inflammatory activation, and dysregulation of collagen production have all been proposed. The purpose of this study is to describe the transcriptosome of lesional morphea skin relative to non-lesional controls.

Methods: Skin samples from adult patients in the Morphea in Adults and Children Cohort (MAC) with active, untreated lesions were collected from the inflammatory border, sclerotic center, and site matched non-lesional skin. Gene expression analysis of the three tissue types was conducted using Illumina Human HT4 arrays. The gene expression profile of each tissue type was then compared to that of corresponding normal tissue in a self-controlled fashion. We considered differentially expressed genes (DEGs) with a cut-off of fold change >2.0 and a $p<0.05$. The data was evaluated without correction and with the Benjamini–Hochberg procedure. Ingenuity Pathway Analysis (IPA) was utilized to identify canonical pathways among differentially expressed genes. The DEGs were compared to known type I interferon genes as collected by Monash University's Interferome database.

Results: Principal components analysis demonstrated a clear difference between gene expression patterns of the inflammatory border and sclerotic center when compared to normal skin and each other. The total number of DEGs when comparing the inflammatory border (IB) and the sclerotic center (SC) grouped together compared to unaffected skin (UA) was 724. The number of genes shared between Morphea skin and UA skin was 397. The number of genes unique to the IB compared with the UA was 647 and to the sclerotic center were 562. Comparison with the Interferome database showed that 35 IB genes and 23 SC genes overlapped with the interferon pathway. Specifically we saw that CXCL10, a major component of the interferon pathway, showed a14.3 fold change when compared to normal skin. Through IPA analysis we showed that the top five pathways include iCOS-iCOSL Signaling in T Helper Cells, CD28 Signaling in T Helper Cells, CTLA4 Signaling in Cytotoxic T Lymphocytes, OX-40 Signaling Pathway, and Dendritic Cell Maturation.

Conclusion: These results demonstrate that gene expression differs between matched pairs of lesional morphea skin and non-lesional skin from the same patient. Interestingly the inflammatory border and sclerotic center showed different levels of gene expression with greater activation of CXCL10 in the IB versus the SC, implicating different molecular mechanisms at play in the initiation of lesions. Our results support the

theory that therapeutics targeting the CXCL10 pathway may lead to future treatments for Morphea.

Disclosure: D. Grabell, None; **A. Kim**, None; **V. Pascual**, None; **S. Assassi**, None; **H. Jacobe**, None.

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Lipoic Acid Plays a Crucial Role In Scleroderma Dermal Fibroblasts. Pei-Suen Tsou[1], Beatrix Balogh[2], Adam J. Pinney[2], George Zakhem[2], Ann Kendzicky[2], Elena Schiopu[2], Dinesh Khanna[2], David A. Fox[2] and Alisa E. Koch[2]. [1]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [2]University of Michigan Medical School, Ann Arbor, MI.

Background/Purpose: Systemic sclerosis (SSc) is a connective tissue disease characterized by vasculopathy and fibrosis of the skin and organs. Increase in oxidative stress and platelet-derived growth factor receptor (PDGFR) activation promote collagen I (Col I) production, leading to fibrosis in SSc. Lipoic acid (LA) and its *active* metabolite dihydrolipoic acid (DHLA) are naturally occurring thiols that act as cofactors and antioxidants. The goal of this study was to examine whether LA, and lipoic acid synthetase (LIAS), the enzyme producing LA, were deficient in SSc patients. The effect of DHLA on the phenotype of SSc dermal fibroblasts was also determined. N-acetylcysteine (NAC), a commonly used thiol antioxidant, was included as a comparison.

Methods: Dermal fibroblasts were isolated from punch biopsies from healthy subjects and patients with diffuse cutaneous SSc. Oxidative stress was measured by dihydroethidium staining and hydrogen peroxide fluorescent assay. Immunofluorescence was performed to probe for LA, Col I and α-smooth muscle actin (αSMA). Matrix mettaloproteinase-1 (MMP-1) and 3, LIAS were measured by ELISA. Expression of phosphatases, PDGFR phosphorylation, and αSMA was measured by Western blotting.

Results: The expression of LA and LIAS in SSc dermal fibroblasts was lower than normal, however LIAS was significantly higher in SSc plasma (normal 79.5$\pm$6.0 vs. SSc 119.5$\pm$14.2 pg/ml, $p<0.05$). DHLA lowered cellular hydrogen peroxide (basal 2487$\pm$252 vs. plus DHLA 1908$\pm$61 fluorescent unit, $p<0.05$), and decreased PDGFR phosphorylation, Col I, and αSMA expression in SSc dermal fibroblasts. It also restored the activities of phosphatases that inactivated the PDGFR. SSc fibroblasts produced lower levels of MMP-1 and 3 then did normal fibroblasts (MMP-1: normal 15161$\pm$3525 vs. SSc 2094$\pm$405 pg/ml; MMP-3: normal 714$\pm$189 vs. SSc 216$\pm$69 pg/ml, both $p<0.05$), with levels increasing after DHLA incubation (MMP-1: 4789$\pm$1406 and MMP-3: 407$\pm$143 pg/ml, $p<0.05$ vs. without DHLA). DHLA showed better efficacy than NAC in most cases.

Conclusion: DHLA decreased PDGFR activation and increased MMPs that degrade Col I. It also lowered αSMA expression in SSc dermal fibroblasts. Since LA and LIAS were deficient in SSc dermal fibroblasts, this might be one of the reasons DHLA was beneficial. DHLA not only acted as an antioxidant but also an antifibrotic since it had the ability to reverse the profibrotic phenotype of SSc dermal fibroblasts.

Disclosure: P. S. Tsou, Arthritis Foundation, 2; **B. Balogh**, None; **A. J. Pinney**, None; **G. Zakhem**, None; **A. Kendzicky**, None; **E. Schiopu**, None; **D. Khanna**, NIH, 2; **D. A. Fox**, None; **A. E. Koch**, Eli Lilly and Company: I am currently employed by Eli Lilly with an adjunct appointment at University of Michigan. My work at Lilly is not relevant to the content of the abstract, 3.

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Elevated 8-Isoprostane In Scleroderma: Implications Of Its Role In Inhibiting Vascular Endothelial Growth Factor-Induced Angiogenesis. Pei-Suen Tsou[1], George Zakhem[2], Beatrix Balogh[2], M. Asif Amin[2], Phillip Campbell[2], Gautam Edhayan[2], Ray Ohara[2], Elena Schiopu[2], Dinesh Khanna[3], Alisa E. Koch[2] and David A. Fox[1]. [1]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [2]University of Michigan Medical School, Ann Arbor, MI, [3]University of Michigan, Ann Arbor, MI.

Background/Purpose: Scleroderma (SSc) is a complex disease characterized by inflammation, vasculopathy, and excessive disposition of extracellular matrix. Various studies have demonstrated a paradoxical increase in angiogenic mediators, such as vascular endothelial growth factor (VEGF), in both the skin and serum of patients with SSc. Despite this, angiogenesis does not occur normally. The signaling of the thromboxane A2 receptor (TXAR), which can be activated by 8-isoprostane (8-IP), has been shown to inhibit angiogenesis as well as VEGF-induced endothelial cell (EC) differentiation and migration. However, its role in SSc has not been examined. In this study we examined whether 8-IP was elevated in patient plasma and conditioned medium (CM) from ECs, and examined its' effect on VEGF-induced angiogenesis in SSc.

Methods: Dermal ECs were isolated from punch biopsies from healthy subjects or patients with diffuse cutaneous SSc. Angiogenesis was assessed by chemotaxis and *in vitro* Matrigel tube formation assays.

Results: SSc patients had significantly higher 8-IP plasma levels (60.9$\pm$8.4 pg/ml) compared to healthy subjects (24.9$\pm$5.0 pg/ml, $p<0.05$). When divided into disease subtypes, patients with diffuse SSc or interstitial lung disease showed elevated 8-IP, while those with limited SSc or pulmonary hypertension did not. Increased oxidative stress was detected in SSc ECs as increased 8-IP in SSc EC CM was observed (15.1$\pm$2.8 vs. 27.8$\pm$3.6 pg/ml, $p<0.05$). To test whether the increased 8-IP levels in CM affected angiogenesis, we performed Matrigel tube formation assay using NL ECs. SSc EC CM decreased VEGF-induced tube formation in NL ECs while addition of vitamin E restored it. In addition, 8-IP inhibited VEGF-induced healthy EC migration, and the inhibition of TXAR or ROCK pathways restored VEGF-induced angiogenesis inhibited by 8-IP. We then measured ROCK activity in NL and SSc ECs before and after VEGF or 8-IP stimulation. Basal ROCK activity was significantly higher in SSc ECs compared to healthy ECs. 8-IP-induced ROCK activation was significantly higher in SSc ECs while VEGF induced significantly higher ROCK activation in healthy ECs.

Conclusion: We show that 8-IP inhibits VEGF-induced migration in healthy ECs through the TXAR/ROCK pathway. SSc ECs produce high levels of 8-IP and exhibit elevated ROCK activity compared to healthy ECs, suggesting that this pathway plays a crucial role in impaired angiogenesis in SSc. This is supported by using vitamin E, which decreases 8-IP, in the Matrigel in vitro assay, in which it restores the inhibitory effect of SSc EC CM on VEGF-induced angiogenesis in healthy ECs. This study provides a potential link between oxidative stress and impaired angiogenesis in SSc, and shows that 8-IP is not just a by-product as a result of oxidative stress, rather it plays a significant role in impaired angiogenesis that characterizes SSc.

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Circulating Cell-free microRNAs in Systemic Sclerosis. Samantha Steen[1], Anting L. Carlsen[1], Line V. Iversen[1], Christoffer T. Nielsen[2], Christian Lood[3], Anders A. Bengtsson[3] and Niels H. H. Heegaard[1]. [1]Statens Serum Institut, Copenhagen, Denmark, [2]University Hospital Rigshospitalet, Copenhagen, Denmark, [3]Lund University, Lund, Sweden.

Background/Purpose: microRNAs (miRNAs) are a class of small non-coding RNAs that regulate gene expression through target mRNAs and are involved in important physiological and pathological processes. Alterations in miRNA expression have been reported in autoimmune diseases including systemic lupus erythematosus (SLE) and rheumatoid arthritis, and in fibrotic disorders such as idiopathic pulmonary fibrosis. Systemic sclerosis (SSc) is characterized by fibrosis, vasculopathy and immunological disturbances, and the differential diagnosis and assessment of SSc disease activity can be challenging. The aim of this study was to identify putative circulating miRNAs in SSc patients as biomarkers for diagnosis, disease complications, and activity.

Methods: Total RNA was purified from platelet-poor plasma from 121 SSc patients, 29 SLE patients and 40 healthy controls, and the expression of 45 different specific miRNAs was determined using a quantitative real-time PCR dynamic array. Expression data and diagnosis and clinical parameters were analyzed for correlations.

Results: Twenty-seven miRNAs were significantly differentially expressed in SSc patients compared with healthy controls ($p < 0.05$). Nineteen miRNAs were down-regulated in SSc (miR-16, -17, -20a, -21, -24, -27a-3p, -29c-3p, -92a, -106a, -142-3p, -145-5p, -146b, -184, -192-5p, -221, -223, -342-3p, -375 and -423-5p), whereas 8 miRNAs were up-regulated in SSc (-29a, -29b-3p, -150, -181b, -203, -409-3p, -590-5p and -638). Ten miRNAs were found to be statistically differentially expressed in SSc patients compared with both healthy controls and SLE patients ($p < 0.05$). Receiver operating characteristic (ROC) analysis underlined the potential use of 4 miRNAs as biomarkers in SSc diagnostics, and revealed a promising 2

miRNA model to discriminate SSc patients from healthy controls when combining miR-106a with miR-181b (AUC = 0.91).

Conclusion: The expression of cell-free circulating miRNAs is altered in SSc compared with healthy controls and SLE patients. A promising 2 miRNA index differentiates SSc patients from healthy controls.

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Bleomycin Delivery By Mini-Osmotic Pump: A Novel Multi-Organ Murine Model For Fibrosis. Rebecca Lee, Elena Tourkina, Richard P. Visconti and Stanley Hoffman. Medical University of SC, Charleston, SC.

Background/Purpose: Systemic sclerosis (SSc, Scleroderma) is a rare but severe systemic connective tissue disorder involving the skin and multiple internal organs, in particular lung, kidney, gastrointestinal tract, and heart. The hallmark pathophysiologic features of this disease include vascular injury, autoimmunity, inflammation, and extensive tissue fibrosis. Bleomycin is routinely used to create a model for SSc lung disease by direct administration into this target tissue. Systemic bleomycin treatment by multiple subcutaneous injections has occasionally been used to induce fibrosis in skin and lungs. However, this method is laborious and expensive, involving frequent injections of high concentrations of bleomycin over long time periods. Furthermore, fibrosis induced by this method has only been reported in locally injected skin and lung. In our study, for the first time, we report a bleomycin induced multi-organ fibrosis murine model for SSc by one-time subcutaneous implantation of a mini-osmotic pump containing bleomycin.

Methods: Mini-osmotic pumps are implanted into 10 week-old CD1 male mice. The pump delivers 100 U/kg bleomycin over 7 days. Mice are sacrificed on day 28. A variety of methods are used to analyze the progression of fibrosis.

Results: This model produces substantial and progressive multi-organ fibrosis, including dermal, pulmonary, renal, cardiovascular, and hepatic, as evaluated histologically and immunohistologically (Fig. 1 and 2). This model also mimics the vasculopathies observed in SSc patients, including loss of capillaries, proliferation of vascular smooth muscle cells, and dilation and hypertrophy of the right ventricle. Because caveolin-1 has been identified as a master regulator of fibrotic tissue remodeling, we evaluated whether systemic treatment of mice with the caveolin-1 scaffolding domain (CSD) peptide might have a beneficial effect on skin fibrosis. Indeed, bleomycin-induced skin thickening was almost completely blocked by CSD treatment ($p < 0.01$).

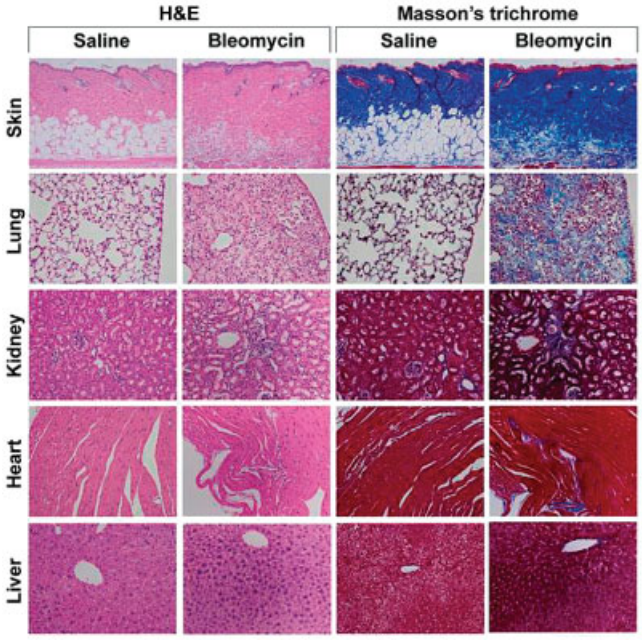

Fig. 1. Tissue morphology changes following bleomycin treatment. Sections are stained with H&E and Masson's trichrome.

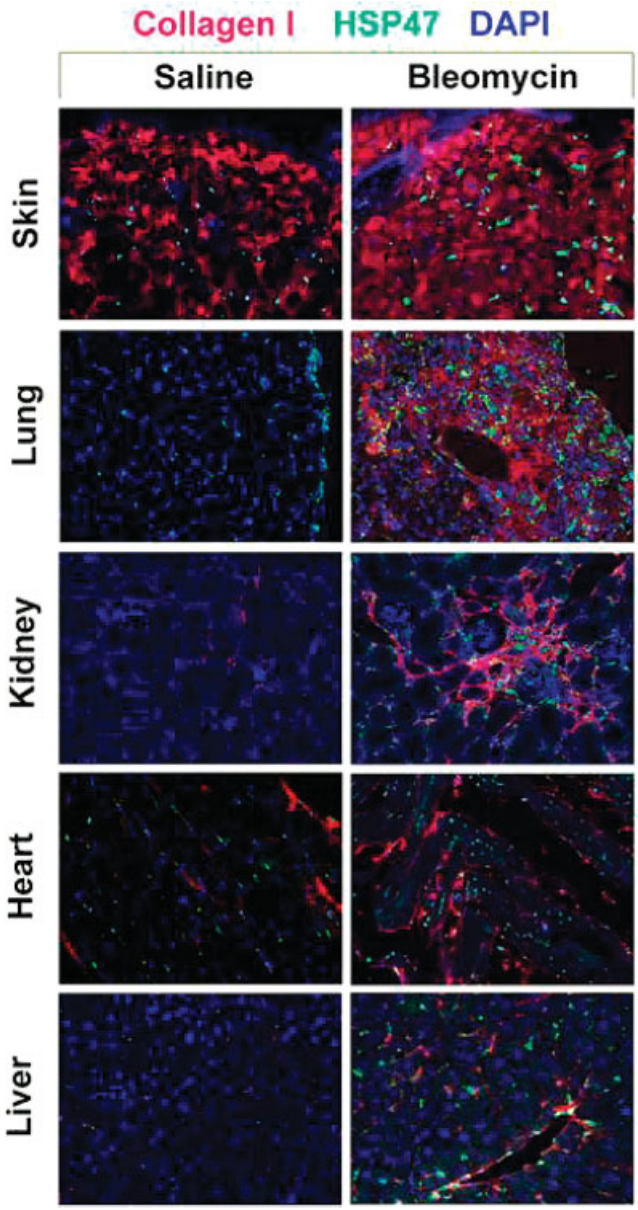

Fig. 2. Extracellular matrix protein expression in murine tissue sections following bleomycin treatment. Sections were stained with antibodies against collagen I and the collagen chaperone HSP47.

Conclusion: Bleomycin delivery by mini-osmotic pump effectively recapitulates the hallmark features of SSc in several organs, thereby providing a convenient model system to evaluate potential treatments for SSc (such as CSD) in each affected organ.

Disclosure: R. Lee, None; **E. Tourkina**, None; **R. P. Visconti**, None; **S. Hoffman**, None.

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Topoisomerase-1 Specific T Cells Exhibit a Proinflammatory Th17 Phenotype and Are Associated With Interstitial Lung Disease In Scleroderma. Andrea Fava[1], Raffaello Cimbro[1], Antony Rosen[1], Qing-Rong Liu[2], Fredrick M. Wigley[3] and Francesco Boin[3]. [1]Johns Hopkins University, Baltimore, MD, [2]NIH/NIDA, Baltimore, MD, [3]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Anti-topoisomerase-1 (Topo-1 or Scl70) autoantibodies are present in 30–45% of scleroderma (SSc) patients and identify a more aggressive disease phenotype with worse clinical outcome and reduced survival. While autoreactive T cells may be involved in SSc patho-

genesis driving tissue inflammation and damage, no study has to date reliably quantified and functionally characterized topo-1-specific T cells in SSc patients.

Methods: Peripheral blood mononuclear cells from 27 (15 Scl70-positive and 12 Scl70-negative) consecutive patients and 4 healthy donors (HD) were stimulated with topoisomerase-1 purified from baculovirus-infected insect cells in the presence of anti-CD40 blocking antibodies and autologous serum. Topo-1-responsive T cells were defined based on the expression of activation markers CD154 and CD69, and their frequency calculated as percentage of CD4+ cells. The polarized functional phenotype (Th1, Th2, Th17, Th1/17) of autoreactive T cells was further determined by the surface expression of specific chemokine receptors (CXCR3, CCR6, CCR4) and their cytokine secretion profile (IFNγ, IL-4, IL-17) quantified by ELISA and qPCR after cell sorting. Comprehensive clinical data were obtained at the time of blood draws.

Results: Topo-1-reactive CD4+ T cells were found in all topo-1-positive subjects compared to one topo-1-negative patient and no HD [p=<0.001 and p=0.005 respectively] with a frequency ranging between 0.11% and 0.42% of CD4+ T cells. Anti-HLA-DR antibodies effectively inhibited topo-1 presentation and the activation of topo-1-responsive CD4+ T cells. Topo-1-specific T cells exhibited a predominant Th17 phenotype compared to the parent CD4+ T cell population [37±16% vs 8±5%, p=0.001]. Among topo-1-positive patients, higher levels of topo-1-reactive CD4+ T cells were associated with presence of interstitial lung disease [p=0.03], lower forced vital capacity (FVC) [rho=−0.657, p=0.011], and lower carbon monoxide diffusing capacity (DLco) [rho=−0.592, p=0.026].

Conclusion: This study establishes a robust and sensitive assay to measure topo-1-reactive T cells, and suggests that Th17 differentiation may be of importance in SSc pathogenesis.

Disclosure: A. Fava, None; **R. Cimbro**, None; **A. Rosen**, None; **Q. R. Liu**, None; **F. M. Wigley**, None; **F. Boin**, None.

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Oxidative Stress-Dependent Activation Of Collagen Synthesis Is Induced In Human Pulmonary Vascular Smooth Muscle Cells By Scleroderma Sera and Predicts Pulmonary Vascular Disease. Francesco Boin[1], Anna Maria Posadino[2], Annalisa Cossu[2], Roberta Giordo[2], Ami A. Shah[1], Gaia Spinetti[3], Gian Luca Erre[2], Costanza Emanueli[4], Giuseppe Passiu[2], Fredrick M. Wigley[1] and Gianfranco Pintus[2]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Sassari, Sassari, Italy, [3]Istitituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Multi Medica, Milan, Italy, [4]University of Bristol, Bristol, United Kingdom.

Background/Purpose: Vascular disease is a dominant component of Systemic Sclerosis (SSc) pathogenesis. Hypoxia and oxidative stress have been linked to endothelial injury, intimal hyperplasia and progressive vessel occlusion in SSc and the aberrant function of vascular smooth muscle cells (VSMC) has been associated with the initiation and the amplification of this process. We hypothesize that in SSc patients with pulmonary vascular disease circulating factors may drive vascular damage by exerting pro-oxidant effects involving VSMC.

Methods: The generation of reactive oxygen species (ROS) and the activation of collagen synthesis was investigated in primary Human Pulmonary Vascular Smooth Muscle Cells (HPVSMC) after exposure to sera obtained from 19 SSc patients with pulmonary vascular disease (PVD) defined by echocardiographic criteria (right ventricular systolic pressure ≥ 45 mmHg), 17 patients with no PVD and 15 healthy donors (HD). Intracellular ROS levels were assessed using the general oxidative stress indicator dichlorodihy drofluorescein diacetate (H_2-DCFDA). Collagen type I (COL1A1) promoter activity was investigated using a GFP-based lentiviral vector, while collagen protein expression was assessed by ELISA in culture supernatants. In selected experiments, pretreatment of cells with diphenyleneiodonium (DPI), a general flavoprotein inhibitor, was performed.

Results: HPVSMC treated with SSc sera from PVD patients significantly increased intracellular ROS levels (248.8 ± 27.5 Relative Fluorescence Units - RFU) compared to no-PVD subjects (155.1 ± 10.5 RFU; p=0.008) and HD (124.9 ± 2.8 RFU; p=0.002). DPI effectively prevented the raise of intracellular ROS, implicating the involvement of Flavin Oxidases (FO) in this process. The pro-oxidant stimulus provided by SSc sera was associated with a parallel increase of both COL1A1 promoter activity (PVD-SSc sera 278.1 ± 24.2 RFU vs 194.4 ± 7.9 RFU; p=0.01 in no-PVD and 164.9 ± 5.1; p=0.002 in HD) and collagen protein expression in HPVSMC. Also this effect was abrogated by DPI pretreatment.

Conclusion: This study provides evidences that sera from SSc patients with pulmonary vascular disease drive pro-fibrotic responses mediated by Flavin Oxidases-derived ROS production in HPVSMC and suggests that antioxidant therapies should be further explored in the treatment of SSc vascular disease.

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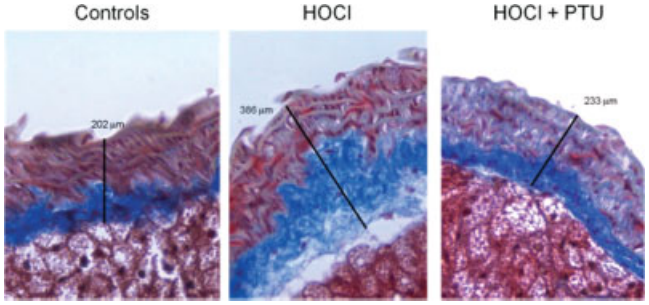
Propylthiouracil Attenuates Aortic Vasculopathy In An Animal Model Of Systemic Sclerosis. Gianluca Bagnato[1], Alessandra Bitto[1], Gabriele Pizzino[1], Neal Roberts[2], Domenica Altavilla[1], Francesco Squadrito[1], Gianfilippo Bagnato[1] and Antonino Saitta[1]. [1]University of Messina, Messina, Italy, [2]University of Louisville, Louisville, KY.

Background/Purpose: Systemic sclerosis (SSc) is a generalized connective tissue disorder of unknown etiology characterized by thickening and fibrosis of the skin and distinctive visceral involvement associated with vascular damage. Traditionally, the vasculopathy of SSc has been considered mainly to affect small arteries and capillaries but there is recent evidence showing that SSc is also associated with large vessel disease. Increased aortic augmentation index and pulse wave velocity in comparison to age and sex matched healthy controls indicate large-vessel involvement in patients with SSc. A second, and as yet poorly accounted for, endocrine feature of scleroderma is its overlap with thyroid abnormalities. Recent experimental data suggest that propylthiouracil (PTU) abrogates the development of cutaneous and pulmonary fibrosis in SSc murine model and reduces the development of plexiform lesions in an animal model of primary pulmonary hypertension. The aim of the study is therefore to evaluate the effect of propylthiouracil administration on intima-media (IM) thickness and ratio in a murine model of systemic sclerosis.

Methods: Chronic oxidant stress SSc was induced in BALB/c mice by daily subcutaneous injections of HOCl for 6 weeks, characterized in detail as the Cochin chronic oxidant stress model of SSc. Mice (n=25) were randomized in three arms: treatment with either propylthiouracil plus HOCl (n=10), HOCl (n=10), or vehicle alone (n=5). Propylthiouracil treatment (12 mg/kg) was initiated 30 minutes after HOCl subcutaneous injection and continued daily for the 6 weeks. Thoracic aorta was evaluated by histological methods. IM thickness and ratio were measured for statistical analysis.

Results: HOCl injections induced an increase in aortic IM thickness when compared to controls by 101% (p<0.0001). In mice treated with HOCl and PTU there was a 86% reduction of IM thickness (p<0.0001). PTU treated animals had a significantly thinner intima layer (−13%, p<0.0001) and media layer (−198%, p<0.0001) compared to HOCl group. IM ratio was also decreased in HOCl treated mice compared to controls (0.72 vs 1.76, p<0.0001) and significantly increased by PTU administration (1.62 vs 0.72, p<0.0001).



Conclusion: Our data suggest that PTU, probably through its antioxidant direct effect or indirectly through thyroid function inhibition, substantially moderates the increase of aortic thickness found in HOCl treated animals reducing collagen deposition in media layer and aortic fibrotic changes.

Disclosure: G. Bagnato, None; **A. Bitto**, None; **G. Pizzino**, None; **N. Roberts**, None; **D. Altavilla**, None; **F. Squadrito**, None; **G. Bagnato**, None; **A. Saitta**, None.

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Formate, Acetate and Acetone: News Biomarkers in Systemic Sclerosis identified by Metabolomics. Emmanuel Chatelus[1], Francois Marie Moussallieh[1], Christelle Sordet[1], Arnaud Theulin[1], Alain Meyer[1], Karim El Bayed[2], Jean Francois Kleinmann[1], Jean Sibilia[1], Jacques-Eric Gottenberg[1] and Izzie Jacques Namer[1]. [1]Strasbourg University Hospital, Strasbourg, France, [2]UMR 7177 CNRS/Strasbourg University, Strasbourg, France.

Background/Purpose: High throughput study of metabolic pathways might help identify new biomarkers and therapeutic targets in autoimmune diseases. Systemic sclerosis (SSc) currently lacks prognostic biomarkers and efficacious and specific treatments. We therefore assessed serum levels of 40 metabolites in patients with SSc and healthy controls using high-resolution magic-angle spinning (HRMAS) proton magnetic resonance spectroscopy.

Methods: The blood samples of 97 successive patients with SSc (median age 59 years (22–85); disease duration 13 years (1–37); limited cutaneous SSc 57%; diffuse cutaneous SSc 43%) and 39 healthy controls were analysed in this study. After cryopreservation at −80°C, the samples were studied with HRMAS proton magnetic resonance spectroscopy (1H-MRS). Spectra were recorded on a Bruker Avance III 500 spectrometer operating at a proton frequency of 500 MHz. The speed revolution of the tube was 3000 Hz. The 1D MR spectra were acquired during 15 min (between 0.5 and 4,7 ppm). Supervised clustering was performed using principal component analysis (PCA).

Results: Supervised clustering of the 97 samples allowed to discriminate all patients with SSc from healthy controls ($R^2Y=0.76$ and $Q^2=0.72$) (Figure 1). Interestingly, 3 metabolites were significantly more expressed in SSc blood samples than in healthy controls: formate, acetate and acetone (median 19.6 *vs* 7.9 μmol/l, $p<0.0001$; 17.7 *vs* 5.4 μmol/l; $p<0.0001$; 10.4 *vs* 8.1 μmol/l, $p=0.043$ respectively). Supervised clustering also allowed to discriminate SSc patients with interstitial lung disease (ILD) from patients without ILD ($R^2Y=0.73$ and $Q^2=0.50$).

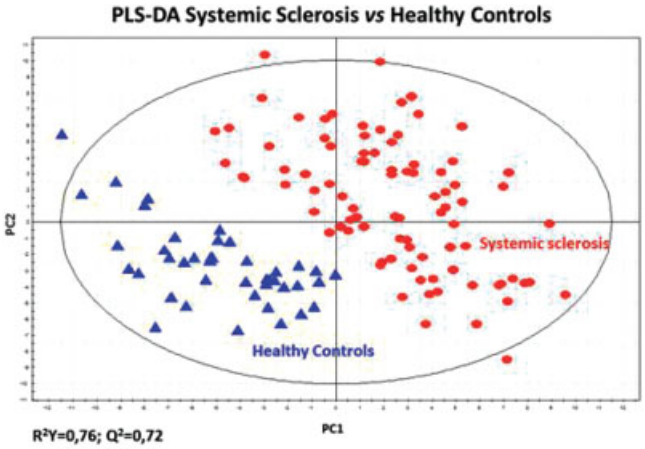

Figure 1 : PLS-DA scores plot based on NMR spectra of blood samples obtained from systemic sclerosis (red plot) and healthy controls (blue triangle)

Conclusion: This first high-throughput analysis of metabolic pathways disclosed a specific metabolomic signature of SSc allowing to discriminate all patients from controls and SSc patients with ILD. This new and very potent means of metabolic analysis may help to increase our knowledge on the pathogenesis of SSc, identify biomarkers, and new therapeutic targets.

Disclosure: E. Chatelus, None; **F. M. Moussallieh**, None; **C. Sordet**, None; **A. Theulin**, None; **A. Meyer**, None; **K. El Bayed**, None; **J. F. Kleinmann**, None; **J. Sibilia**, None; **J. E. Gottenberg**, None; **I. J. Namer**, None.

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DNA hypermethylation of Forkhead box protein 3 (FOXP3) locus leads to quantitative defects of regulatory T cells in systemic sclerosis. Yaoyao Wang[1], Ye Shu[2], Qing Wang[1], Ming Zhao[1], Gongping Liang[1], Qianjin Lu[1] and Rong Xiao[1]. [1]Second Xiangya Hospital, Central South University, Changsha, China, [2]Hunan Children's Hospital, Changsha, China.

Background/Purpose: Systemic sclerosis (SSc) is a systemic autoimmune disease of which the etiology and pathogenesis remains complex and poorly understood. Attention has recently been directed towards regulatory T cells (Tregs) because they are important in maintenance of immunologic self-tolerance as well as negatively regulating immune responses against non-specific stimuli. The normal development and suppressive phenotype of Tregs depends on stable expression of FOXP3. The methylation status of the CpG residues in the proximal promoter region has an essential role in FOXP3 expression. Transcriptional silencing of FOXP3 through hypermethylation in regulatory elements regions has been identified as a hallmark of committed Treg cells and several human diseases. The aim of this study was to investigate on how DNA methylation status of CpG islands in the proximal promoter region within the FOXP3 locus affect FOXP3 expression and defects in Tregs from patients with SSc.

Methods: 18 SSc patients and 16 healthy control subjects(HC) were recruited from the outpatient clinics, inpatient services and medical staff at the Second Xiangya Hospital of Central South University in China. Patients and controls were age- and sex-matched in all experiments.Peripheral blood mononuclear cells were isolated by Ficoll-Hypaque density-gradient centrifugation, and CD4+T cells were isolated by positive selection using immunomagnetic beads, according to protocols provided by the manufacturer. The percentage of CD4+CD25+FOXP3+ Treg cells in peripheral blood mononuclear cells was measured by flow cytometry from SSc patients and HC. FOXP3 expression in CD4+ T cells from patients with SSc and HC was measured by RT-PCR and western blot. Bisulfite sequencing was performed to determine the methylation status of the FOXP3 proximal promoter in CD4+ T cells from SSc patients, HC and in CD4+ T cells with DNA methylation inhibitors.

Results: The percentage of CD4+CD25+FOXP3+ Treg cell was decreased in SSc patients. FOXP3 expression was significantly reduced in patients with SSc. The methylation levels of the DNA regulatory sequences were elevated in patients with SSc compared with healthy controls, and there was a significant inverse correlation between the average methylation level and FOXP3 mRNA expression in patients with SSc. Further more, there was a significant inverse correlation between the the average methylation level and the percentage of Tregs in a cohort of SSc patients. Treatment with a DNA methylation inhibitor led to FOXP3 hypomethylation in the FOXP3 promoter resulting in FOXP3 overexpression and expansion of Tregs. The percentage of Tregs was positively correlated with disease activity.

Conclusion: Hypermethylation of the FOXP3 promoter contributes to the decreased FOXP3 expression and quantitative defects of Tregs in SSc patients correlating with disease activity. These data provide evidence that a quantitative defect of Treg cells could be considered a common biological hallmark of SSc. We propose that this reduction per se could sustain autoimmunity.

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Involvement Of TCR Vdelta1$^+$ NKT Cells In Systemic Sclerosis: Association With Interstitial Pneumonia. Seiji Segawa[1], Daisuke Goto[2], Masanobu Horikoshi[2], Yuya Kondo[3], Naoto Umeda[2], Shinya Hagiwara[2], Masahiro Yokosawa[4], Tomoya Hirota[3], Haruka Miki[1], Hiroto Tsuboi[3], Hiroshi Ogishima[2], Takeshi Suzuki[4], Isao Matsumoto[3] and Takayuki Sumida[3]. [1]University of Tsukuba, Ibaraki, Japan, [2]University of Tsukuba, Tsukuba City, Japan, [3]University of Tsukuba, Tsukuba, Japan, [4]University of Tsukuba, Tsukuba, Ibaraki, Japan.

Background/Purpose: Interstitial pneumonia (IP) is one of the critical complications in patients with several autoimmune diseases. However, the exact mechanism of IP remains elusive. Recently, the pathological role of $\gamma\delta$ T cells was reported in several IP mice models. Previous our data showed that IP in Interleukin (IL)-2 plus IL-18 induced mice was similar to human IP. In this mice model, $\gamma\delta$NKT cells exacerbated IL-2 plus IL-18 induced lung inflammation via the production of IFN-γ. Thus, to examine whether TCR V$\delta1^+$ NKT cells play a crucial role, we carried out the number and function of TCR V$\delta1^+$ NKT cells in systemic sclerosis patients with IP.

Methods: 1) PBMCs were isolated from healthy controls (HC, n=22) and patients with rheumatoid arthritis (RA, n=17), systemic sclerosis (SSc, n=35), and polymyositis/dermatomyositis (PM/DM, n=14). We examined the proportion of TCR V$\delta1^+$ NKT cells in PBMCs by flow cytometry (FCM). 2) In SSc patients with IP, the correlation between proportion of TCR V$\delta1^+$ NKT cells in PBMCs and serum KL-6 levels was analyzed. 3) CD161$^-$ V$\delta1^+$ $\gamma\delta$T and CD161$^+$ V$\delta1^+$ $\gamma\delta$T cells (TCR V$\delta1^+$ NKT cells) in PBMCs were sorted out from HC (n=3). We performed GeneChip analysis using those two cell populations. 4) Cytokine (IFN-γ, TNF-α, IL-4, IL-17) and chemokine (CCL2, CCL3, CCL4, CCL5) secretion assay using TCR V$\delta1^+$ NKT cells from HC and SSc patients was performed. 5) The effect of

culture supernatant of TCR Vδ1$^+$ NKT cells on fibroblast proliferation was evaluated.

Results: 1) The proportion of TCR Vδ1$^+$ NKT cells in PBMCs from SSc patients (mean±SEM, 0.55±0.13%) was significantly higher than that of HC (0.23±0.09%, $p<0.05$), whereas RA (0.38±0.12%) and PM/DM patients (0.23±0.11%) were not. In SSc patients, the proportion of TCR Vδ1$^+$ NKT cells in PBMCs from IP-negative subjects (1.03±0.32%) was significantly higher than that of IP-positive subjects (0.28±0.07%, $p<0.05$). In RA and PM/DM patients, there was no difference between IP-negative and IP-positive subjects. 2) In IP-positive SSc patients, the proportion of TCR Vδ1$^+$ NKT cells correlated negatively with serum KL-6 values ($r=-0.464$, $p<0.05$). 3) 192 genes were highly expressed in TCR Vδ1$^+$ NKT cells compared to CD161$^-$ Vδ1$^+$ γδT cells. One of 192 genes was CCL3 chemokine associating with SSc and IP. 4) Upregulation of CCL3 and downregulation of IFN-γ production were noted in TCR Vδ1$^+$ NKT cells of IP-positive SSc patients upon TCR stimulation compared with HC ($p<0.05$). 5) Fibroblast proliferation was promoted with medium supplemented with culture supernatant derived from IP-positive SSc patients ($p<0.05$), whereas that from HC was not.

Conclusion: TCR Vδ1$^+$ NKT cells might play a regulatory role in the pathogenesis of IP in SSc patients.

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IL6 and CCL2 Co-Regulate Fibroblast Dependent Trans-Endothelial Migration Of Mononuclear Cells and Fibrotic Response In Scleroderma. Rebecca Alade[1], Korsa Khan[2], Xu Shiwen[3], Christopher P. Denton[1] and Voon Ong[4]. [1]UCL Medical School, London, United Kingdom, [2]UCL Medical School, London, United Kingdom, [3]Royal Free Hospital, London, United Kingdom, [4]UCL Medical School, London, England.

Background/Purpose: IL6 is a key mediator recently implicated in activation of extracellular matrix (ECM) proteins in scleroderma (SSc) fibroblasts. CCL2 is a proinflammatory chemokine that is overexpressed in diffuse cutaneous systemic sclerosis (dcSSc). We explored interaction between these two major mediators and their role in the recruitment of inflammatory cells and fibroblast ECM production.

Methods: Dermal fibroblasts were cultured from skin biopsies from healthy controls (n=4) and early stage dcSSc (n=4). Peripheral blood mononuclear cells (PBMCs) were isolated from blood samples of the latter group. Induction of CCL2 in dermal fibroblasts by IL6 trans-signalling (via sIL-6R) and the ability of SSc fibroblast derived CCL2 to regulate migration of PBMCs across an endothelial layer in vitro was studied using Transwell migration assays in a co-culture system. The effect of PBMCs-fibroblast cross-talk on induction of ECM proteins: α-smooth muscle actin (αSMA) and Collagen type-I (Col-I) was assessed using neutralising antibodies against CCL2 and/or IL6 ligand-receptor axis and targeted ectodomain shedding inhibition using TNF-α processing inhibitor-1(TAPI-1).

Results: IL6 trans-signalling significantly increased CCL2 expression (mean ± SEM % basal expression) (33± 2.7% $p<0.03$ and 45±5.6% $p<0.04$) in control and SSc fibroblasts respectively. CCL2 expression was reduced in the presence of anti-IL6R in control fibroblasts (63±6.4%, $p<0.04$), but the reduction is not significant in the presence of SSc fibroblast IL6 trans-signalling increased migration of PBMCs (n=4) by 2.1 fold ($p<0.05$) and 4.5 fold ($p<0.03$) in the presence of control fibroblasts and SSc fibroblasts respectively. The migration of PBMCs was significantly reduced by the addition of neutralising antibodies against CCL2 and IL6R (44± 5.1%, $p<0.05$ and 62 ± 5.4%, $p=0.04$) respectively and both antibodies combined (44± 7.3.2%, $p<0.05$) in the presence of SSc fibroblasts.In response to IL-6 trans-signalling, there was increased expression of ECM proteins: αSMA (53 ± 5.9%, $p<0.04$) and Col-I (70± 2.6%, $p<0.03$) at 24-hour in the presence control fibroblasts and αSMA (37± 5.9%, $p<0.03$) and Col-I (47± 3.6%, $p<0.04$) in the presence of SSc fibroblasts. Activation of ECM was significantly abrogated by anti-IL6R by αSMA (46± 4.9%, $p<0.05$) and (58 ± 5.9%, $p<0.04$) in the presence of control and SSc fibroblasts respectively. TAPI-1 reduced PBMC migration in a concentration dependent manner with maximal effect at 50μM by (55± 4.1 % $p<0.04$) and TAPI-1 reduced synthesis of αSMA (37± 4.8 %, $p<0.05$) and Col-I (41± 3.6%, $p<0.03$) respectively. Together these data support a key role for IL-6 trans-signalling in regulating cell migration in SSc and confirm the potential importance of IL-6 and CCL2 in matrix overproduction

Conclusion: Our data suggests that fibroblast-derived CCL2 expression is in part dependent on IL-6 trans-signalling. The IL-6/CCL2 interplay regulates recruitment of PBMCs and IL-6 trans-signalling with intramembrane shedding of IL-6R mediates the fibrotic response. Thus,CCL2/IL6 interplay may be important in SSc pathogenesis and could be targeted therapeutically.

Disclosure: R. Alade, None; **K. Khan**, None; **X. Shiwen**, None; **C. P. Denton**, Roche-Genentech., 2; **V. Ong**, Roche-Genentech., 2.

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Enhanced Expression Of The Cold-Sensing Receptor-TRPM8 In Scleroderma Endothelial Cells and Skin and Endothelial Dysfunction Following TRPM8 Activation. Yongqing Wang, David R. Giovannucci and Bashar Kahaleh. University of Toledo, Toledo, OH.

Background/Purpose: Cold exposure induces vasospasm and incites reperfusion injury in SSc. The mechanisms responsible for enhanced cold sensitivity in SSc are poorly understood. Transient receptor potential melastatine8 (TRPM8) is a well characterized cold sensing cation channel. To date, TRPM8 expression has not been described in human microvascular endothelial cells (MVEC). In this study we thought to search for TRPM8 expression in SSc MVEC and skin. We also investigated the effects of TRPM8 activation on MVEC gene expression.

Methods: MVEC were isolated from involved SSc skin and from matched healthy control subjects. The expression of TRPM8 was determined by RT-PCR, immunohistochemistry and western blotting. TRPM8 activation in MVEC was triggered by the TRPM8 agonist menthol or by exposure of cells to cold temperature (18C°). The intracellular calcium concentration was determined by Ca^{2+} microfluorometry using the prototypical TRPM8 agonist menthol. The effects of TRPM8 activation on the mRNA expression levels of *ET1*, *NOS3* and *PTGIS* and the expression levels of TRPM8 in SSc-MVEC and SSc skin biopsies were quantitated by real time PCR.

Results: TRPM8 gene and protein expression in HMVEC are demonstrated by RT-PCR, Western blotting and immunohistochemistry. In Ca^{2+} microfluorometry studies, we showed increased MVEC intracellular calcium ($[Ca2^+]_i$) in response to the TRPM8 agonist menthol. The activation of the TRPM8 in HMVEC stimulated by cold significantly increased expression of *ET1* (2.39 folds ± 0.21) and decreased *NOS3* (62% ± 5.1 reduction) and *PTGIS* (61% ± 4.8) expression levels. These effects were attenuated by the addition of the TRPM8 antagonist capsazepine. Similar results were obtained with menthol treated HMVEC. The TRPM8 mRNA expression levels were significantly increased in SSc-MVEC (2.59 fold ± 0.22 vs. control MVEC) and SSc-skin biopsies (25.52 fold ± 2.28 vs. control skin biopsies).

Conclusion: The study demonstrates that human MVEC express functional TRPM8 and that there is increased expression of TRPM8 in SSc skin and in SSc-MVEC. TRPM8 may be involved in cold-induced vascular dysfunction through increase *ET1*, and decrease *NOS3* and *PTGIS* mRNA expression. The increased expression levels of TRPM8 in SSc-MVECs and SSc skin may be involved in enhanced cold sensitivity in SSc. The bulk of TRPM8 skin expression in SSc seems to be extravascular and possibly neuronal.

These results suggest that the blockade of TRPM8 activation could be an effective therapeutic strategy in SSc vasculopathy.

Disclosure: Y. Wang, None; **D. R. Giovannucci**, None; **B. Kahaleh**, None.

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Up-Regulated Expression Of CXCL5 In Circulating Platelets From Patients With Systemic Sclerosis: A Role In Fibrosis. Hidekata Yasuoka, Ken Stern, Yuka Okazaki, Tetsuya Nishimoto, Tsutomu Takeuchi and Masataka Kuwana. Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: Systemic sclerosis (SSc) is a systemic fibroproliferative disease characterized by concomitant occurrence of microvascular injury and autoantibody production. It has long been suggested that many processes are shared by physiological wound healing and pathological fibrosis. During wound healing process, platelets are the first cells that home to the site of injury, and contribute to the initiation phase through release of a variety of growth factors, chemokines, cytokines, and inflammatory mediators. Circulating platelets in patients with SSc are known to have activated phenotype, but there are few data regarding their functional properties. In this study, we identified potentially fibrogenic factors specifically up-regulated in platelets from SSc patients.

Methods: We used peripheral blood samples from 49 patients with SSc and 23 age- and sex-matched healthy controls. Proportions of activated platelets and platelet-derived microparticles were examined by expression of an activation marker CD62P using flow cytometry. Genes up-regulated in SSc platelets were screened with the RT^2 profiler™ PCR array that covered 168 genes, and were subsequently verified by semi-quantitative and TaqMan® quantitative PCR. The protein expression levels of candidate genes were examined by Proteome Profiler or immunoblots combined with densitometry using platelet lysates. We further evaluated roles of platelets or the platelet-derived molecule up-regulated in SSc platelets in production of fibronectin in cultures of human dermal fibroblasts. Finally, effects of CXCL5 on fibronectin production were confirmed in cultures of fibroblasts and SSc platelets in the presence or absence of a chemical antagonist or a neutralizing antibody.

Results: Proportions of activated platelets and microparticles were increased in SSc patients than in healthy controls ($P < 0.05$ for both comparisons). By stepwise screening strategies based on comparisons of gene/protein expression profiles between SSc and control platelets, CXCL5 was identified as a platelet-derived factor up-regulated in SSc patients. Fibronectin production was greater in fibroblast cultures with SSc platelets, compared with those with control platelets ($P < 0.05$). Enhanced fibronectin production in cultures with SSc platelets, but not in cultures with control platelets, was partially abolished by a CXCL5 receptor antagonist or a neutralizing antibody to CXCL5. In addition, recombinant CXCL5 promoted in vitro production of fibronectin from fibroblasts.

Conclusion: These results suggest that circulating platelets in SSc patients are phenotypically and functionally altered, and are involved in the fibrotic process through up-regulation of CXCL5.

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ACR Poster Session A
Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's - Clinical Aspects and Therapeutics I
Sunday, October 27, 2013, 8:30 AM–4:00 PM

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Autoantibody Diversity In Scleroderma Patients With Antinucleolar Antibodies and Negative For Three Major Disease-Specific Markers. Sarada Nandiwada[1], Troy Jaskowski[2], Maureen D. Mayes[3], Minoru Satoh[4] and Anne E. Tebo[1]. [1]University of Utah, Salt Lake City, UT, [2]ARUP Laboratories, Salt Lake City, UT, [3]University of Texas Health Science Center at Houston, Houston, TX, [4]University of Florida, Gainesville, FL.

Background/Purpose: Antinuclear antibodies (ANA) in a nucleolar pattern (antinucleolar antibodies, ANoA) by indirect immunofluorescence technique correlate with several autoantibody specificities and clinical manifestations in scleroderma (systemic sclerosis, SSc). However, the full repertoire of this autoantibody diversity is not completely defined. In this study, we investigated the breadth of antibody specificities by radioimmunoprecipitation (IP) assay in a subset of SSc patients with ANoA but negative for three main disease markers [topoisomerase-I (topo-1/Scl-70), centromere (ACA) and RNA polymerase III (RNAP III)].

Methods: In a cohort of 1000 patients with SSc, we identified 160 individuals with a positive ANoA and negative for ACA by immunofluorescence and topo-1 and RNAP III by ELISA. All 160-serum samples were further evaluated by IP using ^{35}S-methionine labeled K562 cell extract to identify specificities of ANoA in the sera.

Results: Of the 160 patient specimens investigated, 152 (95%) had antibodies previously reported in SSc. No known antibodies were identified in 8 patients (5%). The repertoire of identifiable autoantibodies included scleroderma specific (U3-RNP, Th/To, PM/Scl, topo I, RNAP III) and non-specific (NOR90, U1-RNP, Su, and Ro60) autoantibodies. The distribution of the specific antibodies based on clinical manifestations and ethnicity is summarized in Table 1. The anti-U3RNP antibody was the most prevalent (49%; 78/160) and occurred predominantly in individuals of African American descent (68%; 53/78) with diffuse SSc (72%; 38/53). Although less prevalent in Caucasians and Hispanics, anti-U3-RNP also correlated with diffuse SSc in these groups. Of note, anti-Th/To autoantibodies were found mainly in limited SSc in Caucasians (85%; 22/26) and Hispanics (70%; 7/10). Anti-PM/Scl antibodies were primarily observed in Caucasians (70%; 16/23) and mostly in patients with limited (62%; 10/16) versus diffuse (38%; 6/16) disease.

Table 1. Scleroderma-specific Autoantibody profile based on race and clinical manifestations in antinucleolar antibody-positive patients

	African Americans (n=62)		Hispanic (n=33)			Caucasians (n=65)		
Marker(s)	Limited (n=19)	Diffuse (n=43)	Limited (n=12)	Diffuse (n=19)	SINE (n=2)	Limited (n=37)	Diffuse S (n=27)	SINE (n=1)
U3-RNP (n=78)	15 (28%)	38 (72%)	2 (17%)	10 (83%)	0 (0%)	0 (0%)	13 (100%)	0 (0%)
Th/To (n=39)	1 (33%)	2 (67%)	7 (70%)	2 (20%)	1 (10%)	22 (85%)	3 (12%)	1 (3%)
PM/Scl (n=23)	0 (0%)	2 (100%)	1 (20%)	3 (60%)	1 (20%)	10 (62%)	6 (38%)	0 (0%)
RNAP I/III (n=4)	0 (0%)	0 (0%)	0 (0%)	2 (100%)	0 (0%)	0 (0%)	2 (100%)	0 (0%)
Topo-1 (n=4)	0 (0%)	1 (100%)	1 (50%)	1 (50%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Unknown (n=8)	1 (100%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	3 (50%)	3 (50%)	0 (0%)

Conclusion: Among AnoA positive SSc patients, anti-U3RNP is the most common specificity (85%, 53/62) in African American and Hispanic (36%, 12/33) whereas anti-Th/To is the most prevalent in Caucasians (40%, 26/65). This study further highlights the relevance of autoantibody diversity and ethnicity in the stratification of SSc patients for management.

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Anti-Th/To Antibodies In Various Systemic Rheumatic Diseases Screened By Anti-Rpp25 ELISA. Ann D. Chauffe[1], Eric S. Sobel[1], Michael R. Bubb[1], Westley H. Reeves[1], Michael Mahler[2], Cristina Gascon[3], Jason Y.F. Chan[1], S. John Calise[1], Edward K.L. Chan[1] and Minoru Satoh[1]. [1]University of Florida, Gainesville, FL, [2]INOVA Diagnostics, San Diego, CA, [3]INOVA Diagnostics, Inc., San Diego, CA.

Background/Purpose: Anti-Th/To antibodies (anti-Th) are one of the specificities that show nucleolar staining in indirect immunofluorescence antinuclear antibody test. Anti-Th is associated with systemic sclerosis (SSc), mainly the limited cutaneous variant. However, cases of anti-Th also have been reported in other diseases. Although known for over 20 years, anti-Th is rarely used in routine testing algorithms because immunoprecipitation (IP) is not widely available. One of the components of the Th-complex, namely Rpp25, has been reported as a major autoantigen, recognized by ~80% of anti-Th positive sera in ELISA. The goal of the study was to better characterize the clinical features associated with anti-Th in various autoimmune disease cohorts as identified by anti-Rpp25 ELISA followed by confirmation IP.

Methods: Patients enrolled were seen at Autoimmune Disease Center from 2000 to 2012. All SSc patients' sera had previously undergone RNA-IP. Patients with other rheumatic diseases including 462 systemic lupus erythematosus (SLE), 131 autoimmune inflammatory myopathy (AIM), 63 primary Sjogren's syndrome (SS) and 138 Rheumatoid Arthritis (RA) were screened by anti-Rpp25 ELISA. Borderline and positive cases underwent confirmatory IP. Additionally, antinucleolar staining ANA positives were tested by RNA-IP. The clinical characteristics of the anti-Th (+) patients were then more closely evaluated by reviewing database and chart records.

Results: Overall, anti-Th was confirmed in 17 cases (7 SSc and 10 non-SSc) via Rpp25 ELISA and IP. Prevalence of anti-Th was 6% (7/125) in SSc, 0.6% (3/462) in SLE, 0.7% (1/131) in AIM, 0% (0/138) in RA, 3% (2/63) in SS and 4 others without a rheumatologic diagnosis. Of the 17 anti-Th patients, 15 were Caucasian and 2 were African American and had SLE. The anti-Th SSc patients were mainly the limited cutaneous variant (4/7) and none of them had interstitial lung disease (ILD) or pulmonary arterial hypertension (PAH). Of the non-SSc patients with other rheumatologic diagnoses 3 had SLE, 2 had SS and 1 had AIM but some also had features associated with SSc: 2/6 ILD, 3/6 Raynaud's (RP), 1/6 telangiectasia (TG), 1/6 pitting scars (PS). Four other non-SSc patients without a rheumatologic diagnosis had features typical of SSc: 3/4 RP, 1/4 PS, 3/4 TG, 1/4 ILD, 1/4 PAH which may represent sine-SSc variant.

	Systemic Sclerosis N=7	Other Rheum Diagnosis SLE (3) Sjogren's (2) myositis (1) N= 6	No Rheum Diagnosis N = 4
Female	100% (7/7)	100% (6/6)	75% (3/4)
Caucasian	100% (7/7)	67% (4/6)	100% (4/4)
Age in Years (mean)	48	50	40
ILD	0% (0/7)	33% (2/6)	25% (1/4)
PAH	0% (0/7)	0% (0/6)	25% (1/4)
Raynaud's	86% (6/7)	50% (3/6)	75% (3/4)
Telangiectasia	86% (6/7)	17% (1/6)	75% (3/4)
Pitting Scars	0% (0/7)	17% (1/6)	25% (1/4)

Conclusion: Based on anti-Rpp25 ELISA and IP screening, anti-Th is fairly specific for SSc. However, anti-Th was also found in other connective tissue diseases with features associated with SSc and some cases had feature of SSc without sclerodermatous skin changes, thus may be classified sine-SSc.

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Systemic Sclerosis Disease Subset Is a Better Predictor Of Long Term Outcome Than Autoantibody Profile. Svetlana I. Nihtyanova[1], Voon H. Ong[2] and Christopher P. Denton[1]. [1]Royal Free and University College Medical School, London, United Kingdom, [2]The Royal Free and University College Medical School, London, United Kingdom.

Background/Purpose: Disease subset has been shown to strongly correlate with survival and risk of organ complications in patients with systemic sclerosis (SSc). Nevertheless evidence in the literature suggests that SSc-specific autoantibodies may be a better predictor of SSc-associated morbidity and mortality.

Methods: We explore subset and autoantibodies as predictors of outcome in a large, well-characterised cohort of consecutive unselected SSc patients.

Results: We analysed 649 contemporary SSc patients, 59% with limited cutaneous (lc)SSc and 41% with diffuse cutaneous (dc)SSc. Of those, 25% carried anti-centromere antibody (ACA), 23% anti-topoisomerase-I antibody (ATA), 10.5% anti-RNA polymerase antibody (ARA), 4.6% anti-U3RNP, 6% anti-U1-RNP, 4% anti-Pm-Scl, 18% were ANA positive, but without a defined ENA reactivity, 3.4% were ANA negative and 6% had other rarer antibodies, including Th/To, Ku, Jo1, Ro, La, SL, PL7, PL12, SL and XR.

As previously described, the strongest association with subset was observed in ACA+ patients, of whom 98% had lcSSc, while ARA+ subjects had predominantly dcSSc (91%). Although more frequent in dcSSc patients, 44% of ATA and 40% of anti-U3RNP subjects had lcSSc.

Cox regression analysis confirmed that ATA has the strongest positive association with pulmonary fibrosis (PF) – HR 3.8 (95%CI 2.9–5.1, $p<0.001$) and ACA has the strongest protective effect – HR 0.1 (95%CI 0.05–0.2, $p<0.001$). In this cohort there was also a significant negative association between PF and ARA (HR 0.5, 95%CI 0.3–0.9, $p=0.018$) and anti-U3RNP (HR 0.2, 95%CI 0.05–0.8, $p=0.023$). Although dcSSc is associated with significantly increased risk of PF, the effect of the antibodies was independent of subset.

Anti-U3RNP was associated with an increase (HR 2.9, 95%CI 1.4–5.8, $p=0.003$) while ATA with a reduction (HR 0.4, 95%CI 0.2–0.8, $p=0.01$) of the overall hazard for PH. Incidence of PH did not differ in the two subsets and correction for subset did not alter the predictive value of the antibodies.

We also confirmed the strong association between scleroderma renal crisis (SRC) and ARA (HR 7.5, 95%CI 4.2–13.2, $p<0.001$) and the protective role of ACA in SRC patients (HR 0.06, 95%CI 0.01–0.4, $p=0.005$), which were observed both within the subsets and for the cohort as a whole. There was also a negative association between SRC and ATA (HR 0.4, 95%CI 0.15–0.9, $p=0.037$) in the whole group, but in the subset analysis the effect held only for dcSSc patients. We found no associations between cardiac SSc and any of the antibodies.

The only antibody specificity that demonstrated significant association with survival in the whole cohort was ACA (HR 0.7, 95%CI 0.5–0.9, $p=0.022$), although in the analysis within subsets the association was no longer significant, suggesting that the better survival among ACA+ patients is due to the predominantly limited skin involvement in this group.

Conclusion: While ANA reactivities are strong predictors of organ complications, generally independent of disease subset, they correlate poorly with survival. Disease subset is a much better predictor of mortality and this may reflect severity rather than presence of individual organ-based complications.

Disclosure: S. I. Nihtyanova, None; **V. H. Ong**, None; **C. P. Denton**, None.

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Impact Of Male Sex On Survival In Systemic Sclerosis. Haseena Hussein[1], Peter Lee[2], Cathy Chau[3] and Sindhu R. Johnson[4]. [1]Toronto Scleroderma Research Program, Mount Sinai Hospital, Toronto Western Hospital, University of Toronto, Toronto, ON, [2]Mt. Sinai Hospital, Toronto, ON, [3]Toronto Scleroderma Research Program, Toronto Western Hospital, Mount Sinai Hospital, University of Toronto, Toronto, ON, [4]Division of Rheumatology, Toronto Western Hospital, University Health Network Pulmonary Hypertension Programme, Toronto General Hospital, Mount Sinai Hospital and University of Toronto, Toronto, ON.

Background/Purpose: Systemic sclerosis (SSc) has a female predominance with a female-to-male ratio of 3:1. Sex differences have been seen in many autoimmune diseases; however, little is understood about the effect of sex on SSc disease manifestations and survival. The objectives of this study were to evaluate differences in survival and disease manifestatons between males and females with SSc.

Methods: We conducted a retrospective cohort study of patients from the Toronto Scleroderma Program who fulfilled the American College of Rheumatology (ACR) classification criteria for SSc and were >16 years of age. We evaluated differences in age of onset, disease manifestations, serology, and survival between males and females.

Results: 907 patients (745 females, 162 males) were included. Males more frequently had diffuse SSc than women (45% versus 31%, $p = 0.007$). Men were more likely to have renal crisis (10% versus 7%), abnormal nail fold capillaries (30% versus 25%), digital ulcers (35% versus 32%), esophageal dysmotility (89% versus 85%), telangiectasia (81% versus 77%), and interstitial lung disease (42% versus 32%). Females more frequently had anticentromere antibodies (19% versus 9%), pulmonary arterial hypertension (38% versus 33%), and Raynaud's phenomenon (96% versus 94%). There were 186 deaths (37 males, 149 females). Males had increased mortality compared to females (Hazard Ratio (HR) 1.56, $p=0.02$). The median survival time was 17.3 years for males and 24.7 years for females. After adjusting for differences in SSc subtype, serology and presence of interstitial lung disease, men still had increased mortality compared to females (HR 1.64, $p = 0.009$).

Conclusion: Males with SSc have an increased burden of disease and decreased survival compared to females with SSc.

Disclosure: H. Hussein, None; **P. Lee**, None; **C. Chau**, None; **S. R. Johnson**, None.

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Early Systemic Sclerosis: Marker Autoantibody Positive Patients Have A Faster Pace Of The Disease. Gabriele Valentini[1], Antonella Marcoccia[2], Michele Iudici[1], Serena Vettori[1] and Giovanna Cuomo[1]. [1]Rheumatology Unit, Second University of Naples, Naples, Italy, [2]Angiology Unit, Sandro Pertini Hospital, Rome, Italy.

Background/Purpose: To investigate whether patients affected with any of the 3 subsets of early systemic sclerosis (SSc) i.e. Raynaud's Phenomenon (RP) with SSc marker autoantibody (ACA or anti-Scl70 or anti-RNA polymerase III or anti-fibrillarin or anti-Th/To) and typical capillaroscopic findings (megacapillaries and/or avascular areas) (subset I); or autoantibody positive only (subset II); or capillaroscopy positive only (subset III) (1) and unsatisfying the 2012 ACR/EULAR classification criteria for SSc (2) at admission differ in the lag time to satisfy the new SSc classification criteria.

Methods: Early SSc patients consecutively admitted to a Rheumatology and an Angiology center and unsatisfying the 2012 ACR/EULAR classification criteria for SSc at admission, were subdivided into the 3 above referred subsets and followed-up for 7–101 months (median 45).

They were re-evaluated six-monthly by history, clinical examination, B-mode echoDopplercardiography and Lung functional study including DLCO evaluation and yearly by lung HRCT to assess whether and when each of them satisfied new ACR/EULAR classification criteria i.e. developed a disease score ≥9 (2).

Results: During the follow-up, 11 out of 21 subset I patients (52.3%) (baseline score 8); 10 out of 15 subset II patients (66.6%) (baseline score 6) and 0 out of 24 subset III patients (baseline score 5–7) satisfied the criteria; the difference being significant between each of the 2 autoantibody positive (subsets I and II) and the capillaroscopic positive-autoantibody negative subset (subset I versus III: X^2 by log rank test=17.45, p=0.0001; subset II versus III: X^2 =11.04, p=0.0009), no difference being detected between the 2 autoantibody positive subsets (X^2 =0.55, p=0.454). The 11 subset I patients satisfied the criteria because of the development of teleangectasias in 5 cases; puffy fingers in 3 cases; lung fibrosis in 2 cases; digital ulcers in 1 case. The 10 subset II patients did it because of the development of at least 2 of the following manifestations: scleroderma capillaroscopic pattern in 5 cases, teleangectasias in 5 cases, puffy fingers in 5 cases, digital ulcers in 3 cases, pulmonary hypertension in 1 case and lung fibrosis in 1 case. Despite the unfulfillment of the criteria, among the 24 subset III patients, 21 of whom already presented puffy fingers at baseline, 2 developed telangectasias, 1 digital ulcers, 4 a DLCO<80%.

Conclusion: We have recently pointed out that autoantibody positive early SSc patients differ from subset III patients in the pattern of activation markers (increased serum concentration of procollagen I carbossipropeptide versus increased serum concentration of E-selectin) and preclinical internal organ involvement (higher prevalence of decreased DLCO) (3). Here we point out that autoantibody positive patients present a faster pace of the disease.

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Quantifying Change In Pulmonary Function As a Prognostic Marker In Systemic Sclerosis-Related Interstitial Lung Disease. Owen Moore[1], Susanna Proudman[2], Nicole Goh[3], Tamera Corte[4], Hannah Rouse[1], Oliver Hennessy[1], Vivek Thakkar[5], Joanne Sahhar[6], Janet E. Roddy[7], Peter Youssef[4], Eli Gabbay[7], Peter Nash[8], Jane Zochling[9], Wendy Stevens[5] and Mandana Nikpour[10]. [1]St. Vincent's Hospital, Melbourne, Australia, [2]Royal Adelaide Hospital, Adelaide, Australia, [3]Alfred Hospital, Melbourne, Australia, [4]Royal Prince Alfred Hospital, Sydney, Australia, [5]St Vincent's Hospital, Melbourne, Australia, [6]Monash Medical Centre, Clayton, Australia, [7]Royal Perth Hospital, Perth, Australia, [8]Nambour Hospital, Sunshine Coast, Australia, [9]Menzies Research Institute Tasmania, Hobart, Australia, [10]University of Melbourne, Fitzroy, Australia.

Background/Purpose: Interstitial lung disease (ILD) is a leading cause of mortality in systemic sclerosis (SSc) but it is not severe or progressive in all patients. Serial pulmonary function tests (PFTs) can predict outcomes but there are no established data regarding what is a clinically meaningful decline in these variables in SSc-ILD. We sought to quantify change in pulmonary function as a predictor of outcome in SSc-ILD.

Methods: Patients with SSc with ILD defined by high resolution CT lung scan were identified through a nationwide cohort study. All PFTs performed during follow-up, including forced expiratory volume in one second (FEV1) (L), forced vital capacity (FVC) (L), FEV1/FVC ratio (%), diffusing capacity of the lung for carbon monoxide (DLCO) (ml/min/mmHg) and DLCO by alveolar volume ratio (DLCO/VA) (ml/min/mmHg/L) were retrieved. Demographic and disease-related data were prospectively collected. The rate of change over four years in the absolute value for each variable was calculated for each patient using a regression line of best fit. Percentage change in absolute values over the first year of follow-up from diagnosis of SSc-ILD (±90 days) was determined. The composite outcome variable was deterioration, defined as need for home oxygen or lung transplantation, or death. Univariable Cox regression models were used to determine the relationship between each of rate of decline and percentage decline in each PFT variable and outcome. Receiver operating characteristics (ROC) curves were used to determine the best cut-off points to predict adverse outcomes.

Results: Among 264 patients in whom PFT data were available from time of ILD diagnosis, there were 49 events (38 deaths, 10 prescribed supplemental oxygen, one lung transplant) over a mean (±SD) follow-up of 3.0 (±1.7) years. The rates of decline over time in each of FVC, DLCO & DLCO/VA were significantly predictive of deterioration or death (hazard ratios [HR] of 0.06, 0.637 and 0.06 respectively, p values all <0.0001). Cut-off values of zero (i.e. no overall change in PFTs over four years) gave the optimal sensitivity-specificity trade-off with negative predictive values (NPVs) of 88–96%. The percentage changes in FVC, DLCO and DLCO/VA over one year from diagnosis (±90 days) were significantly associated with outcome (HRs 1.06 [p<0.04], 1.07 [p<0.0001] and 1.05 [p<0.04] respectively). The best trade-off between sensitivity and specificity was a decline in FVC of 10% and in DLCO and DLCO/VA of 15% with NPVs of 92–93%. A decline in DLCO/VA of 15% predicted a poor outcome with a likelihood ratio of 7.62.

Conclusion: The course that SSc-ILD takes is evident within the first 1–4 years following its diagnosis. Patients who have no decline in PFTs over the first 4 years do well. As seen in idiopathic pulmonary fibrosis, a decline within the first year in FVC of 10% or more and DLCO or DLCO/VA of 15% or more bodes badly and identifies patients who should be monitored more closely and considered for therapy.

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Validation Of a Novel Radiographic Scoring System For Calcinosis Affecting The Hands Of Patients With Systemic Sclerosis. Lorinda Chung[1], Antonia Maria Valenzuela Vergara[2], David Fiorentino[3], Kate Stevens[2], Shufeng Li[2], Jonathan Harris[4], Charles E. Hutchinson[5], Shervin Assassi[6], Lorenzo Beretta[7], Santhanam Lakshminarayanan[8], Tatiana Rodriguez Reyna[9], Christopher P. Denton[10], Rebecca G. Taillefer[11], Solene Tatibouet[12], Ariane Herrick[13] and Murray Baron[14]. [1]Stanford Univ Medical Center, Palo Alto, CA, [2]Stanford University School of Medicine, Stanford, CA, [3]Stanford University School of Medicine, Redwood City, CA, [4]Salford Royal Hospital, Manchester, United Kingdom, [5]University of Warwick, Coventry, United Kingdom, [6]University of Texas Health Science Center at Houston, Houston, TX, [7]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [8]University of Connecticut School of Medicine, Farmington, CT, [9]Instituto Nacional de Ciencias Médicas y Nutrición, Mexico City, Mexico, [10]Royal Free and University College Medical School, London, United Kingdom, [11]University of Montreal, Montreal, QC, [12]McGill University, Montreal, QC, [13]University of Manchester, Salford, United Kingdom, [14]Jewish General Hospital, Montreal, QC.

Background/Purpose: Calcinosis affects approximately 25% of patients with systemic sclerosis (SSc) and is associated with substantial morbidity. There are currently no validated outcome measures to assess calcinosis severity. We sought to develop and validate a novel radiographic scoring system for calcinosis affecting the hands of patients with SSc for potential use in future clinical trials.

Methods: We assessed the reliability of two types (termed "simple" and "complex") of radiographic scoring systems using hand radiographs from patients with SSc obtained from the University of Manchester. The simple scoring system defined calcinosis severity as mild (single site of low density), moderate (medium density at one or more sites OR a single site of high density), or severe (more than one site of high or mixed density). The complex scoring system was calculated as the sum of scores for 22 weighted areas affecting each hand: % area coverage (0–100) × density (1–3) × weight for each area (Figure 1). Following a 1-hour teleconference training session, 12 investigators (8 rheumatologists, 1 dermatologist, 3 radiologists) scored 12 hand radiographs in random order using both simple and complex scoring systems. After a minimum of 24 hours, each investigator re-scored at least one radiograph. Inter-rater and intra-rater reliability were assessed using a Fleiss kappa or weighted kappa coefficient for the simple system, and intraclass correlation coefficient (ICC) for the complex system.

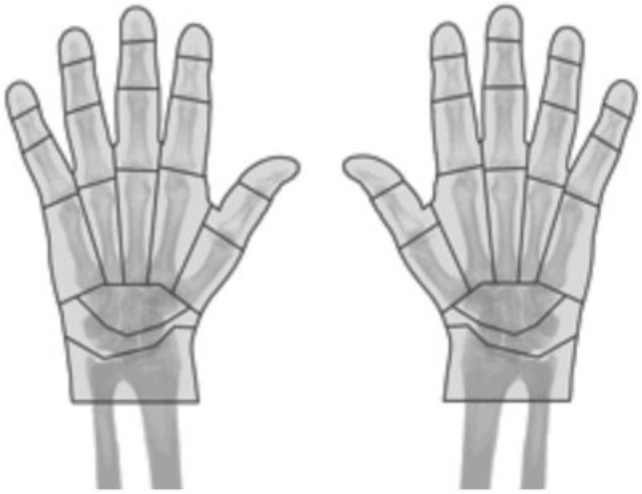

Figure 1. Anatomic Regions of Hand Radiographs for Complex Scoring System

Results: Of 144 assessments, 10 were categorized as mild, 67 as moderate, and 67 as severe using the simple scoring system. The mean time to complete the complex scoring system was significantly longer than the simple scoring system (4.0 vs. 0.4 min, $p<.0001$), and increased with increasing severity of calcinosis (2.0±1.2 min for mild, 3.2±2.3 min for moderate, 5.1±3.7 min for severe). Overall inter-rater reliability for the simple scoring system was poor (kappa=0.39, 95% CI 0.1–0.52), but improved if dichotomized as mild/moderate vs. severe (kappa=0.51, 95% CI 0.26–0.7). Inter-rater reliability was excellent for the complex scoring system (ICC=0.89, 95% CI 0.86–0.92). Intra-rater reliability was moderate for the simple scoring system (kappa=0.67, 95% CI 0.37–0.96), but almost perfect for the complex scoring system (ICC=0.93, 95%CI 0.89–0.97).

Conclusion: We developed a novel radiographic scoring system that accounts for the area coverage, density, and anatomic location of calcinosis affecting the hands in patients with SSc. This scoring system is feasible with excellent reliability and should undergo further validation testing for use in clinical trials.

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Diastolic Dysfunction Amongst Autoantibody Subgroups Of Patients With Diffuse Scleroderma. Cory Perugino, John Stephens, Colin O'Rourke and Soumya Chatterjee. Cleveland Clinic, Cleveland, OH.

Background/Purpose: Scleroderma or systemic sclerosis (SSc) is an autoimmune disease characterized by microangiopathy, tissue hypoxia, and fibrosis. At least seven different autoantibodies have been identified with distinct phenotypic associations. A recent study involving patients with limited and diffuse SSc found the prevalence of diastolic dysfunction to be 23%.[1] Serious cardiac involvement defined as symptomatic heart failure, arrhythmia, or pericardial effusion, has been associated with Scl-70 antibodies when compared to RNA polymerase III (Pol-III) positive patients.[2] The aim of this study was to compare prevalence of subclinical diastolic dysfunction in diffuse SSc patients with Pol-III antibodies or Scl-70 antibodies.

Methods: Forty two patients from a major tertiary referral center with known SSc and Pol-III antibodies provided a cohort of 18 patients after the exclusion of those with limited disease. Similarly, 540 patients diagnosed with SSc were screened for Scl-70 antibodies providing a cohort of 24 patients after the exclusion of those with limited disease phenotype. Demographic and echocardiographic indices for diastology were collected. Welch's two-sample t-test and Pearson's chi-squared test were used for continuous and categorical variables, respectively. Logistic regression was used to compare binary measurements and linear regression models for continuous measurements after adjusting for disease duration. A significance level of 5% was used for all analyses.

Results: By unadjusted analysis, 26% of the Pol-III patients had diastolic dysfunction, compared to 74% of the Scl-70 group. This difference reached statistical significance with a p-value of 0.035. After adjusting for disease duration, the estimated odds ratio of having diastolic dysfunction was 4.2 times higher for Scl-70 patients than for Pol-III patients. Although the latter finding did not reach statistical significance, it can be thought of as a trend with a p-value of 0.052. There was no evidence that the septal E/E′ ratio, lateral E/E′ ratio, E/A ratio, or left ventricular mass index differ between the two groups.

Conclusion: Diastolic dysfunction is prevalent amongst SSc patients with diffuse disease. Scl-70 and Pol-III antibodies are associated with diastolic dysfunction in patient with diffuse SSc. After adjusting for disease duration, Scl-70 patients had a proportionally higher prevalence of diastolic dysfunction than Pol-III patients with a trend towards significance. These autoantibodies may be markers of risk for developing myocardial dysfunction.

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Disclosure: C. Perugino, None; **J. Stephens**, None; **C. O'Rourke**, None; **S. Chatterjee**, None.

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Effects Of Extracoporeal Shock Wave Therapy To The Digital Ulcers Of Scleroderma:a Pilot Study. Shinichiro Saito[1], Yukiko Kamogawa[1], Kyohei Nakamura[1], Ryu Watanabe[1], Tsuyoshi Shirai[1], Yoko Fujita[1], Hiroshi Fujii[1], Yuko Shirota[1], Tomonori Ishii[1], Hideo Harigae[1], Katsuko Kikuchi[1] and Yasushi Kawaguchi[2]. [1]Tohoku University, Sendai, Japan, [2]Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Vasculopathy, immunological abnormalities and excessive tissue fibrosis are key elements in the pathogenesis of Scleroderma (SSc). In winter, patients often display Raynaud syndrome, which sometimes causes digital skin ulcers. As these ulcers do not depend on autoimmune or abnormal coagulation, conventional immunosuppressive therapies and anticoagulants are often ineffective. Extracorporeal shock waves (ESW) have been induced primarily in urology for lithotripsy, as its low energy application has yielded evidence for the successful treatment of myocardial ischemia and skin ulcers caused by diabetes. The rationale of this effectiveness is that, new angiogenesis induced by VEGF produced at arteries in the applied area. We tried to introduce ESWT to skin with Raynaud and digital ulcers of SSc.

Methods: We enrolled 9 SSc patients with newly observed digital ulcers: 8 females and 1 male. All 9 patients had been treated with currently available anti-coagulant therapies, especially 6 patients had received intravenous administration of prostaglandin E_1. One ESW therapies (ESWT) sitting consisted of 100 impulses at 0.08～0.25 mJ/mm^2 per area, 20 areas in both hands and 15 in both feet, totaling 7000 impulses. Sitting were done once a week for 9 weeks. We examined the patients, counting the number of skin ulcers, and checking the Rodnan Skin Score (RSS) as well as patient disability index (HAQ, EQ-5D), pain VAS and objective pain index using PainVision™, before and after ESWT. Additionally, the surface skin temperature of all fingers was measured by thermography.

Results: Numbers of skin ulcers were reduced from 5.4 per person to 1.1 by the last treatment of ESWT. Totally, 18 large ulcers (>5mm) were observed from 9 patients before ESWT, 10 disappeared and average size was diminished from 10.8mm into 3.7mm after ESWT. Average HAQ score of 9 patients was improved from 0.57 to 0.43 and other index as EQ5D and PainVision™ scores also showed improvement. Fingers with the lowest temperatures displayed a rise in temperature. This treatment was minimally invasive and could be repeated without any side effects.

Conclusion: ESWT may be a safe and efficacious treatment that can be used as a type of therapy for indolent digital ulcers caused by SSc.

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HRCT Predictors Of Decline In FVC% predicted—Implications For Cohort Enrichment For Scleroderma Lung Disease (SLD) Trials. Dinesh Khanna[1], Chi-hong Tseng[2], Robert D. Suh[3], Fereidoun Abtin[4], Athol U. Wells[5], Donald Tashkin[6] and Jonathan Goldin[7]. [1]University of Michigan, Ann Arbor, MI, [2]University of California Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [3]Ronald Reagan UCLA Medical Center, Los Angeles, CA, [4]University of California Los Angeles Medical Center, Santa Monica, CA, [5]Department of Radiology, London, United Kingdom, [6]David Geffen School of Medicine at UCLA, Los Angeles, CA, [7]David Geffen School of Medicine at UCLA, Santa Monica, CA.

Background/Purpose: Moderate-to-severe HRCT-defined lung involvement (total lung involvement or fibrosis) is a predictor of decline in FVC% predicted and mortality in SLD. Various staging systems have been proposed to evaluate lung involvement in SLD: 1. Visual read of maximum fibrosis score (MaxFib) calculated from the zone with the worst extent of abnormality (maximum score), 2. Goh and Wells scoring system of limited vs. extensive disease (visual read of HRCT for total lung involvement of >20% vs. < 20% and incorporation of FVC% predicted of >70% or < 70%, if indeterminate HRCT read), and 3. computer-aided diagnosis (CAD) of quantitative scoring for percentage with fibrosis (QLF) and total lung involvement (QILD) Our objective was to evaluate the performance of different staging systems in the placebo cohort of SLS-I over 1-year period.

Methods: QLF and QILD were assessed using the CAD and maximum fibrosis score (MaxFib) was calculated from the zone with the worst extent of abnormality (maximum score) based on average of 2 thoracic radiologists. 3 thoracic radiologists read the baseline HRCTs from the SLS-I for total lung involvement (as proposed by Goh and Wells) and read by 5% increments and for indeterminate results (15–25% lung involvement), FVC% was used to classify patients into limited vs. extensive disease. Paired t-test was used to assess for statistical significance for change in FVC% predicted (relative change) over 1-year.

Results: 79 patients were randomized to placebo group; 55 completed the 1-year study. Of these, 48 had FVC% data at baseline and 12 months and good quality HRCT and were included in the analysis. 60% of patients had MaxFib of >25%, 66% were classified as extensive disease, 11% and 79% had >20% QLF and QILD, respectively. Greater cut off for each staging system was associated with greater decline in FVC% predicted at 1-year (Table).

	N	Decline in FVC% predicted, Mean (SD)	P value
HRCT Fibrosis score			
0–25%	**19**	**1.1 (14.2)**	**.009**
26–100%	**29**	**−9.6 (12.5)**	
Limited disease	**16**	**2.0(15)**	**.009**
Extensive disease	**32**	**−9.0 (12)**	
Whole QILD			
< 20%	**10**	**−0.03 (8.08)**	**.07**
> 20%	**37**	**−6.8 (15.3)**	
Whole QLF			
< 20%	**42**	**−4.2 (13.8)**	**.09**
> 20%	**5**	**−15.4 (15.4)**	

Conclusion: HRCT-defined lung involvement is a predictor of decline in FVC% predicted over 1 year using different staging systems. The choice of system incorporated in a trial depends on the feasibility and available expertise.

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Clinical Characteristics Of Scleroderma Patients With Calcinosis In a Single-Center Cohort. Danielle Velez[1] and Vivien M. Hsu[2]. [1]RWJMS, South Plainfield, NJ, [2]RWJ Med Schl Scleroderma Prog, New Brunswick, NJ.

Background/Purpose: Calcinosis is soft tissue deposition of calcium hydroxyapatite crystals in scleroderma spectrum disorder (SSc) patients. In our cohort, ≤5% of SSc patients have confirmed calcinosis. Common in pressure areas, deposits vary in size and shape, are solid or semi-solid, and range from asymptomatic to widespread and painfully disabling. Risk factors, pathophysiology, and clinical outcomes in SSc-calcinosis patients (SSc-Ca) are unknown, and there is no cure. Therefore, identifying those at risk may lead to understanding of calcinosis development and better management. Herein, we compare clinical characteristics of 17 SSc-Ca patients to 10 control SSc patients without calcinosis.

Methods: Outpatient SSc subjects were invited to enroll as they were seen consecutively in the UMDNJ Scleroderma Program. Clinical information was obtained and calcinosis confirmed by the examining physician or imaging. Fisher's Exact Test was used to measure significance.

Results: Table 1 summarizes clinical characteristics per group. SSc-Ca patients were generally older Caucasian females with limited SSc of longer disease duration, with more bowel (OR 5.71, p = 0.107) and fewer pulmonary complications (OR 0.14, p = 0.046). Calcinosis often presented years after SSc onset (mean 16 y, range 1–41 y). About 1/3 of each group also had polyarthritis or myositis.

Table 1. Clinical characteristics of SSc subjects with and without calcinosis

	Calcinosis (n = 17)	*Control* (n = 10)	*P value*
Gender			
Male	15	5	
Female	2	5	
Race			
Caucasian	16	8	
Non-Caucasian	1	2	
Ave age ± SD (y)	60.3 ± 17.05	48.0 ± 13.75	
SSc mean duration (y)			
From Raynaud	20.9 ± 12.67	10.0 ± 9.76	0.0272
From non-Raynaud	26.3 ± 15.36	9.7 ± 9.99	0.0057
SSc type			
Limited	10	4	
Diffuse	7	6	
Organ involvement (%):			
Small bowel	58	20	0.046
Pulmonary fibrosis	35	80	
Pulmonary hypertension	11	20	
Osteoporosis %	59	10	0.018
% myositis, polyarthritis overlap	35	40	

In this cohort, the most common calcinosis sites were fingertips (100%), IP joints (52%), and elbows (35%). Most subjects (80%) did not consider themselves disabled unless deposits were painful or affected function. Extensive extremity and trunk calcinosis completely disabled 2 patients. Over 50% took analgesics or sought surgical removal as the most common therapy. SSc-Ca patients were more likely to have osteoporosis (OR 12.86, p = 0.018); we observed 2 subjects whose bone density deteriorated rapidly as their disabling calcinosis became widespread.

Laboratory studies showed normal electrolyte and PTH levels in both groups. All subjects were taking vitamin D supplements. The most common antibody was anti-centromere in 44% of SSc-Ca patients and Scl70 in 67% of control patients.

Conclusion: Older Caucasian female subjects with limited SSc more commonly developed calcinosis years after SSc onset, usually involving the hands/fingers. SSc-Ca subjects tended to have osteoporosis, as well as more SSc-related small bowel, but fewer pulmonary complications. It is unclear why some SSc patients develop calcinosis. More studies are needed to evaluate risk factors and clinical outcomes in SSc-Ca patients.

Disclosure: D. Velez, None; **V. M. Hsu**, None.

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Lung Function and Survival In Systemic Sclerosis Associated Interstitial Lung Disease. Samar M. Shadly[1], Sindhu R. Johnson[2], Cathy Chau[3] and Theodore K. Marras[4]. [1]University Health Network Interstitial Lung Diseases Program, University Health Network and Mount Sinai Hospital, Toronto, ON, [2]Division of Rheumatology, Toronto Western Hospital, University Health Network Pulmonary Hypertension Programme, Toronto General Hospital, Mount Sinai Hospital and University of Toronto, Toronto, ON, [3]Toronto Scleroderma Research Program, Toronto Western Hospital, Mount Sinai Hospital, University of Toronto, Toronto, ON, [4]University Health Network Interstitial Lung Diseases Program, University Health Network and Mount Sinai Hospital, University of Toronto, Toronto, ON.

Background/Purpose: We sought to assess for an association between baseline forced vital capacity (FVC) and diffusion capacity (DLCO) with mortality, and to identify threshold values of forced vital capacity (FVC) and diffusion capacity (DLCO) that predict mortality in systemic sclerosis-associated interstitial lung disease (SSc-ILD).

Methods: The Toronto ILD Program and the Toronto Scleroderma Program cohorts were used to identify SSc-ILD patients. Data were retrospectively collected using a standardized electronic database. The primary outcome was time to all-cause mortality or lung transplant. Kaplan Meier analysis was used to evaluate the association of threshold values of baseline FVC and DLCO and survival. Cox proportional hazards models were used to evaluate the adjusted association of FVC and DLCO with mortality or transplantation.

Results: 1200 patients with SSc were screened to identify 188 SSc-ILD patients, 140 (75%) were female, and 69% had never smoked. 55 (29.3%) patients had pulmonary hypertension. The mean±standard deviation (sd) baseline FVC was 78.1%±20.4% predicted, and DLCO was 59.5%±17.9% predicted. The mean (sd) baseline 6-minute walk test distance was 412 (119) meters. 45 (23.9%) patients received immunosuppressive treatment at baseline. 38 (20%) patients died, and five (2.7%) patients underwent lung transplant. Baseline FVC <80% predicted (p=0.003) or DLCO<80% predicted (p=0.01) were associated with mortality. Unadjusted survival analysis found baseline FVC (Hazard Ratio (HR) 0.97 (0.95, 0.98), p <0.001) and DLCO (HR 0.97 (0.96, 0.99), p=0.002) were associated with survival. In the adjusted analysis, FVC (HR 0.93, p=0.007) and smoking history (HR 5.08, p=0.049) were both independently associated with survival, however DLCO (HR 0.98, p=0.33), age (HR 1.00, p=0.77), pulmonary hypertension (HR 1.97, p=0.46), SSc-specific antibodies (HR 0.50, p=0.39), and immunosuppressive use (HR 0.64, p=0.64) were not.

Conclusion: Our study confirms and extends previous findings that even a mild decrease in baseline FVC (< 80%) is predictive of mortality. However, we did not observe a robust association between DLCO and mortality.

Disclosure: S. M. Shadly, None; **S. R. Johnson**, None; **C. Chau**, None; **T. K. Marras**, None.

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Blood Flow In The Hands Of a Predefined Homogeneous Systemic Sclerosis Population: The Presence Of Digital Ulcers and The Improvement With Bosentan. Jessica Meijs[1], Annemie J.M. Schuerwegh[1], Alexandre E. Voskuyl[2], Joanne P.J. Bloemsaat-Minekus[3] and Madelon C. Vonk[4]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands, [3]Actelion, Woerden, Netherlands, [4]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.

Background/Purpose: Digital ulcers (DU) are complications of systemic sclerosis (SSc) and arise as a result of ischaemia due to vasculopathy of the digital arteries (1). Rosato et al (2) found that SSc patients, who had pulmonary arterial hypertension (PAH) and were treated with bosentan, had improved blood flow in the hands over time. However, as patients with active DU were excluded from their study they were unable to relate blood flow to the presence of DU. This is the first study to examine the relationship between blood flow in the hands of SSc patients and the presence of digital ulcers (DU). Additionally, the effect of bosentan on blood flow in the hand was assessed in a subset of patients who had reduced blood flow relative to healthy subjects.

Methods: Adult patients with SSc and a recent history of DU and healthy subjects were included. Patients were classified into 4 subgroups: no current DU or pitting scars; pitting scars only; new DU; or persistent DU. The hand was categorised into three regions of interest (ROI) and blood flow was measured by laser Doppler perfusion imaging at baseline, 4 and 12 weeks. Patients who had a reduction in blood flow of more than 50% relative to healthy control subjects in ROI 1 on baseline, in at least one of the hands, were treated with bosentan for 12 weeks.

Results: Fifty-two SSc patients and 51 healthy subjects and were included in the analysis. There was no significant difference in blood flow in the hand across the patient subgroups at baseline. Sixteen SSc patients had a reduction of blood flow of ≥50% versus healthy subjects and received bosentan. Bosentan significantly (p<0.05) increased the blood flow in the whole hand after 12 weeks compared with baseline (shown in figure 1).

NO FIGURE SUPPLIED FOR ABS0686Figure 1.** Change in blood flow from baseline to week 4 and 12 with bosentan treatment

Conclusion: No relationship was found between blood flow in the hands of SSc patients and presence of DU. After 12 weeks of bosentan treatment the blood flow had increased in the SSc patients but had not normalised to that of healthy subjects.

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Disclosure: J. Meijs, Actelion Pharmaceuticals, 2; **A. J. M. Schuerwegh**, Actelion Pharmaceuticals, 5; **A. E. Voskuyl**, Actelion Pharmaceuticals, 5; **J. P. J. Bloemsaat-Minekus**, Actelion Pharmaceuticals, 3; **M. C. Vonk**, Actelion Pharmaceuticals US, 5.

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Role Of Class II Human Leukocyte Antigens In The Progression From Early To Definite Systemic Sclerosis. Barbara Vigone, Alessandro Santaniello, Maurizio Marchini, Gaia Montanelli, Monica Caronni, Adriana Severino, Stefania Celeste and Lorenzo Beretta. Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

Background/Purpose: Criteria for the diagnosis of Early Systemic Sclerosis (EaSSc) have been formalized by LeRoy and Medsger in 2001 and later validated by Koenig et al (2008), who showed that the vast majority of EaSSc patients develops a definite SSc within few years from EaSSc. The genetic factors that may affect the progression from early to definite SSc are poorly studied.

Methods: One-hundred-fifty-eight consecutive subjects with Raynuad's phenomenon (RP) fulfilling the EaSSc criteria and no other manifestation indicative of SSc (Fransen et al, 2012) at referral were considered. All the patients underwent high-resolution HLA Class II typing by means of PCR with sequence-specific primers ad were retrospectively evaluated in an observational fashion for the appraisal of definite SSc according to the ACR/EULAR proposed criteria for SSc (Pope et al, 2012): patients with a score >9 are classified as definite SSc, where the single items scores are: skin thickening of the fingers of both hands extending proximal to the MCP joints (9); highest between puffy fingers (2) and skin thickening of the fingers (4); highest between digital tip ulcers (2) and pitting scars (3); telangiectasia (2); abnormal nailfold capillaries (2); lung involvement (interstitial lung disease/ PAH- 2), RP (3); SSc-specific antibodies (3). The time-to-event was analyzed by means of Kaplan-Meier and Cox regression analysis; multiple testing correction was performed by 1000-fold permutations test.

Results: One-hundred-nine subjects (69%) developed a definite SSc by the end of the 10-years follow-up period, with a median estimated time-to-progression equal to 45 months from referral. Twenty-eight (17.7%) patients tested positive for anti-Topoisomerase I antibodies, 96 (60.8%) for anti-centromere antibodies (ACA) and 17 (10.8%) for other SSc-specific antibodies. ACA-positivity was associated with a reduced the risk of progression (median=55 vs 23 months, HR=0.67, CI=0.458–0.979, p=0.038). The presence of the HLA DQ5-DR1 haplotype (HLA-DRB1*0101 - HLA-DQA1*0101(4) - HLA-DQB1*0501) strongly reduced the time and the risk of progression (median=108 vs 45 months; HR=0.388, CI=0.211–0.712, p=0.002, permutation p=0.009); the effect of the HLA DQ5-DR1 haplotype was independent from ACA positivity or from the duration of RP in a stepwise multivariate model. Similar results were observed when the single alleles within the HLA-DQ5-DR1 haplotypes were analyzed.

Conclusion: The occurrence of the HLA DQ5-DR1 haplotype reduces the risk of progression from early to definite SSc independently from the autoanticorpal subsets and other factors that may affect the time-to-progression.

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Minimal Clinically Important Investigations In Systemic Sclerosis. Jessica Meijs, Anne A. Schouffoer, Nina Ajmone Marsan, Maarten K. Ninaber and Tom W.J. Huizinga. Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: The optimal management of Systemic Sclerosis (SSc) is a challenge due to the complexity of early diagnosis and identification of patients who are at risk of progressive disease. Furthermore, there is no consensus about minimal clinically relevant treatment effect outcome measurements [1]. Besides that, randomized clinical trials about medications that are disease modifying for SSc in terms of disease activity are scarce [2]. The aim of our study was to examine the minimally clinically important investigations for starting immunosuppression in patients with SSc.

Methods: For this study the baseline visits of SSc patients referred to an academically day patient clinic for a two-day health care program between 2009 and 2012 were recorded. This annual program compromised visits to health care professionals and laboratory investigation, HRCT-thorax, lung function, Cardiopulmonary Exercise Test (CPET), echocardiography, ECG, SSc Health Assessment Questionnaire (SHAQ) and Short Form-36 (SF-36). After 2 weeks a multidisciplinary consultation resulted in a change of treatment if appropriate. The change of treatment was divided in start with immunosuppression versus no start with immunosuppression for the analysis. Logistic regression analysis was used to determine the relationship between start and no start with immunosuppression as dependent variable and clinical parameters as independent variables.

Results: Two hundred twenty-seven patients participated in the day care program for at least one visit. Their mean age was 54 years, 82% of the patients were female and 75 patients had a diffuse cutaneous SSc (DcSSc). Fourteen patients had a previous autologous haemopoietic stem cell transplantation and were excluded for the logistic regression analysis. Forty-six patients started with immunosuppression after visiting the day patient clinic.

The univariate regression analysis showed that DcSSc, younger age, shorter disease duration, shorter duration of Raynaud Phenomenon and organ/skin involvement, contractures, dyspnea, crackles, not suffering from calcinosis, higher MRSS, anti-Scl70 positivity, anticentromere negativity, higher ESR, higher CRP, lower Vital Capacitiy, alveolitis on HRCT, pericardial fluid, and the CPET parameters lower wattage and lower VO2 max of predicted were significantly associated with the start of immunosuppression. Multivariate regression analysis showed that male gender, shorter disease duration, higher MRSS, anticentromere negativity, alveolitis and lower VO2 max of predicted were significantly associated with the start of immunosuppression.

Conclusion: Autoantibodies, MRSS, HRCT-thorax and CPET are minimally clinical important investigations that are advocated in clinical evaluation.

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Subclinical Biventricular Systolic Function Is Impaired In Patients With Systemic Sclerosis: A Speckle Tracking-Based Echocardiographic Study. Sukru Taylan Sahin[1], Selen Yurdakul[2], Neslihan Yilmaz[3], Yonca Cagatay[3], Saide Aytekin[1] and Sule Yavuz[3]. [1]Istanbul Florence Nightingale Hospital, Cardiology, Istanbul, Turkey, [2]Bilim University, Faculty of Medicine, Cardiology Department, Istanbul, Turkey, [3]Bilim University, Faculty of Medicine, Rheumatology Department, Istanbul, Turkey.

Subclinical biventricular systolic function is impaired in patients with systemic sclerosis: A speckle tracking-based echocardiographic study

Background/Purpose: Myocardial involvement is associated with poor prognosis in patients with systemic sclerosis (SSc). In the present study we aimed to evaluate subclinical left ventricular (LV) and right ventricular (RV) systolic dysfunction in SSc patients without any cardiovascular disease, by using a strain imaging method, "speckle tracking echocardiography" (STE).

Methods: Thirty-six SSc patients were screened, 7 patients were excluded because of ischemic heart disease. We studied 29 patients with SSc (diffuse/ limited: 15/14) and 20 age and sex-matched healthy controls(HC), without any cardiac disease and with preserved LV-EF. Conventional echocardiography and STE-based strain imaging were performed to assess biventricular deformation analyse. Association with anti-Scl 70 was sought in patients with SSc.

Results: In SSc patients (Female/Male: 25/4) the mean age was 47.7 years. Anti Scl-70 was positive in 13 (44.8%) patients. Left ventricular conventional echocardiographic measurements (LV end diastolic diameter, LV end systolic diameter and LV EF) were similar between SSc and HC. Regarding RV conventional parameters, right atrium was significantly enlarged, tricuspidal annular plane systolic excursion (TAPSE) was decreased and systolic pulmonary artery pressure was increased in SSc compared to HC ($p<0.001$). Both LV and RV longitudinal peak systolic strain/ strain rate were significantly impaired in SSc, demonstrating subclinical LV and RV systolic dysfunction ($p\leq0.001$) (table).

Table. Conventional echocardiography and Speckle tracking echocardiography (STE) results of SSc patients and healthy controls.

	SSc	HC	p value
Right atrium (cm)	3.71 ± 0.30	3.43 ± 0.20	0.004
TAPSE (cm)	2.01 ± 0.41	2.82 ± 0.54	0.0001
Systolic PAB (mmHg)	34.13 ± 8.96	22.07 ± 3.87	0.0001
LV longitudinal peak systolic strain (%)	13.3 ± 1.51	18.87 ± 3.78	0.0001
LV strain rate (1/s)	0.31 ± 0.11	1.77 ± 0.54	0.0001
RV longitudinal peak systolic strain (%)	11.83 ± 1.93	14.19 ± 2.29	0.001
RV strain rate (1/s)	0.30 ± 0.18	2.66 ± 0.4	0.0001

Values were presented as mean ±SD. TAPSE;tricuspidal annular plane systolic excursion, PAB; pulmonary artery pressure, LV; left ventricle, RV; right ventricle

We obtained significant positive correlation between TAPSE and RV longitudinal peak systolic strain/strain rate ($r=0.744$ and $r=0.706$, respectively, $p=0.0001$). Systolic PAB was negatively correlated with both LV and RV longitudinal peak systolic strain/strain rate (LV: $r=-0.552$ and $r=-0.637$, respectively, $p<0.001$ and RV: $r=-0.547$ and $r=-0.638$, respectively, $p=0.001$). Anti Scl -70 positive patients had impaired LV longitudinal peak systolic strain and strain rate values, compared to the others, however the difference did not reach statistical significance (13.01 ± 1.26 % to 13.04 ± 1.90 %, $p=0.96$ for strain; 0.30 ± 0.06 1/s to 0.31 ± 0.15 1/s, $p=0.79$ for strain rate).

Conclusion: SSc is associated with myocardial systolic dysfunction. Deformation analysis by STE-based strain imaging is a novel promising modality allowing for detailed measurement of early deterioration in biventricular systolic function in patients with SSc.

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Assessment Of The New American and European Classification Criteria For Systemic Sclerosis In The Norwegian Systemic Connective Tissue Disease and Vasculitis Registry. Anna-Maria Hoffmann-Vold[1], Torhild Garen[2], Oyvind Midtvedt[1] and Øyvind Molberg[1]. [1]Oslo University Hospital, Oslo, Norway, [2]Oslo University Hospital Rikshospitalet, Oslo, Norway.

Background/Purpose: To assess the newly established ACR/EULAR classification criteria for systemic sclerosis [1] (SSc) in a large Norwegian SSc registry cohort.

Methods: The Norwegian systemic connective tissue disease and vasculitis registry (NOSVAR) at the Department of Rheumatology, Oslo University Hospital (OUH) was interrogated for all systemic sclerosis (SSc) patients. All the SSc patients included in NOSVAR fulfil either the American Rheumatism Association 1980 classification criteria for SSc (ACR criteria) and/or LeRoy and Medsger's modified criteria for the classification of early SSc. Patients are scored according to the algorithm in the new ACR/EULAR criteria and classified as SSc if scoring 9 points or more. Descriptive statistics are applied to analyse the number of patients meeting the newly established classification criteria for SSc.

Results: NOSVAR includes 381 patients with SSc. 270 SSc patients (71%) fulfil the ACR criteria. The remaining 111 SSc patients meet the modified Medsger and LeRoy criteria for SSc. The mean age at onset is 48 years (SD 0.8), the median disease duration is 10 years (range 1–48 years) and the female to male ratio is estimated to 4:1. The cohort consists of 7 limited (l) SSc patients, 277 limited cutanoeus (lc) SSc patients and 98 diffuse cutaneous (dc) SSc patients. Altogether, 73/381 patients (19%) have bilateral skin thickening extending proximal to the metacarpophalangeal (MCP) joints and are classified as SSc by this criterion alone. Of the remaining 302 patients, 296 gain >9 points by fulfilling other parameters defined in the new ACR/EULAR criteria. Only 6 patients (2%) in the NOSVAR cohort do not meet the new criteria. These 6 patients fulfil only the LeRoy and Medsger's modified SSc criteria and have Raynauds phenomenon, pathological capillaroscopi and a positive antinuclear antibody, but no skin changes.

Conclusion: This study demonstrates the applicability of the new SSc classification criteria in a large, clinical registry cohort. Only 2% of SSc patients in the cohort do not meet the new ACR/EULAR criteria.

References:

1. Van den Hoogen, F *et al*. Classification criteria for Systemic Sclerosis; preliminary results. Annals Rheum Dis 2013;72 (3): 59.

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Descriptive Review Of Morphea Subjects From a Single Cohort Center. Lesley Portugal[1], Muneera Naeem[2], Lakshmi N. Moorthy[3] and Vivien M. Hsu[4]. [1]Robert Wood Johnson Medical School, New Brunswick, NJ, [2]Mountainside Hospital, Montclair, NJ, [3]Robert Wood Johnson Medical School-UMDNJ, New Brunswick, NJ, [4]RWJ Med Schl Scleroderma Prog, New Brunswick, NJ.

Background/Purpose: Morphea, or localized scleroderma, is an idiopathic, rare fibrotic skin disorder that may result in tissue atrophy, pigment changes, and contractures. Disability may range from purely cosmetic, causing great anxiety, to lifelong functional disability.

Methods: We conducted a retrospective chart review of pediatric and adults diagnosed with morphea at UMDNJ, and data on types of morphea, possible triggering events, disease course, complications and therapies. Descriptive analysis was done on all variables.

Results: Table 1 lists the clinical manifestations: there were 26 subjects (2 males), mostly Caucasians females of mean age 45±24 (10–85 years). Five had known associated autoimmune disease. Only 2 patients had a family history of morphea. Thirty-eight percent had a family history of autoimmune disease including SLE, RA, Crohn's and thyroid disease. Types of morphea, and known triggering events are listed in table 1.

Table 1. Clinical manifestations of 26 morphea subjects

Variables	*Frequency* (n = 26)	*% frequency*
Triggering event		
Unknown	23	88
Lovenox injection	1	
Chicken pox	1	
Previous Schamberg's	1	
Morphea type	7	27
Plaque	8	31
Generalized SQ	3	12
Linear	4	12
Coup de Sabre mixed	3	12
Eosinophilic fasciitis	1	< 1

Sizes ranged from small (<3±1.5 cm) to large (16±16 cm) with (85%) associated itching, tightness, dryness, burning, pain, or contracture requiring intervention. More than 90% had more than one lesion involving the trunk or extremity. Generalized SQ and eosinophilic fasciitis were only found in adults. Elevated CPK and inflammatory markers were more common with extensive disease. Extra-cutaneous manifestations presented in 18 subjects, including arthralgias, fatigue, and Raynaud. Two adults had monoclonal gammopathy associated with GSM. Tissue atrophy occurred in 14 subjects and 81% had long-term cosmetic issues (pigmentary changes), pain or depression due to their lesions. One was functionally disabled.

Twenty-four patients received the following therapy: Topical steroid (n=1), intra-lesional steroid (n=1), UV phototherapy (n=1). Immunosuppression was generally used for extensive disease: Methotrexate (n=17) alone or with systemic corticosteroids, etanercept, penicillamine, hydroxychloroquine, cyclosporine and cyclophosphamide. One patient with GSM required skin grafting. Morphea improved but did not resolve in 19 subjects; only one had resolution after 6 years. One patient had a relapse, two progressed and one child had limb length discrepancy. Of 18 patients with extra-cutaneous manifestations, 5 improved concurrently with their skin lesions.

Conclusion: Many morphea subjects sought therapy for their discomfort or complications. Long-term consequences, including joint pains and cosmetic issues, did not always resolve despite improvement of the morphea. More studies are needed to understand the various types of morphea and its clinical consequences to improve long-term outcomes.

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Characterization Of Lower Limb Cutaneous Ulcers In Systemic Sclerosis: The Analysis of 424 Lesions. Jelena Blagojevic[1], Guya Piemonte[2], Laura Benelli[2], Francesca Braschi[2], Ginevra Fiori[2], Felice Galluccio[2], Francesca Bartoli[2], Lorenza Busco[2], Alberto Pignone[2], Giulia Carnesecchi[2], Gemma Lepri[2], Serena Guiducci[2] and Marco Matucci Cerinic[2]. [1]University of Siena, Siena, Italy, [2]University of Florence, Florence, Italy.

Background/Purpose: Cutaneous ulcers reppresent one of the most frequent complications in course of systemic sclerosis (SSc). They are often disabling and difficult to treat. The upper limb ulcers have been evaluated and characterized extensively, but there are only few studies on lower limb ulcers. SSc is characterized by a microangiopathy that represents the hallmark of disease, but concomitant alterations of arterial, venous and lymphatic circulation may contribute to the pathogenesis of the lower limb cutaneous lesions. The aim of the study is to assess the pathogenesis, characteristics and time to healing of the lower limb cutaneous lesions in course of SSc.

Methods: Fifthy-seven consecutive SSc patients with lower limb cutaneous lesions were followed up for four years. All patients performed an accurate health examination and evaluation of cutaneous lesions, routine blood and urine tests with autoantibodies, lipid and glycemic profile and creatinine clearance, videocapillaroscopy and arterial and venous lower limb Color Doppler Ultrasonography. Arteriography was performed in patients with occlusive peripheral arterial disease.

Results: Four hundred and twenty-four (424) lower limb cutaneous lesions were observed. Lesions were divided into: hyperkeratosis, ulcers (loss of tissue) and gangrene. We observed: 275 (64,9%) hyperkeratosis, 144 (33,9%) ulcers and 5 (1,2%) gangrene. The ulcers were subsetted in: primary ulcers (107 (74,3%)), ulcers secondary to hyperkeratosis (17 (11,8%)) and ulcers secondary to calcinosis (20(13,9%)). The mean time to healing was 152 ± 202 days, and recurrence was observed in 31,6% of lesions. The prevalence of amputations was 1,2%. As regards pathogenesis, 16 (28,1%) patients had a significative peripheral arterial disease, 22 (38,6%) had venous insufficiency and 7 (12,4%) presented lymphedema, besides the microangiopathy. Three patients presented simultaneously a peripheral arterial disease and venous pathology. One patient presented lymphedema and venous insufficiency and two patiens had lymphedema and peripheral arterial disease. Four patients with critical arterial stenosis performed the lower limb angiography which confirmed the presence of stenosis with distal distribution.

Conclusion: Our data indicate that lower limb lesions have often a multifactorial pathogenesis in SSc. This is the first study that characterized extensively a large number of lower limb cutaneous lesions in SSc. The comprehension of characteristics and pathogenesis of these lesions is essential for their correct management.

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Pulmonary Involvement In Mixed Connective Tissue Disease: Slow Progression After 10 Years Of Follow-Up. Leticia Kawano-Dourado[1], Olivia M Dias[1], Fernando U Kay[1], Thais E H Gripp[1], Paula S Gomes[2], Ricardo Fuller[3], Bruno G Baldi[1], Ronaldo A Kairalla[1], Carlos R R Carvalho[1] and M.Teresa C. Caleiro[1]. [1]University of Sao Paulo, Sao Paulo, Brazil, [2]Hospital do Servidor do Estado de Sao Paulo, São Paulo, Brazil, [3]University of Sao Paulo, São Paulo, Brazil.

Background/Purpose: Evaluate the progression of interstitial lung disease (ILD) in a 10-year period of a group of 53 MCTD patients previously evaluated 10 years ago.

Methods: Pulmonary function tests (PFTs) and chest HRCT images were performed: current results were compared with the patientxs own results obtained ten years ago (baseline value). HRCT images were analyzed qualitatively and quantitatively. Two thoracic radiologists scored images independently using a global quantitative score (ILD-HRCT), that gives an estimate of lung involvement (0% – 100%), as previously described. Decreases in forced vital capacity (FVC) of 10%/200ml and/or in carbon monoxide diffusing capacity (DLCO) of 15% were considered significant. Structured interview, and retrospective collection of clinical data was also performed. Ethics committee approval: 0099/11.

Results: From the 53 patients, 7 patients lost follow-up, 3 died, and 4 changed diagnosis. Therefore 39 patients were re-evaluated (table 1): 92% underwent PFTs and 86% chest HRCT.

Table 1. Actual characteristics of the MCTD patients

Characteristic	patients
Number of patients	39
Female (%)	39 (100)
Age mean years (range)	53 (32–76)
Mean duration of MCTD symptoms in years (range)	21 (11–40)
Active smokers n (%)	1 (2,7%)
Ex-smokers n (%)	11 (30,5%)
Pulmonary Arterial Hypertension n (%)	2 (5,5%)
Shortness of breath n (%)	22 (56%)
Chronic cough n (%)	16 (41%)
Raynaud n (%)	32 (82%)
Autoantibodies n (%):	
ANA titer > 1/160	39 (100%)
Anti-dsDNA	0 (0%)
ENA titer > 1/1000	39 (100%)
Anti-SM	0 (0%)
Anti-Ro/SSA	11 (28%)
Anti-La/SSB	1 (2.5%)
Rheumatoid Factor	10 (25.6%)

Treatment was given according to the attending physician. All patients received omeprazol. 5% received only chloroquine, 18% received variable doses of corticosteroids and chloroquine, and 77% received corticosteroids, chloroquine and another medication: azathioprine, methotrexate, cyclophosphamide, or leflunomide.

22% of patients had normal HRCT (0% ILD-HRCT score) baseline and follow-up. In the remaining, ground glass opacities and reticulate were the most common image findings. Signs of fibrosis increased in the follow-up images (honeycomb and bronchiolectasis), nevertheless, overall lung involvement was mild and only slightly progressed (note baseline and follow-up ILD-HRCT score, table 2).

Table 2. Evolution of Chest HRCT findings in MCTD patients in 10 years

Image Finding	Baseline (% patients)	Follow-up (% patients)	p
ground-glass opacities (%)	74	77	ns
Reticulate (%)	65	77	ns
pleural irregularities (%)	35	61	0.042
traction bronchiolectasis (%)	32	58	0.041
Honeycomb cysts (%)	13	45	0.005
esophageal dilatation (%)	68	90	0.029
ILD-HRCT score mean ± SD (%)	9.3 ± 10.3	13.7 ± 15.9	0.016

From the subgroup of patients who had normal baseline PFTs, half of them worsened FVC and/or DLCO in follow-up (mean decrease: FVC −10.4% and DLCO −27%). Despite functional loss, 33% remained with normal follow-up chest HRCT images (0% ILD-HRCT score) and 22% with stable ILD-HRCT scores.

From the subgroup of patients with a restrictive pattern in baseline (mild reduction in FVC and FEV_1 with normal DLCO): Half of them presented a reduction in FVC and/or DLCO (mean decrease FVC: −17.5% and DLCO: −33%).

Conclusion: In this cohort, ILD associated with MCTD was mild in extent and slowly progressed in 10 years in half of the patients. These results suggest that a systematic lung assessment should be performed in all subjects with MCTD in a regular basis.

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Peripheral Bone Marrow-Derived Endothelial Progenitor Cells and N-Terminal Probrain Natriuretic Peptide in Scleroderma Mexican Patients With and Without Diastolic Dysfunction: A Preliminary Report. Jesús Sepúlveda[1], Olga Vera-Lastra[2], Maria Pilar Cruz-Dominguez[3], Laura Montiel-Cervantes[1], Joaquín Gómez-León[1], Luis Robles-Espinoza[1], Ramón Lozano-Morales[1], Sergio Mendoza-Alvarez[1], Rubiraida Molina-Aguilar[1], Gabriela Medina[4], Jorge Vela-Ojeda[1] and Luis J. Jara[5]. [1]Instituto Mexicano del Seguro Social, Mexico City, Mexico, [2]MD, Mexico City, Mexico, [3]Hospital de Especialidades Centro Medico Nacional La Raza., Mexico, DF, Mexico, [4]Seris/Zachila s/n La Raza, Mexico City, Mexico, [5]Hospital de Especialidades Centro Medico La Raza, México City, Mexico.

Background/Purpose: Diastolic dysfunction (DD) in systemic sclerosis (SSc) is a marker of increased risk of death. The N-terminal pro-brain natriuretic peptide (NT-proBNP) is a neurohormone released by ventricular and atrial myocytes and cardiac fibroblasts in response to pressure overload. NT-proBNP is highly associated with pulmonary arterial hypertension in SSc and is a potent vasculogenic agent that enhances bone marrow-derived endothelial progenitor cells (EPC) mobilization to cardiac regeneration. Our purpose was to explore the relationship between NT-proBNP levels and peripheral EPC in SSc patients with and without DD.

Methods: Cross-sectional study in 56 SSc adult patients and 28 matched healthy controls. Exclusion criteria: systolic dysfunction, structural cardiopathy, neoplasms, overlap syndrome, diabetes and hypertension. DD (mild, moderate and severe) was determined according to 2009 EAE/ASE guidelines for the evaluation of diastolic function. EPC were characterized in peripheral blood by flow cytometry according to the expression surface markers CD309, CD34 and CD133 and 7AAD as a viability biomarker. CPE were divided in three phenotypes: 1.CD309+CD34+CD133-,2.CD309+CD133+CD34-, and 3. CD309+CD34+CD133+. Serum levels of NT-proBNP were measured by electroquimioluminiscence. SSc patients were divided according to the severity of DD. Statistical analysis data were expressed in median and range and comparison was made with Wilcoxon, Kruskal Wallis and Pearson correlation tests. P value<0.05 was considered significant.

Results: Results are summarized in Table 1. DD prevalence was 62%. NTproBNP was higher in mild, moderate and severe DD. NT-proBNP showed weak linear relation with CD309+CD34+ EPC cells (R=−0.36, p=0.04).

Table 1.

			SSc with DD n=35		
	Healthy controls n= 28	SSc without DD n=21	Mild (n=20)	Moderate or severe (n=15)	P Value
NTproBNP (pg/ml)	21 (15–50)	45.01 (17.3–162.6)	112.5 (35.6–617.5)	251.1 (84.95–965.6)	0.0083
EPC subtypes (cells/μl)					
CD309+CD34+CD133+	1.53 (0.05–5.45)	1.04 (0.07–2.52)	0.47 (0.07–2.91)		0.0007
CD309+CD34+CD133−	0.72 (0.10–3.12)	0.99 (0.16–4.35)	0.90 (0.05–5.51)		0.45
CD309+CD133+CD34−	1.42 (0.32–6.72)	1.19 (0.181–4.68)	1.06 (0.04–3.81)		0.23

Conclusion: NT-proBNP level is increased in patients with SSc and significantly correlates with severity of DD. On the other hand, the EPC subtype CD309+CD34+CD133+, was significantly diminished in patients with DD compared to patients without DD and healthy controls. These results support the role of NT-proBNP and EPC in the development of cardiac disease in SSc patients. A prospective study is necessary in order to define the prognostic significance of NT-proBNP and EPC alterations in SSc mexican patients.

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Combined Pulmonary Fibrosis and Emphysema (CPFE) In Systemic Sclerosis. Nicolas Champtiaux[1], Vincent Cottin[2], Eric Hachulla[3], Dominique Valeyre[4], Hilario Nunes[4], David Launay[5], Alice Berezne[6], Bruno Crestani[7], Loic Guillevin[8], Jean-Francois Cordier[2] and Luc Mouthon[9]. [1]Service de Médecine Interne, hôpital Cochin, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France, [2]Division of Pneumology, Hôpital Louis-Pradel, Hospices Civils de Lyon, Lyon 1, Lyon, France, [3]Internal Medicine, Lille CEDEX, France, [4]Avicenne Hospital (AP-HP), Bobigny, France, [5]Claude Huriez University Hospital, Lille, France, [6]Paris Descartes University, Internal Medicine department, Cochin Hospital, Paris, France, [7]Hôpital Bichat, Paris, France, [8]Cochin University Hospital, Paris, France, [9]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, Paris, France.

Background/Purpose: Combined pulmonary fibrosis and emphysema (CPFE) is a recently defined syndrome, in which centrilobular and/or paraseptal emphysema in upper lung zones coexist with pulmonary fibrosis in the lower lobes. These patients have a characteristic lung function profile, with unexpected subnormal dynamic and static lung volumes, contrasting with a significant reduction of carbon monoxide transfer capacity (DLco) and exercise hypoxemia. CPFE has recently been described in association with connective tissue disease. The aim of this study was to describe the recently individualized syndrome of CPFE in a population of patients with systemic sclerosis (SSc).

Methods: In this multicenter case-control study, we retrospectively investigated data from patients with SSc who also had CPFE. The demographic characteristics of the patients, the results of pulmonary function testing, high-resolution computed tomography, and treatment, and the outcomes of the patients were analysed retrospectively. For each patient with CPFE and SSc, two patients with SSc and pulmonary fibrosis without emphysema were included as controls.

Results: Thirty one SSc patients with CPFE were identified and paired with 62 controls. In one center (Cochin), the prevalence of CPFE was 3.5% in SSc patients, and 8.2 % in SSc with interstitial lung disease. CPFE patients with SSc were more likely to be male (77% vs 18%, $p< 10^{-5}$), smokers (84 vs 37%, $p< 10^{-5}$), and to have a limited SSc (62 vs 26%, $p< 0.01$) than control SSc patients. Pulmonary function testing revealed a marked decrease in DLco at diagnosis (39% vs 50% of predicted, $p<0.001$) and at the end of follow-up (30% vs 44%, $p<0.0001$) in CPFE patients compared to controls, despite similar lung volumes (total lung capacity 78 vs 81%, forced vital capacity 78 vs 78%). Autoantibody profiles did not differ significantly between SSc patients with or without CFPE.

During follow up, CPFE patients with SSc developed more frequently pulmonary hypertension (48 vs 12%, $p<0.0001$), had more frequent unscheduled hospitalisation (48% vs 22%, $p<0.01$) and had decreased survival ($p<0.05$ by Log rank test) as compared to those with SSc and pulmonary fibrosis without emphysema.

Conclusion: The CPFE syndrome presents with distinct pulmonary manifestations within the spectrum of lung diseases occurring in patients with SSc, with a higher risk of pulmonary hypertension and a shorter survival as compared to those with pulmonary fibrosis without emphysema.

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Chronic Periaortitis With Thoracic Aorta Involvement: A New Subtype Of Large Vessel Vasculitis. Alessandra Palmisano[1], Maria Letizia Urban[2], Domenico Corradi[3], Federico Alberici[1], Carlo Salvarani[4], Carlo Buzio[1] and Augusto Vaglio[1]. [1]University of Parma, Parma, Italy, [2]Nephrology University of Parma, Parma, Italy, [3]Pathology University of Parma, Parma, Italy, [4]Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy.

Background/Purpose: Chronic periaortitis (CP) is characterised by a fibroinflammatory tissue arising from the adventitia of the abdominal aorta and the iliac arteries and spreading into the surrounding retroperitoneum. CP is thought to have an autoimmune origin and to arise as a primary aortitis. Involvement of the thoracic aorta and its main branches has been anecdotally described. We analysed frequency and pattern of involvement of the large thoracic arteries in CP patients.

Methods: We studied 77 consecutive CP patients who had appropriate imaging studies to evaluate thoracic vessel involvement (chest contrast-enhanced CT/MRI, angio-CT/MRI, whole-body CT-PET). All patients underwent routine clinical assessment and laboratory tests.

Results: Twenty-eight patients (36.4%) showed thoracic vessel involvement: 21 had thoracic periaortitis, which surrounded an aneurysmal thoracic aorta in 6 cases and also involved the origin of the epiaortic vessels in 9 cases; 7 patients had thoracic aortic aneurysm without periaortitis. Analysis of demographic and clinical features in the groups with and without thoracic involvement showed, in the former, a higher female prevalence (M/F ratio 14/14 vs 39/10, $P=0.010$), a more advanced age at diagnosis [median(interquartile range) 64.5 (58.3–69.-5) vs 56.0 (50–59) years, $P=0.001$], a higher frequency of constitutional symptoms (86% vs. 59%, $P=0.021$), and a shorter relapse-free survival (log-rank $P=0.025$).

Conclusion: Involvement of large thoracic arteries occurs in about one-third of CP patients. This subset of patients with systemic large vessel involvement shows distinct clinical features, such as a higher female prevalence, a higher age at diagnosis, and a higher frequency of systemic symptoms; in addition, patients with thoracic involvement tend to have a frequently relapsing course. These findings raise the question as to whether this CP subset represents a distinct form of large-vessel vasculitis.

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Longitudinal Assessment Of Pulmonary Function In 304 Norwegian Patients With Systemic Sclerosis. Anna-Maria Hoffmann-Vold[1], Torhild Garen[2], Oyvind Midtvedt[1], May-Brit Lund[3], Jan Tore Gran[1] and Øyvind Molberg[1]. [1]Oslo University Hospital, Oslo, Norway, [2]Oslo University Hospital Rikshospitalet, Oslo, Norway, [3]Oslo University Hospital, Rikshopitalet, Oslo, Norway.

Background/Purpose: The purpose of this study was to asses sequential pulmonary function measurements (forced vital capacity [FVC] % predicted) in a large systemic sclerosis (SSc) cohort over a mean observation period of 5.2 (+/− 2.8) years.

Methods: The study cohort included all the 304 SSc patients with sequential pulmonary measurements enrolled in the Norwegian systemic connective tissue disease and vasculitis registry (NOSVAR) at the Department of Rheumatology, Oslo University Hospital (OUH). Lung function measurements were registered at baseline and then prospectively at annual follow-up visits. Altogether, 1125 lung function tests were analysed. Patients were segregated according to their baseline unadjusted FVC % predicted (<70% and >70%). Descriptive statistics were applied to obtain baseline characteristics and the FVC% decline over the observation period. Vital status at 1 January 2013 was provided for all participants by the national population register. Kaplan-Meyer and Cox proportional hazard models were used to analyse survival.

Results: In total, 52 patients (17%) had a baseline FVC <70% (Table 1). Patients with a baseline FVC <70% were more often anti-topoisomerase antibody (ATA) positive than patients with baseline FVC >70% (p-value <0.05). They were also more frequently classified as diffuse cutaneous (dc) SSc (p-value <0.001) and with male gender (p-value <0.001). There were 52 deaths during the observation period and the death rate (22/52, 41%) in patients with a baseline FVC < 70% was significantly higher than in patients with baseline FVC >70% (47/205, 19%). The 10-year survival rate was estimated to 69% and 84% for FVC<70% and FVC>70%, respectively (p-value 0.006, data not shown).

Table 1. Clinical characteristics of 304 SSc patients stratified by baseline FVC%

	Baseline FVC		
	<70%	**>70%**	**p-value**
Number of patients (%)	52 (17)	254 (83)	
Age, years (SD)	52.4 (12.9)	54.3 (14.2)	
Disease duration (SD)	7.0 (7.7)	5.6 (7.0)	
Male sex, no (%)	23 (44)	43 (17)	0.000
Ever smoker, no (%)	15 (29)	67 (27)	0.318
Deceased, no (%)	22 (42)	47 (19)	0.000
SSc type			0.000
Diffuse cutaneous SSc, no (%)	26 (50)	51 (20)	
Limited cutaneous SSc, no (%)	26 (50)	201 (80)	
ATA positive	15 (29)	29 (12)	0.000
ACA positive	9 (17)	115 (46)	0.000
Declining FVC, no (%)	15 (29)	99 (39)	0.264

SSc: systemic sclerosis; ATA: anti-topoisomerase antibody, ACA: ant-centromere antibody

The longitudinal analyses showed that 114/304 patients (38%) had declining FVC values over the study period. The mean +/− SD decline in the FVC was −2.2 +/− 9% per year. No significant predictors were detected for progressive lung disease, but the 10-year survival rate was lower in patients with declining FVC compared to patients who did not display significant decline from their baseline FVC value, 74% versus 93% (p-value 0.03, data not shown).

Conclusion: The data from our large SSc cohort suggest that male gender, ATA and dcSSc are associated with early development of restrictive pulmonary disease, as evaluated by the baseline FVC. Moreover, survival is decreased for SSc patients with baseline FVC <70%. Interestingly, survival was also decreased in patients with progressive fall in FVC and this association was independent of the patients' baseline FVC value.

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Adverse Events With The Use Of Radiotherapy In Patients With Connective Tissue Diseases and Cancer: A Systematic Review and Meta-Analysis. Maria A. Lopez-Olivo[1], Juan A Martínez-López[2], Jean H. Tayar[3], Mahesh Bavineni[4] and Maria E. Suarez-Almazor[5]. [1]University of Texas. M.D Anderson Cancer Center, Houston, TX, [2]Jiménez Díaz Foundation University Hospital, Madrid, Spain, [3]University of Texs, MD Anderson Cancer Center, Houston, TX, [4]Louisiana State University Lafayette, Lafayette, LA, [5]University of Texas MD Anderson Cancer Center, Houston, TX.

Background/Purpose: In the era of modern medicine, radiotherapy remains a cornerstone for the multi-modality cancer treatment.

Methods: We conducted a comprehensive search for any study describing patients with a connective tissue disorder (CTD) who received radiotherapy and reported adverse events (AEs) in electronic databases (MEDLINE, EMBASE, Web of Science, and The Cochrane Library) from inception through March 2013. Our search strategy was restricted to human subjects and studies published in English, French, or Spanish. Study selection, data collection and quality assessment were independently performed by two pairs of investigators. Our primary outcome was the incidence of AEs from radiotherapy in patients with CTDs. Secondary outcomes included: i) predictive factors of AEs ii) effects of radiotherapy on underlying CTD either flares or increased organ damage; and iii) incidence of de novo CTD in patients receiving radiotherapy and iv) Incidence of recurrent malignancies in patients with CTD receiving radiotherapy. Meta-analyses were performed when there were two or more studies with similar outcomes. AEs were recollected and classified in acute (<90 days) and late (>90 days).

Results: 46 publications were included (5 retrospective cohorts, 6 case series (7 publications), and 34 case reports). Study quality raged from fair to moderate. 832 patients received radiation at palliative or curative doses; 558 patients with a CTD and 274 controls. The age of the included patients ranged from 16–72. Pooled incidence of significant AEs was 8% (95%CI: 4%, 14%) for acute and 13% (95%CI 9%, 17%) for late. Patients with a CTD had 2.4 greater odds of developing a significant late AEs compared with patients without a CTD (95%CI 1.1, 3.9). No differences were found in the rate of significant acute AEs. AEs rates were affected by radiation site (abdominal, pelvic and CNS), concurrent CTD therapy (use of DMARDs, NSAIDs, or steroids versus no treatment), and type of CTD. Compared to patients without CTD, increased risk of severe AEs were observed in patients with rheumatoid arthritis (late AEs: Peto OR 3.8; 95%CI 1.4, 10.3) and scleroderma (acute AE: Peto OR 16.5; 95% CI 1.5, 186.2 and late AEs: Peto OR 6.8; 95%CI 4.0, 46.1). Regarding, the effects of radiation on underlying disease 19 out of 25 patients with scleroderma had exacerbation of symptoms, 2 patients improved with steroids and penicillamine. The pooled incidence of de novo CTD was 18% (95%CI 9%, 28%) and malignancy recurrence was observed in 3% of the patients.

Conclusion: We observed statistically significant increased rates of severe late AEs in patients with CTD undergoing radiotherapy. Although, radiotherapy is an essential component of cancer therapy, oncologists should be aware that patients with rheumatic diseases requiring radiotherapy as a part of the treatment regimen might be at a greater risk of developing severe adverse events.

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Severity Of Muscle Weakness Predicts Disability In Scleroderma. Julie J. Paik[1], Fredrick M. Wigley[1], Amanda Mejia[2] and Laura K. Hummers[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Johns Hopkins Bloomberg School of Publich Health, Baltimore, MD.

Background/Purpose: The Health assessment questionnaire disability index (HAQ-DI) is a self-administered questionnaire that is a patient reported outcome which provides a measure of disability responsive to change in clinical trials in scleroderma. The purpose of this study was to determine if the degree of muscle weakness in scleroderma associates with HAQ-DI scores.

Methods: We queried a large, well characterized cohort of patients with scleroderma to determine whether the presence of muscle weakness associates with abnormal HAQ-DI scores. A total of 2481 patients with scleroderma were enrolled in the database from 1990 until 2010. 1723 patients were included in the analyses since these patients had a complete muscle severity assessment. We defined muscle weakness using the Medsger Muscle Severity Score. A value of 0 indicates no weakness, and a value ranging from 1–4 characterizes the patient at various degrees of weakness. The maximum score recorded from all clinic visits was used. The outcome, HAQ-DI, at their most recent visit was used in this analysis.

Multivariate linear regression was used to calculate effect estimates. Muscle severity scores were modeled as a categorical variable, with an effect estimate for each category 1 to 4, with zero as the reference category. Linear regression on the original data, log-transformed data and inverse-transformed data was performed, but in all cases the residuals showed strong non-normality. A generalized linear model using the gamma distribution with identity link was seen to improve model fit.

Results: 407/1733 patients were weak based on their maximum muscle severity score. The mean age was 52.4 ± 13.7 years old among the weak patients. Age and gender were not different in those who were weak vs. not weak. There were also more weak scleroderma patients who were limited subtype rather than diffuse subtype (p<0.0001).

After controlling for age, sex, disease duration, signs of synovitis, disease subtype, level of gastrointestinal severity score (0–4), and lung function (most recent forced vital capacity (<70%)), the severity of weakness was significantly positively associated with higher scores of the HAQ-DI. For every unit of change in the Muscle Severity score at the Score level of >0 and <4, there was a positive association with the disability score (see Table).

	HAQ-DI (score of 0–3)		
Muscle Severity Score (Reference of 0)	Increase in HAQ-DI score	95% Confidence Interval	p-value
1	0.467	(0.33–.610)	< 0.0001
2	0.692	(0.30–1.09)	< 0.001
3	0.950	(0.78–1.82)	0.033
4	1.050	(0.078–2.01)	0.034

Summary: This study demonstrates that a history of muscle weakness is positively associated with self-reported disability as measured by the HAQ-DI.

Conclusion: Muscle weakness is an independent cause of disability among patients with scleroderma.

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Osteoporosis and Fracture Risk In Outpatients With Systemic Sclerosis. Veronica Codullo[1], Flora Inverardi[2], Silvia Breda[3], Laura Bogliolo[4], Francesca De Nard[5], Giovanni Cagnotto[5], Roberto Caporali[6] and Carlomaurizio Montecucco[7]. [1]IRCCS Policlinico San Matteo Foundation, Pavia, Italy, [2]Division of Rheumatology, IRCCS Policlinico San Matteo Foundation and University of Pavia, Pavia, Italy, [3]University of Pavia, IRCCS Foundation Policlinico San Matteo, 27100, Italy, [4]IRCCS Foundation Policlinico San Matteo, Pavia, Italy, [5]University of Pavia/ IRCCS Policlinico San Matteo Foundation, Pavia, Italy, [6]Rheumatology, IRCCS Policlinico San Matteo Foundation and University of Pavia, Pavia, Italy, [7]University and IRCCS Policlinico S. Matteo Foundation, Pavia, Italy.

Background/Purpose: Osteoporosis (OP) is a frequent complication of a number of chronic inflammatory diseases. Only Rheumatoid Arthritis (RA) is included in the FRAX algorythm to calculate fracture risk but also Systemic Sclerosis (SSc) displays many disease-specific OP risk factors (chronic

inflammation, malnutrition, steroid use, etc.) Aim:To determine OP frequency and fracture risk by FRAX in outpatients with SSc

Methods: After consent, in outpatients with SSc (le Roy criteria) of a University Hospital, bone mineral density (BMD) was calculated by Dual Energy X-Ray Absorptiometry (DEXA) at the femoral neck and lumbar spine and FRAX was obtained by the calculation tool (http://www.shef.ac.uk/FRAX). A routine SSc evaluation (according to EUSTAR) was performed as well. Age- and BMI-matched early AR (ACR/EULAR 2010 criteria) patients were enrolled as controls

Results: Seventy-one SSc patients (3:68 M:F, age 66±9yrs, 57:14 limited:diffuse cutaneous, median disease duration 8.5, 2.4–14.7yrs, median disease activity 1, 0.25–2) and 44 AR (11:33 M:F, age 62±12yrs, median DAS28 4.42, 3.94–5) were enrolled. OP was detected in 42/71 (59%) SSc patients. Disease duration was significantly higher in SSc-OP patients (10.5, 4.3–16.6 vs 5.5, 1.6–9.8, $p<0.01$) and it was also significantly associated to OP (OR 1.4, 1.1–1.7, $p<0.01$), even when corrected at a multivariable analysis for other disease-specific features (skin and gastrointestinal involvement, autoantibody subset, median mRSS, disease activity) and OP risk factors (steroid use, smoke, BMI, chronic renal insufficiency). OP in RA patients was significantly lower than in SSc (9/44, 20%, $p<0.001$). Mean femoral BMD was 0.58 (0.53–0.7) in SSc vs 0.72 (0.64–0.82) in RA ($p<0.001$), lumbar mean BMD 0.82 (0.75–0.9) in SSc vs 0.92 (0.81–1) in RA. FRAX for major fracture was not significantly different between groups (low in 47% and 50%, medium in 28% and 40%, high in 25% and 10% of SSc and RA respectively). A diagnosis of SSc was significantly associated to OP (OR=13.2, 4–42.4), even when corrected for steroid use.

Conclusion: We have detected a very high OP frequency in our SSc patients, significantly higher than a control early AR cohort and significantly associated to disease duration. Routine DEXA evaluation and risk factors for OP should always be considered and treated when possible in every SSc patient, especially after 5 years of disease duration

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Extension Of Cardiac Damage Through The Delayed Enhancement Of Cardiac Magnetic Resonance: Predictive Value Of a Combined Approach Based On Clinical and Laboratory Findings, EKG-Holter and Cardiac Magnetic Resonance. Silvia Laura Bosello[1], Giacomo De Luca[1], Agostino Meduri[2], Giorgia Berardi[1], Manuela Rucco[1], Giovanni Canestrari[1], Federico Parisi[1] and Gianfranco Ferraccioli[1]. [1]Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy, [2]INSTITUTE OF RADIOLOGY - Catholic University of the Sacred Heart, ROME, Italy.

Background/Purpose: Cardiac involvement is a relevant prognostic determinant in Systemic Sclerosis (SSc), but the diagnosis is often delayed due to the lack of a specific diagnostic algorithm.

Recent studies, screening the hearts of subclinical consecutive SSc patients by delayed enhancement (DE) - cardiac magnetic risonance (CMR), found that 21–66% had midwall DE-CMR. We studied the hearts of symptomatic SSc patients through CMR and we evaluated the role of a combined approach, based on evaluation of clinical symptoms, laboratory findings, EKG-holter and CMR, to characterize cardiac involvement in SSc-patients.

Methods: Thirty-six SSc-patients with symptoms of cardiac involvement (dyspnea, palpitation) and/or signs of cardiac failure and elevation of cardiac enzymes (MB-CK and/or troponin T) underwent EKG-holter and cardiac magnetic resonance (CMR). Median follow-up was 24±0.2 months.

Results: Major EKG-holter modifications were present in 30.6% of patients. CMR study demonstrated T2 hyperintensity in 3 patients while none of the patients presented early gadolinium enhancement and 18 (50.0%) patients presented late gadolinium enhancement (LGE). We identified 3 different patterns of distribution of LGE: subepicardial, midwall and subedocardial. Eleven patients presented a single pattern of distribution, while 7 patients (38.8%) presented more than one: 61.1% of patients presented a midwall distribution of LGE, 33.3% of patients presented a subepicardial LGE with a linear distribution pattern and 22.2% presented a subendocardial LGE distribution. 38% of patients showed hypokinetic area and only one patient an akinetic area. The mean EF of left ventricle was 61.7±10.8%, and of right ventricle was 58.1±10.3%. Hypokinetic and akinetic area corresponded with the LGE area. The extension of LGE on CMR was evaluated according to a standardized left-ventricular segmentation. When CMR demonstrated a DE, the mean number of involved cardiac segments was 3.3±2.7. Segment number *9* was involved in 44.4% of the patients, followed by segments number *3* and *5* (38.9%) and by segment *2* (27.8%). Patients with major abnormalities on EKG-holter presented a higher number of involved myocardial segments on CMR (3.7±2.3) with respect to the patients without EKG-abnormalities (0.9±1.4), ($p=0.012$). After a mean follow-up of 24±0.2 months, 4 patients (16%) died for arrhythmias or heart failure.

All patients, who died at follow-up, had severe dyspnea, elevated cardiac enzymes, myosytis, major EKG-holter abnormalities, reduction of EF and LGE on CMR at baseline; 75% of patients who died had a subendocardial distribution pattern of LGE on CMR.

Conclusion: Our study suggests that a combined approach, based on clinical presentation, laboratory findings, EKG-holter examination and study of distribution of LGE on CMR, is useful to characterize the extension of myocardial damage and to identify patients with a poor outcome related to heart involvement in SSc.

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Prediction Of Worsening Of Skin Fibrosis In Patients With Diffuse Systemic Sclerosis Using The EULAR Scleroderma Trials and Research (EUSTAR) Registry. Britta Maurer[1], Nicole Graf[2], Beat A. Michel[1], Carola Metzig[3], Vivian Lanius[3], Dinesh Khanna[4] and Oliver Distler[1]. [1]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]graf biostatistics, Winterthur, Switzerland, [3]Bayer Pharma AG, Berlin, Germany, [4]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI.

Background/Purpose: To identify predictive parameters for the progression of skin fibrosis in patients with diffuse cutaneous SSc (dcSSc) to enable 1) risk-stratification in clinical practice and 2) improved cohort enrichment in clinical trials with skin fibrosis as the primary endpoint.

Methods: An observational prospective study using the EUSTAR database was performed. Worsening of skin fibrosis was defined as increase in modified Rodnan skin score (mRSS) >5 points and ≥25% from the 1st to the 2nd visit. Inclusion criteria: dcSSc, ACR criteria fulfilled, mRSS≥7 at 1st visit, valid data for mRSS at 2ndvisit, period in between visits 12±2 months. In the univariate analysis, patients with progressive skin fibrosis were compared to non-progressive patients. Predictive markers with $p<0.2$ were included in the multivariate logistic regression analysis. For validation of the regression models, a second cohort with new patients was extracted from the EUSTAR database 11 months after the first data extraction.

Results: Out of 637 patients fulfilling the inclusion criteria of the original cohort, 9.7% had progressive skin disease. Univariate analysis suggested the following prediction parameters: presence of joint synovitis ($p=0.009$), disease duration ($p=0.023$), mRSS at baseline ($p=0.015$), and the interaction between disease duration (≤15>/15 months, cut-off defined by ROC analysis) and sex ($p=0.020$) as well as the interaction between disease duration and CK elevation ($p=0.047$).

In the multivariate analysis, different prediction models with varying numbers and combinations of the predictors identified in the univariate analysis were compared. The model with the highest prediction success rate (n=8/18, 44.4%) showed an area under the ROC curve of 0.73 (95% CI=0.66–0.79, $p<0.0001$) with an overall accuracy of 89.9% (98.1% for no progression, 14.3% for progression) (Table1).

Table 1. Prediction model for skin progression in dcSSc

Predictors	p-value	OR	95%-CI
Joint synovitis	0.016	2.123	1.147–3.927
Female sex	0.143	0.541	0.238–1.230
Short disease duration* (≤15 months)	0.689	0.752	0.186–3.036
Female sex*short disease duration (≤15 months)	0.033	5.380	1.142–25.342
Low mRSS at baseline (≤22/51)	0.001	6.027	2.113–17.189

Other models with broader inclusion criteria revealed lower prediction success rates, but would simplify the recruiting process (e.g. prediction success rate 23.8% (n=20/84) for a model including low mRSS at baseline (≤22/51) and short disease duration (≤15 months)).

In the validation cohort, out of 188 patients, 6.5% had progressive skin

disease. In the multivariate analysis, essentially the findings from the original cohort were confirmed, including the model in Table 1.

Conclusion: These data from a large cohort analysis including a 2nd verification cohort clearly have an important impact on the future clinical study design in SSc. The identified and validated criteria allow the enrichment for dcSSc patients with progressive active skin fibrosis by up to 4.5-fold.

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Correlation Between Patient Self-Report Of Symptoms Of Raynaud's Phenomenon and Objective Assessment Of Digital Microvascular Perfusion Using Infrared Thermography. Marina Scolnik[1], Bhavisha Vasta[2], Darren Hart[2], Jacqueline A. Shipley[2], Sue Brown[2], Eleanor Korendowych[2], Neil J McHugh[3] and John D. Pauling[3]. [1]Rheumatology Section, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [3]Department of Pharmacy and Pharmacology, University of Bath, Bath, United Kingdom.

Background/Purpose: Patient self-report of digital colour changes form the basis of a clinical diagnosis of Raynaud's phenomenon (RP) and help classify patients with early systemic sclerosis (SSc). There is a high reported prevalence of RP symptoms in fibromyalgia syndrome (FMS) but little evidence of a true vasculopathy. We report the findings of a retrospective study designed to evaluate the relationship between patient self-report of digital colour changes and objective assessment of digital microvascular function using infra-red thermography (IRT) in patients with primary RP, SSc and FMS.

Methods: Retrospective review of all patients referred for thermographic evaluation between 2010 and 2012 was undertaken. Our thermographic protocol includes the completion of a patient-reported questionnaire documenting symptoms of RP. Thermographic assessment of the resting longitudinal thermal gradient of all fingers was undertaken by calculating the mean distal dorsal difference (DDD) at 23°C. A negative DDD is suggestive of digital microvascular dysfunction and a DDD of −1 °C or less has previously been reported as clinically relevant. A subsequent case note review was undertaken to select out patients with a clinician diagnosis of primary RP (ANA negative), SSc (sclerodactyly in conjunction with a SSc-specific autoantibody and/or abnormal nail fold capillaroscopy) and FMS (1990 criteria).

Results: 138 patients were evaluated (83 PRP, 12 SSc, 43 FMS). No pattern of digital colour change discriminated between the three groups (Table). In all groups RP symptoms were most frequently monophasic, with white being the most common colour change. In the SSc group, triphasic colour changes were uncommonly reported but thumb involvement was more common than in the other groups (non-significant). Thermographic assessment revealed most pronounced peripheral microvascular dysfunction in SSc followed by primary RP and then FMS respectively. Using the DDD to differentiate between SSc and FMS, area under ROC curve analysis was 0.7 (95% CI, 0.558– 0.842, p 0.036), with an optimal DDD cutoff of −0.76 (66% sensitivity and 65% specificity). Regression analysis did not identify any relationship between thermographic analysis and specific colour changes, pattern of color change or body area affected by RP. After adjusting for vasodilator use and co-morbidities, only current smoking showed an increased risk for a lower DDD (OR 2.9, CI 95% 1.17–7.23, p 0.02).

* p=0.09 vs. FMS	Primary RP (n=83)	SSc (n=12)	FMS (n=43)
Age, mean (SD)	47.8 (14.8)	53.1 (13.6)	43.8 (10.8)
Females, n (%)	64 (77.1)	10 (83.3)	39 (90.7)
White, n (%)	58 (69.9)	9 (75)	29 (67.4)
Blue, n (%)	36 (43.4)	7 (58.3)	14 (32.6)
Red, n (%)	35 (42.2)	5 (41.7)	21 (48.8)
Purple, n (%)	39 (47)	3 (25)	16 (37.2)
Monophasic, n (%)	23 (27.7)	5 (41.7)	14 (32.6)
Biphasic, n (%)	21 (25.3)	4 (33.3)	11 (25.6)
Triphasic, n (%)	17 (20.5)	1 (8.3)	8 (18.6)
Numbness, n (%)	71 (85.5)	12 (100)	41 (95.3)
Symptoms in absence of cold, n (%)	45 (54.2)	8 (66.7)	25 (58.1)
Thumbs involvement, n (%)	30 (36.1)	7 (58.3)	17 (39.5)
Toes involvement, n (%)	65 (78.3)	8 (66.7)	35 (81.4)
Average DDD °C, median (IQR)	−1.05 (4.83)	−2.2 (4.5)	+0.62 (4.92)
Proportion of patients with a mean DDD <−1.0 °C, n (%)	42 (50.6)	8 (66.7)*	15 (34.9)

Conclusion: Patient self-report of RP symptoms are similar across primary RP, SSc and FMS and do not aid disease classification. Objective assessment using IRT revealed strong trends for differences in baseline digital microvascular function across the 3 groups although relatively low patient numbers for SSc hampered data analysis. Despite a similar burden of patient-reported symptoms of RP, normal thermographic appearances were identified in the majority of patients with FMS.

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Evaluating The Effects Of Combination Aspirin and Dipyridamole (asasantin retard) On Platelet Function, Oxidative Stress and Peripheral Vascular Function In Primary Raynaud's Phenomenon and Systemic Sclerosis. John D. Pauling[1], Jacqueline A. Shipley[1], Darren Hart[1], Ginger L. Milne[2] and Neil J McHugh[3]. [1]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [2]Vanderbilt University, Nashville, TN, [3]Department of Pharmacy and Pharmacology, University of Bath, Bath, United Kingdom.

Background/Purpose: There is evidence of enhanced platelet activation in Raynaud's phenomenon (RP), particularly in systemic sclerosis (SSc). Upon activation, platelets release vasoconstrictive mediators (e.g. thromboxane and serotonin) which may contribute to microvascular compromise. Platelet activation can be inhibited using aspirin (ASA) and dipyridamole (DIP). Pleiotropic effects of DIP include vasodilation and direct antioxidant effects. We investigated the effects of combination ASA and DIP on digital vascular function, platelet function and oxidative stress in primary RP and SSc.

Methods: This was an investigator-led single-centre exploratory open-label phase IIB study. Patients with primary RP and SSc received combination ASA (25mg) and DIP (200mg), given as a single capsule twice daily for 2 weeks. The primary endpoints were the individual components of the Raynaud's Condition Score (RCS) diary. Secondary endpoints included objective assessment of digital vascular response to local cold challenge assessed using infrared thermography (IRT) and laser speckle contrast imaging (LSCI). Platelet function was assessed using light transmission aggregometry (LTA) to adenosine diphosphate (ADP) and arachidonic acid (AA). Plasma levels of p-selectin, soluble CD40 ligand and TGF-beta were measured using ELISA. Urinary levels of 11-dehydro-TxB_2 (metabolite of thromboxane), 2,3-dinor-6-keto-PGF_{1a} (metabolite of prostacyclin) and F_2-isoprostanes (biomarker of oxidative stress) were measured using gas chromatography mass spectrometry.

Results: Nineteen patients were recruited to the study (n=11 SSc). Four patients withdrew due to adverse drug reactions (ADR, headache n=3 and possible allergic reaction n=1). Fifteen patients completed the study (n= 9 SSc). There was significant improvement in the RCS score (median 2.29 [2.27] vs.1.11 [1.52], p=0.006) and the daily frequency of RP attacks (median 2.04 [2.67] vs. 1.32 [2.66], p=0.039). There was no improvement in mean daily duration of RP attacks. There was no improvemnt in objective assessment of digital microvascular responses to cold challenge using IRT or LSCI. There were significant reductions in aggregation to both ADP and AA ($p<0.005$ for all comparisons vs. baseline). The significant reduction in urinary 11-dehydro-TxB_2 levels (398 [198] vs. 157 [170] pg/mg, p=0.001) was lower than expected. There was also a significant reduction in urinary 2,3-dinor-6-keto-PGF_{1a} (147 [93] vs. 135 [130] pg/mg, p=0.017) but no significant change in urinary F_2-isoprostane levels or plasma levels of p-selectin, soluble CD40 ligand and TGF-beta. The commonest ADR was headache, reported in 16/19 (84.2%).

Conclusion: The apparent improvement of RP severity following combination ASA/DIP therapy in patients with primary RP and SSc is likely to be related to placebo effect although the high prevalence of headaches suggests a vasodilatory effect. We did not identify any beneficial effect of treatment on objective assessment of basal digital microvascular perfusion or recovery following local cold challenge. The results of this exploratory study do not support the initiation of larger controlled studies of combination ASA/DIP for peripheral vascular disease in RP or SSc.

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Treatment With Rituximab Reduces Activation Of Scleroderma Dermal Fibroblasts. Paolo Fraticelli[1], Salvatore De Vita[2], Nicoletta Franzolini[3], Silvia Svegliati[4], Cecilia Tonnini[4], Barbara Gabrielli[4], Cathryn Anne Scott[5], Giovanni Pomponio[6], Gianluca Moroncini[4] and Armando Gabrielli[4]. [1]Istituto di Clinica Medica, Università Politecnica delle Marche, Ancona, Italy, [2]Rheumatology Clinic, DSMB, University of Udine, Udine, Italy, [3]Presidio Ospedaliero di San Daniele del Friuli, ASS 4 "Medio Friuli, Udine, Italy, [4]Università Politecnica delle Marche, Ancona, Italy, [5]Università degli studi di Udine ·, Udine, Italy, [6]Ospedali Riuniti, Ancona, Italy.

Background/Purpose: There is evidence that B lymphocytes play a role in the pathogenesis of systemic sclerosis (scleroderma). Stimulatory autoantibodies targeting PDGF receptor and activating normal human fibroblasts *in vitro* have been demonstrated in sera from scleroderma patients(1–3). Rituximab is a monoclonal antibody which selectively targets and depletes CD20+ B lymphocytes. We investigated the biological effects of rituximab in six patients with scleroderma and severe skin involvement.

Methods: Six patients with severe skin fibrosis documented by rapidly increasing skin score not responsive to immunosuppressive treatment were treated with 375 mg/m2 per week of intravenous rituximab for a total of four doses. Primary outcomes were the reduction of the levels of anti-PDGF receptor autoantibodies in patients sera and down-regulation of skin fibroblast activation *in vitro*. Stimulatory autoantibodies to the PDGF receptor were detected with a biological assay using IgG immunopurified from patients serum samples at baseline and 3 and 6 months after treatment. Secondary outcomes included the modified Rodnan's skin score, heath assessment of quality of life (HAQ) and visual analogic scale (VAS) for global wellness. CD19+ lymphocyte count was performed monthly to assess B cell depletion.

Results: Significant reduction of the serum levels of anti-PDGF receptor autoantibodies was observed in all patients 3 months after treatment. However, a slight increase was again detected six months after rituximab infusion. Fibroblasts grown from skin biopsies taken 6 months after treatment showed a significant reduction of type I collagen gene expression and down-regulation of the intracellular signalling triggered by anti PDGFR autoantibodies. A decrease of skin score and improvement of disability indexes paralleled biological results. No infusion reaction or adverse effects were recorded.

Conclusion: A single course of rituximab reduced scleroderma fibroblast activation in vitro and the serum levels of anti PDGFR stimulatory autoantibodies. The data provide further evidence of B-cell involvement in the pathophysiology of scleroderma. Targeting B cells may be a promising treatment for scleroderma patients and large, controlled clinical trials are warranted.

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Effect Of Aminaftone On Raynaud's Phenomenon Secondary To Systemic Sclerosis: A Double-Blind Prospective, Randomized, Placebo-Controlled Pilot Study. Alessandro Santaniello, Barbara Vigone, Monica Caronni and Lorenzo Beretta. Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

Background/Purpose: Raynaud's phenomenon (RP) is a pivotal manifestation of systemic sclerosis (SSc) which reflects an underlying vasculopathy. Endothelial activation with increased circulating levels of Endothelin-1 (ET1) are frequently observed in SSc patients due to a deranged vascular homeostasis. Aminaftone (AMNA) –a derivate of the 4-aminobenzoic acid- was found to be capable of reducing the production of ET-1 in endothelial cell cultures. The present work was conducted to assess the role of AMNA in the treatment of RP and vasculopathy secondary to SSc.

Methods: Single-centre, randomized, prospective, double-blinded comparison of AMNA vs placebo. Patients received either 75 mg AMNA 3 times per day for 12 weeks in wintertime, or matching doses of placebo. We compared the number and the severity of RP attacks at baseline and after 12 weeks; furthermore we investigated the effect of AMNA on serum concentrations of ET1.

Results: Twenty-five patients were randomized to receive AMNA or placebo; 23 patients (12 AMNA; 11 placebo) did complete the study; no drug-related averse events were observed. The two distinct groups were statistically overlapping for baseline clinical and demographical characteristics. An encouraging and strong trend on the reduction of the number of RP attacks in the AMNA vs placebo group was observed (median: −67.9% [−40.7%, −83.3%] vs −44.2% [−15.5%,−54.3%]; p=0.06; Mann-Whitney test); no differences in RP severity scores or Rp duration scores were observed. ET-1 serological concentrations were markedly reduced in the treatment arm compared to the placebo arm (median [IQR]: −43.5% [−25.5%, −46.2%] vs 4.9% [−0.6%, 15.9%]; p=0.02; Mann-Whitney test).

Conclusion: Although the primary clinical endpoint was not met, most likely due to the low sample size, AMNA was found to have meaningful effects on ET-1 serum levels. In light of the results of a previous report showing the non-inferiority of AMNA compared to bosentan in the log-term control of peripheral SS-related vascular clinical manifestations, when bosentan was not indicated, we believe that further wider and more focused studies (e.g. on the prevention of DU) may be warranted to investigate the long-term effect of AMNA in SSc.

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Different Location and Extent Of Impaired Perfusion Of The Choroid Plexus In Primary and Secondary Raynaud's Phenomenon. Francesca Ingegnoli[1], Roberta Gualtierotti[2], Luisa Pierro[3], Elisabetta Miserocchi[4], Giulio Modorati[5], Claudia Del turco[3], Marco Gagliardi[3], Giuseppe Parrinello[3], Tommaso Schioppo[2] and Pier Luigi Meroni[6]. [1]Rheumatology, Istituto G. Pini, University of Milan, Milano, Italy, [2]Division of Rheumatology, Istituto G. Pini, University of Milan, Milano, Italy, [3]Vita-Salute University, San Raffaele Scientific Institute, Milano, Italy, [4]Scientific Institute San Raffaele, University Vita-Salute, Milan, Italy, [5]Ocular immunology and uveitis service, Milano, Italy, [6]Division of Rheumatology, Gaetano Pini Institute, Milano, Italy.

Background/Purpose: Raynaud's phenomenon (RP) is a disorder characterized by systemic vascular dysregulation which has been related with vasospasms and retinal blood flow abnormalities. Nevertheless among the potential complications of RP, eye involvement is often overlooked. The aim of this study was to evaluate the presence of vascular eye involvement measuring the choroidal and macular thickness in a cross-sectional cohort of RP at the first rheumatologic evaluation.

Methods: Thirty adult consecutive RP, without visual symptoms, underwent: clinical evaluation and nailfold capillaroscopy. Sera were tested for anti-nuclear antibodies, anti-dsDNA, anti-extractable nuclear antigens. Patients underwent a complete ocular examination including: best corrected visual acuity; slit lamp biomicroscopy; intraocular pressure measurements and fundus examination; choroidal thickness by Zeiss Cirrus Spectral Domain Optical Coherence Tomography with enhanced depth imaging scan system at the fovea and up to 2 mm at intervals of 1 mm from the fovea in the superior, inferior, nasal and temporal choroid; central foveal thickness (CFT) was also measured. 27 healthy, sex and age-matched, subjects were analysed as control group. Statistical analysis was performed by one-way ANOVA and multiple comparisons.

Results: Eight primary RP (pRP) (median age 53 yrs), 12 early systemic sclerosis (SSc) (median age 57 yrs), 10 RP secondary to suspected connective tissue disease (CTD) (i.e. capillaroscopy abnormalities or antibody positivity and without any symptoms/signs suggesting a CTD) (median age 54 yrs). Slit

lamp biomicrocopy was within normal limits in all patients and fundus examination revealed normal arterial and venous vessels with no capillary abnormalities. The mean best corrected visual acuity was 20/40 and the mean intraocular pressure measurement was 14 mmHg. In pRP, mean choroidal thickness was significantly thinner than healthy controls in the outer nasal (224.8μm vs 289μm; $p<0.05$) and outer temporal (263.3μm vs 299μm; $p<0.05$) regions. In patients with RP secondary to suspected CTD the inner and outer nasal were significantly thinner (244.1μm vs 297.4μm; $p<0.05$ and 199.7μm vs 289μm; $p<0.0001$ respectively). In SSc all the areas examined were significantly thinner than healthy controls except for the inner temporal region which however was decreased: central (250.5μm vs 313.2μm; $p<0.01$), inner inferior (239.9μm vs 293.1μm; $p<0.05$), inner nasal (221μm vs 297.4μm; $p<0.001$), inner superior (243.9μm vs 293.2μm; $p<0.05$), outer temporal (219.3μm vs 299μm; $p<0.001$), outer inferior (229.9μm vs 289.8 μm; $p<0.001$), outer nasal (187μm vs 289μm; $p<0.001$), outer superior (240.4μm vs 293.3μm; $p<0.05$). CFT was also thinner in all the patients than healthy controls although not significant.

Conclusion: A thinner choroidal and macular thickness was observed in all the patients, with progressive decrease from pRP to SSc. These data suggest an early involvement of ocular microcirculation with significant reduction of choroidal perfusion. This process likely starts from the external regions (outer nasal and temporal) in pRP, and becomes more severe and extensive in RP secondary to a suspected CTD and even more severe and in SSc.

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Intravenous Immunoglobulin May Be An Effective Therapy In Scleroderma Patients With Refractory Active Diffuse Cutaneous Disease. Corrie Poelman, Laura K. Hummers, Fredrick M. Wigley, Cynthia Anderson, Francesco Boin and Ami A. Shah. Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: A subset of patients with active diffuse cutaneous scleroderma has refractory disease despite traditional immunosuppressive therapy. In this retrospective observational study, we investigated whether intravenous immunoglobulin (IVIG) improved skin thickening in patients with refractory disease compared to data from historical controls.

Methods: Scleroderma patients receiving IVIG to treat diffuse cutaneous disease that was active despite other therapy were identified from the Johns Hopkins Scleroderma Center database and medical record review. The mean modified Rodnan skin score (mRSS) at baseline was compared to the mRSS at 6, 12, 18 and 24 months post-IVIG initiation by paired t-test. Clinical "responders" at 6 and 12 months were defined by a mRSS decline of at least 5 points based on previously published data examining the minimal clinically important difference. Potential predictors of response were examined by Student's t-test, Fisher's exact test, and logistic regression analysis where appropriate. Changes in mRSS at 6 and 12 months were also compared to data from historical controls of 3 large, negative, multicenter, randomized clinical trials of other medications (D-penicillamine (D-pen), Recombinant Human Relaxin (Relaxin), and Oral Bovine Type I Collagen (Collagen) trials) using the Student's t-test.

Results: Out of 66 patients who received IVIG between 2004–2012, 30 were treated for active diffuse cutaneous disease and were included for analysis. The study population had a mean age of 42.7 $\pm$ 14.4 years at scleroderma onset, were predominantly female (80%) and white (86.7%), and had a mean scleroderma disease duration of 3.9 $\pm$ 5.9 years at initiation of IVIG. Patients received an average of 8.3 $\pm$ 4.6 monthly IVIG cycles. Concomitant medication use included methotrexate (10%), mycophenolate (70%), cyclophosphamide (20%), and corticosteroids (33.3%). The mean baseline mRSS was 29.6 $\pm$ 7.2, and this significantly decreased to 24.6 $\pm$ 9.4 ($N=28$; $p=0.0017$) at 6 months, 22.0 $\pm$ 10.1 ($N=26$; $p<0.0001$) at 12 months, 21.0 $\pm$ 11.5 ($N=23$; $p=0.0002$) at 18 months and 15.3 $\pm$ 6.4 ($N=15$; $p<0.0001$) at 24 months. 15/28 patients and 16/26 patients were "responders" to IVIG therapy at 6 and 12 months, respectively. None of the examined parameters (age, disease duration at IVIG initiation, duration of IVIG therapy, autoantibody status, and concomitant immunosuppressive therapy) were associated with responder status at 6 or 12 months.

The mean baseline mRSS in the IVIG group (29.6 $\pm$ 7.2) was similar to that of the Relaxin trial (27.3 $\pm$ 6.9, $p=0.09$), but was significantly higher than that observed in the D-pen (21.0 $\pm$ 8.0, $p<0.0001$) and Collagen (26.1 $\pm$ 7.8, $p=0.023$) trials. At 6 months, the mean change in mRSS was not significantly different in the IVIG group (-5.3 ± 8.0) compared to the Relaxin trial (-4.8 ± 6.99, $p=0.75$); however, at 12 months the mean change in mRSS was significantly better in the IVIG group (-7.9 ± 8.1) than in the D-pen (-2.5 ± 8.6, $p=0.0044$) and Collagen (-3.4 ± 7.1, $p=0.0047$) groups.

Conclusion: This study suggests that IVIG may be an effective therapy for active diffuse cutaneous disease in patients who have been refractory to other immunosuppressive therapies.

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Nilotinib (Tasigna™) In The Treatment Of Early Diffuse Systemic Sclerosis: A Single Group, Open Label Pilot Clinical Trial – One Year Results. Jessica K. Gordon[1], Cynthia Magro[2], Uzunma Udeh[1], Daniele Lerner[1], Horatio F. Wildman[2], Wei-Ti Huang[1], Mary K. Crow[1] and Robert F. Spiera[1]. [1]Hospital for Special Surgery, New York, NY, [2]Weill-Cornell Medical Center, New York, NY.

Background/Purpose: Tyrosine kinase inhibitors (TKI) are under investigation for the treatment of diffuse cutaneous Systemic Sclerosis (dcSSc.) Nilotinib is a second-generation TKI which selectively antagonizes c-abl and PDGFR and has a different side-effect profile from imatinib and other TKIs. One year follow-up data from a single group, open label, pilot trial are presented here.

Methods: Ten adult patients (pts) with early progressive dcSSc of <3 yrs since the initial SSc symptom excluding Raynaud's were recruited. Pts were treated with nilotinib 400 mg PO twice daily. Pts were excluded if they had a QTc>450 ms. Concurrent immunosuppressive treatment was not allowed. The primary endpoint was safety as assessed by the number of adverse effects (AEs) and serious (S)AEs, and the primary efficacy endpoint was change in the Modified Rodnan Skin Score (MRSS) after 6 mo of treatment. Secondary endpoints include forced vital capacity (FVC), diffusion capacity (DLCO) and other measures. After 6 mo pts were offered continued treatment for 24 mo. Forearm skin biopsies were performed at baseline and after 6 and 12 mo.

Results: Nineteen pts were screened; 5 were excluded due to QTc>450 ms, and 10 were enrolled. At baseline the median age was 46 (IQR 33, 52), 80% were female, 50% were Caucasian, and disease duration was 0.7 yrs (0.5, 1.7). 30% were Scl70+ and 50% were RNAPol3+. 30% had ILD. 40% had tendon friction rubs. 70% had a worsening MRSS in the month prior to baseline, with a mean MRSS increase between screen and baseline of 2.9 ($p=0.02$) in the group.

Seven pts completed 12 mo of treatment and elected to continue on nilotinib. Three pts discontinued nilotinib within the first 3 mo of treatment - 2 due to Grade 1–2 QTc prolongation and 1 due to progression of preexisting coronary artery disease. During the 12 mo period of observation 71 AEs including 2 SAEs were observed; 75% were considered to be at least possibly related to nilotinib. 92% of AEs were grade 1 or 2.

The MRSS was significantly improved by a mean of 4.1 points or 15% at 6 months and by 6.7 or 25% at 12 months in the 7 completers. The physician global assessment improved significantly as well. No significant difference was observed in the FVC, DLCO, or Scleroderma health assessment questionnaire.

	Baseline	6 months	12 months	p-value 6 mo	p-value 12 mo
MRSS	26.9 $\pm$ 5.4	22.7 $\pm$ 8.0	20.1 $\pm$ 7.3	0.02	0.01
FVC (%pred)	77.4 $\pm$ 12.9	75.4 $\pm$ 12.5	71.7 $\pm$ 11.7	0.17	0.054
DLCO (%pred)	72 $\pm$ 9.9	69.9 $\pm$ 18.1	69.3 $\pm$ 12.39	0.56	0.26
Physician Global Assessment	62.5 $\pm$ 10.8	40.2 $\pm$ 12.7	32.3 $\pm$ 15.3	<0.01	<0.01

Skin biopsies were assessed in a blinded fashion by a dermatopathologist. No significant difference in morphology or skin thickness was observed.

Conclusion: Nilotinib was tolerated by the majority of patients in this study. Tolerability was limited primarily by mildly prolonged QTc, which is a known side effect of nilotinib and an exclusion criterion for continuation in this study. QTc elevation can be seen in dcSSc independent of nilotinib therapy and limited patient eligibility. Although this single-group pilot study is not conclusive, significant improvement of MRSS was seen in an early and actively progressing group of patients. Further study of TKI is warranted in a randomized controlled manner.

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Johnson, 1, Novo Nordisk, 2, Ignyta, 5, Takeda, 5, EMD Merck Serono, 5, Biogen-Idec, 5, Idera, 5, MedImmune, 5, Human Genome Sciences/GSK, 5, Roche Genentech, 5; **R. F. Spiera**, Roche Pharmaceuticals, 2, Novartis Pharmaceutical Corporation, 2, GlaxoSmithKline, 2.

ACR Poster Session A
T-cell Biology and Targets in Autoimmune Disease: Signaling Pathways in T-cell Differentiation
Sunday, October 27, 2013, 8:30 AM–4:00 PM

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Interleukin-6 Driven STAT3 Phosphorylation In Circulating Lymphocytes Is Specific For CD4$^+$ T Cells In Early Rheumatoid Arthritis. Amy E. Anderson[1], Christine Routledge[2], Philip Mawson[2], John D. Isaacs[1] and Arthur G. Pratt[1]. [1]Newcastle University, Newcastle upon Tyne, United Kingdom, [2]The Freeman Hospital, Newcastle upon Tyne, United Kingdom.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease, caused by a breakdown in self tolerance. Robust biomarkers are needed which, as well having diagnostic utility, enable its stratification into therapeutically relevant sub-sets. We recently identified a transcriptional signature in circulating CD4$^+$T-cells which predicted RA progression amongst patients attending an early arthritis clinic. As well as appearing most prominently in a diagnostically challenging sub-group of individuals who were seronegative for anti-citrullinated peptide autoantibodies (ACPAs), the signature contained an over-representation of signal transduction and activator of transcription-3 (STAT3) regulated genes, whose expression in turn correlated with serum interleukin (IL)-6. We therefore sought an improved understanding of STAT3 signalling amongst immune cell subsets of an independent early arthritis patient cohort.

Methods: 94 newly presenting patients, naïve to immunomodulatory treatment (including steroids), were recruited from an early arthritis clinic, and followed until diagnoses were confirmed. Basal and IL-6-induced expression levels of p_{Y705}STAT3 (pSTAT3) were determined in T-cell and B-cell subsets using Phosflow, a flow cytometry based method for measuring intracellular phospho-proteins. Contemporaneous serum IL-6, IL-6R and soluble gp130 levels were measured by immuno-assay.

Results: Basal pSTAT3 levels were high in circulating CD4$^+$ T-cells, but low in both CD8$^+$ T-cells and B-cells. Basal pSTAT3 expression correlated with serum IL-6 levels most strongly in CD4$^+$ T-cells and, to a lesser extent, CD8$^+$ T-cells, but not B-cells. The expected pSTAT3 induction following IL-6 stimulation, observed in all subsets, was most pronounced in CD4$^+$ T-cells, and this reflected significantly higher basal IL-6R surface expression in this cell population. Finally, when patients were categorised by diagnostic outcome, ACPA-negative RA patients had significantly higher basal pStat3 in CD4$^+$ T-cells than ACPA-positive RA, inflammatory non-RA and non-inflammatory arthritis patients – a pattern that was not seen in CD8$^+$T-cells or B-cells, and which corroborates our previous observations in respect of STAT3 target gene expression.

Conclusion: Our findings support a particular role for IL-6-driven CD4$^+$ T cell activation, primarily via STAT3, during the induction of RA. Since CD4$^+$ T-cells preferentially express surface IL-6R, a critical role in this setting for *classical* IL-6 signalling (as opposed to *trans* signalling, which is not dependent on IL-6R surface expression) is suggested. Expression of pSTAT3 in CD4$^+$ T-cells may serve as a biomarker for predicting the evolution of RA in ACPA-negative patients and may also be a useful tool for predicting efficacy of therapies which target IL-6 signalling.

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1,25(OH)$_2$D$_3$ Inhibits Th17 Cytokine Production and RORγt Expression Through GATA3/IL4-Dependent and -Independent Mechanisms. Wendy Dankers[1], Jan Piet van Hamburg[2], Anne-Marie Mus[1], Patrick S. Asmawidjaja[1], Johannes van Leeuwen[1], Rudi W. Hendriks[1], Louis Boon[3], Edgar Colin[4] and Erik Lubberts[2]. [1]Erasmus MC, University Medical Center, Rotterdam, Netherlands, [2]Erasmus Medical Center, Rotterdam, Netherlands, [3]Bioceros, Utrecht, Netherlands, [4]ZGT, Almelo, Netherlands.

Background/Purpose: Vitamin D has suppressive effects on autoimmune diseases, such as rheumatoid arthritis (RA). One important mechanism of disease suppression by vitamin D is inhibition of Th17 cytokines and the Th17 transcription factor RORγt. On the other hand, vitamin D induces IL-4 and GATA3. Since GATA3 overexpression inhibits experimental Th17-mediated autoimmunity, we studied the contribution of GATA3 in vitamin D-mediated suppression of Th17 polarization.

Methods: We first sorted CD4$^+$ T cells from the spleen of naïve DBA-1 mice and DBA-1 mice immunized with collagen type II (CII) and cultured them under T helper cell polarizing conditions with or without 1,25(OH)$_2$D$_3$, the active form of vitamin D. Furthermore, splenic CD4$^+$ T cells are sorted from wild-type and CD2-GATA3 transgenic mice and cultured under these conditions. Finally, we performed gene-expression profiling on CCR6$^+$cells from treatment-naïve early RA patients.

Results: In cultures of CD4$^+$ T cells from naïve and CII-immunized mice, 1,25(OH)$_2$D$_3$ inhibits Th17 polarization while inducing IL-4 and GATA3 expression. IL-4 inhibition partly reversed the vitamin D-mediated inhibition of Th17 polarization. To study the role of GATA3, we compared CD4$^+$ T cells from wild-type and CD2-GATA3 transgenic mice after culture under Th17 polarizing conditions. In these cultures 1,25(OH)$_2$D$_3$ reduces Th17 differentiation, but the effect of GATA3 overexpression is stronger. Interestingly, combining GATA3 overexpression and 1,25(OH)$_2$D$_3$ treatment reduced IL-17A and RORγt expression even further. Subsequent analysis of gene expression in wild-type CD4$^+$ T cells cultured under Th17 polarizing conditions showed that NFAT-C2, which is involved in IL-17A production, was downregulated by 1,25(OH)$_2$D$_3$. In addition, gene expression analysis in CCR6$^+$ T cells from patients with RA showed that 1,25(OH)$_2$D$_3$also inhibits Th17 cytokine and RORγt expression in humans, while inducing IL-4 and GATA3 expression.

Conclusion: These data show that vitamin D-mediated regulation of Th17 polarization occurs through GATA3-dependent mechanisms, including direct effects on RORγt expression and IL-4-mediated inhibition of Th17 polarization. Moreover, GATA3-independent mechanisms are involved that may include modulation of NFAT-C2. These mechanisms may play a role in the suppressive effect of vitamin D on RA disease activity.

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Increased IL-23 Receptor Expression Is Observed On KIR3DL2+ CD4+ T Cells In Ankylosing Spondylitis and Correlates With IL-23R Polymorphisms. A. Ridley, C. Cohen, T. Karaderi, S. Kollnberger, I. Wong-Baeza, J. Shaw, P. Wordsworth and P. Bowness. University of Oxford, Oxford, United Kingdom.

Background/Purpose: T helper 17 (Th17) cells are a subset of pro-inflammatory CD4+ T cells implicated in a number of inflammatory arthritides including the Spondyloarthritides (SpAs). Ankylosing Spondylitis (AS), the commonest spondyloarthropathy, has genetic associations both with HLA-B27 and with IL-23 receptor (IL-23R) single nucleotide polymorphisms (SNPs), however the link remains unexplained. We have previously shown that KIR3DL2+ CD4+ T cells are expanded in the peripheral blood of individuals with AS. The aim of the study was to further characterize KIR3DL2+ CD4+ T cells and to correlate IL-23R expression on KIR3DL2+ CD4+ T cells to IL-23R genotype.

Methods: The frequency and expression level of Th17 markers IL-23R, IL-1R and CCR6 on peripheral blood KIR3DL2+ CD4+ T cells was investigated by flow cytometry (n=15) and confirmed by qRT-PCR (n=3). IL-23R expression on paired peripheral blood and synovial fluid samples from SpA patients was investigated by flow cytometry (n=3). Cytokine production by anti-CD2/3/28-stimulated FACS-sorted KIR3DL2+ and KIR3DL2- CD4+ T cells was investigated using multiplex bead analysis. Immunochip GWAS and ENCODE data were integrated to predict functional SNPs in the IL-23R secondary region of association.

Results: KIR3DL2+ CD4+ T cells were increased in the peripheral blood of HLA-B27+ AS patients, as compared to HLA-B27- healthy controls ($p<0.001$, n= 15), confirming previous findings. KIR3DL2+ CD4+ T cells were enriched for expression of the Th17 phenotypic markers IL23R ($p<0.0001$, n=15), CCR6 ($p<0.0001$, n=15) and IL-1R ($p<0.0001$, n=15), compared to KIR3DL2- CD4+ T cells. IL-23R expression levels were also increased on KIR3DL2+ CD4+ T cells compared to KIR3DL2- CD4+ T cells from AS patients ($p<0.0001$, n=15). SNPs in three (non-coding) putative regulatory regions (PRRs) of

IL-23R were identified (PRR1–3). The presence of the AS risk-associated allele at PRR1 correlated with increased expression of IL-23R on KIR3DL2+ CD4+ T cells ($p=0.031$, $n=13$). KIR3DL2+ CD4+ T cells accounted for the majority of peripheral blood CD4+ T cell IL-23R expression in AS patients, and this was significantly greater compared to HLA-B27- healthy controls ($p<0.01$, $n=15$). KIR3DL2+ CD4+ T cells from AS patients produced significantly more IL-17 than KIR3DL2- CD4+ T cells ($p=0.037$, $n=7$). IL-17 production significantly increased in the presence rIL-23 and rIL-1 ($p=0.029$, $n=7$). Lastly IL-23R expression was increased on KIR3DL2+ CD4+ T cells from SpA synovial fluid samples compared to match peripheral blood samples when available ($p=0.017$, $n=3$).

Conclusion: KIR3DL2-expressing cells constitute the majority of peripheral blood CD4+ T IL-23R-expressing cells in AS and produce increased levels of IL-17. Correlation of IL-23R expression on KIR3DL2+ CD4+ T cells with putative regulatory SNPs suggest genetic and epigenetic control of IL-23R expression may contribute to the pathogenesis of AS.

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Interferon Regulatory Factor 2 Haploinsufficiency Deteriorates Imiquimod-Induced Psoriasis-Like Skin Inflammation. Takayuki Kimura, Makoto Sugaya, Makiko Kawaguchi, Sohshi Morimura, Hiraku Suga and Shinichi Sato. The University of Tokyo, Tokyo, Japan.

Background/Purpose: Psoriasis is a T-cell-mediated immunological skin disease with a complex pathogenesis where both genetic and environmental factors are involved. Interferon regulatory factor (IRF)-2 is one of the potential susceptibility genes for psoriasis. IRFs are a family of transcription factors that regulate expression of pro- and anti-inflammatory genes. IRF-2 protein binds the same regulatory sequence as IRF-1, which suppresses transcription of interferon-inducible genes. Topical application of imiquimod, a TLR7/8 ligand, induces psoriasis-like inflamed skin lesions via the IL-17/23 axis. We hypothesized that combination of IRF2 gene status and environmental stimulus (imiquimod) would cause severer skin lesions, serving as a good model of human psoriasis.

Methods: IRF-$2^{+/-}$ and wild-type (WT) mice received a daily topical dose of 62.5 mg imiquimod cream (5%) on a shaved back and ears for 6 consecutive days. Erythema, scaling, and skin thickness were independently scored every day. Total RNA was isolated from skin specimens on day 2 and 5 and reverse-transcribed into cDNA. Macrophage were harvested from peritoneal cavity of naive IRF-$2^{+/-}$ and WT mice and stimulated with 1 or 5 μg/ml of imiquimod for 6 or 24 hours in vitro. Total RNA was isolated and reverse-transcribed into cDNA. Messenger RNA expression of different cytokines was analyzed using a real-time PCR quantification method.

Results: Imiquimod-induced skin inflammation assessed by erythema, scaling, and skin thickness was severer in IRF-$2^{+/-}$ mice than WT mice. In inflamed skin, mRNA expression of TNF-α, IL-12/23p40, IL-23p19, and inducible nitric oxide synthase (iNOS) was increased on day 2, and that of TNF-α, IL-12p35, IL-17A, and iNOS was increased on day 5 in IRF-$2^{+/-}$ mice compared to WT mice. In peritoneal macrophage of IRF-$2^{+/-}$ and WT mice stimulated with imiquimod, mRNA levels of TNF-α, IL-12/23p40, IL-23p19, IL-12p35, IL-36α, and IL-36γ were significantly elevated compared to non-stimulated macrophages. Interestingly, macrophages harvested from IRF-$2^{+/-}$ mice expressed higher levels of TNF-α, IL-12/23p40, IL-23p19 compared to those from WT mice 24 hours after stimulation, while they expressed similar levels of IL-12p35, IL-36α, and IL-36γ. Moreover, elevated mRNA expression of iNOS was observed only in stimulated macrophages derived from IRF-$2^{+/-}$ mice.

Conclusion: These results suggest that IRF-2 haploinsufficiency and a TLR7/8 stimulator regulate cytokine expression in a different manner, developing Th17-associated skin inflammation, which may serve as a good model of human psoriasis.

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Combination Blocking Of Interleukin-6 and Interleukin-21 In Experimental Arthritis Inhibits Their Redundant Role In T Helper 17-Driven Joint Pathology. Debbie M. Roeleveld[1], Marije I. Koenders[2], Renoud J. Marijnissen[1], Cheryl L. Nickerson-Nutter[3], Fons A. van de Loo[1] and Wim B. van den Berg[4]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Rheumatology Research and Advanced Therapeutics, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands, [3]Pfizer, Cambridge, MA, [4]Rheumatology Research and Advanced Therapeutics, Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.

Background/Purpose: Both IL-6 and IL-21 have been described to drive *in vitro* Th17 differentiation in the presence of TGF-β. We explored whether also *in vivo* IL-6 and IL-21 play an exchangeable and redundant role in Th17 differentiation during experimental arthritis, and to what extent combined blocking of these cytokines inhibits Th17 differentiation and suppresses arthritis development.

Methods: To investigate possible synergistic effects of the IL-6 and IL-21 pathways, arthritis development and Th17 cells were first studied in IL-$6^{-/-}$xIL-$21R^{-/-}$ mice and their wild-type (WT) and single-knockout controls during antigen-induced arthritis (AIA). In addition, the effects of combined IL-6R and IL-21 neutralization were studied in DBA-1J mice treated at various stages of collagen-induced arthritis (CIA).

Results: Mice deficient for either IL-6 or IL-21R showed suppressed AIA compared to WT controls. This disease reduction was accompanied by a significant reduction in CD4+IL17+ T cells in the draining lymph nodes as determined by FACS. Interestingly, mice lacking both the IL-6 and IL-21 signaling pathways showed even stronger disease suppression, and a striking reduction in Th17 levels was observed in these mice.

Based upon these findings, we aimed to confirm the synergistic effects of IL-6/IL-21 with a cytokine-neutralization approach using anti-IL-6R antibodies and sIL-21R-Fc treatment during CIA. Antibodies were given as single treatment or in combination, starting from immunization (day 0) or simultaneous with the booster (day 21).

Combined blocking of IL-6R and IL-21 early during arthritis development (day 0) was a very potent approach to prevent arthritis development, reaching a disease incidence of only 40% at day 35 (isotype control 100%, sIL-21R-Fc 100%, anti-IL-6R 60%). Analyzing the mice that did develop arthritis, we observed that the anti-IL-6R/sIL-21R-Fc combination was also clearly more potent in suppressing the arthritis severity in comparison with the single treatments. Interestingly, blocking the IL-6/IL-21 pathways at a later stage during arthritis development (day 21) was clearly less effective and did not show additional effects to anti-IL-6R treatment alone.

Conclusion: Combined blocking of the IL-6 and IL-21 pathways suppresses Th17 differentiation *in vivo* as demonstrated by our IL-6/IL-21R-deficient mice. However, our neutralization study during CIA shows that to influence arthritis development this IL-6/IL-21 blocking approach only has a limited therapeutic window. These findings suggests that to target Th17-driven joint pathology, blocking Th17 effector cytokines like IL-17 and IL-22 might be more effective than attempting to reduce Th17 cell numbers during active disease.

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Protein Phosphatase 5 (PP5) Regulates Methylation Sensitive Gene Expression In CD4+ T Cells. Dipak R. Patel, Gabriela Gorelik and Bruce C. Richardson. University of Michigan, Ann Arbor, MI.

Background/Purpose: CD4+CD28- T cells are enriched in chronic inflammatory diseases like rheumatoid arthritis (RA) and lupus. They are cytotoxic and resistant to apoptosis. Compared to CD28+ cells, CD28- CD4 T cells over-express killer immunoglobulin-like receptors (KIRs) and other pro-inflammatory molecules. These genes are regulated by DNA methylation, so they are over-expressed by CD4 T cells that are demethylated in vitro. This is a result of decreased signaling through the ERK and JNK pathways and, consequently, decreased activity of the DNA methyltransferase enzymes (DNMTs) responsible for DNA methylation. Protein phosphatase 5 (PP5) is a stress induced regulator of gene expression in multiple signaling pathways,

including those involved in aging. It is expressed in CD4+CD28-, but not CD4+CD28+ T cells, and it inhibits both ERK and JNK signaling. We hypothesized that PP5 is over-expressed in CD4+ T cells in patients with RA and lupus, and that over-expressing PP5 in CD4 T cells from healthy donors will induce expression of methylation sensitive genes unique to CD4+CD28- T cells.

Methods: CD4+ T cells were isolated from healthy controls and patients, and PP5 mRNA was measured by RT-PCR. To study the effects of PP5 on gene expression, PBMCs from healthy donors were stimulated with phytohemagglutinin and cultured for 3 days with IL-2. CD4+ T cells were then isolated by negative selection, transfected (Amaxa Nucleofector) with constructs encoding GFP and PP5 or GFP alone, and cultured 24–72 hours. Expression of DNMT1 and methylation sensitive genes was assessed by RT-PCR in sorted CD4+GFP+ T cells. DNMT1 expression was measured 24 hours after transfection, and the other genes were analyzed 72 hours after transfection. Cell surface protein expression was measured by flow cytometry 72 hours after transfection.

Results: Compared to CD4+ T cells from healthy donors, PP5 mRNA is over-expressed in patients with lupus (1.97 fold change $\pm$0.18 SEM, $p=0.03$) and RA (1.6$\pm$0.2, $p<0.05$). When transfected into CD4+ T cells from healthy donors, PP5 increased mRNA levels of KIR (2DL4 gene, 2.4$\pm$0.7 fold, $n=3$, $p=0.04$), perforin (1.38$\pm$0.07 fold, $p=0.03$, $n=3$), CD11a (1.2$\pm$0.1 fold, $p=0.047$, $n=5$), and CD70 (10.5$\pm$4.1 fold, $p=0.03$, $n=7$). PP5 also increased the percentage of cells expressing surface KIRs (33$\pm$7% with control vs. 62$\pm$7% with PP5, $n=7$, $p<0.01$), CD70 (37% with control vs. 63% with PP5), and CD40L (30% with control vs. 54% with PP5). Finally, PP5 caused a corresponding 20$\pm$8% decrease ($n=3$, $p=0.05$) in DNMT1 mRNA expression.

Conclusion: CD4+CD28- T cells, which are enriched in lupus and RA, over-express pro-inflammatory methylation sensitive genes. These data demonstrate, for the first time, that PP5 contributes to the regulation of these genes (KIR, perforin, CD70, CD40L, and CD11a) in CD4+ T cells. PP5 is hypothesized to accomplish this by demethylating regulatory elements in the promoters for these genes, and this is currently being tested. PP5 has not been studied in T cells before, and it potentially links aging and DNA methylation with the pathogenesis of multiple rheumatologic disorders.

Disclosure: D. R. Patel, None; **G. Gorelik**, None; **B. C. Richardson**, None.

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The Active Metabolite Of Spleen Tyrosine Kinase Inhibitor Fostamatinib Abrogates The T Cell Priming Capacity Of Dendritic Cells.

Andrew Platt[1], Ross McQueenie[1], Robert Benson[2], John Butcher[1], Martin Braddock[3], James M. Brewer[1], Iain B. McInnes[1] and Paul Garside[1]. [1]University of Glasgow, Glasgow, United Kingdom, [2]Institute of Infection, Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, United Kingdom, [3]AstraZeneca R&D Alderley Park, Macclesfield, United Kingdom.

Background/Purpose: Spleen tyrosine kinase (SYK) is a core signaling protein that drives inflammatory responses and is fundamental to the propagation of signals via numerous immune-receptors including the B cell receptor (BCR) and Fc receptors (FcRs). The small molecule SYK inhibitor, fostamatinib, has shown evidence of ameliorating inflammation in rheumatoid arthritis (RA) patients. We sought to understand how the active metabolite of fostamatinib, R406, affects the inflammatory response at the cellular level. It has been shown that R406 reduces the response of dendritic cells (DCs) to immune complexes (ICs) and we have previously demonstrated that the area and duration of interaction between T cells and DCs are key determinants in the outcome of an immune response.

Methods: Fluorescence microscopy was combined with CD4+ T cells from T cell receptor transgenic OT-II mice to track antigen-specific interactions between DCs and T cells in vitro.

Results: We have found that R406 reduces the DC-T cell contact area and the number of interactions lasting more than 5 minutes during the initial phase of cellular cross-talk between IC-activated DCs and antigen-specific CD4+ T cells. This led to diminished proliferation with 19.2$\pm$0.5% of OT-II CD4+ T cells undergoing proliferation (and only a maximum of two rounds) after R406 treatment compared with 79.6$\pm$2.0% in vehicle controls. This reduced proliferative capacity of CD4+ T cells was accompanied by reduced expression of the co-stimulatory molecules, ICOS and PD-1, and total blockade of the production of inflammatory cytokines such as IFNg and IL-17.

Conclusion: Our findings indicate a potential mechanism via which this compound may be effective in inhibiting FcR-driven T cell responses and ameliorating chronic articular inflammation.

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Patients With Rheumatoid Arthritis Have Impaired Candida Albicans Specific Th17 Responses But Preserved Oral Candida Albicans Protective Immunity.

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Background/Purpose: Rheumatoid arthritis (RA) patients are susceptible to infections, even after controlling for the effects of medications. Recent data suggest an important role for the IL-17 producing CD4+ Th17 cell subset in the pathogenesis of RA. Development of Th17 cells is dependent on TNFa, IL-6 and T cell co-stimulation, targets for current biologic therapies for RA. In humans, Th17 cells and IL-17 are necessary for immunity to the commensal fungus *Candida albicans*, and response to biologics in RA is associated with reductions in Th17 cells. There is little published data on *Candida albicans* specific responses in RA. Therefore, our aim was to assess *Candida albicans* specific Th17 responses in RA and to determine the effect of biologic therapies on *Candida albicans* specific Th17 responses.

Methods: Subjects for this study were recruited from the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Registry (RACER). We used flow cytometry to compare the fraction of peripheral blood Th17 and Th1 cells between healthy controls ($n=23$) and RA subjects ($n=48$). To assess *C. albicans* specific peripheral blood Th17 responses and capacity for Th17 differentiation, we used ELISA to determine IL-17A production from peripheral blood mononuclear cells (PBMCs) cultured for 5 days from healthy controls ($n=10$) and RA subjects ($n=37$). PBMC were co-cultured with either heat-killed *C. albicans* (HKC) or Th17 polarizing cytokines. Th17 effector responses were determined by measuring oral *C. albicans* colonization and candidacidal killing using saliva collected from healthy control and RA subjects. Healthy control and RA subject data were compared using Mann-Whitney U tests.

Results: Patients with RA had significantly elevated production of IL-17A during PBMC culture without HKC or cytokines as compared to healthy control PBMC ($p=0.02$). However, IL-17A production by RA PBMC during co-culture with HKC was significantly diminished compared to healthy control PBMC ($p=0.006$) despite equal production of IL-17A during PBMC co-culture with Th17 differentiating cytokines ($p=0.91$). The *C. albicans* specific peripheral blood Th17 defect was associated with a higher propensity towards oral colonization with *C. albicans* of RA subjects compared to healthy controls ($p=0.04$), although RA subjects had preserved salivary candidacidal killing capacity compared to controls ($p=0.82$). Furthermore, the *C. albicans* specific defects were not associated with differences between RA and control subjects in either circulating Th17 cell numbers ($p=0.07$) or the distribution of Th17 cells in the CD161+ ($p=0.82$) and CD45RO+ (memory) ($p=0.37$) compartments. There were no differences in *C. albicans* specific responses in subgroups of RA subjects on oral DMARDs vs. biologics.

Conclusion: We found that despite increased basal IL-17A production by RA PBMC and a preserved ability to respond to Th17 inducing cytokines, RA patients have demonstrable impairments in *C. albicans* specific T cell responses and increased oral colonization with *C. albicans*. Fortunately, biologic therapy (as compared to oral DMARD therapy) did not appear to impact *C. albicans* specific responses.

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Mesenchymal Stem Cells and Skin Fibroblasts Both Suppress Early Steps In T Cell Activation In a Nitric-Oxide Dependent Manner.

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Background/Purpose: Mesenchymal stem cells (MSCs) are multipotent cells with capacity to differentiate into osteoblasts, chondrocytes, and adipocytes. A phase II study in Europe has shown intravenous infusion of *ex vivo* expanded MSCs might be an effective treatment for steroid-resistant, acute graft-versus-host disease. This result raised the question of whether a similar therapy would be beneficial for autoimmune diseases. Although some studies have shown that MSCs can suppress T cell proliferation, the mechanism (s) by which MSCs suppress T cell function are not well understood. Also, whether the immunosuppressive functions of MSCs are unique to MSCs or a more general function of stromal cells has been questioned. The purpose of this study is to compare the suppressive effect of MSCs from different sources and skin fibroblasts (FB) on T cell activation, proliferation and differentiation, and to examine whether the underlying mechanisms by which suppression occurs are similar.

Methods: Purified mouse TCRβ+ CD44- CD62L^{high} näive T cells were activated with anti-CD3/anti-CD28 antibodies, either alone or in transwell contact-independent co-cultured with human adipose derived stem cells (ADSC), human bone marrow stromal cells (BMSC), human fibroblasts (FB), human umbilical vein endothelial cells (HUVEC). T cell activation and proliferation was analyzed using carboxyfluorescein diacetate succinimidyl ester (*CFSE*) and FlowJo software. T cell surface markers, intracellular cytokine expression, MSCs and FB surface markers were analyzed by flow cytometry.

Results: ADSC and BMSC, but not FB, demonstrate trilineage differentiation potentials. After three days of co-culture of naïve T cells with ADSC, BMSC, FB or HUVEC, proliferation analysis showed that the percentage of divided cells (division index) was lower in ADSC, BMSC, FB groups compared to T-cell-only group and HUVEC group. However, after T cells had divided at least once, no difference in the further cell division (proliferation index) was observed. This indicates that ADSC, BMSC and FB suppress either activation or commitment to enter the cell cycle, rather than proliferation of activated T cells. Stromal cells needed to be present during the first 24 hours of T cell activation, and could not suppress T cell proliferation when added after that. By using sorted Foxp3$^-$T cells, the suppressive effect of stromal cells on T cell proliferation was shown to be independent of Treg. Analysis of naïve CD8 T cells showed similar results. L-NAME, an inhibitor of inducible nitric oxide synthetase (iNOS) reversed the suppressive effects of BMSC, ADSC and FB at a concentration of 50μM.

Conclusion: Mesenchymal stem cells (ADSC and BMSC) and fibroblasts can suppress T cell activation independent of Treg at a stage prior to the first cell division. This suppression can be reversed by inhibition of iNOS. These results indicate that immunomodulatory function is not unique to MSCs, and may be unrelated to their "stemness". Stromal cells with different tissue origins such as skin-derived fibroblasts probably share similar properties.

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Mammalian Target Of Rapamycin (mTOR) Skews T Cell Lineage Development In Systemic Lupus Erythematosus (SLE). Hiroshi Kato and Andras Perl. SUNY Upstate Medical University, Syracuse, NY.

Background/Purpose: mTOR activity is increased in SLE T cells and its blockade has therapeutic efficacy in SLE. Murine studies showed essential roles of mTORC1 in Th1/Th17 and mTORC2 in Th2 differentiation, whereas mTORC1 and 2 need to be blocked for Treg differentiation. Whether mTOR regulates T cell cytokine expression and Treg development in SLE remains elusive.

Methods: CD3$^+$ T cells were isolated from SLE patients and matched healthy controls (HC). A part of the CD3$^+$ T cells were stained with pS6RP, FoxP3, IFN-γ, IL-4, and IL-17 alone or together following CD4, CD8, and CD25 staining. The rest of the cells were cultured in RPMI culture media with 10% FCS, 1% Penicillin/Streptomycin, and 1% L-glutamine for 3 days in the absence or presence of plate bound anti-CD3 and soluble anti-CD28 with or without 100 nM rapamycin. After 3 day culture, cells were stained as previously described. pS6RP and cytokine expression by CD4$^+$, CD8$^+$, and DN T cells and frequency of CD4$^+$CD25$^+$FoxP3$^+$ Treg were assessed by flow cytometric analysis. Using day 3 T cell lysates, immunoblotting was performed using anti-Akt, anti-pAkt (Ser 473), anti-S6K1, and anti-pS6K1. The signal intensity was normalized to Actin.

Results: On day 0, frequency of pS6RP^{hi} cells was higher in DN T cells than CD4$^+$ or CD8$^+$ T cells (DN T cells: 29.40$\pm$6.37%, CD4$^+$ T cells: 1.04$\pm$0.16%; p=0.00028, CD8$^+$ T cells: 5.02$\pm$0.73%; p=0.00097 in SLE) and was higher in SLE than HC T cells, which was most prominent in DN T cells (29.40$\pm$6.37%, 17.59$\pm$4.47%, p<0.001). Rapamycin inhibited mTORC1 in T cells stimulated *in vitro* for 3 days based on the frequency of pS6RP^{hi} cells (41.85$\pm$7.67%, 1.53$\pm$0.27% in SLE; p<0.0001) and pS6K1 expression in T cell lysates (p=0.002) while it augmented mTORC2 based on pAkt expression (p=0.02). On day 0, SLE T cells had higher frequency of IL-4$^+$ cells, most prominently in CD8$^+$ T cells (7.72$\pm$2.40%, 4.00$\pm$0.45%, p=0.027). After 3 day *in vitro* stimulation, DN T cells had higher frequency of IL-4$^+$ cells than CD4$^+$ or CD8$^+$ T cells (DN T cells: 9.89$\pm$1.85%, CD4$^+$ T cells: 3.08$\pm$0.63%; p=0.0018, CD8$^+$ T cells: 4.94$\pm$0.81%; p=0.014 in SLE). Rapamycin suppressed T cell IL-4 expression, most robustly in DN T cells (9.89$\pm$1.85%, 4.92$\pm$0.80%, p=0.001). Frequency of IFN-γ^+ cells was reduced in SLE (p<0.0001). Rapamycin did not suppress T cell IFN-γ expression. After 3 day *in vitro* stimulation, SLE T cells had higher frequency of IL-17$^+$ cells, which was most prominent in CD4$^+$ T cells (5.31$\pm$1.57%, 2.71$\pm$0.63%, p=0.0196) and was suppressed by rapamycin (5.31$\pm$1.57%, 2.96$\pm$1.12%, p=0.0097). Frequency of Treg was reduced in SLE. Rapamycin blocked mTOR in Treg (pS6RP^{hi} cells: 45.13$\pm$10.97%, 3.39$\pm$0.38% in SLE; p<0.001) and promoted its expansion (11.49$\pm$1.92%, 19.60$\pm$2.80% in SLE; p<0.0001). Neutralization of IL-17 expanded Tregs (p<0.05).

Conclusion: The data indicate the pathogenic relevance of IL-4 and IL-17 in SLE, which are mainly produced by DN T and CD4$^+$ T cells respectively in an mTORC1-dependent manner. In contrast, IFN-γ is conceivably protective against SLE. Rapamycin expands Tregs by blocking mTOR in the Treg and suppressing IL-17. Our study reveals three distinct mechanisms of action by rapamycin in SLE: 1) suppression of DN T cell IL-4 production, 2) suppression of CD4$^+$ T cell IL-17 production, and 3) Treg expansion.

Disclosure: H. Kato, None; **A. Perl**, None.

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Abatacept Efficacy Is Overruled By IL-7 In TSLP-Primed Myeloid Dendritic cell driven T Cell Activation From Rheumatoid Arthritis Patients. F.M. Moret, T.R.D.J. Radstake, J.W.J. Bijlsma, F.P.J.G. Lafeber and J.A.G. van Roon. University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: Abatacept is an effective treatment for a subset of rheumatoid arthritis (RA) patients, interfering in the interaction between antigen-presenting cells and T cells preventing T cell activation. Thymic stromal lymphopoietin (TSLP) and the related cytokine IL-7 are both increased in synovial fluid (SF) of RA patients and are shown to contribute to immunopathological mechanisms in RA. Recently, we have shown that TSLP potently activates CD4 T cells via myeloid dendritic cells (mDCs) depending on antigen presentation and co-stimulation. IL-7 directly acts on T cells and strongly induces T cell-dependent activation of antigen-presenting cells. The aim of this study was to investigate the potential of abatacept in inhibiting TSLP-mDC driven naïve and memory T cell activation in the presence of IL-7 in healthy controls (HC) and RA patients.

Methods: Naïve (Tn), central memory (Tcm) and effector memory (Tem) T cell subsets in PB of HC and in PB and SF of RA patients were assessed based on CD27 and CD45RO expression by flow cytometry. CD4 T cell subsets of HC isolated by flow cytometry and T cells from PB and SF of RA patients isolated by MACS were co-cultured with autologous TSLP-stimulated-mDCs with or without abatacept and/or IL-7 and subsequently T cell proliferation was measured.

Results: CD4 T cell subsets from PB of HC and RA patients were comparable and mainly consisted of Tn and Tcm cells (Tn 42 vs. 46%; Tcm 42 vs. 31%; Tem 8 vs. 10%, respectively), whereas SF of RA patients mainly consisted of Tcm and Tem cells (Tn 6%; Tcm 51%; Tem 34%). Activation of these T cell subsets by TSLP-mDCs from PB was completely blocked by abatacept (Tn: 6948 to 114; Tcm: 2347 to 207; Tem: 5718 to 199 cpm, all p<0.05, respectively). IL-7 strongly increased T cell activation and overruled the inhibitory capacity of abatacept (abatacept+IL-7 vs. abatacept, Tn 4836 vs. 114; Tcm 10128 vs. 207; Tem 11605 vs. 199 cpm, all p<0.05, respectively). This IL-7-induced reversal was associated with strong induction of IFNγ and TNFα secretion. Similarly, CD4 T cell proliferation induced by TSLP-stimulated mDCs from SF of RA patients was completely blocked by abatacept and largely reversed in the presence of IL-7.

Conclusion: Our data indicate that the presence of T cell activating cytokines, like IL-7, in joints of RA patients reduce the inhibitory capacity of abatacept on (TSLP-)mDC driven T cell activation. This could possibly explain the unresponsiveness to abatacept in a subset of patients.

Disclosure: F. M. Moret, None; **T. R. D. J. Radstake**, None; **J. W. J. Bijlsma**, None; **F. P. J. G. Lafeber**, None; **J. A. G. van Roon**, None.

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T Cell Activation Induces Increased mRNA Expression Of The Splicing Factor SF2/ASF But Simultaneous Protein Downregulation Via Proteasome Mediated Degradation. Vaishali R. Moulton, Andrew R. Gillooly and George C. Tsokos. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

Background/Purpose: T cells from patients with systemic lupus erythematosus (SLE) are poor producers of the vital cytokine interleukin (IL)-2. We recently showed that SLE T cells exhibit reduced expression of the splicing factor 2/ Alternative splicing factor (SF2/ASF), more so in patients with worse disease as evidenced by higher SLE disease activity index (SLEDAI) scores compared to those with mild disease. SF2/ASF, a member of the serine arginine (SR) family of splicing proteins is not only a key regulator of alternative splicing via its RNA binding capacity, but also plays roles in transcription and translation by virtue of its protein-protein interaction properties. Increasing the expression of SF2/ASF in T cells from SLE patients restored their IL-2 production, indicating that SF2/ASF is an important regulator of T cell function, and its reduced expression is a potential molecular defect in SLE T cells. How the expression of SF2/ASF is controlled in T cells is not known. The goal of this study was to determine the mechanism/s controlling SF2/ASF expression in human T cells in resting state and during T cell activation.

Methods: T cells were isolated from peripheral blood of healthy volunteers. T cells were activated for various time points (3, 6, 24 hours) with either anti-CD3, anti-CD28 antibodies, or phorbol myristic acid (PMA) plus Ionomycin. mRNA expression was assessed by reverse transcription and real time quantitative PCR. Protein expression was studied by immunoblotting. Actinomycin D was used to block transcription and assess mRNA stability. To assess post translational mechanisms, the lysosome inhibitor Bafilomycin A1 and proteasome inhibitor MG132 were added during activation to block protein degradation.

Results: T cells in resting state expressed SF2/ASF mRNA and protein abundantly. T cell activation increased mRNA expression of SF2/ASF by 3- to 4- fold whereas protein expression did not change much, or even decreased. Stimulating T cells with PMA and Ionomycin similarly resulted in increased mRNA and reduced SF2/ASF protein expression. This discrepancy between mRNA and protein expression suggests that post-transcriptional and/or post-translational mechanisms regulate SF2/ASF expression during T cell activation. The discrepancy was not due to reduced transcript stability, as the rate of SF2/ASF mRNA decay in resting versus activated T cells showed no significant difference. Activating T cells in the presence of inhibitors of the lysosome or proteasome revealed that the proteasome but not lysosome is involved in the degradation of SF2/ASF.

Conclusion: Our results indicate that SF2/ASF mRNA and protein expression are differentially regulated during T cell activation, and that proteasome mediated degradation may represent an important physiologic mechanism to tightly control expression of this essential splicing factor. Our previous work showed that increased ubiquitination and proteasome degradation are important in the downregulation of the CD3 zeta signaling protein in SLE T cells. Therefore proteasome mediated SF2/ASF degradation may represent a molecular mechanism that contributes to its reduced expression in SLE T cells.

Disclosure: V. R. Moulton, None; **A. R. Gillooly**, None; **G. C. Tsokos**, None.

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BAFF Promotes T Follicular Helper Cell Development and Germinal Center Generation In Mice. Song Guo Zheng, Maogeng Chen, Qiang Li and William Stohl. University of Southern California Keck School of Medicine, Los Angeles, CA.

Background/Purpose: BAFF (B cell activating factor belonging to the TNF family) promotes B cells maturation in germinal center. The generation of germinal center depends on T follicular helper cells (Tfh). Overexpression of BAFF and Tfh is found in many autoimmune diseases. However, whether BAFF has effects on Tfh development is still unclear. In this study, we explored the relationship between BAFF and Tfh in mice.

Methods: Mice were immunized with KLH for 10 days for the induction of Tfh in vivo. Mouse naive CD4+ cells cultured with IL-6 and IL-21 were used for Tfh differentiation *in vitro*. BAFF$^{-/-}$, BAFF transgenic (Tg), April$^{-/-}$, BR3$^{-/-}$, TACI$^{-/-}$ and BCMA$^{-/-}$ mice were used for the mechanism studies. To determine if B cells are required, μMT mice, BCL-2 Tg/μMT and BAFF$^{-/-}$/BCL-2 Tg mice were also used. Tfh cells and mature B cell were detected by FACS. Germinal centers were determined by immunofluorescence staining of PNA and IgD. The levels of IgG after KLH immunization were measured by ELISA. The mRNA expression of IL-6and IL-21 was determined by real-time qPCR.

Results: We showed that BAFF but not April promotes the development of Tfh cells in vivo and in vitro. Furthermore, the development of Tfh cells is dependent upon BR3, but independent on BCMA and TACI. BAFF facilitates the generation of germinal center, and promotes B cells maturation and secretion of IgG. B cells are required for BAFF-promoted Tfh cell formation. We demonstrated that BAFF increases IL-21 mRNA expression in CD4+ T cells, and IL-6 mRNA expression in B cells and dendritic cells.

Conclusion: In summary, these findings provide evidence that BAFF promotes Tfh development, germinal center generation and pathogenesis of autoimmune diseases.

Disclosure: S. G. Zheng, None; **M. Chen**, None; **Q. Li**, None; **W. Stohl**, None.

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Abatacept Is Highly Effective At Inhibiting T Cell Priming and Induces a Unique Transcriptional Profile In CD4$^+$ T Cells. Agapitos Patakas[1], Rui-Ru Ji[2], William Weir[1], Sean Connolly[2], Steven G. Nadler[2], James M. Brewer[1], Iain B. McInnes[1] and Paul Garside[1]. [1]University of Glasgow, Glasgow, United Kingdom, [2]Bristol Myers Squibb Co. Research and Development, Princeton, NJ.

Background/Purpose: Absence of co-stimulation in the presence of TCR-stimulation has been proposed to induce tolerance via deletion or anergy. Abatacept is a CTLA-4-Ig molecule that binds with high affinity to CD80/86 on antigen presenting cells (APC). It modulates CD28-mediated T cell co-stimulation and is currently approved for the treatment of rheumatoid arthritis, however it remains unclear whether its use leads to the development of immunological tolerance. The aim of this study was to investigate *in vivo* the capacity of abatacept to regulate development of antigen-specific immunological tolerance.

Methods: In order to generate antigen specific tolerised CD4$^+$ T cells, DO11.10 RAG2$^{-/-}$ mice, which have a CD4 cells specific for ovalbumin (OVA), were fed with OVA in their drinking water (50mg/ml) for 10 days. Priming was induced by s.c. injection of OVA in CFA in the presence of abatacept or control IgG (10mg/kg). The functionality of the generated CD4 populations was confirmed by their ability to respond to antigen rechallenge after adoptive transfer into BALB/c mice. The phenotype of purified CD4 and CD11c cells was assessed by flow cytometry, ELISA and complemented by detailed full genome transcriptional profiling.

Results: While T cells tolerised by ovalbumin feeding were unable to produce IL-2 after *ex-vivo* restimulation, T cells primed in the presence of abatacept produced copious amounts of this cytokine and resembled naïve T cells exposed to antigen for the first time in this respect. Tolerised T cell populations exhibited a significantly higher proportion of T_{REG} and CTLA-4$^+$ cells compared with naïve, primed or 'primed in the presence of abatacept' T cells. The latter were characterised by the absence of T_{REG}, more resembling naïve rather than tolerised T cells. However, abatacept treatment significantly reduced the expression of T cell markers (ICOS, CD71 and CD44) compared with primed and orally tolerised groups. When these T cells were adoptively transferred to BALB/c mice and rechallenged with OVA, only the orally tolerised CD4 cells failed to expand to antigen, suggesting that abatacept treatment does not induce anergy. Furthermore, T cells isolated from abatacept treated mice had a unique transcriptional profile, distinct from naïve, tolerant and primed T cells. Crucially we observed that this state is accompanied by an inhibition of the activation of dendritic cells at the transcriptional level, indicating a level of licensing of these cells by T cells. These results demonstrate that Abatacept treatment significantly modulates T-DC communication resulting in defective cell priming *in vivo* and a unique transcriptional profile which is distinct from anergic tolerance.

Conclusion: This study provides insight into the mode of action of Abatacept and its bidirectional impact upon both T cells and DC. We demonstrate that while abatacept does not induce T cell anergy, it generates a distinct T cell phenotype that most resembles naïve T cells and potentially modulates the function of APCs. This could have significant implications when considering its application in rheumatoid arthritis and other autoimmune conditions.

Disclosure: A. Patakas, None; **R. R. Ji**, Bristol-Myers Squibb Co, 3; **W. Weir**, None; **S. Connolly**, Bristol-Myers Squibb Co, 3; **S. G. Nadler**, Bristol-Myers Squibb Co, 3; **J. M. Brewer**, Bristol-Myers Squibb Co, 2; **I. B. McInnes**, Bristol-Myers Squibb Co, 2; **P. Garside**, Bristol-Myers Squibb Co, 2.

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Dose-Dependent Suppression Of Cytokine Production From T Cells By a Novel Phosphoinositide 3-Kinase Delta Inhibitor. Emily E. Way[1], Kong Chen[1], Kamal D. Puri[2] and Jay K. Kolls[1]. [1]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [2]Gilead Sciences, Inc., Seattle, WA.

Background/Purpose: The use of specific cytokine inhibitors to treat inflammatory autoimmune conditions is common but typically utilizes monoclonal antibodies, fusion proteins, and other molecules whose large size necessitates parenteral administration. There remains a significant need for development of effective small molecule cytokine inhibitors for inflammatory conditions. Phosphoinositide 3-kinase (PI3K) is a direct upstream activator of AKT, and plays a critical role in multiple cell signaling pathways, cell cycle progression, and cell growth, and is thus a potential target for drug development. We examined the effect of a novel PI3Kδ inhibitor, GS-599220, on CD3/CD28 stimulated T-cell cytokine production.

Methods: Mouse Th17 cells were differentiated from naïve T cells in vitro, and GS-599220 was added on day 3 of differentiation prior to re-stimulation with anti-CD3/CD28 beads. On day 4, secretion of T helper signature cytokines by these cells were determined by both Luminex and ELISA, while real time PCR was used to quantify gene expression of these cytokines. The compound toxicity was determined by flow cytometry with 7AAD staining. Th17 cells were also transduced with a retrovirus encoding GFP-labeled myristoylated AKT, which renders the AKT constitutively active, and then treated with GS-599220.

Results: When added to culture after allowing naïve T-cells to polarize into different effector lineages, we observed dose-dependent suppression of multiple cytokines by Luminex and ELISA, including IL-17, IFNγ, and IL-4 from Th17, Th1, and Th2 cells, respectively. Real time PCR confirmed the suppression of cytokine gene expression suggesting the inhibition is mediated at the transcriptional level. Toxicity of this compound to Th17 cells was found to be minimal, indicating that the mechanism of cytokine inhibition is not by cell death. Experiments carried out under conditions free of antigen presenting cells suggest that this compound functions independently of antigen presenting cells and acts directly on the T cells. To investigate the downstream effects of this PI3Kδ inhibitor, constitutively active AKT was introduced into Th17 cells by retroviral transduction. Th17 cells containing constitutively active AKT appear to be resistant to PI3Kδ inhibition, as IL-17 production is not reduced even in the presence of high concentrations of GS-599220, suggesting that this inhibitor is acting through AKT signaling pathways.

Conclusion: These experiments show effectiveness of this small molecule inhibitor of PI3Kδ activity to modulate inflammation in vitro and exhibit promise as a treatment for in vivo models of inflammation.

Disclosure: E. E. Way, None; **K. Chen**, None; **K. D. Puri**, Gilead Sciences, Inc., 3; **J. K. Kolls**, None.

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Localization At The Immunological Synapse Of Adaptor Protein Grb2 and PLC Gamma-1 In Non-Stimulated Peripheral Blood T Lymphocytes From Patients With Systemic Lupus Erythematosus Suggests An In Vivo dysregulated Activation State. Nursamaa Abdoel[1], Mireyma Sanchez[1], Hector Rojas[2], Martin Rodriguez[1] and Ana M. Blasini[1]. [1]Hospital Universitario de Caracas, Caracas, Venezuela, [2]Instituto de Inmunologia, Escuela de Medicina, Universidad Central de Venezuela, Caracas, Venezuela.

Background/Purpose: We previously showed an increased metabolic rate of transmembrane adaptor protein LAT in TCR/CD3 stimulated lupus T cells, associated with delocalization of this adaptor molecule from lipid rafts and from the immunological synapse after TCR/CD3-CD28 stimulation of lupus T cells. Additionally, unstimulated T cells from systemic lupus erythematosus (SLE) patients seem to be in a preactivated state showing augmented phosphorylation of signaling proteins, among other evidences, compared to non-SLE patients and healthy controls. In this study we evaluated the presence of key signaling molecules in lipid rafts of lupus T cells.

Methods: SLE patients were diagnosed according to the American College of Rheumatology criteria. Healthy donors were from the blood bank of *Hospital Universitario de Caracas*. All individuals signed an informed consent previously approved by the Bioethics Committee. Highly enriched T cells, obtained from peripheral blood samples and subjected to RosetteSep™ isolation, were adhered to pLL coated slides and activated for 5 and 15 min at 37°C, with 4.5 μm superparamagnetic polystyrene beads coated with antibodies against CD3ϵ and CD28. The cells were fixed, permeabilized and stained with antibodies recognizing Grb2 and PLCγ1, and CT-B as a lipid raft marker. The cell-bead complexes were evaluated by confocal microscopy and densitometries were obtained using ImageJ, 1.44, National Institutes of Health, USA.

Results: We observed increased localization of adaptor protein Grb2 at the immunological synapse in unstimulated T cells from lupus patients compared to healthy controls (23.46 ± 3.57 vs. 20.67 ± 2.28, MFI ± SME, n=10). PLCγ1 showed the same pattern of increased localization at the immunological synapse in these cells (23.14 ± 4.10 vs. 17.22 ± 2.14, MFI ± SME, n=10). The colocalization of either Grb2 or PLCγ1 with GM1, as well as colocalization of Grb2 and PLCγ1 themselves was similar between SLE patients and healthy controls, suggesting normal coupling of signaling molecules in lipid rafts in lymphocytes from lupus patients.

Conclusion: Since partition of PLCγ1 and Grb2 in lipid rafts occurs after ligation of the TCR, we conclude that our findings suggest an in vivo dysregulated activation state in SLE T cells, which may contribute to known downstream signaling abnormalities such as MAPK activation.

Disclosure: N. Abdoel, None; **M. Sanchez**, None; **H. Rojas**, None; **M. Rodriguez**, None; **A. M. Blasini**, None.

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Tofacitinib Does Not Inhibit Dendritic Cell Maturation and T Cell Proliferation In Vitro. Emmanuelle Le Bras[1], Dagmar Halbritter[2] and Martin Fleck[3]. [1]University Medical Center of Regensburg, Regensburg 93053, Germany, [2]University Medical Center of Regensburg, 93042 Regensburg, Germany, [3]Asklepios Clinic Bad Abbach, Bad Abbach, Germany.

Background/Purpose: Tofacitinib is the first approved Janus Kinase (JAK) Inhibitor for the treatment of rheumatoid arthritis (RA). The JAK/STAT pathway-inhibition leads to dysfunction of several processes of the acquired and innate immunity as well as haematopoesis. Beyond this, JAK3, which is exclusively expressed on haematopoetic cells, is known to be involved in the maturation and activation of dendritic cells (DCs), but its specific role remains controversial. Since DCs play a key role in the pathogenesis of RA, we investigated the in vivo effect of Tofacitinib on DC maturation and allogeneic T cell activation.

Methods: Monocytes were collected from healthy donors and cultured for 5 days in the presence of GM-CSF and IL-4 to generate immature dendritic cells (iDCs). To induce maturation, iDCs were cultured for 2 days in the presence of LPS (10 ng/ml) or a cocktail consisting of IL-1β (10 ng/ml), TNF-α (10 ng/ml), IL-6 (1000 U/ml) and Prostaglandin E2 (1mg/ml) or LPS with or without different concentrations of tofacitinib (10–300 nM). After seven days of culture, mature DCs (mDCs) were harvested and phenotypically characterized using FACS analysis. To evaluate mDC function, mixed leukocyte reactions (MLR) were established by incubation of 5×10^4 allogeneic T cells with different amounts of mDCs at stimulator:responder (S:R) ratios from 1:625 to 1:1 in the presence of different concentrations of tofacitinib, or abatacept. On day 5 of co-culture, 1 μCi of 3H-methylthymidine/well was added and T cell proliferation was determined after 24h using a liquid scintillation counter.

Results: There was no relevant inhibition of DC maturation in the presence of tofacitinib as FACS analysis revealed similar expression patterns for HLA-DR and CD83 in all cultures (HLA-DR+: 55.4%, 45.5%, 62.5%; CD83+: 82%, 74%, 80,3% for tofacitinib concentrations from 10nM, 30nM and 100nM, respectively). Furthermore, expression of co-stimulatory molecules CD80 and CD86 (>92% CD80+ and CD86+ for all tofacitinib concentrations) was not affected by tofacitinib. In addition, proliferation of allogeneic T cells in co-cultures with mDCs was not significantly impaired as similar proliferation rates could be observed at all S:R ratios despite the presence of tofacitinib (mean increase of 27% cpm for all S:R ratios vs untreated mDC after LPS stimulation, mean decrease of 6% cpm for all S:R ratios after stimulation with cytokine cocktail vs. untreated mDC). In contrast, there was a concentration dependent inhibition up to 75% of T cell proliferation in co-cultures treated with abatacept.

Conclusion: The present results demonstrate that DC maturation as well as proliferation of allogeneic T cells in MLR's is not significantly affected by tofacitinib. Therefore, modulation of the JAK pathway in other cell populations might be responsible for the anti-inflammatory effects observed upon tofacitinib treatment in vivo.

Disclosure: E. Le Bras, None; **D. Halbritter**, None; **M. Fleck**, None.

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Adiponectin Promotes The Differentiation Of naïve T Cell To Th17 Cell and Aggravates Collagen-Induced Arthritis. Miaojia Zhang[1], Xiaoxuan Sun[2], Wenfeng Tan[3], Xiaoke Feng[4] and Ke Gan[3]. [1]the First Affiliated Hospital of Nanjing Medical University, Nanjing, CHINA., Nanjing, China, [2]the First Affiliated Hospital of Nanjing Medical University, Nanjing, CHINA, Nanjing, China, [3]the First Affiliated Hospital of Nanjing Medical University, Nanjing, China, [4]the First Affiliated Hospital of Nanjing Medical University, China, Nanjing, China.

Background/Purpose: To investigate a role of Adiponectin (AD) on the differentiation of naïve T cell to Th17 cell and bone erosion in collagen-induced arthritis (CIA) mice.

Methods: Purified naïve T cells were cultured in anti-CD3 mAb and anti-CD28 mAb precoated with TGF-β, IL-6, IL-23 in the presence and absence of AD (0.1, 1 or 10 μg/ml). After 72 hours of culture, the frequencies of Th17 cells were measured by flow cytometry; the expression of ROR-γt and IL-17 were determined by real-time PCR and ELISA. Intraarticularly injected of AD 10 μl (1 μg/1 μl) into the knee joint of CIA mice was to analysis the role of AD on CIA development and Th17 expression in vivo.

Results: The frequencies of Th17 cells were significantly increased with the concentration of AD 10 μg/ml, but AD treatment with 0.1 and 1 μg/ml showed no obvious effect on the differentiation of naïve T cell to Th17 cell. The expression of IL-17 and ROR-γt mRNA were significantly increased oupon AD 0.1 μg/ml and 10 μg/ml AD stimulation. Consistently with mRNA expression, IL-17 levels were significantly elevated in culture supernatants after 10 μg/ml AD treatment. Intraarticular injection of AD into the knee joint of CIA mice aggravated arthritic development and bone erosion, triggered higher expression of IL-17 mRNA and its transcription factor including ROR-γt, IL-21, IL-22 and IL-23 in CIA model.

Conclusion: These findings identify a role of AD on enhancing the differenation of naïve T cell to Th17 cell, contributed to CIA bone erosion in CIA mice.

Disclosure: M. Zhang, None; **X. Sun**, None; **W. Tan**, None; **X. Feng**, None; **K. Gan**, None.

ACR Poster Session A
Vasculitis I
Sunday, October 27, 2013, 8:30 AM–4:00 PM

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Unraveling The Identity Of *FoxP3*$^+$ Regulatory T-Cells In Gpa-Patients. WH Abdulahad, Coen A. Stegeman, MG Huitema, Pieter C. Limburg, Abraham Rutgers, Peter Heeringa and Cees G.M. Kallenberg. University Medical Center Groningen, Groningen, Netherlands.

Background/Purpose: Human *FoxP3*$^+$ Th-cells are heterogeneous in function and include not only suppressive cells (T_{Regs}) but also non-suppressive cells that abundantly secrete proinflammatory cytokines. We have previously shown that *FoxP3*$^+$ Th-cells were increased in GPA-patients during remission as compared to healthy controls (HCs). In this group of patients, however, we observed a defective suppressor function of T_{Regs}, and an increase in the percentage of Th-17 cells. These observations make it tempting to investigate whether increased *FoxP3*$^+$ Th-cells in GPA-patients are attributed to an increase in the cytokine-secreting non-suppressive *FoxP3*$^+$Th-cells.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from 46 GPA-patients in remission and from 22 age- and sex-matched HCs. Expression of CD4, CD45RO, and *FoxP3* were determined by flow cytometric analysis. The expression levels of *FoxP3* and CD45RO were used for distinction between activated suppressor T_{Regs} (*FoxP3*^{High}CD45RO$^+$; $_{AS}T_{Reg}$), resting suppressor T_{Regs} (*FoxP3*^{Low}CD45RO$^-$; $_{RS}T_{Reg}$), and cytokine-secreting non-suppressor T_{Regs} (*FoxP3*^{Low}CD45RO$^+$; $_{NON}T_{Reg}$) cells. Intracellular expression of IFNg, IL-17, and IL-21 were determined in the various FoxP3$^+$ Th-cell subsets after *in vitro* activation of PBMCs by PMA and Ca-Ionophore.

Results: A significant increase in the frequency of $_{NON}T_{Reg}$ cells was observed in GPA-patients as compared with HCs, whereas no differences were detected in $_{RS}T_{Reg}$- and $_{AS}T_{Reg}$ cells between GPA-patients and HCs. The distribution of $_{RS}T_{Reg}$- and $_{NON}T_{Reg}$ cells did not differ between ANCA-negative and ANCA-positive patients, whereas lower percentages of $_{AS}T_{Reg}$ cells were observed in ANCA-positive patients as compared to ANCA-negative patients and HCs. Importantly, a significant increase in the percentage of IL-17$^+$ and IL-21$^+$ cells was seen within the $_{NON}T_{Reg}$cells from ANCA-positive patients (n= 9) when compared to ANCA-negative (n= 10) and HCs (n= 12), whereas no differences were found between ANCA-negative and HCs.

Conclusion: Increased *FoxP3* expression in Th-cells from GPA-patients is related to an increase in a subset of non-suppressive Th-cells. Increased production of IL-17 and IL-21 cytokines, in $_{NON}T_{Reg}$ cells from ANCA-positive patients points towards *FoxP3*$^+$ effector cells and decrease in suppressive T_{Reg} cells in relation to ANCA production.

Disclosure: W. Abdulahad, BMS, 2; **C. A. Stegeman**, None; **M. Huitema**, BMS, 2; **P. C. Limburg**, None; **A. Rutgers**, None; **P. Heeringa**, None; **C. G. M. Kallenberg**, Roche, 8.

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Role Of Innate Immunity In The Pathogenesis Of ANCA-Associated Vasculitis. Angelica Gattamelata[1], Giovanna Peruzzi[2], Rossana Scrivo[1], Roberta Priori[1], Stefania Morrone[3], Angela Santoni[2] and Guido Valesini[1]. [1]Department of Internal Medicine and Medical Specialties, Sapienza University, Rome, Italy, [2]Department of Molecular Medicine, Sapienza University, Rome, Italy, [3]Department of Experimental Medicine, Sapienza University, Rome, Italy.

Background/Purpose: Natural killer cells (NK) represent one of the main effectors of the innate immune response through the defense against viral infections and the production of immunoregulatory cytokines. Recent evidence shows an increase in the expression of TLR2 and TLR9 on NK cells of patients with ANCA-associated vasculitis (AAV) compared with healthy controls (HC). This is of great interest considering that infections are implicated in the pathogenesis of these diseases.

The aim of our study was to characterize NK cells in patients with AAV, assessing their number, phenotype and functional status.

Methods: We enrolled 19 patients with AAV [M/F: 7/12; mean age 60.2 years (range 41–75)] according to the Chapel Hill criteria (11: granulomatosis with polyangiitis, 7: eosinophilic granulomatosis with polyangiitis, 1: microscopic polyangiitis) and 12 HC matched for age and sex with the patients. After obtaining informed consent, clinical data were collected and blood drawing was performed. Peripheral blood mononuclear cells (PBMCs) were isolated from heparinized blood by Lymphoprep gradient centrifugation. NK cells (CD3-CD56+) were evaluated by multi-parameter flow cytometry, distinguishing between cytotoxic CD56^{dim} and immunoregulatory CD56^{bright} NK cells, also divided into two recently identified subpopulations: memory NK cells (CD3-CD56+CD57+) and NK-22 cells (CD3-CD56+NKp44+ CCR6+). In addition, the expression of TLR2 and TLR9 was evaluated on these cells. Finally, NK cells were isolated by magnetic separation to assess the state of activation through the expression of intracellular IFNg following *in vitro* incubation with TLR2 (Pam3CSK4) and TLR9 (CpG ODN) ligands.

Results: We found no differences in the percentage of NK cells between patients (11.3%) and HC (12%). The percentage of CD56^{dim} and CD56^{bright} (80.5% vs 92% and 7.5% vs 8%, respectively), and the percentage of memory NK cells and NK-22 cells (0.550% vs 0.507% and 66% vs 67%, respectively) was comparable between AAV patients and HC. In NK cells, the expression of TLR2 was significantly higher in HC (14.8%) compared to patients (8.12%; p=0.0328) and TLR9 expression showed a tendency to be higher in patients (26%) compared to HC (15%), but the difference was not statistical significant. In the memory NK cells subset the expression of TLR2 was significantly decreased in patients (10.2%) compared to controls (19.2%; p=0.0434), while there was no difference in the expression of TLR9. Interestingly, the stimulation with TLR9 ligand induced a significant production of IFNg in patients (11%) compared to HC (2.8%; p=0.0071). No correlation with clinical and laboratory parameters was found.

Conclusion: The increased production of IFNg after stimulation with the ligand of TLR9 demonstrates a state of NK activation in AAV patients. Hence, TLR9 may be involved in the pathogenesis of these diseases, strengthening the possibility that infections may promote their onset and/or exacerbations. Further experiments are needed to confirm these data and to clarify the meaning of the reduced expression of TLR2 on CD57+ NK cells of patients compared to HC.

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Cell-Mediated Immune Responses To Influenza and Herpesvirus Antigen Stimulation Are Conserved But Adversely Impacted By Immunosuppressive Therapy and Active Infection In Patients With Granulomatosis With Polyangiitis. John McKinnon[1], Robbie Mailliard[2], Dawn McClemens-McBride[2], Donald Jones[2], Charles Rinaldo Jr.[2] and Kathleen Maksimowicz-McKinnon[1]. [1]Henry Ford Hospital, Detroit, MI, [2]University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Reactivation of chronic herpesvirus infections is not uncommon in immunosuppressed patients, including those with granulomatosis with polyangiitis (GPA). The effects of GPA disease and therapy on cell-mediated immunity against herpesviruses are not well established. Although immunosuppressive therapy is clearly associated with viral reactivation disease, data from other cohorts demonstrate that altered immunocompetence from other infections may also be an important contributing factor. We examined the effects of recent and acute infections on cell-mediated immune response against influenza and herpesvirus antigens in a well-characterized cohort of patients with GPA.

Methods: Twenty GPA patients (mean age: 56 years; 55% female; 100% Caucasian) and 5 age-, race-, and gender-matched healthy controls were prospectively enrolled. Disease features, medications, current and recent infection data, and disease activity scores were obtained. Extended ELISPOTs for interferon-gamma (IFNg) production to CEF and VZV antigens were assessed.

Results: GPA patients had a median disease duration of 86.8 (54) months, median BVAS of 1.0 and VDI of 2.0. Prednisone was used in 15 (75%) of the patients (median dose: 12.5 mg) and steroid-sparing immunosuppressive agents in 14 (70) %; two patients were not receiving IS therapy. An active infection was identified in 30% of the patients at study entry, and 50% had a recent serious infection within the past year. GPA patients had a significant decline in IFNg median responses to CEF & VZV antigens with increasing prednisone dose (0mg=450 & 192.1; <11mg= 161.8, 7.3; 11–60mg= 202.5, 24.2; 1000mg= 22.5, 25.5) (p=0.21, 0.041 respectively) and with the number of immunosuppressive agents used (none= 457, 192.5; one= 161.3, 129.3; two or more= 202.5, 18.5) (none vs. one=0.53, 0.8; none vs. two: p=0.095, 0.095). The presence of an active infection at study entry was associated with a decrease in VZV IFNg response (p=0.024). However, prior herpesvirus infection (1 HSV pneumonia, 4 VZV disease) within the past year was associated with higher CEF response (p=0.036) and a trend towards higher VZV responses (p=0.099).

Conclusion: Immunosuppressive therapy and non-viral infections both decrease cell-mediated immune response against herpes viruses, potentially leading to reactivation disease in patients with GPA, as seen in other immunosuppressed populations. Prior herpesvirus infection is associated with increases in both CEF and VZV responses, suggesting a possible "crossover" protective effect against both CMV and VZV reactivation, which could be important when considering the need and timing of prophylactic interventions. .

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C3 Activation Is Associated With The Disease Activity Of Microscopic Polyangiitis. Dan Liu[1], Jin-song Zhou[2], Qing-ping Chen[2], Chao-yang Duan[3], Li Wang[2], Yuan Jia[1] and Ke Li[3]. [1]Peking University People's Hospital, Beijing, China, [2]The Fifth Hospital of Xi'an, Xi'an, China, [3]The Second Affiliated Hospital, Xi'an Jiaotong University, Xi'an, China.

Background/Purpose: Microscopic polyangiitis (MPA) is the most common anti-neutrophil cytoplasmic antibodies(ANCA) associated small-vessel vasculitis with specificity of the ANCA to myeloperoxidase(MPO) of neutrophils. MPA mainly affects kidneys and lungs. The kidneys are the most commonly affected organ; and kidney vasculitis can result in renal failure. The interplay of ANCA, neutrophil and complement activation has been implicated in the pathogenesis of MPA. In this study, we tried to establish the relationship of complement activation and the disease activity of MPA and to identify potential biomarkers for this disease.

Methods: Blood samples were collected from 45 MPO-ANCA positive patients who had clinical diagnosis of MPA in People's Hospital, Peking University, after informed consent. The samples, according to serum C3 levels, were divided into two groups: normal C3 group: ≥0.8 g/L (n=18) and low C3 group: C3<0.8 g/L (n=27). Inflammatory markers (i.e. *ESR,* CRP), renal functional markers (i.e. BUN, creatinine, 24-hour urinary protein level), and lung diseases were evaluated in the two groups. Birmingham Vasculitis Activity Score-version 3 (BVAS[V3]) was calculated. Data was analyzed using corresponding *t* test, chi-square test, linear correlation analysis and binary logistic regression, respectively.

Results: We found that: 1) Compared with normal C3 group, low C3 group had significantly lowered C4 (0.17±0.08 g/L vs 0.25±0.08 g/L) but significantly increased CRP (101±57 mg/L vs 33±33 mg/L), 24-hour urinary protein (1.4±1.3g/d vs 0.6±0.5g/d), BUN (17.08±9.02 mmol/L vs 8.62±5.28 mmol/L) and BVAS(V3) (21.4±3.6 vs 15.4±3.8). 2) BVAS(V3) has a significant linear correlation with serum complement C3 level (R^2=0.43, P<0.01). 3) Morbidity of severe lung injury (i.e. interstitial lung disease, pneumorrhagia) in low C3 group was higher than that in normal C3 group (92.6% vs 33.3%, X^2=17.69, P<0.01). 4) C3, CRP and ESR levels were closely related to the occurrence of severe lung injury, and the logistic regression equation was: $P(y)=1/(1+e^{-2.1+7.54\times C3-0.054\times CRP-0.027\times ESR})$, in which the overall correct percentage was 93.3%.

Conclusion: Serum complement C3 levels were associated with the disease activity and clinical manifestations of MPA. Therefore, serum C3 level may represent as a biomarker for disease activity and an indicator for organ injury of MPA.

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Expansion Of IgA-Plasma Cells As a Sign For Ear-Nose-Throat-Involvment In Granulomatosis With Polyangiitis? Bimba F. Hoyer[1], Adriano Taddeo[2], Qingyu Cheng[1], Laleh Khodadadi[1], Gerd Burmester[1] and Falk Hiepe[1]. [1]Charité University Medicine, Department of Medicine/ Rheumatology and Clinical Immunology and German Rheumatism Research Centre Berlin (DRFZ), Germany, Berlin, Germany, [2]Deutsches Rheuma-forschungszentrum, Berlin, Germany.

Background/Purpose: B cells are playing a major role in granulomatosis with polyangiitis (GPA, formarly known as Wegener's disease). This is reflected by the presence of autoantibodies directed against neutrophil granular encymes (ANCA) in a great majority of patients as well as in the success of B cell depleting therapies in GPA. Renal manifestations are directly mediated by autoantibodies. Whether mucosal plasma cells play a role in ENT-involvment is yet unknown. IgA-ANCA can be found in about 30% of GPA patients (Kelley et al). For a better understanding of the possible role of B cells in GPA we analyzed B cells subsets in the peripheral blood of patients and found major changes correlating with disease activity (BVAS).

Methods: 18 patients with GPA (11 with active disease, 7 in remission) were analyzed by flow cytometry and compared to 17 healthy donors. Stainings for CD19, 20, 27, IgD, IgA and MHCII were performed and analyzed by FlowJo-software. The study was approved by the Charité ethics committee and all patients signed informed consent. Statistical analysis was performed using GraphPadPrism.

Results: Marked differences (p=0,0018) were found regarding the number and frequency of plasmablasts and plasma cells in patients with active disease (6,4 ± 5,06/μl) as compared to patients in remission (2,5 ± 1,6/μl) or healthy donors (2,3 ± 1,2/μl). In patients with GPA a significant higher number of the plasma cells produced IgA as compared to healthy controls (p=0,0028).

The number of plasma cells as well as their frequency correlate with disease activity (r= 0,9135, p<0,0001). Interestingly, no expansion of the double negative memory B cells that has been described in SLE could be seen. For naive B cells significant differences could be detected as well.

Conclusion: The number of plasma cells in active GPA is increased. This implies a central role of plasma cells in the pathogenesis of GPA. A high frequency of these plasma cells is producing IgA, which could play a role in ENT-involvement. Further studies including the analysis of ENT biopsies are needed to further understand their role in disease pathogenesis.

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Plasma Levels Of Fibrin/Fibrinogen Degradation Products Might Be a Useful Indicator Of Disease Activity, Classification and Nephritis Complications In Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Kuninobu Wakabayashi, Nao Oguro, Yoko Miura, Sho Ishii, Shinya Seki, Masayu Umemura, Takahiro Tokunaga, Hiroyuki Tsukamoto, Sakiko Isojima, Hidekazu Furuya, Ryo Yanai, Kumiko Otsuka, Ryo Takahashi, Takeo Isozaki, Nobuyuki Yajima, Yusuke Miwa and Tsuyoshi Kasama. Showa University School of Med, Shinagawa-ku Tokyo, Japan.

Background/Purpose: It is important to determine the biomarkers for assessing disease activity of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Plasma levels of fibrin/fibrinogen degradation products (FDP) are fibrinolytic markers and elevates after any thrombotic event. We hypothesized that plasma levels of FDP reflect to hypercoagulable state and thrombosis in AAV. The purpose of the present study is to investigate whether plasma levels of FDP could be an indicator of disease states and complications of organ involvements in patients of AAV.

Methods: Patients with microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) who were admitted to Showa University Hospital for induction therapy and had their plasma FDP levels checked in the active state from October 2005 to May 2013 were retrospectively included. Plasma FDP levels were compared between the active and inactive states of AAV. Among patients in the active state, vasculitis disease clinical activity was assessed using Birmingham Vasculitis Activity Scores (BVAS), and the relationship between plasma FDP levels and BVAS, scores of each system were discussed. Plasma FDP levels were evaluated for differences in each disease and were compared between patients with and without complications of nephritis, interstitial pneumonia and peripheral neuropathy. Laboratory markers of AAV and nephritis activity were examined to determine their correlations with plasma FDP levels.

Results: Thirty-seven MPA, 12 GPA, and 6 EGPA patients were included. Plasma FDP levels were high in the active state and decreased significantly after therapy ($p<0.001$). Among patients in the active state, plasma FDP levels significantly correlated with BVAS ($r_s=0.35$, $p<0.05$). Especially, positive correlations were observed among plasma FDP levels and the system of general ($r_s=0.57$, $p<0.001$) and renal involvement ($r_s=0.33$, $p<0.05$) in the systems of BVAS. Plasma FDP levels were significantly higher in patients with MPA than in patients with GPA ($p<0.05$) and with EGPA ($p<0.05$). Although plasma FDP levels were significantly higher in patients with nephritis than in patients without nephritis ($p<0.01$), there were no differences between patients with and without complications of interstitial pneumonia and peripheral neuropathy. Plasma FDP levels significantly correlated with serum C-reactive protein levels ($r_s=0.52$, $p<0.001$), peripheral blood neutrophil count ($r_s=0.53$, $p<0.001$), plasma D-dimer levels ($r_s=0.87$, $p<0.001$), serum creatinine levels ($r_s=0.34$, $p<0.05$), estimated glomerular filtration rates ($r_s=-0.43$, $p<0.01$), and urinary N-acetyl-beta-D-glucosaminidase index ($r_s=0.37$, $p<0.05$). Plasma FDP levels were significantly higher in the patients with proteinuria ($p<0.01$) and hematuria ($p<0.05$).

Conclusion: Plasma FDP levels might be a useful indicator of disease activity and complications of nephritis in patients with AAV. Better understanding of the association of thrombosis with inflammation in AAV might lead to development new approaches to therapy.

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The Significance Of Anti-Myeloperoxidase and Anti-Proteinase 3 Antibodies In The Absence Of Anti-Neutrophil Cytoplasmic Antibody Immunofluorescence Positivity. Deepak A. Rao, Joseph F. Merola, William R. O'Brien, Kevin Wei, Samuel U. Takvorian, Paul F. Dellaripa and Peter H. Schur. Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Identification of serum anti-neutrophil cytoplasmic antibodies (ANCA) for the detection of ANCA-associated vasculitis (AAV) is often performed by screening with indirect immunofluorescence (IF), followed by testing of IF-positive samples for anti-proteinase-3 (PR3) and anti-myeloperoxidase (MPO) antibodies. Many institutions, including ours, analyze all samples by IF and anti-PR3/anti-MPO assays simultaneously. This strategy can identify patients with detectable anti-PR3 or anti-MPO antibodies despite a negative IF (IF-/Ab+); however, the significance of this discordant result is not clear. We attempted to determine whether IF-/Ab+ results identified any cases of clinically meaningful systemic vasculitis.

Methods: We conducted a retrospective chart review of all patients tested for serum ANCAs at a large academic center between January 2011 and May 2013 who had a negative IF but detectable anti-PR3 or anti-MPO antibodies (IF-/Ab+). IF was performed on serum diluted 1:20, with cytoplasmic or perinuclear patterns considered positive. Atypical patterns were excluded. Anti-PR3 and anti-MPO assays were performed by immunoassay. AAV diagnosis was based on the European Medicines Agency vasculitis algorithm.

Results: Of 2345 samples tested for ANCAs, 49 samples (2.1%), derived from 38 patients, contained a detectable anti-PR3 or anti-MPO antibody despite a negative IF. By comparison, 1950 samples (83%) had both negative IF and antibody assays, and 123 samples (5.2%), derived from 68 patients, had both a positive IF and a detectable anti-PR3 (44), anti-MPO antibody (77), or both antibodies (2). Of 76 samples with detectable anti-PR3 antibodies, 29 (38%) had a negative IF, while 20 of 115 (17%) anti-MPO-positive samples had a negative IF.

We identified only one case in which a patient with an IF-/Ab+ result was subsequently diagnosed with AAV. A repeat test 1 month later returned IF+/Ab+. Eleven of the IF-/Ab+ cases (29%) represented previously diagnosed and treated AAV, all with positive IF and antibody tests prior to treatment. The majority of patients with IF-/Ab+ results (20/38 (52%)) had non-vasculitic immunologic disorders, including SLE (5) inflammatory bowel disease (3), autoimmune hepatitis (1), Hashimoto's thyroiditis (1), relapsing polychondritis (1), pyoderma gangrenosum (1), hepatitis C (1), and graft versus host disease (1). In the comparator group, 42 of 68 (62%) patients with IF+/Ab+ results were diagnosed with AAV (anti-PR3 17, anti-MPO 25).

Conclusion: A positive anti-PR3 or anti-MPO assay in the absence of positive ANCA IF may rarely lead to a new diagnosis of systemic vasculitis; however, this immune profile can be observed in patients with previously known seropositive (IF+/Ab+) AAV. If one believes that serial ANCA testing is of value in monitoring clinical activity and response to therapy, our data suggest that both IF and specific antibody tests should be monitored, though the utility of this practice is controversial. Further investigation into the clinical implications of persistent antibody-positivity with negative immunofluorescence is warranted.

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Clinical Research Of Microscopic Polyangiitis Combined With Autoimmune Hemolytic Anemia. Dan Liu[1], Qing-ping Chen[2], Hai-hong Yao[1], Ru Li[1], Yin Su[1], Jie Zhang[2], Yu Chen[2], Ke Li[3] and Yuan Jia[1]. [1]Peking University People's Hospital, Beijing, China, [2]The Fifth Hospital of Xi'an, Xi'an, China, [3]The Second Affiliated Hospital, Xi'an Jiaotong University, Xi'an, China.

Background/Purpose: Autoimmune hemolytic anemia (AIHA) and Microscopic polyangiitis (MPA) are both rare autoimmune conditions. AIHA is caused by autoantibody-induced hemolysis (the premature destruction of circulating red blood cells) while MPA is characterized by necrotizing glomerulonephritis and pulmonary capillaritis. Both diseases are mediated by activation of lymphocytes and complement. Here we describe the clinical and laboratory characteristics of MPA patients combined with AIHA, investigate their treatment and prognosis, so as to help to improve the prognosis of such patients.

Methods: MPA was diagnosed in 51 patients referred to Department of Rheumatology, People's Hospital, Peking University. All patients of MPA were divided into 2 groups, non-AIHA group (n=35), and MPA combined with AIHA group (n=16). Clinical and laboratory data were retrospectively analyzed. Disease activity was evaluated by Birmingham Vacuities Activity Score-version 3 (BVAS [V3]). Therapeutic response and prognosis were systemically reviewed during a two-year follow-up period.

Results: Sixteen of the 51 patients were combined with AIHA(31.4%) and 13 of them manifested as the first symptome. Incidence of fever, hypertension, and severe lung injury (i.e. interstitial lung disease, pneumorrhagia) of MPA combined with AIHA group were higher than that in non-AIAH group, fever (81.3% vs. 15%, $X^2=7.50$, $P<0.01$), hypertension

(50% vs. 17.1%, X^2=5.95, P<0.01) and severe lung injury (100% vs. 68.9%, X^2=4.69, P<0.01), respectively. Compared with non-AIHA group, MPA combined with AIHA group had significantly lower levels of RBC (2.3 ± 0.3×10^9/L vs. 3.0 ± 0.7 × 10^9/L), Hb (72.8 ± 15.3 vs. 102.3 ± 20.7g/L), and C3 (0.6 ± 0.2 g/L vs. 1 ± 0.2g/L), while higher level of ESR (103.4 ± 27.9mm/H vs. 76.5 ± 31.1mm/H), IgG (18.5 ± 6.1mg/ml vs. 13.9 ± 6.0mg/ml) and BVAS [V3] (22.3 ± 2.7 vs. 18.3 ± 5.1). In MPA combined with AIHA group, Methylprednisolone of 500mg/day and 40mg/day were used in nine and seven cases, respectively, in which 13 cases had combined with cyclophosphamide, and 1 case combined with mycophenolate mofetil. After 3 months' treatment, Hb level of MPA combined with AIHA group significantly increased (from 72.8 ± 15.3 to 100.1 ± 16.9g/L) while BAVS (V3) has remarkably decreased (from 22.3 ± 2.7 to 3.6 ± 3.2). Five of 16 cases of MPA-AIHA patients died of severe anemia, renal failure and pulmonary fungal infection, another five were rehospitalized for anemia or renal dysfunction; the remaining six underwent gradual improvements of disease.

Conclusion: AIHA can be the first manifestation of MPA. MPA-AIHA patients with hypocomplementemia and multiple organ damage had high mortality. Start treatment with sufficient glucocorticoid combined with immunosuppressant is beneficial to induce remission.

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Antineutrophil Cytoplasmic Antibody-Associated Vasculitis Associated With Systemic Sclerosis In Japan: A Review Of The Literature. Natsumi Nagao, Yuri Sadanaga, Satoko Tashiro, Rie Suematsu, Syuichi Koarada, Akihide Ohta and Yoshifumi Tada. Saga University, Saga, Japan.

Background/Purpose: Cases of Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) during the course of systemic sclerosis (SSc) have recently been reported. Japanese cases of AAV associated with SSc were collected from the literature, and the characteristics of patients in Japan were analyzed.

Methods: A literature review was performed using MEDLINE and the database of the Japan Medical Abstracts Society. The following keywords were used: antineutrophil cytoplasmic antibody; vasculitis; and systemic sclerosis/scleroderma. Case reports, including proceedings and abstracts from Japan that were written in either English or Japanese, were identified. A total of 61 cases were reviewed, including 58 cases from 42 reports (6 in English and 36 in Japanese) and 3 cases from our hospital. The clinical features of SSc-associated AAV were compared with those reported by the AAV survey of the Ministry of Health, Labor and Welfare study group done between 2006 and 2008 in Japan.

Results: In SSc-associated AAV, the average age at onset was 57.0 years, which was 12.4 years earlier than for all AAV patients, and women developed the disease much more frequently than men. In SSc-associated AAV, the male:female ratio was 1:9, whereas the ratio was 1:1 in all AAV. In SSc, the proportions of the diffuse and the limited types were equal; anti-Scl-70 antibody was positive in 35 cases, and anti-centromere antibody was positive in 6 cases. The mean duration between diagnosis of SSc and AAV was 10.3 years (range, 1–41 years). In AAV, alveolar hemorrhage developed in 24%, and rapid progressive glomerulonephritis developed in 81%; both were more frequent than in all AAV as reported by the survey (11% and 63%, respectively). On the other hand, neurological manifestations were less frequent in SSc-associated AAV (24% versus 45%). No cases were positive for anti-PR3 antibody. Twelve cases died, and the most frequent cause of death was infection (7 cases).

Conclusion: SSc-associated AAV in Japan has several characteristics, including younger onset, female predominance, frequent pulmonary and renal manifestations, and long duration from SSc to AAV. It should be noted that this association is not extremely rare, and increased awareness may lead to earlier diagnosis and better prognoses.

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Pulmonary Fibrosis In ANCA-Associated Vasculitis. Cloé Comarmond[1], Bruno Crestani[2], Abdellatif Tazi[3], Baptiste Hervier[4], Sylvain Adam-Marchand[5], Hilario Nunes[6], Fleur Cohen-Aubart[4], Marie Wislez[7], Jacques Cadranel[7], Bruno Housset[8], Célia Lloret-Linares[9], Pascal Sève[10], Christian Pagnoux[11], Sébastien Abad[12], Juliette Camuset[13], Boris Bienvenu[14], Michael Duruisseaux[15], Eric Hachulla[16], Jean-Benoît Arlet[17], Mohamed Hamidou[18], Alfred Mahr[19], Anne-Laure Brun[20], Philippe Grenier[20], Patrice Cacoub[21] and David Saadoun[22]. [1]Hôpital Pitié Salpétrière, Paris, France, [2]Hôpital Bichat, Paris, France, [3]Hôpital Saint-Louis, Paris, France, [4]Pitié-Salpêtrière Hospital, APHP, Paris, France, [5]Centre Hospitalier Universitaire de Tours, Tours, France, [6]Avicenne Hospital (AP-HP), Bobigny, France, [7]Hôpital Tenon, Paris, France, [8]Centre Hospitalier Intercommunal de Créteil, Créteil, France, [9]Hôpital Lariboisière, Paris, France, [10]CHU Lyon, Lyon, France, [11]Rheumatology, Mount Sinai Hospital, Toronto, Canada, Toronto, ON, [12]Avicenne Hospital, Bobigny, France, [13]Centre Hospitalier Victor Dupouy, Argenteuil, France, [14]Division of Internal Medicine, Centre Hospitalier Régional Universitaire de Caen, Côte de Nacre, Caen, France, Caen, France, [15]CHU de Grenoble, Grenoble, France, [16]Internal Medicine, Lille CEDEX, France, [17]HEGP, Paris, France, [18]Nantes University Hospital, Nantes, France, [19]Department of Internal Medicine, Hospital Saint-Louis, Paris, France, [20]Hôpital Pitié-Salpêtrière, Paris, France, [21]Hopital Pitié-Salpétrière, Paris, France, [22]Department of Internal Medicine and Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France.

Background/Purpose: The association of pulmonary fibrosis (PF) with anti neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV), especially microscopic polyangiitis (MPA), is rare but related to poor prognosis. The possible link between PF, occult alveolar hemorrhage, ANCA positivity and specificity, and vasculitis remains unclear. The aim of the current study was to describe the characteristic features and long-term outcome in a large cohort of patients with PF associated to AAV.

Methods: We performed a retrospective study of the characteristics and outcome of 49 patients with PF associated to AAV, diagnosed between 1996 and 2013, and according to the American College of Rheumatology criteria and/or Chapel Hill definitions.

Results: Data were obtained from 30 (61%) men and 19 (39%) women. The median age at diagnosis of AAV was 66.5 [IQR: 57−74] years. Thirty nine (80%) patients had MPA and 10 (20%) had granulomatosis with polyangiitis. Besides constitutional symptoms, main extra-pulmonary manifestations included kidney involvement (57%), peripheral neuropathy (52%), and myalgia (37%). All patients had pulmonary symptoms, including crackles (77%), dyspnea (76%), chronic cough (27%) and/or hemoptysis (10%). The diagnosis of PF preceded the development of vasculitis in 21 (43%) patients, was concomitant in 21 (43%) and occurred subsequently in 7 (14%). At AAV diagnosis, restrictive syndrome was present in 67% of patients. Alveolar hemorrhage was present in 43% of patients. Thoracic computed tomography showed usual interstitial pattern in 39 (80%) patients, nonspecific interstitial pneumonia in 5 (10%) patients, and combined pulmonary fibrosis and emphysema in 5 (10%) patients. ANCA had mostly anti-myeloperoxydase specificity (84%). Hypereosinophilia was frequently observed at diagnosis of AAV (n=15,31%). All patients were treated with steroids as induction therapy, combined with cyclophosphamide (CYC) (n=37, 76%) or rituximab (RTX) (n=1, 2%). The 1-year survival in patients treated with steroids alone or combined with CYC or RTX as induction therapy was of 60% and 92%, respectively (p=0.016). After a median follow-up of 48 [14−88] months, vasculitis relapses occurred in 18 (37%) patients. Eighteen (37%) patients died, related to respiratory failure in 11 (61%) of them.

Conclusion: PF is a rare manifestation of AAV with a very poor prognosis. Induction therapy with CYC might improve the outcome.

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Cardiac Involvement In Granulomatosis With Polyangiitis. Lucy McGeoch[1], Simon Carette[2], David Cuthberston[3], Gary S. Hoffman[4], Nader A. Khalidi[5], Curry L Koening[6], Carol A. Langford[7], Paul A. Monach[8], Larry W. Moreland[9], Philip Seo[10], Ulrich Specks[11], Steven R. Ytterberg[11], Carol McAlear[12], Peter A Merkel[13], Christian Pagnoux[14] and The Vcrc[13]. [1]Mount Sinai Hospital, University Health Network, University of Toronto, Toronto, ON, [2]UHN/MSH, Toronto, ON, [3]University of South Florida, Tampa, FL, [4]Cleveland Clinic Foundation, Cleveland, OH, [5]McMaster University, Hamilton, ON, [6]George E. Wahlen Department of Veterans Affairs Medical Center Salt Lake City and University of Utah, University of Utah School of Medicine, Salt Lake City, UT, [7]Cleveland Clinic, Cleveland, OH, [8]Boston University, Boston, MA, [9]University of Pittsburgh, Pittsburgh, PA, [10]Johns Hopkins Vasculitis Center, Baltimore, MD, [11]Mayo Clinic, Rochester, MN, [12]University of Pennsylvania, Philadelphia, PA, [13]University of Pennsylvania and VA Medical Center, Philadelphia, PA, [14]Division of Rheumatology, Mount Sinai Hospital, Toronto, ON.

Background/Purpose: Prior cohort studies in Europe have found cardiac involvement to be rare in granulomatosis with polyangiitis (GPA) but associated with significant increases in mortality and risk of relapse. The aim of this study was to determine the frequency and associated clinical outcomes of cardiac disease in a large multicenter North American GPA cohort.

Methods: The data source was the Vasculitis Clinical Research Consortium (VCRC) Longitudinal Study of GPA which includes 517 patients satisfying the modified ACR criteria for GPA recruited into the cohort between 2006 and 2013. Information on cardiac disease was reported by expert investigators using a standardized protocol. The demographic and clinical characteristics of patients with GPA-related cardiac involvement at diagnosis or during follow-up were compared to those patients without cardiac disease.

Results: Seventeen (3.3%) patients with cardiac involvement were identified. Cardiac manifestations were observed both at diagnosis (n=9) or during subsequent disease course and/or relapse (n=8). Observed cardiac manifestations included pericarditis (n=8), cardiomyopathy (n=5, including 1 with pericarditis), coronary artery disease (n=4), and valvular disease (n=2, including 1 with CAD). There were no overt differences between patients with GPA with cardiac involvement and those without cardiac disease: 7/17 (41%) patients with cardiac disease were female (vs. 52% in those without cardiac disease; p= 0.36); mean age at diagnosis of patients with cardiac disease was 45.2 ± 19.9 yrs. (vs. 44.8 ± 16.5 yrs. for those without cardiac disease; p= 0.92); and 16/17 (94% [PR3 65%]) with cardiac disease were tested ANCA positive (vs. 81% [PR3 68%] in those without cardiac disease; p=0.33). Frequency of non-cardiac disease manifestations were comparable between the two groups and no significant differences were observed in the immunosuppressant agents. Lag time between symptom onset and diagnosis in the cardiac GPA group was comparable to the non-cardiac GPA group (18 ± 27 mo. vs. 14 ± 36 mo. respectively; p= 0.56).

Mean follow-up from diagnosis was 104 ± 68 mo. for cardiac GPA and 105 ± 71 mo. for non-cardiac GPA (p = 0.92). Rate of relapse was comparable between the 2 groups (53% of cardiac GPA patients experienced ≥1 GPA relapse vs. 66% of the non-cardiac GPA group; p= 0.25). At present, none of the patients with cardiac disease in the cohort have died.

Conclusion: This case series confirms that cardiac involvement in GPA is rare, heterogeneous, and can manifest at disease onset as well as during subsequent relapses. In contrast with previous reports, cardiac involvement was not associated in this population with a higher rate of relapse.

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Clinically Apparent Arterial Thrombosis In Persons With Systemic Vasculitis. Alexander Tsoukas[1], Christian A. Pineau[2], Sasha Bernatsky[2], Lawrence Joseph[1] and Patrick Belisle[3]. [1]McGill University, Montreal, QC, [2]McGill University Health Center, Montreal, QC, [3]Research Institute of the McGill University Health Centre, Montreal, QC.

Background/Purpose: Systemic vasculitides are a group of heterogeneous, autoimmune disorders characterized by inflammation of blood vessels. As with other autoimmune disorders, inflammation and long-term medical therapies may lead to accelerated atherosclerosis, with subsequent arterial thrombosis being a significant adverse outcome. Our first goal is to compare the rate of arterial thrombotic events in patients with systemic vasculitis, namely polyarteritis nodosa (PAN) and granulomatosis with polyangiitis (GPA), with that of the general population. Our second goal is to determine if there is an increased rate of comorbidities related to atherosclerosis within the vasculitis group compared to the general population group.

Methods: Data was collected from the Quebec provincial health administrative database from the years 2002–2006. Incident cases of all systemic vasculitis (ICD 446.x), PAN (ICD 446.0)and GPA (ICD 446.4)were included in the cohort, and age (18–45, >45-<65, and ≥65 years old) and sex-matched controls were taken from the general population. Outcomes included acute myocardial infarction (AMI; ICD 410.x) and cerebrovascular accident (CVA; ICD 433.x, 434.x) which were assessed longitudinally via hospitalization records within the same administrative data. Outcomes in vasculitis cases were compared to those in the general population. Furthermore, the incidence of comorbidities, specifically type II diabetes, hypertension, and dyslipidemia were ascertained in vasculitis patients with adequate followup and compared with the general population.

Results: Within the systemic vasculitis group (n=1672) the incidence rate for AMI was most elevated for 18–45 y.o. females (n=96) at 495.6/100k-py [95% CI 222.7–1103.2] vs. 19.5/100k-py [95% CI 18.6–20.5] in the gen. pop. (relative rate=25.4), and 18–45 y.o. males (n=46) at 1048.8/100k-py [95% CI 471.2–2334.5] vs. 89.5/100k-py [95% CI 87.4–91.6] (RR=11.7). In the PAN/GPA subgroups, similarly elevated rates existed, most significant for young males with PAN at 1683.1/100k-py. The incidence rate for CVA was most elevated in 18–45 y.o. females at 247.2/100k-py vs. 8.8/100k-py (RR=28.1).

Amongst the 45–65 y.o. patients with PAN, there was a RR for AMI of 4.9 in males. In those with GPA, there was no statistical difference in AMI, and a 2–3 RR for CVA. In the ≥65 y.o. group, there was no elevation in RR in any subgroup for either outcome.

In 18–45 y.o. females with systemic vasculitis, there was a incidence of DMII of 10.1% (vs. 0.83% in the gen. pop), dyslipidemia 5.1% (vs. 0.49%), and hypertension 24.1% (vs. 1.37%). In 18–45 y.o. males the incidence of DMII was 7.9% (vs.0.74%), dyslipidemia 13.2% (vs. 1.05%), and hypertension 31.6% (vs.1.46%). In both the 45–65 and ≥65 y.o. groups there was an approximately 2–3 times incidence for the three comorbidities compared to the gen. pop.

Conclusion: Patients with systemic vasculitis have higher incidence rates of arterial thrombotic events, with the most significant difference seen in subjects under the age of 45 y.o. The high incidence of comorbidities is likely an important factor, possibly related to corticosteroid use. However, the difference in rates observed between PAN and GCA may point to possible disease specific factors.

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Granulomatosis With Polyangiitis Central Nervous System Involvement: Presentation and Management. Gonzalo De Luna[1], Benjamin Terrier[1], Pierre Kaminsky[2], Francois Maurier[3], Roser Solans[4], Raphaèle Seror[5], Xavier Puéchal[6], Luc Mouthon[7] and Loic Guillevin[1]. [1]Cochin University Hospital, Paris, France, [2]Université de Lorraine, Nancy, F-54000, France; CHU de Nancy, Orphan disease unit, Nancy, F-54000, France;, Nancy, France, [3]Division of internal Medicine, CHR Metz, Metz, Metz, France, [4]Hospital Vall d'Hebron, Barcelona, Spain, [5]Bicetre university hospital, LE Kremlin-Bicetre, France, [6]Hôpital Cochin, AP-HP, Université Paris Descartes, Sorbonne Paris Cité, Paris, France, [7]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, Paris, France.

Background/Purpose: Granulomatosis with polyangiitis (GPA), a small-sized–vessel vasculitis, commonly involves ear, nose & throat (ENT), lungs and kidneys, and, more rarely, the central nervous system (CNS). Three different pathological CNS-involvement patterns are known: 1) a manifestation of generalized GPA, with vasculitis of small-sized brain or spinal cord vessels; 2) contiguous granulomatous CNS invasion from extracranial sites; 3) intracerebral (meninges (pachymeningitis) or brain) granulomatous lesions. We evaluated GPA CNS clinical features, imaging findings, treatments and outcomes.

Methods: GPA patients with CNS (pachymeningitis, meningitis, stroke, spinal cord and/or hypophyseal) involvement who met ACR criteria and/or Chapel Hill definitions, after excluding other causes, were studied retrospectively. Patient characteristics, treatments and outcomes were analyzed. Neurological sequelae were evaluated with a simplified modified Rankin scale (mRS) by telephone interview at the last follow-up.

Results: We included 31 patients (22 men), whose mean age at GPA diagnosis and onset of CNS involvement were 46±17 and 50±15 years, respectively. The latter was present in 14 (45%) patients at GPA diagnosis, and appeared in the other 17 (55%) after a median follow-up of 69 months. Headache was the main symptom (64%), along with motor (32%) and sensory impairments (41%). CNS lesions were: 19 pachymeningitis (16 cranial and 3 spinal cord), 14 ischemic or 3 hemorrhagic strokes, 5 cerebral vasculitides and/or 2 hypophyseal lesions. Extra-CNS manifestations affected ENT (81%), lungs (58%), peripheral nerves (48%) and kidneys (35%). ANCA detected in 27/31 (87%) patients had PR3 (n=22) or MPO (n=5) specificity.

Induction comprised corticosteroids (CS; 100%) combined with IV (61%) or oral (35%) cyclophosphamide (CYC), or rituximab (RTX; 3%). Maintenance therapy consisted of CS (100%) combined with azathioprine (58%), methotrexate (19%) or RTX (6%).

After 73±56 months of follow-up since GPA CNS onset, CNS manifestations had responded clinically in 26/31 (84%) patients, whereas 5 (16%) patients had refractory CNS GPA. Seven out of the 26 (27%) responders relapsed after a median of 13 months. Relapsed and/or refractory CNS GPA was seen in 9/14 (64%) of patients with initial vascular CNS manifestations but only in 5/19 (26%) of those with granulomatous lesions. Overall, relapsing and/or refractory CNS involvement was more frequently associated with vascular CNS manifestations (P=0.04).

Relapsing and/or refractory CNS (n=12) were treated with CS (100%) and RTX (58%), IV CYC (33%) or oral CYC (8%). All but one achieved remission after new induction regimen. One patient died. Neurological sequelae persisted in 10/31 (32%) patients. Diabetes insipidus related to hypophyseal GPA persisted after induction and maintenance regimens in the 2 patients.

Conclusion: Our series highlights the heterogeneity of GPA CNS involvement. Despite initial severe disease, most patients improved under conventional therapy. Baseline vascular CNS manifestations were more frequently associated with relapsing and/or refractory disease than granulomatous lesions. RTX deserve to be evaluated to treat GPA patients with CNS involvement.

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Safety Of Remission Induction With Rituximab Versus Cyclosphosphamide In Patients 65 and Older With Severe ANCA-Associated Vasculitis. Eli Miloslavsky[1], Ulrich Specks[2], Peter A Merkel[3], Philip Seo[4], Robert F. Spiera[5], Carol A. Langford[6], Gary S. Hoffman[7], Cees G.M. Kallenberg[8], E. William St. Clair[9], Nadia Tchao[10], Linna Ding[11], David Ikle[12], Brett Jepson[12], Paul Brunetta[13] and John H. Stone[14]. [1]Massachusetts General Hopsital, Boston, MA, [2]Mayo Clinic, Rochester, MN, [3]University of Pennsylvania and VA Medical Center, Philadelphia, PA, [4]Johns Hopkins Vasculitis Center, Baltimore, MD, [5]Hospital for Special Surgery, New York, NY, [6]Cleveland Clinic, Cleveland, OH, [7]Cleveland Clinic Foundation, Cleveland, OH, [8]University Medical Center Groningen, Groningen, Netherlands, [9]Duke University Medical Center, Durham, NC, [10]Immune Tolerance Network, Bethesda, MD, [11]NIAID, Bethesda, MD, [12]Rho, Chapel Hill, NC, [13]Genentech, So San Francisco, CA, [14]Massachusetts General Hospital, Boston, MA.

Background/Purpose: Retrospective studies have demonstrated that patients of advanced age with systemic vasculitis experience a higher mortality and adverse events than their younger counterparts. However, no study has prospectively examined the safety of remission induction treatment of Granulomatosis with Polyangiitis (GPA) or Microscopic Polyangiitis (MPA) in patients of advanced age. We analyzed the results of the Rituximab in ANCA-associated vasculitis (AAV) (RAVE) trial in order to evaluate adverse events (AEs) and mortality in patients ≥ 65 years old.

Methods: Randomized controlled trial comparing rituximab (RTX, n=99) to cyclophosphamide (CYC) followed by azathioprine (AZA, n=98) for remission induction in patients with GPA or MPA. Glucocorticoids were tapered over 5 months. Subjects were followed for 18 months.

Results: 55 patients were ≥ 65 years old (36 RTX, 19 CYC/AZA) and 142 patients were < 65 years old (63 RTX, 79 CYC/AZA). Baseline characteristics of both groups are reported in the table. Treatment regimens achieved similar efficacy in both age groups.

While total adverse events were similar between both age groups, patients ≥ 65 had more severe AEs (Grade ≥ 3) than those < 65 (Table). Severe cytopenias occurred more frequently in older patients. All four deaths during the study period occurred in patients ≥ 65 (2 RTX, 2 CYC/AZA).

Table. Baseline characteristics and adverse events

	Under 65 (95% CI)	65 and Older (95% CI)
Mean baseline BVAS/WG	7.84	8.51
Mean baseline creatinine	1.33	1.74
PR3-ANCA	74.6%	45.5%
MPO-ANCA	25.4%	54.5%
Achieved complete remission at 6 mos	61.3%	50.9%
Remained in complete remission at 18 mos	37.3%	32.7%
Mean total prednisone dose (g)	7.07	5.73
Total adverse events/patient year	10.51 (10.07–10.97)	11.50 (10.73–12.3)
Severe adverse events (Grade ≥3)/ patient year	0.52 (0.42–0.63)	1.06 (0.83–1.32)
Severe infections/patient year	0.10 (0.06–0.16)	0.21 (0.12–0.34)
Severe cytopenias/patient year	0.03 (0.01–0.06)	0.23 (0.14–0.37)
Deaths	0	4

Comparing the two treatment arms among patients 65 and older, frequencies of total AEs or severe AEs were similar between the RTX and CYC/AZA groups (11.52/patient year RTX vs 11.44/patient year CYC/AZA; 1.15/patient year (95% CI 0.87–1.50) RTX vs 0.85/patient year (0.52–1.31) CYC/AZA, respectively). Similarly, the frequency of severe cytopenias and severe infections were comparable between the two groups (0.24 (95% CI 0.13–0.42)/patient year RTX vs 0.21 (95% CI 0.07–0.49)/patient year CYC/AZA; 0.22 (95% CI 0.11–0.40)/patient year RTX vs 0.17 (95% CI 0.05–0.43)/patient year CYC/AZA), respectively.

Conclusion: Patients ≥ 65 undergoing remission induction treatment for GPA or MPA may experience more severe adverse events than their younger counterparts, including more frequent severe cytopenias. Both RTX and CYC/AZA-based regimens have a similar adverse event profile in patients ≥ 65 years old.

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Efficacy Of Rituximab For Otolaryngologic (ENT) Manifestations Of Granulomatosis With Polyangiitis (GPA, Wegener's granulomatosis). Lindsay Lally[1], Robert Lebovics[2], Wei-Ti Huang[1] and Robert F. Spiera[1]. [1]Hospital for Special Surgery, New York, NY, [2]St. Luke's-Roosevelt Hospital Center, New York, NY.

Background/Purpose: ENT involvement is the most prevalent manifestation of GPA. Rituximab (RTX) is a proven effective remission induction therapy for severe GPA with vasculitic manifestations. The efficacy of RTX for the granulomatous manifestations of GPA is debated. No previous studies have looked at the efficacy of RTX specifically for ENT manifestations of GPA. The aim of this study was to compare the efficacy of RTX to other therapies for the ENT manifestations of GPA, in a well-characterized cohort.

Methods: Subjects with GPA seen at a tertiary care ENT practice between 2003 and 2013 were identified via ICD-9 code. Charts were reviewed for demographics, organ involvement, ENT disease activity, medications, and procedures at each visit. At each visit subjects had complete ENT exam including endoscopic visualization of the upper airway and audiometry, for those with otologic involvement. Endoscopic exam and assessment of ENT disease activity were all performed by one otolaryngologist with specific expertise in GPA. Primary outcome was ENT disease activity at each visit in subjects on RTX versus those on all other therapy. RTX use was defined a priori as most recent infusion within 6 months or continued B cell depletion at the time of the visit. Secondary outcomes were comparison of ENT disease activity in subjects on RTX to those on MTX, AZA, CYC or TMP-SMX.

Results: 99 subjects with GPA were identified and 975 office visits from the subjects were analyzed. The mean age was 49.8 years, mean disease duration 8.1 years, 68.7% were female, 63.5% had limited disease and 76.8% had positive PR3. 48 subjects never received RTX and 51 received RTX at least once. Comparing patients who ever received RTX to those who did not, those treated with RTX were significantly more likely to have severe disease (48% vs 26%, p=0.027) and were also more likely to have ENT damage at baseline (94% vs73%, p=0.004). There were no other differences between the groups.

Outcomes: There was no active ENT disease at 92.4% of visits for subjects on RTX compared to 53.7% of visits for subjects not receiving RTX (OR 11.0; 95%CI 5.5–22.0, p<0.0001). Adjusting for ENT damage, extent and duration of disease, age, and sex, RTX was still favored (OR 12.0; 95%CI 5.9–24.3, p<0.0001). Subjects on RTX compared to MTX, AZA, CYC, or TMP-SMX were significantly more likely to be in ENT remission, p<.0001 for each comparison (Table 1).

Table 1.

Medication	Visits on Medication, n (%)	Visits with ENT Remission, n (%)	Adjusted OR, 95% CI	P value**
RTX	144 (14.8)	133 (92.4)		
Not RTX*	831 (85.2)	449 (53.7)	12.0 (5.9–24.3)	< .0001
MTX	197 (20.2)	116 (58.9)	11.5 (6.4–24.8)	< .0001
CYC	55 (5.6)	12 (21.8)	52.8 (19.1–145.9)	< .0001
AZA	98 (10.1)	53 (54.1)	8.1 (3.3–19.7)	< .0001
TMP–SMX	113 (11.6)	64 (56.2)	13.4 (5.9–30.6)	< .0001
Other	94 (9.6)	45 (47.9)	17.0 (6.9–41.6)	< .0001

*includes MTX, CYC, AZA, TMP–SMX, other and no therapy (not accounting for corticosteroids)
**mixed linear effect model

Conclusion: RTX is an effective treatment for ENT manifestations of GPA. Subjects treated with RTX were >11 times less likely to have active ENT disease compared to those not on RTX. Those treated with RTX were far less likely to have active ENT disease than those treated with other immunosuppressives. This represents the largest cohort of patients in whom meticulously assessed ENT outcomes with RTX versus other therapies is described and suggests RTX is superior to conventional immunosuppressives for ENT manifestations of GPA.

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Relationship Between Infectious Side Effects and Immunoglobulin Levels In The Maintenance Rituximab Vs Azathioprine For ANCA-Associated Vasculitides Trial. Loic Guillevin[1], Christian Pagnoux[2], Alexandre Karras[3], Chahera Khouatra[4], Olivier Aumaître[5], Pascal Cohen[6], Olivier Decaux[7], Hélène Desmurs-Clavel[8], Pierre Gobert[9], Thomas Quemeneur[10], Claire Blanchard-Delaunay[11], Pascal Godmer[12], Xavier Puechal[13], Pierre-Louis Carron[14], Pierre-Yves Hatron[15], Nicolas Limal[16], Mohamed Hamidou[17], Francois Maurier[18], Thomas Papo[19], Matthias Büchler[20], Bernard Bonnotte[21], Philippe Ravaud[22] and Luc Mouthon[13]. [1]Division of Internal Medicine, Hôpital Cochin, University Paris Descartes, Paris, France, [2]Hôpital Cochin, PARIS, France, [3]Hôpital Européen Georges Pompidou, APHP, Paris, France, [4]CHU Lyon, Lyon, France, [5]Division of internal Medicine, Centre Hospitalier Universitaire, Hôpital Gabriel Montpied, Clermont–Ferrand, Clermont–Ferrand, France, [6]Cochin University Hospital, Paris, France, [7]Rennes University Hospital, Rennes, France, [8]University of Lyon, LYON, France, [9]Centre Hospitalier d'Avignon, Avignon, France, [10]CHR de Valenciennes, Valenciennes, France, [11]Hôpital de Niort, Niort, France, [12]Department of Internal Medicine, Centre Hospitalier Bretagne Atlantique de Vannes, Vannes, France, [13]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, Paris, France, [14]Centre Hospitalier de Grenoble, Grenoble, France, [15]Claude Huriez University Hospital, Lille, France, [16]Hôpital Henri Mondor, APHP, Creteil, France, [17]Nantes University Hospital, Nantes, France, [18]Division of internal Medicine, CHR Metz, Metz, Metz, France, [19]University Paris-7, INSERM U699, APHP, Bichat Hospital, Paris, France, [20]University Hospital of Tours, TOURS, France, [21]Centre Hospitalier de Dijon, Dijon, France, [22]Hopital Hotel Dieu, Paris Descartes University, Paris, France.

Background/Purpose: MAINRITSAN trial (NCT 00748644) results demonstrated that 500 mg of rituximab (RTX) every 6 months was superior to azathioprine (AZA) to maintain ANCA-associated–vasculitis (AAV) remission. Infection frequencies were comparable in the 2 arms, and other SAE were infrequent and resolved in most patients. This study aimed to determine whether globulin levels could be associated with infectious side effects.

Methods: Once remission was obtained with a conventional regimen, patients with newly diagnosed or relapsing AAV were randomly assigned to receive a 500-mg RTX infusion on D1, D15, 5.5 months later, then every 6 months for a total of 5 infusions over 18 months, or AZA (initial dose 2 mg/kg/d) for 22 months. The primary endpoint was the major relapse rate (EULAR/ACR criteria) at 28 months. Other outcome measures were the severe adverse event (SAE) rate (WHO definition) associated with each maintenance regimen. Infectious SAE occurring in both groups were one of the study's secondary endpoints, as were gammaglobulin, IgG and IgM levels (1/3 missing data for valid reasons).

Results: Among the 115 patients (50 men/65 women; mean age, 55±13 years; 92 newly diagnosed and 23 relapsers) study participants (57 RTX arm, 58 AZA arm): 87 had granulomatosis with polyangiitis, 23 microscopic polyangiitis and 5 kidney-limited diseases. The main clinical involvements at diagnosis or last relapse were: 89 (77.4%) ENT, 71 (61.7%) lung and 81 (70.4%) kidney. Major relapses occurred in 20 (17.3%) patients: 3 (3.5%) in the RTX arm and 17 (29.3%) in the AZA arm, with 3 AZA-arm deaths (1 sepsis, 1 pancreatic cancer, 1 mesenteric ischemia). Seven infectious SAE (12.2%) were recorded in the RTX arm and 8 (13.7%) in the AZA arm (Table). Respective RTX- and AZA-arm mean levels (g) of gammaglobulin were: 8.04 (±6.05) and 7.21 (±2.18) at M0, and 7.41 (±2.16) and 8.1 (±2.89) at M28; IgG were 6.06 (±2.66) and 5.44 (±1.58) **at M0**, and 6.87 (±2.50) in the RTX arm and 6.71 (±1.05) **at M28**; IgM were 0.64 (± 0.5) and 0.58 (± 0.51) at M0, and 0.44 (±0.62) and 0.6 (±0.32) at M28.

Infection	RTX 57 patients	AZA 58 patients
Bronchitis	2	0
Tuberculosis	1	0
Bacterial pneumonia	0	1
Pneumocystis jiroveci pneumonia	1	0
Bacterial endocarditis	0	1
Mycobacterial infection	0	1
Prostatitis	0	1
Herpes zoster	1	1
Angiocholitis	0	1
Septicemia	0	1 (died)
Esophageal candidiasis	1	0
Campylobacter jejuni diarrhea	1	1

Conclusion: These trial results demonstrated that 500 mg of RTX every 6 months was not only superior to AZA to maintain AAV remission but as safe as AZA. At the chosen dose, RTX did not significantly decrease gammaglobulin, IgG and IgM levels. The rare infections, observed in both groups, were reflected causes and mechanisms other than Ig levels.

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Rate Of Infection and Development Of Malignancy In Patients With ANCA-Associated Vasculitis Treated With Rituximab: A Meta-Analysis From Randomized Trials. Carolina Mejia-Otero[1], Carlos J. Lozada[2] and Luis Arias-Urdaneta[3]. [1]Mount Sinai Medical Center, Miami, FL, [2]University of Miami Miller School of Medicine, Miami, FL, [3]Mount Sinai Medical Center, Miami Beach, FL.

Background/Purpose: Over the past 40 years failures to achieve remission in a proportion of patients and the potential development of significant adverse effects have been major drawbacks of cyclophosphamide (CYC)-based regimens. Rituximab, an anti-CD20 monoclonal antibody, has compared favorably to CYC-based regimens for remission-induction of ANCA-associated vasulitis (AAV) in controlled clinical trials. It has also been able to maintain clinical remission in some patients for several months of follow up without the need for medication-based maintenance regimens. We intend to describe the rates of major adverse events (malignancy, infections) with

rituximab and control interventions in existing randomized controlled trials for the treatment of AAV.

Methods: All randomized controlled trials of rituximab in patients with AAV were sought in PubMed, EMBASE, and Cochrane databases during December 2012. Pooled treatment effects were estimated using risk ratio (RR) with the Mantel–Haenszel risk ratio in a random-effects model. Heterogeneity was assessed using chi-square tests and I2 statistic; we defined I2 < 25% as low heterogeneity according to the Cochrane Handbook of Systematic Reviews. For statistical analysis, we used Review Manager 5.1

Results: Upon analysis of the pooled data of included trials [1, 2, 3], rituximab was shown to be more efficacious in achieving remission than the control interventions. Even though no statistically significant difference was found in the rates of adverse events, the rate of malignancy tended to be more prevalent in the rituximab group when compared to the control group (P= 0.85, *figure 1*). In contrast, infection rates were more prevalent in the control group when compared to rituximab (P= 0.84, *figure 2*). Patient exposure to several immunosuppressive drugs in these trials, makes appraising the direct responsibility of one agent, rituximab or CYC, in the occurrence of the adverse events reported by investigators a significant challenge. In addition, AAV itself may predispose patients to malignancy or infection. Long-term follow up of the patients from these trials may provide further information about the safety profile of rituximab.

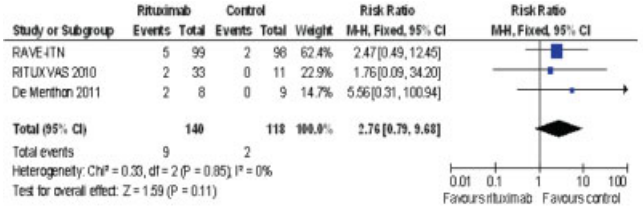

Figure 1. Malignancy rates

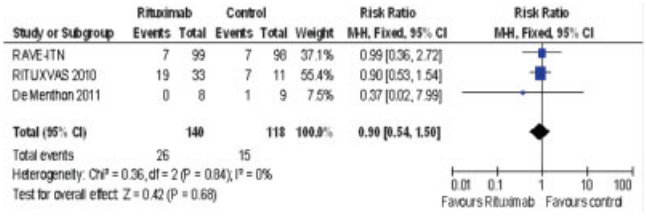

Figure 2. Infection rates

Conclusion: Rituximab has been shown an effective alternative for achieving remission in AAV when compared to the control interventions in this meta-analysis. This therapy may allow long term disease control with fewer side effects in patients with AAV but more randomized control trials are needed.

Disclosure: C. Mejia-Otero, None; **C. J. Lozada**, None; **L. Arias-Urdaneta**, None.

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Glucocorticoid Treatment and Damage In The Antineutrophil- Cytoplasm Antibody Associated Vasculitides. Joanna Robson[1], Helen Doll[2], Ravi Suppiah[3], Oliver Flossmann[4], Lorraine Harper[5], Peter Hoglund[6], David Jayne[7], Alfred Mahr[8], Kerstin Westman[9] and Raashid A. Luqmani[10]. [1]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford, United Kingdom, [2]University of East Anglia, Norwich, United Kingdom, [3]Auckland District Health Board, Auckland, New Zealand, [4]Royal Berkshire Hospital, Reading, United Kingdom, [5]University of Birmingham, Birmingham, United Kingdom, [6]Skane University Hospital, Lund, Sweden, [7]Addenbrookes Hospital University of Cambridge, Cambridge, United Kingdom, [8]Department of Internal Medicine, Hospital Saint-Louis, Paris, France, [9]Skåne University Hospital Malmö, Lund University, Malmö, Sweden, [10]University of Oxford, Oxford, United Kingdom.

Background/Purpose: Granulomatosis with polyangiitis [Wegener's] (GPA) and microscopic polyangiitis (MPA) are antineutrophil-cytoplasm antibody associated vasculitides (AAVs). Damage is quantified by the Vasculitis Damage Index (VDI). Long term (up to 7 years) damage has been described for patients from four European Vasculitis Study Group (EUVAS) trials. The objective of this study is to determine the factors associated with long-term damage in the ANCA-associated vasculitides.

Methods: Data from N=535 patients from four EUVAS trials were studied. A long-term follow up (LTFU) questionnaire at 7 years post diagnosis was completed including VDI and glucocorticoid data. The associations between baseline (age, creatinine and BVAS scores) and follow-up data (number of relapses and duration of glucocorticoids) and damage over LTFU (total VDI scores and individual treatment related damage items) were explored. Multiple regressions were used to look for independent associations between baseline measures, cumulative factors and VDI scores at LTFU.

Results: 296 patients had steroid use and VDI data available at LTFU, with the mean length of use 40.4 (SD 16.7) months. On multiple linear regression, high levels of damage were associated with age at baseline (p=.048), serum creatinine (p=.042), number of relapses (p=.021), and cumulative glucocorticoid use (p=.026). Patients with a longer duration of glucocorticoid treatment [OR=1.21 per 10 months (95%CI 1.3 to 1.42), p=0.019] were more likely to have a total VDI score of ≥5 at LTFU.

Conclusion: Long term damage in the ANCA-associated vasculitides may be predicted by severity of initial disease, age, number of relapses and duration of steroids used; improvement in immunosuppressant therapies is therefore indicated.

Table 1. Independent associations between baseline factoss, relapse and steroid use and (A) overall damage, (B) treatment-related damage

Factor	B (SE)	p-value	OR (95% CI)	p-value
(A) Overall damage	**Total number of items**		**5+ items**	
Age at entry, per 10 years	.243 (.12)	0.048	1.19 (.98–1.43)	0.077
Creatinine, per 100 μmol/l	.164 (.08)	0.042	1.22 (1.06–1.40)	0.005
GFR, per 10	−.010 (.07)	0.891	.99 (.89–1.12)	0.969
CRP, per 10	.018 (.01)	0.06	1.01 (.99–1.03)	0.247
BVAS, per 10 points	.371 (.19)	0.055	1.26 (.94–1.69)	0.124
4+ relapses	1.838 (.79)	0.021	5.28 (1.32–21.0)	0.018
Steroid use, per 10 months	.230 (.10)	0.026	1.21 (1.3–1.42)	0.019
(B) Treatment-related damage	**Total number of items**		**1+items**	
Age at entry, per 10 years	.156 (.06)	0.008	1.18 (.98–1.42)	0.09
Sex (Female)	.457 (.16)	0.005	2.27 (1.32–3.92)	0.003
Creatinine, per 100 μmol/l	.072 (.04)	0.07	1.19 (1.01–1.40)	0.041
GFR, per 10	−.017 (.04)	0.623	.97 (.86–1.09)	0.591
4+ relapses	.474 (.38)	0.209	1.47 (.40–5.37)	0.56
Steroid use, per 10 months	.120 (.05)	0.013	1.22 (1.04–1.43)	0.016

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Efficacy Of Glucocorticoids To Treat Limited Flares In ANCA-Associated Vasculitis. Eli Miloslavsky[1], Ulrich Specks[2], Peter A. Merkel[3], Philip Seo[4], Robert F. Spiera[5], Carol A. Langford[6], Gary S. Hoffman[7], Cees G.M. Kallenberg[8], E. William St. Clair[9], Nadia Tchao[10], Linna Ding[11], David Ikle[12], Brett Jepson[12], Paul Brunetta[13] and John H. Stone[14]. [1]Massachusetts General Hopsital, Boston, MA, [2]Mayo Clinic, Rochester, MN, [3]University of Pennsylvania, Philadelphia, PA, [4]Johns Hopkins Vasculitis Center, Baltimore, MD, [5]Hospital for Special Surgery, New York, NY, [6]Cleveland Clinic, Cleveland, OH, [7]Cleveland Clinic Foundation, Cleveland, OH, [8]University Medical Center Groningen, Groningen, Netherlands, [9]Duke University Medical Center, Durham, NC, [10]Immune Tolerance Network, Bethesda, MD, [11]NIAID, Bethesda, MD, [12]Rho, Chapel Hill, NC, [13]Genentech, So San Francisco, CA, [14]Massachusetts General Hospital, Boston, MA.

Background/Purpose: The great majority of patients with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) achieve disease remission initially, but relapses occur in up to 50% of patients within three years. Most disease flares are limited rather than severe. The most common approach to treating limited flares is to increase the glucocorticoid dose with or without a change in other immunomodulatory therapy. However, the effectiveness of this approach has never been studied.

Methods: This analysis explored the outcomes of patients with a first limited flare in the RAVE trial. Limited flares (BVAS/WG ≤ 3 and no major BVAS/WG items) were treated, per protocol, by increasing prednisone to a dose selected by the investigator. The new prednisone dose was maintained for 1 month before resumption of a protocol-specified taper with an endpoint of 0mg. Patients were followed for 18 months from study entry. The primary

outcome was the percentage of patients who achieved and maintained remission without additional changes in therapy.

Results: 47 patients (24%) experienced limited flares and were treated with an increase in prednisone. 25 limited flares occurred in the rituximab (RTX) group and 22 in the cyclophosphamide/azathioprine (CYC/AZA) group. 38 patients (81%) who flared were PR3-ANCA-positive and 29 (62%) had relapsing disease at baseline. 41 patients (87%) achieved remission before experiencing their first limited flare, which occurred on average 7.6 months (range 1.8–17.2) after entry. 28 patients (60%) who experienced a limited flare were off prednisone at the time of the flare, and the mean daily dose at flare among patients who remained on prednisone was 7.1 mg (range 2.5–20.0). Within the CYC/AZA group, 9% of the patients with limited flares were still receiving CYC and 86% were on azathioprine.

Following the limited flare, patients were followed for an average of 7.0 months (range 0.7–16.3). The average daily prednisone dose used to treat limited flares was 19.5mg (range 2.5–80). 36 patients (77%), (18 RTX and 18 CYC/AZA) achieved remission again, an average of 2.5 months after the increase in prednisone dose. However, 26 patients (55%) were unable to achieve and maintain remission throughout the follow-up period: 15 failed to sustain remission and 11 did not reach remission. 22 patients (47%) had recurrent flares: 13 limited (8 RTX, 5 CYC/AZA) and 9 severe (5 RTX, 4 CYC/AZA). Of these, 9 had discontinued prednisone and 13 patients were receiving 7.7mg (range 2.5–20) of prednisone on average. One patient had persistently elevated BVAS/WG (i.e., did not achieve remission again), and three withdrew from the trial. Only 11 patients (23%) who experienced limited flares were able to achieve remission, discontinue prednisone, and maintain remission through month 18.

Conclusion: Treatment of limited flares in AAV with a temporary increase of glucocorticoids is effective in restoring disease control in most patients, but recurrent flares within a relatively short time period are the rule in this scenario. Alternative approaches to the treatment of limited flares, including continuing glucocorticoids indefinitely or increasing or changing concomitant immunosuppressive therapies, must be considered.

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Efficacy Of Methotrexate For Remission Induction and Maintenance In Granulomatosis With Polyangiitis In Routine Clinical Practice. Megan L. Krause, Misbah Baqir, Rodrigo Cartin-Ceba, Tobias Peikert, Karina Keogh and Ulrich Specks. Mayo Clinic, Rochester, MN.

Background/Purpose: Methotrexate has been shown to be effective for both induction (non-severe disease) and maintenance of remission in patients with Granulomatosis with Polyangiitis (GPA) in the context of controlled clinical trials. Limited data are available regarding the long term efficacy of methotrexate in the routine care of patients with GPA. We conducted this study to determine the outcomes of routine methotrexate use in a cohort of patients with GPA.

Methods: Single center retrospective study of patients of GPA treated with methotrexate for either induction or maintenance of remission between January 1997-December 2012. Measured outcomes included time to remission, time to relapse and adverse effects of methotrexate. Remission was defined as Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) of 0 with prednisone dose < 10 mg/d. Disease relapse was defined as an increase in the BVAS/WG of 1 point or more after having achieved remission. Kaplan Meier estimation with Log-rank test was used for evaluation of the efficacy outcomes.

Results: Seventy-four patients with GPA were treated with methotrexate. Thirty-nine patients (53%) were c-ANCA/PR3 positive, 22 (30%) were p-ANCA/MPO positive and 13 (17%) were ANCA negative. The mean age (standard deviation, SD) at diagnosis was 48.6 (15.3) and 26 (35%) were men. GPA was biopsy proven in 57 patients (77%). At the time of diagnosis, the mean BVAS/WG was 7.0 (SD, 3.9). Of the total cohort, 18 patients (24%) used methotrexate for remission maintenance. The remaining 56 used methotrexate for induction of remission; eleven of these patients (15%) did not achieve remission with methotrexate. From the remaining 45 patients, 35 patients that used methotrexate for remission induction in newly diagnosed non-severe disease achieved remission at a median of 100 days (IQR, 84–153); 10 patients that used methotrexate for remission induction after a relapse were able to achieve remission after a median of 75 days (IQR, 50–114) ($p=0.04$). Nineteen patients relapsed, 15 (31%) in the induction group and 4 (28%) in the maintenance group ($p=0.99$). The time from achieving remission to relapse was 589 days (IQR 260–1153) in the induction group versus 781 days (IQR, 93–863) in the maintenance group, $p=0.7$. The cohort was followed at our institution for a median of 3.5 years (IQR, 1.6–10.3). At the time of conclusion of follow-up, 37 (50%) remained on methotrexate. Methotrexate had to be discontinued in 5 (6.8%) patients due to side effects. Liver toxicity followed by nausea/vomiting were the most commonly experienced adverse events. One patient developed *Pneumocystis jirovecii* pneumonia while on methotrexate.

Conclusion: In this clinical cohort of GPA patients treated with methotrexate, the time to achieve remission was significantly shorter for patients treated for induction after a relapse as compared to patients treated for initial induction. Time to relapse was not different for patients treated with methotrexate for maintenance therapy as compared to patients treated for induction of remission. Methotrexate is well tolerated long-term, and only a minority of patients had to discontinue methotrexate due to adverse events.

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High Clinical Remission Rate With Relatively High Incidence Of Serious Infection In Newly-Onset ANCA-Associated Vasculitides In Japan - A Report From The Nationwide Prospective Cohort Study. Masayoshi Harigai[1], Ken-ei Sada[2], Takao Fujii[3], Masahiro Yamamura[4], Yoshihiro Arimura[5] and Hirofumi Makino[2]. [1]Tokyo Medical and Dental University, Tokyo, Japan, [2]Okayama University, Okayama, Japan, [3]Graduate School of Medicine, Kyoto University, Kyoto, Japan, [4]Okayama Saiseikai Hospital, Okayama, Japan, [5]Kyorin University School of Medicine, Tokyo, Japan.

Background/Purpose: Clinical characteristics and antineutrophil cytoplasmic antibody (ANCA)-serology of ANCA-associated vasculitis (AAV) patients are substantially different between Western and Asian countries. We investigated effectiveness and safety of remission induction therapy currently performed for patients with AAV in Japan using data from a nationwide prospective inception cohort study (UMIN000001648).

Methods: A total of 156 Japanese patients with newly diagnosed AAV (safety population) were registered by 22 university hospitals and referring hospitals from 2009 until 2010, and 155 had follow-up data (effectiveness population). Patients were classified according to the European Medicines Agency (EMEA) algorithm. Patients were evaluated at Months 3, 6, 12, 18, and 24 and at relapse. Remission, survival and renal survival rates were compared among groups by disease classification, disease severity (localized, early systemic, generalized, severe), and concomitant use of cyclophosphamide (CY).

Results: Of 156 patients, 14 patients were classified as having eosinophilic granulomatosis with polyangiitis (EGPA), 33 patients were granulomatosis with polyangiitis (GPA), 78 patients were microscopic polyangiitis (MPA), 31 patients were unclassified (U). Baseline characteristics of 156 patients were as follows: mean age, 68 years old; female, 61%; P-ANCA positive, 83%; C-ANCA positive, 12%; mean serum creatinine, 1.75 mg/dl; mean Birmingham vasculitis activity score (BVAS), 17. As remission induction therapy, all patients started corticosteroid with mean prednisolone-equivalent dosage of 42 mg/day, and 62 (40%) and 54 (35%) were given methylprednisolone pulse therapy and cyclophosphamide, respectively. Of the effectiveness population, 141 (91%) achieved remission by Month 18. The time to remission differ significantly by disease classification ($P=0.0004$, U<EGPA<MPA<GPA), but not by severity or treatment. Although survival rate did not differ by disease classification, the disease severity affected the survival rate significantly ($P=0.0001$, severe<early systemic <generalized<limited). Patients with concomitant use of CY had significantly better survival rate ($P=0.040$). Thirteen (8%) patients reached renal death. There were significant differences of time to renal death among the disease severity ($P=0.0121$, MPA<U<GPA=EGPA) and among disease classification ($P<0.0001$, severe<generalized<early systemic<limited). In the safety population, serious infections (SIs) were the most frequent serious adverse events. During the first six months, 63 SIs developed in 42 patients (88/100 patient-year). The median length of time to the onset of SIs was 57 days. Multivariate analyses revealed that male (HR 2.1, $p=0.024$), severe type (HR 2.2, $p=0.025$), and initial corticosteroid dosages >0.8mg/kg/day (PSL-equivalent) (HR 2.7, $p=0.002$) were identified as predictors for SIs.

Conclusion: More than 90% of newly onset AAV patients achieved BVAS remission in clinical practice in Japan with relatively high incidence of serious infection. Investigation to establish treatment strategy with better benefit-risk balance is warranted.

Disclosure: M. Harigai, Abbott Japan Co., Ltd., Astellas Pharma Inc., Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Mitsubishi Tanabe Pharma Co., Santen Pharmaceutical Co., Ltd, Takeda Pharmaceutical Co., Ltd., Teijin Pharma, Ltd.Mitsubishi Tanabe, 2, Janssen Pharmaceutical K.K., Chugai Pharmaceutical Co., Teijin Pharma, Ltd., 5; **K. E. Sada**, None; **T. Fujii**, Abbott Japan Co., Ltd., Astellas Pharma Inc., Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Daiichi-Sankyo Pharmaceutical Co. Ltd., Eisai Co., Ltd., Mitsubishi Tanabe Pharma Co, Takeda Pharmaceutical Co., Ltd., and Pfizer Japan Inc., 2; **M. Yamamura**, None; **Y. Arimura**, None; **H. Makino**, None.

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Maintenance Treatment In Childhood Granulomatosis With Polyangiitis. Marinka Twilt[1], Rayfel Schneider[1], Diane Hebert[1], Elizabeth Harvey[1], Ronald M. Laxer[1], Sharon Dell[1], Christoph Licht[1] and Susanne M. Benseler[2]. [1]The Hospital for Sick Children, Toronto, ON, [2]Hospital for Sick Children, Toronto, ON.

Background/Purpose: Granulomatosis with Polyangiitis (GPA) is a rare but life threatening disease. Most children present with pulmonary bleeds and/or renal failure. Most treatment regimens are derived from the adult literature, no studies have been performed in pediatric patients.

Methods: All consecutive children diagnosed with GPA since January 2000 in the Hospital for Sick Children were included. Demographic data, data at diagnosis and follow-up data were collected. Descriptive statistics were used for these preliminary results.

Results: 32 children were diagnosed with GPA since January 2000. Twenty-one girls and 11 boys, with a median age of 13.7 years at diagnosis. ANCA was positive in 30 children (26 c-ANCA with 25 anti-PR-3, 4 p-ANCA with 4 anti MPO) and 2 were ANCA negative (1 anti-PR3 positive). Eight children had limited disease and 24 systemic disease. All systemic patients were treated with pulses cyclophospamide iv (mean 7 pulses) and methylprednisone (mean 5 pulses) iv, and 6 children received plasmapheresis. Maintenance treatment in this group consisted of MTX in 7, AZA in 14, MMF in 3 children. In the limited disease group, treatment consited of oral prednisone in all, MTX in 7 children and AZA in 1. Relapses were seen in 14 children. One child did not receive any treatment at time of relapse. Two children with limited disease relapsed, both while still on MTX. 11 children with systemic disease were still on treatment, MTX in 4, AZA in 5, MMF in 2.

Conclusion: Relapses are seen often in childhood GPA when still receiving maintenance treatment. Relapses are higher in children with systemic GPA (50%) compared to limited GPA (25%).

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Fatigue, Pain, and Functional Disability Among Patients With Vasculitis. Antoine G. Sreih[1], Narender Annapureddy[2] and Osama Elsallabi[3]. [1]The University of Pennsylvania, Philadelphia, PA, [2]Rush University Medical Center, Chicago, IL, [3]Creighton University, Omaha, NE.

Background/Purpose: Vasculitis is a heterogeneous group of diseases often resulting in severe morbidity affecting patients' quality of life. These morbidities are generally attributed to disease activity, end-organ damage, and the use of immunosuppressive therapy. Current tools for assessing vasculitis do not include patient-reported outcomes such as fatigue, pain, and functional disability. We measured various clinical outcomes using the Multi-Dimensional Health Assessment Questionnaire (MDHAQ) to determine if the outcomes correlate with disease activity, disease damage, glucocorticoid dose, and laboratory parameters.

Methods: Patients with large vessel vasculitis (LLV) and ANCA-associated vasculitides (AAV) treated at the Rush Vasculitis Clinic from 2010 to 2013 were administered the MDHAQ at every visit. The MDHAQ measures functional disability (score: 0–10), pain and fatigue (visual analogue scales: 0–10), and depression, anxiety, and sleep disturbance (each measure scored 0–3). For all MDHAQ scales higher scores mean worse symptom. The Birmingham Vasculitis Activity Score (BVAS) and the Vasculitis Damage Index (VDI) were used to calculate disease activity and damage, respectively. All evaluations reported here represent the baseline values at first visit.

Results: 51 patients participated in the study: 29 with AAV and 22 with LVV, 40 females, 31 Caucasians, 13 Hispanics, and 7 African-Americans. Mean age was 53.2 years. The mean BVAS was 5.1 ± 1.6 and mean VDI was 2.1 ± 0.3. 91% of patients were on prednisone, mean dose=23.2 ± 2.9 mg/day. Fatigue was the most frequently reported symptom (82%, mean=3.8 ± 0.4) followed by pain (77%, mean=3.2 ± 0.4), sleep disturbance (66%, mean=0.8 ± 0.1), anxiety (42%, mean= 0.52 ± 0.1) and depression (37%, mean= 0.4 ± 0.1). Functional disability was reported by 80% of patients (mean=1.7 ± 0.23). Fatigue, pain, and functional disability did not correlate with BVAS, VDI, dose of glucocorticoids, erythrocyte sedimentation rate (ESR) or hemoglobin level (Table 1).

Table 1. Correlations between fatigue, pain and functional disability with the BVAS, VDI, glucocorticoid dose, ESR and Hemoglobin.

	BVAS		VDI		GC dose		ESR		Hb	
	r	P	r	p	r	p	r	p	r	p
Fatigue	0.08	0.63	0.11	0.46	−0.03	0.82	−0.14	0.44	0.08	0.63
Pain	0.99	0.55	−0.4	0.06	0.04	0.82	0.4	0.06	0.04	0.85
Functional disability	0.04	0.75	−0.05	0.77	0.07	0.61	−0.19	0.25	−0.12	0.5

GC (Glucocorticoid), ESR (Erythrocyte Sedimentation Rate), Hb (Hemoglobin)

Conclusion: Fatigue, pain, and functional disability are frequent self-reported symptoms in patients with AAV and LVV. These symptoms do not correlate with disease activity, damage, glucocorticoid dose, ESR, or hemoglobin level. While disease control is of prime importance, it is also important to address these symptoms that may not reflect disease activity or disease damage but can substantially impact patients' quality of life.

Disclosure: A. G. Sreih, None; **N. Annapureddy**, None; **O. Elsallabi**, None.

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Cardiovascular Outcomes Are Worse In Microscopic Polyangiitis Compared To Granulomatosis With Polyangiitis: Data From An Inception Cohort Of Patients With Anti-Neutrophil Cytoplasm Antibody Associated Systemic Vasculitis. Anna Mistry[1], Joanna Robson[2], Susan L Hogan[3], Caroline Poulton[3], Yichun Hu[3], Ronald Falk[4] and Raashid A. Luqmani[5]. [1]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, UK, Oxford, United Kingdom, [2]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford, United Kingdom, [3]UNC Kidney Centre, University of North Carolina, Chapel Hill, North Carolina, Chapel Hill, NC, [4]UNC Kidney Center, Chapel Hill, NC, [5]Nuffield Orthopaedic Centre, Oxford, United Kingdom.

Background/Purpose: A greater than three-fold increase in cardiovascular mortality as been reported within the first five years of diagnosis of anti-neutrophil cytoplasmic antibody (ANCA) associated systemic vasculitis (AASV) compared to the general population. A 5 year predictive cardiovascular risk model was developed using data derived from a trial cohort, to stratify patients into a high, moderate or low risk of a cardiovascular (CV) event.

We describe the CV events occurring in an inception cohort of patients with a new diagnosis of AASV within the first 5 years of diagnosis and test the validity of the existing predictive risk model in parallel.

Methods: A retrospective case note review was performed on 387 patients recruited to a vasculitis registry with a diagnosis of granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA).

CV events following the diagnosis of GPA or MPA in this cohort were analysed over time and results compared to the predicted rate per 1000 general population matched for age and gender. CV events were then stratified according to proteinase-3 (PR3) or myeloperoxidase (MPO) ANCA positivity. All results were then compared to the data from the published trials cohort.

Patients without pre-existing CV events were used to validate the existing predictive cardiovascular risk model.

Results: 39/387 (10.1%) patients experienced at least one CV event during follow up (0.02 – 27.8 years, median 3.6 years).

The CV event free-survival time was significantly reduced in the MPA patients vs GPA patients (p=0.0077) over 120 months (figure 1). However, no statistical difference was found between MPO or PR3 ANCA positive groups (p= 0.2767).

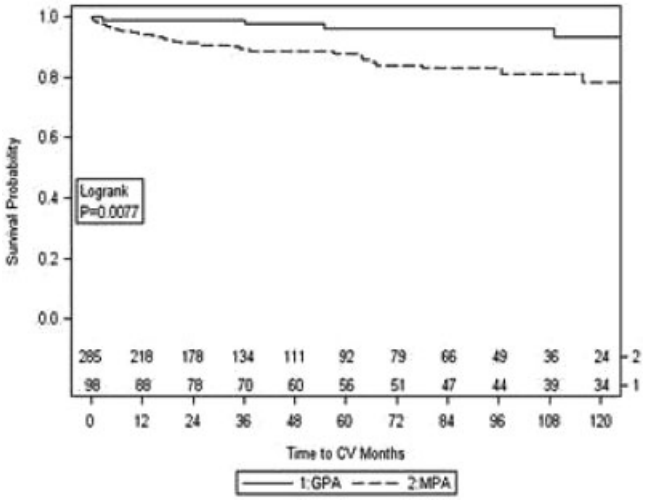

Figure 1. Survival probability against time to cardiovascular events (months): GPA vs MPA

A trend towards more CV events was observed within the AASV group compared to the predicted rates per 1000 general population although this did not reach statistical significance.

Regarding the predictive risk model, the inception cohort data was similar to the trial cohort data in predicting CV events based on age, hypertension and the absence of PR3 status when comparing the percentage of patients per risk group (p=0.5309) and CV events by risk group (p=0.9278).

Conclusion: We demonstrated an overall trend towards more CV events in vasculitis patients compared to the general population, although this does not reach statistical significance.

MPA is associated with significantly more CV events than GPA with events occurring earlier in the disease course. However, there is no difference in CV events between MPO or PR3 positive patients suggesting that clinical phenotype may be more relevant in identifying patients at risk of CV events than serological status.

We have provided further validation for the published 5 year cardiovascular model in this inception cohort, proving its transferability to clinical practice to allow stratification of individual CV risk.

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Validation Of The New Histopathological Classification Of ANCA Glomerulonephritis and Its Association With Renal Outcomes In a Paediatric Population. Marinka Twilt[1], Damien Noone[1], Wesley Hayes[1], Paul Thorner[1], Susanne M. Benseler[2], Ronald M. Laxer[1], Rulan Parekh[1] and Diane Hebert[1]. [1]The Hospital for Sick Children, Toronto, ON, [2]Hospital for Sick Children, Toronto, ON.

Background/Purpose: Anti-Neutrophil Cytoplasmic Antibody (ANCA) associated glomerulonephritides (ANCA GN) include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and Churg-Strauss. A novel histopathologic classification for GPA and MPA has been proposed and validated in adult populations and found to be predictive of long-term renal outcome. We aimed to validate this classification system in a paediatric population and identify clinical predictors of renal outcome.

Methods: We performed a retrospective review of all patients with ANCA GN, diagnosed and followed up until transfer to an adult centre at the Hospital for Sick Children between 1987 and 2012. Renal biopsies were reviewed by a pathologist blinded to patient outcome and classified using the new histopathological classification system of focal, crescentic, mixed, sclerotic and globally sclerotic groups. We determined time to CKD by estimated glomerular filtration rate (eGFR) with repeated creatinine measures using the Schwartz equation, or end stage kidney disease as defined as dialysis dependant. Survival and linear regression analyses were conducted.

Results: The study population consisted of 42 children (69% male) with ANCA GN (21 GPA, 21 MPA) with a median age of 11.96 (+3.52) years and eGFR 36.6 mls/min/1.73m^2 (IQR 15–87.4). Of the 40 patients with a renal biopsy at time of initial diagnosis, 12 (30%) had focal lesions, 20 (50%) crescentic, 3 (7.5%) mixed, 5 (12.5%) sclerotic and no globally sclerotic lesions. 13 (31 %) patients required dialysis at baseline. Survival analysis of time to the composite renal endpoint of at least 3 months of eGFR $<$ 60 ml/min/1.73 m^2 or ESKD differed among all 3 biopsy groups [p (logrank) = 0.0001; figure]. Probability (95% CI) of having an eGFR $<$ 60 mls/min/1.73m^2 at 2 years was 58.5% (35.1–76.0%) in the crescentic/mixed group. The sclerotic group all progressed to ESKD. Linear regression analysis demonstrated an association with slope of eGFR with baseline eGFR (p= 0.01), baseline proteinuria (p=0.037) and need for dialysis (p$<$0.001) after adjustment.

Conclusion: We demonstrate the clinical utility of the new new histopathologic classification system and its ability to clearly discriminate outcomes among paediatric ANCA GN patients. Additional factors predicting outcome include baseline eGFR and dialysis. The new classification can be adopted for both clinical use and research studies.

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Outcome Of Kidney Transplantation In Paediatric Patients With ANCA Associated Glomerulonephritis: A Single-Center Experience. Marinka Twilt[1], Damien Noone[1], Wesley Hayes[1], Paul Thorner[1], Susanne M. Benseler[2], Ronald M. Laxer[1], Rulan Parekh[1] and Diane Hebert[1]. [1]The Hospital for Sick Children, Toronto, ON, [2]Hospital for Sick Children, Toronto, ON.

Background/Purpose: Kidney transplant outcomes for paediatric patients with end stage kidney disease (ESKD) secondary to ANCA GN, particularly granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) is limited. Adult data suggests similar allograft survival post transplant to other causes of ESKD. We aimed to describe our experience of kidney transplantation in paediatric ANCA GN patients.

Methods: We performed a retrospective review of patients with ANCA GN who developed ESKD and were transplanted at the Hospital for Sick Children (HSC) between 2000 and 2012. All patients were diagnosed at HSC and followed until their transfer to an adult center.

Results: Since 2000 there have been 6 paediatric patients transplanted with ANCA GN (5 MPA). 5 patients were ANCA positive at diagnosis: 1 c-ANCA, PR3 positive and 4 p-ANCA MPO positive. Age at ANCA GN diagnosis was 10.4 ± 4.3 (Mean±SD) years (range 4.1 to 15.4). eGFR at diagnosis was 14.1 ± 6.2 ml/min/1.73m^2. Renal biopsy category was crescentic in 4 and sclerotic in 2 by the new histopathological classification. Initial treatments included: steroids 6 [100%], cyclophosphamide 4 [66.69%] and PLEX 1 [16.67%]. 2 patients had disease relapse within the first 6 months. 4 patients required dialysis at diagnosis (HD) and remained dialysis dependent. All 6 were dialysis dependent by 6 months post diagnosis. Time from ANCA GN diagnosis to kidney transplant (Mean±SD) was 31±12 months (range 17–48 months). All patients received induction therapy and maintenance immunosuppression with prednisone, mycophenolate mofetil, and tacrolimus. Median duration of follow up post transplantation was 3.5 years (range 1.25–6.9). eGFR at last follow up was 71.9 ± 34.7 ml/min/1.73m^2 (range 5.7–100.5). 1 patient lost her transplant to biopsy-proven, severe acute cellular rejection due to complete non-adherence to medications after 21 months of stable transplant function. No patient had recurrence of vasculitis.

Conclusion: Short-term patient and allograft survival in paediatric patients with ESKD secondary to ANCA GN is excellent despite aggressive disease, with no recurrence of vasculitis post transplant.

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Survival Of Patients With ANCA-Associated Vasculitides In Chronic Dialysis In France From 2002 To 2011: Data From The National Rein Registry.
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Background/Purpose: Despite dramatic outcome improvement in ANCA-associated vasculitides (AAV), renal involvement is still leading toend-stage renal disease (ESRD) in 20–30% of patients. This study evaluated the survival of AAV patients in chronic dialysis in France.

Methods: All patients starting chronic renal replacement therapy (RRT) secondary to AAV registered in the Renal Epidemiology and Information Network (REIN) registry, between January 1st 2002 and December 31st2011, were included in the study. Survival analysis, censored for renal transplantation, renal function recovery and lost to follow-up, was performed with Kaplan-Meier in AAV patients. AAV patients were compared to non-AAV patients in chronic dialysis matched for age, gender and main comorbidities.

Results: A total of 425 patients starting RRT were registered in the REIN registry (0.7% of incident patients in chronic RRT in France), comprising 166 (39%) patients with microscopic polyangiitis (MPA) and 259 (61%) patients with granulomatosis with polyangiitis (GPA). Renal disease was biopsy-proven for 307 (72%) of them. Within a median follow-up of 23 months, 58 (14%) patients received a renal allograft, 19 (4%) had a renal function recovery allowing dialysis withdrawal and 348 remained in dialysis. Median survival in dialysis was 5.35 years (95% CI, 4.4–6.3) and survival rates at 1, 3 and 5 years were respectively 83%, 65% and 49% in AAV patients, without difference between GPA and MPA. A total of 143 (41%) patients died, after a median of 16 months in dialysis. Causes of death were: cardiovascular (29%), infectious (20%), malnutrition (13%), malignancies (4%), AAV relapse (2%), other miscellaneous (14%) and unknown (18%). After Cox2 multivariate logistic regression, only 3 risk factors were independently associated with mortality in AAV patients: age (HR=1.05 per year, p<0.001), peripheral artery disease (HR=2.62, p=0.003) and the absence of autonomy (HR=2.43 p<0.001). Survival of AAV patients did not differ from that of the 792 non-AAV matched patients in chronic dialysis, but infectious mortality was higher in AAV patients (20% vs 8% p<0,001). The limitation of this study is the absence of registration of immunosuppressive regimen and non fatal AAV relapses in the REIN registry.

Conclusion: Survival of AAV patients in chronic dialysis, although poor, is comparable to the survival of non-AAV matched patients in dialysis, with a similar burden of cardio-vascular mortality, and a higher infectious mortality. This calls for cardio-vascular risk prevention and monitoring of vaccination status in this population.

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Clinical Value Of Commonly-Measured Laboratory Tests In Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss).
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Background/Purpose: Serial measurement of absolute eosinophil count (Eos), serum immunoglobulin E (IgE), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) is common practice in the care of patients with EGPA, yet the value of these tests as longitudinal biomarkers is largely anecdotal.

Methods: Subjects were enrolled in an observational EGPA cohort. Eos, IgE, ESR, and CRP were measured quarterly. BVAS/WG defined disease activity. Correlation among laboratory tests was derived using Spearman's rank order test. The association of tests with disease activity was assessed via GEE logistic regression, adjusting for repeated measures and medication use (prednisone, other immunosuppressants). Survival analysis was used to determine if laboratory tests were predictive of 3-month future flare risk. Analyses were stratified by ANCA status.

Results: Among 141 subjects, there were clinico-demographic differences according to ANCA status (**Table**). Out of 892 observations, the majority (74%) occurred while subjects were taking prednisone or other immunosuppressants. Correlations among Eos, IgE, ESR, and CRP were mostly low or non-significant (range r = −0.08 to 0.43) and differed by ANCA status and medication use. There were few significant, but clinically weak, associations with disease activity (Eos: OR=1.01 per 100 units, 95% CI 1.01–1.02 in both ANCA negative and positive subjects; CRP: OR=1.62 per 10 mg/L increase, 95%CI 1.57–1.67 in ANCA-negative subjects). When BVAS/WG ≥1 defined active disease, only Eos (HR=1.02 per 100 units, 95%CI 1.01–1.03) was predictive of flare. When BVAS/WG ≥3 defined active disease, only ESR was predictive of flare (HR=1.52 per 10 mm/hr increase, 95% CI 1.27–1.71).

Table. Clinical and Demographic Differences in EGPA cohort by ANCA status

Variable	Total	ANCA Negative	ANCA Positive
No. subjects	141	76 (54%)	65 (46%)
No. observations	892	490	402
Sex, female*	82 (58%)	53 (70%)	29 (45%)
Age at first observation, years (median, range)	55 (21–82)	51 (21–82)	57 (23–82)
Race, white	131 (93%)	72 (95%)	59 (91%)
Disease duration at first observation, years (median, range)	1.5 (0–29.8)	1.6 (0–21.7)	1.3 (0–29.8)
On prednisone* # observations	579 (65%)	348 (71%)	231 (57%)
On other medications,# # observations	423 (47%)	245 (50%)	178 (44%)
On either prednisone or other medications, # observations	659 (74%)	376 (77%)	283 (70%)
BVAS_WG	0: 766 (86%) ≥1: 99 (11%) ≥3: 33 (4%)	0: 414 (85%) ≥1: 56 (11%) ≥3: 17 (3%)	0: 352 (88%) ≥1: 43 (11%) ≥3: 16 (4%)
Eosinophil count, 10^3/mm (median, range)	262.0 (0–18,096)	276.0 (0–7,083)	229.4 (0–18,096)
Immunoglobulin E, mg/dL* (median, range)	60.0 (0–21,925)	38.4 (0–21,925)	85.0 (2–7,298)
ESR, mm/hr (median, range)	8.0 (1–94)	8.0 (1–72)	8.0 (1–94)
CRP, mg/L (median, range)	2.2 (0–203)	2.0 (0–98)	2.6 (0–203)

* Indicates statistically significant differences (p<0.01) between ANCA positive and ANCA negative subjects with EGPA. Categorical variables were assessed by Fisher's exact test and continuous variables were assessed by Wilcoxon rank sum test.
# Other medications= azathioprine, cyclophosphamide, methotrexate, or mycophenolate mofetil.

Conclusion: Eos, IgE, ESR, and CRP have limited value as longitudinal biomarkers of disease activity or predictors of flare in EGPA. Only Eos was consistently associated with disease activity but the association was quite weak. The relationship of these labs to each other and their value as biomarkers differed according to ANCA status. These findings question the routine use of these tests to guide therapy in EGPA and suggest that novel biomarkers of disease activity for EGPA are needed.

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Impact Of Cardiac Magnetic Resonance Imaging On Eosinophilic Granulomatosis With Polyangiitis Outcomes: A Long-Term Retrospective Study On 42 Patients. Bertrand Dunogué, Pascal Cohen, Benjamin Terrier, Julien Marmursztejn, Denis Duboc, Olivier Vignaux and Loic Guillevin. Cochin University Hospital, Paris, France.

Background/Purpose: Eosinophilic granulomatosis with polyangiitis (EGPA) cardiomyopathy carries a poor prognosis, and is the main cause of 1st-year and long-term mortality. Morbidity due to chronic cardiac insufficiency is also a major concern. The need for complementary investigations, which may detect cardiac involvement earlier, is crucial to effectively treat these patients early, before the advent of more severe clinical manifestations and cardiac damage. Cardiac magnetic resonance imaging (CMRI) seems to be a sensitive tool to detect EGPA cardiac lesions (defined as late myocardial gadolinium enhancement) in symptomatic but also asymptomatic patients, thereby raising the questions of CMRI specificity and the type(s) of anomalies (active inflammatory and/or fixed fibrotic) detected. This study was undertaken to determine retrospectively the diagnostic and prognostic impacts of such lesions in a cohort of EGPA patients with or without signs of cardiomyopathy who had undergone systematic CMRI screening.

Methods: This retrospective analysis concerned a monocentric cohort of 42 EGPA patients: 25/42 male (59.5%); mean age at diagnosis: 46.5 years; 11/42 (26.2%) ANCA-positive, with a median EGPA duration of 0.42 years before the 1st CMRI screening.

Results: Among the 42 patients, 17 (40.5%), 15 (88.2%) of whom were ANCA-negative, were diagnosed with cardiomyopathy, independently of CMRI findings. CMRI revealed late myocardial gadolinium enhancement in 14/17 (82.4%) patients with cardiomyopathy vs. 11/25 (44%) without cardiomyopathy ($p=0.024$). Using the sole criterion of late myocardial gadolinium enhancement, CMRI sensitivity and specificity for diagnosing cardiomyopathy were, respectively, 82.4% (95% CI: 0.59–0.93) and 56% (95% CI: 0.37–0.73). Among patients with cardiomyopathy who underwent additional CMRI during follow-up (median follow-up: 4.6 years), 6/14 patients' CMRI-detected cardiac lesions had regressed under maintenance therapy, while those of 8/14 patients worsened or stabilized, despite treatment. No differences were found between non-cardiomyopathic patients with or without CMRI anomalies concerning subsequent EGPA cardiac manifestations and outcomes.

Conclusion: CMRI is a sensitive but non-specific method for detecting potential cardiomyopathic EGPA lesions. The diagnostic significance of late myocardial gadolinium enhancement in EGPA patients remains uncertain and should not be the only criterion for cardiomyopathy diagnosis. Furthermore, for patients with no other signs of cardiomyopathy, the CMRI-detected anomalies do not seem to adversely affect prognosis or outcome. However, longer follow-up is needed to assess this apparent absence of impact of CMRI lesions on cardiac outcome in asymptomatic patients.

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Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss Syndrome)—Re-Analysis Of The French Vasculitis Study Group Cohort Using Different Disease Definitions and Cluster Analysis. Christian Pagnoux[1], Pascal N. Tyrrell[2], Chiara Baldini[3], Simon Carette[4], Jean-Francois Cordier[5], Loic Guillevin[6] and French Vasculitis Study Group FVSG[7]. [1]Division of Rheumatology, Mount Sinai Hospital, Toronto, ON, [2]University of Toronto, Toronto, ON, [3]Rheumatology Unit, Pisa, Italy, [4]UHN/MSH, Toronto, ON, [5]Division of Pneumology, Hôpital Louis-Pradel, Hospices Civils de Lyon, Lyon 1, Lyon, France, [6]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, Paris, France, [7]Service de médecine interne, Centre de Références des Vascularites, Université Paris Descartes, APHP, Hôpital Cochin, 75005 Paris, France., Paris, France.

Background/Purpose: Because only 25–40% of the patients are ANCA+ and biopsy is not always taken or helpful, EGPA diagnosis can be challenging. Previous cohort analyses identified several covariates associated with poor outcomes and suggested differences between ANCA+ and ANCA– patients. We reanalyzed the FVSG cohort using different definitions of EGPA and cluster analysis to try to identify other disease subsets.

Methods: FVSG-cohort patients were grouped using the following 4 EGPA definitions: 1) all 383 patients whose EGPA diagnoses met ACR criteria or 1994 Chapel Hill nomenclature according to referral physicians; 2) only the 59 patients with biopsy-proven vasculitides; 3) the 138 with biopsy-proven vasculitis and/or ANCA+; 4) the 267 patients with biopsy-proven vasculitis and/or ANCA+ and/or surrogate manifestations (purpura, gangrene, alveolar hemorrhage, mononeuritis multiplex (MNM), renal disease (glomerulonephritis and/or hematuria)). Exploratory hierarchical cluster analyses were performed on the entire cohort and each subgroup to determine the number of clusters. The parameters, all binary, included in these cluster analysis were: skin manifestations, sinusitis, cardiomyopathy (CM), renal disease, MNM. In subsequent steps, we also included ANCA test results (missing for 35 patients excluded from these cluster analyses). Then K-means nonhierarchical cluster analysis examined the characteristics of the clusters.

Results: Table 1 shows characteristics of the different patient subgroups.

	Definition 2	Definition 3	Definition 4	All others/ Undefined
n	59/383	138/383	267/383	116/383
Sex, (M/F, n)	30/29	74/64	141/126	58/58
Age at diagnosis (yrs)	51	51	51	49
Asthma	93%	94%	96%	80%
ENT manifestations	53%	54%	54%	34%
Lung infiltrate	37%	39%	42%	30%
Alveolar hemorrhage	5%	6%	6%	–
Skin manifestations	39%	41%	49%	16%
Purpura	31%	28%	32%	–
Mononeuritis multiplex	51%	53%	66%	–
CNS	5%	6%	6%	3%
Cardiomyopathy	9%	9%	19%	11%
Severe GI signs	7%	4%	6%	6%
Eye	7%	9%	8%	3%
Renal disease	25%	26%	28%	6%
BVAS at diagnosis	19.4 ± 6.8	21.10 ± 7.6	20.6 ± 7.9	12.0 ± 6.8
ANCA+	55%	82%	45%	–
(ANCA status missing, n)	(6)	(6)	(26)	(9)
Vasculitis relapse	36%	34%	30%	14%
Deaths	12%	7%	14%	6%

Cluster analysis of the entire cohort, not including ANCA, yielded 3 clusters:

- n=128, 89% with definite EGPA (definition 4), 29% ANCA+, 24% with renal disease, 66% with MNM, 27% with CM;
- n=160, 78% met definition 4, 38% ANCA+, 57% with MNM, 18% with CM, 16% with renal disease;
- n=95, only 29% met definition 4, 22% ANCA+, none with skin, renal, CM or MNM, meaning that 71% had undefined disease (others).

Without including ANCA and whichever the EGPA definition used, clusters differed mainly by their CM, MNM or skin-sign distributions. Including ANCA strongly influenced clustering results. Subgroup cluster analysis on the 241 patients with known ANCA status meeting definition 4, yielded 3 clusters:

- n=61, all ANCA+, with 41% ENT signs, 48% MNM, 25% renal disease, 7% CM, but no skin lesions, 31% vasculitis-relapse rate, 5% mortality;
- n=54, all ANCA–, with 89% MNM, 48% ENT signs, 22% CM, 22% renal disease, but no skin disease, 21% relapse rate, 13% mortality;
- n=126 with 37% ANCA+, 94% skin manifestations, 65% ENT signs, 60% MNM, 22% CM, 19% renal disease, 37% relapse rate, 16% mortality.

Conclusion: The results of this study suggest the need to establish rigorous EGPA definitions. Cluster analysis supported and strengthened findings from previous analyses, which showed the main subsets were identified by ANCA status.

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Eosinophilic Granulomatosis With Polyangiitis (Churg–Strauss Syndrome): Comparison Of The Independent French Vasculitis Study Group and Italian–Pisa Patient Cohorts and Cross-Validation Of Cluster Analysis.

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Background/Purpose: Previous analyses of the FVSG- and Pisa-cohort EGPA patients identified several covariates associated with poor outcomes and suggested differences between ANCA+ and ANCA– EGPA-patient subsets. Reanalysis of the FVSG cohort using more stringent (than the 1990 ACR criteria) EGPA definitions and clustering analysis identified 3 main clusters reinforcing the impact of ANCA status. We compared the FVSG and Pisa cohorts and aimed to cross-validate the FVSG-cohort cluster analysis results with Pisa-cohort data.

Methods: We first compared the main characteristics of patients from both cohorts, selecting only those patients with definite EGPA (biopsy-proven vasculitis, ANCA+ and/or surrogate clinical manifestations of vasculitis, i.e. mononeuritis multiplex, purpura, alveolar hemorrhage and/or renal disease [glomerulonephritis and/or hematuria]) and known ANCA status. Hierarchical cluster analysis of FVSG-cohort patients included 6 clustering parameters (cutaneous manifestations, sinusitis, cardiomyopathy, renal disease, mononeuritis multiplex, ANCA) and yielded 3 main clusters, further characterized using K-means nonhierarchical clustering methodology. The same cluster analysis was applied to the Pisa patients.

Results: Table 1 summarizes the main characteristics of both EGPA-patient cohorts with biopsy-proven vasculitis, ANCA+ and/or surrogate clinical vasculitis manifestations.

	Pisa patients N = 51	FVSG patients N = 241	P
Sex, (M/F, n)	24/27	132/109	0.32
Age at diagnosis (yr)	52	51	0.55
Asthma	100%	96%	0.14
ENT manifestations	86%	55%	< 0.01
Lung infiltrate	45%	44%	0.84
Alveolar hemorrhage	2%	6%	0.22
Skin manifestations	61%	49%	0.13
Purpura	49%	33%	0.02
Mononeuritis multiplex	61%	64%	0.72
CNS	4%	6%	0.52
Cardiomyopathy	12%	18%	0.26
Severe GI signs	8%	6%	0.58
Eye	12%	8%	0.37
Renal disease (n with GN)	6% (2)	21% (12)	0.01
BVAS at diagnosis	17.7 ± 7.7	20.8 ± 8.1	0.02
ANCA+	57%	45%	0.12
Vasculitis relapse	27%	32%	0.57
Deaths	6%	12%	0.18

Cluster analysis identified 3 clusters in the Pisa cohort:

- n=21, all ANCA+, with 86% ENT manifestations, 81% peripheral nerve involvement, 48% skin disease, 14%cardiomyopathy, 10% renal disease, 38% vasculitis-relapse rate, 12% died;
- n=14, all ANCA–, with 100% with peripheral nerve involvement, 72% ENT manifestations, 36% skin involvement, 7% cardiomyopathy, 7% renal disease, 29% relapsed, none died;
- n=16, 50% ANCA+, and 100% with ENT, 100% skin signs, 13% cardiomyopathy, but no renal disease and no peripheral nerve involvement, 13% relapsed, 7% died.

As for the FVSG cohort, the main feature distinguishing between clusters was ANCA status. Although, the intermediate ANCA+ (low but not null %) clusters in both cohorts had the lowest frequencies of renal disease, highest of skin disease and intermediate cardiomyopathy, distributions of other EGPA manifestations among clusters differed between the 2 cohorts.

Conclusion: Cluster analysis of 2 independent EGPA-patient cohorts demonstrated that ANCA status is the main parameter distinguishing disease subsets, as previously found with other statistical methods. These exploratory analyses exemplify the advantages and challenges of cluster-analysis methodology. Interpretation of results must be cautious, taking into account the methods used and sample size.

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Cluster Analysis To Explore Clinical Subclassification Of Eosinophilic Granulomatosis With Polyangiitis (Churg–Strauss).

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Background/Purpose: Results from descriptive studies of eosinophilic granulomatosis with polyangiitis (EGPA) suggest distinct clinical subclasses that may be determined by anti-neutrophil cytoplasmic antibody (ANCA) status. We used hierarchical cluster analysis to explore whether EGPA could be subclassified.

Methods: The study was based on patients with clinically diagnosed EGPA followed in 6 tertiary referral centers for vasculitis in Germany, Italy and Poland. Clinical data and ANCA results were collected retrospectively on a standardized case report form. A hierarchical cluster analysis (Ward's method) was performed using the following 12 input variables assessed at diagnosis or at relapse including the main symptoms and organ involvements (general symptoms, arthromuscular, mucocutaneous, ophthalmological, ENT, cardiovascular, gastrointestinal, renal and central nervous system involvement, peripheral neuropathy, non-fixed lung infiltrates) and ANCA positivity. The resulting clusters were described by their most prominent summary characteristics. The distribution of clinical variables was analyzed by ANCA status with chi-square test.

Results: The analyzed dataset included 362 EGPA cases diagnosed between 1984 and 2013. Median age at diagnosis was 50 years and 48% were males; ANCA were detected in 35%. The cluster analysis produced 3 clusters of respectively 158 (cluster 1), 74 (cluster 2) and 130 subjects (cluster 3). They were characterized as follows: cluster 1 by high proportion of renal involvement (43%) and positive ANCA serology (73%); cluster 2 by virtually absent renal involvement (4%) and no ANCA (0%); and cluster 3 by an intermediate phenotype with renal involvement (15%), positive ANCA (9%) and more frequent cardiovascular (57% vs. 33% and 38% for clusters 1 and 2, respectively) and gastrointestinal involvement (44% vs. 22% and 15%). Stratification of the 11 clinical input variables by ANCA status found that ANCA positivity was associated with more frequent arthromuscular involvement ($P = 0.045$), renal involvement ($P < 0.0001$), peripheral neuropathy ($P = 0.011$), constitutional symptoms ($P = 0.006$) while absence of ANCA was associated with more frequent cardiovascular involvement ($P = 0.005$).

Conclusion: Cluster analysis of EGPA, although reinforcing the link between ANCA status and renal, peripheral nervous system and cardiovascular involvement, does not suggest that this disease is composed of clearly separated and mutually exclusive subclasses.

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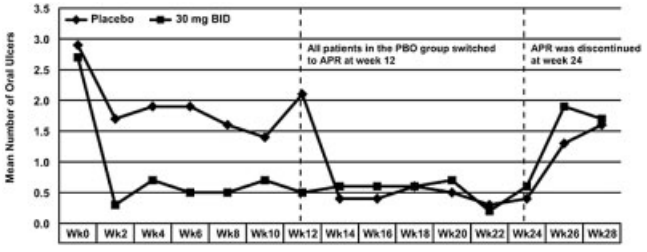
Apremilast For The Treatment Of Behçet's Syndrome: A Phase II Randomized, Placebo-Controlled, Double-Blind Study. Gulen Hatemi[1], Melike Melikoglu[1], Recep Tunc[2], Cengiz Korkmaz[3], Banu Turgut Ozturk[2], Cem Mat[4], Peter A. Merkel[5], Kenneth Calamia[6], Ziqi Liu[7], Lilia Pineda[7], Randall M. Stevens[7], Hasan Yazici[1] and Yusuf Yazici[8]. [1]Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey, [2]Selçuk University, Konya, Turkey, [3]Eskisehir Osmangazi University, Eskisehir, Turkey, [4]Istanbul University, Cerrahpasa Medical Faculty, Dermatology, Istanbul, Turkey, [5]University of Pennsylvania, Philadelphia, PA, [6]Mayo Clinic, Jacksonville, FL, [7]Celgene Corporation, Warren, NJ, [8]NYU Hospital for Joint Diseases and New York University School of Medicine, New York, NY.

Background/Purpose: Mucocutaneous manifestations of Behçet's syndrome (BS) can be resistant to conventional treatment and at times disabling. Apremilast (APR), an oral phosphodiesterase 4 inhibitor, modulates inflammatory pathways. This study investigated the efficacy of APR in BS patients with active oral ulcers (OU).

Methods: This was a phase II, multicenter, randomized, placebo (PBO)-controlled study with an open-label extension. Patients with BS without major organ involvement but ≥2 OU were randomized to APR 30 mg BID or PBO for 12 weeks followed by a 12-week active-treatment period for all patients and a 28-day post-treatment observational follow-up. The primary endpoint was the number of OU at week 12. Secondary endpoints were the number of genital ulcers (GU) at week 12, efficacy over time (AUC for OU and GU, first 12 weeks), disease activity (BSAS, BDCAF), patient-reported outcomes (BDQOL, SF-36), and adverse events (AEs).

Results: 111 patients (mean age 34.5 ± 10.1 years, 69% women) were randomized (55 APR, 56 PBO) and 95 completed the treatment phase (50 APR, 45 PBO). Mean (±SD) number of OU at week 12 was 0.5 ± 1.03 with APR and 2.1 ± 2.58 with PBO ($P<0.0001$). The figure shows the mean number of OU over time. Notably, the beneficial effect of APR on OU started within 2 weeks. There was a sustained effect while on APR, but the effect disappeared shortly after APR was stopped at week 24. Improvement in OU pain (VAS) was significantly higher with APR (−44.7 ± 24.30 vs −16.0 ± 32.54; $P<0.0001$). At week 12, significantly more patients receiving APR had a complete response (OU-free) (71% [39/55], APR; 29% [16/56], PBO; $P<0.0001$). Among the limited number of patients with GU at baseline (n=16), 10/10 receiving APR had a complete response at week 12 vs 3/6 receiving PBO (p=0.036). The mean change from baseline in the BDCAF, BSAS and BDQOL scores were significantly higher in the APR group (APR vs PBO −1.5 ± 1.84 vs −0.1 ± 1.51; $P=0.0007$, −21.2 ± 17.9 vs −5.9 ± 18.2; $p<0.0001$ and −4.5 ± 7.61 vs −1.6 ± 5.3 $P=0.0397$ respectively). There were 2 serious AEs with APR (1 diplegia, 1 anal fissure and hemorrhoids) and 3 with PBO (2 disease flares, 1 fever episode). The diplegia in 1 patient was transient and was not thought to be related to APR.

Conclusion: APR was effective in the treatment of OU, the cardinal manifestation of BS, with an acceptable safety profile. There were also indications of efficacy in several secondary endpoints, including GU, a highly specific lesion for BS. Further trials are warranted to test the efficacy of APR for other manifestations of BS.



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Inhibition Of TGF-Beta Signaling In Articular Chondrocytes Leads To OA-Like Pathological Defects and Pain-Related Behavior Change In Mice. Jia Li[1], Jie Shen[2], Shan Li[1], John Dickerson[1], Jeffrey Kroin[1], Hee-Jeong Im[1] and Di Chen[1]. [1]Rush University, Chicago, IL, [2]University of Rochester, Rochester, NY.

Background/Purpose: TGF-β signaling plays an important role in chondrocyte differentiation and osteoarthritis (OA) pathogenesis. However TGF-β downstream target genes and signaling mechanism in OA development remains poorly understood. In the present studies, we investigated TGF-β signaling in OA development.

Methods: *Tgfbr2* conditional knockout ($Tgfbr2^{Col2ER}$) mice were generated by breeding $Tgfbr2^{flox/flox}$ mice with *Col2-CreER* transgenic mice. Deletion of the *Tgfbr2* gene was achieved by administration of tamoxifen into 2-week-old $Tgfbr2^{Col2ER}$ mice. Changes in histology, gene expression and pain-related behavior were analyzed. *Tgfbr2*/*Mmp13* and *Tgfbr2*/*Adamts5* double KO mice were generated by breeding $Tgfbr2^{Col2ER}$ mice with $Mmp13^{flox/flox}$ mice and $Adamts5^{-/-}$ mice.

Results: Deletion of the *Tgfbr2* gene in articular chondrocytes resulted in up-regulation of *Runx2*, *Atf4*, *Mmp13*, *Adamts5* and *Col10* expression. Histological analysis showed articular cartilage degradation, increased chondrocyte hypertrophy in superficial zone, early osteophyte formation, and increased subchondral bone mass in 3-month-old $Tgfbr2^{Col2ER}$ mice. Loss of entire articular cartilage, formation of extensive osteophytes, and substantially increased subchondral bone mass were observed in 6-month-old $Tgfbr2^{Col2ER}$ mice. Histomorphometric analysis and evaluation with OARSI scoring system showed a significant decrease in articular cartilage area in $Tgfbr2^{Col2ER}$ mice. Significant reduction in spontaneous rearing activity and ambulation counts were also observed in 4-, 5-, 6-, 7-, and 8-month-old $Tgfbr2^{Col2ER}$ mice. To determine if up-regulation of *Mmp13* and *Adamts5* expression is responsible for $Tgfbr2^{Col2ER}$-induced OA development, we generated *Tgfbr2*/*Mmp13* and *Tgfbr2*/*Adamts5* double KO mice. Deletion of the *Mmp13* gene significantly alleviates OA-like pathological changes observed in 3- and 6-month-old $Tgfbr2^{Col2ER}$ mice. In contrast, deletion of the *Adamts5* gene only reversed OA-like phenotype in 3-month-old $Tgfbr2^{Col2ER}$ mice. These changes were confirmed by histomorphometric analysis and by evaluation with OARSI scoring system. We also investigated the signaling mechanism and found that inhibition of TGF-β signaling prevented Runx2 degradation. Runx2 directly bound to its binding site located in the proximal region of the *Mmp13* promoter and activated *Mmp13* transcription. ATF4 interacted with Runx2 and enhanced Runx2-induced *Mmp13* transcription.

Conclusion: In this study, we demonstrate that inhibition of TGF-β signaling in articular chondrocytes leads to a progressive OA-like phenotype in mice. *Mmp13* and *Adamts5* are critical downstream target genes of TGF-β signaling during OA development.

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The Risk Of Myocardial Infarction In Systemic Sclerosis: A Population-Based Cohort Study. Iman Hemmati[1], Hyon K. Choi[2], Kamran Shojania[1], Eric C. Sayre[3] and J. Antonio Avina-Zubieta[4]. [1]University of British Columbia, Vancouver, BC, [2]Boston University School of Medicine, Boston, MA, [3]Arthritis Research Centre of Canada, Richmond, BC, [4]Arthritis Research Centre of Canada, University of British Columbia, Richmond, BC.

Background/Purpose: An increased risk of premature atherosclerosis has been well described in patients with rheumatoid arthritis and systemic lupus erythematosus. However, there is limited data on the risk of atherosclerotic diseases, myocardial infarction (MI) in patients with Systemic Sclerosis (SSc). Moreover, the scarce information has come from selected populations. To fill this knowledge gap, we estimated the risk of newly recorded MI events among incident cases with SSc compared to controls from the general population using physician billing and hospitalization databases that cover the entire population from our province (~ 5 million).

Methods: Our data included all visits to health professionals and hospital admissions covered by the comprehensive provincial medical services plan (from Jan1990 until Dec 2010) and all dispensed medication (from Sept 1995 to Dec 2010); for all individuals >= 18 years of age. We

conducted a matched cohort analysis among patients satisfying at least one of the following criteria: a) diagnosis of SSc on at least two visits within a two-year period between Jan 1996 and Dec 2010 by a non-rheumatologist physician; b) diagnosis of SSc on at least one visit by a rheumatologist or from a hospital. To increase specificity we excluded cases that were not confirmed by a rheumatologist if they were seen at a later point. Ten controls matched by birth year, sex and calendar year of follow-up were selected from the general population for each case. Newly recorded MI events from hospital or death certificate were recorded as an outcome. We estimated relative risks (RRs) comparing SSc with age-, sex- and entry time-matched comparison cohorts, adjusting for potential cardiovascular risk factors.

Results: Among 1,208 individuals with incident SSc (84% female, mean age of 56 yrs [SD 15.0]), 90 developed MI (incidence rate= 20.2 per 1000 person years) (Table 1). Compared with non-SSc individuals (N= 12,080), the age-, sex-, and entry-time-matched RR for MI was 3.8 (95% CI, 2.9 to 4.8). The risk was 9 times greater within the first year after the disease onset and progressively decreases over time. After further adjustment for angina, COPD, obesity, cardiovascular disease, diabetes, hormone replacement therapy, dyslipidemia, non steroidal anti-inflammatory drugs, Cox-2 inhibitors, number of hospitalizations and Charlson's comorbidity index at baseline; the RR remained similar (4.0, 95% CI, 3.1 to 5.3). These results persisted among men, women and different age groups (Table 1).

Table 1. Relative risk of incident MI according to Systemic Sclerosis status.

Incidence Rate Ratios of MI	SSc (n = 1,208)	Non-SSc (n = 12,080)
Cases, N	**90**	281
Incidence Rate/1000 Person-Years	**20.2**	**5.3**
Age-sex-entry time matched RRs (95% CI)	**3.8 (2.9–4.8)**	**1.0**
Multivariable RRs (95% CI)	4.0 (3.1–5.3)	1.0
Disease Duration		
< 1 year	**9.0 (5.8–13.9)**	**1.0**
1–4.9 years	**3.0 (2.0–4.4)**	**1.0**
5+ years	**1.6 (0.8–3.1)**	**1.0**
Female	4.1 (3.0–5.6)	**1.0**
Male	4.2 (2.2–7.9)	**1.0**
Age Group		
< 45	**3.0 (0.7–14.1)**	**1.0**
45–59	**5.2 (2.9–9.4)**	**1.0**
60–74	**3.5 (2.3–5.2)**	**1.0**
75 +	**5.4 (3.2–9.3)**	**1.0**

Conclusion: This large population-based study indicates an increased risk of MI in patients with SSc, especially within the first year of disease diagnosis. These findings support increased monitoring of MI complication and risk factors in those with SSc, particularly during the early phase of SSc diagnosis.

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Inflammatory Disease Due To Dysregulated Nuclear Factor-κB Activation and Impaired Type I Interferon Response Resulting From a *De Novo* Human NEMO Hypomorphic Mutation. Alex Wessel[1], Amy Hsu[2], Jevgenia Zilberman-Rudenko[1], Raphaela Goldbach-Mansky[1], Richard M. Siegel[1] and Eric Hanson[1]. [1]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [2]Laboratory of Clinical Infectious Diseases, NIAID, Bethesda, MD.

Background/Purpose: The NF-kB family of transcription factors regulate innate and adaptive immunity, in addition to driving pro-inflammatory-disease states. The type I interferon response acts in parallel, and is mediated by IRF3 and IRF7 transcription factors. The IRFs are triggered by the RIG-I-like family of receptors (RLRs) in fibroblasts and Toll-like receptors (TLRs) in dendritic cells and macrophages. Both NF-kB activation and the Type I IFN response require the NF-kB essential modulator (NEMO) for normal function. The mechanisms by which NEMO is regulated to integrate various upstream signals to direct transcription in antiviral immune defense and inflammatory disease is unknown. We present the molecular mechanism by which a naturally occurring NEMO mutation associated with inflammatory disease leads to aberrant cell responses.

Methods: Genomic DNA and cDNA from dermal fibroblasts and peripheral blood cells from a patient with optic neuritis, panniculitis and physical characteristics consistent with NEMO mutation were analyzed to determine the genotype and effect on NEMO protein product. Patient cells were stimulated with TNF, anti-CD3/CD28,viral nucleic acid analogs, and RSV and HPIV3 infection. Gene expression profiling, cytokine production and biochemical analysis was performed to characterize and determine the mechanism of aberrant signaling produced by the mutant form of NEMO.

Results: We identified an individual with Ectodermal Dysplasia, a history of *in utero* cytomegalovirus exposure, and persistent inflammatory disease. Sanger sequencing revealed a *de novo* synonymous mutation in *IKBKG*, which encodes NEMO, the NF-kB essential modulator. The mutation results in an mRNA splicing defect which leads to the production of a mutant protein containing an in-frame deletion of 51 residues, lacking a previously identified TANK (TRAF family member-associated NFKB activator) interaction domain. Co-immunoprecipitation studies revealed that the mutant form of NEMO from patient T cells is unable to recruit the IRF3 kinase TANK-binding kinase-1 (TBK1), due to impaired association with TANK. Patient fibroblasts stimulated with the RLR ligand poly(I:C) led to impaired induction of IRF3 response genes *IFNB1*, *CCL5*, *CXCL10*, *IP10*, *OASL*, and *DDX58*. Consequently, dermal fibroblasts infected with RSV or hPIV3 demonstrated increased virus propagation relative to healthy control cells. Impaired gene expression occurred despite enhanced nuclear translocation of IRF3, suggesting that the mechanism of impaired activation is not a simple defect in nuclear localization of the transcription factor. In contrast to the impaired type I IFN response, canonical IKK activation and gene induction in dermal fibroblasts appeared relatively normal following TNF treatment.

Conclusion: These results illustrate a novel mechanism of autoinflammatory disease due to aberrant expression of an alternately spliced NEMO and deficient IRF3-mediated response.

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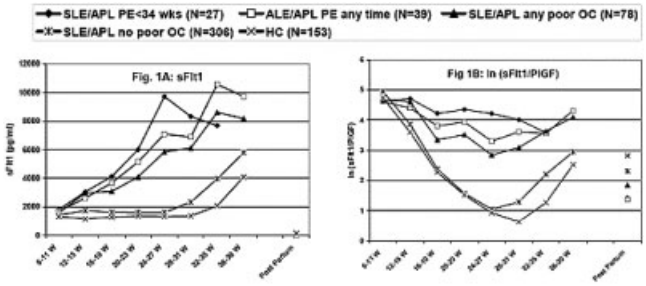
Angiogenic Factor Dysregulation and Risk Of Adverse Pregnancy Outcome In Lupus Pregnancies. Jane E. Salmon[1], Mimi Kim[2], Marta M. Guerra[1], Michael D. Lockshin[1], Ware D. Branch[3], Michelle Petri[4], Carl A. Laskin[5], Joan T. Merrill[6], Lisa R. Sammaritano[1], Jill P. Buyon[7] and S. Ananth Karumanchi[8]. [1]Hospital for Special Surgery, New York, NY, [2]Albert Einstein College of Medicine, Bronx, NY, [3]Univ of Utah, Salt Lake City, UT, [4]Johns Hopkins University School of Medicine, Baltimore, MD, [5]University of Toronto and LifeQuest Centre for Reproductive Medicine, Toronto, ON, [6]Oklahoma Medical Research Foundation, Oklahoma City, OK, [7]NYU School of Medicine, New York, NY, [8]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

Background/Purpose: Pregnant women with lupus and APL are at increased risk for adverse outcomes, particularly preeclampsia (PE), yet identification of those destined for complications remains elusive. Dysregulation of angiogenic factors contributes to pathogenesis of placental insufficiency and preeclampsia. Placentally derived sFlt1 antagonizes proangiogenic proteins (placental growth factor, PlGF; VEGF) which are necessary for development of the placenta and for vascular homeostasis. We prospectively studied patients to determine whether levels of angiogenic factors early in pregnancy would predict outcomes.

Methods: The PROMISSE Study (**P**redictors of p**R**egnancy **O**utcome: Bio**M**arkers **I**n antiphospholipid antibody **S**yndrome and **S**ystemic **L**upus **E**rythematosus) enrolled 384 pregnant women with ≥4 ACR SLE criteria and/or APL and 153 healthy pregnant controls (HC). Subjects were evaluated and blood collected monthly beginning at <12 wks gestation. Exclusion criteria were multi-fetal pregnancy, prednisone >20mg/d, proteinuria >1gm/24hr, and creatinine >1.2 mg/dL. Poor pregnancy outcomes (OC) were defined as preeclampsia, fetal death, neonatal death, preterm delivery <36 wks because of IUGR or placental insufficiency, and/or growth restriction <5th %ile. Levels of angiogenic factors were measured by ELISA and compared between groups at each time point using Wilcoxon rank sum test. In addition, linear mixed effects models were fit to rank transformed data to estimate and compare rates of change in these factors over the entire gestational period.

Results: PE occurred in 10% of pregnancies (27 at <34 wks; 39 at any time) and other poor outcomes in 10%. Compared to SLE patients without poor OC, levels of sFlt1 (Fig 1A) and sFlt1/PlGF ratios were significantly higher as early as 12–15 wks in those destined for PE or other complications, and remained elevated through 31 weeks. The rate of increase in sFlt1 from 6 wks through 31 weeks was higher in patients with PE (<34 wks, any time) or non-PE OC compared to those without poor OC ($p < 0.0001$ all comparisons). In contrast, and consistent with impaired placental development, the rate of increase in PlGF was lower in those destined for poor OC ($p < 0.0001$ all comparisons). Ln sFlt1/PlGF ratios for those who developed PE were markedly and consistently higher throughout pregnancy compared to SLE patients without poor OC or HC ($p<0.0005$ all comparisons) (Fig 1B). Based on ROC analysis, a ln sFLT1/PlGF

ratio cutpoint of 4.14 at the 12–15 wk measure yielded 78% sensitivity and 73% specificity for PE < 34 wk.



Conclusion: We demonstrate that in pregnant SLE and/or APL patients, alterations in the balance of angiogenic factors early in pregnancy are strongly associated with subsequent PE and other poor outcomes. Absolute levels of sFlt1, ratio of sFLt1/PlGF and rate of change of angiogenic factors may be used to identify those at risk before 15 wks, allow early intervention and reveal novel targets for treatment.

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ACR Concurrent Abstract Session
Biology and Pathology of Bone and Joint I: Cartilage Biology and Osteoarthritis
Sunday, October 27, 2013, 2:30 PM–4:00 PM

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Cholesterol Accumulation By Synovial Lining Macrophages Results In Ectopic Bone Formation During Experimental Osteoarthritis. Wouter de Munter[1], Arjen B. Blom[1], Monique M. Helsen[1], Birgitte Walgreen[1], Peter M. van Der Kraan[1], Leo A. Joosten[2], Wim B. van den Berg[3] and Peter L. van Lent[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Department of Medicine, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands, [3]Rheumatology Research and Advanced Therapeutics, Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.

Background/Purpose: Synovial macrophages have previously shown to play a significant role in the etiopathology of experimental collagenase-induced osteoarthritis (OA). In addition to production of pro-inflammatory proteins such as S100A8/9 and IL-1 in early OA, synovial lining macrophages have also shown to play a crucial role in promotion of transforming growth factor-beta (TGFβ) mediated osteophyte formation. In an inflammatory milieu such as OA, accumulated low density lipoprotein (LDL) is oxidized, resulting in high intra-articular levels of oxidized LDL (oxLDL). OxLDL is taken up by macrophages via scavenger receptors, resulting in an more aggressive phenotype. In the present study we investigated whether LDL accumulation by either LDL-receptor deficiency ($LDLr^{-/-}$) or a cholesterol-rich diet leads to increased oxLDL uptake by synovial macrophages and affects synovial activation and osteophyte formation.

Methods: $LDLr^{-/-}$mice and their wild type (WT) controls received either a high cholesterol or control diet for 120 days. Experimental OA was induced by intra-articular injection of collagenase on day 84 and 86. Paraffin sections of OA knee joints were analyzed for cartilage destruction and osteophyte formation using the Pritzker score and image analysis, respectively. ApoB and S100A8 were detected using immunohistochemistry and synovial wash-outs were tested for active TGFβ using a TGFβ reporter gene assay and gene expression. Murine bone marrow derived macrophages were stimulated with 50 μg/mL oxLDL, after which supernatant was functionally tested for active TGFβ presence.

Results: Mice receiving a cholesterol-rich diet not only developed increased serum LDL cholesterol levels, but also showed enhanced ApoB expression in synovial lining macrophages. In line with that, $LDLr^{-/-}$ mice, which already had systemically high basal levels of LDL, showed a much higher accumulation of ApoB in the synovial lining after receiving a cholesterol-rich diet. Although increased LDL levels did not enhance thickening of the synovium, S100A8 expression within macrophages was markedly increased, reflecting an elevated activation status. Even though no effect of LDL accumulation on cartilage destruction was found, both a cholesterol-rich diet and $LDLr^{-/-}$ strongly increased cartilage and bone formation in ligaments with a fold change of 6.7 and 6.1, respectively. Moreover, an increase in osteophyte size was found at the margins of the tibial plateau (4.4 fold increase after a cholesterol-rich diet and 5.3 fold increase in LDLr deficient mice compared to WT mice). To elucidate the mechanism, we finally studied the presence of active TGFβ, which is crucial in driving osteophyte formation, in synovial wash-outs and culture supernatant of oxLDL stimulated macrophages. Using a TGFβ reporter assay, synovial wash-outs of $LDLr^{-/-}$mice and stimulation of macrophages with oxLDL showed an increased presence of functional TGFβ compared to controls (fold change of 1.4 and 2.9, respectively).

Conclusion: Both a cholesterol-rich diet and LDLr deficiency lead to increased synovial activation and ectopic bone formation in experimental OA. Uptake of oxLDL by synovial macrophages leads to activation, rather than production of TGFβ.

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Zinc Finger Protein ZCCHC6 Is Highly Expressed In Osteoarthritic Cartilage and Regulate The Expression Of Interleukin-6 In Human Chondrocytes. Nahid Akhtar, Ahmad Arida and Tariq M. Haqqi. North East Ohio Medical University, Rootstown, OH.

Background/Purpose: Interleukin-1β (IL-1β) is the major cytokine involved in cartilage catabolism in osteoarthritis(OA) and induces the expression of pro-inflammatory cytokine IL-6. Members of cytoplasmic RNA nucleotidyl transferases superfamily catalyze the addition of nucleotides to the 3'end of mRNAs. However, the expression or role of RNA nucleotidyl transferases in regulating cytokine expression in OA is unknown. The aim of this study was to investigate whether RNA nucleotidyl transferase ZCCHC6 is expressed in OA cartilage and whether it is involved in the regulation of IL-6 expression in OA chondrocytes.

Methods: Chondrocytes were derived by enzymatic digestion of human cartilage obtained from OA patients (n=14) undergoing knee joint replacement. Chondrocytes were stimulated with IL-1β (5ng/ml) or treated with Actinomycin D (5 μg/ml) or NF-κB inhibitor SC514 (75 μM). Total RNA from grounded cartilage and from chondrocytes was purified using Qiagen RNeasy kit (Qiagen). Reverse transcription was performed using the Quantitect Reverse Transcription kit and the ZCCHC6 or IL-6 mRNA was quantified using TaqMan assays. SiRNA-mediated depletion of ZCCHC6 in human chondrocytes was used to study the effect on inflammatory cytokine expression using a cytokine array (Ray Biotech). Protein expression of IL-6 was studied using Western immunoblotting and by ELISA in culture supernatants. Data was analyzed using Origin 6.1 software package and $p<0.05$ was considered significant.

Results: Our results showed differential expression of nucleotidyl transferase ZCCHC6 in the damaged cartilage compared to unaffected cartilage. Higher expression of IL-6 (6.0-fold $\pm$ 1.44) in damaged cartilage compared to smooth cartilage (n=3; $p<0.05$) from OA patients was also observed. We further demonstrate that IL-1β stimulation resulted in significant increase in the expression of ZCCHC6 (11.3-fold $\pm$ 1.6) and the mRNA of the inflammatory cytokine IL-6 (4956-fold $\pm$ 40.6) in human chondrocytes (n=4; $p<0.05$). Similar increase in the protein expression of both ZCCHC6 and IL-6 was also observed. Depletion of ZCCHC6 significantly decreased the expression of IL-6 mRNA (~77–95%) and protein in IL-1β-stimulated human chondrocytes. Importantly, IL-6 mRNAs in IL-1β-stimulated human chondrocytes treated with ZCCHC6 siRNA had shorter poly-A tails (n=3; $p<0.05$). Cell supernatants from control or ZCCHC6 siRNA treated chondrocytes stimulated with IL-1β were analyzed using a cytokine array. A subset of cytokines including IL-6 was substantially decreased by loss of ZCCHC6. Our results also showed that the IL-1β-induced activation of NF-κB has no role in the regulation of ZCCHC6 expression in OA chondrocytes (n=3; $p<0.05$). Additionally, OA chondrocytes transfected with ZCCHC6 siRNA also showed a decrease (~99%) in constitutive IL-6 mRNA expression (n=3; $p<0.05$).

Conclusion: Taken together our results demonstrate that ZCCHC6 is highly expressed in damaged human cartilage from OA patients. Furthermore, ZCCHC6 modulates IL-6 expression in human chondrocytes at the post-transcriptional level by influencing cytokine mRNA stability. These

results identify ZCCHC6 as a possible therapeutic target for the treatment of OA.

Disclosure: N. Akhtar, None; **A. Arida**, None; **T. M. Haqqi**, None.

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Inhibition Of X-Box Binding Protein 1 (XBP1) Is Chondroprotective By Promoting Autophagy and Inhibiting Catabolic Responses. Ru L. Bryan[1], Robert Terkeltaub[2] and Ramon Serrano[3]. [1]VA Medical Center/ University of California San Diego, San Diego, CA, [2]VA Medical Ctr/ University of California San Diego, San Diego, CA, [3]VA Medical Center, San Diego, CA.

Background/Purpose: Chondrocyte stress responses to biomechanical injury and joint inflammation, and associated changes in differentiation and function, provide a foundation upon which cartilage injury and OA can be triggered and accelerated. Fundamental proteostasis responses by which cells normally resolve stress include the unfolded protein response (UPR), which restores equilibrium to the stressed ER via a reprogrammed proteome, rich in chaperones and protein folding catalysts. The UPR also regulates oxidative stress responses, inflammation, and cell fate including autophagy. Chondrocyte autophagy is impaired in biomechanical cartilage explant injury, and in aging and OA cartilage. Autophagy repairs damaged cell organelles and is anti-inflammatory, in part by degrading pro-IL-1beta. The UPR can promote autophagy and autophagy promotes normal UPR and mitochondrial functional. UPR-specific XBP1 alternative mRNA splicing generates the potent transcriptional activator XBP1s, which can exert either promote or inhibit autophagy or inflammation depending on cell type and context. In this study, we tested the hypothesis that XBP1 activation is noxious in chondrocytes by impairing autophagy.

Methods: We knocked down XBP1 expression in cultured normal human chondrocytes (passage 1) via siRNA transfection. After 48 hours, the XBP1 knockdown chondrocytes were subjected to SDS-PAGE/Western blot analysis for phosphorylation of the autophagy promoter AMPKα, expression of FOXO1, transglutaminase 2, and the autophagy proteins LC3, and p62. XBP1 knockdown chondrocytes were also treated with IL-1β for 18 hours, and nitric oxide (NO) production and MMP-3 release were measured from the conditioned media by Griess reaction method and Western blot, respectively.

Results: We observed markedly increased activation of XBP1 in human knee OA chondrocytes. In XBP1 knockdown human knee chondrocytes, we observed increased basal levels of expression of the autophagy promoter FOXO1, and increasing LC3 conversion from I to II, and decreased basal levels of expression of p62, indicating induction of autophagy. This was linked with increased basal level of phosphorylation of the autophagy promoter, anti-inflammatory mediator and metabolic super-regulator AMPK in the XBP1 knockdown chondrocytes. Conversely, IL-1β-induced release of NO and MMP-3 was significantly inhibited in the XBP1 knockdown chondrocytes. Last, basal expression of transglutaminase 2, which transduced inflammatory responses of IL-1β and chemokines in chondrocytes, was blunted in the XBP1 knockdown chondrocytes.

Conclusion: This study demonstrated increased UPR-specific XBP1 activation in human knee OA cartilage, and that XBP1 critically transduces noxious functions in chondrocytes, including impairment of autophagy, and pro-catabolic activities, mediated by regulation of AMPK and transglutaminase activity. These findings identify XBP1 as a novel target to limit OA progression.

Disclosure: R. L. Bryan, None; **R. Terkeltaub**, None; **R. Serrano**, None.

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Synovial Wnt and WISP1 Expression Induces Expression Of Cartilage-Degrading Metalloproteinases In The Synovium. Martijn H. van den Bosch[1], Arjen B. Blom[1], Sylvia W. Suen[1], Anke E. van Erp[1], Fons A. van de Loo[1], Esmeralda N. Blaney Davidson[1], Peter M. van der Kraan[1], Peter L. van Lent[1] and Wim B. van den Berg[2]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Rheumatology Research and Advanced Therapeutics, Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.

Background/Purpose: Although many osteoarthritis (OA) patients show significant synovial involvement, consequences are largely unknown. Previously, we found strong upregulation of Wnts 2b and 16 and WISP1, a downstream protein of canonical Wnt signaling, in knee joints in two murine OA models. Wnt signaling has been implicated in OA incidence and modulation of the β-catenin pathway leads to OA-like changes in cartilage. However, the role of the synovium in the induction of OA pathology under the influence of Wnt signaling is unclear. Here we investigated the potential of Wnt signaling to increase the expression of cartilage-degrading enzymes in the synovium.

Methods: Pathway analysis of microarray data from the synovium of a collagenase-induced OA mouse model was done using DAVID software. *In vivo* synovial overexpression of genes from the canonical Wnt signaling pathway was achieved by intra-articular injection of adenoviral vectors. Joint pathology was assessed by histology at several time points after injection. Gene expression was analyzed by qPCR. Human OA synovial specimen were collected from joint replacement surgery and either stimulated or used for outgrowth of OA fibroblasts.

Results: Pathway analysis using DAVID showed that Wnt signaling was enriched in the synovium during experimental OA. To determine the effects of Wnt signaling on synovial tissue, we stimulated human OA synovial specimen with Wnt3a or WISP1, which resulted in increased expression of MMP3, MMP9 and MMP13, whereas expression of the MMP inhibitors TIMP1 and 3 was not altered. Next, we investigated which cell type in the synovium may cause the increased MMP expression. Stimulation of human synovial OA fibroblasts with Wnt3a increased the expression of both MMP3 and MMP13, whereas stimulation of these cells with WISP1 led to an upregulation of MMP3. Stimulation of human THP-1 cells with Wnt3a resulted in highly increased expression of MMP3, MMP9 and MMP13. Stimulation with WISP1 led to increased expression of MMP3. Expression levels of TIMP1 and TIMP3 were not altered. To determine if synovial overexpression of members of the Wnt signaling pathway leads to cartilage damage *in vivo*, we injected adenoviral vectors for Wnt8a, Wnt16 and WISP1 into murine knee joints. These vectors specifically target synovial cells, due to their size. 7 days after overexpression, we found a significant induction of OA pathology at the medial margin of the medial tibial plateau, a preferential site for damage in experimental OA. Lesions were found in 92% (n=12) of the knee joints after Wnt8a overexpression compared to 17% (N=12) for the control virus and 80% (N=5) for Wnt16 overexpression, but only 20% (N=5) for the control virus.

Conclusion: Canonical Wnts produced in the synovium may play an important role in OA pathology. Stimulation of human OA synovium with Wnts and WISP1 increases the expression of MMPs. Fibroblasts and macrophages showed comparable patterns of MMP induction. In addition, synovium specific overexpression of Wnt signaling members, as is found in experimental OA, induces cartilage damage *in vivo*. This underlines synovial Wnt/WISP1 expression to be a potential target for OA therapy.

Disclosure: M. H. van den Bosch, None; **A. B. Blom**, None; **S. W. Suen**, None; **A. E. van Erp**, None; **F. A. van de Loo**, None; **E. N. Blaney Davidson**, None; **P. M. van der Kraan**, None; **P. L. van Lent**, None; **W. B. van den Berg**, None.

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Suppressor Of Cytokine Signaling-3 Is a Critical Regulator Of gp130 Cytokine Signaling In Articular Chondrocytes. Xiao Liu, Kate E Lawlor, Ben A Croker and Ian P Wicks. Walter & Eliza Hall Institute of Medical Research, Parkville, Australia.

Background/Purpose: Cartilage damage is a key feature of inflammatory and degenerative arthritis and an important determinant of patient outcomes. Chondrocytes are the only cells in articular cartilage and are critical for tissue homeostasis. Relatively little is known about how chondrocyte responses to cytokines are regulated. Suppressor of cytokine signaling-3 (SOCS-3) is a negative regulator of the IL-6 cytokine family, which utilizes the common gp130 signaling receptor, in other cell types. We investigated the impact of gp130 cytokines on cartilage and isolated chondrocytes and examined the impact of SOCS-3 deficiency on chondrocytes, *in vitro* and *in vivo*.

Methods: Conditional gene targeting was used to generate mice lacking SOCS-3 in chondrocytes by crossing mice with a floxed allele of *SOCS-3*, with mice transgenic for Cre recombinase driven by the type II collagen (*Col2a1*) promoter ($Socs3^{\Delta/\Delta col2}$ mice). Primary chondrocytes and femoral head cartilage explants were obtained from control and $Socs3^{\Delta/\Delta col2}$ mice. Cartilage explant cultures were stimulated with gp130 cytokines and aggrecanase activity measured using the 1,9-DMMB dye-binding assay and quantitative PCR. STAT1, STAT3 and STAT5 phosphorylation and cytokine/chemokine production in response to gp130 cytokines were measured by flow cytometry and multiplex bead array, respectively. The responses of littermate and $Socs3^{\Delta/\Delta col2}$ mice to intra-articular injections of

gp130 cytokines and to K/BxN serum transfer arthritis were assessed clinically and histologically.

Results: In wild-type articular chondrocytes, all gp130 cytokines activated JAK-STAT signaling and upregulated *Socs3* mRNA expression. Stimulation with Oncostatin M caused the most STAT phosphorylation. $Socs3^{\Delta/\Delta col2}$ cartilage explants and isolated chondrocytes stimulated with gp130 cytokines exhibited prolonged STAT1, STAT3 and STAT5 activation, enhanced *Adamts4* and *Adamts5* production and cartilage degradation. In addition, SOCS-3 deletion in chondrocytes increased the production of multiple inflammatory mediators (IL-6, G-CSF, CXCL1 and CCL2), including receptor activator of NF-kB ligand (RANKL). All features of joint pathology in the acute inflammatory arthritis model – exudate, synovitis, cartilage degradation and bone erosion - were exacerbated in $Socs3^{\Delta/\Delta col2}$ mice compared to $Socs3^{fl/fl}$ littermate controls (see figure). Total histological scores were 9.5 ± 0.78 vs. 6.0 ± 0.96 ($p=0.006$), for $Socs3^{\Delta/\Delta col2}$ and $Socs3^{fl/fl}$ mice, respectively. Furthermore, microarray analysis showed profound and selective effects on gene expression in response to gp130 cytokines, which were heightened in the absence of SOCS3.

Conclusion: Our findings highlight important biological effects of gp130 cytokines on cartilage and provide the first direct evidence for a key regulatory role of SOCS-3 in articular chondrocytes.

Disclosure: X. Liu, None; **K. E. Lawlor**, None; **B. A. Croker**, None; **I. P. Wicks**, None.

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The S100A9 Inhibitor Paquinimod (ABR-215757) Reduces Synovial Activation, Osteophyte Formation and Cartilage Damage In Experimental Osteoarthritis. Rik Schelbergen[1], Arjen B. Blom[1], Tomas Leanderson[2], Helena Eriksson[3], Wim B. van den Berg[4] and Peter L.E.M. van Lent[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Lund University, Lund, Sweden, [3]Active Biotech AB, Lund, Sweden, [4]Rheumatology Research and Advanced Therapeutics, Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.

Background/Purpose: Synovial activation is present in a large subset of osteoarthritis (OA) patients and it is thought to play an important role in the development of OA pathology. Previously, we found that alarmins S100A8 and S100A9 are elevated in the synovium of OA patients and that high S100A8/A9 serum levels correlate with 2-year progression of the disease. Furthermore, in experimental OA these S100-proteins are involved in cartilage degradation and synovial activation. Paquinimod is a quinoline-3-carboxamide compound with immunomodulatory properties that is currently in clinical development for treatment of systemic sclerosis. It targets the S100A9 protein and disrupts the binding of S100A9 to RAGE and TLR-4.

In the current study we investigated the effect of the S100A9-blocking compound paquinimod on experimental osteoarthritis with different degrees of synovial activation.

Methods: Collagenase induced OA (CIOA) was induced by two times intra-articular injection of 1U collagenase and DMM was induced by transsection of the medial anterior meniscotibial ligament leading to destabilization of the medial meniscus (DMM), both in C57Bl6 mice. Paquinimod (3,75 mg/kg) was administered in the drinking water 4 days before induction of OA in both CIOA and DMM and refreshed twice a week. Synovial thickening and cellularity was measured using an arbitrary score from 0–3. OA-like cartilage pathology was scored using a modified Pritzker OARSI score. Osteophyte size was assessed by a blinded observer using imaging software.

Results: First, we assessed the effect of paquinimod on DMM development at day 56. Synovial activation in this surgical model is low, as are S100A8/A9 levels in the synovium. No differences were observed on osteophyte size between paquinimod-treated and non-treated animals at both medial tibia and medial femur. Furthermore, OA-like cartilage pathology was only significantly reduced by paquinimod-treatment at the medial femur (−64%), not at other surfaces and not in the total joint score (−16%).

Then, we treated collagenase-induced OA (CIOA) with paquinimod and evaluated the effects at day 42. In CIOA, synovial activation is high and S100A8/A9 levels in the synovium are significantly higher than those in DMM. Synovial activation was significantly reduced by paquinimod-treatment at the medial side of the patella-femur region (−57%). Osteophyte size was significantly reduced at the medial femur (66%) and cruciate ligaments (−67%). Finally, OA-like cartilage pathology in CIOA was significantly reduced after paquinimod treatment on the medial side of both tibia and femur (−47% and −75% respectively) as well as in the total joint score (−46%).

Conclusion: Paquinimod administered in the drinking water reduces synovial activation, osteophyte formation and OA-like cartilage pathology in CIOA. In contrast, in an experimental OA model where synovial activation is nearly absent (DMM), the effect of paquinimod is marginal.

Paquinimod could prove a very promising treatment for osteoarthritis patients with high synovial activation by blocking S100A9.

Disclosure: R. Schelbergen, None; **A. B. Blom**, None; **T. Leanderson**, Active Biotech, 1, Part-time employee of Active Biotech, 3; **H. Eriksson**, Active Biotech, 1, Active Biotech, 3; **W. B. van den Berg**, None; **P. L. E. M. van Lent**, Active Biotech, 2.

ACR Concurrent Abstract Session
Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis I: Identifying Novel Factors that Facilitate Neovascularization and Cell Trafficking
Sunday, October 27, 2013, 2:30 PM–4:00 PM

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Neovascularization and CD15s Influence Long Distance Migration Of Synovial Fibroblasts From Patients With Rheumatoid Arthritis. Birgit Zimmermann[1], Sina Köppert[1], Stephanie Lefèvre[1], Stefan Rehart[2], Ulf Müller-Ladner[1] and Elena Neumann[1]. [1]Justus-Liebig-University of Gießen, Kerckhoff-Klinik, Bad Nauheim, Germany, [2]Markus-Hospital, Frankfurt, Germany.

Background/Purpose: Rheumatoid arthritis (RA) synovial fibroblasts (SF) are central cells of cartilage destruction and neoangiogenesis. RASF show an increased migratory potential in the synovium towards sites of cartilage degradation. In the SCID mouse model, RASF were able to migrate through the vascular system. The interaction of RASF with endothelial cells (EC) is important for RASF-mediated angiogenesis and migration. Vessel sprouting and EC activation are two key mechanisms induced by interaction of RASF and EC. In this study, the kinetics of vessel growth by RASF in the SCID mouse model was analyzed as well as the E-selectin ligand (CD15s) expression in the synovial membrane, a mechanism potentially involved in RASF adhesion to EC.

Methods: Using 5μm frozen sections RA and osteoarthritis (OA) synovium fluorescence double staining was performed with FITC-labeled anti-CD15s and Cy3-labeled anti-vimentin (fibroblast) antibodies. Medium of cultured RA- and OASF was replaced with RA serum or serum from healthy donors for 48h. Then, cells were stained for CD15s. SCID mouse model (implants n=3–7/time point): the ipsilateral site contained healthy cartilage together with 1.5×10^5RASF in a carrier matrix, the contralateral site contained cartilage without RASF. Neovascularization next to and into the implants was determined after 3 to 60 days. Implant images were taken, implants removed and angiogenesis analyzed by CD31 staining.

Results: CD15s signals were detectable in all RA tissues (n=12). In 67% CD15s signals were co-localized with vimentin, mainly located in sublining (50%) but also located in vessels (33%). After stimulation with RA serum, 80% of RASF (n=5) and 33% of OASF (n=3) showed an increased CD15s expression. Serum stimulation from healthy donors did not alter CD15s. Implant evaluation showed the early presence of truncated vessels (day 3–12) especially at the ipsilateral site which was reduced over time. Vessels in the murine skin close to ipsilateral implants increased in size and perfusion. Late during vascularization, very small vessels sprouted into the carrier matrix (day 9–60). Anti-CD31 staining showed that neoangiogenesis (<10 cell sizes) started at day 9 at both sites. Later (day 18), EC were detectable deep within the carrier matrix (>10 cell layers). Then (> day 27) the whole carrier matrix showed detectable EC signals. At this time the vessel lumen in the implants increased.

Conclusion: CD15s positive RASF were detectable in RA synovium and some of them located in vessels. RA serum increased CD15s expression by RASF which in turn allows RASF to adhere to EC. Implants co-implanted with RASF showed a stronger vessel formation at early time points then RASF-free implants. Vessel formation around and into implants showed an unexpected dynamics, starting with newly formed truncated vessels surrounding the implants especially at the ipsilateral site. Then these vessels disappear and EC invade into the implants, increasing over time. The perfusion of the surrounding vessels increases solely at the ipsilateral site. In summary, RASF

are actively involved in neovascularization showing distinctive pattern in vessel formation. In turn, vascularization allows RASF long distance migration.

Disclosure: B. Zimmermann, None; **S. Köppert**, None; **S. Lefèvre**, None; **S. Rehart**, None; **U. Müller-Ladner**, None; **E. Neumann**, None.

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Adioponectin-Induced p38 MAPK and AMPK Pathways In Rheumatoid Arthritis Synovial Fibroblasts Are Adiponectin Isoform Dependent. Kiran Khawaja[1], Klaus W. Frommer[1], Stefan Rehart[2], Ulf Müller-Ladner[1] and Elena Neumann[1]. [1]Justus-Liebig-University of Gieβen, Kerckhoff-Klinik, Bad Nauheim, Germany, [2]Markus-Hospital, Frankfurt, Germany.

Background/Purpose: Adiponectin, a C1q/tumour necrosis factor (TNF) homologue, was previously known to be secreted by adipocytes. Additionaly, it was found to be synthesized by other cells types like osteoblasts and synovial fibroblasts. Adiponectin levels were found to be high in synovial fluid of rheumatoid arthritis (RA) patients as compared to osteoarthritis patients, hence suggesting a role of adiponectin in the pathophysiology of the disease. Based on this, RA synovial fibroblasts (SF) are the key cells to secrete adiponectin in the synovium *in vivo*. At present, four different adiponectin isoforms are known, namely the globular, low molecular weight (LMW), middle molecular weight (MMW) and high molecular weight (HMW) form. Adiponectin acts by binding to its receptors AdipoR1, AdipoR2, and potentially PAQR3 and PAQR10, which leads to the activation of signaling cascades involving key molecules like AMPK, p38 MAPK, FAK, and ERK. The aim of the present study was to determine the adiponectin receptor expression in RASF and to elucidate the specificity of adiponectin isoforms mediating different signaling pathways in RASF.

Methods: AdipoR1, AdipoR2, PAQR3 and PAQR10 mRNA and protein expression were analyzed in RASF by real-time PCR, Western blotting, and immunocytochemistry. RASF were preincubated with serum-free medium for 30 min with or without signaling inhibitors. Stimulation of RASF was performed using the respective adiponectin isoforms, WT (wild type, contains all isoforms), LMW, globular and MMW/HMW enriched adiponectin isoform (each 10 μg/ml) for 10 min. Then a phosphorylation analysis of p38 MAPK, AMPK, and FAK by Western blotting was performed.

Results: Real-time PCR and Western blotting results showed that cultured RASF express AdipoR1, AdipoR2, and PAQR3 but not PAQR10. This was further confirmed by immunocytochemical analysis. With respect to signaling, phosphorylation of p38 MAPK increased by adiponectin isoform stimulation, with the strongest induction by the MMW/HMW enriched isoform. Similarly, the phosphorylation of AMPK increased in response to adiponectin isoforms and the effect was stronger with the MMW/HMW enriched isoform. On the contrary, although FAK was detectable, no induction or repression in FAK phosphorylation was observed in response to adiponectin isoform stimulation indicating that FAK does not play a role in adiponectin-mediated signaling. The increase in phosphorylation of AMPK was further enhanced by AMPK activator 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) and was reduced by AMPK inhibitor compound C. Compound C caused a further increase in the adiponectin isoform-induced enhanced phosphorylation of p38. Pre-treatment with p38 inhibitor SB203580 did not have any effect on the phosphorylation of AMPK.

Conclusion: Cultured RASF express the adiponectin receptors AdipoR1, AdipoR2 and PAQR3. Adiponectin signaling in RASF is mediated via the p38 MAPK and AMPK pathway but not FAK, and the effect is adiponectin isoform-dependent. The data suggest that the p38 MAPK pathway is a compensatory pathway for the AMPK pathway but not *vice versa*.

Disclosure: K. Khawaja, None; **K. W. Frommer**, None; **S. Rehart**, None; **U. Müller-Ladner**, None; **E. Neumann**, None.

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Citrullination Of ENA-78/CXCL5 Changes Its Receptor Affinity From CXCR2 To CXCR1 and Induces Monocyte Migration. Ken Yoshida, Alisa E. Koch, Ray A. Ohara, Phillip L. Campbell, M. Asif Amin, David A. Fox and Jeffrey H. Ruth. University of Michigan Medical School, Ann Arbor, MI.

Background/Purpose: We previously showed that citrullinated epithelial-derived neutrophil-activating peptide 78/CXCL5 (citENA-78/CXCL5) was significantly higher in rheumatoid arthritis (RA) synovial fluids (SFs) compared to osteoarthritis (OA) and other inflammatory rheumatic diseases (OD) SFs, and its concentration correlates with RA disease activity. Furthermore, we have shown that citrullination of ENA-78/CXCL5 results in conversion from a non-monocyte recruiting to a monocyte recruiting chemokine. We now examine the cellular receptors utilized by citENA-78/CXCL5 to induce monocyte migration in vitro.

Methods: Citrullination of ENA-78/CXCL5 was verified by *mass spectrometry* and Western blot analysis with anti-modified citrulline antibody (AMC). We initially performed polymorphonuclear *neutrophil*(PMN) chemotaxis assays to citENA-78/CXCL5 using a 48-well Boyden chamber system to determine if citrullination altered recruitment activity of ENA-78/CXCL5 for PMNs. Next, we performed monocyte chemotaxis assays to determine whether citENA-78/CXCL5 induced monocyte chemotaxis. Finally, we investigated whether cell recruitment could be inhibited by pertussis toxin (PTX), which is a G protein-coupled receptor antagonist, or with anti-CXCR1 and/or anti-CXCR2 blocking antibodies. For in vivo analysis, C57BL/6 mice were injected intra-articularly (i.a.) with non-cit or citENA-78/CXCL5 to induce inflammation. Immunofluorescence (IF) staining was performed on injected joint tissues using anti-F4/80 antibody, which is specific for monocytes/macrophages, to determine the number of recruited monocytes/macrophages to mouse joints.

Results: citENA-78/CXCL5 was recognized by AMC, while non-citENA-78/CXCL5 was not. Chemotaxis assays showed that citENA-78/CXCL5 induced less PMN migration compared to non-citENA-78/CXCL5, indicating that the binding affinity for PMN chemokine receptors was altered by citrullination of ENA-78/CXCL5. Monocyte chemotaxis assays showed that citrullinated ENA-78/CXCL5 significantly enhanced monocyte migration, while non-citENA-78/CXCL5 did not. PTX completely inhibited citENA-78/CXCL5-induced monocyte chemotaxis, indicating that citENA-78/CXCL5 is binding to a G-protein coupled receptor. Anti-CXCR1 and 2 antibodies both partially reduced the monocyte chemotaxis, and a combination of anti-CXCR1 and 2 antibodies completely inhibited monocyte chemotaxis. Lastly, IF staining showed that citENA-78/CXCL5 recruited more F4/80 positive monocytes/macrophages into mouse knee joints compared to non-citENA-78/CXCL5.

Conclusion: Our results show that citENA-78 induces monocyte migration via CXCR1 and CXCR2, and indicate that citrullination may increase the affinity of ENA-78/CXCL5 for CXCR1. Our data also shows that citENA-78/CXCL5 is a potent recruitment factor for monocytes, but a poor recruitment factor for PMNs. citENA-78/CXCL5 also induced more macrophage accumulation in synovium when injected into mouse knee joints compared to non-citENA-78/CXCL5. These results show that citrullination of ENA-78/CXCL5 can alter its receptor affinity and cellular recruitment properties.

Disclosure: K. Yoshida, None; **A. E. Koch**, Eli Lilly and Company: I am currently employed by Eli Lilly with an adjunct appointment at University of Michigan. My work at Lilly is not relevant to the content of the abstract., 3; **R. A. Ohara**, None; **P. L. Campbell**, None; **M. A. Amin**, None; **D. A. Fox**, None; **J. H. Ruth**, None.

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Cytokine-Mediated Repression Of The Lncrna Hotair Enhances Intracellular Signaling and The Expression Of Adhesion Molecules In Synovial Fibroblasts. Michelle Trenkmann[1], Mojca Frank Bertoncelj[1], Matthias Brock[2], Christoph Kolling[3], Renate E. Gay[1], Beat A. Michel[4], Diego Kyburz[1], Lars C. Huber[2] and Steffen Gay[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Department of Internal Medicine, University Hospital Zurich, Zurich, Switzerland, [3]Schultess Clinic, Zurich, Switzerland, [4]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland.

Background/Purpose: Rheumatoid arthritis (RA) synovial fibroblasts (SF) are characterized by a stably activated phenotype which is, at least in part, because of the epigenetic inheritance of aberrations in gene expression. The histone methyltranferase EZH2 is upregulated in RASF thereby causing the epigenetic repression of specific target genes *via* methylation of histone 3 on lysine 27 (H3K27me3). Long noncoding RNAs (lncRNAs) have recently emerged as powerful regulators of gene expression, e.g. through the interaction with chromatin-associated proteins. In this regard, the lncRNA HOX transcript antisense RNA (HOTAIR) was found to associate with EZH2 and to regulate certain EZH2 target genes. Here we studied the function of HOTAIR in RASF.

Methods: SF were transfected using Lipofectamin 2000 (for siHOTAIR) or AMAXA Nucleofection (for plasmid DNA) and/or stimulated with 10ng/ml TNFα or 1ng/ml IL-1β. Gene expression was measured by quantitative real-time PCR (qPCR) and flow cytometry. Chromatin immunopre-

cipitation (ChIP) was performed with antibodies for histone 3 (H3), H3K27me3 or IgG control and precipitated chromatin was analyzed by qPCR. The activity of intracellular signaling pathways was determined by reporter gene assay (NF-κB; using the pGL4.32 vector and pRL_GAPDH as internal control) and Western blot (p38 phosphorylation).

Results: In OASF (n=13), the expression of HOTAIR was upregulated by 12.7-fold compared with RASF (n=9) (ΔCt 10.6±1.7 vs. 14.3±3.3, p=0.005). Stimulation of OASF (n=5) with TNFα or IL-1β potently decreased HOTAIR levels at 24h (by 65±8% and 50±9%) and 48h (by 52±31% and 49±27%) ($p<0.05$). ChIP analysis revealed increased levels of the repressive H3K27me3 mark at the HOTAIR promoter in RASF (ratio to H3: 0.51±0.35, OASF: 0.25±0.23; p=0.03) showing a strong inverse correlation with its expression (Spearman $R=-0.8725$, $p<0.0001$). Silencing of HOTAIR in OASF significantly increased the TNFα-induced activity of the NF-κB pathway (17±9-fold to 24±14-fold, n=13) whereas p38 phosphorylation was not significantly changed (n=8). In line with this, we found the expression of NF-κB target genes to be upregulated, namely intercellular adhesion molecule 1 (ICAM1) and vascular adhesion molecule 1 (VCAM1). At the mRNA level, ICAM1 and VCAM1 expression was increased after HOTAIR silencing (n=12) both under unstimulated (1.91±0.61- and 2.05±0.99-fold; $p\leq0.005$) as well as TNFα-induced conditions (from 53±23- to 72±43-fold and 4.77±3.39- to 6.31±4.2-fold; $p<0.005$) whereas under IL-1β only ICAM1 mRNA levels were elevated (from 11.9±5.4- to 15.5±6.8-fold; $p<0.005$). These data were confirmed for ICAM1 protein levels measuring its surface expression under TNFα stimulation (n=6, $p<0.01$).

Conclusion: Our data underline the role of the epigenetically repressed lncRNA HOTAIR in the activated phenotype of RASF. Silencing of HOTAIR increased the activity of the NF-κB signaling pathway and the expression of adhesion molecules suggesting a contribution to inflammatory cell infiltration into the joint and, thus, chronic inflammation in RA.

Disclosure: M. Trenkmann, EURO-TEAM, IMI BTCure, IAR Epalinges, KFSP USZ, 2; **M. Frank Bertoncelj**, EURO-TEAM, IMI BTCure, IAR Epalinges, 2; **M. Brock**, None; **C. Kolling**, None; **R. E. Gay**, EURO-TEAM, IMI BTCure, IAR Epalinges, 2; **B. A. Michel**, None; **D. Kyburz**, SNSF, KFSP USZ, 2; **L. C. Huber**, None; **S. Gay**, EURO-TEAM, IMI BTCure, IAR Epalinges, 2.

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Tumor Necrosis Factor Alpha Modifies Chromatin Landscape and Amplifies Inflammatory Responses To Subsequent Stimuli In Synovial Fibroblasts. Angela Lee, Lionel B. Ivashkiv and George D. Kalliolias. Hospital for Special Surgery, New York, NY.

Background/Purpose: Fibroblast-like synoviocytes (FLS) cross-talk with macrophages (Mf) during the course of rheumatoid arthritis (RA). Our group has shown that TNFa, primarily Mf-derived within synovium, induces chromatin modifications and a sustained inflammatory program in FLS. Here we test the hypothesis that chronic TNFa modifies the chromatin landscape in FLS, amplifying responses to subsequent inflammatory stimuli.

Methods: FLS obtained from synovial tissues of patients with RA were chronically exposed to TNFa, then stimulated with interferons (IFNb or IFNg) and were assayed for gene expression by qPCR. NFkB signaling and chromatin modifications were evaluated using western blotting and ChIP assay.

Results: Chronic exposure (72h) of FLS to TNFa leads to super-induction of *CXCL10*, *CXCL11* and *CXCL9* upon subsequent stimulation with IFNb or IFNg (Figure 1A). Notably, these genes reside proximally within the same locus on chromosome 4. These chemokines have been linked to RA pathogenesis and a monoclonal antibody against CXCL10 has shown promising results in a clinical trial. The expression of other classic IFN-target genes upon IFN stimulation is not affected by pre-exposure to TNF (Figure 1B and data not shown), suggesting that the effect of TNF on the IFN-inducible transcriptional program in FLS is gene-specific. After 72h of TNF stimulation, FLS were washed to remove TNF and treated with infliximab (IFX) for 24h to neutralize any residual TNF in the system and then stimulated with IFN. Despite the abrogation of TNF signaling for 24h, the super-induction of *CXCL10*, *CXCL11* and *CXCL9* was retained (Figure 1C), suggesting that TNF has a sustained impact on FLS. In addition, it was observed that chronic TNF stimulation (72h) induces histone depletion, hyperacetylation of residual histones and induction of the active histone mark H3K27Ac at the *CXCL10* promoter (Figure 2A). Exposure of FLS to TNFa for 72h also induced nuclear localization and binding of p65 at the *CXCL10* promoter (Figure 2B) as well as expression of transcription factors STAT1, IRF1 and IRF7 (Figure 2C).

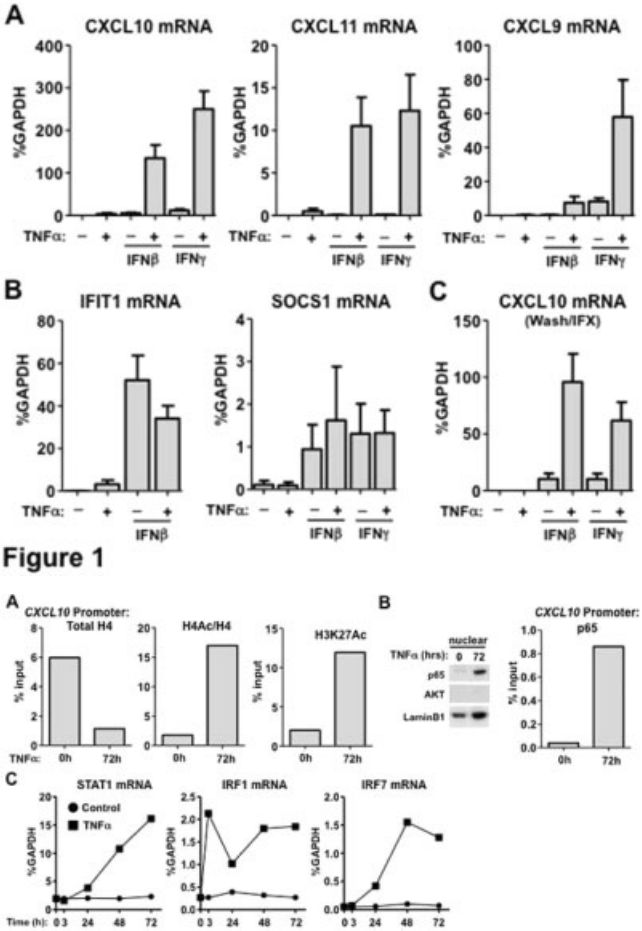

Figure 1

Conclusion: Chronic exposure of FLS to TNFa induces sustained chromatin activation at the *CXCL10* locus, allowing its super-induction upon subsequent IFN stimulation. Since this locus contains binding sites for TNFa-induced p65, STAT1 and IRFs, we will further investigate the potential implication of these transcription factors on the observed activation of chromatin in FLS.

Disclosure: A. Lee, None; **L. B. Ivashkiv**, None; **G. D. Kalliolias**, None.

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A Unique Role For Galectin-9 In Angiogenesis and Inflammatory Arthritis. Martin O'Brien[1], Qiang Shu[2], Pei-Suen Tsou[3], William Stinson[4], Jeffrey H. Ruth[1], Takeo Isozaki[1], Alisa E. Koch[5], David A. Fox[1] and M. Asif Amin[1]. [1]University of Michigan Medical School, Ann Arbor, MI, [2]University of Michigan Medical School and Qilu Hospital of Shandong University, Ann Arbor, MI, [3]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [4]University of Michigan, Ann Arbor, MI, [5]VA Medical Service, Ann Arbor, MI.

Background/Purpose: Galectin-9 (Gal-9) is a mammalian lectin which contributes to T-cell autoimmunity and tumor biology. Here, we examined the contribution of Gal-9 in angiogenesis and inflammatory arthritis, two critical components involved in the pathogenesis of rheumatoid arthritis (RA).

Methods: To determine the role of Gal-9 in angiogenesis *in vitro*, we performed human dermal microvascular endothelial cell (HMVEC) chemotaxis in modified Boyden chambers and Matrigel tube formation assays. We employed the mouse Matrigel plug angiogenesis assay to examine the involvement of Gal-9 in angiogenesis *in vivo*. Inhibitors and siRNA to signaling molecules for Gal-9 were also tested in these assays. We performed a local model of inflammation by injecting Gal-9 in the knees of C57/Bl6 wild type (wt) mice. HMVECs were stimulated with Gal-9 in the presence or absence of chemical inhibitors and Western blots were performed to investigate the phosphorylation of signaling molecules. We also examined the expression of Gal-9 in RA synovial tissue (ST) sections by performing immunohistochemistry.

Results: Gal-9 significantly induced HMVEC migration at 1μg/mL and 2μg/mL ($P < 0.05$), while signaling inhibitors of Erk1/2, p38, and c-Jun inhibited Gal-9-mediated HMVEC migration ($P < 0.05$). Gal-9 increased HMVEC Matrigel tube formation *in vitro*, another facet of angiogenesis, which was significantly reduced by the signaling inhibitors of Erk1/2, c-Jun, and p38 ($P < 0.05$). We confirmed our data by using siRNA directed against signaling intermediates. To examine the role of Gal-9 in angiogenesis *in vivo*, we performed Matrigel plug angiogenesis assays in mice. Gal-9 induced significantly higher ($P < 0.05$) hemoglobin, an indirect measure of angiogenesis, compared to phosphate buffered saline (PBS) injected plugs. Gal-9-mediated angiogenesis was attenuated in the plugs containing Jnk inhibitor, suggesting the importance of Jnk in Gal-9 induced angiogenesis *in vivo*. We found a marked increase in inflammation when wt mouse knees were injected with Gal-9 compared to PBS, suggesting that Gal-9 is a potent proinflammatory mediator. Gal-9-stimulated HMVECs showed a time-dependent increase in Jnk and Erk1/2 phosphorylation. We also found that Jnk is upstream of Erk1/2, as siRNA directed against Jnk decreased Gal-9-activated Erk1/2 phosphorylation in HMVECs. Immunohistochemical staining showed markedly higher expression of Gal-9 in blood vessels in RA compared to osteoarthritis ST sections.

Conclusion: Gal-9 mediates angiogenesis *in vitro* and *in vivo* via Erk1/2 and Jnk pathways. Gal-9 increases mouse knee circumference when injected intraarticularly. Our data suggest a novel role of Gal-9 in angiogenesis and inflammatory arthritis. Gal-9 may be a potential therapeutic target for angiogenesis-dependent diseases such as RA.

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ACR Concurrent Abstract Session
Epidemiology and Health Services Research I: Comorbidities in Rheumatic Diseases
Sunday, October 27, 2013, 2:30 PM–4:00 PM

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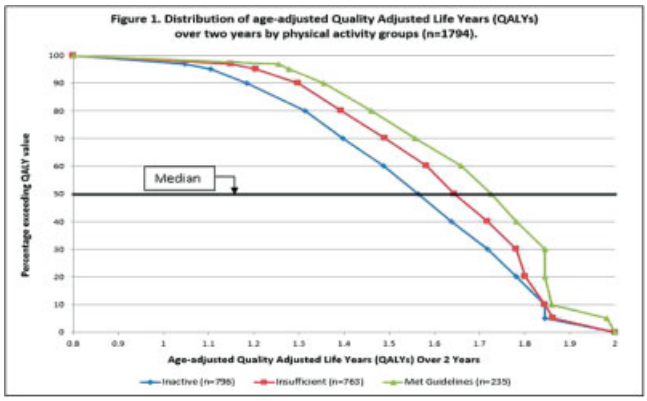
Relationship of Meeting Physical Activity Guidelines and Quality Adjusted Life Years. Kai Sun[1], Jing Song[1], Larry Manheim[1], C. Kent Kwoh[2], Rowland W. Chang[3], Pamela A. Semanik[1], Dorothy D. Dunlop[1] and Charles Eaton[4]. [1]Northwestern University, Chicago, IL, [2]University of Pittsburgh, Pittsburgh, PA, [3]Northwestern University Medical School, Chicago, IL, [4]Brown University, Providence, RI.

Background/Purpose: Regular physical activity is associated with reduced chronic disease burden and mortality. Recognizing the importance of physical activity, there are US federal guidelines for adults that also include persons with arthritis. Improving physical activity may be key to improving overall public health and reducing health care spending. Quality Adjusted Life Year (QALY) is a standard outcome measure used in cost-effectiveness analyses. We analyzed the data from the Osteoarthritis Initiative (OAI) to determine whether increasing levels of physical activity is correlated to larger QALY estimates.

Methods: Physical activity was measured using accelerometers and was classified as 1) Meeting Guidelines (≥150 moderate-to-vigorous [MV] minutes/week acquired in bouts ≥10 minutes); 2) Insufficiently Active (some but <150 MV bout minutes/week) or 3) Inactive (no bouts of MV activity lasting 10 minutes over the week). An SF6-D utility score (range 0–1) was derived from patient reported health status at baseline and 2 year follow-up. The QALY outcome was calculated as the area under utility curve over 2 years (range 0–2). Data were stratified by gender and body mass index (BMI). The relationship of physical activity levels to median QALY adjusted for sociodemographic factors (age, gender, race, education, income) and clinical/health factors (body mass index, medical comorbidity, smoking, presence of radiographic knee osteoarthritis, knee symptoms, and prior knee injury) was derived using median quantile regression.

Results: Median QALYs over 2 years were significantly higher with greater physical activity level in a stepwise fashion as shown by the cumulative frequency curve (figure). Relative to the Inactive group, the median QALYs of the Meeting Guidelines group was 0.162 (95% confidence interval (CI) 0.120–0.204) higher, and that of the Insufficiently Active group was 0.082 (95% CI 0.052–0.110) higher. After adjusting for sociodemographic and clinical/health factors, the differences in median QALYs continued to show a statistically significant linear trend with physical activity level. Similar findings were observed when the cohort was stratified by gender and BMI.



Conclusion: We found a strong graded relationship between greater physical activity and better QALYs. Moving individuals from the Inactive to Insufficiently Active group or from the Insufficiently Active to Meeting Guidelines group could be associated with a 0.08 increase in QALYs over 2 years. An intervention costing $4,000 or less that resulted in such physical activity gains would be cost effective using a $50,000 per QALY gain cutoff. Our analysis further supports the potential effectiveness and cost-effectiveness of interventions to promote physical activity even if recommended levels are not fully attained.

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Low Cardiovascular Mortality Among Early Rheumatoid Arthritis Patients—A Nationwide Register Study 2000–2008. Anne M. Kerola[1], Tuomo Nieminen[2], Lauri J. Virta[3], Hannu Kautiainen[4], Kari Puolakka[5], Tuomas Kerola[6], Timo Pohjolainen[7] and Markku J. Kauppi[6]. [1]Medical School, University of Helsinki, Helsinki, Finland, [2]Division of Cardiology, Helsinki University Central Hospital, Helsinki, Finland, [3]Research Department, the Social Insurance Institution, Turku, Finland, [4]Unit of Primary Health Care, Helsinki University Central Hospital, Helsinki, Finland, [5]Department of Medicine, South Karelia Central Hospital, Lappeenranta, Finland, [6]Department of Internal Medicine, Päijät-Häme Central Hospital, Lahti, Finland, [7]ORTON Rehabilitation Centre, ORTON Foundation, Helsinki, Finland.

Background/Purpose: Increased cardiovascular (CV) mortality in established rheumatoid arthritis (RA) is a widely accepted threat, but in early RA or inception cohorts, growing evidence suggests no increased CV mortality. The aim of this study was to assess the CV mortality in early RA patients diagnosed in the 2000s, and to compare it with the general population.

Methods: All incident RA patients over 16 years of age diagnosed in 2000–2007 were identified from a Finnish nationwide register maintained by the Social Insurance Institution (M05 for RF positive and M06 for RF negative RA). Death certificate data were obtained from the National Population Registry until the end of 2008, and CV disease was identified as the primary cause of death by the ICD-10 codes I00–99. The number of CV deaths was calculated in subgroups according to sex, age, RF status, and calendar year. The cumulative incidence of CV deaths was assessed with adjustment for competing risks—that is, deaths due to causes other than CV disease. The expected number of CV deaths in each subgroup was calculated on the basis of CV death rates in the age- and sex-specific general population (data obtained from Statistics Finland), and a standardized mortality ratio (SMR) was calculated with 95% CIs.

Results: During the 8-year follow-up period, 14,878 new RA patients were identified (68% women, 63% RF positive). The mean age was 55.8 (SD 15.8) years in women and 57.5 (SD 13.9) years in men at the time of RA diagnosis. By the end of 2008, 501 patients had died of CV causes. Cumulative incidence analysis adjusted for competing risks showed that CV mortality at five/eight years after the diagnosis of RA was 2.6%/5.8% in women and 4.4%/8.4% among men (Figure 1). The SMR in the entire RA cohort was 0.57 (95% CI 0.52 to 0.62). The SMRs in subgroups according to sex and RF status varied from the lowest value of 0.43 among the RF negative women to 0.70 among the RF positive men (Table 1). Male sex and the presence of RF increased the risk of CV death: the sub-hazard ratios (sHR)

were 1.73 (95% CI 1.45 to 2.05, p<0.001) and 1.33 (1.10 to 1.60, p=0.003), respectively.

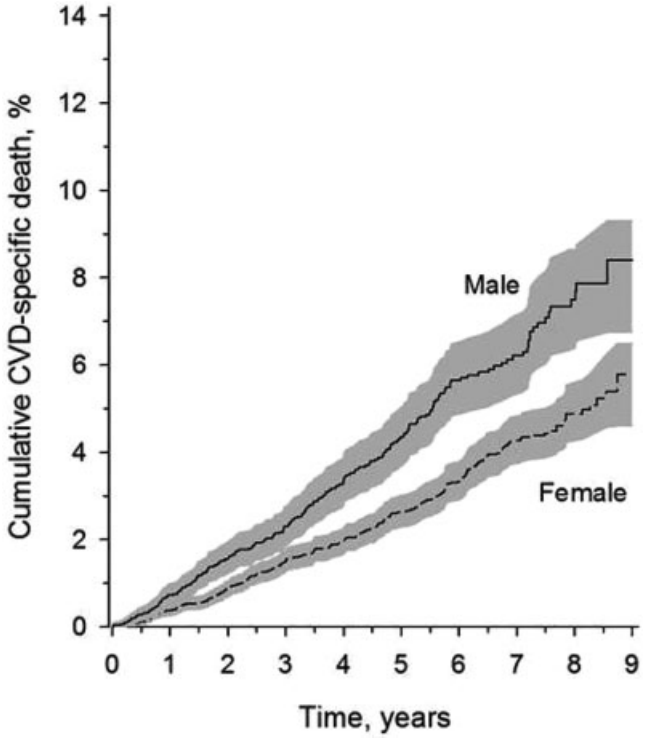

Figure 1. Estimated cumulative incidence functions for cardiovascular-disease-specific (CVD-specific) death among patients with RA.

Table 1.

	Number ofCV deaths	SMR (95% CI)
Total		
Men	214	0.63 (0.55 to 0.72)
Women	287	0.53 (0.48 to 0.60)
RF+		
Men	148	0.70 (0.60 to 0.83)
Women	198	0.60 (0.52 to 0.69)
RF−		
Men	66	0.51 (0.40 to 0.65)
Women	89	0.43 (0.35 to 0.53)

Conclusion: In this nationwide early RA cohort, CV mortality was substantially lower than in the age- and sex-specific general population. This reduction in CV deaths may reflect both the recent advances in the management of systemic inflammation and the improved recognition and treatment of CV risk factors in RA. With longer disease duration, this favorable CV prognosis may deteriorate.

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Serious Infection Rates Among Patients With Systemic Lupus Erythematosus Receiving Corticosteroids and Immunosuppressants. Candace H. Feldman[1], Linda T. Hiraki[2], Francisco M. Marty[3], Wolfgang C. Winkelmayer[4], Jessica M. Franklin[5], Daniel H. Solomon[6], Seoyoung C. Kim[3] and Karen H. Costenbader[7]. [1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital, Harvard School of Public Health, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]Stanford University School of Medicine, Stanford, CA, [5]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, [6]Harvard Medical School, Brigham and Women's Hospital, Division of Rheumatology, Division of Pharmacoepidemiology, Boston, MA, [7]Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Infections are among the leading causes of hospitalization and mortality in patients with systemic lupus erythematosus (SLE); approximately 50% have a serious infection during their disease course. We investigated rates of serious infections requiring hospitalization according to immunosuppressant use in a nationwide cohort of SLE patients.

Methods: We used the Medicaid Analytic eXtract (MAX) data system, with billing claims and demographic information for >24 million Medicaid enrollees from 47 states and Washington, DC, 2000–2006. We identified patients age 18–65 years with prevalent SLE (≥3 visits ≥30 days apart with ICD-9 codes of 710.0). We defined serious infections resulting in hospitalization using a method previously validated in an administrative database. We identified patients ever receiving immunosuppressants (IS; azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus), and corticosteroids (CS) and calculated incidence rates per 100,000 persons-years for bacterial (bacteremia, cellulitis, endocarditis, osteomyelitis, pneumonia, pyelonephritis, septic arthritis, listeriosis), fungal (pneumocystosis, candidiasis, cryptococcosis, aspergillosis, histoplasmosis) and viral (influenza, herpes zoster, cytomegalovirus) infections, occurring ≥7 days after receipt of the drug. We used Poisson regression to determine age, sex, and Medicaid enrollment duration-adjusted infection incidence rate ratios comparing SLE patients receiving no drugs to CS alone and IS and CS combined.

Results: We identified 43,351 patients with SLE. The mean age was 38 years (±12) and mean Medicaid enrollment duration was 3.3 person-years (±2.1). SLE patients were 98% female, 38% Black, 37% White, and 15% Hispanic. 18,659 (43%) patients received a CS alone and 13,913 (32%) received both a CS and an IS. During follow-up there were 13,986 serious bacterial infections: 23% bacteremia, 38% pneumonia and 24% cellulitis. There were also 47 cases of pneumocystosis, 382 cases of herpes zoster, and 114 cases of influenza all requiring hospitalization. The incidence rate for all infections was 1.2 times higher among those receiving a CS alone and combined with an IS, compared to those prescribed neither (**Table**). The incidence rate of viral infections was 2.4 times higher in patients receiving an IS and a CS combined and 1.3 times higher with a CS alone, compared to those prescribed neither.

Table. Incidence Rates of Serious Infections by Subtype among Patients with SLE, 2000–2006*

	Total Infections		Bacterial Infections		Fungal Infections		Viral Infections	
SLE Group	**IR**	**IRR**	**IR**	**IRR**	**IR**	**IRR**	**IR**	**IRR**
No IS or CS N=9197	102.05 (102.01–102.09)	1.0 (ref)	95.80 (95.76–95.84)	1.0 (ref)	3.65 (3.64–3.66)	1.0 (ref)	1.90 (1.90–1.91)	1.0 (ref)
CS Alone N= 18659	120.73 (120.71–120.75)	**1.20 (1.13–1.27)**	112.42 (112.40–112.44)	**1.19 (1.12–1.26)**	4.66 (4.65–4.66)	**1.30 (1.19–1.41)**	2.47 (2.47–2.54)	**1.31 (1.20–1.43)**
IS and CS N=13913	119.51 (119.48–119.53	**1.19 (1.12–1.26)**	109.06 (109.04–109.09)	**1.16 (1.09–1.22)**	5.10 (5.10–5.11)	**1.35 (1.23–1.47)**	4.62 (4.62–4.63)	**2.39 (2.15–2.65)**

*Crude incidence rates (IR) reported per 100,000 person-years with 95% CIs. Incidence rate ratios (IRR) with 95% CIs adjusted for age, sex and Medicaid enrollment duration.

Conclusion: In this large, diverse cohort, SLE patients receiving CS alone and both IS and CS combined had elevated incidence rates of serious infections requiring hospitalization, particularly viral infections. Further studies are needed to evaluate the causality of the observed associations accounting for patients' baseline infection risk and drug-specific effects.

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Mortality Rates, Readmissions and Revascularisation Following a First Myocardial Infarction In Patients With Autoimmune Rheumatic Disease Compared With Controls. Sharon Van Doornum[1], Megan Bohensky[1], Mark Tacey[1], Caroline Brand[1], Vijaya Sundararajan[2] and Ian Wicks[3]. [1]The University of Melbourne, Melbourne, Australia, [2]University of Melbourne, Melbourne, Australia, [3]Royal Melbourne Hospital, Melbourne, Australia.

Background/Purpose: We have previously demonstrated increased case fatality following myocardial infarction (MI) in rheumatoid arthritis (RA) patients[1], however post-MI case fatality has not been inves-

tigated in other autoimmune rheumatic disease (AIRD). The primary aim of this study was to compare mortality rates following a first MI in patients with and without a diagnosis of AIRD. The secondary aims were to compare hospital readmission rates and post-MI revascularisation treatment.

Methods: This was a retrospective cohort study using two population-based linked databases. Cases of MI from 1 July 2001 to 30 June 2007 were identified using International Classification of Diseases (ICD) codes. AIRD status was identified from the index admission or any prior admission in the preceding 3 years using relevant ICD codes. Thirty-day and 1-year mortality rates were calculated from the date of index MI to the date of death (all-cause and cardiovascular causes of death) for patients with AIRD and patients without AIRD (controls). Adjusted odds ratios for mortality were calculated using a logistic regression model fitted with mortality as the outcome, AIRD status as the exposure and with adjustment for age, gender, socio-economic status, geographic location and relevant co-morbidities. Readmissions were defined as admission to hospital within 1 year of the index MI. Procedure codes for percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft (CABG) up to 90 days after the index MI were identified to compare intervention rates.

Results: There were 79,390 individuals with a first MI, of whom 1,409 (1.8%) had AIRD. The 30-day all-cause mortality rate for patients with AIRD was 21.4% compared to 13.4% for controls ($p < 0.001$). At 1 year the AIRD group had an all-cause mortality of 38.6% compared to controls of 22.8% ($p < 0.001$). Adjusted odds ratios for mortality in the AIRD group and AIRD sub-groups are shown in Figure 1. Higher rates of readmissions at 30-days ($p=0.004$) and 1 year ($p=0.003$) were observed in the AIRD group compared to controls, but this was not sustained when considering only subsequent MIs as the cause of readmission. The 90-day rates of PTCA and CABG were significantly lower in the AIRD group compared to controls (PTCA: 15.7% vs 25.9%, $p < 0.001$ and CABG: 3.8% vs 8.7%, $p < 0.001$).

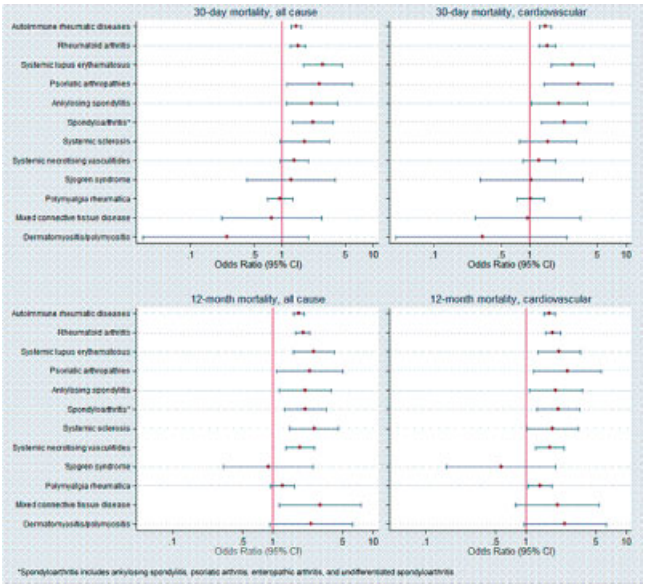

Figure 1. Mortality Risk for AIRD patients who experienced a first MI between 1 July 2001–30 June 2007

Conclusion: We identified a higher risk-adjusted mortality rate for AIRD patients overall and for the majority of patient subgroups at 30-days and 12 months after first MI. We also identified higher readmission rates and lower post-MI revascularisation rates in the AIRD group, suggesting gaps in the current treatment of cardiovascular disease for AIRD patients.

1) Van Doornum et al, Arthritis Rheum. 2006

Disclosure: S. Van Doornum, None; **M. Bohensky**, None; **M. Tacey**, None; **C. Brand**, None; **V. Sundararajan**, None; **I. Wicks**, None.

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Rates Of Malignancies In Patients From 5 Rheumatoid Arthritis Registries Across The World. Johan Askling[1], Niklas Berglind[2], Stefan Franzén[2], Thomas Frisell[1], Christopher Garwood[3], Jeffrey D. Greenberg[4], Meilien Ho[5], Marie Holmqvist[1], Laura Horne[6], Kathy Lampl[6], Kaleb Michaud[7], Fredrik Nyberg[8], Dimitrios A. Pappas[9], George Reed[10], Eiichi Tanaka[11], Trung Tran[12], Suzanne Verstappen[3], Hisashi Yamanaka[11] and Deborah Symmons[3]. [1]Karolinska Institutet, Stockholm, Sweden, [2]AstraZeneca R&D Mölndal, Mölndal, Sweden, [3]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [4]NYU Hospital for Joint Diseases, New York, NY, [5]AstraZeneca R&D Alderley Park, Macclesfield, United Kingdom, [6]AstraZeneca R&D Wilmington, Wilmington, DE, [7]University of Nebraska Medical Center, Omaha, NE, [8]AstraZeneca R&D, Mölndal, Sweden, [9]Columbia University, New York, NY, [10]University of Massachusetts Medical School, Worcester, MA, [11]Tokyo Women's Medical University, Tokyo, Japan, [12]MedImmune LLC, Gaithersburg, MD.

Background/Purpose: The overall incidence of cancer in patients with rheumatoid arthritis (RA) is modestly elevated compared with the general population. The extent to which cancer rates in RA populations vary across cohorts and across patient subsets defined by disease activity or treatment is less known. Available data are often difficult to compare, since background malignancy rates may vary across the world, and due to methodological differences and population differences between studied RA cohorts. We investigated malignancy rates in 5 international RA registries from 4 continents, employing a standard set of analyses and standardizing rates to a common population.

Methods: Participating RA registries were CORRONA (USA), SRR (Sweden), NOAR (UK), CORRONA International (East Europe, Latin America, India) and IORRA (Japan). Within each registry, we analyzed a primary cohort of all RA patients from January 2000 to last available data of each register (2010–2013), and several subcohorts as defined by disease activity, treatment status, calendar time, duration of follow-up and prior comorbidity for sensitivity analyses. Malignancy rates with 95% confidence intervals were estimated, and were standardized for age, sex and, in 1 sensitivity analysis, also for HAQ, using the distributions from a typical RA trial program population.

Results: There was remarkable consistency in crude malignancy rates across registries (Table). Sex and age standardization reduced heterogeneity further, with standardized rates of malignancy excluding nonmelanoma skin cancer (NMSC) varying from 0.56 to 0.87 per 100 person-years (Table). Within each registry, rates were generally also consistent across the sensitivity analyses, which also differed little from the main analyses based on the full cohort (data not shown).

Table. Incidence of malignancies excluding NMSC, and of malignant lymphomas, in the primary cohorts (RA patients from Jan 1, 2000) from 5 RA registries

Registry	N	Events	PY*	Crude Incidence/ 100 PY	Standardized† Incidence/100 PY (95% CI)
Malignancies excluding NMSC					
CORRONA	24,176	694	74,751	0.93	0.64 (0.58–0.71)
SRR	18,527	1078	79,241	1.36	0.87 (0.80–0.94)
NOAR	1564	129	10,695	1.21	0.77 (0.60–0.99)
CORRONA-INT	2727	11	1812	0.61	0.56 (0.27–1.07)
IORRA	7770	241	33,582	0.72	0.65 (0.57–0.75)
Lymphoma					
CORRONA	24,176	62	75,655	0.08	0.06 (0.04–0.08)
SRR	18,527	82	81,459	0.10	0.06 (0.04–0.08)
NOAR	1564	10	10,931	0.09	0.09 (0.03–0.21)
CORRONA-INT	2727	1	1812	—‡	
IORRA	7770	23	33,951	0.07	0.06 (0.04–0.10)

* PY, person-years.
† Standardized according to the age and sex distribution in a typical RA clinical trial program.
‡ NA, not available. Too few events - incidence rates not calculated.

Conclusion: A consistent methodology and analysis with standardization of rates facilitated comparison across registries and demonstrated that in real world RA populations from different countries and with variations in RA management and comorbidity, rates of overall malignancy excluding NMSC and of lymphoma were surprisingly consistent across and within the cohorts.

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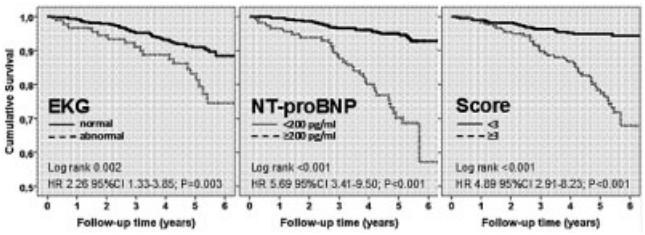
Outcome In Patients With Rheumatoid Disease: Simple Screening Tools Predict Cardiovascular Events and Death. Stefan Kleinert[1], Margret Breunig[2], Hans-Peter Tony[1], Martin Feuchtenberger[3], Marc Schmalzing[1], Christian Kneitz[4], Stefanie Lehmann[5], Christiane Angermann[1], Georg Ertl[1] and Stefan Störk[5]. [1]University Hospital Würzburg, Würzburg, Germany, [2]University Hospital Würzburg, Würzburg, Wuerzburg, Germany, [3]Kreiskliniken Altötting-Burghausen, Burghausen, Germany, [4]Hospital Südstadt, Rostock, Germany, [5]University of Würzburg, Würzburg, Germany.

Background/Purpose: Patients with rheumatoid disease (RD) have an increased mortality risk compared to the normal population, mainly due to cardiovascular (CV) disease. Only a proportion of this risk increase seems explained by traditional cardiovascular risk factors. It is therefore difficult to identify patients with RD at high risk. We identified patients at increased risk for CV diseases and mortality by a screening program that is suitable for clinical practice in rheumatology, and quantified long-term outcome.

Methods: 612 consecutive patients attending the rheumatology outpatient department of the University Hospital underwent a comprehensive CV risk assessment including medical history, patient questionnaires, ECG, and laboratory measurements including natriuretic peptides (NT-proBNP). Screening was regarded "positive" if any of the following was present: European CV disease risk assessment Score (SCORE) ≥3% or NTproBNP≥200 pg/ml or any pathological ECG pattern. Patients were followed for a median of 5.5 years.

Results: 312 subjects suffered from rheumatoid arthritis (RA; 80% female, mean age 54 yrs), and 260 from systemic autoimmune diseases (SAI; 77% female, mean age 51 yrs). Across all subjects, SCORE was ≥3% in 31%, 20% had a NTproBNP level ≥200 pg/ml, and 16% had a pathological ECG. All-cause mortality in RA/SAI was 6.2%/5.6%, respectively; frequency of cardiac events (ie, myocardial infarction, stroke, cardiac decompensation, resuscitation) was 5.8%/7.3%, respectively. The figure shows KM-plots for the 3 screening strategies, and unadjusted hazard ratios with 95%CI. In an age- and sex-adjusted multivariable model, only NTproBNP≥200 pg/ml conferred independent prognostic information with HR 2.8 (1.55–5.03; p<0.001) and an area under the ROC curve of 80%.



Conclusion: RD patients at high risk for death and CV events can be identified using simple screening tools. In patients with a SCORE ≥3% or NTproBNP ≥200 pg/ml are further diagnostics and closer long-term follow-up seem justified.

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ACR Concurrent Abstract Session
Miscellaneous Rheumatic Diseases
Sunday, October 27, 2013, 2:30 PM–4:00 PM

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IgG4+ Plasmablasts Are A Novel Biomarker In IgG4-Related Disease. Mollie Carruthers[1], Hamid Mattoo[2], Zachary S. Wallace[1], Vinay Mahajan[2], Shiv Pillai[1] and John H. Stone[1]. [1]Massachusetts General Hospital, Boston, MA, [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: IgG4-related disease (IgG4-RD) is an immune-mediated disorder that responds to B cell depletion with rituximab (RTX). We detected IgG4+ plasmablasts in the sera of patients with IgG4-RD and observed a general correlation with disease activity. We examined the relationship between disease activity and IgG4+ plasmablast concentration more closely in eight patients treated with RTX.

Methods: This study was approved by the institutional review board and all subjects provided informed, written consent. All patients had histopathologic proof of their IgG4-RD diagnoses, and their clinical features were consistent with this diagnosis. Patients were selected for rituximab treatment based on previous refractoriness to glucocorticoids or disease activity at one or more organ sites. Rituximab (1000 mg) was administered in two doses at days 0 and 15. Absolute plasmablasts/ml were measured by flow cytometry, gated on IgG4+, CD38+, CD27+ and CD19 lo. Clinical visits and laboratory evaluations were performed at baseline and approximately 3 months later. One subject had the baseline plasmablast concentration measured 2 weeks after RTX, and another had the measurement at 5 months post-RTX treatment. The IgG4-RD responder index (IgG4-RD RI) was used to measure disease activity. Concentrations of plasmablasts before and after RTX were compared using a paired t-test.

Results: IgG4+ plasmablast concentrations decreased dramatically following RTX (Figure 1). The mean absolute IgG4+ plasmablast counts per ml before and after treatment were 3692 (range: 610 to 5772) and 422 (range: 1 to 156), respectively (p=0.004). The IgG4-RD RI declined in a similar fashion, from a mean of 13±4 to 3±2 (p=0.0001). Three patients had baseline serum IgG4 concentrations <140 mg/dl yet still had substantial blood plasmablast elevations, with a mean of 5279 PB/ml (range: 4530 to 5772). The mean serum IgG4 concentration also decreased significantly following RTX, from 284 mg/dl (range: 58 to 638) to 177 mg/dl (range: 47 to 387 mg/dl)(p=0.025).

Conclusion: The IgG4+ plasmablast level falls significantly 3 months after treatment with RTX, corresponding to improvements in disease activity in IgG4-RD. IgG4+ plasmablasts may be an important biomarker in IgG4-RD for diagnosis, serial assessment of disease activity, and a gauge for the need for treatment.

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Ophthalmic Manifestations Of IgG4-Related Disease: A Single-Center Experience. Zachary S. Wallace, Vikram Deshpande and John H. Stone. Massachusetts General Hospital, Boston, MA.

Background/Purpose: IgG4-related disease (IgG4-RD) is an inflammatory disorder responsible for fibrosing, tumefactive lesions that can present in nearly any anatomic location. The orbital manifestations of IgG4-RD, termed IgG4-related ophthalmic disease (IgG4-ROD), include lacrimal gland involvement in most cases. However, the extraocular muscles, orbital soft tissues, sclera, and local nerves may also be affected. We review the orbital manifestations of IgG4-RD based on the experience at our center and characterize the natural history, pathology, and treatment of these IgG4-RD complications.

Methods: We identified 27 patients in our IgG4-RD Registry with orbital manifestations. Six cases were excluded because no pathology was available for review. All 21 cases included had histopathologically-confirmed IgG4-RD diagnoses. We then performed a retrospective medical records review.

Results: Patients with IgG4-ROD had a mean age of 50 years (range: 21–79) at the time of symptom onset and were approximately balanced with regard to gender distribution (male 57%, female 43%).The lacrimal gland, affected in 13/21 cases (62%) was the most commonly involved orbital structure. Dacryoadenitis typically led to proptosis. Most patients (71%) had bilateral ophthalmic disease as well as extra-orbital involvement. The salivary glands, abnormal in 40% of those with IgG4-ROD, comprised the most common site of extra-orbital disease. The average serum IgG4 concentration was 721 mg/dL (range: 28 to 4780; normal < 125). The mean serum concentration was higher in patients with bilateral disease and in those with extra-orbital manifestations. Among patients with dacryoadenitis, all were anti-Ro and anti-La negative. The histopathological and immunostaining features of every biopsy specimen were consistent with consensus criteria. Nine of 10 patients treated with rituximab responded to this therapy.

Conclusion: Ophthalmic involvement is a common manifestation of IgG4-RD and can affect nearly every anatomic structure of the orbit. Consideration of IgG4-RD and accurate diagnosis by biopsy have important implications for prognosis and treatment following the distinction of this condition from Sjögren syndrome (SjS), granulomatosis with polyangiitis (GPA, formerly Wegener's), sarcoidosis, lymphoma, infection, and other disorders. Rituximab holds promise as an effective steroid-sparing agent or therapy for steroid-resistant cases.

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Antibodies Against Drp-4 and Macropain Subunit C2 As a Potential Marker Of Aosd. Niklas T. Baerlecken[1], Nils Pursche[2], Torsten Witte[3], Reinhold E. Schmidt[1], Marius Hoepfner[1], Frank Moosig[4], Wolfgang L. Gross[5], Eugen Feist[6] and Dirk Foell[7]. [1]Medical University Hannover, Hannover, Germany, [2]Medical University of Hannover, Hannover, Germany, [3]Medical University Hannover, Hanover, Germany, [4]University Hospital Schleswig Holstein and Klinikum Bad Bramstedt, Bad Bramstedt, Germany, [5]Medical University at Lubeck, Lubeck, Germany, [6]Charite University Hospital, Berlin, Germany, [7]University of Muenster, Muenster, Germany.

Background/Purpose: Making the diagnosis of adult-onset Still's disease (AOSD) is mainly based on the exclusion of inflammatory, infectious and malignant diseases. There are no specific clinical or laboratory findings for AOSD. Therefore, we aimed to identify new autoantibodies as diagnostic tools for AOSD.

Methods: As a screening procedure, we studied sera of 3 patients with AOSD using a protein array loaded with more than 28000 human recombinant proteins (imagenes biolifesciences, Berlin). Sera of patients with spondyloarthritis (SpA), rheumatoid arthritis (RA), eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis (GPA), HIV infection, B-NHL, chronic regional pain syndrome, giant cell arteritis (GCA), polymyalgia rheumatica (PMR), multiple sclerosis, osteoarthritis, Takayasu arteritis and sarcoidosis served as controls.

In the next step, we next established ELISAs in order to measure the respective autoantibodies in larger patient numbers.

Results: Using the protein array, we detected IgG antibodies against the two new autoantigens Macropain subunit C2 and DRP-4 in 2/3 AOSD patients, respectively, but in none of the 50 controls.

Using the ELISA, we measured autoantibodies binding to peptides of Macropain subunit C2 and Dihydropyrimidinase-related protein 4 (DRP-4) in the sera of patients with AOSD and other inflammatory disorders. The results are summarized in the table (AOSD* = patients with active AOSD before the onset of treatment, systemic JIA = systemic juvenile idiopathic arthritis, PsoA = psoriatic arthritis, BD = blood donors):

	AOSD (n=78)	AOSD* (n=39)	Systemic JIA (n=50)	SpA/ PsoA (n=58)	RA (n=66)	GPA (n=29)
MP + DRP-4	43%	56%	0%	19%	5%	10%
MP	54%	59%	0%	24%	9%	10%
DRP-4	43%	56%	3%	28%	8%	10%

	PMR/ GCA (n=60)	Sjögren's syndrome (n=29)	SLE (n=38)	febrile infections (n=63)	Malignant Disease (n=37)	BD (n=147)
MP + DRP-4	15%	0%	5%	18%	3%	1%
MP	22%	0%	11%	21%	3%	1%
DRP-4	20%	3%	8%	21%	5%	2%

Conclusion: The new autoantibodies against Macropain subunit C2 and DRP-4 are associated with AOSD and may be useful as a diagnostic tool of AOSD. In addition, these markers clearly differentiate AOSD from systemic juvenile idiopathic arthritis.

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Serum Leucine-Rich Alpha-2 Glycoprotein As a Marker For Disease Activity In Adult-Onset Still's Disease. You-Jung Ha[1], Jung-Soo Song[2], Eun-Jin Kang[3], Sang-Won Lee[1], Yong-Beom Park[1], Soo-Kon Lee[1] and Sang Tae Choi[2]. [1]Yonsei University College of Medicine, Seoul, South Korea, [2]Chung-Ang University College of Medicine, Seoul, South Korea, [3]Busan Medical Center, Busan, South Korea.

Background/Purpose: Leucine-rich α2-glycoprotein (LRG) is a plasma protein which contains leucine-rich repeats. Though physiological functions of LRG have not been clarified yet, it has been reported that LRG could be a marker of granulocytic differentiation and its expression was up-regulated during neutrophil differentiation. Serum LRG levels were significantly elevated in some chronic inflammatory diseases such as ulcerative colitis and rheumatoid arthritis. However, there are no studies about the association between serum LRG level and disease activity and severity in patients with adult-onset Still's disease (AOSD). This study aimed to investigate whether the serum LRG level is elevated in AOSD patients and its correlation with disease activity and severity.

Methods: We enrolled 39 patients with AOSD and 39 age- and sex- matched healthy controls. Forty-five serum samples were obtained from patients with AOSD during active or inactive disease and were assayed for LRG by enzyme-linked immunosorbent assay (ELISA). Clinical and laboratory data related to disease activity were collected at the same time. Disease severity was determined by modified Pouchot's score.

Results: Serum LRG concentrations were significantly elevated in AOSD patients compared with healthy control (126.2 $\pm$ 40.9 ng/mL vs 22.4 $\pm$ 6.2 ng/mL, $p < 0.001$). Patients with active AOSD had a significantly higher LRG level than those with inactive disease (132.9 $\pm$ 34.6 ng/mL vs 67.1 $\pm$ 50.2 ng/mL, $p = 0.009$). Serum LRG showed modest correlation with C-reactive protein ($\gamma = 0.349$, $p = 0.029$), serum lactate dehydrogenase ($\gamma = 0.360$, $p = 0.031$) and ferritin ($\gamma = 0.533$, $p < 0.001$), but not with white blood cell counts or erythrocyte sedimentation rate. Serum LRG did not show correlation with AOSD systemic scores, reflecting disease severity. Serum LRG levels decreased significantly after treatment in all 6 active patients with AOSD who had follow-up evaluations ($p = 0.007$).

Conclusion: Serum LRG levels were increased in patients with AOSD and well correlated with disease activity measures. These findings suggest that plasma LRG may be a useful serologic marker for monitoring disease activity of AOSD.

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Efficacy Of Tocilizumab In Refractory Adult-Onset Still's Disease: Multicenter Study Of 32 Patients. Francisco Ortiz-Sanjuan[1], Ricardo Blanco[2], Javier Narvaez[3], Esteban Rubio Romero[4], Alejandro Olivé[5], Santos Castañeda[6], Adela Gallego Flores[7], M. Victoria Hernández[8], Cristina Mata[1], Inmaculada Ros Vilamajo[9], Alberto Sifuentes Giraldo[10], M Caracuel[11], Mercedes Freire[12], Catalina Gómez Arango[13], José Llobet[14], Sara Manrique Arija[15], Carlos Marras[16], Concepcion Moll Tuduri[17], Chamaida Plasencia Rodriguez[18], Rosa Roselló[19], Ana Urruticoechea[20], Maria Luisa Velloso Feijoo[21], Javier Loricera[1], Vanesa Calvo-Rio[1] and Miguel A González-Gay[1]. [1]Hospital Universitario Marqués de Valdecilla. IFIMAV. Santander. Spain, Santander, Spain, [2]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain, [3]Hospital Universitario de Bellvitge, Barcelona, Spain, [4]HU Virgen del Rocío, Sevilla, Spain, [5]Hospital Universitario Germans Trias i Pujol, Badalona, Spain, [6]Hospital Universitario de La Princesa, IIS Princesa, Madrid, Spain, [7]Hospital de Mérida, Mérida, Spain, [8]Hospital Clinic, Barcelona, Spain, [9]Hospital Son Llàtzer, Palma de Mallorca, Spain, [10]H Ramón y Cajal, Madrid, Spain, [11]Hospital de Córdoba., Córdoba, Spain, [12]Hospital Universitario Juan Canalejo. La Coruña, La Coruña, Spain, [13]HU Basurto, Bilbao, Spain, [14]H Sant Pau, Barcelona, Spain, [15]HRU Carlos Haya, Málaga, Spain, [16]Hospital Universitario Virgen de la Arrixaca, Murcia, Spain, [17]H Mateu Orfila, Mahón, Spain, [18]HU La Paz, Madrid, Spain, [19]H San Jorge, Huesca, Spain, [20]Hospital Can Misses, Ibiza, Spain, [21]H Valme, Sevilla, Spain.

Background/Purpose: Adult-onset Still's disease (AOSD) is frequently refractory to standard immunosuppressive drugs and it may require biological therapy. Tocilizumab (TCZ) has demonstrated efficacy in clinical isolated cases or in small series. We assessed the efficacy of TCZ in AOSD.

Methods: Multicenter study of 32 patients with AOSD from 20 hospitals diagnosed according to Yamagouchi's criteria (J Rheumatol 1992; 19:424). TCZ was used due to lack of efficacy to standard synthetic immunosuppressive drugs or lack of adequate response to at least 1 biologic agent.

Results: The 32 patients (24 women/ 8 men), had a mean age of 37.9±16.4 (range 16–74) and an average duration of AOSD of 5.6±5.0 years (range 0.1–17) before TCZ onset. In addition to steroids, they had previously received the following drugs: Methotrexate (29 patients), Anakinra (14), Etanercept (7), Adalimumab (6) and Infliximab (4). TCZ standard dose was 8 mg/k/iv/4 weeks.

At TCZ onset, the most frequent manifestations were joint (31 cases), cutaneous (17) and fever (19), along with increase of ESR or CRP (25 cases), anemia (14) or leucocytosis (18). Following TCZ clinical and analytical response was observed from the beginning (1st month) that was maintained over time **(TABLE)**.

	Basal	Month 1	Month 3	Month 6	Month 12
Joint manifestations, %	96.9%	68.8%	43.8%	25%	31.3%
Fever, %	59.4%	6.3%	6.3%	3.1%	3.1%
Cutaneous manifestations, %	53.1%	15.6%	12.5%	6.3%	6.3%
Leukocyte/mm3, mean ±SD	13650 ± 5978.4	8709 ± 4242.2	7898 ± 4188.7	7364 ± 3384.5	8630 ± 3709.5
ESR, mean±SD (mm/1st/hour)	49.8 ± 18,1	8.8 ± 10.8	5.9 ± 5.3	6.2 ± 5.7	8.0 ± 9.5
CRP, mg/dL mean±SD	23.2 ± 35.8	3.1 ± 6.0	0.8 ± 2.1	0.9 ± 2.7	0.8 ± 1.6
Prednisone dosage, mean±SD	15.2 ± 0.3	9.3 ± 7.0	6.0 ± 5.1	4.5 ± 5.4	4.8 ± 8.2
Prednisone dosage, median [IQR]	12.5 [7.5–20]	7.5 [5–15]	5 [2.5–10]	2.5 [0–7.5]	1.3 [0–7.5]

After a mean follow-up of 18.4 ±12.5 months, skin manifestations disappeared in 16 of 17 of the patients (94.1%), fever in 18 of 19 (94.7%) and joint manifestations in 25 of 31 (80.6%). In the laboratory findings, there was also improvement in most cases with normalization of the leucocytosis in 11 of 18 (61.1%) patients, anemia in 13 of 14 (92.9%), ESR in 18 of 24 (75 %), CRP in 22 of 25 (88%), hepatic enzymes (AST/ALT) in 3 of 4 (75 %) and ferritin seric levels in 11 of 14 (78.6%). The median [IQR] dose of prednisone was reduced from 15.1 [7.5–20] to 6.1 [0.0–7.5] mg/day.

Conclusion: In refractory AOSD, TCZ yields early and maintained clinical-laboratory improvement, even in cases that are refractory to other biologic agents. Although TCZ shows global efficacy, joint manifestations are more refractory than systemic manifestations.

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Sirolimus Plus Prednisone For Erdheim-Chester Disease: A Pilot Trial. Davide Gianfreda[1], Federico Alberici[1], Maricla Galetti[2], Maria Nicastro[2], Carlo Buzio[1] and Augusto Vaglio[1]. [1]University of Parma, Parma, Italy, [2]Nephrology University of Parma, Parma, Italy.

Background/Purpose: Erdheim-Chester disease (ECD) is an extremely rare form of non-Langerhans cell histiocytosis. The pathogenesis of ECD is unclear: while most authors suggest the hypothesis of an inflammatory disease, others claim it is a neoplastic disorder. ECD often has a fatal course (3-year mortality 25–60%) and has no established treatment. Interferon-α is often used but it has severe toxicity and poor efficacy on CNS and cardiovascular lesions.

The mTOR inhibitor sirolimus (SRL) is an immunosuppressive drug with known anti-neoplastic properties. We tested the efficacy and safety of prednisone (PDN) and SRL in a series of patients with multisystemic, active ECD. We also assessed mTOR activity in patients' biopsies as a potential predictor of treatment efficacy.

Methods: We enrolled all patients with active, multisystemic ECD (either at first diagnosis or with progressive disease refractory to other treatments) referred to our Department between 2003 and 2011.

PDN was given at the initial dose of 0.75 mg/kg/day for 1 month, tapered to 2.5–5 mg/day over 6 months; SRL was given at a daily dose of 2–3 mg, with a target trough level of 8–10 ng/mL. If disease stabilization or remission was achieved, treatment was continued chronically.

Where available, frozen tissue biopsies were used to assess mTOR activity: for this purpose, the levels of phospho-p70S6K (Thr389) and phospho-mTOR (ser 2448) in total proteins extracted from the biopsies were determined by Western blotting.

Results: Nine consecutive ECD patients were enrolled; six were newly diagnosed and untreated, the remaining three were refractory to previous treatments (interferon-α, PDN and colchicine, PDN and cyclophosphamide). The median follow-up from diagnosis was 41 months (range 12–164). At the end of the follow-up, seven patients were alive and experienced quiescent disease; of the remaining two, one died 12 months after diagnosis because of progressive CNS involvement, and one 25 months after diagnosis because of small cell lung cancer.

One of two patients had a complete cardiac response (complete remission of pericarditis), 1/2 a complete response in the lungs and 2/5 a complete remission in cutaneous lesions. Partial responses were observed at the following sites: long bones in 2/8 cases, CNS in 1/2 cases, retroperitoneum-perirenal space in 5/7 cases, hypothalamic-pituitary axis in 1/4 cases, skin in 1/5 cases. One patient had a progression in retroperitoneal involvement.

Treatment-related toxicity was mild; only one patient had to stop treatment because of sirolimus-related pneumonia.

The three available biopsies (2 retroperitoneal, 1 skin) exhibited high levels of phospho-p70S6K and phospho-mTOR, confirming that the mTOR pathway is activated in ECD. Given the paucity of available frozen tissue samples, we could not evaluate whether mTOR activity was a predictor of response to SRL.

Conclusion: The combination of PDN and SRL is a potential treatment for multisystemic ECD; it usually induces disease stabilization and in some cases objective responses, and has a good tolerability. The mTOR pathway seems to be activated in ECD lesions; further studies are needed to explore whether phospho-p70S6K and phospho-mTOR tissue expression predict response to SRL therapy.

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Pediatric Rheumatology: Clinical and Therapeutic Disease: Juvenile Idiopathic Arthritis
Sunday, October 27, 2013, 2:30 PM–4:00 PM

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Predictors and Sustainability Of Clinical Inactive Disease In Polyarticular Juvenile Idiopathic Arthritis Given Aggressive Therapy Very Early In The Disease Course. Carol A. Wallace[1], Edward H. Giannini[2], Steven J. Spalding[3], Philip J. Hashkes[4], Kathleen M. O'Neil[5], Andrew S. Zeft[3], Ilona S. Szer[6], Sarah Ringold[7], Hermine I. Brunner[2], Laura E. Schanberg[8], Robert P. Sundel[9], Diana Milojevic[10], Marilynn G. Punaro[11], Peter Chira[12], Beth S. Gottlieb[13], Gloria C. Higgins[14], Norman T. Ilowite[15], Yukiko Kimura[16], Anne Johnson[2], Bin Huang[17] and Daniel J. Lovell[2]. [1]Seattle Childrens Hosp & Research Institute, Seattle, WA, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]The Cleveland Clinic, Cleveland, OH, [4]Shaare Zedek Medical Center, Jerusalem, Israel, [5]Riley Hospital for Children, Indianapolis, IN, [6]Rady Childrens Hosp San Diego, San Diego, CA, [7]Seattle Children's Hospital, Seattle, WA, [8]Duke University Medical Center, Durham, NC, [9]Boston Children's Hospital and Harvard Medical School, Boston, MA, [10]University of California, San Francisco, San Francisco, CA, [11]Texas Scottish Rite Hospital, Dallas, TX, [12]Indiana University School of Medicine, Riley Hospital for Children, Indianapolis, IN, [13]Cohen Children's Medical Center of New York, New Hyde Park, NY, [14]Nationwide Childrens Hosp, Columbus, OH, [15]The Children's Hospital at Montefiore, Bronx, NY, [16]Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [17]Cincinnati Children's Hospital Medical Center/ University of Cincinnati School of Medicine, Cincinnati, OH.

Background/Purpose: The double-blind, randomized placebo-controlled Trial of Early Aggressive Therapy in Polyarticular Juvenile Idiopathic Arthritis (TREAT) compared the ability of 2 aggressive treatment regimens to produce clinical inactive disease (CID) within 6 mos of starting therapy. An exploratory phase lasting up to 1 year from baseline determined if patients could achieve CID after switching to the more aggressive treatment arm (M-E-P: etanercept 0.8 mg/kg/wk, MTX 0.5 mg/kg/wk given subcutaneously, prednisolone 0.5 mg/kg/d tapered to zero by 17 wks) from the less aggressive arm (MTX: MTX as in the M-E-P Arm, placebo prednisolone, placebo etanercept), and achieve clinical remission on medication (CRM; 6 continuous mos of CID). The purposes of this analysis were to determine lapsed time on-therapy to the first occurrence, and sustainability of CID and if predictors of CID exist.

Methods: Eighty-five patients aged 2–17 yrs with active RF (+) or (−) polyarticular JIA (poly-JIA) less than 12 mos in duration (median 4.2 mos) were randomized to either M-E-P (N=42) or MTX (N=43) and assessed for CID using the Wallace Criteria at mos 1, 2, 4, 5, 6, 7, 8, 10 and 12 mos or discontinuation. Patients in either group who failed to achieve an ACR Pedi 70 at 4 mos, or CID at 6 mos were switched to open-label M-E-P for the remainder of the study. Descriptive measures, the Mann-Whitney U and Fisher's Exact tests were the chief statistical methods.

Results: CID was observed at least once in 30 (71%) of those who started on M-E-P and in 28 (65%) of MTX starts (17 of these 28 achieved CID only after switching to open-label M-E-P). Median number of days on aggressive therapy until the first occurrence of CID was 168.5 and 192 for those who started M-E-P and MTX groups respectively. M-E-P starts spent a median of 139.5 (42%) days of follow-up with CID, compared to a median of 79 (24%) days for MTX starts (p=0.016). M-E-P starts had CID at 117 of 347 (34%) follow-up visits while MTX starts had CID at 81 of 337 (24%) visits. When data were combined from the blinded and open-label (all patients receiving M-E-P) phases, CID was observed at 154 of 481 (32%) visits by patients on M-E-P, compared to 43 of 203 (21%) visits while receiving MTX alone.

Baseline characteristics were not statistically predictive of CID except for disease duration prior to enrollment. Patients with duration ≤3 mos at enrollment had CID at a median of 40% of visits, while those with disease >3 mos had CID for a median of only 11% of visits (p<0.0001).

Among 49 patients who achieved an ACR Pedi 70 at 4 mos, 42 (86%) attained CID, compared to 16 of 36 (44%) who failed to achieve the early response (p=0.0001). All 12 patients (9 M-E-P and 3 MTX) who achieved CRM met the ACR Pedi 70 at 4 mos.

Conclusion: Aggressive therapy given early in the disease course of poly-JIA results in a large proportion of patients achieving CID within 12 mos. There is a tendency for a combination of an anti-TNF agent, MTX and prednisolone to produce more sustainable CID than does high dose MTX monotherapy. A short disease duration prior to start of aggressive therapy and attainment of an ACR Pedi 70 by 4 mos are significant predictors of achieving sustained CID.

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Efficacy and Safety Of Tocilizumab In Patients With Polyarticular-Course Juvenile Idiopathic Arthritis: 2-Year Data From Cherish. Hermine I. Brunner[1], Nicolino Ruperto[2], Zbigniew Zuber[2], Rubén J. Cuttica[3], Ricardo Xavier[2], Inmaculada Calvo[2], Nadina Rubio[2], Ekaterina Alekseeva[2], Vyacheslav Chasnyk[4], Jose Chavez[2], Gerd Horneff[3], Violetta Opoka-Winiarska[2], Pierre Quartier[2], Alberto Spindler[2], Caroline Keane[5], Kamal N. Bharucha[6], Jianmei Wang[5], Daniel J. Lovell[1], Alberto Martini[2] and Fabrizio De Benedetti[7]. [1]PRCSG, Cincinnati, OH, [2]PRINTO, Genoa, Italy, [3]Pediatric Rheumatology International Trials Organization (PRINTO)-Istituto Gaslini, Genova, Italy, [4]Saint-Petersburg State Pediatric Medical University, Saint-Petersburg, Russia, [5]Roche, Welwyn Garden City, United Kingdom, [6]Genentech, South San Francisco, CA, [7]IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy.

Background/Purpose: Efficacy and safety of tocilizumab (TCZ), an interleukin-6 receptor inhibitor, were previously demonstrated at week 40 of CHERISH, a phase 3 trial in patients with polyarticular-course juvenile idiopathic arthritis (pcJIA).[1] The purpose of this analysis was to investigate the efficacy and safety of TCZ over 104 weeks of treatment in pcJIA.

Methods: Patients 2–17 years old with ≥6 months' active pcJIA who failed methotrexate received open-label (OL) TCZ (weight ≥30 kg, 8 mg/kg [n=119]; weight <30 kg, randomized [1:1] to 8 [n=34] or 10 [n=35] mg/kg) every 4 weeks for 16 weeks. Patients with JIA American College of Rheumatology (ACR)30 response or better at week 16 entered a 24-week double-blind withdrawal period and were randomized (1:1) to placebo or continuation with TCZ. Patients with JIA ACR30 flare or who completed the withdrawal period entered an OL extension through week 104.

Results: One hundred eighty-eight patients entered the lead-in period, 166 entered the withdrawal period, 160 entered the OL extension period, and 155 completed 104 weeks. In patients who received TCZ throughout the study, JIA ACR responses and improvement in JIA ACR core components (Table) were maintained through week 104. The safety population comprised 188 patients with 307 patient-years (PY). Rates/100PY of adverse events (AEs) and serious AEs (SAEs) were 406.5 and 11.1, respectively; infections were the most common AE (151.4) and SAE (5.2). Alanine aminotransferase and aspartate aminotransferase elevations ≥3× upper limit of normal occurred in 6.4% and 2.7% of patients, respectively. Grade 3 neutropenia and grade 2/3/4 thrombocytopenia occurred in 5.9% and 1.6% of patients, respectively. Low-density lipoprotein cholesterol ≥110 mg/dL occurred in 16.2% of patients.

Table. JIA ACR50/70 Responses and Percentage Change From Baseline in Components,[a] mean ± SD

	All TCZ (N = 82)	
	Week 40	**Week 104**
JIA ACR70 responders,[b] n (%)	65 (79.3)	71 (86.6)
JIA ACR90 responders,[b] n (%)	41 (50.0)	58 (70.7)
ACtive joints (0–71)	−82.4 ± 24.9	−87.7 ± 27.1
Joints with limitation in ROM (0–67)	−73.5 ± 30.7	−81.3 ± 31.7
Patient global[c] (VAS 0–100 mm)	−62.5 ± 76.3	−75.4 ± 43.8
Physician global (VAS 0–100 mm)	−85.3 ± 16.8	−89.7 ± 23.7
CHAQ-DI (0–3)	−66.0 ± 44.7	−76.7 ± 34.7
ESR (mm/h)	−76.5 ± 22.0	−76.2 ± 27.3

[a] Patients who withdrew are excluded.
[b] Patients who withdrew due to nonsafety reasons are nonresponders. Patients who withdrew due to safety are included using last observation carried forward.
[c] Parent rated.
CHAQ-DI, Childhool Health Assessment Questionnaire Disability Index; ESR, erythrocyte sedimentation rate; ROM, range of motion; VAS, visual analog scale.
Crude incidence rates for ACS in the cohorts

Conclusion: Efficacy of TCZ was maintained through 2 years of treatment in patients with pcJIA, with no change in safety profile from that reported previously.[1]

Reference:

1. Brunner H et al. *Arthritis Rheum* 2012;64:2012.

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Methotrexate Polyglutamates in Erythrocytes Are Associated With Lower Disease Activity in Juvenile Idiopathic Arthritis Patients. Maja Bulatovic Calasan[1], Ethan den Boer[2], Maurits C.F.J. De Rotte[2], S.J. Vastert[1], Sylvia Kamphuis[3], Robert De Jonge[2] and Nico M. Wulffraat[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Erasmus Medical Center, Rotterdam, Netherlands, [3]Eramus MC Sophia Children's Hospital, Rotterdam, Netherlands.

Background/Purpose: Methotrexate polyglutamates (MTX-PG) could be biomarkers of MTX response and adverse effects and could thus be used

as a therapeutic drug monitoring (TDM) tool to steer tailor-made therapeutic decisions. The aim of this study was to determine association of erythrocyte MTX-PG with disease activity and adverse effects in a prospective juvenile idiopathic arthritis (JIA) cohort.

Methods: One hundred thirteen JIA patients were followed from MTX start until 12 months. Erythrocyte MTX-PGs with 1 to 5 glutamate residues were measured at 3 months with tandem mass spectrometry. The outcomes were Juvenile Arthritis Disease Activity Score (JADAS)-27 and adverse effects. To determine associations of MTX-PGs with JADAS-27 at 3 months and during one year of MTX treatment, linear regression and linear mixed model analyses were used. To determine associations of MTX-PGs with adverse effects during one year of MTX treatment, logistic regression was used. Analyses were corrected for, JADAS-27 at baseline and co-medication.

Results: Median JADAS-27 decreased from 12.7 (IQR: 7.8–18.2) at baseline to 2.9 (IQR: 0.1–6.5) at 12 months. Higher concentrations of MTX-PG3 (β: −0.006, p=0.005), MTX-PG4 (β:−0.015, p=0.004), MTX-PG5 (β: −0.051, p=0.011) and MTX-PG3–5 (β: −0.004, p=0.003) were associated with lower disease activity at 3 months. Higher concentrations of MTX-PG3 (β: −0.005, p=0.028), MTX-PG4 (β: −0.014, p=0.014), MTX-PG5 (β: −0.049, p=0.023) and MTX-PG3–5 (β: −0.004, p=0.018) were associated with lower disease activity over one year. None of the MTX-PGs was associated with adverse effects.

Conclusion: In the first prospective study in JIA, long-chain MTX-PGs were associated with lower JADAS-27 at 3 months and during one year of MTX treatment. Erythrocyte MTX-PG could be a plausible candidate for therapeutic drug monitoring of MTX in JIA.

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Efficacy and Safety of Adalimumab in Pediatric Patients With Enthesitis Related Arthritis. Rubén Burgos-Vargas[1], Shirley M.L. Tse[2], Gerd Horneff[3], Aileen L. Pangan[4], Kristina Unnebrink[5] and Jaclyn K. Anderson[6]. [1]Hospital General de Mexico, Universidad Nacional Autonoma de Mexico, Mexico City, Mexico, [2]University of Toronto, The Hospital for Sick Children, Toronto, ON, [3]Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany, [4]AbbVie Inc., North Chicago, IL, [5]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany, [6]AbbVie, North Chicago, IL.

Background/Purpose: Enthesitis related arthritis (ERA) is a subcategory of juvenile idiopathic arthritis (JIA) which primarily affects peripheral joints and entheses but also can involve the sacroiliac joints and spine. It causes long-term effects on both physical and quality aspects of a child's life. Adalimumab (ADA) has been previously demonstrated to be effective in polyarticular JIA. The purpose of this study was to evaluate the efficacy and safety of adalimumab compared to placebo in children and adolescents with ERA.

Methods: This is a phase 3, multicenter, randomized, double-blind (DB) study in patients (pts) aged ≥6 to <18 years (yr) with ERA (ILAR criteria) with active disease not responsive to ≥1 nonsteroidal anti-inflammatory drug and ≥1 disease-modifying antirheumatic drug. Active disease was defined as ≥3 active joints (swelling or loss of motion + pain/tenderness) and enthesitis in ≥1 location. Pts were randomized 2:1 to receive blinded ADA (24 mg/m^2 BSA up to 40 mg every other week (wk) [eow]) or placebo (PBO) for 12 wks followed by open-label (OL) ADA eow up to 144 wks. The primary endpoint was % change from baseline (BL) in the number of active joints with arthritis (AJC) at wk 12. Secondary variables assessed included enthesitis count (EC), tender and swollen joint counts, and American College of Rheumatology (ACR) Pediatric (Pedi) 30/50/70 responses. Results are summarized through 52 wks of treatment. Safety was assessed in terms of adverse events (AE).

Results: 46 pts were randomized (31 to ADA, 15 to PBO). No pts discontinued during the DB period; however, 7 pts early escaped to OL ADA. Mean age was 12.9±2.9 yrs. At BL, mean duration of ERA symptoms was 2.6±2.3 yrs; mean AJC was 7.8±6.6, and mean EC was 8.1±8.4. The % change from BL at wk 12 in AJC was greater in the ADA group vs. PBO (−62.6±59.5 vs −11.6±100.5, P=0.039). Most secondary variables showed numerically greater, but not statistically significant improvement at wk 12 in favor of ADA vs. PBO (Table). Treatment response was maintained with continued ADA therapy up to 52 wks (% change from BL at wk 52 in AJC, −88.7±26.1). During the DB period AE incidence rates were similar [ADA/PBO (%)]: any AE (67.7/53.3), serious AE (3.2/0, 1 pt in the ADA group [abdominal pain and headache]), and infectious AEs (29.0/20.0). Among pts who received at least 1 dose of ADA through wk 52, any AE, serious AEs, and infectious AEs were reported in 91.3%, 10.9%, and 76.1%, respectively. No deaths, TB, or malignancies were reported.

At Week 12		ADA (N=31)	PBO (N=15)
Change from Baseline[a] (mean ± SD)	# enthesitis sites (0-35)	−4.4 ± 6.2	−2.7 ± 5.0
	Tender joint count (0-72)	−7.9 ± 8.3	−4.5 ± 9.0
	Swollen joint count (0-68)	−3.5 ± 5.6	−2.4 ± 4.7
ACR Pedi Response[b] (n, %)	ACR Pedi30 responder	21 (67.7)	10 (66.7)
	ACR Pedi50 responder	20 (64.5)	7 (46.7)
	ACR Pedi70 responder	16 (51.6)	4 (26.7)

[a] LOCF. [b] NRI. SD, standard deviation.

Conclusion: ADA reduced the signs and symptoms of ERA at wk 12 and efficacy was sustained up to 52 wks. The safety profile observed in pediatric patients with ERA was consistent with that observed in children aged ≥4 years treated for polyarticular JIA.

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Recent Trends In Medication Usage for the Treatment of Juvenile Idiopathic Arthritis and the Influence of TNF Inhibitors. Melissa L. Mannion, Fenglong Xie, Jeffrey R. Curtis and Timothy Beukelman. University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: The pharmacologic management of JIA has changed dramatically with the advent of tumor necrosis factor inhibitors (TNFi), but the impact of TNFi on medication usage in routine clinical practice has not been well-studied. Using national administrative claims from a large commercial U.S. health insurer, we investigated the use of medications in the treatment of JIA over the last 8 years. We examined medication use by calendar year, as well as medication use before and after new TNFi use among individual patients.

Methods: Using data from January 2005 through September 2012, we identified children <17 years old with > 1 physician diagnosis code consistent with JIA. In the analyses of medication use by year, only subjects with full medical and pharmacy benefits for the entire enrollment period of the calendar year were included. Use of TNFi, methotrexate (MTX), non-steroidal anti-inflammatory drugs (NSAID), and oral glucocorticoids (GC) was determined using pharmacy and infusion claims. Significant changes in medication usage over time were evaluated with the Cochran-Armitage test for trend. New TNFi users were defined by no receipt of any TNFi in the 6 months immediately prior to starting. New TNFi users were required to have a minimum of 6 months of follow-up after starting TNFi, and only the earliest episode of new TNFi use for each patient was included. Among prevalent users of NSAID and GC, we used paired t-tests to compare the number of filled prescriptions for NSAID and the cumulative mean daily GC dose (in prednisone equivalents) in the 6 months before and after new TNFi use.

Results: Including all years of the study, we identified 4,261 individuals with ≥1 JIA diagnosis code. Their median age was 11 years (IQR 7–14) and 64% were female. The proportion of TNFi users increased during the study period from 8.7% in 2005 to 22.3% in 2012 (p<0.0001). Over the same time period, the proportion of MTX users increased from 18.4% to 23.2% (p=0.02), the proportion of NSAID users decreased from 49% to 40% (p=0.02), and the proportion of GC users was relatively unchanged (19.8% to 16.1%; p=0.4). We identified 344 new users of TNFi (70% etanercept, 19% adalimumab, 10% infliximab). Among 194 prevalent NSAID users, the number of NSAID prescriptions decreased in the 6 months following new TNFi use (mean 2.8 prescriptions before versus 2.0 after; p<0.0001). Among 126 prevalent GC users, the cumulative mean daily dose was significantly reduced in the 6 months following new TNFi use (mean decrease 3.4 mg/day; p<0.0001). Many new TNFi users (195/344, 57%) had not filled a prescription for MTX in the previous 6 months. Of these without recent MTX use, only 11% (21/195) used MTX in the 6 months following new TNFi use. Overall, 38% (129/344) had any concurrent MTX use in the 6 months following new TNFi use.

Conclusion: TNFi use in the treatment of JIA increased 2–3 fold over the last 8 years with a concurrent smaller increase in MTX use. New use of TNFi was associated with a reduction in the number of NSAID prescriptions and mean daily GC dose. The relatively small proportion of patients with recent or concurrent use of MTX around the time of new TNFi use suggests that TNFi may be replacing, rather than complementing, MTX therapy in many patients.

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Second TNF-Inhibitor Or Alternative Biologic In Juvenile Idiopathic Arthritis (JIA) Patients Failing a First TNF-Inhibitor. Kirsten Minden[1], Klaus Tenbrock[2], Gerd Horneff[3] and Hans-Iko Huppertz[4]. [1]pediatric rheumatology, Berlin, Germany, [2]University Aachen, Aachen, Germany, [3]Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany, [4]Prof. Hess Childrens Hospital, Bremen, Germany.

Background/Purpose: Patients with incomplete response to initial anti-TNF treatment often are switched to other biologic treatments. However, little is known about the efficacy of switching to a second anti-TNF or a non-TNF biologic treatment since comparative clinical trials are lacking.

Methods: Data of the German BIKER registry were used to analyse treatment response after switching from a TNF-inhibitor to a second TNF-inhibitor or to a non-TNF-inhibitor biologic. Efficacy analyses were performed with the patients′ disease activity assessed by the Juvenile Arthritis Disease Activity Score (JADAS)-10 and functional status assessed by the Childhood Health Assessment Score-Disability Index (CHAQ-DI) as outcomes.

Results: 1725 JIA patients receiving Etanercept (ETA) as first biologic were identified in the BIKER registry. 279 patients received a second biologic, which was again a TNF-inhibitor in 219 (Adalimumab (ADA) 190, Infliximab (INF) 30, Golimumab (GOL) 5,) and a non-TNF inhibitor biologic in 60 cases (Abatacept (ABA) 16, Anakinra (ANA) 31, Tocilizumab (TOC) 13). Switchers more often had systemic JIA (15.1% vs 6.6%; $p<0.001$; Odd-R 2.5(1.7–3.7)) but less often enthesitis related arthritis (ERA) (9.7% vs.15. 9%; $p=0.008$, Odd-R 0.6 (0.4–0.9)) than non-switchers. Comparison of JADAS10 at last follow up to start of ETA gave a marked improvement of disease activity while a considerable residual disease activity persisted. 215 JIA patients had follow up forms after switching to a second biologic enabling the analysis of efficacy. After switching the biologic agent, a decrease of disease activity parameters could be observed in all cohorts. At last follow up, lowest JADAS10 (mean±SD) was reached in the patient cohort switching from ETA to ADA (6.2±6.1) followed by INF (9.7±9.9) and TOC (10.2±7.2). Patients on ABA had higher JADAS10 (12.5±10.2) at last follow up (table 1). Also the CHAQ-DI decreased in all cohorts. Lowest CHAQ-DI (mean±SD) was reached in patients switching from ETA to INF (0.21±0.52) or ADA (0.29±0.46), followed by TOC (0.4±0.67) and ABA (0.73±0.78). Follow-up data from few patients only switching to GOL and from patients switching to ANA (all but 3 systemic JIA) were not shown.

Switching from Etanercept to:	Time of analysis	JADAS-10	CHAQ-DI
Adalimumab N=163	first on ETA	17.1+/−7.4	0.72+/−0.70
	last on ETA	8.4+/−7.0	0.40+/−0.54
	first on ADA	9.9+/−8,0	0.37+/−0.52
	last on ADA	6.2+/−6.1	0.29+/−0.46
Infliximab N=19	first on ETA	19.4+/−8.0	1.03+/0.71
	last on ETA	10.9+/−9.5	0.44+/−0.58
	first on IFN	10.7+/−9.2	0.47+/−0.66
	last on IFN	9.7+/−9.9	0.21+/−0.52
Tocilizumab N=20	first on ETA	18.9+/−6.0	0.93+/−0.85
	last on ETA	9.4+/−7.5	0.67+/−0.76
	first on TOC	13.2+/−10.0	0.75+/−0.72
	last on TOC	10.2+/−7.2	0.40+/−0.67
Abatacept N=13	first on ETA	18.3+/−6.−3	0.68+/−0.56
	last on ETA	13.5+/−10.5	0.43+/−0.62
	first on ABA	17.4+/−6.5	0.57+/−0.51
	last on ABA	12.5+/−10.2	0.73+/−0.78

Conclusion: JIA patients failing ETA can successfully be switched to another biologic. Interestingly, switching within the class of biologics, from a first TNF- to a second TNF-inhibitor also gave favourable results.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects I: Treatment Strategies in Rheumatoid Arthritis
Sunday, October 27, 2013, 2:30 PM–4:00 PM

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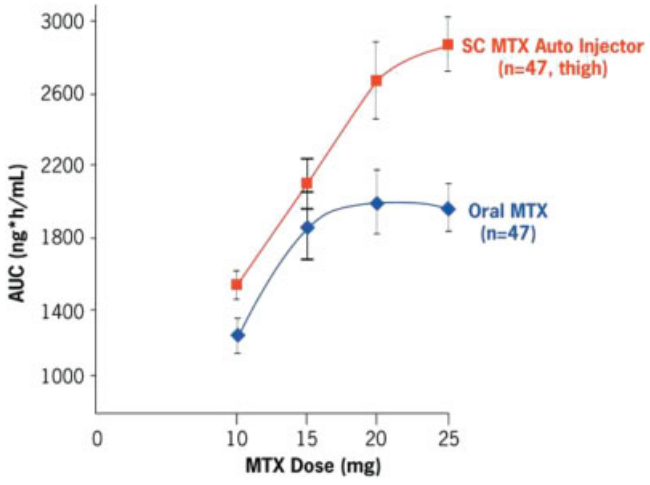
Drug Exposure Limitations of Oral Methotrexate (MTX) At Doses >15mgs May be Overcome By Using a Subcutaneous MTX Auto-Injector in Patients With Rheumatoid Arthritis (RA). Michael H. Schiff[1], Lee S. Simon[2], Bruce Freundlich[3], Jonathan Jaffe[4] and Kaushik J. Dave[4]. [1]University of Colorado, Denver, CO, [2]SDG LLC Consulting, West Newton, MA, [3]University of Pennsylvania, Philadelphia, PA, [4]Antares Pharma Inc, Ewing, NJ.

Background/Purpose: MTX is the cornerstone of RA therapy but absorption saturability limitations compromise oral MTX bioavailability (BA). Parenteral MTX exhibits a dose-proportional increase in exposure throughout the dosing range, possibly leading to better efficacy. Parenteral MTX is used by < 5% of U.S. clinicians due to lack of familiarity and availability and the challenges of self-injection. To address these issues, an investigational, single-use, self-administered SC MTX auto-injector (MTXAI) was developed with 10-, 15-, 20-, and 25-mg fixed doses. This study compares the relative BA of MTXAI vs oral MTX to demonstrate safety and tolerability of MTXAI in RA pts.

Methods: In this 12-week, open-label, crossover study, 49 adults with RA already receiving MTX for ≥3 months were given 10, 15, 20, or 25 mg MTX, based on their current dose and disease control, via random assignment (1:1:1) to oral MTX, MTXAI (abdomen), or MTXAI (thigh). Blood samples for PK analysis were collected predose and at 13 timepoints from 0.25 to 12 hours postdose and were analyzed by liquid chromatography-mass spectrometry. Mixed model analysis derived AUC, C_{max}, and T_{max} PK parameters. Dose-normalized parameter ratios were calculated. Safety was assessed by the incidence of treatment-emergent AEs (TEAEs), changes in safety laboratory parameters and vital signs, and administration site AEs.

Results: Mean age was 61 years; mean body mass index, 30.7 kg/m^2; and mean disease duration, 13 years; 63% of pts were female. PK analysis of MTXAI (thigh) vs. oral MTX showed that BA of MTXAI was consistently greater at all dose levels (Figure). MTXAI thigh and MTXAI abdomen PK measures were similar. Although oral MTX plateaued at 15 mg, MTXAI had no plateau, resulting in a higher exposure than comparable oral doses. Relative BA (AUC of MTXAI vs. oral MTX) at 10, 15, 20, and 25 mg were 121%, 114%, 131%, and 141%. Ratio of the dose-normalized AUC (0–24 h) and C_{max} of MTXAI vs. oral MTX were 127.61 (90%CI: 122.30–133.15) and 94.88 (90%CI: 87.95–102.37). Few TEAEs were reported with MTXAI; observed AEs were transient, manageable, and required no medical treatment. Two serious AEs were considered unrelated to treatment, including a death from a myocardial infarction in a 79-year-old man with cardiac history that occurred several weeks after the study. MTX and MTXAI were otherwise safe and well tolerated.



Conclusion: SC MTX delivered by auto-injector has a linear absorption compared to oral MTX, which plateaued at doses >15 mg. Pts receiving oral MTX with an inadequate clinical response may benefit from higher drug exposure levels by switching to SC MTX via MTXAI. This study confirms existing findings that higher systemic exposure to MTX is not associated with increased rates of AEs.

Disclosure: M. H. Schiff, Antares Pharma, 5; **L. S. Simon**, Savient Pharma, 1, See notes section for full list., 5; **B. Freundlich**, Antares Pharma, Celgene, BMS, 5, Pfizer Inc, 1; **J. Jaffe**, Antares Pharma, 3; **K. J. Dave**, Antares Pharma, 3.

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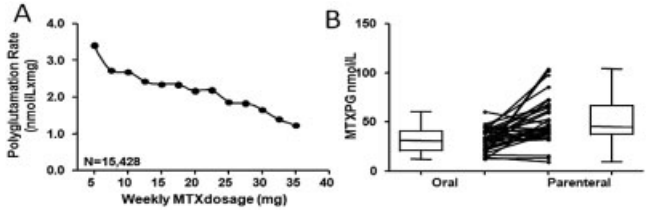
Methotrexate Exposure Assessment In Routine Clinical Rheumatology Practice: Effect Of Dosing and Route Of Administration On Polyglutamate Levels. Roy A. Kaplan[1], Brigid Freyne[2], Derren Barken[3] and Thierry Dervieux[3]. [1]Private Practice / Scripps Health, Encinitas, CA, [2]Private Practice, Murietta, CA, [3]Exagen Diagnostics, Vista, CA.

Background/Purpose: Large interpatient variability in Methotrexate (MTX) absorption and intracellular activation to methotrexate polyglutamates (MTXPGs) can explain, in part, the large spectrum of MTX response in patients with rheumatic diseases. We sought to identify the contributors to the large inter-subject variability in MTX exposure during the course of clinical care of patients with rheumatoid diseases.

Methods: Red blood cells (RBC) MTXPG levels were requested by treating physicians during the course of clinical care of patients with rheumatic diseases. Of all RBC MTXPG measurements performed, a total 15,428 measurements from 12,725 patients were available with weekly MTX dosing information as provided by the requesting physicians. In a subset of 2571 test results from 2261 patients the route of MTX administration (oral vs. parenteral) was provided. MTX RBC $MTXPG_3$ levels were measured in our accredited clinical laboratory using liquid chromatography and reported as nmol/L packed RBCs. A dose normalized polyglutamation rate defined as the amount of MTXPG produced per mg MTX administered (nmol/Lxmg) was calculated. To maintain patient privacy, all specimens were de-identified prior to the analysis. The statistical analyses consisted of multivariate linear regressions, and non parametric tests to assess differences between groups.

Results: There was a large interpatient variability in MTX polyglutamation. Median MTX dose administered was 17.5 mg/week (Interquartile [IQ] range: 15–20 nmol/L), median MTXPG levels were 36 nmol/L (IQ range: 21–54 nmol/L) and median MTX polyglutamation rate was 2.1 nmol/Lxmg (IQ: 1.2–3.0 nmol/Lxmg). The proportion of patients having undetectable MTXPG (<2 nmol/L), a potential indicator of non-adherence was 7.6%. Multivariate linear regression analysis revealed that lower MTX polyglutamation rates was associated with higher MTX dosage ($p<0.001$), lower patient age ($p<0.001$) and oral (vs. parenteral) administration of MTX ($p<0.01$) (Global $R^2=0.12$; $n=2571$). The impact of MTX dosing on MTX polyglutamation is highlighted in the Figure (panel A). In 31 patients who switched from oral to parenteral MTX without change in MTX dose (median 20 mg/week, range 15–25 mg), RBC MTXPG levels were determined 18 weeks (median) apart (range 8–65 weeks). The switch from oral to parenteral MTX was associated with a 1.4-fold increase in MTXPG levels (32 nmol/L [range 12–60 nmol/L] vs. 44 nmol/L [range 9–102 nmol/L]; $p<0.01$) (Figure, panel B).



Conclusion: These findings are consistent with the notion that MTX polyglutamation is a saturable process at higher MTX dosage. Switching from oral to parenteral administration of MTX produces higher levels of RBC MTX polyglutamates.

Disclosure: R. A. Kaplan, None; **B. Freyne**, None; **D. Barken**, Exagen, 3; **T. Dervieux**, Exagen, 3.

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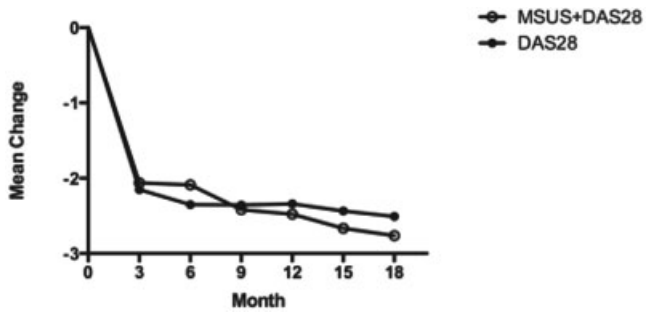
Targeting Ultrasound Remission In Early Rheumatoid Arthritis - Results Of The Taser Study. James Dale[1], Anne Stirling[2], Iain B. McInnes[1] and Duncan Porter[2]. [1]University of Glasgow, Glasgow, United Kingdom, [2]Gartnavel General Hospital, Glasgow, United Kingdom.

Background/Purpose: The TaSER study (NCT00920478) is an open label randomized clinical trial with blinded assessments of outcome. It was designed to test whether the efficacy of DAS28 driven treat-to-target DMARD strategies could be improved by the addition of regular musculoskeletal ultrasound (MSUS) disease activity assessment.

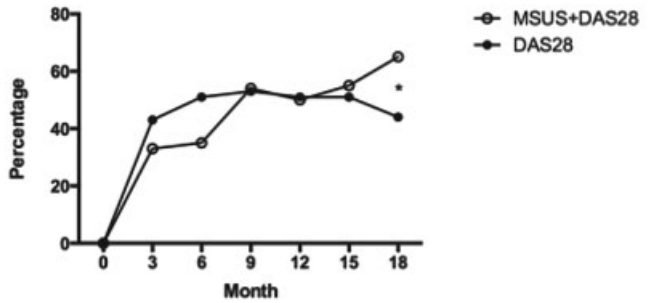
Methods: 111 untreated early UA/RA patients (symptom duration <1 year) were randomized to step-up DMARD escalation strategies guided by either DAS28 alone (target = DAS28<3.2) or DAS28+MSUS assessment of a limited joint set (target = PD signal in ≤1 joint). In the MSUS group, ultrasound assessment was undertaken in patients in LDAS, or moderate DAS but with minimal synovitis ($28SJC^2 1$). The follow-up period was 18 months. In the first 3 months both groups received identical treatment. Thereafter, treatment was escalated whenever the appropriate target was not achieved; through the addition of new DMARDs, DMARD dose optimisation, and/or IA/IM steroid. The sequence of DMARD escalation was: MTX □ MTX/SSZ/HCQ □ scMTX/SSZ/HCQ □ etanercept/scMTX/SSZ/HCQ.

Outcomes were assessed every 3 months by a metrologist who was blinded to randomization group. The primary clinical outcome was the mean improvement in DAS44. Secondary outcome measures included: mean improvement in ACR core set variables and DAS44 remission rate. Radiological outcomes included the MRI RAMRIS score and Total Sharp Score (results still to be analysed).

Results: 110 (99%) patients fulfilled 2010 ACR/EULAR RA classification criteria. Both groups were well matched for disease duration (median 4m), baseline DAS (4.4), ACPA+ve (60%) and HAQ (1.6 v 1.5). The DAS28 group contained a higher proportion of females (60% vs 78%, p 0.031). Both groups experienced significant improvements in DAS44 (mean change in DAS44 −2.51 [DAS28] vs −2.76 [MSUS]; 95%CI −0.84, 0.33; p 0.39) and HAQ (−0.79 v −1.06; 95%CI −0.57, 0.031: p0.08). The DAS28 group had a numerically higher rate of DAS44 remission after 3 months (43% v 33%; p=0.32). However, after 18 months, more patients in the MSUS groups had attained DAS44 remission (44% v 65%; p=0.046). There was no difference in DAS44, HAQ or ACR core set variables at any time point.



Graph 1. Mean change in DAS44 from baseline



Graph 2. Proportion of patients achieving DAS44 remission (* $p<0.05$)

Conclusion: Both groups exhibited similar, very robust improvements in clinical outcomes. MSUS disease activity assessment was not associated with improved clinical outcomes except a higher rate of DAS44 remission after 18 months.

Disclosure: J. Dale, Pfizer Inc, 2; **A. Stirling**, None; **I. B. McInnes**, Pfizer Inc, 2, Astra Zeneca, 2, UCB, 5, BMS, 2, Pfizer Inc, 5, Astra Zeneca, 5; **D. Porter**, Pfizer Inc, 2, Medimmune, 5.

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Clinical and Radiological Outcomes Of Two Years Remission Steered Treatment In Early Arthritis Patients. L. Heimans[1], K.V.C. Wevers-de Boer[1], G. Akdemir[1], H.K Ronday[2], T.H.E. Molenaar[3], J. H. L. M. Van Groenendael[4], A.J. Peeters[5], I. Speyer[6], G. Collee[7], P.B. de Sonnaville[8], B.A. Grillet[9], T.W.J. Huizinga[1] and C.F. Allaart[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Haga Hospital, The Hague, Netherlands, [3]Groene Hart Hospital, Gouda, Netherlands, [4]Franciscus Hospital, Roosendaal, Netherlands, [5]Reinier de Graaf Gasthuis, Delft, Netherlands, [6]Bronovo Hospital, Den Haag, Netherlands, [7]MCH, The Hague, Netherlands, [8]Admiraal de Ruyter hospital, Goes, Netherlands, [9]Zorgsaam Hospital, Terneuzen, Netherlands.

Background/Purpose: To evaluate outcomes after 2 years of remission steered therapy in early arthritis patients.

Methods: 610 patients with early rheumatoid or undifferentiated arthritis (UA) were treated with methotrexate (MTX) and tapered high dose of prednisone. Patients in early remission (DAS<1.6) after 4 months, tapered prednisone to zero and when remission persisted after 8 months, also tapered MTX. Patients not in early DAS-remission were randomized to either MTX+hydroxychloroquine+sulphasalazine+prednisone (arm 1) or to MTX+adalimumab (arm2). Based on 4-monthly DAS evaluations, medication was restarted, increased or switched in case of no remission and tapered or stopped in case of remission. Proportions of DAS-remission, drug free remission (DFR) and radiological damage progression (increase Sharp-vanderHeijde Score ≥0.5) were analyzed separately for the treatment strategies and patients with RA and UA.

Results: 387 patients achieved early DAS-remission, 83 patients were randomized to arm 1 and 78 to arm 2 and 50 did not follow the protocol. After 2 years, 301/610 (49%) of all patients were in DAS-remission and 131/610 (21%) in DFR. Of the early remission group, 241/387 (62%) were in DAS-remission and 110/387 (28%) were in DFR. In arm 1, 22/83 (27%) were in DAS-remission compared to 24/78 (31%) in arm 2 (p=0.76), 7/83 (8%) were in DFR in arm 1 and 7/78 (9%) in arm 2 (p=0.90). Remission defined according to the proposed ACR/EULAR remission criteria was achieved in 138/610 (23%) patients; 117/387 (30%) in the early remission group, 2/83 (2%) in arm 1 and 14/78 (18%) in arm 2 (arm 1 vs. 2 p=0.001). There were no significant differences in DAS-remission rates between patients with RA (234/479, 49%) and patients with UA (64/122, 52%) (p=0.25). UA patients more often achieved DFR (41/122 (34%)) than RA patients (89/479 (19%), p<0.001). Over the first 2 years, DAS or HAQ were not significant different between arm 1 and 2 (mean difference (95%CI) DAS 0.01 (−0,2;0,2) and HAQ 0.1 (−0.1;0.2)).Of the total study population, 51/610 (8%) had radiological progression (increase SHS'0.5), in the early remission group 34/387 (9%) patients showed progression, in arm 1 9/83 (11%) and in arm 2 5/78 (6%) (p arm 1 vs. arm 2=0.31). Median (IQR) SHS progression in all groups was 0 (0-0).

	Early remission n = 387	Arm 1 n = 83	Arm 2 n = 78	p-value arm 1 vs. arm 2
Baseline				
Age in years, mean + SD	52 ± 14	49 ± 14	51 ± 14	0.20
Female, n (%)	240 (62)	64 (77)	58 (74)	0.68
ACPA positive, n (%)	225 (58)	40 (48)	37 (47)	0.99
RA(2010), n (%)	298 (77)	66 (80)	66 (85)	0.32
DAS, mean + SD	3.0 ± 0.8	3.6 ± 0.9	3.6 ± 1.0	0.91
HAQ, mean + SD	1.0 ± 0.7	1.4 ± 0.6	1.4 ± 0.6	0.47
Total SHS, median (IQR)	0 (0–0.5)	0 (0–0)	0 (0–0)	0.75
2 years				
DAS, mean + SD	1.3 ± 0.8	2.0 ± 0.7	1.9 ± 0.9	0.45
HAQ, mean + SD	0.4 ± 0.5	0.9 ± 0.7	0.8 ± 0.7	0.55
DAS-remission, n (%)	241 (62)	22 (27)	24 (31)	0.76
Drug free remission, n (%)	111 (29)	6 (7)	7 (9)	0.73
ACR/EULAR remission, n (%)	117 (30)	2 (2)	14 (18)	0.001
Total SHS, median (IQR)	0 (0–0.5)	0 (0–1.1)	0 (0–0)	0.12
SHS progression≥0.5, n (%)	34 (9)	9 (11)	5 (6)	0.31

Conclusion: Patients who achieved early remission after 4 months most often achieved (drug free) remission after 2 years. Patients in arm 1 and 2 achieved lower but comparable (drug free) DAS-remission rates, probably due to remission steered treatment adjustments. This may also explain negligible radiographic damage progression. These results suggest that there is a window of opportunity where effective anti-rheumatic therapy can induce lasting remission and non-progression.

Disclosure: L. Heimans, None; **K. V. C. Wevers-de Boer**, None; **G. Akdemir**, None; **H. K. Ronday**, None; **T. H. E. Molenaar**, None; **J. H. L. M. Van Groenendael**, None; **A. J. Peeters**, None; **I. Speyer**, None; **G. Collee**, None; **P. B. de Sonnaville**, None; **B. A. Grillet**, None; **T. W. J. Huizinga**, Tom WJ Huizinga has received lecture fees/consultancy fees from Merck, UCB, Bristol Myers Squibb, Biotest AG, Pfizer, Novartis, Roche, Sanofi-Aventis, Abbott, Crescendo Bioscience, Nycomed, Boeringher, Takeda, and Eli Lilly, 5; **C. F. Allaart**, None.

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A Strategy For Selecting Individuals With RA For Reduction Of Anti-TNF Therapy Using Combined Clinical and Ultrasound Assessment. Christopher R. Holroyd[1], Brian Davidson[1], Sarah Bennett[1], David Waghorn[1], Caron Underhil[1], Cyrus Cooper[2], Antonia Calogeras[1], Elaine M. Dennison[2], Nicholas C. Harvey[2], Ray Armstrong[1], Stephan Gadola[3] and Christopher J. Edwards[4]. [1]University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, [2]MRC Lifecourse Epidemiology Unit, Southampton, United Kingdom, [3]University of Southampton, Southampton, United Kingdom, [4]NIHR Wellcome Trust Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom.

Background/Purpose: Reducing the dose of biological therapy may be possible for patients with rheumatoid arthritis (RA) who have achieved remission or low disease activity (LDA). However, patients in clinical remission may have synovitis detectable by ultrasound (US) and continue to accrue damage. We aimed to develop a strategy using both clinical and US assessment in a biologics review clinic to increase the likelihood of selecting the correct patients for biological therapy dose reduction, thereby minimising the chance of damage in those with subclinical synovitis.

Methods: All patients with RA (ACR criteria) receiving biologic therapies were reviewed in a biologics review clinic. At each appointment, patients underwent DAS28 assessment and US of their MCPs, PIP(2–5) and wrist joints (Esoate Mylab70). Synovitis was detected by power doppler (PDUS) and scored on a 0–3 semi-quantitative scale. PDUS remission was defined as a score of 0. Patients in clinical and US remission (DAS28<2.6 & PDUS=0) had the dose of anti-TNF therapy reduced by a third (adalimumab (ADA) to 40mg 3 weekly, etanercept (ETN) to 50mg every 10 days, infliximab (INF) reduced to 2mg/kg per infusion, certolizumab (CZB) reduced to 200mg every 3 weeks, golimumab (GOL) reduced to 50mg every 6 weeks). Patients were followed-up and if disease flared they were advised to ring a helpline to arrange an urgent clinic visit where a repeat DAS28 and US assessments were performed, and if needed the dose was increased back to baseline.

Results: 321 RA patients attended the clinic. All had fulfilled local requirements for biological therapy eligibility (including DAS28>5.1, and failed 32 non-biological DMARDs). Baseline demographics showed mean age 59.4 years, 75.4% female, mean time from diagnosis to first biological therapy 10.8years, mean pre-biologic DAS28 5.69, baseline biologic ADA 112, ETN 58, INF 41, GOL 5, CZB 5, rituximab 73, tocilizumab 25, abatacept 2. 179(55.8%) patients were receiving their first biological, 197(61.4%) received a biologic & methotrexate in combination. 101 (31.5%) patients were in DAS28 remission and 45 (15%) were in LDA. PDUS remission was present in 42.9% and of those in clinical remission 69(72.6%) had a PDUS score of 0. Biological reduction was agreed by 56(81.2%) patients and of these, 42(75%) have remained on a reduced dose at a mean of 8.7 months. 14 patients have flared and returned to baseline treatment at a mean of 5.9 months. Of patients flaring DAS28 score increased by mean 0.6. 11(78.6%) had a DAS28>2.6 and 50% had a PDUS=0.

Conclusion: A strategy using clinical assessment and US may increase the likelihood of correctly selecting patients with RA who could successfully reduce the dose of their biological therapy whilst maintaining

clinical and ultrasound remission. This strategy may minimize the risk of ongoing joint damage in those who reduce therapy.

Disclosure: C. R. Holroyd, None; **B. Davidson**, None; **S. Bennett**, None; **D. Waghorn**, None; **C. Underhil**, None; **C. Cooper**, None; **A. Calogeras**, None; **E. M. Dennison**, None; **N. C. Harvey**, None; **R. Armstrong**, None; **S. Gadola**, None; **C. J. Edwards**, Pfizer, AbbVie, MSD, Roche, UCB, Celgene, Samsung Bioepis, Jansen, BMS, 8.

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Remaining Pain Is Common In Early RA Patients Treated With Methotrexate—Results From The EIRA Cohort and The Swedish Rheumatology Quality Register. Reem Altawil[1], Saedis Saevarsdottir[2], Sara Wedren[1], Lars Alfredsson[3], Lars Klareskog[2] and Jon Lampa[4]. [1]Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [2]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [3]Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden, [4]Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Although treatment with methotrexate is often efficient in decreasing inflammation and joint destruction in RA, several patients report remaining pain at follow-up (Taylor P et al, J Int Med Res 2010), and the potential discrepancy between decrease in inflammation and pain needs to be explored further. We investigated the frequency and possible predictors of remaining pain after 3 months treatment with MTX as the only DMARD treatment in early RA, with special focus on the patients who had a good clinical response to MTX.

Methods: The study base was cases reported to the Epidemiological investigation of RA (EIRA) cohort 1996–2009 who had follow-up data in the Swedish Rheumatology Quality Register (1996–2010), a total of 1241 patients (69% women). Disease activity was measured with the 28-joint based disease activity score (DAS28) and the EULAR response criteria were used to evaluate clinical response to treatment. The primary endpoint was 'remaining pain' at the 3 months follow-up visit, defined as pain according to a 100 mm visual analog scale above 20 mm (VAS pain >20 mm), which has earlier been stated as a cutoff for patient reported significant pain (Wolfe F et al, J Rheumatol 2007). The association between baseline parameters and remaining pain was evaluated by logistic regression and expressed as odds ratios (OR) with 95% confidence interval (95%CI), adjusted for age at onset/treatment start, gender and cigarette smoking status.

Results: Median VAS-pain was 54 mm at baseline and 25 mm at the 3 months follow-up visit. Remaining pain was observed in 57% of all patients at the 3 months follow-up. The frequency of EULAR good/moderate/no response was 40%/38%/22% respectively, and in these response groups, the frequency of remaining pain was 29%/70%/83% respectively. In the EULAR good responder group (n=421), remaining pain was associated with more disability at baseline (HAQ; adjusted OR 2.2, 95%CI=1.4–3.4 per unit increase) and less inflammation (erythrocyte sedimentation rate, ESR; adjusted OR 0.81; 95%CI=0.70–0.93 per 10 mm increase). In line with this, patients who were EULAR good responders and had a remaining pain at follow-up exhibited lower ESR ($p<0.02$) and higher HAQ ($p<0.02$) at baseline compared to patients with less pain. Moreover, increase in VAS pain during the treatment period was observed in 19% of the whole cohort and frequencies of increased pain in the response groups were 9%/15%/45% respectively.

Conclusion: Majority of early RA patients starting methotrexate monotherapy at diagnosis have remaining pain after 3 months. Further, almost 1/5 of the patients actually exhibit increase in VAS pain during treatment. Despite good response to methotrexate, almost a third of those patients have remaining pain, and in moderate responders, more than two thirds of the patients have remaining pain. Remaining pain despite a good response to MTX is associated with more disability and less inflammation at baseline. These results are in line with the hypothesis that a subgroup of early RA patients exhibits pain that is not inflammatory mediated and where non-RA causes and alternative treatment strategies can be discussed.

Disclosure: R. Altawil, None; **S. Saevarsdottir**, None; **S. Wedren**, None; **L. Alfredsson**, None; **L. Klareskog**, None; **J. Lampa**, None.

ACR Concurrent Abstract Session
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Safety Issues
Sunday, October 27, 2013, 2:30 PM–4:00 PM

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Tofacitinib, An Oral Janus Kinase Inhibitor: Analysis Of Malignancies Across The Rheumatoid Arthritis Clinical Program. X. Mariette[1], J. R. Curtis[2], E. B. Lee[3], B. Benda[4], I. Kaplan[5], K. Soma[5], R. Chew[5], J. Geier[6], L. Wang[5] and R. Riese[5]. [1]Paris-Sud University, Paris, France, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Seoul National University, Seoul, South Korea, [4]Pfizer Inc, Collegeville, PA, [5]Pfizer Inc, Groton, CT, [6]Pfizer Inc, New York, NY.

Background/Purpose: Tofacitinib is a novel, oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). This analysis extended the evaluation of malignancies that occurred in the tofacitinib RA program from the Phase (P) 2, P3, and long-term extension (LTE) studies based on the data cut off of April 2013 (except where indicated).

Methods: Data were pooled from 6 randomized P2, 6 randomized P3 studies and 2 open-label LTE studies. Patients (pts) in P3 and LTE (LTE pts rolled over from the P2 and P3 studies) studies were treated with tofacitinib 5 or 10 mg twice daily; P2 included additional dosages.

Results: A total of 5674 patients (12669 pt-yr) received tofacitinib in the P2, P3 and LTE studies. One hundred and five pts receiving tofacitinib (all doses) reported malignancies (excluding non-melanoma skin cancer [NMSC]); the most common types of malignancies were lung and breast cancer. There were 10 lymphoma cases. The overall incidence rate (IR, events per 100 pt-yr) for all malignancies (excluding NMSC) and lymphomas were 0.83 (95% confidence interval [CI]: 0.69, 1.00) and 0.076 (0.04, 0.14), respectively. The IRs (95% CI) for all malignancies (excluding NMSC) broken down into 0–6, 6–12, 12–18, 18–24, 24–30, 30–36, 36–42, and >42 months based on exposure to study drug were 0.70 (0.44, 1.11), 0.62 (0.37, 1.05), 0.94 (0.59, 1.49), 1.04 (0.64, 1.66), 0.83 (0.47, 1.46), 1.00 (0.57, 1.76), 0.79 (0.36, 1.76), and 0.93 (0.46, 1.85), respectively. The standardized incidence ratios (SIRs) (95% CI) (as compared with the US Surveillance Epidemiology and End Result database) for all malignancies (excluding NMSC) and lymphomas were 1.07 (0.88, 1.30) and 2.58 (1.24, 4.74), respectively. The SIRs (95% CI) for lung and breast cancer were 1.93 (1.12, 3.09) and 0.71 (0.37, 1.24), respectively (data cut off April 2012). Thirty eight pts experienced NMSCs, for an IR of 0.45 (95% CI: 0.33, 0.62) (data cut off April 2012). By comparison, the IR of NMSC in patients treated with anti-TNF was 0.47 (0.37, 0.59) in a meta-analysis of randomized controlled trials[1] and ranged from 0.23 to 0.35 in a meta-analysis of registries.[2]

Conclusion: The malignancies that occurred in the tofacitinib RA program, including more than 12000 pt-yr of drug exposure, are consistent with the type and distribution of malignancies expected for patients with moderately to severely active RA. The IRs for all malignancies (excluding NMSC), lung cancer, breast cancer, and lymphomas are consistent with published estimates in RA patients treated with biologic and non-biologic DMARDs.[3–6]

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The Risk Of Serious Infections In Patients Receiving Rituximab For Rheumatoid Arthritis: Results From The British Society For Rheumatology Biologics Register-Rheumatoid Arthritis. Lucía Silva-Fernández[1], Mark Lunt[1], Audrey S. Low[1], Kath D. Watson[1], BSRBR Control Centre Consortium[1], Deborah P. Symmons[1], Kimme L. Hyrich[2] and On behalf of the BSRBR[3]. [1]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Sciences Centre, Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom, [3]British Society for Rheumatology, London, United Kingdom.

Background/Purpose: In the United Kingdom (UK), rituximab (RTX), an anti-CD20 monoclonal antibody, is currently used to treat patients with rheumatoid arthritis (RA) who have failed initial anti-tumor necrosis factor (TNF) therapy. There is a concern over whether B-cell depletion and potential resultant hypogammaglobulinaemia may result in an increased risk of serious infections (SI). The aim of this study was to determine if RTX influences the risk of SI when used in routine clinical practice.

Methods: The British Society for Rheumatology Biologics Register-RA is an ongoing national prospective cohort study of subjects with RA recently started on biologic therapy. To date, over 20000 subjects have been recruited. Patients who had failed a first anti-TNF and were switched to either a second anti-TNF or RTX between 2001–2012 were identified from the study cohort. All patients were followed by physician and patient questionnaires every six months for the first three years and annual physician questionnaires thereafter, in which data on drug therapy and serious adverse events were reported. Deaths were identified by flagging with UK National Health Service Information Centre. SIs were defined as those requiring intravenous antibiotics and/or hospitalization, or those resulting in death. Subjects were followed until 01/31/2013, first serious infection, death or treatment discontinuation allowing for a lag window (90 days after first missed dose of anti-TNF and 12 months following each course of RTX), whichever came first. The rates of SI in both cohorts (anti-TNF switched to another anti-TNF vs anti-TNF switched to RTX) were compared using Cox proportional hazards model adjusted using inverse probability of treatment weighting (IPTW) (see variables included in table).

Results: In total, 525 subjects experienced at least one SI (448 in 4048 anti-TNF treated subjects and 77 in 1433 RTX treated subjects) occurred during 14155 and 2621 person-years (pyrs) of observation respectively (incidence rate 31 versus 29 per 1000 pyrs) (Table). After adjustment using IPTW, there was a lower overall risk of SI for patients receiving rituximab than for those receiving a second anti-TNF: hazard ratio (HR) for RTX 0.50 (95% CI 0.33, 0.76). However, the median time to first SI was shorter in the RTX cohort. Analysis limited to patients who initiated their second biologic after RTX approval in 2006 gave similar results.

	Second anti-TNF (n=4048)	Rituximab (n=1433)
Age (years), mean (SD)	56.4 (12.3)	59.5 (11.8)
Gender: n (%) female	79.3	77
RA disease duration (years), Median (IQR)	14 (8, 21)	15 (9, 22)
DAS28 score at switch, mean (SD)	5.4 (1.5)	5.9 (1.3)
HAQ at switch, mean (SD)	1.9 (0.6)	1.9 (0.6)
Steroid use (%)	57	68
Past serious infection on initial anti-TNF therapy: n (%)	342 (8.5)	198 (19.9)
Follow-up (pyrs)	14155	2621
Median follow-up (pyrs; IQR)	2.7 (0.8, 6)	1.5 (0.8, 2.5)
Number of first serious infections	448	77
Median time to infection (years; IQR)	1.4 (0.4, 3.2)	0.5 (0.2, 1.4)
Crude incidence rate of SI per 1,000 pyrs (95% CI)	31 (28, 34)	29 (23, 36)
Unadjusted HR (95% CI)	Referent	0.62 (0.49, 0.80)
Age and gender adjusted HR (95% CI)	Referent	0.56 (0.44, 0.72)
Fully adjusted by IPTW HR (95% CI)*	Referent	0.50 (0.33, 0.76)

*IPTW HR adjusted by age, disease duration, Disease Activity Score (DAS)-28 score and Heath Assessment Questionnaire (HAQ) when initiating the second biologic, gender, smoking, use of steroids before switching to a second biologic, reason for stopping first anti-TNF, previous serious infection, number of prior disease modifying anti-rheumatic drugs (DMARDs) used before initiating biologic treatment, diabetes, lung involvement, heart disease, liver disease, renal disease, previous cancer, tuberculosis and year of starting first biologic drug.

Conclusion: The rate of SI in patients starting a second biologic is similar to that previously observed for a first anti-TNF therapy although our data suggest patients selected to switch to RTX may have a lower risk of SI compared to patients who switch to a second anti-TNF.

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Tumour Necrosis Factor Inhibitors and The Risk Of Acute Coronary Syndrome In Rheumatoid Arthritis—a National Cohort Study. Lotta Ljung[1], Johan Askling[2], Solbritt M. Rantapää-Dahlqvist[1], Lennart T.H. Jacobsson[3] and The ARTIS Study Group[2]. [1]Umeå University, Umeå, Sweden, [2]Karolinska Institutet, Stockholm, Sweden, [3]Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

Background/Purpose: The high risk of ischemic heart disease (IHD) in patients with rheumatoid arthritis (RA) has been linked to inflammation and disease severity. Treatment with tumour necrosis factor inhibitors (TNFi) can modify cardiovascular risk factors and are often effective in reducing disease activity. The objective of the study was to evaluate the risk of acute coronary syndromes (ACS) in patients treated with TNFi for RA compared with the risk in bio-naïve RA patients and in the general population.

Methods: In the Swedish Biologics Register we identified a cohort of patients, with RA and no previous IHD, starting their first TNFi 2001–2010 (n=7,704, mean age 57.1 years, 75.9% women). Matched bio-naïve referents were randomly selected (3:1, n=23,112) from the underlying national cohort of all individuals with two or more outpatient diagnoses of RA (one of which at a dept. for Rheumatology or internal medicine) as identified in the National Patient Register. Furthermore, a matched comparator cohort (5:1, n=38,520) was randomly selected from the Population Register. Covariates were obtained from the Patient register (joint surgery, disease duration, and prevalent diagnoses of hypertension, diabetes, chronic pulmonary disease, infection, cerebrovascular disease and other atherosclerotic disease,) and Statistics Sweden (educational level and previous work disability). Three exposure windows were defined; *Actively on TNFi* – Until date of termination of TNFi therapy +90 days, *Short term exposure* – limiting the follow-up on TNFi to 2 years, and *Ever exposed to TNFi*. The outcome, incident ACS, was defined as a primary discharge diagnosis of myocardial infarction, or unstable angina, or myocardial infarction as the underlying cause of death. Incidence rates were calculated and Cox Proportional Regression models were utilized for risk estimations.

Results:

Crude incidence rates for ACS in the cohorts

	TNFi exposed RA pts (n = 7,704)		Bio-naive RA comparator (n = 23,112)		General population comparator (n = 38,520)	
Exposure window	ACS (n)	Crude IR per 1,000 pyar	ACS (n)	Crude IR per 1,000 pyar	ACS (n)	Crude IR per 1,000 pyar
Short term exposure	74	6.3 (5.0–8.0)	316	9.0 (8.0–10.0)	216	3.3 (2.8–3.7)
Actively on TNFi	137	5.7 (4.8–6.7)	476	8.6 (7.8–9.4)	394	3.3 (3.0–3.7)
Ever exposed to TNFi	221	6.8 (5.9–7.7)	680	9.0 (8.4–9.7)	602	3.6 (3.4–3.9)

The fully adjusted hazard ratios, HR (95%CI), for TNFi exposed compared with bio-naïve RA patients were for *Short term exposure* 0.78 (0.61–1.01), *Actively on TNFi* 0.73 (0.60–0.89), and *Ever exposed* 0.82 (0.70–0.95). Comparing the bio-naïve RA cohort with the general population fully adjusted models resulted in the HRs *Short term exposure* 2.27 (1.88–2.73), *Actively on TNFi* 2.10 (1.82–2.43), and *Ever exposed* 2.03 (1.80–2.29) for the risk of ACS. The corresponding HRs for the TNFi cohort compared with the general population referents were 1.65 (1.23–2.22), 1.50 (1.21–1.85), and 1.61 (1.36–1.92) respectively.

Conclusion: In this nation-wide, population-based, matched cohort study treatment with TNFi was associated with a modest reduction of the risk of ACS in patients with RA. Compared with the general population the risk of ACS in RA was increased, although less pronounced among the TNFi exposed patients. The decrease in risk could be attributable to the TNFi *per se,* or correspond to a higher degree of inflammatory control in the treatment group.

Disclosure: L. Ljung, Bristol Myers Squibb, 5; **J. Askling**, Pfizer Inc, 2; **S. M. Rantapää-Dahlqvist**, None; **L. T. H. Jacobsson**, Pfizer, 2, Pfizer, 5, UCB, 5, Abbvie, 5; **T. ARTIS Study Group**, Merck, BMS, Pfizer, Abbott Laboratories, SOBI, UCB, and Roche, 9.

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Good Response On Tumour Necrosis Factor Inhibitors Are Associated With a Decreased Risk Of Acute Coronary Syndromes In Patients With Rheumatoid Arthritis. Lotta Ljung[1], Lennart T.H. Jacobsson[2], Solbritt M. Rantapää-Dahlqvist[1], Johan Askling[3] and The ARTIS Study Group[3]. [1]Umeå University, Umeå, Sweden, [2]Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [3]Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Inflammatory activity, as well as traditional cardiovascular risk factors, have been suggested to underlie the increased risk of coronary disease in patients with rheumatoid arthritis (RA). Treatment with tumour necrosis factor inhibitors (TNFi) may often effectively reduce disease activity in RA patients. The objective of the study was to evaluate whether level of response to TNFi in RA are associated with the risk of developing an acute coronary syndrome (ACS).

Methods: In the Swedish Biologics Register we identified a cohort of patients, with RA and no previous IHD, who had been on TNFi treatment > 2 months 2001–2010 (n=7,361). For each patient 5 matched referents were randomly selected from the Population Register. Information on inflammatory activity (ESR, CRP, DAS28, CDAI) for the patients was extracted from the register at start and from a visit 5 (±3) months after start of therapy. Data on the primary exposure, EULAR response at 5 months, was available in 4,931 (67%) individuals, mean age 57.1 years, 75.9% women. Covariates were extracted from the Patient register (prevalent hypertension, diabetes, chronic pulmonary disease, infection, and atherosclerotic disease, joint surgery, disease duration) and Statistics Sweden (educational level and work disability). The outcome, incident ACS, was defined as a primary discharge diagnosis of myocardial infarction or unstable angina, or myocardial infarction as the underlying cause of death. Incidence rates were calculated and Cox Proportional Hazard Regression models were utilized for risk estimations.

Results: A good EULAR response was observed in 37.8% (n=1866), a moderate response in 37.0% (n=1824) and no response in 25.2% (n=1241) of the patients. During the 1st year after the response evaluation 33 ACS were observed among the patients, and during year 1 and 2 after exposure 59 ACS were observed, resulting in crude incidence rates of (IR (95%CI)) 7.18 (5.10–10.10) and 6.90 (5.34–8.90) per 1,000 person-years, respectively. Among the general population comparators the corresponding IRs were 3.05 (2.42–3.86) and 3.37 (2.86–3.97). Relative risks for ACS among the response classes compared with non-responders and general population referents are presented in table.

Fully adjusted relative risks the year after evaluations for the secondary exposures were; ESR<20 vs. ESR≥20 HR 0.34 (0.16–0.74), $CRP^2$10 vs. CRP>10 HR 0.77 (0.38–1.54), DAS28 remission vs. non-remission HR 0.21 (0.05–0.88) and CDAI remission vs. non-remission HR 0.44 (0.06–3.27).

Conclusion: Good EULAR response after 5 months of treatment with TNFi in RA patients was associated with a significantly decreased risk of ACS, as was ESR<20 and DAS28 remission. In patients with good response on therapy no significant increase in the risk of ACS was detectable in comparison with the risk in general population during the 2 years after the evaluation.

Disclosure: L. Ljung, Bristol Myers Squibb, 5; **L. T. H. Jacobsson**, Pfizer, 2, Pfizer, 5, UCB, 5, Abbvie, 5; **S. M. Rantapää-Dahlqvist**, None; **J. Askling**, Pfizer Inc, 2; **T. ARTIS Study Group**, Merck, BMS, Pfizer, Abbott Laboratories, SOBI, UCB, and Roche, 9.

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Risk Of Cancer Recurrence Or New Tumors In RA Patients With Prior Malignancies Treated With Various Biologic Agents. Anja Strangfeld[1], Dagmar Pattloch[2], Peter Herzer[3], Edmund Edelmann[4], Silke Zinke[5], Martin Aringer[6], Joachim Listing[7] and Angela Zink[8]. [1]German Rheumatism Research Center, a Leipniz Institute, Berlin, Germany, [2]German Rheumatism Research Center, Berlin, Berlin, Germany, [3]University of Munich, Munich, Germany, [4]Rheumatologist, Bad Aibling, Germany, [5]Rheumatological Office, Berlin, Germany, [6]University Clinical Center Technical University of Dresden, Dresden, Germany, [7]German Rheumatism Research Center, Berlin, Germany, [8]German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany.

Background/Purpose: If patients with rheumatoid arthritis (RA) have a history of malignancy, the choice of treatment is an important clinical question. The aim is to control disease activity with a minimum of risk for recurrence. During the past years we have observed in our register that rheumatologists tend to prefer rituximab over other biologic agents for the treatment of patients with prior malignancies. Our aim was to analyse the risk for recurrence or new tumors under different treatment regimens.

Methods: We used data from the German biologics register RABBIT which observes patients with RA from start of treatment with any approved biologic agent or with a nonbiologic (nb) DMARD. Only patients with a history of malignancy were included in our analysis. All data until 30st of October 2012 were used. Because of a possibly different risk for recurrences patients with prior lymphoma and skin cancer were looked at separately from patients with other malignancies.

Results: At time of the analysis 10,168 patients comprising 36,595 patient years of observation (PY) were included in the register. 367 patients (3.6%) had a history of cancer at time of enrollment. A remarkably high proportion of patients with prior malignancies (28%) were treated with rituximab. The mean time of observation in the register was 3 years for patients with prior lymphomas and 2.6 years for those with prior solid malignancies. The rates for recurrences or new incident tumors are shown in the table.

	Start of treatment with			
	nonbiologic DMARDs	**Rituximab**	**antiTNF agents***	**Other biologics§**
Total number of patients	3399	770	5231	768
PYobserved	12,190	2236	20,446	1722
Patients with **prior lymphomas**, n (%)	10 (0.3)	24 (3.1)	6 (0.1)	2 (0.3)
Median yearsbetween lymphoma and start of treatment	7.6	4.0	1.3	3.6
Recurrence rate/100 PY# (n events)	0	**3.4** (2)	**4.5** (1)	0
CI		0.4–12.3	0.1–25.3	
Patients with **prior solid malignancies**, n (%)	112 (3.3)	77 (10)	109 (2.1)	32 (4.2)
Median years between malignancyand start of treatment	5.9	3.3	6.8	5.2
Recurrence rate/100 PY# (n events)	**3.6** (13)	**3.9** (7)	**5.7** (21)	**4.0** (3)
CI	1.9–6.1	1.6–8.0	3.5–8.8	0.8–11.7
Patients with **prior skin cancer**				
Prior melanoma, n	6	4	7	1
Prior basal cell carcinoma, n	3	1	7	5
Prior squamous cell carcinoma, n	–	3	1	2
Total of patients with prior skin cancer	**9**	**8**	**15**	**10**
Recurrences, n events	0	0	3	1

* antiTNF agents: adalimumab, etanercept, infliximab, certolizumab pegol, golimumab
§ other biologics: abatacept, anakinra, tocilizumab
# PY= patient years between enrollment (start of treatment) and new or recurrent malignancy or end of observation, whichever came first

Conclusion: Our data suggest that patients with a history of lymphomas, solid malignancies or skin cancer do not have higher recurrence rates when treated with rituximab in comparison to treatment with nbDMARDs. This finding is strengthened by the fact that the median time between prior solid malignancy and start of treatment was remarkably shorter in patients receiving rituximab than in all other treatments.

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Perioperative Use Of Anti-Rheumatic Agents Does Not Increase Early Postoperative Infection Risks: A Veteran Affairs' Administrative Database Study. Zaki AbouZahr[1], Andrew Spiegelman[2], Maria Cantu[3] and Bernard Ng[4]. [1]Baylor College of Medicine, Houston, TX, [2]Michael E DeBakey Veteran Affairs Medical Center, Houston, TX, [3]Baylor College Of Medicine, Houston, TX, [4]Michael E. DeBakey VA Medical Center, Houston, TX.

Background/Purpose: Evidences for perioperative management of disease modifying anti-rheumatic drugs (DMARDs) and biologic agents (BA) are sparse, and limited mainly to methotrexate & specific surgeries (orthopedics). Such data may not be generalizable to other surgeries or DMARDs/BA. The use of administrative database is difficult here due to lack of validated methods to predict stopping of DMARDs/BA before surgery. Using novel techniques to predict stopping of DMARDs/BA, we used data from Veterans Affairs (VA) to compare infection risks of RA patients who stopped versus continued DMARDs/BA perioperatively over a 10-year period from 2000–2009.

Methods: We identified 6548 RA patients in VA administrative databases using validated algorithms & included only those on 1 DMARD or BA in the perioperative period. Those on multiple DMARDs/BA were excluded to simplify result interpretation.

We predicted drug stoppages by calculating × = medication stop date closest to the surgery - next start date. y = surgery date-stop date was used to determine if the drug was stopped before or after surgery. To validate this method, two

investigators independently reviewed clinic notes from the Houston VA facility for actual start or stop dates before or after surgery. A third investigator reviewed and resolved conflicting chart review results. ROC analyses were performed to obtain optimal x and y values to distinguish if DMARDs/BA were stopped and if it occurred before or after surgery.

The primary endpoints were wound infections within 30 days of surgery, according to the modified 1992 US Centers for Disease Control and Prevention criteria for postoperative infection, and other infections including pneumonia, UTI and sepsis. Propensity scores were used to match factors that may influence infection rates such as comorbidity scores, chronic steroid use, smoking, diabetes mellitus, etc.

Results: In the validation part of the study, ROC analyses found that $x \geq 33$ days best predicted stoppage of DMARD/BA (AUC=0.954) and $y \geq -11$ best predicted that DMARD/BA was stopped before surgery (AUC=0.846).

Risk of post-op general infection or wound infection in RA patients who stopped DMARDs/BA before surgery were not significantly different compared with those who did not stop these agents. Those who stopped BA after surgery had significantly higher odds of post-op wound (OR 13.7, p=0.014) and post-op general infections (OR 9.2, p=0.005) compared to those who did not stop BA. Similarly stopping DMARDs after surgery was associated with increased risk of post op wound infection (OR 3.08, p=0.000) and post op general infection (OR 1.68, p=0.024) compared with not stopping treatment. Treatment was stopped postoperatively likely because of post-operative infection.

Conclusion: Using our novel technique of identifying DMARDs/BA discontinuation, we showed that there was no significant difference in post-op infection risk whether stopping anti-rheumatic treatment preoperatively or not. Our results grouped all types of surgeries and different DMARDs/BA. Further analyses looking at different types of surgeries and individual DMARDs/BA will be helpful to evaluate possible differences in infection risks between individual DMARDs/BA in different types of surgeries.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis-Autoantibodies and Citrullinated Proteins
Rheumatoid Arthritis - Autoantibodies and Citrullinated Proteins
Sunday, October 27, 2013, 2:30 PM–4:00 PM

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A Genome Wide Association Study Of Rheumatoid Arthritis Without Antibodies Against Citrullinated Peptides. Lara Bossini-Castillo[1], Carolien de Kovel[2], Henrik Kallberg[3], Marieke J.H. Coenen[4], Paul P. Tak[5], Marcel D. Posthumus[6], Cisca Wijmenga[7], Thomas W.J. Huizinga[8], Annette H.M. van der Helm-van Mil[8], Luis Rodriguez-Rodriguez[9], Isidoro Gonzalez-Alvaro[10], Miguel Angel Gonzalez-Gay[11], Irene E. van der Horst-Bruinsma[12], B.A.C Dijkmans[12], G. J. Wolbink[13], Roel A. Ophoff[2], Piet L.C.M. van Riel[14], Lars Klareskog[3], J.B.A. Crusius[15], Elisabeth Brouwer[16], Javier Martin[17], Niek de Vries[5], René E.M. Toes[8], Leonid Padyukov[3] and Bobby P.C. Koeleman[2]. [1]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Granada, Spain, [2]Department of Medical Genetics, UMCU Utrecht, Utrecht, Netherlands, [3]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [4]Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [5]Division of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Center / University of Amsterdam, Amsterdam, Netherlands, [6]University of Groningen, University Medical Center, Groningen, Netherlands, [7]University Medical Hospital Groningen, University of Groningen, Groningen, Netherlands, [8]Leiden University Medical Center, Leiden, Netherlands, [9]Hospital Clínico San Carlos, Madrid, Spain, [10]Hospital Universitario de La Princesa, Madrid, Spain, [11]Hospital Universitario Marqués de Valdecilla. IFIMAV. Santander, Santander, Spain, [12]VU University Medical Center, Amsterdam, Netherlands, [13]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [14]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [15]Vrije Universiteit Medical Center, Amsterdam, Netherlands, [16]University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [17]Instituto de Parasitologia y Biomedicina López-Neyra, IPBLN-CSIC, Granada, Spain.

Background/Purpose: Rheumatoid arthritis (RA) is a common autoimmune disease that is associated with a progressive loss of the joints induced by a chronic inflammation of the joint synovium. The production of anti-citrullinated peptide/protein antibodies (ACPA) is a common but not essential characteristic of RA patients, which is thought to be influenced by the genetic background. To date, the genetic background of ACPA negative patients (ACPA-) remains widely unknown. Therefore, our goal was to analyze the genetic risk factors that contribute to ACPA- RA.

Methods: We performed a large scale genome wide association study in three European cohorts comprising 1,148 ACPA- RA patients and 6,008 controls. Meta-analysis with previously published data was performed as follow-up for selected signals (reaching a total of 1,922 ACPA- RA patients and 7,087 controls). The HLA region underwent a specific imputation process which inferred the classical HLA alleles, polymorphic amino acid positions and SNPs. Finally, we recursively searched for models which better explained the association in the HLA region following a step-wise strategy.

Results: The combined analysis of the three cohorts identified a peak of association in the HLA-region and 34 non-HLA *loci* showed suggestive associations. These signals were selected for follow-up using meta-analysis with a previous report. The meta-analysis confirmed the association of the HLA region, a suggestive association in the *CLYBL locus* (rs9557321, $p = 5.82\times10^{-8}$) and two *tier 2* associations (rs518167 in *GRM5*; rs3790022 in the *RNASEH2B-FAM124A* region). In addition, we observed nominal associations in previously known susceptibility *loci*. In the case of the *TNPO3-IRF5* region, rs12531711 showed a remarkable risk association with ACPA-RA in the combined analysis ($p = 4.35\times10^{-5}$).

After the imputation in the HLA region, the most significant association corresponded to the HLA-DRB1 Leu67 variant (p-value $= 9.41\times10^{-10}$). Furthermore, we identified two additional independent amino acid signals: HLA-B Asp9 and HLA-DRB1 Thr181. Finally, we confirmed that the model including all the previously mentioned amino acid variants was the most parsimonious explanation and accounted for the observed genome-wide associations in this region.

Conclusion: The present report analyzed the genetic component of a large cohort of ACPA- RA patients compared to non-affected controls following a genome-wide strategy. Our results replicated previous findings in different *loci* and revealed a novel suggestive susceptibility factor, *CLYBL*. Moreover, we provided a deep insight into the influence of the HLA region in ACPA-RA. This study supported the existence of an ACPA- specific genetic component and highlighted the importance of comprehensive genetic analysis of large ACPA- RA cohorts.

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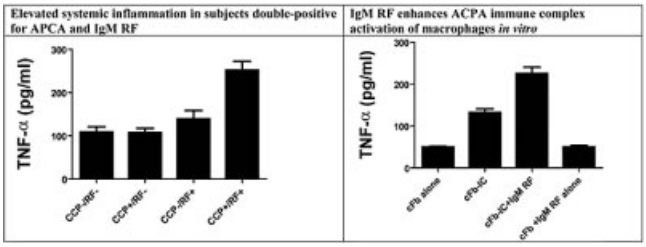
IgM Rheumatoid Factor As a Potentiator Of Anti-Citrullinated Protein Antibody Mediated Inflammation In Rheumatoid Arthritis. Jeremy Sokolove[1], Danye Cheng[1], Dannette S. Johnson[2], Ted R. Mikuls[3] and William H. Robinson[4]. [1]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [2]Jackson VA and University of Mississippi Medical Center, Jackson, MS, [3]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [4]Stanford University School of Medicine, Stanford, CA.

Background/Purpose: The co-occurrence of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) is well described in rheumatoid arthritis (RA), and has been associated with increased disease severity. However, the mechanisms underlying the potential interaction between these two distinct, but often co-existent, autoantibodies has not been well defined.

Methods: Multiplex cytokine profiles, plasma CRP levels, and disease activity scores (DAS28) were assessed in a cohort of 1,467 Veterans with RA (89% male). Patients were categorized into subgroups including double-negative (negative ACPA and RF; n=204), ACPA-positive (n=96), RF-positive (n=135), or double-positive (ACPA and RF positive; n=1031). Levels of each cytokine, CRP, and DAS28 score were compared between the double-negative, ACPA+, RF+, or double-positive subgroups using the Kruskal Wallis test with Tukey's multiple comparison post-test. Molecular interaction between ACPA and RF was investigated using an *in-vitro* immune complex (IC) stimulation assay in which IgG derived from RA patient sera was incubated with citrullinated fibrinogen (cFb) to form cFb-IC in the presence or absence of monoclonal IgM RF. The stimulatory capacity of these immune complexes to activate macrophages was assessed by measuring TNFa production.

Results: Compared with the double-negative subgroup, the double-positive subgroup (possessing ACPA and RF) exhibited significantly higher levels of DAS28, CRP, and multiple inflammatory cytokines including TNFa, IL-1b, IL-6, IL12p70, and IL-17A (all $P<0.001$). Notably, compared to the ACPA+/RF- subgroup, there was a similar increase in the levels of DAS28, CRP, and key inflammatory cytokines among the double-positive population (all $P<0.001$). *In vitro* stimulation of monocyte-derived macrophages by ACPA-immune complexes demonstrated significantly increased cytokine production with the addition of monoclonal IgM rheumatoid factor as compared to ACPA-immune complexes alone ($P=0.003$)

Conclusion: The combined presence of ACPA and IgM RF mediates increased proinflammatory cytokine production *in vitro*, and is associated with significantly increased systemic inflammation and disease activity in patients with RA. Compared to the double-negative subgroup, those with ACPA or RF alone demonstrated no increase in markers of inflammation or disease activity, while levels were consistently elevated among the double-positive subgroup. Our data suggest that the ability of IgM RF to enhance the capacity of ACPA-immune complexes to stimulate macrophage cytokine production is responsible for the increased level of inflammatory mediators and disease activity in double-positive individuals, thereby providing a mechanistic link by which RF enhances the pathogenicity of ACPA-ICs in RA.



Disclosure: J. Sokolove, None; **D. Cheng**, None; **D. S. Johnson**, None; **T. R. Mikuls**, Roche/Genentech and Biogen IDEC Inc., 2; **W. H. Robinson**, None.

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Inducible Bronchus Associated Lymphoid Tissue In The Lung Is Associated With Seropositivity For Rheumatoid Arthritis-Related Autoantibodies In Subjects With and Without Clinically Diagnosed Rheumatoid Arthritis. M. Kristen Demoruelle, Adam W. Bagley, Mark C. Parish, David E. Heinz, V. Michael Holers, Carlyne D. Cool and Kevin D. Deane. University of Colorado School of Medicine, Aurora, CO.

Background/Purpose: Data suggest the lung may be a site of RA-related autoantibody (Ab) generation including findings of airways inflammation prior to onset of articular RA (Demoruelle 2012; Fischer 2012), and the presence of RA-related Abs in sputum but not blood in subjects at risk for future RA (Willis and Demoruelle 2013, in press). The mechanisms by which RA-related Abs may be generated in the lung are unknown; however, inducible bronchus-associated lymphoid tissue (iBALT) is known to form in the lung in response to inhaled antigens, can release Abs in the airways, and contains plasma cells generating RA-related Abs in RA (Rangel-Moreno 2006). Therefore, we hypothesize that iBALT formation is a mechanism by which RA-related Abs are generated in the lung, and aim to establish an association between iBALT and serum RA-related Abs.

Methods: We obtained stored blood and lung tissue from 48 subjects from the NIH Lung Tissue Research Consortium that includes subjects undergoing lung biopsy for clinical management of any underlying disease. Routine histologic staining of the lung was performed and interpreted in a blinded fashion by a trained pathologist. Lymphoid follicles consistent with iBALT and follicles with areas of inflammation organized into germinal centers (GCs) were quantified. Serum was tested for RA-related Abs: CCP2 (IgG, Axis-Shield), CCP3.1 (IgA/IgG, INOVA), and RF isotypes (IgM/A/G, INOVA). Differences in prevalence of positivity were compared using chi-squared/Fishers exact testing.

Results: Subjects with iBALT had similar rates of ever smoking (74% v. 64%, p=0.54), were younger (median age 60 v. 68, p=0.02), more often female (78% v. 44%, p=0.02), and more often had interstitial lung disease (ILD) (61% v. 8%, p<0.01) compared to subjects without iBALT. Nine subjects had a clinical diagnosis of RA; of these, 9 (100%) had airways disease or ILD, 9 (100%) were positive for ≥1 serum RA-related Ab, and 8 (89%) had iBALT. In the 39 subjects without RA, 35 (90%) had airways disease or ILD, 13 (33%) were positive for ≥1 serum RA-related Ab, and 15 (38%) had iBALT. In comparing all subjects, the prevalence of iBALT and GCs was associated with serum RA-related Ab positivity (Table).

Prevalence of serum RA-related autoantibody positivity in subjects with and without inducible bronchus-associated lymphoid tissue*

	iBALT present (N=23; 8 with RA)	iBALT absent (N=25; 1 with RA)	p-value	GC present (N=7; 5 with RA)	GC absent (N=41; 4 with RA)	p-value
CCP2 (+)	7 (30.4%)	0 (0%)	<0.01	4 (57.1%)	3 (7.3%)	<0.01
CCP3.1 (+)	8 (34.8%)	2 (8.0%)	0.03	4 (57.1%)	6 (14.6%)	0.03
CCP2 and/or CCP3.1 (+)	9 (39.1%)	2 (8.0%)	0.02	4 (57.1%)	7 (17.1%)	0.04
RF-IgA (+)	8 (34.8%)	2 (8.0%)	0.03	3 (42.9%)	7 (17.1%)	0.35
RF-IgM (+)	7 (30.4%)	2 (8.0%)	0.07	5 (71.4%)	4 (9.8%)	<0.01
RF-IgG (+)	7 (30.4%)	5 (20%)	0.51	3 (42.9%)	9 (22.0%)	0.34
Any RF isotype (+)	12 (52.2%)	6 (24.0%)	0.07	5 (71.4%)	13 (31.7%)	0.09

*48 subjects were included that had a variety of underlying diseases that resulted in a lung biopsy for clinical management including: 14 with interstitial lung disease (3 of which also had airways disease), 29 with emphysema and/or respiratory bronchiolitis, 1 with sarcoidosis, 2 with lung cancer, and 2 with normal lung tissue.

Conclusion: iBALT is associated with serum RA-related Abs in subjects with and without RA. While these pilot results are driven by subjects with diagnosed RA, when combined with the published data discussed above, this association suggests that iBALT may be a mechanism of RA-related Ab generation. Notably, iBALT can develop in response to inflammation, and given our prior findings of airways inflammation associated with RA-related Abs in absence of synovitis, iBALT may be a mechanism of RA-related Ab generation prior to synovitis in RA. Going forward we will expand these studies to additional subjects to evaluate the generation of RA-related Abs within iBALT, and factors (e.g. microbial) that may trigger iBALT and Ab development in subjects with and without classified RA.

Disclosure: M. K. Demoruelle, None; **A. W. Bagley**, None; **M. C. Parish**, None; **D. E. Heinz**, None; **V. M. Holers**, None; **C. D. Cool**, None; **K. D. Deane**, None.

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Influence Of Smoking On Citrullinated Proteins and *Porphyromonas Gingivalis* In The Lung: A Priming Site For Autoimmunity In RA. Elena B. Lugli[1], Patrick Venables[2], Raquel Correia[3], Karin Lundberg[4], Ken Bracke[5] and Guy Brusselle[5]. [1]Kennedy Institute of Rheumatology, Oxford, United Kingdom, [2]University of Oxford, Oxford, United Kingdom, [3]Univerity of Oxford, Oxford, United Kingdom, [4]Rheumatology unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [5]Gent University, Gent, Belgium.

Background/Purpose: Anti-citrullinated peptide/protein antibodies (ACPA) may be detected in RA serum more than 10 years before onset of disease, suggesting that the autoimmune response begins outside the joint. Because smoking and periodontitis are risk factors for RA, it has been suggested that smoke inhalation or invasive infection with *Pophyromonas gingivalis* leads to citrullination of proteins in the lung. In this study, we examine human lung tissue by immunoblotting from 41 subjects with well-defined smoking status for the presence of citrullinated proteins, PAD2, PAD4 and *P. gingivalis* DNA.

Methods: Uninvolved tissue samples were dissected from lobectomy specimens from 41 subjects (10 never smokers, 10 COPD ex-smokers, 10 smokers without airflow limitation and 11 COPD smokers). The tissue was homogenised and examined by immunoblotting for the presence of citrullinated proteins with AMC. PAD2, PAD4, α-enolase, citrullinated α-enolase, vimentin and fibrinogen were detected using specific antibodies. Band intensities were scored quantitatively using a BioRad Quantity One Analysis Sofware or semi-quantitatively from 0–3 by two blinded observers. Recombinant proteins were used as positive controls and blots with secondary antibodies alone were carried out to exclude non-specific cross-reactivity. *P. gingivalis* was detected by nested PCR using primers spanning the PPAD gene.

Results: Citrullinated proteins were found in all lung tissues, both smokers and non-smokers. There was a trend towards increased citrullination in the lungs of the smokers with and without COPD but this did not reach statistical significance by either densitometry or semi-quantitative scoring of band intensities. There was a similar, but not significant, trend for increased expression of PAD2 amongst the smokers. PAD4 and the RA antigens, α-enolase, vimentin and fibrinogen, were observed in all lung tissue in comparable amounts regardless of disease and smoking status. There was also evidence of citrullination of α-enolase provided by co-migration of a ~50kDa

band recognised by AMC and an anti-citrullinated enolase antibody, and by 2D electrophoresis showing multiple isoforms of the antigen.

P. gingivalis DNA was detected most frequently in all the never smokers (100%) compared to the COPD ex-smokers (10%); smokers without COPD (10%); and least frequently in COPD smokers (0%) (Chi-square test, $p<0.001$).

Conclusion: We have demonstrated widespread citrullination of proteins in lung tissue from never smokers, with a slight increase with smokers. The inverse relationship between smoking and the detection of *P. gingivalis* DNA was initially surprising, but in keeping with previously published studies. These data support the hypothesis that the lung is a site for priming the ACPA response, though the mechanism is likely to be more complex than smoking inducing PAD enzymes or *P. gingivalis* infection.

Disclosure: E. B. Lugli, None; **P. Venables**, None; **R. Correia**, None; **K. Lundberg**, None; **K. Bracke**, None; **G. Brusselle**, None.

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Alveolar Bone Loss Is Associated With Disease Activity and ACPA Expression In Rheumatoid Arthritis. Ted R. Mikuls[1], Jeffrey Payne[2], Fang Yu[3], Geoffrey M. Thiele[3], Shawneen Gonzalez[2], Jeffrey Markt[4], Jeremy Sokolove[5], William H. Robinson[6], Richard J. Reynolds[7], Grant W. Cannon[8], David McGowan[9], Gail S. Kerr[10], Robert Redman[11], Andreas M. Reimold[12], Garth Griffiths[12], Mark Beatty[2], Marian Schmid[2], Paul Johnson[2], Debra Bergman[4], Bartlett C. Hamilton III[13], Alan R. Erickson[14] and James R. O'Dell[4]. [1]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [2]University of Nebraska Medical Center, Lincoln, NE, [3]Univ of Nebraska Med Ctr, Omaha, NE, [4]University of Nebraska Medical Center, Omaha, NE, [5]Stanford University, Palo Alto, CA, [6]Stanford University School of Medicine, Stanford, CA, [7]University of Alabama at Birmingham, Birmingham, AL, [8]Salt Lake City VA and University of Utah, Salt Lake City, UT, [9]George E. Wahlen VA Medical Center, Salt Lake City, UT, [10]Washington DC VAMC, Georgetown and Howard University, Washington, DC, [11]Washington DC VA, Georgetown and Howard University, Washington, DC, [12]Dallas VA and University of Texas Southwestern, Dallas, TX, [13]University of Nebraska Medical Center and Omaha VA Medical Center, Omaha, NE, [14]Omaha VA and University of Nebraska Medical Center, LaVista, NE.

Background/Purpose: Periodontitis (PD) has been implicated in rheumatoid arthritis (RA) pathogenesis including the expression of anti-citrullinated protein antibody (ACPA). ACPA, in turn, have been shown to be robust predictors of radiographic progression in RA with recent evidence suggesting that ACPA targeting citrullinated vimentin could directly mediate disease-related bone damage. We sought to examine the relationship of alveolar bone loss (a feature of PD) with RA disease activity and autoantibody expression, including ACPA.

Methods: Panoramic radiographs were collected in RA patients and scored by two investigators (ICC 0.85) blinded to PD status. Patients were categorized into low, moderate, or high tertiles based on the mean bone loss across sites (up to 24 sites were examined per patient). PD was defined using a standardized periodontal exam and the criteria of Machtei et al (J Periodontol, 1990). ACPA concentrations were measured via 2ndgeneration ELISA (aCCP2) and by a bead-based multiplex antigen array on the BioPlex Platform, the latter to assess distinct antigen-specific ACPA. Associations of moderate and high bone loss (vs. low) with disease characteristics were examined using multivariable (MV) regression (covariates: age, gender, race, BMI, smoking, HLA-DRB1 SE, PD prednisone use, sicca symptoms, and others) identified through stepwise selection. Antigen-specific ACPA responses were compared across tertiles in aCCP2 positive patients using Significance Analysis of Microarrays (SAM) with separate analyses in ever and never smokers.

Results: RA patients (n = 274) were primarily male (63%), Caucasian (78%), ever smokers (62%), and had a mean age of 59 (±12) years. Approximately 1 in 3 patients (35%) had PD. Of those with PD, most had high (66%) and moderate (24%) levels of bone loss with fewer showing low bone loss (10%). Disease characteristics based on alveolar bone loss are shown (Table). Following MV adjustment, increased alveolar bone loss remained significantly associated with higher values of aCCP2, DAS-28-CRP, HAQ, tender joint counts, and joint space narrowing scores. Microarray analyses limited to aCCP2 positive patients demonstrated that ACPA targeting citrullinated vimentin and histone were significantly increased (q-value < 0.1%) in the moderate and high bone loss groups vs. low group, irrespective of smoking status.

Table. RA-related measures of disease activity & severity based on low, moderate, or high tertile of alveolar bone loss (unadjusted p-values shown)

	Low (n=88)	Moderate (n=85)	High (n=101)	P-Value
Tender joint count (0–28)	2.6 (4.8)	3.0 (4.2)	4.0 (4.9)	0.002
Swollen joint count (0–28)	3.0 (3.5)	3.4 (4.7)	4.2 (4.3)	0.041
DAS-28-CRP	2.4 (1.2)	2.6 (1.1)	3.0 (1.1)	<0.001
HAQ disability (0–3)	0.6 (0.7)	0.8 (0.7)	1.0 (0.7)	0.001
Pain (0–10)	2.7 (2.5)	3.0 (2.4)	3.9 (2.7)	0.007
Anti-CCP2, U/ml	145 (122)	162 (117)	203 (119)	0.007
RF, IU/ml	200 (519)	273 (465)	281 (490)	0.002
Total Sharp Score	13.2 (16.4)	18.1 (20.4)	25.8 (25.4)	0.003
Erosion Score	2.7 (4.7)	4.4 (7.8)	5.7 (8.7)	0.041
JSN Score	10.5 (13.3)	13.8 (14.5)	20.1 (19.3)	<0.001

Conclusion: Alveolar bone loss, a well-recognized feature of chronic PD, is strongly associated with increased RA disease activity. Furthermore, these results suggest that ACPA targeting, potentially of both vimentin and histones could represent potentially important links between RA and alveolar bone loss, providing novel insight into the disproportionate frequency of periodontal bone damage that has been reported in RA.

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Citrulline Specific CD4+ T Cells Exhibit a Th1 Memory Phenotype In Rheumatoid Arthritis Subjects and Their Ex Vivo Frequency Is Influenced By Both Disease Duration and Biologic Therapy. Eddie James[1], Mary Rieck[1], Jennifer Pieper[2], John Gebe[3], Betty Yue[3], Megan Tatum[3], Charlotta Sandin[4], Lars Klareskog[5], Vivianne Malmström[6] and Jane Buckner[7]. [1]Benaroya Research Institute, Seattle, WA, [2]Karolinska Institutet, Rheumatology Unit, Stockholm, Sweden, [3]Benaroya Research Institute at Virginia Mason, Seattle, WA, [4]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [5]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [6]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [7]Translational Research Program, Benaroya Research Institute, Seattle, WA 98101, USA,, Seattle, WA.

Background/Purpose: Rheumatoid arthritis is thought to be a T cell mediated disease, based on its strong association with HLA class II alleles, clinical responsiveness to T cell directed therapies and the presence of CD4 T cells in rheumatoid joints. Understanding the character and antigen specificity of auto-reactive T cell responses in RA has been elusive, in part due to the limited identification of the most relevant epitopes and inability to interrogate responses directly ex vivo. The presence of ACPA in the serum of patients and association of these antibodies with HLA-DR4 alleles provides a clue to the specificity of pathogenic T cells and implicates their probable importance in the development and progression of RA.

Methods: We developed a panel of HLA-DR0401 tetramers, selecting citrullinated peptides from four different synovial antigens and verifying their immunogenicity in HLA-DR4 transgenic mice. This panel of tetramers was used to directly examine the frequency and cell surface phenotype of T cells specific for citrullinated peptides in subjects with DR0401 haplotypes using an ex vivo magnetic enrichment procedure.

Results: Citrullinated-antigen specific CD4 T cells were detectable in peripheral blood samples from both healthy subjects and RA patients. In comparison to healthy subjects, RA patients had significantly higher frequencies of citrullinated-antigen specific T cells ($p=0.0069$) and a greater proportion of these cells displayed a T_H1 memory phenotype ($p<0.0001$). Among RA subjects the frequency of citrullinated-antigen specific T cells was significantly higher within the first 5 years after disease onset ($p=0.0018$) and was decreased among patients on biologic therapies ($p<0.0001$) and this difference was seen irrespective of disease duration, indicating an independent effect.

Conclusion: This study represents the first evidence that the frequency and phenotype of citrullinated-antigen specific T cells vary with respect to important disease parameters and are therefore a potential biomarker in at risk

individuals and subjects with RA. These findings link the presence of ACPA in patient serum with T cells specific to citrullinated epitopes and suggest that the pathogenic T cells in established RA are of a Th1 lineage.

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ACR Concurrent Abstract Session
Spondylarthropathies and Psoriatic Arthritis: Clinical Aspects and Treatment: Therapeutics and Outcomes in Psoriatic Arthritis
Sunday, October 27, 2013, 2:30 PM–4:00 PM

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Results Of a Randomised Controlled Trial Comparing Tight Control Of Early Psoriatic Arthritis (TICOPA) With Standard Care: Tight Control Improves Outcome. Laura C. Coates[1], Anna R. Moverley[1], Lucy McParland[2], Sarah Brown[2], Howard Collier[2], Jennifer Law[2], Sarah R. Brown[2], Neil Corrigan[2], Nuria Navarro-Coy[2], Paul Emery[3], Philip G. Conaghan[1] and Philip S. Helliwell[1]. [1]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [2]Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, United Kingdom, [3]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom.

Background/Purpose: The aim of this study was to assess the impact of tight control of early psoriatic arthritis (PsA) in a randomised-controlled trial (RCT) using a treat-to-target approach.

Methods: In this UK multicentre, open-label RCT, 206 patients with early DMARD naive PsA (<24 months symptom duration) were randomised 1:1 to receive either tight control (TC) (4 weekly review) or standard care (StdC) (12 weekly review) for 48 weeks. Patients assigned to the TC group followed a strict treatment protocol with escalation of therapy if minimal disease activity (MDA) criteria[1]were not met. All patients in the TC arm were started on methotrexate with rapid escalation to 25mg after 6 weeks if tolerated. After 12 weeks of therapy, patients were escalated to combination DMARDs if they had not achieved MDA. After a further 12 weeks, patients were either escalated to anti-TNF therapy if they had ≥3 tender and swollen joints (as per UK NICE guidelines) or to an alternative DMARD in combination with methotrexate if they were not in MDA but had <3 active joints. Patients assigned to the StdC group were treated by a rheumatologist with no set protocol and no limitations.

The primary outcome was ACR20 response at 48 weeks. Key secondary outcomes included ACR50 and 70, and PASI75 at 48 weeks. Treatment arms were compared using multivariate logistic regression adjusting for arthritis classification and centre. Missing ACR response component data was imputed using multiple imputation for the intention to treat (ITT) population.

Results: 206 patients were recruited from 8 UK centres from 2008–2012 with 101 randomised to TC and 105 to StdC. By week 48, 12 patients had withdrawn (5 TC, 7 StdC) and 12 lost to follow-up (6 TC, 6 StdC). Patients had a median age of 45 (range: 18–80), 52% were male and 71% presented with polyarthritis; these characteristics were similar across treatment arms. In the ITT population, there was significant evidence that the odds of achieving ACR20 at 48 weeks were greater in the TC arm compared to the StdC arm (odds ratio (OR): 1.91, 95% CI: 1.03, 3.55, p=0.0392). The odds of achieving ACR50 (OR: 2.36, 95% CI: 1.25, 4.47, p=0.0081) and ACR70 (OR: 2.64, 95% CI: 1.32, 5.26, p=0.0058) were also greater in the TC arm compared to the StdC arm. Results for patients with non-missing data are displayed below.

Outcome measure	Patients with all data available (N)	Tight Control	Standard Care
		N (%) achieving outcome	
ACR20	172	55 (61.8)	37 (44.6)
ACR50	170	44 (51.2)	21 (25.0)
ACR70	172	33 (38.4)	15 (17.4)
PASI75*	156	44 (58.7)	27 (33.3)
		Median improvement in score (range)	
Enthesitis*	145	2 (−12, 13)	1 (−8, 14)
LDI*	53	38 (0, 276)	58.5 (−6, 157)
mNAPSI*	110	3 (−18, 41)	2 (−22, 32)

* only evaluated if involvement at baseline

The most commonly reported adverse events (AEs) were nausea, liver function test abnormalities and infections (e.g. common cold). AEs were reported in 88% of patients, (97% TC vs 80% StdC). 33 serious AEs (SAEs) (25 TC, 8 StdC) were reported across 20 patients (14 TC, 6 StdC) during the course of the study. There were no deaths or unexpected SAEs.

Conclusion: Tight control of PsA disease activity using a treat-to-target approach significantly improves joint and skin outcomes for newly diagnosed PsA patients with no unexpected SAEs seen.

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1. Coates et al, Arthritis and Rheum 2010

Disclosure: L. C. Coates, None; **A. R. Moverley**, None; **L. McParland**, None; **S. Brown**, None; **H. Collier**, None; **J. Law**, None; **S. R. Brown**, None; **N. Corrigan**, None; **N. Navarro-Coy**, None; **P. Emery**, None; **P. G. Conaghan**, Pfizer Inc, Janssen Pharmaceutica Product, L.P., 5, Bristol-Myers Squibb, Pfizer Inc, 8; **P. S. Helliwell**, Pfizer Inc, 5.

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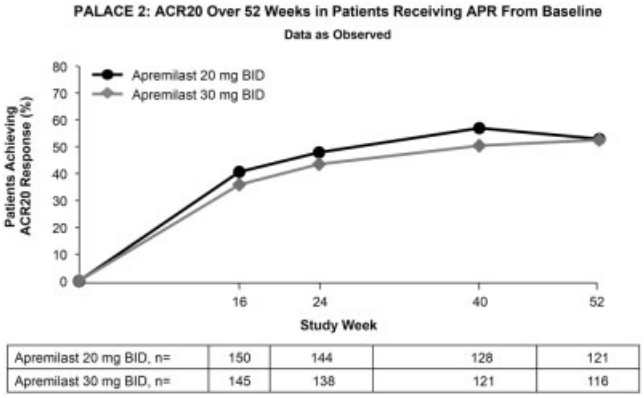
Long-Term (52-Week) Results Of a Phase 3, Randomized, Controlled Trial Of Apremilast, An Oral Phosphodiesterase 4 Inhibitor, In Patients With Psoriatic Arthritis (PALACE 2). Maurizio Cutolo[1], Gary E. Myerson[2], Roy M. Fleischmann[3], Frédéric Lioté[4], Federico Díaz-González[5], Filip Van den Bosch[6], Helena Marzo-Ortega[7], Eugen Feist[8], Kamal Shah[9], ChiaChi Hu[9], Randall M. Stevens[9] and Airi Poder[10]. [1]University of Genova, Genova, Italy, [2]Arthritis and Rheumatology of Georgia, Atlanta, GA, [3]Metroplex Clinical Research Center, University of Texas Southwestern Medical Center, Dallas, TX, [4]Hôpital Universitaire Lariboisière, Paris, France, [5]University of La Laguna, Hospital Universitario de Canarias, La Laguna, Spain, [6]Gent University Hospital, Gent, Belgium, [7]Leeds Musculoskeletal Biomedical Research Unit and University of Leeds, Leeds, United Kingdom, [8]Charite University Hospital, Berlin, Germany, [9]Celgene Corporation, Warren, NJ, [10]Clinical Research Centre Ltd, Tartu, Estonia.

Background/Purpose: Apremilast (APR), an oral phosphodiesterase 4 inhibitor, works intracellularly to modulate pro- and anti-inflammatory mediators. PALACE 2 compared the efficacy and safety of APR with placebo (PBO) in pts with active PsA despite prior DMARDs and/or biologics.

Methods: Pts were randomized 1:1:1 to PBO, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline (BL) DMARD use. At wk 16, pts with <20% reduction from BL in swollen and tender joint counts qualified for protocol-defined early escape; those on PBO were re-randomized to APR20 or APR30 and those on APR remained on the initial APR dose. At wk 24, all remaining PBO pts were re-randomized to APR20 or APR30 through wk 52. Patients taking concurrent DMARDs were allowed to continue stable doses (MTX, sulfasalazine, leflunomide, or a combination).

Results: 484 pts were randomized and received ’1 dose of study drug (PBO, 159; APR20, 163; APR30, 162). At wk 16 (primary endpoint), a significantly greater proportion of pts treated with APR20 (38.4%; $P=0.0002$) and APR30 (34.4%; $P=0.0024$) achieved an ACR20 response vs PBO (19.5%). For those pts originally randomized to APR and completing 52 wks of study, improvements were maintained or increased over 52 wks for multiple endpoints, including: (1) ACR20 response of 52.9% (APR20) and 52.6% (APR30) (Figure); (2) HAQ-DI mean change from BL (SD) of −0.192 (0.573) for APR20 pts and −0.330 (0.509) for APR30 pts; (3) SF-36 Physical Functioning domain score mean change from BL (SD) of 5.05 (7.96) for APR20 pts and 6.35 (8.67) for APR30 pts; and (4), in these pts with BL BSA ≥3%, PASI-75/PASI-50 achievement of 27.1%/49.2% in APR20 pts and 39.3%/58.9% in APR30 pts. Pts randomized to APR at wks 16 and 24 demonstrated results consistent with those originally randomized to APR. APR was generally well tolerated. Adverse events (AEs) occurring in ≥5% of all pts exposed to APR through wk 52 were diarrhea, nausea, upper respiratory tract infection, headache, and nasopharyngitis. The majority of AEs were mild or moderate in severity and predominantly did not lead to discontinuation. Serious AEs (SAEs) occurred in 4.7% (APR20) and 5.1% (APR30) of pts as treated. No new safety findings were identified and the incidence of pts experiencing any AE was comparable over the 0–24 and 0–52 wk periods. No imbalance in the exposure-adjusted incidence rates of major adverse cardiac events, serious infections including systemic opportunistic infection, or malignancies between APR and PBO was observed. No cases of TB (novel or reactivation) were reported in the APR treatment groups; TB screening was not required per protocol.



Apremilast 20 mg BID, n=	150	144	128	121
Apremilast 30 mg BID, n=	145	138	121	116

Conclusion: Over 52 wks, APR demonstrated long-term efficacy in the treatment of PsA, including clinically meaningful improvements in signs and symptoms and physical function. APR had an acceptable safety profile and was generally well tolerated for up to 52 wks.

Disclosure: M. Cutolo, BMS, Sanofi and Actelion, 2; **G. E. Myerson**, Abbvie, Actelion, Amgen, BMS (Bristol-Myers Squibb), Bioventus, GSK (Glaxo Smith Cline), Lilly, Pfizer, Primus, Roche (Genentech), Takeda, UCB, 5; **R. M. Fleischmann**, Celgene, 2, Celgene, 5; **F. Lioté**, Celgene, 5; **F. Díaz-González**, Celgene, 2; **F. Van den Bosch**, AbbVie, Celgene, Merck, Pfizer, UCB, Janssen, 5; **H. Marzo-Ortega**, None; **E. Feist**, None; **K. Shah**, Celgene Corporation, 3; **C. Hu**, Celgene Corporation, 3; **R. M. Stevens**, Celgene Corporation, 3; **A. Poder**, Celgene, 2.

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Apremilast, An Oral Phosphodiesterase 4 Inhibitor, Is Associated With Long-Term (52-Week) Improvements In Enthesitis and Dactylitis In Patients With Psoriatic Arthritis: Pooled Results From Three Phase 3, Randomized, Controlled Trials.

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Background/Purpose: Apremilast (APR), an oral phosphodiesterase 4 inhibitor, works intracellularly to modulate pro- and anti-inflammatory mediators. The PALACE 1, 2, and 3 trials compared the efficacy and safety of APR with placebo (PBO) in pts with active PsA despite prior DMARDs and/or biologics.

Methods: Pts were randomized 1:1:1 to PBO, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline DMARD use. At wk 16, pts with <20% reduction from baseline in swollen and tender joint counts qualified for protocol-defined early escape; those on PBO were re-randomized to APR20 or APR30 and those on APR remained on the initial APR dose. At wk 24, all remaining PBO pts were re-randomized to APR20 or APR30 through wk 52. Pts taking concurrent DMARDs were allowed to continue stable doses (MTX, sulfasalazine, leflunomide, or a combination). In order to increase the number of pts with pre-existing enthesopathy and/or dactylitis, data were pooled across PALACE 1, 2, and 3. Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), ranging from 0–13, is the number of painful entheses out of 13 entheses. The dactylitis count, ranging from 0–20, is the number of digits on the hands and feet with dactylitis present; each digit is rated as 0 (no dactylitis) or 1 (dactylitis present).

Results: APR administration resulted in statistically significant and clinically meaningful improvement in ACR20 response (primary endpoint) in all 3 PALACE trials. In pts originally randomized to APR and with pre-existing enthesopathy (n=634) and/or dactylitis (n=428), APR was associated with improvements in the severity of enthesitis and dactylitis over the 52-wk period, as evidenced by reductions in MASES and dactylitis count. At wk 24, median changes in MASES were −21.1%, −40.0% (P=0.0789), and −50.0% (P=0.0167) in pts receiving PBO, APR20, and APR30, respectively. In those pts originally randomized to APR and completing 52 wks of study, median change in MASES was −66.7% with APR20 and APR30 (Table). A MASES score of 0, indicating no pain at any of the entheses assessed, was achieved by 41.4% of APR20 and 37.4% of APR30 pts. At wk 24, median changes in dactylitis count were −66.7%, −75.0% (P=0.2158), and −79.3% (P=0.0609) in pts receiving PBO, APR20, and APR30, respectively. At wk 52, both doses resulted in a median 100% decrease in dactylitis count. Dactylitis count decreased to 0 in 66.9% of APR20 and 65.9% of APR30 pts. Pts randomized to APR at wks 16 and 24 demonstrated results consistent with those originally randomized to APR. No new safety findings were identified and the incidence of pts experiencing any AE was comparable over the 0–24 and 0–52 wk periods.

Conclusion: Over 52 wks, APR continued to demonstrate efficacy in the treatment of PsA, including improvements in enthesitis and dactylitis. APR demonstrated an acceptable safety profile and was generally well tolerated for up to 52 wks.

Impact of APR on Enthesitis and Dactylitis at Week 52 in Patients Receiving APR From Baseline

MASES*	APR20 (n=307)	APR30 (n=327)
Baseline, median	4.0	4.0
Median percent change from baseline*	−66.7	−66.7
Proportion of patients achieving a score of 0§, %	41.4	37.4
Dactylitis count*	**APR20 (n=207)**	**APR30 (n=221)**
Baseline, median	2.0	2.0
Median percent change from baseline*	−100.0	−100.0
Proportion of patients achieving a score of 0‡, %	66.9	65.9

*In patients with pre-existing enthesopathy or dactylitis, the n reflects randomized patients; actual number of patients available for each end point may vary. Reductions in MASES and dactylitis count indicate improvement.
§MASES ranges from 0 to 13, with zero indicating no pain at any entheses assessed and 13 indicating the presence of pain at all entheses assessed.
‡Dactylitis count is the sum of scores for each of the 20 digits, with individual digits scored as 0=absence or 1=presence of dactylitis.

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Clinical Response To Brodalumab, An Anti-Interleukin-17 Receptor Antibody, In Subjects With Psoriatic Arthritis.

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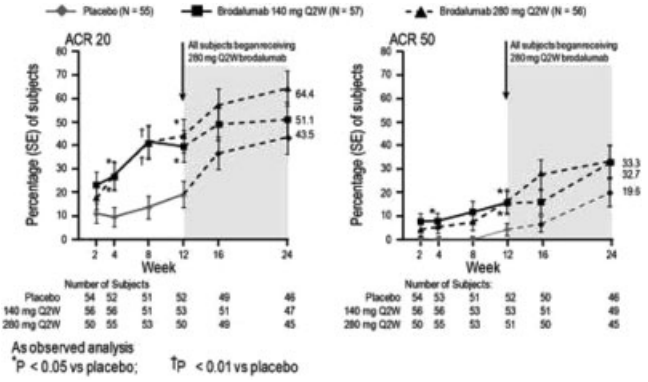
Background/Purpose: Psoriasis-associated skin and joint disorders are characterized by ongoing inflammation mediated by similar molecular pathways. IL-17 plays a potential role in the pathogenesis and ongoing inflammation of psoriatic disease. We sought to assess the efficacy and safety of brodalumab, a human anti-IL-17 receptor A monoclonal antibody, in patients with psoriatic arthritis (PsA).

Methods: Adults (age 18 to 75 years) with active PsA (Classification Criteria for Psoriatic Arthritis and ≥3 tender and ≥3 swollen joints) for ≥6 months were randomized to brodalumab (140 or 280 mg Q2W) or placebo. At week 12 subjects could enroll in an open-label extension (OLE) in which all subjects received 280 mg brodalumab. Outcomes based on available data up to week 24 from the ongoing study included American College of Rheumatology 20% response (ACR20), ACR50, and ACR70, changes in DAS 28 and ACR response components, and adverse events (AEs).

Results: At baseline, the majority of enrolled subjects (113 brodalumab and 55 placebo) were female (64%), white (94%), and rheumatoid factor negative (92%). Mean (SD) age, weight, and duration of PsA at baseline were 52 (12) years, 91 (21) kg, and 9 (8) years, respectively. 156 subjects entered in the OLE (52 prior placebo, 53 prior 140 mg, 51 prior 280 mg).

ACR20 was achieved at week 12 by 37% and 39% of subjects in the 140- and 280-mg brodalumab groups, respectively, compared with 18% of placebo subjects ($p < .05$) (Fig. 1). The percent of ACR20 responders (observed) increased at week 24 (44%, 51%, 64%, in prior placebo, prior 140 mg, and prior 280 mg groups, respectively) (Fig. 1). The percent of ACR50 responders (observed) across all groups increased from week 12 to week 24 (Fig. 1). There were improvements in other secondary endpoints such as DAS 28, CDAI, and several components of the ACR from baseline to week 12 that continued through week 24 in all treatment groups.



AEs were balanced among treatment groups and placebo, with 85% of subjects reporting an AE during the OLE. The most commonly reported adverse events were nasopharyngitis, arthralgia, psoriatic arthropathy, upper respiratory tract infection, and oropharyngeal pain. SAEs were reported in 11 subjects during the full study through data cutoff (double-blind phase and OLE). No deaths, clinically significant neutropenia (≥ Grade 2), or mycobacterial/fungal/opportunistic infections were reported in this study.

Conclusion: Brodalumab treatment was associated with significant clinical response with continued improvement from week 12 to 24. The benefit:risk profile supports continued evaluation of brodalumab for treatment of PsA.

Disclosure: M. C. Genovese, Amgen Inc., 2, Amgen Inc., 5; **P. J. Mease**, AbbVie, Amgen, BiogenIdec, BMS, Celgene, Crescendo, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, Vertex, 2, AbbVie, Amgen, BiogenIdec, BMS, Celgene, Crescendo, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, Vertex, 5, AbbVie, Amgen, BiogenIdec, BMS, Crescendo, Genentech, Janssen, Lilly, Pfizer, UCB, 8; **M. W. Greenwald**, Amgen Inc., 2, Amgen Inc., 5; **C. T. Ritchlin**, Amgen, Janssen, UCB, Abbott (AbbVie), Regeneron, 5, Amgen, Janssen, UCB, 2; **A. Beaulieu**, Amgen Inc., 2, Amgen Inc., 5; **A. Deodhar**, AbbVie, Merck-Sharp-Dohme, Pfizer and UCB, 5, AbbVie, Merck-Sharp-Dohme, Pfizer and UCB, 8, AbbVie, Amgen, Novartis, UCB, 2; **R. Newmark**, Amgen Inc., 1, Amgen Inc., 3; **J. Feng**, Amgennc., 1, Amgen Inc, 3; **N. Erondu**, Amgen Inc., 1, amgen Inc., 3; **A. Nirula**, Amgen Inc., 1, Amgen Inc., 3.

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HLA-B*0801 Is Strongly Associated With Asymmetrical Sacroiliitis and HLA-B*27 With Symmetrical Involvement In Psoriatic Arthritis: Results Of a Long-Term Follow-Up Study Examining Clinical and Genetic Predictors Of Radiographic Sacroiliitis. Muhammad Haroon[1], Agnes Szentpetery[1], Phil Gallagher[1], Robert Winchester[2] and Oliver FitzGerald[1]. [1]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [2]Columbia University, New York, NY.

Background/Purpose: Psoriatic arthritis (PsA) is characterised by involvement of both the appendicular and axial skeleton. Little is known about the clinical predictors of sacroiliitis (SI), especially regarding underlying patient's characteristics, life style, correlation with skin disease and with severity of psoriatic disease. The objectives of our study were: 1) To investigate the prevalence of SI in an ethnically homogenous cohort of established PsA, 2) to identify clinical and genetic predictors of SI in patients with PsA, 3) to describe different radiographic patterns of SI and their potential associations with clinical and genetic characteristics.

Methods: A cohort of 283 PsA patients, fulfilling CASPAR criteria, was included. Following informed consent, patients underwent a detailed skin and rheumatologic assessment including PASI, body surface area for Psoriasis (PsO), CRP, ESR, smoking, BMI status, alcohol intake, education status, family history of PsO and/or PsA, PsA duration, age of PsO/PsA onset, enthesitis, dactylitis, erosions, osteolysis, arthritis mutilans, clinically deformed joints, PsO and/or PsA requiring TNFi treatment, HAQ, DLQI, Bristol Rheumatoid Arthritis Fatigue Numeric Rating Scale (BRAF-NRS), and EQ5D. In addition, HLA-B*27 and B*080101 status was recorded, which we have recently shown are the key genetic markers of radiographic SI (www.rheumatology.org/education/annual/2012_abstract_supplement.pdf). Unilateral or bilateral grade 2 radiographic changes were required for inclusion as having SI. SI involvement was further defined as asymmetrical when radiographic scoring grades were discordant between the 2 SI joints and as unilateral when the opposite SI joint was completely uninvolved.

Results: 70 patients (25%) had radiographic SI; all either had present or past history of backache. Mean age of patients with SI was 51.6±11 years, and 53.5% were male. Unilateral SI was present in 14 patients (27%); bilateral SI in 38 patients (73%). Of those with bilateral involvement, SI was asymmetrical in 28 (73%) patients. HLA-B*0801 was significantly associated with asymmetrical SI, which included those with unilateral SI or asymmetrical bilateral involvement ($p=0.001$), and in striking contrast, HLA-B*2705 was significantly associated with bilateral symmetrical SI ($p=<0.001$). On backward step-wise multiple regression analysis, model predicted significant association of peripheral joint erosions (OR 1.91, $p=0.03$), PASI maximum (OR 1.05, $p=0.03$), younger PsA age of onset (OR 0.93, $p=<0.001$), presence of HLA-B*0801 (OR 2.9, $p=0.001$) and HLA-B*2705 (OR 2.39, $p=0.02$) with SI.

Conclusion: Twenty five percent of PsA patients developed SI on long-term follow up. PsA developing at younger age, severe skin PsO, peripheral joint erosions, HLA-B*0801 and HLA-B*2705 are clinical and genetic predictors for the development of SI. We report for the first time that there are two separate principal patterns of HLA antigens explaining 2 clinically distinct sub-types of radiographic SI.

Disclosure: M. Haroon, None; **A. Szentpetery**, None; **P. Gallagher**, None; **R. Winchester**, None; **O. FitzGerald**, Pfizer, Abbott, UCB, Roche, MSD, BMS, 2, Janssen Pharmaceutica Product, Pfizer, Abbott, Roche, MSD, BMS, 5, Pfizer, Abbott, UCB, Roche, Janssen, 8.

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Low Diagnostic Utility Of Candidate Definitions For a Positive MRI Of The Spine In Axial Spondyloarthritis. Ulrich Weber[1], Veronika Zubler[1], Zheng Zhao[2], Robert GW Lambert[3], Kaspar Rufibach[4], Stanley Chan[3], Susanne Juhl Pedersen[5], Mikkel Ostergaard[6] and Walter P. Maksymowych[3]. [1]Balgrist University Hospital, Zurich, Switzerland, [2]Department of Rheumatology, University of Alberta and PLA General Hospital, Beijing, PR China, Beijing, China, [3]University of Alberta, Edmonton, AB, [4]rePROstat, Basel, Switzerland, [5]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [6]Copenhagen Center for Arthritis Research, Glostrup, Denmark.

Background/Purpose: A recent consensus statement based on a systematic literature review by the Assessment of SpondyloArthritis International Society suggested the presence of ≥3 corner inflammatory lesions (CIL) or of several corner fat lesions (CFL) as candidate definitions for a positive MRI of the spine in axial spondyloarthritis (SpA) [1]. The goals of this study were to determine data-driven cut-off values for spinal CIL and CFL yielding a specificity ≥90%, and to evaluate their diagnostic utility in non-radiographic axial SpA (nr-axSpA) and ankylosing spondylitis (AS).

Methods: The study sample comprised 2 independent cohorts A/B of 130 consecutive patients with back pain ≤50 years newly referred to 2 university clinics, and 20 healthy controls (HC). Patients were classified according to clinical examination and pelvic radiography as having nr-axSpA (n=50), AS (n=33), or mechanical back pain (MBP; n=47). Spinal MRI were assessed by 4 blinded readers according to the standardized CanDen module. Readers recorded bone marrow edema and fat infiltration in the central and lateral compartment of 23 discovertebral units. We calculated cut-off values for CIL and CFL to obtain ≥90% specificity and the corresponding area under the curve (AUC) with confidence interval (CI). Finally, we tested the diagnostic

utility (mean sensitivity/specificity over 4 readers) of cut-off values for spinal MRI as proposed in the literature ('3 CIL [1] and ≥5 CFL [2]) for nr-axSpA and AS patients in both cohorts.

Results: In cohorts A/B, ≥3 CIL were reported in 43.4%/25.0% of nr-axSpA patients, 61.1%/42.7% of AS patients, and 25.0%/10.6% of MBP patients (and in 17.5% of HC in cohort A). Corresponding numbers for ≥5 CFL were 31.6%/43.5%, 47.2%/54.2%, and 32.1%/24.2% (and 23.8%). For cohorts A/B, the rounded lesion cut-offs to obtain ≥90% specificity were 3/2 CIL and 7/10 CFL, respectively. The corresponding AUC for CIL were 0.69 (CI 0.49–0.84) and 0.69 (CI 0.47–0.85) in the 2 cohorts, and for CFL 0.60 (CI 0.43–0.75) and 0.71 (CI 0.56–0.82), respectively. The diagnostic utility of the spinal thresholds of ≥3 CIL and of ≥5 CFL was low in both cohorts when comparing nr-ax SpA versus MBP.

Diagnostic utility of candidate definitions for a positive MRI of the spine in cohorts A/B

Lesion cut-off	Mean Sensitivity	Mean Specificity	Positive LR	Negative LR
nr-axSpA vs MBP				
≥3 CIL	0.43/0.25	0.75/0.89	1.74/2.36	0.75/0.84
≥5 CFL	0.32/0.44	0.68/0.76	0.98/1.80	1.01/0.75
≥7 CFL	0.21/0.34	0.86/0.82	1.47/1.86	0.92/0.81
≥10 CFL	0.12/0.21	0.89/0.90	1.11/2.13	0.99/0.88
AS vs MBP				
≥3 CIL	0.61/0.43	0.75/0.89	2.44/4.03	0.52/0.64
≥5 CFL	0.47/0.54	0.68/0.76	1.47/2.23	0.78/0.61
≥7 CFL	0.36/0.47	0.86/0.82	2.53/2.58	0.75/0.65
≥10 CFL	0.19/0.45	0.89/0.90	1.81/4.55	0.90/0.61

LR: Likelihood Ratio

Conclusion: In this controlled study, the definitions of a positive spinal MRI proposed in a recent consensus statement showed low diagnostic utility in nr-axSpA. While a cut-off of ≥2/≥3 CIL for a positive spinal MRI was optimal, the threshold for CFL was as high as 10.

References.

[1] Hermann KG et al. ARD 2012;71:1278. [2] Bennett A et al. ARD 2010;69: 891.

Disclosure: U. Weber, None; **V. Zubler**, None; **Z. Zhao**, None; **R. G. Lambert**, None; **K. Rufibach**, None; **S. Chan**, None; **S. J. Pedersen**, None; **M. Ostergaard**, None; **W. P. Maksymowych**, None.

ACR Concurrent Abstract Session
Systemic Sclerosis, Fibrosing Syndromes and Raynaud's – Pathogenesis, Animal Models and Genetics I: Therapeutic Interventions in Preclinical Animal Models of Sclerodermaoderma

Sunday, October 27, 2013, 2:30 PM–4:00 PM

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CC-220: A Clinical Stage Immunomodulatory, Antifibrotic Drug For Systemic Sclerosis. Jörg HW Distler[1], Yongqing Wang[2], Pawel Zerr[3], Katrin Palumbo[4], Gerald Horan[5], Peter Schafer[5] and Bashar Kahaleh[2]. [1]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]University of Toledo, Toledo, OH, [3]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [4]University of Erlangen-Nuremberg, Erlangen, Germany, [5]Celgene Corporation, Summit, NJ.

Background/Purpose: Systemic Sclerosis (SSc) is an autoimmune fibrotic disease in which B cells may play a crucial role in pathogenesis. CC-220 is an immunomodulatory drug with antifibrotic activity in early clinical development. CC-220 binds with high affinity to cereblon, part of the DCX (DDB1-CUL4–X-Box) ubiquitin ligase complex, and regulates ubiquitination of target proteins including key regulators of hematopoietic cell differentiation and activation. CC-220-treatment suppresses B cell proliferation, differentiation, Ig secretion, and cytokine production. In addition to its B cell suppressive properties, CC-220 has demonstrated antifibrotic activity both *in vitro* and *in vivo*. This combination of B cell suppressive and antifibrotic properties makes CC-220 an intriguing potential therapeutic for SSc. To better characterize its activity, we evaluated CC-220 in primary cells from SSc patients and in mouse models of scleroderma.

Methods: Primary dermal fibroblasts were isolated from both normal volunteers and SSc patients and cultured for 24 hours in presence of CC-220 or vehicle control. Gene expression was evaluated by quantitative RT-PCR. Dermal thickening was induced in mice by intradermal injection of bleomycin every other day for 3 weeks. CC-220 was orally administered at 30 mg/kg daily and skin samples were processed for histology, hydroxyproline analysis and quantitative RT-PCR. Tight skin-1 (Tsk) mice were similarly treated for 5 weeks.

Results: CC-220 had little to no effect on basal or TGFβ-stimulated expression of profibrotic genes in normal fibroblasts. However, in fibroblasts derived from SSc patients, CC-220 treatment induced a robust, dose-dependent normalization of the expression of key fibrotic mediators including COL1a1, α-SMA, PAI-1, FN and MMP1. We next wondered if this broad therapeutic effect, specific to the SSc fibroblasts, might be mediated by epigenetic mechanisms, so we measured expression of the DNA methyltransferase, Dnmt1. Dnmt1 is elevated in SSc fibroblasts, and CC-220 induced a dose-dependent decrease in expression, suggesting that CC-220 may mediate its antifibrotic activity, at least in part, via regulation of epigenetic modifiers.

To evaluate its antifibrotic potential *in vivo*, CC-220 was tested in a bleomycin-induced skin fibrosis model and in Tsk mice, a genetic model of scleroderma skin disease. In the bleomycin model, CC-220 treatment significantly prevented dermal thickening and inhibited expression of profibrotic genes in the skin, including COL1a1 and TGFβ1. In Tsk mice, CC-220 treatment resulted in highly significant decreases in dermal thickness and in skin collagen content as measured by hydroxyproline. Gene expression of COL1a1 and CTGF are elevated in the skin of Tsk mice and were significantly decreased by CC-220 treatment.

Conclusion: CC-220 potently regulates key profibrotic factors and has demonstrated antifibrotic efficacy *in vitro* and *in vivo*. The combined antifibrotic efficacy and B cell suppressive activity make it a promising candidate for treatment of SSc.

Disclosure: J. H. Distler, Celgene, 2; **Y. Wang**, None; **P. Zerr**, None; **K. Palumbo**, None; **G. Horan**, Celgene, 3; **P. Schafer**, Celgene, 3; **B. Kahaleh**, Celgene, 2.

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Activation Of The Signal Transducer and Activator Of Transcription 3 By Transforming Growth Factor-Beta Promotes Fibroblast Activation and Tissue Fibrosis. Barbora Sumova[1], Katrin Palumbo-Zerr[2], Clara Dees[3], Pawel Zerr[2], Oliver Distler[4], Georg Schett[3], Ladislav Senolt[5] and Joerg H. W. Distler[2]. [1]Department of Rheumatology of the First Faculty of Medicine, Institute of Rheumatology and Connective Tissue Research Laboratory, Prague, Czech Republic, [2]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]University of Erlangen-Nuremberg, Erlangen, Germany, [4]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [5]Institute of Rheumatology, Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic.

Background/Purpose: Systemic sclerosis (SSc) is characterized by uncontrolled activation of fibroblasts resulting in tissue fibrosis in which the TGFβ signaling plays a main role. Signal transducer and activator of transcription 3 (STAT3) is a transcription factor belonging to the family of seven proteins transmitting the signals from plasma membrane receptors to nucleus with subsequence modulation of gene transcriptions involved in angiogenesis, immune responses and metastasis. Nuclear translocation occurs upon phosphorylation by several receptors tyrosine kinases, particularly by Janus kinase 2 (JAK2). In the present study, we evaluated the role of STAT3 as a downstream mediator of TGFβ signaling pathway in the pathogenesis of SSc and analyzed the potential of STAT3 inhibition as a novel anti-fibrotic approach.

Methods: Activation of STAT3 in the human skin and in murine models was analyzed by IF staining for phosphorylated and thereby activated STAT3 (pSTAT3). Selective inhibitors of JAK2 and STAT3 and knockdown strategies were used to interfere with JAK2 and STAT3 signaling *in vitro* and *in vivo*. The anti-fibrotic potential of STAT3 inhibition was evaluated in two mouse models of SSc: bleomycin-induced fibrosis and fibrosis induced by overexpression of a constitutively active TGFβ receptor type I (TBR).

Results: Increased activation STAT3 signaling with accumulation of pSTAT3 in fibroblasts was observed in the skin of SSc patients and in murine models of SSc. Stimulation with TGFβ increased the expression of STAT3 protein and induced nuclear accumulation of pSTAT3 in cultured fibroblasts. Pre-incubation with specific JAK2 inhibitor abrogated the TGFβ induced induction of STAT3 as well as nuclear accumulation of pSTAT3, demonstrating that TGFβ activates STAT3 in a JAK2 dependent manner. Inactiva-

tion of STAT3 with the selective STAT3 inhibitor S3I-201 significantly reduced the stimulatory effects of TGFβ on the protein collagen level (−56%, p=0.05) and the mRNA level of *Col1a1* (−71%, p=0.0095) and *Col1a2* (−35 %, p=0.0095) and myofibroblast differentiation in cultured human fibroblasts. The same results were observed when STAT3 was inactivated by conditional knockout in murine fibroblasts. Moreover, treatment with S3I-201 (10 mg/kg) exerted potent anti-fibrotic effects in bleomycin- and TBR induced fibrosis. In the model of bleomycin induced fibrosis, treatment with the specific STAT3 inhibitor decreased dermal thickening by 33% (p=0.0009), hydroxyproline (HP) content by 51 % (p=0.001) and myofibroblast counts by 55 % (p=0.0009) Potent anti-fibrotic effects with reduced dermal thickening, decreased HP content and reduced myofibroblast counts were also observed in TBR induced fibrosis.

Conclusion: We characterize STAT3 as a novel downstream mediator of the profibrotic effects of TGFβ in SSc. We demonstrate that TGFβ activates STAT3 and that this activation is required for the profibrotic effects of TGFβ. Inhibition of STAT3 prevents fibroblast activation and shows potent antifibrotic effect in different preclinical models of SSc. These findings may have direct translational implications considering that several STAT3 inhibitors are currently in clinical trails.

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Inhibition Of Casein Kinase II Reduces TGFβ Induced Fibroblast Activation and Ameliorates Experimental Fibrosis. Yun Zhang. Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, Erlangen, Germany.

Background/Purpose: Casein kinase-2 (CK2) is a highly conserved serine/threonine kinase. CK2 is a tetramer composed of 2 catalytic subunits (α or α') and 2 β regulatory subunits, which are essential for cell viability. CK2 is discussed as a target for cancer therapy and is currently evaluated in clinical trials. Recently, we have shown that targeting of JAK2 might be an interesting molecular approach for the treatment of systemic sclerosis (SSc).

Methods: Activation of CK2, JAK2, and STAT3 in human skin and in experimental fibrosis were determined by immunohistochemical analysis. CK2 signaling was inhibited by the selective CK2 inhibitor 4, 5, 6, 7-Tetrabromobenzotriazole (TBB). The mouse models of bleomycin-induced and TGF-β receptor I (TBR)-induced dermal fibrosis were used to evaluate the anti-fibrotic potential of specific CK2 inhibition *in vivo*.

Results: Increased expression of CK2 was detected by immunohistochemistry in skin sections of SSc patients, particularly in fibroblasts. Inhibition of CK2 by TBB in cultured fibroblasts completely abrogated the stimulatory effects of TGFβ on collagen release (p<0.05). After TBB treatment, stress fiber formation and α-smooth muscle actin (α-SMA) expression in TGFβ-stimulated fibroblasts were significantly reduced by 97% (p=0.0064) and 69% (p=0.0280). Besides reduced fibroblast activation, western blot analyses showed complete normalization of the levels of phosphorylated JAK2 (pJAK2) in the cytoplasm and of phosphorylated STAT3 (pSTAT3) in the nucleus of TGFβ-treated fibroblasts upon preincubation with TBB (p=0.0004 and p=0.0214). In addition, treatment with TBB effectively prevented bleomycin-induced fibrosis in mice with decreased dermal thickness by up to 70% (p<0.0001) and efficient reductions in myofibroblast counts by up to 68% (p=0.0002). TBR-induced fibrosis in mice was strongly ameliorated by TBB with efficient reductions of dermal thickening by 75% (p<0.0001). Myofibroblast counts and hydroxyproline content also decreased by 59% and 40% (p<0.0001 and p=0.0193), respectively. In both murine models, we observed reduced pJAK2 and pSTAT3 expression as analyzed by immunohistochemistry.

Conclusion: We demonstrate that CK2 is activated in SSc and prove that inhibition of CK2 reduces canonical TGF-β signaling and prevents experimental fibrosis in different preclinical models. Considering the potent antifibrotic effects of CK2 inhibition, our study might have direct translational implications. These data provide first evidence that targeting CK2 may be a novel therapeutic approach for fibrotic diseases.

Disclosure: Y. Zhang, None;

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Activation Of Liver X Receptors Inhibits Experimental Fibrosis By Interfering With Interleukin-6 Release From Macrophages. Christian Beyer[1], Jürgen Beer[1], Katrin Palumbo-Zerr[1], Pawel Zerr[1], Alfiya Distler[1], Clara Dees[1], Louis E. Munoz[1], Gerhard Krönke[1], Oliver Distler[2], Steve Anderson[3], Georg A. Schett[4] and Joerg H. W. Distler[1]. [1]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Rheumatology and Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [3]Lexicon Pharmaceuticals Inc., The Woodlands, TX, [4]University of Erlangen-Nuremberg, Erlangen, Germany.

Background/Purpose: Liver X receptors (LXRs) are orphan nuclear receptors with emerging roles in metabolic and autoimmune diseases. Here, we investigated the role of LXRs in experimental skin fibrosis and evaluated their potential as anti-fibrotic targets for systemic sclerosis (SSc) and other fibrotic diseases.

Methods: We studied the role of LXRs in bleomycin-induced skin fibrosis and in tight skin-1 (Tsk-1) mice, reflecting different subtypes of fibrotic disease. To dissect the role of both LXR isoforms in fibrosis, we generated LXRα- and LXRβ-knockout mice as well as LXR-α/β-double-knockout mice. To establish the mode of action of the anti-fibrotic effects of LXRs, we investigated the effects of LXRs on fibroblasts and macrophages.

Results: LXR activation by the LXR agonist T0901317 had potent anti-fibrotic effects in both bleomycin-induced skin fibrosis and Tsk-1 mice as assessed by skin thickness, hydroxyproline content, and the number of myofibroblasts. The anti-fibrotic activity of LXRs was particularly prominent in the inflammatory bleomycin-model in which LXR activation reduced skin thickening by up to 64%, the hydroxyproline content by up to 91% and the number of myofibroblasts by up to 91%.

LXRα-, β- and LXRα/β-knockout mice showed a similar response to bleomycin challenge as wildtype animals. In line with these results, low levels of the LXR target gene ABCA-1 in the skin of bleomycin-challenged and control mice suggested a weak baseline activation of the anti-fibrotic LXR signaling, which, however, could be specifically activated by T0901317. The specificity of T0901317 on LXRs was again reflected by the LXRα/β-knockout mice in which the LXR agonist lacked anti-fibrotic activity.

Of note, fibroblasts were not the direct targets of the anti-fibrotic effects of LXRs. By contrast, LXR activation inhibited macrophage infiltration in fibrotic tissue and decreased the release of the pro-fibrotic cytokine interleukin-6 from macrophages, resulting in reduced fibroblast activation and collagen release.

Conclusion: We identified LXRs as novel therapeutic targets for SSc and other fibrotic diseases, a yet unknown aspect of these nuclear receptors. Our data suggest that LXR activation might be particularly effective in patients with inflammatory disease subtypes. Activation of LXR interfered with the release of interleukin-6 from macrophages and, thus, inhibited fibroblast activation and collagen release.

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Bosentan Improves Vascular Abnormalities In Endothelial Cell-Specific Fli1 Knockout Mice By Increasing The DNA Binding Ability Of Fli1 - a Possible Mechanism Explaining The Effect Of Bosentan On Scleroderma Vasculopathy. Kaname Akamata[1], Yoshihide Asano[1], Takashi Taniguchi[1], Takehiro Takahashi[1], Yohei Ichimura[1], Tetsuo Toyama[1], Maria Trojanowska[2] and Shinichi Sato[1]. [1]University of Tokyo Graduate School of Medicine, Tokyo, Japan, [2]Boston University, Boston, MA.

Background/Purpose: Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by initial vascular injuries and resultant fibrosis of skin and certain internal organs. Although there have been no established treatments against SSc, recent studies have demonstrated that bosentan, a dual endothelin receptor antagonist, reverses nailfold capillary changes in SSc patients. However, the molecular mechanism explaining this observation still remains unknown. Therefore, we herein investigated the mechanism underlying the reversal effect of bosentan on SSc vasculopathy by using endothelial cell (EC)-specific Fli1 knockout mice (Fli1 ECKO mice), which mimic the functional and morphological abnormalities characteristic of SSc vasculopathy.

Methods: Eight-week-old Fli1 ECKO mice were administered intraperitoneally with bosentan for 4 weeks. The expression levels of VE-Cadherin, PECAM1, a-SMA, and Fli1 were evaluated by immunohistochemistry. Vascular structure in the back skin was visualized by intravenously injected FITC-dextran. Vascular permeability was evaluated by the degree of Evans blue dye extravasation. The effects of bosentan on c-Abl, PKC-d, and Fli1 in human dermal microvascular ECs (HDMECs) were evaluated by immunoblotting.

Results: The structural and functional abnormalities, including stenosis of arterioles, dilation of capillaries, and increased vascular permeability, of small dermal blood vessels were improved by the administration of bosentan in Fli1 ECKO mice. Bosentan reversed the abnormal expression of various genes regulating EC-pericyte interaction, EC-EC interaction, and degradation of vascular basement membranes in dermal microvascular ECs isolated from Fli1 ECKO mice. In HDMECs, bosentan suppressed the activity of c-Abl and PKC-d, resulting in decreased phosphorylation levels of Fli1 at threonine 312. Consistent with the evidence that, when unphosphorylated, the DNA binding ability and the protein stability of Fli1 are increased, Fli1 protein levels were elevated along with the increase of its DNA binding, while Fli1 mRNA levels were not affected, after the exposure to bosentan in those cells.

Conclusion: Bosentan reverses the functional and morphological abnormalities of Fli1 ECKO mice at least partially by increasing the transcriptional activity and the protein levels of Fli1 through post-translational modification without affecting its mRNA expression. These results suggest that the efficacy of bosentan on SSc vasculopathy, in which Fli1 deficiency due to the epigenetic mechanism is deeply involved, is partly attributable to its reversal effect on Fli1 transcriptional activity and expression in SSc endothelial cells.

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Activating Transcription Factor 3 Regulates Canonical Transforming Growth Factor Beta Signaling In Experimental Fibrosis. Tatjana Mallano[1], Katrin Palumbo-Zerr[1], Christian Beyer[1], Clara Dees[2], Jingang Huang[1], Tsonwin Hai[3], Georg A. Schett[2] and Joerg H. W. Distler[1]. [1]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]University of Erlangen-Nuremberg, Erlangen, Germany, [3]The Ohio State Biochemistry Program, The Ohio State University, Columbus, USA, Colombus, OH.

Background/Purpose: Activating transcription factor 3 (ATF3), a member of the activating transcription factor/cAMP-responsive element binding protein (ATF/CREB) family of transcription factors is induced by various types of cellular stress including oxidative stress. Here, we analyzed ATF3 as a downstream mediator of TGF- β signaling in fibroblast activation and tissue fibrosis in systemic sclerosis (SSc).

Methods: Activation of ATF3 expression in the skin and dermal fibroblasts was determined by real-time PCR, Western blot and immunohistochemistry. To investigate the role of ATF3 in fibrosis, ATF3 knock-out mice and wildtype littermates were evaluated in the mouse models of bleomycin-induced dermal fibrosis and dermal fibrosis induced by overexpression of a constitutively active TGF-β receptor I (TBR). The content was determined by haematoxylin-eosin and trichrome stainings, by immunohistostaining for aSMA and hydroxyproline assays respectively. In vitro cultured fibroblasts were used and measure collagen release by SirCol and study target genes by RT-PCR. Co-immunoprecipitation (Co-IP) and Smad reporter assay were performed to study physical and functional interactions between ATF3 and Smad3.

Results: An increased expression of ATF3 was detected in the upper layer of the dermis of SSc patients on fibroblasts double stained for ATF3 and anti-prolyl-4-hydroxylase ($p= 0.0016$). The overexpression of ATF3 persisted in cultured SSc fibroblasts with increases of 292% ($p= 0.043$). TGF-β induces ATF3 with an increase of 256% ($p= 0.01$). ATF3 knock-out fibroblasts were less sensitive to the pro-fibrotic effects of TGF-β with impaired induction of collagen mRNA and protein upon stimulation with TGF-β. In the model of bleomycin-induced fibrosis, dermal thickening was decreased by 70% ($p= 0.02$), the hydroxyproline content by 73% ($p= 0.035$) and the myofibroblast counts by 80% ($p= 0.0003$) in AFT3 knockout mice compared to wild type littermates. ATF3 knockout mice were also protected from TBR induced fibrosis with significant decreases in dermal thickening ($p= 0.003$), accumulation of collagen ($p= 0.001$) and myofibroblast differentiation ($p= 0.002$). Function studies demonstrated that ATF3 interacts with Smad3 to regulate the pro-fibrotic effects of TGF-β. Co-IP demonstrated that TGF-β induces binding of ATF3 to Smad3. Reporter study and analyses of the expression of classical Smad target genes such as PAI-1 demonstrated that the binding of ATF3 to Smad3 stimulates the transcriptional activity of Smad3. The activity in Smad3 reporter assays and the expression of PAI-1 upon stimulation with TGF-β were both strongly reduced in ATF3 knockout fibroblasts compared to control cells (decreases of 56 %, $p= 0.004$ and 85 %, $p= 0.02$, respectively).

Conclusion: We demonstrate for the first time a key-role of ATF3 in fibroblast activation and tissue fibrosis in SSc. Targeting of the ATF3 reduced the stimulatory effect of TGF-β on cultured fibroblasts by interfering with canonical Smad signaling. Moreover, knockdown of ATF3 protected from experimental fibrosis in different mouse models. Considering the potent anti-fibrotic effects observed in this study, ATF3 might be a candidate for molecular targeted therapies of SSc.

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ACR/ARHP Combined Session

ACR/ARHP Combined Rehabilation Abstract Session

Sunday, October 27, 2013, 2:30 PM–4:00 PM

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The Value Of History and Physical Examination Findings In The Diagnosis Of Symptomatic Meniscal Tear Among Middle-Age Subjects With Knee Pain. Jeffrey N. Katz, Yan Dong, John Wright, Stephanie Chen, Scott Martin, Laurel Donnell-Fink, Benjamin N. Rome and Elena Losina. Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Clinicians often rely on mechanical symptoms (e.g. clicking, catching, popping, giving way) and tests such as the McMurray sign in the diagnosis of symptomatic meniscal tear (MT). While the diagnostic value of these findings has been validated in younger patients with traumatic MT, there is limited data on the utility of the history and physical exam in the diagnosis of symptomatic MT in middle-age and older persons.

Methods: We enrolled patients $>$ 45 years old presenting with unilateral knee pain to 2 academic orthopedists. A research associate completed a standardized medical history and musculoskeletal physical exam. The history included mechanical symptoms and other items such as symptom duration and diffuse vs. localized location. The exam included identification of tender areas, motion, provocative tests and performance tests. The orthopedist, blind to this standardized assessment, rated his confidence that patients' symptoms were attributable to MT from 0 (certain the symptoms are NOT from MT) to 100 (certain that symptoms ARE from MT). We defined the primary outcome ("expert diagnosis of MT") as confidence $>$ 70. History and physical exam findings associated with this outcome ($p < 0.05$ or OR > 1.5 or < 0.75) in bivariate analyses were advanced to multivariate models. Findings associated in the model ($p < 0.05$) with expert diagnosis of MT were included in an additive index, with weights proportional to adjusted OR's. We calculated the proportion of subjects with particular index scores that had expert diagnosis of MT.

Results: The sample consisted of 80 persons who provided history and physical exam data. Median age was 62 years (range 47, 90) and 66% were female. 28% had expert diagnosis of MT. In bivariate analyses, none of the traditional mechanical symptoms (locking, clicking, catching, popping, giving way) were associated with expert's diagnosis of MT, nor was the McMurray test. History findings associated with expert diagnosis of MT included having localized pain (that the subject could point to with 1 finger) and pain present for $<$ 1 year. Physical exam findings associated with expert diagnosis of MT were joint line tenderness, absence of anserine bursa tenderness and knee pain with the step down test. These history and exam findings were aggregated into an additive index with 1 point for each positive feature and 1 subtracted for anserine bursal pain. 6% (1/17; 95% CI 0–17%) of subjects with -1 or 0 points had expert diagnosis of MT, while 21% (9/43; 95% CI 9–33%) of those with 1–2 points and 60% (12/20; 95% CI 38–82%) of those with 3–4 points had expert diagnosis of MT.

Conclusion: In this sample of middle-age and older subjects with knee pain, select history and physical findings identified subjects with low ($\sim$6%) risk of expert diagnosis of MT and a group with moderate risk of $\sim$60%. These findings suggest that the history and physical exam may be useful in the diagnosis of MT, but that emphasis on the "mechanical symptoms" traditionally thought to be associated with meniscal tear may not be useful in

determining whether those symptoms are attributable to MT in older patients with knee pain.

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Cost-Effectiveness and Cost-Utility Of a One-Year Coaching Program For Healthy Physical Activity In Rheumatoid Arthritis. Nina Brodin[1], Malin Lohela Karlsson[2], Emma Swärdh[1] and Christina H. Opava[3]. [1]Karolinska Institutet, SE 14183 Huddinge, Sweden, [2]Karolinska Institutet, Stockholm, Sweden, [3]Karolinska Institutet, Huddinge, Sweden.

Background/Purpose: Economic evaluations of interventions, as a complement to the effect evaluation, intend to inform decision makers about whether an intervention provides good value for the money. Since resources in healthcare are scarce, there is an increased demand from decision makers for economic evaluations. Economic evaluations of non-pharmacologic care in RA are still not as commonly presented as evaluations of the costs related to medications, for example. At the CARE VI meeting, the importance of such evaluations was acknowledged. Thus, the aim of the present study was to describe cost-effectiveness and cost-utility of a one-year coaching program aimed at increasing daily physical activity in RA, previously studied in the Physical Activity in Rheumatoid Arthritis (PARA) study.

Methods: The protocol for the PARA study is available at http://www.controlled-trials.com/ISRCTN88886304/. Costs were collected and estimated retrospectively. The study was performed from 2000 to 2004 and all costs were deflated using gross domestic product with 2005 as a reference year. Cost-effectiveness was calculated based on the intervention cost per patient, with respect to health status (EuroQol visual analog scale, EQ-VAS) and activity limitation (Health assessment questionnaire, HAQ). To calculate cost utility, Quality adjusted life years (QALY) was used based on the EuroQol-5D.

Results: The cost of the one-year intervention program was estimated to €44 224 of which 65% were for treatment and 35% for education, project activities and administration. Estimated difference in total societal cost between the intervention (IG) and control (CG) was €372 per patient. ICER for one point (1/100) of improvement in EQ-VAS was estimated to €72. By offering the intervention exclusively to more affected patients (MO), both the effectiveness and cost-effectiveness were improved. The estimated ICER for a one-point improvement in EQ-VAS was €35 for MO in the IG compared to MO in the CG. By offering the intervention to MO in the IG only, and not to less affected patients (LE), an extra point of improvement in EQ-VAS would cost €21. An extra gain in QALY for this group would cost €3585 and for one extra point (1.0) of improvement in HAQ, the cost would be €1517.

Conclusion: The intervention resulted in improved effect on EQ-VAS for the intervention group with a cost of €72 per extra point. The result reveals that the cost per QALY and ICER for improvement in health status was lower in the subgroup with more affected patients (MO) in the IG compared to in the CG with the same level of disability. The cost per QALY and ICER for improvement in health status was even lower when comparing more affected patients (MO) to less affected patients (LE) within the IG. This indicates that from a societal perspective, it would be more cost-effective to offer this kind of intervention exclusively to more affected patients with RA, than to all patients with RA.

Disclosure: N. Brodin, None; **M. Lohela Karlsson**, None; **E. Swärdh**, None; **C. H. Opava**, None.

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Psychosocial Determinants Of Total Knee Arthroplasty Outcomes 2 Years After Surgery. Aparna Ingleshwar[1], Maria A. Lopez-Olivo[2], Glenn C. Landon[3], Sherwin J. Siff[3], Andrea Barbo[4] and Maria E. Suarez-Almazor[5]. [1]The University of Texas, MD Anderson Cancer Center, Houston, TX, Houston, TX, [2]University of Texas. M.D Anderson Cancer Center, Houston, TX, [3]St. Luke's Episcopal Health System, Houston, TX, [4]MD Anderson Cancer Center, Houston, TX, [5]University of Texas MD Anderson Cancer Center, Houston, TX.

Background/Purpose: To explore potential psychosocial and demographic factors that influence Total Knee Arthroplasty (TKA) outcomes and satisfaction at 24 months.

Methods: A prospective cohort study was conducted. Outcome measures of interest were: WOMAC and SF-36 recorded at baseline and 24 months post-surgery, and SkiP, recorded at 24 months. Independent variables included: the Medical Outcome Study–Social Support Scale (MOS-SSS); Depression, Anxiety and Stress scale (DASS); brief COPE inventory; Health Locus of Control (MHLC); Arthritis Self-efficacy Scale (ASES) and the Life Orientation Test–revised (LOT). Spearman rank correlations between baseline predictors and outcomes at 24 months were calculated. Stepwise multiple linear regression was performed to determine the influence of various patient psychosocial domain characteristics at baseline, on the outcomes at 24 months. For each outcome, a model that considered the baseline outcome measure as one of the predictors and a model that did not consider this were run. Patient's age and sex were forced into all models.

Results: There were 178 TKA patients who had baseline and 24 month scores. Patients' mean age was 65±9 years; 65% were women. Results from the bivariate correlations between psychosocial and demographic characteristics, and outcomes at 24 months showed that; only problem-solving coping, emotional coping and the belief that others have control over one's health were not significantly correlated with any of the outcomes of interest ($p>0.05$). Regression analyses with baseline outcomes adjustment indicated that; older age, higher BMI, less tangible support, and lower optimism were associated with worse pain and function scores (total adjusted R^2: pain=0.15 and function=0.21). Older age, higher BMI and a greater number of comorbidities was associated with lower PCS domain scores (total adjusted R^2= 0.33); whereas being depressed ($p<0.001$) and having lower optimism ($p<0.001$) was associated with reduced MCS scores (total adjusted R^2= 0.43). Being employed ($p<0.001$) and less dysfunctional coping ($p=0.01$) was associated with greater satisfaction with knee procedure (total adjusted R^2: 0.12). Similar results were obtained in the models without baseline outcomes adjustment except for MCS component scores wherein; increased BMI ($p=0.04$), greater number of comorbidities ($p=0.03$), lower tangible support ($p=0.03$) and higher stress ($p=0.03$) was associated with lower MCS scores (total adjusted R^2= 0.43).

Conclusion: Psychosocial factors such as; level of tangible support, depression, problem-solving coping, dysfunctional coping and optimism were associated with pain, function and satisfaction in patients after TKA. Thus, in order to achieve clinical success following TKA, physicians must also consider their patients' psychosocial status. Further research is needed to study suitable intervention strategies targeting these identified psychosocial determinants.

Disclosure: A. Ingleshwar, None; **M. A. Lopez-Olivo**, None; **G. C. Landon**, None; **S. J. Siff**, None; **A. Barbo**, None; **M. E. Suarez-Almazor**, None.

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Is The Severity Of Knee Osteoarthritis On MRI Associated With Outcome Of Exercise Therapy? Jesper Knoop[1], Joost Dekker[2], Marike van der Leeden[2], Martin van der Esch[1], J.P. Klein[2], David J. Hunter[3], Leo D. Roorda[1], Martijn P.M. Steultjens[4] and Willem F. Lems[2]. [1]Reade, centre for rehabilitation and rheumatology, Amsterdam, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands, [3]University of Sydney, Sydney, Australia, [4]Glasgow Caledonian University, Glasgow, Scotland.

Background/Purpose: To evaluate associations between severity of knee osteoarthritis (OA) on MRI and treatment outcome in knee OA patients treated with exercise therapy.

Methods: Ninety-five participants with knee OA in a 12-week exercise program had obtained 3.0 Tesla MRI scans of the knee joint, prior to treatment. MRI data were systematically assessed for OA severity of multiple features (cartilage loss, bone marrow lesions, osteophytes, effusion/synovitis, and meniscal abnormalities) according to the BLOKS scoring system. Regression analyses were performed to analyze associations between OA severity on MRI and outcome of exercise therapy, i.e. changes in activity limitations (WOMAC physical function; primary outcome), pain (NRS), and upper leg muscle strength, and treatment response (OMERACT-OARSI criteria).

Results: Improvements of on average 24%, 34%, and 21% in WOMAC physical function, NRS pain and upper leg muscle strength, respectively, after 12-week exercise therapy were found. Moderate-to-severe patellofemoral (PF) cartilage loss was significantly associated with less improvements in both activity limitations ($p=.01$) and upper leg muscle strength ($p=.04$), while moderate-to-severe PF osteophytes with less improvements in upper leg muscle strength ($p<.01$). Severity of other features on MRI were not found to be associated with treatment outcome.

Conclusion: Effectiveness of exercise therapy was found to be independent of OA severity on MRI, except for cartilage loss and osteophytes, both in the PF compartment. Our study suggests that all grades of OA severity on MRI can benefit from professionally supervised exercise therapy, although effects might be reduced in patients with advanced PF OA.

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Ethnic Variations At Time Of Surgery and During Follow-Up In Patients Undergoing Total Knee Arthroplasty. Aparna Ingleshwar[1], Andrea Barbo[2], Glenn C. Landon[3], Sherwin J. Siff[3], Sofia De Achaval[4] and Maria E. Suarez-Almazor[5]. [1]The University of Texas, MD Anderson Cancer Center, Houston, TX, Houston, TX, [2]MD Anderson Cancer Center, Houston, TX, [3]St. Luke's Episcopal Health System, Houston, TX, [4]U.T. MD Anderson Cancer Center, Houston, TX, [5]University of Texas MD Anderson Cancer Center, Houston, TX.

Background/Purpose: Literature reports sizable improvements in pain and function in patients having undergone Total Knee Arthroplasty (TKA) procedure. However, significant disparities exist in the utilization of this procedure by racial groups. Hence, the aim of this study is to evaluate the role of race on TKA outcomes.

Methods: Patients were recruited from 2 orthopedic clinics. Outcomes measured included: i) WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) measuring pain, stiffness and function (higher scores=worse outcomes), ii) SF-36 measuring mental (MCS) and physical (PCS) health status. Scores at baseline, 6 and 24 months were generated and absolute change (Δ= Baseline score – 6/24 months score) was calculated. ANOVA was used to determine whether: scores at baseline, 6 and 24 months, independently, varied among the racial groups and; the absolute and percent change scores (at 6 and 24 months) varied among the racial groups. Multiple regression analysis was conducted to evaluate the association of race and other demographic characteristics with 6 and 24 months TKA outcomes; with and without controlling for baseline outcomes.

Results: 247 of 615 patients screened completed baseline of which 241 completed 6 months and 178 completed 24 months assessments. Of the 247; 162 (66%) were females, 114 (46%) were <65 years, 172 (70%) were White, 62 (25%) were African American and, 11 (4%) were Hispanic. Although African Americans compared to Whites had consistently greater pain and function WOMAC scores at all three time periods, this difference was statistically significant only pre-operatively (pain- 62 vs 52, $p<0.05$ and function- 62 vs 52, $p<0.05$). With respect to SF-36 scores: compared to Whites, Hispanics had significantly lower MCS scores (55 vs 48, $p<0.05$) only at 6 months, whereas, neither clinically nor statistically significant differences in PCS scores were observed between the two groups at any time period. In regards to absolute change: African Americans compared to Whites, experienced greater improvements in pain (Δ: 41 vs 33, NS) and function (Δ: 40 vs 20, $p<0.05$) which was not observed at 24 months. In spite of adjusting for age, gender, marital status, educational attainment and baseline outcomes; being Hispanic was still associated with lower MCS scores ($p=0.02$) at 6 months, and being African American was still associated with lower functional status at 24 months ($p=0.04$).

Conclusion: When compared to Whites, African American patients started out with a lower preoperative status. Yet, they achieved greater gains in pain and function than White patients, within 6 months. However, by 24 months these improvements leveled off such that no significant difference in change was observed between the two groups. Controlling for demographic characteristics and baseline outcomes, ethnicity was predictive of TKA outcomes such that; being Hispanic was associated with lower mental health at 6 months and being African American was associated with poorer functional status at 24 months. Further research is needed to explore potential behavioral and psychosocial determinants that explain reduced pain and functional outcomes in African American patients.

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Relationships Between Clinical Outcome Measures and Gait Variables Before and After Total Hip Arthroplasty. Kharma C. Foucher[1] and Omar Behery[2]. [1]University of Illinois at Chicago, Chicago, IL, [2]Rush University Medical Center, Chicago, IL.

Background/Purpose: Inadequate clinical response in a substantial portion of total hip arthroplasty (THA) patients, [1] as well as gait deficits after THA [2] have been well-documented. However, the relationships between different types of outcome measures is not always obvious. A more detailed understanding of the relationships between clinical scores and gait variables could lead to new management strategies that would improve outcomes in both domains. The purpose of this study was to determine whether gait variables are related to clinical scores before or after THA, and whether changes in gait variables are related to changes in clinical scores.

Methods: From an IRB-approved repository, we identified 125 subjects (Age 61 $\pm$ 10 years; BMI 29 $\pm$ 5 kg/m^2; 62 Female, 63 Male) who had been evaluated before and 1 year after primary unilateral THA. Harris Hip Scores (HHS) were used to summarize clinical status (preop 57 $\pm$ 14, postop 91 $\pm$ 11). From standard gait analysis data, we selected 3D peak external hip moments and sagittal plane dynamic hip range of motion (HROM) from trials collected at each subject's self-selected normal walking speed. Pearson correlations revealed that speed was significantly correlated with several gait variables before or after surgery, and that change in speed was significantly correlated with change in HHS and gait variables ($R = 0.199$ to 0.660, p values ≤ 0.026). We therefore decided to use first order partial correlation coefficients to evaluate relationships between HHS and gait variables while controlling for speed.

Results: There were significant correlations between preop HHS and HROM ($R_{|speed} = 0.296$, $p = 001$), postop HHS and the peak external rotation moment ($R_{|speed} = 0.234$, $p=0.009$) and the change in HHS and the change in both HROM ($R_{|speed} = 0.252$, $p = 0.005$) and peak internal rotation moment ($R_{|speed} = 0.270$, $p = 0.002$). There were no other statistically significant relationships ($p \geq 0.158$).

Conclusion: To our knowledge, this is the first study linking specific gait variables to clinical outcome measures. After controlling for the relationship between walking speed and both clinical and gait variables, higher preop- and postop- clinical scores, or more clinical improvement, was associated with higher values of range of motion or hip rotational moments. Because the hip abductors play an important secondary role in maintaining rotational control during stance, we found the relationships between HHS and rotational moments particularly notable. It is possible that addressing subtle abductor dysfunction in the transverse plane could improve both gait and clinical outcomes for some patients. Future prospective studies, however, are needed to fully evaluate the time-course of clinical recovery and gait recovery.

References:
1) Hawker et al., Arthritis Rheum 2013; 65(5):1243–5. 2) Ewen et al., Gait Posture 2012; 36(1):1–6.

Disclosure: K. C. Foucher, None; **O. Behery**, None.

ARHP Concurrent Abstract Session
ARHP Exemplary Abstracts
Sunday, October 27, 2013, 2:30 PM–4:00 PM

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Factors That Affect Tender and Swollen Joint Counts In Rheumatoid Arthritis. Christine L. Amity[1], Marisa Eckels[2], Kenneth N. Gold[3], Kelly A. Reckley[4], Niveditha Mohan[5], Stephen R. Wisniewski[6], Elizabeth A. Schlenk[7], Marc C. Levesque[7] and Terence W. Starz[8]. [1]Univ of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh Medical Center, Pittsburgh, PA, [3]Arthritis & Internal Medicine, Pittsburgh, PA, [4]University of Pittsburgh School of Medicine, Pittsburgh, PA, [5]Univ of Pittsburgh Arth Inst, Pittsburgh, PA, [6]University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, [7]University of Pittsburgh, Pittsburgh, PA, [8]Arth & Internal Med Associates, Pittsburgh, PA.

Background/Purpose: Quantitative joint counts are used to determine rheumatoid arthritis (RA) disease activity and are increasingly important for routine clinical practice to optimize patient care. Several factors make quantitative joint assessments challenging. The purpose of this study was to determine how osteoarthritis (OA), fibromyalgia (FM), body mass index

(BMI), handedness and disease activity affect tender and swollen joint counts by examining their effects on the inter-rater reliability of tender and swollen joint counts in a usual care setting.

Methods: 72 RA patients (54 F, 18M) recruited from the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry underwent standardized 28-joint assessments performed by two registered nurses and two rheumatologists at a single clinic visit. A Manual Tender Point (TP) Survey to determine the presence of FM ($\geq$ 11/18 TPs) took place during the same visit. Hand X-rays within 1 year of the clinic visit were graded for the presence of OA by a blinded, independent rheumatologist. BMI and disease duration were obtained from registry data. Subjects were classified according to Clinical Disease Activity Index (CDAI) as being in remission-low (CDAI $\leq$ 10) or moderate-high (CDAI $>$ 10) disease activity. Intra-class correlations and 95% CIs were determined for tender and swollen joints, stratified by variables of interest.

Results: The overall agreement among raters was moderate for tender and swollen joints (ICC = 0.48 and ICC = 0.56, respectively). The agreement among raters for swollen joints was similar in subjects with and without OA, with disease duration $<$ or $\geq$ 3 years, with BMI $<$ or $\geq$ 30 and with remission-low or moderate-high disease activity (ICC = 0.17 to 0.56). For tender joints, agreement was also moderate between disease duration and BMI subgroups (ICC = 0.47 to 0.64). However there were significant differences in agreement for tender joints for subjects with OA versus without (ICC = 0.33 (0.12, 0.50) vs. ICC = 0.65 (0.55, 0.72), respectively), and for subjects in remission-low disease activity versus moderate-high (ICC = 0.13 (−0.03, 0.29) vs. ICC = 0.52 (0.39, 0.63), respectively).

Conclusion: Agreement between raters was only moderate for tender and swollen joint counts. The presence of OA and lower disease activity reduced inter-rater reliability significantly. These results indicate that new methods of assessing joint disease activity may be needed for many of the patients seen in usual care settings as opposed to clinical trials where subjects are generally younger, have less OA and higher levels of disease activity. Our future analyses will focus on the level of agreement between nurses and physicians, on the level of agreement at the individual joint level, and on multivariable analyses that incorporate all factors that may affect inter-rater agreement of tender and swollen joint counts.

Disclosure: C. L. Amity, Genentech and Biogen IDEC Inc., 2; **M. Eckels**, None; **K. N. Gold**, None; **K. A. Reckley**, Genentech and Biogen IDEC Inc., 2; **N. Mohan**, None; **S. R. Wisniewski**, None; **E. A. Schlenk**, None; **M. C. Levesque**, Genentech and Biogen IDEC Inc., 2, Genentech and Biogen IDEC Inc., 5; **T. W. Starz**, None.

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Cardiovascular Diseases In Rheumatoid Arthritis: Can Early Treatment With Disease-Modifying Antirheumatic Drugs Alter The Risk? Rishi Desai[1], Jaya Rao[2], Richard Hansen[3], Gang Fang[2], Matthew Maciejewski[4] and Joel Farley[2]. [1]Brigham & Women's Hospital, Harvard Medical School, Boston, MA, [2]University of North Carolina, Chapel Hill, NC, [3]Auburn University, Auburn, AL, [4]Duke University, Durham, NC.

Background/Purpose: Atherosclerosis is known to be accelerated in rheumatoid arthritis (RA) patients resulting in an increased cardiovascular (CV) risk. Structural damage to joints occurs aggressively within the first few years of RA diagnosis, so it is possible that development of atherosclerosis may also be rapid during the early stages of RA. Little evidence exists on the association between use of disease-modifying antirheumatic drugs (DMARDs) and the risk of CV events in early RA patients. Our study evaluated this association in this previously understudied population.

Methods: A nested case-control study was conducted using data from a large US insurance claims database (2008–2010) representing commercial and Medicare supplemental plans. The population of interest was early RA patients, which included newly diagnosed RA patients with no medical claims indicating RA in the prior year. These patients were followed up for the outcome of a composite CV event including acute myocardial infarction, unstable angina, angina pectoris, chronic heart failure, other forms of chronic heart diseases, and cerebrovascular accident. Patients with the outcome were defined as cases on their event date. Twelve age-, sex-, and cohort entry month-matched controls were selected for each case using incidence density sampling. Seven mutually exclusive exposure categories were defined hierarchically: 1) no DMARD use, 2) past use of only non-biologic DMARDs, 3) current use of only non-biologic DMARDs, 4) past use of TNF-inhibitors, 5) current use of TNF- inhibitors, 6) past use of non-TNF biologics, and 7) current use of non-TNF biologics. Any use of these DMARDs in the period of 6 months prior to the event date was defined as current use and any use preceding that period was defined as past use. Duration of treatment was defined as a continuous variable representing cumulative days of use. Conditional logistic regression models were used to derive estimates for incidence rate ratios (IRR).

Results: Of the 15,951 RA patients of the base cohort, 466 cases of an incident CV event were identified during follow-up. Cases were matched with 5,592 controls. In our multivariate analyses adjusting for baseline factors as well as treatment history with medications, current use of TNF-inhibitors and current use of non-biologic DMARDs were found to be associated with a reduced risk of an incident CV events compared to no DMARD use (IRR 0.62 95% CI 0.40–0.98 & IRR 0.66 95% CI 0.48–0.89 respectively). Duration of use for both TNF-inhibitors and non-biologic DMARDs was found to be associated with a reduced risk of CV events in a linear manner (for each additional month of treatment, IRR 0.95 95% CI 0.90–1.00 & IRR 0.97 95% CI 0.94–1.00 respectively).

Conclusion: Treatment with TNF-inhibitors and non-biologic DMARDs may help in reducing the risk of incident CV events in patients newly diagnosed with RA compared to no treatment with DMARDs.

Table. Adjusted incidence rate ratios for a cardiovascular event in rheumatoid arthritis patients using various DMARDs

Exposure	n (cases)	n (controls)	Adjusted* IRR (95% CI)
DMARD use indicator			
No DMARD use	79	775	Ref.
Current TNF-I	39	518	0.62 (0.40–0.98)
Current nbDMARD	302	3879	0.66 (0.48–0.89)
Current other biologic	14	57	1.93 (0.96–3.87)
Past TNF-I	1	28	0.24 (0.03–1.85)
Past nbDMARD	28	323	0.68 (0.40–1.13)
Past other biologic	3	12	2.32 (0.61–8.84)
DMARD use duration indicators			
Each additional month of cumulative TNF-I use	–	–	0.95 (0.90–1.00)
Each additional month of cumulative nbDMARD use	–	–	0.97 (0.94–1.00)
Each additional month of cumulative other biologics use	–	–	1.06 (0.99–1.13)

Abbreviations-DMARDs:Disease modifying antirheumatic drugs, TNF-I: Tumor necrosis factor-α inhibitors, nbDMARDs: non biologic DMARDs, IRR: Incidence rate ratio

* Adjusted for pre-index NSAID use, steroid use, non-biologic DMARD use, cardiovascular medication use, diabetes, hypertension, hyperlipidemia, chronic obstructive pulmonary disease and cancer in addition to matching with age, gender, duration of RA and cohort entry month and year.

Disclosure: R. Desai, Biogen Idec, 1; **J. Rao**, None; **R. Hansen**, None; **G. Fang**, None; **M. Maciejewski**, Amgen, 1; **J. Farley**, None.

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Physical Activity Behavior In Patients With Arthritis. Gustavo J. Almeida and Sara R. Piva. University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: The physical activity (PA) guidelines issued by the US Health and Human Services (HHS) recommend that adults with arthritis should perform at least 150 min/week of PA at moderate or higher intensity spread in bouts of at least 10 minutes of PA. Although it has been extensively discussed that physical inactivity is a problem among adults with arthritis, relatively little is known about the pattern of their daily activities measured in real-time by an accelerometer-based monitor. The purposes of this study were (1) to characterize the time that adults with arthritis spent in daily activities of various intensity levels and (2) to examine whether adults with arthritis meet the PA recommendations from the HHS guidelines.

Methods: Adults with rheumatoid arthritis (RA) and with end-stage knee osteoarthritis post total knee replacement (TKA) participated in this cross-sectional study. The SenseWear Armband (Bodymedia, Pittsburgh, PA) was used to measure PA. Subjects wore the Armband for a period of 7 days, 24 hours a day. PA was characterized as the time spent per day in sedentary (0 to 0.99 metabolic equivalent [MET]), light (1 to 1.99 MET), lifestyle (2 to 2.99 METs) and moderate (3 METs and above) intensity activities. We also calculated the number of 10-minute bouts of moderate activity per day for each subject. Subjects who performed 15 bouts of moderate PA per week were considered to meet the HHS guidelines. Disability in subjects with RA was measured using the Health Assessment Questionnaire (HAQ) and in subject post TKA it was measured by the Western Ontario and McMaster

Universities Arthritis Index (WOMAC). Descriptive statistics were run for the demographics, biomedical and PA data.

Results: Complete data were obtained in 68 subjects post TKA and 100 subjects with RA. Descriptive statistics are depicted in the Table. In general, our sample consisted of mainly females who were well educated. Subjects post TKA appeared to be older and heavier than subjects with RA. In general, both groups presented with mild to moderate disability. The results indicated that around 16 hours a day were spent in sedentary, 3 hours in light, 2 hours in lifestyle, and 30 minutes in moderate activities. From the 30 minutes in moderate activity dispersed throughout the day, subject performed only 1 bout of 10 minutes of continuous moderate activity per day. Only 12% of subjects with RA and 12% of subjects post TKA met the HHS guidelines. Subjects post TKA had similar pattern of activities in comparison to subjects with RA.

Table. Demographic and biomedical characteristics and physical activity behavior of the study sample. Data are presented as mean ± standard deviation, unless otherwise indicated.

	All (N=168)	TKA (n=68)	RA (n=100)
Demographics			
Age in years	63 ± 10	69 ± 7	58 ± 8
Female (%)	129 (77)	45 (66)	84 (84)
Height in cm	163 ± 8	166 ± 9	162 ± 8
Weight in kg	76 ± 22	82 ± 13	73 ± 22
BMI	28 ± 7	30 ± 4	27 ± 7
Race – White (%)	109 (65)	63 (94)	96 (96)
Education			
High School (%)	67 (40)	29 (43)	38 (38)
College (%)	48 (29)	22 (33)	26 (26)
Disease Characteristics			
RA duration in years		—	14 (6; 21)§
Time post TKA in months		6 (5; 34)	—
Functioning in RA measured by the HAQ		—	0.6 (0.3; 1)§
Functioning in TKA measured by the WOMAC		24 ± 14	—
Physical Activity variables*			
Time in Sedentary Activity (hours/day)	16:31 (11:41; 18:13)§	16:31 (11:41; 18:13)§	15:42 (12:51; 18:25)§
Time in Light	3:06 (2:28; 4:10)§	3:06 (2:28; 4:10)§	3:25 (2:24; 6:25)§
Time in Lifestyle	2:08 (1:15; 2:55)§	2:08 (1:15; 2:55)§	2:23 (1:08; 3:13)§
Time in Moderate	0:33 (0:18; 1:03)§	0:33 (0:18; 1:03)§	0:36 (0:19; 1:07)§
Number of 10-minute bouts	1 (0; 3)§	2 (0; 3)§	1 (0; 3)§
Met PA criteria (%)	20 (12)	8 (12)	12 (12)

TKA= total knee arthroplasty; RA= rheumatoid arthritis; BMI= body mass index; HAQ= Health Assessment Questionnaire; WOMAC= Western Ontario and McMaster Universities Arthritis Index; PA= physical activity; §= median (25th–75th percentile); *Sum of time in several levels of physical activity do not total 24 hours because subjects did not wear monitors during shower/bath and also because the data represents medians rather than means.

Conclusion: According with the HHS guidelines, adults with arthritis in this study were in general sedentary. Only a small proportion (12%) met the HHS guidelines. Subjects post TKA and subjects with RA seem to have similar PA behavior.

Disclosure: G. J. Almeida, None; **S. R. Piva**, None.

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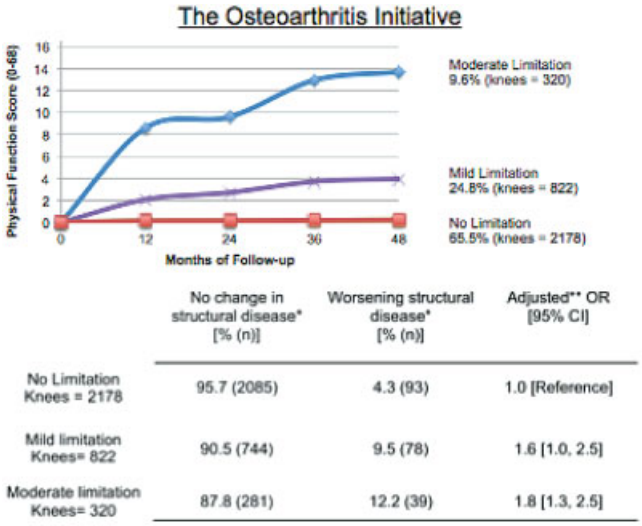
The Association Of Worsening Structural Disease With Trajectories Of Decline In Physical Function In Knee Osteoarthritis: Results From Two Cohort Studies. Daniel K. White[1], Tuhina Neogi[1], Jingbo Niu[1], Uyen Sa D.T. Nguyen[1], David T. Felson[1], Barton L. Wise[2], C.E. Lewis[3], Michael C. Nevitt[4], James Torner[5] and Yuqing Zhang[1]. [1]Boston University School of Medicine, Boston, MA, [2]UC Davis School of Medicine, Sacramento, CA, [3]University of Alabama, Birmingham City, Brimingham, AL, [4]University of California, San Francisco, San Francisco, CA, [5]University of Iowa, Iowa City, Iowa City, IA.

Background/Purpose: Knee osteoarthritis (OA) is the most common cause of functional limitation in older adults. It is not known, however, what proportion progress to a trajectory of functional decline and to what extent worsening of structural damage is associated with decline, particularly among initially well-functioning adults. We examined trajectories of physical function in adults with or at high risk of knee OA who started without functional limitation, and examined the relation of structural worsening to these trajectories.

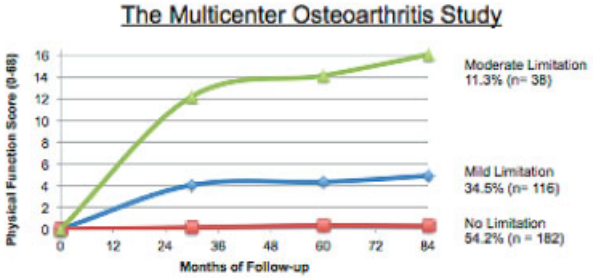
Methods: We utilized data from the Osteoarthritis Initiative (OAI) and the Multicenter Osteoarthritis (MOST) to describe function trajectories over 48- and 84-months, respectively. Physical function was measured with the WOMAC physical function (PF) subscale (0–68) for each knee in OAI and each person in MOST. We included only participants with WOMAC-PF=0 (i.e., no functional limitation) at baseline. We used a group-based method (Proc Traj) to identify homogeneous clusters of developmental trajectories in MOST and OAI. We then examined the relation of worsening structural disease to the trajectory of subsequent functional decline. Since MOST had few high-functioning participants, we conducted this analysis in OAI only. Structural worsening was defined as any increase in Kellgren and Lawrence (KL) or joint space narrowing grade, or a new total knee replacement from 0- to 24-months. We examined the association of worsening structural disease (0- to 24-months) with trajectories of subsequent physical function (24- to 72-months) using multinomial logistic regression, adjusting for age, sex, body mass index, and baseline KL grades in OAI.

Results: Our study sample comprised 3,320 knees in OAI (age 63.3 ± 9.2 yrs, 53.4% female, BMI 27.4 ± 4.4 at 24-month visit) and 336 people in MOST (age 61.3 ± 8.0 yrs, 53.9% female, BMI 29.6 ± 4.8 at the baseline visit). We identified 3-trajectories in OAI and MOST (Figures). For OAI, the 1st trajectory, no limitation, had stable WOMAC-PF, with an average value < 1 at the last follow-up and included 65.6% of all knees. The 2nd trajectory, mild limitation, progressively worsened 1.0 unit/year to 4/68 at the last follow-up and included 24.8%. The 3rd trajectory, moderate limitation, progressively worsened 3.4 units/year to 13.7/68 at the last follow-up and included 6.3%. We observed similar trajectories in the MOST study. Worsening structural disease was associated with 1.6 to 1.8 times the odds of a trajectory of worsening function compared with those with no change in OAI (Table).



	No change in structural disease* [% (n)]	Worsening structural disease* [% (n)]	Adjusted** OR [95% CI]
No Limitation Knees = 2178	95.7 (2085)	4.3 (93)	1.0 [Reference]
Mild limitation Knees= 822	90.5 (744)	9.5 (78)	1.6 [1.0, 2.5]
Moderate limitation Knees= 320	87.8 (281)	12.2 (39)	1.8 [1.3, 2.5]

* Structural disease change was any worsening in KL grade, joint space narrowing, or a new TKR from the 0 to 24 month OAI visit. Functional trajectories started at the 24 month OAI visit.
**Adjusted for age, sex, Body Mass Index, and baseline KL grade



Conclusion: In initially well-functioning people with or at high risk of knee OA, a minority has progressive worsening of physical function, with worsening structural disease contributing to risk of this decline. Such findings

highlight the importance of addressing methods to maintain and improve function even among those with knee OA who are well-functioning.

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Comprehensive Behavioral Intervention Compared To Standard Of Care Exercise Program After Total Knee Arthroplasty: A Pilot Randomized Trial. Sara R. Piva, Maria Beatriz Catelani and Gustavo J. Almeida. University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Although the overall outcome of total knee arthroplasty (TKA) is favorable, surgery alone fails to resolve many of the substantial functional limitations and physical inactivity that began long before the surgery. To improve these persistent limitations, exercise programs need to be performed at doses sufficiently high to promote sizable improvements in physical function (PF). In addition, physical activity (PA) promotion should be part of the rehab program. The aim of this study was to determine the effectiveness of comprehensive behavioral intervention (CBI) - that uses intense exercises and promotes activity participation - compared to a standard of care (SC) exercise program to improve PF and PA in patients after TKA.

Methods: Double blinded pilot randomized clinical trial. Patients who underwent unilateral TKA 3 – 6 months prior were assigned into 2 groups, the CBI or SC. Subjects in both groups completed 12 weeks of supervised exercise followed by 12 weeks of exercise program. Clinical outcomes were collected prior to (baseline) and after intervention (6 months). Self-reported PF was measured by the Western Ontario and McMaster Universities Arthritis Index- PF score (WOMAC-PF) and the PF subscale of the RAND-36. Patient-identified problem areas in daily functioning were measured by the Canadian Occupational Performance Measure (COPM), which considers both the importance and the satisfaction with the performance areas. Performance-based PF was measured by the chair-raise test, gait velocity, and the stair climbing test. An objective accelerometer-based monitor was used to quantify PA during light (2 to 2.99 metabolic equivalents – METs) and moderate intensities (above 3 METs). Changes between groups were compared using independent sample t-test or Wilcoxon according with data distribution.

Results: Sample included 44 subjects (70% female, age 68 ± 0.98 years, and BMI 30.0 ± 0.6 Kg/m2). Results are reported in the Table. Both groups reported improved PF. PF measured by the RAND-36 was statistically significant larger in the CBI than in the SC, whereas group differences in the WOMAC- PF did not reach significance. Both groups improved performance and satisfaction in the COPM. Subjects in the CBI group significantly improved in the Stair Climb test compared to the SC group. Group differences in gait velocity and chair-raise test were not significant. While not significant, subjects in the SC group decreased PA while the ones in the CBI increased PA.

Table Baseline and 6-month physical function and physical activity outcomes in the CBI and SC groups. Data represent mean ± SD or median (Q25; Q75).

	Group	Baseline	6 months	Change (6 mo – baseline)	Percentage Change	p-value
WOMAC – Physical Function*	SC	17.68 ± 2.21	12.8 ± 2.42	−5.35 ± 2.09	−30%	0.503
	CBI	19.09 ± 1.99	11.42 ± 1.50	−7.05 ± 1.34	−37%	
RAND-36 – Physical Function**	SC	66.14 ± 3.97	70.25 ± 5.41	6.75 ± 3.86	10%	0.037
	CBI	56.14 ± 4.80	76.05 ± 3.74	16.58 ± 2.30	30%	
COPM – Performance**	SC	36.38 ± 2.71	59.74 ± 5.74	23.18 ± 4.48	64%	0.360
	CBI	34.27 ± 3.16	63.34 ± 4.70	29.0 ± 4.39	85%	
COPM – Satisfaction**	SC	27.63 ± 3.26	56.70 ± 6.78	28.62 ± 5.50	104%	0.176
	CBI	22.36 ± 2.74	61.93 ± 5.37	39.15 ± 5.27	175%	
Chair-raise Test (sec)	SC	13.16 ± 0.68	13.74 ± 1.67	0.68 ± 1.53	5%	0.444
	CBI	14.26 ± 0.81	11.97 ± 0.63	−1.69 ± 0.40	−12%	
Gait Velocity (m/sec)	SC	1.106 ± 0.38	1.183 ± 0.06	0.06 ± 0.04	6%	0.679
	CBI	1.037 ± 0.04	1.147 ± 0.04	0.08 ± 0.03	8%	
Stair Climbing Test (sec)	SC	15.5 ± 0.997	15.59 ± 1.66	0.07 ± 1.47	0.5%	0.006
	CBI	19.03 ± 1.54	14.19 ± 0.98	−4.43 ± 1.00	−23%	
Light Intensity PA (min/d)	SC	123.5 (82.5; 176.8)	83.5 (42.0; 158.0)	−5.5 (−62.8; 14.0)	−5%	0.167
	CBI	99.5 (44.8; 157.5)	124.0 (61.0; 142.0)	12.0 (−26.0; 21.0)	12%	
Moderate Intensity PA (min/d)	SC	38.5 (18.3; 70.8)	33.0 (17.3; 61.8)	−1.0 (−25.3; 21.8)	−3%	0.999
	CBI	24.5 (9.3; 47.8)	34.5 (12.5; 47.7)	4.5 (−23.5; 12.0)	18%	

*Lower scores represent better function; ** Higher scores represent better function

Conclusion: Subjects in the CBI group experienced larger improvements in PF as measured by the RAND-36 and the stair climbing test. Although we observed a trend towards larger changes in COPM-satisfaction and light intensity PA in the CBI group, the negative results may be due to the small sample of this pilot study. Results indicate that the CBI may be a promising intervention for patients post TKA.

Disclosure: S. R. Piva, None; **M. B. Catelani**, None; **G. J. Almeida**, None.

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The Validity Of The Satisfaction With Appearance Scale and The Brief Satisfaction With Appearance Scale For Patients With Limited and Diffuse Systemic Sclerosis. Rina M. Sobel-Fox[1], Sarah D. Mills[1], Shadi Gholizadeh[1], Erin L. Merz[1], Philip J. Clements[2], Suzanne Kafaja[2], Vanessa L. Malcarne[3], Dinesh Khanna[4] and Daniel E. Furst[2]. [1]SDSU/UCSD Joint Doctoral Program in Clinical Psychology, San Diego, CA, [2]David Geffen School of Medicine, UCLA, Los Angeles, CA, [3]Department of Psychology, San Diego State University, Psychology, San Diego, CA, [4]University of Michigan Medical School, Ann Arbor, MI.

Background/Purpose: The Satisfaction with Appearance Scale (SWAP) was originally developed to evaluate body image dissatisfaction (BID) among burn victims, and was later adapted for use in patients with systemic sclerosis (SSc). A short form of the measure (Brief-SWAP) was derived from the full version. Both measures yield factor-analytically derived subscales. Although both versions have been validated for use in SSc, their factor structures have never been compared for use with patients with limited versus diffuse SSc. Because these groups may have very different appearance issues, the purpose of the current study was to determine the comparability of the factor structures of 1) the SWAP and 2) the Brief-SWAP for patients with limited versus diffuse SSc.

Methods: Participants were adults participating in the UCLA Scleroderma Quality of Life Study with rheumatologist-diagnosed limited (n = 103) or diffuse (n = 82) SSc. The 14-item SWAP evaluated BID, and the six items that comprise the Brief-SWAP were taken from the full measure. Prior research has shown that the SWAP has four subscales evaluating Social Distress, Facial Features, Non-facial Features, and Perceived Social Impact; the Brief-SWAP has two subscales evaluating Social Discomfort and Dissatisfaction with Appearance. Multiple group confirmatory factor analysis was used to determine if the factor structures of the SWAP and the Brief-SWAP were the same for individuals with limited and diffuse SSc. Both statistical (chi squared [χ^2]), and descriptive (RMSEA, CFI, SRMR) indicators of model fit were considered. For RMSEA and SRMR, values $< .08$ and $< .05$ were considered to indicate acceptable and good model fit, respectively. For CFI, values $> .90$, and $> .95$ were considered to indicate acceptable and good model fit, respectively. A model was determined to fit well if at least two of the three descriptive fit indices met the criteria for acceptable model fit.

Results: For the 14-item SWAP, the four factors satisfactorily fit the data from persons with diffuse SSc (χ^2 [71, N = 82] = 120.271, $p < .001$; RMSEA = .092, CFI = .923, SRMR = .075), but not from persons with limited SSc (χ^2 [71, N = 103] = 199.547, $p < .001$; RMSEA = .133, CFI = .873, SRMR = .070), suggesting that the commonly used subscales might not be informative for persons with limited disease. In contrast, for the Brief-SWAP, fit indicators supported the two hypothesized factors for persons with either limited or diffuse disease. Interestingly, the variance in scores on the two factors was greater for persons with limited SSc. This indicated that severity of BID, as measured by the Brief-SWAP, varied more widely in persons with limited disease, versus those with diffuse disease, in the present sample.

Conclusion: The four-factor structure of the 14-item SWAP may not evaluate BID among patients with limited SSc as well as it does among patients with diffuse SSc. Conversely, the two-factor model of the Brief-SWAP, which evaluates Social Discomfort and Dissatisfaction with Appearance, was found to function equivalently across disease subtypes when measuring BID. Therefore, the two-factor structure of the Brief-SWAP can be confidently used to measure body image dissatisfaction in patients with either limited or diffuse SSc.

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ACR Concurrent Abstract Session
Fibromyalgia, Soft Tissue Disorders and Pain: Diagnosis and Disease Epidemiology
Sunday, October 27, 2013, 4:30 PM–6:00 PM

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Recommendations for the Classification and Diagnosis of Fibromyalgia Syndrome Provided By Independently Developed Evidence-Based Interdisciplinary Guidelines Spanning Three Continents. Mary-Ann Fitzcharles[1], Yoram Shir[1], Jacob N. Ablin[2], Dan Buskila[3], Howard Amital[4], Peter Henningsen[5] and Winfried Häuser[5]. [1]McGill University Health Centre, Montreal, QC, [2]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [3]Ben-Gurion University, Beer-Sheva, Israel, [4]Department of Medicine B, Center for Autoimmune Diseases, Sheba Medical Center, Tel-hashomer, Israel, [5]Klinikum Saarbrücken, Saarbrücken, Germany.

Background/Purpose: Fibromyalgia (FM), often disputed and challenged, has emerged as a clear cluster of symptoms and co-morbidities, characterized by subjective complaints without physical or biomarker abnormality. Areas of debate include classification, value of diagnostic label, tender point examination, and best clinical care setting. Recommendations in recent guidelines addressing these issues were examined for consistencies and differences.

Methods: Systematic searches from January 2008 to February 2013 of the US-American National Guideline Clearing House, the Scottish Intercollegiate Guidelines Network, Guidelines International Network and Medline for evidence-based guidelines for the management of FM were conducted. Inclusion criteria required that the guideline was commissioned by a scientific organisation, guideline group was interdisciplinary, systematic search strategy was outlined, criteria for classification of evidence and recommendations were stated and the process for establishing recommendations was outlined. Only guidelines addressing FM were accessed.

Results: The literature search yielded 24 citations (19 excluded for duplication, 1 without criteria for assigning evidence, 1 not scientific society commissioned) with three guidelines independently developed in Canada, Germany and Israel included. Recommendations concerning definition, classification, clinical diagnosis and general principles of care were based predominantly on expert consensus, with limited literature evidence. All three countries justified the need for guidelines based on high FM prevalence, controversies surrounding diagnosis/management, reduced health-related quality of life and high health care costs with unanimity for the following parameters: FM was defined by the 1990 ACR classification criteria; FM should be clinically diagnosed by a typical cluster of symptoms, following a composite history, physical examination, and selected laboratory tests, to exclude another somatic disease; diagnosis confirmation with 2010 ACR diagnostic criteria if desired; importance of assigning a diagnostic label; education regarding the nature of the disorder to include a biopsychosocial model, planned treatment strategy and expected outcome; recognition that FM is a continuum disorder; coexistence with another medical (e.g.) rheumatic condition and mental disorder. Differences between guidelines were reflected in the concept of FM as representing a clinical construct of pain and other symptoms, a functional somatic syndrome, or a central hypersensitivity syndrome identified by each, tender point examination replaced by examination for soft tissue tenderness by 2, care in the primary care setting by 2, and 1 discouraging focus on a triggering event.

Conclusion: Guidelines from three continents showed remarkable consistency regarding the clinical concept of FM, acknowledging the need to provide confidence in a clinical diagnosis, importance of assigning a diagnostic label, and acceptance that FM is neither a distinct rheumatic nor mental disorder, but a cluster of symptoms spanning a broad range of medical disciplines.

Disclosure: M. A. Fitzcharles, Purdue Pharma L.P., 5, Eli Lilly and Company, 5, Pfizer Inc, 5, Valeant, 5; **Y. Shir**, Purdue Pharma L.P., 8, Paladin Labs, 8, Paladin Labs, 5; **J. N. Ablin**, Pfizer Inc, 8; **D. Buskila**, None; **H. Amital**, Pfizer Inc, 2; **P. Henningsen**, Novartis Pharmaceutical Corporation, 5; **W. Häuser**, Pfizer Inc, 5, Daiichi Pharmaceutical Corporation, 5, Abbott Laboratories, 5.

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A Paradigm Change for Treatment Strategies for Fibromyalgia Syndrome Reflected By Recommendations of Recent Evidence-Based Interdisciplinary Guidelines Developed Independently in Three Countries. Jacob N. Ablin[1], Dan Buskila[2], Howard Amital[3], Mary-Ann Fitzcharles[4], Yoram Shir[4], Peter Henningsen[5] and Winfried Häuser[5]. [1]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [2]Ben-Gurion University, Beer-Sheva, Israel, [3]Department of Medicine B, Center for Autoimmune Diseases, Sheba Medical Center, Tel-hashomer, Israel, [4]McGill University Health Centre, Montreal, QC, [5]Klinikum Saarbrücken, Saarbrücken, Germany.

Background/Purpose: Although the ideal treatment for fibromyalgia (FM) remains elusive, the medical community requires direction in the care of these patients. The literature however abounds with copious reports of various treatments that drive health-care costs, but provide ever increasing confusion for patients and physicians. We have compared treatment recommendations for FM provided by recent evidence-based guidelines.

Methods: Systematic searches from January 2008 to February 2013 of the US-American National Guideline Clearing House, the Scottish Intercollegiate Guidelines Network, Guidelines International Network and Medline for evidence-based interdisciplinary guidelines on the management of FM were conducted. Inclusion criteria required that the guideline was commissioned by a scientific organisation, the guideline group was interdisciplinary, the systematic search strategy was outlined, criteria and process for classification of evidence and recommendations were stated.

Results: Three evidence-based interdisciplinary guidelines for the treatment of FM in Canada, Germany and Israel fulfilled inclusion criteria. All three guidelines emphasized a patient-tailored approach according to key symptoms. Non-pharmacologic strategies were the major positive first choice recommendation for all with emphasis on aerobic exercise, cognitive behavioural therapy and multicomponent therapy (exercise and psychological). Acupuncture, hypnosis/guided imagery and Tai Chi were recommended by the German and Israeli guideline, whereas the Canadian guidelines indicated only short term benefits for acupuncture, and categorized hypnosis/guided imagery and Tai Chi as psychological and exercise interventions respectively with some evidence for effect, but none were specifically recommended. Pharmacologic treatments were less enthusiastically recommended by all three groups. With the qualifier that drugs provide only modest effect, the Canadian and Israeli guidelines gave strong recommendation for the anticonvulsants (gabapentin and pregabalin) and serotonin noradrenaline reuptake inhibitors, whereas these drug categories received only weak recommendation by the German guideline. All groups cautioned about the side effects of drugs manifesting as symptoms of FM. Use of strong opioids was discouraged by all, with the Israeli and German guideline providing specific negative recommendation for many other drug categories including non-steroidal agents, systemic steroids, benzodiazepines, thyroid hormone replacement, amongst others. Although not providing specific negative treatment recommendations, the Canadian guidelines cited lack of evidence to support many treatments which would therefore constitute "off-label" use.

Conclusion: Recent evidence-based interdisciplinary guidelines concur on the importance of treatments tailored to the individual patient and further emphasize the necessity of self-management strategies which include exercise and psychological techniques. Contrary to popular perception, drug treatments were recommended with reservation regarding both efficacy and side effect profile.

Disclosure: J. N. Ablin, Pfizer Inc, 8; **D. Buskila**, None; **H. Amital**, Pfizer Inc, 2; **M. A. Fitzcharles**, Purdue Pharma L.P., 5, Eli Lilly and Company, 5, Pfizer Inc, 5, Valeant, 5; **Y. Shir**, Purdue Pharma L.P., 8, Paladin Labs, 8, Paladin Labs, 5; **P. Henningsen**, Novartis Pharmaceutical Corporation, 5; **W. Häuser**, Pfizer Inc, 5, Daiichi Pharmaceutical Corporation, 5, Abbott Laboratories, 5.

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Fibromyalgia, Somatic Symptoms, and Mental Illness In View Of The 2013 Diagnostic and Statistical Manual Of Mental Disorders. Frederick Wolfe[1], Brian T. Walitt[2], Robert S. Katz[3] and Winfried Häuser[4]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]Washington Hospital Center, Washington, DC, [3]Rush Medical College, Chicago, IL, [4]Klinikum Saarbrücken, Saarbrücken, Germany.

Background/Purpose: Pain research conceptualizes fibromyalgia (FM) as a Physical or Somatic Symptom Disorder (PSD or SSD). However, the 2013 Diagnostic and Statistical Manual of Mental Disorders (DSM-5) identifies an SSD mental disorder (DSM-SSD) when there are findings of "positive symptoms (distressing somatic symptoms + excessive thoughts,

feelings, and behaviors in response to these symptoms)," whether or not the symptoms are "medically explained." FM is defined on the basis of somatic symptoms and concerns arose that DSM criteria would turn FM into a mental disease. We examined DSM mental illness in patients with rheumatoid arthritis (RA), including those with FM. We utilized RA patients to provide a large subject base and appropriate control subjects, and to avoid self-selection for severity.

Methods: We used the Patient Health Questionnaire-15 (PHQ-15), a validated assessment of somatic symptom severity, to operationalize the DMS-5 SSD definition. For mental illness Definition 1 a DSM-SSD positive individual had to have at least 2 "severe" symptoms ("bothered a lot") and a total PHQ-15 somatic symptom severity classification of "medium" (10–14) or "high" (>=15). A second, more restrictive definition (Definition 2) required the total PHQ-15 symptom severity classification to be high (>=15). We diagnosed FM according to the survey modified 2010 FM criteria.

Results: Of the 4718 RA patients, 22.1% were definition 1 DSM-SSD positive and 6.7% definition 2 positive (Table 1). When FM (+) patients were considered, 68.8% and 28.8% satisfied mental illness 1 and 2 definitions. 19.8% of RA patients also satisfied ACR2010 criteria. The probability of satisfying the mental illness definitions increased as a function of polysymptomatic distress (fibromyalgianess) (Figure 1). Persons who met either definition had more abnormal scores for all severity and outcome measures, including functional status, pain, quality of life, household income, etc.

	FM (−) (80.2%)	FM (+) (19.8%)	All
Mental illness 1 (%)	10.7	68.8	22.1
Mental illness 2 (%)	1.2	28.8	6.7
PHQ-15	5.6	12.3	6.9
Polysymptomatic distress	63.0	19.3	8.7

Conclusion: There are serious problems of face validity when mental illness is defined on the basis of "excessive thoughts, feelings, and behaviors" in response to somatic symptoms, as somatic symptoms form the basis of rheumatic diseases. In addition, somatic symptoms increase in number and severity with increasing pain, and no clear direction of causality can be discerned. If somatic symptoms are to be expected in rheumatic diseases, then it all comes down to "excessive", a term that cannot be reliably or validity defined. The high rates mental illness identified by the DSM-SSD definition in our study suggest the mental illness classification is invalid.

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The Prevalence Of Fibromyalgia In The General Population – a Comparison Of The ACR 1990, 2010 and Modified 2010 Classification Criteria. Gareth T. Jones[1], Marcus Beasley[1], Fabiola Atzeni[2], Elisa Flüβ[1], Piercarlo Sarzi-Puttini[2] and Gary Macfarlane[1]. [1]University of Aberdeen, Aberdeen, United Kingdom, [2]Rheumatology Unit, L. Sacco University Hospital, Milan, Italy.

Background/Purpose: In 1990 the ACR published criteria for the classification of fibromyalgia (FM), based on widespread pain and tenderness. In 2010 new criteria were published which were based on widespread pain and somatic symptoms and explicitly excluded individuals that a clinician considered had a disorder that would otherwise explain the pain. Then, in 2011, the 2010 criteria were modified (hereafter referred to as the 2010m criteria) to allow their use in research, without the requirement of a clinical history or examination. To our knowledge, there have been no studies investigating the population prevalence of FM in a manner that allows comparison between the three sets of criteria. The aim of the current study was to determine the prevalence of FM in the general population and, specifically, to compare differences in prevalence, when using different criteria.

Methods: In the UK, 96% of the population are registered with a general practitioner providing an ideal population sampling frame. Postal questionnaires were sent to 4500 randomly selected individuals, aged >=25yrs, registered with a general practitioner in the Grampian region, Scotland (UK). The questionnaire included questions on pain and somatic symptoms, and on prior rheumatological diagnoses: osteoarthritis, rheumatoid arthritis, osteoporosis, SLE, scleroderma, ankylosing spondylitis and gout.

All participants with chronic widespread pain, or who met the 2010m FM criteria, were invited to attend a clinical research facility, as were a random sample of participants who did not meet these criteria. At the clinic, participants completed an additional questionnaire; and underwent a full examination by a rheumatologist, including clinical history and tender-point examination.

Using the information collected it was possible to classify participants according to each of the ACR 1990, 2010 and 2010m FM criteria. The population prevalence of each was determined by weighting back to the initial general practice sample, by the inverse of the sampling fraction.

Results: 1604 (36%) participants returned a questionnaire, 269 participants were invited, of whom 104 (39%) attended the clinical examination. Of these, 32 met at least one of the FM criteria (31%). Weighting back to the general population, the prevalence of FM using the ACR 1990, 2010 and 2010m criteria was 1.9% (95%CI: 0.8–3.1%); 1.2% (0.3–2.1%); and 5.3% (4.7–6.0%), respectively. The gender ratio (female: male) varied across criteria from 11.2 (1990) to 6.7 (2010) and 2.3 (ACR 2010m) and 56%, 29% and 48% of participants who met these criteria, respectively, also reported the prior diagnosis of another rheumatological condition.

Conclusion: This is the first study to produce population estimates of the prevalence of FM using the three different ACR classification criteria. Prevalence estimates are considerably higher, and a greater proportion of men are classified as having FM with the 2010m criteria in comparison to either of the criteria requiring clinician input (1990 and 2010). Further, depending on which set of criteria are employed, between one-third and one-half of participants who meet the criteria have coexistant other rheumatological disorders.

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A Cytokine/Chemokine Multiplex Assay That Is Sensitive and Specific For Fibromyalgia Compared To Controls, Systemic Lupus Erythematosus, and Rheumatoid Arthritis. Daniel J. Wallace[1], Igor Gavin[2], Oleksiy Karpenko[2] and Bruce S. Gillis[2]. [1]Cedars-Sinai Medical Center, Los Angeles, CA, [2]University of Illinois College of Medicine at Chicago, Chicago, IL.

Background/Purpose: Fibromyalgia (FM) is a chronic pain and fatigue syndrome that affects about 6 million adults in the United States. The clinical diagnosis of FM has been based on subjective evaluations paired with the exclusion of other diseases. No confirmatory objective laboratory benchmark has been available. To investigate potential FM biomarkers, we previously determined whether cytokine/chemokine production is altered in FM patients by comparing their in vitro peripheral blood mononuclear cell (PBMC) cytokine/chemokine responses to mitogenic activators with matched healthy controls. A multiplex immunoassay (Luminex™) was used on PBMC supernatants. Based on a larger multiplex array exploratory pilot study, a custom panel of antibody-conjugated beads for eight cytokines/chemokines (IL-5, IL-6, IL-8, IFN-g, IL-10, MIP-1a, MIP-1b, MCP-1) was used. This panel was 93% sensitive for the diagnosis of FM. The current study was designed to address the specificity of the panel for FM vs SLE and RA.

Methods: After IRB informed consent, a total of 25 SLE and 25 RA patients, fulfilling ACR criteria, were recruited and compared with 101 FM patients and 91 controls. Peripheral blood was harvested and PBMC isolated by differential centrifugation on Ficoll. These cells were cultured overnight in medium alone or in the presence of mitogenic activators; PHA or PMA in combination with ionomycin. The supernatant cytokine/chemokine concentrations were determined using the Luminex multiplex immunoassay bead array technology. Data was ported to "R" statistical software for appropriate analysis. The standard curve was fitted with a 5-PL model and the concentrations of the analytes were quantified according to this curve. The two sided t-test was used to test whether the mean concentrations of each chemokine and cytokine were the same in every group. Each patient's profile was scored, as previously described, and ported to statistical software for appropriate analysis.

Results: Compared to FM, cytokine/chemokine levels from stimulated RA and SLE PBMC supernatants were significantly different ($p<0.002$). The concentrations of all cytokines except for IL-8 in RA were significantly lower in FM than in SLE or RA at 1% false discovery rate. In SLE and RA, 68% and 76%, respectively, tested negative for the FM profile. This was lower than

healthy controls at 89%. Concomitant corticosteroid use might explain this since in steroid naïve SLE and RA, the negative FM profile increased to 86% and 83%, respectively. There was no statistically significant difference at the 95% confidence level between the concentrations of chemokines and cytokines in SLE and RA patients except for MIP-1b ($p=0.042$), which was higher in the SLE cohort.

Conclusion: These data demonstrate that lowered cytokine/chemokine profiles from stimulated PBMC may represent a biomarker that is relatively sensitive and specific for FM compared to SLE and RA. It remains unclear if these differences are directly related to the pathogenesis of FM or if subsequent measurements will be useful in longitudinal outcome studies. This test may represent the first objective laboratory marker for an otherwise enigmatic and clinically defined rheumatic disease.

Disclosure: D. J. Wallace, EpicGenetics, 5; **I. Gavin**, EpicGenetics, 3; **O. Karpenko**, EpicGenetics, 3; **B. S. Gillis**, EpicGenetics, 4.

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Endogenous Pain Modulation In The Ehlers-Danlos Syndrome, Hypermobility Type. Inge De Wandele. Ghent University, Ghent, Belgium.

Background/Purpose: The Ehlers-Danlos Syndrome (EDS) is the most prevalent heritable connective tissue disorder. More than 90% of individuals are classified as having the hypermobility type (EDS-HT). Patients typically demonstrate generalized severe joint hypermobility, associated with recurrent joint dislocations. Although pain is the number one complaint in EDS-HT, causing severe disability in daily life, the underlying pain mechanisms and the nature of pain are unknown. Therefore, this study aims to assess the nature of pain (nociceptive / neuropathic / dysfunctional pain) and the endogenous pain modulation in EDS-HT.

Methods: Patients with EDS-HT were compared with a healthy control group (CON), and a fibromyalgia group (FM). The latter was included, because FM has been the subject of a lot of research regarding endogenous pain modulatory deficits, and because of the large symptomatic overlap with EDS-HT. All patients filled out a Margolis Pain Diagram, the Pain Detect Questionnaire (PDQ) and questionnaires regarding cognitive-emotional sensitization (Pain Catastrophizing Scale - PCS, Hospital Anxiety and Depression Scale - HADS, Tampa Kinesiophobia Scale - TSK, Pain Vigilance and Awareness Scale – PVAQ). After a thorough anamnesis regarding medical history, the somatosensory system was evaluated. Thermal quantitative sensory testing was performed on the right trapezius and left tibialis anterior to determine the sensory thresholds for cold and warmth, and the pain thresholds for cold and heath. Next, pressure pain thresholds were examined on the right trapezius and quadriceps. Further, endogenous pain modulation was assessed by evaluating wind-up (WU), conditioned pain modulation (CPM) and exercise induced analgesia (EIA). WU was assessed by applying 10 pressure stimuli (at the pressure pain threshold) on the trapezius and quadriceps and by evaluating the subsequent increase in VAS score. CPM was induced by immersing the left hand into a 46° water bath and evaluating the subsequent decrease in VAS score (for a pressure stimulus at the pressure pain threshold). EIA was assessed by comparing the pressure pain threshold before and after a submaximal bicycle test (Aerobic Power Index Test).

Results: Regarding the nature of pain, the EDS-HT group showed characteristics of neuropathic pain, with 89.5% of patients being classified by the PDQ as having possible or probable neuropathic pain. In addition, the EDS-HT group also showed characteristics of dysfunctional pain. The Margolis pain diagram showed a more widespread pain in patients with EDS-HT ($p<0.001$). WU at the trapezius was significantly higher in patients with EDS-HT and FM compared to controls ($p=0.046$). EIA was significantly reduced at the quadriceps in EDS and FM ($p=0.041$). By contrast, CPM did not significantly differ between groups ($p=0.903$). Cognitive emotional sensitization was present in the EDS-HT group (significantly higher scores on the PCS, HADS and TSK compared to controls; $p<0.01$).

Conclusion: Patients with EDS-HT suffer from nociceptive, as well as neuropathic and dysfunctional pain. The endogenous pain modulation is disrupted by a reduced pain inhibition, which is comparable to FM.

Disclosure: I. De Wandele, None.

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Level and Determinants Of Health Related Quality Of Life In Childhood-Onset Systemic Lupus Erythematosus. Jordan T. Jones[1], Shannen L. Nelson[2], Janet Wootton[3], Brianna Liberio[4], Alexandria J. Greenler[1], Jennifer L. Huggins[1], Laura E. Schanberg[3] and Hermine I. Brunner[1]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Duke University Medical Center, Durham, NC, [4]University of Cincinnati College of Medicine, Cincinnati, OH.

Background/Purpose: Childhood-onset lupus (cSLE) is a chronic autoimmune disease and its effect on health-related quality of life (HRQoL) has not been systematically established, nor does certainty exist around what cSLE factors most impact HRQoL. Physician assessment of disease activity and disease activity measures exist, but are not inclusive. Chronic disease can impair developmental tasks achieved by adolescence, leading to functional disability. The *objectives* of this study were to document the degree of HRQoL impairment with cSLE and delineate HRQoL domains most affected by cSLE.

Methods: Two population-based cohorts of ALL cSLE patients (n= 86; 7 – 20 years) followed at two tertiary pediatric rheumatology centers were studied 3 times over a 12 month period. *Pediatric PROMIS™* Short Forms (Anger, Anxiety, Depression, Fatigue, Mobility, Upper Extremity, Pain Interference, Peer Relationships), Functional Disability Inventory [FDI; range 0 – 60], and the Child Health Questionnaire [CHQ]) were completed by patients and parents. Disease activity was measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and treating physicians completed a visual analog scale of cSLE activity (0–10; 0=inactive). Average PROMIS T-scores, CHQ physical function (PFS) and psychosocial summary scores (PSS) in healthy children are at 50 (SD 10), while a FDI score $\geq$ 13 signifies at least moderate functional disability.

Results: At enrollment 23% of the patients (mean age was 15.7 yrs [SD 2.44], average disease duration of 6 yrs, and SLEDAI score of 6.13 [SD 6.15])had at least moderate functional disability (FDI $\geq$ 13) . There was more than minimal pain (VAS $\geq$ 3) in 46% of the patients. A large proportion of cSLE patients had markedly decreased HRQoL (score $\leq$ 1 SD below mean of healthy; see Figure 1). The presence of functional disability correlated with decreased mobility, higher pain, and more fatigue (Pearson correlations; all $r > 0.69$). Conversely, none of the HRQoL measures correlated with the SLEDAI or MD-rated disease activity (all $r< 0.2$).

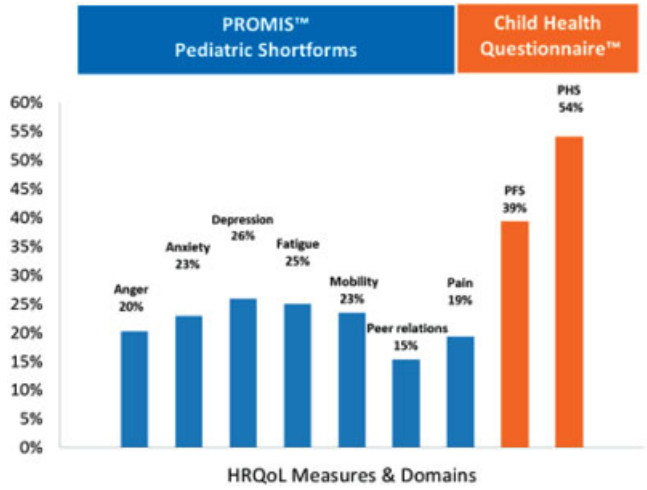

Figure 1.

Table 1. Pearson Correlation Coefficients

	PROMIS PEDIATRIC SHORT FORMS								CHILD HEALTH QUESTIONNAIRE		
Pearson correlations	**FDI**	**VAS Pain**	**Anger**	**Anxiety**	**Depression**	**Fatigue**	**Mobility**	**Pain**	**Peer Relations**	**PHS**	**PFS**
MD ratedcSLE activity	0.078	0.162	0.110	0.153	0.105	0.125	−0.288	0.240	0.135	0.159	−0.138
SLEDAI	0.176	0.166	0.229	0.119	0.073	0.189	−0.413*	0.297	0.158	0.189	−0.035
Functional Disability (FDI)	1	0.551*	0.352*	0.428*	0.379*	0.750*	−0.696*	0.691*	−0.077	−0.002	−0.459*
VAS Pain	0.551*	1	0.420*	0.342	0.343	0.624*	−0.416*	0.607*	−0.182	−0.162	−0.163
PROMIS Short Forms											
Anger	0.352*	0.420*	1	0.539*	0.670*	0.391*	−0.435*	0.397*	−0.235	−0.169	−0.056
Anxiety	0.428*	0.342	0.539*	1	0.691*	0.568*	−0.408*	0.614*	−0.222	−0.031	−0.195
Depression	0.379*	0.343	0.670*	0.691*	1	0.484*	−0.396*	0.454*	−0.275	−0.197	−0.243
Fatigue	0.750*	0.624*	0.391*	0.568*	0.484*	1	−0.644*	0.774*	−0.046	−0.153	−0.358
Mobility	−0.696*	−0.416*	−0.435*	−0.408*	−0.396*	−0.644*	1	−0.601*	0.158	0.023	0.551*
Pain	0.691*	0.607*	0.397*	0.614*	0.454*	0.774*	−0.601*	1	−0.080	−0.111	−0.439*
Peer Relations	−0.077	−0.182	−0.235	−0.222	−0.275	−0.046	0.158	−0.0802	1	0.01	0.074
CHQ											
PHS	−0.002	−0.162	−0.169	−0.0309	−0.1968	−0.1527	0.0229	−0.1109	0.01	1	0.0632
PFS	−0.4591*	−0.1628	−0.0561	−0.1954	−0.2426	−0.3577*	0.5505*	−0.4387*	0.0744	0.0632	1

* Denotes < 0.001;

Conclusion: cSLE is often associated with decreased HRQoL, despite comprehensive treatment provided at tertiary pediatric rheumatology centers. Psychosocial aspects of heath are diminished, with depression being common and functional disability attributed to pain, fatigue, and mobility limitations. Traditional measures of cSLE activity do not capture HRQoL outcomes adequately which may limit achievement of optimal health outcomes with cSLE.

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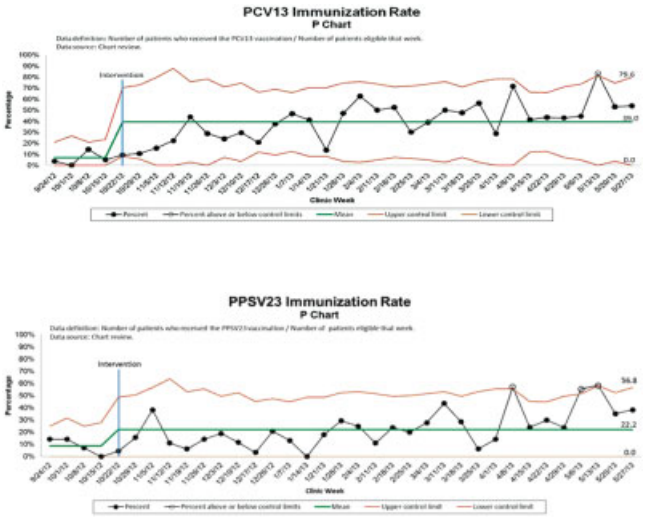
Improving Pneumococcal Vaccination Rate In The Pediatric Rheumatology Clinic. Julia G. Harris[1], Kristyn I. Maletta[2], Bixiang Ren[2] and Judyann C. Olson[3]. [1]Children's Hospital of Wisconsin, Milwaukee, WI, [2]National Outcomes Center, Children's Hospital of Wisconsin, Milwaukee, WI, [3]Medical College of Wisconsin, Milwaukee, WI.

Background/Purpose: This quality improvement project was conducted to increase pneumococcal vaccination rates in eligible Pediatric Rheumatology Clinic patients. *Streptococcus pneumoniae* is a leading cause of bacteremia, meningitis, pneumonia, sinusitis, and acute otitis media. Many patients in the Pediatric Rheumatology Clinic are at increased risk of pneumococcal disease secondary to a deficient immune system and/or immunosuppressive medications. Infections remain one of the leading causes of hospitalization and death in patients with certain rheumatic diseases. The Centers for Disease Control and Prevention recommends both the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23) for this high-risk population.

Methods: Baseline immunization rates were assessed for eligible clinic patients over a four week period. Eligible patients include children at least two years old and adults with systemic lupus erythematosus and patients currently on or starting an immunosuppressive medication. Interventions included a presentation to rheumatology providers and nurses, creation of clinic document with immunization algorithm, previsit planning, placing reminders on patient clinic forms, and sending letters to out-of-state patients. Chart reviews of eligible patients occurred throughout the study period. Control charts were established to portray change in immunization rate.

Results: The pre-intervention immunization rate for 90 eligible Pediatric Rheumatology Clinic patients was 6.7% for PCV13, 8.9% for PPSV23, and 0% for both vaccines. Data from 31 weeks were analyzed following the interventions for a total of 679 eligible patient visits and 265 separate patients. The average post-intervention immunization rate was 39.0% for PCV13, 22.2% for PPSV23, and 16.3% for both vaccines. These rates are statistically higher than the pre-intervention rates ($p<0.001$, $p=0.003$, and $p<0.001$, respectively). The final eight weeks of assessment showed a shift above the mean in pneumococcal rates for both PCV13 and PPSV23.



Conclusion: Pneumococcal vaccination is an important part of the care for systemic lupus erythematosus patients and pediatric rheumatology patients on immunosuppressive medications. Simple interventions through this quality improvement project led to a marked increase in pneumococcal vaccination rates in this vulnerable population.

Disclosure: J. G. Harris, None; **K. I. Maletta**, None; **B. Ren**, None; **J. C. Olson**, None.

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Applying Choosing Wisely: Identifying Inefficiencies Of Antinuclear Antibody Subserology Testing In a Safety Net Health System. Lisa A. Davis[1], Barbara L. Goldstein[2], Vivian Tran[1], Angela Keniston[1], Jinoos Yazdany[3], Joel M. Hirsh[1], Amy Storfa[1] and Joann Zell[2]. [1]Denver Health and Hospital Authority, Denver, CO, [2]National Jewish Health, Denver, CO, [3]University of California, San Francisco, San Francisco, CA.

Background/Purpose: In 2013, the American College of Rheumatology participated in the American Board of Internal Medicine Foundation's Choosing Wisely® campaign, developing a Top 5 List of things physicians and patients should question. Among the top 5 items in rheumatology was "do not test ANA (antinuclear antibody) sub-serologies without a positive ANA and clinical suspicion of immune mediated disease." The goal of this study was to analyze ANA and sub-serology ordering patterns in a large safety net hospital, and to identify areas where there may be room for value improvement.

Methods: We identified all ANA and sub-serology testing and results at Denver Health, a large safety net hospital, between 1/1/2005 and 12/31/2011 via query of the electronic medical records. We included the following antibodies among the sub-serology testing: Ro (SSA), La (SSB), double stranded DNA, centromere, ribonuclear protein, Smith, Scl-70 and Jo-1. Finally, we identified the timing of the ANA and the sub-serologies, and using logistic regression, we identified predictors of the ANA and profile being sent simultaneously. Variables for logistic regression included demographics, insurance type and if the laboratory was sent by primary or specialty care.

Results: During the seven years, a total of 2800 ANA tests were ordered, of which 9.7% had multiple ANAs. Thus we analyzed 2662 index ANA studies. Of those patients with both an ANA and at least one sub-serology ordered at any time (n=339,) 46.7% (n=157) had these laboratory tests sent at the same patient encounter. A subspecialty care appointment predicted that the ANA and sub-serologies were sent concurrently (OR 8.41, 95% CI 5.46–12.96, p-value <0.0001). Only 4 individuals (1.5%) were found to have at least one positive sub-serology in the setting of a negative index ANA (see Figure).

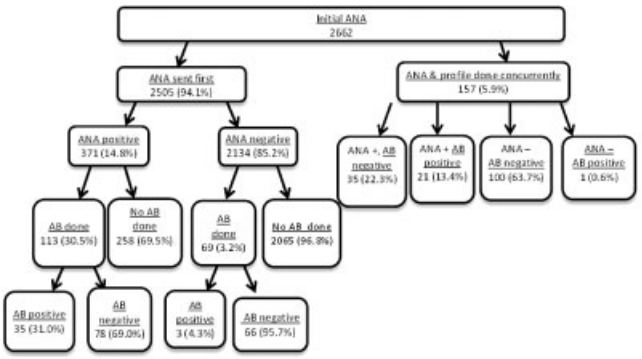

Figure. ANA and sub-serology ordering patterns between 2005–2011 at Denver Health (AB: at least one of the following was ordered: SSA, SSB, Smith, Centromere, Ribonuclear protein, Double stranded DNA, Jo-1 and Scl-70)

Conclusion: In this study, we showed that of the 2662 index ANAs, approximately 6% (157) of tests were accompanied by sub-serologies at the same patient encounter. A negative ANA predicted negative sub-serologies with rare exception in these patients. This brings into question the value of sending an ANA and sub-serologies simultaneously, which may not be cost effective or clinically indicated, and demonstrates an area for value improvement in rheumatology.

Disclosure: L. A. Davis, None; **B. L. Goldstein**, None; **V. Tran**, None; **A. Keniston**, None; **J. Yazdany**, None; **J. M. Hirsh**, None; **A. Storfa**, None; **J. Zell**, None.

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Do Rheumatologists (and Other Specialists) Practice What We Preach? A Study Of Serology Ordering Patterns With Attention To Subserologies When The Antinuclear Antibody By Enzyme Linked Immunosorbent Assay Is Negative; And The Clinical Significance Of These Positive Subserology Results.

David Bulbin[1], Alicia Meadows[1], Alfred E. Denio[1], H. Lester Kirchner[2], Sandi Kelsey[1] and Harold Harrison[1]. [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Health System, Danville, PA.

Background/Purpose: The American College of Rheumatology (ACR) was asked by the American Board of Internal Medicine to contribute to the "Choosing Wisely" campaign. The first recommendation from the ACR was: Don't test Antinuclear Antibody (ANA) subserologies without a positive ANA and clinical suspicion of immune-mediated disease. Rheumatologists likely presume that non-rheumatologists often use a "shotgun" approach when ordering ANA and subserologies. However, we wanted to look at how often physicians including rheumatologists used this "shotgun" approach that the ACR cautions against. We also investigated the clinical relevance of a positive subserology when the ANA is negative and the financial impact of such shotgun testing.

Methods: We conducted a retrospective study of the Geisinger integrated health system that examined ANA and subserology ordering practices of all physicians. Data from 2010–2012 was collected from the EPIC electronic health record and Sunquest lab system. We reviewed physician serology ordering rationale to determine the relevance of positive subserology when the ANA was negative. Subserologies included were DSDNA, Anti-Smith, RNP, SSA/SSB, SCL70 and JO1. We classified the reasoning for ordering a subserology prior to knowledge of ANA result as either justified or not justified. The subserology was justified if there was a high clinical suspicion of a specific systemic autoimmune inflammatory disease whose associated subserology is not included in the screening ANA (i.e. SSA/SSB. JO1 AB). Finally, we completed a 2010–12 cost analysis for unjustified subserology ordering.

Results: Of the 51 patients with negative ANA and a positive subserology, 41 had positive SSA/SSB, 7 Anti-Smith, 5 RNP, 2 SCL70, 0 JO1, and 0 DSDNA. 51% (26/51) of the patients had subserology orders placed by a rheumatologist at the same time as the ANA, prior to ANA results. 22% (11/51) had testing ordered by Neurologists and the other 27% (14/51) were ordered by primary physicians and other specialties. 75% of the patients had both ANA and subserology testing ordered concurrently. 75% of cases had unjustified reasoning for the subserology order. Positive subserologies when the ANA was negative did not have any clinical relevance. The cost analysis showed an average cost of tests ordered at $631.00 per patient totaling $32843 for all 51 patients. This was a small fraction of the total cost of all unjustified subserologies ordered, if one includes the NEGATIVE subserologies when the ANA was negative.

Conclusion: Rheumatologists do not always "practice what we preach." Rheumatologists ordered the majority of unjustified subserologies. We have demonstrated that there is significant waste of healthcare resources by the inappropriate ordering of subserologies, and that most of that waste is by rheumatologists. Positive subserologies when the ANA was negative did not have clinical importance. Of interest, we discovered that the ANA by Enzyme Linked Immunosorbent Assay (ELISA) assays and the subserology ELISA assays used by our lab were from two different manufacturers. The methodology difference could explain the positive subserology tests in patients with negative ANA's.

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Human Papillomavirus Vaccine Uptake Among Children and Young Adults With Autoimmune Diseases.

Candace H. Feldman[1], Linda T. Hiraki[2], Joyce Lii[3] and Seoyoung C. Kim[3]. [1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital, Harvard School of Public Health, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Autoimmune diseases such as lupus and inflammatory bowel disease are associated with increased rates of human papillomavirus (HPV), the most common sexually transmitted disease and the primary cause of cervical cancer. In 2006 and 2009 the U.S. Food and Drug Administration approved two 3-dose series HPV vaccines for use in 9–26 year-old females and males. Studies show the HPV vaccine to be safe and efficacious in patients with autoimmune diseases. We investigated whether HPV vaccine uptake is higher among those with autoimmune diseases compared to the general population.

Methods: Using a U.S. commercial insurance claims database from 2005–2012, we identified children and young adults age 9–26 with ≥12 months of continuous enrollment and ≥2 autoimmune disease diagnosis codes ≥7 days apart. We defined the index date as the calendar month and year of the second autoimmune disease diagnosis code. We matched these individuals by age, sex, and index date to randomly selected controls without any autoimmune disease diagnosis codes (1:4 ratio). We excluded individuals with a history of malignancy or organ transplant. Vaccination was defined as ≥1 HPV vaccine code (CPT 90649 or 90650) following the index date, after 2006. Baseline covariates for stratified analyses included age, sex, region, healthcare utilization and comorbidities. We also examined vaccine uptake in the 21 states that passed HPV-related legislation from 2008–2012, compared to states that did not. We obtained p-values comparing proportions of HPV vaccine uptake in the two cohorts.

Results: We identified 29,255 children and young adults with autoimmune diseases and 117,020 without. The mean age was 19 years (SD 5); 59% were female. The autoimmune disease cohort had a higher number of physician visits, abnormal pap smears, and sexually transmitted diseases (all p-values<0.01). Both cohorts had low percentages of HPV vaccine uptake overall, with 8.5% with autoimmune diseases and 9.1% without receiving ≥1 vaccine (p=0.34) (**Table)**. Among females, 13.1% with autoimmune diseases and 14.1% without received ≥1 vaccine (p<0.01); <5% of females in both groups completed a 3-dose series (p=0.57). Vaccinations were equally distributed geographically except for the Northeast which had a higher percent with autoimmune diseases receiving ≥1 HPV vaccine (p=0.02). In states with HPV-related legislation, 7.1% with autoimmune diseases and 7.5% without received ≥1 vaccine, compared to 6.5% with autoimmune diseases (p=0.04) and 7.4% without (p=0.5) in states without legislation.

Conclusion: HPV vaccine uptake is profoundly low among children and young adults both with and without autoimmune diseases despite its known efficacy. Heightened public health efforts are necessary for the general population and for those with autoimmune diseases given their increased risk of persistent HPV infection.

Table. HPV Vaccine Uptake Among Children and Young Adults in the U.S. With and Without Autoimmune Diseases*

	Autoimmune Disease Cohort* N=29,255	Non-autoimmune Disease Cohort N=117,020	p-value
Abnormal Pap Smears at Baseline	549 (1.9)	1698 (1.5)	**<0.01**
HPV Vaccine: Overall – N(%)			
≥1	2495 (8.5)	10680 (9.1)	0.34
3 (Completed series)	866 (3)	3364 (2.9)	0.87
HPV Vaccine: Females-N (%)			
≥1	2388 (13.7)	10264 (14.1)	**<0.01**
3	861 (4.7)	3343 (4.6)	0.57
HPV Vaccine: Males-N (%)			
≥1	107 (0.97)	416 (0.90)	0.49
3	5 (0.1)	21 (0.1)	0.99
≥1 HPV vaccine: Females by age group – N (%)	N= 2388	N=10264	
9–14	872 (36.6)	2734 (37.4)	0.47
15–20	1045 (43.7)	4319 (41.1)	**0.02**
21–26	471 (19.7)	2111 (20.6)	0.33
≥1 HPV vaccine: Males by age group – N (%)	N=107	N=416	
9–14	70 (65.5)	225 (54.1)	**0.03**
15–20	33 (30.8)	171 (41.2)	**0.05**
21–26	4 (3.7)	20 (4.8)	0.63
≥1 HPV vaccine by U.S. region– N (%)			
Northeast	406 (16.3)	1264 (11.8)	**0.02**
Midwest	694 (27.8)	3325 (31.1)	0.09
South	1034 (41.4)	4433 (41.5)	0.95
West	361 (14.5)	1654 (15.5)	0.63

*Autoimmune diseases include: juvenile idiopathic arthritis, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, psoriatic arthritis, inflammatory bowel disease, vasculitis, multiple sclerosis, dermatomyositis, scleroderma, ankylosing spondylitis, Goodpasture's syndrome, and sarcoidosis.

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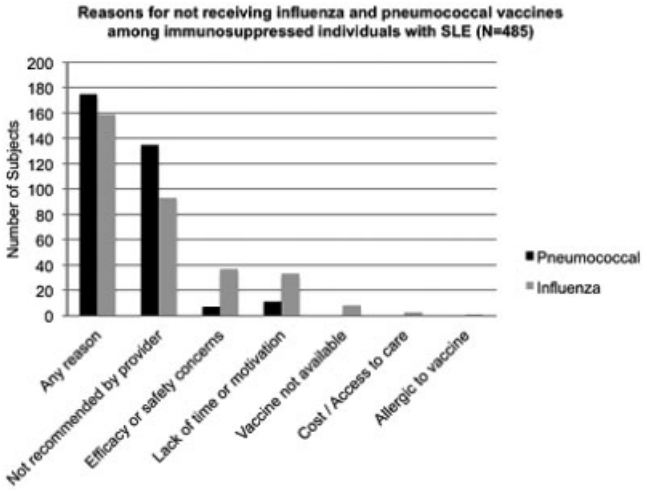
Reasons For Failure To Obtain Influenza and Pneumococcal Vaccines Among Immunosuppressed Individuals With Systemic Lupus Erythematosus. Erica F. Lawson, Laura Trupin, Emily von Scheven, Edward H. Yelin and Jinoos Yazdany. UC San Francisco, San Francisco, CA.

Background/Purpose: Infection is the third-leading cause of death in individuals with systemic lupus erythematosus (SLE) in developed countries. Nearly half of those deaths are attributed to pneumonia, making vaccination against influenza and pneumococcus critical to prevention of mortality. Nonetheless, previous work has shown that a significant number of SLE patients fail to receive these vaccinations (Yazdany, 2010). The goal of this study was to better understand why individuals with SLE fail to receive influenza and pneumococcal vaccines.

Methods: Data derive from the 2009 cycle of the Lupus Outcomes Study (LOS), an annual longitudinal telephone survey of individuals with confirmed SLE. Subjects were included in the analysis if they had taken immunosuppressive medications in the past year and reported whether they had received influenza and pneumococcal vaccines. We assessed any prior receipt of pneumococcal vaccine and receipt of influenza vaccine in the past year. Subjects who did not receive a vaccine were asked whether their physician had recommended it. If the vaccine was recommended but not received, subjects were given itemized response options to elicit reasons for not receiving vaccination. We used bivariate statistics and logistic regression (adjusting for age, gender, race, insurance status, and physician specialty) to assess frequency and predictors of reported reasons for not obtaining influenza or pneumococcal vaccines.

Results: Among 508 subjects who received immunosuppressive medications, 485 reported whether they had received vaccines. Mean age (±SD) was 50 years (±12), 93% were female, and 40% were non-white. Nearly all had insurance coverage: 53% through employers, 40% with Medicare and 5% with Medicaid. Among subjects who did not receive the influenza vaccine (N=175), the most common reason was lack of doctor recommendation (45%), followed by efficacy or safety concerns (21%), and lack of time or motivation to obtain the vaccine (19%). Reasons for not receiving the pneumococcal vaccine (N=159) were similar, with lack of doctor recommendation the most common (85%), followed by lack of time (7%) and efficacy or safety concerns (4%). Subjects age 65 or older were more likely to receive a recommendation for pneumococcal vaccine than younger subjects (43% vs. 11%, p=0.02). Multivariate models to assess predictors of vaccine recommendation were not statistically significant.

Conclusion: The most common reason why individuals with SLE did not receive pneumococcal and influenza vaccines was that physicians failed to recommend them, follwed by concerns about safety and efficacy of vaccines and time constraints. Physicians were more likely to recommend pneumococcal vaccination for older subjects. Data suggest that increasing vaccination rates in SLE will require improved process quality at the provider level, as well as addressing patient concerns and barriers.



Disclosure: E. F. Lawson, None; **L. Trupin**, None; **E. von Scheven**, None; **E. H. Yelin**, None; **J. Yazdany**, None.

ACR Concurrent Abstract Session
Imaging of Rheumatic Diseases: Imaging in Vascular and Extra-articular
Sunday, October 27, 2013, 4:30 PM–6:00 PM

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Salivary Gland Ultrasonography: A Highly Specific Tool For The Early Diagnosis Of Primary Sjögren's Syndrome. Nicoletta Luciano[1], Chiara Baldini[1], Gaia Tarantini[2], Rachele Pascale[2], Francesca Sernissi[1], Linda Carli[1], Francesco Ferro[1], Rosaria Talarico[1], Marta Mosca[3], Davide Caramella[2] and Stefano Bombardieri[1]. [1]Rheumatology Unit, Pisa, Italy, [2]Department of Diagnostic and Interventional Radiology, University of Pisa, Pisa, Italy, [3]Rheumatology Unit, University of Pisa, Pisa, Italy.

Background/Purpose: Recently, Cornec D. et al. reported that salivary gland ultrasonography (SGUS) was characterized by a sensitivity of 65.8% and a specificity of 95.3%, in patients with primary Sjögren's syndrome (pSS) and a disease duration of ≤5 years, thus encouraging the use of SGUS for the early diagnosis of pSS. Aims of this study were:1) to validate SGUS diagnostic accuracy in a different cohort of patients with sicca symptoms duration of ≤5 years; 2) to correlate the SGUS score with minor salivary gland biopsy focus score (MSGB/FS) and unstimulated salivary flow rate measured by sialometry.

Methods: Patients with suspected pSS and symptoms duration of ≤5 years were consecutively enrolled in this study. The diagnosis of pSS was made according to the AECG criteria. SGUS was carried out by the same radiologist blinded to the diagnosis and the following US parameters were recorded: size, parenchymal echogenicity and inhomogeneity in the parotid and submandibular glands on both sides. A previously reported ultrasound scoring system (De Vita et al 1992, cut-off≥1) was used to grade the echostructure alterations of the salivary glands. Statistical analysis was performed using SPSS v16.

Results: This study included 50 patients with pSS and 57 with no-SS sicca symptoms. The mean age of the pSS group was lower than non-SS group (47(13) vs 53(12) yrs, p=0.006).No further differences between the two groups were observed with respect to gender, frequency and duration of dry-mouth and dry-eye related symptoms. Patients with pSS showed a significantly higher SGUS score in comparison with controls (mean (SD)=2.1 (1.8) vs 0.0 (0.4), p=0.000). The SGUS cut-off≥1 showed a sensitivity (SE) of 66%, a specificity (SP) of 98%, a positive predictive value (PPV) of 97% and a negative predictive value (NPV) of 73% for pSS diagnosis. An inverse correlation was observed between the SGUS score and the age of the patients (r=−26, p=0.006) with younger patients frequently presenting multiple hypoechoic areas. The SGUS score was also correlated with both the MSGB/FS (r=55, p=0.000) and the salivary flow rate (r=−40, p=0.000).

Conclusion: This study confirmed the good performance that SGUS for the early non-invasive diagnosis of pSS. Further research in larger international cohort of patients is mandatory in order to assess the role of SGUS in the diagnostic algorithm of pSS.

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Salivary Gland Ultrasonography Improves The Diagnostic Performance Of ACR 2012 Classification Criteria For Sjögren's Syndrome, Even In The Early Stages Of The Disease. Divi Cornec[1], Sandrine jousse-Joulin[2], Thierry Marhadour[3], Jacques-Olivier Pers[1], Yves Renaudineau[1], Alain Saraux[4] and Valerie Devauchelle-Pensec[5]. [1]Brest Occidentale University, Brest, France, [2]Brest university medical school, EA 2216, UBO and CHU de la Cavale Blanche,, Brest, France, [3]CHU de la Cavale Blanche, Brest, France, [4]CHU Brest et Université Bretagne Occidentale, Brest, France, [5]Brest Occidentale university, Brest, France.

Background/Purpose: Recently published ACR classification criteria for primary Sjögren's syndrome (pSS) include only 3 objective tests: 1) a serological item: anti-SSA/SSB antibodies or [antinuclear antibody (ANA) titer ≥1:320 and rheumatoid factor (RF) positivity], 2) an Ocular Staining Score (OSS) ≥3, and 3) focus score ≥1 on salivary gland biopsy (SGB). None of these tests explore the function or the morphology of the salivary glands. In a recent study, we have shown that salivary gland ultrasonography (SGUS) has good diagnostic properties for SS.Our objective was to evaluate if SGUS could improve the diagnostic properties of ACR 2012 criteria.

Methods: The pSS Brittany cohort includes patients with suspected pSS (sicca symptoms, parotidomegaly or extraglandular manifestations suggestive of pSS). All patients had a standardized clinical and biological evaluation and a SGB. Ophtalmologic evaluation used fluorescein and lissamine green to assess the presence of keratoconjunctivitis sicca, allowing the subsequent calculation of the OSS. SGUS was performed on bilateral parotid and submandibular glands. Their echostructure was quoted on a scale between 0 and 4, as previously published. A SGUS score ≥2 was considered pathologic. The gold standard for the analysis was a clinical diagnosis of pSS performed by a group of experts, unaware of the of the SGUS score.

Results: 101 patients were included in this study (mean age 57.4±13.0 years, symptoms duration 6.7±6.1 years, 94.1% females). The diagnosis of pSS was made in 45 patients, and 34 patients fulfilled ACR criteria. Sensitivity (Se) and specificity (Sp) of the different items for the diagnosis of pSS were respectively: 60.0% and 96.4% for the serological item of ACR criteria; 82.2% and 82.1% for the focus score ≥1; 55.6% and 58.9% for the OSS ≥3; 60.0% and 87.5% for SGUS. ACR criteria displayed 64.4% Se and 91.1% Sp. We created a new criteria set including the 3 items of ACR criteria and SGUS; these criteria were considered positive for all patients fulfilling almost 2 of these 4 items. The adjunction of SGUS to ACR criteria increased their Se to 84.4%, for a similar 89.3% Sp. This improvement of ACR criteria diagnostic performance was also found when we restricted the analyses to patients with disease duration of less than 5 years.

Conclusion: The diagnosis properties of ACR classification criteria for pSS are notably improved by the addition of the SGUS score. SGUS should be included in future consensual classification criteria for pSS.

Disclosure: D. Cornec, None; **S. jousse-Joulin**, None; **T. Marhadour**, None; **J. O. Pers**, None; **Y. Renaudineau**, None; **A. Saraux**, None; **V. Devauchelle-Pensec**, None.

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Systemic Lupus Erythematosous and Primary Sjogren's Syndrome May Display Joint Erosions On MRI As Well As Healthy Control, But Cannot Be Considered As Erosive Disease Such As Rheumatoid Arthritis: An MRI Observational Study Of 90 Subjects. Frédérique Gandjbakhch[1], Violaine Foltz[1], Jérôme Renoux[2], Nahalie Cozic[3], Nathalie Costedoat-Chalumeau[4], Damien Sene[5], Guillaume Mercy[6], Zahir Amoura[7], Jean-Charles Piette[7], Nathalie Morel[8], Pierre Bourgeois[9] and Bruno Fautrel[10]. [1]APHP, Pitié Salpétrière Hospital, Universite Paris 6, Paris, France, [2]Pitie-Salpetriere Hospital, Paris, France, [3]APHP, Pitie Salpetriere Hospital, department of statistics, Paris, France, [4]Hopital Cochin, Paris, France, [5]Hopital Lariboisière, Paris, France, [6]APHP, Pitie-Salpétrière Hospital, paris, France, [7]CHU Pitié-Salpêtrière, Paris, France, [8]Groupe Hospitalier Pitié-Salpétrière, Paris, France, [9]APHP, Pitie-Salpetriere Hospital, Paris 6, Paris, France, [10]Paris 6 – Pierre et Marie Curie University; AP-HP, Rheumatology, Pitié-Salpêtrière Hospital, - GRC-UPMC 08 – EEMOIS, Paris, France.

Background/Purpose: Recent studies tend to demonstrate presence of MRI erosion in Systemic Lupus Erythematosous (SLE) and primary Sjogren's syndrome (pSS). The objective of this study was to describe MRI characteristics (erosion and osteitis, i.e. bone marrow oedema) of patients with SLE and pSS without association with rheumatoid arthritis (RA) compared to "positive control",i.e. RA and "negative control" (sex/age-matched healthy controls).

Methods: pSS, SLE, RA and HC were prospectively included from 2 university departments (rheumatology and internal medicine) between 2009 and 2011. Inclusion criteria were: 1- for lupus and primary SS: disease duration >2 years, no association with RA defined as no arthritis, no ACPA, normal X rays of hand and feet. 2-for Healthy controls (HC): no history of tender or swollen joint or rheumatic disease. 3- for RA: established RA with duration>2 years. MRI of MCP2 to 5 and wrist of the dominant hand was performed for all subjects using a dedicated MRI (ESAOTE Cscan 0.2 Tesla) in coronal and axial plans using T1 and STIR sequences, without gadolinium injection, in order to evaluate erosion and osteitis according to the OMERACT definitions. Adaptation of the OMERACT definition for erosion was used in order to differenciate physiological cortical break, i.e. vascular foramen and erosion due to pathological process. MRIs were evaluated by 2 independent readers, blindly to clinical and radiographic data using RAMRIS scores for erosion and osteitis. Statistics were performed using SAS 9.3 software.

Results: 90 subjects were included prospectively in the study: 19 pSS, 21 SLE, 30 RA and 20 HC. 83 % of RA patients were erosive on Xrays, 86% and 72 % were RF and ACPA positive. All SLE and pSS patients had normal Xrays of hand and feet (inclusion criteria). All patients and HC had at least one cortical break seen in 2 plans on MRI of hand and wrist without statistical difference between the groups. Frequencies and scores for erosion and for osteitis were statistically different between RA and SLE/pSS while no statistical difference was seen between SLE/pSS and HC (Table). Sensitivity and specificity were respectively for erosion: 0.93 and 0.38, for erosion with grade ≥2: 0.4 and 0.88 and for osteitis: 0.77 and 0.78. A cut-off of RAMRIS erosion was determined at 9 and could discriminate SLE/pss and RA patients (AUC= 0.8007) with good sensitivity (0.68) and specificity (0.84).Erosions in wrist and MCP3 were frequent in all groups, while erosions in MCP2, MCP4 and MCP5 were more frequently observed in RA with statistical difference between the groups.

	RA (n=30)	Lupus (n=21)	SS (n=19)	HC (n=20)	SLE/pSS vs RA	SLE/pSS vs HC
Patient with at least one Cortical break, n(%)	30 (100%)	21 (100%)	19 (100%)	20 (100%)	NS	NS
Patient with at least one erosion, n(%)	28 (93%)	12 (57%)	13 (68%)	12 (60%)	0.004	1
Patient with at least one erosion ≥grade2, n(%)	22 (69%)	9 (43%)	7 (36%)	5 (25%)	0.019	0.39
Patient with at least one osteitis, n(%)	23 (77%)	3 (14%)	5 (26%)	5 (25%)	<.0001	0.74
Patient with at least one erosion and one osteitis, n(%)	22 (69%)	3 (14%)	5 (26%)	5 (25%)	<.0001	0.74
RAMRISerosion	21.6±10.34	13.02±5.59	11.56±5.73	10.69±4.54	0.0003	0.40
RAMRISosteitis	2.29±4.69	0.17±0.67	0.11±0.27	0.29±0.79	0.0005	0.63

Conclusion: MRI Cortical break are frequent in SLE and pSS as well as in HC. Erosions may be seen in SLE and pSS but can be distinguished from erosions of RA. Distinction of physiological cortical break and pathological

erosion may lead to better interpretation of MRI and further consensus on MRI definition of these 2 items should be to consider.

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Capillaroscopy Compared With Color Doppler Ultrasound Of Digital Arteries For Distinguishing Primary From Secondary Raynaud's Phenomenon. Wolfgang A. Schmidt[1], Katharina Pagel[2], Bernd Schicke[3] and Andreas Krause[4]. [1]Med Ctr Rheumatology Berlin Buch, Immanuel Krankenhaus Berlin, Berlin, Germany, [2]Medical Ctr Rheumatol Berlin Buch, Immanuel Krankenhaus Berlin, Berlin, Germany, [3]Tumorzentrum Berlin, Berlin, Germany, [4]Immanuel Krankenhaus Berlin, Berlin, Germany.

Background/Purpose: Raynaud's phenomenon (RP) is commonly seen in rheumatology practice. Differentiating primary from secondary RP is important for disease management and prognosis. How does capillaroscopy compare to color Doppler ultrasound (US) of the finger arteries for distinguishing primary from secondary RP? How often do these imaging techniques detect abnormalities in nailfold arteries or finger arteries in patients with connective tissue diseases?

Methods: Consecutive patients with RP or with suspected connective tissue disease and healthy controls who presented within a 12-month period in a tertiary rheumatology referral center were examined.

Nailfold capillaroscopy of the 2nd to 5th fingers was done bilaterally with a Nikon Stereoscopic Zoom Microscope SMZ1000 including a camera control unit DS-Us, in search for scleroderma, dermatomyositis and other connective tissue disease patterns as previously described (Cutolo M, et al. Best Pract Res Clin Rheumatol 2008;22:1093–108).

Bilateral color Doppler US of the radial, ulnar, all common palmar and all proper digital arteries was performed after a hot water bath of the hands in search for occlusions and stenoses as previously described (Schmidt WA, et al. J Rheumatol 2008;35:1591–8). An Esaote MyLab Twice US machine, equipped with a 6–18 MHz linear probe, was used.

Capillaroscopy and US images were stored electronically. Both investigators were not aware of the results of the other examination. After diagnostic work-up the results of US and capillaroscopy were compared with the final diagnosis.

Results: Twenty healthy controls and 165 patients were included. Final diagnoses included primary RP (52 patients), systemic sclerosis (49 patients), myositis (15 patients), other connective tissue diseases such as SLE (13 patients), MCTD (12 patients), UCTD (10 patients), Sjögren's syndrome (4 patients) and vascular diseases such as vasculitis (5 patients), antiphospholipid syndrome (3 patients), and arteriosclerosis (2 patients). Table 1 shows the results.

Table 1.

Diagnosis	N	Consistent results of US and capillaroscopy	Only US positive	Only capillaroscopy positive	Kappa
Controls	20	100%	0%	0%	N.A.
Primary RP	52	71%	10%	19%	−0.10
Systemic sclerosis	49	88%	8%	4%	0.81
Myositis	15	67%	7%	27%	0.68
Other connective tissue diseases	39	80%	5%	15%	0.73
Vascular disease	10	50%	20%	30%	0.51
Total	185	79%	7%	14%	0.58

The highest rate of abnormalities was found in systemic sclerosis (capillaroscopy, 92%; US 96%). In myositis (87%; 67%) and other connective tissue diseases (82%; 72%) capillaroscopy more often displayed abnormal results than US. In primary RP, US and capillaroscopy were positive in 10% and 19% respectively. None of these patients showed abnormalities in both US and capillaroscopy.

Conclusion: Although capillaroscopy and US are assessing different anatomical structures, each technique helps distinguish primary from secondary RP. Abnormalities are particularly common in systemic sclerosis. Capillaroscopy is more sensitive in other connective tissue diseases. However, it is more frequently positive also in primary RP. The agreement between US and capillaroscopy is good to moderate.

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Aortic Wall Thickness In Patients Without Aortitis: a Computed Tomography-Based Study Of 100 Patients. Afif Nakhleh, Irina Rukhkyan, Vladimir Wolfson, Itzhak A. Rosner, Majed Odeh and Gleb Slobodin. Bnai Zion Medical Center, Haifa, Israel.

Background/Purpose: Thickening of the aortic wall, probably the earliest CT sign of aortitis, is frequently missed as there are no accepted criteria for normal aortic wall thickness (AWT). Studies based on CT-assessed AWT in healthy persons and patients with prevalent co-morbidities are scarce, and do not allow determination of reference values for the definition of increased AWT necessary for the diagnosis of aortitis by CT. On the other hand, the substantial difference in the techniques of MRI and CT prevent the blind extrapolation of MRI-based definitions onto CT imaging. The present study was conducted to assess the relationship of CT-measured AWT with patient-related and disease-related factors in a large cohort of patients without aortitis.

Methods: CT scans of 100 consecutive patients without known aortic disease, hospitalized at the Bnai Zion Medical Center were reviewed and AWT measured at three levels: 1. thoracic descending aorta at the level of the bifurcation of the pulmonary artery; 2. abdominal aorta at the level of celiac artery origin; 3. abdominal aorta one slice below the level of the origin of renal arteries. Patients' charts were analyzed and demographic data and data on co-morbidities extracted. Correlations with measured AWT were calculated.

Results: By bivariate analysis, AWT had significant positive correlation with patient age ($r=0.68$, $p=0.000$; $r=0.6$, $p=0.000$; $r=0.62$, $p=0.000$, for 3 levels, respectively), the presence of arterial hypertension (2.11 ± 0.6 mm vs 1.7 ± 0.8 mm, $p=0.001$; 2.14 ± 0.8 mm vs 1.64 ± 0.5 mm, $p=0.004$; 2.05 ± 0.7 mm vs 1.51 ± 0.6 mm, $p=0.000$, for 3 levels, respectively) and calcifications of the aortic wall (2.24 ± 0.6 mm vs 1.63 ± 0.7 mm, $p=0.000$; 2.3 ± 0.8 mm vs 1.58 ± 0.5 mm, $p=0.000$; 2.16 ± 0.7 mm vs 1.52 ± 0.6 mm, $p=0.000$, for the 3 levels, respectively). The aortic wall had a tendency to be thicker in males (2.04 ± 0.8 mm vs 1.79 ± 0.6 mm, $p=0.089$; 2.00 ± 0.6 mm vs 1.85 ± 0.8 mm, $p=0.325$; 1.95 ± 0.7 mm vs 1.69 ± 0.7 mm, $p=0.071$, for the 3 levels, respectively) and in patients with known coronary artery disease (2.18 ± 0.6 mm vs 1.86 ± 0.7 mm, $p=0.04$; 2.11 ± 0.7 mm vs 1.76 ± 0.72 mm, $p=0.069$; 2.21 ± 0.6 mm vs 1.86 ± 0.76 mm, $p=0.073$, for the 3 levels, respectively), being independent on the presence of diabetes mellitus, hyperlipidemia or malignancies. Multivariate analysis showed significant positive correlation of AWT only with patient age and the presence of aortic calcifications ($p=0{,}000$ and $p=0.034$ for the thoracic descending aorta, $p=0.021$ and 0.001 for the upper abdominal aorta, $p=0.001$ and $p=0.005$ for the infrarenal abdominal aorta, respectively).

Table 1. AWT in different age groups

AWT in mm (median, range)	<50 years median 40.5 years (16 patients)	50–59 years median 54 years (11 patients)	60–69 years median 64 years (15 patients)	70–79 years median 74 years (33 patients)	≥80 years median 84.5 years (25 patients)
Level 1	1.3 (0.5–2.05)	1.4 (0.15–1.8)	1.65 (1.3–4.75)	2.05 (0.5–2.85)	2.38 (1.6–2.85)
Level 2	1.4 (0.5–1.75)	1.55 (0.2–1.7)	1.7 (1.25–5.95)	2.15 (0.75–3.0)	2.33 (0.7–3.05)
Level 3	1.2 (0.5–1.75)	1.4 (0.9–1.5)	1.5 (1.0–5.4)	2 (1.2–3.0)	2.1 (1.2–4.1)

Conclusion: The 'normal' range of AWT varies with age, and may also vary with co-morbidities. These data may serve as a reference and should be considered in interpretation of the CT-appearance of the aortic wall when assessing for aortitis.

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Ultrasound Evaluation Of The Greater Trochanter Pain Syndrome: Bursitis Or Tendinopathy? Cristian Quiroz[1], Santiago Ruta[1], Javier Rosa[1], David A. Navarta[1], Ricardo Garcia-Monaco[2] and Enrique R. Soriano[3]. [1]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Radiology and Imagenology Department, Hospital italiano de Buenos Aires, Buenos Aires, Argentina, [3]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina.

Background/Purpose: Greater trochanteric pain syndrome (GTPS) is a common clinical problem that may be caused by a variety of either

intra-articular o peri-articular pathologies. Inflammation of the trochanteric bursa has been postulated for a long time as the main cause of pain at trochanteric level. However, some studies have questioned the real involvement of the trochanteric bursa in the GTPS, and tendinopathy of the gluteus medius and/or minimus has been proposed as an important cause of this syndrome. The aim of the present study was to evaluate the prevalence of different US abnormal findings in patients with GTPS.

Methods: A retrospective analysis was carried out from the electronic medical records of consecutive patients complaining of a GTPS who underwent an US assessment of the greater trochanter between January 2011 and February 2013 at a Rheumatology Unit. US assessment was performed in all cases by the same experienced rheumatologist using a MyLab 70 XV (Esaote Biomedica, Genoa, Italy) machine equipped with a broadband 4–13 MHz linear probe. The presence or absence of the following US abnormal findings was investigated: 1) tendinopathy (tendinosis, calcific tendinosis and/or tendon tear) of the gluteus medius and/or minimus; 2) trochanteric bursitis (fluid distension). Additionally, we investigated if patients had also magnetic resonance imaging (MRI) evaluation of the hip within the 30 days before or after US evaluation.

Results: A total of 124 US examinations of the greater trochanter in 96 patients (28 underwent bilateral US evaluation) were included for the analysis. Eighty-seven patients (90.6%) were female and the mean age (SD) was 64.3 years (14.7). Sixty-eight (55%) US examinations were ordered by rheumatologists and the others by general practicioners, orthopedics and internal medicine consultants. Tendinopathy of the gluteus medius and/or gluteus minimus, as the only US abnormal finding, was detected in 62 out of 124 (50%) examinations. Bursitis, as the only US abnormal finding, was found in 5 out of 124 (4%) examinations. Eighteen (14.5%) US examinations showed a combination of both tendinopathy of the gluteus medius and/or gluteus minimus and trochanteric bursitis. Calcifications were found in 12 out of 80 (15%) tendinopathies. In 39 (31.5%) US examinations no abnormalities were detected. Twenty-five patients had also unilateral MRI evaluation of the hip. The unweighted kappa values between US and MRI for the detection of tendinopathy of the gluteus medius and/or gluteus minimus and trochanteric bursitis were 0,746 (95% CI: 0.477–1.014) and 0.715 (95% CI: 0.415–1.014), respectively.

Conclusion: Tendinopathy of the gluteus medius and/or minimus was the most frequent US abnormal finding in patients with GTPS. Trochanteric bursitis was less common and had associated tendinopathy in the majority of the cases. There was good agreement between US and MRI. These results support the role of pathology of the gluteus tendons as the major cause of pain in patients with GTPS.

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ACR Concurrent Abstract Session
Metabolic and Crystal Arthropathies I
Sunday, October 27, 2013, 4:30 PM–6:00 PM

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Cost-Effectiveness Of Urate Lowering Strategies For The Management Of Gout. Eric Jutkowitz[1], Karen Kuntz[2], Laura T Pizzi[3] and Hyon Choi[4]. [1]University of Minnesota, Minneapolis, MN, [2]Division of Health Policy and Management, School of Public Health, University of Minnesota, Minneapolis, MN, [3]Thomas Jefferson University, Philadelphia, PA, [4]Boston University School of Medicine, Boston, MA.

Background/Purpose: The new 2012 ACR guidelines for the management of gout have provided updated recommendations; however, the employed method do not address the societal costs of the recommendations. We evaluated the cost-effectiveness of 5 first-line urate-lowering therapy (ULT) strategies (incorporating dose-escalation reflective of real practice) for the management of gout over a lifetime.

Methods: We developed a Markov model to calculate lifetime health benefits, costs, and incremental cost-effectiveness ratios (ICERs) of 5 ULT strategies: 1) no ULT, 2&3) allopurinol and febuxostat used as single therapy options, 4) allopurinol-febuxostat sequential therapy, and 5) febuxostat-allopurinol sequential therapy. We investigated two ULT dosing scenarios: 1) fixed dosing (febuxostat[80 mg daily]; allopurinol [300 mg daily]), 2) dose escalation (febuxostat [up to 120mg daily]; allopurinol [up to 800mg daily]). The fixed dosing scenario is reflective of recent randomized trials, whereas the dose-escalation scenario is reflective of real practice. Health states in the model reflected those that could occur during a gout patient's lifetime: controlled (serum urate acid (SUA) <6.0 mg/dl), or uncontrolled (SUA ≥ 6.0 mg/dl). Within each state we accounted for gout flares and ULT associated adverse events, including allopurinol hypersensitivity syndrome. Costs were evaluated from a payer perspective. Cost and utility estimates were obtained from the literature and discounted by 3% per year. Gout flares and ULT associated adverse events were associated with a disutility. Sensitivity analyses were conducted to evaluate the impact of parameter uncertainty.

Results: In both dosing scenarios (fixed and escalating), allopurinol as a single-line option was the least costly option (discounted lifetime cost = $12,004 and $10,477, respectively) and was more effective than no ULT (**Table**). In both dosing scenarios, allopurinol- febuxostat sequential therapy was more costly and more effective than allopurinol single therapy, with an ICER of $24,400/quality-adjusted life year (QALY) (fixed dosing) and $33,500/QALY (dose escalation). In both dosing scenarios, febuxostat -allopurinol sequential therapy had a cost-effectiveness ratio $>$$300,000/QALY, and febuxostat single therapy cost more and was less effective than febuxostat -allopurinol sequential therapy (dominated) (**Table**). The allopurinol- febuxostat sequential therapy result in the dose escalation scenario was sensitive to the cost of febuxostat and time spent on a given ULT without control.

Table. Costs, effectiveness,and cost-effectiveness of 5 ULT strategies for gout over a lifetime

Strategy	Fixed Dosing			Dose Escalation		
	Lifetime Costs	QALY (Yr)	ICER	Lifetime Costs	QALY (Yr)	ICER
Allopurinol Single Therapy	$12,004	12.813	Reference	$10,477	13.341	Reference
No ULT	$13,395	12.363	Dominated	$13,395	12.363	Dominated
Allopurinol-febuxostat sequential therapy	$27,578	13.451	$24,400	$19,142	13.599	$33,500
Febuxostat-allopurinol sequential therapy	$32,821	13.457	$873,800	$31,529	13.639	$309,700
Febuxostat Single Therapy	$35,938	13.413	Dominated	$35,257	13.380	Dominated

Notes: No ULT is dominated (costs more and is less effective) by allopurinol as an only treatment option.
Dominated strategies are excluded in the incremental cost-effectiveness ratio

Conclusion: Allopurinol single therapy is cost saving compared to no ULT. Allopurinol-febuxostat sequential therapy appears to be cost-effective as compared with allopurinol single therapy. Febuxostat single therapy and febuxostat-allopurinol sequential therapy are unlikely to be cost-effective.

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Impact of Urate Lowering Therapy On Renal Disease Progression in Patients With Hyperuricemia. Gerald D. Levy[1], T. Craig Cheetham[2], Nazia Rashid[3] and Fang Niu[2]. [1]Southern California Permanente Medical Group, Downey, CA, [2]Kaiser Permanente, Downey, CA, [3]Kaiser Permanente Southern California, Downey, CA.

Background/Purpose: The relationship between elevated serum Uric Acid [sUA] and progression of chronic kidney disease is well established.[1–3] There are a several small studies on the impact of Urate Lowering Therapy (ULT) on renal progression or ESRD.[4–6] This large study evaluated patients with hyperuricemia and the impact of ULT on renal function.

Methods: This retrospective, database study identified 111,992 patients with a serum uric acid level (sUA) of $\geq$ 7mg/dl [Index Date (ID)] from January 1, 2002 to December 31, 2010. Patients with at least 12 months of Health Plan membership including drug benefit prior to ID were studied. All patients had at least one sUA and Glomerular Filtration Rate (GFR) level within the 6 months period prior to the ID and at least one sUA and GFR in the follow up period following the ID (follow up period). A $\geq$ 30% reduction in GFR, initiation of dialysis or a GFR $\leq$ 15 ml/min were defined as Outcome Events. All subjects were ULT naïve to allopurinol, probenecid and febuxostat in the 12 months before the ID. At ID, subjects were $\geq$18 years of age, without chronic kidney disease (CKD) 4 or 5, on dialysis, HIV, non-remission cancer, proteinuria, nephrolithiasis, or organ transplantation. Patients who met inclusion criteria were followed until they had an Outcome Event, disenrolled, died, the end of the follow up period or the conclusion of the study, 12/31/2011.. The cohort was subdivided into three groups: never treated (NT), ULT time on therapy of $<$80% ($<$80%) and time on therapy of $\geq$80%

(≥80%). Cox proportional hazards regression model was used to determine factors associated with renal function decline.

Results: A total of 16,186 patients met inclusion criteria with 11,192 NT patients, 3,902 with <80% and 1,092 with ≥80%. The ≥80% group tended to be older, male with more co-morbidities compared to NT or <80% groups. The ≥80% group received ULT earlier than <80% group with 43.5% compared to 16.9% starting within 2 weeks of ID and 94% compared to 41% starting within 4 months. Allopurinol accounted for 98.3% of ULT and deaths were equally represented amongst the groups at 1.2%. Factors associated with outcome events were age, female gender, hypertension, diabetes, congestive heart failure, previous hospitalizations, higher sUA at baseline and rheumatoid arthritis. Time on therapy of ≥80% was not associated with outcome events 1.07 (0.76–1.52, p=0.68) however those patients with a sUA <6mg/dL had a significant 37% reduction in events p=<0.0001 HR 0.63 (0.5–0.78). See Table 1.

Table 1. Cox Proportional Hazard Model for Risk Factors

Results After Statistical Analysis	Hazard Ratio	95% CI	p value
Age at Index	1.03	1.02–1.04	<0.0001
Gender: F vs M	1.49	1.25–1.78	<0.0001
Ethnicity			
Asian vs White	0.86	0.64–1.14	0.29
Black vs White	1.05	0.85–1.31	0.64
Hispanic vs White	0.94	0.71–1.24	0.65
Co-Morbities			
Hypertension	1.50	1.17–1.93	0.00
Obesity	0.96	0.79–1.18	0.71
Diabetes	1.96	1.64–2.35	<0.0001
Dyslipidemia	0.92	0.77–1.11	0.39
Cardiovascular Ds	1.15	0.93–1.42	0.21
Congestive Heart Failure	1.39	1.04–1.85	0.03
Osteoarthritis	1.05	0.86–1.29	0.62
Rheumatoid Arthritis	1.46	0.84–2.54	0.19
Concomitant medications			
NSAIDs	0.85	0.72–1.01	0.07
Colchicine	1.08	0.82–1.42	0.58
Corticosteroids	0.92	0.73–1.17	0.49
Patient characteristics			
Previous Hospitalizations	1.33	1.12–1.59	0.00
GFR at Baseline	1.01	0.99–1.01	0.12
sUA levels at Baseline	1.11	1.04–1.19	0.00
Gout Diagnosis at Index	1.00	0.81–1.24	0.99
Role of therapy and (sUA<6)			
<80% Time on Rx vs Never	1.27	1.05–1.55	0.01
≥80% Time on Rx vs Never	1.08	0.76–1.52	0.68
sUA at Goal vs Not at Goal	**0.63**	**0.5–0.78**	**<0.0001**

Conclusion: Serum Uric Acid is an independent risk factor for progressive renal function decline. Time on ULT was not associated with a reduction in renal disease progression, but in patients who achieved the ACR goal of sUA <6mg/dL[7] there was a 37% reduction in outcome events.

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Monosodium Urate Crystal Induced Macrophage Inflammation Is Attenuated By Chondroitin Sulfate: Pre-Clinical Model For Gout Prophylaxis?

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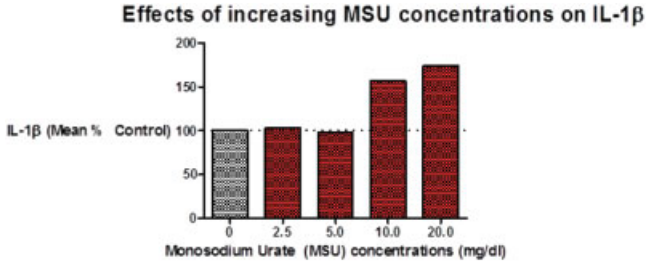
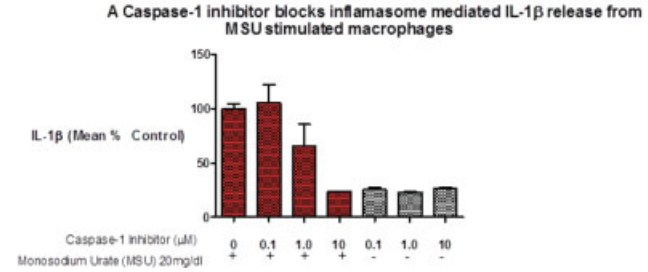
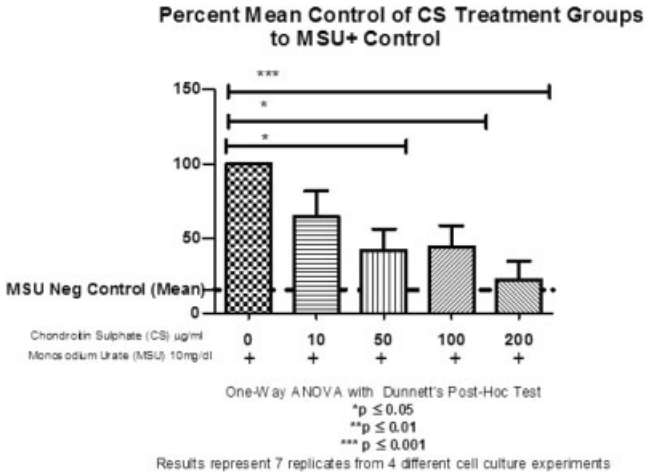
Background/Purpose: Gout is one of the most common forms of inflammatory arthritis and is characterized by acute episodes of joint pain. Monosodium urate (MSU) crystals are taken up by macrophages resulting in NLRP3 inflammasome activation and IL-1beta production. The ACR guidelines recommend a daily prophylactic agent, such as colchicine, NSAIDs or corticosteroids, to prevent acute gout flares at the time of initiation of urate-lowering therapy; however, all these agents are associated with possible intolerance or comorbidities. Chondroitin Sulphate (CS), a natural glycosaminoglycan of the extracellular matrix, has some clinical benefit in symptomatic osteoarthritis but has never been tested in gout. *In vitro*, CS has anti-inflammatory effects on chondrocytes and synoviocytes but its effect on macrophages is unknown. The purpose of our study was to evaluate the *in vitro* effects of CS on MSU-stimulated cytokine production of macrophages.

Methods: THP-1 monocytes were differentiated into mature macrophages using a phorbol ester followed by MSU crystal stimulation in the absence and presence (4 hours prior) of CS in a physiologically achievable range of concentrations (10–200μg/ml). Cell culture media was removed at 24h and analyzed by immunoassay for IL1β. The specificity of inflammasome activation by MSU crystals was tested with a caspase-1 inhibitor (0.01μM-10 μM). Lipopolysaccaride (LPS, 50μg/ml), a toll-like receptor activator, served as a positive control for IL-1 β production.

Results: MSU crystals ≥10mg/dll consistently increased IL-1β production by macrophages (Figure 1); this effect was inhibitable by the caspase-1 inhibitor confirming inflammasome activation as the source of this cytokine (Figure 2). Increasing levels of CS resulted in a significant dose-dependent inhibition of MSU stimulated IL-1β production from macrophages (Figure 3).







Conclusion: Increasing levels of CS attenuate MSU crystal induced macrophage inflammation, suggesting a possible role for CS in gout prophylaxis.

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Knee Effusion: Sensitivity and Specificity Of Ultrasound For The Identification Of Calcium Pyrophosphate Crystals. Erika Catay[1], Santiago Ruta[1], Javier Rosa[1], David A. Navarta[1], Marina Scolnik[2], Ricardo Garcia-Monaco[3] and Enrique R. Soriano[4]. [1]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Rheumatology Section, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [3]Radiology and Imagenology Department, Hospital italiano de Buenos Aires, Buenos Aires, Argentina, [4]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina.

Background/Purpose: Calcium pyrophosphate deposition disease (CPPD) is an important cause of arthritis mainly in elderly people. The final diagnosis is based on the identification of calcium pyrophosphate (CPP) crystals in the synovial fluid (SF).Our objective was to evaluate the sensitivity and the specificity of ultrasound (US) and conventional radiography for the detection of CPP crystals in patients with knee effusion.

Methods: Consecutive patients > 50 years old with knee effusion on clinical examination seen at the out-patient Rheumatology Unit who underwent aspiration of SF including microscopic investigation of SF samples, were included. In all patients, US and conventional radiography (CR) of the involved knee were performed after arthrocentesis. US examinations were carried out by a rheumatologist trained in this imaging technique who was blinded to all clinical and CR data. A MyLab 70 XV (Esaote Biomedica, Genoa, Italy) machine equipped with a broadband 4–13 MHz linear probe was used. US scanning technique was performed according to standard methods, including suprapatellar views (transverse and longitudinal) with knee in maximal possible flexion to assess femoral hyaline cartilage and lateral and medial longitudinal views with knee extended (as possible) to evaluate lateral and medial meniscal fibrocartilage, respectively. The following US abnormal findings were considered indicative of CPPD: 1) hyperechoic bands within the femoral hyaline cartilage layer; 2) hyperechoic sparkling spots in meniscal fibrocartilage. CR were read by an experienced rheumatologist blinded to all clinical and US data searching for radiological evidence of chondrocalcinosis. SF was analyzed by an experienced biochemist, blinded to clinical and imaging data, using plain light and polarizing light microscopy.

Results: A total of 75 knees were evaluated in the same number of patients [39 male; mean age (SD): 66.6 years (15.7)]. Twenty-four patients had previous diagnosis of primary knee osteoarthritis (OA), 15 rheumatoid arthritis, 10 CPPD (McCarty criteria), 8 psoriatic arthritis and 5 systemic lupus erytematosus. Thirteen patients had knee effusion without definitive diagnosis of any rheumatic condition. Analysis of synovial fluid revealed CPP crystals in 15 out of 75 (20%) examined knees from 9 patients with previous diagnosis of CPPD, 3 patients with previous diagnosis of primary knee OA and 3 patients without previous definitive diagnosis of a rheumatic condition.

Table shows the US and cr diagnostic test properties for the detection of CPP crystals using SF findings as the gold standard.

	Synovial fluid analysis		Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
	Positive	Negative				
Ultrasound						
Positive	9	2	60% (32.33–83.57)	96.67% (88.45–99.50)	81.82% (48.24–97.18)	90.62% (80.69–96.46)
Negative	6	58				
Conventional radiology						
Positive	6	10	40% (16.43–67.67)	83.3% (71.47–91.69)	37.5% (15.29–64.53)	84.75% (73–92.76)
Negative	9	50				

Conclusion: US showed high specificity with good sensitivity to detect CPP crystals in patients with knee effusion. Compared with CR, US had better specificity and sensitivity. US may be used in daily rheumatologic practice when CPPD is suspected.

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Diet-Induced Obesity Results In a Pro-Inflammatory Resting Environment With No Impact On Monosodium Urate Crystal-Induced Inflammation. Odette Shaw[1], Bregina Pool[2], Nicola Dalbeth[2] and Jacquie Harper[1]. [1]Malaghan Institute of Medical Research, Wellington, New Zealand, [2]University of Auckland, Auckland, New Zealand.

Background/Purpose: Obesity-related diseases, including gout, are associated with low-grade chronic inflammation. Although there is evidence that adipose resident macrophages have a pro-inflammatory M1-like phenotype, the impact of obesity on the inflammatory phenotypes of resident macrophage and infiltrating monocytes in other tissues is not clear. This study sought to determine if diet-driven obesity alters the inflammatory phenotype of non-adipose tissue resident macrophages and changes the inflammatory response to monosodium urate (MSU) crystals.

Methods: C57BlJ6 mice were fed normal chow containing 5.3% fat or high fat chow containing 23.5% fat for 12 weeks and then challenged with 3mg MSU crystals intraperitoneally (n=30 per group). Peritoneal lavage was carried out at 0, 8 and 18 hours. Peritoneal monocyte and neutrophil numbers were determined by flow cytometry and cytokine levels were quantified by ELISA. Purified resident peritoneal macrophages and 18 h MSU-recruited monocytes were stimulated *ex vivo* with MSU crystals and cytokine levels were measured.

Results: Mice receiving the high fat diet had higher weight, visceral adipose tissue, blood glucose and circulating insulin levels, compared to mice fed normal diet. The obese mice had significantly higher basal levels of the pro-inflammatory cytokine IL-6, the neutrophil and monocyte chemokines (KC and MCP-1 respectively) and the inflammatory differentiation factor GM-CSF in peritoneal fluid (Figure). This elevated inflammatory profile did not increase the numbers of peritoneal monocyte/macrophages or neutrophils in unchallenged obese mice compared to controls. Naïve, unstimulated resident macrophages from obese mice produced elevated levels of pro-inflammatory cytokines but produced less upon MSU crystal stimulation *ex vivo*. Consistent with this pattern, the elevated basal levels of peritoneal cytokines observed in obese mice decreased during MSU crystal-induced inflammation *in vivo* and there was a trend towards decreased MSU crystal-induced cell infiltration. IL-1b responses to MSU crystals were not different in the two groups.

Conclusion: Obesity induces a high basal pro-inflammatory environment outside the adipose tissue that may originate from the development of a GM-CSF-driven inflammatory resident macrophage phenotype. However, this phenotype does not translate into in an increased inflammatory response to MSU crystal stimulation. These data suggest that a heightened inflammatory background does not predict exacerbation of MSU crystal-induced inflammation.

Figure. NO FIGURE AVAILABLE. High fat diet increased basal cytokine levels but did not alter cytokine production following MSU-induced inflammation. Mice were fed on low fat (NFD) or high fat (HFD) diet for 12 weeks. Mice were then injected i.p. with MSU crystals for 8 or 18h. Mean (SEM) peritoneal lavage (A) IL-6, (B) KC, (C) MCP-1 and (D) GM-CSF.

Disclosure: O. Shaw, None; **B. Pool**, None; **N. Dalbeth**, None; **J. Harper**, None.

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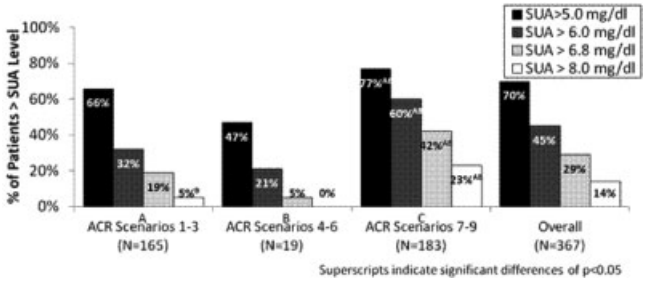
Many Gout Patients Treated By Rheumatologists Do Not Meet Established Treatment Goals Despite Long-Term Urate Lowering Therapy: Results Of a Gout Patient Encounter Survey. Max I. Hamburger[1], Michael H. Pillinger[2], Robert Sederman[3] and Gary Fernandez[4]. [1]Rheumatology Associates, Melville, NY, [2]NYU School of Medicine, Division of Rheumatology, New York, NY, [3]C1 Consulting, LLC, Summit, NJ, [4]Savient Pharmaceuticals, Bridgewater, NJ.

Background/Purpose: In Oct 2012, the ACR published guidelines for the management of gout. These guidelines recommend pharmacologic treatment that results in a sufficient lowering of the serum urate level to durably improve signs and symptoms of gout, including palpable and visible tophi, with a target of <6 mg/dl at a minimum, and often <5 mg/dl. (Khanna et al. Arthritis Care & Research 2012; 64 10:1431–46.) The extent to which current practice among rheumatologists aligns with these guidelines is unknown, and the areas in which the guidelines may help improve gout treatment remain to be determined. Our purpose was to assess symptoms, treatment, and out-

comes among gout patients treated by US rheumatologists and identify any gaps in current practice per the new ACR recommendations.

Methods: We recruited a national sample of rheumatologists to report gout patient encounters prospectively between Jan 15 and Feb 22, 2013. Anonymous patient data collected included demographics, gout symptoms, rheumatologist assessment of control, gout medications and treatment changes. We applied the ACR working case "scenarios" used in the guideline process and grouped patients by increasing severity: ACR scenarios 1–3 (intermittent symptoms, no tophi), scenarios 4–6 (intermittent symptoms, ≥ 1 tophus) and scenarios 7–9 (Chronic Tophaceous Gouty Arthropathy). We defined "Higher Dose ULT" (Urate Lowering Therapy) as >300mg/day of allopurinol or ≥80 mg/day of febuxostat.

Results: 127 rheumatologists submitted 2,380 patient encounter forms. Patients were mostly male (79%) with mean age of 61 years. 68% of encounters were ACR scenarios 1–3, 4% were 4–6 and 28% were 7–9. 24% of patients were on Higher Dose ULT. Among those on Higher Dose ULT, 50% had an SUA >6 mg/dl, including 36% in ACR scenarios 1–3, 28% in 4–6 and 68% in 7–9. Despite elevated SUA levels, 45% of encounters did not result in a dose increase or change in ULT at the visit. Figure 1 shows that many patients have an SUA >6 mg/dl, even after 6 months on Higher Dose ULT.



Conclusion: Our results suggest that a high percentage of gout patients treated by rheumatologists are not at ACR recognized treatment goals, even after 6 months on Higher Dose ULT. The new ACR treatment guidelines recommend these patients should be considered for an increase in ULT dose or other treatment change, but no change was made in nearly 1/2 of encounters. These findings indicate gout management is currently suboptimal and inadequately aggressive for many patients. Further study is needed to determine the long-term impact of the new ACR treatment guidelines.

Disclosure: M. I. Hamburger, Savient, 8, Savient, 2, Savient, 9; **M. H. Pillinger**, Takeda Pharmaceuticals, 2, Savient Pharmaceuticals, 2; **R. Sederman**, Savient, 5; **G. Fernandez**, Savient, 3.

ACR Concurrent Abstract Session
Osteoporosis and Metabolic Bone Disease: Clinical Aspects and Pathogenesis
Sunday, October 27, 2013, 4:30 PM–6:00 PM

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Ten-Year Incidence of Self-Reported Nonvertebral Fractures in 9,720 Japanese Patients With Rheumatoid Arthritis: A Prospective Observational Cohort Study. Kensuke Ochi[1], Takefumi Furuya[1], Eisuke Inoue[2], Katsunori Ikari[1], Atsuo Taniguchi[1], Hisashi Yamanaka[1] and Shigeki Momohara[1]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]Tokyo Women's Medical University, Tokyo, Japan.

Ten-Year Incidence of Self-reported Nonvertebral Fractures in 9,720 Japanese Patients with Rheumatoid Arthritis: A Prospective Observational Cohort Study

Background/Purpose: Although rheumatoid arthritis (RA) is a risk factor for osteoporosis and fracture, few studies have described the correlation between disease activity of RA and incidence of fracture in patients with RA. We previously reported that disease activity in our Institute of Rheumatology Rheumatoid Arthritis (IORRA) cohort improved significantly from 2001 to 2010; however, the change in the incidence of fractures in this period is unknown. This study aimed to investigate the change in the incidence of nonvertebral fractures between 2001 and 2010.

Methods: The IORRA is a prospective observational cohort study of Japanese RA patients at the Institute of Rheumatology, Tokyo Women's Medical University. A total of 9,720 patients (82% female; mean age, 56 years) with RA were enrolled in the IORRA cohort study from 2000 to 2010. Clinical parameters, including physician's assessment, patient's assessment, and laboratory data, were collected biannually in April and October. All participants self-reported the occurrence of a nonvertebral fracture within the previous 6 months and the fracture sites. Statistical analysis was performed using the *f*Ô test with a confidence interval of 95%.

Results: From 2001 to 2010, the percentage of patients with DAS28 remission increased from 7.8% to 39.7%, the mean score on the Japanese version of the health assessment questionnaire decreased from 0.82 to 0.65, prednisolone intake decreased from 51.4% (mean, 4.7 mg/day) to 41.3% (mean, 4.1 mg/day), and bisphosphonate intake increased from 5.0% to 23.4%. The incidence of nonvertebral fracture was 1.19% in 2001 and 1.79% in 2010, with no apparent change (mean, 1.78% [0.23%]; Figure 1). The incidence of fracture increased dramatically after the age of 45 years in women, while the increase was linear in men. The mean age of fracture (year) and the mean incidence of fracture (%) were 61.8 (12.7) and 0.36 (0.05) in the ribs, 65.9 (11.1) and 0.07 (0.03) in the pelvis, 66.8 (10.4) and 0.11 (0.04) in the shoulder, 67.4 (10.4) and 0.12 (0.04) in the wrist, 68.4 (9.4) and 0.18 (0.06) in the hip, and 62.5 (10.6) and 0.13 (0.04) in the ankle, respectively. Overall incidence of nonvertebral fracture was significantly higher in the autumn/winter than in the spring/summer ($p = 0.02$).

Conclusion: Despite the improvement in disease activity and functional disability, the incidence of nonvertebral fracture appears to show no apparent change between 2001 and 2010 in our patients with RA.

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Romosozumab Administration Is Associated With Significant Improvements In Lumbar Spine and Hip Volumetric Bone Mineral Density and Content Compared With Teriparatide. H K Genant[1], S Boonen[2], M A Bolognese[3], C Mautalen[4], J P Brown[5], C Recknor[6], S Goemaere[7], K Engelke[8], Y-C Yang[9], M Austin[9], A Grauer[9] and C Libanati[9]. [1]UCSF & Synarc Inc., San Francisco, CA, [2]Leuven University Division of Geriatric Medicine, Leuven, Belgium, [3]The Bethesda Health Research Center, Bethesda, MD, [4]Centro de Osteopatias Medicas, Buenos Aires, Argentina, [5]CHU de Québec Research Centre and Laval University, Québec, QC, [6]United Osteoporosis Centers, Gainesville, GA, [7]Ghent University Hospital, Ghent, Belgium, [8]Synarc Germany, Hamburg, Germany, [9]Amgen Inc., Thousand Oaks, CA.

Background/Purpose: Sclerostin is an osteocyte-derived inhibitor of osteoblast activity. Romosozumab, a monoclonal antibody to sclerostin stimulates bone formation and decreases bone resorption. In a phase 2 study, romosozumab administered for 12 months increased areal bone mineral density (BMD) at the lumbar spine (LS) and total hip (TH) as measured by dual X-ray absorptiometry compared with placebo (Pbo), alendronate, and teriparatide (TPTD) in postmenopausal women with low bone mass. Here we describe the effect of romosozumab on LS and TH volumetric BMD (vBMD), and bone mineral content (BMC) as measured by quantitative computed tomography (QCT) in this trial.

Methods: This international, randomized, Pbo-controlled, phase 2 study enrolled postmenopausal women of 55–85 years with LS, TH, or femoral neck T-score ≤–2.0 and ≥–3.5. Measurements with QCT were performed at the "total" LS (mean of L1 and L2 entire vertebral bodies) and TH in subjects receiving Pbo, subcutaneous TPTD (20 μg QD), and romosozumab (210 mg QM). Percentage change from baseline in integral and cortical vBMD and BMC, and trabecular vBMD was evaluated at 12 months. The analyses included subjects with baseline and ≥1 post-baseline QCT measurements.

Results: Treatment with romosozumab resulted in significant increases in integral vBMD and BMC at the "total" LS and TH from baseline, and compared with Pbo and TPTD (Figure). TPTD and Pbo were similar at the TH, but not the LS. In the trabecular and cortical bone compartments, differences between romosozumab and TPTD were observed. Trabecular vBMD increased from baseline with both romosozumab and TPTD at the LS and TH (both $P<0.05$). These gains in trabecular vBMD were similar with romosozumab and TPTD at the LS (18.3% vs 20.1%, respectively), but

significantly larger with romosozumab at the TH (10.8% vs 4.2%, $P=0.01$). Cortical vBMD gains were larger with romosozumab compared with TPTD at the LS (13.7% vs 5.7%, $P<0.0001$) and TH (1.1% vs –0.9%, $P=0.12$). Cortical BMC gains were larger with romosozumab compared with TPTD at both the LS (23.3% vs 10.9%, $P<0.0001$) and TH (3.4% vs 0.0%, $P=0.03$).

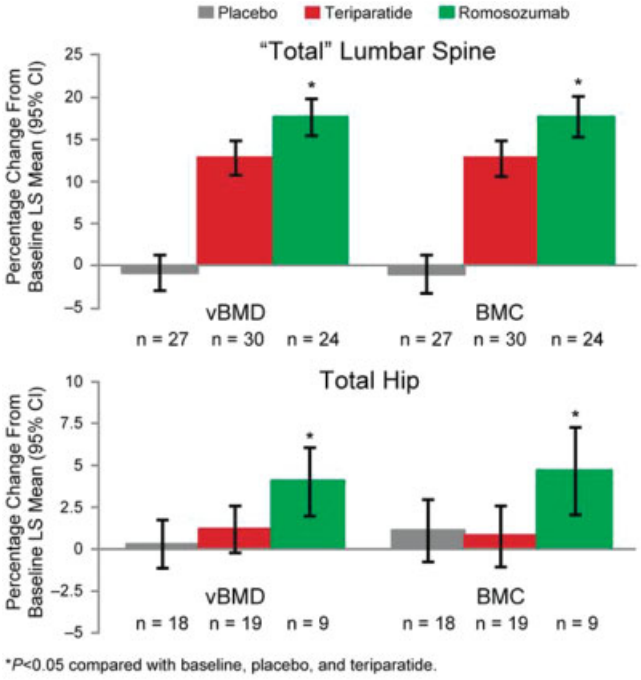

Figure. Percentage Change in Integral vBMD and BMC From Baseline at 12 Months.

Conclusion: Romosozumab significantly increased vBMD and BMC at the "total" LS and TH compared with Pbo and TPTD in postmenopausal women with low bone mass. The gains, observed in the trabecular and cortical compartments, support the continued clinical investigation of romosozumab as a potential treatment for women with postmenopausal osteoporosis with established BMD deficits and at increased fracture risk.

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Further Reduction In Nonvertebral Fracture Rate Is Observed Following 3 Years Of Denosumab Treatment: Results With Up To 7 Years In The Freedom Extension. Jonathan D. Adachi[1], Serge Ferrari[2], Carol Zapalowski[3], Paul D. Miller[4], Jean-Yves Reginster[5], Ove Törring[6], Nadia Daizadeh[3], Andrea Wang[3], Cynthia O'Malley[3], Rachel B. Wagman[3] and E. Michael Lewiecki[7]. [1]McMaster University, Hamilton, ON, [2]Geneva University Hospital, Geneva, Switzerland, [3]Amgen Inc., Thousand Oaks, CA, [4]Colorado Center for Bone Research, Lakewood, CO, [5]University of Liège, Liège, Belgium, [6]Karolinska Institutet, Södersjukhuset, Stockholm, Sweden, [7]New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM.

Background/Purpose: Some antiresorptives reduce nonvertebral fracture incidence in the first 3 years of treatment; however, evidence for further reduction of nonvertebral fractures with prolonged therapy is limited. The effects of denosumab (DMAb) treatment for up to 10 years are being evaluated in the 3-year FREEDOM study and its 7-year extension. Here we compare the nonvertebral fracture rate during the first 3 years of DMAb with that in the following 4 years of treatment.

Methods: During the extension, all subjects received 60 mg DMAb Q6M. Here, long-term subjects received 7 years of DMAb (3 years in FREEDOM followed by 4 years in the extension); subjects from the cross-over group received 4 years of DMAb (3 years of placebo in FREEDOM followed by 4 years of DMAb in the extension). Nonvertebral fracture rates for the first 3 years of DMAb were compared with rates in the 4th year of DMAb in each group separately and combined. For the long-term group only, the nonvertebral fracture rate in the first 3 years of DMAb was also compared with the fracture rate during the subsequent 4 years. Adjusted rate ratios (95% CIs) between observational periods were computed via generalized estimating equation (GEE) Poisson regression.

Results: Of 5928 women eligible for the extension, 4550 (77%) enrolled (N=2343 long-term; N=2207 cross-over). In the long-term group, the nonvertebral fracture rate was 1.98 per 100 subject-years during years 1–3 of DMAb (FREEDOM). This rate decreased during year 4 (extension) to 1.43 (rate ratio=0.73; $P=0.096$), and the rate remained low at 1.45 during years 4–7 (rate ratio=0.74; $P=0.016$; Table). Similarly for the cross-over group, the fracture rate was 2.20 during years 1–3 of DMAb (extension) and decreased to 1.03 at year 4 (rate ratio=0.48; $P=0.004$). Combining the long-term and cross-over groups yielded a fracture rate of 2.08 during the first 3 years of DMAb (FREEDOM or extension) that decreased to 1.27 at year 4 (rate ratio=0.62; $P=0.002$).

Conclusion: Three years of DMAb treatment significantly reduced the nonvertebral fracture rate compared with placebo. When DMAb was continued for an additional 4 years, the fracture rate remained low and was significantly lower than that in the first 3 years of treatment. Contributing factors that might explain this observation include sustained reduction in bone resorption, continued gains in hip BMD and bone mass, decrease in cortical porosity, and increases in cortical/trabecular strength observed with DMAb treatment.

Disclosure: J. D. Adachi, Amgen Inc., Eli Lilly, Merck, Novartis, 5, Amgen Inc., Eli Lilly, Merck, Novartis, Warner Chilcott, 7, Amgen Inc., Eli Lilly, Merck, Novartis, 2; **S. Ferrari**, Amgen Inc., GSK, Lilly, MSD, Bioiberica, 5, Novartis Pharmaceutical Corporation, 9, Amgen Inc., MSD, 2; **C. Zapalowski**, Amgen Inc., 1, Amgen Inc., 3; **P. D. Miller**, Amgen Inc., Lilly, Merck, 5, Novartis Pharmaceutical Corporation, 9, Warner-Chilcott, 7, Amgen Inc., Lilly, Merck, Radius, 2; **J. Y. Reginster**, Servier, Novartis, Negma, Lilly, Wyeth, Amgen Inc., GSK, Roche, Merckle, Nycomed, NPS, Theramex, UCB, 5, Merck Sharp and Dohme, Lilly, Rottapharm, IBSA, Genevrier, Novartis, Servier, Roche, GlaxoSmithKline, Tejin, Teva, Ebewee Pharma, Zodiac, Analis, Theramex, Nycomed, Novo-Nordisk, Nolver, 8, Bristol-Myers Squibb, Merck Sharp and Dohme, Rottapharm, Teva, Lilly, Novartis, Roche, GlaxoSmithKline, Amgen, Servier, 2; **O. Törring**, Amgen Inc., Takeda, GSK, Eli Lilly, 5; **N. Daizadeh**, Amgen Inc., 1, Amgen Inc., 3; **A. Wang**, Amgen Inc., 1, Amgen Inc., 3; **C. O'Malley**, Amgen Inc., 1, Amgen Inc., 3; **R. B. Wagman**, Amgen Inc., 1, Amgen Inc., 3; **E. M. Lewiecki**, Amgen Inc., Lilly, Merck, 5, Amgen, Lilly, Novartis, 7, Amgen, Lilly, Novartis, 2.

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Vertebral Fractures In The 3 Year Period Following Steroid Initiation Among Children With Chronic Illnesses. Johannes Roth[1], Jinhui Ma[1], David A. Cabral[2], Peter B. Dent[3], Janet E. Ellsworth[4], Adam M. Huber[5], Kristin M. Houghton[6], Roman Jurencak[1], Bianca A. Lang[7], Maggie Larche[3], Claire MA Leblanc[8], Brian Lentle[6], MaryAnn Matzinger[1], Paivi M. Miettunen[9], Kiem Oen[10], Claire Saint-cyr[11], Rosie Scuccimarri[12], Nazih Shenouda[1], Leanne M. Ward[1] and The Canadian STOPP Consortium[13]. [1]University of Ottawa, Ottawa, ON, [2]BC Children's Hospital, Vancouver, BC, [3]McMaster University, Hamilton, ON, [4]University of Alberta, Edmonton, AB, [5]IWK Health Centre and Dalhousie University, Halifax, NS, [6]University of British Columbia, Vancouver, BC, [7]Dalhousie University, Halifax, NS, [8]McGill University, Montréal, QC, [9]University of Calgary, Calgary, AB, [10]University of Manitoba, Winnipeg, MB, [11]Université de Montréal, Montreal, QC, [12]Montreal Children's Hospital and McGill University, Montréal, QC, [13]National Pediatric Bone Health Working Group, Ottawa, ON.

Background/Purpose: To describe the pattern and frequency of incident vertebral fractures (VF) in glucocorticoid (GC)-treated children and to determine the clinical factors at baseline that are associated with incident VF.

Methods: In children with leukemia, rheumatic disorders and nephrotic syndrome, VF were assessed prospectively each year following GC initiation for 3 years, according to the Genant semi-quantitative method. An incident VF was defined as a new fracture in a previously normal vertebral body or worsening of an existing fracture. The 3-year cumulative VF incidence rate was then calculated. Multivariable Poisson regression was used to examine associations between the 3-year total number of incident VF and clinical factors *at baseline*, including diagnosis, age, gender, pubertal stage, height

and body mass index (BMI) Z-scores, calcium and vitamin D intake, physical activity, back pain, and lumbar spine (LS) bone mass density (BMD) Z-score. In addition, prevalent VF (at baseline) as well as cumulative GC exposure and the number of days in receipt of GC until the baseline visit were also assessed for their relationship with 3-year, incident VF.

Results: 404 children were enrolled at a median age of 6.2 years, range 1–17; 50% boys; 188 (46%) had leukemia, 136 (34%) rheumatic conditions, and 80 (20%) nephrotic syndrome. The baseline study visit occurred at a median of 18 days following steroid initiation (inter-quartile range 11–24 days). Forty-four (11%) children had VF at baseline, while 134 incident VF were detected in 55 children over the 3 years. Overall, 17% of children (95% CI 13–22) had at least one incident VF over the 3 years. The proportions of children with incident VF were as follows: Leukemia: 24% (95% CI 16–32); rheumatic disorders: 13% (95% CI 6–19); nephrotic syndrome 9% (95% CI 1–17). The annual proportion of children with incident VF peaked at 12 months and declined thereafter ($p=0.04$). Among those with incident VF, 24/55 children (44%) had 1 or more moderate or severe fracture. Most of the VF were new fractures in previously normal vertebral bodies (86%), compared to worsening of existing VF. In Poisson multivariable modeling assessing *baseline* clinical factors, the following were associated with higher, 3-year VF incident rates: the presence of VF at baseline (incidence Rate Ratio (RR) 6.3, 95% CI 3.2–12.4), female gender (RR 1.8; 95% CI 1.0–3.3), pre-pubertal status (RR 2.1; 95% CI 0.8–5.4), and lower BMD Z-scores (RR 1.4; 95% CI 1.1–1.7). Underlying diagnosis and back pain at baseline were highly correlated with these significant factors (co-linear). Other factors at baseline were not significantly associated with incident VF.

Conclusion: Within 3 years of steroid initiation, 17% of children had incident VF. VF incidence peaked at 12 months, and almost half of the VF were moderate or severe. Of the factors measured *at baseline*, prevalent VF were most strongly associated with incident VF over the ensuing 3 years. Female gender, pre-pubertal status and low BMD at baseline were also associated with 3-year incident VF (for every 1 standard deviation reduction in spine BMD Z-score, there was a 40% increased incident VF risk).

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Use Of Non Steroidal Anti-Inflammatory Drugs Prevent Bone Loss In Patients With Early Inflammatory Back Pain: Results From The DESIR Cohort. Karine Briot[1], Simon Paternotte[1], Corinne Miceli-Richard[2], Maxime Dougados[3] and Christian Roux[1]. [1]Paris Descartes University, Paris, France, [2]Université Paris Sud, Le Kremlin Bicêtre, France, [3]Paris- Descartes University, Paris, France.

Background/Purpose: To assess the 2-year bone mineral density (BMD) changes at lumbar spine and hip in a large cohort of patients with early inflammatory back pain (IBP) suggestive of axial Spondyloarthritis (SpA), and to assess determinants of bone loss.

Methods: of the 708 patients of the DESIR cohort (IBP of less than 3 years duration suggestive of axial SpA), 265 (54% males, mean age 34.4 years) had BMD measurements at baseline and 2 years. Low BMD was defined as Z score ≤ -2 (at at least one site) and significant bone loss was defined by a decrease in BMD$\geq$0.03g/cm^2. Clinical, biological (erythrocyte sedimentation rate ESR and C reactive protein CRP, bone formation inhibitors markers (sclerostin and DKK-1 serum levels)), imaging (X-rays, spine and sacroiliac joints MRI) parameters and therapies were assessed. AntiTNF users were defined as those who received antiTNF at 2 years. The dependant variable of this study was the bone loss (decrease in BMD$>$ 0.03 g/cm2) at either lumbar spine or hip site. Independant variables included both the ones collected at baseline (age, gender, BMI, BASDAI, ADSAS CRP, ESR, CRP, HLA B27, current use of NSAIDS use, ASAS NSAIDs score, X-rays sacroiliitis, bone marrow oedema on sacroiliac or spine MRI, lean and fat masses, sclerostin and DKK-1) and 2-year longitudinal variables (BMI, BASDAI, ADSAS CRP, ESR, CRP, current NSAIDS use, ASAS NSAIDs score, lean and fat masses, intake of antiTNF). Parameters were tested in univariate and multivariate analyses; accuracy of models was measured by the area under the curve (AUC).

Results: Thirty nine patients (14.7%) patients had low BMD at baseline. 2-year BMD significantly changed from baseline at lumbar spine (+1.3 (6.4) %, p=0.02) and total hip (−0.3 (4.0) %, p=0.02). 95 patients (35.8%) had a 2-year significant bone loss (at lumbar spine or hip), 59 (22.4%) at lumbar spine and 46 (18.0%) at total hip. 187 (70.6%) had current use of NSAIDS at baseline and 89 (33.6%) received anti-TNF at 2 years (mean duration 5.7 (9.1) months). Significant 2-year lumbar spine bone loss was associated in multivariate analysis with age (OR=1.06 (1.00 – 1.12), p=0.017) (AUC= 0.608). In multivariate analysis, current use of NSAIDS at baseline (OR=0.38 (0.19–0.76), p=0.006) had a protective effect on hip bone loss (AUC= 0.608). In patients without anti-TNF treatments at 2 years (n=176): male gender was the only predictor of lumbar spine bone loss (OR= 2.4 (1.13–5.09), p=0.023) (AUC= 0.608). In these patients, current use of NSAIDS (OR= 0.09 (0.02 – 0.5), p= 0.006) and 2-year increase in BMI (OR= 0.55 (0.37–0.85), p=0.003) had protective effects on hip bone loss whereas 2-year increase in fat mass was associated with hip bone loss (OR=1.18 (1.02–1.42), p=0.046) (AUC=0.833).

Conclusion: Among patients with early IBP among whom a third received antiTNF during the follow-up, BMD are in the normal range and 35% have significant bone loss over 2 years. Current use of NSAIDS has a protective effect on hip bone loss in patients with or without antiTNF.

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Reduced Hip Cortical Porosity Upon Denosumab Treatment: A Likely Mechanism Contributing To The Reduction Of Hip Fracture Risk In Women With Osteoporosis. R. M. Zebaze[1], C. Libanati[2], M. R. McClung[3], J. R. Zanchetta[4], D. L. Kendler[5], A. Høiseth[6], A. Wang[2], A. Ghasem-Zadeh[1] and E. Seeman[1]. [1]Austin Health, University of Melbourne, Melbourne, Australia, [2]Amgen Inc., Thousand Oaks, CA, [3]Oregon Osteoporosis Center, Portland, OR, [4]Instituto de Investigaciones Metabólicas, Buenos Aires, Argentina, [5]University of British Columbia, Vancouver, BC, [6]Curato Røntgen, Oslo, Norway.

Background/Purpose: Nonvertebral fracture risk is significantly influenced by cortical thickness, area, mass, and porosity because all of these contribute to bone strength. In particular, increased cortical porosity, a marker of structural decay, is associated with an exponential worsening in bone fragility. Cortical porosity is the result of unbalanced and accelerated intracortical remodeling upon Haversian canal surfaces which enlarge, coalesce, and fragment the cortex. Reducing remodeling will limit worsening of porosity but for individuals already at increased risk for fracture, reducing porosity is a preferred outcome. Using multi detector computer tomography (MDCT) hip images from the FREEDOM study, we previously reported that hip cortical mass and thickness improved over 3 years of denosumab (DMAb) administration and postulated that this could be explained by infilling of porosity in the inner cortical region adjacent to the medullary canal. Here, we used a subset of these images to evaluate changes in hip porosity.

Methods: FREEDOM was a 3-year, randomized, double-blind trial that enrolled postmenopausal women with a lumbar spine or total hip T-score <-2.5 but not <-4.0 at both sites. Women were randomly assigned to placebo (Pbo) or 60 mg DMAb every 6 months. Percentage porosity in both the compact and the trabecularized (outer and inner transitional zones) cortical volumes of the subtrochanter region were measured using StrAx1.0 software (Zebaze et al., *Bone* 2013) from MDCT hip images obtained at baseline and year 3 (Pbo, n=22; DMAb, n=28).

Results: Cortical porosity was larger as a function of proximity to the medullary canal; the percentage volume occupied by porosity at baseline was 72% in the inner transitional zone adjacent to the medullary compartment, 37% in the outer transitional zone, and 29% in the compact-appearing cortex. Cortical porosity correlated positively with serum CTX ($p=0.017$) and negatively with hip strength estimated using finite element analysis ($p=0.027$). DMAb reduced porosity compared with baseline and Pbo at year 3 across the entire cortex (Figure) and in each cortical sub-compartment, reaching treatment effect (DMAb–Pbo) improvements of –1.8% (inner transitional zone), –5.6% (outer transitional zone), and –7.9% (compact-appearing cortex) (all $p<0.001$).

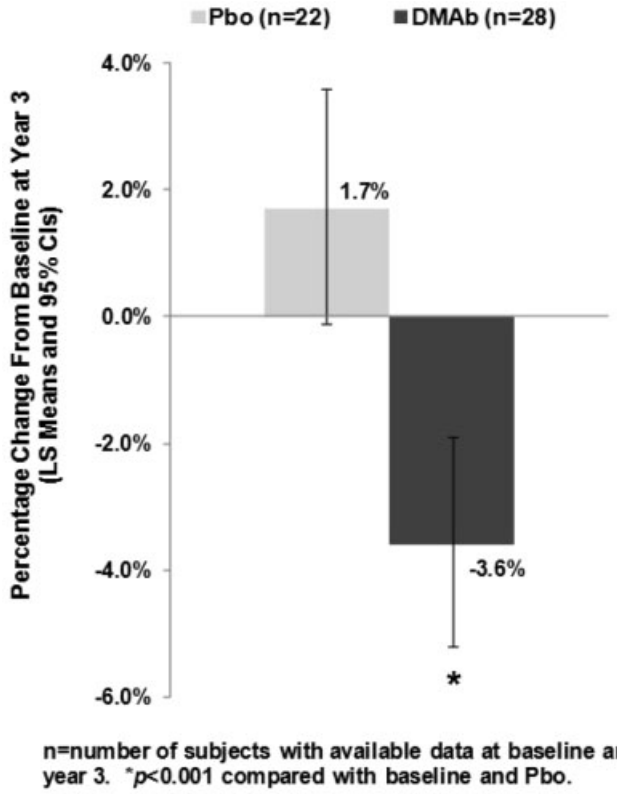

Figure. Percentage Change From Baseline at Year 3 in Cortical Porosity at the Hip

Conclusion: This is the first report of *in vivo* hip porosity changes in response to a pharmacological therapy. Since reductions in cortical porosity equate to increased mineralized bone matrix mass and both are relevant to strength, these improvements are expected to contribute to the observed reductions in nonvertebral fractures associated with DMAb administration.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects II: Identifying Rheumatoid Arthritis in At-Risk Populations
Sunday, October 27, 2013, 4:30 PM–6:00 PM

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Serum Immunoglobulin Free Light Chains and Rheumatoid Arthritis: A Population-Based Study. John M. Davis III[1], S. Vincent Rajkumar[1], Cynthia S. Crowson[1], Xiaoli Deng[2], Angela Dispenzieri[1], Dirk R. Larson[1], Terry M. Therneau[1], Eric L. Matteson[1], Robert A. Kyle[1], Jerry Katzmann[1] and Sherine E. Gabriel[1]. [1]Mayo Clinic, Rochester, MN, [2]Peking University Third Hospital, Beijing, China.

Background/Purpose: Serum immunoglobulin free light chains (FLCs) represent biomarkers of B-cell activation and have been associated with rheumatoid arthritis (RA) as well as all-cause mortality in the general population. The objective of this study was to evaluate the relationships of serum FLCs to pre-clinical disease, RA characteristics, and mortality in persons with RA compared to non-RA subjects.

Methods: A population-based study during the period of 1995 – 2003 was performed by cross-linking a large cohort in the general population with available serum FLC data with our established RA inception and prevalence cohorts. FLCs were measured using commercial immunonephelometric assays. The estimated glomerular filtration rate (eGFR) was estimated using the CKD-EPI formula. Levels of serum κ, λ, and total FLCs and their trends relative to RA incidence were compared between RA and non-RA subjects. Associations between RA disease characteristics and serum total FLCs were assessed using linear and logistic regression models, adjusting for age and sex. Among the population with normal κ-to-λ ratio (0.26 – 1.65), Cox models were used to determine the association between serum FLCs and mortality, adjusting for age, sex, serum creatinine, and the RA × FLC interaction variable.

Results: Among 16,609 subjects, 270 fulfilled criteria for RA at the time of the serum FLC measurement. The patients with RA were slightly older (mean age 67 vs. 65 years, $p<0.001$) and more frequently female (68% vs. 55%, $p<0.001$). The mean κ-to-λ ratio was similarly normal in both groups ($p = 0.9$), and there was no difference in the proportions of RA and non-RA subjects with an abnormal κ-to-λ ratio, which by definition indicates monoclonal gammopathy (3.3% vs. 4.1%, $p=0.48$). Significant elevations of κ, λ and total FLCs were observed in the RA compared to non-RA subjects (mean total FLCs: 4.2 vs. 3.3 mg/dL, $p<0.001$). These findings were not explained by any difference in the mean eGFR, which was similar between the groups (64.8 vs. 65.2 mL/min/1.73 m^2, $p=0.56$). Serum FLCs became elevated 3 – 5 years before the clinical onset of RA and remained elevated during follow-up (Figure). Total FLCs were associated with severe extra-articular manifestations (odds ratio = 3.64; 95% confidence interval [CI]: 1.26, 10.58) but not with rheumatoid factor or the sedimentation rate. Finally, total FLCs were associated with increased mortality in the RA population (hazard ratio = 1.07 per mg/dL; 95% CI: 1.03, 1.11), though the effect on mortality appeared to be attenuated in RA compared to non-RA subjects, perhaps due to treatment with immunosuppressive therapies or to other competing factors.

Conclusion: Serum FLCs are significantly elevated in patients with RA compared to the general population. The elevation of serum FLCs precedes the clinical onset of disease. Serum FLCs may be useful in monitoring B-cell activity and in assessing prognosis.

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Anti-Carbamylated Protein Antibodies Are Present Prior To The Diagnosis Of Rheumatoid Arthritis and Predict Future Disease Onset. Ryan W. Gan[1], Leendert A. Trouw[2], Jing Shi[2], René E.M. Toes[2], Tom W. J. Huizinga[2], Gary O. Zerbe[3], Kevin D. Deane[4], Jess Edison[5], William R. Gilliland[5], Jill M. Norris[1] and V. Michael Holers[4]. [1]Colorado School of Public Health, Aurora, CO, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Colorado School of Public Health / University of Colorado Anschutz Medical Campus, Aurora, CO, [4]University of Colorado School of Medicine, Aurora, CO, [5]Walter Reed National Military Medical Center, Bethesda, MD.

Background/Purpose: Anti-cyclic citrullinated peptide-2 (CCP2) can be present in serum years before a diagnosis of rheumatoid arthritis (RA), and is highly specific (>95%) for the future onset of RA: however, its sensitivity for future RA is relatively low. Thus, novel autoantibodies (Abs) that are highly sensitive and specific for RA would be a valuable predictive tool. Recently, Shi and colleagues (Shi et al, *PNAS,* 2011) discovered that anti-carbamylated protein (anti-CarP) was not sensitive (43%), but highly specific (95%) for classified RA as well as present prior to the onset of classifiable RA in subjects with arthralgia but no inflammatory arthritis who were positive for CCP and/or rheumatoid factor (RF)(IgM) (Shi et al, *A&R*, 2013). Herein we utilized a unique sample set of military subjects to determine if serum anti-CarP antibodies are present before RA diagnosis, and compared the diagnostic accuracy of anti-CarP to other RA-related Abs.

Methods: Stored pre-diagnosis serum samples from military personnel were obtained from 82 RA cases and 82 controls matched on case age at diagnosis, sex, and race. We tested the pre-RA diagnosis samples from cases and controls for anti-CarP Fetal Calf Serum (FCS) and anti-CarP Fibrinogen (Fib), as well as RF by nephelometry, RF isotypes (IgM, IgG, and IgA), CCP2 (Axis-Shield), and CCP3.1 (Inova). The cutoffs for anti-CarP were determined using the mean +2 SD of log-transformed levels from 41 randomly selected military controls. The diagnostic accuracy of Abs for future RA were assessed in prediagnosis serum and logistic regression was used to determine the association between RA case status and antibody

positivity in prediagnosis serum, comparing RA cases to the 41 remaining controls.

Results: RA cases, cutoff controls, and controls had similar demographic characteristics. The diagnostic accuracy in prediagnosis serum for each Ab is presented in the Table. Anti-CarP FCS was 29.9% sensitive (SENS) and 95% specific (SPEC) for future RA; anti-CarP Fib was 17.9% SENS and 95.1% SPEC. There was a strong association between RF and/or CCP positive RA case status and anti-CarP FCS positivity in prediagnosis serum (OR: 8.3, 95% CI: 1.8–37.7, p<0.01); however, there was a non-significant association between seropositive RA case status and anti-CarP Fib positivity in prediagnosis serum (OR: 4.3, 95% CI: 0.9–20.8, p=0.07).

Table: Sensitivity and specificity for RA-related autoantibodies in prediagnosis serum samples, including only seropositive (RF and/or CCP positive) RA cases.

Antibody	Sensitivity (%) of 67 cases with RA	Specificity (%) of 41 controls	Positive Predictive Value (%)	Negative Predictive Value (%)
Anti-CCP 2	50.8	100.0	100.0	55.4
Anti-CCP 3.1	56.7	75.6	79.2	51.7
RF	52.2	85.4	85.4	52.2
RF IgM	55.2	87.8	88.1	42.9
RF IgG	25.4	82.9	70.8	40.5
RF IgA	55.2	87.8	88.1	54.5
Anti-CCP2 and/or ≥ 2 RF Isotypes	58.2	90.2	90.7	56.9
Anti-CarP FCS	29.9	95.1	90.9	45.3
Anti-Carp FCS and/or ≥ 2 RF Isotypes	49.3	85.4	84.6	50.7
Anti-CarP Fib	17.9	95.1	85.7	41.5
Anti-Carp Fib and/or ≥ 2 RF Isotypes	47.8	85.4	84.2	50.0

Conclusion: Our results suggest that anti-CarP antibodies, are present in RA cases before clinically apparent disease, and the presence of anti-CarP FCS is strongly associated with future onset of RA (Positive Predictive Value=90.9%). Identification of novel antibodies such as anti-CarP FCS can elucidate disease mechanisms and predict the onset of RA.

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How To Predict That Early Arthritis Without Rheumatoid Factor and ACPA Becomes Rheumatoid Arthritis According To ACR/EULAR 2010 After a 3-Years Follow-Up? Results From The Espoir Cohort. Gaël Mouterde[1], Cédric Lukas[2], Nathalie Rincheval[3], Alain Saraux[4], Philippe Dieude[5] and Bernard Combe[6]. [1]Montpellier 1 University, Lapeyronie Hospital, Montpellier, France, [2]Lapeyronie Hospital, Montpellier, France, [3]Institut Universitaire de Recherche Clinique, Montpellier, France, [4]CHU Brest et Université Bretagne Occidentale, Brest, France, [5]Rheumatology departement & INSERM U699, Paris Diderot university, APHP, Bichat hospital, Paris, France, [6]Lapeyronie Hospital, Montpellier I university, Montpellier, France.

Background/Purpose: To describe disease course of patients without rheumatoid factor (RF) and anti-citrullinated protein auto-antibodies (ACPA) in an inception cohort of early arthritis patients. To determine baseline predictors of development of rheumatoid arthritis (RA) according to ACR/EULAR 2010 criteria at 3 years in these patients.

Methods: Patients presenting with synovitis of at least 2 joints for 6 weeks to 6 months were included in the multicenter French ESPOIR cohort. Following data were collected at baseline for those who were negative for IgM RF and ACPA (anti-CCP2): clinical and biological features of arthritis, HLA-DRB1* typing, socio economic factors, comorbidities, radiographs of hands, wrists, and feet (modified Sharp score). RA was defined according to the 2010 ACR/EULAR classification criteria (1) at any visit during the first 3 years of follow-up or by typical RA erosion (2). Alternative diagnoses were reported among patients who did not fulfill ACR/EULAR criteria. Logistic regression was performed to evaluate the association between RA diagnosis at 3 years and baseline variables.

Results: Of the 813 recruited patients, 406 (49.9%) were negative for both RF and anti-CCP2. They had the following characteristics: age 49±13 years, females 77%, mean disease duration: 102+/−50 days, median morning stiffness: 45mn [IQR 15 – 90], median pain at rest: 34/100 [IQR 12 – 58], median tender joint count (TJC) 6 [IQR 3 – 13], DAS28 4.95±1.3, HAQ score 0.93±0.68, CRP 18.6±34.2 mg/l. 70 (19.3%) patients had typical RA erosions on X-ray; 57 (14.1%) had antinuclear antibodies (ANA) and 39 (9.6%) were RF-IgA positive. 246/387 patients (63.6%) fulfilled ACR/EULAR 2010 criteria for RA at baseline and 269/374 (71.9%) at 3 years. In this seronegative cohort, diagnosis of RA at 3 years was associated with the following initial factors: symmetric involvement (OR=3 [1.41; 6.39], p=0.004), morning stiffness (>median: 45 min) (OR=2.48 [1.34; 4.57], p=0.004), pain at rest on a VAS (>median: 34/100) (OR=2.14 [1.14; 4.01], p=0.017), number of tender joints (>median: 6) (OR=3.51 [1.78; 6.92], p<0.001) and presence of feet erosions (OR=2.96 [1.19; 7.40], p=0.020). Presence of ANA (OR=0.38 [0.17; 0.87], p=0.021), transaminases elevation (OR=0.52 [0.28; 0.94], p=0.032) and living in the south of France (OR=0.45 [0.22; 0.90], p=0.024) had a protective effect against progression to RA. No association between extra-articular manifestations, HLA-DR3 and "seronegative RA" was observed. Among the 105 patients who did not fulfill ACR/EULAR 2010 criteria for RA at 3 years, 44 had another definite diagnosis: psoriatic arthritis (n=10), spondyloarthritis (n=7), erosive hand osteoarthritis (n=5), connective tissue disease and vasculitis (n=8), polymyalgia rheumatica or RS3PE syndrome (n=3).

Conclusion: Patients with early arthritis and without RF and ACPA are more prone to have RA at 3 years if they have inflammatory pain, symmetric involvement of numerous joints and typical feet erosions. Detection of ANA and transaminases elevation should suggest non RA diagnosis.

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Do We Need To Lower The Cut Point Of The 2010 ACR/EULAR Classification Criteria For Diagnosing Rheumatoid Arthritis?! M. van der Ven[1], J.J. Luime[1], A.H. Gerards[2], C. Alves[1], P.J. Barendregt[3], D. van Zeben[4], M.H. de Jager[5], P.B.J. de Sonnaville[6], B.A. Grillet[7] and J.M.W. Hazes[1]. [1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]Vlietland Hospital, Schiedam, Netherlands, [3]Maasstad Hospital, Rotterdam, Netherlands, [4]Sint Franciscus Gasthuis, Rotterdam, Netherlands, [5]Albert Schweitzer Hospital, Dordrecht, Netherlands, [6]Admiraal de Ruyter Ziekenhuis, Goes, Netherlands, [7]Zorgsaam Hospital, Terneuzen, Netherlands.

Background/Purpose: The 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA) were recently developed to facilitate the study of persons at earlier stages of the disease. Part of the patients in whom arthritis persists over time does not fulfil the ACR/EULAR 2010 criteria (≥6/10 points) at first consultation. Krabben et al [2013] showed that neither ACPA fine-specificity nor the Leiden prediction rule were able to identify these patients. The developers of the criteria suggest that there is a scope to use other cut points for different purposes. We used the 2010 criteria for diagnostic purposes and evaluated the effect of lowering the cut point to 5/10 points for diagnosing RA.

Methods: Clinical data used were from the Rotterdam Early Arthritis Cohort (REACH). This ongoing, prospective cohort study was set up in the greater Rotterdam area in July 2004. Demographic and clinical characteristics of each patient were recorded at baseline. For the present study we included patients with at least one joint with clinical synovitis as required for the implementation of the ACR/EULAR 2010 criteria (n=557). Outcome after one year was the use of methotrexate (MTX) or persistent disease defined as synovitis present at physical examination after 1 year and no other explanation for the synovitis was present. Sensitivity and specificity of the 2010 criteria for this outcome were determined at each cut point.

Results: Following implementation of the 2010 criteria we identified the undifferentiated arthritis patients (□6/10 points; n=328), the so-called 2010 UA patients. After 12 months follow-up 35% (n=115) of the 2010 UA patients (□6/10 points) used MTX (n=96) or had persistent disease (n=19). Table 1 shows the baseline characteristics of the cases (n=115) and the non-cases (n=213). 63% of the patients in the group with 5 out of 10 points of the 2010 criteria used MTX or had persistent disease. The area under the receiver operator characteristic curve (AUC) of the 2010 criteria for the use of MTX or persistent disease after 12 months was 0.78 (SE 0.02). Sensitivity and specificity for the cut point of 6 were 60% and 79% respectively. With the cut point of 5, sensitivity will increase to 73% and specificity will decrease to 70%. The patients that would be falsely diagnosed as having RA and start treatment when using the cut point of 5 included polyarthritis (n=18) and osteoarthritis (n=2).

Table 1. Baseline characteristics of 2010 UA patients who used MTX or had persistent disease after 1 year follow-up (case) and of those patients in whom arthritis did not persist over time (non-case).

	UA2010 case (n=115)	UA2010 non-case (n=213)
Women (%)	79 (69)	143 (67)
Age, years (mean, SD)	53 (15)	50 (16)
SJC (median, IQR)	5 (3–7)*	2 (1–4)*
TJC (median, IQR)	8 (4–12)*	4 (2–10)*
RF positive (%)	9 (8)	10 (5)
ACCP positive (%)	3 (3)	9 (4)
ESR (median, IQR)	21 (10–37)	13 (6–26)
CRP (median, IQR)	6 (3–31)	5 (2–16)
Morning stiffness, min (median, IQR)	60 (30–120)	45 (30–120)
DAS score (mean, SD)	4.5 (1.0)*	3.8 (1.1)*
Erosions (%)	13 (12)	9 (5)
Symptom duration, days (median,IQR)	95 (52–160)	90 (35–168)
HAQ (mean, SD)	0.9 (0.6)	0.8 (0.6)
Symmetry (%)		
*MCP	67 (58)	86 (41)
*PIP	54 (47)	72 (34)
*MTP	12 (10)	17 (8)
*Wrist	41 (36)	41 (19)

SD = standard deviation, IQR = interquartile range. Independent T-test or Wilcoxon-Mann-Whitney test was used for group comparisons for continuous variables. T-test was executed when variables are presented as mean. Wilcoxon-Mann-Whitney test was executed when variables are presented as median. Frequencies were compared using a Chi-square test. *p-value <0.001

Conclusion: By lowering the cut point of the 2010 criteria from 6 to 5 points, we were able to identify a substantial proportion of UA patients who develop RA within 1 year with higher sensitivity, but with the loss of some specificity. Hereby early treatment can be initiated, leading to optimal use of the window of opportunity.

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Spontaneous Remission In Patients Fulfilling The 2010 Classification Criteria For Rheumatoid Arthritis: The Impact Of Duration Of Joint Swelling. Ellen Sauar Norli[1], Elisabeth Lie[2], Gina Hetland Brinkmann[3], Olav Bjørneboe[1], Halvor Nygaard[4], Anne Julsrud Haugen[3], Patrik Stolt[5], Cathrine Thunem[6], Tore K. Kvien[2] and Maria Mjaavatten[2]. [1]Martina Hansens Hospital, Gjettum, Norway, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Østfold Hospital Trust, Fredrikstad, Norway, [4]Revmatismesykehuset Lillehammer, Lillehammer, Norway, [5]Innlandet Hospital Trust, Brumunddal, Norway, [6]Betanien Hospital, Skien, Norway.

Background/Purpose: In 2010 the new ACR/EULAR classification criteria for rheumatoid arthritis (RA criteria) were published. The prospects for early diagnosis and treatment have increased over the past decades, partly driven by the theory of a window of opportunity. The theory even implies the possibility of preventing development of RA if aggressive treatment is started early. We wanted to study the 2-year outcome of patients with arthritis of less than 16 weeks duration who fulfilled the RA criteria at baseline, according to the duration of joint swelling at first visit.

Methods: 1084 patients (age 18–75 years) were included in the NOR-VEAC (Norwegian Very Early Arthritis Clinic) study from 2004 to 2010, i.e. before the RA criteria were implemented.

Patients with crystal arthritis, septic arthritis, osteoarthritis and arthritis due to trauma were excluded. 234 patients (21.6%) fulfilled the RA criteria at baseline. 202 of these had information about DMARD use and were included in the current study, and168 (83.2%) had 2-year follow-up data.

The relationship between spontaneous resolution of arthritis (defined as no swollen joints at last visit and never used DMARDs) and duration of joint swelling, as well as other factors, was examined. Duration was treated as a non-linear continuous variable as well as divided into categories. Mann-Whitney U, Fisher's exact and Chi-Square tests were used for the statistical analyses.

Results: Duration of joint swelling [median (25–75 percentiles)] was 64 (38–83) days, mean (SD) age 52 (14) years, 62% were females, 60% anti-CCP positive, and 69% anti-CCP and/or RF positive. 23/202 (11.4%) had spontaneous resolution of arthritis.

There was a statistically significant relationship between duration of disease and tendency of spontaneous resolution of arthritis (Mann-Whitney U p=0.01). In cases with very short (0–2 weeks) duration, the arthritis resolved without DMARDs in 9/23 patients (39.1%). The corresponding proportion for 2–6 weeks duration was 5/36 (13.9%), and for >6 weeks duration 9/143 (6.3%). The patients with resolving arthritis less often had positive anti-CCP (p<0.001),were more seldom current daily smokers (p=0.01) and had less RA criteria points (p=0.02). There were no significant differences between the groups with regard to sex (p=0.50), age (p=0.28), 68-swollen (p=0.34) and 28-tender (p=0.97) joint counts, SR (p=0.42), CRP (p=0.50), BMI (p=0.51), fatigue (p=0.93), joint pain (p=0.13), patient global (p=0.28), assessor global (p=0.37), HAQ (p=0.27) or distribution of mono-, oligo- and polyarthritis (p=0.62).

Conclusion: When the duration of joint swelling was very short, the arthritis resolved without initiation of DMARD treatment in a considerable proportion of patients who fulfilled the RA criteria at baseline. Patients with arthritis of more than 6 weeks duration experienced spontaneous resolution less frequently.

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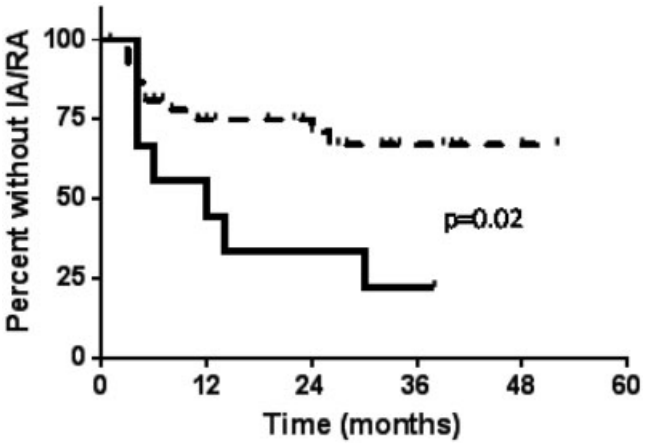
Health Fair Evaluations To Identify Subjects At-Risk For Future Inflammatory Arthritis and Rheumatoid Arthritis. Kristen E. Beck[1], M. Kristen Demoruelle[1], Christopher C. Striebich[2], Kaylynn Aiona[3], Marie L. Feser[4], Lezlie A. Derber[4], Stacey Brake[5], Jill Lysengen[6], Laura Rosseisen[6], Julia J. Rhiannon[1], Stuart M. Weisman[4], Jill M. Norris[3], V. Michael Holers[1] and Kevin D. Deane[1]. [1]University of Colorado School of Medicine, Aurora, CO, [2]University of Colorado Denver, Aurora, CO, [3]Colorado School of Public Health, Aurora, CO, [4]University of Colorado School of Medicine, Division of Rheumatology, Aurora, CO, [5]Health Fair, Denver, CO, [6]Arthritis Foundation, Great West Region, Denver Office, Denver, CO.

Background/Purpose: Multiple studies demonstrate that there is a preclinical period of rheumatoid arthritis (RA) when autoantibodies (Abs) including RF and anti-CCP are abnormal in absence of clinically apparent inflammatory arthritis (IA). Furthermore, RF and CCP abnormalities are highly predictive of future classifiable RA. However, most data regarding preclinical RA and prediction of future disease are derived from retrospective studies or referral clinics for symptomatic patients, and little is known from prospective community-based studies. Therefore, in a community health fair we identified and followed subjects with abnormalities of RA-related Abs in the absence of IA to evaluate predictive factors for development of IA/RA.

Methods: Volunteers were tested for serum anti-CCP3 (INOVA) at a Colorado health fair from 2008–2012. Subjects with CCP3 positivity (≥20 units) without IA by physical examination were invited for biannual follow-up that included assessment of demographic factors, environmental exposures, joint symptoms, joint examination by a trained study physician or nurse, and testing of CCP3 and CCP3.1 (INOVA), CCP2 (Axis-Shield), RF by nephelometry (Dade-Behring) and specific isotypes IgG/M/A (INOVA), C-reactive protein (CRP), and the shared eptiope (SE). The primary outcomes were the development of IA (≥1 swollen joint), and RA by 1987 and/or 2010 criteria at a research visit or clinical evaluation by a rheumatologist outside of the study.

Results: 7178 volunteers were initially evaluated, and 158 (2%) were CCP3(+) without IA; 47 of 158 (30%) invited subjects agreed to further study and were followed for a median of 27 months (range 1–52). Of these, 18/47 (38%) developed IA or RA all within 36 months: 10 with transient IA defined as ≥1 swollen joint(s) not present at an evaluation ~6 weeks later, and 8 with RA (7 by 1987 and 8 by 2010 criteria). The factor most strongly associated with the development of either IA or RA was CCP2 >3x normal plus positivity for any RF assay at any level (OR 5.5, 95% CI 1.2–25.3; sensitivity [SENS] 39%, specificity [SPEC] 90%, positive predictive value [PPV] 70%). This same Ab profile exhibited a stronger association with development of classified RA (OR 11.3, 95% CI 2.0–62.8; SENS 63%, SPEC 87%; PPV 50%). The timing of development of IA or RA is presented in the Figure. Age, sex, smoking, family history of RA, baseline joint symptoms, CRP and SE were not significantly associated with developing IA/RA.



Conclusion: A health fair evaluation using initial CCP3 testing is able to identify subjects at-risk for future IA or RA. In particular, during follow-up, CCP2 >3x normal and RF positivity were most strongly associated with development of IA or RA. This method of identifying subjects at risk for RA is useful for understanding the natural history of disease development, and may ultimately be used to identify candidates for RA prevention.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Efficacy of Approved Biologics II
Sunday, October 27, 2013, 4:30 PM–6:00 PM

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Sustained and Consistent Clinical Benefit With Intravenous Golimumab Therapy In Patients With Active Rheumatoid Arthritis Despite Methotrexate Therapy: Results Through 1-Year Of a Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled Trial. Clifton O. Bingham III[1], Rene Westhovens[2], Alan M. Mendelsohn[3], Lilianne Kim[3], Kim Hung Lo[3] and Michael E. Weinblatt[4]. [1]Johns Hopkins University, Baltimore, MD, [2]University Hospital KU Leuven, Leuven, Belgium, [3]Janssen Research & Development, LLC., Spring House, PA, [4]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: To report on sustainability and consistency of ACR component scores with intravenous (IV) golimumab (GLM) 2mg/kg+methotrexate (MTX) through wk52 in pts with active rheumatoid arthritis (RA).

Methods: 592 pts with active RA (≥6/66 swollen, ≥6/68 tender joints, C-reactive protein (CRP) ≥1.0mg/dL, rheumatoid-factor and/or anti-cyclic-citrullinated-peptide-antibody positive at screening) despite MTX ≥3 months (stable 15–25mg/wk, ≥4wks) participated in this multicenter, international, randomized, double-blind, placebo-controlled Phase 3 study. Pts were randomized (2:1) to IV GLM 2mg/kg or placebo (PBO) infusions at wks0&4 and q8w; pts continued stable MTX. PBO pts started GLM 2mg/kg at wk16 (early escape; <10% improvement in tender&swollen joints) or wk24 (crossover by design), so that all patients received GLM between wks 24–52.

Results: Significant and rapid clinical improvement in all ACR component scores was observed through wk24 (Table). Among pts with ≥20% improvement in ACR20 response or who achieved "good" or "moderate" response per 28-joint disease activity score employing CRP (DAS28-CRP) at wk24, approximately 80% maintained response through wk52. GLM+MTX treatment yielded sustained improvement across ACR components, including swollen and tender joint counts, pt assessments of pain and disease activity, physician assessment of disease activity, and the Health Assessment Questionnaire-Disability Index (Table).

Table. Median improvement in ACR components through 1-year

	PBO→GLM 2mg/kg + MTX	GLM 2 mg/kg + MTX
Randomized pts	197	395
Swollen joints (0–66)		
Baseline, median	12.0	12.0
% improvement at wk14/24/36/52	25.0%/27.3%/66.7%/81.8%	68.2%/75.0/77.8%/85.7%
Tender joints (0–68)		
Baseline, median	22.0	24.0
% improvement at wk14/24/36/52	12.8%/13.6%/57.9%/68.2%	61.5%/64.0%/66.7%/70.6%
Pt pain (0–10 cm VAS)		
Baseline, median	6.9	6.5
% improvement at wk14/24/36/52	7.4%/10.8%/30.0%/34.7%	38.1%/42.9%/41.5%/41.4%
Pt disease activity (0–10 cm VAS)		
Baseline, median	6.9	6.6
% improvement at wk14/24/36/52	7.3%/13.9%/31.1%/37.0%	37.1%/40.5%/40.0%/41.5%
Physician disease activity (0-1- cm VAS)		
Baseline, median	6.3	6.3
% improvement at wk14/24/36/52	14.5%/23.7%/54.0%/57.4%	52.1%/54.5%/59.7%/61.1%
HAQ-DI (0–3)		
Baseline, median	1.6	1.6
% improvement at wk14/24/36/52	6.7%/8.7%/26.7%/25.0%	28.6%/30.0%/31.3%/30.0%
Serum CRP (mg/dL)		
Baseline, median	1.7	2.0
% improvement at wk14/24/36/52	29.3%/21.4%/56.0%/57.3%	77.8%/76.8%/64.9%/65.8%

CRP=C-reactive protein, GLM=golimumab, HAQ-DI=Health Assessment Questionnaire-Disability Index, MTX=methotrexate, PBO=placebo

Conclusion: In pts with active RA despite MTX, IV GLM+MTX yielded sustained clinical improvement that was consistent across ACR components, with no new safety signals observed through 1-year.

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Microrna Expression Profiles Associated With Response To Adalimumab and Methotrexate Versus Methotrexate: A Placebo-Controlled Clinical Trial. Sophine B. Krintel[1], Christian Dehlendorff[2], Merete L. Hetland[3], Kim Hørslev-Petersen[4], Klaus K. Andersen[2], Peter Junker[5], Jan Pødenphant[6], Torkell Ellingsen[7], Palle Ahlqvist[8], Hanne M. Lindegaard[9], Asta Linauskas[10], Annette Schlemmer[11], Mette Y. Dam[12], Ib Hansen[13], Hans Chr Horn[14], Anette Jørgensen[12], Johnny Raun[4], Christian G. Ammitzbøll[12], Mikkel Østergaard[15], Kristian Stengaard-Pedersen[12] and Julia S. Johansen[16]. [1]Copenhagen University and Glostrup Hospital, Copenhagen, Denmark, [2]Danish Cancer Society Research Center, Copenhagen, Denmark, [3]DANBIO, Center for Rheumatology and Spine Diseases, Glostrup Univ Hospital, Glostrup, Denmark, [4]University of Southern Denmark, Graasten, Denmark, [5]University of Southern Denmark, Odense, Denmark, [6]Copenhagen University at Gentofte, Hellerup, Denmark, [7]Silkeborg Regional Hospital, Silkeborg, Denmark, [8]University of Southern Denmark, Vejle, Denmark, [9]Odense University Hospital, Odense, Denmark, [10]Vendsyssel Hospital, Hjørring, Denmark, [11]Aalborg University Hospital, Aalborg, Denmark, [12]Arhus University Hospital, Aarhus, Denmark, [13]Viborg Hospital, Viborg, Denmark, [14]Vejle Hospital, Vejle, Denmark, [15]Copenhagen University Hospital Glostrup, Copenhagen, Denmark, [16]Herlev Hospital, Herlev, Denmark.

Background/Purpose: The response to anti-TNF therapy varies widely between patients with rheumatoid arthritis (RA). MicroRNAs (miRNAs) are suggested to influence susceptibility to RA and disease severity. We aimed to investigate the association between miRNAs and treatment response in pre-treatment whole blood from 180 patients with early RA (treatment-naïve, disease duration <6 months) enrolled in the OPERA Study, a prospective, investigator-initiated, double-blinded, placebo-controlled study (1).

Methods: Patients were randomized 1:1 to methotrexate (MTX) 7.5 mg weekly (increased to 20 mg/week within two months) in combination with adalimumab (n=89) or placebo-adalimumab (n=91) 40 mg subcutaneously every other week. Both groups received intra-articular glucocorticoid injections (i.a. GC). Treatment response after 1 year was assessed according to EULAR response, DAS28(CRP) remission, and ACR/EULAR Boolean remission criteria. Expression of miRNAs was determined using TaqMan® Human MicroRNA LDA, A Card v2.0 (Applied Biosystems). Raw Cycle

threshold (CT) values of each miRNA were pre-processed using Quantile, 120 most expressed, and Rank normalizations. We performed interaction analyses to identify miRNAs associated differently with response to MTX + adalimumab and MTX + placebo-adalimumab. The overall test for no interaction between miRNAs and treatment was achieved by means of Kolmogorov-Smirnov. Potential predictive miRNAs were included in a multivariate model and backwards eliminated using the Bayesian Information Criterion. All effects were reported for a CT inter-quartile range increase.

Results: Kolmogorov Smirnov tests indicated interactions between miRNAs and treatment using EULAR response as outcome parameter (120 most expressed, p=0.008; Quantile, p=0.003; and Rank normalization, p=0.011). After backwards elimination, miR-22 and miR-886.3p demonstrated interaction with treatment using EULAR response as outcome parameter, Table 1. Nomograms suggested that in patients treated with adalimumab, the combination of low miR-22 and low miR-886.3p expression had the highest probability of EULAR good response (95%), whereas patients with high miR-22 and high miR-886.3p had the lowest probability of EULAR good response (65%).

Table 1. Multivariate estimated effects for 120 most expressed miRNAs, Rank, and Quantile normalization.

miRNA	Treatment	Normalization	OR	95% CI	p-value
miR-22	Adalimumab	120 most expressed	15.32	3.43–137.06	0.001
miR-22	Adalimumab	Rank	10.26	2.29–96.66	0.01
miR-22	Adalimumab	Quantile	12.18	2.30–140.45	0.01
miR-22	Placebo	120 most expressed	0.54	0.22–1.28	0.17
miR-22	Placebo	Rank	0.60	0.26–1.40	0.22
miR-22	Placebo	Quantile	0.71	0.29–1.80	0.46
miR-886.3p	Adalimumab	Rank	2.06	0.79–6.39	0.16
miR-886.3p	Adalimumab	Quantile	2.01	0.82–5.88	0.15
miR-886.3p	Placebo	Rank	0.33	0.11–0.78	0.02
miR-886.3p	Placebo	Quantile	0.40	0.14–0.97	0.06

Conclusion: In a one-year randomized, placebo-controlled, double-blind clinical trial of treatment-naïve patients with early RA, which compared adalimumab+MTX+i.a.GC with placebo+MTX+i.a.GC, we found that expression of miR-22 and miR-886.3p in pre-treatment whole blood was predictive of EULAR good response to adalimumab. Validation studies are needed to investigate the utility of these miRNAs as predictive biomarkers.

[1] Hørslev-Petersen K et al. Ann Rheum Dis Online First 7 mar 2013

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Prediction Of TNF Inhibitor Response In Rheumatoid Arthritis Patients Using Single Cell Network Profiling Of Intracellular Immune Signaling.

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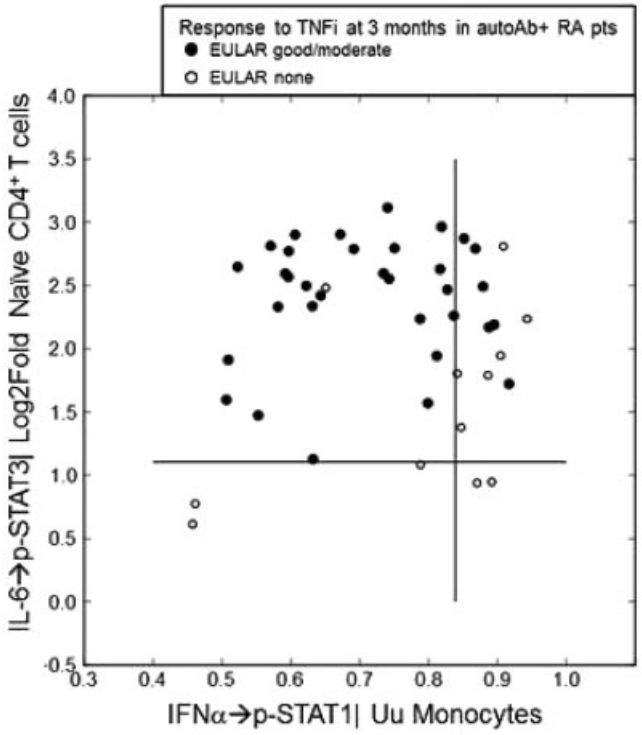
Background/Purpose: Biomarkers predictive of drug efficacy are lacking in rheumatoid arthritis (RA) and would be useful in clinical practice and clinical trials. Single cell network profiling (SCNP) is a multiparametric flow cytometry-based assay that measures induced changes in intracellular signaling proteins, providing a functional measure of pathway activity and immune networking in multiple cell subsets without physical separation. Induced signaling was measured in specific subsets of monocytes, B and T cells from RA patients (pts) initiating new treatment, and analyzed to build models to predict treatment response.

Methods: PBMCs from RA pts (n=87) starting TNF inhibitors (TNFi) were examined by SCNP of 42 nodes (combinations of modulator and intracellular readout) within 21 immune cell subsets. RA pts were a subset of ~200 from the Treatment Efficacy and Toxicity in Rheumatoid Arthritis Database and Repository (TETRAD). Blood samples were collected before initiating treatment with TNFi (adalimumab, etanercept, infliximab, golimumab). Clinical data included disease activity (DAS28) and EULAR response criteria at baseline, 3, 6, and 12 months. For the 53 evaluable patients, statistical analyses, including ordinal logistic regression and multivariate modeling, were performed to identify signaling profiles associated with response to TNFi after controlling for baseline DAS28 and age.

Results: Immune cell subsets from RA pts collected before initiating TNFi treatment exhibited heterogeneity in their induced intracellular signaling. Of note, T cell receptor (TCR) and IFNa modulation produced cell subset-specific signaling profiles that were associated with EULAR response at 3 months. Specifically, TCR→p-CD3z in CD4−CD45RA$^+$ T cells was weakest in pts that had a good EULAR response to TNFi (p=0.04). Similarly, donors with weak IFNa→p-STAT5 in B cells were more likely to have a good response to TNFi (p=0.007). In contrast, IL-6→p-STAT3 in naïve CD4$^+$ T cells was weakest in autoantibody (RF/ACPA)-positive (autoAb+) pts with no response (p=0.01). Although TNFa→p-p38 in monocytes was associated with baseline DAS28, this signaling was not predictive of TNFi response. Combining signaling nodes produced a model of TNFi response in autoAb+ donors defined by IL-6→p-STAT3 in naïve CD4$^+$ T cells and IFNa→p-STAT1 in monocytes with an area under receiver operating characteristic curve (AUC) of 0.91 in the full dataset, or 0.64 cross-validated.



Conclusion: These data provide the first evidence that measurement of peripheral blood immune cell function can: 1) identify patients likely to respond to TNFi, and 2) reveal the biology associated with TNFi response or lack thereof, thus providing information on therapeutic strategies. SCNP has revealed predictive biomarkers that, once replicated in future studies, may enable patient stratification in clinical practice and clinical trials.

Disclosure: J. Ptacek, Nodality, Inc., 3; **R. Hawtin**, Nodality, Inc., 3; **B. Louie**, Nodality, Inc., 3; **E. Evensen**, Nodality, Inc., 3; **J. Cordeiro**, Nodality, Inc., 3; **B. Mittleman**, Nodality, Inc., 3; **M. Atallah**, Nodality, Inc., 3; **A. Cesano**, Nodality, Inc., 3; **C. O. Bingham III**, None; **S. Cofield**, None; **J. R. Curtis**, None; **M. I. Danila**, None; **R. A. Furie**, None; **M. C. Genovese**, None; **M. C. Levesque**, None; **L. W. Moreland**, None; **P. A. Nigrovic**, None; **J. R. O'Dell**, None; **W. H. Robinson**, None; **N. A. Shadick**, Crescendo Biosciences, Medimmune, BMS, Genentech, Abbott and AMGEN, 2; **E. W. St Clair**, None; **C. C. Striebich**, None; **G. M. Thiele**, None; **P. K. Gregersen**, None; **S. L. Bridges Jr., None.**

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Results From The RATE-RA Study: A Multicenter, Single-Arm Study To Evaluate The Safety Of Administering Rituximab At a More Rapid Infusion Rate In Patients With Rheumatoid Arthritis. Charles H. Pritchard[1], Maria W. Greenwald[2], Joel M. Kremer[3], Norman B. Gaylis[4], William Rigby[5], Steve Zlotnick[6], Carol Chung[6], Birgit Jaber[7] and William Reiss[6]. [1]Drexel University College of Medicine, Willow Grove, PA, [2]Desert Medical Advances, Palm Desert, CA, [3]Center for Rheumatology, Albany Medical College, Albany, NY, [4]Arthritis & Rheumatic Disease Specialties, Aventura, FL, [5]Geisel School of Medicine at Dartmouth, Lebanon, NH, [6]Genentech Inc., South San Francisco, CA, [7]F. Hoffmann-La Roche Ltd., Basel, Switzerland.

Background/Purpose: The FDA-approved dose of rituximab (RTX) in rheumatoid arthritis (RA) is 2 × 1000 mg IV infusions given 2 weeks apart (1 course), with recommended times of 4.25 hours (h) and 3.25 h for infusions 1 and 2, respectively. The objective of this analysis was to assess the safety of administering the second infusion of a RTX course and subsequent infusions at a more rapid rate over 2 h.

Methods: Patients (pts) with moderate-to-severe RA and an inadequate response to TNF inhibitors who were either RTX-naïve or RTX-experienced (up to 2 prior courses, last course 6–9 months before baseline) were eligible. All pts received methotrexate and were premedicated with IV methylprednisolone, antihistamines and analgesics prior to all RTX infusions. All pts received the first infusion (Infusion 1) on Day 1 over 4.25 h, the standard rate. The second infusion (Infusion 2) on Day 15 was over 2 h (Infusion 1 and 2 = course 1), as were both Infusions 3 and 4 (course 2) 6 months later. The primary endpoint was the incidence of infusion-related reactions (IRRs) during or within 24 h of Infusion 2 of course 1.

Results: The 351 enrolled pts had the following characteristics: RTX-naïve (n=306; 87.2%); RTX-experienced (n=45 of which 24 [6.8%] and 21 [6.0%] had received 1 or 2 prior RTX courses, respectively); mean age 55.5 (SD 11.5) y, with 19.7% of pts aged ≥65 y; and mean RA disease duration 12.5 (SD 9.7) y. The incidence of IRRs during or within 24 h of Infusion 1 was 16.2% (95% CI 12.5%, 20.5%) (none serious), consistent with that derived from historical clinical trial data (20.7%).[1] Infusion 2 was given to 337 pts (96.0%) over 2 hours; 333 completed the infusion and received the full 1000 mg dose, 4 pts did not complete the infusion (3 for AEs [none serious], 1 for another reason). Of these 333 pts, 5 (1.5%) required an infusion time >2.5 h. The incidence of IRRs for Infusion 2 (Figure 1, primary endpoint) was 6.5% (95% CI, 4.1%, 9.7%) (22 pts experienced a total of 30 events), similar to historical data for infusion 2 given at the standard rate (8.1%).[1] All IRRs for Infusion 2 were CTC grade 1 or 2 except two grade 3 (hypertension and headache), with no grade 4 events. The most commonly observed IRRs for Infusion 2 were nausea (1.2%) and chills (0.9%). Course 2 data indicate a low incidence of IRRs for Infusions 3 (secondary endpoint) and 4. No serious IRRs or SAEs were reported during or within 24 h of Infusions 1 and 2 (course 1) or Infusions 3 and 4 (course 2).

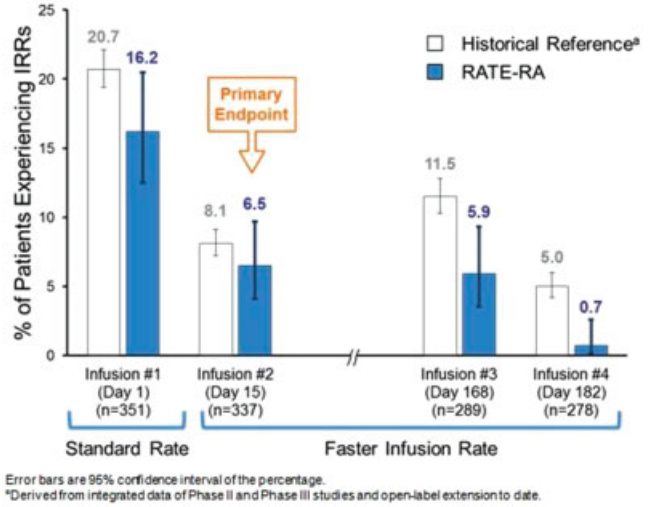

Figure. IRRs During or Within 24 Hours of Each RTX Infusion

Conclusion: The incidence of IRRs occurring during or within 24 h of the second infusion of RTX when administered at an increased 2 h rate is similar to the historical incidence. The incidence of IRRs for subsequent infusions is also similar to the historical incidence. The overall safety data were consistent with the known RTX safety profile. These data of RTX at a faster infusion rate provide clinically relevant information for HC providers and patients.

1. van Vollenhoven, et al. ACR 2012: poster 459.

Disclosure: C. H. Pritchard, Genentech, Pfizer, Abvie, 8; **M. W. Greenwald**, Genentech/Roche, 2; **J. M. Kremer**, Genentech, Pfizer, Lilly, UCB, Novartis, 2, Genentech, Pfizer, Lilly, BMS, 5; **N. B. Gaylis**, Genentech/Roche, 2, Genentech/Roche, 5; **W. Rigby**, Roche Pharmaceuticals, 5; **S. Zlotnick**, Genentech Inc., 3; **C. Chung**, Genentech Inc., 3; **B. Jaber**, F. Hoffmann-La Roche Ltd, 3; **W. Reiss**, Genentech, Inc., 3.

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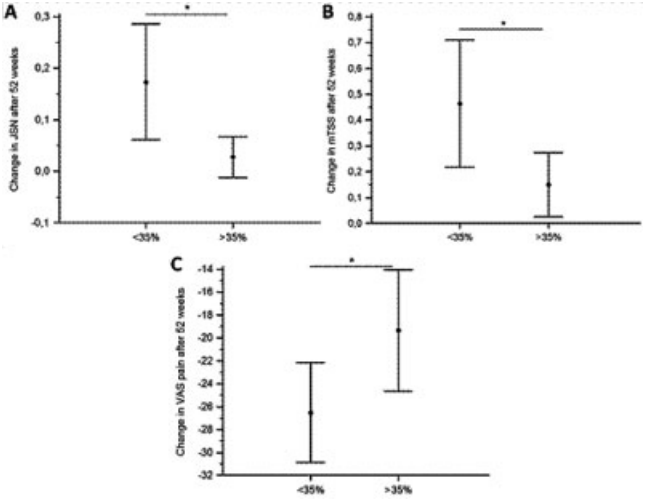
Responders To Tocilizumab Identified By Serological Measurement Of Connective Tissue Type I Collagen In Patients With Rheumatoid Arthritis. Anne Sofie Siebuhr[1], Anne C. Bay-Jensen[1], Diana J. Leeming[1], Adam Platt[2], Inger Byrjalsen[1], Claus Christiansen[3], Désirée van de Heijde[4] and Morten Asser Karsdal[1]. [1]Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, [2]Roche Products Ltd, Welwyn Garden City, United Kingdom, [3]Center for Clinical and Basic Research and C4Pain, Aalborg, Denmark, [4]Leiden Univerisity, Leiden, Netherlands.

Background/Purpose: As biological treatments for rheumatoid arthritis (RA) are only effective in a subpopulation of patients and the treatment can have serious side effects, there is a need to identify patients who will benefit from a particular treatment. The serum Protein Fingerprint, type I collagen degradation mediated by MMP-cleavage (C1M), is a biomarker of connective tissue destruction. We investigated 1) whether baseline (BL) C1M levels were correlated with structural status, progression and pain, 2) how C1M changed with time and treatment with tocilizumab (TCZ) and 3) if C1M could be a potential early surrogate marker of treatment efficacy with TCZ.

Methods: LITHE biomarker study (n=585) was a 1-year phase III, double-blind, placebo (PBO)-controlled, parallel group study of TCZ 4 or 8 mg/kg every 4 weeks, in RA patients on stable doses of methotrexate (MTX). C1M was tested in serum from BL and week 2, 4, 16, 24 and 52. Spearman's correlations was analysed between BL level of C1M (log transformed) and clinical measures. The associations between BL serum C1M and change in JSN and mTSS were investigated in the PBO group by regressions analysis, including CRP, age, BMI, disease duration and BL JSN/mTSS. Change in C1M levels were studied as a function of time and treatment. Lastly, in patients receiving TCZ the level of change within 1-year in structural progression and pain were investigated in two groups based of the change in C1M level until week 16: 1; <35% change in C1M and 2; >35% change in C1M and analysed by Student's T-test.

Results: BL C1M was significantly correlated with change in JSN at week 24 (r=0.38 p<0.0001) and at week 52 (r=0.63, p<0.0001) and with changes in mTSS at 24 (r=0.21 p<0.012) and 52 weeks (r=0.58, p<0.0001). BL C1M was weakly negatively correlated with change in VAS pain at 24 weeks (r=−0.1, p<0.05). However, BL C1M was not correlated to BL JSN (rho=0.12) or mTSS (rho=0.14), but highly correlated with BL VAS pain (rho=0.3). Serum C1M was dose-dependently reduced by TCZ8 (p<0.0001) and TCZ4+MTX (p<0.05) as compared to PBO. Change in C1M at 16 weeks after treatment initiation in the TCZ groups was related to the level of radiographic changes over 1 year (p<0.05). Surprisingly, VAS pain had a negative relationship with change in C1M at 16 weeks.



Conclusion: MMP-mediated tissue degradation is imperative in joint destruction, as those patients with the highest levels of C1M were significantly more likely to progress in JSN and mTSS compared to those with a low level. Surprisingly, pain showed the reverse relationship with C1M. C1M may assist in identifying those patients that are rapid progressors. Interestingly, TCZ dose-dependently inhibited C1M level already after 2 weeks, suggesting almost immediate onset of joint protection. C1M may both be a surrogate marker of structural efficacy and enable prognostic identification of those patients that are in most need of treatment.

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Serological Biomarkers Of Specific Mode Of Action For Early Identification Of Rheumatoid Arthritis Patients Who Respond To Anti-IL6 Or Anti-TNF Treatment. Anne C. Bay-Jensen, Natasja Stæhr Gudman, Anne Sofie Siebuhr, Claus Christiansen and Morten Asser Karsdal. Nordic Bioscience, Biomarkers and Research, Herlev, Denmark.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized debilitating joint destruction, if not treated aggressively in the patient in most need of treatment. Personalized health care is needed in RA, as response rates are low compared to the potential side effects and cost of treatment. Anti-IL6 and anti-TNF treatments are approved for treatment of RA patients, however with varying response rates. A unique class of serological biomarkers, which are measures of extracellular matrix turnover, also called protein fingerprint, may describe specific disease mode of actions. We investigated whether early measurement after treatment initiation could identify patients that would respond to either anti-IL6 or anti-TNF treatment.

Methods: Following tissue-specific biomarkers were measured in 800 RA patients treated with either methotrexate, tocilizumab, infliximab, entercept or adalimumab; VICM (citrullinated and MMP-degraded vimentin), C1M (MMP-degraded type I collagen), C3M (MMP-degraded type III collagen), CRPM (MMP-degraded CRP), C2M (MMP-degraded type II collagen), CTx (cathepsin K degraded type I collagen), osteocalcin (bone formation), and CRP (acute phase reactant). The baseline levels and changes in the biomarkers were investigated was investigated for each of the treatment groups. Logistic regression and classification and regression tree analysis were used to assess whether the markers alone or together could predict treatment response evaluated by DAS28 changes. Data was corrected for multiplicity.

Results: Methothraxate had a small effect on CRP, but not on any of the other markers. Tocilizumab significantly suppressed ($p<0.0001$) the level the connective tissue markers MMP3, VICM, C1M, C2M, C3M, CRPM and significantly increased ($p<0.05$) the level of the bone markers CTx and ostoecalcin. In contrast, cartilage degradation measured by C2M, was not inhibited anti-TNF treatment. A simple combination of the biomarkers (C1M, C3M, C2M, osteocalcin and CRPM) was able to double the DAS28 response rate of tocilizumab 27 to 54%. When including the change from baseline to 4 or 16 weeks in cartilage degradation or bone formation the rate was increased to 64%. Similar segregation could be reached for the anti-TNF group, however with a different set of markers; C1M, C3M, VICM and CRPM.

Conclusion: Distinct mode of action profiles were identified for each of the different treatment groups by measurement of the unique protein fingerprint markers. This may assist in identification of the patients, in any inflammatory disease, who respond most optimally to given interventions, with fewer AEs, and thus provide a stronger risk/benefit/cost value proposition to patients and payers.

Disclosure: A. C. Bay-Jensen, Nordic Bioscnce, 3; **N. S. Gudman**, Nordic Bioscience, 3; **A. S. Siebuhr**, Nordic Bisocience, 3; **C. Christiansen**, Nordic Bioscience Diagnostic, 1, Nordic Bioscience Diagnostic, 6; **M. A. Karsdal**, Nordic Bioscience, 3.

ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Lupus Nephritis and Genetics
Sunday, October 27, 2013, 4:30 PM–6:00 PM

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Role Of Urinary Podocyte Number and Urinary Podocalyxin Level As Biomarkers Of Glomerulonephritis In Systemic Lupus Erythematosus and ANCA-Associated Vasculitis. Hiroshi Kajiyama[1], Keiju Hiromura[2], Daisuke Ikuma[1], Hidekazu Ikeuchi[2], Hiroyuki Kurosawa[3], Yoshiaki Hirayama[3], Fumio Gondaira[3], Masanori Hara[4], Yoshihisa Nojima[2] and Toshihide Mimura[1]. [1]Saitama Medical University, Saitama, Japan, [2]Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan, [3]Denka Seiken Co. Ltd., Niigata, Japan, [4]Yoshida Hospital, Niigata, Japan.

Background/Purpose: Podocytes are glomerular visceral epithelial cells functioning as molecular sieves not to allow high molecular weight protein to leak from glomerular capillary wall. The decreased number of podocyte per glomerulus due to death or detachment from glomerular basement membrane leads to severe proteinuria, irreversible glomerulosclerosis and end stage kidney disease. Podocalyxin (PCX) is one of the podocyte markers, expressed on the apical cell membrane and shed in urine from injured podocytes. It has been reported that two different urine PCX-related biomarkers, urine numbers of PCX-positive cells (podocytes) and urine levels of PCX are associated with glomerular lesions, such as in IgA nephropathy and diabetic nephropathy. However, the role of these biomarkers in systemic lupus erythematosus (SLE) and ANCA-associated vasculitis (AAV) remain to be elucidated.

Methods: Urine numbers of podocytes (U-Pod) were determined by counting PCX-positive cells in sediments from urine samples. PCX staining was done by indirect immunofluorescent method. Urine levels of PCX (U-PCX) were measured by sandwich ELISA, normalized to urine creatinine levels. Patients with proteinuria (defined as more than 0.2 urine protein/creatinine ratio) and/or renal failure (defined as estimated GFR less than 60 mL/min/1.73m^2) were defined as KD(+), and patients who had neither proteinuria nor renal failure were defined as KD(−). Patients with SLE and AAV were recruited from our hospitals between October 2010 and March 2013. SLE-KD(+) (n=61), SLE-KD(−) (n=22), AAV-KD(+) (n=17) and AAV-KD(−) (n=6). Renal histology of lupus nephritis was classified according to ISN/RPS classification. Statistical analysis was done using Mann-Whitney test. $P<0.05$ was defined as statistical significance. Each value was described as mean ± standard deviation.

Results: U-Pod was significantly higher in the KD(+) group than in the KD(−) group both in SLE (7.9±24.9 vs 0.2±0.6 cells/mL, $P<0.0001$) and in AAV (0.7±1.0 vs 0.0±0.0 cells/mL, $P=0.0048$). However, there was not a statistical difference in U-Pod between the SLE-KD(+) group and the AAV-KD(+) group ($P=0.397$). In contrast, although U-PCX was significantly higher in the KD(+) group than in the KD(−) group in SLE (362.2±298.8 vs 128.9±113.5 μg/gCr, $P=0.0012$), U-PCX tended to be lower in the KD(+) group than in the KD(−) group in AAV (100.3±117.6 vs 206.3±169.5 μg/gCr, $P=0.06$). In addition, U-PCX was significantly higher in the SLE-KD(+) group than in the AAV-KD(+) group ($P<0.0001$). Among 36 patients with biopsy-proven lupus nephritis, U-Pod was significantly higher in patients with Class IV lesion (diffuse proliferative lesion) than in those without Class IV lesion (20.0±38.6 vs 0.7±0.6 cells/mL, $P=0.0025$). U-PCX tended to be higher in patients with Class V lesion (membranous lesion) compared to that in those without class V lesion (549.1±344.5 vs 347.8±274.0 cells/mL, $P=0.058$), although it did not reach statistical significance.

Conclusion: Our data suggest that podocyte injury estimated by U-PCX is more severe in lupus nephritis compared to AAV nephritis. In addition, the combination of U-Pod and U-PCX may predict the histological features of lupus nephritis.

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Time To Renal Flare and Renal Disease Activity Over a 1 Year Period Is associated With Urinary TWEAK Levels In Patients With Systemic Lupus Erythematosus. Nicolas Wisniacki[1], Chris Stebbins[2], Jadwiga Bienkowska[3], Susan Gawlak[2], Donald Bennett[4], Yuhong Xiang[2], Andrea Dearth[5], Linda C. Burkly[2], Ann Ranger[5], Carrie Wager[2], Laurence S. Magder[6] and Michelle Petri[7]. [1]Biogen Idec, Maidenhead, United Kingdom, [2]Biogen Idec, Cambridge, MA, [3]Biogen Idec Inc., Cambridge, MA, [4]Biogen idec, Cambridge, MA, [5]Biogen Idec Inc, Cambridge, MA, [6]University of Maryland, Baltimore, MD, [7]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: TNF-like weak inducer of apoptosis (TWEAK) is a member of the TNF superfamily that signals through its distinct, highly inducible receptor, FGF-inducible molecule 14 (Fn14) on renal epithelial and mesenchymal cell types. The TWEAK/Fn14 pathway mediates key pathologic processes involved in renal disease in SLE. Previous studies have demonstrated that lupus patients with active renal disease have higher levels of urinary TWEAK (uTWEAK) compared to those without active renal disease. Furthermore, uTWEAK levels correlated significantly with renal disease activity on the same day as assessed by the renal SLE Disease Activity Index (SLEDAI) scores. However, the value of uTWEAK to predict SLE disease activity during follow up is unknown. The aim of this study was to explore the ability of uTWEAK levels to predict SLE renal and non-renal disease activity in the subsequent year after measurement.

Methods: The SPARE study is a prospective, longitudinal, observational study conducted at single center. Consecutive adult patients attending the SLE clinic were eligible if they met the ACR Criteria for SLE. At baseline, uTWEAK levels were measured by ELISA and normalised with urinary creatinine. Patients within uTWEAK quartiles were compared with respect to the frequency of disease activity measured at clinic visits in the following year. Estimates of differences and p-values were based on generalized estimating equations (GEE) models to account for repeated visits from the same patient. Cox proportional hazards models were fit to time to first renal flare within the first year, adjusting for either log2-transformed or quartile of uTWEAK along with sex, race, complement (C3, C4), and dsDNA; p-values for uTWEAK were based upon the effect estimates. Renal flares were defined as increase in SLEDAI renal descriptors or doubling of urine protein/cr.

Results: 293 patients were included in the analysis: 91% were female; 59% Caucasian and 33% African American. The mean age was 46.2 (±12) years. Patients with higher uTWEAK at baseline were more likely to have renal SLEDAI, uPCR >0.5, PGA >1 and SLEDAI >3 during the follow-up year (Table 1). There were no differences in the non-renal SLEDAI score components or levels of anti-dsDNA and complement. The variables associated with time to first renal flare within one year of follow up included male gender, asian race, complement, dsDNA and uTWEAK. The median time (days) to renal flare declined with increasing quartile of uTWEAK (q1=323 / q2=195 / q3=183 / q4=141; p=0.05 for comparing hazard q4 to q1). In the model where log2-transformed uTWEAK was treated as a continuous variable, each 2-fold increase in uTWEAK corresponded to 1.34 times the instantaneous risk of having a flare in the first year (p=0.04).

Variable	Low uTWEAK Patient n=73 Visit n=310	Medium low uTWEAK Patient n=73 Visit n=294	Medium high uTWEAK Patient n=73 Visit n=300	High uTWEAK Patient n=74 Visit n=313	P-value	Adjusted P-value for race	Adjusted P-value for trend
PGA >1	13%	15%	16%	27%	0.099	0.135	0.0098
SLEDAI ≥3	22%	21%	27%	30%	0.42	0.24	0.044
urine protein/cr ≥0.5	5%	5%	12%	15%	0.12	0.20	0.012
Anti-dsDNA ≥ 10	24%	19%	21%	21%	0.90	0.91	0.62
C3 <79	7%	10%	16%	15%	0.15	0.20	0.12
C4 <12	8%	10%	14%	11%	0.62	0.70	0.62
ESR >20	58%	46%	50%	45%	0.30	0.58	0.66
Any SLEDAI Renal	3%	5%	9%	12%	0.013	0.016	0.0088
Any SLEDAI Musculoskeletal	2%	3%	2%	5%	0.40	0.38	0.14
Any SLEDAI Immunologic	32%	26%	31%	28%	0.85	0.82	0.85
Any SLEDAI Skin	31%	31%	28%	23%	0.53	0.92	0.84
Any SLEDAI Hematology	3%	5%	5%	4%	0.87	0.85	0.14

Conclusion: Shorter time to renal flare and increased renal disease activity over a 1 year period is associated with higher urinary TWEAK levels in patients with SLE

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Association Of a Neutrophil Gene Signature Comprised Of Low Density Granulocyte (LDG)-Enriched Genes With Both Future Systemic Lupus Erythematosus Disease Activity and Poor Longterm Outcomes. Michelle Petri[1], Laurence S. Magder[2], Hong Fang[1], Jadwiga Bienkowska[3], Andrea Dearth[4], Norm Allaire[3] and Ann Ranger[4]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD, [3]Biogen Idec Inc., Cambridge, MA, [4]Biogen Idec Inc, Cambridge, MA.

Background/Purpose: Neutrophils and neutrophil death (NETosis) have a role in the pathogenesis of SLE. A neutrophil gene signature (NGS) exists in SLE, although its association with the clinical phenotype is unknown. We explored the association of a neutrophil gene signature comprised of genes significantly upregulated in low-density granulocytes (LDGs) with both future disease activity and long-term outcomes.

Methods: 292 SLE patients (91.1% female; 58.9% Caucasian, 33.9% African-American, mean age (SD) 46.5 (±11.9) years were included. Gene expression levels were assessed in peripheral blood RNA samples using microarray (Affymetrix). The LDG-associated gene signature was comprised of 8 genes reported in the literature to be significantly upregulated in LDGs relative to normal-density neutrophils. The LDG–associated NGS "score" was calculated for each patient based on the geometric mean of the expression levels (chip signal intensity) of the 8 genes in the signature. Three groups based on NGS scores were compared. GEE models (to account for repeated measures) were used.

Results: The mean LDG-associated NGS was somewhat lower in African Americans (mean=5.4) relative to Caucasians (mean=5.8) and other ethnicities (mean=6.4), p=0.0087. It was also somewhat higher in men than women (mean 6.2 vs. 5.7, p=0.067). The NGS was strongly associated with global disease activity over the next year, serologies (anti-dsDNA and low complement), and future organ-specific activity (renal, cutaneous and arthritis) (Table 1). An elevated LDG-associated NGS was also strongly associated with a history of poor outcomes (myocardial infarction, deep venous thrombosis, diabetes, malignancy).

Table 1. %visits with various types of disease activity over 1 year, by LDG-associated NGS tertiles

Variable	1st Tertile Neutrophil Patient n=97 visit n=406	2nd Tertile Neutrophil Patient n=98 visit n=395	3rd Tertile Neutrophil Patient n=97 visit n=409	P-value	Adjusted P-value for Ethnicity	Adjusted P-value for Trend
Physician Global Assessment >1	13%	17%	24%	0.057	0.045	0.0064
SLEDAI ≥2	48%	53%	62%	0.054	0.0034	0.0010
Urine Protein/Creatinine Ratio (≥0.5)	8%	7%	14%	0.16	0.11	0.037
Anti-dsDNA ≥ 10	9%	23%	32%	<0.0001	<0.0001	0.0006
C3 <79	9%	7%	19%	0.014	0.022	0.0012
C4 <12	9%	7%	16%	0.088	0.14	0.0046
ESR >20	41%	51%	59%	0.014	0.0007	0.0005
Any SLEDAI Renal	5%	6%	11%	0.073	0.052	0.0038
SLEDAI Arthritis	1%	2%	6%	0.020	0.020	0.0031
Any SLEDAI Skin	25%	30%	30%	0.57	0.030	0.016
Any SLEDAI Heme	6%	4%	4%	0.69	0.67	0.31

Table 2. Association between SLICC/ACR Damage Index and the LDG-associated NGS in SLE

Variable	Low Neutrophil (<5) (%, N=107)	Med Neutrophil (5–6) (%, N=92)	High Neutrophil (>6) (%, N=93)	Adjusted P-value for Ethnicity
Myocardial Infarction	0.0	6.5	5.4	0.0056
Deep Venous Thrombosis	1.9	0.0	6.5	0.016
Diabetes	4.7	6.5	14.1	0.024
Malignancy	2.8	12.1	15.2	0.0043

Conclusion: The LDG-associated NGS associates with SLE clinical and serologic activity over the next year. This is the first gene signature to be associated with myocardial infarction, deep venous thrombosis and malignancy. The NGS may be a promising biomarker of disease activity. Given that atherosclerotic disease is the major cause of death in late SLE, this gene signature may be the "missing link" in understanding how SLE accelerates atherosclerosis.

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Sex Bias In Autoimmune Diseases: Increased Risk Of 47,XXX In Systemic Lupus Erythematosus (SLE) and Sjögren's Syndrome (SS) Supports The Gene Dose Hypothesis.

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Background/Purpose: Female preponderance is a hallmark of most autoimmune diseases, the mechanism for which is unknown. We hypothesize that this is a consequence of a gene dose effect from the X chromosome. Here we tested a prediction of the gene does hypothesis: that triple X (47,XXX, which is found in 1 in ~1,100 live female births) would be increased in female predominant diseases (e.g. Systemic Lupus Erythematosus [SLE], Sjogren's Syndrome [SS], Primary Biliary Cirrhosis [PBC] and Rheumatoid Arthritis [RA]) compared to diseases without a female predominance (e.g. sarcoidosis, granulomatosis with polyangiitis [GP]) or to healthy controls.

Methods: Chromosome X aneuploidies were identified using single nucleotide polymorphisms (SNP) array and confirmed by karyotyping, FISH, or quantitative PCR.

Results: 47,XXX was found in eight of 2,948 SLE patients and in three of 1,206 SS patients, but in none of the 4,976 controls, all female (OR≥28.64, 95% CI 1.65-∞, p=0.00037; and OR≥28.84, 95% CI 1.49-∞, p=0.00745; respectively). These data suggest that one female with SLE and one female with SS has 47,XXX of approximately every 391 female SLE cases and 351 SS female cases. In addition, we identified one individual with 47,XXX from 1,179 female cases with PBC and one from 943 female cases with Sarcoidosis. No individuals were identified with 47,XXX in 453 female cases with RA or 247 female cases with GP, providing no evidence in these underpowered samples that individual with a 47,XXX karyotype have an increased risk for PBC, RA, GP or Sarcoidosis (p>0.05 for each).

Conclusion: The 47,XXX karyotype is present in excess among females with either SLE or SS, consistent with the X chromosome gene dose hypothesis of pathogenesis. We estimate the prevalence of SLE and SS is ~2.5 and ~2.8 times higher than expected in individuals with 47,XXX when compared to 46,XX females and ~25 and ~39 times higher when compared to 46,XY males respectively. That Klinefelter's syndrome (47,XXY) males carry the same SLE disease risk as females with 46,XX karyotype further support the hypothesis that the X chromosome dose contributes to the sex-bias of SLE, independently of phenotypic sex and most hormone and cultural differences between male and female life.

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Treatment Of Lupus Nephritis With Abatacept Plus Low-Dose Pulse Cyclophosphamide Followed By Azathioprine (the Euro-Lupus Regimen): Twenty-Four Week Data From a Double-Blind Controlled Trial.

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Background/Purpose: Studies in murine models for SLE have shown that CTLA4Ig can ameliorate murine lupus nephritis. Moreover, the combination of CTLA4Ig plus intravenous cyclophosphamide (IVC) acts synergistically in mice to reverse lupus nephritis. The purpose of this study (the ACCESS Trial) was to determine whether these observations in mice could be translated into an effective treatment for lupus nephritis in people.

Methods: Subjects with biopsy-proven class III or IV lupus nephritis (with or without class V) and urine protein:creatinine ratio (UPCR) >1 were enrolled in the trial. All subjects received low-dose IVC (500 mg q 2 wks × 6) followed by azathioprine (2 mg/kg/d up to a maximum of 200 mg/dose), per the Euro-Lupus nephritis (ELN) regimen. Subjects were randomized 1:1 to receive either saline (n=68) or abatacept (ABA) (n=66) intravenously at weeks 0, 2, 4, and then every four weeks. ABA was dosed based on weight: <60 kg, 500 mg; 60–100 kg, 750 mg; >100 kg, 1 gm. In addition, subjects received oral prednisone beginning at 60 mg/d and tapered to 10 mg/d within 12 weeks. The primary outcome measure was complete response (CR) at 24 weeks, defined as: (i) UPCR <0.5; (ii) serum creatinine normal or, if abnormal, within 25% of baseline; and (iii) adherence to the steroid regimen. Partial response required a >50% improvement in UPCR and otherwise mirrored the CR criteria.

Results: A racially and ethnically diverse population of North American subjects was enrolled (39% African American and 40% Hispanic/Mestizo). The groups were well matched for baseline characteristics, including race, ethnicity, severity of nephritis, and biopsy class. At 24 weeks, the CR rate in the ABA group was 22/66 (33%) compared to 21/68 (31%) in the control group (p=0.85). Total response (CR+PR) was 59% in both groups (39/66 vs 40/68). Among African American subjects, 33% (9/27) of subjects in the ABA group achieved CR, compared to 16% (4/25) in the control group (p=0.20). Twice as many subjects in the ABA group experienced disappearance of anti-dsDNA Ab (24% vs 11%), but the difference was not statistically significant (p=0.22). Patient global assessment improved by 74% in the ABA group compared to 38% in the control group (p=0.051). There was no difference between the groups at week 24 in mean UPCR, anti-dsDNA and complement levels, BILAG score, SF-36 (physical and mental), frequency of serious adverse events (SAEs), or withdrawals (total or lupus-related). The rate of infectious SAEs was 0.3/yr in the ABA group compared to 0.2/yr in the control group (NS).

Conclusion: The ACCESS trial did not achieve its primary goal of demonstrating a benefit for ABA plus ELN compared to ELN alone at 24 weeks. However, it achieved an important secondary objective by providing the first systematic examination of the ELN regimen in a racially and ethnically diverse North American population. The response rate of >30% CR within 24 weeks in the ELN control group is higher than has been reported in prior lupus nephritis trials (including studies of mycophenolate mofetil and high-dose IVC), suggesting that the ELN regimen may have

broad applicability. Subjects in the ACCESS trial are still undergoing blinded evaluation to examine outcome at later time points.

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Fatigue In SLE Is Associated With Upregulation Of Interferon-Alpha Related Gene Transcripts. Maureen A. McMahon, Jennifer M. Grossman, Bevra H. Hahn, Lori Sahakian, Isao Matsuura, Elaine Lourenco and Brian Skaggs. UCLA David Geffen School of Medicine, Los Angeles, CA.

Background/Purpose: Fatigue is a major complaint in at least 80% of SLE patients, and is often listed as the most disabling symptom of the disease; however, fatigue often does not improve significantly with standard treatments that reduce disease activity assessed by standard measures (SLEDAI). Defining altered biologic pathways in SLE patients with severe fatigue might provide clues to disease pathways that have not been previously identified – or have been identified but not appreciated for their importance in SLE fatigue. One possible pathway of interest is the IFNa pathway, well appreciated in SLE disease activity and recently identified as important in patients with chronic fatigue syndrome. We hypothesized that gene expression studies comparing patients classified by high fatigue scores and low disease activity and patients with low fatigue scores/low disease activity might identify new or previously underappreciated pathways of SLE pathogenesis.

Methods: We administered the Fatigue Severity Score (FSS) to a subset of SLE patients participating in a longitudinal SLE in atherosclerosis cohort study. Monocyte RNA was isolated from peripheral blood of 5 SLE patients with severe fatigue (defined as '6 on FSS) and 8 SLE subjects with mild fatigue ($\leq$ 4 on FSS), all of whom had low disease activity (SELENA-SLEDAI $\leq$ 4). Whole genome transcript analysis was performed using Affymetrix Human U133+2.0 chips. dChip software (Li lab, Harvard) was utilized to determine differentially expressed transcripts. The Database from Annotation, Visualization, and Integrated Discovery (DAVID) program (http://david.abcc.ncifcrf.gov) was utilized to examine if any functional groups of genes were altered. To examine whether a subset of IFNa-regulated genes were dysregulated, differentially expressed genes were entered into the Web-based database www.interferome.org. Differential transcript expression was confirmed by quantitative PCR.

Results: The mean FSS score in the high fatigue group was 6.7 $\pm$ 0.5 vs. 2.8 $\pm$ 0.8 in the low fatigue group. Approximately 300 transcripts were differentially expressed between the high and low fatigue groups (fold change $\geq$1.2 or $\leq$−1.2, p$\leq$0.05). Three gene families were significantly altered in this comparison: the immune response gene category (Benjamini corrected p-value 3.8 e-8), regulation of apoptosis (2.5 e-6), and response to virus (2.8 e-3). 35% of the dysregulated transcripts were IFNa-regulated genes (expected 'interferome' transcripts would be ~8%), and most were upregulated in patients with high fatigue. Dysregulation of five interferome genes was confirmed by qPCR analysis: ICAM1 (1.86-fold up, p=0.01), IRF1 (2.24-fold up, p=0.03), JAK2 (3.60-fold up, p=0.04), OAS-L (1.94-fold up, p<0.01), and TLR4 (2.63-fold up, p=0.01).

Conclusion: Upregulation of IFNa-regulated transcripts, already known to associate with SLE disease activity, appear to also associate with high fatigue in patients with low SLEDAI. Targeting IFNa pathways with specific therapeutic agents might be beneficial in patients suffering from fatigue, even in the absence of traditional high disease activity measurements.

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ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Human Etiology and Pathogenesis I
Sunday, October 27, 2013, 4:30 PM–6:00 PM

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Lupus Neutrophil Extracellular Traps Render High Density Lipoprotein Oxidized and proatherogenic. Carolyne K. Smith[1], Anuradha Vivekanandan-Giri[2], Jason S. Knight[3], Paul Ryan Thompson[4], Subramaniam Pennathur[2] and Mariana J. Kaplan[3]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan Nephrology, Ann Arbor, MI, [3]University of Michigan Rheumatology, Ann Arbor, MI, [4]The Scripps Research Institute, Jupiter, FL.

Background/Purpose: Cardiovascular risk is significantly increased in systemic lupus erythematosus (SLE) patients. This phenomenon cannot be explained by the Framingham risk equation. Previous reports suggest that high density lipoprotein (HDL) becomes oxidized in autoimmune diseases such as rheumatoid arthritis and SLE. We previously demonstrated that phagocyte-derived myeloperoxidase (MPO) oxidizes HDL and renders the lipoprotein atherogenic by impairing reverse cholesterol transport. Neutrophil extracellular traps (NETs) are an innate antimicrobial mechanism wherein granulocytes extrude their chromatin and antimicrobial peptides, including MPO. Nitric oxide synthase (NOS) is also capable of generating the reactive nitrogen species required for HDL oxidation and is highly present in neutrophils. As a subset of lupus granulocytes termed low density granulocytes (LDGs) display an enhanced capacity to form NETs, we hypothesized that the MPO and NOS present in these structures may represent sources of HDL oxidation, thereby leading to vascular damage and acceleration of atherogenesis.

Methods: Two oxidation products, 3-chlorotyrosine and 3-nitrotyrosine were quantified by tandem mass-spectrometry (MS/MS) in plasma and HDL derived from healthy controls and lupus subjects. Site-specific nitration and chlorination of apoA-1 peptides were also quantified by MS/MS. Plasma MPO levels were determined. Isolated NETs from control neutrophils and LDGs were incubated with control, unoxidized HDL in the absence or presence of MPO- and/or NOS-specific inhibitors. The resulting levels of HDL oxidation were then quantified by MS/MS.

Results: Lupus subjects demonstrated higher levels of MPO, and altered HDL function. There was marked increase in 3-nitrotyrosine and MPO-specific 3-chlorotyrosine content in HDL from SLE subjects. Oxidative peptide mapping revealed site-specific unique oxidation signatures on apoA1 in lupus patients. NETs were significant inducers of HDL oxidation, and this phenomenon was enhanced in NETs isolated from LDGs compared to control neutrophils. HDL oxidation by NETs was blocked with incubation of NOS- and/or MPO-specific inhibitors *in vitro*.

Conclusion: Accelerated NET formation by LDGs leads to enhanced HDL oxidation and renders the lipoprotein proatherogenic. These observations further support the concept that aberrant NET formation in lupus leads to damage of the endothelium and promotes atherosclerosis.

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Atherosclerosis and Cardiovascular Disease In Systemic Lupus Eryhematosus Are Related To An Inflammatory/Oxidative Status Linked To The Autoimmune Condition and The Clinical Activity Of The Disease. Effect Of Statins Treatment. Chary Lopez-Pedrera Sr.[1], Patricia Ruiz-Limon[1], Carlos Perez-Sanchez[1], M[a] Angeles Aguirre[1], Nuria Barbarroja[1], Tomás Cerdó-Ráez[2], Maria Laura Bertolaccini[3], Munther A. Khamashta[3], Antonio Rodriguez-Ariza[1], Yolanda Almaden[4], Husam Khraiwesh[5], Jose Antonio Gonzalez-Reyes[6], Jose Manuel Villalba[6], Eduardo Collantes[7] and M[a] Jose Cuadrado[8]. [1]IMIBIC-Reina Sofia Hospital, Cordoba, Spain, [2]Imibic, Córdoba, Spain, [3]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [4]Imibic, Códoba, Spain, [5]UCO, Córdoba, Spain, [6]University of Cordoba, Cordoba, Spain, [7]Hospital Reina Sofia, Cordoba, Spain, [8]The Rayne Institute, London, United Kingdom.

Background/Purpose: Atherosclerosis (AT) and cardiovascular disease (CVD) are enhanced systemic lupus erythematosus (SLE). Although there is evidence that statins have anti-inflammatory properties, their mechanism of

action remains incompletely understood. Aims: i) To determine if the proinflammatory SLE profile is related to their oxidative status, and associated to the autoimmune condition and the clinical disease activity; ii) to test the anti-inflammatory effectiveness of fluvastatin.

Methods: The study was conducted in 85 SLE patients and 62 healthy donors. Flow cytometry, ELISA and enzymatic assays were used to evaluate markers of inflammation and oxidative stress. Carotid-intimate media thickness (CIMT) was used as surrogate marker of AT. Microarray expression profiling was used in paired samples of SLE monocytes from 27 patients before and after of fluvastatin treatment.

Results: Increased TF and PAR2 levels were found in monocytes from SLE patients, which also displayed higher plasma levels of VEGF, IL-2, -6, -8, -17, -23, MCP-1, MIP1α and tPA. SLE monocytes displayed an altered mitochondrial membrane potential (MMP) and increased levels of peroxides, peroxynitrites, and antioxidant enzymes. Correlation and association studies demonstrated the existence of an interplay among parameters related to autoimmunity, oxidative stress and inflammation in the development of the disease and on the increased risk of athero-thrombosis in SLE patients. Real time RT-PCR showed that monocytes were major players in the altered expression of the above mentioned proinflammatory parameters.

The in vivo treatment of SLE patients with fluvastatin for one month led to a significant reduction in the activity of the disease and the levels of anti-dsDNA. Analysis of blood cells and serum showed that one month of fluvastatin treatment effectively attenuated SLEDAI and the lipid levels, and reduced the oxidative status and the vascular inflammation. Array studies on monocytes demonstrated that a total of 799 genes displayed significant changes in expression after 1 month of fluvastatin treatment. Many new target genes and pathways modulated by fluvastatin were uncovered. IPA analysis revealed a network of these genes involved in cholesterol and lipid metabolism, inflammation, oxidative stress and mitochondrial activity. Electron microscopy analysis of mitochondria in monocytes from fluvastatin treated SLE patients showed a significant increase in the number of mitochondria in that cells, pointing at an induced process of mitochondrial biogenesis. The increased expression of a set of genes involved in those processes (i.e. PGC1a, PPAR1a, NRF, Sirt-1) confirmed that hypothesis.

Conclusion: i) Several mediators of autoimmunity, inflammation, and endothelial dysfunction orchestrate in conjunction the pathophysiology of atherothrombosis in SLE ii) A redox-sensitive pathway seems to play a key role in the elicitation of that pathological processes. iii) Fluvastatin has significant anti-inflammatory effects on SLE monocytes, which may partly explain the beneficial pleiotropic effects of statins on cardiovascular disease in the setting of SLE.

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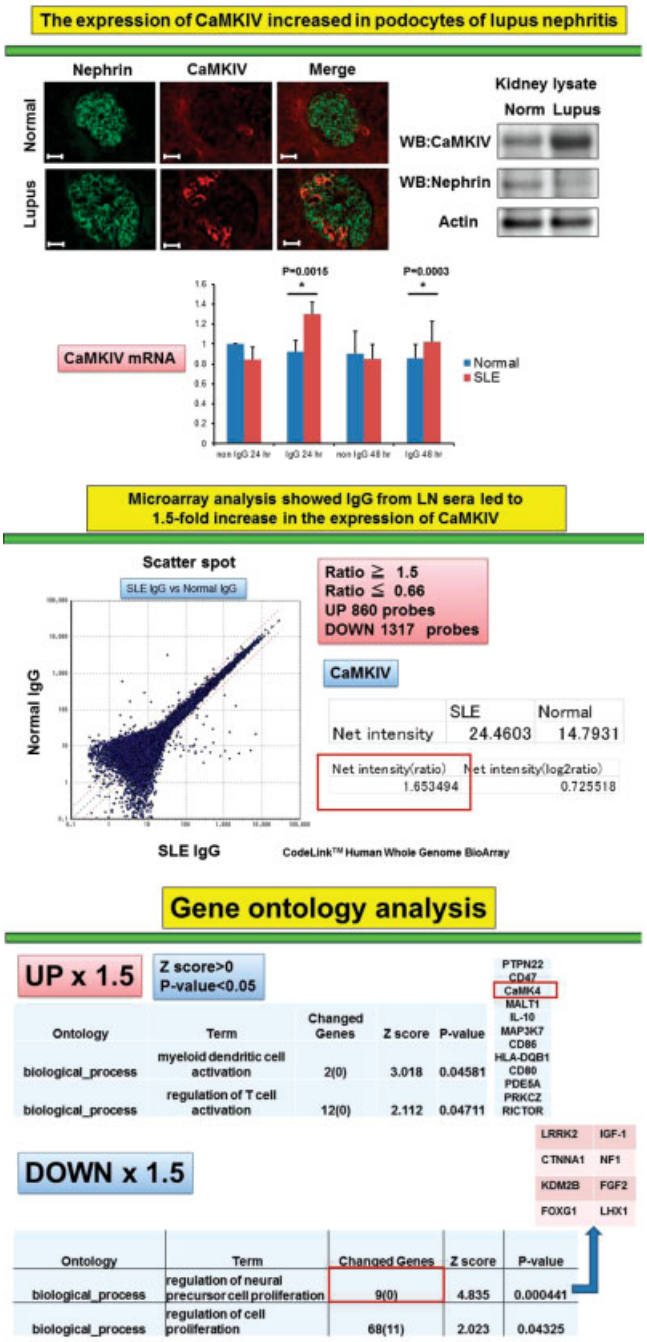
Role of Calcium/Calmodulin Kinase IV On Podocyte Function in Lupus Nephritis. Kunihiro Ichinose[1], Takeshi Ushigusa[2], Tomohiro Koga[3], George C. Tsokos[4] and Atsushi Kawakami[2]. [1]Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [4]BIDMC, Harvard Medical School, Boston, MA.

Role of calcium/calmodulin kinase IV on podocyte function in lupus nephritis

Background/Purpose: Kidney podocytes and their slit diaphragms settle the integrity of renal basement membrane and prevent urinary protein loss. T cell from patients with systemic lupus erythematosus display increased expression of calcium/calmodulin kinase IV (CaMKIV). Here we evaluated the expression of CaMKIV in kidney biopsy specimens from patients with lupus nephritis (LN) and in a human podocyte cell line (AB8/13) after exposure to IgG from sera of patients with LN

Methods: We examined the expression level of nephrin, a podocyte marker and CaMKIV in normal and LN kidney specimens by immunofluorescence staining. We cultured human podocytes with IgG purified from sera of normal individuals and LN patient for 24 hr and analyzed CaMKIV mRNA levels by real time PCR. We also performed microarray analysis to determine gene expression.

Results: Although the expression levels of nephrin were decreased, CaMKIV expression was found increased in podocytes of LN kidney biopsy specimens. The levels of nephrin and CaMKIV correlated in an inverse manner. Interestingly, culture of AB8/13 podocytes in the presence of IgG from LN sera led to 1.5-fold increase in the expression of CaMKIV mRNA. Gene array analysis revealed that the expression of genes related to the cell activation including CaMKIV increased significantly ($P<0.05$) and the regulation of neural precursor cell proliferation decreased significantly ($P<0.01$) in podocytes treated with IgG from LN patients.



Conclusion: Our data demonstrate increased expression of CaMKIV in LN podocytes which may represent the result of exposure to IgG. We suspect that increased CaMKIV expression may contribute to the inability of podocytes to maintain the integrity of glomerular basement membrane in LN patients.

Disclosure: K. Ichinose, None; **T. Ushigusa**, None; **T. Koga**, None; **G. C. Tsokos**, None; **A. Kawakami**, None.

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Podocytes Take Up Adsdna Autoantibody Complexes. Anja Hillmann[1], Elisabeth Jung[1], Annika Engbers[1], Hedda Wardemann[2], Annett M. Jacobi[1] and Thomas Pap[1]. [1]University Hospital Münster, Münster, Germany, [2]Max Planck Institute for Infection Biology, Berlin, Germany.

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease, resulting in inflammation and tissue damage in several organs. This autoimmune reaction is caused by autoantibodies, e.g. against dsDNA (adsDNAabs). Most patients with SLE develop joint pain and about 70% develop renal symptoms, partly with lupus nephritis leading to proteinuria. It is still unclear why the kidney and especially the postmitotic podocytes are involved in such a dramatic manner during SLE.

Methods: Antibodies were isolated from SLE-patients, cloned and produced recombinantly in HEK293 cells. Living podocytes were treated with equal amounts of adsDNAabs and control antibodies in time and concentration dependent experiments and examined by immunofluorescence and Western Blot. To investigate the uptake mechanism, antibodies were pretreated with DNaseI. To analyze the degradation mechanism, treated cells were incubated with e.g. Bafilomycin.

Results: adsDNAabs are taken up by cultivated podocytes selectively in a concentration and time dependent manner and turn up in cytosolic aggregates. After treatment of the antibodies with DNAseI, the uptake decreases significantly. In recovery experiments, we could show that these aggregates are eliminated over time in media without adsDNAabs. The aggregates co-localize with different autophagy related proteins. Western Blot analyzes show that autophagy is upregulated after treatment with adsDNAabs. The degradation of adsDNAabs is reduced in experiments under autophagy inhibiting conditions (treatment with Bafilomycin A) and number of aggregates after the inhibition of autophagy rises significantly up to twofold. The number of aggregates of podocytes treated with a control antibody or antibodies against other autoantigens (e.g. Ro) is almost zero.

Conclusion: Podocytes are postmitotic and highly complex cells. Loss of these cells leads to kidney injury and proteinuria. During lupus-nephritis, podocytes are destroyed. We could show that these cells take up adsDNAabs selectively in a complex with their target and are harmed by these antibody-aggregates. Our results indicate that the antibody-complexes in the cells are degraded via autophagy. This should be considered for future therapeutic approaches in lupus nephritis.

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Quantitative Cell Distance Mapping In Human Nephritis Reveals Organization Of *In Situ* Adaptive Immune Responses. Marcus R. Clark, Vladimir M. Liarski, Natalya Kavernia, Maryellen L. Giger, Anthony Chang, Yahui Peng and Daniel F. Brandt. University of Chicago, Chicago, IL.

Background/Purpose: Inflammatory infiltrates contain multiple cell types that could interact in myriad ways to amplify *in situ* immune responses. However, there currently are no methods available to quantitatively assess such interactions in human tissue.

Methods: Therefore, we developed a novel computational approach which we term cell distance mapping (CDM) that, when coupled to confocal microscopy, enabled us to quantitatively assess the spatial relationships between different cell populations.

Results: When applied to human lupus nephritis (LuN), CDM revealed that T follicular helper (T_{FH})-like cells commonly infiltrated the renal tubulointerstitium with almost half in cognate pairs with B cells. Furthermore, in the absence of evident germinal center (GCs), the overall spatial organization of B cells and T_{FH} cells in LuN was similar to that observed in tonsil GC light zones. T_{FH}-like cells ($CD4^+ICOS^+PD\text{-}1^+$) were also observed in T cell-mediated renal transplant rejection (TCMR) cases. However, the T_{FH}-like cells in TCMR infrequently formed cognate pairs with B cells. Furthermore, the TCMR T_{FH}-like cells did not organize the B cells around them. Finally, while IL-21 expression was high in tonsil GC and LuN T_{FH}-like cells, it was barely detectable in the T_{FH}-like cells infiltrating the tubulointerstitium in TCMR.

Conclusion: These results suggest that even in areas of diffuse inflammation, CDM reveals cellular organizations and inter-cell interactions associated with *in situ* adaptive immunity. Furthermore, we propose that CDM can discriminate between functional and non-functional T_{FH} cells *in situ*.

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ACR Concurrent Abstract Session
Vasculitis I

Sunday, October 27, 2013, 4:30 PM–6:00 PM

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A Single Amino Acid In The β1 Chain Of HLA-DR Explains The Majority Of The HLA Association With Giant Cell Arteriti. Javier Martin[1], F. David Carmona[2], Jose Ezequiel Martin[3], Aurora Serrano[1], Lara Bossini-Castillo[1], Roser Solans[4], Jose A. Miranda-Filloy[5], Santos Castañeda[6], Maria C. Cid[7], Jose A. Hernandez[8], Inmaculada C. Morado[9], Javier Narvaez[10], Ricardo Blanco[11], Bernardo Sopeña[12], M. Jesus García-Villanueva[13], Jordi Monfort[14], Norberto Ortego-Centeno[15], Ainhoa Unzurrunzaga[16], Begoña Marí-Alfonso[17], Cesar Magro[15], Ana Hidalgo-Conde[18], Marta Conde-Jaldon[19], María F. González-Escribano[19], Paul de Bakker[20], Bobby P.C. Koeleman[21] and Miguel A. González-Gay[22]. [1]Instituto de Parasitologia y Biomedicina Lopez-Neyra (IPBLN-CSIC), Granada, Spain, [2]Consejo Superior de Investigaciones Científicas, Armilla (Granada), Spain, [3]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Granada, Spain, [4]Hospital Vall d'Hebron, Barcelona, Spain, [5]Hospital Xeral-Calde, Lugo, Spain, [6]Hospital Universitario de La Princesa, IIS Princesa, Madrid, Spain, [7]Hospital Clínic. University of Barcelona. IDIBAPS, Barcelona, Spain, [8]Hospital Clinic. University of Barcelona, IDIBAPS,, Barcelona, Spain, [9]Hospital Clínico San Carlos, Madrid, Spain, [10]Hospital Universitario de Bellvitge, Barcelona, Spain, [11]Hospital Universitario Marqués de Valdecilla, IFIMAV, Santander, Spain, [12]Complejo Hospitalario Universitario de Vigo (CHUVI), Vigo, Spain, [13]Hospital Ramón y Cajal, Madrid, Spain, [14]Hospital del Mar, Barcelona, Spain, [15]Hospital Clínico San Cecilio, Granada, Spain, [16]Hospital de Galdakano, Vizcaya, Spain, [17]Corporació Sanitaria Parc Taulí, Instituto Universitario Parc Taulí, UAB, Sabadell, Spain, [18]Hospital Universitario Virgen de la Victoria, Málaga, Spain, [19]Hospital Universitario Virgen del Rocío, Sevilla, Spain, [20]University Medical Center Utrecht, Utrecht, Netherlands, [21]Department of Medical Genetics, UMCU Utrecht, Utrecht, Netherlands, [22]Hospital Universitario Marqués de Valdecilla. IFIMAV. Santander. Spain, Santander, Spain.

Background/Purpose: Giant cell arteritis (GCA) is a polygenic inflammatory disease affecting medium- and large-sized blood vessels in people elder than 50-years old. Although it is clear that GCA has an important genetic component, very little is known about the genetic susceptibility to this vasculitis. In order to better understand the genetic association of the HLA region with this disease, we aimed to carried out for the first time a comprehensive fine-mapping of this genomic region to identify the causative variants and/or amino acids responsible for the GCA predisposition.

Methods: 556 biopsy-proven GCA patients and 1,951 controls from Spanish Caucasian ancestry were genotyped using the *Illumina Infinium Immunochip* genotyping platform. Subsequently, we isolated the genotyping data from the extended major histocompatibility complex (xMHC) region, located in chromosome 6, and used a previously validated imputation method to analyze the variation within the xMHC region of single-nucleotide polymorphisms (SNPs), classical HLA alleles and variable amino acids. For the imputation, we used the Beagle software and a reference panel comprised of 5,225 individuals of European origin with genotyping data of about 8,961 common SNPs and insertion-deletion polymorphisms across the xMHC region, and four digits genotyping data of the HLA class I and II molecules. Control quality filters were performed with the Eigensoft and Plink software.

Results: The accuracy reached after comparing 4 digit types with the corresponding imputed data was >90% for *HLA-DQA1*, *HLA-DRB1* and *HLA-B*. As expected, one of the highest association peaks was HLA-DRB1*0404 (P=1.97×10–11, OR=2.91, CI 95%=2.13–3.98), but HLA-DQA1*0301 was also firmly associated (P=4.81×10-09, OR=1.70, CI 95%=1.42–2.03). Consequently, different amino acid positions of both DRβ1 and DQα1 chains were strongly associated with disease predisposition ($P<5\times10$-8). However, the presence of a histidine in the position 13 of the DRβ1 molecule defined almost all the association of the HLA region with GCA. Only the addition of an arginine amino acid at position 56 of the

HLA-DQα1 chain improved marginally the model (likelihood-P=0.018). Both amino acids are located in the binding pocket of their corresponding molecule and, therefore, may interact with the antigen.

Conclusion: Our results show that one amino acid located at the binding pocket of the HLA-DRβ1 chain is responsible for almost all the HLA association with GCA.

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The Functional *PTPN22* Variant R620W Is Strongly Associated With Giant Cell Artetitis Predisposition. F. David Carmona[1], Sarah L. Mackie[2], Aurora Serrano[3], Ana Marquez[4], Roser Solans[5], Jose A. Miranda-Filloy[6], Jose Hernández-Rodríguez[7], Maria C. Cid[7], Santos Castañeda[8], Inmaculada C. Morado[9], Javier Narvaez[10], Ricardo Blanco[11], Bernardo Sopeña[12], M. Jesus García-Villanueva[13], Jordi Monfort[14], Norberto Ortego-Centeno[15], Ainhoa Unzurrunzaga[16], Begoña Marí-Alfonso[17], Julio Sánchez-Martín[18], Eugenio de Miguel[19], Cesar Magro[15], Enrique Raya[20], Niko Braun[21], Joerg Latus[21], Øyvind Molberg[22], Benedicte A. Lie[22], Frank Moosig[23], Torsten Witte[24], Ann W. Morgan[2], Miguel A. González-Gay[11] and Javier Martin[3]. [1]Consejo Superior de Investigaciones Científicas, Armilla (Granada), Spain, [2]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [3]Instituto de Parasitologia y Biomedicina Lopez-Neyra (IPBLN-CSIC), Granada, Spain, [4]Instituto de Parasitología y Biomedicina 'López-Neyra' (IPBLN-CSIC), Granada, Spain, [5]Hospital Vall d'Hebron, Barcelona, Spain, [6]Hospital Xeral-Calde, Lugo, Spain, [7]Hospital Clínic. University of Barcelona. IDIBAPS, Barcelona, Spain, [8]Hospital Universitario de La Princesa, IIS Princesa, Madrid, Spain, [9]Hospital Clínico San Carlos, Madrid, Spain, [10]Hospital Universitario de Bellvitge, Barcelona, Spain, [11]Hospital Universitario Marqués de Valdecilla. IFIMAV. Santander. Spain, Santander, Spain, [12]Complejo Hospitalario Universitario de Vigo (CHUVI), Vigo, Spain, [13]Hospital Ramón y Cajal, Madrid, Spain, [14]Hospital del Mar, Barcelona, Spain, [15]Hospital Clínico San Cecilio, Granada, Spain, [16]Hospital de Galdakano, Vizcaya, Spain, [17]Corporació Sanitaria Parc Taulí, Instituto Universitario Parc Taulí, UAB, Sabadell, Spain, [18]Hospital Universitario 12 de Octubre, Madrid, Spain, [19]Hospital Universitario La Paz, Madrid, Spain, [20]University Hospital San Cecilio, Granada, Spain, [21]Division of Nephrology, Robert-Bosch-Hospital, Stuttgart, Germany, [22]Oslo University Hospital, Oslo, Norway, [23]University of Luebeck, Bad Bramstedt, Germany, [24]Medical University Hannover, Hanover, Germany.

Background/Purpose: The *PTPN22*/*CSK* signaling represents one of the common susceptibility pathways in autoimmunity. Considering that the genetic basis of giant cell arteritis (GCA), an autoimmune vasculitis of complex etiology, remains poorly understood, we decided to analyze whether variations within the *PTPN22* and *CSK* genes are associated with GCA predisposition and/or severity in a well-powered case/control cohort.

Methods: The study comprised a discovery cohort from Spanish Caucasian ancestry of 623 biopsy-proven GCA cases and 1,729 unaffected controls, and a replication Caucasian cohort from three different European countries (UK, Norway and Germany) consisting of 288 biopsy-proven GCA patients and 6,407 unaffected controls. Two non-synonymous functional *PTPN22* polymorphisms (rs24746601/R620W and rs33996649/R263Q) and two additional *CSK* variants that have been associated with systemic sclerosis (rs1378942) and systemic lupus erythematosus (rs34933034) were genotyped using TaqMan© probes. The statistical analyses were performed with Plink.

Results: A clear association of the *PTN22* classical polymorphism rs24746601/R620W with GCA was observed in the discovery cohort, which was maintained after FDR correction for multiple testing (corrected P=1.06E-04, OR=1.62, CI 95%=1.29–2.04). This association was further confirmed in the replication set of independent European cohorts, whose meta-analysis also reached statistical significance (P_{MH}=0.015, OR=1.38, CI 95%=1.07–1.77). A strong association signal was observed when the four European cohorts were combined (P_{MH}=2.00E-06, OR=1.51, CI 95%=1.28–1.79). The comparison between the analysed clinical phenotypes (*i.e*. polymyalgia rheumatica, visual ischemic manifestations, and irreversible occlusive disease) and the control set also yielded significant *P*-values for *PTPN22* R620W; however, no association was observed when the GCA cases positive and negative for each clinical characteristic were compared, suggesting that this *PTPN22* variant is associated with the whole disease. None of the other analyzed polymorphisms showed evidence of association either with the global disease or with the different phenotypes.

Conclusion: Our results clearly indicate that the autoimmune-disease associated *PTPN22* polymorphism rs24746601/R620W confers risk to develop GCA.

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Association Between Human Leukocyte Antigen-B's Amino Acid Variation and Disease-Susceptibility To Takayasu's Arteritis. Hajime Yoshifuji[1], Chikashi Terao[1], Kosaku Murakami[1], Daisuke Kawabata[1], Koichiro Ohmura[1], Takao Fujii[1], Yasushi Kawaguchi[2], Hisashi Yamanaka[2] and Tsuneyo Mimori[1]. [1]Graduate School of Medicine, Kyoto University, Kyoto, Japan, [2]Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: HLA-B52 and HLA-B51 are frequently seen in Asian population and are almost identical except two amino acid residues(the 63rd and 67th), but HLA-B52 is related with susceptibility to Takayasu's arteritis (TAK) while HLA-B51 is related with susceptibility to Behçet's disease. To understand the mechanisms, we analyzed the variation of HLA-B amino acid sequences in TAK patients.

Methods: We collected DNA of 173 TAK patients from Kyoto University Hospital and Tokyo Women's Medical University Hospital, genotyped their HLA-B alleles, and compared them with those of 2000 healthy controls.

Results: HLA-B52 was strongly related with TAK susceptibility ($P < 0.000000000000001$), while HLA-B51 was not ($P = 0.39$). Analysis of HLA-B's amino acid variations revealed that 171H (histidine at 171st position) compared with 171Y was a risk factor ($P < 0.00000001$), and 67F compared with 67notF (S, Y, C or M) was a protective factor ($P < 0.0001$) of TAK susceptibility. Both the 171st and 67th amino acids are located at the groove of HLA-B protein, implying immune response is related to the pathogenesis. Both HLA-B52 and HLA-B51 have the TAK-susceptible 171H. While HLA-B52 has the TAK-susceptible 67S, HLA-B51 has the protective 67F. That is a plausible reason why HLA-B51 was not related with TAK susceptibility. Besides, we also searched for single nucleotide polymorphisms (SNPs) of non-HLA genes that related to TAK susceptibility and found several candidates of genes.

Conclusion: The difference of HLA-B's 67th amino acid residue was supposed to divide the susceptibilities to TAK or Behçet's disease. Further analyses are needed to know what kind of peptides show affinities to the HLA-B's groove.

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Intermittent Fever, Immune Dysregulation, and Systemic Vasculopathy Due To Loss-Of-Function Mutations In Adenosine Deaminase2. Qing Zhou[1], Dan Yang[2], Andrey Zavialov[3], Amanda Ombrello[1], Hyesun Kuehn[4], Jae Jin Chae[1], Anton Zavialov[3], David Chin[1], Deborah Stone[1], Camilo Toro[1], Joshua Milner[5], Chyi-chia Lee[6], Edward Cowen[6], Fabio Candotti[1], Elaine Remmers[1], Susan Moir[5], Raman Sood[1], Shawn Burgess[1], Massimo Gadina[7], Sergio Rosenzweig[5], Michael Hershfield[8], Daniel L. Kastner[1], Manfred Boehm[2] and Ivona Aksentijevich[1]. [1]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [2]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, [3]University of Turku, Turku, Finland, [4]Clinical Center, National Institutes of Health, Bethesda, MD, [5]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, [6]National Cancer Institute, National Institutes of Health, Bethesda, MD, [7]National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD, [8]Duke University Medical Center, Durham, NC.

Background/Purpose: We observed a syndrome characterized by intermittent fevers and livedoreticularis, systemic inflammation, hepatosplenomegaly, cytopenias, vasculopathy, and early-onset lacunar strokes in five unrelated patients. We suspected a genetic cause because the disorder presented in early childhood.

Methods: We performed whole-exome and candidate gene sequencing on the patients and their unaffected parents. Patient samples were analyzed by ELISA, immunoblotting, immunohistochemistry, flow cytometry, and cytokine profiling. Morpholino knockdowns in zebrafish embryos were used to study gene function.

Results: Our patients were compound heterozygous for 5 missense mutations(G47A, A109D, H112Q, R169Q, Y453C) anda 28kb genomic deletion in *CECR1* encoding adenosine deaminase2 (ADA2).All mutations are either novel or present at low frequency (<0.001) in several large databases, consistent with the recessive inheritance. The Y453C mutation was present in an NHLBI exomedatabase in 2 siblings who suffered from late-onset ischemic stroke. This finding indicatesthat heterozygous mutations in ADA2 might be associated with susceptibility to adult stroke.Computer modeling based on the crystal structure of the human ADA2 suggests that *CECR1* mutations either disrupt protein stability or impair ADA2 enzyme activity. Patients had at least a 10-fold reduction in blood ADA2, and dramatically reduced ADA2-specific adenosine deaminase activity in blood and $CD14^+$ monocytes. In contrast to patients with ADA1 deficiency and severe combined immunodeficiency, there was no accumulation of deoxyadenosine or its toxic metabolites in patients' blood suggesting new functional role of ADA2 addition to its enzyme activity. *cecr1b*knockdown caused intracranial hemorrhages in zebrafish embryossuggesting defects in vessel development.The intracranial hemorrhage phenotype was rescued with wild type human *CECR1* mRNA, but not by the R169Q mutant mRNA.Skin, liver, and brain biopsies from patients showed a diffuse vasculopathy, with evidence of impaired endothelial integrity and endothelial cellular activation.

Conclusion: Recessive mutations in *CECR1* cause ADA2 deficiency manifesting with diffuse vasculopathy, systemic inflammation, and early-onset stroke. Ex vivo experiments with patients' cells, in vitro cell culture studies, and animal model data suggest an important role for ADA2 in vascular and leukocyte development, consistent with its proposed role as a growth factor.ADA2 replacement with the fresh frozen plasma transfusions, enzyme therapies with recombinant ADA2, gene therapy, and hematopoietic stem cell transplantation are possible treatment options.

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The Relative Risk Of Aortic Aneurysm In Patients With Giant Cell Arteritis Compared With The General Population. Joanna Robson[1], Amit Kiran[2], Joseph Maskell[3], Andrew Hutchings[4], Nigel K. Arden[5], Bhaskar Dasgupta[6], William Hamilton[7], Akan Emin[8], David Culliford[3] and Raashid A. Luqmani[2]. [1]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford, United Kingdom, [2]University of Oxford, Oxford, United Kingdom, [3]University of Southampton, Southampton, United Kingdom, [4]London School of Hygiene and Tropical Medicine, London, United Kingdom, [5]Oxford NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, United Kingdom, [6]Southend University Hospital, Westcliff-on-sea, United Kingdom, [7]University of Exeter Medical School, Exeter, United Kingdom, [8]The Royal College of Surgeons of England, London, United Kingdom.

Background/Purpose: To evaluate the risk of aortic aneurysm in patients with giant cell arteritis (GCA) when compared with age, gender and location matched controls from the general population.

Methods: Parallel cohort study. General Practice Research Database (GPRD). 6999 men and women with giant cell arteritis (GCA). Non-GCA patients matched on a 6:1 ratio on the following three parameters: same GP practice, year of birth (+/− 3 years) and gender. A competing risk model using aortic aneurysm as the primary outcome and death as the competing risk, was used to determine the relative risk (subhazard ratio) between non-GCA and GCA subjects, after adjustment for cardiovascular risk factors.

Results: Comparing the GCA cohort with the non-GCA cohort, using a multivariable model with adjustment for BMI, smoking, alcohol, hyperlipidaemia, lipid lowering medication, hypertension, anti-hypertensives, diabetes, cardiovascular disease, cerebrovascular disease and peripheral vascular disease; the subhazard ratio for aortic aneurysm (95% CI) was 1.92 (1.52 to 2.41). Significant predictors of aortic aneurysm were as follows:being an ex-smoker 2.64 (2.03 to 3.43), current smoker 3.37 (2.61 to 4.37), previous prescription of anti-hypertensives 1.57 (1.23 to 2.01), previous history of diabetes 0.32 (0.19 to 0.56) and previous history of cardiovascular disease 1.98 (1.50 to 2.63). In a multivariable model of the GCA cohort alone, male gender 2.10 (1.38 to 3.19), smoking 3.79 (2.20 to 6.53), and diabetes 0.19 (0.05 to 0.77) were significant predictors of aortic aneurysm.

Table 1. Subhazard ratios (95% CI) using the competing risk model for each non-GCA/GCA cohort (imputed data)

	non-GCA (n=41994)		GCA (n=6999)	
Characteristics	**univariable**	**multivariable**	**univariable**	**multivariable**
Age (years)	1.03 (1.02, 1.04)***	1.00 (0.99, 1.02)	0.99 (0.98, 1.00)+	0.97 (0.94, 1.00)
Age caregories (reference <65 years)	3.30 (2.23, 4.89)***	3.21 (1.86, 5.53)***	1.04 (0.66, 1.63)	2.14 (0.95, 4.80)
BMI ($kg \cdot m^{-2}$)	0.99 (0.97, 1.02)	1.00 (0.97, 1.03)	0.99 (0.95, 1.03)	1.00 (0.96, 1.04)
Gender (reference female)	3.95 (3.11, 5.01)***	3.49 (2.70, 4.,52)***	2.36 (1.59, 3.49)***	2.10 (1.38, 3.19)**
Smoking (Reference no)				
ex	3.02 (2.24, 4.08)***	2.08 (1.52, 2.85)***	2.58 (1.49, 4.47)**	2.20 (1.22, 3.98)**
yes	3.02 (2.21, 4.13)***	3.00 (2.17, 4.14)***	4.24 (2.50, 7.16)***	3.79 (2.20, 6.53)***
Alcohol (reference no)				
ex	1.66 (0.90, 3.03)*	1.16 (0.63, 2.14)	0.68 (0.20, 2.34)	0.62 (0.19, 1.99)
yes	1.28 (0.85, 1.92)	0.94 (0.62, 1.43)	1.26 (0.72, 2.21)	0.91 (0.52, 1.60)
Previous history of hyperlipidaemia	1.88 (1.14, 3.11)*	1.37 (0.80, 2.34)	1.04 (0.38, 2.82)	1.19 (0.40, 3.53)
Previous prescription of lipid lowering medication	1.97 (1.44, 2.71)***	1.21 (0.83, 1.76)	0.77 (0.37, 1.60)	0.69 (0.31, 1.50)
Previous history of hypertension	1.16 (0.89, 1.51)	0.92 (0.68, 1.24)	0.91 (0.57, 1.43)	0.93 (0.55, 1.58)
Previous prescription of anti-hypertensives	1.72 (1.36, 2.16)***	1.42 (1.06, 1.89)*	1.23 (0.83, 1.83)	1.62 (1.00, 2.61)*
Previous history of diabetes	0.54 (0.30, 0.97)*	0.32 (0.18, 0.58)***	0.22 (0.05, 0.88)*	0.19 (0.05, 0.77)*
Previous history of cardiovascular disease	2.83 (2.10, 3.81)***	1.65 (1.20, 2.29)**	1.38 (0.77, 2.47)	1.28 (0.72, 2.29)
Previous history of cerebrovascular disease	1.36 (0.88, 2.09)+	09.88 (0.56, 1.38)	0.82 (0.38, 1.77)	0.79 (0.36, 1.73)
Previous history of peripheral vascular disease	2.93 (1.68, 5.13)***	1.84 (1.04, 3.25)*	0.70 (0.17, 2.86)	0.68 (0.17, 2.72)

+p-values <0.2, *p-value <0.05, **p-value <0.01, ***p-value <0.0005.

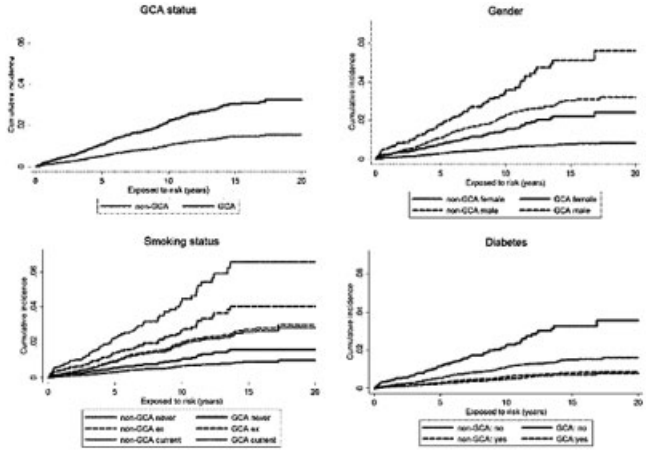

Figure 1. Cumulative incidence of AA events

Conclusion: This study demonstrates a two-fold increased risk of aortic aneurysm in patients with GCA. Other risk factors for aortic aneurysm, including male gender, age, and smoking, are important in patients with GCA and the general population. The message for clinicians and policymakers is therefore that the diagnosis of GCA should be considered within the context of the range of risk factors for aortic aneurysm, rather than acting as a prompt for a specific screening programme. This study also demonstrates for the first time the protective effect of diabetes in the development of aortic aneurysms in patients with GCA.

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Increased Rho Kinase (ROCK) Activity In Temporal Artery Biopsies From Patients With Giant Cell Arteritis (GCA). Lindsay Lally[1], Navneet Narula[2], Alessandra B. Pernis[1], Wei-Ti Huang[1], Uzunma Udeh[1] and Robert F. Spiera[1]. [1]Hospital for Special Surgery, New York, NY, [2]Weill Cornell Medical College, New York, NY.

Background/Purpose: ROCKs are implicated in the pathogenesis of many vascular diseases. ROCK activation is associated with Th17 differentiation and production of Th17-associated cytokines, IL-17 and IL-21. Th17 cells and related cytokines are present in increased levels in the vascular inflammatory infiltrate in active GCA. ROCK activity in GCA is unknown. The aim of this study was to assess ROCK activity in temporal artery biopsy (TAB) specimens in GCA versus controls.

Methods: All TAB performed at a tertiary care center over a 5 year period were identified. Charts were reviewed for clinical information; included subjects had TAB specimens and clinical information available. Subjects were categorized according to 1990 ACR criteria and TAB status into 3 groups: GCA with positive TAB, GCA with negative TAB and age-sex-matched controls.

Paraffin-embedded temporal artery specimens were stained for Phospho-Ezrin/Radixin/Moesin (pERM), a surrogate of ROCK activity, using immunohistochemical (IHC) stain. IHC stained slides were reviewed by a pathologist blinded to clinical status. Three separate areas (endothelium, adventitia and vaso vasorum) were scored for intensity of staining on a scale of 0–2 for total possible composite score of 6. Primary outcome was biopsy pERM intensity score in subjects with GCA compared to controls.

Results: Nineteen subjects with GCA had positive TAB, 17 subjects had GCA with negative TAB and18 age-sex-matched controls were analyzed. Mean age was 77.9±9.1years and 81.4% were female (Table 1). Biopsy pERM intensity scores ranged from 2–6 with 28.3% scores ≤4 and 72.2% of scores >4 (high). 79.4% of high scores occurred in GCA subjects compared to controls (p=0.0033). Compared to controls, GCA subjects with either positive or negative TAB showed statistically significantly higher pERM intensity scores (p=0.035 and p=0.0083 respectively). Adjusting for comorbid diabetes, hypertension, prednisone use, and statin use, GCA subjects still had significantly higher pERM intensity scores compared to controls (OR 7.3; 95%CI 1.9–25.9, p=0.0046). High score for diagnosis of GCA had sensitivity of 86%, specificity of 55.6%. Comparing GCA with negative TAB to controls, high score had sensitivity of 90.4% and negative predictive value of 90.9%.

Table 1.

	GCA (n=36)			
	Biopsy Positive (n=19)	Biopsy Negative (n=17)	Control (n=18)	P value
Age, yr± SD	78.4±9.2	76.6±7.9	78.4±10.5	0.81
Female, n (%)	14 (74)	16 (94)	13 (72)	0.2
Prednisone Dose mg, mean±SD	55.6±17.9	50.6±17.1	47.2±27.2	0.5
Hypertension, n (%)	8 (44)	10 (59)	12 (67)	0.39
Diabetes, n (%)	1 (6)	6 (35)	4 (22)	0.11
Statin, n (%)	5 (28)	8 (47)	11 (61)	0.13
IHC score				0.0159
≤4	4 (21)	1 (6)	10 (56)	
>4	15 (79)	16 (94)	8 (44)	

Conclusion: Subjects with GCA had more intense pERM staining in TAB specimens compared to age and sex-matched controls regardless of whether TAB was positive or negative, independent of prednisone dose, statin use, or vascular comorbidities. In this population, high pERM staining score had a sensitivity comparable to what is reported as sensitivities of TAB routine histopathology itself and suggests it may be a useful adjunctive diagnostic tool especially in patients with suspected GCA and negative TAB. The ROCK pathway warrants further investigation in GCA as inhibition of this pathway is a potential therapeutic target.

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Characterization Of Low Back Symptoms In a Community-Based Sample Of Older Adults: The Johnston County Osteoarthritis Project. Adam P. Goode[1], Kelli D. Allen[2], Timothy S. Carey[3] and Joanne M. Jordan[4]. [1]Duke University, Durham, NC, [2]Duke and Durham VA Medical Center, Durham, NC, [3]Cecil G. Sheps Center for Health Services Research University of North Carolina, Chapel Hill, NC, [4]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC.

Background/Purpose: The majority of research in low back pain has focused on the middle-aged segment of the population. As such, there is a gap in knowledge about low back pain among older adults (>=65 years). The purpose of these analyses is to describe differences in clinical characteristics between older adults with and without low back symptoms.

Methods: The sample for these analyses consists of 1,010 participants >=65 years of age who participated in the Johnston County Osteoarthritis Project from 2008–11. Participants had a mean age of 74.1 (SD 6.5), 69% were female, 29% were African American, and had mean body mass index (BMI) of 30.4 (SD 6.4). Low back symptoms were defined at clinical interview by "On most days do you have the symptoms of pain, aching or stiffness in your lower back?" General function was measured with the Health Assessment Questionnaire (HAQ) and, among those with reported low back symptoms, disease specific function with the Roland-Morris Low Back Pain Disability Questionnaire (RMDQ). The Centers for Epidemiological Questionnaire Scale (CES-D) was categorized at <16 or >=16 to represent mild depressive symptoms. Self-reported physical activity was measured as moderate (i.e., at least 10 minutes at a time, such as brisk walking, bicycling, vacuuming, gardening or anything else that causes small increases in breathing or heart rate) or vigorous (i.e., at least 10 minutes at a time, such as running, aerobics, heavy yard work, or anything else that causes large increases in breathing or heart rate). Lateral lumbar spine films were graded at each lumbar level in a semi-quantitative fashion (0–3) for disc space narrowing (DSN) and osteophytes (OST) according to the Burnett Atlas. Differences were determined by Chi-square tests.

Results: Fifty-nine percent (n=599) of older adults reported the presence of low back symptoms. The Table provides sample sizes, proportions and p-values for each clinical characteristic by low back symptom status. Among those with low back symptoms, self-reported general function (i.e., HAQ) was significantly (p<0.001) lower, depressive symptoms were significantly (p<0.001) greater and the reported mean RMDQ score was 7.6 (SD 6.9), indicating a perceived 31.7% disability. Those with low back symptoms were less likely (p=0.03) to report participation in weekly moderate physical activity. A similar finding was present with vigorous activity but not statistically significant. Particpants with low back symptoms had more severe DSN (p=0.04), whereas OST severity was similar between the groups.

Characteristic	No Low Back Symptoms	Low back symptoms	p-value
HAQ, n (%)			<0.001
0	114 (27.0%)	60 (16.2%)	
1	194 (45.9%)	118 (31.9%)	
2	115 (27.2%)	192 (51.9%)	
CES-D, n (%)			<0.001
<16	544 (93.8%)	334 (86.3%)	
>=16	36 (6.2%)	53 (13.7%)	
Moderate Physical Activity	423 (70.6%)	251 (64.0%)	0.03
Vigorous Physical Activity	72 (14.1%)	35 (10.6)	0.08
DSN, n (%)			0.04
0	117 (20.3%)	55 (14.4%)	
1	183 (31.7%)	115 (30.2%)	
2	150 (26.0%)	104 (27.3%)	
3	127 (22.0%)	107 (28.1%)	
OST, n (%)			0.10
0	45 (9.1%)	18 (5.3%)	
1	242 (49.0%)	160 (47.5%)	
2	142 (28.7%)	117 (34.7%)	
3	65 (13.2%)	42 (12.5%)	

Conclusion: These findings highlight the impact low back symptoms have across multiple health domains in older adults. Interventions to increase

physical activity have been shown to improve multiple outcomes among middle-aged adults, but the effectiveness is unknown in older adults. Clinical trials of physical activity are needed in this subgroup, which is particularly susceptible to declining general function.

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Sex-Specific Employment Participation Restriction Across Occupational Groups Among Working-Age (18–64 years) U.S. Adults With and Without Arthritis. Kristina A. Theis[1] and Louise Murphy[2]. [1]Centers for Disease Control and Prevention, Atlanta, GA, [2]CDC, Atlanta, GA.

Background/Purpose: Previous research has shown arthritis-attributable work limitation to be high (~30%) among U.S. adults with arthritis and for employment to be ~20% lower among adults with arthritis compared with those without arthritis. Women with arthritis typically are less likely to be employed than women without arthritis and all men. The purpose of this study is to estimate, for the first time, the overall and sex-specific prevalence of employment participation restriction (PR) among adults ≥18 years with and without arthritis and also to examine differences by occupational groups.

Methods: 2011 National Health Interview Survey (NHIS) data were analyzed (Adult Functioning and Disability Supplement and Sample Adult Core [n = 16,540; response rate = 63%]). NHIS is an annual, multistage probability survey by in-person interview designed to represent the U.S. civilian, non-institutionalized population. Arthritis diagnosis was identified by "Have you ever been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?" Several activities were queried with the root: "For each of the following activities, please tell me if you do the activity, don't do the activity, or are unable to do the activity." Employment PR was ascertained by a response of "unable to do" for the activity: "Working outside the home to earn an income." Five major occupational groups were categorized according to Bureau of Labor Statistics classifications: 1) management, professional, and related; 2) service; 3) sales and office; 4) natural resources, construction, and maintenance; 5) production, transportation, and material moving. Occupation among those who were working/had ever worked was classified based on their current/most recent job. Weighted proportions with 95% confidence intervals (CI) were calculated accounting for complex sample design (SAS 9.2).

Results: Overall, 5.9% (5.4–6.4) of respondents reported employment PR; the proportion was approximately four times higher among those with arthritis (17.5% [5.8 million]) compared with those without arthritis (3.5% [5.5 million]). For each occupational group, employment PR was 2.5–8 times greater among those with arthritis(Table). Among those with arthritis, the group with the greatest sex-specific difference was production, transportation, and material moving, with employment PR approximately double among women (32.0%) compared with men (14.9%).

Prevalence of Participation Restriction in Employment by Arthritis Status, Sex, and Occupational Group among Working-Age (18–64 year old) U.S. Adults, NHIS, 2011

	Men				Women			
	Arthritis		No Arthritis		Arthritis		No Arthritis	
Occupational Group	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Management, professional, & related	6.8	3.8–9.7	N/A	–	9.7	6.8–12.6	1.5	0.9–2.2
Service	18.0	11.2–24.8	2.0	0.8–3.1	26.4	21.4–31.4	4.0	2.8–5.1
Sales & office	15.1	9.6–20.6	3.6	2.1–5.1	19.1	14.5–23.7	3.2	2.3–4.1
Natural Resources, construction, & maintenance	19.8	13.4–26.2	4.3	2.7–5.8	N/A	–	N/A	–
Production, transportation, & material moving	14.9	10.5–19.3	5.8	3.8–7.8	32.0	23.0–41.0	5.9	3.2–8.6

Conclusion: High prevalence of employment PR for people with arthritis across all occupational groups compared with their non-arthritis peers indicates greater employment PR burden; women have higher employment PR burden than men. Exploration of effective interventions to reduce employment PR, including potential differences in benefits by sex, is necessary to mitigate the negative effects of employment PR.

Disclosure: K. A. Theis, None; **L. Murphy**, None.

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Foot Pain, But Not Foot Structure Or Foot Function, Are Associated With Self-Reported Physical Limitations: The Framingham Foot Study. Alyssa B. Dufour[1], Patricia P. Katz[2], Virginia A. Casey[3], Marian T. Hannan[1] and Hylton B. Menz[4]. [1]Hebrew SeniorLife & Harvard Medical School, Boston, MA, [2]University of California, San Francisco, San Francisco, CA, [3]Hebrew SeniorLife, Boston, MA, [4]La Trobe University, Bundoora, Victoria 3086, Australia.

Background/Purpose: The purpose of this cross-sectional study was to examine the relation between self reported physical limitations and foot pain, foot structure and foot function in older men and women of the Framingham Foot Study (FFS).

Methods: 1860 participants in the FFS completed the foot questionnaire, which included foot pressure measurements and questions on physical limitations. The presence of foot pain was defined (y/n) using the question "On most days, do you have pain, aching, or stiffness in either of your feet?" Foot structure and foot function were defined using standing and walking foot pressure scans from a Tekscan Matscan system, respectively. The modified arch index describes foot structure as planus, cavus or referent using sex-specific quintiles from the population distribution. The center of pressure excursion index measures dynamic foot function as pronated, supinated, or referent using sex-specific quintiles from the population distribution.

An overall physical limitations score was derived from items assessing difficulty (none vs. any [little, some, a lot, unable]) for 9 activities such as remaining balanced while standing; standing in one place; getting in/out of a car, a chair, or bed; putting on socks/stockings; and up/down 1 flight of stairs. We created an overall score by summing the number of tasks with limitations (range 0–9) and also a mean difficulty score across all levels of difficulty in the 9 items, range 0–4. Linear regression estimated the association between physical limitation score and foot pain, foot structure and foot function, adjusting for age, height, weight and sex.

Results: Of the 1860 participants, 55% were women and mean age was 65 yrs (SD=10.6). 37% had no physical limitation. The average overall physical limitations score was 2 (SD=2.4) and average mean difficulty score was 0.36 (SD=0.50). 27% reported foot pain, 34% were pronators, 27% were supinators, 24% had cavus foot and 29% had planus foot.

Those with foot pain reported more physical limitations than those without ($p<.0001$). Foot structure and foot function were not associated with the overall physical limitation score in adjusted models (Table). Remarkably similar results were seen for the mean difficulty score as seen with the overall physical limitations score.

Table. Least squares means (lsmeans) and p-values from a linear regression between the overall physical limitations score and foot pain, foot structure and foot function.

		Crude		Adju sted (age, height, weight, sex)	
	Raw means	lsmeans	p-value	lsmeans	p-value
Foot Pain	3.13	3.12	<.0001	3.03	<.0001
No Foot Pain	1.70	1.71	Ref	1.74	Ref
Foot Function					
Supinator	1.98	1.98	0.41	2.09	0.68
Pronator	2.16	2.16	0.60	2.13	0.44
Referent	2.08	2.09	Ref	2.04	Ref
Foot Structure					
Planus	2.48	2.48	<.0001	2.16	0.36
Cavus	1.86	1.86	0.48	2.08	0.73
Referent	1.95	1.96	Ref	2.04	Ref

Conclusion: Foot pain is strongly associated with self-reported physical limitations, but foot structure and foot function are not. Persons may adapt to their own foot structure and foot function so that it does not limit physical activity. Objective measures of physical limitations are needed to provide other insights into the links with foot pain.

Disclosure: A. B. Dufour, None; **P. P. Katz**, None; **V. A. Casey**, None; **M. T. Hannan**, None; **H. B. Menz**, None.

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Foot Symptoms Increase Odds Of Falling: The Johnston County Osteoarthritis Project. Yvonne M. Golightly[1], Marian T. Hannan[2], Alyssa B. Dufour[2], Amanda E. Nelson[3], Adam Dore[1] and Joanne M. Jordan[3]. [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]Hebrew SeniorLife & Harvard Medical School, Boston, MA, [3]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC.

Background/Purpose: Foot symptoms (symptoms=pain, aching, and stiffness) are common in older adults and are associated with poorer physical function, but their contribution to risk of falling is understudied. The purpose of this cross-sectional study was to examine whether presence and severity of foot symptoms were associated with falls in a community-based cohort of African American and Caucasian men and women 50+ years old.

Methods: Of 1,690 Johnston County Osteoarthritis Project participants who completed questionnaires about falls from 2006–2010, complete data on foot symptoms, history of falls, and participant characteristics were available for 1,406 participants (mean age 68 ± 9 years, mean body mass index [BMI] 32 ± 7 kg/m^2, 66% women, 30% African American, 22.4% with <12 years of school). Falls (yes/no) were queried as: "In the last 12 months, have you had any falls of any type?" If they responded "yes", they reported the number of falls. Presence of foot symptoms (yes/no) was defined based on the question: "On most days, do you have pain, aching or stiffness in your left/right foot?" Foot symptom severity was recorded as none (referent), mild, moderate, or severe. Logistic regression models were used to estimate the association between foot symptoms and falls (defined two ways as ≥1 fall and ≥2 falls), adjusting for history of falls, age, BMI, gender, race, education (12+ years vs. <12 years) and other lower body symptoms at the low back, hip, or knee. Statistical interaction between foot symptoms and each covariate was examined, with a p-value of <0.10 for interaction considered statistically significant.

Results: Foot symptoms were reported by 341 (24.3%) participants, and symptoms were severe for 4.3% of participants, moderate for 10.7%, and mild for 9.3%. In the past 12 months, 26.9% of participants reported 1 or more falls and 10.5% reported 2 or more falls. 22.2% participants had a history of falls, and 60.1% had other lower body symptoms. Foot symptoms were associated with falls during the past 12 months (Table). Compared to those without foot symptoms, those with foot symptoms had 60% higher odds of sustaining at least one fall and 90% higher odds of sustaining at least 2 falls. The odds of falling increased with greater foot symptom severity (Table). There were no interactions between foot symptoms and any of the covariates.

Table. Odds ratios and 95% confidence intervals for the association between foot symptoms and falls during the past 12 months, adjusting for history of falls, age, BMI, race, gender, education, and other lower body symptoms.

Falls	Foot Symptoms	# of fallers/ n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Any falls vs. no falls	Symptoms:			
	Yes	128/341 (37.5)	1.96 (1.57, 2.63)	1.62 (1.23, 2.15)
	No	250/1065 (23.5)		
	Severity:			
	None	250/1065 (23.5)	1.00	1.00
	Mild	44/131 (33.6)	1.65 (1.12, 2.43)	1.38 (0.92, 2.07)
	Moderate	54/150 (36.0)	1.83 (1.28, 2.63)	1.52 (1.04, 2.24)
	Severe	30/60 (50.0)	3.26 (1.93, 5.51)	2.68 (1.54, 4.68)
2 or more falls vs. 0 or 1 fall	Symptoms:			
	Yes	61/341 (17.9)	2.48 (1.74, 3.53)	1.92 (1.32, 2.80)
	No	86/1065 (8.1)		
	Severity:			
	None	86/1065 (8.1)	1.00	1.00
	Mild	22/131 (6.8)	2.30 (1.38, 3.82)	1.84 (1.09, 3.13)
	Moderate	26/150 (17.3)	2.39 (1.48, 3.85)	1.95 (1.18, 3.22)
	Severe	13/60 (21.7)	3.15 (1.64, 6.05)	2.00 (1.01, 3.98)

Conclusion: Foot symptoms were significantly associated with falls during the past 12 months, with odds increasing with greater severity of foot symptoms. Surprisingly, there were no interactions, especially by race or BMI. Fall prevention measures may target foot interventions specifically to reduce foot symptoms or to slow progression of symptom severity to prevent future falls.

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Smokers and Overweight Persons Are At Increased Risk Of New Onset Of Severe Foot Pain and Persistent Severe Foot Pain In a Population Study. Alyssa B. Dufour[1], Hylton B. Menz[2], Arunima Awale[3], Thomas J. Hagedorn[3], Virginia A. Casey[3], Patricia P. Katz[4] and Marian T. Hannan[1]. [1]Hebrew SeniorLife & Harvard Medical School, Boston, MA, [2]La Trobe University, Bundoora, Victoria 3086, Australia, [3]Hebrew SeniorLife, Boston, MA, [4]University of California, San Francisco, San Francisco, CA.

Background/Purpose: Few studies have evaluated risk factors for patterns of foot pain in the general population, let alone over time. An understanding of the possible predictors is the first step towards evidence-based interventions. The purpose of this study was to examine risk factors for the onset and persistent of severe foot pain in men and women of the population-based Framingham Foot Study (FFS).

Methods: The longitudinal FFS included 648 participants who attended baseline (BL, 2002–5) and follow-up (FU, 2005–8) exams. The presence of foot pain at both BL and FU was queried using the question "On most days, do you have pain, aching, or stiffness in either of your feet?" If participants had foot pain, severity was then queried as mild, moderate or severe. We dichotomized pain severity into 2 pain groups: moderate/severe versus none/mild for each foot. Two separate analyses were done to examine 1) onset of moderate/severe pain versus none/mild pain and 2) persistent severe/moderate pain versus resolving severe/moderate pain. Two per-foot analyses using logistic regression and generalized estimating equations were used to examine the association between onset versus no foot pain and persistent versus resolving foot pain with potential risk factors (age, sex, body mass index (BMI), current smoking, knee pain, hip pain, and low back pain). Models were also examined by sex.

Results: At BL, average age was 65 years (range 36–86, SD=9), BMI was 29 kg/m^2 (SD=5), 51% were female and mean follow-up time was 3 years (range 1–6). 85% had no pain, 5% had onset, 7% had resolving, and 3% had persistent pain. Female sex and current smoking was associated with a 2–3 fold increased odds of onset of pain. Increased BMI was associated with a 16–20 fold increased odds of persistent versus resolving pain (Table).

Table. Odds ratios (OR) and 95% confidence intervals (CI) for the per-foot analysis between onset and persistent moderate/severe foot pain and risk factors in 648 participants (1296 feet)

	Onset (N_1=67 feet) vs. No Pain(N_0=1104 feet)			Persistent (N_1=40 feet) vs. Resolving (N_0=85 feet)		
	n/ N_1	OR (95% CI)	p-value	n/ N_1	OR (95% CI)	p-value
Age (10 yr incr)		1.23 (0.92,1.64)	0.16		1.06 (0.60,1.87)	0.84
Female sex	42/67	1.98 (1.03,3.82)	0.04	28/40	1.14 (0.41,3.18)	0.80
BMI 25–30 vs <25	27/67	1.26 (0.54,2.93)	0.59	16/40	20.67 (2.39,178.74)	0.01
BMI 30+ vs <25	25/67	1.24 (0.57,2.71)	0.59	23/40	16.31 (1.91,139.41)	0.01
Current smoking	14/67	2.76 (1.21,6.28)	0.02	6/40	2.92 (0.69,12.31)	0.15
Knee pain	23/67	1.26 (0.70,2.27)	0.45	15/40	1.11 (0.54,2.31)	0.78
Hip pain	9/67	0.67 (0.29,1.58)	0.36	7/40	0.52 (0.22,1.22)	0.13
Low back pain	29/67	1.69 (0.87,3.26)	0.12	29/40	1.66 (0.57,4.82)	0.35

In the sex-specific models, current smoking maintained its effect with onset pain, but was non-significant (OR_{men}=3.4, p=.07; OR_{women}=2.4, p=.11). The elevated odds of persistent pain remained for overweight (OR=14, p=.20) and obese men (OR=7, p=.10) but not for women. These non-significant results are not surprising given the small numbers in individual cells.

Conclusion: A larger study with longer follow-up is needed to identify risk factors and patterns of foot pain over time. Looking at foot disorders, in addition to pain, is also of interest. Nevertheless, in our study current smoking regularly appears to be linked with onset of moderate to severe foot pain, which is in agreement with common clinical observations that smokers develop more foot problems than non-smokers. Additionally, increased BMI was suggestively linked to persistent moderate to severe foot pain compared to those whose pain resolved.

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The Effect Of Obesity On Physical Function: The Osteoarthritis Initiative Study. Jingbo Niu[1], Daniel K. White[1], David T. Felson[1], Michael C. Nevitt[2] and Yuqing Zhang[1]. [1]Boston University School of Medicine, Boston, MA, [2]University of California, San Francisco, San Francisco, CA.

Background/Purpose: Previous studies assessing relationship between obesity and physical function used linear regression model that assumes effects of obesity on physical function were the same across the distribution of outcome variable. However, if this assumption is not true, linear regression model may fail to reveal important associations and fail to identify persons who might be best targeted for obesity modification. Quantile regression provides a more complete picture of the relationship between obesity and physical function when both lower and upper or all quantiles are of interest. We used quantile regression to examine the distribution-specific effect of obesity on physical function.

Methods: The *Osteoarthritis Initiative* (*OAI*) Study is an observational study of people 45–79 years with or at high risk of knee osteoarthritis. Body Mass Index (BMI) was calculated from standardized assessments of height and weight and categorized into 3 groups: normal ($< 25 kg/m^2$), overweight ($25 - <30 kg/m^2$), and obese ($\geq 30 kg/m^2$). Physical function was measured with knee-specific WOMAC function (range: 0–68) at the 12-month visit. The knee with higher (worse) WOMAC function score was used to represent a person's function level. We performed sex-specific quantile regression models to assess association between BMI categories and WOMAC function percentiles from 30^{th} to 90^{th} with increase by 10^{th} adjusting for age, race, and CES-D score. We also performed a traditional linear regression model.

Results: 4,243 subjects (mean age 62.3, 58% women, 81% Whites, mean CES-D score 62.3) were included in analysis. In men, WOMAC function score among obese subjects was $>$ 6 units worse at the 70^{th}, 80^{th}, and 90^{th} percentile, but only 0.4 unit worse at the 30^{th} percentile compared with the score for those in a normal BMI category. Similarly, WOMAC function score among obese women was $>$ 9 units worse at the 70^{th}, 80^{th}, and 90^{th} percentile, but only 2.2 units worse at the 30^{th} percentile of WOAMC physical function score than score for those in a normal BMI category. A similar pattern was observed for subjects who were overweight though with attenuated effects (see table). Such findings were not revealed when using a linear regression approach.

Table. WOMAC function score and BMI categories (normal BMI as reference)

Mean/percentiles of WOMAC function score	Men		Women	
	overweight beta (95% CI)	obesity beta (95% CI)	overweight beta (95% CI)	obesity beta (95% CI)
mean	1.81 (0.60, 3.03)†	3.77 (2.50, 5.05)‡	1.94 (0.85, 3.02)‡	5.94 (4.83, 7.04)‡
30^{th}	0 (−0.13, 0.13)	0.42 (0.04, 0.79)*	0.13 (−0.04, 0.30)	2.20 (1.69, 2.72)‡
40^{th}	0.12 (−0.09, 0.34)	1.07 (0.66, 1.49)‡	0.60 (0.14, 1.06)*	3.85 (3.21, 4.49)‡
50^{th}	0.67 (0, 1.33)*	2.09 (1.22, 2.97)‡	1.05 (0.35, 1.75)†	5.10 (4.20, 6.01)‡
60^{th}	1.83 (0.81, 2.84)‡	4.25 (2.65, 5.84)‡	2.10 (0.98, 3.22)‡	6.98 (5.45, 8.50)‡
70^{th}	2.54 (1.01, 4.07)†	6.30 (4.20, 8.39)‡	3.22 (1.52, 4.93)‡	9.20 (7.26, 11.14)‡
80^{th}	3.46 (1.21, 5.71)†	8.01 (5.60, 10.42)‡	3.99 (2.00, 5.99)‡	10.49 (8.47, 12.52)‡
90^{th}	3.53 (−0.09, 7.15)	8.65 (4.59, 12.71)‡	5.21 (2.62, 7.81)‡	11.42 (8.52, 14.31)‡

*P-value <0.05, †P-value <0.01, ‡P-value <0.001

Conclusion: Using quantile regression model we demonstrated that the magnitude of association between obesity and physical function score was greater among subjects with worse physical function than those with better function. When research interest focuses on bounded outcomes, such as pain or function assessed with visual analogue scale, quantile regression models may provide more valuable insights into the relationships than methods that use single summary effect measure, such as difference in mean or median.

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ARHP Concurrent Abstract Session
Psychology/Social Sciences/Pediatrics
Sunday, October 27, 2013, 4:30 PM–6:00 PM

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A Qualitative Study Of The Educational Needs Of Children With Scleroderma and Their Parents. Cindy F. Mendelson[1], Ana-Alicia Huerta[2], Jane Kastning[1], Bernadette Vargas[1] and Janet L. Poole[1]. [1]University of New Mexico, Albuquerque, NM, [2]Univeristy of New Mexico, Albuquerque, NM.

Background/Purpose: Scleroderma is a rare disease, especially in childhood. Skin changes can be physically disfiguring which can lead to lowered self-esteem, especially during the adolescent years when physical appearance is emphasized. No psycho-educational programs exist to help children and their families cope with disease management, prognosis and psychosocial issues. A qualitative interview study was conducted to determine the appropriate content, delivery methods and targeted audience to be included in a psycho- educational program for children with scleroderma and their parents

Methods: Participants were recruited through the Scleroderma Foundation (SF) website and at the annual conference. Participants completed consent and assent forms, a demographic questionnaire and the Childhood Health Assessment Questionnaire (CHAQ). Parents and children then participated in either focus groups (FG) or interviews. Two in person FG were convened at the SF annual conference; one with children and one with their parents, similarly two online FG were conducted, with children and parents who were unable to interview in person. Five child/parent interviews were also conducted: one in person and four via telephone. The telephone, in person, and FG interviews were audio recorded and transcribed. The documents from the online FG were downloaded for analysis.

Interview and FG questions centered on key information needed at time of diagnosis, desired content, format and target audience for a self-management program, managing questions from peers, and desired content on transition for pediatric to adult services. Data analysis was directed at identifying common themes. Key interview questions served as the initial organizing framework for data analysis Participants' responses to these questions were coded for key themes independently by the analysts and then reviewed for agreement. Differences were resolved by returning to the transcripts to reexamine the data jointly and discussing the data and themes until consensus was achieved.

Results: Eleven dyads (6 with jSSc, 5 with JLS) were included in the study. The majority of the children were female (90.9 %); all were White non-Hispanic. Mean age of the children was 14.5 years, their mothers was 46.5 years, the mean CHAQ disability score was 0.41. Analysis of the data revealed 8 themes: Lack of Scleroderma Information, Uncertain Future, Need for Internet Resources, Isolation, Disease Management, Health Professional Face to Face Time, Helping Explain to My Peers, and Self-Advocacy.

Conclusion: This is the first study to assess the educational needs of children with scleroderma and their parents. The psychosocial themes that emerged from this study are consistent with the low CHAQ disability scores and reflect children are affected psychologically and socially. Patient education for children with chronic diseases is valuable in helping the child and family cope with disease management, prognosis and psychosocial issues.

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Worse Mental Health In Employed Adult Patients With Juvenile Idiopathic Arthritis (JIA): More Than Just A Job. Nadia E. Aikawa[1], Jms Gordo[2], R Krieger[3], LE Paula[4] and Claudia Goldenstein-Schainberg[5]. [1]Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, [2]Faculdade de Medicina, Universidade de São Paulo, Sao Paulo, Brazil, [3]Universidade de Sao Paulo, Sao Paulo, Brazil, [4]Faculdade de Medicina, Universidade de São Paulo, Sao PAulo, Brazil, [5]Reumatologia, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: Work status and unemployment are significant future concerns among individuals with JIA, because roughly 20% patients enter adulthood with clinically active disease and disabled. Functional impairment allied to work condition may affect one's physical and mental health with an important impact in social relationships and economic aspects. Therefore we aimed to determine the employment rate and the prevalence of work disability among a cohort of adult patients with JIA from a tertiary rheumatology center and to determine possible associated risk factors.

Methods: Forty-three adult JIA patients according to 2004 revised ILAR criteria were enrolled in this cross-sectional study. Working status and labor activity were assessed through a self-administered questionnaire encompassing educational level, occupation, current/previous work, employment and withdrawal rate. Demographic data, JIA characteristics, clinical activity (DAS28>2.6), functional class (1991 ACR criteria), HAQ and SF-36 scores, therapeutic intervention, comorbidities, physical activity and sedentary status (WHO definitions) were recorded. The prevalence of work disability was calculated using 95% confidence interval, and compared to all parameters; quantitative variables were analyzed using Mann-Whitney or student test and qualitative variables by tests of association (chi-square test).

Results: Mean age of JIA patients was 29+7.4yrs (range 19–41) with mean JIA duration of 17.2+12.3yrs (range 3–33); 63% were males and 37% females. JIA subtypes were: 64% polyarticular (9/27= RF+), 11% oligoarticular, 9% systemic, 9% ERA, 2% extended oligoarticular, 2% psoriatic

arthritis. Serum RF was positive in 21%, ANA in 21% and 7% had uveitis. At the time of the study, 72% JIA patients (n=31) were employed whereas 28% (n=12) were not working. In the latter group, 83% (n=10) were prematurely retired due to JIA related disability. Further analysis comparing 31 patients currently working vs. 12 not working revealed similar age (25.3 vs. 29.5yrs, P=0.09), sex ratio, poly onset JIA (22 vs. 6 P=0.37), good education level >12 yrs at school (31 vs. 9, P=0.38), ACR functional class I (P=0.96), practice of regular physical activity (9 vs. 0, P=0.89) and singles (26 vs. 8, P=0.15). Both groups were also comparable for HAQ (0.62 vs. 0.59, P=0.47) and DAS 28 scores (2.51 vs. 2.07, p=0.64) with similar arthroplasty rate (8 vs. 4, p=0.42). Frequencies of hypertension (3 vs. 1, P=0.99), dyslipidemia (1 vs. 1, P=0.12), diabetes (1 vs. 0, P=0.99), depression (1 vs. 0, P=0.99) and smokers (3 vs. 1, P=0.99) were also alike in both groups. Unexpectedly, employed patients had a significantly higher SF 36 mental health component score (84.0 vs. 70.42, P = 0.01).

Conclusion: The present study provides evidence that disease related incapacity remains a matter of concern for adult JIA individuals with a high rate work disability and retirement. Worse mental health in employed patients is intriguing and may indicate that intense affirmative disability actions to remove possible disabling barriers and to adapt to restrictive environments are necessary. Moreover, further attention focused on enhanced strategies and policy for inclusion of JIA patients in the job market is urged.

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Lupus and Reproductive Health Considerations: A Pilot Training For Reproductive Health Care Providers Serving Teens and Young Adults. Jillian A. Rose[1], Dariana M. Pichardo[2], Monica C. Richey[1], Josephine Isgro[3] and Roberta Horton[1]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital For Special Surgery, New York, NY, [3]Morgan Stanley Children's Hospital of New-York Presbyterian, Columbia University Medical Center, New York, NY.

Background/Purpose: Health disparities (our target communities continue to experience some of the highest rates of sexually transmitted disease and teen pregnancy in the country) related to reproductive health and lupus points to the need for sound interventions. Effective reproductive health care is crucial for teens/young adults with lupus given the multiple risk of pregnancy & high risk of sexual transmitted disease that often make medical management of lupus complex. As previously published, health professionals are often unprepared to counsel women with chronic illnesses about the potential adverse side effects of pregnancy and contraception on underlying disease. Providers may often hesitate to prescribe contraception to women with lupus due to concerns about the risk of lupus complications. Our national lupus support and education program is offered to people with lupus and their families in underserved Latino and African American communities. As part of our community service plan, we collaborated with a pediatric rheumatologist from an affiliated urban medical center, an internal rheumatology nurse practitioner and social worker to develop educational trainings to increase awareness of lupus and related treatment considerations among local reproductive health care providers in traditionally underserved areas.

Methods: Trainings were conducted at 3 reproductive health care centers that provide comprehensive care to culturally diverse teen/young adults. A 5-item post evaluation tool (Likert-scale and open-ended questions) was used to assess whether the program met its learning objective, and overall satisfaction

Results: A total of 85 health care providers attended the trainings, of which 67 completed evaluations. 94% strongly agreed/agreed that the training contributed to their professional learning and development; 85% strongly agreed/agreed that the training will enhance their work with clients. Participants reported that the training increased their understanding of contraception options and pregnancy management in lupus patients. All participants strongly agreed/agreed that their awareness/ understanding of this area of lupus has increased as a result of the traning; 76 % strongly agreed/ agreed that they would change their practice in some way as a result of the training; ie. "I will include calcium and vitamin D to medications for lupus patients". 98% strongly agreed/agreed that the program met its educational objectives and 94% strongly agreed/agreed that they were satisfied with the training. When asked to describe how this training contributed to their learning and further care of patients, themes focused on awareness of teen lupus related issues, pregnancy concerns, and appropriate contraception options. i.e., "I am better equipped to manage lupus patients in reproductive health/primary care setting."

Conclusion: This pilot program has allowed us to enhance awareness, and access to trusted reproductive health care services in the community for our lupus patients. In addition, it has helped to foster mutual collaborations that enhance awareness and understanding of lupus.

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Longitudinal Patterns Of Depression In Lupus. Patricia P. Katz, Chris Tonner, Laura Trupin and Jinoos Yazdany. University of California, San Francisco, San Francisco, CA.

Background/Purpose: Depression is commonly reported in systemic lupus erythematosus (SLE), yet information is lacking about long-term patterns of depression. We examined a longitudinal SLE cohort to identify the proportions of individuals who were depressed at least once and who were persistently depressed over the 9-year observation period.

Methods: Data derive from the UCSF Lupus Outcomes Study (LOS), in which participants are interviewed by phone annually. Participants are recruited from medical and community settings, and all have confirmed SLE diagnoses. During each interview, the Center for Epidemiologic Studies Depression scale (CESD) is administered. We defined depression using two lupus-specific cut-points – a score of 20 was used to approximate any mood disorder, and a score of 24 to define probable major depressive disorder (MDD) (1) – and conducted separate analyses for each. Once individuals met a depression criterion, their CESD score was considered elevated until it dropped below the cut-point by 3 points (i.e., 0.5 standard deviation). Those whose CESD score remained within 0.5 SD of the cut-point (i.e., ≥ 17 for mood disorder, ≥21 for MDD) were classified as remaining depressed. Those whose CESD score dropped below 17 (or 21) were classified as remitting. In order to determine longitudinal patterns of depression, we included only individuals who had completed at least three annual interviews.

Results: Of 1008 individuals who participated in at least 3 annual interviews, mean age was 46 (± 13) years, 92% were female, and mean SLE duration was 12 (±9) years. 340 (34%) met the criterion for mood disorder and 256 (25%) met the criterion for MDD at the first interview. Among those who met the mood disorder criterion, 135 remained in this classification. An additional 220 individuals met the mood disorder criterion in a later interview; 44 of them remained in this classification once they met the criterion. In total, 560 (56%) were classified with a mood disorder in at least one interview, and179 (18%) were persistent in this classification once reaching it (Table). For MDD, 47% met the criterion in at least one interview, and 13% were persistent.

Table. Prevalence of mood disorder and major depressive disorder over time

	CESD ≥ 20: Any mood disorder % (n)	CESD ≥ 24: Major depressive disorder % (n)
Never depressed	44% (448)	53% (531)
Depressed at ≥1 interview	56% (560)	47% (477)
Remained depressed once meeting criterion	18% (179)	13% (128)
Depressed at all interviews	13% (135)	9% (89)

Conclusion: In this large cohort of individuals with lupus, over half met the criterion for a mood disorder and just under half met the criterion for major depressive disorder in at least one interview. Thirteen percent and 9% met these criteria in all interviews; 18% and 13% were persistently depressed once meeting the mood disorder or MDD criterion, respectively. Results underscore the high prevalence of depressive disorders in lupus, the persistence of such disorders in a sizable group of individuals, and the need for effective prevention and treatments.

(1) Julian L, et al. Using the CES-D to screen for depression in SLE. *Arthritis Care Res* 2011; 63:884–890

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The Role Of Social Relationships and Perceived Independence In The Employment Participation Of Young Adults With Rheumatic Disease.

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Background/Purpose: Participating in employment is an important milestone in the transition to adulthood for young people living with rheumatic disease and can be influenced by relationships with those closest to them including parents, spouses or friends. To date, little research has looked at social relationships and their impact on the work experiences of young adults living with rheumatic disease. This study aims at examining the nature of social relationships and their influence on perceived independence and participation in employment in young adults (18 to 30 years of age) living with systemic lupus erythematosus (SLE) and juvenile arthritis (JA).

Methods: 143 young adults (Mean age = 23.3, SD = 3.5,) with SLE (n = 78) and JA (n = 65) completed an online survey. In addition to collecting information on demographics, health (e.g. pain, fatigue, disease activity, activity limitations) and employment status, the Lubben Social Network Scale was administered to measure social contacts and perceptions of support using eight items (e.g. "How many relatives do you see or hear from at least once a month?"). Responses to items were provided on a 5-point scale (0 = none; 5 = nine or more) and a total score was produced. Participants were also asked about perceived overprotection that characterized their relationships with those closest to them (1 = not at all; 5 = a great deal). Seven items assessing independence were developed for the study and administered to participants (1 = not at all; 5 = a great deal). Bivariate analyses were conducted to examine the interrelationships between variables and multivariable log-Poisson analysis examined factors associated with employment.

Results: More than half of participants (59.4%) were employed at the time of the survey. 26% were students and the remaining were not working. Respondents indicated having a well-managed health condition with low average pain, fatigue, disease activity and HAQ-PROMIS scores. Participants reported moderate to high perceptions of independence (Mean = 3.6, SD = .60) and social support (Mean = 22.1, SD = 7.3) as well as low overprotection (Mean = 2.8, SD = 1.4). Despite low average scores, over one quarter (27.1%) reported 'quite a bit' to 'a great deal' of overprotection. At the bivariate level, perceived independence was related to greater social support and less overprotection ($p < .05$). At the multivariable level greater perceptions of independence were significantly associated with a greater likelihood of participating in employment (PR = 1.3, 95%CI 1.0–1.6). When controlling for psychosocial variables, health factors were not significantly related to being employed.

Conclusion: For young adults with rheumatic disease perceptions of independence play an important role in determining one's likelihood of participating in paid work and should be promoted. This study also showed that the role of others is more complex than simply providing support. Young adults experiencing less overprotection may have more opportunities for independence that may in turn foster employment. Future research needs to unpack the relationship between psychosocial factors and employment in greater detail.

Disclosure: A. Jetha, None; **E. M. Badley**, None; **D. Beaton**, None; **M. A. Gignac**, None.

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Appearance Dissatisfaction, Social Discomfort, and Helplessness In Patients With Systemic Sclerosis.

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Background/Purpose: Systemic sclerosis (SSc) is a progressive, autoimmune disease with no known cure. It is related to a wide spectrum of adverse health outcomes including marked appearance changes (AC), particularly on the face, mouth, and hands. Despite the prevalence of AC among SSc patients, dissatisfaction with appearance is relatively unexplored in this group. Given that disease-related disfigurement can be unpredictable and uncontrollable, there is reason to hypothesize that AC may be associated with feelings of helplessness. Further, as there are personal (i.e., body image) and interpersonal (i.e., social relationships) aspects to AC, both were examined as correlates of helplessness. The present study examined the relationship between satisfaction with appearance and helplessness in patients with SSc

Methods: As part of the UCLA Quality of Life (QOL) Study, a sample of patients (N = 191) completed the Brief Satisfaction With Appearance Scale (Brief-SWAP) and the Arthritis Helplessness Index (AHI). The Brief-SWAP is a self-report measure comprised of two positively correlated subscales evaluating Dissatisfaction with Appearance and Social Discomfort. The AHI is a self-report measure designed to capture perceived loss of control among arthritic patients, and is comprised of two negatively correlated subscales - Internality and Helplessness.

Results: Hierarchical linear regression was utilized to examine the relationship between the Brief-SWAP and the AHI in two separate models controlling for disease severity using the modified Rodnan Skin Score. A significant main effect (p = .009) was found for social discomfort (e.g., comfort in the presence of strangers) as a statistical predictor of helplessness (e.g., my arthritis is controlling my life), such that greater social discomfort due to SSc-related AC was associated with greater feelings of helplessness. Dissatisfaction with appearance was not a significant predictor ($p > .05$) of helplessness. In the model predicting internality, neither social discomfort nor subjective dissatisfaction with appearance demonstrated significant main effects ($p > .05$) after controlling for disease severity. Age (M = 53.8; SD = 14.8) was examined as a potential moderator in both models, but no significant interaction effects were found.

Conclusion: Given the extent of AC among SSc patients, this is an area that deserves greater study in order to increase understanding of the spectrum of outcomes associated with body disfigurement. A limitation of this study is that the variance in age in the present sample was limited and may have precluded finding a significant age interaction effect. These findings suggest that social distress due to disease-related AC is associated with greater feelings of helplessness among SSc patients, while dissatisfaction with appearance is not. The findings further suggest that neither social distress nor dissatisfaction with appearance is associated with internality.

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Diagnostic Autoantibody Signatures Of Rheumatoid Arthritis Patients Identified With a Bead-Based Assay Approach. Angelika Lueking[1], Petra Budde[1], Stefan Vordenbäumen[2], Carmen Theek[1], Heike Goehler[1], Martin Gamer[1], Peter Schulz-Knappe[1] and Matthias Schneider[3]. [1]Protagen AG, Dortmund, Germany, [2]Univ. Duesseldorf, Düsseldorf, Germany, [3]Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany.

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease typically characterized by chronic inflammation, accumulation of self-reactive B-cells and production of autoantibodies of which anti–cyclic citrullinated peptide (anti-CCP) antibodies and rheumatoid factor (RF) have diagnostic utility. 30% of RA patients remain sero-negative making the early diagnosis of RA more difficult. Our goal is to develop a novel autoantibody-based diagnostic test that allows to correctly diagnosing CCP-negative early RA patients.

Methods: We performed a large-scale screen of 5800 proteins in a total of 250 serum samples of patients with stable RA, patients with SLE and healthy volunteers. An automated bead-based Luminex xMAP technology enables to measure the reactivity of autoantibodies to up to 500 different antigens in one single serum sample. All proteins are produced from *E.coli*, are highly purified by affinity capturing, sequenced by mass spectrometry, and each protein is coupled in optimized concentration to individual color coded Luminex beads. Biostatistical analysis was performed using univariate as well as multivariate statistical algorithms.

Results: 144 novel antigens were identified in RA patients. The auto-antibody profile of RA patients is heterogeneous with some overlap between CCP-positive and CCP-negative patients. We therefore evaluated panels comprising five to ten antigens for identification of CCP-negative RA patients. One panel with six antigens showed a specificity comparable to CCP in CCP-negative patients. Another panel was able to detect about 60% of CCP-negative. Comparison to an active control group consisting of 100 SLE patients, an AUC was obtained of 0.78, with high a specificity of 0.86 and a lower sensitivity of 0.54.

Conclusion: CCP-negative RA patients can be identified based on specific set of autoantibodies. Further studies are currently conducted to validate the biomarker panels in early RA patients.

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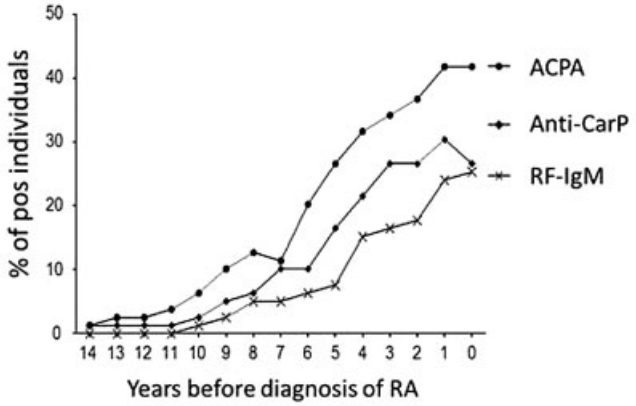
Anti-Carbamylated Protein Antibodies (Anti-CarP) Precede The Onset Of Rheumatoid Arthritis. Jing Shi[1], Lotte A. van de Stadt[2], E.W.Nivine Levarht[1], Tom W. J. Huizinga[1], Dörte Hamann[3], Dirkjan van Schaardenburg[2], René E.M. Toes[1] and Leendert A. Trouw[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [3]Sanquin Diagnostic Services, Amsterdam, Netherlands.

Background/Purpose: Anti-citrullinated protein antibodies (ACPA) and IgM-Rheumatoid Factor (IgM-RF) are auto-antibodies that can be detected many years before the clinical diagnosis of Rheumatoid Arthritis (RA) [1]. Since ACPA and IgM-RF are known as predictive and prognostic markers of RA, it is conceivable that these antibodies play a pathogenic role in RA. In recent studies we discovered anti-carbamylated protein (anti-CarP) antibodies as a prognostic marker in RA [2]. In addition anti-CarP antibodies are associated with a conversion to RA in patients that suffer from arthralgia [3]. In this study we analyzed whether anti-CarP antibodies can also be detected prior to the onset of the symptoms of RA and which auto-antibody appears first over time.

Methods: Sera of 79 RA patients obtained prior to the onset of symptoms and 141 age and sex matched controls that were regular blood donors from Amsterdam, The Netherlands, were tested for the presence of anti-carbamylated fetal calf serum (Ca-FCS) antibodies, anti-cyclic citrullinated peptide 2 (CCP2) antibodies and RF-IgM. A median of 5 (IQR 4–6) sequential pre-RA sera, obtained at 1–6 year intervals was available for analysis.

Results: Anti-CarP antibodies were present in 27% of the serum samples that were drawn just prior to the diagnosis of RA of blood donors compared to 4% of the matched control samples. Anti-CarP antibodies were present in both ACPA positive and ACPA negative patients. Of the 79 individuals that developed RA, 42% were positive for anti-CCP2 antibodies and 25% for IgM RF.

Analysis of the longitudinal samples revealed that anti-CarP antibodies could be detected many years before the onset of symptoms (median 5 years) (Figure 1). Comparing the first appearance of the three autoantibody families revealed that both ACPA and anti-CarP antibodies appear (similarly) earlier in time as compared to IgM-RF.



Conclusion: Next to ACPA and IgM-RF also the newly identified anti-CarP antibodies appear many years before the onset of clinical symptoms of RA.

1. Nielen MM, *et al*. Arthritis Rheum. 2004; 50:380–6.
2. Shi J, *et al*. Proc. Natl. Acad. Sci. U.S.A 2011; 108:17372–7.
3. Shi J, *et al*. Arthritis Rheum. 2013; 72(1) 148–50

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Neutralization Of Anti-Citrullinated Protein Antibodies - a Way To Go? Catia Cerqueira[1], Elena Ossipova[1], Monika Hansson[2], Linda Mathsson[3], Lars Klareskog[2], Johan Rönnelid[3] and Per Johan Jakobsson[2]. [1]Rheumatology unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [2]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [3]Uppsala University, Uppsala, Sweden.

Background/Purpose: In a previous study, we have identified endogeneously citrullinated sites in fibrinogen from RA synovial tissue (Hermansson M. et al. Proteomics Clin Appl, 2010). Within the alpha chain, Arg573 and Arg591 were found citrullinated with an occupancy rate in the range of 1–2% and in the β-chain, Arg72 and Arg74 were also found citrullinated. In the present study, we demonstrate that citrullinated fibrinogen peptides are autoantigenic and can be used as probes for development of anti-citrullinated protein antibodies (ACPA) neutralizing compounds opening new opportunities for treatment of CCP positive RA patients.

Methods: The autoantigenic potential was investigated using the Phadia's ImmunoCAP ISAC® system. Citrullinated and unmodified fibrinogen peptides were immobilized onto a glass slide in an arrayed fashion and serum from 404 CCP positive and 532 CCP negative RA patients and 461 healthy controls from the EIRA cohort were tested. We also assayed the identified citrulline fibrinogen peptides for their ability to prevent purified ACPA (Ossipova E. et al. 2013, submitted) to bind to CCP (CCPlus® ELISA, Euro-Diagnostica AB). Peptides were individually or in combinations incubated with different ACPA pools and the blocking efficiency was expressed as percent of inhibition and IC50. Corresponding arginine peptides were used as controls.

Results: We found that 31% (87% are CCP positive) of patients were positive to Cit573 peptide. For the Cit591 peptide, the corresponding numbers were 10% (65%), for the Cit74 peptide 28% (68%) and for the Cit72 peptide 20% (68%). Interestingly, citrullinated 573 and Cit591 peptides revealed a maximum of 77% and 48% ACPA inhibition, respectively. When equally mixed, these peptides displayed an additive higher degree of ACPA neutral-

ization (84%). In contrast, Cit74 and Cit72 peptides reached a more modest maximum inhibition of 26% and 30%, respectively. This experiment was repeated using a different set of ACPA pool and then the efficiencies were lower for Cit573 (47%) but similar for Cit591 (51%). Logically, the efficiency of specific citrullinated compounds will depend on the individual ACPA specificities.

Conclusion: Here we demonstrate extensive autoantibody reactivity against in vivo citrullinated fibrinogen epitopes found in RA synovial membranes. These peptides can now be used as additional biomarkers for studies of ACPA sub-specificity profiles as recently reported (Brink M. et al. Arthritis Rheum, 2013). We also demonstrate that these citrullinated peptides can be used as neutralizing agents blocking a significant portion of ACPA binding to CCP. These results open novel possibilities for the design of personalized ACPA blockers preventing for instance the osteoclastogenesis and bone loss induced by ACPA (Harre U. et al. J Clin Invest, 2012).

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B-Cell Responses To De Novo Identified Citrullinated Fibrinogen Peptides Are Associated With PTPN22 Risk Allele. Vijay Joshua[1], Loes Schobers[2], Lena Israelsson[1], Johan Rönnelid[3], Monika Hansson[4], Anca I Catrina[5], Ger JM Pruijn[2] and Vivianne Malmström[6]. [1]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [2]Department of Biomolecular Chemistry, Radboud University, Nijmegen, Netherlands, [3]Uppsala University, Uppsala, Sweden, [4]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [5]Rheumatology Unit, Department of Medicine, Karolinska Institute, Stockholm, Sweden, [6]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Antibodies against citrullinated proteins are common in patients with rheumatoid arthritis (RA) and appear prior to the onset of the disease [1]. Many of the citrullinated epitopes have been identified and studied to varying details. Using an unbiased approach via mass spectrometry, the levels of citrullinated (cit) fibrinogen (Fib) peptides were demonstrated to be elevated in the synovial fluid of RA patients compared to non-RA patients [2]. Here we aim to identify the presence of autoantibodies against these citrullinated peptides.

Methods: An in-house ELISA was established against 5 citrullinated fibrinogen epitopes (cit-Fib α-35, cit-Fib α-216, 218, cit-Fib α-263, 271, cit-Fib α-425,426 and cit-Fib β-60,72,74) and serum from a cohort of patients with established RA (n=347) and disease controls with psoriatic arthritis (PSA) or ankylosing spondylitis (AS) (n=268) were analyzed. Cut-off for the ELISA was set at 98 percentile, based on reactivity in a cohort of healthy controls (n=152). The RA patients were genotyped with regard to HLA-DR alleles and PTPN22 R620W. The RA cohort has previously been screened for anti-CCP2 antibodies and antibodies against cit-fibrinogen protein (cFib) [3].

Results: Autoantibodies against the different citrullinated fibrinogen epitopes were present in the following frequencies in the RA patients compared to the PSA/AS patients, cit-Fib α-35 (RA-20%, PSA/AS-2%), cit-Fib α-216,218 (13%, 2%), cit-Fib α-263,271 (21%, 2%), cit-Fib α-425,426 (17%, 2%) and cit-Fib β-60,72,74 (4%, 0%). The presence of autoantibodies against these epitopes was associated with the presence of anti-CCP2 antibodies and antibodies against whole cit-fibrinogen. No genetic association was found between the presence of HLA shared epitope and antibodies to the different cit-Fib epitopes, while an association was observed between the PTPN22 risk allele and positivity to cit-Fib α-35 and cit-Fib α-263,271.

Conclusion: Fibrinogen is readily citrullinated in the rheumatic joint and our data show that several of the citrullinated epitopes are targeted by autoantibodies in the context of RA, but not in PSA/AS. Our data further emphasizes that the anti-citrulline response is broad with many parallel immune responses. Association between the presence of these autoantibodies with the PTPN22 risk carriers suggest that cit-Fib reactive B-cells would normally be deleted during the B-cell tolerance check points [4].

[1] Rantapää-Dahlqvist S., *et. al*., Arthritis Rheum. 2003
[2] Raijmakers R., *et. al*., Arthritis Res Ther. 2012
[3] Snir O., *et. al*., Arthritis Rheum. 2010
[4] Menard L., *et. al.*, J Clin Invest. 2011

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High Throughput Epitope Mapping Of Autoantibodies In BXD2 Mice Reveals The Generation Of Autoantibodies Against Citrullinated Antigens At The Predicted Major Immunogenic Sites. Jennie Hamilton, Qi Wu, PingAr Yang, Hui-Chen Hsu and John D. Mountz. University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Increased polyreactive B cells have been identified in patients with systemic lupus erythematous (SLE) and rheumatoid arthritis (RA). Such autoantibodies (autoAbs) were also identified in BXD2 mice that spontaneously develop IgG Immune complex glomerulonephritis and erosive arthritis. Most naturally occurring polyreactive autoantibodies are primarily IgM, germline and low affinity. Pathogenic autoAbs including anti-citrullinated protein antibodies, however, evolve through somatic hypermutation and class-switch recombination, suggesting that antigen (Ag)-selected affinity maturation is required. The purpose of this study is to identify and characterize the dominant autoAbs and their epitopes in BXD2 mice to determine if pathogenic autoAbs indeed react to immunodominant epitopes of self antigens.

Methods: A PEPperPRINT Autoimmunity Microarray which covers 2,733 linear B-cell autoepitopes from the Immune Epitope Database (IEDB) was used to identify BXD2 autoepitopes. Top peptides were selected based on the strength of reactivity and concordance with predictions made by DiscoTope, a structure-based computational program that predicts discontinuous B cell epitopes from protein three dimensional structures.

Results: The dominant epitopes recognized by BXD2 autoantibodies are those commonly found in human SLE and RA patients. The strongest response was observed with peptides of the 60 and 65 kDa heat shock proteins. Serum was also strongly reactive against a variety of arginine-rich peptides, including several that show shared consensus sequence derived from antigens U1 small nuclear ribonucleoprotein (U1snRNP), 70 kDa and small nuclear ribonucleoprotein Sm D1 (snRNP Sm D1), and 52 kDa Ro protein. The array further revealed reactivity with several citrulline-modified peptides, including fibrinogen beta chain (PA[Cit]KQCSKEDGGGWWY and WYNZCHAANPNGA[Cit]YY) as well as glucose regulated protein 78 (GRP78) (ALSSQHQAA[Cit]IEIESFYE). X-ray crystallography information is available for these two Ags. DiscoTope analysis shows that citrullination occurs in the highly immunogenic sites and are the immunoreactive epitopes of BXD2 autoantibodies.

Conclusion: The present results suggest that BXD2 mice exhibit a high tendency to develop autoAbs against nucleosome proteins and stress response proteins. Such results are consistent with our recent report showing defective marginal zone macrophages in clearance of apoptotic self antigens in BXD2 mice. Although cross-reactivtive epitopes are found, BXD2 autoAbs also react to autoAg at the major immunogenic sites that exhibit protein citrullination, suggesting that specific Ag engagement and selection are involved in the formation of autoAb producing B cells. Tetramers against the dominant epitopes are currently being generated to evaluate the immune checkpoint loss that leads to the generation of these B cells.

Disclosure: J. Hamilton, None; **Q. Wu**, None; **P. Yang**, None; **H. C. Hsu**, None, 2; **J. D. Mountz**, None, 2.

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Accentuated Expression Of RANKL In Switched Memory B Cells From Patients With Rheumatoid Arthritis. Yuri Hirosaki, Hiroaki Niiro, Shunichiro Ota, Naoko Ueki, Hirofumi Tsuzuki, Siamak Jabbarzadeh-Tabrizi, Kumiko Noda, Naoyasu Ueda, Naoyasu Ueda, Atsushi Tanaka, Masahiro Ayano, Sho Ueda, Satomi Hisamoto, Daisuke Oryoji, Mitsuteru Akahoshi, Yojiro Arinobu, Hiroshi Tsukamoto, Takahiko Horiuchi and Koichi Akashi. Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan.

Background/Purpose: Clinical efficacy of B-cell depletion therapy underscores a pathogenic role of B cells in autoimmune diseases such as rheumatoid arthritis (RA). In addition to generating pathogenic antibodies, B cells can function as potent effector cells by an Ab-independent mechanism. RANKL is a member of the tumor necrosis factor (TNF) family and plays a key role in osteoclastogenesis and inflammatory bone loss. A recent study suggested that B cells, but not T cells, are a major source of RANKL in the joints of patients with RA. In this study, we have elucidated underlying mechanisms of RANKL expression in B cells from normal subjects and RA patients, and determined the impacts on osteoclast differentiation.

Methods: Levels of RANKL mRNA and protein in B cells from peripheral blood of normal subjects and RA patients were evaluated using quantitative RT-PCR and flow cytometry, respectively. Highly pure B cell subsets were enriched using cell sorter. To validate the functional significance of osteoclast differentiation, B cells were co-cultured with osteoclast precursor cells and the formation of tartrate-resistant acid phosphatase (TRAP)-positive cells were assessed thereafter.

Results: In the absence of stimuli, human B cells only marginally expressed RANKL mRNA and protein. Combined stimulation of B cells with anti-Ig and anti-CD40, however, significantly induced RANKL expression. The experiments using signaling inhibitors suggested the involvement of several pathways in its expression. Among B cell subsets, switched-memory (CD27+IgD-) B cells, a normal counterpart of pathogenic B cells in the joints, expressed RANKL at the highest levels. Consistent with these findings, these subsets induced osteoclast formation as assessed by TRAP staining. Finally, switched-memory B cells from RA patients expressed RANKL at higher levels than normal subjects.

Conclusion: Our current findings shed the light on a pathogenic role of switched-memory B cells in bone damage associated with RA via production of RANKL, and regulation of RANKL expression in B cells may pave an avenue in developing a novel treatment for this devastating disease.

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IL-6R Inhibition Reduces Activation Of Different Peripheral Memory B Cell Subsets In RA. Zafar Mahmood[1], Khalid Muhammad[1], Marc Schmalzing[2], Petra Roll[1], Kathrina Eckert[1], Thomas Dörner[3] and Hans-Peter Tony[2]. [1]University of Würzburg, Würzburg, Germany, [2]University Hospital Würzburg, Würzburg, Germany, [3]Charité university medecine/ German Rheumatism Research Centre Berlin (DRFZ), Berlin, Germany.

Background/Purpose: Enhanced B cell activity has been proposed as part of the pathogenesis of rheumatoid arthritis also based on the clinical experiences obtained by B cell targeted therapies able to modulate memory B cells. Human peripheral memory B cells can be distinguished by the phenotypic expression of CD27 and IgD defining three major B cell subpopulations: CD27+IgD+ pre-switch, CD27+IgD- post-switch and CD27-IgD- double negative memory B cells. We analyzed these different memory populations in RA and under IL6R blockade.

Methods: B cells from RA patients were phenotypically analyzed by 8 color flow cytometry at baseline, week 12 and week 24 under tocilizumab (TCZ) treatment. Memory B cell subsets were defined by CD27 and isotype surface expression. B cell activation was identified by surface staining with CD95 and intracellular Ki-67 staining. Mutation frequencies of VH gene rearrangements were analyzed by single B cell RT-PCR. Statistical analysis was performed using Mann Whitney U test.

Results: The Ig receptor mutational frequency was highest in class switched CD27+/IgD- memory B cells with 6.1±0.3% compared to CD27-/IgD- (3.5±0.2%) largely containing memory-like B cells and CD27-/IgD+ pre-switch memory B cells (4.1±0.2%). The phenotypically analyzed isotype profile in RA patients (n=40) and healthy donors (n=18) revealed that the memory B cell pool was a heterogeneous population of IgA, IgG and IgM expressing cells. The CD27-/IgD- B cell memory population showed a clear dominance of IgG followed by IgA and IgM (~70%, 20% and 10% respectively), whereas CD27+IgD- class switched B cells had an equal distribution of IgA and IgG. Under IL-6R inhibition by TCZ, the distribution of Ig isotypes remained stable at week 12 and 24. Surface and intracellular staining of B cells showed a significantly higher percentage of CD95 (14.0±1.4%, p=0.016) and Ki-67 expression (3.0±0.3%, p=0.041) in B cells of RA as compared to HD (CD95: 7.5±1.0% and Ki-67: 1.9±0.2% which was highest in post-switched memory B cells in RA (CD95: 38.4±2.1% and Ki-67: 8.1±1.0%). In post-switched memory B cells, IL-6R inhibition significantly decreased the expression of CD95 to 21.1±3.4 % and Ki-67 to 4.8±0.7% at week 12 with p=0.0004 and p=0.0081 respectively.

Conclusion: Our data suggest that the three major peripheral memory B cell populations, pre-, post-switch as well as CD27-/IgD- B cells harbour different numbers of mutations in their Ig receptors. These B cell subsets are activated in RA with enhanced CD95 and Ki-67 expression compared to healthy individuals and which can be reduced by IL-6R inhibition *in vivo.* The CD27-/IgD- B cell pool displays a significantly higher proportion of IgG bearing cells compared to post-switch B cells which is not modulated by IL-6R inhibition.

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Role Of CD20+ B Cells As Antigen-Presenting Cells In Arthritis. Estefania Armas-Gonzalez[1], Ana Diaz-Martin[1], María Jesús Dominguez-Luis[1], Maria Teresa Arce-Franco[1], Ada Herrera-Garcia[1], Vanesa Hernandez[1], Alicia Usategui[2], Jose L. Pablos[2], Sagrario Bustabad[1] and Federico Diaz-Gonzalez[3]. [1]Hospital Universitario de Canarias, La Laguna. Tenerife, Spain, [2]Instituto de Investigación Hospital 12 de Octubre, Madrid, Spain, [3]University of La Laguna, Hospital Universitario de Canarias, La Laguna, Spain.

Background/Purpose: B cells participate in the pathogenesis of rheumatoid arthritis (RA) through a mechanism still not fully understood. In RA, B cells are believed to plays roles in: 1) the production of autoantibodies, 2) the release of proinflammatory cytokines, and 3) T-cell activation by acting as antigen-presenting cells. Objective: To study the potential involvement of B cells as antigen-presenting cell in the arthritis synovial microenvironment.

Methods: The presence of class II molecules (HLA-DR) and costimulatory molecules (CD86 and CD40) in CD20+ cells was studied by immunohistochemistry in biopsies of RA synovium. The surface-expression levels of CD27, class II molecules (HLA-DP, -DQ and -DR) and CD86 were analyzed by double-staining flow cytometry on CD20+ cells from peripheral blood (PB) and synovial fluid (SF) from 14 patients with RA and 12 with psoriatic arthritis (PA). The surface-expression levels of CD40 and CD20 on CD19+ and CD138- cells were studied in cells from both compartments by triple labeling. The expression of the interferon-induced protein, IFIT-4, which is involved in the differentiation into dendritic cells, was assessed by quantitative RT-PCR in immunoselected CD20+ cells from SF and PB of RA patients.

Results: Immunohistochemical studies showed that CD20+ B cells present in the RA synovial infiltrate express molecules involved in antigen presentation (HLA-DR) and costimulation (CD40 and CD86). In the patients included in this study the percentage of mononuclear CD20+ cells in SF (2.12±0.69%) was lower than in PB (7.44±0.62%). Flow cytometry analysis showed a significant increment in the expression levels of CD27 on B-cells from SF versus PB in both RA and PA patients, indicating that memory B cells are recruited into the inflamed synovium. CD20+ cells from SF showed an increased expression of HLA-DR and -DQ compared to PB in both RA and PA patients. HLA-DP was also elevated in SF with respect to PB in RA, although in PA, a significantly lower expression of HLA-DP was observed in SF with respect to PB. Surface expression of CD86 was higher in B cells from SF compared to those from PB in both pathologies. CD40 expression increased in SF compared to PB in PA patients; otherwise, a decrease was observed in SF with respect to PB in RA patients. Interestingly, a CD20 expression was lower in B cells (CD19+, CD138-) from SF in both RA (69.82±17.22%) and PA (54.44±15.66%) patients with respect to PB (considered 100%). Finally, qRT-PCR showed approximately a 5-fold increase in IFIT-4 mRNA content in B cells from SF compared to PB in RA patients

Conclusion: These data show that the B cells present in the synovial microenvironment express an antigen-presenting cell phenotype, which suggests that this cell type may participate in RA pathogenesis via antigen presentation.

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B-Regulatory-, $CD19^{+}CD20^{+}CD24^{high}CD38^{high}$ -Cells Are Functionally Impaired In Patients With Rheumatoid Arthritis and Healthy First Degree Relatives Compared With Controls. Mikael Brink[1], Kristina Lejon[2], Lisbeth Ärlestig[3] and Solbritt Rantapää Dahlqvist[4]. [1]Umeå University, Umea, Sweden, [2]Umeå Universitet, Umeå, Sweden, [3]Umeå University, Umeå, Sweden, [4]Umeå University Hospital, Umeå, Sweden.

Background/Purpose: Rheumatoid arthritis (RA) is a complex disease with both genetic- and environmental risk factors. By studying first degree relatives (FDR) of RA patients which shares some of the genetic and

environmental risk factors, may shed light on the pathogenic mechanisms of RA. A subset of B-cells, identified by their IL-10 producing abilities, when stimulated with CD-40 the B-regulatory cells ($CD19^+CD20^+CD24^{high}CD38^{high}$) has been suggested to be less functional in expressing IL-10 in patients with Systemic lupus erythematosus compared with cells from healthy individuals. As a downstream protein of CD-40 stimulation, signal transducer and activator of transcription 3 (Stat-3) expression can be used as a pseudo- marker for IL-10 expression and response to CD-40 stimulation.

In FDR, regarded as high risk population we aim to analyze B-regulatory cells to investigate their Stat-3 response with and without CD-40 stimulation and compare it with healthy controls and RA- patients.

Methods: Mononuclear cell isolation was done with blood samples from 23 FDR and 26 RA patients and 11 control individuals from northern Sweden. Two million cells, either with or without anti-CD40-antibody stimulation was analyzed with LSRII flow cytometer (Becton-Dickinson, San Jose, CA) for Stat-3 expression in $CD19^+CD20^+CD24^{high}CD38^{high}$-cells (B-regulatory cells). Samples with a robust coefficient of variation in flow cytometry variables >150 was excluded for subsequent analyses. Anti-CCP2 antibody analysis was performed by ELISA (Euro-Diagnostica). HLA-DRB1 alleles were genotyped using polymerase chain reaction sequence-specific primers. Genotyping of the *PTPN22* 1858C/T polymorphism was performed using a Taqman instrument. Continuous data were compared by non-parametric analysis using the Mann-Whitney U-test for two groups and the Kruskal-Wallis test comparing several groups. For within-patient comparisons the Wilcoxon signed-rank test was used.

Results: Comparing the Stat-3 levels with and without CD-40 stimulation in B-regulatory cells on individual level, a significant increase was found in controls ($p=0.018$) while no change of significance was found in the FDR nor in the RA patients. No significant differences could be found in Stat-3 expression in B-regulatory cells when stratified for HLA-SE or *PTPN22* T-carrier. No significant difference could be found between the three studied populations (Controls/FDR/Patients) regarding; Stat-3 expression, relative cell number to parent ($CD19^+CD20^+$) or relative cell number to grandparent population, in neither CD40-stimulated nor unstimulated B-regulatory cells, respectively.

Conclusion: We have demonstrated that the B-regulatory cells of RA-patients and their FDR could be functionally impaired when measuring the Stat-3 response on CD40 stimulation, compared with healthy controls. HLA-SE and *PTPN22* 1858T genotype did not affect Stat-3 expression. This could indicate that defective B-regulatory cells play a role in the predisposition for RA.

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Regulatory B Cells Suppress Skin Inflammation in a Murine Model of Psoriasis. Koichi Yanaba[1] and Shinichi Sato[2]. [1]The University of Tokyo, Tokyo, Japan, [2]University of Tokyo Graduate School of Medicine, Tokyo, Japan.

Background/Purpose: Psoriasis is a cutaneous disorder characterized by widespread erythematous plaques with adherent scales. Recent studies have revealed that both T helper (Th) 17 and Th1 cells play critical roles in disease development. Histologically, psoriasis is characterized by marked thickening of the epidermis with an inflammatory infiltrate predominantly composed of Th17 and Th1 cells. These infiltrated cells stimulate keratinocytes to produce cytokines, which further amplifies the inflammatory response.

The application of imiquimod occasionally leads to the development of psoriasis in humans. Imiquimod is a potent agonist for Toll-like receptors-7 and -8, and has been used therapeutically in the treatment of a variety of other skin disorders. In mice, the daily topical application of imiquimod induces the appearance of inflamed skin lesions resembling human psoriasis. This experimental method has therefore served as a convenient animal model of the disease.

B cells mediate multiple functions that influence immune and inflammatory responses. Recently, it has been demonstrated that B cells and specific B cell subsets can also negatively regulate immune responses in mice, validating the existence of regulatory B cells. A potent subset of regulatory B cells with a phenotype of $CD1d^{hi}CD5^+$ was recently found to regulate contact hypersensitivity and experimental autoimmune encephalomyelitis in an interleukin (IL)-10-dependent manner. This regulatory B cell subset is called B10 cells to distinguish them from other regulatory B cell subsets that may exist and to identify them as the predominant source of B cell IL-10 production. B10 cell subset is found within the spleen of naïve wild-type mice at 1–2% of the total B cell count, whereas CD19-deficient ($CD19^{-/-}$) mice have few, if any, B10 cells. At present, the contribution of regulatory B cells to imiquimod-induced skin inflammation is unclear. Therefore, we examined the importance of regulatory B cells in imiquimod-induced skin inflammation in $CD19^{-/-}$ and wild-type mice.

Methods: We treated $CD19^{-/-}$ and wild-type mice with imiquimod for 6 days and quantitatively evaluated the severity of skin inflammation.

Results: $CD19^{-/-}$ mice developed more severe skin inflammation, both clinically and pathologically, than wild-type mice. Splenic B10 cells entered the circulation and migrated to draining lymph nodes during imiquimod-induced skin inflammation, thereby suppressing interferon-g and IL-17 production. Remarkably, the adoptive transfer of spleen B10 cells from wild-type mice ameliorated skin inflammation, whereas either splenic B10 cells from $IL\text{-}10^{-/-}$ mice or non-B10 cells from wild-type mice were without effect.

Conclusion: IL-10-producing regulatory B10 cells regulated imiquimod-induced skin inflammation. Further studies are needed to determine the precise mechanisms by which regulatory B cells attenuate the severity of psoriasis. Nonetheless, the current results may provide new insights and therapeutic approaches for treating psoriasis.

Disclosure: K. Yanaba, None; **S. Sato**, None.

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B Cell Derived IFN-γ Contributes To The Negative Regulation Of T-Regulatory Cell Differentiation In Arthritis. Susan Olalekan, Yanxia Cao and Alison Finnegan. Rush University Medical Center, Chicago, IL.

Background/Purpose: Depletion of B cells using a monoclonal antibody against CD20 expressed on mature B cells has proven efficacious in patients with rheumatoid arthritis (RA). We have previously shown in our mouse model of RA, proteoglycan induced arthritis (PGIA), that depletion of B cells leads to enhanced T regulatory cell (Tregs) numbers and activity essential in the suppression of arthritis. This increase in Treg numbers and function correlated with a decrease in $CD4^+$ T cell IFN-γ production. In this study, we investigate the effects of B cells on the generation of Tregs and how IFN-γ contributes to this process.

Methods: An anti-CD20 mAb was used to deplete B cells in $FOXP3^{egfp}$ reporter mice 5 days after immunization intraperitoneally (i.p.) with a recombinant protein for the G1 domain of the human proteoglycan in adjuvant. Mice were sacrificed 4 days after B cell depletion. Naïve and memory $CD4^+CD25^-$ T cells based on CD62L expression were isolated from wild type (WT) and IFN-γ knockout ($IFN\text{-}\gamma^{-/-}$) mice and cultured under Treg differentiating conditions in the presence of proinflammatory cytokines IL-12 and IFN-γ. Flow cytometry was performed and Tregs were phenotyped as $CD4^+$ $Foxp3^+$ cells. ELISA was used to measure cytokine production. In the in vivo transfer model $CD4^+CD62L^+Foxp3^-$ T cell were sorted from transgenic animals and transferred into congenic animals that were later immunized and B cell depleted. Mixed bone marrow chimeras were created by transferring bone marrow cells from B cell deficient and $IFN\text{-}\gamma^{-/-}$ mice in a 1:1 ratio into irradiated recipients. These mice were later immunized i.p. with G1 in adjuvant 3 times at 3 week intervals. Paws were examined every other day for arthritis.

Results: We show that in vitro IFN-γ suppresses the differentiation of $CD4^+CD25^-CD62L^+$ T cells into $Foxp3^+$ Tregs. $CD4^+CD25^-CD62L^-$ T cells were resistant to Treg differentiation and this resistance correlates with copious IFN-γ production. Through an in vivo transfer model of transgenic T cells into congenic mice, we find that $CD4^+CD62L^+Foxp3^-$ T cells are converted into Tregs more effectively in B cell depleted mice as compared to the control group. To determine if IFN-γ is responsible for the suppression of Treg generation, we setup an in vitro Treg differentiation assay using WT and $IFN\text{-}\gamma^{-/-}$ $CD4^+CD25^-CD62L^+$ T cells in the presence of TGF-β and WT or $IFN\text{-}\gamma^{-/-}$ B cells. We find that $IFN\text{-}\gamma^{-/-}$B cells resulted in an increase in Treg differentiation in comparison to WT B cells. Chimeras with a specific deficiency in IFN-γ in B cells also show an increase in the percentage of Tregs.

Conclusion: Our findings demonstrate that B cell derived IFN-γ can negatively regulate the generation of Tregs in arthritis.

Disclosure: S. Olalekan, None; **Y. Cao**, None; **A. Finnegan**, None.

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Fms-Like Tyrosine Kinase 3 Signaling Is Essential For Differentiation Of Antigen Specific Plasma Cells During Experimental Arthritis. Mattias Svensson, Kersti Månsson, Karin Andersson, Mats Bemark, Mikael Brisslert and Maria Bokarewa. University of Gothenburg, Gothenburg, Sweden.

Background/Purpose: Signaling through the tyrosine kinase receptor Flt3 plays an important role in early B-cell development. Mice lacking either Flt3 or its ligand (Flt3L) have reduced numbers of pre-B-cells in the bone marrow (BM) but normal numbers of mature B-cells in the periphery and normal serum levels of Igs. Flt3L is included in a predictive model for the development of rheumatoid arthritis (RA). We have previously shown that Flt3L is increased in RA patients and that interfering with Flt3 signaling during experimental arthritis reduces antibody production. In the present study we investigate how Flt3 signaling on activated B-cell affects terminal differentiation and antibody production during experimental arthritis.

Methods: C57/Bl6 mice deficient for Flt3L (FLKO) and their wild type (WT) counterparts were immunized with mBSA on day 0 and day 7. On day 21, arthritis was induced by an intraarticular injection of mBSA. Mice were sacrificed on day 14 or day 28 and splenocytes and bone marrow cells were isolated. B-cell populations were analyzed using flow cytometry and B-cell associated transcription factors by qPCR. Also, isolated splenocytes stimulated with either LPS or LPS+IL-4, were cultured for antibody and germ-line transcript measurements.

Results: mBSA immunization and LPS activation in vitro induced Flt3 expression on splenic B-cells. Flt3 expressing B-cells represented an activated population recognize by higher expression of MHCII, CD80, CD86 and CD40 when compared to B-cells not expressing the receptor. Lack of Flt3 signaling was associated with enlarged plasma cell population in spleen ($P=0.0014$) and bone marrow ($P = 0.016$), supported by high gene expression of transcription factors IRF4, Blimp1 and XBP1 essential for plasma cell maturation. FLKO mice had increased serum levels of IgM and impaired affinity maturation of mBSA specific IgG1 antibodies. The low IgG1 production by FLKO mice was supported by low formation of germ-line transcripts for IgG1. Stat6 activation (pStat6) controlling IgG1 switch was low FLKO mice compared to WT.

Conclusion: We show that antigen stimulation induces expression of Flt3 on mature B-cells during arthritis. Flt3 signaling is essential for differentiation of antigen specific plasma cells during experimental arthritis. Functional Flt3/Stat6 pathway regulates class switch recombination of IgG1.

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Blocking The Complement Receptor 2 (CR2) Ligand-Receptor Interaction With a Novel Mouse Anti-Mouse CR2 Monoclonal Antibody Decreases Antigen-Specific Humoral Immune Responses and The Evolution Of Collagen-Induced Arthritis. Rosa Rodriguez[1], Liudmila Kulik[1], Joshua Thurman[1], Jonathan Hannan[1], Steve Tomlinson[2] and V. Michael Holers[1]. [1]University of Colorado School of Medicine, Aurora, CO, [2]Medical University of South Carolina, Charleston, NC.

Background/Purpose: The CR2/CD19 complex on B cells serves as a co-receptor for membrane IgM and amplifies B cell responses through physical associations of the bound antigen with the complement C3 activation fragment designated C3d. Prior studies have used *Cr2* −/− mice which lack CR2 expression; however, because the mouse CR2 protein is derived through an alternately spliced mRNA from the same gene as the complement receptor 1 (CR1) protein, a C3b/C4b receptor, one cannot discern whether the primary immune effect is due to deficiency of one or the other receptor, or whether compensatory mechanisms play important roles in the gene-targeted mice. To better understand the unique role of CR2 in autoimmune disease, while minimizing manipulation of CR1, we have generated a novel mouse monoclonal antibody (mAb), designated 4B2, to mouse CR2 that uniquely blocks the CR2/C3d interaction.

Methods: mAb 4B2 (IgG1) was generated in *Cr2*−/− mice by immunizing with recombinant mouse CR2 spanning the ligand-binding site within short consensus repeat domains 1–4 and fusion with the 653 myeloma cell line. A mouse model of collagen-induced arthritis (CIA) was used, and more recently a mouse model of lupus-like disease is being used to study the effects of blocking the CR2/C3d ligand-receptor interaction with mAb 4B2.

Mice were immunized twice with sheep red blood cells (SRBC) to evoke a primary and secondary antibody response in the presence or absence of a single pre-injection of mAb 4B2. Using the CIA model, the durability of the inhibitory effect of 4B2 was measured, and B cell levels were recorded. Immune responses to antigen were measured in CIA mice pretreated with 4B2, or control isotype mAb. In CIA, mice pre-treated with 4B2 or control mAb were injected with bovine type II collagen, and IgG2a antibodies to mouse and bovine type II collagen (mCII and bCII, respectively) were measured. Peripheral and splenic B and CD4+ T cells were measured as well as B cell subpopulations from spleen. Additionally, a clinical scoring system was used to evaluate arthritis.

Results: Mice pre-injected with 4B2 antibody demonstrated reduced levels of anti-SRBC IgG1 levels. Mice with CIA treated with 4B2 demonstrated a 6 week blockade of CR2 and significantly decreased anti-mCII and anti-bCII IgG2a. No anti-idiotype antibodies were generated to 4B2. Splenic B cell follicular, transitional, immature and marginal zone subpopulations were not changed. B and T cell hematopoietic changes were not seen. Clinical disease activity was substantially decreased in mice treated with mAb 4B2. Additionally, 4B2 is being used in studies of (NZBxNZW)F1 mice, which spontaneously develop lupus-like disease.

Conclusion: We have shown that the mouse monoclonal antibody to CR2, 4B2, is able to block CR2/C3d interaction and decrease immunological responses to model antigens as well as the development of CIA. Studies using 4B2 in (NZBxNZW)F1 mice are being undertaken to determine whether chronic blockade of the CR2/C3d interaction can be used as a therapeutic approach in lupus. Chronic inhibition of the CR2/C3d interaction can be further studied with this new tool as a potential therapeutic approach in other mouse models of autoimmune and inflammatory disease.

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Role Of B Cells and/Or Autoantibodies In Pulmonary Manifestations Of Inflammatory Arthritis. Lisa K. Peterson[1], Jeremy Sokolove[2], Paul Jedlicka[3], Lauren J. Lahey[2], William H. Robinson[4] and Leonard L. Dragone[1]. [1]National Jewish Health, Denver, CO, [2]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [3]University of Colorado Denver, Aurora, CO, [4]Stanford University, Palo Alto, CA.

Background/Purpose: RA is a systemic condition affecting approximately 1% of the general population leading to progressive arthritis and extra-articular manifestations (ExRA), including interstitial lung disease (RA-ILD). RA-ILD is a major cause of morbidity and mortality due to its progression despite the use of therapies that effectively treat arthritis. These observations suggest that the articular and RA-ILD manifestations may have overlapping but unique features related to their pathogenesis, which could be identified and specific therapies started if biomarkers for RA-ILD were available. A significant obstacle to advancing our ability to predict the development of RA-ILD is the limited availability of relevant experimental mouse models that have a predictable kinetics of developing RA-ILD.

Methods: To enable mechanistic and biomarker studies, we created a mouse disease model based on SKG mice which develop inflammatory arthritis as well as ExRA manifestations upon zymosan exposure. Our model utilizes Double SKG Src-Like adaptor protein (SLAP)-Knockout mice (DSSKO) that are arthritis-resistant to the disease trigger (zymosan), yet develop progressive lung inflammation with histologic features of the clinical manifestations of RA-ILD that occurs with predictable kinetics. To examine the contributions of lymphocytes to the pulmonary manifestations associated with inflammatory arthritis using adoptive transfer and antibody-mediated cell depletion.

To identify autoantibodies associated with autoimmune lung disease in zymosan-treated DSSKO mice we performed arthritis autoantigen arrays on a well-characterized cohort of DSSKO mice with lung disease but without arthritis and SKG mice with arthritis but without lung disease. As a complement to this approach, generated B cell hybridomas and screened them against lung tissue lysates by ELISA and western blot. Specific autoantigens were then identified using mass spectrometry.

Results: Transfer of $CD4^+$ T cells from DSSKO mice into $RAG2^{-/-}$ mice induced arthritis in the absence of the lung disease. Thus, CD4+ T cells are not sufficient to induce lung disease. In contrast, B cell depletion studies using an anti-CD20 monoclonal antibody eliminated lung disease in DSSKO mice, implicating B cells and/or autoantibodies in lung disease pathogenesis.

In addition, DSSKO mice developed distinct profiles of anti-citrullinated antibodies compared to arthritis-prone (SKG) controls. DSSKO mice developed autoantibodies to several citrullinated antigens previously detected in the serum of humans with RA, though the exact relationship to RA-ILD pathogenesis is unknown.

Conclusion: B cells and/or autoantibodies are required for autoimmune lung disease in zymosan-treated DSSKO mice. DSSKO mice developed a distinct profile of autoantibodies to antigens that have been detected in the serum of humans with RA, but the relationship to RA-ILD pathogenesis is unknown. Therefore, identification of autoantibodies that develop during lung disease in DSSKO mice may reveal new biomarkers for RA-ILD. Identified autoantibodies could potentially also be used to determine their contribution to disease pathogenesis.

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Redox Dependent Conformational Changes Of The Autoantigen La Are Responsible For Its Shuttling, Translocation and a Pathophysiological Role Of Anti-La Autoantibodies. Irene Michalk[1], Nicole Berndt[1], Claudia C. Bippes[1], Holger Bartsch[1], Stefanie Koristka[1], Claudia Arndt[1], Anja Feldmann[1], Biji T. Kurien[2], Robert Hal Scofield[3], A. Darise Farris[4], Judith A. James[5], Marc Cartellieri[1] and Michael Bachmann[1]. [1]Carl Gustav Carus TU-Dresden, Dresden, Germany, [2]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [3]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation; Department of Medicine, University of Oklahoma Health Sciences Center; US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [4]Oklahoma Medical Research Foun, Oklahoma City, OK, [5]Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: Since their detection a pathophysiological role of antibodies (abs) to extractable nuclear autoantigens including anti-La abs has been controversially discussed. Stainings of anti-La abs point to an exclusive nuclear localization. However, we and others have also seen an intracellular shuttling and an occurrence on the cell surface. All conditions leading to a translocation of La onto the cell surface were later found to induce apoptosis. Therefore, a pathophysiological contribution of anti-La abs appears rather unlikely. And, even until today, the mechanisms underlying the shuttling and translocation of the autoantigen are still largely unclear.

Methods: Ten novel monoclonal abs (mabs) were established, characterized by epitope mapping and used for analysis of intra- and cell surface localization of La by immunoblotting, ELISA, epifluorescence microscopy and FACS. The observed redox dependent localization was confirmed by analysis of native and cystein mutant (GFP) La forms. In addition to mabs, human anti-La abs directed to redox dependent forms of La were isolated from autoimmune sera, tested for binding to cell surface La and induction of an ADCC using Chromium-release and FACS-based cytotoxicity assays.

Results: Reactivities of novel anti-La mabs were found to depend on reducing/non-reducing conditions when analyzed by immunoblotting or ELISA. The sensitivity to oxidation was lost when all three cystein residues present in La were mutated. Oxidation of native La protein or cystein mutants in which only one or two cystein residues were mutated leads to inter- and intra cystein disulfide bonds, and thereby to the formation of dimers and higher oligomers *in vitro* and *in vivo*. Oxidative stress results in oxidation of La and causes a separation from a redox dependent nuclear retention partner. Thereafter, La translocates to the cytoplasm and its reentry into the nucleus is blocked resulting in a cytoplasmic enrichment. Oxidation of La can occur in a cell type specific manner. E.g. LPS treatment causes a translocation only in cells expressing TLR4. Dying cells can release La. Released La binds strongly to the surface of neighbouring intact cells. The binding depends on the cell type and the oxidative status of the protein. Only oxidized La binds strongly to the surface of cells including to epithelial, endothelial, blood DCs and other APCs but not to NK- or T cells. Surface bound La is available for binding of anti-La abs, thereby mediating ADCC. Furthermore, it can bind nucleic acids including DNA which improves the binding of other autoantibodies such as anti-DNA abs. Such La/nucleic acid complexes can lead to maturation of DCs.

Conclusion: Under physiological conditions the shuttling of La is favoured to a nuclear localization. Redox dependent conformational changes of La alter this balance resulting in an enrichment of La in the cytoplasm. Dead cells release La which then binds to the surface of intact living cells in a redox dependent manner. Anti-La abs can bind to surface La and cause an ADCC. These redox dependent alterations explain why anti-La abs can become of pathophysiological relevance only under conditions causing acute phases of disease in autoimmune patients.

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B Cell Subsets and Dysfunction Of Regulatory B Cells In IgG4-Related Diseases and Primary Sjögren Syndrome: The Similarities and Differences. Wei Lin[1], Lixia Jin[2], Wen Zhang[1], Hua Chen[1], QingJun Wu[1], Yunyun Fei[1], Yan Zhao[1], Xiaofeng Zeng[1] and Fengchun Zhang[1]. [1]Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, China, [2]Tsinghua University, Beijing, China.

Background/Purpose: IgG4 related disease (IgG4-RD) is a chronic, multisystem-involved autoimmune disease. Abnormally activated and differentiated B cells may play important roles. Regulatory B cells (Breg) are newly defined B cell subgroups with immunosuppressive functions. In this study, we investigated the differences of B cell subsets, the expressions of co-stimulatory molecules on B cells, and the function of Breg cells in the peripheral blood of patients with IgG4-RD, primary Sjögren's syndrome (pSS), and healthy donors.

Methods: We recruited 38 newly diagnosed IgG4-RD patients, 38 newly diagnosed pSS patients and 30 healthy volunteers were included as disease and healthy controls. To analyze B cell subsets and B cell activity, PBMCs were surface stained with CD19, CD24, CD38, BAFF-R, CD40, CD80 and CD86 mAbs and then detected by flow cytometry. The function of Bregs was tested by co-culturing of isolated CD19+CD24^{hi}CD38^{hi} Breg cells with purified CD4+CD25- effector T cells. Serum cytokines were measured by ELISA. Correlation of clinical data and laboratory findings were measured as well.

Results: Compared with pSS patients and healthy controls, IgG4-RD patients had a lower frequency of peripheral mature B cells and Breg cells. Interestingly, CD19+CD24-CD38hi B cell subsets were significantly higher in peripheral blood B cells from new-onset IgG4-RD patients than in pSS patients and healthy controls. The expression of BAFF-R and CD40 on B cells was significantly lower in IgG4-RD patients compared with those in pSS patients and healthy controls. Whereas, the expression of CD86 and CD80 on B cells was significantly increased in IgG4-RD patients compared with those in pSS patients and healthy controls. Unlike healthy B cells, CD19+CD24hiCD38hi Breg cells from pSS patients were lack of suppression function.

Conclusion: B cells in patients with IgG4-RD and pSS display a variety of abnormalities including disturbed B cell subpopulations, abnormal expression of key signaling molecules, co-stimulatory molecules. A significantly increased B cell subset, CD19+CD24-CD38hi B cells may play an important role in the pathogenesis of IgG4-RD.

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B Cell Subset Phenotypes In Patients With Granulomatosis With Polyangiitis (Wegener's). Atul A. Khasnis[1], Carol A. Langford[2], L Calabrese[2], Julia M. Sugalski[3], Michael Lederman[3] and Donald D. Anthony[4]. [1]Cleveland Clinic Foundation, Cleveland, OH, [2]Cleveland Clinic, Cleveland, OH, [3]Case Western Reserve University, Cleveland, OH, [4]Case Western Reserve University, Cleveland VA Medical Center, University Hospitals of Cleveland, Cleveland, OH.

Background/Purpose: B cells are pathogenic in granulomatosis with polyangiitis (Wegener's) (GPA). Rituximab (RTX), an anti-CD20 monoclonal antibody, is effective therapy however B cell reconstitution patterns after RTX are unknown. We present pilot data on B cell subsets in GPA patients compared to healthy controls in addition to GPA patients with active disease or remission as well as patients who are treated with RTX or non-biologic immunosuppression.

Methods: GPA patients were enrolled into: Group I (Active), Group II (Remission) and Group III (Controls). We have currently recruited 4 patients into Group 1, 13 patients into Group 2 and 5 patients in Group 3. Frozen

peripheral blood mononuclear cells were stained with isotype control, anti-CD19, anti-CD10, anti-CD20, anti-CD27, anti-CD38 and anti-CD21 antibodies. B cell subset frequencies were measured as CD19+ cell proportions that are CD10+CD27− (immature transitional - IT), CD10−CD21+CD27− (naive), CD10−CD21+CD27+ (resting memory - RM), CD10-CD21−CD27+ (mature activated - MA), CD10−CD21−CD27− (tissue like memory-TLM) and CD20-CD38+ (plasmablasts). Median proportions were compared using the Wilcoxon rank sum test with $P < 0.05$ considered significant.

Results: In all GPA subjects (n=17), we observed a decrease in total lymphopenia (P=0.03; 45.5 vs 66.2) and significantly decreased naïve B cell frequencies (P=0.04; 28.4 vs. 70.1) as compared to controls (n=5). GPA patients with active disease (n=4) had a significantly increased proportion of IT B cells (P=0.04; 27.85 vs. 0) compared to patients in remission. Patients in remission (n=13) who had received RTX had significantly decreased naïve B cell (P=0.03; 17.6 vs. 59.45) as compared to patients receiving non-biologic immunosuppression therapy (n=6). There were no statistically significant differences between other B cell subsets when comparing GPA patients with controls, active disease with remission, and comparing RTX with non-biologic immunosuppression.

Conclusion: Patients with GPA appear to have a skewed B cell profile compared to healthy controls and this is altered during active disease with a potentially increase in the IT B cell subset. Despite clinical remission observed with RTX, GPA patients continue to have lower frequencies of naïve B cells.

Table 1. B cell subset analyses comparing: 1) GPA patients with controls, 2) Active disease with remission and 3) patients in remission after RTX versus non-biologic immunosuppression

	GPA vs. controls			Active vs. remission			RTX vs. non-RTX		
Parameter**	GPA (n= 17)	Controls (n = 5)	p value	Active GPA (n = 4)	GPA in remission (n = 13)	p value	RTX group (n = 7)	Non-RTX group (n = 6)	p value
Total lymphocytes	45.50	66.2	**0.03**	39.45	53.00	0.41	53	50.35	0.94
CD19+ cells	0.70	6.43	0.16	8.52	0.70	0.62	0.15	2.17	0.23
Immature transitional	0.00	0.03	0.37	0.51	0.00	**0.05**	0	0	0.38
Mature activated	8.45	3.28	0.19	22.86	8.45	0.62	13.9	4.73	0.37
Resting memory	19.90	13.8	0.65	11.59	20	0.41	16.1	27.1	0.23
Tissue like memory	18.20	8.5	0.24	19.5	18.2	1.00	30	11.26	0.18
Naive	28.40	70.1	**0.04**	26.9	28.4	0.61	17.6	59.45	**0.03**
Plasmablast	5.1	2.96	0.25	0.22	0.69	0.82	3.61	0.54	0.44

** All numbers represent B cell subset frequencies

Disclosure: A. A. Khasnis, None; **C. A. Langford**, Bristol-Myers Squibb, 9, Genentech and Biogen IDEC Inc., 9; **L. Calabrese**, None; **J. M. Sugalski**, None; **M. Lederman**, None; **D. D. Anthony**, None.

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Autoantibodies to the Th/To Complex Are the Most Common Antibodies in Systemic Sclerosis (SSc) Patients Without Other Autoantibodies. Michael Mahler[1], Jason Y.F. Chan[2], Edward K.L. Chan[2], Minoru Satoh[2], Marie Hudson[3], Murray Baron[4], James Wick[5] and Marvin J. Fritzler[5]. [1]INOVA Diagnostics, San Diego, CA, [2]University of Florida, Gainesville, FL, [3]McGill University, Montreal, QC, [4]Jewish General Hospital, Montreal, QC, [5]University of Calgary, Calgary, AB.

Background/Purpose: Antinuclear antibodies (ANA) play an important role in the diagnosis of systemic sclerosis (SSc) being present in about 80–90% of the patients. In the majority of ANA positive SSc patients, SSc-specific and SSc-associated antibodies can be detected (i.e. antibodies to centromere, Scl-70, RNA Pol-III, PM/Scl, Ro52/TRIM21 and U1RNP). However, in a significant portion of ANA positive SSc patients, no fine specificities can be detected when conventional diagnostic protocols are used. Several studies demonstrated limited sensitivity for the detection of autoantibodies (especially anti-nucleolar antibodies) using solid phase screening assays in SSc patients. Recently, it was found that anti-Rpp25 antibodies are an important autoantigenic component of the Th/To complex. However, it remains unknown how much anti-Th/To and anti-Rpp25 antibodies contribute to ANA positivity in SSc patients. Consequently, the present study aimed to define the prevalence of autoantibodies to Rpp25 in SSc patients without other SSc-specific or SSc-associated antibodies.

Methods: Sera from 874 Canadian SSc patients were tested for ANA and various SSc-specific and SSc-associated antibodies including antibodies to common extractable nuclear antigens (ENA) and to those contained in a SSc line immunoassay (Euroimmun, Germany). Samples without those antibodies (n=54, later referred to as ANA+/ENA-) were analyzed by immunoprecipitation (IP) analysis of proteins and RNAs and for anti-Rpp25 antibodies (n=51) by a chemiluminescent immunoassay (CIA, QUANTA Flash, INOVA Diagnostics, US) and Rpp25 ELISA (University of Florida, US).

Results: Anti-Th/To antibodies were the most common antibody in ANA+/ENA-negative SSc patients; being found in 18/54 (26%) of the patients as determined by IP. A total of 51 of these samples were available for additional testing by CIA and ELISA. Anti-Rpp25 antibodies were detected in 12 (23.5%, CIA) or 10 (19.6%, ELISA) of 51 patients when using the recently established cut-off values. ROC analysis showed similar discrimination between Th/To IP positive (n=18) and negative samples (n=33) by CIA and ELISA (AUC 0.89 *vs.* 0.86; $p=0.7491$). The positive percent agreements between IP and CIA or ELISA were 12/18 (66.7%, 95% Confidence interval 41.0–86.7%) or 10/18 (56.7%, 95% CI 30.8–78.5%), respectively. Negative percent agreements were 100% for both assays (95% CI 89.4–100.0%).

Conclusion: Autoantibodies to the Th/To autoantigen are important in SSc patients who have been considered to be negative for SSc-specific or SSc-associated antibodies by widely available commercial assays. Rpp25 has been confirmed as a major target of these anti-Th/To antibodies. Diagnostic assays for the detection of anti-Th/To and anti-Rpp25 antibodies hold promise to improve the diagnosis and management of SSc. Rpp25 might also help to improve solid phase screening assays for the detection of autoantibodies in SSc patients.

Disclosure: M. Mahler, Inova Diagnostics, Inc., 3; **J. Y. F. Chan**, None; **E. K. L. Chan**, None; **M. Satoh**, None; **M. Hudson**, None; **M. Baron**, None; **J. Wick**, None; **M. J. Fritzler**, Inova Diagnostics, Inc., 5.

ACR/ARHP Poster Session B
Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis I
Monday, October 28, 2013, 8:30 AM–4:00 PM

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The Role of HIF-1 and HIF-2 During Angiogenesis and Metabolic Adaptation of Human Microvascular Endothelial Cells Towards Hypoxia. Martin Hahne[1], Cindy Strehl[1], Manuela Jakstadt[1], Paula Hoff[1], Timo Gaber[1], Gerd-Rüdiger Burmester[2] and Frank Buttgereit[3]. [1]Charité University Medicine, Berlin, Germany, [2]Charite University Hospital, Berlin, Germany, [3]Charité - Universitätsmedizin Berlin, Berlin, Germany.

Background/Purpose: Hypoxia is a feature of RA synovitis. In the present study, we focused on the two transcription factors Hypoxia inducible factor (HIF)-1 and (HIF)-2. These factors are known to regulate the cellular and metabolic responses to pathophysiologically reduced oxygen tension thereby promoting both angiogenesis and metabolic adaptation of endothelial cells. However, functional differences and similarities between these factors in these regards have not been investigated so far. Our aim was to knockdown either HIF-1α or HIF-2α in human microvascular endothelial cells (HMEC), respectively, in order to understand the differential impact of HIF-1 and HIF-2 on the angiogenic and metabolic transcriptome under hypoxic versus normoxic conditions.

Methods: Specific knockdown of either HIF-1α or HIF-2α was achieved using lentiviral-based shRNA technology. Angiogenic and metabolic transcriptome was studied by performing gene expression studies (Agilent Human Whole Genome 60K Microarrays) of (un-)transduced HMECs incubated under normoxia (18% O2) vs. hypoxia (1% O2) for 20h. Obtained data were analyzed by the classification of significantly regulated genes ($\geq$2-fold change, $p<0.01$) into angiogenic and metabolic processes using Panther database.

Results: In untransduced HMECs, we identified 73 angiogenesis related genes in 11 different pathways and 17 cellular metabolism related genes in 9 different pathways, respectively, which are differentially expressed under hypoxia vs. normoxia. Interestingly, in both HIF-1α and HIF-2α knockdown cells, hypoxia was still capable of inducing a differential gene expression pattern, but the effect was much less pronounced if compared with cells without knockdown.

Analysis of effects on *angiogenesis* related processes (VEGF pathway, HIF activation, EGFR pathway) showed that 74% of the differentially expressed genes are controlled by both HIF-1 and HIF-2. Another 14% of the regulated genes depend on the presence of HIF-1, among them the genes *GRB2*, *PDGFRB*, *PLD*, *WNT5A* and *MMP3.* The remaining 12% of regulated genes are under the control of HIF-2, among them the genes *DLL3*, *HSP27b2*, *NOTCH4*, *PKC* and *MMP1.*

The differentially regulated genes encoding proteins/enzymes involved in the *cellular metabolism* (i.e. glycolysis, ATP synthesis, TCA cycle) were found to be to 80% controlled by both HIF-1 and HIF-2, respectively. The remaining 20% are dependent on the presence of HIF-1, among them the genes *FOXJ1*, *FOXQ1* and *Cyt C.*

Conclusion: Both HIF-1α and HIF-2α are key regulators driving the adaptation of endothelial cells towards hypoxia with overlapping functions. However, they do differ in their capacity to regulate *cellular energy metabolism* and *angiogenesis*. This leads us to conclude that HIF-1α affects angiogenesis via indirect effects on cellular energy metabolism as indicated by the regulation of metabolic transcriptome to one fifth. In contrast, HIF-2α does influence angiogenesis more directly via regulating the synthesis of proangiogenic factors (as has been previously shown).These findings provide new insights into the divergent regulation of angiogenesis in inflamed (hypoxic) tissues by HIF-1 and HIF-2 and are, therefore, considered to be of clinical relevance in RA.

Disclosure: M. Hahne, None; **C. Strehl**, None; **M. Jakstadt**, None; **P. Hoff**, None; **T. Gaber**, None; **G. R. Burmester**, None; **F. Buttgereit**, None.

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The Bioenergetic Role of HIF-1 and HIF-2 During Angiogenesis of Human Microvascular Endothelial Cells. Martin Hahne[1], Cindy Strehl[1], Manuela Jakstadt[1], Paula Hoff[1], Timo Gaber[1], Gerd-Rüdiger Burmester[2] and Frank Buttgereit[3]. [1]Charité University Medicine, Berlin, Germany, [2]Charite University Hospital, Berlin, Germany, [3]Charité - Universitätsmedizin Berlin, Berlin, Germany.

Background/Purpose: Hypoxia is a feature of inflamed tissues. The transcription factors Hypoxia inducible factor (HIF)-1 and (HIF)-2 regulate the cellular and metabolic responses to reduced oxygen tensions thereby promoting angiogenesis with implications on the pathogenesis of rheumatoid arthritis (RA). However, functional differences and similarities between these factors in regard to bionergetics have not been investigated so far. Our aim was to knockdown either HIF-1α or HIF-2α in human microvascular endothelial cells (HMEC) in order to investigate resulting effects on angiogenesis and bioenergetics under hypoxia vs. normoxia. In previous studies we showed that HIF-2α does directly influence angiogenesis via regulating the synthesis of proangiogenic factors. In this study we focused on the regulation of bioenergetics by HIF-1α and HIF-2α, respectively.

Methods: Specific knockdown of either HIF-1α or HIF-2α was achieved using lentiviral-based shRNA technology. Angiogenesis of transduced HMECs was studied by investigating both tubuli and node formation under hypoxic (<1% O2) versus normoxic (~18% O2) conditions.

Expression of genes involved in the metabolic response to hypoxia *(GAPDH, PGK, GLUT1, LDHA)* was quantified by realtime RT-PCR. The bioenergetic status of the cells was quantified via ATP/ADP measurements.

Results: Knockdown of HIF-1α resulted in a loss of both hypoxia induced node ($p<0.01$) and tubuli formation ($p=0.09$). Also HIF-2α knockdown was followed by a significant reduction of hypoxia induced formation of tubuli ($p<0.05$).

Focusing on bioenergetic aspects, we found hypoxia to significantly induce the gene expression of *PGK* ($p<0.001$), *LDHA* ($p<0.05$) and *GAPDH* ($p<0.05$) in control cells. Interestingly, knockdowns of HIF-1α and HIF-2α, respectively, did not affect the hypoxic induction of *PGK* and *LDHA* expression.

In both HIF-1α ($p=0.01$) and HIF-2α ($p=0.13$) knockdown cells, hypoxia was still capable of inducing *GAPDH*, but the effect was considerably less pronounced in HIF-1α knockdown cells. Hypoxia did not significantly up-regulate *GLUT1* (encoding the glucose transporter 1), neither in control nor in HIF-1α or HIF-2α knockdown cells.

However, the knockdown of HIF-2α resulted in significantly decreased expression levels of *GLUT1* under hypoxia ($p<0.01$).

We also found the ATP/ADP ratio to be similar in control, HIF-1α knockdown and HIF-2α knockdown cells under normoxia. Under hypoxia, however, HIF-1α knockdown cells showed a significantly reduced ATP/ADP ratio ($p<0.05$)–indicating that less ATP is available–compared to HIF-2α knockdown cells.

Conclusion: HIF-1α and HIF-2α are both key regulators of angiogenesis. However, they do differ in their potency to regulate cellular energy metabolism. We show here HIF-1α to affect angiogenesis via effects on cellular energy metabolism as indicated by the reduced expression of *GAPDH* and the diminished ATP/ADP ratio. In contrast, HIF-2α has rather modest effects on cellular energy metabolism but has been shown to affect angiogenesis directly via regulating the synthesis of proangiogenic factors. These findings provide new insights into regulation of angiogenesis in inflamed (hypoxic) tissues and are, therefore, considered to be of clinical relevance in RA.

Disclosure: M. Hahne, None; **C. Strehl**, None; **M. Jakstadt**, None; **P. Hoff**, None; **T. Gaber**, None; **G. R. Burmester**, None; **F. Buttgereit**, None.

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Blockade Of TNFα Produced By TSLP-Primed CD1c Myeloid Dendritic Cells Skews T Cell Response To Th2 Activity In Rheumatoid Arthritis Patients. F.M. Moret, T.R.D.J. Radstake, J.W.J. Bijlsma, F.P.J.G. Lafeber and J.A.G. van Roon. University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: Thymic stromal lymphopoietin (TSLP) is well known for its potent activation of myeloid dendritic cells (mDCs) to induce Th2-mediated immune responses. Additionally, TSLP and its receptor play a crucial role in promoting Th17-driven collagen-induced arthritis. Recently, we have shown that increased intra-articular TSLP concentrations in RA patients potently activate TSLPR-expressing mDCs from peripheral blood (PB) and synovial fluid (SF) of RA patients to secrete T cell attractant chemokines and to potently increase Th1, Th17 and Th2 activity. Since TNFα is a crucial pro-inflammatory and tissue-destructive mediator in RA, we assessed the capacity of TSLP to regulate TNFα production by CD1c mDCs and the effects of TNFα blockade in T cell regulation.

Methods: CD1c mDCs, isolated from PB or SF of RA patients, were primed with TSLP for 20 hours without or with anti-TNFα mAb and cytokine production was measured by multiplex immunoassay. Washed TSLP-activated mDCs primed without or with anti-TNFα mAb were added to autologous CD4 T cells in the absence of additional stimuli, cultured for 6 days and subsequently proliferation was measured. Additionally, T-cell cytokine production was measured by ELISA upon restimulation with ionomycin/PMA.

Results: Upon incubation with TSLP, mDCs from PB and SF potently stimulated TNFα production of autologous CD4 T cells as compared to unprimed mDCs (ratio T cell:DC 5:1, PB from 3498 to 9225 pg/ml, $p=0.001$ and SF from 8951 to 18415 pg/ml, $p<0.05$). TSLP significantly stimulated the production of TNFα by mDCs from PB and SF (PB from 99 to 378 pg/ml, $p<0.05$ and SF from 170 to 355 pg/ml, $p<0.05$). Blockade of TNFα during TSLP-priming of mDCs did not affect T-cell differentiating cytokine production but significantly decreased MIP1α and enhanced TARC production (MIP1a:TARC ratio, TSLP-mDCs versus anti-TNFα-TSLP-mDCs, ratio 40 vs. 3, $p<0.05$, respectively). Co-culturing TSLP-primed-mDCs that had been treated with anti-TNFα mAb together with T cells did not affect IFNγ and IL-17 production but significantly increased IL-4 production as well as the IFNγ:IL-4 ratio (TSLP-mDCs versus anti-TNFα-TSLP-mDCs, ratio 11 vs. 5, $p<0.05$, respectively).

Conclusion: TSLP induces TNFα production by CD1c mDCs and mDC-activated CD4 T cells of RA patients. Blockade of TNFα produced by TSLP-primed-mDCs results in the enhancement of Th2 activity by promoting Th2 attracting chemokine production and T cell skewing towards Th2 activity. Considering the inhibitory capacity of Th2 cells in RA, this suggests that TNFα blockade in RA patients contributes to reduced immunopathology by increasing the Th2-inducing potential of TSLP.

Disclosure: F. M. Moret, None; **T. R. D. J. Radstake**, None; **J. W. J. Bijlsma**, None; **F. P. J. G. Lafeber**, None; **J. A. G. van Roon**, None.

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The Endocannabinoid Anandamide Modulates Adhesion, Proliferation and The Production Of Inflammatory Mediators In Rheumatoid Arthritis Synovial Fibroblasts By Activating CB_1, TRPV1, TRPA1 and Non-Cannabinoid Receptor Targets. Torsten Lowin, Angelika Graeber and Rainer H. Straub. Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, University Hospital of Regensburg, Regensburg, Germany.

Background/Purpose: In rheumatoid arthritis (RA), synovial fibroblasts (SF) secrete large amounts of IL-6, IL-8 and matrixmetalloproteinases (MMPs) which are crucial for cartilage destruction. RASFs are sensitive to the action of cannabinoids and they express cannabinoid receptors type I and II (CB_1 and CB_2), the vanilloid receptor (TRPV1) as well as endocannabinoid

degrading enzymes (FAAH and COX-2). Cannabinoids are regarded as antiinflammatory and since anandamide (AEA) is found in RA synovial fluid we investigated how this endocannabinoid affects adhesion, proliferation and production of inflammatory mediators of RASF.

Methods: Adhesion was assessed by the XCELL*igence* system. Proliferation was quantified by the amount of incorporated fluorescent dye into cellular DNA. MMP-3 and cytokines were detected by ELISA. Collagen II induced arthritis was used a s a mouse model of RA.

Results: AEA dose-dependently decreased IL-1β induced production of MMP-3, IL-6 and IL-8 in RASFs and OASFs under normoxic conditions (20% O_2). The efficacy of AEA was significantly enhanced by addition of the COX-2 inhibitor nimesulide. The effects of AEA were not inhibited by CB_1, CB_2 or GPR55 antagonists but were blocked by the TRPV1 antagonist capsazepine in RASFs but not OASFs. Under hypoxic conditions (1% O_2) and TNF stimulation, the effects of AEA on cytokine and MMP-3 production were blocked by TRPA1 and TRPV1 antagonists. In mixed synovial cell cultures however, AEA increased the production of TNF (100%) which was enhanced by inhibition of AEA degradation. Furthermore, AEA increased adhesion of OASFs and RASFs to fibronectin. Adhesion was modulated by CB_1, GPR55 and TRPV1 antagonists in OASFs but not in RASFs. Combined FAAH and COX-2 inhibition blocked the stimulatory effect of AEA on adhesion in OASF.Proliferation was decreased by AEA in RASFs and OASFs via a cyclooxygenase-2 but not via CB_1, CB_2 or TRPV1 dependent mechanism. Elevation of endogenous AEA by inhibition of its degradation showed beneficial effects in collagen-induced arthritis in mice.

Conclusion: In conclusion, AEA promotes an antiinflammatory phenotype of RASFs and OASFs by activating/desensitizing TRPV1 and TRPA1 under hypoxic conditions. Furthermore, COX-2 inhibition is necessary to fully exploit the therapeutic potential of AEA. This might be important in RA where low oxygen and abundant cytokine expression up-regulate COX-2 in the joint.

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Effect Of Neutralizing IL-17A and IL-17F Antibodies On Host Resistance To Acute *Mycobacterium Tuberculosis* Infection In Mice In Comparison With Neutralizing TNF-α Treatment. Michael Kammüller[1], Franco Di Padova[1], Christian Antoni[2], Salah-Dine Chibout[1], Timothy Wright[3], Marie-Laure Bourigault[4], Noria Segueni[4], Stephanie Rose[4], Bernhard Ryffel[4] and Valerie Quesniaux[4]. [1]Novartis Institutes for Biomedical Research, Basel, Switzerland, [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [3]Novartis Pharma AG, Basel, Switzerland, [4]UMR7355 CNRS and University of Orleans, Orleans, France.

Background/Purpose: Antibodies targeting IL-17A or IL-17RA are in clinical trials for the treatment of several autoimmune diseases. However, these therapies, by blocking critical mediators of innate and adaptive immunity, may carry the risk of an increased susceptibility to infections. While *M. tuberculosis* infections can be an important complication of anti-TNFα therapies, the role of the Th17/IL-17 pathway in host resistance to this intracellular pathogen is less clear.

Methods: The effect of neutralizing IL-17A or IL-17F during acute *M. tuberculosis* infection was evaluated in a 4-week aerosol mouse model. *M. tuberculosis* (strain H37Rv, 1000 CFU) infected C57BL/6 mice were treated once per week i.p. with 0.5 mg (approximately 20 mg/kg) of anti-mouse IL-17A or F antibodies, 0.25 mg (approximately 10 mg/kg) of anti-mouse TNFα antibody, and respective isotype control antibodies, starting 1 day before the infection. Disease symptoms, lung and spleen weight, pulmonary bacterial burden and lung histopathology were assessed at day 28.

Results: IL-17A or IL-17F blockade like the isotype controls did not alter body, lung, and spleen weights, pulmonary bacterial burden and lung histopathology after 28 days. On the other hand, in mice treated with a neutralizing anti-TNFα antibody, body weight was drastically decreased, while lung and spleen inflammation and pulmonary bacterial burden were clearly increased by day 28. These changes were associated with a worsening of the microscopic observations in the lung with the anti-TNFα antibody. TNFα-deficient mice succumbed by day 28 to severe infection under these experimental conditions.

Conclusion: Overall, these results confirm the importance of TNFα in host resistance to *M. tuberculosis* infection, and highlight that anti-IL-17A or anti-IL-17F cytokine blockade for 4 weeks *in vivo* do not impair immunity in an acute mouse *M. tuberculosis* infection model.

Disclosure: M. Kammüller, Novartis Institutes for Biomedical Research, 3, Novartis Institutes for Biomedical Research, 1; **F. Di Padova**, Novartis Institutes for Biomedical Research, 3; **C. Antoni**, Novartis Pharmaceutical Corporation, 3; **S. D. Chibout**, Novartis Institutes for Biomedical Research, 3; **T. Wright**, Novartis Pharma AG, 3; **M. L. Bourigault**, Novartis Institutes for Biomedical Research, 2; **N. Segueni**, Novartis Institutes for Biomedical Research, 2; **S. Rose**, Novartis Institutes for Biomedical Research, 2; **B. Ryffel**, Novartis Institutes for Biomedical Research, 2; **V. Quesniaux**, Novartis Institutes for Biomedical Research, 2.

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Hypoxia and Signal Transducer and Activator Of Transcription 3 Signalling Interactions Regulate Pro-Inflammatory Pathways In Rheumatoid Arthritis. Wei Gao[1], Jennifer McCormick[2], Mary Connolly[3], Emese Balogh[3], Douglas J. Veale[1] and Ursula Fearon[2]. [1]Translational Rheumatology Research Group, Dublin, Ireland, [2]St. Vincent's University Hospital, Dublin 4, Ireland, [3]Translation Research Group, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland.

Background/Purpose: Signal Transducer and Activator of Transcription 3 (STAT3), a critical transcription activator in angiogenesis, plays a crucial role in the pathogenesis of Rheumatoid Arthritis (RA). Hypoxia and Notch signalling regulate angiogenesis, cell proliferation, invasion and survival. This study was to examine the effect of hypoxia on STAT3-induced pro-inflammatory pathways in RA.

Methods: Expression of phospho-STAT3 in synovial tissue and RA synovial fibroblasts (RASFC) was assessed by immunohistology/immunofluorescence. Primary RASFC and synoviocyte cell lines (K4IM) were cultured under 3% hypoxia and normoxia conditions±Stat3-siRNA, HIF-siRNA or WP1066 (potent STAT inhibitor). HIF1α, p-STAT3 and Notch-1IC (intracellular domain) protein expression were analyzed by Western blot. Functional mechanisms were quantified by invasion chamber, matrigel and wound repair assays. IL-6, IL-8, IL-10 and MMP-3 were quantified by ELISA. Notch-1 receptor, its DLL-4 ligand and downstream target genes (*hrt-1, hrt-2*) were quantified by Real-time PCR. Finally the effect of WP1066 on spontaneous secretion of pro/anti-inflammatory cytokines was examined in RA synovial explants *ex-vivo*.

Results: Increased p-STAT3 expression was demonstrated in RA synovium compared to healthy control ($p<0.05$) and 3% hypoxia induced nuclear translocation of p-STAT3 in RASFC. Hypoxia induced p-STAT3 and HIF1α expression, an effect blocked by Stat3-siRNA and WP1066. Hypoxia-induced cell invasion, migration and cytokine production were inhibited by Stat3-siRNA (all $p<0.05$) and WP1066 (all $p<0.05$). While HIF1α siRNA inhibited hypoxia-induced p-STAT3 expression, Stat3-siRNA also inhibited hypoxia-induced HIF1α. Furthermore hypoxia-induced Notch-1IC, DLL4, *hrt-1* and *-2* expression were significantly inhibited by STAT3 blockade ($p<0.05$). Finally, in RA synovial explant cultures *ex-vivo,* STAT3 blockade decreased spontaneous secretion of IL-6, IL-8 and MMP3 ($p<0.05$), and induced IL-10 ($p<0.05$).

Conclusion: This is the first study to provide evidence of a functional link between HIF1α, STAT3 and Notch-1 signalling in the regulation of pro-inflammatory mechanisms in RA, and further supports a role for STAT blockade in the treatment of RA.

Disclosure: W. Gao, None; **J. McCormick**, None; **M. Connolly**, None; **E. Balogh**, None; **D. J. Veale**, AbbVie, 2, Pfizer Inc, 2, MSD, 2, Roche Pharmaceuticals, 2, Pfizer Inc, 5, Roche Pharmaceuticals, 5, Abbott Laboratories, 8, Pfizer Inc, 8, MSD, 8, Roche Pharmaceuticals, 8; **U. Fearon**, None.

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Characterizing The Expression and Function Of CCL28 and Its Corresponding Receptor CCR10 In The Pathogenesis Of RA. Zhenlong Chen[1], Seung-jae Kim[1], Michael V. Volin[2], Suncica Volkov[1], William Swedler[1], Nadera J. Sweiss[1] and Shiva Shahrara[1]. [1]University of Illinois at Chicago, Chicago, IL, [2]Chicago College of Osteopathic Medicine Midwestern University, Downers Grove, IL.

Background/Purpose: This study was conducted to determine the expression pattern and function of CCL28 and its corresponding receptor CCR10 in the pathogenesis of rheumatoid arthritis (RA).

Methods: Expression of CCL28 and CCR10 was examined in RA compared to osteoarthritis (OA) and normal (NL) synovial tissue (ST) and/or fluid (SF) by histological studies and real-time RT-PCR. Next, the factors

modulating CCL28 and CCR10 expression were identified in RA peripheral blood (PB) *in vitro* differentiated macrophages and endothelial cells by real-time RT-PCR. Based on the elevated expression of CCR10 on RA blood vessels, significance of CCL28 expressed in RA SF was evaluated on human endothelial progenitor cell (EPC) migration and tube formation. Finally, the mechanism by which CCL28 mediates angiogenesis was determined in knockdown CCR10 endothelial cells by Western blot analysis, endothelial chemotaxis and tube formation.

Results: We demonstrate that expression of CCL28 and CCR10 are markedly higher in RA and OA ST lining macrophages and sublining endothelial cells compared to NL ST. Consistently, comparable levels of CCL28 were expressed in RA and OA SF which were 4 to 33 fold greater than those detected in RA and NL serum. Since both CCL28 and CCR10 are mainly expressed in RA myeloid and endothelial cells, we asked whether their expression levels are regulated in a similar manner in these cells. Interestingly we found that expression of CCL28 and CCR10 was very responsive to stimulation in RA PB *in vitro* differentiated macrophages and was similarly enhanced by TNF-a (8–18 folds), IL-1b (6–32 folds) or IL-6 (12–18 folds) treatment. In contrast, concentrations of CCL28 and CCR10 were differentially regulated in endothelial cells. We show that while in endothelial cells, IL-1b (5 fold) or IL-17 (3 fold) were responsible for increasing CCL28 mRNA levels, CCR10 (11 fold) expression levels were modulated by TNF-a stimulation. We uncovered that CCL28 can strongly attract endothelial cells starting at 0.1 ng/ml, indicating that CCL28 (up to 3300 pg/ml expressed in RA SF) can contribute to migration of endothelial cells at a physiologically relevant concentration. We further document that ligation of SF CCL28 to endothelial CCR10 is involved in RA angiogenesis, as neutralization of CCL28 in RA SF or blockade of CCR10 on human EPCs significantly reduce RA SF induced endothelial migration and tube formation. To determine the mechanism by which CCL28 promotes RA angiogenesis, endothelial cells stimulated with CCL28 were examined for activation of MAPK and AKT pathways. We found that while ERK was phosphorylated by CCL28 stimulation in endothelial cells, JNK, p38 and AKT pathways were unaffected by this process. We further show that knockdown of endothelial CCR10 significantly reduces CCL28 mediated ERK phosphorylation as well as endothelial migration and tube formation compared to the control siRNA cells.

Conclusion: We found that CCL28 and CCR10 are coexpressed in RA ST blood vessels and as a result, ligation of RA SF CCL28 to endothelial CCR10 facilitates endothelial cell migration and tube formation through activation of ERK pathway. This study identifies for the first time the presence and function of CCL28 as a novel mediator of RA angiogenesis.

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Interleukin-12B Is Up-Regulated By Decoy Receptor 3 In Specifically Rheumatoid Synovial Fibroblasts. Koji Fukuda[1], Yasushi Miura[2], Toshihisa Maeda[1], Shinya Hayashi[1] and Masahiro Kurosaka[1]. [1]Kobe University Graduate School of Medicine, Kobe, Japan, [2]Kobe University Graduate School of Health Sciences, Kobe, Japan.

Background/Purpose: Decoy receptor 3 (DcR3) is a secreted decoy tumor necrosis factor receptor and competitively binds and inhibits the TNF family including Fas-ligand (FasL), LIGHT, and TL1A. DcR3 is overexpressed in tumor cells and might benefit tumors by helping them to avoid cytotoxic and regulatory effects of the ligands. We previously reported that DcR3 overexpressed in rheumatoid synovial fibroblasts (RA-FLS) stimulated by TNFα protects the cells from Fas-induced apoptosis. We recently reported that DcR3 induces VLA-4 expression in THP-1 macrophages to inhibit cycloheximide-induced apoptosis, and that DcR3 binds to TL1A expressed on RA-FLS resulting in the negative regulation of cell proliferation induced by inflammatory cytokines. Therefore, DcR3 may regulate gene expressions in RA-FLS by binding to TL1A on RA-FLS as a ligand. In the present study, we studied interleukin (IL)-12B as one of the key molecules in DcR3-TL1A signaling in RA-FLS based on the genes expression profiles regulated by DcR3.

Methods: *Microarray assay.* Four individual lines of primary cultured RA-FLS were incubated with either recombinant human DcR3-Fc protein or control IgG1 for 12 hours. Gene expressions were detected by microarray assay and the profiles were analyzed. *Real-time polymerase chain reaction (real-time PCR).* RA and osteroarthritis (OA) -FLS were stimulated with various concentration of DcR3-Fc or control IgG1 for 12 hours. Further, RA-FLS were incubated with DcR3-Fc for 12 hours after overnight preincubation with anti-TL1A antibody. The relative expression levels of IL-12B mRNA were quantified by real-time PCR. *Western blotting.* RA-FLS was stimulated with DcR3-Fc or control IgG1 for 24 hours. The expression of IL-12B p40 protein in RA-FLS was investigated by western blotting.

Results: Microarray data analysis revealed that DcR3 up-regulates or down-regulates the expression of various genes n RA-FLS. Among the most significantly regulated 100 genes by DcR3, 45 genes were up-regulated and 55 genes were down-regulated. The profiles indicated that shared p40 subunit (IL-12B) of IL-12 and IL-23 was up-regulated by DcR3-Fc (fold change 1.65). Real-time PCR revealed that DcR3-Fc significantly increased the expression of IL-12B mRNA in RA-FLS in a dose dependent manner (113% with 10ng/ml, 135% with 100ng/ml, and 218% with 1000ng/ml) compared with control IgG1. In contrast, DcR3-Fc did not increase IL-12B mRNA in OA-FLS. Anti-TL1A antibody inhibited the up-regulation of IL-12B expression in RA-FLS induced by DcR3-Fc. Western blotting confirmed that IL-12B p40 protein in RA-FLS was increased when stimulated with DcR3-Fc.

Conclusion: IL-12 consisted of IL-12A (p35) and IL-12B induces Th1 immune responses. Meanwhile, IL-23 consisted of IL-23A (p19) and IL-12B is involved in the inflammatory pathway via IL-17. In this study, we revealed that DcR3 increased the expression of IL-12B in RA-FLS in a disease-specific fashion by binding to membrane-bound TL1A as a ligand. DcR3 may affect the pathogenesis of RA through IL-12B.

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Adenosine A2A Receptor Activates The Pro-Fibrotic Wnt / β-Catenin Signaling In Human Dermal Fibroblasts. Miguel Perez-Aso[1] and Bruce N. Cronstein[2]. [1]New York University School of Medicine, New York, NY, [2]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Upon adenosine formation in stress conditions, the adenosine A_{2A} Receptor ($A_{2A}R$) activation promotes wound healing, but it is also detrimental in fibrotic conditions such as scarring, scleroderma and liver fibrosis. Although we have previously shown that the $A_{2A}R$ regulates scarring and fibrosis by fine-tuning the collagen1 to collagen3 balance in human dermal fibroblasts, the intracellular pathway leading to collagen production upon $A_{2A}R$ activation remains unclear. β-catenin is a central mediator of pro-fibrotic Wnt signaling in systemic sclerosis (Beyer et al. 2012) and the pro-fibrotic growth factor TGF-β1 targets the β-catenin pathway (Caraci et al. 2008). We therefore sought to determine whether $A_{2A}R$ stimulates Wnt / β-catenin signaling in human dermal fibroblasts.

Methods: Cells were stimulated for 24h with the specific $A_{2A}R$ agonist CGS21680, in the presence or absence of the $A_{2A}R$ antagonist SCH58211. β-catenin was knock-down with siRNA and collagen1, collagen3 and β-catenin expression were analyzed by western-blotting. Subcellular distribution of β-catenin was studied by cellular fractionation and confocal microscopy.

Results: The A2A agonist CGS21680 stimulated, in a dose-dependent fashion, a significant increase in β-catenin expression (increase over non-stimulated control: CGS21680 0.1μM 139.6$\pm$10.3%, $P<0.01$ n=5; 1μM 163.7$\pm$18.8%, $P<0.001$ n=3; 10μM 151.6$\pm$7.1%, $P<0.001$ n=5) and preincubation with the A2AR antagonist SCH21680 1μM prevented this effect (two-way ANOVA $P<0.01$, n=5). Subcellular fractionation after incubation with CGS21680 (1μM) showed a preferential increase of β-catenin in the nucleus, as assessed by Western Blot Analysis and confocal images demonstrate colocalization of the nuclear marker DAPI and β-catenin after A2AR stimulation. As expected, CGS21680 1μM stimulated an increase of both collagen1 (1.4 and 2.5 fold increase over control) and collagen3 (2.8 and 2.2 fold increase over control) but, interestingly, β-catenin knock-down prevented the CGS21680-mediated increase in collagen3, but not collagen1.

Conclusion: These results strongly support the hypothesis that activation of the A2AR leads to cross-talk with the pro-fibrotic Wnt / β-catenin signaling system. These findings suggest a mechanism for changes in the collagen1: collagen3 ratio in animal models of hypertrophic scars and scleroderma in which A2AR blockade or deletion prevents fibrosis and in which adenosine concentrations are dramatically increased.

Disclosure: M. Perez-Aso, None; **B. N. Cronstein**, Canfite Pharma, 1, NIH, Gilead, Takeda, AstraZeneca, 2, NYU School of Medicine, 3, Merck-SeronoBristol-Myers Squibb, Novartis, CanFite Biopharmaceuticals, Cypress Laboratories, Regeneron (Westat, DSMB), Endocyte, Protalex, Allos, Inc., Savient, Gismo Therapeutics, Antares Pharmaceutical, Medivector, 5, Multiple patents on adenosine receptors and bone metabolism, pharmacology, 9.

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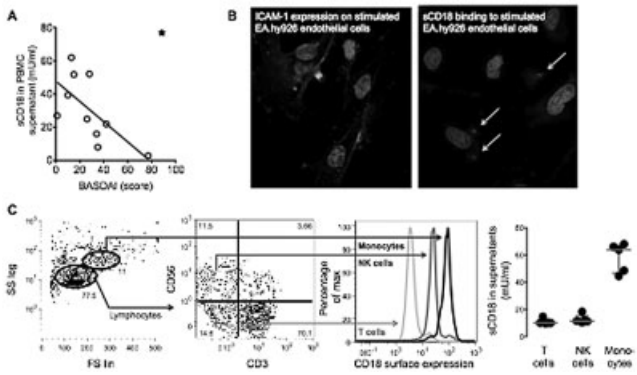
Decreased Plasma Levels Of Soluble CD18 Link Leukocyte Migration and Disease Activity In Spondyloarthritis. Tue W. Kragstrup[1], Babak Jalilian[2], Malene Hvid[2], René Østgård[2], Berit Schiøttz-Christensen[3], Anne G. Jurik[4], William H. Robinson[1], Thomas Vorup-Jensen[2] and Bent Deleuran[4]. [1]Stanford University School of Medicine, Stanford, CA, [2]Aarhus University, Aarhus, Denmark, [3]Private practice, Aarhus, Denmark, [4]Aarhus University Hospital, Aarhus, Denmark.

Background/Purpose: Spondyloarthritis (SpA) comprise a group of diseases characterized by inflammation of the entheses and joints of the axial skeleton primarily driven by innate immune cells such as monocytes, fibroblasts and granulocytes.(1) The family of CD18 integrins is pivotal in guiding leukocytes to sites of inflammation and has been shown to form soluble complexes in the blood (sCD18).(2) CD18 hypomorphic mice develop a disease resembling psoriatic arthritis, demonstrating that decreased CD18 expression can result in development of SpA-like disease.(3) Here, we investigated whether sCD18 plays a role in SpA disease pathogenesis.

Methods: The level of sCD18 in plasma from a well characterized study population with 84 SpA patients and age- and sex-matched healthy controls was analyzed with a time resolved immunoflourometric assay (TRIFMA). Shedding of CD18 from peripheral blood mononuclear cells was studied by using flow cytometry and TRIFMA. Binding of sCD18 to endothelial cells and fibroblast-like synovial cells (FLS) was studied by using confocal microscopy.

Results: Plasma levels of sCD18 were decreased in SpA patients compared with healthy volunteers ($P< 0.001$). The sCD18 levels exhibited an inverse correlation with the BASDAI ($P< 0.05$), the level of morning stiffness ($P< 0.05$), the BASMI ($P< 0.05$), the physician global assessment score ($P< 0.01$), and the sacroiliac MRI activity score ($P< 0.05$) in multiple regression models, including multivariate analysis to account for differences in CRP levels. Remarkably, this situation could be simulated in vitro. First, CD18 shedding from SpA PBMC correlated inversely with the BASDAI ($P< 0.05$), suggesting insufficient generation (Fig 1A). Second, sCD18 in plasma adhered to inflammation induced ICAM-1 on endothelial cells and FLS, indicating increased consumption (Fig 1B). Importantly, both ICAM-1 expression and CD18 shedding were increased by TNFα, suggesting that sCD18 plays a role in regulating leukocyte migration during the normal immune response. CD18 was primarily shed from monocytes, supporting the notion that alterations in innate immunity dominate the inflammatory processes in SpA (Fig 1C).



Conclusion: Taken together, the failure of SpA patients to maintain normal sCD18 levels may reflect insufficient CD18 shedding from monocytes to counterbalance the capture of sCD18 complexes to inflammation induced ICAM-1. This results in increased availability of ICAM-1 molecules on the endothelium and in the synovium facilitating increased leukocyte migration to the entheses and joints and increased inflammatory burden. In this way, our findings on sCD18 link leukocyte migration with SpA disease activity.

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Inhibitor Of DNA Binding 1 Mediates Angiogenesis In Rheumatoid Arthritis By Recruitment Of Endothelial Progenitor Cells. Takeo Isozaki[1], Alisa E. Koch[1], M. Asif Amin[1], Ali S. Arbab[2], Gautam Edhayan[1], Christine M. Ha[1], Pei-Suen Tsou[3], Sean C. Friday[1], David A. Fox[3] and Jeffrey H. Ruth[1]. [1]University of Michigan Medical School, Ann Arbor, MI, [2]Henry Ford Hospital and Medical Centers, Detroit, MI, [3]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI.

Background/Purpose: Endothelial progenitor cells (EPCs) are known to induce vasculoproliferative responses within rheumatoid arthritis (RA) synovial tissue (ST). Inhibitor of DNA-Binding 1 (Id1) is a transcription factor shown to be actively transcribed in only progenitor cells, making it a possible marker for identifying EPCs in neovascular responses in RA ST. We previously showed that Id1 is not only expressed in RA STs, but is also secreted and upregulated in RA synovial fluid (SF). The identification of Id1 in RA tissues indicates progenitor cells are active in the RA joint, and may serve as a potential target for limiting neovascularization in the RA ST. This study further examines the cellular sources, angiogenic and chemotactic potential, and cell signaling properties of Id1.

Methods: Severe combined immunodeficient (SCID) mice were implanted with RA ST and allowed to engraft for six weeks. Mice were injected i.v. with fluorescently dye-tagged EPC's while receiving simultaneous intragraft injections with either human Id1 (10 nM) or PBS. Another group of SCID mice grafted and injected similarly, received intragraft injections of RA SF immunodepleted with either non-specific IgG ("sham depleted"), or Id1 immunodepleted with a neutralizing antibody. For signal transduction analysis, human dermal microvascular endothelial cells (HMVECs) and EPCs were plated and stimulated with human Id1. Cell lysates were made and Western blot analysis was used to determine the kinetics of protein kinase expression. We also examined whether Id1 induces HMVECs to form blood vessels, measured as an increase in plug hemoglobin (Hb) concentration normalized to plug weight, using the mouse Matrigel plug angiogenesis assay. Finally, to determine the cells secreting Id1, we cultured monocytes, HMVECs, EPCs and fibroblasts and measured the supernatants for Id1 expression by ELISA.

Results: There was a significant increase in EPC migration to engrafted RA ST in the SCID mouse chimera to intragraft injections of Id1. Using the same RA ST SCID mouse chimera system, we found that intragraft injections of RA SF immunodepleted of Id1 resulted in a 50% reduction in EPC recruitment compared to mice injected similarly with sham depleted RA SF (*$p<0.05$). Cell signaling experiments to Id1 showed Jnk was upregulated in both HMVECs and EPCs, and P38 only in EPCs. We also show that Id1 induces *in vivo* blood vessel formation, and that inhibiting HMVEC associated Jnk with silencing RNA reverses Id1 induced HMVEC vessel formation in Matrigel plugs *in vivo*. Lastly, we show that monocytes and especially fibroblasts, but not HMVECs and EPCs, actively secrete Id1, indicating that mature fibroblasts may be a primary source of Id1 in RA SF.

Conclusion: Our data indicates that Id1 induces EPC recruitment in the RA ST SCID mouse chimera, and that by depleting RA SF of soluble Id1, we can attenuate EPC migration by 50%. Id1 was also found to be potently angiogenic in the mouse Matrigel angiogenesis assay, and activates Jnk signaling pathways in HMVECs and EPCs. Lastly, we found that fibroblasts actively secrete Id1 and may be a primary source for its expression in SF. These studies identify Id1 as both a regulatory transcription factor and a unique angiogenic target within the RA synovium.

Disclosure: T. Isozaki, None; **A. E. Koch**, Eli Lilly and Company, 3; **M. A. Amin**, None; **A. S. Arbab**, None; **G. Edhayan**, None; **C. M. Ha**, None; **P. S. Tsou**, None; **S. C. Friday**, None; **D. A. Fox**, None; **J. H. Ruth**, None.

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A Disintegrin and Metalloprotease-17 (ADAM-17) Is Expressed In Rheumatoid Arthritis and Mediates Monocyte Migration. Takeo Isozaki, Nao Oguro, Shinya Seki, Yoko Miura, Sho Ishii, Hiroyuki Tsukamoto, Takahiro Tokunaga, Masayu Umemura, Hidekazu Furuya, Ryo Yanai, Sakiko Isojima, Kuninobu Wakabayashi, Nobuyuki Yajima, Yusuke Miwa and Tsuyoshi Kasama. Showa University School of Med, Shinagawa-ku Tokyo, Japan.

Background/Purpose: Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized byinflammation and joint destruction. Migration of monocytes/macrophages into the synovium is important in a variety of vasculoproliferatine states in RA. A disintegrin and metalloprotease (ADAM) are a family of proteases that are responsible for the liberation of a variety of

types of cell surface expressed proteins. ADAM-17 has been shown to cleave a number of inflammatory mediators from the cell surface including CX3CL1 and CXCL16. In this study, we examined the expression of ADAM-17 in RA and the role it plays ininflammation.

Methods: ADAM-17 expression was determined in serumand synovial fluids from normal (NL) subjects, osteoarthritis (OA) patients and RA patients using enzyme linked immunosorbent assay. We also measured ADAM-17 in RA serum after treatment with tocilizmab (6, 12 and 24 week). To determine whether ADAM17 was expressed by THP-1 cells (human acute monocytic leukemia cell line)and whether it was regulated byphorbol 12-myristate 13-acetate (PMA), quantitative polymerase chain reaction (qPCR) was performed. In order to confirm the role of ADAM-17 in inflammation, we did THP-1 chemotaxis assay. To block the expression of ADAM-17, THP-1cells were transfected with siRNA against ADAM-17. After treatment with ADAM-17 siRNA, THP-1cell chemotaxis assay wasperformed towards RA synovial fluids and monocyte chemotactic protein-1 (MCP-1)/CCL2.

Results: ADAM-17 in RA serum (n=23) was significantly higher than NL serum (n=7) (mean ± SEM RA serum 2093 ± 538 pg/ml and NL serum 0 ± 0pg/ml). ADAM-17 in RA synovial fluids (n=10) was also significantly higher than OA synovial fluids (n=7) (mean ± SEM RA synovial fluids 1645 ± 952 pg/ml and OA synovial fluids 5±4 pg/ml). After treatment with tocilizmab, ADAM-17 in serum was significantly decreased [pre 486 ± 126pg/ml (n=21), 12 week 215 ± 114 (n=15) and 24 week 98 ± 98 (n=12); $p<0.05$ between pre and 12 week, pre and 24 week]. The expression of ADAM-17 messenger RNA (mRNA) in THP-1 cells was induced by stimulation withPMA after 1 hour (2.6 fold increased). ADAM-17 siRNA treated THP-1 cells had decreased migration compared with control siRNA treated THP-1 cells towards RA synovial fluids (6± 2number of cells migrated and 33 ± 12 number of cells migrated, $p<0.05$). ADAM-17 siRNA treated THP-1 cells had also decreased migration compared with control siRNA treated THP-1 cells towards MCP-1/CCL2 (27 ± 4 number of cells migrated and 146 ± 18 number of cells migrated, $p<0.05$).

Conclusion: These data show that ADAM-17 is overexpressed in RA, and is decreased after treatment. ADAM-17 is involved monocyte migration, and this study suggests that ADAM-17 may play a role in RA inflammation. ADAM-17 may be a potential target in inflammatory disease like RA.

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Reduction Of Circulating Blood Neutrophils In Mice By Anti-IL-6R Alpha Monoclonal Antibody is Not Due To Apoptosis Or Blockade Of Neutrophil Differentiation. Ludmila Kelly, Vilma Decman and Dimitris Skokos. Regeneron Pharmaceuticals, Inc., Tarrytown, NY.

Background/Purpose: Blockade of IL-6/IL-6Rα signaling is associated with a reduction of circulating neutrophils in the blood of patients treated with anti-IL-6Rα mAb but the mechanism is unknown. Due to the lack of IL-6Rα mAb effect on neutrophils in naïve mice, we established a mouse model of dexamethasone (DEX)-induced neutrophilia to explore the impact of anti-IL-6Rα mAb on neutrophil distribution, differentiation and recovery in vivo.

Methods: Wild type C57Bl/6 or IL-6Rα$^{Hu/Hu}$/IL-6$^{Hu/Hu}$ mice were injected with anti-mouse (REGN844) or anti-human IL-6Rα mAb (REGN88, sarilumab), respectively. DEX was injected 2 hrs after mAb injection to induce a temporary increase of neutrophils in the periphery. Mice were euthanized 4 hrs after DEX injection, and blood, spleen, and bone marrow were evaluated for neutrophil levels by flow cytometry. Neutrophil apoptosis was assessed by active Caspase-3 staining in the above tissues. In another experiment, mice were injected with cyclophosphamide (CTX), resulting in temporary neutropenia. Recovery of neutrophils in peripheral blood in the presence or absence of IL-6Ra mAb was monitored for six days after CPM injection.

Results: Treatment of naïve C57Bl/6 mice with IL-6Rα mAb alone did not affect neutrophil levels in blood, spleen or bone marrow. We found that IL-6Rα mAb reversed the DEX effect in both mouse strains (Figure 1). This reversal was not associated with apoptosis as assayed by active Caspase-3 staining in spleen and bone marrow in C57Bl/6 mice. Furthermore, in IL-6Rα$^{Hu/Hu}$/IL-6$^{Hu/Hu}$ mice treated with CTX, neutrophil numbers in blood recovered to a comparable level in the presence of IL-6Rα mAb or hIgG1 isotype (Figure 2), indicating that differentiation and exit of neutrophils from bone marrow was not affected by IL-6Rα mAb treatment.

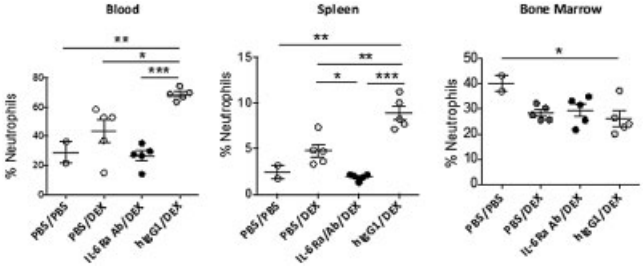

Figure 1. IL-6Ra antibody blocks the dexamethasone-induced neutrophilia in blood and spleen of IL-6$^{Hu/Hu}$/IL-6$^{Hu/Hu}$ humanized mice.

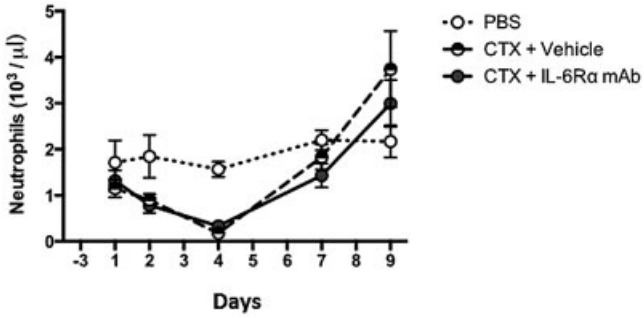

Figure 2. Il-6Rα mAb does not interfere with neutrophil recovery in blood after cyclophosphamide treatment in IL-6$^{Hu/Hu}$/IL-6$^{Hu/Hu}$ humanized mice (p=NS).

Conclusion: In a mouse model of DEX-induced neutrophilia, IL-6Rα mAb treatment negated the DEX effect in both C57Bl/6 and IL-6Rα$^{Hu/Hu}$/IL-6$^{Hu/Hu}$ mice. This effect was not associated with Caspase-3 mediated apoptosis, although alternative apoptotic pathways should be explored. IL-6Rα mAb did not prevent the recovery of neutrophils in blood following CPM treatment. These data suggest that the reduction in circulating neutrophil counts observed with IL-6Rα mAb treatment are not due to effects within the bone marrow and may be due to effects on neutrophil margination.

Disclosure: L. Kelly, Regeneron, 3, Regeneron, 1; **V. Decman**, Regeneron, 3, Regeneron, 1; **D. Skokos**, Regeneron, 3, Regeneron, 1.

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Novel Function Of Soluble Interleukin-6 Receptor As An Antagonist Of Interleukin-27-Mediated Anti-Inflammatory Responses. Misato Hashizume[1], Keiko Esaki[1], Keiko Yoshimoto[2], Hideto Kameda[2], Tsutomu Takeuchi[2] and Yoshihiro Matsumoto[1]. [1]Chugai Pharmaceutical Co., Ltd., Gotemba, Japan, [2]Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: The immunological roles of interleukin 27 (IL-27) have been reported in various rheumatic diseases, such as rheumatoid arthritis (RA), lupus, systemic sclerosis and psoriasis. The role of IL-27 in the immune response is not fully understood, although pro- and anti-inflammatory responses to IL-27 were reported. IL-27 is a heterodimeric cytokine composed of IL-27p28 and EBI3, which are analogous to IL-6 and soluble IL-6 receptor (sIL-6R) respectively, and exerts its biological activities through binding to IL-27 receptor which is composed of alpha subunit and gp130. Since IL-6 and IL-27 are similar in terms of their structures and the way of signaling pathway, we hypothesized that sIL-6R binds to IL-27. In this study, we investigated a possible role of sIL-6R in regulating IL-27 signaling.

Methods: Surface Plasmon Resonance (SPR) analysis was used to examine the binding of IL-27 to sIL-6R. CD14$^+$ cells were isolated from peripheral blood of RA patients. CD14$^+$ cells were incubated with IL-27, sIL-6R and anti-gp130 antibody for 30 minutes, and the expression of SOCS3, which is a negative regulator of inflammatory cytokine signaling, was measured by western blotting. MCP-1 was measured by ELISA in the culture supernatant of CD14$^+$ cells incubated with M-CSF, TNF-α, IL-27, sIL-6R, anti-IL-6 antibody, anti-IL-6R antibody (tocilizumab) and anti-gp130 antibody. The number of osteoclasts was counted after tartrate-resistant acid phosphatase staining in CD14$^+$cells cultured with RANKL and M-CSF in the presence of IL-27, sIL-6R and tocilizumab for 4 days.

Results: SPR analysis showed that binding curves were generated from experiments in which IL-27 was exposed to a high-density of sIL-6R coated on a sensor chip, showing that IL-27 bound to sIL-6R. IL-27 induced the expression of SOCS3 in $CD14^+$ cells, which was suppressed by the addition of sIL-6R to the culture. Neutralizing antibody to gp130O'Dell JR et al. Therapies for Active Rheumatoid Arthritis after Methotrexate Failure. N Engl J Med. 2013.

Table. Discontinuation rates and median survival for patients on triple therapy.

	Discontinuation Definitions	
	First-Strict	Second-Relaxed
Time at risk (patient years)	742.2	918.0
Discontinuation rate per year	0.408	0.235
Median survival (months)	14	28
Discontinuation rates (95% CI) after:		
1 year	0.501 (0.449, 0.551)	0.627 (0.621, 0.719)
2 years	0.391 (0.339, 0.442)	0.538 (0.482, 0.590)
3 years	0.291 (0.242, 0.343)	0.438 (0.381, 0.494)

Disclosure: S. Pedro, Natinal DataBank for Rheumatic Disease, 3; **F. Wolfe**, None; **H. Jalal**, None; **K. Michaud**, University of Nebraska Medical Center, 3, National Data Bank for Rheumatic Diseases, 3.

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Mir-34a In Rheumatoid Arthritis: Characterisation Of Elevated Synovial Expression and Association With Treatment Resistance. Clare E Tange[1], Stefano Alivernini[2], Derek S. Gilchrist[1], Lynn Crawford[1], Ashleigh-Ann Rainey[1], Derek Baxter[1], Iain B. Mcinnes[1] and Mariola Kurowska-Stolarska[1]. [1]University of Glasgow, Glasgow, United Kingdom, [2]Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy.

Background/Purpose: Cells of the monocyte/macrophage lineage are critical to RA pathogenesis: unravelling mechanisms underlying macrophage inflammatory gene expression should elucidate novel disease-associated pathways and thereby biomarkers and therapeutic targets. MicroRNA (miR) comprise small, non-coding RNA species that are key regulators of mammalian gene expression. We sought to define the expression and regulation of novel miR species that regulate RA macrophage biology.

Methods: Blood (PB; healthy controls & RA patients with defined treatment characteristics) or synovial fluid (SF; RA) CD14+ cells were purified using histopaque centrifugation & autoMACS bead separation. $CD14^+$ cells were matured with M-CSF or GM-CSF for up to 7 days, or stimulated with various TLR ligands. For T cell -macrophage interaction, $CD4^+$ T cells were cultured with TNF, IL-2, IL-6, prior to 24hr co-culture with M-CSF-matured $CD14^+$ cells. miR expression and copy number was variously quantified in cells or tissues via TLDA, validatory qPCR & *in situ* hybridisation with specific primers and DIG or FITC labelled probes, respectively.

Results: Prior TLDA elicited several dysregulated miRs in RA SF compared to PB $CD14^+$ cells, including miR-34a. Fold change and copy number PCR assays confirmed elevated miR-34a in RA SF cells ($n=10$; $p<0.01$). Crucially miR-34a was also elevated in PB $CD14^+$ cells from biologic-resistant RA patients compared to cDMARD good responders or matched healthy controls ($n=19$–30), associating miR-34a expression with chronic, treatment-resistance. miR-34a expression correlated with disease activity assessed by swollen joint count. *In situ* hybridisation demonstrated elevated miR-34a expression in RA compared with non-inflammatory and inflammatory OA synovial tissues ($n=6$); double fluorescent staining confirmed expression in lining and sub-lining layer CD68+ macrophages, plus adjacent cells of FLS morphology. miR-34a was rapidly upregulated during monocyte maturation induced by adherence, M-CSF or GM-CSF, but was not further enhanced by addition of TLR ligands (LPS, CLO97, PAM3, PolyIC, CpG). Similarly co-culture with RA derived SF (10%) enhanced miR-34a expression in monocytes. Finally, cognate interactions between CD4+ T cells and macrophages further enhanced miR-34a expression in the latter cells.

Conclusion: miR-34a expression is elevated in RA SF macrophages and in PB monocytes of treatment resistant RA patients where it correlates with clinical disease activity measures. miR-34a is upregulated by the maturation rich synovial microenvironment and by interactions with activated T cells. Putative miR-34a molecular targets include NOTCH1 rendering it a plausible novel immune regulator in synovitis.

Disclosure: C. E. Tange, None; **S. Alivernini**, None; **D. S. Gilchrist**, None; **L. Crawford**, None; **A. A. Rainey**, None; **D. Baxter**, Roche Pharmaceuticals, 2; **I. B. Mcinnes**, Roche Pharmaceuticals, 2; **M. Kurowska-Stolarska**, Roche Pharmaceuticals, 2.

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CXCL13 Is a Marker Of Joint Involvement In Early Rheumatoid Arthritis. Stinne Greisen[1], Tue Rasmussen[1], Karen Schelde[1], Kristian Stengaard-Pedersen[2], Merete Lund Hetland[3], Kim Hørslev-Petersen[4], Bent Deleuran[5] and Malene Hvid[1]. [1]Aarhus University, Aarhus, Denmark, [2]Arhus University Hospital, Aarhus, Denmark, [3]The Danish Rheumatologic Database (DANBIO), Glostrup Hospital., Copenhagen, Denmark, [4]University of Southern Denmark, Graasten, Denmark, [5]Aarhus University Hospital, Aarhus, Denmark.

Background/Purpose: CXCL13 is central in the formation of lymphoid follicles in secondary and tertiary lymphoid tissue. It attracts CXCR5-expressing B cells and follicular helper T cells (T_{FH}). CXCL13 has previously been associated with disease in RA. We examined the role of CXCL13 and CXCR5 in early rheumatoid arthritis (eRA) and in a murine collagen induced arthritis (CIA) model.

Methods: CXCL13 was measured by ELISA in plasma from 76 treatment naïve eRA patients (disease $<$ 3 month), at baseline and after 6 months of treatment. Treatment was methotrexate (MTX) ($n=39$) or MTX + Adalimumab (ADA) ($n=37$). Clinical disease was assessed by: DAS28, VAS, CRP, no. of swollen joints (SJ28+40), SDAI, IgM-RF and ACPA. Healthy volunteers (HV) ($n=38$) were age and gender matched with eRA patients. Negative selected CD14+ cells from healthy blood donor buffy coats were cultured with GM-CSF (100 ng/ml) and IL-4 (40 ng/ml) to acquire monocyte derived dendritic cells (Mo-DC). At day 6 Mo-DC were stimulated with: LPS, CD40L, IL-21, TGFb, PD-1, CXCL13, OX40, TNFa, IL-22, LIGHT etc. Up regulation of CXCL13 and CXCR5 mRNA was evaluated by PCR with GAPDH as reference. CIA was induced in DBA/1 mice. Arthritis was scored according to the Mean Arthritis Score (MAS). Adoptive transfer was done with CXCR5+/− splenocytes from CIA mice to healthy DBA/1 mice, boosted with incomplete Freunds adjuvant. Mice were sacrificed at day 48, and paws embedded in paraffin were stained. Statistical correlations were assessed by Spearman's rho. Data are expressed as median (IQR).

Results: Treatment reduced CXCL13 plasma levels by 30% (baseline: 149.3 pg/ml (74.8 pg/ml–245.0 pg/ml vs. 6 months: 48.1 pg/ml (26.9 pg/ml–93.0 pg/ml), $p<0.001$). At 6 months CXCL13 levels were similar to levels observed in HV (50.3 pg/ml (29.2 pg/ml–92.7 pg/ml), $p=0.99$). Patients in the MTX group had 50% reduction in plasma CXCL13 compared with ADA ($p=0.015$). We observed correlation with baseline CXCL13 and disease parameters in both groups (VAS, SDAI and SJ28+40 (all $r=0.3$–0.4, all $p<0.05$)). CXCL13 mRNA expression in Mo-DC was only up regulated by TNFa, LIGHT and IL-22, whereas CXCR5 also was up regulated by PD-1 and CXCL13. Adoptive transfer of CXCR5+ splenocytes from CIA mice resulted in a more severe inflammation and cartilage destruction, compared with CXCR5- and total splenocytes. Adoptive transfer of similar cell types from healthy mice did not result in arthritis development in the recipient mice.

Conclusion: CXCL13 plasma levels were significantly elevated in eRA patients and decreased to levels comparable with HV within 6 months of treatment. Treatment with ADA resulted in a more prominent decrease in CXCL13 levels, supporting a close connection between TNF a inhibition and CXCL13 production, also supported by CXCL13 up regulation by TNFa. CXCL13 serves as a prominent marker of joint involvement, evaluated by the close association with number of swollen joints and the VAS score. The high degree of joint inflammation and destruction in mice receiving CXCR5+ cells, points to a memory development within this cellular subset, and considering the upregulation of CXCR5 by TNFa and CXCL13 the importance of these two chemokines in joint involvement is supported.

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Synergism Between Granulocyte-Macrophage Colony Stimulating Factor and Interleukin-17 Causes Joint Damage Via The Production Of Interleukin-23, Receptor Activator Of NF-κB Ligand and S100A8. Annemarie E.M. Van Nieuwenhuijze[1], Fons A.J. Van de Loo[2], Birgitte Walgreen[1], Miranda B. Bennink[2], Monique M. Helsen[1], Liduine Van den Bersselaar[1], Ian P. Wicks[3], Wim B. Van den Berg[4] and Marije I. Koenders[4]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Rheumatology Research and Advanced Therapeutics, Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [3]Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia, [4]Rheumatology Research and Advanced Therapeutics, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands.

Background/Purpose: T helper-17 (Th17) cells are important mediators of inflammatory diseases, and are the main pathogenic cell type in many animal models of autoimmunity. Recent studies highlight a surprising role for T-cell derived granulocyte-macrophage colony stimulating factor (GM-CSF) in the pathogenicity of Th17 cells. We examined the mechanism by which interleukin 17 (IL-17) and GM-CSF contribute to cartilage- and bone damage of synovial joints during experimental arthritis, and provide a rationale for combination therapy in auto-inflammatory conditions.

Methods: Collagen-induced arthritis was elicited in DBA/1J mice. Neutralizing antibodies to IL-17 and/or GM-CSF were administered after onset of disease for 14 days. Arthritis progression was followed by macroscopic scoring of the paws (maximum score of 12 per mouse). In addition, the effect of local over-expression of IL-17 and/or GM-CSF was studied by adenoviral transfection in naïve knee joints. Knee- and ankle joints, synovial tissue and serum from both experiments were analyzed in detail for the presence of cytokines, chemokines, and matrix metalloproteinases (MMPs). Cartilage- and bone damage was determined by histological analysis.

Results: Combined therapeutic treatment of mice during arthritis ameliorated disease progression. Macroscopic joint inflammation was significantly reduced, from a total score of 5.6 ± 0.4 for mice treated with isotype control antibodies to 2 ± 0.6 for mice treated with combination therapy. Treatment with anti-IL-17 or anti-GM-CSF alone resulted in scores of 3.4 ± 0.5 and 3.5 ± 0.4, respectively. Anti-IL-17 specifically reduced the transcription of IL-23 in the synovium, whereas anti-GM-CSF inhibited production of MMPs, Receptor Activator of NF-κB Ligand (RANKL), and monocyte-chemotactic protein-1 (MCP-1, CCL2). Serum IL-6 was reduced in all treatment groups compared to control mice. To provide further insight in local additive or synergistic effects of IL-17 and GM-CSF, overexpression of IL-17, GM-CSF or the combination was achieved with adenoviral vectors. Inflammatory infiltrate and cartilage- and bone damage developed in all groups from day 1 after adenoviral transfer, with the most severe effect observed in the combination group. On day 7, partial destruction of joint architecture was apparent in knee joints after combined overexpression of IL-17 and GM-CSF. Overexpression of IL-17 alone caused a specific increase in synovial IL-6 production. Overexpression of GM-CSF alone induced IL-1β, S100A8 and MMP13 in synoviocytes. A strong synergistic effect of combined overexpression was seen on the production of the endogenous damage-associated molecular patterns (DAMP) ligand S100A8, the osteoclast activator RANKL and the Th17 differentiation factor IL-23.

Conclusion: We show that IL-17 and GM-CSF cause joint damage through synergistic effects on inflammatory mediators in synovial joints. In view of the moderate success of therapeutic IL-17 or GM-CSF blockade in rheumatoid arthritis, combined inhibition of IL-17 and GM-CSF might be an option for patients that do not fully respond to inhibition of the separate cytokines.

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Mir-125a: A Novel Regulator Of IL-6 and TLR Driven Pathways In RA Pathogenesis. Ashleigh-Ann Rainey, Derek S. Gilchrist, Clare E Tange, Marina Frleta, Lynn Crawford, Derek Baxter, Iain B. Mcinnes and Mariola Kurowska-Stolarska. University of Glasgow, Glasgow, United Kingdom.

Background/Purpose: Molecular mechanisms driving disease initiation and chronicity in RA are incompletely understood. There is increasing interest in the role played therein by microRNAs–small RNA species that mediate post-transcriptional regulation of integrated pathways in mammalian cells. We recently profiled miRs in RA synovial fluid (SF) CD14+ macrophages in comparison to peripheral blood (PB) monocytes and identified dysregulation of miR-125a, which has not previously been associated with RA pathophysiology. Herein we aimed to characterise its expression and functional significance.

Methods: Matched PB & SF CD14+ cells were isolated from RA patients (n=10). Additional PB samples were obtained from RA DMARD good responders (n=17), recurrent non-responders (n=11) and matched healthy controls (n=17). Primary human monocytes and THP-1 cells were stimulated with TLR ligands (LPS, PAM3, PolyIC, CLO97) and differentiated using M-CSF or GM-CSF for up to 7 days. Copy number of miR-125a was evaluated using qPCR. Targeted pathways were identified using prediction algorithms (e.g. TargetScan) and transcriptional profiling of SF CD14+ cells. Direct molecular interactions were confirmed using luciferase reporters. miR-125a or control mimic were transfected into THP-1 cells and IL-6R expression was evaluated by flow cytometry.

Results: miR-125a was up-regulated in RA SF CD14+ macrophages compared to PB controls ($p=0.002$). Moreover, miR-125a was up-regulated in RA PB CD14+ monocytes compared with healthy controls, regardless of DMARD response status ($p<0.02$). Copy number of miR-125a in resting control PB monocytes was low. Extensive activation profiling revealed M-CSF, GM-CSF & 10% RA SF all induced miR125a expression at discrete time-points between 24h & 7ds. Of TLR ligands tested, only TLR4 agonism increased miR125a. Prediction algorithms identified members of the IL-6 signalling pathway (IL-6R, gp130) as potential targets of miR-125a. Luciferase reporter assays thereafter confirmed functional target interactions. Transfection of THP-1 cells with miR-125a but not control mimic reduced IL-6R membrane expression measured by FACS. miR-125a also targeted the negative regulators of TLR signalling, TNFAIP3 and IRF4, assessed by TargetScan and luciferase reporter. Commensurate with this IRF4 was down-regulated in RA PB monocytes (both DMARD good & recurrent non-responders) compared to healthy donors.

Conclusion: Inflammatory cytokines, maturation factors and articular DAMPs drive elevated miR-125a expression in monocyte/macrophage lineages. miR-125a, in turn represents a novel molecular pathway that cross regulates IL-6R and TLR pathway activation in RA macrophages. We conclude that miR-125a represents an intriguing molecular marker with therapeutic and biomarker potential.

Disclosure: A. A. Rainey, None; **D. S. Gilchrist**, None; **C. E. Tange**, None; **M. Frleta**, None; **L. Crawford**, None; **D. Baxter**, Roche Pharmaceuticals, 2; **I. B. Mcinnes**, Roche Pharmaceuticals, 2; **M. Kurowska-Stolarska**, Roche Pharmaceuticals, 2.

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Non-Canonical NF-Kappa B Signaling Enhances Angiogenesis In a Novel 3D Spheroid Model Of Rheumatoid Arthritis Synovial Inflammation. Chrissta X. Maracle, Ae-Ri Noort, Katinka P.M. van Zoest and Sander W. Tas. Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands.

Background/Purpose: Angiogenesis plays a crucial role in rheumatoid arthritis (RA) synovitis and is regarded as a switch from acute to chronic inflammation. Previously, we have demonstrated that NF-kappaB inducing kinase (NIK) mediated non-canonical NF-kappaB signaling contributes to pathological angiogenesis in endothelial cells (EC). However, many of the current *in vitro* models of angiogenesis focus solely on EC and do not include interactions with other cell types. RA synovial fibroblasts (RASF) are important contributors to angiogenesis in synovial inflammation, and thus a model including both RASF and EC would more accurately represent the pathophysiology of RA angiogenesis.

Objective: To develop better *in vitro* models to study the interaction between RASF and EC and to further delineate the role of the non-canonical NF-kappaB pathway in pathological angiogenesis.

Methods: First, we utilized a 2 dimensional (2D) model to evaluate the effects of non-canonical NF-kappaB signaling on angiogenesis. RASF and human umbilical cord EC (HUVEC) were co-cultured in the presence or absence of lymphotoxin (LT), LIGHT, or growth factors (bFGF/VEGF). EC were visualized through immunohistochemical staining of CD31, which was semi-quantitatively scored. Next, we developed a novel 3 dimensional (3D) model in which HUVEC and RASF were labeled with green or orange cell tracker dye, respectively, and incubated overnight to form spheroids. Subsequently, the spheroids were harvested and plated in a collagen solution, and medium with or without LT, LIGHT or growth factors (bFGF/VEGF) was added. After 48 hours, spheroids were fixed and imaged through confocal

microscopy. Cumulative EC sprout length and the number of sprouts was quantified using Leica QWin Plus software.

Results: The 2D culture model revealed an increase in CD31 positive area under all stimulation conditions, with LIGHT inducing almost a 2-fold increase ($p<0.05$). Confocal analysis of the 3D model showed that spheroids containing HUVEC and RASF formed sprouts under all conditions and that LT and LIGHT caused significant increases ($p<0.05$) in cumulative sprout length. Interestingly, the total number of sprouts formed by each spheroid also increased significantly. Preliminary results indicate that siRNA-mediated knock-down of NIK in EC leads to a clear reduction in cumulative sprout length, as well as in total sprout numbers.

Conclusion: Both the 2D and 3D model demonstrate that activation of the non-canonical NF-kappaB pathway via LT and LIGHT enhances angiogenesis. However, in contrast to the 2D model, the 3D model allows visualization of actual blood vessel formation. Importantly, preliminary results demonstrate that the observed increase in angiogenesis is at least in part NIK-dependent. This suggests that NIK may be a novel therapeutic target to block pathological angiogenesis in RA, thereby halting disease progression. Of interest, it is also possible to incorporate immune cells in the 3D model to study their contributions to pathological angiogenesis in RA synovial inflammation, which makes this a valuable tool for future studies.

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Interleukin-34 Regulates Angiogenesis and Cell Proliferation In Inflammatory Arthritis, This Effect Is Potentiated By Hypoxia. Emese Balogh[1], Mary Connolly[1], Monika Biniecka[1], Jennifer McCormick[2], Douglas J. Veale[2] and Ursula Fearon[2]. [1]Translation Research Group, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [2]St. Vincent's University Hospital, Dublin 4, Ireland.

Background/Purpose: Interleukin-34 (IL-34) is a cytokine implicated in macrophage differentiation, angiogenesis and osteoclastogenesis in inflammatory arthritis (IA). IA is characterized by synovial hypoxia, increased oxidative stress and altered angiogenesis. Our objectives was to investigate the role of IL-34 in the regulation of angiogenesis and hypoxia in IA.

Methods: Patients with active IA (RA n=18; PsA n=5) were recruited and underwent knee arthroscopies with a subgroup of (n=6) pre-post TNF-inhibitoric (TNFi) therapy investigations. Synovial tissue (ST) was collected and *in vivo*ST oxygen levels (tpO2) were measured. Synovial IL-34 expression was assessed by immunohistology (IHC) compared to control synovium. IL-34 expression was correlated to angiogenic marker (VEGF, Ang-2, Tie-2) expressions and proliferation marker expression (Ki67). Colocalisation of IL-34 with actin and vimentin was examined by dual-immunofluorescence (IF). IA fibroblast-like synoviocytes (IAFSCs, n=8) and human microvascular endothelial cells (HMVECs) were stimulated with IL-34 under normoxia and 3% hypoxia, then proliferation and tube formation assays were performed. IL-34 induced IASFC VEGF expression was measured by ELISA. Baseline mRNA levels of IASFCs were compared to osteoarthritic fibroblasts (OASFCs) by RT-PCR and followed up after TNFα stimulation. The effect of IL-34 on matrix metalloproteinase expression (MMP-2, MMP-9) was examined by zymography, IL-34 induced mononuclear cell (PBMC) adhesion to HMVECs was examined by adhesion assay.

Results: The baseline mean tpO_2 level was hypoxic at 25.94 mmHg (3.3%). IL-34 expression was observed through the synovium with higher expression in the vascular (VC) regions compared to the lining (LL) and sub-lining (SL). Expression levels were higher in any layers than in the healthy synovium ($p<0.05$). Synovial IL-34 expression correlated with VEGF ($r=0.60$, $p=0.011$), Tie2 ($r=0.50$, $p=0.021$), Ang2 ($r=0.70$, $p=0.013$) and Ki67 ($r=0.56$, $p=0.025$) and with macroscopic vascularity ($r=0.47$, $p=0.043$). Posttherapeuthic synovial IL-34 expression significantly decreased in SL and VC layers ($p=0.039$, $p=0.026$) with a simultaneous tpO_2increase from 20.9 to 23.2 mmHg. Baseline synovial IL-34 expression showed colocalisation with actin and vimentin. Basal IL-34 mRNA expression was higher in IASFCs than in OASFCs ($p<0.05$), the previous one was further potentiated by TNFα stimulation ($p<0.05$). IL-34 induced IASFC proliferation and HMVEC tube formation (all $p<0.05$), this effect was potentiated by 3% hypoxia ($p<0.05$). Furthermore IL-34 induced VEGF expression in IASFCs and stimulated PBMC adhesion to HMVECs as well as facilitated MMP-2 and MMP-9 expression in vitro.

Conclusion: IL-34 is strongly associated with synovial inflammation and promotes synovial angiogenesis and cell proliferation, an effect that is potentiated by hypoxia.

Disclosure: E. Balogh, AbbVie, Pfizer, MSD, Roche, 2; **M. Connolly**, AbbVie, Pfizer, MSD, Roche, 2; **M. Biniecka**, AbbVie, Pfizer, MSD, Roche, 2; **J. McCormick**, AbbVie, Pfizer, MSD, Roche, 2; **D. J. Veale**, AbbVie, Pfizer, MSD, Roche, 2, Pfizer, Roche, 5, Abbott, Pfizer, MSD, Roche, 8; **U. Fearon**, AbbVie, Pfizer, MSD, Roche, 2.

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The Interleukin 33/miR29 Axis Regulates Differential Collagen Production In Tendinopathy. Dr Neal L Millar[1], Derek S. Gilchrist[1], Mariola Kurowska-Stolarska[2], Prof George AC Murrell[3] and Prof Iain B. McInnes[1]. [1]University of Glasgow, Glasgow, United Kingdom, [2]Institute of Infection, Immunity and Inflammation, College of Medical, Veterinary and Life Sciences University of Glasgow, Glasgow, United Kingdom, [3]Orthopaedic Research Institute, Sydney, Australia.

Background/Purpose: Tendon disorders comprise the commonest musculoskeletal clinical presentation and accordingly represent a significant unmet clinical need in rheumatology. Recent animal and human studies have highlighted a central role for inflammation and subsequent matrix remodeling in tendon pathophysiology. Interleukin-33 (IL-33) acting via its receptor ST2 is increasingly recognized as a critical endogenous tissue danger signal that can initiate inflammation.

We investigated the role of the IL-33/ST2 signaling pathway on tendon pathology in animal and human models of tendinopathy.

Methods: Fifteen torn supraspinatus tendon (established pathology) and matched intact subscapularis tendon (representing 'early pathology') biopsies were collected from patients undergoing arthroscopic shoulder surgery. Human tendon-derived primary cells were derived from hamstring tendon tissue obtained during hamstring tendon ACL reconstruction. The impact of microRNA 29 upon tenocyte biology ex vivo was measured using quantitative RT-PCR, collagen I/III ELISAs and luminex cytokine multiplexes.

Results: We show here that human and mouse tendons over express IL-33 when damaged, and drives tenocytes to undergo an early switch in collagen matrix production toward a collagen III phenotype. Moreover, administration of rh IL-33 in an in vivo model of tendinopathy results in reduced biomechanical tendon strength at early time points while neutralizing antibodies to IL-33 attenuates these changes. Furthermore we highlight a key regulatory role for the microRNA29 family in IL-33 induced collagen matrix changes through direct targeting of the soluble ST2 receptor and Collagen III. In particular we show that miR29a selectively targets Collagen III through distal polyadenylation sites.

Conclusion: For the first time we provide evidence that IL-33/miR-29 pathway orchestrates inflammatory and matrix responses following tissue injury, and thus may offer future strategies to treat tendon diseases.

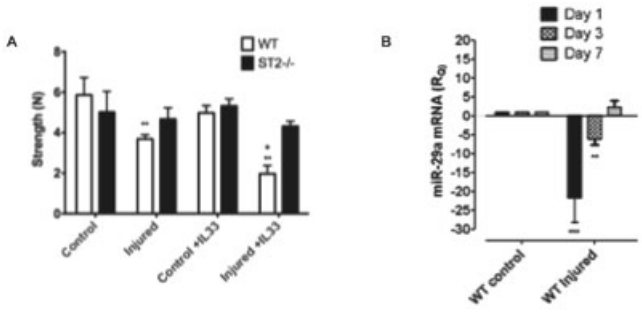

Figure 1. (A) rhIL-33 results in a significantly decreased load to failure in WT uninjured mice on Days 1 and 3 of the treatment protocol. More significantly WT injured mice had 45% less load to failure if treated with rhIL-33 on days 3 post injury with a 20% decrease in strength at 21 post injury compared to PBS injection alone. (B) miR29a levels in WT versus WT injured mice showing significant down regulation at early time points post injury which mirrored over expression of the IL33/ST2 axis.

Disclosure: D. N. L. Millar, None; **D. S. Gilchrist**, None; **M. Kurowska-Stolarska**, None; **P. G. A. Murrell**, None; **P. I. B. McInnes**, None.

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Dual Neutralization Of TNF and IL-17 Provides Greater Efficacy In Collagen Induced Arthritis Through Regulation Of a Gene Transcription Program That Includes CXCL1 and CXCL5. Carolyn Cuff[1], Chung-Ming Hsieh[1], Suzanne Mathieu[1], Anwar Murtaza[2], Margaret Hugunin[1], Shaughn Bryant[1], Robert O'brien[1], Lisa Olson[1] and Jeffrey Voss[1]. [1]AbbVie Pharmaceuticals, Worcester, MA, [2]Broad Institute, Cambridge, MA.

Background/Purpose: Dual neutralization of TNF and IL-17 is hypothesized to provide greater efficacy in rheumatoid arthritis (RA) and inflammatory diseases compared to either monotherapy as these cytokines cooperatively up-regulate cytokines and metalloproteinases. Moreover, dual blockade has been reported to provide greater efficacy in mouse collagen induced arthritis (CIA) compared to either monotherapy. To better understand the mechanism of this apparent cooperativity, we conducted a series of experiments utilizing the mouse CIA model.

Methods: CIA was induced in DBA/1 mice according to standard method and animals were treated with vehicle, anti-TNF antibody (8C11, 12 mg/kg), anti-IL-17 (MAB421, 12 mg/kg), or both antibodies twice a week for 3 weeks beginning at the onset of disease. Affymetrix gene chips were used to measure RNA expression in the paw. PCR was used to analyze chemokine expression in fibroblast like synoviocyte (FLS) culture. ELISA and MSD were utilized to measure chemokines in paw homogenate on day 7 of disease.

Results: Neutralization of mouse TNF or IL-17 alone with antibodies resulted in a significant but partial inhibition of arthritic score (36% and 43% inhibition, respectively, $p < 0.05$). However, when the 2 cytokines were neutralized by administration of anti-TNF and anti-IL-17 mAbs, arthritic score was significantly reduced to a greater extent (60%; $p < 0.05$). Combination treatment was also more effective at preventing bone destruction vs anti-TNF alone as determined by micro-CT analysis (80% vs 42%, $p < 0.05$). Microarray analysis of paw RNA from mono or dual cytokine inhibition identified pathways that could account for the enhanced efficacy. Consistent with cooperative gene regulation observed in vitro, these data demonstrated that combination treatment regulated a unique subset of disease related genes that were not regulated by monotherapy. Among other molecules, the protein level of the chemokines CXCL1 and CXCL5 were inhibited in paw homogenates by the combination treatment (73% and 70% respectively, $p < 0.05$) whereas monotherapies had little effect. TNF and IL-17 concordantly regulated CXCL1 and CXCL5 mRNA expression in both mouse and human FLS cultures, indicating the cooperative regulation of mediators of arthritis by TNF and IL-17 may translate to human tissues.

Conclusion: These data provide a mechanistic basis for the increased efficacy achieved by dual blockade of TNF and IL-17 in mouse CIA and support the rationale for testing dual TNF/IL-17 blockade in the treatment of RA.

Disclosure: C. Cuff, AbbVie, 3, AbbVie, 1; **C. M. Hsieh**, AbbVie, 3, AbbVie, 1; **S. Mathieu**, AbbVie, 3, AbbVie, 1; **A. Murtaza**, None; **M. Hugunin**, abbvie, 3, abbvie, 1; **S. Bryant**, AbbVie, 1, AbbVie, 3; **R. O'brien**, AbbVie, 3; **L. Olson**, Abbott Immunology Pharmaceuticals, 3; **J. Voss**, Abbott Immunology Pharmaceuticals, 3.

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Targeting CD1c-Expressing Mdcs To Inhibit Tcell Activation and Thymus and Activation Regulated Chemokine (TARC)-Dependent Chemotaxis In RA. M.R. Hillen, F.M. Moret, F.P.J.G. Lafeber, C.E. Hack, T.R.D.J. Radstake and J.A.G. van Roon. University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: Recently, we demonstrated strong Th1 and Th17 cytokine induction by $CD1c^+$ myeloid dendritic cells (mDCs) from synovial fluid and identified thymic stromal lympopoeitin (TSLP) as an important activator of these cells. CD1c-expressing mDCs and CD4 T cells are potent producers of Thymus and activation regulated chemokine (TARC), which is a chemotactic factor that attracts cells expressing CCR4, including CD4 T cells with Th2, Th17 and Treg phenotypes. TARC is known as a critical mediator in atopic diseases but is also present at sites of inflammation in autoimmune diseases. In synovial fluid (SF) of rheumatoid arthritis (RA) patients CCR4 is expressed on Th17 cells and mast cells that together are indicated to make up most IL-17 producing cells, suggesting that TARC plays an important role in attraction of IL-17 producing cells to the synovium. In addition, TARC can attract mDCs and fibroblasts. This study aimed to investigate if TARC is associated with RA pathogenesis and whether depletion of CD1c mDCs prevents production of high TARC concentrations.

Methods: TARC ELISA was performed on SF of 100 RA and 50 OA patients. Mononuclear cells (MC) were isolated from the blood of healthy controls (HC) and blood or SF of RA patients and juvenile idiopathic arthritis (JIA) patients. CD1c mDCs were isolated with MACS and stimulated with TSLP for 24 hours and TARC levels were measured in supernatants. Alternatively, CD1c-expressing cells were depleted from MC using MACS and TARC levels were measured upon stimulation with TSLP or IL-7.

Results: SF from RA patients contained significantly higher concentrations of TARC as compared to SF from OA patients (78.9 vs 9.2 pg/mL, $p<0.0001$). Isolated CD1c mDCs from the synovial fluid of RA patients produced TARC directly *ex vivo* and produced significantly higher TARC levels compared to paired mDCs from the blood (26.4 vs 1.2 pg/mL, $p<0.01$). CD1c mDCs and SFMCs from RA and JIA patients produced more TARC compared to paired PB counterparts when stimulated with TSLP (926 vs 128 pg/mL, $p<0.01$) (or IL-7, $p<0.01$). Moreover, depletion of CD1c cells from MC significantly reduced TARC production induced by stimulation with TSLP (mean inhibition 61%, $p=0.004$).

Conclusion: Increased TARC levels correlate with the percentages of CD1c-expressing mDCs present in RA SF; these mDCs produce enhanced TARC levels directly *ex vivo* and production is increased upon stimulation with TSLP. TARC production is markedly decreased when CD1c cells are depleted. Considering the strong potential of SF $CD1c^+$ mDCs to activate CD4 T cells and to induce Th1 and Th17 cytokine secretion as well as the potent attraction of a range of inflammatory cells by TARC, targeting CD1c mDCs could be a novel therapeutic approach in RA.

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Changes In Circulating Visfatin Levels By Different Anti-Rheumatic Treatments: A Comparison Among Synthetic Disease Modifying Anti-Rheumatic Drugs, Tumor Necrosis Factor Blockade and B-Cell Depletion For Rheumatoid Arthritis. Hana Hulejová[1], Markéta Kuklová[2], Herman F. Mann[3], Mária Filková[4], Olga Kryštufková[5], Karel Pavelka[6], Ondrej Sglunda[4], Jiri Vencovsky[1] and Ladislav Senolt[1]. [1]Institute of Rheumatology, Prague, Czech Republic, [2]Institute of Rheumatology, Department of Experimental Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [3]Institute of Rheumatology, Prague, Prague, Czech Republic, [4]Institute of Rheumatology and Department of Rheumatology of the First Faculty of Medicine, Charles University in Prague, Czech Republic, Prague, Czech Republic, [5]Institute of Rheumatology, and Dept. of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, Prague, Czech Republic, [6]Department of Clinical and Experimental Rheumatology, Charles University, Prague, Czech Republic.

Background/Purpose: Visfatin is an insulin mimetic adipokine that has been originally described as a pre-B cell colony-enhancing factor. Association between elevated visfatin levels, disease activity and radiographic disease progression in rheumatoid arthritis (RA) were demonstrated, although the data are not consistent. The aim of this study is to investigate whether serum visfatin levels are affected by different treatments in various stages of RA.

Methods: Serum visfatin levels were determined by ELISA assay in patients with early RA (n=40) starting synthetic disease modifying anti-rheumatic drugs (DMARDs), in patients with established RA starting biologic DMARDs-adalimumab (n = 70) or rituximab (n = 31). Early RA was characterized as symptom duration £ 6 months. Fasting blood samples were collected from all patients at baseline and after three months of treatment. Visfatin levels were also evaluated in healthy controls (n=44). Disease activity was assessed based on DAS28 score. Serum levels of C-reactive protein (CRP), rheumatoid factors and anti-cyclic citrullinated peptides (anti-CCP) were measured.

Results: Baseline levels of visfatin were higher in patients with RA compared with healthy controls and correlated positively with CRP levels ($r = 0.456$, $p = 0.003$) and DAS28 ($r = 0.383$, $p = 0.015$) in patients with early RA, but not in patients with established disease. In addition, serum levels of visfatin significantly decreased after 3 months of treatment in patients with early RA (from 1.92 ± 1.17 to 0.99 ± 0.67 ng/ml; $p<0.0001$). Accordingly, in patients with established disease, treatment with adalimumab resulted in significant decrease of serum visfatin levels (from 2.27 ± 2.02 to 1.77 ± 1.66, $p < 0.05$), and treatment with rituximab resulted in significant decrease of serum visfatin levels (from 1.92 ± 1.66 to 0.94 ± 0.70, $p < 0.005$). The change of visfatin levels correlated positively with the change of CRP ($r = 0.393$, $p = 0.013$) and DAS28 ($r = 0.425$, $p = 0.007$) between baseline and 3 months in patients with early RA.

Conclusion: This study shows for the first time that circulating visfatin levels are decreased following synthetic as well as biologic DMARDs in various stages of RA; however, circulating visfatin is associated with disease activity only at early phase of the disease.

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The Anti-IL-17A Monoclonal Antibody Secukinumab (AIN457) Inhibits Pro-Inflammatory Mediator Release From Human Primary Synoviocytes Costimulated With IL-17 and TNF. Christine Huppertz, Marija Curcic Djuric, Robert Hennze and Frank Kolbinger. Autoimmunity, Transplantation and Inflammatory Disease, Novartis Institutes for BioMedical Research, Novartis Pharma AG, Basel, SWITZERLAND, Basel, Switzerland.

Background/Purpose: Fibroblast-like synoviocytes (FLS) are targets of the pro-inflammatory IL-17 cytokines and a major source of inflammatory mediators in the inflamed synovium in rheumatoid arthritis (RA). We have determined the activity of IL-17A and IL-17AF (the heterodimer of IL-17A and IL-17F) to augment the effects of TNF or IL-1β on FLS derived from RA patients (RA-FLS) as described in a separate study. Since the newly developed anti-IL-17A antibody secukinumab has shown promise in various clinical trials including RA, we provide here further evidence how it interferes with IL-17 pathways by investigating the in vitro neutralizing activity of secukinumab on the release of key pro-inflammatory FLS products upon costimulation with TNF combined with IL-17A or IL-17AF and upon costimulation with IL-1β and IL-17A.

Methods: RA-FLS were stimulated for 18h with IL-1β (300 pM) combined with IL-17A, or with TNF (60 pM) combined with either IL-17A (30 pM) or IL-17AF (1 nM). Secukinumab or control antibody was given shortly before cytokine stimulation of RA-FLS. The release of IL-6, IL-8, CXCL-1 and CCL2 was determined by homogeneous time resolved fluorescence technology or AlphaLISA. RA-FLS cell lines were obtained from Cell Application Inc.

Results: While IL-17A was weak as a single stimulus, co-stimulation of primary human RA-FLS with IL-17A and TNF synergistically potentiated the effect of TNF on the release of the pro-inflammatory cytokines IL-6, IL-8 and CXCL-1 (Gro-α). Interestingly, CCL2 (MCP-1) release was not potentiated but was only dependent on TNF, indicating a different mechanism or regulation of this chemokine. Secukinumab potently inhibited the potentiated release of IL-6 induced by IL-17A/TNF costimulation at picomolar concentrations with an IC50 value of 0.14 $\pm$ 0.02 nM, but had no effect on basal TNF-induced release of IL-6. Similar results were obtained for the inhibition of IL-8 and CXCL-1 release. CCL2 release was not attenuated by secukinumab, which is in line with CCL2's dependency on the TNF pathway. As we had observed a lower potency of IL-17AF compared to IL-17A to co-stimulate mediator release, IL-17AF was administered at 34 higher concentrations to induce similar maximum IL-6 levels. The effect of secukinumab on IL-17AF/TNF stimulated mediator release were similar to those observed for IL-17A but were less potent, consistent with the lower binding affinity of secukinumab to IL-17AF and the higher IL-17AF cytokine levels required in the in vitro experiment. Combination of IL-1β with IL-17A showed no potentiating effect on pro-inflammatory cytokines. In line with this, there was no significant effect of secukinumab on mediator release from IL-17/IL-1β co-stimulated FLS.

Conclusion: The data show that secukinumab completely neutralizes the amplifying effect of IL-17 on TNF-stimulated RA synovial fibroblasts, one of the key target cells in rheumatoid arthritis. It is anticipated that this blockade contributes to the therapeutic effect of secukinumab seen in RA clinical trials.

Disclosure: C. Huppertz, Novartis Pharma AG, 3; **M. Curcic Djuric**, Novartis Pharma AG, 3; **R. Hennze**, Novartis Pharma AG, 3; **F. Kolbinger**, Novartis Pharma AG, 3.

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CX3CR1 Deficiency Attenuates Imiquimod-Induced Psoriasis-Like Skin Inflammation By Predominant Infiltration Of M2 Macrophages. Sohshi Morimura, Makoto Sugaya and Shinichi Sato. The University of Tokyo, Tokyo, Japan.

Background/Purpose: CX3C chemokine receptor 1 (CX3CR1), a receptor for CX3CL1, has been identified as a key mediator of macrophage migration into injured tissue or inflammation sites. It has recently been reported that serum CX3CL1 levels were significantly elevated in patients with rheumatoid arthritis (RA). Psoriasis is a common skin condition that causes skin redness and irritation. Some patients with psoriasis suffer from arthritis, which is clinically similar to RA, suggesting that both psoriatic arthritis and RA *have* the same *underlying* immunological cause. Thus, we hypothesized that CX3CL1 and CX3CR1 also play important roles in the development of psoriasis. To elucidate the role of CX3CL1 and CX3CR1 in a mouse model of psoriasis, psoriasiform skin inflammation triggered by topical application of imiquimod, an agonist of Toll-like receptor (TLR) 7, was assessed in CX3CR1-deficinet mice and wild-type (WT) mice.

Methods: CX3CR1$^{-/-}$ and WT mice received a daily topical dose of 62.5 mg imiquimod cream (5%) on a shaved back and ears for 6 consecutive days. Erythema, scaling, and skin thickness were independently scored every day. Total RNA was isolated from ears 24 and 48 hours after the start of topical application and mRNA expression levels of cytokines were investigated. Furthermore, macrophages were harvested from peritoneal cavity of naive CX3CR1$^{-/-}$ and WT mice and cultured in the presence or absence of CX3CL1. Cytokine expression in macrophages was examined at mRNA levels by quantitative RT-PCR and at protein levels using enzyme-linked immunosorbent assay. We also investigated macrophage populations by checking expression of M1 and M2 macrophage markers.

Results: Imiquimod-induced skin inflammation assessed by erythema, scaling, and skin thickness was milder in CX3CR1$^{-/-}$ mice than WT mice. In inflamed skin, mRNA expression levels of IL-12/IL-23p40, IL-23p19, IL-12p35, IL-17A, IL-17F, IL-22, IL-1β, IL-6, TNFα, IL-36α, and IL-36γ were significantly decreased in CX3CR1$^{-/-}$ mice compared to WT mice. The number of macrophages harvested from peritoneal cavity of naive CX3CR1$^{-/-}$ mice were about one third of that of WT mice. The expression levels of IL-1β, IL-6, TNFα in macrophages of CX3CR1$^{-/-}$ mice were significantly lower than that of WT mice. Addition of CX3CL1 into the culture media, however, decreased expression of these cytokines in WT macrophages, suggesting that loss of interactions between CX3CL1 and CX3CR1 did not directly cause decrease in cytokine expression. In inflamed skin of CX3CR1$^{-/-}$ mice, MCP-1 (a M1 macrophage marker) mRNA expression levels were significantly lower, while mRNA levels of MRC-1, Arginase 1, and Ym1/2 (M2 macrophage markers) were significantly higher than in WT mice. Similar findings were observed in peritoneal macrophages, suggesting that difference in macrophage populations was one possible reason for different cytokine expression.

Conclusion: CX3CL1 and CX3CR1 play important roles for infiltration of M1 macrophages both in the skin and peritoneal cavity. Predominance of M2 macrophages in CX3CR1$^{-/-}$ mice may account for decreased expression of IL-1β, IL-6, and TNFα and milder imiquimod-induced skin inflammation.

Disclosure: S. Morimura, None; **M. Sugaya**, None; **S. Sato**, None.

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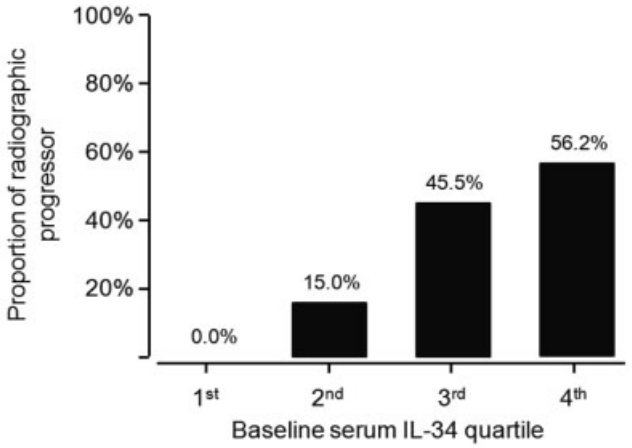
Baseline Serum Interleukin-34 Levels Predict Radiographic Progression In Rheumatoid Arthritis Patients. Sung Hae Chang[1], Byoung Youg Choi[1], Hyon Joung Cho[1], Hye Jin Oh[2], Eun Ha Kang[1], Yeong Wook Song[3] and Yun Jong Lee[1]. [1]Seoul National University Bundang Hospital, Seongnam-si, South Korea, [2]Seoul National University Hospital, Seoul, South Korea, [3]Seoul National University College of Medicine, Seoul, South Korea.

Background/Purpose: Interleukin-34 (IL-34), a novel cytokine playing a critical role in osteoclastogenesis, recently was reported that its expression increases in the synovial tissue and sera of patients with rheumatoid arthritis (RA). However, there has been no study on an association between IL-34 and RA-associated joint damage. We evaluated whether baseline serum IL-34 levels predict radiographic progression in RA patients.

Methods: Sera were obtained from consecutive patients with RA (n=100) and ankylosing spondylitis (AS, n=36). Fifty-nine gender- and age-matched healthy individuals served as controls. Synovial fluid (SF) samples were collected from another 18 patients with RA and 19 with osteoarthritis (OA). Clinical data were recorded at the time of sampling.

Radiologic damage was assessed according to the modified Sharp/van der Heijde score (SHS) at baseline and at follow-up (n=78), an average of 1.7 years later. The IL-34 concentrations were determined by an enzyme-linked immunosorbent assay.

Results: Serum IL-34 levels were significantly higher in patients with RA ($p=4.02 \times 10^{-4}$) or AS ($p=2.15 \times 10^{-5}$) than those in controls. RA patients showed significantly higher SF IL-34 levels in the SF samples than OA patients ($p=3.62 \times 10^{-5}$). In RA, serum IL-34 levels were significantly associated with rheumatoid factor positivity (p=0.011), current smoking status (p=0.002), ESR levels (r=0.258, p=0.010), and C-reactive protein levels (r=0.262, p=0.008). ¥ÄSHS/year was positively correlated with serum IL-34 levels (r=0.474, p=0.029). Moreover, baseline IL-34 level quartiles was an independent predictor for radiographic progression in RA patients (odds ratio 4.765 [95% CI 19.810–11.461], $p=4.89 \times 10^{-4}$, Figure 1).



Multivariate regression results for radiographic progression

Variables	Regression coefficients (β)	*p* values	Odds ratios [95% CI]
IL-34 quartiles	1.561	4.89×10^{-4}	4.765 [1.981, 11.461]
RF positivity	0.762	0.524	2.142 [0.206, 22.278]
WBC	0.000	0.156	1.000 [1.000, 1.001]
CRP	-0.009	0.613	1.565 [0.761, 3.220]

Figure 1. Proportions of patients with subsequent radiographic progression according to the quartiles of baseline serum IL-34 levels.

Conclusion: These results suggest that IL-34, a novel osteoclastogenic cytokine, play a role in RA-associated joint damage and it can be a biomarker for predicting the subsequent radiographic progression in RA patients.

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Correlating The *In Vivo* Production Of IFNγ To Disease Parameters In TLR9-Induced Macrophage Activation Syndrome (MAS) In Mice. Vanessa Buatois[1], Laurence Chatel[1], Laura Cons[1], Sabrina Lory[1], Maureen Deehan[1], Jennifer Sims[2], Cristina de Min[1], Marie Kosco-Vilbois[1] and Walter Ferlin[1]. [1]NovImmune S.A., Geneva, Switzerland, [2]Integrated Biologix GmBH, Basel, Switzerland.

Background/Purpose: Cytokine release is the hallmark feature in mice given repeated injections of the TLR9 agonist, CpG-containing oligodeoxynucleotides (CpG-ODN), resulting in pathology resembling the human disease, MAS. However, an anti-IL-10 Receptor (R) monoclonal antibody (mAb) must be co-administered with CpG-ODN to induce more severe human MAS symptoms including hemophagocytosis (herein referred to as fulminant-MAS). Use of an anti-mouse IFNγ mAb, XMG1.2, has demonstrated the dependence of disease manifestation on this cytokine. This study exploits an *in vivo* principle that secreted IFNγ, in the presence of XMG1.2, produces a complex that has a relatively long-half-life and consequently allows cytokine accumulation in the serum which can be quantitated (Finkelman, 1999). An accumulation of complex, from body tissues into the serum, thus, is a reflection of the total IFNγ production of the cytokine in the body. Our *in vivo* results characterize and correlate the production of IFNγ to the clinical and laboratory parameters in murine models of MAS and fulminant-MAS.

Methods: C57BL/6 mice received i.p. injections of CpG-ODN on days 0, 2, 4, 7 and 9. Neutralizing IL-10R, mAb 1B1.3A at 200μg/mouse (days 0, 2, 4 & 6), and anti-mouse IFNg, mAb XMG1.2 at 100 mg/kg (days 1, 3 & 6) were administered *i.v*. Q-PCR was used to analyze inflammatory gene expression. Luminex multiplex technology was used to detect serum cytokines. Blood parameters were measured using a haematological counter. Serum concentrations of the cytokine-drug complex were determined by an ELISA method developed for purpose.

Results: TLR9 agonism resulted in a multi-phasic production of IFNγ evidenced by a spike in serum cytokine levels following each CpG-ODN injection. Therapeutic blockade of IFNγ by XMG1.2 reduced body weight loss, splenomegaly, normalized white blood cell counts, significantly reversed the decrease in other laboratory parameters (e.g. platelets, haemoglobin and red blood cells) and controlled hyperferritinemia. IFNγ measured from CpG-ODN mice co-treated with XMG1.2, which accumulated as a complex in the serum, reached steady state levels of 233 ng/ml. This represented a 200-fold increase over serum IFNγ levels measured in mice treated with CpG-ODN alone (1 ng/ml). Expression of IFNγ induced inflammatory genes demonstrated that spleen and liver are major sites of IFNγ production. Interestingly, although the fulminant-MAS model presented a more severe pathology, *in vivo* production of IFNγ production was determined to be equivalent in the two models. Nonetheless, blockade of IFNγ in mice with fulminant-MAS also improved key disease features including body weight loss, splenomegaly, anemia, hyper-cytokinemia, lymphopenia. Notably, XMG1.2 treatment also decreased the platelet loss in mice with fulminant MAS. Ongoing experiments are focused on determining how the blockade of IFNγ influences the consumptive anemia of inflammation observed in these mice.

Conclusion: The substantial production of IFNγ in tissues is intimately associated with the clinical and laboratory features in the CpG-induced model of MAS. These data support the potential therapeutic strategy for IFNγ neutralization in patients afflicted with this severe form of MAS.

Disclosure: V. Buatois, NovImmune S.A., 3; **L. Chatel**, NovImmune S.A., 3; **L. Cons**, NovImmune S.A., 3; **S. Lory**, NovImmune S.A., 3; **M. Deehan**, NovImmune S.A., 3; **J. Sims**, NovImmune S.A., 5; **C. de Min**, NovImmune S.A., 3; **M. Kosco-Vilbois**, NovImmune S.A., 3; **W. Ferlin**, NovImmune S.A., 3.

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Myeloid Deletion Of SIRT1 Aggravates Serum Transfer Arthritis But Ameliorate Collagen-Induced Arthritis. Sang-Il Lee[1], Yun-Hong Cheon[1], Won Seok Lee[2] and Ji-Min Kim[3]. [1]Gyeongsang National University School of Medicine, Jinju, South Korea, [2]Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Keimyung University School of Medicine, Daegu, South Korea.

Background/Purpose: SIRT1 plays a pivotal role in regulating the inflammatory response. Thus, we assessed the role of SIRT1 in K/BxN serum transfer arthritis as a model of inflammatory arthritis using a myeloid cell-specific SIRT1 knockout (mSIRT1 KO) mouse. To further understand how SIRT1 regulates autoimmunity, we also evaluated collagen-induced arthritis (CIA) using mSIRT1 KO mice.

Methods: mSIRT1 KO mice were generated by using the loxP/Cre recombinase system. K/BxN serum transfer arthritis and CIA were induced in mSIRT1 KO ($SIRT1^{loxP/loxP}$ LysM-$Cre^{+/+}$) and their age-matched littermate loxP control ($SIRT1^{loxP/loxP}$ LysM-$Cre^{-/-}$) mice. Arthritis severity was assessed by clinical and pathological scoring. The levels of inflammatory cytokines in the serum and joints were measured by ELISA and quantitative polymerase chain reaction. The migration, M1 polarization, cytokine production, osteoclastogenesis, and p65 acetylation were assessed in bone marrow-derived monocytes/macrophages (BMMs). The each subset of T cells and dendritic cells was analyzed by flow cytofluorometry in lymph node and spleen.

Results: The mSIRT1 KO mice showed more severe inflammatory arthritis accompanied by aggravated pathological findings than control in K/BxN serum transfer model. These effects were paralleled by higher levels of IL-1 and TNF-α and increased TRAP-positive osteoclasts and

F4/80$^+$ macrophages in the synovium of mSIRT1 KO mice. BMMs from the mSIRT1 mice displayed hyperacetylated p65 and increased NF-κB binding activity than control. However, unlike passive K/BxN arthritis, SIRT1 deficiency in CIA was associated with lower arthritic, radiographic, and pathologic severity. These effects were paralleled by lower levels of numerous inflammatory cytokines in the ankles and lymph nodes of mSIRT1 KO mice. In CIA, the proportion of Th1 and Th17 cells and CD80/86-positive dendritic cells was significantly decreased in mSIRT1 KO mice than controls.

Conclusion: Our study suggests that SIRT1 plays a complex role in regulating inflammation and adaptive immunity and, depending on the model, either enhances or suppresses rheumatoid arthritis.

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The Role Of S100A4 As a Biological Marker Of Immune Response In Early Rheumatoid Arthritis. Lucie Andrés Cerezo[1], Klára Prajzlerová[1], Martina Remáková[1], Herman F. Mann[2], Michal Tomcík[1], Karel Pavelka[2], Jiri Vencovsky[1] and Ladislav Senolt[1]. [1]Institute of Rheumatology, Prague, Czech Republic, [2]Institute of Rheumatology, Prague, Prague, Czech Republic.

Background/Purpose: We have previously demonstrated that S100A4 is up-regulated in established rheumatoid arthritis (RA) and that S100A4 regulates apoptosis and synthesis of matrix degrading enzymes in synovial fibroblasts. The aim of the present study was to: 1) characterize whether S100A4 reflects disease activity and/or response to treatment in patients with early RA and 2) determine whether S100A4 regulates production of pro-inflammatory cytokines in mononuclear cells.

Methods: Serum samples were obtained from 59 patients with early RA (symptom duration ≤ 6 months) before and 3 months after treatment with disease modifying anti-rheumatic drugs (DMARDs) and also from 41 healthy individuals. Disease activity score (DAS28-CRP) was assessed at baseline and after 3 and 12 months. S100A4 levels were analyzed by ELISA. Peripheral blood mononuclear cells (PBMCs) and CD3+ T-cells isolated from patients with established RA were stimulated with S100A4, S100A8 and S100A12 proteins (each 1μg/ml). Production of interleukin IL-1β, IL-6 and tumor necrosis factor alpha (TNF-α) was measured by ELISA. Receptor for advanced glycation end products (RAGE) and Toll-like receptor-4 (TLR-4) signalling were examined. For signalling pathway blocking studies, inhibitors of MyD88, NFkB and MAP kinases p38, erk1/2, jnk were used. Activation of MAP kinases was determined by Western blotting.

Results: S100A4 serum levels were significantly higher in patients with early RA compared with healthy controls ($p<0.001$) and significantly decreased after 3 months of treatment ($p<0.001$).

Although S100A4 levels did not correlate with disease activity, in female patients, high S100A4 levels (>1000 ng/ml) at baseline predicted worse response to treatment (DAS28 ≥ 3.2) after 3 and 12 months of therapy (PPV 0.28, OR (95% CI) 2. 846 (1.837, 4.410), p= 0.006 and PPV 0.60, OR (95% CI) 2.700 (0. 992, 7.351), P=0.046). Interestingly, higher S100A4 levels (>1000 ng/ml) at 3 months predicted worse response to treatment (DAS28 ≥ 3.2) in all patients after 12 months (PPV=0.33, OR (95% CI) 2.36 (1.17, 4.74), p=0.04).

Stimulation of PBMCs with S100A4 significantly up-regulated production of IL-1β, IL-6 and TNF-α compared with unstimulated cells ($p<0.001$). Importantly, production of the cytokines was markedly enhanced in response to S100A4 compared with S100A8 and S100A12 proteins. Extracellular S100A4 induced production of the pro-inflammatory cytokines ($p<0.01$) also in CD3+ T-cells. Furthermore, enhanced production of pro-inflammatory cytokines in S100A4 stimulated PMBCs was at least partly mediated via TLR-4, but not RAGE, and by the activation of transcription factor NFkB and MAP kinases p38 and erk1/2.

Conclusion: This is the first study to demonstrate that S100A4 is elevated in patients with early RA and that S100A4 induces inflammatory response mediated by the TLR-4 signalling pathway in mononuclear cells. Taken together, we suggest that high levels of S100A4 may represent a potential biomarker of insufficient treatment response and/or therapeutic target for immune mediated diseases such as RA.

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Serum Cytokine Changes In Rituximab-Treated Rheumatoid Arthritis Patients. Tamarah D. de Jong[1], Saskia Vosslamber[1], Wilco de Jager[2], Hennie G. Raterman[1], Alexandre E. Voskuyl[1], Kyra A. Gelderman[1] and Cornelis L. Verweij[1]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: Although rituximab therapy is successful in the majority of rheumatoid arthritis (RA) patients, 30–40% of patients do not respond. The mechanism behind this is yet unknown, as B cell depletion generally takes place in all patients. This study aims to explore changes in serum cytokines during rituximab therapy in established RA patients.

Methods: Serum was collected from 18 established RA patients before and at 1, 3, 6, 9 and 12 months after start of rituximab therapy. A panel of 34 cytokines was measured by a multiplex immunoassay platform (Luminex). Rituximab responder status was determined by the change in disease activity score after 6 months; Patients with DDAS28>1.2 were considered responders.

Results: During rituximab therapy, CXCL13 showed a significant decrease in all patients (median 1.9-fold decrease (IQR 1.4–3.3)), irrespective of responder status. This pattern appeared to coincide with B cell depletion, suggesting that CXCL13 reflects B cell levels in the circulation.

No differences were observed between responders and non-responders after 1 and 3 months of therapy. However, at 6, 9 and 12 months, CXCL10 appeared to be regulated differently between responders and non-responders (R vs. NR, T6/T0 p=0.004, T9/T0 p=0.003, T12/T0 p=0.001). CXCL10 showed a relative increase compared to baseline in the non-responders and no increase or even a decrease in responders. The fold changes in CXCL10 correlated to the DDAS28 at 6 months, indicating that this reflects disease activity rather than a mechanistic effect of rituximab. Most strikingly, IL-12 was not detectable in most of the non-responders until 6 months, but showed a sudden increase after 9 months of therapy. This increase was not observed in the responders (R vs. NR T9/T6 p=0.030, Fisher's exact p=0.049). In contrast to CXCL10, no correlation was observed between DDAS28 and the fold change in IL-12.

Conclusion: This study shows that during rituximab therapy, cytokine changes occur in the patient serum, both related and unrelated to the clinical response. CXCL13 seems to reflect B cells levels in the circulation, whereas the dynamics of CXCL10 and IL-12 during therapy are regulated differently between responders and non-responders during rituximab treatment. These findings indicate different pharmacological effects of rituximab between responders and non-responders.

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Interleukin 10 Negatively Correlates With Glycoprotein VI-Related Platelet Activation In Rheumatoid Arthritis (RA): A Novel Potential Target Of Cardiovascular Morbidity In RA. Leann Bell[1], Anne M. Madigan[1], Paul A. MacMullan[1], Eimear Dunne[2], Paola M. Bagaglia[1], Laura J. Durcan[1], Dermot Kenny[2] and Geraldine M. McCarthy[1]. [1]Mater Misericordiae University Hospital, Dublin 7, Ireland, [2]RCSI, Dublin 2, Ireland.

Background/Purpose: Patients with rheumatoid arthritis (RA) die prematurely of cardiovascular disease (CVD). Platelet mediated thrombosis is a major cause of CVD. Platelets amplify inflammation in RA via the collagen receptor, glycoprotein (GP) VI. When platelets are activated, the GPVI receptor is shed and present in plasma as soluble GPVI (sGPIV). Since sGPVI is a marker of global platelet activation, we investigated whether sGPVI differs in patients with active RA in comparison with

patients with low RA disease activity. Moreover, since cytokines associated with disease activity in RA may effect platelet activation, we also assessed the relationship between sGPVI and plasma cytokine levels in this cohort.

Methods: We prospectively assayed blood samples from healthy donors (n=5), patients with active RA (n=13), and controlled RA (n=10), respectively. Disease activity assessment comprised of serological markers (ESR, CRP, fibrinogen), patient measures (VASDA), evaluator global assessment, and the DAS-28 score. Platelet activation was assessed by measuring sGPVI. Plasma was centrifuged at 720g and then 20000g to ensure that no platelets or platelet derived microparticles were present in the sample and sGPVI levels were measured by ELISA. Serum levels of tumor necrosis factor (TNF)α, interleukin (IL)1β, IL6, IL8, IL10, IL12p70 and interferon (IFN)δ were measured by multiplex ELISA and a Spearman's rank-order correlation was used to test significance.

Results: Mean plasma sGPVI was significantly higher in patients with active RA (14 $\pm$7ng/ml;(mean$\pm$SEM) $p<0.005$) compared to both stable RA (5$\pm$1ng/ml) and controls (5$\pm$2ng/ml) demonstrating that platelet activation occurs in active RA. Mean plasma IL-10 was significantly higher in stable RA patients (39$\pm$31 pg/ml; $p<0.005$) compared to both active RA and controls (15$\pm$8 and 2.24$\pm$0.33pg/ml respectively). There was no association with any measured cytokine and sGPVI levels apart from IL-10, which was negatively correlated with sGPVI in these 28, matched plasma samples (-0.432; $p \leq 0.045$).

Conclusion: Platelet hyper-reactivity in patients with active RA likely contributes to the associated adverse cardiovascular outcomes. sGPVI is a marker for platelet activation in active RA. The anti-inflammatory cytokine IL10, known to play a modulatory role in endothelial cell damage and platelet adhesion, may negatively regulate platelet activation in active RA. These effects of IL-10 could potentially be exploited in the management of RA.

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ACR/ARHP Poster Session B
Medical Education

Monday, October 28, 2013, 8:30 AM–4:00 PM

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Self-Perceived Efficacy of a Workshop On Musculoskeletal Clinical Anatomy. Miguel A. Saavedra[1], José E. Navarro-Zarza[2], J. Alvarez-Nemegyei[3], Juan J. Canoso[4], Robert A. Kalish[5], Pablo Villaseñor-Ovies[6] and Cristina Hernández-Díaz[7]. [1]Hospital de Especialidades, Centro Medico La Raza Instituto Mexicano del Seguro Social Mexico D.F., México D.F., Mexico, [2]Mexican Taskforce for the Advancement of Clinical Anatomy, Mexico, Mexico, [3]Instituto Mexicano del Seguro Social, Merida, Mexico, [4]ABC Medical Center and Tufts University, Mexico City, Mexico, [5]Tufts Medical Center, Boston, MA, [6]Hospital Angeles Tijuana, Tijuana, Mexico, [7]Instituto Nacional de Rehabilitación, Mexico City, Mexico.

Background/Purpose: Knowledge of musculoskeletal anatomy is suboptimal at many levels of rheumatology training and practice. In a recent practical anatomy pre-test administered prior to a clinical anatomy workshop rheumatology fellows, practicing rheumatologists and non-rheumatologists from 7 American countries (unpublished) scored a mean of less than 50% correct on a series of anatomic questions thought important to rheumatologic practice. We now report the results of a self-assessed competence questionnaire completed after our workshop took place.

Methods: The workshop on clinical anatomy consisted of a regional demonstration of anatomy, physical examination and simulated injections using clinical vignettes, anatomical drawings and attendee cross examination. The post-workshop questionnaire included the same twenty questions with the practical identification or demonstration of anatomic structures replaced by a self-assessment of competence. A five point Likert scale ranging from not competent to highly competent was used yielding a maximum score of 100. A total of 144 participants from 5 of the original 7 countries were asked to participate with 2 countries not included due to anticipated communication barriers. The initial request was sent one month after the workshop and monthly thereafter to a total of 3 requests. Comparison of self-assessment scores of anatomic competence between fellows, rheumatologists and other participants, as well as comparison of participants from the different countries, was calculated by ANOVA. Efficacy of the workshop was determined by the comparison of the pre-workshop (as assessed by instructors) and the post-workshop (self-assessed) scores by the t test for paired samples.

Results: The overall response rate was 74.3% (107 respondents, inter-country range 56–100). A significantly higher overall self-assessed competence score was noted after the workshop as compared to the pre-workshop score (74.7$\pm$13.1 v.s. 48.1$\pm$13.1; $p<0.0001$). Interestingly, marked score differences noted between countries in the pre-workshop tests (inter-country range: 42.8$\pm$20.5 to 62.7$\pm$15.8;) were no longer present in the post-workshop assessments (inter-country range 66.7$\pm$12.6 to 80.2$\pm$10.6). Likewise, whereas rheumatology fellows scored significantly higher in the pre-test assessment than non-rheumatologists, in the post-workshop self-assessment there were no significant differences in the scores of the three groups.

Conclusion: We found a uniformly high level of self confidence in the identification of key anatomical items following an intensive workshop in clinical anatomy despite significant differences between countries and between professional groups in the pre-workshop test. A limitation to our study is that scores from two dissimilar assessment methods, a practical clinical musculoskeletal anatomy pre-test and a self-rated competency assessment, were compared. Nonetheless based on these limited data we are optimistic that our clinical anatomy workshop can positively impact knowledge and skills in this important area for rheumatologists and that further assessment of the utility of our workshop is warranted.

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Assessment and Promotion of a National Immunology Curriculum for Adult Rheumatology Residents. Dharini Mahendira[1], Shirley L. Chow[2], Sari Herman-Kideckel[3] and Heather McDonald-Blumer[4]. [1]St Michael's Hospital, University of Toronto, Toronto, ON, [2]University of Toronto, Toronto, ON, [3]University of Toronto, North York, ON, [4]Division of Rheumatology, Mount Sinai Hospital; Osteoporosis Program, Toronto General Hospital, Toronto, ON.

Background/Purpose: Immunologic mechanisms play an integral role in understanding the pathogenesis and management of rheumatic conditions. Currently, there is limited access to standardized formal instruction in immunology for rheumatology trainees across Canada. This is despite the belief that a comprehensive immunology curriculum is essential for adult rheumatology trainees to meet the competencies mandated by the Royal College of Physicians and Surgeons of Canada. The goals of this project were (1) to describe the structure of current immunology curricula amongst adult rheumatology training programs across Canada and (2) to identify and compare the perceived learning needs of rheumatology trainees from the perspective of both the trainees and Program Directors.

Methods: Rheumatology trainees and Program Directors from adult rheumatology programs across Canada completed an online questionnaire. Information on student demographics, past immunology training and overall satisfaction with current immunology training was collected in an anonymous manner. All participants ranked a comprehensive list of immunology topics by order of perceived importance. A modified two step Delphi approach was implemented to obtain consensus on immunology topics.

Results: 15 Program Directors and 38 rheumatology trainees were contacted between March 2012 and May 2012. From this group, 42% of trainees and 66% of Program Directors responded, with a total 49% response rate. Of the rheumatology trainees, 67% had prior experience in immunology, consisting of undergraduate and graduate courses. Teaching format and formal teaching hours varied between sites. Notably, only 42% of Program Directors and 31% of trainees felt the current method of teaching immunology was effective. Results illustrate concordance between Program Directors and trainees for the highest ranked topics, which include innate immunity, adaptive immunity, and cells and tissues of the

immune system. However, there was discordance amongst other topics. Notably, diagnostic laboratory immunology and therapeutics were ranked higher by Program Directors as compared to trainees. Part two of the modified Delphi was conducted amongst Program Directors and completed by December 2012. Only six of the original twelve Program Directors participated in the second phase of the Delphi. The results of round two demonstrated consistency with topic ranking generated from round one.

Conclusion: There is a need to improve immunology teaching in rheumatology training programs. Results illustrate high concordance between many of the topics ranked by trainees and Program Directors. However, discordance is seen with other topics, including diagnostic immunology and therapeutics. To our knowledge, this is the first study to examine perceived immunology education needs of adult rheumatology trainees at a national level. It provides the groundwork for further development of immunology curricula for rheumatology trainees.

Disclosure: D. Mahendira, None; **S. L. Chow**, None; **S. Herman-Kideckel**, None; **H. McDonald-Blumer**, None.

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Electronic Learning Module Enhances Rheumatology Education. Malini Juyal[1], Avis Ware[1], John Houk[1] and Rina Mina[2]. [1]University of Cincinnati, Cincinnati, OH, [2]Cincinnati Children's Hospital Medical Center/University of Cincinnati School of Medicine, Cincinnati, OH.

Background/Purpose: Electronic-learning (e-learning) has recently increased in use. Blended learning combines e-learning with traditional training. At the University of Cincinnati Division of Rheumatology, only traditional methods have been used for the education of resident and medical student rotators. Covering all aspects of basic rheumatology can be challenging in this short exposure time in addition, existing conventional teaching methods may not always allow the learners to retain and apply what they have learned.

The objective of this study was to determine if blended learning leads to better learning than traditional methods currently utilized during the four-week Rheumatology rotation for residents and students.

Methods: A digital CD module on Rheumatoid Arthritis (RA) was designed using Lectora® software following established methods, compliant with the learning industry standard SCORM (Sharable Content Object Reference Model). This included interactive links for a learner-directed process. Rotators were randomly allocated to two groups: 1) traditional and 2) blended. Both groups received comparable lectures and clinical exposure. The blended group also utilized the module. Performance was assessed using pre- and post-tests. The difference between the group scores was calculated using the Wilcoxon signed-rank test. The blended group also evaluated the CD module using five point Likert scales to determine, ease of use, navigation, and acceptability.

Results: In the traditional group, the median post-test score stayed the same (P-value=NS) versus the blended group, which increased by three and a half points (P-value=0.002) (Table 1). The pre-test scores for both groups were not statistically different. Learners with an interest in Rheumatology scored generally higher. The questionnaire revealed that 88% (N=15) thought they had a better understanding about RA than they did before using the module, 82% (N=14) of learners favored using the module, and agreed it was useful for future exams, and 94% (N=16) thought access to other rheumatology modules would be beneficial. There was no difference between the baseline scores of the two groups. Baseline characteristics were also similar, regarding age, sex and level of training.

Table 1. Difference Between Pre and Post-Test Scores

	Traditional Group (No Module, N=8)		
Variable	**Median**	**Range**	**P-value**
Pre-test Scores	31	20–35	NS
Post-test Scores	31	28–39	
	Blended Group (With Module, N=19		
Pre-test Scores	30	23–36	0.002
Post-test Scores	33.5	26–40	

Conclusion: In this pilot study, blended learning resulted in improved learning for residents and medical students during the rheumatology rotation. Implementation of this module will likely enhance trainee learning in the Rheumatology rotation.

Disclosure: M. Juyal, None; **A. Ware**, None; **J. Houk**, None; **R. Mina**, None.

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Impact Of a Nurse-Led Program On Comorbidity Management In Rheumatoid Arthritis (RA): Results Of a Prospective, Multicenter, Randomized, Controlled Trial. Martin Soubrier[1], Elodie Perrodeau[2], Melanie Gilson[3], Alain G. Cantagrel[4], Xavier le Loet[5], René-Marc Flipo[6], Sandrine Guis[7], Gael Mouterde[8], Liana E. Euller-Ziegler[9], Thierry Schaeverbeke[10], Bruno Fautrel[11], Alain Saraux[12], Isabelle Chary-Valckenaere[13], Gérard Chales[14], Emmanuelle Dernis[15], Pascal Richette[16], Xavier Mariette[17], Francis Berenbaum[18], Jean Sibilia[19], Philippe Ravaud[20] and Maxime Dougados[21]. [1]CHU CLERMONT-FERRAND, Clermont-Ferrand, France, [2]Epidemiologist, Paris, France, [3]CH Grenoble Hopital Sud, Grenoble, France, [4]Hopital Purpan, Toulouse CEDEX 9, France, [5]CHU de ROUEN, Rouen, France, [6]Hôpitaux Universitaires de Lille, France, France, [7]Aix Marseille Univ; AP-HM, Marseille, France, [8]Montpellier 1 University, Lapeyronie Hospital, Montpellier, France, [9]L Archet Hospital (University), Nice CEDEX 3, France, [10]Groupe Hospitalier Pellegrin, Bordeaux, France, [11]UPMC-Paris 6 University, Paris, France, [12]CHU de la Cavale Blanche, Brest Cedex, France, [13]Nancy Teaching Hospital, Nancy, France, [14]CHU RENNES, Rennes, France, [15]Centre Hospitalier, Le Mans, France, [16]Hôpital Lariboisière, Paris, France, [17]Bicêtre University Hospital, Le Kremlin Bicetre, France, [18]AP-HP, St Antoine Hospital, Paris, France, [19]CHU Hautepierre, Strasbourg, France, [20]Hopital Hotel Dieu, Paris Descartes University, Paris, France, [21]Cochin Hospital, Paris, France.

Background/Purpose: Patients with rheumatoid arthritis (RA) are at an increased risk of developing numerous comorbid conditions that affect both mortality and RA outcome.

Objectives: To evaluate the impact of a nurse-led program on comorbidity (cardiovascular disease [CVD], infection, cancer and osteoporosis) management in RA.

Methods: *Design:* Prospective, randomized, controlled, open-label, six-month trial between March 2011 and December 2012.

Setting: Outpatient clinic.

Participants: Patients aged 18 to 80 years with non-active RA for at least three months (ACR criteria).

Intervention: After written informed consent was obtained, the study treatment was randomly allocated (i.e. either comorbidity evaluation by a nurse or using a self-assessment program). *Study treatment:* Data was collected by a nurse as recommended by the French Society of Rheumatology (SFR). In the event of inconsistencies, the patient was informed. A report summarizing the program results was prepared by the nurse and sent to the patient's attending physician and rheumatologist.

Outcome variables: Number of actions taken for comorbidities, in line with the recommendations, in the six months following the program. The actions taken into account for CVD were: introduction of lipid-lowering or anti-platelet therapy, smoking cessation, blood pressure measurement, purchase of a sphygmomanometer, weight loss, creatinine measurement, nephrological consultation; for infection: vaccinations; for cancer: mammography, Pap smears, digital rectal examination and/or consultation with a urologist, fecal occult blood testing, colonoscopy and consultation with a dermatologist; and for osteoporosis: DEXA scan, increased alimentary calcium uptake, initiation of calcium and/or vitamin D supplementation and/or anti-osteoporosis medication, Increased physical activity and alcohol discontinuation.

Results: The 970 recruited patients, 488 of whom were assigned to the active group and 482 to the control group, did not differ in terms of baseline characteristics. During the six-month follow-up, the number of actions taken per patient was statistically higher in the comorbidity group: 4.54+2.08 vs. 2.65+1.57 ($p<0.001$); incidence rate ratio (IRR): 1.78 (1.61–1.96). This increase in actions taken concerned CVD (IRR: 1.44 [1.30–1.61]), infection (IRR 1.81 [1.43–2.30]), cancer (IRR: 1.65 [1.40–1.94]) and osteoporosis (IRR 3.45 [2.91–4.09]).

Conclusion: This study demonstrates the short-term benefit of a nurse-led program on RA comorbidity management.

Trial registration: NCT #0131652.

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Redesign Of a Rheumatology Curriculum For Internal Medicine Residents: Results Of Needs Assessment Survey. Susan F. Kroop[1], Cecilia P. Chung[2] and Charlene M. Dewey[3]. [1]Vanderbilt University Medical School, Nashville, TN, [2]Vanderbilt University, Nashville, TN, [3]Vanderbilt University School of Medicine, Nashville, TN.

Background/Purpose: We plan to improve internal medicine (IM) resident competence in caring for patients with rheumatologic disease and increase resident interest in rheumatology as a career. To achieve this goal, we conducted a needs assessment to help inform curriculum revisions to enhance our rheumatologic ambulatory curriculum.

Methods: After interviewing IM and Rheumatology faculty we constructed a 16-item online self-assessment resident survey tool. This tool assessed confidence (0=not confident, 100=extremely confident) in performing a rheumatologic history, exam and common rheumatology procedures (knee injection and aspiration, and shoulder and trochanteric bursa injection), ordering and interpreting rheumatologic labs (ESR, CRP, RF, CCP, ANA), and caring for patients with osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia. Additional questions included demographics, interest in rheumatology as a topic and career, and current career choice. Between February and May, 2013, we invited categorical PGY1 residents, just prior to the onset of their one week rheumatology ambulatory block, and all PGY3 residents to complete the Web-based survey. The results from the resident surveys were analyzed via two-sample Wilcoxon rank-sum (Mann-Whitney) test. IRB-approval and consent was obtained prior to completing the survey.

Results: Eighty-six percent (19/22) PGY1 IM residents and 70% (6/37) of PGY3 IM residents responded. Twenty-three of 45 residents (51%) were females. Twelve (27%) residents planned careers in General IM vs. 33 (73%) in IM subspecialties. There was no significant difference in any self-assessed confidence ratings when analyzed by gender or career plans. Table 1 summarizes the results. Overall PGY3 residents self-assessed their confidence ratings higher than PGY1s in all categories. There was no difference in interest in rheumatology between the PGY1 and PGY3 groups but there was significantly less interest in rheumatology as a career in the PGY3 group (p=0.002). Self-rated confidence in joint procedures was consistently lower for both groups compared to history, exam, lab interpretation and patient care.

Table 1. Self rated confidence survey results of PGY1 and PGY3 IM residents Feb-May 2013; Visual analogue scale (0–100).

Self-rated confidence in performing:	PGY1 (median, IQR)	PGY3 (median, IQR)	P value	95% Confidence Interval of difference in medians
Rheumatology History taking	50 (27–64)	65 (50–76)	0.014	−4, −27
Rheumatologic exam	30 (18–52)	59 (37–65)	0.005	−6, −32
Knee injection	10 (2–35)	34 (17–50)	0.006	−6, −33
Knee aspiration	12 (2–20)	42 (30–62)	<0.001	−17, −42
Shoulder injection	5 (1–13)	19 (2–34)	0.041	0, −21
Trochanteric bursa injection	5 (0–14)	20 (6–34)	0.019	−1, −22
Self-rated confidence in ordering and interpreting:				
ESR	63 (50–69)	72 (61–81)	0.004	−5, −25
CRP	59 (48–68)	73 (64–84)	<0.001	−7, −25
ANA	50 (32–59)	62 (50–76)	0.011	−5, −30
RF	55 (39–64)	65 (56–71)	0.032	−1, −21
CCP	57 (38–84)	70 (61–88)	0.161	5, −29
Self-rated confidence in care of patient with:				
OA Care	53 (44–75)	68 (64–75)	0.023	−2, −22
RA Care	43 (28–52)	59 (35–66)	0.011	−3, −26
Gout Care	64 (49–80)	82 (73–85)	0.001	−5, −26
SLE Care	31 (22–51)	50 (38–67)	0.006	−7, −27
Fibromyalgia Care	31 (19–42)	56 (38–74)	<0.001	−12, −38
Self-rated interest in:				
Topic of Rheumatology	62 (56–73)	60 (36–72)	0.260	−4, 21
Career in Rheumatology	49 (29–58)	17 (0–38)	0.002	11, 35

Conclusion: Our results suggest we need to enhance training of procedural skills in our ambulatory curriculum. Further study on factors that influence a resident to consider rheumatology as a career is needed. Encouragement and support for rheumatology as a career should be given early and throughout training.

Disclosure: S. F. Kroop, None; **C. P. Chung**, None; **C. M. Dewey**, None.

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The "Mini-Residency" In Musculoskeletal Care: An Efficient and Effective Mixed Method Model For Continuing Professional Education. Michael J. Battistone[1], Andrea M. Barker[1], Marissa Grotzke[1], J Peter Beck[1], Robert Z. Tashjian[1], Timothy A. Huhtala[1], Grant W. Cannon[1] and Patrice Kennedy[2]. [1]Salt Lake City VA and University of Utah, Salt Lake City, UT, [2]Salt Lake City VA, Salt Lake City, UT.

Background/Purpose: The societal burden of musculoskeletal (MSK) disease is amplified by the limited number of subspecialists. Developing knowledge and skills of primary providers is projected to be cost-effective in addressing this. The George E. Wahlen VA Salt Lake City Health Care System (VASLCHCS) has established an interprofessional "mini-residency" in MSK care to serve this purpose.

Methods: The mini-residency, held on the campus of VASLCHCS, is a one-week immersive experience. Content is introduced in didactics, reinforced in hands-on sessions with peer teaching and technologically enhanced simulations, and applied in the clinic in supervised patient encounters. Course evaluation was informed by Kirkpatrick's model of assessing educational effectiveness, and Phillip's concept of return on investment. Outcome measures included a post-course survey (5-point scale; 1 = "not at all satisfied"; 5 = "extremely satisfied"), qualitative comments in telephone interviews, and the number of joint injections performed after training.

Results: Thirteen of the first fourteen participants completed course evaluations (93% response rate).

Participant Satisfaction (Kirkpatrick Level 1)	• 97% agreed or strongly agreed across all satisfaction items (mean =4.67); all respondents (100%) strongly agreed they would recommend the MSK Mini-residency to others (mean=5.00).
Learning/Skill Acquisition (Kirkpatrick Level 2)	• 100% agreed or strongly agreed across all learning items.
Application/Job Impact	• 100% indicated the training was able to affect practice outcomes.
	• 100% felt trained and more comfortable performing a full shoulder and knee examination.
(Kirkpatrick Level 3)	• 100% are more comfortable performing MSK procedures.
	• Respondents indicated they conducted more thorough exams and had had fewer referrals

Credentials of Participants	States Represented	Number of Injections Performed In 6 Months Following Training
MD (11), NP (9), PA (3)	CO, GA, ID, MN, MT, UT, VA, WA, WI, WY	385 total
		Average per provider = 30
		Range 0–120; s.d. = 42

Conclusion: An interprofessional "mini-residency" in musculoskeletal care is an effective model of continuing medical education. This program is highly rated, results in an expanded scope of practice for most participants, and providers who participated in this course report an increase in the numbers of joint injections they perform in their primary care settings.

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Less Is More? A Targeted Intervention Results In Substantial Improvement In rheumatologists' Ordering Of Anti Nuclear Antibodies (ANA) In Patients With Rheumatic Complaints. Nienke Lesuis[1], Ester Piek[1], Hatice Demirel[1], Ronald F. van Vollenhoven[2] and Alfons A. den Broeder[1]. [1]Sint Maartenskliniek, Nijmegen, Netherlands, [2]Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), the Karolinska Institute, Stockholm, Sweden.

Background/Purpose: Anti-Nuclear Antibodies (ANA) are found both in patients with (non-)rheumatic diseases and in healthy controls[1]. ANA testing is useful in the diagnostic process of Systemic Lupus Erythematodus (SLE), Systemic Sclerosis (SSc), Mixed Connective Tissue Disease (MCTD), Sjögren Syndrome (SS), Polymyositis (PM) and dermatomyositis (DM)[1,2]. Laboratory tests in general, are often used inappropriate which leads mainly to overuse of tests.[3] This was recently recognized by the American College of Rheumatology and the ANA is now included in the top 5 list of 'things physicians and patients should question'.[4] Therefore we aimed to assess the

characteristics of ANA testing by rheumatologists in patients visiting the rheumatology outpatient clinic of the Sint Maartenskliniek (SMK) and Maartenskliniek Woerden (MKW), the Netherlands, before and after a targeted educational intervention.

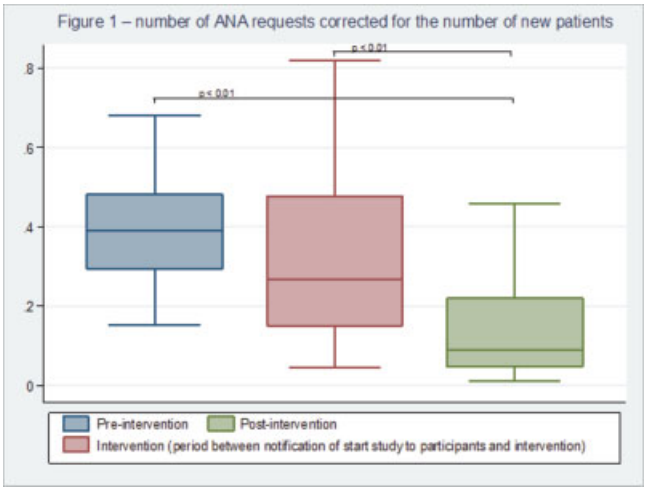
Methods: The characteristics (number, result, final diagnosis) of all ANA tests conducted by rheumatologists between 1-1-2010 and 31-1-2012 (25 months) were compared with the ANA tests done in the four months after the intervention. For fair comparison, the absolute ANA count was corrected for the number of new patients seen at the outpatient clinic in the same period. The intervention consisted of a one-hour, group training in which the individual ordering behavior from the pre-intervention period was given, followed by general background information on ANA test characteristics and the correct use of ANA testing. Directly afterwards all rheumatologists received individual information on their own ANA orders in comparison with their colleagues.

Results: All rheumatologists working in both the pre- and post-intervention period at the outpatient clinic participated (n=20). The characteristics of the ANA tests they ordered pre- and post-intervention are summarized in table 1. At both locations a large decrease in the number of ANA tests was seen after the intervention; when corrected for number of new patients seen the decrease was 77% (figure 1).

Table 1. ANA characteristics before and after the targeted intervention

	SMK & MKW (n=20)	
Characteristic	**Pre-intervention**	**Post-intervention**
Number of ANAs	3702	187
Number of unique patients	3615	185
Number of ANAs per new patient (median; p27–p75)	0.39; 0.29–0.48	0.09; 0.05–0.22
Mean age patients (year; SD)	52 ± 16	47 ± 16
Women (%)	75	81
Most frequent final diagnosis*		
1	UAM	UAM
2	RA	RA
3	FMS	FMS
ANA associated disease** (%)	6	7
Negative ANAs (%)	71	67

* UAM, undifferentiated arthralgia/myalgia; RA, rheumatoid arthritis; FMS, fibromyalgia; OA, osteoarthritis
** SLE, SSc, PM, DM, MCTD and SS



Conclusion: The finding that our single session intervention resulted in a sizable reduction in number of ANA's requested, while inter-individual variation and final diagnoses remained unchanged, suggests that excessive usage of ANA tests was reduced without a reduction in appropriate use of the ANA test.

References:
[1]Solomon DH et al. Arthritis Rheum 2002.[2]Colglazier CL et al. South Med J 2005. [3]van Walraven C et al. JAMA 1998. [4]Yazdany J. Arthritis Care Res 2013.

Disclosure: N. Lesuis, None; **E. Piek**, None; **H. Demirel**, None; **R. F. van Vollenhoven**, None; **A. A. den Broeder**, None.

967

'Bending' Ethical Norms To Serve Patients' Interests: Tensions In Medical Professionalism. C. Ronald MacKenzie[1], Inmaculada de Melo-Martin[2], Michele Meltzer[3] and Elizabeth A. Kitsis[4]. [1]Hospital for Special Surgery, New York, NY, [2]Weill Cornell Medical College, New York, NY, [3]Jefferson Universtiy, Philadelphia, PA, [4]Albert Einstein College of Med, Bronx, NY.

Background/Purpose: The rheumatic diseases are a common cause of short and long-term disability. Affecting all sectors of the population, they diminish wellbeing, affect quality of life, and have a significant social impact. In spite of the benefits of early treatment and ever more effective therapies, access to rheumatologic services is often inadequate, involving long wait times, and difficulties finding providers; moreover the cost of effective therapy renders treatment unaffordable for many. A just system would mitigate these impediments to care, but in unjust context physicians might find themselves in situations of ethical conflict. We herein focus on the effects that the current practice context has on how rheumatologists' view their ethical responsibilities.

Methods: A survey consisting of 14 closed-ended and 2 open-ended questions, was developed, pilot tested, and sent electronically to 5,500 members of the ACR in the United States. A second email requesting participation was sent to increase the response rate. Reported herein are the results of the open-ended component.

Results: A pressing ethical issue for many rheumatologists is their perceived need to 'bend' ethical norms and compromise ethical principles in order to serve their patients' interests. In the survey physicians report ways in which they see themselves as 'bending' ethical standards and presented justifications as to why they do so. Examples include, 'embellishment' of symptoms to help patients obtain prior authorization; downcoding to help the less fortunate; stretching the truth to obtain drugs and testing; and label patients with certain diagnosis that they do not have so as to obtain coverage for medications or physical therapy. The ethical implications of these challenges for the physicians' sense of integrity, their responsibilities towards their patients, and the impact on justice in the health care system are considered.

Conclusion: The results of our questionnaire indicate that, in the context of inadequate access to care, rheumatologists wrestle with ethical dilemmas concerning how to fulfill their responsibilities to their patients. As the delivery of medical care takes places in a particular social context, the extent to which the context involves unjust conditions forces healthcare practitioners to struggle with ethical conflicts, making trade-offs that are often not sufficiently recognized. In order to provide solutions to the resultant ethical and professional challenges faced daily by physicians, an awareness of this problem and its consequences is necessary.

Disclosure: C. R. MacKenzie, None; **I. de Melo-Martin**, None; **M. Meltzer**, None; **E. A. Kitsis**, None.

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Success Of Educational Intervention In Improving The Management Of Rheumatoid Arthritis. Nimish Mehta and Ronald Viggiani. Medscape, LLC, New York, NY.

Background/Purpose: In many patients with rheumatoid arthritis (RA), the disease is not adequately controlled and only a minority of patients attain the goal of consistent remission or low disease activity. Underlying clinical practice gaps and educational needs were identified and a study was conducted to determine if an online educational intervention specifically designed to address the identified practice gaps could improve knowledge and competence of rheumatologists with respect to evidence-based management of patients with RA.

Methods: A cohort of practicing rheumatologists participated in an innovative educational intervention that used a problem-based learning model and short-branching technology. Clinical decision questions included at 3 critical points in each of the 2 case vignettes provided tailored feedback and clinical consequences related to the specific answer selected. Learners who did not make the correct decision on the first attempt were allowed a second opportunity to make a decision. Each case also included knowledge assessment questions pre- and post-intervention. The education launched on August 31 2012 and data were collected through November 13, 2012 (76 days). A paired 2-tailed t-test was used to assess differences in mean scores between knowledge assessment questions pre- and post-education. Pearson's $\chi 2$ statistic was used to measure changes in responses to individual questions. For

the consequence-based clinical decision questions a test of proportions was used to determine the effectiveness of the feedback provided for incorrect first attempts. P value of less than .05 indicates statistical significance.

Results: A total of 456 rheumatologists participated in the activity during the data collection period and 146 (who answered all questions) were included in the analysis. Evaluation of the knowledge assessment questions demonstrated statistically significant improvements (n = 146; $P < .05$), with an overall large effect size of 0.829. Improvements post-guidance in specific clinical decisions were as follows:

- 52% improvement post education in determination of the level of RA disease activity objectively using a predefined metric ($P = .01$).
- In a patient who developed new or worsening symptoms consistent with heart failure while receiving treatment with anti-TNF agents, 38% more rheumatologists recommended evaluation with transthoracic echocardiogram post education ($P = .01$).
- Post education, 62% more rheumatologists correctly identified Clinical Disease Activity Index as the validated metric that incorporates both patient- and clinician-derived data ($P = .001$).
- 76% improvement in switching to correct biologic therapy for a patient with RA who developed CHF while receiving treatment with an anti-TNF agent and had to discontinue methotrexate due to adverse effects ($P = .07$).

Conclusion: Statistically significant improvement in knowledge and competency of rheumatologists who completed the educational intervention was demonstrated in a number of areas. Technology-enhanced educational interventions utilizing consequence-based feedback can significantly impact rheumatology practices in the management of patients with RA.

Disclosure: N. Mehta, None; **R. Viggiani**, None.

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Increasing Rheumatology Exposure To Internal Medicine Residents: 3 Year Analysis Of A Web-Based Image Of The Month. Steven J. Katz University of Alberta, Edmonton, AB.

Background/Purpose: A previous study has demonstrated a web based Image of the Month can increase rheumatology exposure for internal medicine residents over 1 year with minimal additional manpower or financial resources. It remains unclear whether or not this effect would persist over a longer duration, or in the transition from junior to senior resident. This study examines this question with an analysis of 3 years' experience of the web based Image of the Month.

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

Results: The Image of the Month webpage has posted images monthly for 35 months since July 2010. There was no cost to implement the program as the website already existed and there was pre-existing funding for the book prize. The rheumatologist required no more than 15 minutes monthly to administer the contest. The webpage had 2517 visits (average 72 visits/month) between July 2010 and May 2013. Resident participation was constant over time ($p>0.05$), with 46/80 (57.5%) residents participating in 2010/11, 49/85 (57.6%) in 2011/12, and 59/92 (64.1%) in 2012/13, with each resident participating on average 3.6, 4.2, and 3.2 times/year respectively. Rheumatology exposure was also improved consistently ($p>0.05$), as there were 35/80 (43.8%) residents in 2010/11 who did not complete a rheumatology rotation but participated in the Image of the Month, 34/85 (40%) in 2011/12, and 40/92 (43.5%) in 2012/13. There was a small decrease in participation as residents transitioned from a junior to senior level, as the 2010/11 first year resident cohort went from 25 participants to 20 in their second and third years of residency, while the 2011/12 first year cohort went from 20 to 19 participants in their second year of residency.

Conclusion: The Image of the Month webpage successfully improves rheumatology exposure to internal medicine residents with minimal resources required. Further, increased exposure remains persistent over time as most residents continue to participate as they gain seniority. Further study is necessary to determine the impact this exposure may have on the musculoskeletal clinical skills of internal medicine residents.

Disclosure: S. J. Katz, None;

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Incorporating The Health Literacy Universal Precautions Toolkit Quick Start In Academic Rheumatology Practices: Carolina Fellows Collaborative. Adam Dore[1], John Dye[2], Lara Hourani[3], Betsy Hackney[1], Lisa G. Criscione-Schreiber[2], Faye N. Hant[4], Kenneth S. O'Rourke[5], Beth L. Jonas[1] and Leigh F. Callahan[6]. [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]Duke University School of Medicine, Durham, NC, [3]Medical University of South Carolina, Charleston, SC, [4]Medical Univ of South Carolina, Charleston, SC, [5]Wake Forest School of Medicine, Winston-Salem, NC, [6]University of North Carolina, Chapel Hill, NC.

Background/Purpose: Gaps in health literacy (HL) are associated with increased medication errors, higher health care costs, and inadequate care of chronic medical conditions. Previous studies have shown a large number of rheumatology patients have low HL. To address this, a Health Literacy Universal Precautions Toolkit (HLUPTK) has been developed for rheumatology practices (HLUPTK-R), including a Quick Start for patient encounters. The Quick Start consists of 3 tools: encouraging questions, the teach-back method, and brown-bag medication review. The purpose of this project is to evaluate the implementation of the HLUPTK-R Quick Start into academic rheumatology practices in the Carolina Fellows Collaborative (CFC).

Methods: At the winter meeting of the CFC, the HLUPTK-R Quick Start was introduced to participants through a 20 minute presentation and included an overview of HL. Prior to the presentation, the participants were asked to complete a questionnaire to evaluate their awareness of HL. After the presentation, participants were given paper and electronic versions of the HLUPTK-R Quick Start and asked to incorporate the Quick Start techniques into their rheumatology practice. Eight weeks later, the participants completed a second questionnaire which assessed their impression of the presentation and experience with incorporating the techniques into their practice.

Results: Eighteen participants filled out the pre-questionnaire and were present for the HLUPTK-R Quick Start and HL presentation. Sixteen participants (89%) knew what HL was prior to the presentation, with 10 having learned about HL during their residency training (56%). No participants stated they had previously learned about HL during their fellowship training. Only 6 participants (33%) believed their practice was currently promoting HL for their patients. The post-assessment questionnaire was returned by 13 participants (72%), all of whom incorporated HLUPTK-R Quick Start techniques into their practice. Ten (77%) of those who returned the post-questionnaire agreed that their knowledge of HL was improved and agreed that incorporating the HLUPTK-R Quick Start techniques made a positive impact on patient care. All 13 participants believed the Quick Start techniques were helpful in their practice. The encouraging questions technique was used by all participants who returned the post-questionnaire (13), 8 (62%) used the teach-back method, and 5 (39%) used the medication review technique. Seven participants (39%) thought incorporating the HL techniques added time to the patient's visit. However, all 7 thought the extra time was "worth-while". Lastly, all 13 participants stated they would continue to support interventions to promote HL in their practice.

Conclusion: By introducing the HLUPTK-R Quick Start to rheumatologists of the CFC, we were able to raise awareness and knowledge of HL. A majority of the participating rheumatologists used HL techniques into their practice, believed it was beneficial for their patients, and would support interventions to benefit HL in their practice. We advocate widespread dissemination of the HLUPTK-R Quick Start into rheumatology training programs.

Disclosure: A. Dore, None; **J. Dye**, None; **L. Hourani**, None; **B. Hackney**, None; **L. G. Criscione-Schreiber**, None; **F. N. Hant**, None; **K. S. O'Rourke**, None; **B. L. Jonas**, None; **L. F. Callahan**, None.

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A Needs Assessment and Review Curriculum Of Content Of Teaching On Systemic Lupus Erythematosus. Mo Yin Mok, Yi Lo and Chak Sing Lau. University of Hong Kong, Hong Kong, Hong Kong.

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease that is more common among Asians compared with Whites but the prevalence of SLE is significantly low compared with common chronic medical diseases in westernised city like Hong Kong.

This study aimed to evaluate medical student knowledge on SLE and their feedback on teaching on SLE related topics at a medical school in Hong Kong.

Methods: Senior medical students were recruited to complete a self administered questionnaire regarding learning, teaching and subjects regarded as important in SLE.

Results: A total of 124 (109 MBBS IV, 15 MBBS V) medical students from the University of Hong Kong were recruited. Majority of students acquired knowledge on SLE from standard sources provided by curriculum teaching including lectures (98.4%), textbook (96.7%), patient contact (86.1%) and problem based learning sessions (64.8%). A significant proportion of students (77.0%) also obtained knowledge from internet and e-learning. An addition of 36.4% of students also preferred learning from extra-curricular sources including education leaflets from professional societies, family contact and television program. Most students regarded knowledge on clinical presentations (45.4%), diagnosis (49.6%) management and treatment (76.5%) as the most fundamental knowledge an average doctor should know more about SLE. Renal disease was considered most important (36.7%) among all organ involvement in SLE teaching. Only 8.4% of students regarded epidemiology and pathogenesis as essential but overall importance of subjects on epidemiology and pathogenesis, management and complications ranked 4.0/5, 4.3/5 and 4.2/5 respectively. These senior medical students graded their confidence in knowledge in SLE as 3.4/5. In general, the quality (3.9/5) and quantity (3.5/5) of teaching regarding SLE is good. Majority (85.1%) of students preferred to be taught by rheumatologists where as only 15.8% regarded rheumatology nurse as important sources.

Conclusion: Majority of students were satisfied with current curriculum teaching and valued clinical management with higher priority than epidemiology and pathogenesis among the taught subjects. Extra-curricular sources of learning including information from professional societies and rheumatology nurse may be considered as adjunct to teaching.

Disclosure: M. Y. Mok, None; **Y. Lo**, None; **C. S. Lau**, None.

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Retrospective Self-Assessment Of Pre-Course Competency: A Useful Tool For Musculoskeletal Curriculum Assessment In a Multi-Center, Interprofessional Cohort. Michael J. Battistone[1], Andrea M. Barker[1], J Peter Beck[1], Marissa Grotzke[1], Timothy A. Huhtala[1], Jorie Butler[2], Amy C. Cannella[3], David I. Daikh[4], Meika A Fang[5], Antonio A. Lazzari[6], Pedro Roldan[7], Joan Marie Von Feldt[8] and Grant W. Cannon[1]. [1]Salt Lake City VA and University of Utah, Salt Lake City, UT, [2]Salt Lake City VA, Salt Lake City, UT, [3]Omaha Veterans Affairs Hospital and University of Nebraska Medical Center, Omaha, NE, [4]University of California, San Francisco, San Francisco, CA, [5]VA Greater Los Angeles Healthcare System, Los Angeles, CA, [6]Boston VA Medical Center, Boston, MA, [7]Leesburg VA CBOC, Leesburg, FL, [8]Univ of Pennsylvania/Philadelphia VAMC, Philadelphia, PA.

Background/Purpose: Value of traditional pre- and post-course assessments is uncertain. Having learners re-evaluate pre-course competency after a course may be a more useful tool for curriculum evaluation. This project explores whether "retrospective" self-assessments provide a more useful measure of program effectiveness than traditional pre- and post-course assessments.

Methods: The Department of Veterans Affairs created a program in musculoskeletal care for primary providers. To date, this has involved 130 participants across six national sites. Prior to the course, providers used a 5-point Likert scale to rate proficiency in approaching shoulder, knee, and back pain. Curriculum included focused didactics and small group hands-on practice sessions with simulated patients for shoulder and knee exams. In contrast, back pain was addressed through a single didactic session. After the program, providers retrospectively rated pre-course proficiency on the same dimensions, as well as post-course proficiency. Paired t-tests compared mean prospective and retrospective assessments.

Results: Post-course ratings were higher than pre-course ratings across all items. Retrospective ratings of pre-course competency in assessing shoulder and knee pain were significantly lower than initial, prospective pre-course ratings. In contrast, retrospective ratings for competency with back pain were not significantly lowered.

	Mean Pre-course Ratings		Mean Paired Difference	Mean Post-course Ratings	Pre-Post Change	
	Prospective	Retrospective	(SEM; p)		Post-Pro	Post-Retro
Shoulder Pain						
I can examine and diagnose shoulder pain without MRI	3.1	2.7	0.3 (0.09; 0.001)	4.7	1.6	2.0
I can evaluate patients effectively	3.2	2.8	0.3 (0.08; <0.001)	4.8	1.6	2.0
I can develop a appropriate plan	3.3	3.0	0.2 (0.09; 0.011)	4.7	1.4	1.7
I understand when to order imaging	3.4	3.1	0.3 (0.09; 0.003)	4.8	1.4	1.7
I understand when to refer	3.6	3.3	0.2 (0.08; 0.007)	4.7	1.1	1.4
Knee Pain						
I can examine and diagnose knee pain without MRI	3.2	2.9	0.3 (0.08; 0.01)	4.7	1.5	1.8
I can evaluate patients effectively	3.3	3.0	0.2 (0.07; 0.01)	4.7	1.4	1.7
I can develop an appropriate plan	3.5	3.1	0.3 (0.08; 0.01)	4.6	1.1	1.5
I understand when to order imaging	3.6	3.2	0.2 (0.08; 0.03)	4.7	1.1	1.5
I understand when to refer	3.7	3.3	0.3 (0.09; 0.01)	4.7	1.0	1.4
Back Pain						
I can identify patients with low back for whom MRI is appropriate	3.8	3.6	0.04 (0.09; 0.65)	4.5	0.7	0.9
I can develop a reasonable management plan	3.8	3.7	0.01 (0.09; 0.91)	4.5	0.7	0.8
I understand when to refer	3.8	3.7	0.07 (0.09; 0.42)	4.6	0.8	0.9

Conclusion: Lower retrospective pre-course ratings were seen only in course elements that involved multiple methods of instruction. Multi-modal skill acquisition may lead to a more critical assessment pre-course proficiency. Incorporating retrospective pre-course self-assessment may distinguish educational programs that most effectively teach new skills.

Disclosure: M. J. Battistone, None; **A. M. Barker**, None; **J. P. Beck**, None; **M. Grotzke**, None; **T. A. Huhtala**, None; **J. Butler**, None; **A. C. Cannella**, None; **D. I. Daikh**, None; **M. A. Fang**, None; **A. A. Lazzari**, None; **P. Roldan**, None; **J. M. Von Feldt**, None; **G. W. Cannon**, None.

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Basic Musculoskeletal Ultrasound Curriculum Among Internal Medicine Residents: A Pilot Study. Gaurav Gulati[1] and David George[2]. [1]University of Cincinnati College of Medicine, Cincinnati, OH, [2]The Reading Hospital and Medical Center, West Reading, PA.

Background/Purpose: Musculoskeletal Ultrasound (MSKUS) is becoming an important component of rheumatology practice. Given increasing appreciation of bedside ultrasound, residency programs are beginning to include ultrasound training in their curriculum. Time and resources are barriers to implementation. We performed a pilot study to assess the feasibility of incorporating introductory MSKUS education into an Internal Medicine (IM) Residency Program.

Methods: A limited MSKUS curriculum for IM residents was created, with knee ultrasound as focus of our pilot study. After IRB approval, participants were recruited and consented. Educational program included reading material; two one hour lectures on anatomy, biophysics and pathology; and a 30 min hands on practicum. A pre and post test for medical knowledge was performed, and a minimum 80 % score was required to proceed.

Residents then received individual technique training on two knees, with identification of effusion as principal objective. They were supervised for cognitive and technical skill by experienced rheumatology faculty.

An Observed Structured Clinical Exam (OSCE) was performed. Each resident performed MSKUS on two patient knees. Residents were assessed for proper probe placement, machine use and identification of knee effusion. In addition, they were tested on five still images. Feedback questionnaires were completed by residents and faculty. Analysis was performed using paired t-test for pre and post tests and survey results were collated.

Results: All fifteen enrolled residents completed their training but twelve could complete the OSCE. Pre and post results [TABLE 1] demonstrated significant improvement in knowledge for all three curricular components ($p < 0.001$). Final OSCE scores ranged from 7 to 10 on a 10 point scale. Faculty evaluated all residents' cognitive and technical skills as excellent or good. All participants rated reading material, orientation and supervision as great or good on the four point Likert scale. Program was thought to be a valuable learning experience by all participants. Although 66.7% participants thought the exposure to patients before OSCE was adequate, others suggested 3 to 20 additional supervised procedures. Based upon resident performance and faculty time commitment, faculty rated overall learning experience as good.

Table 1. Outcomes Data Analysis (Paired t-test)

Variable	Pretest Values Mean	Pretest Values SD	Posttest Values Mean	Posttest Values SD	p-value
Pre-Post Total (20)	6.45	1.62	17.48	1.13	<0.001
Biophysics (12)	3.88	1.32	11.13	0.63	<0.001
Pathology (4)	0.97	0.90	3.07	0.68	<0.001
Anatomy (4)	1.60	0.92	3.28	0.50	<0.001

Conclusion: Our study was a pilot project to assess incorporating introductory MSKUS training into an IM Residency training program, addressing feasibility, perceived value, and observed competence. Based upon our preliminary results, the curriculum is a feasible and time efficient addition to training and was considered valuable by both faculty and residents. Further studies are needed to assess methods to reinforce core training for all residents, offer advanced curriculum for a subset of interested residents, and assure MSKUS for IM residents complements their ultrasound training in other subspecialties.

Disclosure: G. Gulati, None; **D. George**, None.

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Medical Student Perceptions Of Point-Of-Care Ultrasound In Musculoskeletal Education. Minna J. Kohler[1], Joshua Rempell[2] and Margaret Seton[2]. [1]Massachusetts General Hospital/Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Point-of-care ultrasound (POC US) is increasingly being incorporated into clinical care among rheumatologists and other specialties to expedite diagnosis and assist in needle and vascular access guidance for improved accuracy and patient safety. POC US is also emerging as an educational tool for medical students for better understanding of anatomy, physiology, pathology, physical diagnosis skills, and problem-based learning. A survey of students was performed to document student-perceived value in the use of POC US as an educational tool and to assess student interest in rheumatology after POC US exposure.

Methods: We describe our experience incorporating POC US into a 2nd year medical student musculoskeletal (MSK) pathophysiology course to introduce basic concepts of arthritis, tendinitis, and crystal-induced arthropathies. A 40 minute case-based lecture describing the use of MSK US in the care of rheumatology patients was provided followed by a 1.5 hour hands-on US session. Instructors guided students (1:5 ratio) to use portable US equipment to scan patients with osteoarthritis, tendinitis, gout, and pseudogout. Anatomic and pathologic findings on US were identified while patients simultaneously described their clinical symptoms. Seven Likert scale formatted questions were administered to survey students after completion of the US teaching session.

Results: Thirty students were surveyed by email. 24(80%) students responded. Among those who responded, prior awareness of US use in rheumatology was reported: 14(58.3%) were somewhat aware of US being used in rheumatology and thought it is used in other specialties, 2(8%) were minimally aware and had not seen it used in other specialties, and 8 (33%) were not aware at all of US use. Twenty-two (91.7%) felt that the hands-on US session added a great deal of value to the course, while 2(8.3%) felt it somewhat added value to the course. All students desired more hands-on US exposure; additionally 4(16.7%) were interested in learning more US by class lectures, and 2(8.3%) desired more class lectures and online didactics. The effects of US exposure on increasing understanding of concepts and increasing interest in rheumatology are shown in the Table.

Table.

Effect of Hands-on US Exposure	N (%)
Better understanding of anatomy	22 (91.7%)
Better understanding of pathology	20 (83.3%)
Better understanding of physical exam skills	12 (50.0%)
Better understanding of physiology	2 (8.3%)
Raised consideration for pursuing rheumatology as a specialty	4 (16.7%)
Wanted to learn more about rheumatology but uncertain what specialty to pursue	14 (58.3%)
Wanted to learn more about rheumatology but wants to pursue another specialty	4 (16.7%)

Conclusion: Hands-on POC US teaching in medical student MSK education is highly valued by students. Exposure to MSK US increased their understanding of anatomy, pathology, and physical exam skills, increased their desire to learn, and additionally increased their interest in learning more about rheumatology as a potential specialty to pursue.

Disclosure: M. J. Kohler, None; **J. Rempell**, None; **M. Seton**, None.

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Outcomes-Based Program Evaluation Of a Musculoskeletal Ultrasound Curriculum. Hitasha Singh[1] and Karina D. Torralba[2]. [1]University of Southern California, Los Angeles, CA, [2]University of Southern California Keck School of Medicine, Los Angeles, CA.

Background/Purpose: The Los Angeles County-University of Southern California Rheumatology fellowship program has incorporated musculoskeletal ultrasound (MSUS) in its curriculum since 2009. The following teaching approaches have been used: 1) 8-hour correlative history-physical exam-MSUS didactic and hands-on scanning workshop, 2) twice monthly cadaver-based procedural simulation, and 3) weekly MSUS clinic. We aimed to evaluate the effectiveness of this curriculum in the acquisition and utilization of MSUS-knowledge and skills (MSUS-KS).

Methods: Program evaluation was done through: 1) Likert-scale based survey of current and past fellows (2010–2013, (N=15)), noting satisfaction with organization and content, confidence, and MSUS-KS utilization, 2) written feedback from 3 faculty members regarding challenges faced, 3) MSUS-clinic utilization review via sampling of 50 cases referred and seen by fellows since 2010 (reasons for referral, interventions, patient outcomes); and 4) review of competency-based electronic portfolios (ePFs) for learning evidences. Ultrasound School of North American Rheumatologists (USSONAR) fellow program participation was also considered. Descriptive statistics were used to analyze data.

Results: 11/15 fellows responded to the survey (6 current, 5 graduates; 4 were USSONAR participants). There was a favorable response towards organization and content of the workshop-didactic sessions, and clinic. Suggested improvements included: limiting simulations to once monthly, correlative dissection; and disease-specific (i.e. synovitis) didactics. Immediate feedback from faculty was useful. 10/11 agreed with understanding MSUS indications and limitations, and had an improved understanding of clinical anatomy. There was at least 50% neutral-disagree responses regarding confidence in using MSUS, ability to identify pathology; and amongst graduates, regarding application of MSUS-KS in practice. Faculty cited a learning curve, striking a balance between developing their own MSUS-KS while also achieving confidence and competency in teaching this field. ePFs showed documentation through procedure logs and journal article reviews; USSONAR fellows had more number of evidences. Referrals to MSUS clinic were mainly by fellows sending patients from continuity clinics, and majority were for rheumatoid arthritis disease activity evaluation. 38% of patients had management changes as a result of MSUS findings. 20 patients underwent MSUS-guided injection; 80% had symptom relief at follow-up.

Conclusion: This program evaluation indicates feasibility in the usage of these various teaching approaches as part of a MSUS curriculum. Faculty development and learner participation are vital towards successful implementation; USSONAR participation can complement learning. Feedback can be used to improve curricular content and organization, and assessment. Measures are needed ensure lifelong learning. Although this study involved a limited number of fellows in one program, it provides a realistic view of how to incorporate MSUS into a fellowship curriculum.

Disclosure: H. Singh, None; **K. D. Torralba**, None.

976

Experiential Learning In Musculoskeletal Ultrasound. Hitasha Singh[1] and Karina D. Torralba[2]. [1]University of Southern California, Los Angeles, CA, [2]University of Southern California Keck School of Medicine, Los Angeles, CA.

Background/Purpose: The Los Angeles County Medical Center-University of Southern California Rheumatology fellowship program has incorporated MSUS in its curriculum since 2009. Apart from didactics with hands-on workshops, cadaver-based simulation, a weekly 4-hour musculoskeletal ultrasound clinic (MSUSc) was incorporated with an early rheumatoid arthritis (ERA) clinic to teach knowledge and skills (MSUS-KS). The MSUSc was also established to address MSUS needs of patients which could not feasibly be done during other clinics. The objective of this study was to

assess the utilization of a dedicated MSUSc by fellows as part of curricular program evaluation.

Methods: A sampling of 50 charts seen at the MSUSc July 2009-May 2013 was done. Charts were reviewed mainly for: reasons for referral, pre-existing diagnoses, anatomic sites evaluated, intervention (synovitis evaluation, guided injection) and outcomes (pain resolution, diagnosis change) were noted. A Likert-scale based survey by current and graduate fellows was done to determine effectiveness of MSUSc teaching, and effectiveness of the overall curriculum. Review of electronic portfolios (ePFs) was done to assess evidences of learning.

Results: Majority of the patients were seen within a week's time from date of referral from a fellow continuity clinic. The most common pre-clinic diagnoses were: RA (35), psoriatic arthritis, OA (2 each), gout, pseudogout, vasculitis, mixed connective tissue disease, entrapment neuropathy (1 each), and tendinopathy (3). Majority of referrals were for initial diagnostic evaluations (29), treatment monitoring (10), mass evaluation (1), therapeutic injections without prior attempt (9). Of cases referred for initial diagnostic evaluation, 9 were injections without prior attempts, 8 were diagnostic scans followed by injection based on scan findings. Scans for RA initial diagnostic ultrasound were more common and included fingers (15), wrist (11), knee (11), and elbow joints (7). Majority of scans for synovitis showed positive power Doppler (23). Of 11 tendinopathy evaluations, positive doppler (3), and tendon tears (3) were noted. Of 20 patients that had injections, 80% reported pain relief. Overall 38% of patients had a change in treatment based on the ultrasound findings or procedure.

Of 15 fellows surveyed, 11 responded. 90% were agreeable regarding MSUSc provision of adequate patients, and efficient opportunities for procedures. All noted better understanding of MSUS indications and limitations. There were 50% neutral-disagree responses regarding overall confidence in doing MSUS, pathology identification. Immediate attending feedback and self-directed learning were cited as MSUSc advantages. All ePFs showed mainly procedure logs and journal article reviews as evidence of MSUS learning with most of procedures done during MSUSc.

Conclusion: This is an initial attempt to assess the effectiveness of learning MSUS-KS through various teaching approaches including experiential learning in a MSUSc and its applicability towards patient care. Feedback obtained from fellows can be used to improve curricular content and guide proper competency-based assessments.

Disclosure: H. Singh, None; **K. D. Torralba**, None.

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Development Of a Tool To Assess Internal Medicine Residents' Confidence In Their Musculoskeletal Examination Skills. Lisa G. Criscione-Schreiber[1], Eric Schreiber[2], Murat Arcasoy[3] and Kenneth S. O'Rourke[4]. [1]Duke University Health System, Durham, NC, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, [3]Duke University School of Medicine, Durham, NC, [4]Wake Forest School of Medicine, Winston-Salem, NC.

Background/Purpose: Published literature shows that internists have poor confidence in their ability to perform the musculoskeletal (MSK) exam. Confidence is an important self-assessment; lack of confidence drives individuals towards improvement efforts, but lack of confidence in physical exam skills can yield reliance on expensive imaging modalities and over-referral to specialists. Therefore, educators should develop effective interventions to teach the MSK exam and determine those efforts' effects on practitioners' confidence. There are no published validated surveys to assess confidence in performing a comprehensive MSK exam.

Methods: We designed a pilot MSK exam confidence survey based on a previously validated 15-item MSK student assessment for confidence in knee and shoulder exams. Our survey included 10 multi-item questions designed to measure confidence in several examination tasks for the knees, back/spine, shoulders, and hands/wrists. Confidence was measured on a 10-point Likert Scale (1=not at all confident to 10=very confident). The pilot survey was administered to internal medicine residents at Duke University before a didactic session on performing the MSK exam. We performed psychometric analyses of the instrument. Survey responses were analyzed in two dimensions: 1) the joint area in which confidence was assessed, and 2) specific task confidence (taking a pain history, assessing for swelling or range of motion, using information gained to make diagnoses or guide medical decision making, ability to perform provocative maneuvers).

Results: 19 surveys were collected (14 PGY1 residents, 4 PGY2, 1 PGY4). Only PGY1 responses were analyzed; 3 incomplete surveys were not analyzed. The discrimination for the entire test was 0.726 (joint domain R values 0.5–0.75), which is very good. The reliability was also high; Cronbach's alpha for all scored items was 0.975 (joint domain values 0.906–0.925). For response analysis, confidence was highest for knee examination (mean 6.34) and lowest for hands (mean 5.92). In task domains, participants were most confident in assessing range of motion of joints (mean 7.71) and least confident in their ability to use the joint exam to guide medical decision making (5.05), identify and name deformities (5.182), use the joint exam to make diagnoses (5.27), and perform provocative diagnostic maneuvers (5.295). Extremes of confidence were rarely endorsed, giving an item frequency distribution that was highly skewed towards the center (overall item mean 6.016).

Conclusion: We established content and internal structure validity for a 10-question multi-item survey to assess residents' confidence in their ability to perform a comprehensive musculoskeletal examination. Confidence was relatively similar among joint areas and varied more based on MSK exam task. Based on these results, we have modified the survey, contracting response options to 6 with a descriptive rather than numerical Likert scale to improve validity. Testing of this modified survey is ongoing. Future directions include validation by testing the relationship of measured confidence to actual performance of a comprehensive MSK exam.

Disclosure: L. G. Criscione-Schreiber, None; **E. Schreiber**, None; **M. Arcasoy**, None; **K. S. O'Rourke**, None.

978

Inter-Professional Training Programs For Primary Care Providers Can Successfully Educate Practitioners With Dramatically Different Educational and Training Background Through a Common Mini-Residency Training Program. David I. Daikh[1], Michael J. Battistone[2], Andrea M. Barker[2], Andy L. Avins[3], Marissa Grotzke[2], Meika A Fang[4], Antonio A. Lazzari[5], Amy C. Cannella[6], Pedro Roldan[7], Joan Marie Von Feldt[8] and Grant W. Cannon[2]. [1]San Francisco VA Medical Center and University of California, San Francisco, San Francisco, CA, [2]Salt Lake City VA and University of Utah, Salt Lake City, UT, [3]San Francisco VA Medical Center, San Francisco, CA, [4]VA Greater Los Angeles Healthcare System, Los Angeles, CA, [5]Boston VA Medical Center, Boston, MA, [6]Omaha Veterans Affairs Hospital and University of Nebraska Medical Center, Omaha, NE, [7]Leesburg VA CBOC, Leesburg, FL, [8]Univ of Pennsylvania/Philadelphia VAMC, Philadelphia, PA.

Background/Purpose: Musculoskeletal (MSK) problems present frequently during outpatient visits to primary care providers. Training in the diagnosis and care of MSK disease varies based on the specific discipline and on the degree of emphasis placed on these problems by training programs. Providers may also have different learning styles and post-training experiences that influence their comfort and competence with MSK problems. We examined the impact of prior training and experience on providers' perceived level of competence before and after participation in a novel intensive 3 day MSK "mini-residency" training program including physicians (MD), physician assistants (PA) and nurse practitioners (NP) from six VA health systems across the country.

Methods: Providers engaged in a three-day intensive, multi-method training program that included specific training in the approach to common shoulder and knee problems. Participants were surveyed regarding training and clinical experience with MSK problems. We compared experience with self-reported competency and performance in observed structured clinical examinations (OSCE) of the shoulder and knee.

Results: Participants had significant heterogeneity in their educational and training experience with MSK disease.

	Professional School Education (%)		Residency Training (%)		Post-training Experience (%)	
Discipline	≤6 hrs	>12 hrs	≤ 6 hrs	>12 hrs	<5 yrs	>10 yrs
MD	42.5	29.7	49.1	33.6		
NP/PA	68.4	23.1	46.4	25.0	19.2%	50.0%
OSCE Rating (maximum 5.0)						
Shoulder	4.53	4.62	4.60	4.56	4.77	4.57
Knee	4.15	4.17	4.26	4.08	4.41	4.07

95.4% of 109 participants reported that they frequently see common MSK conditions in practice. However, there were no significant differences in their confidence level in the evaluation and management of common MSK conditions prior to taking the course, or in specific self-reported baseline competencies based on these differences in training or experience. Providers exhibited significant improvements in post-course evaluations, with no significant differences in improvement in self-rated competencies or in objective skill assessments across education, experience, or practice specialty.

Surprisingly, providers with less than 5 years post-training experience performed better on the post-course OSCE than those with 10 or more years ($p = 0.022$ and 0.017 for shoulder and knee, respectively).

Conclusion: Providers have widely varying education and training in MSK problems. Higher performance in OSCE among providers recently completing training may reflect easier acceptance of a systematic physical examination approach or greater comfort with the OSCE format. Despite differences in prior training and experience, participation in a focused, structured, multi-method training experience can lead to improved MSK competency, even among experienced clinicians from varied backgrounds.

Disclosure: D. I. Daikh, None; **M. J. Battistone**, None; **A. M. Barker**, None; **A. L. Avins**, None; **M. Grotzke**, None; **M. A. Fang**, None; **A. A. Lazzari**, None; **A. C. Cannella**, None; **P. Roldan**, None; **J. M. Von Feldt**, None; **G. W. Cannon**, None.

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Southern Hemisphere Educational Partnership For Pediatric Arthritis and Rheumatological Diseases (SHEPPARD): An International Educational Program. Ricardo A. G. Russo[1], Marìa M. Katsicas[2], Kate Webb[3] and Christiaan Scott[3]. [1]Hospital de Pediatria Garrahan, Buenos Aires, Argentina, [2]Hospital de Pediatrìa Garrahan, Buenos Aires, Argentina, [3]Red Cross War Memorial Children's Hospital, Cape Town, South Africa.

Background/Purpose: Cooperation and collaboration between developing countries can be mutually beneficial and create the basis for a longstanding, Third World-centered educational program aimed at increasing the pediatric support for Pediatric Rheumatology (PR). The objective of this presentation is to describe a binational (Argentina-South Africa), bicontinental, educational program aimed at increasing the pediatric support for PR in developing countries with similar health problems.

Methods: This is an ongoing program aimed at combining the expertise from 2 centers in different developing countries to deliver a program in professional education. This program was approved and supported by an ILAR educational grant. Its objectives are: 1) To provide pediatricians with education and training in the management of patients with juvenile rheumatic diseases to facilitate early diagnosis, referral and follow up 2) To develop permanent communication means for bidirectional contact between local teams and specialized centers. 3) To establish an integrated South Africa-Argentina (SA-A) teaching modality, adapted to the needs of these developing countries. Strategies used were: selection of 6 pediatricians working in underserved areas of SA-A based on availability and interest in the field; 3 months-long rotations in Pediatric Rheumatology centers in Cape Town and Buenos Aires; supervised patient-centered education and personalized training of pediatricians where they applied to a 10-item curriculum-based program; visiting professorships to those areas for education of basics of PR for pediatricians through patient-based teaching sessions and interactive discussions; periodic, problem-based, SA-A teleconference rounds where expertise in clinical, epidemiological and educational aspects of PR from both centers were shared and promoted new developments in patient care and professional education. A tailored educational program included specific competency-based educational goals for each trainee as well as community-based epidemiological research and team-based, patient-oriented care adapted to the specific local needs of the trainee′s setting. Post-training assessment of trainees' skills and knowledge was performed through multiple choice tests and Objective Structured Clinical Examination, as well as trainees′ satisfaction through a structured survey.

Results: Six pediatricians (3 in Argentina and 3 in South Africa) received a comprehensive training according to the educational program. They were successfully evaluated and returned to their local setting, where they are currently involved in the care of children and adolescents with rheumatic conditions. Visiting professorships resulted in the delivery of basics of PR to over 200 pediatricians in different cities of underserved areas of SA-A. All trainees expressed high degree of satisfaction with their experience. Their activities are periodically monitored through combined trainer-trainee case discussions.

Conclusion: This project developed an ongoing, successful educational strategy that may be used as a model for training in PR in other regions of the developing world. Evaluation of the impact of the program on care delivery will follow.

Disclosure: R. A. G. Russo, None; **M. M. Katsicas**, None; **K. Webb**, None; **C. Scott**, None.

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Promoting Critical Appraisal Self-Efficacy and Peer Connectivity With An Epidemiology Curriculum For Rheumatology Trainees. Juliet Aizer[1], Jessica Berman[2], Anne R. Bass[1], Stephen A. Paget[1] and Lisa A. Mandl[3]. [1]Hospital for Special Surgery Weill Cornell Medical College, New York, NY, [2]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, [3]Hospital for Special Surgery, New York, NY.

Background/Purpose: Self-efficacy and peer connectivity are important in career choice, productivity, and persistence. Applying adult, critical, and social learning theory, we broadened a traditional journal club format into an Epidemiology Curriculum for Rheumatology trainees, to foster critical appraisal self-efficacy and peer support in clinical research.

Methods: Rheumatology faculty at a single center developed learning objectives with input from trainees. All year 1 adult and pediatric rheumatology trainees, as well as those in years 2 and 3 of the clinical/translational research track participated. The group met 27 times from 9/2012–6/2013.

Clinically relevant, methodologically important articles were reviewed in 19 sessions. Participants joined facilitators to critique articles through questions on study design, chance, bias, confounding, generalizability and significance. Participants identified knowledge gaps, reflected on related clinical and research experiences, suggested alternative methodologic approaches, and debated implications. Faculty facilitated 16 sessions. With faculty support, 3rd year trainees each facilitated 1 session. Each of 5 2nd year trainees had one session to present their own research in progress. Challenges were highlighted and solutions sought through peer consultation followed by reflection and follow up to address barriers.

Baseline and year-end questionnaires examined trainees' experience, critical appraisal skills, attitudes, behaviors and suggestions. Perspectives on curriculum format/content were also captured mid-year and year-end. The primary outcome was change in critical appraisal self-efficacy.

Results: 12 trainees participated; all had experience in clinical research. 75% had taken epidemiology courses. After exposure to the curriculum, the proportion of participants reporting "a lot" of confidence in their "ability to critically evaluate study design" increased from 16% to 58%, ($p=0.09$, Fisher Exact Test). Self-efficacy regarding ability to evaluate bias, statistics and quality of a study increased by 17%, 8%, and 17%, respectively.

17% reported more thorough reading habits. 33% reported an increase critically evaluating study results.

Participants considered the epidemiology curriculum worthwhile, with positive personal impact. Participants highlighted the importance of a comfortable learning environment and clinical relevance in article selection.

Participants presenting research in progress attributed revision of study aims, hypotheses, protocols, and analyses to the curriculum. Participants developed timelines to achieve the goals of research dissemination. Peers' perspectives and solutions were considered valuable. Research discussions enhanced participants' sense of peer connectivity and likelihood to discuss research.

Conclusion: Although small numbers preclude statistically significant results, application of adult, critical, and social learning theory in an Epidemiology Curriculum for Rheumatology trainees has the potential to promote self-efficacy related to critical appraisal, peer connectivity, and clinical research project development.

Disclosure: J. Aizer, None; **J. Berman**, None; **A. R. Bass**, None; **S. A. Paget**, None; **L. A. Mandl**, None.

981

Competency and Confidence In Musculoskeletal Medicine For The First Graduating Class Of a New Medical School. Shazia Bég University of Central Florida, Orlando, FL.

Background/Purpose: Musculoskeletal problems are among the most common patient complaints in the United States. Despite this, studies show that medical students and interns are not adequately prepared in these topics. The University of Central Florida College of Medicine (UCF) is a new medical school with an integrated curriculum that graduated its charter class of in May 2013. At UCF a four week module that includes topics in rheumatology and orthopedics is taught in the second year. The purpose of this study was to test the UCF charter class on basic topics in musculoskeletal medicine to assess their competence in this area and compare it to the national average and to their juniors who have had an improved curriculum.

Methods: A basic-competency examination in musculoskeletal medicine has been previously validated and used since 1999 by various medical schools. It has 25 short-answer questions covering topics seen in primary care settings. This exam was taken by UCF second year medical students (M2) during their musculoskeletal module and by UCF fourth year medical students (M4) just before their graduation. A Likert-Scale questionnaire was administered to M4 class to rate their self-confidence in musculoskeletal physical examination skills. M4 students were asked if they had taken an elective in orthopedics or rheumatology (MSK). The exam was scored anonymously according to a standardized answer key.

Results: A total of 79 second-year (M2) and 35 fourth-year (M4) medical students took the quiz. The mean score for the M2 class was 80% (sd=10.9), M4 class was 58% (sd=13.1). The pass rate using 60% cut off was 96.2% for M2 and 54.3% for M4 ($p<0.001$). The pass rate using 73% cut off was 82.3% for M2 and 8.6% for M4 ($p<0.001$). The pass rate for UCF M2 and M4 classes was higher than the national average pass rate of 18% for medical school graduates using the same exam in 1998. Using the 60% cut off for the M4 class, those who had taken an MSK elective had a pass rate of 76.5% compared to 33.3% in those who did not take such an elective ($p=0.01$). For the M4 class, confidence level in physical exam skills was as follows: back exam: poor=5.7%, fair to good=94%; shoulder exam: poor=25.7%, fair to good= 74.3%; knee exam: poor=17.1%, fair to good=82.8%. M4 students who had an MSK elective were more confident in back exam ($p=0.014$) compared to those who did not take an elective, but there was no significant difference between shoulder ($p=0.85$) and knee ($p=0.39$) exam confidence levels between the two groups, although the trend was towards more confidence in the group that had taken an MSK elective.

Conclusion: Pass rate using a validated musculoskeletal exam for the UCF graduating class was better than the national average but was still poor overall. Pass rate was significantly better in the second year class who had the improved curriculum. M4 students who had taken a MSK elective had significantly higher pass rates and trended towards having higher confidence in physical exam skills compared to those who had not taken such an elective. Musculoskeletal medicine education needs to be improved in all four years of undergraduate medical education to increase confidence and performance in the real world where there is a high demand for these skills.

Disclosure: S. Bég, None;

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Preferred Strategies For Delivering Treatment Information To People With Rheumatoid Arthritis, Osteoarthritis and Osteoporosis. Maria A. Lopez-Olivo[1], Robert Volk[2], Maria Jibaja-Weiss[3] and Maria E. Suarez-Almazor[4]. [1]University of Texas. M.D Anderson Cancer Center, Houston, TX, [2]UT MD Anderson Cancer Center, Houston, TX, [3]Baylor College of Medicine, Houston, TX, [4]University of Texas MD Anderson Cancer Center, Houston, TX.

Background/Purpose: To explore the perceptions of people with rheumatoid arthritis (RA), osteoarthritis (OA), and osteoporosis (OP) regarding their preferred delivery methods for obtaining treatment information.

Methods: Six focus groups and 18 cognitive interviews were conducted with patients recruited from publicly funded clinics (1 per disease in English and Spanish) and 2 focus groups and 4 cognitive interviews to rheumatologists. In general, patients had low health literacy and were multiethnic. Patients with RA were at least 18 years old and had a diagnosis of RA; patients with OA were 50 or older and had a diagnosis of knee OA (unilateral or bilateral). We included only female patients with OP that were at least 50 years old and at least 3 years post-menopausal.

Results: Content analyses revealed that the preferred media for patients obtaining treatment information were a) passive sources, (i.e., TV and DVDs) and b) active sources (i.e., workshops and classes). The preferred messengers were patients affected by the disease and physicians (specifically rheumatologists). Real life stories and testimonials narrating both successful outcomes with treatment adherence and complications of no adherence were preferred. There was discrepancy by the best method to receive information between patients and providers. Physicians stated that the preferred delivery method to provide information was written material (brochures, booklets and pamphlets). There were diverse perspectives about the key treatment messages to share with people with these conditions. The 3 key messages preferred by most patients and physicians were: 1) understanding the condition, 2) complications of non-adherence, and 3) side-effects.

Conclusion: The methods, key messages, and messengers identified in this study illustrate the need of combined efforts from consumer organizations and health providers for more adequate ways to effectively deliver treatment information to individuals with lower levels of education experiencing these chronic conditions.

Disclosure: M. A. Lopez-Olivo, None; **R. Volk**, None; **M. Jibaja-Weiss**, None; **M. E. Suarez-Almazor**, None.

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Teaching Musculoskeletal Care Through An Inter-Disciplinary and Inter-Professional Clinical Training Program Successfully Provides Trainees With Knowledge and Skills Required To Deliver Excellent Musculoskeletal Care. Grant W. Cannon[1], Andrea Barker[1], J Peter Beck[1], Jeffery Berdan[1], Marissa Grotzke[1], Timothy A. Huhtala[1], Patrice Kennedy[2], Phillip Lawrence[2], JoAnn Rolando[1] and Michael J. Battistone[1]. [1]Salt Lake City VA and University of Utah, Salt Lake City, UT, [2]Salt Lake City VA, Salt Lake City, UT.

Background/Purpose: While musculoskeletal (MSK) complaints are some of the most common reasons for primary care and specialty visits, little time is dedicated to this important topic in training curricula. To address this critical need, we developed an inter-disciplinary and inter-professional program involving primary care (PC), rheumatology (RHE), orthopaedic surgery (OrS), endocrinology (END), and physical medicine specialists (PM&R) to train physicians and associated health professionals in MSK care.

Methods: Through funding from the Office of Academic Affiliations (OAA) of the Department of Veterans Affairs (VA), we developed an intensive week of training that combines didactics, simulations, and clinical experiences to establish a Center of Excellence (COE) for patient centered MSK care. A significant component of this experience is an inter-disciplinary clinic for evaluation of patients with complex MSK disorders. During COE clinic visits, patients are seen by a team of specialists including trainees, attending physicians, and advanced practice clinicians in the specialties listed above. The trainees and practitioners of this inter-professional and inter-disciplinary team evaluate patients and implement a comprehensive management plan. Faculty assess trainee competence through direct observation in clinical experiences and an objective structured clinical exam (OSCE).

Results: To date, 40 physician trainees (30 PC, 3 RHE, 1 OrS, 1 END, 5 PM&R) and 8 associated health trainees (4 DNP, 2 PA, 1 Physical therapist, 1 Pharmacist) have been involved in COE training. A review of the first 140 patients seen in the COE MSK inter-disciplinary clinic documents a rich clinical training opportunity with an average of 2.4 ± 1.5 complaints per visit, and patients being seen by 2.8 ± 1.2 disciplines. The chief MSK complaint by patients was classified according to the following areas (OrS, RHE, END, PC); however, as noted, the vast majority of patients had multiple MSK diagnoses.

	Chief Complaint	Co-Morbid Conditions	Most common diagnoses
OrS	73%	91%	Osteoarthritis, shoulder, knee & spine complaints
RHE	22%	38%	Rheumatoid arthritis, gout, other MSK diseases
END	4%	49%	Osteoporosis, vitamin D deficiency
PC	1%	26%	Fibromyalgia, chronic pain

Trainees reported high satisfaction with the intensive training and COE MSK clinic. Self-assessment of knowledge and skills for several of the key elements evaluated for physician trainees is listed below.

Competency Assessment	Pre-course	Post-course	Change
Comprehensive shoulder and knee pain evaluation	16.7%	100%	83.3%
Manage shoulder and knee pain	11.1%	94.4%	83.3%
Manage gout	22.2%	94.4%	72.2%
Indication for joint injection	5.6%	94.4%	88.9%
Shoulder/Subacromial injection using simulation	27.8%	100.%	72.2%
Knee aspiration using simulation	50.0%	94.4%	44.4%
Perform joint aspirations and injections on patients	23.5%	100.%	76.5%
Diagnose and manage patients with osteoporosis	35.3%	100%	64.7%

There was marked improvement in MSK knowledge and skills in all areas of training with reported improvement in clinical competence confirmed on OSCE.

Conclusion: The COE in MSK disease provides a comprehensive training program in MSK disease. The employment of an inter-disciplinary and inter-professional training model gives trainees the unique opportunity to learn to manage patients with MSK disease in a rich collaborative setting.

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ACR/ARHP Poster Session B
ARHP Education/Community Programs
Monday, October 28, 2013, 8:30 AM–4:00 PM

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Development and Usability Testing Of The Arthritis Health Journal: An Online Tool To Promote Self-Monitoring In People With Rheumatoid Arthritis. Erin Carruthers[1], Paul M Adam[2], Hilary Horlock[3], Linda C. Li[4], Anne F. Townsend[1], Charles H Goldsmith[5], Beverly Mitchell[3] and Diane Lacaille[6]. [1]Arthritis Research Centre of Canada, Richmond, BC, [2]Mary Pack Arthritis Centre, Vancouver, BC, [3]Provincial Health Services Authority, Vancouver, BC, [4]University of British Columbia, Vancouver, BC, [5]Simon Fraser University, Burnaby, BC, [6]Arthritis Research Centre of Canada, University of British Columbia, Richmond, BC.

Background/Purpose: Patient passports have been used in chronic diseases to promote the active involvement of patients in their care, and have led to better treatment and health outcomes. In rheumatoid arthritis (RA), the 'Treat to Target' approach emphasizes the importance of regular assessment and modifying therapy until the target (remission or low disease activity) is reached. Active involvement of RA patients in monitoring their own disease activity could facilitate this approach by providing early warning when targets are not being met. The Arthritis Health Journal (AHJ) is a patient-centered online tool that helps patients track symptoms, monitor disease activity and develop action plans. This study aims to evaluate user satisfaction with the AHJ and to identify usability issues that will help refine the tool.

Methods: Development of the AHJ was guided by a series of semi-structured interviews with patients and rheumatologists. The tool consists of six sections: 1) symptom and exercise log; 2) disease activity assessment; 3) mood assessment; 4) medical information; 5) goals and action plans; 6) health reports.

Two iterative cycles of usability testing were conducted with people with RA using the concurrent think-aloud protocol, in which participants are asked to verbalize their thoughts while performing a set of tasks. Sessions were audio-recorded and field notes were taken. The System Usability Scale (SUS) was used to evaluate the usability of the tool (min-max=0–100; higher=more user friendly) and simple content analysis was performed to identify issues and refine the tool.

Results: Usability testing was conducted with nine participants with RA–five in the first iteration and four in the second iteration. Mean (SD) RA duration was 11y (12.6); mean (SD) age was 51.6y (10.2). All participants were female and most (89%) were college or university educated. Mean (SD) daily internet use was 4h (2.2). The tool's overall usability was good, with a mean (SD) SUS score of 84.7 (7.7).

Participants responded positively to the content and design of the AHJ, reporting particular satisfaction with the ability to view patterns over time and relationships between symptoms and other aspects of their disease or management. Graphical representation of results was viewed as an effective method of displaying these patterns.

Aspects of the interface that were modified after the first iteration led to improved satisfaction in the second iteration. Ensuring font types, sizes and colours were easy to read was essential to user satisfaction. Participants rarely read text or instructions, so long blocks of text were replaced with simple and succinct instructions, and key points were emphasized to ensure important details were understood. Particularly, instructions regarding time frame in analog scale questions (e.g. in the past week) tended to be ignored or go unnoticed, until questions were reformatted in the second iteration to more clearly emphasize the time frame.

Conclusion: Direct observation methods provided valuable insight into the use of online tools to promote active involvement of patients in their care. While general satisfaction was high, usability testing revealed important issues that warranted improvement to refine the prototype.

Disclosure: E. Carruthers, None; **P. M. Adam**, None; **H. Horlock**, None; **L. C. Li**, None; **A. F. Townsend**, None; **C. H. Goldsmith**, None; **B. Mitchell**, None; **D. Lacaille**, None.

985

Efficacy Study Of Multimedia To Educate Rheumatoid Arthritis Patients. Julie A. Unk. Washington Univ School of Med, St. Louis, MO.

Background/Purpose: The level of health literacy varies among rheumatoid arthritis (RA) patients in their ability to understand and act upon information presented in a clinic appointment. The purpose of this randomized trial was to improve patient clinician communication in the rheumatology office by assessing the efficacy of multimedia compared to a handout for RA patients with the goals of improving patients' scores on the self reported Medication Adherence Questionnaire (MAQ) at one month post intervention. Scores of the Brief Illness Perception Questionnaire (BIPQ), Health Assessment Questionnaire (HAQ), and program evaluation were also assessed.

Methods: 200 RA patients in a Midwestern rheumatology outpatient clinic were recruited over 10 months. All participants provided informed consent. They were randomized 1:1 to receive a handout or a 15 minute audio visual Power Point program. At baseline all participants completed a demographics questionnaire, MAQ-5 questions, BIPQ-8 questions, and HAQ identified only by study number. Participants randomized to the handout group took the document home to read. Participants randomized to the multimedia group were shown the program while in the office and sent home with a handout and CD copy of the program. At baseline all participants were sent home with the 3 follow up questionnaires (MAQ, BIPQ, and HAQ) and program evaluation to complete and mail back. At one month all participants were called and reminded to complete and return the forms. Study data were entered and managed using the Research Electronic Data Capture tool (REDCap).

Results: The multimedia group had significant improvement in the MAQ score of skipped doses ($p=0.006$) and experienced significantly fewer physical and emotional symptoms compared to the handout group ($p=0.03$, $p=0.03$ respectively). Both groups had improvement in MAQ and BIPQ scores. No change was seen in the HAQ scores of either group. Upon program evaluation both groups equally reported a better understanding of rheumatoid arthritis.

Conclusion: Multimedia was superior to handout to educate RA patients about adherence to medications which resulted in improved physical and emotional symptoms. Healthcare providers should use multimedia to educate RA patients about causes of disease, RA effects on the body, treatments for RA, self-care strategies, and resources to access more information about their disease. Multimedia can be used as a tool to address health literacy and improve patient clinician communication.

Disclosure: J. A. Unk, None;

986

Participant and Educator Feedback Informs Delivery Of An Interprofessional Inflammatory Arthritis Education Program Using Telemedicine In Rural Communities. Carol Kennedy[1], Kelly Warmington[2], Carol Flewelling[1], Rachel Shupak[3], Angelo Papachristos[4], Caroline Jones[4], Dorcas Beaton[5], Sydney C. Lineker[6] and Denise Linton[1]. [1]St. Michael's Hospital, Toronto, ON, [2]Hospital for Sick Children, Toronto, ON, [3]St. Michaels Hospital, Toronto, ON, [4]St Michael's Hospital, Toronto, ON, [5]Scientist, Institute for Work & Health, Toronto, ON, [6]The Arthritis Society, Toronto, ON.

Background/Purpose: Telemedicine-based approaches to healthcare service delivery are known to improve access to care, as well as the efficiency, quality and timeliness of healthcare service provision in sparsely populated areas. Arthritis care providers working in rural communities recognized that patients with inflammatory arthritis had limited access to appropriate patient education and could benefit from the Prescription for Education (RxEd) program (a one-day education session for adults with inflammatory conditions delivered by an interprofessional team of specialized arthritis care providers).

The one-day program was adapted to include the use of interactive videoconferencing as a method of delivery. Adaptive strategies for educators

(local presenters and rural site clinical leads) included two workshops (Telemedicine Best Practices and Adult Education Principles; Improved Public Speaking) designed to optimize the instructive value of the videoconferencing technology.

The objectives of this presentation are: 1) To explore the feasibility of and participant satisfaction with the use of telemedicine to deliver the RxEd program in rural communities; 2) To use process outcome data to inform improvements in the delivery of future sessions.

Methods: Participants included adults with inflammatory arthritis attending the RxEd program locally or at one of four rural sites (remote). Participants completed course evaluations immediately post-program. Educators completed post-program reflective logs (including qualitative perceptions of videoconferencing technology, interaction between sites, small group learning activities). In addition, a debriefing meeting was held (RxEd educators, telemedicine coordinators, researchers) to discuss collected data and identify delivery modifications to be implemented in future sessions.

Results: Forty-nine persons (12 local; 37 remote, across 4 sites) attended the inaugural RxEd Telemedicine session. Forty-three completed the post-program course evaluation (12 local; 31 remote). Preliminary findings indicate that remote participants were satisfied with the quality of the videoconference (% responding with 'agree' or 'strongly agree'): could hear presenter (97%), could see who was speaking at remote sites (83%), could see slides (87%), adequate facilitation of interaction between sites (90%), could hear discussion between sites (73%).

Educators' post-program reflection logs (n=9) captured feedback about the quality of the videoconferencing, interaction between sites, and small group learning activities. Many of the concerns identified by the educators were consistent with participant feedback. Suggested improvements included: the use of two screens where possible and direct frontal camera angles; equality of interaction with remote sites; slide modifications to improve readability on screen and in handouts; and slight changes in program delivery.

Conclusion: Findings from this pilot session confirm that it is feasible to extend the RxEd program to rural communities using telemedicine. Several areas for improvement of the Telemedicine delivery have been identified and will be addressed where possible.

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Improving Access To Subspecialty Care For Underserved Communities: A Rheumatology Patient Navigator Pilot Intervention. Candace H. Feldman[1], Gregory A. Culley[2], Erika Brown[3], Chanele R. Assencoa[2], LeRoi S. Hicks[4] and Daniel H. Solomon[5]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Family Health Center of Worcester, Inc., Worcester, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]UMass Memorial Medical Center, Worcester, MA, [5]Harvard Medical School, Brigham and Women's Hospital, Division of Rheumatology, Division of Pharmacoepidemiology, Boston, MA.

Background/Purpose: Early and sustained access to rheumatology care can improve access to disease-modifying medications and reduce disparities in outcomes. In one state, more than one-half of community health center (CHC) medical directors felt that their predominantly low-income, underserved patients required better access to rheumatology care. We pilot tested an intervention that utilized a patient navigator- a layperson trained to provide a range of education, advocacy and care coordination services- to improve access to rheumatology and musculoskeletal care.

Methods: We partnered with a CHC that cares for over 30,000 patients each year, 95% with income levels below 200% of poverty. The CHC medical director identified an affiliated community health worker to serve as the patient navigator. We developed a rheumatology/musculoskeletal disease curriculum to train the navigator and provided comprehensive patient resources and pamphlets for distribution. We identified established patients with rheumatic and musculoskeletal diseases by ICD-9 code, and primary care providers (PCPs) confirmed whether each patient would benefit from the navigator's assistance. All patients requiring a new rheumatology appointment were also referred to the navigator. We conducted semi-structured interviews with patients to assess need and tracked all navigator services provided.

Results: Of the 695 patients initially identified by ICD-9 code with possible rheumatic and musculoskeletal diseases, 125 were referred to the navigator; 29 also required new rheumatology appointments. On average, 5 new referrals (range 2–10) were received weekly. After 3 months, 31 (28%) patients were actively working with the navigator, 81 (72%) patients' PCPs were actively in communication with the navigator, and 62/81 (77%) of these patients were in the process of being engaged (outreach attempts made or waiting for appointments to be scheduled). Two of the 125 (2%) patients declined participation. Among the 31 actively engaged patients, navigator's services included direct coordination of appointments and repeated reminders prior to the visit (n=26, 84%), facilitation of communication between providers (n=31, 100%), transportation arrangements (n=7, 23%), financial services including provisions for affordable medications (n=4, 13%), coordination of live interpreters (n=2, 6%), and organization of senior services (n=2, 6%). Of the 29 patients scheduled to see rheumatologists, 14/17 (82%) successfully kept their appointments and 12 appointments are upcoming.

Conclusion: This CHC-based rheumatology navigator pilot demonstrates the feasibility and acceptability of subspecialty navigators to improve access to care for underserved patients. Further research is needed to assess the effectiveness and costs of the patient navigator.

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Lupus Education For Providers Serving The Asian American Community: Hospital For Special Surgery's LANtern® (Lupus Asian Network) Initiative. My-Lan N. Tran[1], Roberta Horton[2], Michael D. Lockshin[2] and Arthur Yee[2]. [1]Hospital for Special Surgery, New York City, NY, [2]Hospital for Special Surgery, New York, NY.

Background/Purpose: Lupus affects Asian Americans 2–3 times more than their white counterparts, with studies demonstrating health disparities in severity and outcomes. Our hospital's national support and education program for Asian Americans with lupus and their loved ones, as part of our community service plan initiative, piloted a collaborative effort to raise awareness about lupus as an Asian American health concern with community providers in healthcare and social services.

Methods: Our program identified and formulated collaborative partnerships with three key stakeholders with longstanding histories of servicing a lower socioeconomic and immigrant population within the Asian American community. We coordinated and delivered specifically designed professional education for medical practitioners in primary care, pediatrics, obstetrics-gynecology, and psychiatry, in addition to programs for health professionals in women's health and mental health, and social services providers. Post-program measures assessed the degree to which these programs contributed to professional learning, enhanced clinical practice, increased interest to learn more about lupus, and overall degree of satisfaction. We also launched an *e-News* publication as a forum for professionals serving the Asian American community.

Results: A total of 10 lupus education programs and 2 *e-News* publications were delivered in 2010–2012. Seven of these programs were for healthcare providers on lupus topics relevant to their professional interests and areas of practice. Of the 94 evaluations completed, 98% strongly agreed/agreed that the presentations contributed to their professional learning, and 96% strongly agreed/agreed that the content would enhance their clinical practice. Responses to open-ended questions underscored how the presentations contributed to their care of lupus patients, for example, "to use helpful clinical pearls in future clinical assessment", and "awareness of subtle presentation of the disease, early diagnosis, treatment and maintenance would result in better outcome."

For the 3 programs tailored for social service providers, the 63 evaluations submitted reflected that 97% strongly agreed/agreed that their awareness of lupus had increased as a result of these presentations. Regarding what was most learned, responses included "what lupus is, and how much of an impact it is to patients and family", and "lupus can affect anyone and differently."

The pilot issue of our e-News was sent to 150 recipients; the 2nd issue reached > 400 interested professionals, an increase of 266%.

Conclusion: Early identification and appropriate treatment of lupus may significantly influence its progression and impact. To our knowledge, this is the first initiative directed toward increasing knowledge of lupus for

providers serving the Asian American community. Our professional education, with topics specifically relevant to providers' areas of practice, yielded a positive impact in potential care outcomes. The increase in our e-News reach also demonstrated an interest among providers in learning more about lupus as an Asian American health issue, as well as the potential power of this form of messaging.

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Reproductive Counseling Program For Lupus Patients At The Systemic Lupus Erythematosus-Antiphospholipid Syndrome Center Of Excellence At Hospital For Special Surgery. Katherine Kim[1], Alana B. Levine[2], Monica C. Richey[2], Nadine H. Spring[2], Elizabeth Schulman[3], Lisa R. Sammaritano[2], Shari E. Gelber[4] and Jane E. Salmon[2]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]Hospital for Special Surgey, New York, NY, [4]New York Presbyterian Hospital, New York, NY.

Background/Purpose: Maternal exposure to mycophenolate mofetil (MMF) during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Responding to this observation, the Food and Drug Administration (FDA) mandated a risk evaluation and mitigation strategy (REMS) for MMF in October 2012. MMF is currently used to treat a variety of conditions including systemic lupus erythematosus (SLE) and lupus nephritis. The HSS SLE-APS Center of Excellence (COE) serves a large number of female patients of child-bearing potential. Based on these facts, we developed a survey to better understand the reproductive counseling needs of our cohort. The objectives were: a) To understand SLE patients' pregnancy intentions and assess their current patterns of contraceptive use. b) To assess the level of contraceptive and reproductive counseling offered by the HSS SLE-APS COE and determine the need for and patient interest in contraceptive and reproductive patient education.

Methods: An anonymous, 9-question paper survey was offered to patients of the HSS SLE-APS COE from December 2010 to September 2011. Survey questions assessed attitudes about pregnancy, patterns and type of contraceptive use, prior pregnancy and contraceptive counseling by healthcare providers, and patients' interest in participating in new reproductive health educational programs offered by the COE.

Results: Sixty-six patients completed the survey; 53 (80%) were female. 23 (35%) patients could recall a discussion with COE healthcare providers regarding contraceptive use; 22 (33%) remembered such a conversation about pregnancy. 56% were interested in participating in a contraception class and 53% were interested in a pregnancy class (Table 1).

Table 1.

Pregnancy Intentions (n=66)	
Pregnant	4 (6%)
Trying to become pregnant	4 (6%)
WouldnÂ't mind becoming pregnant	13 (20%)
Trying to avoid pregnancy	29 (44%)
Not possible to become pregnant	18 (27%)
Haven't considered pregnancy	2 (3%)
Contraceptive use (n=66)	
Never	13 (20%)
Rarely	6 (9%)
Sometimes	11 (17%)
Most of the time	8 (12%)
Always	14 (21%)
Not applicable	14 (21%)
Contraceptive type (n=34)	
None	56%
Barrier	35%
Estrogen/progesterone pill	3%
Progesterone only pill	3%
Progesterone injection	3%

Conclusion: Our survey demonstrated a striking deficiency in recall of contraceptive and reproductive counseling by patients in our COE. Over half of survey participants were interested in a formal educational program on these topics. Based on data from this survey and the FDA's mandate, the SLE-APS Center of excelence now offers a personalized, one-on-one, patient education session taught by a registered nurse for SLE patients taking MMF. Similar sessions for patients receiving cyclophosphamide, methotrexate, and azathioprine are being developed.

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Utilizing Facebook Chats To Convey Health Information To Lupus Patients At The Systemic Lupus Erythematosus-Antiphospholipid Syndrome Center Of Excellence At Hospital For Special Surgery. Nadine H. Spring[1], Elyse Bernstein[1], Su Jin Kim[1], Monica C. Richey[1], Jessica Rowshandel[2] and Jane E. Salmon[1]. [1]Hospital for Special Surgery, New York, NY, [2]SLE Lupus Foundation, New York, NY.

Background/Purpose: The SLE-APS Center of Excellence at Hospital for Special Surgery (HSS) uses Facebook chats as a means to increase awareness, reach a wider audience, allow for interaction between patients and health care providers, and answer patients' questions about lupus. To date, three chats have been completed. These lupus Facebook chats help to educate patients about their disease and the importance of maintaining relationships with their rheumatologists.

Objective: To determine whether collaboration with a disease-specific foundation increases patient awareness of and participation in lupus Facebook chats.

Methods: Three chats have been completed. The first two were promoted through advertising and promotion on the HSS's Facebook and Twitter accounts, targeted pitching of lupus bloggers and awareness groups, word of mouth, and by flyers. For the third chat, HSS collaborated with the S.L.E. Lupus Foundation and they used similar advertising. Participants were instructed to like the HSS Facebook page and post their questions. A panel of rheumatologists, an obstetrician-gynecologist, social workers, physical therapists, nutritionists, and a rheumatology nurse practitioner responded to as many questions as possible over one hour. Remaining questions were distributed to the experts for answers and turned into a blog series on "HSS on the Move" (www.hss.edu/onthemove).

Results: The first chat (May 2012) focused on lupus and medications. 2,280 users saw the chat post, with 60 questions and comments from 20 users. Promotional Facebook posts before the chat were shared 247 times. HSS reported 14 twitter mentions and five retweets. The HSS page received 30 new likes on the day of the chat, and 21 users liked the chat post. The second chat (October 2012) discussed lupus, pregnancy, and reproductive health. There were 2,203 people who saw the chat with 25 questions and comments from 12 users. The promotional Facebook posts were shared 81 times and eight users retweeted. The HSS page received 34 new likes the day of the chat. In May 2013, HSS collaborated with the SLE Lupus Foundation for the third chat on lupus and general health. 6,624 people saw the chat. The HSS Facebook page received 332 new likes on the day of the third chat. The month's daily average was 34 likes. The chat post drew 78 likes. There were 123 participants representing six countries and 28 States. Participants posted 162 questions and comments with 61 answered during the hour. The promotional Facebook posts before the chat (from HSS and the S.L.E. Foundation) were shared 288 times. The S.L.E. Lupus Foundation tweeted an additional 18 times in promotion of the chat.

Conclusion: Participation level was higher when the topics were more general. Lower participation in the second chat may relate to the private nature of the topic and concerns of privacy. Collaboration with the SLE Lupus Foundation increased patient awareness of the chat and participation. This experience suggests that partnering with disease-specific community organizations can enhance delivery of health education programs. More data from participants are needed to determine how they learned about the chat, why they joined, and how to increase comfort in asking difficult questions in an open forum.

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Utilization Of An Informational Needs Assessment To Develop An Education Program For Patients With Ankylosing Spondylitis (AS) and Related Axial Spondyloarthritis (SpA). Rita Kang[1], Rebecca Morton[1], Christopher Hawke[2], Laura A. Passalent[2], Robert D. Inman[3], Dinny Wallis[2], Joan Blair[2], Alison Lake[1], Heather Sloman[1], Marc Doucet[4], Debra MacGarvie[1] and King Wong[4]. [1]University Health Network-Toronto Western Hospital, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON, [3]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON, [4]University Health Network, Toronto, ON.

Background/Purpose: The effectiveness of education programs for patients with arthritis has been well documented. Despite this, there has been minimal investigation into patient education specifically for ankylosing spondylitis (AS) and axial spondyloarthritis (SpA). The current evidence suggests that only 40% of patients with AS are being referred for education. AS patient education programs have demonstrated positive effects with respect to mobility, function, self efficacy, and depression, however many of these effects are not sustained over the long term. Effective patient education programs are built on carefully executed needs assessments.

The objective of this study was to identify what patients with AS and SpA feel their current informational needs are. In addition, the method of preferred information access was also assessed, i.e. group classes vs. pamphlet etc. This information will be used to develop a comprehensive interprofessional patient education program for patients with AS and SpA attending the Toronto Western Hospital Spondylitis Clinic, Toronto, Ontario, Canada.

Methods: Patients with AS and SpA were emailed a link with an Informational Needs Assessment Survey. This included five multiple choice sections: 1. Demographics, 2. Disease, Diagnosis and Prognosis, 3. Management, 4. Relationships, 5. Emotions and an open ended question at the end of the survey. Descriptive statistics and bivariate analyses were used for data analysis. Qualitative statistical methods were utilized to address the open ended question section.

Results: The response rate was 32.1%, of which 66.1% were male. The sample group was primarily older adults, with 22.3% between the ages of 31 to 40, 23.2% between the ages of 41 to 60. The sample group was well educated, with 50.0% completing college or university and 24.1% completing graduate school. The average number of years since diagnosis was 11 years. Of those who completed the survey, 21 (19.4%) were newly diagnosed (diagnosed between 2010–2012) and 87 (80.6%) were diagnosed earlier than 2010. The Disease, Diagnosis and Prognosis and Management sections were found to be the most important informational needs. In addition: website, on-line audio/ video and E-learning were cited as the most useful ways to receive information in all five sections. Qualitative analysis indicated three major themes concerning patients including medication/pain, fatigue/activity/work and long term prognosis.

Conclusion: Based on the needs assessment, it was determined to develop an e-learning module for this patient population followed by self-management focused face-to-face sessions. It is anticipated this unique education program for patients with AS and SpA will be a successful model using best practice in patient education.

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ACR/ARHP Poster Session B
Epidemiology and Health Services II
Monday, October 28, 2013, 8:30 AM–4:00 PM

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Promise Of Behavioral Economics: Delay Discounting and Physical Activity In Patients With Musculoskeletal Diseases. Elena Losina[1], Yan Dong[1], Stephanie Chen[1], Ran Schwarzkopf[2], Laurel Donnell-Fink[1], David Lerner[1] and Jeffrey N. Katz[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]University of California Irvine Medical Center, Orange, CA.

Background/Purpose: Despite strong evidence that physical activity (PA) is associated with better quality of life, less pain and better functional status in persons with musculoskeletal diseases, uptake of PA in this population is low. PA is also associated with delayed rewards, which people tend to value less than immediately tangible benefits. Behavioral economics studies document that preference for smaller immediate rewards, as compared with larger delayed rewards – defined as delay discounting – is related to obesity, substance abuse and drug dependence. We sought to examine the relationship between delay discounting and uptake of PA in patients with musculoskeletal diseases.

Methods: We conducted a cross-sectional study among patients attending an arthritis clinic in a tertiary medical center. Patients completed a questionnaire in which they were asked to choose between pairs of hypothetical monetary rewards in which one reward (e.g. $100) is offered immediately and an alternative, larger reward is offered after a time delay (e.g. $200 after one year). The amounts of the rewards ranged from $100 to $50,000 and the time frames ranged from no delay to a delay of 10 years. The delay discounting factor (DDF) was derived using a hyperbolic function and divided into quartiles. We assessed engagement in PA with the Yale Physical Activity Scale, using the overall Activity Dimensions Summary Index (ADSI) as well as the Vigorous Activity and Leisurely Walking indices. We conducted a multivariate regression analysis to establish the association between delay discounting and PA scores, adjusted for age, sex, BMI and race.

Results: The analysis is based on 172 study subjects with a mean age of 56 years (SD 14). 69% were female, the mean BMI was 29 (SD 7), and 34% were obese (BMI>30 kg/m^2). The primary reasons for seeing a rheumatologist were back pain (46%), osteoarthritis (29%) and rheumatoid arthritis (23%). The average value of ADSI was 49 (SD 29). Mean values of both vigorous and walking PA indices were 3 (range 0–12). After adjusting for age, sex, obesity and race, a greater extent of delay discounting (greater preference for immediate rewards) was statistically significantly associated with lower overall PA ($p=0.0168$), as well as lower vigorous ($p=0.0032$) and walking ($p=0.0370$) activity indices (less engagement in physical activity). Adjusted least squared means for ADSI ranged from 38 in the highest quartile of DDF to 54 in the lowest quartile of DDF. Corresponding adjusted means for vigorous PA ranged from 3.4 for the lowest quartile of DDF to 1.7 for the highest quartile of DDF. A similar trend was observed for walking.

Conclusion: Delay discounting, characterized by preference for smaller immediate rewards rather than larger delayed rewards, is associated with lower levels of PA among persons with musculoskeletal conditions. These data provide rationale and support for the development of incentives-based interventions, built on the principals of behavioral economics, to increase the perception of immediate rewards associated with PA among persons affected by musculoskeletal diseases. Such interventions may serve as a means of improving engagement in PA in persons affected by these conditions.

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An Analysis Of Healthcare Resource Utilization Among Patients Undergoing Total Knee Arthroplasty In The United Kingdom. Mireia Raluy[1], Michael Schoenfeld[2], Dimitra Lambrelli[1], Meng Wang[1], Ning Wu[3], Shih-Yin Chen[3] and Russel Burge[2]. [1]United BioSource Corporation, London, United Kingdom, [2]Eli Lilly and Company, Indianapolis, IN, [3]United BioSource Corporation, Lexington, MA.

Background/Purpose: Elective total knee arthroplasty (eTkA) is among the most commonly performed surgical procedures. The typical reasons for eTkA are pain and decreased quality of life (QoL) from osteoarthritis. These patients can be at risk of various clinical complications, mobility impairment, muscle weakness, decreased ability to perform daily activities. The purpose of this study was to assess the patient characteristics, healthcare resource use, and costs among eTkA patients in large UK-based general practitioner and hospital databases.

Methods: The Clinical Practice Research Datalink (CPRD) linked to the Hospital Episode Statistics (HES) was used to estimate resource use in adult eTkA patients. Inclusion criteria: patients had no GP visits or inpatient stays with OPCS (4.6) procedure codes suggesting eTkA (W-40, 41, 42) in 7 days to 1 year prior to index date (hospital stay for eTkA) with at least 1 year of computerized data pre- and post-index hospitalization. Elective TKA related medical costs (British Pound Sterling, 2012) were calculated by multiplying resource units by official publicly available costs from the NHS perspective.

Results: This study included 12,737 patients with mean age of 71 years, of whom approximately 26% were within 18–65 years of age. Pre-index, opioids (53%), NSAIDs (48%), and acetaminophen (34%) were the most common medications, followed by oral steroids (24%) and antidepressants (17%). Nearly all patients had osteoarthritis (98.6%). Other common comorbidities were pulmonary disease (22.4%), cancer (14%), renal disease (13.9%), and osteoporosis (6.8%). The Charlson Comorbidity Index (mean score was 1.3. For the index hospitalization, average length of stay was 6.2 days and average costs (standard deviation [SD]) were £5,397 (2,459). After index hospitalization the majority of patients (97.5%) were discharged to their place of residence and 1.6% were discharged to another NHS hospital. During their index hospitalization the majority of patients (98.0%) were treated by trauma and orthopedics; almost one-fourth (23.8%) were treated by general medicine. The mean (SD) total healthcare cost in the pre-index period was £2,507 (4168), driven mainly by inpatient costs that were £1,858. Average outpatient costs were £592 and pre-index pharmacy costs were £57. During the post-index follow up, mean (SD) overall cost was £2068 (6519), with average inpatient costs of £1,526.

Conclusion: This study described resource utilization, pain medications usage, and costs among patients undergoing eTkA in the UK. These estimates may provide a better understanding of the ubiquitous economic burden of this condition.

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The Economic Burden Of Osteoarthritis In Americans: Analysis From a Privately Insured Population. Susanne X. Wang[1], Arijit X. Ganguli[1], Dendy Macaulay[2], William Reichmann[3], Jeroen Medema[1] and Mary A. Cifaldi[1]. [1]AbbVie Inc., North Chicago, IL, [2]Analysis Group, Inc., New York, NY, [3]Analysis Group, Inc., Boston, MA.

Background/Purpose: Osteoarthritis (OA) is the most common form of arthritis and leading cause of working age disabilities. Over 27 million US adults have clinical OA, and different types of burdens exist based on the disease stages and locations. The burden of OA by joint location, age, or comorbidity has not been well studied. The objective of this study was to assess the excess healthcare resource use and costs attributable to OA by joint location, age, and comorbidity in a privately insured population.

Methods: 428,084 OA patients aged 18+ were selected from a US-based employer claims database (1999–2011). Controls were selected from the same database by matching OA patients 1:1 by age, gender, index date, and follow-up, to patients who never had OA in their claims histories. Descriptive analyses were used to compare baseline characteristics and study period medical resource use and costs, inflated to 2011 USD using annual medical CPI data (Bureau of Labor Statistics). Statistical comparisons were made using McNemar's test for categorical variables and the Wilcoxon signed-rank test for continuous variables.

Results: Among all the OA patients studied, 181,379 had a primary claim of knee OA; 48,617 had hip OA; 29,340 had hand OA; and 30,549 had spine OA. The average age of OA patients was 63 years and 59% were female. At baseline, OA patients tended to have a greater comorbidity burden than controls ($P< 0.001$). The occurrence of the 4 most common comorbidities between the OA group and controls were hypertension (45% vs 30%, respectively), cardiovascular disease (16% vs 9%, respectively), diabetes (16% vs 10%, respectively), and depression (8% vs 4%, respectively). OA patients aged 18+ incurred total annual medical costs of $8,644 vs $2,273 in controls ($P< 0.001$). 20% of all OA patients had at least 1 primary joint arthroplasty, 1% had a revision joint arthroplasy, and 2% had arthrodesis. The cost per surgery ranged from $16,000 to $25,000. On average, a hip arthroplasty cost $18,425 and a knee arthroplasty cost $17,433. Annual pharmacy cost was $2,179 for OA patients and $1,096 for controls. OA-related healthcare costs are summarized by joint locations, age, and comorbidity in **Table 1**.

Table 1. OA-Related Mean Cumulative One-Year Costs by Joint Location, Age, and Comorbidity

Subgroup	Total Medical*	Inpatient	Outpatient	Physical or Occupational Therapy	Pharmacy
Overall	$ 8,644	$3,533	$4,921	$265	$2,179
Joint location					
Knee	$ 9,466	$4,178	$5,093	$292	$2,086
Hip	$12,478	$7,473	$4,818	$295	$2,047
Hand	$ 6,705	$1,505	$5,004	$221	$2,256
Age group, y					
18–44	$10,857	$3,398	$7,070	$440	$1,794
45–64	$12,799	$5,400	$7,144	$395	$2,258
65+[†]	$ 3,510	$1,429	$2,002	$ 84	$2,156
Comorbidity					
Hypertension	$ 8,917	$3,855	$4,857	$232	$2,519
CVD	$10,844	$4,993	$5,575	$157	$3,150
Diabetes	$10,815	$4,709	$5,859	$242	$3,358

CVD=cardiovascular disease; OA=osteoarthritis.
* Total medical costs are equal to the sum of inpatient, outpatient, and emergency room costs.
[†] Costs for 65+ may be underestimated because payments observed here are supplements to Medicare.

Conclusion: Patients with OA incur greater medical and pharmacy costs than those without OA. The burden of OA varies substantially by joint location. Surgical procedures are the most significant cost among all categories, and therefore is also the main driver of the total cost. In contrast, pharmacy costs are rather small due to no disease-modifying OA drug (DMOAD) available. Hand OA had lower cost than knee and hip due to lack of DMOAD and effective surgery. In summary, OA presents a great disease and economic burden. The current treatment options are limited to generic symptom-modifying drugs and late-stage surgical management of the disease, but the latter is only available for certain joints.

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Quality Of Life, Productivity Impairment, Disease Severity and Health Care Costs In Relation To Functional Impairment In Psoriatic Arthritis Patients In The Czech Republic. Jiri Stolfa[1], Liliana Sedova[1], David Suchy[2], Jiri Klimes[3], Milan Vocelka[3] and Tomas Dolezal[3]. [1]Charles University Prague, Prague, Czech Republic, [2]University hospital Plzen, Plzen, Czech Republic, [3]Charles University, Prague, Czech Republic.

Background/Purpose: Our aim was to describe the QoL, productivity impairment, clinical indicators and health care costs in relationship to functional status described by Health assessment questionnaire (HAQ) in Psoriatic arthritis patients. This relationship is highly important to justify the investment into health care.

Methods: We have organized a prospective multicentre non-interventional observational study with Psoriatic arthritis (PsA) patients in 4 specialized centres for treatment of rheumatic diseases in the Czech Republic. There is 3 years of follow-up planned with 6 months period between each time point observation. The data presented here comes from the first visit, where demographics, clinical, QoL data and productivity were directly collected from patients. Health care consumption was assessed retrospectively reviewing individual patient's medical record (with 6 or 12 months recall period from the first visit). Clinical data were described by DAPsA, QoL measured by EuroQol questionnaire (EQ-5D), work impairment by Work Productivity and Activity Impairment (WPAI) in relationship to HAQ categories. Validated Czech versions of all questionnaires were used. Patients are stratified according to their HAQ in 6 categories, i.e. 0–0.5>, 0.5–1.0>, 1.0–1.5>, 1.5–2.0>, 2.0–2.5>, 2.5–3.0>. Within health care consumed, we focus on medication (classical DMARDs, corticosteroids and biological drugs), out-patient & in-patient care, complement and instrumental examination and out-of pocket money. Health care expenditures are annualized and presented as an average costs per patient. Patients are analysed as the whole cohort and specifically by the presence of biologic treatment.

Results: We have already included 164 patients with PsA, 63 on biological drugs, mean patient age was 57.3 years, mean time from diagnoses of PsA was 25.9 years, 52% were female. With higher

functional impairment, described by HAQ, there is an increase in age, time from diagnoses, percentage of work impairment and also decrease in work-active patients. There is also deterioration in clinical impairment (DAPsA) and QoL observed with worse functional status. There is almost the same height of total costs in each HAQ category in the cohort of patients treated with biologics, as these drugs are the biggest costs driver. However, there is a cost increase in the category with highest HAQ in the cohort not treated with biologics. See results table, where all values are presented as mean values, n.a.-not applicable.

Patients on biologic drugs

HAQ category	HAQ	No.	Age (Years)	Time from Dx(Years)	% women	Costs (EUR)	% of work-active	% WPAI	DAPsA	EQ-5D
0–0.5>	0.2	28	48.0	22.0	39.3%	11,481	82.1%	18.0%	7.5	0.830
0.5–1.0>	0.8	12	51.8	25.5	50.0%	11,604	58.3%	24.9%	8.5	0.733
1.0–1.5>	1.2	10	51.3	25.2	60.0%	12,375	30.0%	45.3%	13.7	0.607
1.5–2.0>	1.8	10	62.7	29.3	40.0%	10,303	10.0%	50.0%	21.2	0.510
2.0–2.5>	2.4	3	59.7	34.3	66.7%	13,181	33.3%	0.0%	32.5	0.375
2.5–3.0>	n.a.	0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Mean/total	**0.83**	**63**	**52.1**	**24.9**	**46.0%**	**11,482**	**55.6%**	**27.9%**	**12.0**	**0.704**

Patients without biologic drugs

HAQ category	HAQ	No.	Age	Time from Dx(Years)	% women	Costs (EUR)	% of work-active	WPAI %	DAPsA	EQ-5D
0–0.5>	0.1	51	56.6	24.9	43.1%	301	66.7%	14.0%	9.1	0.788
0.5–1.0>	0.9	22	63.0	26.8	68.2%	481	36.4%	26.3%	13.3	0.649
1.0–1.5>	1.3	20	62.7	28.7	55.0%	542	10.0%	40.0%	18.0	0.527
1.5–2.0>	n.a.	0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
2.0–2.5>	2.3	3	73.7	41.3	100.0%	411	0.0%	n.a.	24.5	0.381
2.5–3.0>	2.8	5	72.2	23.6	100.0%	1,218	0.0%	n.a.	24.8	0.216
Mean/total	**0.73**	**101**	**60.5**	**26.5**	**55.4%**	**400**	**43.6%**	**20.7%**	**13.0**	**0.665**

Whole cohort of patients

HAQ category	HAQ	No.	Age	Time from Dx(Years)	% women	Costs (EUR)	% of work-active	WPAI %	DAPsA	EQ-5D
0–0.5>	0.2	79	53.6	23.8	41.8%	4,264	72.2%	15.5%	8.5	0.803
0.5–1.0>	0.9	34	59.1	26.3	61.8%	4,407	44.1%	25.7%	11.6	0.679
1.0–1.5>	1.3	30	58.9	27.5	56.7%	4,486	16.7%	43.2%	16.6	0.554
1.5–2.0>	1.8	10	62.7	29.3	40.0%	10,302	10.0%	50.0%	21.2	0.510
2.0–2.5>	2.4	6	66.7	37.8	83.3%	6,796	16.7%	0.0%	28.5	0.378
2.5–3.0>	2.8	5	72.2	23.6	100.0%	1,218	0.0%	n.a.	24.8	0.216
Mean/total	**0.80**	**164**	**57.3**	**25.9**	**51.8%**	**4,657**	**48.2%**	**23.7%**	**12.6**	**0.680**

Conclusion: Patients with worse functional impairment (based on HAQ) revealed impairment of their QoL, work productivity and revealed also worse clinical outcomes. We present total health care costs according to the functional impairment. The findings attributed to higher HAQ impairment (i.e. HAQ $>$ 2.0) must be interpreted with caution because of lower number of patients in these categories.

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Predictors and Modeling of Costs in Rheumatoid Arthritis. Jonas Eriksson[1], Thomas Frisell[2], Johan Askling[3] and Martin Neovius[1]. [1]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Karolinska Institutet, Stockholm, Sweden, [3]Karolinska University Hospital, Stockholm, Sweden.

Background/Purpose: Costs in RA are substantial with 2–3 times higher mean annual costs than in the general population, but with a skewed cost distribution.[1] As a first step in identifying potential high cost patients, our aim was to identify predictors of costs, and assess the accuracy of prediction models in prevalent and incident RA patients using data from nationwide Swedish registers.

Methods: A prevalent cohort of RA patients ≥18y on Jan 1, 2010, was identified from the Swedish National Patient Register (requiring ≥2 visits listing RA) and the Swedish Rheumatology Quality Register, and followed until Dec 31, 2010. From the same registers, patients with the 1st visit listing RA in 2009, with a 2nd visit within one year, were identified to the incident cohort, and were followed for 1 year. Costs for inpatient care, nonprimary outpatient care, prescription drugs, and work loss, as well as explanatory variables, were retrieved from national registers. A linear regression model was used in a training set including 90% of the prevalent patients, and validated in the remaining 10%. The corresponding proportions in the smaller incident cohort were 50%/50%.

Results: 21,682 prevalent RA patients 18–64y were identified. The model included sex, age, time since register identification with RA, rheumatoid factor, hospital admission days and days of work loss the previous year, and any hospital admission/outpatient visit for chronic obstructive pulmonary disease, ischemic heart disease, and diabetes mellitus the previous 3 years. Predictions from the linear regression model performed well at the middle and higher end of the cost distribution, but poor in the lower cost segments (R^2=0.79; Figure).

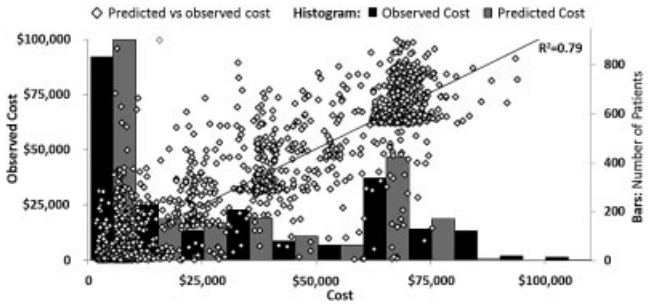

Figure. Scatter plot and histogram of predicted vs observed costs in working age prevalent RA (n=2168)

For the working age incident cohort (n=1378), the same variables were included plus annual income. Also this model performed better in the middle and higher cost segments than in the lower cost end of the distribution (R^2=0.59).

In both models work loss days was the strongest predictor, where 1 more day of work loss the previous year was associated with a $165 (95%CI 163–166) higher annual cost in prevalent patients and $145 (95%CI 133–157) higher in incident patients. For patients ≥65y, a linear regression model including available variables from national data sources resulted in poor cost prediction (R^2<0.15).

Conclusion: Reasonable prediction of annual costs in working age prevalent and incident RA patients was possible, while a satisfactory prediction model in older patients may need additional explanatory variables.

Reference:

1. Eriksson J, et al. EULAR 2012; Abstract no: OP0121.

Disclosure: J. Eriksson, None; **T. Frisell**, None; **J. Askling**, Pfizer Inc, 2; **M. Neovius**, Pfizer, 6.

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Does Biologic Treatment For Rheumatoid Arthritis Offset Health Care Costs In Patients With Rheumatoid Arthritis? An Instrumental Variable Approach Using Administrative Data. Nick Bansback[1], Eric Fu[2], Daphne Guh[2], Huiying Sun[2], Wei Zhang[2], Diane Lacaille[3] and Aslam H. Anis[1]. [1]University of British Columbia, Vancouver, BC, [2]Centre for Health Evaluation and Outcome Sciences, Vancouver, BC, [3]Arthritis Research Centre of Canada, University of British Columbia, Richmond, BC.

Background/Purpose: Expenditure on biologic therapies for rheumatoid arthritis (RA) accounts for the highest pharmaceutical spending in many western healthcare systems. Given their clinical benefit with marked reduction in symptoms and prevention of joint damage, biologics are expected to lead to reduced treatment related costs, such as joint surgeries or physician visits. Despite over a decade of routine use, there is currently no direct evidence supporting an association between biologic use and subsequent reductions in healthcare utilization. The objective of this study was to estimate the impact of biologic treatment compared to DMARDs on other healthcare utilization using instrumental variable (IV) techniques to control for confounding by indication.

Methods: From a population-based cohort of all patients with a rheumatologist diagnosis of RA identified from administrative data, we selected patients that mimick eligibility for reimbursement for biologics between 2003–2007 based on DMARD use history and having 3-year follow-up under the care of rheumatologists since eligibility. Patients receiving biologics in the first follow-up year form the treatment group whereas others who never received biologics throughout the follow-up form the control group. The data contains patient-level information on hospitalizations, physician visits (including investigations and procedures), and prescription medications. Since disease severity is known to be associated with treatment received and healthcare use, but is not directly captured in administrative data, conventional risk-adjustment

approach might not adequately adjust for this confounding by indication. We use an IV based on the prescribing rheumatologist's preference for biologic use at the time of treatment assignment to address the issue of unobserved confounder.

Results: The final analysis included 314 and 486 patients in the biologic and DMARD groups, respectively. As expected, conventional multivariable regression adjusting for observed confounders, but not necessarily for confounding by indication, did not attribute biologic use with cost offsets. The IV analysis results suggest that RA-related costs in the biologic group, compared to the DMARD group, in the 2- and 3-year follow up periods, was 22.5% (95% CI: −21.0%–90.0%) and 48.3% (2.0%–115.6%) more for physician visits but 45.9% (−63.7%–82.1%) and 32.7% (−97.4%–77.0%) less for medications excluding biologics or DMARD, whereas the odds ratios of hospitalization were 2.308 (0.44–12.00) and 3.64 (0.71–18.68), respectively. A similar pattern was observed for total resource utilization.

Conclusion: While RCTs are the gold standard for determining causal relationships, such studies would be infeasible to investigate this important question. Through the use of established econometric methods and a population-based administrative dataset, this study finds no signal that biologic use offsets health care costs in the short-term. Limitations include large confidence intervals common in IV studies, and follow-up of 3 years, which may be too short to observe cost savings from joint replacement prevention.

Disclosure: N. Bansback, None; **E. Fu**, None; **D. Guh**, None; **H. Sun**, None; **W. Zhang**, None; **D. Lacaille**, None; **A. H. Anis**, None.

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Adequacy Of Drug Coverage and Cost-Sharing For Medicare Beneficiaries With Rheumatoid Arthritis. Jinoos Yazdany[1], R. Adams Dudley[2], Randi Chen[3] and Chien-Wen Tseng[4]. [1]University of California, San Francisco, San Francisco, CA, [2]University of California San Francisco Philip R. Lee Institute for Health Policy Studies, San Francisco, CA, [3]Pacific Health Research and Education Institute, Honolulu, HI, [4]University of Hawaii and Pacific Health Research and Education Institute, Honolulu, HI.

Background/Purpose: Biologic and non-biologic disease-modifying anti-rheumatic drugs (DMARDs) significantly reduce pain, disability and mortality in rheumatoid arthritis (RA). We evaluated how well RA drugs are covered by Medicare Part D plans, and what copays are typically required.

Methods: We conducted a cross-sectional analysis of all Medicare Part D stand-alone plans' and Medicare Advantage plans' formularies (n=2,737) in 50 states and Washington D.C. using the January 2013 Centers for Medicare and Medicaid Services (CMS) Prescription Drug Plan Formulary and Pharmacy Network Files. Special Needs Plans (n=643) were excluded since they target subgroups of beneficiaries (e.g. institutionalized, chronic/disabling conditions, dually eligible for Medicaid) and may have specialized formularies. We used the default maintenance dose given by Epocrates©. To calculate the national average of the percentage of plans covering a drug and account for the fact that plans cover varying geographic regions, we first calculated the percentage of plans covering a drug in each county, averaged these percentages across all counties in the state, and then averaged across all 50 states and Washington D.C. We also examined prior authorization requirements and calculated the mean copays for each drug across all states.

Results: All plans covered at least 1 biologic DMARD, but 91% of formularies required providers to first obtain prior authorization (PA) for covered drugs. Across biologic DMARDs, coverage (with PA) ranged from 29% (anakinra) to 100% (adalimumab, etanercept, infliximab, rituximab; **see Table)**. In addition, the vast majority of plans (87%) charged a percentage co-insurance, requiring patients to pay on average 30% of drug costs. Thus, mean copays for biological DMARDs ranged from $255 to $650 per month. In contrast, for five non-biologic DMARDs (methotrexate, leflunomide, sulfasalazine, minocycline, hydroxychloroquine), nearly all plans provided coverage without requiring a PA. For these non-biologic DMARDs, approximately 90% of plans charged a fixed dollar copayment (range $5 to $11 per month); **see Table**.

Table Coverage for Rheumatoid Arthritis Drugs in U.S. Medicare Part D Plans.

Drug	Plans covering drug *(%)*	Plans covering drug without prior authorization *(%)*	Plans Charging Percent Co-insurance *(%)*	Mean Co-insurance *(%)*	Average Copay *Mean (SD) ($)*
Biologic					
Abatacept	54	4	100	30.1	601 (22)
Adalimumab	100	7	100	30.0	583 (12)
Anakinra	40	4	100	29.9	517 (19)
Certolizumab	59	1	100	29.6	650 (16)
Etanercept	100	7	100	30.0	547 (11)
Golimumab	42	1	100	29.6	580 (17)
Infliximab	100	7	100	30.0	255 (5)
Rituximab	100	8	87	29.5	611 (25)
Tocilizumab	40	1	99	29.7	335 (14)
At least 1 biologic DMARD	100	9	87	30.3	275*
Non-biologic					
Azathioprine	100	34	10	18.1	7 (1)
Cuprimine	60	60	59	30.6	83 (6)
Cyclophosphamide	94	2	20	27.4	32 (3)
Cyclosporine	100	12	22	25.1	34 (2)
Hydroxychloroquine	100	100	10	18.1	5 (1)
Leflunomide	100	100	13	19.3	11 (1)
Methotrexate	100	85	13	19.8	5 (1)
Minocycline	100	94	10	18.1	7 (1)
Sulfasalazine	100	100	10	18.1	5 (1)
At least 1 non-biologic DMARD	100	100	11	18.2	4*

*mean copay of least expensive drug covered.

Conclusion: Although most health plans serving Medicare beneficiaries cover at least one biologic DMARD, nearly all require a PA and charge a percent coinsurance. Medicare beneficiaries with RA who require biologic therapies can expect very high mean copays regardless of which Part D plan they choose, likely posing a significant financial barrier for many patients.

Disclosure: J. Yazdany, None; **R. A. Dudley**, None; **R. Chen**, None; **C. W. Tseng**, None.

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Cost Consideration For Biologics For Patients With Rheumatoid Arthritis In a Pharmacy Benefit Management Setting. Ning Wu[1], Yuan-Chi Lee[1], Neel Shah[2] and David J. Harrison[2]. [1]United BioSource Corporation, Lexington, MA, [2]Amgen Inc., Thousand Oaks, CA.

Background/Purpose: Of the seven biologics FDA-approved for the treatment of moderate to severe rheumatoid arthritis (RA) as of August 2011, etanercept, adalimumab, certolizumab, and golimumab were subcutaneously (SC) administered; abatacept, infliximab, and rituximab were intravenous (IV) infusions. Utilization of these agents is often controlled by Pharmacy Benefits Managers (PBMs) using various methods which can affect dosing in clinical practice, gaps in therapy, treatment persistence and switching, and in turn the costs. This study describes the annual cost of biologics per treated patient with RA using administrative claims from a PBM.

Methods: The Medco Database was used to identify adults (18–63 years) with a claim for etanercept, adalimumab, infliximab, abatacept, rituximab, golimumab, or certolizumab between July 1, 2008 and August 31, 2011 preceded by ≥180-days of enrollment. The first claim for biologics was used to define the index agent and date. Patients had to be continuously enrolled for ≥360 days post-index and have a diagnosis of RA between 180 days before and 30 days after the index date. Patients with other conditions for which some of these agents are indicated (e.g. psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, non-Hodgkin's lymphoma, or chronic lymphocytic lymphoma) were excluded. Annual cost per treated patient equaled total dose for the index biologic and all other biologics taken in the post-index period multiplied by wholesale acquisition cost (WAC) as of June 1, 2013, plus the costs associated with administrations, calculated as number of infusions multiplied by the 2013 Medicare Physician Fee Schedule costs.

Results: In the 4,736 patients with RA in this study, etanercept (40.3%), adalimumab (27.9%), and infliximab (19.0%) were the most frequently prescribed biologics followed by abatacept (7.1%), rituximab (3.7%), golimumab (1.2%), and certolizumab (0.7%). Mean age was 51.2 years (SD 9.1) and 78.5% were female. Among the three most commonly prescribed biologics, the annual cost per treated patient was lowest for patients on etanercept ($21,706), followed by infliximab ($22,030) and

adalimumab ($23,150). Among the other agents, cost per treated patient was highest for certolizumab ($21,630), followed by golimumab ($20,526), abatacept ($17,386), and rituximab ($16,571).

Conclusion: Of the three most frequently prescribed biologics for RA, the annual cost per treated patient was the lowest for etanercept. Cost may be an additional consideration when choosing biologic treatments for RA.

Disclosure: N. Wu, Amgen Inc, 9; **Y. C. Lee**, Amgen, 9; **N. Shah**, Amgen Inc., 1, Amgen Inc, 3; **D. J. Harrison**, Amgen Inc., 1, Amgen Inc., 3.

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Comparison Of The Cost-Effectiveness Of The Treatment Strategies With and Without Biological Response Modifiers For Patients With Recently Diagnosed Rheumatoid Arthritis Following A Clinical Guideline For Treatment Selection. An Tran-Duy[1], Annelies Boonen[1], Wietske Kievit[2], Piet L.C.M. van Riel[2], Mart A.F.J. van de Laar[3] and Johan L. Severens[4]. [1]Maastricht University Medical Center, Maastricht, Netherlands, [2]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [3]Medisch Spectrum Twente & University of Twente, Enschede, Netherlands, [4]Erasmus University Rotterdam, Rotterdam, Netherlands.

Background/Purpose: In clinical practice, management of rheumatoid arthritis (RA) is characterized by a sequence of drugs which is determined based on patient characteristics, notably disease activity and treatment history. However, existing cost-effectiveness models do not reflect this clinical process of treatment decisions. In the last decade, biologic response modifiers (BRMs) became available in the treatment of RA. While these drugs show large efficacy in trials, they are expensive. This study aimed at quantifying the cost-effectiveness of the treatment strategy including BRMs (Strategy B) compared with the treatment strategy without BRMs (Strategy A) following a formal guideline for treatment of recently diagnosed RA.

Methods: A discrete event simulation model was developed to simulate life-time health utility and costs of individual patients using a societal perspective. Treatment effect on DAS28 and time to events were estimated using Dutch observational studies (DREAM and Nijmegen Inception cohorts). Long-term progression of HAQ was quantified using a linear mixed model. Health care and sick leave costs were estimated using two-part models. Health utilities (EQ-5D) were predicted using a mixture model with adjusted limited dependent variable. Treatment decisions were based on the recommendations of the Dutch Society for Rheumatology for treatment of RA. A number of 10,000 theoretical patients were tracked individually until death. For uncertainty analysis of the model outcomes, Monte Carlo simulations were performed with 1,000 sets of parameters sampled from the probability distributions. SAS, R and Delphi were used for data analysis and model development.

Results: The recommended treatment selection based on DAS28 and treatment history was well simulated. Incremental cost per quality-adjusted life year gained (ICER) in Strategy B compared with Strategy A was €124,095. At willingness-to-pay thresholds above €119,167 per QALY, Strategy B dominated Strategy A in terms of cost-effectiveness but the probability that the Strategy B is cost-effective never exceeded 0.87.

Conclusion: Incorporation of the treatment decisions based on a clinical guideline in a cost-effectiveness model for RA is feasible, which makes the model more realistic. Our model can be used as a tool to assess the effects of changes in clinical practice of RA management on disease progression of patients and on the corresponding incremental cost-effectiveness.

Disclosure: A. Tran-Duy, Pfizer B.V., The Netherlands, 2; **A. Boonen**, Pfizer B.V., The Netherlands, 5; **W. Kievit**, None; **P. L. C. M. van Riel**, None; **M. A. F. J. van de Laar**, None; **J. L. Severens**, Pfizer B.V., The Netherlands, 2.

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Long-Term Effectiveness and Cost Per Effectively Treated Patient With Biologics Used In Rheumatoid Arthritis. Vernon F. Schabert[1], Jason Yeaw[2], Jonathan Korn[2], Caroleen Quach[3], David J. Harrison[4], Huifeng Yun[5], George Joseph[6], David H. Collier[4] and Jeffrey R. Curtis[7]. [1]IMS Health, Alexandria, VA, [2]IMS Consulting Group, Alexandria, VA, [3]University of North Carolina at Chapel Hill, Gillings School of Public Health, Chapel Hill, NC, [4]Amgen Inc., Thousand Oaks, CA, [5]University of Alabama at Birmingham, Birmingham, AL, [6]Former Amgen Employee, Thousand Oaks, CA, [7]University of Alabama at Birmingham, School of Public Health, Birmingham, AL.

Background/Purpose: Previous work compared one-year cost per effectively treated patient with biologics for rheumatoid arthritis (RA) using a published, claims-based algorithm.[1] Longer term comparisons are important since RA requires lifetime treatment. Using the same algorithm, treatment effectiveness (as a proxy for low disease activity or remission) and cost per effectively treated patient in the second year of biologic treatment for patients who met effectiveness criteria at the end of the first year was estimated.

Methods: Data were obtained from the IMS PharMetrics Plus™ database, comprising adjudicated medical and pharmaceutical claims for 150 million enrollees (40 million annually). The first-year cohort included patients with RA aged 18–63, initiating biologic treatment with etanercept, adalimumab, infliximab, or abatacept between Jan 1, 2007 and Dec 31, 2010, without diagnoses for other approved indications for these biologics or any biologic use for RA in the 6 months before initiation. Patients had to be continuously enrolled for 6 months before and 12 months after initiation; the subset of patients whose initial biologic was classified as "effective" by the algorithm and who were enrolled for a second year were included in this analysis. The algorithm defined lack of effectiveness as: medication possession ratio (MPR) $<80\%$ (or fewer infusions than specified on US label), increase in biologic dose or frequency, switching biologics, adding new non-biologic Disease Modifying Anti-Rheumatic Drugs, initiation or increase of glucocorticoid dose, or >1 parenteral or intra-articular injection. Cost was based on patient and health plan paid amounts for biologic drugs and drug administration from the claims.

Results: Of 16,011 patients in the initial cohort, 1,999 met eligibility criteria for the second-year effectiveness analysis: etanercept (n=994), adalimumab (n=620), infliximab (n=229), and abatacept (n=156). Mean age was 50.8 (SD 8.9), 71.8% were female. In the second year, 44.9% of abatacept, 47.4% of adalimumab, 47.2% of etanercept, and 45.4% of infliximab patients met criteria for effectiveness. Second-year cost per effectively treated patient as defined in the algorithm was $48,176 for abatacept, $37,082 for adalimumab, $37,306 for etanercept, and $36,954 for infliximab. From the prior study, comparable results were (31.0% and $50,141 etanercept, 28.6% and $56,941 adalimumab, 20.2% and $114,089 infliximab, 28.6% and $73,516 abatacept)[1].

Conclusion: Despite similar effectiveness in the second year, cost per effectively treated patient was lower for TNF blockers (etanercept, adalimumab, and infliximab) than for abatacept.

Disclosure: V. F. Schabert, None; **J. Yeaw**, IMS Health, 5; **J. Korn**, None; **C. Quach**, Amgen, Inc., 3; **D. J. Harrison**, Amgen Inc., 1, Amgen Inc., 3; **H. Yun**, None; **G. Joseph**, Amgen Inc, 1, Pfizer Inc, 1, Sanofi-Aventis Pharmaceutical, 3; **D. H. Collier**, Amgen Inc., 1, Amgen Inc., 3; **J. R. Curtis**, Roche/Genetech, 2, UCB, 2, Janssen Pharmaceutica Product, L.P., 2, Corrona, 2, Amgen, 2, Pfizer Inc, 2, BMS, 2, Crescendo, 2, AbbVie, 2, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

1002 WITHDRAWN

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Measuring Economic Value of Morning Stiffness; Consistency Over 1 Year. Risto Tuominen. University of Turku, Turku, Finland.

Background/Purpose: Economic evaluation of health care activities requires often measuring clinical symptoms and their changes also in monetary terms. Patients with rheumatoid arthritis (RA) may experience morning stiffness (MS), which varies over time, reflecting both short-term fluctuation in symptoms and long-term disease progression. A method that has been successfully applied to measure symptoms of RA is contingent valuation, and particularly its form called Willingness-To-Pay approach (WTP). In this method, patients are asked the maximum amount they would be willing to pay in order to reach a certain health status. In earlier studies patients with more severe symptoms have been willing to pay higher amounts than those with less symptoms. However, it is not known whether the fluctuation in symptoms is reflected in the amounts produced by WTP method. In order to serve as a useful method for monetary valuation of symptoms, WTP approach should produce values which reflect also the changes in symptoms.

The aim of this study was to determine the within-patient variation in duration of MS over 1 year, and the corresponding monetary equivalents assigned to its changes using WTP methodology.

Methods: The sample (n=100) comprised patients with RA from Turku University Hospital, Finland. All patients were interviewed twice by a trained interviewer using the same interview, 1 year apart. Patients estimated duration of MS in minutes. They were also asked to estimate how much they would be willing to pay on a daily basis if MS could be reduced by 25%, 50%, 75% and 100%. Weighted average of the monetary assessment for MS reduction was computed. Statistical evaluation was based on paired samples t-test, one way analysis of variance and linear regression model.

Results: After 1 year, there was a highly significant reduction in average MS duration from 44.7 minutes to 41.4 minutes ($p<0.001$); duration was reduced in 34.7% of patients, unchanged in 34.7% and prolonged in 30.6%. Weighted group average WTP for MS duration reduction was € 13.75 in the first interview and € 14.26 a year later ($p<0.001$). Changes in MS duration were reflected in within-patient WTP estimates. Among patients with reduced MS, weighted average WTP was reduced by € 18.46, in patients with unchanged duration, weighted average WTP increased by € 4.89, and in patients with increased duration of MS, weighted average WTP increased by € 13.46 ($p<0.05$). This pattern was statistically significant ($p<0.05$) for hypothetical reduction in MS duration of 50%, 75% and 100%, but not for 25% reduction in MS duration. Changes in duration of MS explained significantly ($p<0.05$) the variation in change of WTP for reduction, also when level of income was simultaneously controlled ($R^2=0.325$).

Conclusion: Duration of MS varied considerably over the 1 year follow-up. WTP estimates and their changes corresponded closely to changes in MS duration. WTP method can be considered a valid method to evaluate the impact of morning stiffness in patients in monetary terms.

Disclosure: R. Tuominen, None;

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Cost-Effectiveness Analysis Of Two Rituximab Based Therapeutic Regimens For Longstanding Rheumatoid Arthritis. Luca Quartuccio[1], Rossella Di Bidino[2], Matteo Ruggeri[3], Domenico Biasi[4], Franco Schiavon[5], Leonardo Punzi[6], Silvano Adami[4], Americo Cicchetti[3] and Salvatore De Vita[1]. [1]Rheumatology Clinic, DSMB, University of Udine, Udine, Italy, [2]HTA Unit, "A. Gemelli" Teaching Hospital, Rome, Italy, [3]Faculty of Economics, Catholic University of the Sacred Heart, Rome, Italy, [4]Rheumatology Clinic, University of Verona, Verona, Italy, [5]Rheumatology Clinic, University of Padova, Padova, Italy, [6]University of Padova, Rheumatology Unit, Padova, Italy.

Background/Purpose: Socioeconomic costs of rheumatoid arthritis (RA) are very high. Biologic therapies with different biologic targets are now available for moderate to severe RA, and these drugs increased the overall direct costs of RA. Thus, therapeutic strategies to improve the cost-effectiveness of the biologics are welcome. Rituximab (RTX) is generally administered intravenously 1 g × 2 (day 1- day 15, regimen 1) and the retreatment is scheduled at the time of clinical relapse. A more intensive regimen has been proposed: 1 g × 2 (day 1- day 15, regimen 2) every six months, following the "treat to target" approach (1). The aim of this study is to compare the cost-effectiveness of two regimens of RTX administration in longstanding RA patients.

Methods: An observational retrospective study was conducted in three Centers. One hundred and two patients suffering from moderate to severe longstanding RA (disease duration more than two years) were enrolled. 47 followed regimen 1, while 55 patients were treated with regimen 2. All the patients were followed for at least one year. A cost effectiveness analysis (CEA) based on a Markov Model were conducted on the basis of sample data collected and scientific literature. Markov Model represented natural evolution of RA and was composed by four states: Treatment, Response, Relapse, and Death. An hypothetical cohort of 300.000 populated the model and was followed till death adopting a societal perspective. Pharmaceutical, direct health, and indirect costs were estimated as well as health quality. Univariate and probabilistic sensitivity analysis (PSA) were done. CEA was conducted for the whole sample of patients and for a subgroup of them (those with rheumatoid factor and/or anti-cyclic citrullinated peptide).

Results: Results for the overall sample show at 10–20–30 year that regimen 1 is less costly and associated with an higher QoL compared to regimen 2. PSA at 10 years estimated a probability of 94.20% for regimen 1 to be cost-effective given a willingness to pay of 30000 € /QALY. The subanalysis in seropositive patients showed that regimen 1 is more cost-effectiveness than regimen 2. PSA at 10 years estimated a probability of 90% for regimen 1 to be cost-effective given a willingness to pay of 30000 € /QALY. Significant differences in the baseline HAQ and DAS 28 scores were estimated ($p<0.0001$, and $p=0.002$, respectively, Mann Whitney U test), although both groups of patients showed a median baseline high disease activity and disability [regimen 1 vs regimen 2: 1.5 (0.5–2.75) vs. 2.7 (0.375–3) for HAQ, and 5.9 (3.5–8.4) vs. 5.0 (2.9–7.0) for DAS28]. At 12 month, the difference in the HAQ scores persisted ($p=0.0004$), while there was no difference in the DAS28 ($p=0.86$).

Conclusion: In longstanding RA, a less intensive regimen of RTX with retreatment at clinical relapse seems to be at least equivalent of the more intensive regimen with retreatment every six months. RTX regimen choice may be oriented by the clinical judgment on the balance between the disease activity and the level of disability, and the evaluation of the irreversible/reversible component ratio in the HAQ score. A similar evaluation in patients with early disease is required.

1. Emery P, et al. Rheumatology (Oxford). 2011;50(12):2223–32.

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Generalization and Extrapolation Of Treatment Effects From Clinical Studies In Rheumatoid Arthritis. Sandhya C. Nair[1], Wietske Kievit[2], R W Janse[3], Johannes WJ Bijlsma[4], Floris Lafeber[5], Jaap Fransen[2] and P.M.J. Welsing[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [3]Medical student, Utrecht, Netherlands, [4]University Medical Centre Utrecht, Utrecht, Netherlands, [5]UMC Utrecht, Utrecht, Netherlands.

Background/Purpose: Randomized clinical trials (RCTs) are accepted as the 'gold standard' to evaluate the efficacy/effectiveness of treatment. However, generalizing results from RCTs to daily practice poses a challenge with treatment effectiveness often being different. Pragmatic clinical trials have been posed as a solution. The objective was to identify whether pragmatic clinical trials are indeed generalizable to clinical practice and investigate how efficacy estimates from RCTs can be translated into effectiveness estimates for daily practice populations.

Methods: Data from pragmatic clinical trials of the Utrecht Rheumatoid Arthritis Study Cohort and the observational Nijmegen inception cohort study with comparable inclusion criteria (RA < 1 year disease duration and no prior DMARD use) were used. Patient characteristics were compared between the studies. The treatment effectiveness of MTX and Hydroxychloroquine both compared to the so-called Pyramid approach were compared between the pragmatic trials and observational data using a modified comprehensive cohort design analysis. Change from baseline in DAS28 and HAQ and EULAR good- and moderate response both at 6 months were the outcomes studied in the regression analyses. To study extrapolation of the treatment effect from Phase II/III clinical trials to clinical practice, published results from recent clinical trials evaluating biological treatment compared to control therapy were used. A metaregression analysis was performed to study the influence of population and treatment characteristics on ACR50% response at 6 months. Relative risk (RR) and risk difference (RD) were studied as outcome.

Results: Age, higher disease activity and response to treatment were higher in patients included in the pragmatic trial as compared to daily practice and rheumatoid factor positive patients were lower. DAS28 and HAQ generally improved more in trial patients as compared to daily practice. Using EULAR response as outcome, the relative effect of treatment (relative risk) was not found to be different. For extrapolating RCT results, glucocorticoid use, disease duration and co treatment with DMARD increased the RR in the study. Higher values of baseline DAS28 and HAQ decreased RD and the use of corticosteroids increased RD.

Conclusion: Pragmatic clinical trials might be directly generalizable only regarding relative treatment effects. In extrapolating RCT results to daily practice, population characteristics associated with disease activity, disease duration and treatment history or co-treatment need to be taken into account, regardless whether the treatment effect is expressed absolute or relative. Extrapolations of RCT results could also considerably impact costs-effectiveness results.

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One-Year Change Of Employment and Work Productivity In Patients With Systemic Lupus Erythematosus From The Southeastern United States. Deepak Sree[1], S. Sam Lim[1], Hong Kan[2], Priti M. Jhingran[2], Charles T. Molta[3], Gaobin Bao[1] and Cristina Drenkard[1]. [1]Emory University, Atlanta, GA, [2]GlaxoSmithKline, Research Triangle Park, NC, [3]GlaxoSmithKline, King of Prussia, PA.

Background/Purpose: Different factors influence employment and work productivity in systemic lupus erythematosus (SLE) patients, including disease activity, cognitive impairment, comorbidities, education, and psychosocial factors. Previous studies have mostly been done in predominantly White SLE populations. This study assesses work loss and factors that impact change in work productivity over a 1-year period in patients with SLE who are primarily Black.

Methods: GOAL is a prospective cohort of SLE patients who provide patient-reported measures at least annually. It is derived primarily from the Georgia Lupus Registry, a population-based registry established in metropolitan Atlanta, Georgia. Data were collected in 2 Waves (2011–12 and 2012–13). We assessed demographic and disease factors associated with work loss over 1 year. Change in work productivity was measured in patients using the Work Productivity and Activity Impairment (WPAI) tool. Three measures were used to examine the change in WPAI: % of work time missed, % of overall work productivity impairment, and % of impairment to perform daily activities. Demographic and disease factors assessed at Wave 1 were evaluated as potential predictors of 1-year change in WPAI outcomes.

Results: Of 511 SLE patients employed at disease diagnosis, 252 aged 18–64 remained employed at the time of the Wave 1 survey and 225 completed the WPAI questionnaire. One-hundred-seventy-three patients who were employed at Wave 1 responded to the Wave 2 survey. Of them, 153 (88%) continued to be employed. Lower education attainment (p=0.01), worse physical health (p=0.002) and greater disease activity (p=0.04) were significantly associated with work loss over 1 year, while living with a partner tended to be a protective factor (p=0.09). One-hundred-thirty-six patients who were employed for 2 consecutive years responded to Waves 1 and 2 WPAI surveys. Their mean disease duration and education level were 13 years and 16 years, respectively; 95% were female and 65% were Black.

Category	N cases	Work Time Missed*	P value	Overall Work Productivity Impairment*	P value	Daily Activities Impairment*	P value
Demographics							
Age							
18–34 (Ref)	30	−0.1 ± 13.9	-	0.2 ± 29.5	-	−5.3 ± 30.0	-
35–54	85	3.0 ± 25.0	0.30	2.6 ± 33.3	0.77	−1.5 ± 21.2	0.41
≥55	21	−0.8 ± 14.6	0.92	−5.2 ± 24.0	0.69	−1.9 ± 17.2	0.60
Race							
Black	89	**4.2 ± 25.6**	**0.088**	5.0 ± 35.0	0.083	−2.8 ± 23.4	0.79
White (Ref)	44	−2.7 ± 7.7	-	−6.4 ± 19.7	-	−2.0 ± 22.2	-
Marital Status							
Married or cohabited	71	1.7 ± 21.6	0.46	0.1 ± 31.0	0.58	**−5.2 ± 19.5**	**0.020**
All others (Ref)	65	1.7 ± 21.8	-	1.7 ± 31.4	-	0.6 ± 25.7	-
Education attainment							
≤High School	22	6.3 ± 22.4	0.16	**15.1 ± 25.8**	**0.002**	1.4 ± 24.6	0.44
Some College	32	−1.0 ± 18.5	0.91	1.0 ± 38.2	0.80	−5.6 ± 26.8	0.87
≥College (Ref)	82	1.6 ± 22.5	-	−3.0 ± 28.5	-	−2.2 ± 20.7	-
Disease Status							
Disease Activity							
Mild (0–15) (Ref)	90	2.4 ± 22.9	-	0.4 ± 31.0	-	−1.7 ± 21.0	-
Severe (≥16)	46	0.5 ± 18.9	0.92	1.9 ± 31.8	0.87	−3.9 ± 26.1	0.49
Organ Damage							
No damage (Ref)	59	1.1 ± 19.4	-	−2.4 ± 31.4	-	−1.9 ± 24.0	-
Mild (1–2)	55	4.7 ± 24.9	0.17	4.8 ± 34.1	0.62	−4.0 ± 23.4	0.42
Severe (>3)	22	−3.8 ± 17.3	0.18	0.0 ± 21.1	0.94	0.0 ± 18.3	0.87
Overall Health							
Excellent or Very Good (Ref)	40	3.2 ± 19.9	-	3.5 ± 29.2	-	1.8 ± 23.7	-
Good	65	0.4 ± 21.3	0.81	−4.8 ± 29.8	0.14	−3.1 ± 23.4	0.23
Fair or Poor	31	2.6 ± 24.6	0.43	9.4 ± 34.7	0.44	−6.5 ± 19.9	0.10
Mental Health Score (SF−12)							
<50	67	0.4 ± 20.0	0.96	1.7 ± 34.4	0.69	−5.4 ± 26.9	0.13
>50 (Ref)	69	3.1 ± 23.1	-	0.1 ± 27.8	.	0.4 ± 17.6	-
Physical Health Score (SF-12)							
≤50	87	2.1 ± 26.4	0.31	−0.5 ± 34.5	0.28	−4.4 ± 20.2	0.35
>50 (Ref)	49	1.0 ± 7.6	-	3.3 ± 24.2	-	1.0 ± 26.7	-

* Mean of % change ±SD: negative values indicate improvement

Conclusion: SLE has a profound impact on employment. In patients having endured more than one decade of disease, the majority become unemployed. Education, physical health and disease activity are associated with short-term work loss, while social support tends to be protective. In those who remain employed, lower education attainment is the only factor predictive of 1-year work productivity impairment. Although not statistically significant, there was a trend towards Black race being negatively associated with work productivity. Patients who live with a partner have better daily life activities performances than those who are single, divorced or widowed. Notably, disease factors do not impact 1-year changes in work productivity. Further research is needed to better understand the pathways through which education, social support and disease status impact short-term work loss and productivity in SLE.

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Dose Of Corticosteroid, Risk Of Adverse Events and Healthcare Resource Utilization In Systemic Lupus Erythematosus. Wei-Shi Yeh[1], Shih-Yin Chen[2], Kathleen McCarty[1], Qian Li[2], Yuan-Chi Lee[2] and Nathalie Franchimont[1]. [1]Biogen Idec Inc., Weston, MA, [2]United BioSource Corporation, Lexington, MA.

Background/Purpose: Gluco-corticosteroids (GCs) are frequently used to treat autoimmune disease and their chronic use has long been known to cause adverse events (AEs). The purpose of this study was to examine the relationship between dose of GCs, risk of AEs, and healthcare resource utilization (HRU) in patients with systemic lupus erythematosus (SLE).

Methods: This retrospective study used a US commercial insurance claims database from January 2007 through December 2011. SLE patients were identified using ICD-9 CM code 710.0 from ≥2 outpatient or 1 inpatient claims. Use of oral GCs was examined for 12 months from the date of first observed SLE diagnosis (index date). Patients receiving ≥60 days of GCs were categorized based on their average daily oral dose of prednisolone (or equivalent) as follows: low (≤7.5mg), medium (7.5mg<dose≤15mg), and high (>15mg) dose groups. A cohort of SLE patients who did not receive any oral GCs was selected as the reference group. Potential AEs associated with chronic GCs were identified from literature and a total of 36 conditions were examined. HRU of outpatient/emergency department (ED) visits, hospitalizations, prescriptions, and total health costs were examined for 12 months post index date. Rates of AEs were compared with the reference group using Chi-square tests. Trend tests of dose response were conducted for dichotomous variables using Cochran-Armitage test and for continuous variables fitted via generalized linear regression.

Results: We identified 46,785 commercially-insured SLE patients with no GCs use and 5,221, 4,965, and 4,136 patients with low, medium, and high dose of GCs, respectively. Their mean age was 46.8, 47.0, 45.1, and 42.8 years and the proportion of males was 9.2, 9.7, 10.8, and 13.3%, respectively. Some but not all steroid-related AEs were observed at a higher frequency among GCs users than non-users. A positive dose-relationship was observed for myopathy, atherosclerosis, hypertension, heart failure, Cushingoid syndrome, and bacterial infection (all $P<0.05$). Among the patients receiving GCs, the proportion of patients having ED visit (29.7, 37.7, and 47.0%, $P<0.01$) and hospitalization (18.3, 24.8, and 42.8%, $P<0.01$) increased significantly with the dose of GCs. Similar trends were observed in annual average number of non-ED outpatient visits (25.0, 28.8, and 34.5, $P<0.01$) and non-steroid prescriptions and refills (42.9, 48.3, and 51.4, $P<0.01$). The annual average total health costs for the low, medium, and high dose groups of GCs users were $21,815, $27,635, and $45,339, respectively ($P<0.01$).

Conclusion: Higher dose of GCs is associated with more AEs and greater HRU in SLE. Although the association may be confounded by SLE disease severity, this finding highlights the value of future effective SLE treatments with steroid-tapering effect.

Disclosure: W. S. Yeh, Biogen Idec Inc., 3; **S. Y. Chen**, Biogen Idec Inc., 2; **K. McCarty**, Biogen Idec Inc., 3; **Q. Li**, Biogen Idec Inc., 2; **Y. C. Lee**, Biogen Idec Inc., 2; **N. Franchimont**, Biogen Idec Inc., 3.

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Longitudinal Analysis Of Direct Medical Costs For Systemic Sclerosis Patients: A Population-Based Study. Natalie McCormick[1], Carlo A. Marra[2], Eric C. Sayre[3] and J. Antonio Avina-Zubieta[4]. [1]University of British Columbia, Vancouver, BC, [2]Univ of British Columbia, Vancouver, BC, [3]Arthritis Research Centre of Canada, Richmond, BC, [4]Arthritis Research Centre of Canada, University of British Columbia, Richmond, BC.

Background/Purpose: Patients with systemic sclerosis (SSc) have considerable morbidity which may be associated with high health resource utilization.

Studies on health use and costs are scarce and the few available have short follow-up from clinic-based samples. To address this knowledge gap, we have estimated the longitudinal health care costs of cases with SSc. We measured physician visits, hospitalizations, and dispensed medication data that cover the entire SSc population of our province.

Methods: Data Source: Universal coverage is a feature of our healthcare system and administrative data captures *all* funded health services (outpatient visits, tests and hospitalizations) and *all* dispensed medications from 1996 through 2010 (regardless of funding source).

Cases: A population-based cohort of SSc was identified using the following algorithm: **a)** diagnosis of SSc on at least two visits within a two-year period between Jan 1990 and Dec 2010 by a non-rheumatologist physician; **b**) diagnosis of SSc on at least one visit by a rheumatologist or from hospitalization. To increase specificity we excluded cases that were not confirmed by a rheumatologist if they were seen at a later point.

Cost Calculation: Costs for outpatient services and prescriptions were summed directly from paid claims. Case-mix methodology was used to cost hospitalizations. Costs are reported in 2010 Canadian dollars.

Results: We identified 1,456 SSc cases (82% female, mean (SD) age of 55.3 (±14.9) years) contributing 7,824 total patient-years (PY). Over 15 calendar years the cumulative costs for SSc cases totalled **$83,507,123** and averaged $10,673 per-PY with $2,475 (23%) from outpatient services, $5,360 (50%) from hospitalizations, and $2,837 (27%) from prescription medications. Cases who were hospitalized at least once over the period averaged 1.9 (±3.0) admissions per-PY.

After adjustment to 2010 dollars, annual mean per-PY costs increased by 8%, from $9,513 in 1996 to $10,261 in 2010. Mean per-PY outpatient costs decreased by 14% and hospital costs by 15% (see table). In contrast, mean per-PY prescription costs increased by 109% (from $1,740 in 1996 to $3,641 in 2010), and the mean number of prescriptions per-PY increased by 56% (from 29 to 46).

	Mean Per-Patient-Year Costs (2010 Canadian dollars)				Mean Per-Patient-Year Dispensed Prescriptions
Year	Overall	Outpatient	Hospital	Medication	
1996	$ 9,513	$2,714	$5,059	$1,740	29
1997	$11,657	$2,851	$6,901	$1,905	30
1998	$11,396	$2,680	$6,741	$1,975	31
1999	$11,329	$2,550	$6,784	$1,995	31
2000	$11,111	$2,369	$6,789	$1,953	32
2001	$ 9,411	$2,479	$4,969	$1,963	34
2002	$10,363	$2,598	$5,549	$2,216	34
2003	$11,906	$2,512	$6,782	$2,612	35
2004	$10,446	$2,398	$4,970	$3,078	36
2005	$11,050	$2,456	$5,662	$2,933	37
2006	$10,322	$2,480	$4,502	$3,341	40
2007	$10,933	$2,467	$5,240	$3,226	43
2008	$ 9,895	$2,375	$4,067	$3,453	43
2009	$11,048	$2,389	$5,206	$3,453	45
2010	$10,261	$2,333	$4,287	$3,641	46
Overall	**$10,673**	**$2,475**	**$5,360**	**$2,838**	**38**
Fifteen-Year %-Change	**8%**	**−14%**	**−15%**	**109%**	**56%**

92% of the cohort's cumulative healthcare costs came from the 67% of SSc cases (n=977) that were hospitalized at least once. These cases had a substantially larger increase in prescription drug costs over the 15 years (by 193%, $1,791 to $5,253 per-PY) than never-hospitalized cases (by 42%, $1,283 to $1,824).

Conclusion: This is the first longitudinal and population-based study assessing the direct medical costs of patients with SSc. As outpatient and hospital costs decrease, medication use and costs continue to rise. Given there are no specific disease modifying anti-rheumatic drugs for SSc, our results suggest the long-term costs of SSc cases may be driven by ongoing complications and comorbidities of this disease.

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Association Of Depressive Symptomatology and Life and Job Satisfaction In Patients With Rheumatoid Arthritis. Jutta G. Richter[1], Dr. Ralph Brinks[2], Thomas Muth[1], Mia Vidakovic[1], Tobias Koch[1], Peter Angerer[1] and Matthias Schneider[3]. [1]Heinrich-Heine-University, Duesseldorf, Germany, [2]Univ. Duesseldorf, Duesseldorf, Germany, [3]Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany.

Background/Purpose: Life satisfaction (LS) has become an important outcome measure in healthcare, is a relevant indicator of job satisfaction, and might be influenced by depression. The objectives of the study were to investigate life and job satisfaction and the influence of self-reported depressive symptomatology (DS) in patients (pts) with rheumatoid arthritis (RA) to consider these aspects in future treatment concepts.

Methods: Self-administered questionnaires (Qs) were applied to RA pts and controls (c) not suffering from rheumatic diseases. General life satisfaction Q (FLZ) captured ten domains of satisfaction (see Table 1). Scores are expressed as age & sex standardized stanines (a method of scaling test scores on a normalized nine-point standard scale with a mean of 5 and a standard deviation of 2). DS was measured by the German long version of the Center for Epidemiological Studies Depression Scale (ADSL). A separate Q assessed self-reported clinical data. Ethics approval was obtained.

Results: 267 pts (85.0% female (f)) and 177 c (90.3% f) contributed data. Pts' mean age was 47.7±10.0 (c 42.8±9.8) years, mean disease duration 9.0+8.0 years, mean HAQ 1.1±0.5 (c 0.4±0.1). 85.5% self-reported at least one comorbidity (range 0–8, c 45.2%, range 0–4). In pts 81.7% received at least one immunosuppressive medication (range 0–6), 43.8% steroids < 7.5mg, 9.0% steroids >7.5mg and 61.4% NSAIDS.

Pts' mean general LS was 236.7±39.6 (c 263.9±31.7, p<1e-15), mean satisfaction with health was significantly lower in pts (26.3±8.6; c 38.6±7.2, p<1e-15). In the FLZ subscales job & profession, finances, self, sexuality and friends pts scored significantly lower than c. Pts' ADS-L score was 18.2±10.7 (c 9.8±6.8, p<1e-15). 27.1% pts and 4.6% c (p<1e-9) scored >23 on the ADS-L which is indicative of depression.

A logistic regression calculated the association between LS (sub-)scale-stanines and DS. Table 1 depicts odds ratios (OR). If the health stanine increases by one unit, a person's risk with respect to an outcome of DS decreases by a factor of 0.409. For RA pts it increases by an additional factor of 1.710. In all FLZ-scales RA pts had a higher risk of DS. Highest OR was detected in the job & profession subscale.

Table 1. Logistic regression: FLZ-(sub-)score-stanine, group affiliation, self-reported depressive symptomatology (0 in the p-value column means $p < 10^{-16}$)

	Stanine			RA vs controls		
FLZ (Sub-)Score	OR	95%-ci	p-value	OR	95%-ci	p-value
Health	0.409	0.392–0.426	5.18e-10	1.710	1.627–1.796	0
Job & profession	0.581	0.571–0.590	2.68e-09	8.536	5.596–13.021	0
Finances	0.725	0.716–0.735	0.000106	7.201	5.168–10.033	0
Leisure	0.699	0.691–0.706	1.39e-06	7.406	5.222–10.502	0
Partner/relationship	0.667	0.658–0.677	1.68e-06	6.642	4.336–10.176	0
Children	0.732	0.721–0.743	0.000378	6.826	3.702–12.588	7.66e-10
Self	0.528	0.518–0.538	4.8e-11	5.560	3.957–7.813	0
Sexuality	0.636	0.628–0.645	7.84e-08	5.861	4.079–8.420	0
Friends and relatives	0.645	0.636–0.654	2.09e-07	6.406	4.528–9.063	0
Home	0.733	0.723–0.744	0.000322	8.479	5.711–12.589	0
General LS	0.446	0.433–0.459	2.44e-11	3.357	2.414–4.668	6.06e-13

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Conclusion: RA pts showed low satisfaction in 10 areas of LS and significantly more pts were indicative of depression. Significant ORs were detected in all FLZ scales, domains that are potentially modifiable. The high OR in the job and profession subscale indicates that beside DS social and job related satisfaction issues should predominantly targeted. Apart from already established (QoL) assessments (e.g. HAQ, SF36) routine care and further clinical studies might gain from additional assessments of LS and ADSL as outcome parameters.

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Association Of Depressive Symptomatology and Life and Job Satisfaction In Patients With Systemic Lupus Erythematosus. Jutta G. Richter[1], Thomas Muth[1], Ralph Brinks[2], Mia Vidakovic[1], Tobias Koch[1], Peter Angerer[1] and Matthias Schneider[3]. [1]Heinrich-Heine-University, Duesseldorf, Germany, [2]Univ. Duesseldorf, Duesseldorf, Germany, [3]Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany.

Background/Purpose: Life satisfaction (LS) has become an increasingly important outcome measure in healthcare, is a relevant indicator of job satisfaction and might be associated with depression. The objectives of the study were to investigate life and job satisfaction and the association of self-reported depressive

symptomatology (DS) in patients (pts) with systemic lupus erythematosus (SLE) to consider these aspects in future treatment concepts and studies.

Methods: Self-reported questionnaires (Qs) were applied to SLE pts and controls (c) not suffering from rheumatic diseases. General life satisfaction Q (FLZ) captured ten domains of satisfaction (see Table1). According to Q's analysis, scores are expressed as age and sex standardized stanines (a method of scaling test scores on a normalized nine-point standard scale (1–9) with a mean of 5 and a standard deviation of 2). DS was measured using the German long version of the Center for Epidemiological Studies Depression Scale (ADS-L). A separate Q assessed self-reported clinical data. Ethics committee approval had been obtained.

Table 1. Logistic regression: FLZ-(sub-)score-stanine, group affiliation, self-reported depressive symptomatology (0 in the p-value column means $p < 10^{-16}$)

	Stanine			SLE vs controls		
FLZ (Sub-)Score	**OR**	**95%-ci**	**p-value**	**OR**	**95%-ci**	**p-value**
Health	0.462	0.446–0.478	6.32e-09	2.245	2.033–2.480	0
Job and profession	0.674	0.664–0.685	8.06e-06	9.396	6.314–13.982	0
Finances	0.695	0.686–0.705	1.87e-05	8.549	5.983–12.214	0
Leisure	0.666	0.657–0.675	1.7e-06	7.483	5.281–10.604	0
Partner/relationship	0.808	0.799–0.818	0.0053	7.644	5.278–11.070	0
Children	0.708	0.695–0.723	0.000623	8.193	4.366–15.373	5.77e-11
Self	0.500	0.489–0.511	6.8e-11	6.710	4.618–9.748	0
Sexuality	0.687	0.677–0.697	1.17e-05	6.146	4.468–8.455	0
Friends and relatives	0.636	0.627–0.644	3.23e-08	7.960	5.510–11.500	0
Home	0.711	0.700–0.722	0.000143	8.933	5.938–13.439	0
General LS	0.483	0.471–0.495	7.92e-11	4.260	3.065–5.920	0

Results: 252 pts (95.6% female (f)) and 177 controls (90.3% f) contributed data. Patients' mean age was 40.1±9.4 (c 42.8±9.8) years, mean disease duration 10.5±7.3 years, mean HAQ 0.8±0.4 (c 0.4±0.1). 86.0% reported at least one comorbidity (range 0–10, c 45.2%, range 0–4). 77.4% received at least one immunosuppressive medication (range 0–3). 40.5% were on steroids <7.5mg, 16.3% on steroids >7.5mg, 34.0% took NSAIDS.

The mean general LS of pts was 237.8±39.6 (c 263.9±31.7, p<4e-10). Except in partner/relationship pts scored significantly lower in all FLZ-subscales compared to c. Pts mean ADS-L Score was 18.1±11.0, c 9.8±6.8 (p<6e-16). 30.0% pts and 4.6% c (p<3e-10) scored >23 on the ADS-L which is indicative of depression.

A logistic regression model calculated the association of LS (sub-)scale-stanines and DS. Table 1 depicts odds ratios: If the health stanine increases by one unit, a person's risk with respect to an outcome of DS decreases by a factor of 0.462. For pts, it increases by an additional factor of 2.245. In comparison to c, SLE pts had a higher risk of DS in all FLZ (sub)scales.

Conclusion: SLE pts showed reduced satisfaction in 10 areas of life and significantly more pts were indicative of depression. Significant ORs were detected in all FLZ scales, domains that are potentially modifiable. The very high OR in the job and profession subscale indicates that beside depression social and job related satisfaction issues should predominantly targeted. Besides from already established (QoL) assessments (e.g. HAQ, SF36) routine care and further clinical studies might gain from the additional assessment of LS and DS as outcome parameters.

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1011

Psychiatric and Cardiovascular Comorbidities As Causes Of Work Disability Among Individuals With Rheumatoid Arthritis. Anne M. Kerola[1], Tuomo Nieminen[2], Markku J. Kauppi[3], Hannu Kautiainen[4], Tuomas Kerola[3], Lauri J. Virta[5], Timo Pohjolainen[6] and Kari Puolakka[7]. [1]Medical School, University of Helsinki, Helsinki, Finland, [2]Division of Cardiology, Helsinki University Central Hospital, Helsinki, Finland, [3]Department of Internal Medicine, Päijät-Häme Central Hospital, Lahti, Finland, [4]Unit of Primary Health Care, Helsinki University Central Hospital, Helsinki, Finland, [5]Research Department, the Social Insurance Institution, Turku, Finland, [6]ORTON Rehabilitation Centre, ORTON Foundation, Helsinki, Finland, [7]Department of Medicine, South Karelia Central Hospital, Lappeenranta, Finland.

Background/Purpose: A remarkable proportion of rheumatoid arthritis (RA) patients stop working before the normal age of retirement. Initial research data suggests that comorbidities, with depression in particular, may increase work disability (WD) rates in RA. The aim of this study was to determine the contribution of psychiatric and cardiovascular (CV) comorbidities to WD among RA patients.

Methods: All incident, non-retired patients with RA (aged 18–64 years, RA diagnosed in 2000–2007) were identified from a Finnish nationwide register maintained by the Social Insurance Institution. From another register maintained by the Finnish Centre for Pensions, data on WD in the RA cohort as well as the entire Finnish population was obtained up until December 31, 2008. The data included all permanent disability pensions and WD periods which had continued for at least one year at the end of the follow-up. The incidence of WD caused primarily by CV diseases, psychiatric disease, and RA was analyzed. The primary cause of WD was identified by the ICD-10 codes I00–99 for CV diseases, F20–69 for psychiatric diseases, and M05 or M06 for RA as the first (i.e. the most important) diagnosis in the register.

Results: We identified a cohort of 7,831 patients with RA who were available for work full-time (71% women, mean age 46 [SD 11]). During the follow-up (median 4.0 years, IQR 2.2–6.3), 1,095 (14.0%) patients became disabled for work. In two out of three cases, the primary cause was RA, whereas psychiatric diseases constituted the second-most important cause (Table). After adjusting for competing risks, 12.0% (95% CI 11.5 to 12.4), 1.3% (1.2 to 1.5), and 0.5% (0.4 to 0.6) of the RA patients lost their capacity for work primarily due to RA, a psychiatric comorbidity, or a CV disease, respectively (Figure). A CV cause was more frequent among men, but no difference was found between the sexes in psychiatric causes. Compared with the overall Finnish population, the age- and sex-specific standardized incidence ratios of WD due to CV or psychiatric comorbidities were 1.75 (95% CI 1.23 to 2.51) and 0.99 (95% CI 0.80 to 1.23), respectively.

Table. Primary causes of work disability according to ICD-10 disease class.

	Male n (%)	**Female n (%)**	**All n (%)**
Total	414	681	1095
M00–M99	321 (77.5)	552 (81.1)	873 (79.7)
** of which M05 or M06 (RA)*	**277 (66.9)*	**462 (67.8)*	**739 (67.5)*
Mental and behavioral disorders F00–F99	27 (6.9)	64 (9.4)	91 (8.3)
** of which F20–F69*	**23 (5.6)*	**59 (8.7)*	**82 (7.5)*
I00-I99	16 (3.9)	14 (2.1)	30 (2.7)
Other	50 (12.1)	51 (7.5)	101 (9.2)

M00–M99 Diseases of the musculoskeletal system and connective tissue.
F00–F99: Mental and behavioral disorders.
F20–F69: Schizophrenia, schizotypal and delusional disorders.
Mood disorders; neurotic, stress-related, and somatoform disorders; behavioral syndromes associated with physiological disturbances and physical factors; disorders of adult personality and behavior.
I00–I99 Diseases of the circulatory system.

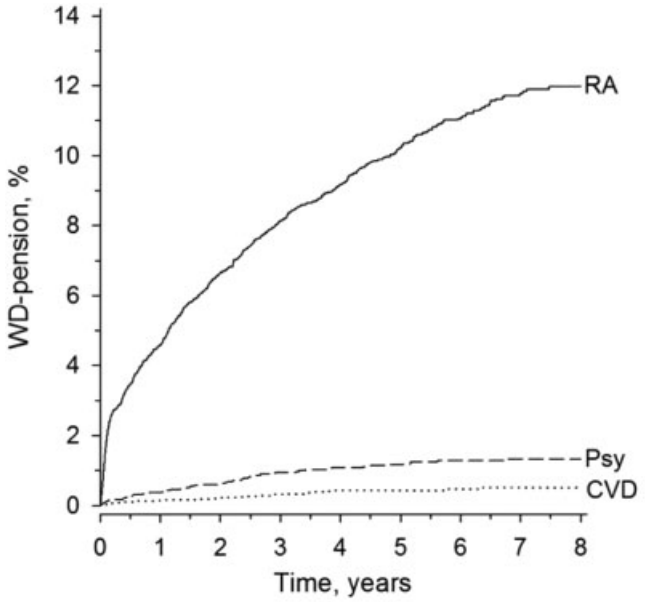

Figure. Competing risk-adjusted cumulative incidence functions for work disability (WD) due to rheumatoid arthritis (RA) as well as psychiatric (Psy) and cardiovascular diseases (CVD) after the diagnosis of RA.

Conclusion: In this cohort of RA patients from 2000–2007, psychiatric or CV comorbidities were the primary causes of WD much less frequently than RA itself. This may, however, represent only a part of their overall contribution to WD, as they may enhance the devastating impact of RA on working capacity without being the leading cause of WD. The risk of WD due to CV disease is higher in RA than in the general population, but psychiatric comorbidities do not appear to cause WD beyond the population level in early RA.

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Disease Severity, Quality Of Life, and Productivity Loss Among Patients With Ankylosing Spondylitis In Germany. Jürgen Braun[1], Herbert Kellner[2], Regina Max[3], Markus Rihl[4], Elmar Schmitz-Bortz[5], Hendrik Schulze-Koops[6], Silke Zinke[7], Tao Fan[8], Qian Ding[8] and Ramon Lyu[8]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Centre for Inflammatory Joint Diseases, Munich, Germany, [3]University of Heidelberg, Heidelberg, Germany, [4]German Society for Rheumatology Association, Traunstein, Germany, [5]Rheumatism Practice in Hattingen, Hattingen, Germany, [6]University of Munich, Munich, Germany, [7]Rheumatological Office, Berlin, Germany, [8]Merck & Co., Inc, Whitehouse Station, NJ.

Background/Purpose: Ankylosing Spondylitis (AS) is a chronic, inflammatory form of arthritis that primarily affects the spine, which can cause significant pain and lead to bone ankylosis, deformities in the spine, and peripheral joint damage over time. Diminished quality of life, reduced productivity, and unemployment associated with AS present a significant burden to patients and society. The purpose of this study is to describe disease severity and morbidity in terms of patient-reported quality of life (QoL) and productivity loss and explore factors associated with productivity loss in patients with AS in Germany.

Methods: A multi-center observational study using 12-month retrospective chart review, with prospective paper-based questionnaires at the index visit and 3 months thereafter was conducted. Patients completed Short-form 36 (SF-36), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Work Productivity and Activity Impairment (WPAI). Physicians completed the Bath Ankylosing Spondylitis Metrology Index (BASMI) and current disease activity. Descriptive analyses of QoL, utility values derived from SF-36 domains, disease activity, and work productivity impairment were performed. Adjusted multivariate regression was used to explore the variables associated with productivity loss.

Results: A total of 106 patients in 15 AS care centers across Germany were recruited. The majority of patients were men (75%), with a mean age of 46.5 ± 13.2 years and time since diagnosis of 14.6 ± 10 years. The main disease manifestation was inflammatory spinal pain (37%), followed by spinal deformities (27%) and hyperkyphosis (21%). Two-thirds of patients had co-morbidities including hypertension (28%), arthritis (25%), and psoriasis (15%). The main treatment was biological drugs in 72 patients (68%), followed by NSAIDs (53%) and Immunosuppressants (21%).

Physician evaluated the current disease activity with a mean of 2.8 ± 2.1. The mean of BASMI was 3.9 ± 1.8 at index visit, with the highest limitations in lumbar flexion at mean of 5.5 ± 2.7 and lateral spinal flexion at a mean of 4.5± 2.6.

The SF-36 summary means of physical health and mental health were 43.8 ± 8.9 and 46.9 ± 11.7. The lowest mean in the 8 domains was general health with 50.2 ± 19, followed by vitality with 52.7 ± 20.7 and bodily pain with 53.3 ± 24.4. The mean of SF-36 utility values was 0.7 ± 0.1.

Among 76 employed patients, 80% of the patients reported a mean of 2 ± 4 hours/week missed work due to AS at the index visit. Two-thirds of patients reported means of 26% of impairment while working and 31% of activity impairment due to AS. Limitation in physical functioning and BASDAI can explain 68% of productivity loss (Adjusted $R2=0.6765$, $P<0.0001$).

Conclusion: German AS patients had lower QoL and experienced substantial sick leave or impairment while working due to AS conditions. Productivity loss was significantly associated with limitation in physical functioning and BASDAI score.

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Estimating the Monetary Value of annual Productivity Gained in Early Active RA Patients Receiving Etanercept Plus Methotrexate: Results From the Prize Study. Wei Zhang[1], Nick Bansback[2], Huiying Sun[1], Ronald Pedersen[3], Sameer Kotak[4] and Aslam H. Anis[1]. [1]Centre for Health Evaluation and Outcome Sciences, Vancouver, BC, [2]University of British Columbia, Vancouver, BC, [3]Pfizer Inc, Collegeville, PA, [4]Pfizer Inc., New York, NY.

Background/Purpose: Determining the effect of treatment on work productivity of subjects with rheumatoid arthritis (RA) is an important topic given that most sufferers develop the disease between 35 to 50 years of age and many experience functional loss that translates into reduced productivity and work disability. The Valuation of Lost Productivity (VOLP) is a validated instrument developed to estimate productivity impacts from a societal perspective according to the human capital (economic) approach to measuring worker productivity. The VOLP was included in the PRIZE trial: a phase IV, 121-week, prospective, 3-phase (open-label followed by randomized double-blind, and tapering/observational phases), parallel-group, multicenter, outpatient study.

Objective: To assess productivity changes (gains), as measured by the VOLP, in phase 1 of the PRIZE trial.

Methods: In Phase 1, MTX- and biologic-naïve patients with early, active RA (symptom onset ≤12 months from enrollment; DAS28 >3.2) received open-label ETN50/MTX for 52 weeks. The VOLP was completed approximately every 13 weeks. The changes in three main VOLP outcomes from baseline to week 52 were measured: 1) 3-month paid work productivity gains, the sum of increased worked hours after adjusting for absenteeism, presenteeism and employment status changes; 2) 7-day unpaid work productivity impact; 3) Total 3-month monetary productivity gains as the sum of paid and unpaid work productivity gains. Productivity impacts included direct impact of a worker's own productivity as well as the spillover effect when team productivity is impacted and/or substitute worker productivity is considered. Bootstrapping methods were used to test the changes in VOLP outcomes.

Results: A total of 196 patients were employed at baseline and had at least one scheduled follow-up visit. The average age was 46 years and 68% were female. The patients had a high disease activity (DAS28=5.91) and moderate functional disability (HAQ=1.22). The paid work loss was about 111.7 hours in the past 3 months at baseline and decreased to 60.1 hours at week 52, with a gain of 33.43 hours per 3 months. Similarly, the gain in unpaid work was about 4 hours per week. Total costs of lost productivity in the past 3 months were €3,483 at baseline and were reduced to €843 at week 52, with total monetary gains of €1322 per 3 months. All the three main VOLP outcomes were improved significantly over the 52 weeks.

Outcomes	Week0	Week52	Gains†	P value†
Employed (N)	**196**	**143**		
Paid work productivity loss in the past 3 months (N)	**162**	**135**		
Paid work loss, hours (SD)	111.71 (116.84)	60.11 (140.91)	33.43(164.41)	0.035
Unpaid work productivity loss in the past 7 days (N)	**167**	**143**		
Unpaid work loss, hours (SD)	6.27 (11.11)	1.79 (5.86)	4.22(12.33)	0.001
Total costs of lost productivity in the past 3 months (N)	**141**	**124**		
Total costs, € (SD)	3483.48 (8482.03)	842.77 (2242.33)	1322.42 (4378.08)	0.017

Bolded values are the numbers of non-missing values used to generate the outcomes below.
† for patients whose outcomes at week 0 and week 52 were both observed.

Conclusion: Combination therapy with ETN50/MTX was associated with a significant productivity gain for patients with early RA who were still observed at week 52.

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Test-Retest Reliability Of Five Global Measures Addressing At Work Limitations/Productivity Loss In Patients With Rheumatological Conditions. Sarah Leggett[1], Annelies Boonen[2], Diane Lacaille[3], Dorcas Beaton[4], Bruno Fautrel[5], Ailsa Bosworth[6], Catherine Hoffstetter[7], Sabrina Dadoun[5], Carlo Alberto Scirè[8], Sofia Hagel[9], Mihai Bojinca[10], Carina Mihai[11], Antje Neuen[12], Pam Rogers[13], Denise Linton[14], Ingemar Petersson[15] and Suzanne Verstappen[16]. [1]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [2]Maastricht University Medical Center, Maastricht, Netherlands, [3]Arthritis Research Centre of Canada, University of British Columbia, Richmond, BC, [4]Scientist, Institute for Work & Health, Toronto, ON, [5]APHP, Pitié-Salpêtrière University Hospital, Paris, France, [6]National Rheumatoid Arthritis Society, Maidenhead, United Kingdom, [7]Patient partner, Toronto, ON, [8]Epidemiology Unit -Italian Society for Rheumatology, Milano, Italy, [9]Lund University and Skåne University Hospital, Lund, Sweden, [10]"Dr. I. Cantacuzino" Hospital, Bucharest, Romania, [11]Carol Davila University of Medicine and Pharmacy & Cantacuzino Hospital, Bucharest, Romania, [12]University Hospital Maastricht, Internal Medicine, Division of Rheumatology, Maastricht, Netherlands, [13]Arthritis Research Centre, Vancouver, BC, [14]St. Michael's Hospital, Toronto, ON, [15]Lund University, Department of Orthopedics, Clinical Sciences Lund, Lund, Sweden, [16]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: There are a number of single item global measures available to explore at-work productivity loss (presenteeism) in patients with rheumatological conditions. However, test-retest data are not available for all these measures and comparison data are lacking. The purposes of this study were i) to test-retest five at-work productivity loss global measures, including: Work Productivity Scale–Rheumatoid Arthritis (WPS-RA), Work Productivity and Activity Impairment Questionnaire (WPAI), Work Ability Index (WAI), Quality and Quantity questionnaire (QQ),and WHO Health and Performance Questionnaire (HPQ), ii) to explore the correlations between the 5 measures, and iii) to investigate the association between the 5 scales and disease activity.

Methods: In this international study 50 patients with a diagnosis of inflammatory arthritis or osteoarthritis in paid employment were recruited from 7 countries (United Kingdom, Sweden, France, The Netherlands, Romania, Italy, and Canada). At baseline and 2 wk follow up, participants completed the five 10-point global measures (WPAI; *0=no effect on work–10=completely prevented from working,* WPS-RA; *0=no interference–10=complete interference,* WAI; *0=unable to work–10=work ability at its best,* QQ; *0= practically nothing/very poor quality–10=normal quantity/very good quality,* HPQ; *0=worst performance–10=top performance).* VAS general well-being was also recorded at 2 wks. Test-retest reliability was assessed applying intra-class correlation (ICC) statistics. ICCs of 0.75 and 0.95 are generally regarded as good at respectively group and individual level. Spearman correlations were calculated to determine the association between the two week global scores and between each scale with the VAS general well-being score.

Results: 54% of the study population was female; mean age was 44 (SD 10.2) yrs and median symptom duration 9.5 [IQR 5–15] yrs. Median VAS general well-being was 28 [IQR 12–55]. 72% of the study population had a non-manual occupation. ICC correlations were moderate at a group level: WPAI (r=0.65), WPS-RA (r=0.66), WAI (r=0.81), QQ-quantity (r=0.70), QQ-Quality (r=0.68) and HPQ (r=0.62). The correlations between the 5 at-work productivity measures ranged from good (WPS-RA vs WPAI, r=0.92) to moderate (QQ-quality and QQ-quantity with all 4 other measures) (see table). Correlations between each of the individual measures and VAS general well-being were low to moderate.

Table. Spearman correlations between 5 at-work productivity loss measures and VAS general well-being

	WPAI	WPS-RA	WAI	QQ–Quantity	QQ–Quality	HPQ-question C	VAS well-being
WPAI	1						
WPS-RA	0.92	1					
WAI	−0.68	−0.70	1				
QQ–quantity	−0.58	−0.59	0.57	1			
QQ–quality	−0.58	−0.60	0.38	0.75	1		
HPQ-question c	−0.71	−0.71	0.73	0.63	0.54	1	
VAS well-being	0.56	0.66	−0.62	−0.37	−0.40	−0.60	1

Conclusion: Overall, test-retest results of the 5 existing at-work productivity loss measures and the correlation between these 5 measures were moderate. The latter probably reflecting differences in concepts, recall periods, and references used in these measures. The moderate association between the global at-work productivity measures and VAS general well-being suggests that the impact of arthritis on work is only partly captured by generic health measures.

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Quality Of Life, Productivity Impairment, Disease Severity and Health Care Costs In Relation To Functional Impairment In Ankylosing Spondylitis Patients In The Czech Republic. Liliana Sedova[1], Jiri Stolfa[1], David Suchy[2], Andrea Smrzova[3], Jiri Klimes[4], Milan Vocelka[4] and Tomas Dolezal[4]. [1]Charles University Prague, Prague, Czech Republic, [2]University hospital Plzen, Plzen, Czech Republic, [3]University hospital Olomouc, Olomouc, Czech Republic, [4]Charles University, Prague, Czech Republic.

Background/Purpose: Our aim was to describe the quality-of-life (QoL), productivity impairment, clinical indicators and health care costs in relationship to functional status described by Bath Ankylosing Spondylitis Functional Index (BASFI) in Ankylosing spondylitis (AS) patients. This relationship is highly important to justify the investment into health care.

Methods: We have organized a prospective multicentre non-interventional observational study with AS patients in 4 specialized centres for treatment of rheumatic diseases in the Czech Republic. A three-year follow-up is planned with 6 months period between each time point observation. The data presented here comes from the first visit, where demographics, clinical, QoL and productivity data were directly collected from patients. Health care consumption was assessed retrospectively reviewing individual patient's medical record (with 6 or 12 months recall period from the first visit). Clinical data were described by ASDAS-CRP, QoL measured by EuroQol questionnaire (EQ-5D), work impairment by Work Productivity and Activity Impairment (WPAI) with respect to BASFI categories. Validated Czech versions of all questionnaires were used. Patients are stratified according to their BASFI in 10 categories. Within health care consumed, we focus on medication (classical DMARDs, corticosteroids and biological drugs), out-patient & in-patient care, complement and instrumental examination and out-of pocket expenses. Health care expenditures are annualized and presented as an average costs per patient. Patients are analysed as the whole cohort and specifically by the presence of biologic treatment.

Results: We have already included 225 patients with AS, 200 on biological drugs, mean patient age was 43.4 years, mean time from diagnoses of AS was 13.8 years, 24.4% were female. With higher functional impairment, described by BASFI, there is trend in age increase, increase in time from diagnosis, percentage of work impairment and also decrease in percentage of work-active patients. There is also deterioration in clinical impairment (ASDAS-CRP) and QoL observed with worse functional status. There is almost the same height of total costs in each BASFI category as 89% of all patients are treated with biologics, which are the most important costs driver. See results table, where all values are presented as mean values, na-not applicable.

Patients on biologic drugs

BASFI category	BASFI	No.	Age	Time from Dx (years)	% women	Costs (EUR)	% of work active	% WPAI	ASDAS-CRP	EQ-5D
0–1>	0.4	50	38.0	9.8	32.0%	12,733	88.0%	6.1%	1.2	0.900
1–2>	1.5	40	41.1	11.7	22.5%	11,960	82.5%	21.4%	1.6	0.782
2–3>	2.5	34	46.1	15.3	14.7%	13,371	73.5%	26.0%	2.1	0.731
3–4>	3.4	23	44.9	16.2	26.1%	11,866	69.6%	23.8%	2.3	0.668
4–5>	4.5	20	44.0	16.3	30.0%	13,551	55.0%	34.0%	1.9	0.661
5–6>	5.4	15	45.2	17.9	20.0%	11,894	46.7%	36.6%	2.4	0.656
6–7>	6.6	7	42.4	7.7	14.3%	12,621	57.1%	47.5%	2.6	0.665
7–8>	7.3	4	52.5	18.3	0.0%	11,397	75.0%	68.9%	3.1	0.651
8–9>	8.4	5	47.8	18.6	0.0%	15,287	20.0%	40.0%	3.5	0.501
9–10>	9.3	2	46.0	13.5	0.0%	12,479	50.0%	95.3%	3.0	0.521
Mean/total	2.7	200	42.7	13.5	23.0%	12,637	72.5%	21.9%	1.9	0.752

Patients without biologic drugs

BASFI category	BASFI	No.	Age	Time from Dx (years)	% women	Costs (EUR)	% of work active	% WPAI	ASDAS-CRP	EQ-5D
Mean/total	4.2	25	49.0	16.6	36.0%	483	52.0%	34.1%	2.9	0.596

Whole patient cohort

BASFI category	BASFI	No.	Age	Time from Dx (years)	% women	Costs (EUR)	% of work active	% WPAI	ASDAS-CRP	EQ-5D
0–1>	0.4	53	37.6	9.5	32.1%	12,026	84.9%	6.7%	1.2	0.899
1–2>	1.5	44	41.5	11.3	25.0%	10,898	84.1%	23.6%	1.7	0.772
2–3>	2.5	37	46.2	14.7	18.9%	12,303	73.0%	25.2%	2.1	0.724
3–4>	3.4	26	46.3	17.4	30.8%	10,534	69.2%	24.9%	2.3	0.664
4–5>	4.5	22	44.0	17.0	27.3%	12,370	59.1%	33.2%	2.0	0.656
5–6>	5.4	19	48.9	19.3	21.1%	9,528	47.4%	37.3%	2.6	0.621
6–7>	6.6	7	42.4	7.7	14.3%	12,621	57.1%	47.5%	2.6	0.665
7–8>	7.4	6	49.3	14.5	0.0%	8,134	50.0%	68.9%	3.3	0.608
8–9>	8.5	9	50.0	22.4	11.1%	8,684	11.1%	40.0%	3.7	0.444
9–10>	9.3	2	46.0	13.5	0.0%	12,479	50.0%	95.3%	3.0	0.521
Mean/total	2.9	225	43.4	13.8	24.4%	11,286	70.2%	22.7%	2.0	0.734

Conclusion: Patients with worse functional impairment revealed more significant impairment of their QoL, work productivity and revealed also worse clinical outcomes. We present total health care costs according to the functional impairment. The findings attributed to higher BASFI impairment (BASFI > 6.0) and to patients not treated with biologics should be interpreted with caution because of lower number of patients in these categories.

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Presenteeism Predicts Sick Leave Better Than Basdai and/Or BASFI In A Longitudinal Cohort Of Patients With Ankylosing Spondylitis (EASIC). Thien Thi Vinh Nguyen[1], An Tran-Duy[2], Frank Heldmann[3], Juergen Braun[3], Herbert Thijs[1] and Annelies Boonen[2]. [1]Hasselt University, Hasselt, Belgium, [2]Maastricht University Medical Center, Maastricht, Netherlands, [3]Rheumazentrum Ruhrgebiet, Herne, Germany.

Background/Purpose: Sick leave (SL) is a critical socioeconomic consequence of ankylosing spondylitis (AS). This study aimed at exploring the role of presenteeism relative to BASDAI and BASFI in predicting SL in patients adequately treated with the TNF-α inhibitor infliximab using longitudinal data analysis.

Methods: The EASIC database is an open label extension of the ASSERT trial and includes 103 patients with AS from six European countries that were treated with infliximab. Demographic, clinical and work-related data were collected at baseline and every six months over a 2-year period. Sick leave represented the number of non-working days in the last six months. Presenteeism represented the AS impact on productivity of patients at work and is measured as a single item (0: no effect; 10: strong effect). We fitted a number of statistical models, including standard/zero-inflated Poisson/Negative Binomial (NB) fixed/mixed effects models. Based on exploratory data analysis and expert opinion, covariates considered in the models included time, gender, baseline age, disease duration, BASDAI, BASFI, BASMI, presenteeism and work-status (part-/full- time), and pair-wise interactions between them. Model selection was based on Akaike information criterion (AIC), Bayes information criterion (BIC) and likelihood ratio test. SAS 9.2 was used for data analysis.

Results: Of all patients (n=103), 84% had full-time job; 86% were male; mean (SD) age was 41 (9.6); mean monthly presenteeism ranged from 2 to 3; mean (SD) BASDAI and BASFI were 3.2 (1.7) and 3.5 (1.4), respectively. Of patients with paid jobs, 35% had SL > 0 with a mean (SD) of 8 (10) days over two years. The ratio of the deviance of Poisson regression to its degrees of freedom indicated overdisperson, suggesting that the standard Poisson models were not appropriate. The likelihood ratio tests comparing the NB models with the Poisson models were significant (p-value < 0.001) in favor of the NB over the Poisson models. Because the overdispersion was due to excess of zero, the zero-inflated NB (ZIBN) models were considered better than the standard NB models. AIC resulting from the ZINB fixed model was smallest, suggesting that the ZINB fixed effect model was the best choice.

In the first part of the best fitting ZINB fixed effect model (which predicts the probability of having zero day of SL), the intercept and the only slope for presenteeism at 6 months (PRES.LAG6) in the past were significantly different than zero. In the second part (which predicts the number of non-zero SL), the intercept and only slopes for time and PRES.LAG6 were significantly different than zero. An increase of one unit in presenteeism yielded an increase by 29% in the expected SL.

Conclusion: In patients with adequately controlled AS, our findings show that presenteeism is a better predictor for SL over time than BASDAI and/or BASFI. Limitations of this study include small sample size, short follow-up time and the absence of work-related factors among the predictors.

Disclosure: T. Thi Vinh Nguyen, None; **A. Tran-Duy**, None; **F. Heldmann**, Merck Pharmaceuticals, 2; **J. Braun**, Merck Pharmaceuticals, 2; **H. Thijs**, None; **A. Boonen**, Merck Pharmaceuticals, 2.

1017 WITHDRAWN

1018

Methodology Of Determining An Appropriate Look-Back Period To Identify Autoimmune Rheumatic Disease In a Study Of Post-Myocardial Infarction Mortality. Mark Tacey, Megan Bohensky and Sharon Van Doornum. The University of Melbourne, Melbourne, Australia.

Background/Purpose: Hospital administrative datasets offer an opportunity to study the relatively rare occurrence of auto-immune rheumatic diseases (AIRD). Under-coding is a known limitation however. "Look-back" periods can be used to compensate for under-coding within the ("index") admission of interest by identifying AIRD codes in preceding admissions for each patient. However if the timespan of the dataset is fixed, increasing the look-back period to identify more AIRD patients reduces the duration of the primary analysis period (Figure 1). This study aimed to examine the effect of different look-back periods for identifying AIRD patients in an evaluation of the relationship between AIRD status and mortality following myocardial infarction (MI).

Methods: This study utilises a population-based hospital admission dataset with data available from 1 July 1998 to 30 June 2007. MI and AIRD status were identified using relevant International Classification of Diseases (ICD) codes. Six scenarios were defined for ascertainment of AIRD status (A to F: Figure 1), ranging from no look-back to a 5 year look-back period. Thirty-day and 1-year mortality rates were calculated from the date of the index MI. A logistic regression model was fitted with mortality as the outcome, AIRD status as the exposure and adjustment for relevant covariates. We compared the relationship between AIRD status and post-MI mortality for each scenario.

Results: As the duration of the look-back period increased (progressing from scenario A to F), the prevalence of AIRD increased from 0.7% (n=632 of 86,841 patients: scenario A) to 2.2% (n=998 of 45,447 patients: scenario F). The number of patients identified with MI decreased from scenario A to F due to the progressive reduction in the duration of the primary analysis period. Adjusted odds ratios for all-cause mortality for the AIRD group are shown in Figure 2. When no look-back period was used, no significant relationship between AIRD and 30-day mortality was identified (OR = 1.13, 95%CI 0.90–1.42). As the look-back period increased, a statistically significant relationship was obtained with an increase in the odds ratio, before stabilising with a look-back period of 3 years or longer in duration.

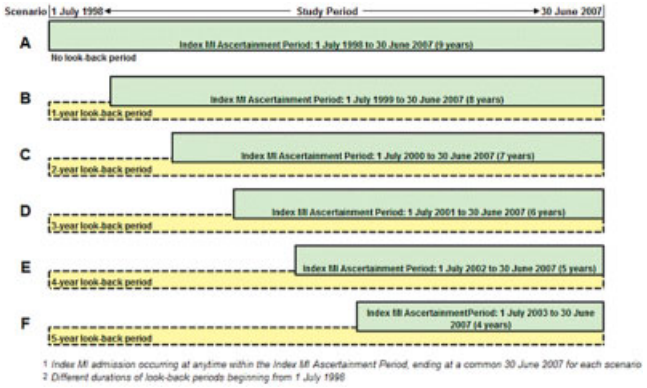


Figure 1. Index MI ascertainment and look-back period scenarios

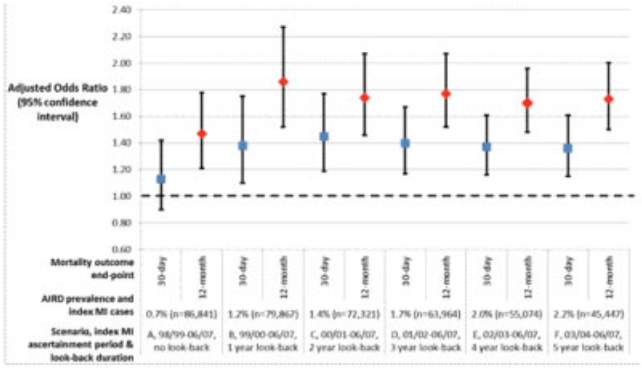


Figure 2. Adjusted Odds Ratio for 30-day and 12-month mortality for AIRD patients

Conclusion: Using a look-back period to identify AIRD status changed the significance of our findings. Based on the dataset in question, there is no advantage of extending the look-back period beyond a duration of three years, with an analysis period of six years.

Disclosure: M. Tacey, None; **M. Bohensky**, None; **S. Van Doornum**, None.

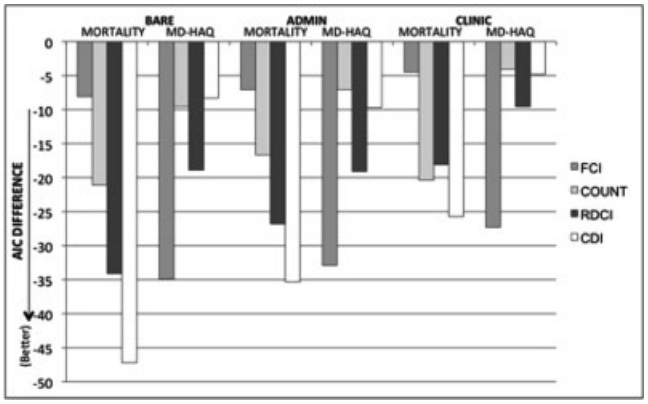
1019

Comparison Of Comorbidity Indexes In a Clinical and Administrative Rheumatoid Arthritis Cohort: A Case For The Rheumatic Diseases Comorbidity Index. Bryant R. England[1], Harlan Sayles[1], Ted R. Mikuls[2], Dannette S. Johnson[3] and Kaleb Michaud[4]. [1]University of Nebraska Medical Center, Omaha, NE, [2]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [3]Jackson VA and University of Mississippi Medical Center, Jackson, MS, [4]National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: Quantifying comorbidities contribution to disability and mortality is important for assessing prognosis and standardizing cohorts in rheumatic disease research. A comorbidity index has been developed specifically for individuals with rheumatic diseases. We compared the Rheumatic Diseases Comorbidity Index (RDCI) with the Charlson-Deyo index (CDI) and Functional Comorbidity Index (FCI) using a nationwide cohort of RA patients.

Methods: The RDCI, range 0–9, combines 11 comorbidities: lung disease, hypertension, MI, stroke, heart disease, cancer, fracture, diabetes, depression, GI problem and ulcer. The predictive value of the RDCI, CDI, FCI, and a generic comorbidity count (COUNT) for outcomes of functional disability and mortality were tested in the Veterans Affairs RA registry by access to administrative ICD9 diagnosis codes. Functional disability was measured by MD-HAQ. Comorbidity indices were fixed at baseline values and patient visits were limited to first visits within each of twenty-one six-month phases from January 2003 to March 2013. Best fit via Cox proportional hazard for mortality and Generalized Estimating Equations for disability models was determined by the Akaike Information Criterion (AIC) where a lower AIC signifies a better model fit. Indices were compared in three models: a bare model [age, sex, and race]; an admin model [bare+ visit frequency, BMI, prednisone, and MTX]; and clinic model [admin+ ESR, nodules, RF+, and patient activity scale].

Results: Each index improved the fit of all models (see Figure). Comorbidity indices decreased AIC most in the bare model and least in the clinic model. CDI decreased AIC most in the mortality analysis while performing worst in MD-HAQ. FCI decreased AIC the most in MD-HAQ analysis but performed worst in mortality. RDCI performed well in both mortality and MD-HAQ analysis.



Conclusion: The RDCI quantifies the contribution of comorbidity to both MD-HAQ and mortality well, while other indices were better predictors of only one outcome. In the first study that compares comorbidity indices with administrative data such as ICD9 codes, RDCI performed well and shows promise for future use in observational studies obtaining data from electronic medical records. Furthermore, we demonstrate when choosing a comorbidity index, the outcome of interest and the variables within the model should guide index selection.

Disclosure: B. R. England, None; **H. Sayles**, None; **T. R. Mikuls**, None; **D. S. Johnson**, None; **K. Michaud**, None.

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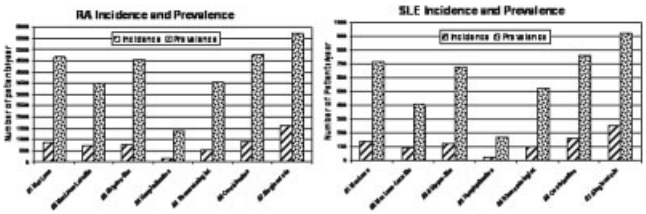
The Impact Of Diagnostic Decision Rules Used In Administrative Healthcare Databases On The Frequency Of Rheumatoid Arthritis and Systemic Lupus Erythematosus. John G. Hanly, Kara Thompson and Chris Skedgel. Dalhousie University and Capital Health, Halifax, NS.

Background/Purpose: To compare the incidence and prevalence of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) in administrative databases using different diagnostic decision rules.

Methods: A retrospective cohort study was performed using administrative health care data from a population of 1 million people with access to universal healthcare. Information was available on hospital discharges and physician billings over a 13 year period. Each RA and SLE case was matched 4:1 by age and gender to randomly selected controls. Seven decision rules, validated against the diagnosis confirmed by a rheumatologist, were used to identify RA and SLE cases and to examine the incidence and prevalence of both diseases.

Results: The overall accuracy of the decision rules for RA cases varied between 68.9–82.9% with a kappa statistic between 0.26–0.53. The sensitivity varied from 20.7–94.8% and the specificity between 62.5–98.5%. For SLE the overall accuracy of the decision rules varied between 88.2–95.6% with a kappa statistic between 0.53–0.86. The sensitivity varied from 41.0–86.6% and the specificity between 92.4–99.9%. The number of incident cases per year was between 176–1610 (0.02–0.17% population) for RA and between 29–255 (0.003–0.027% population) for SLE. The number of prevalent cases per year was between 1384–5722 (0.15–0.61% population) for RA and between 172–920 for SLE (0.018–0.098% population).



Conclusion: The performance of decision rules for the identification of incident and prevalent RA and SLE cases in administrative healthcare databases is variable and should be considered when compareing results across studies.

Disclosure: J. G. Hanly, None; **K. Thompson**, None; **C. Skedgel**, None.

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Application Of a Novel Measure Of Socioeconomic Status Using Individual Housing Data In Rheumatology Research. Young Juhn, Sherine E. Gabriel, Cynthia S. Crowson, Jennifer Rand-Weaver and Elizabeth Krusemark. Mayo Clinic, Rochester, MN.

Background/Purpose: We recently developed and validated an index of socioeconomic status (SES) termed HOUSES (HOUsing-based index of SocioEconomic Status) to address unavailability of SES measures in routinely used data sources for clinical research concerning health disparities. While HOUSES has been associated with various childhood health outcomes, whether HOUSES is associated with adult health outcomes is unknown. Our objective was to assess whether HOUSES (a measure of SES) is associated with risk of and mortality after rheumatoid arthritis (RA).

Methods: We conducted a population-based case-control study among all residents of a geographically-defined area with RA who were identified using 1987 American College of Rheumatology criteria for RA from January 1, 1988 to December 31, 2007. HOUSES was formulated based on z-score for four real property data (housing value, actual square footage, and numbers of bedrooms and bathrooms) and analyzed in categorical (quartiles) and continuous variables. Self-reported educational level and pertinent risk factors for RA were obtained. Logistic regression was used to examine the association between HOUSES and risk of RA. Cox models were used to examine the association between HOUSES and mortality rate during the follow-up after RA adjusting for age, gender, index year of RA, comorbid conditions known to be associated with risk of RA, and therapy for RA.

Results: There were 650 eligible patients who developed RA during the study period and 1:1 matched controls without RA; 604 of RA (93%) and 564 of controls (87%) were successfully geo-coded to real property data. Of these 604 subjects, 418 (69%) were female; the mean age (±SD) was 56±15.6 years, the mean follow-up was 7.7±5.1 years. HOUSES was associated with risk of developing RA (mean±SD: 0.5±3.8 for controls vs. −0.2±3.1 for RA cases, p=0.003) (odds ratio: 1.06 per 1 unit decrease in HOUSES; 95%CI: 1.02–1.09). This association persisted after adjustment for smoking status and body mass index. Cumulative mortality rates at 15 years following RA were 33% (95%CI: (27–39), 27% (21–33), 24% (18–30), and 25% (19–31) for patients in the first (lowest SES), second, third, and fourth quartiles (highest SES) of the HOUSES

index, respectively. The lowest quartile of HOUSES was significantly associated with increased mortality after RA compared to higher quartiles of HOUSES (HR: 1.74; 95%CI: 1.10–2.74; p-value=0.017) adjusting for RA characteristics, comorbidities and RA therapies. The association between HOUSES and mortality after RA was not explained by other known risk factors for mortality after RA. RA therapy such as disease modifying drugs including biologics were not associated with HOUSES nor accounted for the association between HOUSES and mortality after RA.

Conclusion: Lower SES (as measured by HOUSES) is associated with increased risk of RA and mortality after RA. To reduce the gap in differential mortality after RA among individuals with different SES, clinicians or health care systems need to consider their preventive and therapeutic strategies in the patients' social context.

Disclosure: Y. Juhn, None; **S. E. Gabriel**, None; **C. S. Crowson**, None; **J. Rand-Weaver**, None; **E. Krusemark**, None.

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Initiation Of Biologic Therapy: The Patient Perspective. Amir Goren[1], Susan C. Bolge[2], Duncan Brown[3], Roxanne Meyer[4] and Seth Ginsberg[5]. [1]Kantar Health, New York, NY, [2]Janssen Scientific Affairs, LLC, Horsham, PA, [3]Kantar Health, New York, NY, [4]Janssen Scientific Affairs, LLC, Horsham, NY, [5]Creaky Joints, New York, NY.

Background/Purpose: Current guidelines for the treatment of rheumatoid arthritis (RA) recommend that patients who are not adequately responding to treatment with disease modifying anti-rheumatic drugs (DMARDs), most often methotrexate, initiate treatment with biologic therapy. However, from the patient perspective, there may be many other factors which influence this decision. This study describes the experience of patients who are considering biologic therapy to manage their RA.

Methods: Study patients were recruited through two sources: the patient advocacy organization, CreakyJoints, and the Lightspeed Research consumer panel. Patients were U.S. adults (aged ≥18), diagnosed with RA, and currently treated by a rheumatologist with DMARDs. Patients had no history of biologic use but had discussed biologic therapy with their physician. Data were collected directly from patients through a self-administered, web-based questionnaire.

Results: Among the 243 patients who completed the study, the mean (SD) time that elapsed since discussions about biologic therapy began was 1.3 (1.8) years over a mean (SD) of 2.7 (2.6) office visits. Rheumatologists were most likely to initiate the discussion (54%), but 23% of patients reported initiating it. A majority of patients (>73%) reported discussing the following aspects of biologic therapy either somewhat or in detail: ability to improve well-being or daily functioning; ability to improve mobility or range of motion; ability to slow or stop joint damage; potential side effects; how treatment is taken/administered; and frequency of administration. However, fewer than 39% of patients reported discussing the subcutaneous injection experience, the intravenous infusion experience, or financial and treatment support programs. Most patients believe they are the primary decision maker: 25% make the final decision about treatment and 49% make the final decision after considering their rheumatologist's recommendation. When making treatment decisions, 74% of patients reported that they consider both their current and future situations, though 15% only consider the present and 10% only consider the future.

Conclusion: Patients with RA are active participants in the process of initiating biologic therapy. Rheumatologists should actively engage their patients in the shared-decision making process for initiating biologic therapy. As demonstrated by previous research, effective communication between patients and providers may have a positive impact on patient satisfaction and adherence to therapy.

Disclosure: A. Goren, Janssen Scientific Affairs, LLC, 5; **S. C. Bolge**, Janssen Scientific Affairs, LLC, 3; **D. Brown**, Janssen Scientific Affairs, LLC, 5; **R. Meyer**, Janssen Scientific Affairs, LLC, 3; **S. Ginsberg**, Janssen Scientific Affairs, LLC, 5.

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Openness To and Preference For Biologic Therapy Among Patients With Rheumatoid Arthritis Prior To Biologic Initiation: Patient and Prescriber Perspectives. Susan C. Bolge[1], Duncan Brown[2], Amir Goren[3], Roxanne Meyer[4] and Seth Ginsberg[5]. [1]Janssen Scientific Affairs, LLC, Horsham, PA, [2]Kantar Health, New York, NY, [3]Kantar Health, New York, NY, [4]Janssen Scientific Affairs, LLC, Horsham, NY, [5]Creaky Joints, New York, NY.

Background/Purpose: Currently two modes of administration are available for biologic therapies used to treat rheumatoid arthritis (RA): subcutaneous injection (SQ) and intravenous infusion (IV). Patient preference for mode of administration may be among the factors influencing choice of therapy. The purpose of this study was to explore openness to and preference for biologic therapy among patients with RA prior to biologic initiation from the perspectives of both patients and prescribers.

Methods: Data were collected online from both patients and prescribers through self-administered questionnaires. Patients were U.S. adults (aged ≥18), diagnosed with RA, currently treated by a rheumatologist with disease modifying anti-rheumatic drugs (DMARDs), and with no history of biologic use but had discussed biologics with their physician. Prescribers were board certified rheumatologists, practicing for 2–25 years, spent ≥50% of their time in a clinical setting seeing ≥50 RA patients per month, and were not government employees or employed by or consultants to pharmaceutical companies. A total of 243 patients were recruited through the patient advocacy organization CreakyJoints (n=101) and a consumer panel (n=142); 103 prescribers were recruited through a physician panel.

Results: Among all study patients, 53% were open to both SQ and IV therapies, 16% were open only to SQ, 14% were open only to IV, and 16% were open to neither. However, prescribers believed that 41% of patients are open to considering both SQ and IV therapies, 34% are open only to SQ, 13% are open only to IV, and 12% are open to neither. When asked about preference for SQ vs. IV therapy, 22% of patients had no preference, while 49% preferred SQ and 28% preferred IV. Prescribers believed that 31% of patients have no preference, while 52% prefer SQ and 16% prefer IV. Patient openness to and preference for SQ vs. IV therapy was further influenced by frequency of administration, time to complete an infusion, and site of care.

Conclusion: More patients may be open to both SQ and IV biologic therapy and more patients may prefer IV biologic therapy than rheumatologists currently believe. Rheumatologists are well positioned to guide the shared-decision making process with patients to ensure that patients are provided with information about all appropriate biologic therapy options and that patient preferences are considered when making prescribing decisions.

Disclosure: S. C. Bolge, Janssen Scientific Affairs, LLC, 3; **D. Brown**, Janssen Scientific Affairs, LLC, 5; **A. Goren**, Janssen Scientific Affairs, LLC, 5; **R. Meyer**, Janssen Scientific Affairs, LLC, 3; **S. Ginsberg**, Janssen Scientific Affairs, LLC, 5.

1024

Modeling The Benefit Risk Profiles Of a New Janus Kinase Inhibitor Tofacitinib Compared Tottumour Necrosis Factor Inhibitor Biologic Treatments Incorporating Conjoint Derived Patient Preference Weights. Michael P. Ingham[1], Shannon Cartier[2], Raphael J. DeHoratius[3], Jack McGowan[3] and Eric Sabot[2]. [1]Janssen Scientific Affairs, LLC, Horsham, PA, [2]Optum, Eden Prairie, MN, [3]Janssen Services, LLC, Horsham, PA.

Background/Purpose: Tofacitinib (Tofa) was recently approved in the U.S. There are no data comparing the benefit risk profile of Tofa to tumor necrosis factor inhibitors (TNFi). This analysis included a conjoint survey of rheumatology patients' preferences, followed by a benefit-risk assessment combining multiple benefits and risks associated with Tofa vs. TNFi.

Methods: The patient preference study investigated 10 attributes, Patient cost, ACR20, Oral vs Injection vs Infusion, Injection site/infusion reactions, Nausea, Herpes Zoster, Malignancies, and Cholesterol elevation. Attribute "levels" were assigned from pivotal trial data, meta-analyses, FDA documents and prescribing information. Levels encompassed a plausible range of values. Each patient was asked to complete a preference selection for 15 choice tasks, based on a randomized design using a 5-attribute partial profile. A Multi-Criteria Decision Analysis (MCDA), a tool from the EMEA risk-benefit project, was used to assess the overall benefit-risk profile, incorporating differences in outcomes and using the conjoint survey to weight each attribute's relative importance. The base case profile identified Tofa as having a less robust ACR20 response, higher incidence of malignancy and herpes zoster risk, greater impact on cholesterol, lower levels of injection site/infusion reactions and oral vs injection/infusion.

Results: 386 patients had evaluable data from the conjoint preference study. 71% were female and median age was between 60 and 64. Fifty-one patients (13%) were bio-naïve. Attributes that showed the greatest impact on preference perception between top and bottom levels included out-of-pocket costs, injection site reactions, dose interval/mode and impact on cholesterol. There was little difference between injection site reactions levels of none and 4/100 patient years (PY), as well as between dose interval/mode of oral at 730 doses per year and injections at 12 times per year. For dose interval/mode, the least preferred option was injections 26–52 times per year. Based on base case profiles assigned to individual products, 42% of patients would choose golimumab, 34% an oral DMARD and 24% infliximab. If all Tofa risk

attribute differences vs TNFi were removed, 53% would choose Tofa, 28% golimumab and 19% infliximab. Etanercept and Adalimumab preferences were sensitive to rate of injection site reactions. The MCDA estimated a greater combined score for TNFi compared to Tofa, indicating that from a patient perspective TNFi are a more favorable treatment option overall. A major contributing factor to this outcome was the relative importance that patients placed on risk attributes which favored the TNFi profile.

Conclusion: Patients appear sensitive to relatively small changes in tolerability and safety profiles of rheumatology treatments. Benefit and risk profiles can have significant mitigating influence over patient preferences related to convenience of treatment. This reinforces the need for full and clear disclosure to patients of the benefit and risks of treatments in RA and the importance of patient involvement in treatment decisions, since lack of preference can have an impact on adherence.

Disclosure: M. P. Ingham, Janssen Scientific Affairs, LLC, 3; **S. Cartier**, Janssen Scientific Affairs, LLC, 5; **R. J. DeHoratius**, Janssen Biotech., 3; **J. McGowan**, Janssen Scientific Affairs, LLC, 3; **E. Sabot**, Janssen Scientfic Affairs, LLC, 5.

1025

Mapping The Health Assessment Questionnaire On a Preference Based Utility Measure In a Large Canadian Rheumatoid Arthritis Cohort: Results From The Ontario Best Practices Research Initiative. Mark Tatangelo[1], George A. Tomlinson[2] and Claire Bombardier[1]. [1]University of Toronto, Toronto, ON, [2]Toronto General Hospital, Toronto, ON.

Background/Purpose: mANMClinical trials are limited in demonstrating the cost effectiveness of biologic therapies, as these studies often do not collect measures required for economic analysis. Thus we sought to provide a validated algorithm, allowing utility scores to be estimated using mapping (also known as "cross-walking") of the Health Assessment Questionnaire Disease Index (HAQ-DI) onto a standardized utility measure (EQ-5D).

Methods: We studied 5971 patient visits for 1911 patients included in the Ontario Best Practices Research Initiative, a clinical registry of RA patients followed in routine care (2008–2013). Data were collected every 6 months and include patient demographics, socioeconomic status, clinical variables, disease activity measures, and HAQ-DI and EQ-5D. Each patient's EQ-5D score was converted to a utility value using a Canadian tariff. EQ-5D utility values were then predicted from HAQ-DI scores using a linear random effects model. HAQ-DI scores were entered as predictors in the model. Random effects for each patient were fitted for intercepts and slopes for the effect of HAQ-DI. Linearity was assessed by fitting non-parametric estimate calculated by mean EQ-5D grouped by HAQ scores.

Results: The estimated fixed effect change in EQ-5D for each point of the HAQ-DI scores is −0.15 (SE=0.0027, P<0.001), with a $RMSE$= 0.099, and R^2=0.68. Examination of the residual plots suggested mild departures from normality with slightly smaller variance for large EQ-5D values (Figure 1). EQ-5D health utility scores showed a ceiling effect, with 1621 observations achieving a utility value of 1 (perfect health).

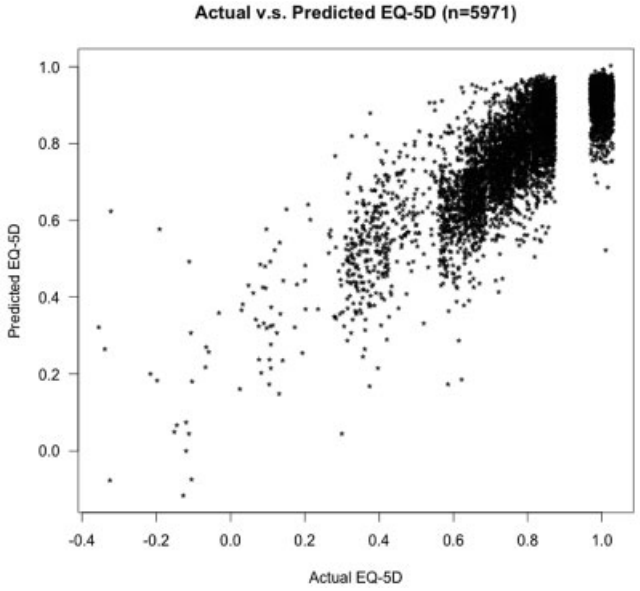

Figure 1.

Conclusion: Preference based utility values like the EQ-5D can be estimated using measures such as the HAQ. These results are important because they allow for accurate prediction of average utility values from functional measures included in current clinical trials. This model will allow for economic analyses of the benefit of biologic rheumatic drugs in Quality Adjusted Life Years that are meaningful to payers. Future analysis will use each HAQ item to predict EQ-5D utility score, and external validation of the algorithm.

Disclosure: M. Tatangelo, None; **G. A. Tomlinson**, None; **C. Bombardier**, None.

1026

Impact Of Basing Rheumatoid Arthritis Disease Activity Measurement and Treatment Recommendations On Patient Instead Of Physician Joint Assessments. Yomei Shaw[1], Daisy Bang[2], Heather Eng[1], Stephen R. Wisniewski[1], Mark S. Roberts[1] and Marc C. Levesque[2]. [1]University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Current guidelines recommend treatment for rheumatoid arthritis (RA) be informed by a measure of disease activity such as the Disease Activity Score-28 (DAS28-CRP), which includes physician assessments of tenderness and swelling in joints. We explored the impact of basing disease activity measurement and treatment recommendations for RA patients on patient joint assessments rather than physician assessments.

Methods: 364 RA subjects enrolled in the Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry and their physicians performed independent and blinded exams of 28 joints for tenderness and swelling during routine clinic visits. Subjects assessed their own joints assisted by a web-based tool that provided illustrations and instructions. We measured discrepancies in the DAS28-CRP, disease activity categories and treatment recommendations (following American College of Rheumatology (ACR) guidelines for therapy adjustment) when based on patient vs. physician assessments. Treatment recommendations were compared with actual treatment decisions for 342 subjects.

Results: Mean DAS28-CRP scores based on patient assessments were higher than when based on physician assessments (mean ±SD, 3.49 ±1.50 vs. 3.02 ±1.25; p<0.0001). In 56% of 364 cases, the patient and physician-based DAS28-CRP led to categorization in the same disease severity level; in 44% of cases the patient and physician-based scores led to discrepant categorizations. In 84% of cases the physician and patient-based scores would yield the same recommendation regarding therapy adjustment, but in 16% of cases they would yield different recommendations. When evaluating actual decisions against treatment recommendations based on ACR guidelines (n=342), only 8.77% of patients actually adjusted therapy, compared to 33.33% and 39.18% recommended to adjust therapy according to physician and patient DAS28-CRP, respectively (Table 1). Actual rates of therapy adjustment were low among those subjects recommended to adjust therapy (16.7% when assessed by physician DAS28-CRP and 14.9% when assessed by patient DAS28-CRP (Table 1)).

Table 1. Physician- and patient-DAS28-CRP based treatment recommendations versus actual decisions (n = 342)

		Actual decisions		
		Therapy adjusted (n = 30, 8.77%)	Therapy not adjusted (n = 312, 91.23%)	Row total (%) (n = 342, 100%)
Physician-DAS28-CRP-based treatment recommendation	Recommended to adjust therapy (n, row %)#	19 (16.7%)	95* (83.3%)	114 (33.33%)
	Not recommended to adjust therapy (n, row %)	11* (4.8%)	217 (95.2%)	228 (66.67%)
Patient-DAS28-CRP-based treatment recommendation	Recommended to adjust therapy (n, row %)*	20 (14.9%)	114* (85.1%)	134 (39.18%)
	Not recommended to adjust therapy (n, row %)	10* (4.8%)	198 (95.2%)	208 (60.82%)

* Undertreated, *Overtreated.
# Both physician and patient-DAS28 based recommendations were significantly different from actual decisions (p < 0.0001), but not significantly different from each other (p = 0.1307).

Conclusion: Although discrepancies in disease severity categorization occurred frequently (44% of the time), discrepancies in RA treatment recommendations arose less frequently (16% of the time) as a result of differences in patient and physician joint exams. Regardless of whether

treatment recommendations were based on patient or physician joint exams, actual treatment decisions often appeared to be inconsistent with disease severity, primarily because therapy was often not adjusted despite > 3 months of moderate to high disease activity. Further research will explore disease and health-related outcomes associated with miscategorizing disease severity and under-treating RA patients.

Disclosure: Y. Shaw, Genentech and Biogen IDEC Inc., 2; **D. Bang**, None; **H. Eng**, Genentech and Biogen IDEC Inc., 2; **S. R. Wisniewski**, Genentech and Biogen IDEC Inc., 2; **M. S. Roberts**, None; **M. C. Levesque**, Genentech and Biogen IDEC Inc., 2, UCB, 5, AbbVie, 9, Crescendo, 5, Baxter Healthcare, 5.

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Factors Associated With Decisions To Adjust Therapy For Rheumatoid Arthritis Patients In Moderate To High Disease Activity. Yomei Shaw[1], Chung-Chou H. Chang[2], Heather Eng[1], Ilinca D. Metes[2], Stephen R. Wisniewski[1], Mark S. Roberts[1] and Marc C. Levesque[2]. [1]University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: The American College of Rheumatology (ACR) recommends treating rheumatoid arthritis (RA) to the target of low disease activity or remission with traditional and biologic disease-modifying anti-rheumatic drugs (DMARDs). However, significant numbers of RA patients do not receive care consistent with these recommendations. Previously, we found that age, race, physician age, current use of a biologic, Disease Activity Score-28 joint (DAS28-CRP), and RA duration were significantly associated with decisions to adjust DMARD therapy for RA patients with moderate to high disease activity. Here, we present an update to our findings with new covariates added to the analysis, including income and comorbidities, which were adjusted for to prevent confounding bias in the effects of age and race.

Methods: Data was drawn from the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Research (RACER) observational registry (2010–13) on visits where patients had moderate to high disease activity for at least 3 months. Therapy adjustment was defined as adding, switching, or increasing the dose of oral or biologic DMARD therapy. To assess this binary outcome, a generalized linear model with logit link was used. Generalized estimating equations (GEE) with clustering by patient were used to account for correlation between different visits for each patient. Variables significant in univariable GEE analyses (Wald test on coefficient has $p<0.2$) were entered into a multivariable model, then backwards selection was used to choose the final model by removing variables with $p>0.05$. The model controlled for patient demographic and disease characteristics: age, race, gender, RA duration, DAS28-CRP, Short Form 12 (SF12) physical and mental components, Health Assessment Questionnaire (mdHAQ), and two new variables (income and Charlson comorbidity index).

Results: There were 562 visits for 255 patients with moderate to high disease activity for at least 3 months. Therapy was adjusted at 23.1% of visits. The odds ratios (OR; [95% CI]) of adjusting therapy were decreased by longer disease duration (0.965; [0.943,0.987]), physician age (0.955; [0.932,0.978]), current use of biologic therapy (0.394; [0.240,0.648]), and lower DAS28-CRP (0.640; [0.455,0.900]). Age and race were no longer significant.

Conclusion: In the RACER observational cohort, 76.9% of RA patients with moderate/high disease activity for at least 3 months did not have DMARD therapy adjusted. Physician age, duration of RA, lower DAS28, and current use of biologic therapy decreased the likelihood of therapy adjustment. The fact that age and race were no longer significant upon the addition of Charlson comorbidity index and income to the model suggests that these new variables may partially explain the previously observed effects of age and race. These results can be used to improve treat-to-target strategies in clinical practice. Our future research will explore how other factors such as prior use of DMARDs/corticosteroids, insurance coverage, and risk aversion may influence treatment decisions for RA patients with moderate/high disease activity.

Disclosure: Y. Shaw, Genentech and Biogen IDEC Inc., 2; **C. C. H. Chang**, None; **H. Eng**, Genentech and Biogen IDEC Inc., 2; **I. D. Metes**, Genentech and Biogen IDEC Inc., 2; **S. R. Wisniewski**, Genentech and Biogen IDEC Inc., 2; **M. S. Roberts**, None; **M. C. Levesque**, Genentech and Biogen IDEC Inc., 2, UCB, 5, AbbVie, 9, Crescendo, 5, Baxter Healthcare, 5.

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Development Of Patient-Reported Outcomes Measurement Information System (PROMIS®) Gastrointestinal (GI) Symptoms Item Bank. Dinesh Khanna[1], Lin Chang[2], Gil Y. Melmed[3], Roger Bolus[4], Puja Khanna[1], Ron Hays[5] and Brennan Spiegel[5]. [1]University of Michigan Medical Center, Ann Arbor, MI, [2]David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA, [3]Cedar-Sinai Medical Center, Los Angeles, CA, [4]Research Solutions Group, Encinitas, CA, [5]University of California, Los Angeles, Los Angeles, CA.

Background/Purpose: The National Institutes of Health PROMIS® roadmap initiative is a cooperative research program designed to develop, evaluate, and standardize item banks to measure patient-reported outcomes (PROs) across different medical conditions as well as the US population (www.nihpromis.org). PROMIS includes items banks that assess self-reported physical, mental, and social health. The aim of this study was to develop GI Symptoms measures applicable to patients with GI illness and the general population.

Methods: A systematic review was conducted to find relevant articles assessing PROs in GI diseases and a conceptual model was proposed for different GI symptoms scales (Spiegel et al Am J Gastroentrol 2011). The individual items from extant instruments were grouped based on different symptoms. This was complemented by 12 focus groups including 102 patients with GI conditions to evaluate their symptoms. New items were developed based on extant items and input from the focus group participants followed by cognitive debriefing in 28 patients with GI conditions. Preliminary items were administered to the patients (irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), systemic sclerosis (SSc), and other common GI disorders) and the US General Population (GP, based on 2010 census data). Patients were recruited from academic, Veterans Affairs, and private practices and completed the survey predominantly on the web using SurveyMonkey® software and the US GP using the Cint®. Items were finalized based on psychometric analyses including categorical confirmatory factor analyses and item response theory modeling to estimate item thresholds and discrimination parameters.

Results: 102 items were developed after qualitative analysis (N=130 patients) and administered to 865 patients with GI conditions and 1177 participants from the US GP. Patients were older (mean age 48 vs. 45 years), more educated (86% vs. 62% with >=some college degree), and reported greater moderate to very-severe overall GI symptoms in the past 1 week (57% vs. 26%). Patients' self-reported GI conditions included IBS (40%), GERD (33%), IBD (28%), chronic constipation (24%), SSc (16%), and other GI conditions. Confirmatory factor analyses provided support for 8 scales: Gastroesophageal reflux (13 items), disrupted swallowing (7 items), diarrhea (5 items), bowel incontinence/soilage (4 items), nausea and vomiting (4 items), constipation (9 items), belly pain (6 items), and gas/bloat/flatulence (12 items). All scales are calibrated using the two-parameter IRT graded response model and scored on a T-score metric with a mean of 50 and SD of 10 in the U.S. general population.

Conclusion: Using NIH PROMIS framework, we have developed a 60-item GI Symptoms scale that can be used for clinical care and trials.

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Quality Of Life In Rheumatoid Arthritis: Cross-National Comparison Study Between US and South Korea. Yoon-Kyoung Sung[1], Kazuki Yoshida[1], Femke H.M. Prince[1], Michelle A. Frits[1], Jung-Yoon Choe[2], Won Tae Chung[3], Jisoo Lee[4], Eun-Mi Koh[5], Dae-Hyun Yoo[6], Simon M. Helfgott[1], Nancy A. Shadick[1], Michael E. Weinblatt[1], Sang-Cheol Bae[6] and Daniel H. Solomon[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Catholic University of Daegu School of Medicine, Daegu, South Korea, [3]Dong-A University Hospital, Busan, South Korea, [4]Ewha Womans University Mokdong Hospital, Seoul, South Korea, [5]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [6]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea.

Background/Purpose: Quality of life (QOL) is a well-established outcome for rheumatoid arthritis (RA) trials. To perform trials with QOL as an outcome involving many countries, it is valuable to compare QOL measures

across countries. The objective of this study was to compare health-related quality of life (HRQOL) of rheumatoid arthritis (RA) patients between United States (US) and South Korea.

Methods: Two year follow-up data on health and HRQOL measured with EuroQoL-5 dimension (EQ-5D) between 2009 and 2011 were compared between US-based (BRASS) and Korean-based (KORONA) cohorts. A total of 1,166 subjects (187 from BRASS and 979 from KORONA) were included in this study to compare the cross-sectional differences in QOL in 2009 and the longitudinal two-year change through 2011. We performed multivariate linear regression analyses to identify factors associated with QOL and its changes in each cohort.

Results: The mean (standard deviation) of EQ-5D score (1.0 being the best possible score) of BRASS subjects was 0.82 (0.16) and that of KORONA subjects was 0.69 (0.25) ($P < 0.01$) at baseline in 2009 (see table). Disease activity score (DAS) 28 ($P<0.01$) and modified health assessment questionnaire (MHAQ) score ($P<0.01$) were inversely associated high QOL in both cohorts. Income level ($P<0.01$) was positively and the number of comorbidities ($P<0.01$) was negatively associated with QOL only in KORONA (see table). Mean changes in QOL were not different between cohorts ($P=0.17$). Only changes in DAS28 and MHAQ during 2 years were significantly associated with the change in QOL in both cohorts.

Table. Multivariate linear regression analyses of predictors for utility score in 2009 and change until 2011

	EQ-5D in 2009				ΔEQ-5D between 2009 and 2011			
Cohort	BRASS (161)		KORONA (947)		BRASS (159)		KORONA (934)	
R^2(adjusted R^2)	0.57 (0.53)		0.59 (0.58)		0.27 (0.21)		0.28 (0.27)	
	B (95% CI)	*P*	B (95% CI)	*P*	B (95% CI)	*P*	B (95% CI)	P
Intercept	0.77 (0.63~0.92)	<0.01	0.96 (0.85~1.07)	<0.01	0.11 (−0.07~0.30)	0.23	−0.12 (−0.25~0.02)	0.10
Age	0.001 (−0.001~0.003)	0.30	−0.0001 (−0.001~0.001)	0.83	−0.0009 (−0.003~0.001)	0.43	0.001	0.17
Disease duration	0.001 (−0.001~0.003)	0.22	0.0002 (−0.001~0.002)	0.79	0.0002 (−0.002~0.003)	0.88	0.001	0.46
Income	*0.02 (−0.002~0.04)*	*0.07*	**0.03 (0.01~0.05)**	**<0.01**	0.003 (−0.02~0.03)	0.80	−0.01 (−0.04~0.01)	0.28
Education	*0.03 (−0.01~0.07)*	*0.09*	−0.02 (−0.05~0.01)	0.19	−0.04 (−0.09~0.01)	0.13	*0.03 (0~0.07)*	*0.07*
Number of comorbidity	0.01 (−0.01~0.04)	0.32	**−0.02 (−0.04~−0.01)**	**0.01**	−0.02 (−0.05~0.02)	0.35	0.01 (−0.01~0.08)	0.54
Female	−0.01 (−0.05~0.04)	0.80	*−0.03 (−0.06~0.002)*	*0.06*	−0.01 (−0.07~0.04)	0.62	0.002 (−0.04~0.04)	0.93
Rheumatoid Factor	0.02 (−0.02~0.06)	0.28	0.01 (−0.03~0.04)	0.68	0.01 (−0.04~0.06)	0.68	0.03 (−0.01~0.08)	0.17
Biologic DMARD	*0.03 (−0.004~0.07)*	*0.08*	0.004 (−0.04~0.04)	0.85	−0.01 (−0.06~0.03)	0.63	−0.04 (−0.09~0.02)	0.17
NSAID	−0.02 (−0.05~0.02)	0.30	−0.004 (−0.03~0.02)	0.72	0.03 (−0.02~0.07)	0.21	0.02 (−0.01~0.04)	0.27
Steroid	−0.004 (−0.04~0.05)	0.86	−0.01 (−0.03~0.02)	0.50	−0.04 (−0.10~0.02)	0.17	−0.01 (−0.04~0.02)	0.58
DAS28-CRP	**−0.04 (−0.05~−0.03)**	**<0.01**	**−0.05 (−0.06~−0.03)**	**<0.01**				
Modified HAQ	**−0.18 (−0.24~−0.13)**	**<0.01**	**−0.35 (−0.38~−0.32)**	**<0.01**				
Δ DAS28-CRP					**−0.03 (−0.04~−0.01)**	**<0.01**	**−0.04 (−0.05~−0.03)**	**<0.01**
Δ Modified HAQ					**−0.17 (−0.23~−0.10)**	**<0.01**	**−0.28 (−0.31~−0.24)**	**<0.01**

*P<0.05; BRASS, Brigham Rheumatoid Arthritis Sequential Study; KORONA, KORean Observational study Network for Arthritis; OR, odds ratio; CI, 95% confidence interval; HAQ, health assessment questionnaire

Conclusion: In this cross-national comparison study, changes in QOL and predictors for QOL were comparable between US-based BRASS and Korean-based KORONA, in spite of the differences in baseline characteristics and QOL level in each population.

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Readability of Participant Information and Consent Forms for Rheumatology Clinical Trial Participants. Stephen Hall[1], Gail Grant[2] and Christina Meyer[2]. [1]Melbourne Rheumatology, Melbourne, Australia, [2]emeritus research, melbourne, Australia.

Background/Purpose: To determine the readability of written information (Participant Information and Consent Forms [PICS]) provided to clinical trial participants prior to enrolment into a clinical trial. General recommendations for reading age are that reading materials should be at educational level of year 8 or below

Methods: PICS over a time frame 2003–2013 from a dedicated clinical trials site were assessed for reading age. 81 industry derived PICs for musculoskeletal studies, 4 investigator initiated PICS and 3 non–drug study PICS were reviewed using a number of validated reading age tools -Flesch Reading Ease; Gunning FOG; Flesch-Kincaid Grade Level; The Coleman Liau Index; The SMOG Index; Automated Reading Index; Linsear Write Formula readability scores-to estimate readability of specific subsections. Specific sub-sections of the PICs from industry sponsored studies were reviewed–confidentiality/privacy section and the Risk Section.

Results: Only 4% of documents conformed to a recommended reading age of year 8 or below. The majority of documents had high reading ages with 93–96% pitched at year 10 or greater. 34–70% required reading levels of college graduate or postgraduate. A study of a small number of non-industry studies demonstrated similar results

Conclusion: Current information materials provided to potential clinical trial participants fall far short of recommended readability levels potentially compromising the process of informed consent. Further attention needs to be paid to this aspect of clinical trials

Disclosure: S. Hall, None; **G. Grant**, None; **C. Meyer**, None.

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Health Literacy Predicts Discrepancies Between Traditional Written Rheumatoid Arthritis Patient Assessments and Verbally-Administered Assessments. Joel M. Hirsh[1], Lisa A. Davis[2], Itziar Quinzanos[3], Angela Keniston[1] and Liron Caplan[4]. [1]Denver Health and Hospital Authority, Denver, CO, [2]Univ. of Colorado Sch. of Medicine, Aurora, CO, [3]University of Colorado School of Medicine, Aurora, CO, [4]Denver Veterans Affairs Medical Center, Denver, CO.

Background/Purpose: Patient assessments of disease activity (PtGA) and general health (GH) measured by visual analog scale (VAS) are widely used in rheumatoid arthritis (RA) clinical practice and research. These require comprehension of the question's wording and the translation of disease activity onto a written VAS, which is problematic for patients with poor vision, limited health literacy (HL), and others unable to complete forms due to hand deformities or neurologic or muscular disorders. The objective of this study was to validate verbally-administered versions of patient assessments and identify factors that might explain discrepancies between verbal and written measures.

Methods: We enrolled RA patients at the Denver Health rheumatology clinic in our study. Subjects completed the traditional written PtGA and GH and one of the verbal assessments. Subjects provided a verbal numeric response after reading the question, having the question read to them in person, or hearing the question over the phone. Spearman correlations comparing written and verbal assessments were determined. Multivariate logistic regression was performed to explain any discrepancies.

Results: Our subjects (n=300) were predominantly female, unmarried and currently unemployed. This cohort was diverse, consisting of approximately half non-white and 58% Hispanic. Limited HL was a common finding as 28% of patients had either inadequate or marginal HL. The verbally administered instruments showed good, but not excellent, correlation with traditional written VAS forms (Spearman coefficients 0.59 to 0.74; $p<0.001$ for all correlations). Approximately one-third of patients provided verbal PtGA and GH responses that were discrepant by more than 2 standard deviations with their PtGA-VAS and GH-VAS, respectively. Twenty-three percent of subjects were unable to complete the one of the VAS assessments without assistance. HL predicted missing written data and discrepancies between verbal and written assessments ($p<0.05$ for all correlations, see Table).

Table. Final multivariate logistic regression models predicting: 1) odds of a discrepancy between verbally-administered and written patient assessments; and 2) odds of a missing patient assessment score.

Variable	Odds Ratio	Std. Err.*	p-value	95% CI	
Odds of a verbally-administered PtGA and traditional written PtGA-VAS discrepancy					
S-TOFHLA comprehension score	0.959	0.012	0.001	0.936	0.983
Odds of a verbally-administered GH and traditional written GH-VAS discrepancy					
S-TOFHLA numeracy score	0.940	0.028	0.042	0.887	0.998
Odds of a missing PtGA value					
S-TOFHLA comprehension score	0.899	0.021	0.000	0.859	0.941
Age (years)	0.952	0.018	0.011	0.917	0.989
Odds of a missing GH value					
S-TOFHLA comprehension score	0.965	0.010	0.001	0.946	0.985

* Std. Err = standard error; CI = confidence interval; PtGA = patient global assessment, as utilized in disease activity score with 28 joint count (DAS28); VAS = visual analog scale; S-TOFHLA = short test of functional health literacy in adults; GH = global health assessment, as utilized in multi-dimensional health assessment questionnaire (MDHAQ).

Conclusion: Verbally-administered PtGA and GH are appropriate for use in population based-studies and randomized control trials, where the results are important for the cohort as a whole. Providers should use verbal versions of PtGA and GH with caution while caring for individual patients unable to complete traditional written version. Limited HL is widely prevalent and a barrier to obtaining patient-oriented data.

Disclosure: J. M. Hirsh, None; **L. A. Davis**, None; **I. Quinzanos**, None; **A. Keniston**, None; **L. Caplan**, None.

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Shared Decision-Making In The Choice Of Biologic Medication: The Patient Perspective. Susan C. Bolge[1], Helen Eldridge[2] and Michael P. Ingham[1]. [1]Janssen Scientific Affairs, LLC, Horsham, PA, [2]Janssen Services, LLC., Titusville, NJ.

Background/Purpose: There has been increasing focus on the importance of patients participating in the treatment decision-making process with their physicians. Previous research has demonstrated that effective physician-patient communication, a key component of shared decision-making, has a positive impact on patient satisfaction and adherence to therapy.[1] The purpose of the study is to understand the patient role in decisions about mode of administration when initiating biologic therapy.

Methods: In November 2011 through March 2012, semi-structured telephone interviews were conducted with 405 patients diagnosed with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, currently using biologic therapy administered through subcutaneous injection (SQ), and residing in the United States. In August through September 2010, a similar study was conducted among a broader group of immunology patients currently using biologic therapy administered through intravenous infusion (IV), of which 209 were diagnosed with a rheumatology condition. The purpose of both studies was to better understand the patient experience with biologic therapies.

Results: Among rheumatology patients currently using SQ biologic therapy, only 45.2% were offered an IV option prior to initiating SQ therapy. However, most SQ patients reported that they themselves made the decision to use a SQ therapy either independently (24.6%) or in partnership with their physician (56.8%). Only 15.3% of patients reported that their physician made the decision independently. Among rheumatology patients currently using IV biologic therapy, slightly more than half (54.1%) were also offered a SQ option prior to initiating IV therapy. As was the case with current SQ users, most current IV users reported that they themselves most greatly influenced the decision to use an IV therapy either independently (15.0%) or in partnership with their physician (44.2%), while 32.7% of patients reported that their physician most greatly influenced the decision.

Conclusion: While many patients report being active decision makers, most often in partnership with their physician, patient decisions are quite frequently based on only a subset of the available biologic options. For patients to be active participants in the shared-decision making process, they need to understand both SQ and IV options. Rheumatologist offices are well positioned to ensure that patients are provided the information and options needed to fully engage in the shared decision-making process.

[1]Elwyn G, et al. Shared decision-making in primary care: the neglected second half of the consultation. Br J Gen Pract 1999;49:477–82.

Disclosure: S. C. Bolge, Janssen Scientific Affairs, LLC, 3; **H. Eldridge**, Janssen Scientific Affairs, LLC, 3; **M. P. Ingham**, Janssen Scientific Affairs, LLC, 3.

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Psychological status correlates of disease activity and sleep quality in patients with Ankylosing Spondylitis: A case-control study. Mingcan Yang[1], Yutong Jiang[1], Zhiming Lin[2], Zetao Liao[3], Qiuxia Li[4], Yanli Zhang[1] and Jieruo Gu[5]. [1]Third affiliated hospital of Sun Yat-sen University, Guangzhou, China, [2]third affiliated hospital of Sun Yat-sen Universtiy, Guangzhou, China, [3]THIRD AFFILIATED HOSPITAL OF SUN YAT-SEN UNIVERSIT, Guangzhou, China, [4]The Affiliated Third Hospital of Sun Yat-san University, Rheumatology, Guangzhou, China, [5]Third Affiliated Hospital of Sun Yat-sen University, Guang-Zhou, China.

Background/Purpose: The objective of this study was to compare psychological status and sleep quality between the patients with AS patients and healthy controls, and to discover the correlation between anxiety, depression and sleep disturbances, to evaluate the associated factors of disease specific variables in AS patients and to detect independent factors contributing to psychological variables.

Methods: A nationwide face-to-face epidemiological investigation was performed in multiple centers of China. The demographic data, clinical symptoms/signs and psychological assessment data including Zung self-rating anxiety scale (SAS), Zung self-rating depression scale (SDS) and the Pittsburgh Sleep Quality Index questionnaire (PSQI) were collected using questionnaires. Mann-Whitney U test and t test was used in independent groups for parametric variables, whereas the Spearman correlation analysis and multiple stepwise regression analysis were used to assess correlation between parametric variables.

Results: 683 AS patients by the revised New York criteria for AS and 697 age-, sex-, education- matched healthy controls were enrolled in the study. (1) Compared with healthy controls, AS patients suffered from more severe psychological disorders and sleep disturbance ($P<0.001$), and the prevalence rate of comorbidity of anxiety- depression-sleep disorders was significantly higher (32.3%vs. 2.4%, $p<0.001$) . (2) Spearman rank correlation analysis found the following variables to be significantly associated with the SAS score: disease duration, morning stiffness and duration, overall pain, back pain, BASDAI, BASFI, SDS score and all components of the PSQI score positively and years of education negatively ($P<0.05$). The SDS score were significantly associated with degree and duration of morning stiffness, overall pain, back pain, BASDAI, BASFI, SAS and all components of the PSQI score positively, and years of education negatively($P<0.05$). (3) In multiple regression analysis, SAS and SDS contributed most to each other, with standardized coefficients of 0.674 and 0.598 respectively. Meanwhile SAS ($P=0.000$) and SDS ($P=0.031$) contributed significantly to sleep disorder.

Conclusion: A large number of AS patients were reported to have anxiety, depression, sleep disturbance. Various psychological abnormalities factors influence one another, there is anxiety-depression-sleep disorders comorbidity phenomenon. Psychological abnormalities factors associated with disease activity in AS patients, there was physical-psychological comorbidity phenomenon.

Disclosure: M. Yang, None; **Y. Jiang**, None; **Z. Lin**, None; **Z. Liao**, None; **Q. Li**, None; **Y. Zhang**, None; **J. Gu**, None.

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The Part Of Function (Health assessment Questionnaire) In The SF-6D and EQ-5D Utility Measures Varies Over Time In Early Arthritis (ESPOIR cohort): Questionable Validity Of Deriving Quality Adjusted Life Years From HAQ. Cécile Gaujoux-Viala[1], Anne-Christine Rat[2], Kossar Hosseini[3], Rene-Marc Flipo[4], Francis Guillemin[3] and Bruno Fautrel[5]. [1]EA 2415, Montpellier I University, Nîmes University Hospital, Rheumatology Department, Nîmes, France, [2]Université de Lorraine, Nancy, F-54000, France; Inserm, CIC-EC CIE6, Nancy, F-54000, France; CHU de Nancy, Clinical Epidemiology and Evaluation Department, Nancy, F-54000, France; CHU de Nancy, Rheumatology department, Nancy, France, [3]CHU Nancy, Clinical Epidemiology and Evaluation, Université de Lorraine, Paris Descartes University, APEMAC, EA 4360, Nancy, France, [4]Hopital R Salengro CHRU Lille, Lille, France, [5]Paris 6–Pierre et Marie Curie University; AP-HP, Rheumatology, Pitié-Salpêtrière Hospital,-GRC-UPMC 08–EEMOIS, Paris, France.

Background/Purpose: There is growing emphasis on the cost-effectiveness of treating early arthritis (EA). As few studies directly record the utility measures needed for economic analyses, mapping is often used. Health Assessment Questionnaire (HAQ) is 'converted' into utility using regression. The use of such transformed data by regulatory bodies which determine drug availability raises concern as it involves mathematical transformation between measures which may not be clinically equivalent and with potentially variable interrelationships over time.

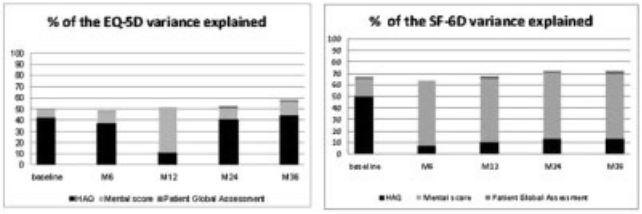
We aimed 1) To assess characteristics associated with SF-6D and EQ-5D utility measures in EA 2) To check whether these associations are stable over 3 years.

Methods: - *Patients:* included in the French nationwide cohort of EA ESPOIR (at least 2 swollen joints for less than 6 months and suspicion of RA).

- *Data available:* SF-6D and EQ-5D utility measures were longitudinally assessed in 813 patients with EA (at baseline, 6 months, 1, 2 and 3 years). Bio-clinical variables and X-rays were also recorded.

- *Analysis:* The determinants of SF-6D and EQ-5D utility measures at each time-point were assessed by multivariate linear regressions in 618 EA patients followed over 3 years. Partial R-squares were used to assess the relative importance of variables to the variation in EQ-5D and SF-6D scores.

Results: At baseline, SF-6D was essentially determined by function, HAQ explaining 50.2% of the variance, whereas after 6 months, SF-6D was essentially determined by mental status (the Arthritis Impact Measurement Scale 2–Short Form) (55.8 to 57.6% of the variance) and the HAQ represented only 7.3 to 13.2%. At each time-point, EQ-5D was essentially determined by function, HAQ explaining 36.9 to 44.2% of the variance, except at 1 year, it was essentially determined by mental status, explaining 40.8% of the variance and the HAQ only 11% (figure).



Conclusion: The major impact of functional ability and mental status, and the variability of the utility determinants over time in addition of the bimodal distribution of the EQ-5D raise concerns about mapping to estimate utilities from clinical instruments. Evaluation of treatment cost-utility should not be based on utility data transformed from HAQ.

Disclosure: C. Gaujoux-Viala, None; **A. C. Rat**, None; **K. Hosseini**, None; **R. M. Flipo**, None; **F. Guillemin**, None; **B. Fautrel**, None.

1035

Psoriatic Arthritis and Mortality-a Nationwide Study. Thorvardur Jon Love[1], Thor Aspelund[2], Alexis Ogdie[3], Joel M. Gelfand[4], Hyon K. Choi[5], Vilmundur Gudnason[2] and Bjorn Gudbjornsson[6]. [1]Landspitali University Hospital, Reykjavik, Iceland, [2]The Icelandic Heart Association, Kopavogur, Iceland, [3]University of Pennsylvania, Philadelphia, PA, [4]University of Pennsylvania., Philadelphia, PA, [5]Boston University School of Medicine, Boston, MA, [6]Faculty of Medicine, University of Iceland, Reykjavik, Iceland.

Background/Purpose: Psoriatic arthritis is an inflammatory arthritis that causes significant morbidity. While a study from a single research clinic in Canada published in the 1990′s suggested an increased mortality rate compared to that seen in the general population, two recent studies from the UK reported no increased mortality, one based on a single center similar to the Canadian study, and the other based on a sample from the general population. We have performed a study of the mortality rate among all known cases of psoriatic arthritis diagnosed since 1971 in Iceland compared to the general population of the same country.

Methods: We used a list of all known patients in Iceland with a diagnosis of psoriatic arthritis assembled in 2002–2003 for a cross-sectional study of psoriatic arthritis in Iceland. The list includes both those patients who were still alive in 2002, as well as those who had died before the study began. This list has been validated by examining close to 200 patients, showing that about 85% had active disease in 2003 and more than 80% fulfilled the CASPAR criteria applied post-hoc. Using national identification numbers and the Icelandic national mortality database we were able to determine the year of death for all individuals who died before end of year 2012, making death ascertainment complete. Using data on age- and sex stratified 1-year survival for the Icelandic population available for each year starting in 1971 we were able to compare the survival of patients with psoriatic arthritis to the expected survival of the age- and sex-matched population starting the year that each psoriatic arthritis diagnosis was made.

Results: The list of psoriatic arthritis patients contained 346 individuals and data on the date of diagnosis of psoriatic arthritis was available for 340. Of these, 293 were diagnosed in 1971 or later and could be used for comparison to the population statistics, with 6747 patient years of follow-up. The mean age at the time of diagnosis was 42.3 years (95%CI 40.1–44.4), with 57 diagnosed in the 1970′s, 98 diagnosed in the 1980‘s, 137 diagnosed in the 1990′s and 1 diagnosed in 2001. This is equivalent to an incidence rate of 3.8 (2.9–5.0), 5.7 (4.6–7.0), and 7.2 (6.1–8.6) incident cases per year per 100.000 individuals age 18 or older for each of the three whole decades included in the study.

Out of 107 men with psoriatic arthritis, 28 had died by the end of 2012, and the same was true for 42 of 186 women with psoriatic arthritis. The age- and sex-specific expected number of deaths updated annually based on year of diagnosis was 27 men and 39 women. The age- and sex-standardized mortality ratio of psoriatic arthritis patients compared to the general population was 1.06 (95% CI 0.84–1.13), p=0.64.

Conclusion: There was no increased death rate among psoriatic arthritis patients compared to the general population.

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The Independent Impact Of Depression On Incident Myocardial Infarction In Psoriatic Disease: A Population-Based Cohort Study. Lindsay C Burns[1], Jan P. Dutz[1] and Hyon K. Choi[2]. [1]University of British Columbia, Vancouver, BC, [2]Arthritis Research Centre of Canada, Richmond, BC.

Background/Purpose: Psoriasis (PsC) and psoriatic arthritis (PsA) represent common, lifelong inflammatory diseases of the skin and joints (respectively) that are associated with substantial cardiovascular and psychiatric morbidity. Considering that depression is associated with deleterious cardiovascular outcomes, we investigated the potential long-term impact of depression on myocardial infarction (MI) risk in this patient population.

Methods: Our analysis employed linked administrative health data, including physician visits, hospital admissions, and death records from Apr 1991 to Mar 2006, and all dispensed medications from Apr 1996 to Mar 2006, for the entire adult (≥18 years) population of British Columbia, Canada (4.1 million individuals). Inclusion in our incident PsC/PsA exposure cohort required one of the following: 1) ≥2 ICD-9 physician diagnostic codes specific for PsC/PsA within a 2 year period between Apr 1996 and Mar 2006; 2) ≥1 specific ICD-9 diagnostic code from a dermatologist (for PsC), a rheumatologist (for PsA), or from hospital. Five unexposed, general population controls were matched to each PsC/PsA case by age, sex, and follow-up time (index date). Individuals with diagnoses of PsC, PsA, or MI prior to the baseline were excluded. Depression was defined by physician or hospital diagnosis, and MI was defined by hospitalization or death certificate. We used Cox proportional hazards models to estimate the independent impact and potential effect modification of depression in psoriatic disease compared to matched controls, adjusting for age, sex, comorbidities, health resource utilization, and socioeconomic status.

Results: Among 10,041 cases of incident PsC/PsA (51% male, mean age of 49 years), 268 incident MI events occurred (incidence = 5.8 per 1,000 person-years [PY]). The incidence of depression in PsC/PsA was 3.4 per 1,000 PY and the corresponding 10-year prevalence estimate was 21.6%. Individuals with PsC/PsA were more likely to be depressed (adjusted OR, 1.26) than controls. Incident depression increased the risk of incident MI by 80% in PsC and PsA (adjusted RR, 1.8; 95% CI, 1.3–2.5). Further, depression was found to modify the risk of MI in psoriatic conditions such that an increased risk was only observed among psoriatic individuals with depression (RRs = 1.6, $P<0.01$ vs. 1.1, *ns*).

Conclusion: These population-based data suggest that depression is a prevalent and independent risk factor for MI among patients with PsC and PsA. Moreover, our findings suggest that depression acted as a major effect modifier in the context of PsC and PsA, such that PsC and PsA only led to an increased risk of MI among individuals with depression. These data underscore the need to actively screen for depression among PsC and PsA patients and closely monitor cardiovascular health in this high-risk group to improve long-term survival.

Main Effects of PsC/PsA and Incident Depression on Risk of MI

Parameter	RR (95% CI)*
PsC/PsA cohort (ref, matched controls)	1.14 (0.97–1.34)
Incident depression	1.80 (1.29–2.51)

Effect of PsC/PsA on Risk of MI According to Prevalent Depression Strata

Parameter	RR (95% CI)*
PsC/PsA cohort (ref, matched controls)	
With depression	1.58 (1.24–2.03)
Without depression	1.14 (0.97–1.35)

*All RRs adjusted for age, sex, Charlson Comorbidity Index, socioeconomic status, history of hospitalizations, chronic obstructive pulmonary disease, obesity, alcoholism, liver disease, cerebrovascular accidents, hypertension, sepsis, varicose veins, peripheral vascular disease, congestive heart failure, chronic renal disease, inflammatory bowel disease, malignant neoplasms, trauma, and fractures, assessed in the year prior to the index date

Disclosure: L. C. Burns, None; **J. P. Dutz**, None; **H. K. Choi**, None.

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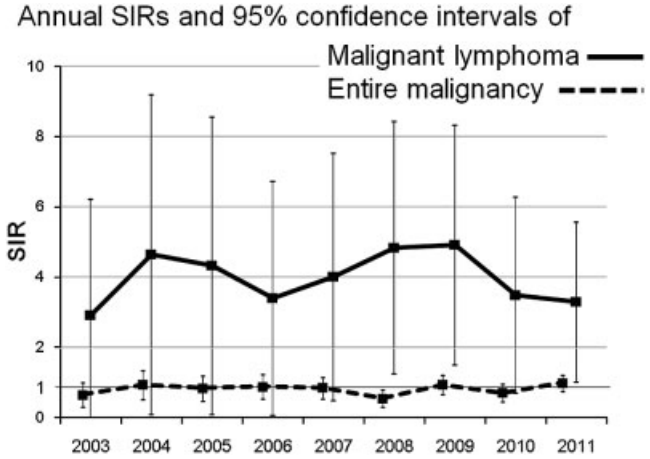
Incidence Of Malignancy In Patients With Rheumatoid Arthritis From a Japanese Large Observational Cohort (NinJa). Atsushi Hashimoto[1], Noriyuki Chiba[2], Jinju Nishino[3], Toshihiro Matsui[4] and Shigeto Tohma[1]. [1]Sagamihara Hospital, National Hospital Organization, Sagamihara, Japan, [2]Morioka National Hospital, NHO, Iwate, Japan, [3]Nishino Clinic, Orthopedics and Rheumatology, Tokyo, Japan, [4]National Hospital Organization Sagamihara Hospital, Kanagawa, Japan.

Background/Purpose: Patients with rheumatoid arthritis (RA) die mainly of cardiovascular/cerebrovascular diseases, respiratory diseases, infections, or malignancies. In recent years, the ratio of infections and respiratory diseases associated with RA as causes of deaths has been decreasing, whereas that of malignancies increasing. A possible reason is recent changes in RA therapy, namely, elevated dose of methotrexate (MTX) or popularized biologics. Incidence of malignancies varies depending on studies because it is strongly affected by regional or racial differences among cohorts. This study is to disclose incidence and risk of malignancy in Japanese patients with RA.

Methods: Data from RA patientsregistered in a nationwide Japanese cohort database (**NinJa:** National Database of Rheumatic Diseases by iR-net in Japan) from 2003 to 2011 were used. To adjust difference of population composition and compare the incidence of malignancy between RA patients and general population, standardized incidence rates (SIRs) were calculated. An SIR is a ratio between actually obtained number of malignancies from the cohort and expected number estimated using incidence of age- and sex-matched Japanese population.

Results: In 9 years the cohort comprised of 55003 patient-years (80% females and 18% males) yielded 444 malignancies, which contained 300 (69%) females and 137 (31%) males, including 6 patients with multiple malignancies. Most frequent malignancy was lung cancer (n=71) followed by gastric (n=59) and breast cancer (n=53). SIR for entire malignancies was 0.96 (95% confidence interval 0.87–1.05), which was consistent with that in the general population. SIRs for malignant lymphoma (ML) in both sexes (SIR 4.01) and bladder cancer in females (SIR 2.80) were significantly higher, whereas several malignancies including rectal cancer in both sexes (SIR 0.49), colon cancer in females (SIR 0.89), or liver cancer in both sexes (SIR 0.28) had significantly lower SIRs. Number of patients on MTX therapy and their dose of MTX have been increasing, while annual SIRs for entire malignancies and ML remained steady (figure).



Conclusion: RA patients had no higher incidence for entire malignancies but should be cared for several malignancies including ML.

Disclosure: A. Hashimoto, None; **N. Chiba**, None; **J. Nishino**, None; **T. Matsui**, None; **S. Tohma**, None.

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Impact Of Biological Treatment On Overall Mortality and On Incidence Of Second Cancers In Arthritis Patients-A Follow-Up Study From The Danish Danbio Registry. Lene Dreyer[1], Lene Mellemkjær[2], Inger Marie Jensen Hansen[3] and Merete Lund Hetland[4]. [1]Copenhagen University Hospital at Gentofte, Copenhagen, Denmark, [2]Danish Cancer Society Research Center, Copenhagen, Denmark, [3]OUH Svendborg Hospital, Svendborg, Denmark, [4]The Danish Rheumatologic Database (DANBIO), Glostrup Hospital., Copenhagen, Denmark.

Background/Purpose: It is largely unknown whether it is safe to treat arthritis patients with a previous malignancy with biologics. Only a few studies have address the question of whether therapy with biologics influences the malignancy rate and mortality in patients with prior cancer and the results are conflicting. We aimed to study 1) the overall mortality and 2) the incidence of second cancers in arthritis patients treated with or without biologics after a primary cancer diagnosis.

Methods: A total of 23,233 arthritis patients (RA:15,286, PSA:3196, MB: 2189, other:2562) registered in the nationwide DANBIO database between January 2000 and Dec 2011 were included and linked to the Central Population Register (information on dates of death or emigration) and the Danish Cancer Registry (identification of all cancer cases). Follow-up for death and second cancer started at the date for diagnosis of the primary cancer or at entry in DANBIO whatever came latest. Information on recurrence of cancers was not available. Hazard Ratio (HR) for death and second cancer among arthritis patients ever receiving biologics compared with patients never receiving biologics were calculated using Cox proportional hazard models, adjusted for age, sex and calendar time.

Results: A total of 2972 patients with a primary cancer were identified. Of these, 262 had been treated with biologics *before* the primary cancer diagnosis, 501 *after* and 244 *both* before and after, while 1965 cancer cases *never* had received biologics. The first biological treatment given *after* the primary cancer diagnosis among 745 patients were: adalimumab(25%), etanercept(23%), infliximab(29%), rituximab(16%) and other(7%). Among the 2972 cancer patients, HR for death in patients *ever* treated with biologics compared to *never* treated was slightly increased: 1.26(95%CI: 1.04–1.53). The same was observed among the non-cancer patients HR 1.38(95%CI 1.16–1.64) (data not shown). An increased risk for overall mortality including (HR 1.49) and excluding (HR 1.50) non-melanona skin cancer were observed in patients treated with biologics only before first cancer diagnosis. An increased risk of developing a second cancer was observed in arthritis patients treated with biologics *both* before and after primary cancer diagnosis, when non-melanoma skin cancers were excluded from the calculations (HR= 5.29), table.

Risk of death and second cancer in arthritis patients treated with biologics (bio) after a primary cancer.

Type of first cancer	Outcome	Bio treatment	Events	Person-years	HR (95% CI)
All types	Death				
		Never bio	300	4155	1 (ref)
		Bio only *after* first cancer	59	1765	0.96 (0.70–1.32)
		Bio only *before* first cancer	111	457	1.49 (1.16–1.91)
		Bio *both* before and after first cancer	32	614	0.83 (0.56–1.21)
All types excluding non-melanoma skin cancer[1]	Death				
		Never bio	257	2924	1 (ref)
		Bio only *after* first cancer	41	1024	1.07 (0.73–1.56)
		Bio only *before* first cancer	118	365	1.50 (1.18–1.93)
		Bio *both* before and after first cancer	27	236	0.95 (0.63–1.44)
All types	All types of second cancer				
		Never bio	51	3793	1 (ref)
		Bio only *after* first cancer	22	1610	1.30 (0.76–2.25)
		Bio only *before* first cancer	9	454	1.19 (0.55–2.60)
		Bio *both* before and after first cancer	12	598	1.52 (0.79–2.94)
All types excluding non-melanoma skin cancer[1]	All types excluding non-melanoma skin cancer				
		Never bio	47	2584	1 (ref)
		Bio only *after* first cancer	13	885	1.66 (0.82–3.36)
		Bio only *before* first cancer	8	338	0.47 (0.21–1.04)
		Bio *both* before and after first cancer	19	240	5.29 (2.98–9.40)

[1] Arthritis patients with non-melanoma skin cancer before entry in DANBIO but diagnosed with another cancer type after entry were included in the analysis.

Conclusion: Arthritis patients treated with biologics had a slightly increased mortality (≈30%) compared to patients never treated with biologics, and this increase was independent of whether they got cancer or not. Treatment with biologics *after* a primary cancer was associated with an increased risk for a second cancer.

Disclosure: L. Dreyer, None; **L. Mellemkjær**, None; **I. M. Jensen Hansen**, None; **M. L. Hetland**, None.

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Risk Of High-Grade Cervical Dysplasia In Women With Systemic Inflammatory Diseases. Seoyoung C. Kim[1], Robert J. Glynn[1], Edward Giovannucci[2], Sonia Hernandez-diaz[3], Jun Liu[1], Sarah Feldman[1], Elizabeth W. Karlson[4], Sebastian Schneeweiss[1] and Daniel H. Solomon[5]. [1]Brigham and Women's Hospital, Boston, MA, [2]Harvard School of Publich Health, Boston, MA, [3]Harvard School of Public Health, Boston, MA, [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [5]Harvard Medical School, Brigham and Women's Hospital, Division of Rheumatology, Division of Pharmacoepidemiology, Boston, MA.

Background/Purpose: Human papillomaviruses (HPV) are causes of high-grade cervical dysplasia and cervical cancer. Persistent HPV infection, the major risk factor for cervical cancer, is associated with several factors including HPV genotypes, age, coexisting infection, and immune function. Several prior studies suggested that the risks of any cervical dysplasia and HPV infection were increased in immunocompromised patients including those with HIV, organ transplantation, and systemic inflammatory diseases (SID). The objective of this study was to assess the risk of high-grade cervical dysplasia, a surrogate endpoint for cervical cancer, in women with SID including inflammatory bowel diseases (IBD), rheumatoid arthritis (RA), psoriasis, and systemic lupus erythematosus (SLE).

Methods: Using U.S. commercial insurance claims data (2001–2012), we conducted a population-based cohort study to examine the incidence rates (IR) of high-grade cervical dysplasia in women with SID including inflammatory bowel disease (IBD), rheumatoid arthritis (RA), psoriasis, and systemic lupus erythematosus (SLE). To have comparable health care utilization with the SID cohort, we selected women with hypertension as the non-SID cohort, matched on age and index date with a 4:1 ratio. The index date was defined as the dispensing date of the first immunomodulating drug after ≥ 2 diagnoses of one of the SID and the first anti-hypertensive drug after ≥2 diagnoses of hypertension for non-SID women. High-grade cervical dysplasia was defined by a validated claims-based algorithm with a positive predictive value of ’81%. Crude and multivariable Cox models estimated the hazard ratios (HR) of high-grade cervical dysplasia in SID versus non-SID women. Separate Cox models were used to calculate HRs for IBD, RA, psoriasis, and SLE subcohorts compared to the non-SID. Our full model was adjusted for age, smoking, prior abnormal cervical dysplasia or sexually transmitted diseases, comorbidities, medications, and health care utilization.

Results: Over the mean follow-up of 2.1 years, the IR of high-grade cervical dysplasia per 100,000 person-years was 94.2 among women with SID (n=133,333) and 73.4 in non-SID women (n=533,332). The fully adjusted HRs were 1.12 (95% CI 0.92–1.35) for all SID combined compared to non-SID. For the SID subcohorts, the fully adjusted HR was significantly increased in women with RA (1.46, 95% CI 1.07–2.01) and SLE (1.49, 95% CI 1.01–2.19), but not among those with IBD (1.06, 95% CI 0.78–1.44) or psoriasis (0.96, 95% CI 0.73–1.26). (**Table**) In women with baseline immunosuppressive use and with prior abnormal Papanicolaou smears, our results were unchanged.

Table. Hazard ratios (95% confidence intervals) for high-grade cervical dysplasia

Adjustment	SID* (n=133,333)	IBD (n=25,176)	Psoriasis (n=34,665)	RA (n=58,979)	SLE (n=14,513)	Non-SID* (n=533,332)
N, outcome	259	59	58	102	40	818
Unadjusted	**1.28 (1.11–1.47)**	**1.50 (1.16–1.96)**	1.11 (0.85–1.45)	1.13 (0.92–1.38)	**1.90 (1.38–2.6)**	Referent
Partial[a]	**1.24 (1.07–1.44)**	1.18 (0.90–1.55)	0.98 (0.77–1.31)	**1.38 (1.12–1.71)**	**1.61 (1.17–2.23)**	Referent
Full[b]	1.12 (0.92–1.35)	1.06 (0.78–1.44)	0.96 (0.73–1.26)	**1.46 (1.07–2.01)**	**1.49 (1.01–2.19)**	Referent

* age and index date-matched, [a] adjusted for age, comorbidity score, and no. of prescription drugs. [b] further adjusted for HPV risk factors, comorbidities, medications, health care utilization and preventive health care use.
The likelihood ratio test of the global null hypothesis showed no significant heterogeneity between the SID subcohorts (p=0.1).

Conclusion: Our study showed that RA and SLE were associated with a 1.5-times increased risk of high-grade cervical dysplasia after adjusting for potential confounders, although the absolute risk was generally low.

Disclosure: S. C. Kim, Pfizer Inc, 2, Pfizer and Asisa, 9; **R. J. Glynn**, AstraZeneca, 2, Novartis Pharmaceutical Corporation, 2; **E. Giovannucci**, None; **S. Hernandez-diaz**, Novartis Pharmaceutical Corporation, 5, GlaxoSmithKline, 5; **J. Liu**, None; **S. Feldman**, None; **E. W. Karlson**, None; **S. Schneeweiss**, WHISCON, LLC, 5, Boehringer Ingelheim, 2, Novartis Pharmaceutical Corporation, 2, Pfizer Inc, 2, Booz and Company, 5; **D. H. Solomon**, Lilly, Amgen, CORRONA, 2, Lilly, Novartis, BMS, Pfizer, 6, Lilly, BMS, Novartis, 9.

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Use Of TNF Inhibitors Is Associated With a Reduced Risk Of Diabetes In RA Patients. Siri Lillegraven[1], Jeffrey D. Greenberg[2], George W. Reed[3], Katherine C. Saunders[4], Jeffrey R. Curtis[5], Leslie R. Harrold[6], Marc C. Hochberg[7], Dimitrios A. Pappas[8], Joel M. Kremer[9] and Daniel H. Solomon[10]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]NYU Hospital for Joint Diseases, New York, NY, [3]CORRONA, Inc., Worcester, MA, [4]CORRONA, Inc., Southborough, MA, [5]University of Alabama at Birmingham, Birmingham, AL, [6]University of Massachusetts Medical School, Worcester, MA, [7]University of Maryland, Baltimore, MD, [8]Columbia University, College of Physicians and Surgeons, New York, NY, [9]Center for Rheumatology, Albany Medical College, Albany, NY, [10]Harvard Medical School, Brigham and Women's Hospital, Division of Rheumatology, Division of Pharmacoepidemiology, Boston, MA.

Background/Purpose: Inflammation may contribute to diabetes risk, and some studies indicate that certain DMARDs might be associated with a reduced risk of diabetes. Most studies in RA have not included confirmed diabetes cases, information about disease activity, BMI and DMARD utilization. The objective of the present study was to assess the association between DMARD exposure and incident diabetes in a large multi-center observational cohort of RA patients.

Methods: The study population consisted of RA patients followed in CORRONA, a longitudinal multi-center cohort. Five mutually exclusive DMARD treatment categories were defined: 1) TNFi, incl. combinations with nonbiologic (nb) DMARDs 2) Other biologic (b) DMARDs, incl. combinations with nbDMARDs 3) Methotrexate, MTX without concomitant bDMARDS or hydroxychloroquine (HCQ) 4) HCQ without concomitant bDMARDs or MTX, and 5) Other nbDMARDs (e.g. LEF, CsA, SSZ), without concomitant TNFi, MTX or HCQ. Patients who did not attend at least one follow-up visit, who had a diagnosis of diabetes at index date of the DMARD regimen, did not receive the DMARD treatments of interest or who had other arthritic diagnoses were excluded. Incident cases of diabetes were confirmed through case ascertainment based on medical records and patient interviews. Incidence rates (IR) and incidence rate ratios (IRR) were calculated. Cox regression models were fitted to estimate the risk of incident diabetes, adjusting for propensity score (including variables such as age, BMI, steroid use and CDAI). The comparison group for all analyses was “Other nbDMARDs”.

Results: We identified 21775 eligible treatment regimens-9880 TNFi regimens, 1756 other bDMARD, 7441 MTX, 1496 HCQ and 1202 other nbDMARD regimens. The mean (SD) age at start of treatment was 58(13) years, mean disease duration 10(10) years and mean CDAI 13.4(12.4). 76% were women and 30% used oral steroids. The mean duration of the treatment regimens ranged from 1.5–2.4 years, and 82 incident cases of diabetes of interest were confirmed. The IRs, IRRs and results from Cox regression models are presented in the table. Diabetes development was significantly reduced in patients receiving TNFi compared to patients receiving other nbDMARDs (e.g. LEF, CsA, SSZ). Use of HCQ, MTX, and other bDMARDs also trended toward a reduced risk, but confidence intervals did not exclude the null. Similar results were found in models adjusted directly for BMI, and in models adjusting for propensity score quintiles. Higher steroid dosages were associated with an increased risk of diabetes in separate models.

	DM IR, cases per 1000 person-years (95% CI)	Crude IRR	HR (95% CI) Propensity score adjusted model	P-value for Cox regression model
TNFI	1.46 (1.03, 2.00)	0.47 (0.21, 1.07)	0.35 (0.13, 0.91)	0.03
Other bDMARDs	1.53 (0.51, 3.63)	0.50 (0.15, 1.70)	0.44 (0.08, 2.57)	0.36
MTX	2.08 (1.45, 2.29)	0.68 (0.30, 1.54)	0.67 (0.44, 1.02)	0.34
HCQ	1.29 (0.43, 3.07)	0.42 (0.12, 1.44)	0.45 (0.13, 1.53)	0.21
Other nbDMARDs	3.07 (1.37, 6.03)		Ref	

Conclusion: After controlling for variables such as BMI, disease activity and steroid use, RA patients treated with TNF inhibitors had a reduced risk for development of diabetes.

Disclosure: S. Lillegraven, None; **J. D. Greenberg**, CORRONA, 1, AstraZeneca, CORRONA, Novartis, Pfizer, 5; **G. W. Reed**, CORRONA Inc., 3, UMASS Medical School, 5; **K. C. Saunders**, CORRONA Inc., 3; **J. R. Curtis**, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, Abb Vie, 2, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, Abb Vie, 5; **L. R. Harrold**, CORRONA, Inc., 5; **M. C. Hochberg**, AbbVie Inc., 5, Amgen, 5, BMS, 5, Genentech/Roche, 5; **D. A. Pappas**, Novartis, 9; **J. M. Kremer**, Corrona, Inc, 1, Corrona Inc., 3; **D. H. Solomon**, Amgen, Lilly, CORRONA, 2, UpToDate, 7, Pfizer, Novartis, Lilly, BMS, 6.

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Non-Differential Reporting Of Myocardial Infarction To a National Observational Drug Safety Study Using Linked Data: Linkage Of The British Society For Rheumatology Biologics Register For Rheumatoid Arthritis and The Myocardial Ischaemia National Audit Project. Audrey SL Low[1], Deborah P. Symmons[2], Mark Lunt[3], Louise K. Mercer[1], Christopher Gale[4], Kath Watson[1], British Society for Rheumatology Biologics Registers (BSRBR) Control Centre Consortium[1], William G. Dixon[5], Kimme L. Hyrich[6] and On behalf of the BSRBR[7]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academic Health Science Centre, Manchester, United Kingdom, [3]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [4]Department of Cardiology, York Teaching Hospital NHS Foundation Trust, York, United Kingdom, [5]The University of Manchester, Manchester, United Kingdom, [6]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Sciences Centre, Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom, [7]British Society for Rheumatology, London, United Kingdom.

Background/Purpose: The BSRBR-RA was established to compare the long term safety of anti tumour necrosis factor (TNFi) drugs with non-biologic drugs (nbDMARD) in subjects with rheumatoid arthritis (RA). Serious adverse events (SAEs) are identified by physician and patient reporting as well as linkage to the national death register. We used myocardial infarction (MI) as an example to explore whether there is differential under-reporting of SAEs to BSRBR between treatment groups by linking BSRBR-RA to the Myocardial Ischaemia National Audit Project (MINAP). MINAP aims to collect data on all hospitalisations with MI in England and Wales.

Methods: This analysis was limited to subjects living in England and Wales. BSRBR and MINAP were linked using deterministic matching with combinations of these parameters: first and last names, birthdate, postcode, unique National Health Service number and sex. Events from both datasets were matched by subject using a 30-day window. Matched and unmatched events were verified using the American Heart Association/European Society of Cardiology criteria for MI. Deaths from MI (reported as the underlying cause of death using ICD-10 via death register linkage) were also included as verified MIs. Age, sex, treatment group, MI phenotype, whether the subjects received cardiology care at the same hospital as their rheumatology care and location of deaths due to MIs were explored as possible reasons for non-overlap between datasets using descriptive statistics. The risk of MI was compared between subjects receiving nbDMARDs and ever-exposed to TNFi using a Cox regression model, adjusted for deciles of propensity scores (PD) (Table) using i) MIs verified from BSRBR only and ii) all MIs verified from either BSRBR or MINAP. Subjects were censored at first MI, death, last physician follow-up or 04/20/2010, whichever came first.

Results: In total, 310 verified MIs were recorded during the observation period, of which 75% were captured in BSRBR-RA, 64% captured in MINAP and 39% were captured in both datasets (Table). A fifth of the BSRBR-RA-only MIs was deaths due to MI occurring outside hospital and therefore could not have been captured by MINAP. There were no differences in the age, sex, treatment group, site of MI care or MI phenotype between matched and unmatched MIs. When additional MIs from MINAP were included in the analysis, the adjusted risk estimate for MI in subjects receiving TNFi compared to nbDMARD did not differ to estimates obtained using MIs from BSRBR-RA only: BSRBR-only MIs; hazard ratio (HR) 0.56 (95%CI 0.35, 0.91); including MINAP MIs: HR 0.59 (95%CI 0.40, 0.88).

Table.

	BSRBR-RA-only MIs	Matched BSRBR-RA-MINAP MIs	MINAP-only MIs	p-value*
Number of verified MIs	112	120	78	-
Median age at MI, years (IQR)	67 (59,73)	65 (58,72)	68 (62, 74)	0.09
Female gender, n (%)	70 (63)	74 (62)	44 (56)	0.67
Proportion of subjects receiving TNFi at time of MI, n (%)	64 (57)	67 (56)	41 (53)	0.09
Proportion of subjects with ST elevation MI, n (%)	Data not collected by BSRBR-RA	63 (53)	33 (42)	0.63
Proportion of subjects treated for MI at a different hospital for MI care to rheumatology care, n (%)	Data not collected by BSRBR-RA	71 (59)	40 (51)	0.28
Number of deaths from MI verified by death certificate using ICD-10	44	5	0	-
Deaths from MI occurring outside hospital, n (%)	21 (48)	0	0	0.04

*Chi-squared test for categorical variables, Kruskal-Wallis test for continuous variables. Variables in PD: age, gender, disease duration, DAS28, HAQ score, steroid use, number of previous nbDMARDs, entry year to study, hypertension, diabetes, smoking, chronic lung disease, aspirin, statin, NSAID/COX2-inhibitor use, all at baseline.

Conclusion: A degree of under-reporting of MIs exists in BSRBR but is non-differential between nbDMARD and TNFi subjects. The additional 78 (25%) MIs from MINAP did not alter the risk estimate but increased its precision. Our findings suggest linkage with other datasets is an important method of increasing event capture and enriching data for analysis.

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1042

Comparison Of Medication Usage Following Myocardial Infarction In Patients With Autoimmune Rheumatic Disease Versus Controls. Sharon Van Doornum[1], Mark Tacey[1], Megan Bohensky[1], Caroline Brand[2], Vijaya Sundararajan[3] and Ian Wicks[4]. [1]The University of Melbourne, Melbourne, Australia, [2]The Royal Melbourne Hospital, Melbourne, Australia, [3]University of Melbourne, Melbourne, Australia, [4]Royal Melbourne Hospital, Melbourne, Australia.

Background/Purpose: We have previously demonstrated that RA patients have higher post-myocardial infarction (MI) case fatality than controls [1] and that treatment with secondary prevention medications is lower in RA patients than matched controls [2]. More recently we have demonstrated that post-MI case fatality is also higher in the larger group of patients with autoimmune rheumatic disease (AIRD) such as lupus, spondyloarthritis, scleroderma and systemic necrotising vasculitis [manuscript in preparation]. The aim of this study was to compare the utilization of lipid-lowering agents (statins), beta-blockers (BB) and angiotensin converting enzyme inhibitors (ACE-I) following MI in patients with AIRD compared to patients without AIRD.

Methods: A retrospective cohort study utilising a population-based dataset containing statewide hospital admission data linked with medication utilisation data. Data were available from 1 July 2001 to 30 July 2009. Cases of MI were identified from hospital admission data based on relevant International Classification of Diseases (ICD) codes. AIRD status was identified from the index MI admission or any admission in the preceding 5 years using relevant ICD codes. Relevant co-morbidities including cardiovascular risk factors were identified using ICD codes from the index MI admission. Adjusted odds ratios (OR) for post-MI treatment with each of the specified medications in AIRD patients compared to non-AIRD patients were estimated using a logistic regression model with adjustment for age, gender, socio-economic status, geographic location and relevant co-morbidities.

Results: There were 21,126 individuals with an index MI, of whom 518 (2.5%) were identified as AIRD patients. The rate of statin use within 12 months post MI for patients with AIRD was 52.7% compared to 69.8% for patients without AIRD ($p<0.001$). A decreased rate of BB and ACE-I use was also identified for AIRD patients compared to non-AIRD patients (BB: 49.4% vs 55.6 %, $p<0.005$ and ACE-I: 50.2% vs 58.3%, $p<0.001$). The adjusted OR for statin use within 12 months post MI for AIRD patients was 0.57 (95% CI: 0.45–0.73). The adjusted ORs for usage of BB and ACE-I in AIRD patients within 12 months of the MI were reduced but not statistically significant after adjustment for covariates (BB: OR = 0.86, 95% CI: 0.69–1.08 and ACE-I: OR = 0.84, 0.68–1.03).

Conclusion: Treatment with statins in the 12 months following MI is significantly lower for patients with AIRD, even after adjustment for potential confounders. Lower rates of usage of BB and ACE-I were also found, although these differences were not statistically significant after adjustment for relevant co-variates.

[1] Van Doornum et al. 2006
[2] Van Doornum et al. 2010

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1043

Musculoskeletal Hospital Admissions Among Patients Treated For Rheumatoid Arthritis Between 1999 and 2010 Compared With The General Population In The Netherlands. I D Bezemer[1], L M A Houweling[1], E Alemao[2], F J A Penning-van Beest[1] and M Hochberg[3]. [1]PHARMO Institute for Drug Outcomes Research, Utrecht, Netherlands, [2]Bristol-Myers Squibb, Princeton, NJ, [3]University of Maryland, Baltimore, MD.

Background/Purpose: Advances in treatment for RA may have resulted in a decrease in musculoskeletal hospital admissions. This study aimed to assess the trends in hospital admissions among patients receiving treatment for RA in the past decade compared with the general population.

Methods: Patients with RA in the PHARMO Database Network treated with any disease-modifying antirheumatic drug (DMARD) between 1999 and 2010 were identified. Population controls were randomly matched 2:1 to patients with RA by age and sex. Patients and controls were followed from the first DMARD dispensed and the matched index date, respectively, until death, end of study period or end of database registration, whichever occurred first. Musculoskeletal hospital admissions and procedures were assessed during follow-up. Incidence rates (IRs) of the first musculoskeletal hospitalization after the index date were calculated and compared using Cox proportional hazards regression.

Results: Between 1999 and 2010, 24,762 patients with RA treated with DMARDs were identified. The IR of musculoskeletal admissions per 100 person years (pt-yrs) decreased from 10.4 (95% CI] 9.4, 11.5) in 1999 to 3.2 (95% CI 2.9, 3.5) in 2010, while the reference population IR was stable at 1.3 per 100 pt-yrs. The largest improvement among patients with RA occurred around 2003; the period in which biologic DMARDs (bDMARDs) were introduced. Therefore, a second comparison was made between 2078 patients with RA (8%) treated with bDMARDs (index date=first bDMARD dispensed) and 4156 patients with RA (17%) treated only with conventional DMARDs, matched by age, sex and timing of first DMARD dispensed (any) in the database. Between 2003 and 2010, the IR of musculoskeletal hospital admissions per 100 pt-yrs decreased from 27.1 (95% CI 20.4, 35.2) to 7.8 (95% CI 6.0, 9.9) among bDMARD users and from 9.9 (95% CI 7.4, 12.9) to 3.2 (95% CI 2.6, 4.1) among the matched conventional DMARD users. Also, the IR of musculoskeletal procedures per 100 pt-yrs decreased from 4.3 (95% CI 2.7, 6.3) to 1.8 (95% CI 1.3, 2.4) among bDMARD users and from 1.6 (95% CI 0.7, 2.9) to 0.7 (95% CI 0.4, 1.1) among the matched conventional DMARD users. Compared with the general population, bDMARD users in 2010 remained six times more likely to be hospitalized for a musculoskeletal event (hazard ratio 6.5 [95% CI 4.2, 10.0]).

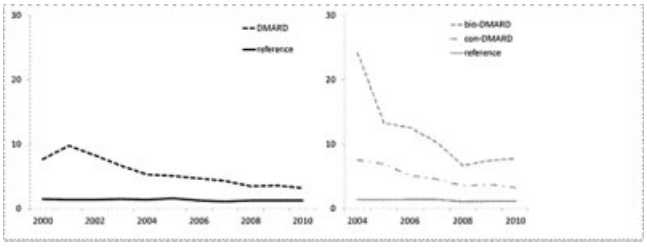

Figure. IRs per 100 pt-yrs of musculoskeletal hospital admissions among DMARD users and matched references.

Conclusion: The IR of musculoskeletal hospital admissions among patients in the Netherlands treated for RA decreased from 1999 to 2010. The largest reduction occurred during the period when bDMARDs were introduced. However, the rates have stabilized in recent years and hospital admission rates in 2010 remained twice as high for patients with RA as the general population, and six times higher in patients receiving bDMARDs.

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1044

Temporal Associations Of Prevalent Depression With The Different Domains Of Rheumatoid Arthritis Disease Activity. Alan Rathbun, Leslie R. Harrold and George Reed. University of Massachusetts Medical School, Worcester, MA.

Background/Purpose: Depression (DEP) is a common psychiatric comorbidity of rheumatoid arthritis (RA), yet little is known of its temporal effect on disease activity and symptoms. The study aim was to evaluate how the lifetime prevalence of DEP influenced longitudinal changes in the different domains of RA disease activity.

Methods: RA patients with self-reported DEP data and ≥ 1 follow-up visit were identified from a national observational cohort of > 34,000 individuals (The Consortium of Rheumatology Researchers of North America; CORRONA). Linear mixed models estimated the association between the lifetime prevalence of DEP and changes in disease activity over 2-years. Outcomes were the clinical disease activity index (CDAI), tender and swollen joint counts (TJC and SJC), patient and physician global assessment (PGA and EGA), patient-reported pain, health assessment question (HAQ), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). To account for potential confounders, patients with and without prior DEP were matched (1:1) using a propensity score. Propensity score models incorporated covariates selected a priori and were the following: baseline disease severity, gender, race, ethnicity, age, health insurance, marital status, employment, alcohol use, smoking, exercise, BMI, and composite comorbidity. The matching was performed separately for each outcome measure. Model based estimates of disease activity were generated and trends over time between the two groups tested.

Results: The rates of change by DEP status were significantly different for the CDAI, TJC, PGA, EGA, pain, and HAQ. Patients without prior DEP had greater decreases in disease activity. Baseline, 1-year, and 2-year CDAI estimates in those without prior DEP were: 15.7 [14.7–16.6], 11.4 [10.5–12.4], and 7.2 [6.1–8.3]; compared to patients with prior DEP: 15.8 [14.8–16.7], 12.9 [11.9–13.8], and 10.0 [8.9–11.1]. The component measures displayed similar trends. Also, this effect was greater for the patient-reported outcomes. Baseline, 1-year, and 2-year PGA estimates in those with no prior DEP were: 3.7 [3.5–3.8], 3.1 [2.9–3.2], and 2.5 [2.3–2.7]; and in patients with prior DEP: 3.7 [3.5–3.8], 3.6 [3.4–3.7], and 3.4 [3.2–3.6]. In contrast, baseline, 1-year, and 2-year EGA estimates in patients without prior DEP were: 2.7 [2.6–2.9], 2.0 [1.8–2.1], and 1.2 [1.0–1.4]; and in those with prior DEP: 2.7 [2.5–2.9], 2.1 [1.9–2.3], and 1.5 [1.3–1.7]. Similar results were obtained for the TJC, a measure assessed via the patient and physician, when compared to the SJC, which is evaluated solely by clinicians.

Table 1. Model based estimates of disease activity by lifetime depression status at baseline, 1 year, and 2 years, among propensity score matched samples.

Prior Depression	Variable	N	Baseline	Year 1	Year 2
No	CDAI***	4250	15.66 [14.69–16.63]	11.43 [10.46–12.39]	7.19 [6.11–8.28]
Yes	CDAI***	4250	15.75 [14.79–16.72]	12.87 [11.90–13.84]	9.99 [8.90–11.08]
No	TJC***	4,455	4.96 [4.50–5.43]	3.33 [2.87–3.79]	1.70 [1.18–2.22]
Yes	TJC***	4,455	5.01 [4.55–5.48]	4.02 [3.55–4.48]	3.02 [2.50–3.55]
No	SJC	4,469	4.06 [3.64–4.49]	2.98 [2.55–3.40]	1.89 [1.42–3.36]
Yes	SJC	4,469	4.13 [3.70–4.56]	3.05 [2.63–3.48]	1.98 [1.51–2.45]
No	PT Global***	4,285	3.67 [3.53–3.81]	3.08 [2.94–3.22]	2.49 [2.31–2.67]
Yes	PT Global***	4,285	3.68 [3.54–3.82]	3.55 [3.41–3.69]	3.42 [3.23–3.60]
No	MD Global***	4,427	2.74 [2.57–2.92]	1.97 [1.79–2.14]	1.19 [1.00–1.39]
Yes	MD Global***	4,427	2.70 [2.52–2.88]	2.11 [1.93–2.28]	1.51 [1.32–1.71]
No	PT Pain***	4,320	4.02 [3.87–4.17]	3.33 [3.18–3.48]	2.64 [2.45–2.83]
Yes	PT Pain***	4,320	3.99 [3.84–4.14]	3.83 [3.68–3.98]	3.66 [3.47–3.85]
No	HAQ***	4,260	1.06 [1.03–1.10]	0.98 [0.94–1.01]	0.89 [0.85–0.93]
Yes	HAQ***	4,260	1.06 [1.03–1.10]	1.04 [1.01–1.08]	1.02 [0.98–1.07]
No	Log CRP	1,453	0.73 [0.68–0.77]	0.67 [0.63–0.72]	0.62 [0.56–0.67]
Yes	Log CRP	1,453	0.68 [0.63–0.72]	0.65 [0.61–0.70]	0.63 [0.57–0.69]
No	Log ESR	2,219	1.24 [1.22–1.25]	1.22 [1.21–1.24]	1.21 [1.19–1.23]
Yes	Log ESR	2,219	1.23 [1.21–1.25]	1.21 [1.19–1.23]	1.19 [1.17–1.21]

Prior depression by follow-up time interaction: * P <0.05; ** P <0.01; *** P <0.001

Conclusion: The results suggest that the presence of prior DEP in RA impacts prospective changes in metrics reported by the patient: pain, functional status, and global assessment; and to some extent measures reported by providers, but not the number of swollen joints or acute phase reactants.

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1045

Under Reporting Of Cataracts In Randomised Controlled Trials Investigating The Use Of Systemic Glucocorticoids In Patients With Rheumatoid Arthritis. Rachel J. Black and William G. Dixon. The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Oral glucocorticoid (GC) therapy is used in more than half of patients with rheumatoid arthritis (RA). Cataracts are a recognised treatment-related side effect of GC use. However, the magnitude of the risk, its relationship with dose, or whether screening for cataracts should be undertaken in patients on GC therapy is not clear. The aim of this study was to determine the incidence of cataracts in the active and placebo arms of RCTs of systemic GC therapy in patients with RA. Because of early concerns about possible under-reporting in the trials, a second aim was to compare the observed incidence in the RCTs to the incidence of cataracts in the general population.

Methods: Twenty two RCTs of systemic GC therapy in patients with RA were reassessed to identify incident cataracts in the placebo and treatment arms. The number of person years at risk (pyr) and the resultant incidence rates/ 1000pyr were calculated for the combined RCT population, then for the GC and control groups separately. The incidence rate ratio for GC use was calculated using Poisson regression. Two large observational studies (The Beaver Dam Eye Study and The Blue Mountains Eye Study) reporting the incidence of cataract in the general population were identified. Both studies reported the age and gender-specific cumulative incidence of cataracts over 5 years and 10 years. The mean of the incidence rates across the two studies was used to generate a general population incidence rate for the age-specific strata. Indirect standardisation was used to calculate the expected number of cases in the RCTs, were the RCT patients to have had the same incidence rate as the general population. A standardised incidence ratio was then calculated using the number of observed and expected cases.

Results: In the 22 RCTs, there were 2250 patients with a mean age of 56 years (weighted by duration of follow up), contributing 3764pyr. There were 13 cases of cataract reported in 3 of the 22 RCTs, giving an overall incidence rate of 3.5 per 1000pyr. The RCTs contributed 1884pyr to the GC group and 1880pyr to the control group. There were 7 cases of cataract reported in the GC group and 6 in the control group, generating incidence rates of 3.7 and 3.2 / 1000pyr in the GC and control group, respectively. The incidence rate ratio for GC use was 1.16 (95%CI 0.39–3.46). Using the general population incidence for patients aged 55–64 years of 46.7 per 1000pyr, the expected number of cataracts was 176. This generates a standardised incidence ratio of 0.07 (95%CI 0.03–0.21).

Conclusion: The incidence of cataracts was 16% higher in GC-treated compared to control patients with RA using all available RCTs. However the lack of precision (wide confidence intervals) due to small numbers means that this calculation is inconclusive. The observed number of cataracts was around 15 times lower than expected in both arms, suggesting huge under-reporting. Such under-reporting results in low confidence of any measured risk from these studies emphasising the need for well designed observational studies and better reporting of steroid-side effects in future RCTS.

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Comparison Of The Incidence Of Influenza Like Illness In Pregnant Women With Rheumatoid Arthritis and Women Without Rheumatoid Arthritis Who Receive An Influenza Vaccination. Yunjun Luo, Diana L. Johnson, Ronghui Xu and Christina D. Chambers. University of California, San Diego, La Jolla, CA.

Background/Purpose: Influenza infection poses significant risk to pregnant women, therefore it is recommended that all pregnant women be vaccinated. However, it is unknown whether the protective effect of influenza vaccine is the same for pregnant women with rheumatoid arthritis (RA) as it is for pregnant women without autoimmune disease.

Methods: Data were obtained from an ongoing prospective cohort study of pregnancy outcome among women in the U.S. and Canada. We included women enrolled between 2009 and 2012 who either had a current diagnosis of RA or were healthy women without autoimmune disease. All women had completed multiple standard maternal telephone interviews during pregnancy that contained structured questions on the receipt of influenza vaccination and the occurrence of a diagnosis of influenza-like illness (ILI) during pregnancy. Using time varying vaccine exposure during pregnancy, and adjusting for the timing of the flu season during pregnancy, we estimated the hazard ratio (HR) and its 95% confidence interval (CI) for ILI in a Cox regression model comparing women who reported receipt of an influenza vaccine some time in pregnancy to women without vaccine during pregnancy. We addressed the potential differential effect of influenza vaccination on risk of ILI by testing an interaction term in the model (influenza vaccination by RA status). For those women who were vaccinated, only ILI reported subsequent to vaccination was included as an event.

Results: There were 1,233 subjects available for analysis: 825 women received influenza vaccine during pregnancy and 408 women did not receive vaccine; 245 women had RA and 988 women were without autoimmune disease. Among RA subjects, 144 (58.8%) were vaccinated and among subjects without autoimmune disease, 681 (68.9%) were vaccinated. Nine (3.7%) of the women with RA and 55 (5.6%) of the women without autoimmune disease reported a diagnosis of ILI at some time in pregnancy. Six (4.2%) vaccinated RA women and 28 (4.1%) vaccinated women without autoimmune disease reported ILI at some time in pregnancy. The adjusted HR for ILI in women vaccinated vs. women not vaccinated was 1.19 with 95% CI of 0.64, 2.24. The interaction term for vaccine exposure and autoimmune disease was not statistically significant ($p = 0.16$).

Conclusion: We found no evidence of a difference in the incidence of ILI after vaccination is pregnant women with RA compared to women without autoimmune disease.

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1047

Rates Of Hospitalized Infections In Rheumatoid Arthritis Patients From 5 Rheumatoid Arthritis Registries Across The World. Hisashi Yamanaka[1], Johan Askling[2], Niklas Berglind[3], Stefan Franzén[3], Thomas Frisell[2], Christopher Garwood[4], Jeffrey D. Greenberg[5], Meilien Ho[6], Marie Holmqvist[2], Laura Horne[7], Eisuke Inoue[1], Kathy Lampl[7], Kaleb Michaud[8], Dimitrios A. Pappas[9], George Reed[10], Deborah Symmons[4], Eiichi Tanaka[1], Trung Tran[11], Suzanne Verstappen[4] and Fredrik Nyberg[12]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Karolinska Institutet, Stockholm, Sweden, [3]AstraZeneca R&D Mölndal, Mölndal, Sweden, [4]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [5]New York Hospital for Joint Disease, New York, NY, [6]AstraZeneca R&D Alderley Park, Macclesfield, United Kingdom, [7]AstraZeneca R&D Wilmington, Wilmington, DE, [8]University of Nebraska Medical Center, Omaha, NE, [9]Columbia University, New York, NY, [10]University of Massachusetts Medical School, Worcester, MA, [11]MedImmune LLC, Gaithersburg, MD, [12]AstraZeneca R&D, Mölndal, Sweden.

Background/Purpose: Rheumatoid arthritis (RA) patients are at increased risk of infection due to both RA itself and immunomodulating treatments. Infection rates are often difficult to compare across studies, since the rates may vary across the world, and due to methodological and demographic differences between studied populations or cohorts. We investigated rates of hospitalized infection in 5 RA registries from 4 continents, employing a standard set of analyses and standardizing rates to a common population.

Methods: Participating registries were CORRONA (USA), SRR (Sweden), NOAR (UK), CORRONA International (East Europe, Latin America, India) and IORRA (Japan). The definition of hospitalized infections was harmonized as much as possible across registries. Within each registry, we analyzed a primary cohort of all RA patients from January 2000 to last

available data of each registry (2010–2013), and several subcohorts for sensitivity analyses, defined by disease activity, treatment status, calendar time, duration of follow-up and prior comorbidity. Rates were standardized for age, sex and, in 1 sensitivity analysis, also for HAQ, using the distributions from a typical RA trial program population.

Results: There was relatively high consistency in rates across registries, and sex/age standardization increased consistency further (Table 1). Generally, the primary cohorts provided the lowest or close to lowest rate (Table 2). In most registries, the highest rates were seen in subcohorts (either biologic naïve or with prior biologic treatment) with only 18 months follow-up after treatment change (Table 2). Additional standardization for HAQ score according to a trial patient distribution led to increased rates in all registries (Table 2).

Table 1. Incidence of hospitalized infection in the primary cohorts (RA patients from Jan 1, 2000) from 5 RA registries

Registry	N	Events	PY*	Crude Incidence/ 100 PY	Standardized† Incidence/100 PY (95% CI)
CORRONA	19,537	701	43,473	1.61	1.30 (1.18–1.42)
SRR	18,527	1909	76,855	2.48	1.62 (1.52–1.72)
NOAR	1564	231	10,366	2.23	1.56 (1.30–1.88)
CORRONA-INT	2727	28	1812	1.55	1.51 (0.99–2.24)
IORRA	10,255	690	59,680	1.16	1.14 (1.05–1.25)

† Standardized according to the age and sex distribution in a typical RA clinical trial program.
* PY, person-years.

Table 2. Incidence of hospitalized infections in the primary cohorts and selected sensitivity analyses from 5 RA registries.

Standardized incidence* per 100 person-years (with 95% confidence intervals)				
CORRONA	SRR	NOAR	CORRONA-INT	IORRA
Main analysis, primary cohort followed from Jan 1, 2000				
1.30 (1.18–1.42)	1.62 (1.52–1.72)	1.56 (1.30–1.88)	1.51 (0.99–2.24)	1.14 (1.05–1.25)
Sensitivity analysis A: Standardization for HAQ score in addition to sex and age, primary cohort				
1.90 (1.64–2.21)	2.03 (1.85–2.23)	1.86 (1.51–2.28)	2.17 (1.29–3.55)	1.84 (1.60–2.13)
Sensitivity analysis B: Subcohort of biologics-naïve patients followed from treatment change for 18 months (nested within primary cohort)				
3.03 (2.09–4.30)	2.11 (1.79–2.49)	2.67 (1.35–4.89)	NA†	1.00 (0.78–1.28)
Sensitivity analysis C: Subcohort of previously biologics-treated patients followed from treatment change for 18 months (nested within primary cohort)				
1.70 (1.25–2.30)	3.50 (2.75–4.43)	-‡	-‡	-‡

* Standardized according to the age and sex distribution (and in Sensitivity Analysis A also HAQ score) in a typical RA clinical trial program.
† Not available. Too few events - incidence rates not calculated.
‡ Too small cohort for reliable analysis.

Conclusion: This study constitutes the first attempt to compare the incidence of hospitalized infections internationally using existing RA cohorts. Consistent methodology, outcome definitions and analysis with standardization of rates facilitated comparison across registries. In most registries there is evidence of higher infection rates initially after starting treatment. The main analysis may be a good averaged estimate of risk over the longer term but may underestimate short-term risk. HAQ standardization appears useful to further address potential bias due to differences between registries and a typical trial population. Remaining differences between registries may reflect true regional differences in risk factors, populations and health care, although residual population and methodological differences are possible.

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Generalizability Of a U.S. Rheumatoid Arthritis Registry: A Comparison Of Participants' Vs. Non-Participants' Characteristics. Jeffrey R. Curtis[1], Lang Chen[2], Huifeng Yun[2], Leslie R. Harrold[3], Jeffrey D. Greenberg[4] and Joel M. Kremer[5]. [1]University of Alabama at Birmingham, Division of Clinical Immunology and Rheumatology, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]University of Massachusetts Medical School, Worcester, MA, [4]New York Hospital for Joint Diseases, New York, NY, [5]Center for Rheumatology, Albany Medical College, Albany, NY.

Background/Purpose: Observational registries provide a valuable complement to clinical trials yet might suffer from limited generalizability referent to the desired population of interest. We compared characteristics of older patients enrolled in a large U.S. rheumatoid arthritis (RA) registry compared to RA patients treated by non-participating rheumatologists throughout the U.S.

Methods: We used national data from the U.S. Medicare program from 2006–2010 and linked it to the Consortium of Rheumatology Researchers of North America (CORRONA) registry. Linkage was accomplished using deterministic methods on multiple non-unique identifiers and achieved $>$ 96% accuracy. RA patients were identified in Medicare on the basis of having at least one ICD-9 diagnosis code for RA (714.X) from a rheumatologist. Demographics, comorbidities, and drug utilization were examined in Medicare data during the most recent consecutive 12 month period with full fee-for-service coverage including pharmacy benefits. Characteristics of CORRONA RA patients were compared to characteristics of RA patients of non-CORRONA rheumatologists. Differences were quantified as standardized mean differences (SMDs), with values $<$ 0.1 considered clinically irrelevant.

Results: A total of 620,111 RA patients in Medicare treated by 3,834 non-CORRONA rheumatologists were identified and their characteristics compared with 5,643 RA patients treated by 282 CORRONA rheumatologists (Table). Mean age and sex were similar; CORRONA patients were more likely to be recruited in the Northeast and West. The prevalence of common comorbidities was comparable. During the 12m observation period, CORRONA RA patients were more likely to use biologics (22 vs. 12%) and somewhat less likely to use oral glucocorticoids (33 vs. 38%). Health services utilization was similar between CORRONA and non-CORRONA RA patients.

Table. Characteristics of Older RA Patients Enrolled in CORRONA vs. RA Patients of Non-CORRONA Rheumatologists

Patient Characteristic	CORRONA Patients	Non-CORRONA Patients	Standardized Mean Differences
Age, years	72.3 (9.9)	72.7 (11.1)	0.03
Female sex, %	74.6	73.8	0.02
Caucasian race	89.5	85.2	0.18
Region, %			
Northeast	30.2	17.4	0.038
Midwest	25.1	23.4	0.303
West	12.7	15.9	0.091
South	32.1	43.3	0.233
Rural Residence, %	21.7	23.4	0.06
Comorbidities, %			
COPD	13.5	14	0.01
Diabetes	18	21.9	0.08
Myocardial infarction	1.3	1.5	0.02
History of cancer	10.5	10.1	0.01
RA Medications, %			
Oral glucocorticoids	33.3	37.9	0.11
Methotrexate	30.9	21.7	0.21
Any biologic	22.3	12.4	0.27
Healthcare utilization			
Number of physician visits, mean ± SD	13.9 ± 10.2	14.2 ± 10.9	0.02
Any hospitalization, %	26.2	28.9	0.06

Conclusion: Despite some differences in regional geographic representation, older RA patients enrolled in CORRONA were generally similar in their characteristics to older RA patients of other rheumatologists not participating in CORRONA, although were more likely to receive biologic therapies. Based upon these findings, results from this U.S. registry may be generalizable to a national U.S. RA population.

Disclosure: J. R. Curtis, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, Abb Vie, 2, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, Abb Vie, 5; **L. Chen**, None; **H. Yun**, None; **L. R. Harrold**, Corrona, 5, Takeda, 2; **J. D. Greenberg**, CORRONA, 1, AstraZeneca, CORRONA, Novartis, Pfizer, 5; **J. M. Kremer**, Corrona, Inc, 1, Corrona Inc., 3.

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Formal Education Level Explains Variation In Rheumatoid Arthritis (RA) Core Data Set Measures and Indices In Korean Patients At Higher Levels Of Significance Than Age, Sex, and Duration Of Disease. Sung-Hoon Park[1], Isabel Castrejón[2], Jung-Yoon Choe[1], Seong-Kyu Kim[1], Hwajeong Lee[1], Sang Gyu Kwak[1] and Theodore Pincus[2]. [1]Catholic University of Daegu School of Medicine, Daegu, South Korea, [2]NYU Hospital for Joint Diseases and New York University School of Medicine, New York, NY.

Background/Purpose: Poor health is associated with low socioeconomic status (SES), with higher prevalence, greater severity and earlier mortality of many diseases, including rheumatoid arthritis (RA). However, a variable describing SES is not included in many clinical research reports, in contrast to age, sex and duration of disease, which are almost always included as potential confounders of differences between patients in clinical status, treatment responses and outcomes. The most easily measured SES variable is formal education level (EDUC), which has been interpreted as an available surrogate for patient actions and attitudes that may affect health. We analyzed the possible significance of EDUC, age, sex and duration of disease to explain variation in RA Core Data Set variables and 4 RA indices, in a cohort of Korean RA patients seen in usual care.

Methods: MDHAQ and all 7 RA Core Data Set measures were collected in 397 consecutive patients with RA seen in a Korean setting by 4 rheumatologists. Patients were classified in 3 EDUC categories: <7 years (elementary school, n=76; mean age 62.9 years), 7–12 years (high school, n=228; mean age 55.8), and >12 years (college, n=93; mean age 42.9). Possible associations with EDUC were analyzed for each of the 7 RA Core Data Set measures and 4 RA indices: DAS28, SDAI, CDAI and RAPID3 [an index of only the 3 patient self-report Core Data Set measures found on an MDHAQ: physical function, pain and patient global estimate of status (PATGL)]. The data were analyzed by multivariate generalized linear model (GLM) with a log link, and a Poisson distribution was applied to examine difference in 7 Core Data Set measures among EDUC, adjusted for age, sex and disease duration, and by regressions for each Core Data Set variable, with EDUC, age, sex and disease duration as independent variables.

Results: Patients with lower EDUC had higher scores, indicating greater severity, for all Core Data Set measures, statistically significant for tender joint count (TJC), physical function, pain, PATGL and ESR, and all 4 indices–DAS28, SDAI, CDAI and RAPID3–adjusted for age, sex and disease duration ($p < 0.01$; data not shown). No significant differences were seen for swollen joint count (SJC), physician global estimate (DOCGL) or CRP. In a series of regressions, EDUC was the only significant variable to explain variation in TJC, pain, PATGL, DOCGL, SDAI, CDAI and RAPID3. EDUC and disease duration explained variation in DAS28 significantly, and only disease duration explained variation in ESR. None of the 4 independent variables was significant to explain variation in SJC, physical function, or CRP.

Table. Beta coefficient (p value) of regressions including 4 possible independent variables to explain variation in ACR Core Data Set measures and composite indices

Dependent variables	Independent variables			
	Age	Sex	Disease duration	EDUC
TJC	<0.001 (0.999)	0.475 (0.483)	0.289 (0.292)	−0.130 (0.034)
SJC	−0.009 (0.331)	−0.004 (0.989)	0.130 (0.239)	−0.021 (0.430)
Physical function	0.016 (0.097)	0.129 (0.633)	0.012 (0.256)	−0.051 (0.053)
Pain	−0.008 (0.621)	0.559 (0.196)	−0.001 (0.957)	−0.140 (0.001)
PATGL	−0.017 (0.232)	0.681 (0.091)	0.011 (0.505)	−0.016 (0.007)
DOCGL	−0.018 (0.048)	0.259 (0.300)	−0.014 (0.163)	−0.072 (0.003)
ESR	−0.206 (0.109)	1.351 (0.709)	0.504 (0.001)	−0.539 (0.123)
CRP	−0.010 (0.341)	0.272 (0.346)	0.001 (0.917)	−0.027 (0.326)
DAS28	−0.010 (0.153)	0.181 (0.363)	0.021 (0.009)	−0.059 (0.002)
SDAI	−0.054 (0.231)	1.684 (0.184)	0.040 (0.436)	−0.365 (0.003)
CDAI	−0.044 (0.294)	1.411 (0.233)	0.039 (0.418)	−0.337 (0.003)
RAPID3	−0.009 (0.798)	1.369 (0.156)	0.022 (0.567)	−0.297 (0.002)

Conclusion: Significant associations of low EDUC with greater disease severity according to most RA Core Data Set measures and 4 indices were seen in 397 Korean RA patients. EDUC was more likely than age, sex or duration of disease to explain variation in most Core Data Set measures and RA indices. EDUC should be included in all clinical databases.

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Population-Based Analysis Of Treatment Patterns For Recently Diagnosed Rheumatoid Arthritis Patients In The United States. Martin M. Crane[1], Boyka Stoykova[2], Julie Priest[1], Nasha Wang[1], Henry Krzywy[1] and Rahul Ganguly[1]. [1]GlaxoSmithKline, Durham, NC, [2]GlaxoSmithKline, Uxbridge, United Kingdom.

Background/Purpose: As treatment paradigms for rheumatoid arthritis (RA) continue to evolve, population-based studies can help assess which strategies are being used in "real-world" practice for the complete spectrum of clinical RA. This approach can also relate therapy to the consumption of other health-care resources such as RA-related surgery or hospitalization which are fundamental for RA economic models. Herein we describe treatment patterns in RA patients newly diagnosed in 2009 and followed for two years.

Methods: A retrospective cohort analysis of adults (age ≥20) with complete medical and pharmacy insurance claims from 1 Jan 2008 to 31 Dec 2011 was used. "Incident RA" required a primary diagnosis at two separate visits 30 days apart in 2009 and no prior claims for RA. Databases employed were the Marketscan Commercial Claims and Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits (MSCB) databases from Truven Health Analytics. Information on demographics, co-morbidities and treatments including conventional (cDMARD) and biologic (bDMARD) therapy and sequencing thereof was obtained for the entire follow-up period. Selected results were informally compared to a similar analysis in 2006 [Arth Rheum 2010;62(Suppl10):18].

Results: There were 8.02 million persons who met study criteria from which 8,507 RA cases were newly diagnosed in 2009. Incidence was 1.06/1000 persons at risk (1. 5 in females; 0.57 in males). 18% of incident patients received a bDMARD in year one (versus 21% in 2006) and 67% a cDMARD. Among the former, TNF inhibitors were the most commonly prescribed (94%). Over two years of follow-up, 23% of patients were prescribed bDMARDs but 22% of them were subsequently switched to a different biologic. A total of 26% of patients did not receive a DMARD over the two years (as compared to 28% in 2006). Corticosteroids were given to 77% of patients during the 2-year follow-up.

Treatment patterns over the 24 months after RA diagnosis were as follows (Table 1):

Table 1.

				bDMARDs								
	No Tx	cDMARDs	NSAIDs/ Cox2/CS	ETA	ADA	INF	CER	GOL	ABA	RTX	TOC	Total
0–12 months	827 (9.7%)	5,718 (67%)	6,767 (80%)	699 (45%)	532 (34%)	279 (18%)	47 (3%)	61 (3.9%)	102 (6.6%)	41 (2.6%)	NA	1,552 (18%)
0–24 months	520 (6.1%)	6,020 (71%)	7,361 (87%)	927 (47%)	734 (37%)	358 (18%)	100 (5%)	110 (5.6%)	189 (9.5%)	82 (4.1%)	35 (1.8%)	1,981 (23%)

ETA-etanercept, ADA - adalimumab, INF - infliximab, CER - certolizumab pegol, ABA - abatacept, RTX - rituximab, TOC - tocilizumab.

Of patients who used bDMARDs, 78% had only one, 17% had two, 4% had three, and 1% had four different biologics over the study period. The most common first line biologic was ETA (45%), followed by ADA (27%), and INF (22%), while second line biologic choices were ADA (43%), INF (22%), and ABA (13%).

Conclusion: The majority of newly diagnosed patients received anti-rheumatic therapy. The proportion of cDMARDs and bDMARDs were similar in 2006 and 2009. Switching among biologics was not uncommon. There were 26% (versus 28% in 2006) who had not received anti-rheumatic treatment over the two years of follow-up.

Disclosure: M. M. Crane, GlaxoSmithKline, 3, GlaxoSmithKline, 1; **B. Stoykova**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **J. Priest**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **N. Wang**, GlaxoSmithKline, 3; **H. Krzywy**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **R. Ganguly**, GlaxoSmithKline, 1, GlaxoSmithKline, 3.

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Sociodemographic, Health System, and Community Characteristics Associated With Initiation Of Biological Dmards In RA. Edward H. Yelin[1], Chris Tonner[2], Seoyoung C. Kim[3], Jeffrey N. Katz[3], John Z. Ayanian[3] and Daniel H. Solomon[4]. [1]UC San Francisco, San Francisco, CA, [2]University of California, San Francisco, San Francisco, CA, [3]Brigham and Women's Hospital, Boston, MA, [4]Harvard Medical School, Brigham and Women's Hospital, Division of Rheumatology, Division of Pharmacoepidemiology, Boston, MA.

Background/Purpose: The use of biologic DMARDs for RA has improved outcomes, but it is unknown whether there are disparities in

initiation of these agents by sociodemographic, medical, health system, and community characteristics.

Methods: We analyzed data from the UCSF Rheumatoid Arthritis Panel for the years 1999 through 2011. Panel participants are drawn from a random sample of Northern California rheumatologists, with enrollments in 1982/1983, 1985, 1989, 1999, and 2003. Principal data collection is by a structured annual phone survey. We used Cox regression to estimate the effect of individual- and community-level characteristics on the first initiation of a biological DMARD. Individual-level characteristics include sociodemographics (age, gender, race, ethnicity, marital status, formal education, annual household income), medical (HAQ, # painful and # swollen joints and # comorbid conditions, Geriatic Depression Score, and use of oral steroids, non-biological DMARDs, and NSAIDS), and health system (having any health insurance, including for medications; HMOs vs. fee-for-service; and # of rheumatologist visits in prior year). Community-level characteristics include # of rheumatologists per capita, presence of a federally qualified health center in local area, and living in area of concentrated poverty.

Results: 527 persons were in the RA Panel in 1999. 83% were female, 83% whites, 7% Hispanics, 41% ≤ high school, and 38% had household income < 30,000/year. Mean (Std) age was 61 (14), RA duration was 20 (11) years, and HAQ score was 1.1 (0.7). Among the 527 persons, 20% had initiated biological therapy by 2000, 40% by 2005, and 43% by 2011. In fully adjusted Cox regression models that include all medical characteristics, younger age [Hazard Ratio (HR) for ages 19–54 =1.89 (95%CI 1.24, 2.87); HR for 55–69=1.25 (0.84,1.87)], Hispanic ethnicity [HR 2.02 (1.05, 3.86], household incomes >$30,000/year [HR1.61 (1.12, 2.32)], being married or with a partner [HR 1.39 (1.00, 1.92)], and living in a rural setting [HR 1.96 (1.28, 2.99)] were associated with a higher probability of initiating a biologic DMARD. The following characteristics were associated with a lower probability: having no [HR 0.18 (0.08, 0.40)] or only 1–4 rheumatology visits in the year prior to interview [HR 0.60 (0.45, 0.81)] and living in an area with Federally qualified health centers [HR 0.63 (0.41, 0.96)]. After adjustment, no medical characteristics were associated with initiation of a biologic DMARD.

Conclusion: These results indicate that many sociodemographic and community characteristics influence the initiation of biologic DMARDs, suggesting attention to these characteristics to improve access to such treatment.

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Glucocorticosteroids and Mortality Risk In Rheumatoid Arthritis-Results Of a Population Based Study. Diane Lacaille[1], J. Antonio Avina-Zubieta[1], Eric C. Sayre[2], Michal Abrahamowicz[3] and John Esdaile[1]. [1]Arthritis Research Centre of Canada, University of British Columbia, Richmond, BC, [2]Arthritis Research Centre of Canada, Richmond, BC, [3]McGill University, Montreal, QC.

Background/Purpose: Glucocorticosteroids (GC) are frequently used in the management of rheumatoid arthritis (RA). Due to their metabolic and immunosuppressive effects, they could increase the risk of mortality, yet suppression of disease activity, a known predictor of premature mortality, could also reduce the risk of mortality in RA. We evaluated the association between exposure to GC and risk of mortality in RA, using a population-based incident RA cohort with administrative health data.

Methods: Using administrative billing data, we assembled a population-based cohort including all incident RA cases between 01/1996 and 03/2006, followed until 03/2010. Cases with GC use prior to RA onset were excluded. Administrative data were obtained on all medications since 09/1995; MD visits, hospitalizations, and tests since 01/1990. The Cox proportional hazard model (PHM) was used to estimate risk of death associated with GC exposure. Time analyzed was from index RA date to death or end of follow-up. GC exposure was defined as any dispensed prescription for oral GC during follow up, and was measured using three time-dependent exposure variables, in separate models, representing current dose (in mg prednisone equivalent), past cumulative dose and past cumulative duration of exposure . We used propensity scores (PS) to control for the observed differences between GC users and non-users, calculated at the time of initiating GC, using markers of RA severity, as well as co-morbidities increasing risk of death. Variables for which there was residual imbalance across PS quintiles were also included as covariates in the model. PHM analyses were also adjusted for age, gender, calendar year of inclusion, PS, as well as time-dependent variables representing exposure to RA medications that could influence mortality risk (MTX, biologics and NSAIDs).

Results: Our sample includes 18,215 incident RA cases (mean (SD) age: 57.2(17.1), 66.5% females) providing a mean of 7.1 years and a total of 128,799 person-years of follow-up, with 5,326 RA cases (29.2%) exposed to GC. We observed 2,881 deaths. Exposure to GC was associated with an increased risk of death in all models (Table 1). Female gender, current MTX and biologic use, and later calendar year of inclusion were associated with a reduced risk of death; whereas age, smoking, Charlson comorbidity score and markers of RA severity were associated with an increased risk of death. Limitations of our study are those inherent to observational study, including possible effect of residual or unmeasured confounding, and selection bias from non-random allocation of treatment.

Table 1.

Model	GC exposure measurement	Risk of all cause mortality aHR (95% CI)	p value
1	Current dose (per 5 mg)	1.22 (1.21;1.24)	<0.0001
2	Cumulative dose (per 1 gm)	1.11 (1.10;1.12)	<0.0001
3	Cumulative duration (per 1 yr)	1.30 (1.26;1.35)	<0.0001
4	Current dose (5mg)	1.22 (1.20;1.24)	<0.0001
	Cumulative duration (1 yr) in same model	1.26 (1.22;1.31)	<0.0001 <0.0001

Conclusion: In a population-based cohort, exposure to GC was associated with a significant increase in mortality. Given the increased mortality risk of RA, this has important implications for health care providers and people with arthritis.

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Physician Proclivity To Use Oral Glucocorticoids Among Rheumatoid Arthritis Patients. Huifeng Yun[1], Fenglong Xie[1], Elizabeth S. Delzell[1], Lang Chen[1], Emily Levitan[1], James Lewis[2], Kenneth G. Saag[1], Timothy Beukelman[1], Kevin L. Winthrop[3], John Baddley[1] and Jeffrey R. Curtis[4]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Pennsylvania, Philadelphia, PA, [3]Oregon Health & Science University, Portland, OR, [4]University of Alabama at Birmingham, Division of Clinical Immunology and Rheumatology, Birmingham, AL.

Background/Purpose: It is unclear if the elevated risks of adverse events in rheumatoid arthritis (RA) patients are due to use of biologics or DMARDs, glucocorticoids (GCs), or features associated with the disease itself. The selection of RA medications is potentially confounded due to disease severity (i.e. channeling). Physician proclivities to use specific medications have been shown in prior analyses to be partially independent of patient factors and may reduce confounding in observational analyses. Therefore, we evaluated variability in physicians' proclivity to use oral GCs among older RA patients.

Methods: Using 2009 Medicare data, we identified patients who had at least two RA diagnosis codes from rheumatologists. We classified patients as oral GC users if they had at least one prescription for >= 30 days' supply. Rheumatologists were identified in the data using NPI numbers.

We calculated proclivity to use GCs for each rheumatologist as a proportion, computed as the number of their RA patients who used GCs divided by total number of all their RA patients, and categorized each rheumatologist into one of 4 groups based on quartiles. For each rheumatologist, this proportion was plotted against the number of RA patients in their practice.

The analysis was repeated in the subgroup of patients who also used biologics in 2009. Physician variability in steroid use was examined based upon inter-quartile ranges of the proportion of their patients using GCs, as well as measures of central tendency (i.e. skewness and kurtosis). Weighted Kappa statistics evaluated whether assignment of physicians' steroid proclivity to quartiles was consistent between the main analysis and the subgroup analysis.

Results: We identified 313,108 RA patients (27,474 of whom used biologics) treated by 4,003 rheumatologists in 2009 Medicare data. Overall, 81,422 (26%) pts were oral GC users; 12,306 (44.8%) in the biologic subgroup used GCs.

The proportion of patients using oral GCs was plotted for each U.S. rheumatologist (Figure) and demonstrated substantial variability between physicians. After restricting to patients on biologics, there was greater

physician variability in use of GCS for their patients than in the main analysis (not shown). The weighted kappa statistic comparing physician's proclivity to use GCs using all their RA patients vs. proclivity to use GCs in the biologic-using subgroup was 0.32 (95% confidence limits: 0.30–0.35) indicating low to moderate agreement.

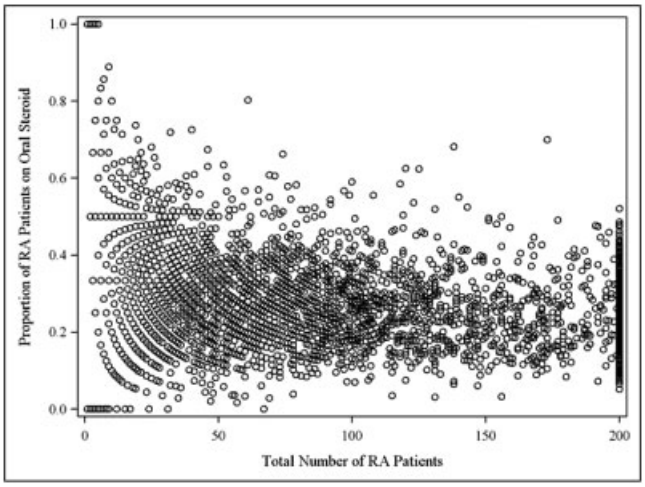

Figure. Proportion of rheumatologist's RA patients on glucocorticoids per practice in 2009

Conclusion: The frequency with which rheumatologists' prescribe oral GCs for RA patients was highly variable and was even greater for patients using biologics. Further work is ongoing to examine whether this approach might be effect to reduce unmeasured or residual confounding associated with glucocorticoid use.

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Use Of Oral and Subcutaneous MTX In a Commercially Insured Rheumatoid Arthritis Population. Jeffrey R. Curtis[1], Fenglong Xie[1], Jie Zhang[1], Lang Chen[1], Huifeng Yun[1], Michael H. Schiff[2], Timothy Beukelman[1] and Seth Ginsberg[3]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Colorado, Denver, CO, [3]Creaky Joints, New York, NY.

Background/Purpose: Methotrexate (MTX) is the most commonly used medication in rheumatoid arthritis (RA), although use of oral and subcutaneous (SQ) preparations in real-world settings has not been well characterized.

Methods: Using national data from a large commercially insured population in the U.S. from 2005–2011, we identified RA patients (pts) on the basis of 2 RA diagnosis codes initiating oral MTX (no prior use ever, minimum of 6m clean period) who also had no prior use of hydroxychloroquine (HCQ), sulfasalazine (SSZ), leflunomide (LEF) or biologic use and had at least one year of follow-up available. Subsequent dose escalation of oral MTX or switch to SQ MTX, HCQ, SSZ, and LEF were characterized. Subsequent use and timing of addition of biologics was examined for those had at least one switch, adjusting for multiple potential confounders using Cox proportional hazards models with switch date as time zero.

Results: New oral MTX users (n=4,048) were 74.2% women, had mean +-SD age of 51.1+−11.9 years and contributed a median (IQR) follow-up of 2.4 (1.6, 3.6) years; 28.1% never changed dose of oral MTX and remained at their starting dose; common doses included 10.0 mg/week (24.9%) and 15.0mg/week (26.3%). Of all patients, only 48.2% used oral MTX at >= 20mg/week at any time. Overall, 73.8% stayed on oral MTX (with or without dose increase) and did not add or switch to HCQ, SSZ, LEF, or SQ MTX. The remainder switched or added HCQ (14.0%), SSZ (6.2%), LEF (9.5%) or switched to SQ MTX (2.9%). The median (IQR) dose of oral MTX prior to switch to SQ was 15.0 (15.0, 20.0) mg/week and occurred at a median (IQR) of 322 (146,527) days.

Overall, 35.3% of the cohort subsequently initiated a biologic, mostly (90.3%) anti-TNF therapy. Of these individuals, 46.0% never used MTX at a dose of >= 20mg; 21.9% never used MTX at a dose of >= 15mg. Among pts who used biologics after switch to SQ MTX, the median (IQR) interval of time between switching to SQ MTX and initiation of a biologic was 113 (65, 233) days. Among patients who increased dose or switched to SQ MTX or other nbDMARDs, (n=2,685) and after multivariable adjustment, there were no significant differences in subsequent biologic initiation between patients who switched to SQ MTX vs. added or switched to SSZ, LEF or HCQ.

Conclusion: Titration to higher doses of oral MTX and use of SQ MTX preparations among RA patients is uncommon, even for patients who subsequently used biologics. Further work to optimize MTX in RA is warranted.

Disclosure: J. R. Curtis, Roche/Genentech, UCB, janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2, Roche/Genentech, UCB, janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **F. Xie**, None; **J. Zhang**, Roche/Genentech, 2; **L. Chen**, None; **H. Yun**, None; **M. H. Schiff**, Antares biopharma, Abbvie, BMS, Pfizer, Amgen, Roche, UCB, 5; **T. Beukelman**, Genentech and Biogen IDEC Inc., 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 2; **S. Ginsberg**, None.

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Discontinuation Rates In Patients With RA Of Triple Disease Modifying Antirheumatic Therapy. Sofia Pedro[1], Frederick Wolfe[1], Hawre Jalal[2] and Kaleb Michaud[3]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]University of Minnesota, Minneapolis, MN, [3]National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: Drug discontinuation rates are measures of effectiveness and are needed in health economic models. While a recent RCT demonstrated statistical equivalence of efficacy with etanercept [1], little is known regarding the real-world use and discontinuation rates of triple therapy, which includes methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ).

Methods: We evaluated the treatment discontinuation rates of triple therapy in rheumatoid arthritis using a large observational cohort, the National Data Bank for Rheumatic diseases. We initially defined discontinuation as when all 3 DMARDs (MTX, SSZ & HCQ) were not taken (First). Since we cannot verify if triple therapy was purposely prescribed, our second discontinuation definition occurred when the patient was no longer on any combination of the 3 DMARDs or if they added a biologic (Second). In both cases missing data between periods on triple therapy were assumed to remain on treatment. Kaplan-Meier survivor functions were used to analyze discontinuation rates.

Results: From 10,156 patients on biologics and DMARDs, 388 (3.8%) initiated triple therapy at some point between 1998–2012. From these 304 (78.4%) discontinued triple therapy according to our first definition with 121 (39.8%) immediately switching to or adding another DMARD while 183 (60.2%) dropped one or two of the 3 drugs. A total of 216 (55.7%) discontinued according to our second definition. The discontinuation rate of triple therapy by our two definitions were 40.8% (First) and 23.5% (Second) per year (See Table). The median survival on triple therapy was 14 months (IQR 6–45 months), and doubled to 28 months (IQR: 10–112 months) when using the second definition. At 24 months, the discontinuation rates were: 39.1% (95% CI 33.9%–44.2%) and 53.4% (95% CI 48.2%–59.0%), for first and second definitions respectively. After triple therapy, patients tended to switch/add more DMARDs afterwards (59.3%) than biologics (41.2%).

[1] O'Dell JR et al. Therapies for Active Rheumatoid Arthritis after Methotrexate Failure. N Engl J Med. 2013

Table. Discontinuation rates and median survival for patients on triple therapy.

	Discontinuation Definitions	
	First-Strict	**Second-Relaxed**
Time at risk (patient years)	742.2	918.0
Discontinuation rate per year	0.408	0.235
Median survival (months)	14	28
Discontinuation rates (95% CI) after:		
1 year	0.501 (0.449, 0.551)	0.627 (0.621, 0.719)
2 years	0.391 (0.339, 0.442)	0.538 (0.482, 0.590)
3 years	0.291 (0.242, 0.343)	0.438 (0.381, 0.494)

Conclusion: This is the first study to provide discontinuation rates of triple therapy using community experience in the biologic era. Overall discontinuation rates were high and patients tended to switch between several combinations of MTX, SSZ, and HCQ. Future work is needed to identify rates of prescription and patient/physician preferences for triple therapy.

Disclosure: S. Pedro, Natinal DataBank for Rheumatic Disease, 3; **F. Wolfe**, None; **H. Jalal**, None; **K. Michaud**, University of Nebraska Medical Center, 3, National Data Bank for Rheumatic Diseases, 3.

1056

Adherence To Methotrexate Therapy Among Patients With Rheumatoid Arthritis In Denmark: A Registry Based Cohort Study. Henning Bliddal[1], Robin Christensen[1], Mikkel Østergaard[2], Tove Lorenzen[3], Michael Sejer Hansen[4], Peter Vestergaard[5] and Stine A Eriksen[5]. [1]The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, Frederiksberg, Denmark, [2]Copenhagen University Hospital Glostrup, Copenhagen, Denmark, [3]Department of Rheumatology, Region Hospital Silkeborg, Silkeborg, Denmark, [4]Gildhøj Privathospital, Copenhagen, Denmark, [5]Aalborg University, Aalborg, Denmark.

Background/Purpose: Conflicting data have been presented on patient compliance with methotrexate (MTX) prescription. A Danish study found a mean period of 12.3% of the prescribed years in reality being non-covered by MTX[1], while recent data from Canada indicate that a rather large percentage of patients do not comply with the prescription of MTX[2]. The objective was to elucidate and quantify the use of MTX after a primary prescription for rheumatoid arthritis (RA).

Methods: The study was a register based cohort study including patients with a hospital diagnosis extracted from the National Hospital Discharge Register of RA (ICD10 codes M05.X, M06.X), diagnosed after January 1, 1998 and aged ≥18 years at the date of first diagnosis/contact. The register has a nationwide coverage, and an almost 100% capture of contacts[3]. Data was extracted of all patients registered as MTX users in the Pharmacies Register from 1996 onwards. Any drugs bought are registered with an ATC code, number and dosage of product, form of medication (tablets, injections etc.), and date of sale. Stability of MTX use was defined as regular MTX prescriptions of 100 tablets of 2.5 mg delivered from a pharmacy > 1 per year with cut-off of 6, 9, or 12 months respectively corresponding to an average weekly dose of minimum 10; 7.5; and 5 mg respectively.

These sources of information were linked through the Central Person Register Number which is a unique registration code given to every inhabitant–to some degree similar to the American social security number - that allows registration on an individual basis. The project was approved by the Danish National Data Protection Agency.

Results: The study population consisted of 5,368,354 inhabitants in Denmark, among whom 4,191,428 were ≥ 18 years during the study period. 39,286 had the diagnosis of ICD10: M05 or M06 after January 1st 1998 and n= 18,703 were found to have used a prescription of MTX, representing 47.6 per cent of all subjects diagnosed with RA at a hospital in the period 1998–2011. Of these subjects, 2,200 (12 %) only used a prescription on MTX once, Figure 1. The median adherence in days almost doubled from the estimated dose of 10 mg to 5 mg per week: 5 mg: 5433 days, 7.5 mg: 4002 days, 10 mg: 2768 days.

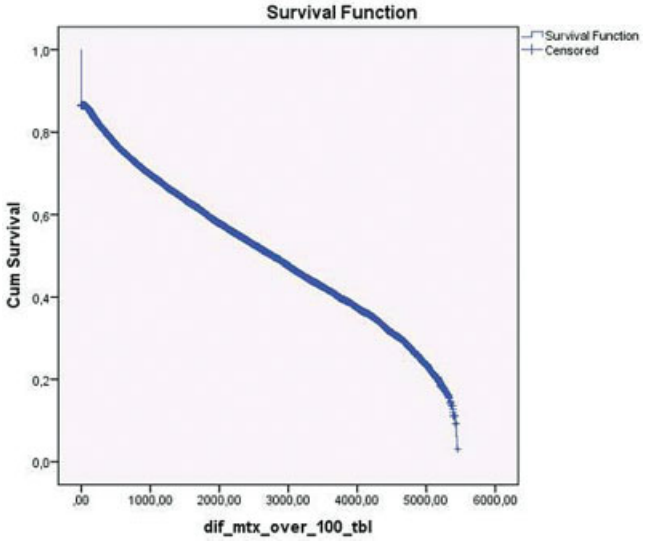

Figure 1. Kaplan-Meyer plot of the remaining subjects on MTX therapy the period 1998–2012. In this plot, the assumption was that the subject had a prescription of > 1 per year, i.e. a minimum average dose of ≥10 mg per week. The last part of the curve, i.e. > 5,000 days is dipping, presumably due to lack of sufficient follow-up time after the last prescription.

Conclusion: Adherence to MTX therapy was decreasing with increasing defined minimum doses 10; 7.5; and 5 mg weekly respectively. The median treatment time on these doses, however, was very long, e.g. 7.5 years on the 10 mg dose. Even so, the results indicate that patients taper their MTX over the years.

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Regional Variations In Rheumatoid Arthritis Treatment and Health Outcomes Across The United States. Susan C. Bolge[1], Roxanne Meyer[2] and Kathy Annunziata[3]. [1]Janssen Scientific Affairs, LLC, Horsham, PA, [2]Janssen Scientific Affairs, LLC, Horsham, NY, [3]Kantar Health, Princeton, NJ.

Background/Purpose: Current ACR guidelines call for treatment of rheumatoid arthritis (RA) with non-biologic or biologic disease modifying anti-rheumatic drugs (DMARDs). The National Quality Forum has listed the prescribing of a DMARD as a specific measure of quality of care. This study seeks to evaluate regional variations in RA treatment and health outcomes.

Methods: Data were obtained from the 2012 U.S. National Health and Wellness Survey, a cross-sectional, self-administered, Internet-based survey of the general adult (aged 18+) population. Respondents reporting a diagnosis of RA (n=1088) were included in the analyses. Current treatments were obtained through a prompted list and categorized into a hierarchy: biologics; non-biologic DMARDs without biologics; other medication classes including steroids, opioids, and NSAIDS but without biologics or non-biologic DMARDs; untreated. Health outcomes included the SF-36v2, the Work Productivity and Activity Impairment (WPAI) questionnaire, and healthcare resource use in the previous six months.

Results: Variations in RA treatment are presented in the table. The Mountain region has the greatest use of biologic and non-biologic DMARDs (60%), as well as the greatest physical functioning (SF36v2 summary score 40.7), the least activity impairment (39%), and among the lowest proportion of ER (18%) and hospital use (11%). The East South Central region had the greatest proportion of patients who were untreated or undertreated with medications other than DMARDs (61%), while also having among the poorest mental and physical functioning (SF36v2 summary scores 43.3 and 38.0, respectively), the greatest activity impairment (52%), and the greatest proportion of ER (32%) and hospital use (22%).

Table. Current Treatment for RA within the U.S. Census Regions

	Biologics	Non-biologic DMARDs	Other Medication Classes	Untreated
New England (n=36)	28%	14%	39%	19%
Middle Atlantic (n=171)	33%	20%	25%	21%
East North Central (n=191)	25%	27%	29%	18%
West North Central (n=72)	21%	33%	28%	18%
South Atlantic (n=238)	28%	24%	29%	18%
East South Central (n=63)	11%	29%	37%	24%
West South Central (n=104)	38%	18%	25%	17%
Mountain (n=76)	34%	26%	17%	22%
Pacific (n=137)	39%	18%	25%	19%

Conclusion: These data suggest that there are regional variations in the care received by patients with RA in the U.S. as well as associated variations in patient outcomes. Initiatives to improve quality of care may benefit from a regional approach that considers these existing variations.

Disclosure: S. C. Bolge, Janssen Scientific Affairs, LLC, 3; **R. Meyer**, Janssen Scientific Affairs, LLC, 3; **K. Annunziata**, Janssen Scientific Affairs, LLC, 5.

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Concomitant Methotrexate Use and The Risk Of Drug Discontinuation For Adalimumab Compared With Etanercept In Anti-TNF-Naïve Rheumatoid Arthritis Patients: A Nationwide Population-Based Cohort Study. Hsin-Hua Chen[1], Der-Yuan Chen[2], Chao-Hsiung Tang[3], Ya-Wen Yang[4], Chi-Hui Fang[4] and Nicole Huang[1]. [1]National Yang-Ming University, Taipei, Taiwan, [2]Taichung Veterans General Hospital, Taichung, Taiwan, [3]Taipei Medical University, Taipei, Taiwan, [4]Pfizer Limited, Taipei, Taiwan.

Background/Purpose: To evaluate possible interaction effect by concomitant methotrexate (MTX) use on the risk of drug discontinuation for adalimumab (ADA) compared with etanercept (ETN) in anti-tumor necrosis factor (anti-TNF)-naïve patients with rheumatoid arthritis (RA).

Methods: This retrospective nationwide population-based cohort study identified 4592 anti-TNF-naïve RA patients (age at diagnosis ≥ 16 years) in whom ETN (n = 2,609) or ADA (n = 1,983) was initiated using administrative data. The outcome was the time to anti-TNF drug discontinuation. We defined drug discontinuation as non-persistence of prescription for more than 84 days. After adjusting for baseline characteristics and concomitant use of disease modifying anti-rheumatic drugs (DMARDs), the risk of drug discontinuation for ADA compared with that of ETN was quantified by calculating relative risk (RR) with 95% confidence intervals (CI) using Cox proportional hazard regression analysis for the follow-up time before and after one year. Subgroup analysis was conducted based on the average weekly dose of concomitant methotrexate use (i.e. not use, ≤10 mg, >10mg).

Results: During the first year of follow-up, 562 of 1,982 ADA users and 682 of 2,609 ETN users withdrew anti-TNF drugs after 1,507 and 2,094 person-years of follow-up respectively, and the incidence rates of drug withdrawal were 0.37 and 0.33 case per person-year. The crude and adjusted RRs of drug discontinuation for ADA compared with ETN were 1.16 (95% CI, 1.04–1.30) and 1.10 (95% CI, 0.98–1.23). The adjusted RR with 95% CIs for those with 0, ≤10mg/week and >10 mg/week concomitant MTX use were 0.83 (0.64–1.06), 0.91 (0.75–1.11) and 1.53 (1.28–1.82) respectively (p for interaction <0.001). If the follow-up time exceeded one year, 376 of 969 ADA users and 616 of 866 ETN users discontinued anti-TNF drugs after 1,012 and 1,846 person-years of follow-up respectively, and the incidence rates of drug discontinuation were 0.37 and 0.33 case per person-year. The crude and adjusted RRs of drug discontinuation for ADA compared with ETN were 1.07 (95% CI, 0.94–1.22) and 0.98 (95% CI, 0.86–1.12). The adjusted RRs with 95% CIs for those with 0, ≤10mg/week and >10 mg/week concomitant MTX use were 0.85 (0.68–1.06), 0.93 (0.77–1.15) and 1.42 (1.06–1.90) respectively (p for interaction 0.026).

Table 1. The adjusted relative risks with 95% confidence intervals of drug discontinuation for ADA compared with ETN

Follow-up time	No MTX use	≤10 mg/week	10 mg/week	P value for interaction
Within 1 year	0.83 (0.64–1.06)	0.91 (0.75–1.11)	1.53 (1.28–1.82)	<0.001
After 1 year	0.85 (0.68–1.06)	0.93 (0.77–1.15)	1.42 (1.06–1.90)	0.026

Note: Cox proportional hazard regression analyses per conducted after adjusting for the variables with p values less than 0.2 in univariate comparisons between adalimumab and etanercept, including sex, age at anti-TNF initiation, RA duration, Charlson comorbidity index (≤1, >2) within one year before anti-TNF use, the use of MTX (not use, ≤10 mg/week, >10 mg/week), leflunomide, salazopyrin, non-steroid anti-inflammatory drugs within one year before and after anti-TNF use, and average daily prednisolone equivalent (≤5 mg, >5 mg) within one year before anti-TNF use.

Conclusion: Among anti-TNF naïve RA patients, compared with ETN users, ADA users had a significantly higher risk of drug discontinuation if the concomitant MTX dose was more than 10 mg/week.

Disclosure: H. H. Chen, Pfizer Limited, 2; **D. Y. Chen**, Pfizer Limited, 2; **C. H. Tang**, Pfizer Limited, 2; **Y. W. Yang**, Pfizer Limited, 3; **C. H. Fang**, Pfizer Limited, 3; **N. Huang**, Pfizer Limited, 2.

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Perinatal and Early Life Risk Factors For Systemic Lupus Erythematosus In a National Cohort Of Women. Christine G. Parks, Aimee D'Aloisio and Dale Sandler. NIH/NIEHS, Research Triangle Park, NC.

Background/Purpose: Growing evidence supports the role of perinatal and early life exposures in risk for chronic adult diseases. We examined perinatal and early life environmental risk factors for SLE in a national cohort of women ages 35–74 at enrollment in 2003–2009.

Methods: Questionnaire data were collected on maternal and perinatal factors and characteristics of longest childhood residence. Prevalent SLE cases (N=124; median age 54, interquartile range, IQR 47–60; diagnosis age 43, IQR 33–50) were identified based on self-reported diagnosis after age 17, and confirmed by current or past use of disease modifying anti-rheumatic drugs (DMARDs) for SLE. Non-cases were women who did not report SLE or discoid lupus (N=50,465; median age 55 years, IQR 50–61). Odds Ratios (OR) and 95% Confidence Intervals (CI) were estimated by logistic regression, adjusting for age and race/ethnicity.

Results: Most cases were non-Hispanic whites (69% vs. 84% non-cases), but cases were more likely to be African-American (19% vs. 9%; OR=2.4; 95%CI 1.5, 3.8) or Hispanic (9% vs. 5%; OR=2.2; 95%CI 1.2, 4.1). Low birth weight (<2500 grams) was associated with risk of SLE (vs. 3000-<3500 grams; OR=2.2, 95%CI 1.2, 3.9), with a significant inverse linear dose-effect for increasing birth weight based on data for 84 cases and 36,477 non-cases. Premature birth (>4 weeks vs. full-term) was also associated with SLE (OR=3.0; 95%CI 1.4, 6.5), but only 47 cases and 15,996 non-cases reported gestational age. An association of SLE with young maternal age (<18 vs. 18–34 years) was not significant after adjusting for race/ethnicity (OR=1.7; 95%CI 0.71, 3.2), and no associations were seen for prenatal smoking exposure (maternal or household), having been breastfed, birth order, or sibling number. SLE was associated with having a mother who worked on a farm during pregnancy (OR=1.7; 95%CI 1.1, 2.7). Considering longest childhood residence, SLE cases were more likely to have lived on a farm (OR= 1.6; 95%CI 1.0, 2.6) and reported pesticides were regularly (at least monthly) applied in and around the home (OR=2.3; 95%CI 1.3, 4.1). SLE was not associated with residential well water or childhood socioeconomic status (household education, income, food insecurity).

Conclusion: Our observed association of premature birth with DMARD-treated SLE is consistent with other studies, but could not be separated from the effect of low birth weight. Findings on maternal farm work, childhood farm residence and household pesticide application require confirmation, but are supported by previous evidence on adult farming and pesticide exposures associated with systemic autoimmune diseases, including SLE.

Disclosure: C. G. Parks, None; **A. D'Aloisio**, None; **D. Sandler**, None.

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Perinatal Risk Factors For Systemic Lupus: A Register-Based Case-Control Study. Elizabeth V. Arkema[1] and Julia F. Simard[2]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Stanford University School of Medicine, Stanford, CA.

Background/Purpose: One's own fetal environment has been linked to future heart disease, breast cancer, and rheumatoid arthritis. Prior work showed that among older women in the US, high birthweight and preterm birth were associated with an increased risk of SLE. Risk factors were self-reported in relatively crude categories, and data were limited on other factors of interest and unavailable for younger individuals or males. In systemic sclerosis and lupus, some have investigated links between birth order and future disease. Therefore we used population-based registers to study the association between perinatal factors and lupus in the Swedish population born 1973 onwards.

Methods: Cases were identified in the National Patient Register with at least two visits with an SLE-specific discharge diagnosis (using ICD codes) and at least one SLE-discharge from a specialty department. General population controls were matched (5:1) on birth year, sex, and residential county when the case was first identified. Using the Medical Birth Register, we obtained data on the case's mother's health and age during pregnancy and characteristics of labor and delivery. Restricting our study population to singleton births yielded 774 cases and 3337 controls. Birthweight was reported in grams and categorized according to standard definitions. Preterm birth was defined using gestational age in weeks and categorized. Parity was included as a continuous variable and an indicator for first born. Odds ratios and 95% CIs were estimated using conditional logistic regression models. Analyses were conducted for the entire population and separately for males and females. In sensitivity analysis, birthweight and preterm status were redefined using similar definitions to previous studies.

Results: High birthweight was not a risk factor for SLE in this younger population. Results were generally similar by sex. Preterm birth (<37 weeks) was not significantly associated with future risk of SLE overall, nor when very preterm was considered separately. Recategorizing these variables as they had been analyzed in the Nurses' Health Studies did not appreciably change the results, nor did adjustment for maternal age, smoking in early pregnancy, and maternal BMI. Being first born was associated with 20%

lower odds of SLE- this was driven by the association in females (OR=0.77, 95% CI=(0.64, 0.94)). Similarly parity was associated with SLE (OR=1.12, 95% CI=(1.02, 1.23)).

Conclusion: Lower parity and being born first were associated with reduced odds of SLE. Unlike previous work, high birthweight did not appear to be a risk factor, however this may be consistent with birth cohort trends when we examined previous published works.

Disclosure: E. V. Arkema, None; **J. F. Simard**, None.

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Clinical Phenotypes and Disease Burden Of Discoid Lupus Erythematosus In a Sample Of Systemic Lupus Erythematosus Patients In The Southeastern United States. Leslie Anne Cassidy, Gaobin Bao, Charmayne M. Dunlop-Thomas, S. Sam Lim and Cristina Drenkard. Emory University, Atlanta, GA.

Background/Purpose: The rash of discoid lupus erythematosus (DLE) has been reported in 10–25% of patients with systemic lupus erythematosus (SLE). Prior reports suggest that DLE may be protective against severe disease in SLE; however, most studies have consisted of convenience samples of predominantly White patients. Although the incidence and prevalence of SLE is 3–4 times higher among individuals of African descent, and recent findings suggest that Blacks are more susceptible to DLE than Whites, no study has yet been conducted with a representative sample of Black SLE patients. We examined the association of DLE with clinical manifestations and disease outcomes in a predominantly Black community-based cohort of SLE patients in the Southeastern United States.

Methods: Data was collected from the Wave 1 (2011–12) annual survey of Georgians Organized Against Lupus (GOAL). GOAL is a large prospective cohort of validated SLE patients primarily derived from the Georgia Lupus Registry (GLR), a population-based registry of lupus patients in Atlanta, Georgia. GOAL includes patients of the full sociodemographic spectrum and collects self-reported data on health status, disease activity, and organ damage. SLE was defined by the presence of at least 4 American College of Rheumatology (ACR) criteria, or 3 ACR criteria and a diagnosis of SLE by a rheumatologist. DLE was assessed by chart review according to dermatologist or rheumatologist clinical evaluation with or without biopsy confirmation. We examined the association of DLE with clinical features and disease status, calculating the OR and 95% CI adjusted for demographic variables and disease duration.

Results: Among 767 SLE patients, 196 (26%) had DLE. DLE was present in 168/597 (28%) Blacks *versus* 25/156 (16%) Whites (p=0.008), and 18/45 (40%) males *versus* 178/722 (25%) females (p=0.02). Mean educational attainment (years) was 13.7 (SD 2.8) and 14.4 (SD 2.9) in patients with and without DLE, respectively (p=0.004), and mean disease duration (years) was 15.5 (SD 10.4) and 12.6 (SD 8.1) in these two respective groups (p=0.0001).

Association of DLE with Clinical Manifestations and Disease Outcomes

	Discoid Rash		
Characteristics	Yes (n=196)	No (n=571)	Adjusted OR (95%CI)^
Clinical Manifestations+			
Malar rash	91 (46.4)	183 (32)	**1.84 (1.29–2.63)**
Photosensitivity	86 (43.9)	153 (26.8)	**2.31 (1.60–3.32)**
Oral ulcers	71 (36.2)	154 (27)	**1.66 (1.15–2.40)**
Arthritis	149 (76)	448 (78.5)	0.84 (0.56–1.26)
Serositis	77 (39.3)	226 (39.6)	0.94 (0.66–1.34)
Renal Disorder	56 (28.6)	180 (31.5)	0.84 (0.57–1.23)
Neurologic Disorder	13 (6.6)	61 (10.7)	**0.46 (0.23–0.90)**
Hematologic Disorder	137 (69.9)	391 (68.5)	0.98 (0.67–1.42)
Immunologic Disorder	119 (60.7)	396 (69.4)	**0.66 (0.46–0.95)**
Antinuclear Antibody	178 (90.8)	512 (89.7)	1.20 (0.66–2.18)
Renal Involvement*	63 (32.1)	220 (38.5)	**0.68 (0.46–0.99)**
Disease Outcomes			
Health Status Excellent/Very Good (ref)	24 (12.6)	85 (15.5)	-
Good	61 (32.1)	187 (34.1)	1.05 (0.60–1.85)
Fair/Poor	105 (55.3)	277 (50.5)	1.14 (0.67–1.96)
Disease Activity Score (SLAQ) Mild (0–10) (ref)	45 (23.7)	158 (28.7)	-
Moderate (11–16)	43 (22.6)	122 (22.2)	1.26 (0.76–2.07)
Severe (17+)	102 (53.7)	270 (49.1)	1.29 (0.85–1.97)
Organ Damage Score (BILD) No Damage (ref)	36 (18.9)	162 (29.5)	-
Mild (1–2)	75 (39.5)	206 (37.5)	1.38 (0.87–2.21)
Severe (3+)	79 (41.6)	182 (33.1)	1.41 (0.87–2.28)

Values are depicted as number (%) of individuals unless otherwise specified. ^Adjusted for gender, race, education, age at diagnosis, and disease duration. +With the exception of renal involvement, clinical manifestations are defined according to the ACR Criteria for the Classification of SLE. *Defined as positive proteinuria or red blood cell casts, lupus nephritis stated by rheumatologist or nephrologist (with or without renal biopsy), or end stage renal disease (ESRD) secondary to lupus nephritis.

Conclusion: DLE occurred in 26% of SLE patients, suggesting a stronger association of discoid rash with systemic manifestations than formerly believed. Males and Blacks were primarily affected. Consistent with prior studies, we found an association of DLE with non-specific cutaneous manifestations in SLE patients. Notably, DLE appears to be protective of renal and neurological involvement. Our findings may reflect more accurately the true epidemiology of DLE in high-risk SLE populations given the demographic makeup of this community-based cohort. Despite differences in clinical phenotypes, disease outcomes were similar in patients with and without DLE. Over 50% of patients reported poor health, organ damage, or severe disease activity, regardless of the presence of DLE. Our data suggest that environmental factors play a major role in outcomes of high-risk SLE patients.

Disclosure: L. A. Cassidy, None; **G. Bao**, None; **C. M. Dunlop-Thomas**, None; **S. S. Lim**, GlaxoSmithKline, 2; **C. Drenkard**, GlaxoSmithKline, 2.

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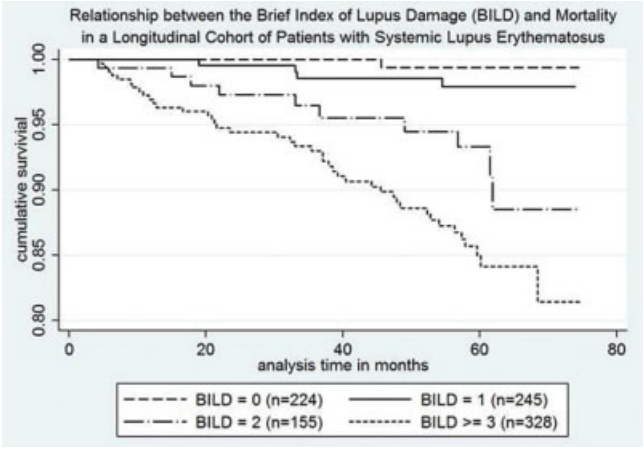
The Brief Index Of Lupus Damage As a Predictor Of Mortality In a Cohort Of Patients With Systemic Lupus Erythematosus. Stephanie Rush, Laura Trupin, Jinoos Yazdany and Patricia P. Katz. University of California, San Francisco, San Francisco, CA.

The Brief Index of Lupus Damage as a Predictor of Mortality in a Cohort of Patients with Systemic Lupus Erythematosus.

Background/Purpose: To examine whether a validated patient-reported measure of lupus damage, the Brief Index of Lupus Damage (BILD), is a predictor of mortality in a longitudinal cohort of patients with systemic lupus erythematosus (SLE).

Methods: Data were gathered from the UCSF Lupus Outcomes Study (LOS), an annual phone interview in which the BILD was administered beginning in 2007. We analyzed the initial BILD score for all participants. BILD scores were divided into 4 categories corresponding to 0, 1, 2, and ≥ 3 points (higher scores represent more damage). The number of deaths up to 75 months of follow-up was determined. Kaplan-Meier life table analysis was used to compare mortality rates by categories of the BILD. Using Cox proportional hazard models, multivariate analyses of possible predictors of mortality were performed. In addition to disease damage, predictors examined included a self-reported disease activity measure (Systemic Lupus Activity Questionnaire, SLAQ), non-white ethnicity, education beyond high school, gender, age, and disease duration.

Results: Among 952 subjects completing the BILD, the mean age was 49 years, 92% were female, 63% Caucasian, the mean disease duration was 16 years, and the median BILD score was 2 (range 0–13). During the follow-up period there were 57 deaths (6.0%). The mean follow-up time was 58 months (range 4–75). Kaplan-Meier analysis showed significantly higher mortality with increasing BILD scores (see figure). In Cox proportional hazards models adjusting for age, gender, disease duration, and SLAQ score, a BILD score of 2 (hazard ratio [HR]: 12.4; 95% confidence interval [CI]: 1.6–97.4), and a BILD score of ≥ 3 (HR: 21.4; 95% CI 2.9–159.2) were associated with higher risk of death over the follow-up period. Race, education, gender and SLE disease activity were not associated with increased mortality risk.



Conclusion: Independent of age, sex, race, disease duration and activity, a higher BILD score was a strong predictor of mortality in this cohort. Given the established relationship between SLE damage and mortality, the results

provide further validation of this patient-reported damage index and support its usefulness in clinical research.

Disclosure: S. Rush, None; **L. Trupin**, None; **J. Yazdany**, None; **P. P. Katz**, None.

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The Influence Of Socioeconomic and Race In Damage Score In Patients With Systemic Lupus Erythematosus. Roberto Teixeira[1], Eduardo F. Borba[2], Georges Christopoulos Sr.[3] and Emilia Sato[4]. [1]UNIVERSIDADE FEDERAL DE SÃO PAULO, SAO PAULO, Brazil, [2]Rheumatology Division; University of São Paulo, São Paulo, Brazil, [3]SANTA CASA DE MISERICORDIA DE MACEIO, MACEIO, Brazil, [4]Universidade Federal de São Paulo, São Paulo, Brazil.

Background/Purpose: The association between socioeconomic status and damage in Systemic lupus erythematosus patients is confounded by the influence of race in various previous studies. The objective of the study was to evaluate the association between socioeconomic status and Quality of life and damage in SLE patients.

Methods: SLE patients (ACR criteria), age ≥ 18 y.o. with at least 12 months of diagnosis were included. Socioeconomic status was evaluated by monthly income and years of formal education. The race was self-reported as white and nonwhite. The study was approved by Institutional Ethic Committee. Assessments were performed by questionnaire and review of medical charters; Mex-SLEDAI score; SF-36 and SLEQOL questionnaire. Statistical analysis: descriptive analysis, median, mean, t-student; Mann-Whitney, chi square, ROC curve to establish cut-off, Pearson and Spearman correlation test, univariate and multivariate regression test were used. $P<0.05$ was considered significant.

Results: 523 patients (96% female / 51.2% nonwhite) with mean age of 37,8±11,4 years were included. The mean years of study were 10.2±3.5. 63,7%; of patients did not work. The mean SLEDAI score was 1,82±2,83 and the per capita income was US$ 402.7± 610.95 and the family income was US$ 1,147.62 ± 1,713.40. Arthritis, photosensivity, hematological involvement and AAN positivity were the most frequent ACR criteria. Hypertension, fibromyalgia, and hypothyroidism were the most frequent comorbidities. Corticosteroids and antimalarials were most common treatment. The median prednisone dose was 15mg/day. Patients with income > US$ 402.7 used lower prednisone/day (P= 0,029 and more frequently antimalarial (P= 0,002). Persistent proteinuria and clearance < 50 ml/min were the most frequent damage. The mean SLICC/ACR ID was 1,4±1,52. Patients with SLICC > 0 had lower income (p= 0,039) and nonwhite patients had SLICC higher than white one (P= 0,005). The SLICC was correlated with disease duration (P < 0,001) and with patient age (P< 0,001), and negatively correlated with years of formal education (P = 0,001). Patients who were working had SLICC lower than those were not working (P <0,001). Univariate analysis showed that those with income < US$ 402.7 have 1,6 time more likely to have SLICC > 0 (P= 0,009); nonwhite patients have 1,6 times more likely to have SLICC > 0 (P= 0,009) and each additional year of study decreases by 91% the chance to have SLICC > 0. Multivariate analysis showed that race (P=0.044) and years of study were the best predictors of damage (P= 0,033). The lowest scores of the SF-36 were physical, emotional and mental domain. The SLICC correlated significantly with functional capacity; physical aspect; emotional aspect and physical domain. The SLICC score correlated significantly with SLEQOL total score, physical function, occupational activity and treatment.

Conclusion: Disease duration, age of the patients and mainly race and socioeconomic status are important factors that influence the onset of damage. The damage interferes with the quality of life, especially the physical domain of patients with SLE.

Disclosure: R. Teixeira, None; **E. F. Borba**, CNPq 303165/2008-1 to EFB; Federico Foundation to to EFB, 2; **G. Christopoulos Sr.**, None; **E. Sato**, None.

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Trends In Hospitalizations Due To Organ Damage In Patients With Systemic Lupus Erythematosus In Canada, 2006–2010. Amyn Sayani, Neerav Monga, Marni Freeman and Jorge Alfonso Ross Terres. GlaxoSmithKline, Inc., Mississauga, ON.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is an autoimmune disease that can affect multiple organs in the body, including the heart, kidney and lung, leading to increasing damage over time. Hospitalizations associated with organ damage in SLE patients across Canada have not been previously reported. The purpose of this study was to describe trends and provincial variations in hospitalizations due to organ damage in SLE patients in Canada between 2006–2010.

Methods: Aggregate hospitalization data for most common organ manifestations (kidney, lung, pericarditis, Libman-Sacks disease) associated with SLE was obtained from the Canadian Institute for Health Information's (CIHI) Discharge Abstract and Hospital Morbidity database, based on ICD–10 coding, for 2006–2010. Hospitalizations associated with organ damage were reported as a function of total hospitalizations due to SLE in Canada. Provincial data was grouped into geographical regions for ease of reporting. Length of stay (LOS) was categorized and reported by gender and province.

Results: Overall, total count of hospitalizations due to organ damage decreased over the study period (2006: 525; 2010: 416). Hospitalization due to kidney involvement was the most common reason for all SLE hospitalizations in Canada (2006: 48.2%; 2010: 41.7%), followed by lung involvement (2006: 9.1%; 2010: 6.8%), pericarditis (2006: 5.2%; 2010: 6.2%), Libman Sacks (2006: 0.6%; 2010: 0.5%), and other (2006: 36.9%; 2010: 44.8%). In all provinces, hospitalizations due to kidney involvement accounted for almost half of all SLE hospitalizations: BC reported the highest rates in 2006 (52.4%), but falling by 2010 (42.7%). A decreasing trend in SLE hospitalizations due to kidney involvement was seen in all provinces, except the Maritimes. Hospitalizations due to lung involvement showed the highest decrease in BC between 2006 (13.5%) and 2010 (4.9%): similar decreases were seen in other provinces and Canada-wide (2006: 9.1%; 2010: 6.8%). In contrast, hospitalizations due to lupus pericarditis increased over this time period, with the highest increase recorded in BC (2006: 2.4%; 2010: 8.4%). There was an increasing trend for patients with kidney involvement to stay longer in hospitals (12+ days; 2006: 33.2%; 2010: 35.6%), when compared to LOS due to any SLE-related hospitalizations (2006: 29%; 2010: 26.6%). Overall, more females than males were hospitalized for organ involvement, but males LOS was longer. Limitations to the study include the possibility of double counting events due to a lack of patient level data.

Conclusion: Kidney involvement accounted for almost half of all hospitalizations related to SLE in Canada, consistent with reported higher incidences of lupus nephritis (1–3). Overall, trends in hospitalizations tended to decrease over the time period, suggesting possibly better care of SLE patients. However, when patients did enter hospital, they tended to stay longer, which may suggest that with current medications, disease progression continues and may lead to greater downstream costs in the Canadian health care system.

Disclosure: A. Sayani, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **N. Monga**, GlaxoSmithKline, 3; **M. Freeman**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **J. Alfonso Ross Terres**, GlaxoSmithKline, 1, GlaxoSmithKline, 3.

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Acute Myocardial Infarction Variation Among U.S. Medicaid Recipients With Systemic Lupus Erythematosus By Race and Ethnicity, 2000–2006. Medha Barbhaiya[1], Candace H. Feldman[1], Jessica M. Franklin[2], Jun Liu[3], Joanne M. Foody[4], Michael A. Fischer[2], Daniel H. Solomon[1] and Karen H. Costenbader[1]. [1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA.

Background/Purpose: SLE patients have elevated rates of acute myocardial infarctions (MI), but the sociodemographic groups that are most affected have not been well studied. We examined acute MI rates among SLE patients in different sociodemographic groups enrolled in Medicaid, the program providing medical insurance to low income individuals in the U.S., from 2000 to 2006.

Methods: From Medicaid Analytic eXtract (MAX) data, containing all billing claims from 2000–2006 for Medicaid patients from 47 U.S. states and Washington, D.C., we identified patients aged 18–65 with prevalent SLE (>3 SLE International Classification of Disease, 9threvision, [ICD-9 codes] of 710.0, >30 days apart). Demographic data included age, sex, race/ethnicity, U.S. region of residence (Northeast, Midwest, South or West) and calendar year. Within MAX inpatient claims files, ICD-9 code were used to identify all inpatient diagnoses for acute MI (ICD-9 codes 410.XX). CVD event incidence rates per 1,000 person-years with 95% CIs for patients with SLE in each sociodemographic group were calculated. We also performed Cox regression models stratified by sex and race/ethnicity, and adjusting for age,

calendar year and U.S. region, to calculate hazards ratios for acute MIs in this population.

Results: We identified 43,351 patients with prevalent SLE. 40,417 (93%) were female. Racial and ethnic breakdown was: African American (35%), White (35%), Hispanic (14%), Asian (3%), and Native American (1%). The incidence rate for acute MI was 6.26 (95%CI 5.86, 6.69) per 1,000 person-years for the entire SLE population. Incidence rates were higher among males than females for all race/ethnicities (except for Native Americans for whom there were no events among males). (**Table**) Among women with SLE, Asians and Hispanics had the lowest incidence rates for acute MIs. Among males, incidence rates were also highest among White and African American patients, and lower in Asian and Hispanic SLE patients. Adjusted hazard ratios for acute MIs were significantly lower among Hispanic women compared to White women; however, they were not statistically lower among Asian women compared to White women. Although not statistically significant, lower hazard ratios for acute MIs were found in all non-White groups of men with SLE as well.

Table. Incidence Rates and Adjusted Hazards Ratios for Hospitalizations for Acute Myocardial Infarctions among Medicaid patients with SLE in the U.S. by Race and Ethnicity, 2000–2006

SLE Patients in Medicaid*	Total Individuals	N events	IR**	95% CI	Person-years	HR***	95% CI
			Females				
White	14,010	296	6.34	5.66–7.11	46,672	1.0 (ref.)	-
African American	14,195	277	5.93	5.27–6.67	46,702	1.05	0.89–1.24
Asian	1,095	****	**2.81**	**1.51–5.22**	3,558	0.68	0.36–1.28
Hispanic	5,887	63	**3.14**	**2.45–4.02**	20,045	**0.66**	**0.50–0.87**
Native American	519	11	6.65	3.68–12.01	1,654	1.21	0.66–2.22
Other/ Multiple	2,667	72	7.71	6.12–9.71	9,344	1.23	0.95–1.60
			Males				
White	1,007	44	15.89	11.82–21.35	2,769	1.0 (ref.)	-
African American	877	22	8.68	5.72–13.18	2,535	0.63	0.38–1.07
Asian	102	****	3.28	0.46–23.29	305	0.36	0.05–2.66
Hispanic	373	****	**3.78**	**1.42–10.07**	1,057	0.40	0.14–1.15
Native American	41	0	****	****	88	****	****
Other/ Multiple	176	****	11.12	5–24.75	540	0.81	0.34–1.93

*Race/ethnicity missing for 2043 females and 359 males
**IR: incidence rate, events per 1,000 patient-years
***HR: hazard ratio, adjusted for age, calendar year and region of the U.S.
****Cell size <11 suppressed per Centers for Medicare and Medicaid Services policies
Bold: confidence intervals are significant compared to White patients as reference group

Conclusion: We found marked sex and race/ethnicity-specific variation in acute MI incidence rates and adjusted hazards ratios among Medicaid patients with SLE. The rates were higher among Whites and African American individuals. Further research is necessary to understand whether there is variation in acute MI prevention, cardiac risk factors, presentation, diagnosis and management among SLE patients in different sociodemographic groups.

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Depression Screening In Patients With Systemic Lupus Erythematosus From The Southeastern United States: Missing Opportunities For Early Diagnosis and Treatment. Cristina Drenkard, Charmayne M. Dunlop-Thomas, Gaobin Bao and S. Sam Lim. Emory University, Atlanta, GA.

Background/Purpose: Depression can be found in 20–60% of SLE patients and has substantial impact on quality of life, disease outcomes and health care costs. Although pathways are not fully unraveled, immune and disease-related factors have been found associated with depression in SLE. In the general population, racial minorities, women and people from lower socioeconomic status (SES) have increased risk. Thus, SLE patients of minority groups and SLE women carry additional factors to those directly associated with the disease. Depression screening, one of the preventive care services recommended by the United States Preventive Services Task Force (USPSTF) for adults receiving care in clinical practices, has shown to improve outcomes when it is combined with further treatment. However, no study has examined the provision of depression screening in adult SLE patients. We assessed depression screening and the contributing factors associated with being screening in a high-risk SLE cohort from the Southern US.

Methods: We used a cross-sectional design to examine Wave 2 data (2012–2013) from the Georgians Organized Against Lupus Cohort (GOAL). GOAL participants are validated SLE patients primarily derived from the Georgia Lupus Registry, a population-based lupus registry established in metropolitan Atlanta, GA, US. GOAL includes patients of the full sociodemographic spectrum and collects self-reported measures on health care utilization and health conditions. We assessed the proportion of SLE patients screened for depression in the past year using two screening questions recommended by the USPSTF. The prevalence of depression was assessed using the Hospital Anxiety and Depression Scale (HADS). We used Chi^2 tests and Student t-test to examine demographic and disease factors associated with being screened for depression.

Results: Among 519 respondents of the ongoing Wave 2 GOAL survey, 163 (31%) had depression and 113 (22%) had both depression and anxiety. Only 59% of patients indicated that they were screened for depression. Among 213 patients not screened, 18% reported symptoms compatible with depression.

Table 1. Factors Associated with Being Screened for Depression

Characteristic	Screened for Depression: Yes (n = 306)	Screened for Depression: No (n = 213)	P Value
Sociodemographics			
Age at Survey (Mean ± SD)	45.9 ± 13.0	47.3 ± 12.2	0.22
Gender			
Female	284 (58.1)	205 (41.9)	0.10
Male	22 (73.3)	8 (26.7)	
Race			0.05
Black	239 (61.6)	149 (38.4)	
White	63 (51.6)	59 (48.4)	
Education Attainment			<0.03
High School or lower	89 (64.0)	50 (36.0)	
Some College	116 (63.0)	68 (37.0)	
College or higher	100 (51.6	94 (48.5)	
Working Status			0.001
Employed	100 (49.5)	102 (50.5)	
Unemployed	133 (65.2)	71 (34.8)	
Living Below Poverty Level			0.005
Yes	115 (66.9)	57 (33.1)	
No	157 (53.6)	136 (46.4)	
Insured			0.26
Yes	253 (57.9)	184 (42.1)	
No	53 (64.6)	29 (35.4)	
Disease-related factors			
Overall Health			<0.0001
Excellent/Very Good	39 (42.9)	52 (57.1)	
Good	104 (54.5)	87 (45.6)	
Fair/Poor	161 (69.7)	70 (30.3)	
MCS (Mean ± SD)	41.3 ± 11.0	48.5 ± 10.1	<0.0001
PCS (Mean ± SD)	37.8 ± 10.1	42.9 ± 11.0	<0.0001
Disease Activity			<0.0001
Mild (0–10)	62 (40.5)	91 (59.5)	
Moderate (11–16)	70 (60.3)	46 (39.7)	
Severe (17+)	174 (69.6)	76 (30.4)	
Organ Damage			0.12
No Damage	76 (55.1)	62 (44.9)	
Mild (1–2)	102 (55.7)	81 (44.3)	
Severe (3+)	128 (64.7)	70 (35.4)	
Healthcare Use in the Past Year			
Rheumatologist			0.10
Yes	252 (57.7)	185 (42.3)	
No	49 (68.1)	23 (31.9)	
Primary Care Physician			0.32
Yes	231 (60.0)	154 (40.0)	
No	63 (54.8)	52 (45.2)	
Cardiologist			0.03
Yes	101 (66.5)	51 (33.6)	
No	192 (56.3)	149 (43.7)	
Emergency Department			0.001
Yes	171 (66.5)	86 (33.5)	
No	132 (52.2)	121 (47.8)	
Hospital Admission			0.0002
Yes	106 (72.1)	41 (27.9)	
No	198 (54.4)	166 (45.6)	

Unless otherwise indicated, values are depicted as number of individuals (%) within each category MCS: mental component summary; PCS: physical component summary. MCS and PCS were assessed with SF-12.

Conclusion: We found important gaps in the quality of screening for depression among SLE patients. Over 40% were not screened and among them, 18% had depression. Thus, a substantial number of SLE patients missed the opportunity of early diagnosis and treatment. Patients from disadvantaged groups, such as Blacks, unemployed or of lower education, as well as those

with worse disease health status were more likely to be screened. However, even within those high-risk groups, at least 30% of cases were not screened. Depression screening was more frequent in patients who visited a cardiologist, the emergency department or were hospitalized in the past year. This study underscores the need for better performances in screening for depression services provided to SLE patients.

Disclosure: C. Drenkard, GlaxoSmithKline, 2; **C. M. Dunlop-Thomas**, None; **G. Bao**, None; **S. S. Lim**, GlaxoSmithKline, 2.

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Incidence and Prevalence Of Systemic Lupus Erythematosus: A 2010 Nation-Wide Population-Based Study Using French National Administrative Databases. Laurent Arnaud[1], Jean-Paul Fagot[2], Michel Païta[2], Alexis Mathian[3], Anne Fagot-Campagna[2] and Zahir Amoura[1]. [1]Hôpital Pitié-Salpêtrière, AP-HP, UPMC Univ Paris 06 & French National Reference Center For Systemic Lupus and Antiphospholipid Syndrome, Paris, France, [2]Caisse Nationale d'Assurance Maladie des Travailleurs Salariés, Paris, France, [3]Pitié-Salpêtrière Hospital, APHP, Paris, France.

Background/Purpose: To date, only a small number of studies have examined the epidemiology of systemic lupus erythematosus (SLE) on a nation-wide basis. These studies were restricted to specific age groups and/or non-representative insurance schemes. In our study, we used French national administrative databases to analyse the 2010 prevalence and incidence rates of SLE on a nation-wide basis.

Methods: The largest French health insurance scheme covers 88% of the population or 58,186,535 individuals. Patients with SLE were identified if they had full coverage for a chronic disease with a M32 code (ICD-10th) in the health insurance information system, or if they had a M32 code in the hospital discharge database in 2010.

Results: Overall, 27,390 individuals were identified as having SLE, 88% were female. The crude 2010 prevalence of SLE was 47.1/100,000, and the WHO age-standardized rate 40.8/100,000. The crude 2010 annual incidence of SLE was 3.32 cases per 100,000 with peaks in females aged 30–39yo (9.11/100,000) and in males aged 50–59yo (1.78/100,000). Major differences in regional age-standardized prevalence rates were observed, with the lowest rates in the North-West metropolitan areas and the highest in Caribbean overseas areas, ranging from 26 to 118/100,000.

Conclusion: This is the largest nation-wide study of SLE population to date, based on 58 million beneficiaries of the French health insurance system. Variations in regional rates may reflect ethnic differences. Rates may be underestimated as beneficiaries may not request full coverage and may not be hospitalised for SLE. The prevalence and incidence rates may however provide useful guidance to improve SLE care.

Disclosure: L. Arnaud, None; **J. P. Fagot**, None; **M. Païta**, None; **A. Mathian**, None; **A. Fagot-Campagna**, None; **Z. Amoura**, None.

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An In-Depth Analysis Of The Prevalence and Socio-Demographic Factors Associated With Lupus Nephritis In Major Industrialized Countries. Guiping Yang and Anne Tuomari. Teva Pharmaceuticals, Inc., Frazer, PA.

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune disease with incidence and prevalence well studied and documented worldwide. Lupus nephritis (LN) is a severe manifestation of SLE causing dramatic morbidity and mortality. We performed a study looking at large epidemiologic database and found that the information differed from what has been reported in clinical literature. Since healthcare cost distribution is often determined on the basis of large 3rdparty payer or government databases rather than data from academic clinical investigative studies, the social and demographic information from this study would have an important impact on how health resources are allocated.

Methods: The worldwide pattern of LN prevalence and socio-demographic influences were identified by combining the information from Kantar's Epi Database®, the National Health and Wellness Survey (NHWS) and available original research literatures. The association between the prevalence of LN and potential socio-economic factors was assessed for the United States and Europe (France, Germany, Italy, Spain and the United Kingdom) using a stratification-projection algorithm strategy commonly used for rare diseases. The LN diagnostic criteria in WHO served to define patients. All statistical tests on differences were conducted using Student's t-test or the Chi-square approach.

Results: The overall prevalence rate adjusted by gender and age equaled 40.9 per 100,000 patients in the US, but the averaged rate in Europe (15.7) was lower than half of the US ($p=0.03$), with specific numbers as 16.1 in France, 11.2 in Germany, 28 in Italy, 13 in Spain and 10.3 in the UK. In the US, patients ages 31–60 were at higher risk (58%) to develop LN. Female gender presented as a major risk factor (84%, $p=0.02$). Only 2% of the cases were pediatric patients (0–15 years old, $p=0.01$). Almost half of prevalent cases were black patients (46%), followed by Whites (27%) and Hispanics (20%). Geographically, the southern region was dominant in LN prevalence (42%) with the vast majority in urban areas (85%). Around 40% of LN patients were commercially insured through employers, followed by Medicare (34%) and Medicaid (13%), while self-insured subjects accounted for only 6%. Within Europe, the socio-demographic breakdown of LN by region and ethnicity was complex and country specific, but the patterns in gender and age distributions were similar to those in the US. LN patients were mainly insured by national public plans (60–86%).

Conclusion: The prevalence rates of LN in the US and Europe were very low. Female gender was a determinant factor contributing to higher LN prevalence. Adults were more likely to develop LN than children. Most patients were insured commercially in the US and by national health plans in Europe. Quantification and characterization of the LN population from epidemiologic database is key to informing treatment decisions, supporting new therapy development for this severely ill population as well as determining effecient health resource allocation.

Disclosure: G. Yang, Teva Pharmaceuticals, Inc., 3; **A. Tuomari**, Teva Pharmaceuticals, Inc., 3.

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Racial Differences In Systemic Lupus Erythematosus Patients' Treatment Preferences: A Two-Site Study. Ernest R. Vina[1], Tammy O. Utset[2], Michael J. Hannon[3], Nicole Roberts[3], Christopher M. Masi[4] and C. Kent Kwoh[5]. [1]University of Pittsburgh and VA Pittsburgh Healthcare System, Pittsburgh, PA, [2]University of Chicago Department of Medicine, Chicago, IL, [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, [4]NorthShore University Health System, Evanston, IL, [5]University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Racial disparities in systemic lupus erythematosus (SLE) exist, with African-American (AA) patients experiencing higher lupus damage scores and disease activity than white (WH) patients. Racial differences in SLE patients' treatment preferences may contribute to these differences and are only partly understood. The goals of the study are to determine whether there are racial differences in willingness to: 1) receive cyclophosphamide (CYC) when physician recommended or 2) participate in a research clinical trial (RCT) involving an experimental medication among SLE patients. We also seek to determine which demographic, clinical and psychosocial characteristics impact racial differences in either measure of treatment preference.

Methods: Data from 163 AA and 180 WH SLE patients recruited from two university clinics were evaluated. Structured interviews and chart reviews were conducted to determine socio-demographic characteristics, clinical factors, perceptions of medications and disease, and beliefs and attitudes towards providers and the healthcare system. Logistic regression models were performed to evaluate the impact of patient characteristics, including race, on preferences for treatment.

Results: AAs, compared to WHs, were less likely to have more than a high-school graduate degree ($p=0.004$), be employed ($p=0.024$), have higher income ($p<0.001$), have private insurance ($p<0.001$) and be married (<0.001). Among patients who had never received CYC (n=293), 62.9% AAs, compared to 87.6% WHs, were willing to receive the medication ($p<0.001$). This difference persisted (OR 0.37 [95% CI, 0.16–0.87]) after adjusting for socio-demographic variables, clinical characteristics, and perceptions about CYC and physicians. Income ($30,001–50,000 vs. <$10,000, OR 4.07 [95% CI, 1.15–14.33]; >$50,000 vs. <$10,000, OR 4.45 [95% CI, 1.24–15.97]) and higher perception of CYC effectiveness (OR 1.41 [95% CI, 1.25–1.59]) were other significant determinants of willingness to receive CYC in the adjusted model.

Among patients who had never participated in a RCT (n=326), 64.9% AAs, compared to 84.3% WHs were willing to do so ($p<0.001$). This difference persisted (OR 0.41 [95% CI, 0.20–0.83]) after adjusting for socio-demographics, clinical variables related to SLE and patients' perceptions of physicians. SLE damage index score (4 vs. 0, OR 0.23 [95% CI, 0.07–0.74]), current number of immunosuppressive medications (1 vs. 0, OR 3.65 [95% CI, 1.14–11.73]; ≥2 vs.

0, OR 5.45 [95% CI, 1.62–18.30]) and higher trust in physicians (OR 1.04 [95% CI, 1.00–1.08]) were also independently associated with willingness to participate in a RCT in the adjusted model.

Conclusion: Variations in lupus patients' treatment preferences are associated with income, medication history, perceived medication effectiveness and trust in physicians. Race remains an independent determinant of preferences after adjusting for these variables. While some factors related to racial differences in patient preferences are relatively fixed, other factors, including medication beliefs and trust in providers, are potentially modifiable and could be addressed to reduce outcome disparities.

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Characteristics and Medication Use Patterns Among Belimumab Users In a Commercially Insured Population With Systemic Lupus Erythematosus. Xuehua Ke[1], Jeetvan Patel[2], Hong Kan[2], Debra F Eisenberg[1] and Alan Oglesby[2]. [1]HealthCore Inc, Wilmington, DE, [2]GlaxoSmithKline, Research Triangle Park, NC.

Background/Purpose: Belimumab is a B lymphocyte stimulator-specific inhibitor approved for treatment of systemic lupus erythematosus (SLE). The purpose of the study was to describe medication use patterns among belimumab users in a commercially insured population.

Methods: This is a retrospective cohort study of newly initiated belimumab users in the HealthCore Integrated Research Database during an intake period of 3/1/2011 through 9/30/2012. Newly initiated belimumab users were defined as those with ≥1 belimumab medical or pharmacy claim within the intake period and without belimumab use prior to index date (i.e., first belimumab claim date in the intake period). Patients were required to have ≥6 months pre- and post- index eligibility and ≥1 SLE diagnosis during the study period of 03/01/2010–09/30/2012. Demographics included age, gender, insurance type, and geographic region. SLE severity and comorbidities were reported in the 6 month pre-index period. Physician specialties associated with belimumab prescriptions in the post-index period were examined. First discontinuation of belimumab use (defined as a gap of >105 days between 2 administrations of belimumab) and concomitant medication use was assessed in the post-index period.

Results: 108 newly initiated belimumab users were identified with a mean age of 44 years, and 93.5% were female. Patients were more concentrated in west region (43.5%) and more were enrolled in preferred provider organization plans (60.2%). 18.5%, 66.7% and 14.8% of patients were categorized as mild, moderate and high SLE severity, respectively. The most prevalent pre-index SLE related comorbidities were cardiac disease (34.3%), hypertension (29.6%), and myositis (26.9%). During the post-index period, 32.4% and 12.0% of patients received belimumab prescriptions from rheumatologists and family/general practitioners/internal medicine physicians, respectively. 42.6% of patients discontinued belimumab use during the follow-up period. The mean [SD] length of belimumab therapy prior to the first discontinuation was 236 [154] days. Among patients who continuously used oral SLE medications prior to the index date, 58.1%, 32.1%, and 30.3% discontinued use of oral steroids, immunosuppressants and antimalarials, respectively within 1 month of belimumab initiation. Additionally, use of SLE medications was found to decrease from the first to sixth month of the post-index period: oral steroids (41.7% vs. 38.0%), immunosuppressants (38% vs. 36.1%) and antimalarials (52.8% vs. 48.2%).

Conclusion: This study described demographics and clinical profiles of newly-initiated belimumab users and utilization of SLE therapies in real-world US settings. Discontinuations of oral steroids, immunosuppressants and antimalarials were observed over 6 months after belimumab initiation. Impact of belimumab use on overall health resource utilization and cost needs further evaluation.

Disclosure: X. Ke, None; **J. Patel**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **H. Kan**, GlaxoSmithKline, 3; **D. F. Eisenberg**, HealthCore Inc, 3; **A. Oglesby**, GlaxoSmithKline, 1, GlaxoSmithKline, 3.

1071

Prevalence Of Systemic Lupus Erythematosus and Lupus Nephritis In The United States: Analysis Of Commercial and Public Insurance Billing Data. Kunal Gandhi[1], Evo Alemao[1], Hugh Kawabata[1] and Jan L. Hillson[2]. [1]Bristol-Myers Squibb, Princeton, NJ, [2]Bristol-Myers Squibb, Seattle, WA.

Background/Purpose: Prevalence estimates of Systemic Lupus Erythematosus (SLE) in the U.S. vary, with numbers ranging from 161,000 (Helmick, 2008) to 1.5 million (Lupus Foundation of America). Renal involvement (Lupus Nephritis; LN), the most common serious manifestation of SLE is reported to develop in up to two-thirds of patients cared for in specialty centers. In the absence of population-based data, it is difficult to estimate the burden of SLE and LN in the US population.

Objective: To estimate the prevalence of SLE and LN among commercially insured and Medicare and Medicaid enrolled populations in the US.

Methods: Subjects with at least 12 months of continuous enrollment were selected from the following administrative databases: Truven MarketScan® Commercial Claims & Encounters Data (n=30,912,744), Truven MarketScan® Medicaid Multi-State data (n=3,979,342) and Centers for Medicare and Medicaid Services Medicare data (n=46,520,716). SLE cases were defined as minimum of 3 claims (ICD-9-CM 710.0) occurring within 2009. LN cases were defined using Chibnik, 2010 requiring at least 2 visits to the nephrologists or at least 2 LN diagnoses (ICD-9-CM codes 580–586, 791.0) within 12 months from SLE index date. Sensitivity analyses were conducted by varying the ascertainment criteria for SLE and LN. Overall and age, gender- specific SLE and LN prevalence rates per 100,000 were computed. An estimate of the total number of SLE and LN patients was projected by applying these prevalence rates to the 2009 U.S. population (~306 million).

Results: The overall prevalence of SLE was 81, 106 and 144 per 100,000 in the Commercial, Medicaid and Medicare databases respectively; leading to a projection of 313,436 SLE patients in US population. The prevalence of LN was 15, 31 and 40 per 100,000, in the three databases respectively; leading to a projection of 63,256 LN patients. The age-specific prevalence of SLE and LN were highest between ages of 18 and 64 years (112 and 22 per 100,000, respectively) compared to children (7 and 3 per 100, 000) and those over 65 (102 and 22 per 100,000). SLE and LN prevalence was greater in females (227 and 52 per 100,000, respectively) as compared to males (30 and 10 per 100,000), consistent with previous reports. Although only 15.1% of all US citizens were insured by Medicare as of 2009, 26.2% of all SLE patients were on Medicare; the majority of the latter (51.5%) were under 65, indicating the impact of disability in this disease.

Conclusion: Based on an analysis of billing records from 81 million subjects, the disease burden of SLE and LN in the US is estimated at 313,436 (100 per 100,000) and 63,256 (20 per 100,000) respectively. The estimate for SLE is consistent with the conservative published estimates, and reflects the stringent case definition applied. This proportion of SLE with LN (20%) is significantly lower that reported in cohort studies, suggesting that cohorts incorporate a more severe subset of the population identified by the present algorithms. Both SLE and LN were more frequent in the publically insured population, with highest rates among Medicaid subjects less than 65 years of age, consistent with the high risk of disability associated with this disease.

Disclosure: K. Gandhi, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **E. Alemao**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **H. Kawabata**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **J. L. Hillson**, Bristol-Myers Squibb, 3.

ACR/ARHP Poster Session B
ARHP Epidemiology and Public Health
Monday, October 28, 2013, 8:30 am–4:00 PM

1072

Gene-Environment Interaction Between HLA-DRB1 Shared Epitope and Occupational Textile Dust Exposure In The Risk Of ACPA-Positive Rheumatoid Arthritis In Female Patients: Evidence From The Malaysian Epidemiological Investigation Of Rheumatoid Arthritis Case-Control Study. Chun Lai Too[1], Nor Asiah Muhamad[1], Leonid Padyukov[2], Lars Alfredsson[3], Camilla Bengtsson[4], Lars Klareskog[2] and Shahnaz Murad[5]. [1]Institute for Medical Research, Jalan Pahang. Kuala Lumpur, Malaysia, Kuala Lumpur, Malaysia, [2]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [3]Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden, [4]Karolinska Institutet, Stockholm, Sweden, [5]Institute for Medical Research, Jalan Pahang, Kuala Lumpur, Malaysia.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease with interacting genetic and environmental factors contributing to its etiology. In this study, we investigated the association between textile dust exposure and the risk of developing RA in the Malaysian population.

Methods: The RA patients and controls were from the Malaysian Epidemiological Investigation of rheumatoid arthritis (MyEIRA) case-control study. The data from a total of 910 female patients with early RA and 910 age matched female population controls were analyzed. Information from interview-reported occupational exposure to textile dust defined as exposed / never exposed was examined for association between occupational textile dust exposure and the risk of developing anti-citrullinated protein antibodies (ACPA)-positive and negative RA. The odds ratio (OR) with 95% confidence interval (CI) was calculated. Interaction was evaluated by calculating attributable proportion (AP) due to interaction, with 95% CIs.

Results: Our data showed that occupational exposure to textile dust was significantly associated with an increased risk of developing RA among female patients compared to female controls (OR=3.16, 95% CI 1.71–5.83). Stratification analysis by ACPA status demonstrated significantly increased risk for developing both the ACPA-positive RA (OR=2.64, 95% CI 1.36–5.13) and ACPA-negative RA (OR=4.43, 95% CI 2.15–9.13) among female patients. We observed a strong association and interaction between occupational textile dust exposure and SE-positive for the risk of developing ACPA-positive RA in Malaysian female patients (OR=35.49, 95% CI 4.67–269.82; AP=0.85, 95% CI 0.53–1.16).

Conclusion: This is the first study demonstrating that the risk of developing ACPA-positive RA in female patients is associated with a strong gene-environment interaction between occupational textile dust exposure and HLA-DRB1 shared epitope in an ethnically diverse Malaysian population.

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1073

Longitudinal Decline In Steps/Day In Older Adults With Or At High Risk Of Knee OA. Daniel K. White[1], Roger Fielding[2], K. Douglas Gross[3], Michael C. Nevitt[4], Cora E. Lewis[5], James Torner[6] and Tuhina Neogi[1]. [1]Boston University School of Medicine, Boston, MA, [2]Tufts University, Boston, MA, [3]MGH Institute of Health Professions, Boston, MA, [4]University of California, San Francisco, San Francisco, CA, [5]University of Alabama, Birmingham, Birmingham, AL, [6]University of Iowa, Iowa City, Iowa City, IA.

Background/Purpose: Walking is the most common type of physical activity older adults employ for physical activity, which, when performed regularly, confers important health benefits. When people develop knee osteoarthritis (OA), it is thought that they are likely to decrease the amount of walking they engage in due to pain and functional limitations. Whether this occurs in reality is not known. The impact of psychological health (e.g., depressive symptoms) on declines in walking activity in such individuals is also not known. The purpose of this study was to examine change in objectively measured walking activity over a 2-year period, and evaluate its relation to radiographic knee OA (ROA), knee pain, and psychological health.

Methods: The Multicenter Osteoarthritis Study (MOST) is a NIH-funded longitudinal cohort of older adults who have or are at high risk of knee OA. Steps/day over 7 days were objectively measured with a StepWatch monitor at 2 study visits, two years apart. We calculated the absolute change in mean steps/day between visits. We also evaluated mean change by categories of baseline disease status, i.e., ROA, frequent knee pain, or symptomatic knee OA (ROA + knee pain), and baseline psychological health status, i.e., presence of depressive symptoms and catastrophizing, using linear regression, adjusting for age, sex, and body mass index (BMI).

Results: Of the 1,318 subjects with the necessary data obtained (Age 66.9 ± 7.7, 59% women, BMI 30.6 ± 5.9), absolute steps/day declined significantly, albeit only slightly, from a mean of 9,173 steps/day at baseline to 9,004 steps/day 2-years later (i.e., 168 fewer steps ± 2,268, p = 0.007). Those with depressive symptoms walked 927 ± 2,495 fewer steps/day 2-years later compared with 124 ± 2,959 fewer for people without depressive symptoms (p=0.007). People with symptomatic knee OA walked 421 ± 3,100 fewer steps/day, which was not statistically significantly different than people without either ROA or frequent knee pain, who walked 517 ± 3,694 fewer steps/day 2-years later. The other factors assessed were not statistically significantly associated with change in steps/day.

Conclusion: Declines in walking activity over a 2-year period were minimal overall, and appeared to be more likely related to psychological health in people with or at high risk of knee OA rather than having painful knee OA itself. Specifically, depressive symptoms were significantly associated with >900 fewer steps/day 2-years later, which is a clinically meaningful difference and beyond the 168 fewer steps/day due to aging. Given the multiple benefits of physical activity, maintaining or improving steps/day in people with knee OA is important. Our findings support the notion that addressing psychological- rather than disease- and pain-factors is promising to minimize declines in daily walking in people with or at high risk of knee OA.

Disclosure: D. K. White, None; **R. Fielding**, None; **K. D. Gross**, None; **M. C. Nevitt**, None; **C. E. Lewis**, None; **J. Torner**, None; **T. Neogi**, None.

1074

Obesity and Life-Space Mobility Among Older Mexican Americans With and Without Arthritis. Soham Al Snih[1], Rafael Samper-Ternent[2], Amit Kumar[1] and Kenneth J. Ottenbacher[1]. [1]University of Texas Medical Branch, Galveston, TX, [2]Universidad Javeriana. Hospital San Ignacio, Bogota, Colombia.

Background/Purpose: To examine the relation between obesity and life-space Assessment (LSA) mobility at 2-year of follow-up among older Mexican Americans with and without arthritis.

Methods: Two-year prospective study of Mexican-American men and women aged >75 years and older residing in five southwestern states in the U.S. Data on socio-demographic variables, medical conditions, disability, body mass index (BMI), and the LSA were collected. The LSA is an instrument that assesses the range, independency, and frequency of movement in the past four weeks preceding the interview. The LSA composite scores ranged from 0 to 120, with higher scores representing greater mobility.

Results: Out of 624 subjects, 65.5 % reported arthritis. Mean score for the LSA instrument was 40.8 (SD=20.7) in subjects with arthritis and 45.5 (SD=20.0) in subjects without arthritis. Multiple regression analysis stratified by arthritis was conducted. The association between obesity (BMI ≥ 30 Kg/m^2) and the LSA mobility in subjects with arthritis was statistically significant (β= –6.49, SE=2.22, p=0.0036), after controlling for all covariates. The association between obesity (BMI ≥ 30 Kg/m^2) and the LSA mobility in subjects without arthritis was non-significant (β= −0.75, SE=3.20, p=0.8157), after controlling for all covariates.

Conclusion: The association between obesity and lower Life-Space mobility differed by arthritis status in older Mexican Americans. Among subjects with arthritis, obesity maintained a negative and independent association with Life-space mobility in models controlling for all factors that can influence mobility patterns. Conversely, obesity did not seem to affect life-space mobility in subjects without arthritis.

Disclosure: S. Al Snih, None; **R. Samper-Ternent**, None; **A. Kumar**, None; **K. J. Ottenbacher**, None.

1075

Patient Characteristics Associated With Insomnia and Sleep Apnea In Knee and Hip OA. Kelli D. Allen, Hayden B. Bosworth, Cynthia Coffman, Amy Jeffreys, Eugene Z. Oddone, William S. Yancy Jr. and Christi Ulmer. Duke and Durham VA Medical Center, Durham, NC.

Background/Purpose: There is increasing recognition that sleep quality is a key outcome among patients with osteoarthritis (OA), but little is known about how clinical or demographic factors influence sleep quality in patients with OA. This study examined patient characteristics associated with insomnia and sleep apnea among patients with hip and knee OA.

Methods: Participants were 300 veterans enrolled in a clinical trial examining a patient and provider intervention for managing OA at the Durham Veterans Affairs Medical Center (mean age = 61, SD=9, 91% male, 50% non-white–primarily African American). All measures were obtained from a baseline interview. Self-reported sleep problems were assessed with the Insomnia Severity Index (ISI; range of 0–28, higher scores indicate more severe insomnia) and the Berlin Questionnaire (BQ; categorizes patients as "high risk" or "low risk" of having sleep apnea). We fit multivariable linear (ISI) and logistic (BQ) regression models to examine the associations of the following patient characteristics with insomnia and sleep apnea: age, gender, race (white vs. non-white), self-reported general health (excellent, very good, good vs. fair, poor), body mass index (BMI), diagnosis of post-traumatic stress disorder (PTSD), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale, depressive symptoms (Patient Health Questionnaire-8), and number of joints affected by arthritis.

Results: The mean ISI score was 11.4 (SD = 8.0); this value is slightly above the cut-point for detecting insomnia. 66% of participants were categorized as being at high risk for sleep apnea based on the BQ. In the

multivariable model of ISI scores, factors associated with more insomnia symptoms included younger age (b = −0.09, 95% Confidence Interval (CI) = −0.16, −0.02; p=0.01), PTSD diagnosis (b = 1.68, 95% CI = 0.26, 3.09; p=0.02), higher WOMAC pain score (b = 0.37, 95% CI = 0.18, 0.55; p<0.001), and more depressive symptoms (b = 0.85, 95% CI = 0.71, 0.98; p<0.001). The only variables associated with high risk for sleep apnea in the multivariable model were greater BMI (odds ratio = 1.13, 95% CI = 1.06–1.21; p<0.001)) and more depressive symptoms (odds ratio = 1.13, 95% CI = 1.06–1.20; p<0.001).

Conclusion: Sleep problems, particularly apnea symptoms, were very common in this sample of patients with hip and knee OA. Depressive symptoms were associated with symptoms of both insomnia and sleep apnea, but other patient characteristics associated with symptoms of insomnia vs. apnea were different. These results highlight the importance of screening for both insomnia and sleep apnea among patients with OA, particularly among those who may be at greater risk due to factors such as depression, PTSD, greater pain severity, and high BMI.

Disclosure: K. D. Allen, None; **H. B. Bosworth**, None; **C. Coffman**, None; **A. Jeffreys**, None; **E. Z. Oddone**, None; **W. S. Yancy Jr.**, None; **C. Ulmer**, None.

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Individuals With Knee Or Hip OA and Low SES Are Likely To Be Physically Active. Rebecca J. Cleveland[1], Kamil E. Barbour[2], Jordan B. Renner[1], Joanne M. Jordan[3] and Leigh F. Callahan[4]. [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]Centers for Disease Control and Prevention, Atlanta, GA, [3]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC, [4]University of North Carolina, Chapel Hill, NC.

Background/Purpose: Osteoarthritis (OA) is a major cause of disability and pain in adults over the age of 45. It has been shown that physical activity (PA) can ease pain and improve quality of life for individuals with hip and knee OA, and may lessen disability. Despite these important health benefits of PA, many with OA do not exercise. Although socioeconomic factors (SES) have been associated in lower PA levels in population-based studies, they have not been meaningfully evaluated among individuals with lower body large joint OA.

Methods: We used cross-sectional data from the first follow-up and cohort replenishment of the Johnston County Osteoarthritis Project (1999–2004) which included 1,404 adults aged 45 and older with radiographic OA (rOA) of the knee and/or hip. rOA in a joint was defined as a Kellgren-Lawrence grade of ≥2. Symptomatic (sxOA) is a subset of those with rOA and symptoms in the same joint. The Minnesota Leisure Time Physical Activity questionnaire was used to collect PA information in the past year. Leisure time PA (LTPA) was assessed as a 4-level variable according to 2008 Physical Activity Guidelines for Americans based on min/wk of PA (0–9, 10-<150, ≥150-<300, ≥300 min/wk), and a dichotomous variable based on meeting Health and Human Services guidelines of ≥150 min/wk of moderate-vigorous PA. Individual SES measures were years of education (EDUC; <12 years, ≥12 years) and occupation type (managerial, non-managerial); community SES was measured using Census block group poverty rate (<12%, 12-<25%, ≥25%). All logistic regression models concurrently examined SES measures for associations with PA levels among those with rOA and sxOA separately, adjusting for age, gender, race, body mass index, occupational PA, and history of injury to matching joint, using the lowest LTPA category as the referent.

Results: Participants meeting recommended PA levels tended to be younger, male, white race, not obese, not have sxOA, with EDUC ≥12 yrs and in a managerial occupation. Among those with rOA, compared to those with EDUC ≥12 yrs, those with EDUC <12 yrs were less likely to participate in high LTPA levels (≥300 min/wk; adjusted odds ratio [aOR]=0.52; 95% confidence interval [CI]=0.34–0.79) and less likely to meet recommended LTPA levels (aOR=0.68; 95% CI=0.51–0.89). Similarly, among the subset of individuals with sxOA, those with EDUC <12 yrs were less likely to meet recommended LTPA levels (aOR=0.65; 95% CI=0.45–0.95). Further, individuals with sxOA living in high poverty block groups were less likely to engage in moderate (aOR=0.34; 95% CI=0.14–0.80), or high levels of LTPA (aOR=0.50; 95% CI=0.25–1.02). Occupation type was not associated with LTPA levels.

Conclusion: In both rOA and sxOA, those with lower SES were less likely to be active or to meet HHS recommendations for PA. Since individuals with lower SES are also more likely to have OA, targeting these groups about the benefits of PA is imperative.

Table 1. Odds ratio (OR)‡ and 95% confidence intervals (CI) for associations of SES variables with physical activity levels among those with knee and/or hip radiographic OA (rOA) and a subset of those with symptomatic* rOA

	Inactive (0–<10 min/week)	Low (10–<150 min/week)	Moderate (150–<300 min/week)	High (=300 min/week)	Meets recommended physical activity levels (=150 min/week) No	Meets recommended physical activity levels (=150 min/week) Yes
Radiographic OA (n = 1404)	n = 228	n = 495	n = 242	n = 439	n = 723	n = 681
Education						
Less than 12 yrs education‡	1.0 (ref)	0.76 (0.51–1.13)	0.65 (0.40–1.04)	0.52 (0.34–0.79)	1.0 (ref)	0.68 (0.51–0.89)
Occupation						
Non-managerial occupation†	1.0 (ref)	1.30 (0.87–1.94)	1.03 (0.65–1.63)	0.96 (0.64–1.44)	1.0 (ref)	0.82 (0.63–1.06)
Block group Poverty§						
Medium (12–25%)	1.0 (ref)	1.20 (0.78–1.84)	0.94 (0.58–1.51)	1.21 (0.78–1.86)	1.0 (ref)	0.96 (0.74–1.26)
High (>25%)	1.0 (ref)	0.64 (0.37–1.10)	0.55 (0.29–1.04)	0.94 (0.54–1.63)	1.0 (ref)	1.04 (0.72–1.51)
Symptomatic rOA* (n = 751)	n = 143	n = 282	n = 123	n = 203	n = 425	n = 326
Education						
Less than 12 yrs education‡	1.0 (ref)	0.58 (0.33–1.02)	0.75 (0.40–1.41)	0.95 (0.56–1.60)	1.0 (ref)	0.65 (0.45–0.95)
Occupation						
Non-managerial occupation†	1.0 (ref)	0.91 (0.52–1.60)	1.22 (0.65–2.30)	1.30 (0.76–2.22)	1.0 (ref)	0.85 (0.59–1.23)
Block group Poverty§						
Medium (12–25%)	1.0 (ref)	1.17 (0.64–2.14)	0.70 (0.36–1.34)	1.11 (0.62–1.97)	1.0 (ref)	0.89 (0.61–1.31)
High (>25%)	1.0 (ref)	0.69 (0.32–1.49)	0.34 (0.14–0.80)	0.50 (0.25–1.02)	1.0 (ref)	0.82 (0.49–1.39)

‡ Adjusted for age, gender, race, body mass index, occupational activity and past injury in corresponding joint; simultaneously adjusted for other SES measures
‡ Symptomatic OA is a subset of those with rOA who have pain in the same joint
* Referent = High school education or greater
† Referent = Managerial occupation
§ Referent = Block group poverty rate less than 12%.

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Less Time Spent In Sedentary Behavior Is Associated With Better Future Physical Function: Objective Data From The Osteoarthritis Initiative. Jungwha Lee[1], Jing Song[2], Rowland W. Chang[1], Linda S. Ehrlich-Jones[3], Pamela A. Semanik[2], Min-Woong Sohn[2] and Dorothy D. Dunlop[2]. [1]Northwestern University Medical School, Chicago, IL, [2]Northwestern University, Chicago, IL, [3]Rehabilitation Institute Chicago, Chicago, IL.

Background/Purpose: Public health physical activity interventions often focus on increasing exercise but give limited attention to reducing sedentary behavior. This study examined whether objectively measured time spent in sedentary behavior is related to subsequent physical function independent of time spent in moderate-to vigorous-intensity physical activity (MVPA) among adults with knee osteoarthritis (OA).

Methods: The Osteoarthritis Initiative cohort included 962 patients with radiographic knee OA, ages 49–83 years at baseline (48-month clinic visit) when physical activity was monitored. Physical function was assessed at baseline and 2 years using the 20-meter walk test (feet/second)) and chair stand rate (per minute). Average daily sedentary behavior and MVPA assessed by accelerometer monitoring was based on 4 or more valid monitoring days (i.e.,10 or more wear hours in a day) for each participant. The percentage of daily wear hours spent in sedentary behavior (minutes when activity counts< 100) was calculated. The relationship of baseline sedentary behavior percentage quartiles to subsequent (2-year) physical function was examined by multiple linear regression models adjusted for demographic factors (age, sex, race/ethnicity, and education), health factors (comorbidity, BMI, knee pain, knee OA severity, presence of knee symptoms) and average daily MVPA minutes.

Results: Adults with knee OA spent on average 66% of their daily time in sedentary behavior (range 28~89%).

For both chair stand rate and gait speed, the most sedentary people had the poorest physical function after 2 years. Compared to the most sedentary group (quartile 1), age-adjusted physical function average was significantly higher in less sedentary behavior groups (chair stand rate: 28.6, 32.1, 31.4, 32.7 stands/minute, P<0.0001; gait speed: 4.19, 4.48, 4.48 and 4.42 feet/second, P=0.0002). These trends persisted in multivariable analyses that controlled for demographic factors, health factors, and MVPA.

Conclusion: Being less sedentary is associated with better future physical function independent of time spent in physical activity. Maintaining physical function may be improved by pairing messages to limit sedentary activities with those promoting increasing levels of physical activity in adults with knee OA.

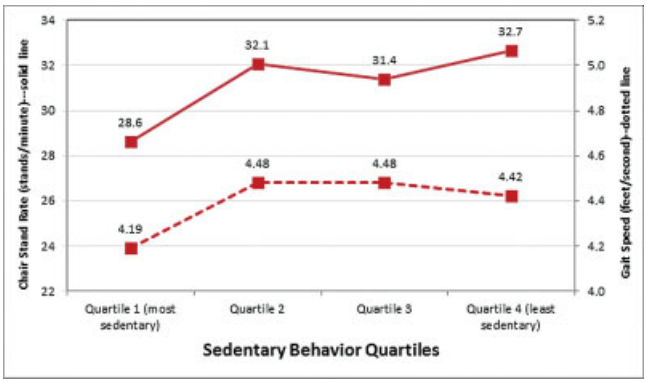

Figure. Average Chair Stand Rate (stands/minute) and Gait Speed (feet/second) at 2 Years, by Sedentary Behavior Quartiles at Baseline, adjusted for age (n=962).

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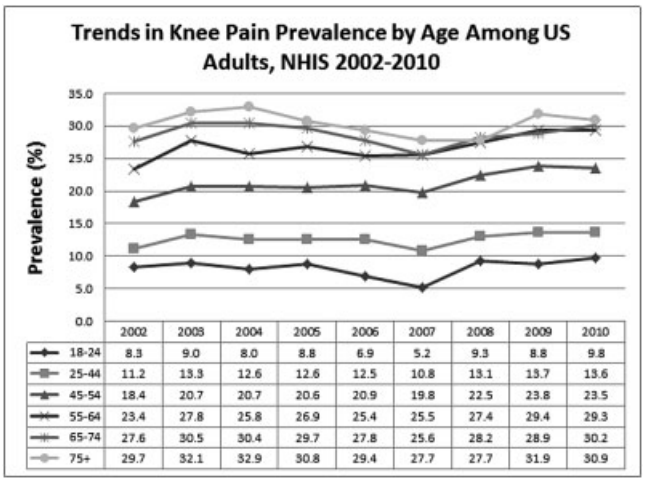
Trends In Prevalence Of Knee Pain Among US Adults, National Health Interview Survey 2002–2010. Jennifer M. Hootman[1], Charles G. Helmick[2] and Yvonne M. Golightly[3]. [1]Centers for Disease Control and Prevention, Kennesaw, GA, [2]Centers for Disease Control and Prevention, Atlanta, GA, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC.

Background/Purpose: Aging of the population as well as the obesity epidemic will play a significant roll in future cases of arthritis and other lower extremity orthopedic conditions. The purpose of this study is to examine trends in the prevalence of knee pain among adults age 18 and older, overall and by age and sex.

Methods: The National Health Interview Survey, conducted annually, targets the civilian, non-institutionalized population and gathers data on a variety of health topics. From 2002–2010 the adult sample size ranged from 21,781 to 31,428. Adults were asked if they had joint pain in the past 30 days not including the back or neck. For those responding "yes", respondents were then asked what joints were affected. Prevalence (%) and 95% confidence intervals (CI) of knee pain were calculated using statistical weights to account for the complex survey design. Prevalence was also stratified by age group (18–24, 25–44, 45–64, 65–74, 75+) and sex and graphed age to show trends over time. Percent increase was calculated using the formula: prevalence 2010–prevalence 2002/prevalence 2002*100. Statistical significance was determined by non-overlapping 95% CIs.

Results: The age adjusted prevalence of knee pain increased significantly from 16.5% (CI 15.6–17.4) in 2002 to 19.6% (CI 18.5–20.7) in 2010. In each year, knee pain prevalence was higher with increasing age and highest for the 75+ age group. (Figure) More than 1 in 4 adults aged 55–64 and 65–74 and 75+ reported having knee pain each year. Knee pain prevalence increased significantly over the 9 years in all age groups. The age groups with the largest percent increase were 25–44 (21.4%), 45–64 (27.7%), and 55–64 (25.2%). Women had higher prevalence of knee pain than men for all years, but prevalence increased more in men (23.0%) versus women (15.3%).



	2002	2003	2004	2005	2006	2007	2008	2009	2010
18-24	8.3	9.0	8.0	8.8	6.9	5.2	9.3	8.8	9.8
25-44	11.2	13.3	12.6	12.6	12.5	10.8	13.1	13.7	13.6
45-54	18.4	20.7	20.7	20.6	20.9	19.8	22.5	23.8	23.5
55-64	23.4	27.8	25.8	26.9	25.4	25.5	27.4	29.4	29.3
65-74	27.6	30.5	30.4	29.7	27.8	25.6	28.2	28.9	30.2
75+	29.7	32.1	32.9	30.8	29.4	27.7	27.7	31.9	30.9

Fig. 1. The effect of fatigue and pain on the physical activity of RA patients.

Conclusion: Knee pain prevalence is high and has increased over time for all age groups with adults aged 25–44 and 45–64 showing the largest increases. The findings suggest a large burden of knee pain among working age adults. Public health and worksite wellness efforts should consider implementing evidence based interventions aimed at reducing knee pain such as physical therapy, aerobic and muscle strengthening exercises, and weight loss. The data also support the need for increasing the number of primary care, rheumatology and orthopedic health professionals in the workforce to be best able to address the growing burden of knee pain in the population.

Disclosure: J. M. Hootman, None; **C. G. Helmick**, None; **Y. M. Golightly**, None.

1079

Physical Activity and Rheumatoid Arthritis: State Of The Art. Jasper van Kuijk, Sanne van Dartel and Han Repping-Wuts. Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.

Background/Purpose: Growing body of research supports the benefit of physical activity in Rheumatoid Arthritis (RA) patients. Physical activity improves some of the most important RA patient outcomes: function, quality of life and pain, without any proven harmful effects on disease activity. However, little is known about physical activity levels among RA patients.

Objectives of this study were to determine how many RA patients meet the Dutch public health recommendation for physical activity, which is at least 30 minutes of moderate-intensity physical activities on at least 5 days a week, and to assess the main personal barriers of RA patients with regard to physical activity.

Methods: A questionnaire, consisted of three parts, was used to answer the objectives. The first part included several general questions describing the population. In this part also the fatigue and pain score of the patients was determined. The second part comprised the Short QUestionnaire to ASses Health-Enhancing Physical Activity (SQUASH) and the final part was the *'guideline for sport participation' (RSO).*The aim of the RSO questionnaire was to assess the main motivation to exercise and the advices by health care providers concerning physical activity. Completing the questionnaire took about 15–20 minutes on www.bewegen-en-reuma.nl. Four different ways of promoting the hyperlink of the questionnaire were used trying to obtain a population which is representing the total RA population. To analyze the answers SPSS was used. One-sample t-tests were performed to compare the RA population with the general Dutch population.

Results: 141 patients completed the questionnaire. The proportions of RA patients meeting the physical activity recommendation were similar to those of the general population (Table 1). Fatigue and pain did have an impact on the achieving of the recommendation for physical activity in RA patients (Fig. 1). 59,1% of the RA population did not receive any advice with regard to physical activity by professional health care providers and 35,5% of the patients is not informed at all about options for physical activity.

Table 1.

	Meeting recommendation for physical activity (%)			Minutes of activity/week
	RA population (n=141)	General population (n=2295)	*p*-value	RA population (n=141)
Total	58,9	59,3	0,917	1578
Female	55,7	59,7	0,386	1590
Male	73,1	58,3	0,108	1528
Age				
<65	61,1			1603
>=65	56,3	48,4	0,385	1325
BMI				
<25	58,5	59,1	0,963	1582
25–30	71,7	56,2	0,034	1761
>30	39,3	50,6	0,239	1277
Disease activity				
Light	86,7			1793
Moderate	58,9			1625
Severe	36,8			1149
Disease duration (yr)				
=<5	62,1			2215
5–16	53,3			1608
16–26	63,2			1346
>25	58,6			1200
Work				
No	58,6	58,5	0,986	1270
Yes	59,5	64,7	0,503	2304

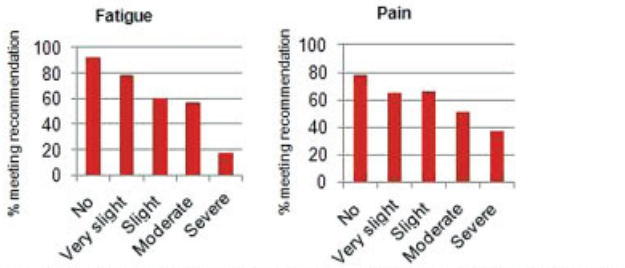


Fig. 1: The effect of fatigue and pain on the physical activity of RA patients

Conclusion: No significant differences were seen between the RA population and the general population in achieving the recommendation for physical activity. RA patients are being informed and advised insufficiently with regard to physical activity. More stimulation and motivation by health care providers is needed to overcome exercise barriers and therefore to help patients in becoming or staying physically active.

Disclosure: J. van Kuijk, None; **S. van Dartel**, None; **H. Repping-Wuts**, None.

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Incidence Of Coronary Heart Disease Associated With Arthritis: A Canadian Population-Based Cohort Study. Orit Schieir[1], S. Hogg-Johnson[2], Richard H Glazier[3] and Elizabeth M. Badley[4]. [1]University of Toronto, Toronto, ON, [2]Institute for Work and Health, and Dalla Lana School of Public Health, University of Toronto, Toronto, ON, [3]nstitute for Clinical Evaluative Sciences, Sunnybrook Health Sciences Centre, Toronto, ON, [4]Division of Health Care and Outcomes Research, Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto, Toronto, ON.

Background/Purpose: Several individual types of arthritis have been associated with increased coronary heart disease (CHD) morbidity in clinical studies, but whether arthritis overall increases the risk of developing CHD is unknown. The objective of the present study was to estimate the extent to which arthritis is associated with the time-to-first occurrence of CHD in a Canadian population-based sample.

Methods: The present study was a secondary analysis of the longitudinal Canadian National Population Health Survey (NPHS), a nationally representative community sample followed every 2 years from 1994/95 through 2010/11. Standardized questionnaires were administered including information on chronic conditions, socio-demographic variables and lifestyle/health behaviours. Deaths were linked to the Canadian Vital Statistics Database. Arthritis was ascertained by self-reported physician diagnosis. CHD was ascertained by self-reported physician diagnosis or death due to ischaemic heart disease (ICD-10 codes I20-I25) or heart failure (ICD-10 codes I50.0-I50.9). Additional covariate information considered in the present analysis included: age, sex, education, body mass index (BMI), smoking, physical inactivity, activity limitation, self-reported physician-diagnosed diabetes and hypertension, and sum of non-cardiovascular comorbidities. Updated values of arthritis, age, education, smoking and comorbidity count were analyzed as time-varying covariates. Discrete-time survival analysis stratified by gender was used to estimate hazard rates for incident CHD associated with arthritis.

Results: The analytical cohort included 13, 369 Canadians age 18 years or older without prevalent CHD or a past history of CHD at baseline. After adjusting for all covariates, arthritis was associated with a 75% increased risk for incident CHD in women (HR: 1.75, 95% CI: 1.39, 2.20) but was not associated with a significant increased risk for CHD in men (HR: 0.95, 95% CI: 0.74–1.22). Women with arthritis who reported concomitant activity limitation had over a 2.5 times higher risk for incident CHD than those without arthritis or activity limitation (HR: 2.55, 95% CI: 1.91, 3.38), adjusted for all covariates. Older age, being a current smoker, baseline diabetes and hypertension, higher BMI and non-cardiovascular comorbidities were also independently associated with incident CHD.

Conclusion: These Canadian population-based estimates suggest that women with arthritis have a significant increased risk for developing CHD, and that women with related activity limitation indicative of more severe arthritis may represent a particularly high-risk population. These data support considering cardiovascular prevention strategies in women with arthritis.

Disclosure: O. Schieir, None; **S. Hogg-Johnson**, None; **R. H. Glazier**, None; **E. M. Badley**, None.

1081

The Effects of Coexisting Cervical Myofascial Pain Syndromes On Pain and Disability of the Computer Users With Cumulative Trauma Disorders. Hakan Genc[1], Ozgul Bozkurt Tuncer[2], Hatice Rana Erdem[3], Baris Nacir[1], Aynur Karagoz[1] and Burcu Duyur Cakit[1]. [1]Ministry of Health, Ankara Training and Research Hospital, Ankara, Turkey, [2]Ministry of Health, Yuksekova Public Hospital, Hakkari, Turkey, [3]Ahi Evran University, Kirsehir, Turkey.

Background/Purpose: Coexisting cervical myofascial pain syndromes (MPS) can have serious effects on pain and disability of computer users with cumulative trauma disorders (CTD). The aims of this study are to evaluate the existence of cervical MPS in computer users with CTD and to investigate the effects of coexisting cervical MPS on pain and disability of computer users.

Methods: 170 computer users were included in the study. Computer users were classified as complainant group (CDT+) who have complaints concerning to neck, back and upper extremity (group 1) and non-complainant group (CTD-) who have no complaint (group 2). 55 age, sex and body mass index matched non-computer user, healthy hospital stuff were recruited as the control group (group 3). All participants were asked to fill our questionnaire form including detailed risk factor query and physical examination. Pain assessment was made by visual analog scale. The existence of MPS was evaluated using specific diagnostic crtiteria. The existence of active trigger points on trapezius, levator scapula, multifidus, sternocleidomastoideus, rhomboideus and deltoideus muscles were evaluated and noted. In order to measure the general disability levels of the participants, Quick DASH Score (QDS) was used, besides to measure their disability levels during work, Quick DASH Work Score (QDWS) was used.

Results: The mean ages of the 114 participants with CTD (77 females and 37 males) was 31.3±6.3 years, of the 56 with non-CTD (33 females and 23 males) was 30.9±6.7 years and of the 55 controls (34 females and 21 males) was 31.7±5.8 years. Statistically significant differences weren't found between the groups with respect to sex, mean ages and body mass indexes. 114 (77%) of the computer users had CTD. The presence of cervical MPS in complainant group (n:87) was statistically significantly higher than non-complainant (n:8) and control (n:8) groups ($p<0.001$). When compared to non-complainant and control groups, QDS and QDWS were significantly higher in complainant group ($p<0.01$–$p<0.05$). In the presence of accompanying MAS, pain intensity, QDS and QDWS increased significantly ($p<0.01$–$p<0.05$).

Conclusion: The existence of cervical MPS is a serious factor in the increase of disability and pain levels of CTD patients. We believe that the evaluation of cervical MPS and treatment of the syndrome have a great importance in the treatment of CTD which can cause serious disability and workforce loss.

Disclosure: H. Genc, None; **O. Bozkurt Tuncer**, None; **H. R. Erdem**, None; **B. Nacir**, None; **A. Karagoz**, None; **B. Duyur Cakit**, None.

1082

The Effects of Prolotherapy in Patients With Subacromial Impingement Syndrome. Eylem Akcan Hannan[1], Akyuz Gulseren Sr.[2] and Nertila Hysenaj[3]. [1]Marmara Univesrsity School of Medicine, Istanbul, Turkey, [2]Marmara University School of Medicine, Istanbul, Turkey, [3]Private Vital Hospital, Istanbul, Turkey.

Background/Purpose: Recent treatments for subacromial impingement syndrome (SIS) are palliative. Dextrose injection which is called prolotherapy has emerged as a treatment option for chronic situations such as tendinitis and bursitis. The aim of the study is to investigate the effects of dextrose injection in patients with chronic shoulder pain caused by subacromial impingement syndrome.

Methods: In this single-center, randomized placebo controlled, single blind, prospective study, 80 patients with chronic SIS who met the study criteria received two dextrose injections in the affected shoulder at two weeks intervals. The patients were randomly assigned into two therapy groups, either

dextrose or other control (lidocaine) groups. The injections were repeated two times with two weeks between injections. Clinical assessments included measurement of range of motion (ROM), pain assessment via Visual Analog Scale (VAS), shoulder functions and daily living activities through University of California (UCLA) shoulder rating scale, the Constant-Murley shoulder outcome score and The Quick Disabilities Arm, Shoulder and Hand (q-DASH) questionnaire were performed at the pre-injection visit, and at the 1-, 3- and 6- month follow-up visits. Magnetic resonance imaging (MRI) evaluation was conducted before the first injection and compared with MRI's taken again on the third month following the second injection.

Results: There were no adverse events reported. The study demonstrated significant improvements in VAS, UCLA, Constant and q-DASH scores in both injection groups. However, there was no significant difference between the two groups in terms of all these clinical scales. Shoulder flexion, abduction, internal and external rotations showed significant improvements in both groups in the first 3 months in accordance to other findings. Nevertheless, while the range of shoulder flexion did not improve in the control group during the last three months, this range of motion continued to improve significantly in treatment group over the same period.

Conclusion: Long-lasting improvements in ROM compared with the lidocaine injection demonstrated could potentially be used to inspire larger, blinded, and randomized clinical trials to determine the most efficient dextrose concentration, the optimal dosage interval, detailed findings on the MRIs and compare with other treatment techniques for the treatment of chronic SIS.

Disclosure: E. Akcan Hannan, None; **A. Gulseren Sr.**, None; **N. Hysenaj**, None.

1083

Something Ventured, Something Gained: Alternative Therapies For FMS and RA. Robert S. Katz[1], Hannah Bond[2], Jessica L. Polyak[2], Lauren Kwan[2], Alexandra Small[3] and Susan Shott[4]. [1]Rush Medical College, Chicago, IL, [2]Rheumatology Associates, Chicago, IL, [3]University of Illinois Medical School, Chicago, IL, [4]Rush University Medical Center, Chicago, IL.

Background/Purpose: Many patients with rheumatologic diseases resort to unproven alternative therapies. We compared FMS and RA patients with respect to the use and effectiveness of alternative therapies.

Methods: 211 office patients with FMS (150; 130 women and 20 men; mean age 51 + 12) or RA (61; 45 women and 16 men; mean age 55 + 15) completed a questionnaire about alternative therapies for treating FMS or RA. Patients rated therapies as 1 = not helpful, 2 = mildly helpful, 3 = moderately helpful, and 4 = very helpful. The chi-square test of association was done to compare FMS and RA patients with respect to percentages, and the two-sided Mann-Whitney test was done to compare them with respect to the ratings, using a 0.05 significance level.

Results: Significantly higher percentages of FMS patients reported having used meditation (44% vs. 26%, p = 0.025), massage (76% vs. 58%, p = 0.020), diet changes (75% vs. 56%, p = 0.018), exercise (92% vs. 79%, p = 0.013), and physical therapy (59% vs. 39%, p = 0.017) compared to RA patients. FMS patients were also more likely to report having tried herbal supplements (47% vs. 31%), biofeedback (21% vs. 9%), and chiropractic treatment (43% vs. 31%) (ns). For FMS patients, the most helpful therapies were yoga, exercise, massage, physical therapy, water therapy, and a gluten-free diet (median ratings = 3), followed by meditation, diet changes, herbal supplements, vitamins/minerals, acupuncture, biofeedback/cognitive behavioral therapy, chiropractic treatment, and tai chi (median ratings = 2), with hypnosis as least helpful (median rating = 1). For RA patients, the most helpful therapies were chiropractic treatment and water therapy (median ratings = 4 and 3.5), followed by yoga, meditation, exercise, massage, biofeedback/cognitive behavioral therapy, physical therapy, and tai chi (median ratings = 3), and diet changes, herbal supplements, vitamins/minerals, acupuncture, and a gluten-free diet (median ratings = 2), with hypnosis as least helpful (median rating = 1). The efficacy ratings were significantly different for FMS and RA patients only for chiropractic treatment efficacy, with lower ratings reported by FMS patients (median 2 vs. 4, p = 0.007).

Conclusion: FMS patients were more adventuresome than RA patients when it came to trying alternative therapies. Many of these therapies had high efficacy ratings for FMS and/or RA patients.

Disclosure: R. S. Katz, None; **H. Bond**, None; **J. L. Polyak**, None; **L. Kwan**, None; **A. Small**, None; **S. Shott**, None.

1084

Age Distribution of Women With Idiopathic and Traumatic Fibromyalgia. Robert S. Katz[1] and Frank Leavitt[2]. [1]Rush Medical College, Chicago, IL, [2]Rush University Medical Center, Chicago, IL.

Background/Purpose: Fibromyalgia has both idiopathic and post traumatic forms. The idiopathic type is insidious in onset, becoming established without a known triggering event. The post-traumatic form is defined by the presence of a triggering event such as a significant illness, an injury or an accident. The purpose of this study is to examine the age distribution of the two forms of onset in order to determine if either form is age-linked.

Methods: Age of onset and the presence of a triggering event were investigated in 169 female patients who met ACR criteria for fibromyalgia. In response to the question "Did a specific event or condition trigger your symptoms of fibromyalgia", 97 (57.4%) recorded yes and formed the post-traumatic group. Forty two percent (42.6%) recorded no and formed the idiopathic group

Results: The mean age of post-traumatic FMS patients was 47.1±11.6 years and for idiopathic FMS patients was 49.7± 12.8 years. The mean age of symptom onset was 35.3 ±11.7 years in the post-traumatic group and 37.1±12.3 years in the idiopathic group. Differences between groups on the two variables were non-significant.

Table 1. illustrates that the age distribution in both forms of fibromyalgia is similar**.** The two forms of FMS occurred in people of all ages, and ranged from 8 to 65 in the post-traumatic group and 6 to 63 in the idiopathic group. The frequency of onset in both forms is highest between the ages of 30 and 49.

Distribution in age of Onset in Two Forms of Fibromyalgia

	Triggered	Idiopathic
Age 6 to 17	10 (10.3%0)	5 (6.9%)
Age 18 to 29	19 (19.6%)	15 (20.8%)
Age 30 to 39	30 (30.9%)	17 (23.6%)
Age 40 to 49	27 (27.8%)	24 (33.3%)
Age 50 to 65	11 (11.3%)	11 (15.3%)

Conclusion: It is curious that the mean age of onset in the group with post-traumatic FMS (35.3 y.o.) was similar to the mean age of onset in patients with idiopathic FMS (37.1 y.o.). Neither the idiopathic nor the post-traumatic form of FMS appears age dependent. Onset can be encountered both early and late in life with approximately 10% of each form occurring before the age of 18 and after the age of 50. FMS onset peaks in the 3rd, 4th and 5thdecades in women.

The similar pattern of onset is puzzling since one is presumably an internally generated process and the other occurs on an apparently chance basis, such as after car accidents. One theory is that the idiopathic form of fibromyalgia is also stress driven but on a more subtle basis. Like the post-traumatic form, it also occurs because cumulative stress builds, in an unnoticed manner, and exceeds a critical threshold dependent on life circumstances.

Disclosure: R. S. Katz, None; **F. Leavitt**, None.

1085

I Work Out: Exercise Appears To Increase FMS Pain. Robert S. Katz[1], Ben J. Small[2] and Susan Shott[3]. [1]Rush Medical College, Chicago, IL, [2]Rush University Medical School, Chicago, IL, [3]Rush University Medical Center, Chicago, IL.

Background/Purpose: A basic tenet of the treatment of FMS is that exercise decreases symptoms of the illness. We compared FMS and RA patients to assess their ability to exercise and the impact of exercise on their pain.

Methods: 211 office patients with FMS (150; 130 women and 20 men; mean age 51 + 12) or RA (61; 45 women and 16 men; mean age 55 + 15) completed a questionnaire about their ability to exercise, types of exercise, and effect of exercise on their pain (rated as 1 = much worse, 2 = moderately worse, 3 = somewhat worse, 4 = no change, 5 = somewhat better, 6 = moderately better, and 7 = much better). The chi-square test of association was done to compare FMS and RA patients with respect to percentages, and the two-sided Mann-Whitney test was done to compare them with respect to the ratings, using a 0.05 significance level.

Results: 71% of FMS patients and 67% of RA patients reported exercising (ns). FMS patients were less likely to report being able to exercise

(74% vs. 87%, ns). The exercise impact ratings were significantly worse for FMS patients compared to RA patients (median 3 vs. 4, p = 0.017). 60% of FMS patients reported that exercise made their pain somewhat, moderately, or much worse, compared to 35% of RA patients. 20% of FMS patients reported that exercise made their pain much worse, compared to only 6% of RA patients. Walking was by far the most common type of exercise, reported by 66% of FMS patients and 70% of RA patients. All other types of exercise were reported by 20% or fewer FMS or RA patients. High-impact exercise such as jogging was rarely reported by FMS or RA patients.

Conclusion: Almost two-thirds of FMS patients reported that exercise made their pain worse, compared to only about a third of RA patients. Exercise programs that can be tolerated by FMS and RA patients need to be designed with input from patients. Although exercise is generally recommended for FMS patients, current exercise programs appear likely to make their pain worse.

Disclosure: R. S. Katz, None; **B. J. Small**, None; **S. Shott**, None.

1086

The Straight Neck in Fibromyalgia. Robert S. Katz[1] and Anthony Farkasch[2]. [1]Rush Medical College, Chicago, IL, [2]Rheumatology Associates, Chicago, IL.

Background/Purpose: In patients with fibromyalgia a straight neck is based on calculating the Cobb angle, a standard radiographic measurement, of lateral view radiographs of the cervical spine. Most fibromyalgia patients have lost the normal cervical lordosis. We re-evaluated cervical spine radiographs of fibromyalgia patients to determine what proportion of FMS subjects have straight necks.

Methods: The lordotic curve of cervical spine radiographs was measured by analyzing the Cobb angle in 138 consecutive patients in a rheumatology office practice. All patients met the ACR criteria for fibromyalgia and complained of moderate to severe neck pain. 23 additional patients with fibromyalgia followed in the same rheumatology practice had cervical radiographs reviewed visually by both a rheumatologist and an X-ray technician, but did not also have the Cobb angle measured (visual inspection group) The amount of visual curvature was noted by each as 1 (straight neck), 2 (slight lordotic curve) and 3 (normal lordotic curve).

Results: 98 of 138 (71%) fibromyalgia patients had a straight spine (Cobb angle less than 14 degrees). 24 of 138 (17%) fibromyalgia patients had a small lordotic curve of the lateral view of cervical spine radiographs (Cobb angle 14–18 degrees). 16 of 138 (12%) patients had a normal Cobb angle (more than 18 degrees) and a normal lordotic curve.

20 (87%) of 23 additional fibromyalgia patients (visual inspection group) had a straight cervical spine by visual inspection. They had lost the normal lordotic curve. 3 (13%) fibromyalgia patients had a slightly curved cervical spine. No fibromyalgia patient had a normal cervical lordosis by visual inspection of lateral views of radiographs of the cervical spine. The Cobb angle in 10 rheumatic disease controls was 22.5 degrees (and reported to be 26.8 degrees in healthy controls).

Conclusion: 88 % of fibromyalgia patients in this study had a straight neck based on measuring the Cobb angle, and 90 % had a straight neck (loss of the lordotic curve) by visualizing the lateral view of cervical spine radiographs. The cause of the straight cervical spine in fibromyalgia is unknown. Speculation of the pathophysiology includes chronic muscle contraction and tightness of other soft tissues.

A straight cervical spine in the absence of other radiological abnormalities might assist in the diagnosis of fibromyalgia, and it may be important in attempting to understand the pathophysiology of this disorder.

Disclosure: R. S. Katz, None; **A. Farkasch**, None.

1087

Abnormalities Of Central Processing Mechanisms In Fibromyalgia. Robert S. Katz[1] and Bhagwan T. Shahani[2]. [1]Rush Medical College, Chicago, IL, [2]University of Illinois College of Medicine, Chicago, IL.

Background/Purpose: Fibromyalgia may be associated with central pain processing abnormalities, including central sensitization. In this study, we describe three patients, two females (41 and 48 years old) and one male (49 years old) who had no evidence of peripheral neuropathy on detailed electrophysiological studies. Each individual patient described a different sensory perception to the same controlled stimulus, suggesting abnormalities of central processing mechanisms.

Methods: Detailed electrophysiological studies including motor sensory nerve conduction as well as late response studies were performed using a TECA EMG machine. Patients were asked to report the sensation they felt when electrical stimulation was delivered to peripheral nerves. The stimulus consisted of single electrical pulses of 0.1to 0.5 msec. duration. The stimulus intensity was adjusted to deliver a supramaximal stimulation.

Results: Motor and sensory nerve conduction as well as late response studies were within normal limits, suggesting that none of these patients had any evidence of peripheral neuropathy. Supramaximal electrical stimulation of peripheral nerves at the level of the ankles in the first patient produced a "burning" pain in the feet, which was so intense that she could not control crying during the study. In the second patient, a single electrical stimulus delivered to the peroneal and tibial nerves produced a ticklish feeling, which elicited uncontrollable laughter on the part of the patient. In the third patient, electrical studies of median and ulnar nerves produced a dull tapping sensation without any discomfort or dysesthesias.

Conclusion: Electrical stimulation of mixed peripheral nerves produced a distinctly different sensory response in each of these three patients with FMS. The stimulus parameter used for this study activated only myelinated fibers; small unmyelinated nerve fibers (C-fibers) were not stimulated. The different types of sensations, including burning and a ticklish sensation experienced by our patients, therefore must have resulted from activation of large and small diameter myelinated nerve fibers. Since the peripheral nervous system was intact in these patients, the perception of burning, tickling, and the dull tapping feeling must be related to abnormalities of central processing mechanisms.

Many of the clinical symptoms of FMS may be related to abnormalities of processing and/or modulating mechanisms in the central nervous system. Depending upon the central mechanism involved, the same stimulus may result in different sensory perceptions. The physiological mechanisms of excitatory postsynaptic potentials (EPSP), inhibitory postsynaptic potentials (FPSP), and presynaptic inhibition, as well as the levels of neurotransmitters and neuromodulation may play a part in producing specific clinical symptoms. Better understanding of these physiological mechanisms will result in better diagnoses and treatment of patients with FMS.

Disclosure: R. S. Katz, None; **B. T. Shahani**, None.

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Fibromyalgia and Parental Medical Histories Of Depression and Alcoholism. Robert S. Katz[1], Ben J. Small[2], Sharon M. Ferbert[3] and Susan Shott[4]. [1]Rush Medical College, Chicago, IL, [2]Rush University Medical School, Chicago, IL, [3]Advocates for Funding Fibromyalgia Treatment, Education and Research(AFFTER), Libertyville, IL, [4]Rush University Medical Center, Chicago, IL.

Background/Purpose: We had found in a previous study suggestions of an increased prevalence of depression in the mothers and alcohol abuse in the fathers of fibromyalgia patients. We re-examined this finding in a group of fibromyalgia patients.

Methods: 115 FMS patients and 63 control patients with other rheumatic diseases answered a rheumatology office questionnaire that included questions about whether their mother or father had been diagnosed with or had symptoms of depression, alcoholism, or FMS. The chi-square test of association and Fisher's exact test were used to compare FMS and control patients with respect to percentages. The Mann-Whitney test was done to compare these groups with respect to age. A 0.05 significance level was used and all tests were two-sided.

Results: 81.7% of the FMS patients and 61.9% of the control patients were women (p = 0.004). The mean age was 48.1 ± 12.3 years for FMS patients and 50.7 13.6 for control patients (p = 0.092). 33.0% of FMS patients and 8.1% of control patients reported a depression diagnosis or symptoms in their mothers (p < 0.001). 26.3% of FMS patients reported a depression diagnosis or symptoms in their fathers, compared to 10.0% of control patients (p = 0.013). Although FMS patients were more likely than control patients to report an alcoholism diagnosis or symptoms in their mothers (9.6% vs. 4.8%. p = 0.38) and fathers (19.2% vs. 10.0%, p = 0.18), the differences were not statistically significant. FMS patients were significantly more likely than control patients to report a FMS diagnosis or symptoms in their mothers (26.4% vs. 3.2%. p < 0.001), but not in their fathers (6.2% vs. 0%, p = 0.083).

Conclusion: FMS patients were significantly more likely than control patients to report that their parents had a diagnosis or symptoms of depression, and significantly more likely to report that their mothers had the diagnosis or symptoms of FMS. No statistically significant differences were found with respect to paternal FMS or maternal or paternal alcoholism.

Disclosure: R. S. Katz, None; **B. J. Small**, None; **S. M. Ferbert**, None; **S. Shott**, None.

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Synergistic Effects Of Transcranial Direct Current Stimulation and Trigger Point Injection For Treatment Of Myofascial Pain Syndrome: A Pilot Study With Randomized, Single-Blinded Trial. Shi-Uk Lee[1], Chang Han Lee[1] and Yoon-Hee Choi[2]. [1]Seoul National University Boramae Medical Center, Seoul, South Korea, [2]Seoul National University Bundang Hospital, Seoul, South Korea.

Background/Purpose: Chronic pain caused by myofascial pain syndrome (MPS) results in generalized and debilitating conditions. Trigger point injection (TPI) is the mainstay of MPS management to reduce acute and localized pain. Other adjunctive intervention to modulate the central pain pathway might be helpful if they are combined with TPI. Transcranial direct current stimulation (tDCS) which is a form of neurostimulation has been reported to be safe and effective in treating chronic pain by changing cortical excitability.

The purpose of this study was to determine whether there is synergistic effect of tDCS and TPI to reduce pain in patients with MPS.

Methods: Subjects: Patients (n=21, 8: M1, 7: DLPFC, 6: sham) with newly diagnosed MPS of shoulder girdle muscles.

Interventions: Patients were randomized into one of 3 groups (2 active and 1 sham stimulation groups) and received TPI. Immediately after TPI, tDCS (2mA, 20min for 5 consecutive days) was administered. For active stimulation groups, tDCS was applied over 2 different locations (primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC)).

Outcome Measures: Visual Analogue Scale (VAS), Pain Threshold Test (PTT) and short form of the McGill Pain Questionnaire (SF-MPQ) was measured prior to and immediately after stimulation for 5 consecutive days.

Results: The mean VAS values were decreased in all three groups after 5 days. There was a significant change between before and after stimulation only in the DLPFC group. The significant change in the mean VAS value was shown from after the second stimulation session (p= 0.031) and those remained significant until the last stimulation session (p=0.027).

Conclusion: tDCS over DLPFC may have synergistic effects with TPI to reduce pain in patient with myofascial pain syndrome. tDCS over DLPFC can be used to reverse central pain pathway by modulating cortical plasticity.

Disclosure: S. U. Lee, None; **C. H. Lee**, None; **Y. H. Choi**, None.

1090

Suprascapular Nerve Block For Shoulder Pain In The First Year After Stroke: A Randomised Controlled Trial. Zoe Adey-Wakeling[1], Maria Crotty[1] and E. Michael Shanahan[2]. [1]Flinders University, Adelaide, Australia, [2]Flinders University, Bedford Park, South Australia, Australia.

Background/Purpose: Shoulder pain is a significant complication of hemiplegic stroke in at least 25% of cases. The evidence base for the treatment of hemiplegic shoulder pain is poor. Suprascapular nerve block has been shown to be safe and effective in the treatment of shoulder pain associated with rheumatoid arthritis and degenerative shoulder conditions but its usefulness in a stroke population is unknown.

Methods: We undertook a randomised controlled trial assessing the effectiveness of suprascapular nerve block compared with placebo in a population of stroke patients with hemiplegic shoulder pain. The primary outcome was pain severity measured on a vertical visual analogue scale (VAS), and secondary outcomes are disability (Modified Rankin Scale, Croft Disability Index) and quality of life (EuroQol Health Questionnaire). All participants were assessed at baseline, and then at 1, 4 and 12 weeks post intervention. Both groups continued to receive routine physiotherapy and standard ward care.

Results: Patients who received a suprascapular nerve block (SSNB) consistently demonstrated superior and statistically significant pain reduction at all follow up time points. Mean VAS reduction in the SSNB group was at least 18mm greater when compared to the scores of those who received the placebo injection. The number needed to treat with suprascapular nerve block to reduce one stroke survivor's pain by 50% at four weeks is 4. No significant differences were noted between groups in regards to function or quality of life. No adverse events associated with the intervention were reported.

Conclusion: Suprascapular nerve block is a safe and effective treatment modality in patients with hemiplegic shoulder pain.

Disclosure: Z. Adey-Wakeling, None; **M. Crotty**, None; **E. M. Shanahan**, None.

1091

Altered Intrinsic Brain Connectivity In The Salience Network Of Fibromyalgia Patients At Rest. Seong-Ho Kim. Division of Rheumatology, Inje University College of Medicine, Haeundae Paik Hospital, Busan, South Korea.

Background/Purpose: Recent studies employing resting-state functional magnetic resonance imaging (fMRI) have demonstrated altered intrinsic brain connectivity in patients with fibromyalgia (FM); however, few studies have addressed the issue of the salience of pain in FM. In this study, we investigated the possible alteration in the salience processing of pain in patients with FM.

Methods: A total of 44 female subjects (20 FM patients and 24 healthy controls) underwent resting-state fMRI. Independent component analysis (ICA) was used for evaluation of resting-state salience network (SN) connectivity. Correlation analyses were performed for determination of correlation between changes in mood and intrinsic connectivity in brain regions within the MPN. The Beck depression inventory (BDI) and Beck anxiety inventory (BAI) were used for assessment of mood changes.

Results: Compared with healthy control subjects, the significant increase in functional connectivity of anterior insula within the SN was found in patients with FM. The increase in functional connectivity within the SN was not associated with symptoms of depression and anxiety.

Conclusion: Increased functional connectivity suggests spontaneous altered activity in the salience of pain in patients with FM implicating enhanced spontaneous salience to pain.

Disclosure: S. H. Kim, None.

1092

Low Dose Naltrexone In The Treatment Of Fibromyalgia. Samy Metyas[1], Karen Yeter[2], John Solyman[3] and D. Arkfeld[2]. [1]Assistant clinical professor Of Rheumatology at USC, covina, CA, [2]University of Southern California Keck School of Medicine, Los Angeles, CA, [3]Research Associate, Covina, CA.

Background/Purpose: Fibromyalgia is a chronic pain disorder characterized by diffuse musculoskeletal pain, fatigue, sleepdisturbance and cognitive impairment. A significant number of fibromyalgia patients do not respond adequately to the current drugs (pregabalin, milnacipran, duloxetine) approved for fibromyalgia treatment by the Food and Drug Administration (FDA). Thus, there is still a need for adjunctive therapies. Naltrexone is an opioid receptor antagonist used to treat alcohol and opioid dependence. It is hypothesized that low dose naltrexone causes transient blockade of opioid receptors centrally resulting in a rebound of endorphin function which may attenuate pain in fibromyalgia.

Objectives: The aim of this study was to determine the effect of low dose naltrexone on symptoms in fibromyalgia.

Methods: This was a prospective, open label study carried out at a single center. Twenty-five patients diagnosed with fibromyalgia (according to the American College of Rheumatology criteria) participated. Naltrexone was started at a doseof 3 mg at night time and could be titrated up to a maximum of 4.5 mg at night time. Patients were permitted to continue pregabalin, milnacipran, or duloxetine. The primary outcome measure was the Revised Fibromyalgia Impact Questionnaire (FIQR) at month 3. Adverse reactions were also recorded.

Results: Twenty-four females and 1 male were enrolled. Twenty-two patients completed the study. Seven (32%) patients were on naltrexone monotherapy throughout the study. There was a 19.5% overall improvement in FIQR at month 3 with naltrexone therapy. Eleven (50%) had an average of a 41% improvement in the FIQR. The patients reported decreases in anxiety, pain and sleeping habits from baseline. Two patients discontinued the drug because they felt it was ineffective and 1 patient discontinued because of diarrhea.

Conclusion: Treatment with low dose naltrexone may be an effective, highly tolerable and inexpensive treatment for fibromyalgia. Further controlled trials are needed.

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1. Ramanathan S, Panksepp J, Johnson B. Is fibromyalgia an endocrine/endorphin deficit disorder?Is it low dose naltrexone a new treatment option? *Psychosomatics* 2012;53:591–4.

Disclosure: S. Metyas, None; **K. Yeter**, None; **J. Solyman**, None; **D. Arkfeld**, None.

1093

SPA Therapy In The Treatment Of Chronic Shoulder PAIN Due To Rotator Cuff Tendinopathy: Rotatherm, A Large Randomized Multicentre Trial. Isabelle Chary-Valckenaere[1], Damien Loeuille[1], Nicolas Jay[1], François Kohler[1], Christian F Roques[2], Michel Boulange[1] and Gérard Gay[1]. [1]Nancy University Hospital, Nancy, France, [2]Université Paul Sabatier, Toulouse, France.

Background/Purpose: To determine whether spa therapy has a beneficial effect on pain and disability in the management of shoulder pain due to chronic rotator cuff lesions.

Methods: This multicentre randomized prospective clinical trial included patients with chronic shoulder pain due to rotator cuff tendinopathy who were attending French spa resorts as outpatients between March 2009 and April 2010. Subjects were randomized into two groups: spa therapy (18 days of standardized treatment) and control (spa therapy delayed for six months). All patients continued usual treatments during the 6-month follow-up period. The main endpoint was the mean change in the DASH score at six months. The effect size (ES) of spa therapy was calculated and the proportion of patients reaching minimal clinically important improvement (MCII) was compared between groups. Secondary endpoints were the mean change in SF-36 components, treatments use, and tolerance.

Results: 186 patients were included in the study (94 controls and 92 in the spa therapy group) and analyzed by intention to treat. At six months, the mean change in the DASH was statistically significantly greater among spa therapy patients than controls (−32.6% and −8.15%, respectively ($p<0.001$)) with an ES at 1.32 (95%CI: −1.68; −0.97). A significantly greater proportion of spa therapy patients reached MCII (59.3% versus 17.9%). Spa therapy was well tolerated, with a significant impact on SF-36 components but not on drug consumption.

Conclusion: Spa therapy provides a highly statistically significant beneficial effect on pain and function in patients with chronic shoulder pain after 6 months compared with usual treatment alone.

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Hyperbaric Oxygen Ameliorates Fibromyalgia Symptoms and Functional Impairment–A Randomized Prospective Trial. Shai Efrati[1], Jacob N. Ablin[2], Yair Bechor[1], Shir Daphna-Tekoah[3], Gregory Fishlev[4], Yifat Faran[3], Jacob Bergan[1], Mony Friedman[1] and Dan Buskila[5]. [1]Asaf-Harofeh medical center, Beer Yaacov, Zerifin, Israel, [2]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [3]Ashkelon Academic College, Ashkelon, Israel, [4]Assaf Harofeh Medical Center, Beer Yaacov, Zerifin, Israel, [5]Ben-Gurion University, Beer-Sheva, Israel.

Background/Purpose: Fibromyalgia Syndrome (FMS), considered to represent a prototype of central nervous system sensitization, is a common condition characterized by chronic widespread pain and diffuse tenderness, along with symptoms of fatigue [1,2]. Hyperbaric oxygen (HBOT) has the capacity to induce neuroplasticity in different chronic brain pathologies [3]. The current study evaluated the utility of HBOT for influencing central sensitization as a therapeutic modality for FMS.

Methods: A prospective, randomized, controlled, two-group trial. The population included 60 female patients of ages 21–67years diagnosed with FMS for at least 2 years. Patients were randomized into two groups: a treated group and a cross group. The patients in the treated group were evaluated twice: at baseline and after HBOT. Patients in the cross group were evaluated three times: baseline, after control period of no treatment, and after HBOT. The following HBOT protocol was practiced: 40 sessions, 5 days/week, 90 minutes, 100% oxygen at 2ATA.

At each time point, level of pain was evaluated by physical examination including tender point count and dolorimetry, as well as extensive evaluation of parameters relating to quality of life, presence of widespread pain, fatigue, physical and social function, and symptoms related to anxiety, depression, and somatization.

Results: A significant reduction of all FMS symptoms such as pain (threshold and number of tender points) and fatigue was apparent following HBOT, sessions as well as significant improvement in distress symptoms. Moreover, the quality of life and functional capability of all patients were significantly improved following HBOT sessions. No improvement in any parameter was found during the control period of patients in the cross group.

Conclusion: The results indicate that HBOT can lead to significant improvement in all FMS symptoms as well as significant improvement in patients' quality of life.

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(3) Efrati S, Fishlev G, Bechor Y, Volkov O, Bergan J, Kliakhandler K et al. Hyperbaric oxygen induces late neuroplasticity in post stroke patients–randomized, prospective trial. PLoS One 2013; 8(1):e53716.

Disclosure: S. Efrati, None; **J. N. Ablin**, Pfizer Inc, 8; **Y. Bechor**, None; **S. Daphna-Tekoah**, None; **G. Fishlev**, None; **Y. Faran**, None; **J. Bergan**, None; **M. Friedman**, None; **D. Buskila**, None.

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Pooled Safety Data From Randomized, Controlled Trials Of Diclofenac Sodium Topical Gel 1% In Subjects With Acute Pain. Roy D. Altman[1], Helmut Pabst[2], Hans-Georg Predel[3], Bruno Giannetti[4], Ian Burnett[5], Morris Gold[6] and Evan F. Ekman[7]. [1]UCLA, Los Angeles, CA, [2]Independent Physician, Gilching, Germany, [3]German Sports University, Cologne, Germany, [4]CRM clinical trials GmbH, Rheinbach, Germany, [5]Novartis Consumer Health, Nyon, Switzerland, [6]Novartis Consumer Health, Parsippany, NJ, [7]Southern Orthopaedic Sports Medicine, Columbia, SC.

Background/Purpose: Diclofenac sodium topical gel (DSG) 1% is clinically proven to be effective and well-tolerated for treatment of osteoarthritis pain and could be appropriate to treat acute conditions, such as ankle sprains and soft tissue injuries. Current treatment options include oral non-steroidal anti-inflammatory drugs (NSAIDs), which may be associated with an increased risk of systemic side effects (eg, gastrointestinal), and topically applied rubefacients, which could be ineffective. Previous pharmacokinetic studies have demonstrated that topically applied diclofenac gel results in low systemic exposure. Three randomized, placebo-controlled phase III clinical trials were conducted to assess the efficacy and safety of DSG 1% in subjects with acute ankle sprain or soft tissue injury/contusion. Safety data from the 3 controlled trials were pooled and are presented in this analysis.

Methods: Two trials were conducted in ankle sprain and 1 trial in contusion. The 3 trials were similar in design and subject population except for the site of the acute injury. Treatment was 3 g DSG 1% or placebo to affected ankle q.i.d. for 7 days or 2 g DSG 1% or placebo to the contusion q.i.d. for 2–7 days, until resolution. AEs were reported either during subject visits or in subject diaries in each trial. The 3 AE databases were pooled for an overall safety analysis. Blood samples were collected for laboratory safety analyses before randomization and at end of study.

Results: Safety data were available for 615 subjects (mean age 30.9±12.0 years). A total of 7788 doses of DSG 1% (N=310) and 7670 doses of placebo (N=305) were applied over the 3 trials. There were no meaningful differences in the incidence of AEs between treatment groups. AEs occurred in 19 DSG 1% subjects (6.1%) and 16 placebo subjects (5.2%). Most were mild and self-resolving. Eight were considered treatment-related: 2 AEs in 1 DSG 1% subject (dry skin and erythema) and 6 AEs in 4 placebo subjects (application site pruritus, joint warmth, erythema, rash and pruritus [2]). There was 1 serious AE in the placebo group (distortion of wrist and rupture of scapholunate ligament), not considered to be treatment-related. Gastrointestinal, hepatic, and renal AEs were rare (≤2 events reported), while hematological and cardiac AEs were absent. Mean values for liver function test results, (alanine aminotransferase, aspartate aminotransferase, and total bilirubin) were within normal ranges at baseline and end of study and did not suggest any clinically significant systemic alterations during the course of the study. The overall safety profile of DSG 1% was similar to that of placebo.

Conclusion: DSG 1% applied 4 times daily for 7 days was found to be well-tolerated and no specific safety concerns were identified in these controlled clinical trials. Overall, the safety profile of DSG 1% demonstrates that it could be an appropriate treatment option for patients with acute painful conditions who have a need to minimize the systemic absorption of NSAIDS.

Disclosure: R. D. Altman, Novartis Consumer Health, 5; **H. Pabst**, Novartis Consumer Health, 9; **H. G. Predel**, Novartis Consumer Health, 9; **B. Giannetti**, Novartis Consumer Health, 9; **I. Burnett**, Novartis, 1, Novartis Consumer Health, 3; **M. Gold**, Novartis, 1, Novartis Consumer Health, 3; **E. F. Ekman**, Novartis Consumer Health, 9, Evan Ekman, 5.

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Is Vitamin D Deficiency a Risk Factor For The Development Of Statin Induced Myalgia, In Patients Treated With Statin? Ozlem Tasoglu[1], Yesim Kutsal[1], Irfan Tasoglu[2], Oya Ozdemir[1] and Yildiz Erdoganoglu[3]. [1]Hacettepe University Faculty of Medicine, Ankara, Turkey, [2]Türkiye Yuksek Ihtisas Training and Research Hospital, Ankara, Turkey, [3]Hacettepe University, Ankara, Turkey.

Background/Purpose: Vitamin D deficiency has become pandemic in the industrializing societies. Recently, the role of vitamin D deficiency in the development of statin myopathy has started to be discussed. The purpose of this study is to compare the serum vitamin D levels and objective muscle strength measures in males with or without myalgia who were under statin treatment.

Methods: Seventeen patients (mean age: 49,1± 7,9) with a diagnosis of statin induced myalgia and 23 patients (mean age: 50,6± 9,0) without myalgia were included in this study. The patients in the two groups were matched according to age, level of physical activity and sunlight exposure. After a detailed physical examination, serum 25-OH vitamin D levels were measured. The patients with myalgia were asked to complete a 10 cm Visual Analog Scale (VAS) and McGill-Melzack Pain Questionnaire. The measurement of grip strength were performed using Jamar type hydraulic hand dynamometer, and isometric/isokinetic measurements of the biceps and quadriceps muscles were performed using Biodex System 3 device.

Results: Statin dosages (mg) were: 19,1±16,7 (myalgia) and 17,0±7,7(without myalgia) (p value: 0,639) and durations (month) were: 32,9±28,4 (myalgia) and 40,4±39,4 (without myalgia (p value: 0,606).There was no significant difference in the mean values of vitamin D levels in both groups (myalgia: 34,8 ng/mL, without myalgia:31,9 ng/mL). In general, the patients with statin induced myalgia had an intermittant pain in the proximal parts of their extremities. They declared that the pain was induced by activity or exercise and reduced with rest. The mean VAS score was determined as 4.0 cm (min:1.3, max:8.4). No statistically significant correlations were found between the vitamin D levels and any of the pain parameters in the myalgia group (p>0,05). Furthermore, the measurement with the hand dynamometer and the isometric and isokinetic muscular strength analyses for both groups were found to be similar except for the biceps isokinetic 120° TT/VA.

Conclusion: The male patients with or without statin induced myalgia have similar serum vitamin D levels and muscle strength. Thus, it seems like vitamin D deficiency might not be a risk factor for the development of statin induced myalgia.

Disclosure: O. Tasoglu, None; **Y. Kutsal**, None; **I. Tasoglu**, None; **O. Ozdemir**, None; **Y. Erdoganoglu**, None.

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A Potential Use Of Neurotropin™, a Novel Neuro-Modulating Medication, For The Treatment Of Chronic Pain and Fibromyalgia. Kenji Miki[1], Ryota Hashimoto[2], Kenrin Shi[3] and Masao Yukioka[1]. [1]Yukioka Hospital, Osaka, Japan, [2]Osaka University Graduate School of Medicine, Suita, Japan, [3]Osaka University Hospital, Suita, Japan.

Background/Purpose: To date, no established treatment for chronic pain including fibromyalgia has been specified in Japan. Neurotropin, a non-protein extract isolated from the inflamed cutaneous tissue of vaccinia virus-inoculated rabbits, is often prescribed for mild to severe chronic musculoskeletal pain such as backache, lumbago and stiff neck in Japan. It is also prescribed for fibromyalgia, and its annual overall sales excesses 200 million USD solely in Japan. We conducted a study on efficacy of Neurotropin on chronic pain including fibromyalgia.

Methods: Among 175 patients with chronic pain, Neurotropin was prescribed for 113 patients in whom psychiatric disorders were absent or not contributing to the pain symptom. Of these, 84 patients met both 1990 classification criteria for fibromyalgia by American College of Rheumatology (ACR) and 2010 preliminary diagnostic criteria for fibromyalgia also proposed by ACR. The mean age of the patients was 51.5 year old (range, 13~81). All patients were assessed and diagnosed by experienced rheumatologists with necessary laboratory and imaging examinations, and any presence or absence of psychiatric disorders were also assessed by an experienced psychiatrist. Neurotropin was firstly introduced as monotherapy with the mean daily dosage of 15 Neurotropin unit. When the efficacy was insufficient after 1 month intake of Neurotropin, other neuro-modulating medications such as selective serotonin reuptake inhibitors (SSRI), serotonin-noradrenaline reuptake inhibitor (SNRI), tricyclic anti-depressants (TCA) and clonazepam were added. Intravenous tramadol was administered only when pain relief by above drugs were insufficient. The degree of pain was assessed by 10cm VAS scale (0, no pain; 10, the worst pain that the patient had ever experienced), and the efficacy was rated as "good", 50% or greater improvement in VAS scale at the final evaluation; "fair", 20%–50% improvement; and "poor", less than 20% improvement or worsening. Correlation between the dosage of Neurotropin and outcome was studied by Spearman's rank correlation test.

Results: After 1 month of Neurotropin intake, 23 patients expected to continue it as monotherapy but remaining 90 patients needed additional medications. Among 23 patients with monotherapy, the efficacy was "good" in 14 patients, "fair" in 6, and "poor" in 3. In the remaining 90 patients, the concomitant drugs were SSRI in 18 patients, SNRI in 4, TCA in 37 and clonazepam in 31. Then, only when these combined therapy of oral neuro-modulating drugs failed, intravenous tramadol was administered in 16 patients. Finally, the overall efficacy of Neurotropin was rated as "good" in 63 patients, "fair" in 39, and "poor" in 11, and its dosage and outcome demonstrated significant correlation either in total ($p=0.0416$), or in monotherapy ($p=0.0073$).

Conclusion: Neurotropin, a novel neuro-modulating drug which activates the descending inhibitory system from brain to peripheral nerve, was effective for the treatment of fibromyalgia and chronic pain.

Disclosure: K. Miki, None; **R. Hashimoto**, None; **K. Shi**, None; **M. Yukioka**, None.

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Safety and Efficacy Of Influenza Vaccination In Patients Suffering From Fibromyalgia. Jacob N. Ablin[1], Valerie Aloush[1], Ayelet Brill[2], Mark Berman[1], Merav Barzilai[1], Dan Caspi[1], Michal Mandelboim[3], David Levartovsky[4], Ari Polachek[5], Yonatan Wolman[1], Daphna Paran[6], Michael Barkagan[1] and Ori Elkayam[2]. [1]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [2]Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [3]Sheba Medical Center, Ramat Gan, Israel, [4]Tel Aviv Medical Ctr, Tel Aviv, Israel, [5]Tel Aviv Medical Center, Tel Aviv, Israel, [6]Tel Aviv Sourasky Medical Ctr, Tel-Aviv university, Tel Aviv, Israel.

Background/Purpose: Fibromyalgia syndrome (FMS) is considered to result from exposure of a genetically susceptible individual to various "triggers" including physical trauma, stress etc. Viral infections have also been linked to FMS etiology. A possible role of vaccination in FMS etiology has been raised. Gulf war syndrome, an entity with considerable clinical overlap with FMS, has been linked with exposure to multiple vaccinations. The possibility that vaccination–related adjuvants induce a multisystem disorder characterized by symptoms such as fatigue, cognitive impairment and arthralgia has also been raised. In view of this background, the aim of the current study was to evaluate the efficacy and safety of influenza vaccination in FMS patients.

Methods: Patients (19) were recruited at a specialized FMS clinic. After informed consent, patients underwent physical and dolorimetric examination and fulfillment of ACR 1990 FMS classification criteria was documented. Patients answered the Fibromyalgia Impact Questionnaire (FIQ) as well as the widespread pain index (WPI) and Symptoms severity scale (SSS) - components of the 2010 diagnostic criteria. 38 Healthy subjects were recruited as controls. All participants were vaccinated with inactivated split virion influenza vaccine, recommended by the WHO and serum was collected for antibody titer determination.

Six weeks after vaccination, patients were re-evaluated. Sera were tested by Haemagglutination (HI) against the three antigens included in the vaccine: A/California (H1N1), A/Perth (H3N2) and B/Brisbane. Humoral response was defined as either a fourfold or more rise in titer, or a rise from a non-protective baseline level of <1/40 to 1/40. Geometric mean titers of antibodies were calculated.

Results: No severe vaccination reactions were observed. As shown in the table, no significant change was observed between WPI, SSS and FIQ values before and after vaccination, indicating no worsening of FMS symptoms.

FMS patients (n=19)	Pre-Vaccination	Post-vaccination	P value
WPI (SD)	13.3 (4.7)	11 (5.4)	0.19
SSS (SD)	9.1 (1.6)	9.0 (2.7)	0.88
FIQ (SD)	67.3 (14.2)	65.9 (22.0)	0.82

Vaccine immunogenicity: Six weeks after vaccination, FMS patients displayed significant increases in geometric mean titers of HI antibody against H1N1 and B/Bri viruses: from 29.9 to 387.9 ($p=0.0011$), from 82.9 to 460.9 ($p=0.0007$) and from 28.8 to 96.0 ($p=0.08$) respectively. The rates of sero-protection (defined as antibody levels above 1/40) increased from 22.9% for H1N1 to 89.5% post vaccination. Significant increase in HI antibody titers were also demonstrated among healthy controls: H1N1 ($p=0.000435$), B/Bri ($p=0.000331$) and Perth ($p=0.004953$).

Conclusion: Influenza vaccination was both safe and effective in FMS patients. Neither severe adverse reactions nor significant worsening of FMS symptoms were recorded following vaccination and serological evidence of sero-conversion was observed, similar to healthy controls. In view of these results, FMS patients should be encouraged to undergo influenza vaccination according to standard WHO recommendations.

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IgG Autoantibodies Against p29ING4 In Early-Stage Type I Complex Regional Pain Syndrome (CRPS) and In Other Inflammatory Diseases Involving The Joints. Niklas T. Baerlecken[1], Torsten Witte[2], Reinhold E. Schmidt[1], Christina Lansche[1], Michael Bernateck[3] and Nils Pursche[3]. [1]Medical University Hannover, Hannover, Germany, [2]Medical University Hannover, Hanover, Germany, [3]Medical University of Hannover, Hannover, Germany.

Background/Purpose: Complex regional pain syndrome (CRPS, a.k.a. RSD) usually occurs after limb injury, especially fractures of the distal radius and elective hand surgery. Recent research has shown that some patients respond to treatment with immunglobulins supporting an autoimmune pathogenesis of CRPS. There are, however, no diagnostic markers of CRPS.

Methods: We screened both sera of patients with early-stage type I CRPS and spondyloarthritis (SpA), rheumatoid arthritis (RA), granulomatosis with polyangitis (GPA) for new autoantibodies by using a protein array. Protein-array Human Fetal Brain Cat. Lib. No. 888 was obtained from imagenes biolifesciences (Berlin, Germany,).

In order to study larger numbers of serum samples, we then established ELISA prototypes using the recombinant p29ING4 protein and the synthetic peptides with aminoacid sequence MAAGMYLEHYLDSIENLPFELQRN and DKHIRRLDTDLARFEADLKEK of p29ING4. For the evaluation of the autoantibodies, we used sera of 36 patients with early-stage type 1 CRPS before starting standard-treatment with glucocorticoids, and as controls of patients with SpA (n=50), RA (n=38), GPA (n=40), and blood donors (BD)(n=96).

Results:

	CRPS	SpA	RA	GPA	BD
recombinant p29ING4	39%	32%	21%	8%	2%
Aa1-23	28%	28%	45%	5%	2%
Aa94-114	42%	36%	8%	3%	2%
Combining all antigens	75%	62%	53%	8%	7%

Conclusion: IgG autoantibodies binding to p29ING4 are most frequently in early-stage type I CRPS compared to SpA, RA, GPA and BD supporting the autoimmune pathogenesis of CRPS.

Our findings could help both in the differential diagnosis of different kinds of arthritis and might be an interesting diagnostic marker of CRPS.

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Relationship Between Body Mass Index, Fat Mass and Muscle Mass Withmusculoskeletal Pain In Community Residents. Young-Il Seo[1], Hyun Ah Kim[2], Nam H. Cho[3] and Jong Jin Yoo[4]. [1]Hallym university sacred heart hospital, Kyunggi, South Korea, [2]Hallym University Sacred Heart Hospital, Kyunggi, South Korea, [3]Ajou University School of medicine, Suwon, South Korea, [4]Armed Forces Capital Hospital Seongnam Republic of Korea, Seongnam si, South Korea.

Background/Purpose: The association between parameters related to obesity like fat mass, fat/muscle mass ratio and metabolic syndrome and musculoskeletal pain has scarcily been assessed. The objective of the present study was to evaluate the relationship between fat mass, muscle mass, fat/muscle mass ratio and metabolic syndrome and musculoskeletal pain including widespread pain in community residents.

Methods: In the Korean Health and Genome Study, 1530 participants completed pain questionnaire and underwent dual x-ray absorptiometry calculating body composition. Widespread pain was defined as pain above the waist, below the waist, on both sides of the body and in the axial region. Three other categories of pain in these analyses were pain in two or more regions that did not meet the criteria for widespread pain, pain in one region, and no pain. Metabolically obese normal weight (MONW) was defined as the presence of more than 3 features of metabolic syndrome and normal BMI. Tests for a linear trend across categories of pain constellations were performed using Mantel-Haenszel chi-square tests for categorical variables and the F-statistics from linear regression models for continuous variables.

Results: BMI, fat mass, muscle mass and fat mass/muscle mass ratio were significantly correlated with pain categories, however, the correlation was only significant among women. The presence of widespread pain was significantly associated with BMI, fat mass and fat/muscle mass ratio after multivariate analysis, however, the association was significant only among women. The prevalence of MONW was 16.4% (12.7% in men, 19.4% in women). Compared to non-obese subjects without metabolic syndrome features, widespread pain was more common in subjects with MONW subjects.

Conclusion: Fat mass, fat/muscle mass ratio and metabolic syndrome as well as BMI was significantly correlated with musculoskeletal pain.

Disclosure: Y. I. Seo, None; **H. A. Kim**, None; **N. H. Cho**, None; **J. J. Yoo**, None.

1101

Neuromuscular Taping On Patients With Fibromyalgia May Be a Useful Tool To Relief Muscular Pain. Camillo Giacomelli, Antonino Santagati, Arianna Consensi, Alessandra Rossi, Stefano Bombardieri and Laura Bazzichi. Rheumatology Unit, Pisa, Italy.

Background/Purpose: Fibromyalgia (FMS) is an illness characterized by an anomalous perception of the painful stimuli that are supposed to be attributable to a combination of interactions among neurotransmitters, nociceptive routes, individual psychological characteristics, hormones and the nervous system. Moreover the FM patients frequently showed a muscular stiffness. The use of an elastic tape, neuro muscular Tape, in medicine practice has recently gained popularity and may help improve postural control deficits and pain relief in several conditions. The purpose of this study was to examine the immediate effects of neuro muscular Taping on pain and functionality in FM patients.

Methods: We enroll 40 FM patients, all female, mean age 49.80 $\pm$ 13.79 yrs. A specialist in neuro muscular tape applications, applied the tape on superior fibers of the trapezius, and after 1 hour we evaluate by a goniometer the inclination and rotation of the neck and by a VAS scale, the pain related to the neck. We excluded the patients with a clinical condition that could interfere with measurement, such as cervical hernia or traumatic neck condition.

Results: We found a significative reduction in neck pain after the tape application ($p<0.001$). Moreover we observe that degree rotation (left and right) and lateral inclination in FM patients had increase after the tape application. In table 1 we summarize the significant results of the application of the tape. Any correlation between age and clinical parameters were found. In any case we observed a local reaction.

Table 1. clinical data of FM patients

	Before tape application	After tape application	p value
VAS pain	7.050 ± 1.825	3.850±1.494	<0.0001
Right rotation (Degree)	43,28 ± 12,43	57,38 ± 10,23	<0.001
Left rotation (Degree)	44,83 ± 11,44	57,80 ± 9,608	<0.001
Right inclination (Degree)	14,10 ± 5.55	19,80 ± 5.94	<0.001
Left inclination (Degree)	13,38 ± 5.66	19,95 ± 6.013	<0.001

Conclusion: The neuromuscular taping is a non-invasive technique that require a specific skills to obtain satisfactory results. Moreover the application of Neuro muscular taping is generally well tolerated by the patients, and the local reaction is very rare. This is a preliminary work that underline the beneficial effects of neuro muscular tape application in FM patients. The improvement of local pain could be associated to a reduction of muscular stiffness, which leads to an increase of motility. The limit of the study was the absence of the control group, for example a placebo group. We actually conducted a study with a prolonged observation and with a control group.

Disclosure: C. Giacomelli, None; **A. Santagati**, None; **A. Consensi**, None; **A. Rossi**, None; **S. Bombardieri**, None; **L. Bazzichi**, None.

1102

The Correlation Among Macromastia, Spinal Pain, Thoracic Kyphosis and Fall Risk. Ulku Akarirmak[1], Hidayet Sari[1], Murat Uludag[1], Sibel Ozbayrak[1], Hasan Battal[1], Hasan Huseyin Gokpinar[1] and Sukru Aras[2]. [1]Istanbul University Cerrahpasa Medical School, Istanbul, Turkey, [2]Private Capa Hospital, Istanbul, Turkey.

Background/Purpose: Large breasts are commonly associated with musculoskeletal symptoms such as neck, shoulder, and back pain, as well as stiff neck, painful brasserie strap grooving, and intertrigo in the inframammary folds. We aimed to show if there is any correlation among size of breasts, spinal pain, thoracic kyphosis (Cobb) angle and fall risk in a group of women with macromastia.

Methods: Seventy women diagnosed with macromastia included to the study. The complaints, physical examination findings and radiographyc thoracic kyphosis angle were recorded. The "Tetrax Interactive Posturography and Balance System" (Tetrax System, Ramat Gan, Israel) was used for assessment of fall risk.

Results: The mean age of patients was 43.6 ± 11.8 (21–66), and body mass index (BMI) was 30.9 ± 5.1. All patients had painful brasserie strap grooving, and persistent intertrigo in the inframammary folds. The rate of back, neck, shoulder and low back pain were 91.4%, 52.8%, 44.5%, 27.2%, respectively. Duration of musculoskeletal pain was 8.4 ± 5.7 years (1–23). The mean thoracic kyphosis (Cobb) angle was 40.6 ± 12.1 (range, 17–64). In the present study, it was found a very strong correlation between the breast size and BMI (r:0.780, p=0.0001). There was also a moderate correlation between breast size and posturographyc falling index (r:0.300, p=0.048).

Conclusion: Macromastia might be also associated with increased thoracic kyphosis and fall risk as well as musculoskeletal symptoms such as neck, back and shoulder pain.

Disclosure: U. Akarirmak, None; **H. Sari**, None; **M. Uludag**, None; **S. Ozbayrak**, None; **H. Battal**, None; **H. H. Gokpinar**, None; **S. Aras**, None.

1103

Brain Derived Neurotrophic Factor Is Elevated In Patients With Rheumatoid Arthritis and Secondary Fibromyalgia. Able Lawrence, Venkatesh Pai, Rajni Srivastava, Vikas Agarwal, Ramnath Misra and Amita Aggarwal. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background/Purpose: Secondary Fibromyalgia is seen in 15% of patients with rheumatoid arthritis (RA). Neurotrophins are elevated in patients with active arthritis and BDNF is elevated in primary Fibromyalgia. We did a cross sectional and longitudinal study to evaluate the association of FMS and tender points with RA disease activity, depression and neurotrophins in patients with RA.

Methods: Female patients of RA with and without Fibromyalgia (ACR 1990 criteria) were recruited. RA disease activity was assessed by DAS28-3v, depression by BPHQ and health related quality of life by WHO HRQoL Bref. Plasma neurotrophins NGF, BDNF, NT3 and NT4 were tested by ELISA. Longitudinal analysis was done using linear mixed model analysis using a fixed effects model adjusting for covariates.

Results: We recruited 40 female patients with RA and secondary FMS and 43 with RA and no FMS. Mean age was 42.2 yrs (20– 66), duration of RA 5.9 yrs (0.6– 22) and mean age of onset was 36.4 yrs (16–59). Of these 38 patients had two or more visits and 14 had 3 visits. At baseline, patients with FMS had more depression by BPHQ (12.8 vs 8) and tender points (14.8 vs 3.4) compared to those without FMS while HAQ, DAS28, age and ESR were similar.

FMS status, DAS28-3v, swollen joints, and HAQ-DI were independent predictors of fibromyalgia tender points with standardized regression coefficients of 0.75 (p<0.001), 0.13 (p<0.05), 0.16 (p<0.005) and 0.14 (p<0.05) respectively. Quality of life was significantly decreased in physical, psychological, social and environmental domains in patients with fibromyalgia even after controlling for disease activity, HAQ-DI and depression with mean differences of 5.71 (p<0.001), 6.06 (p<0.001), 9.19 (p<0.001) and 2.99 (p<0.001) respectively.

At baseline patients with RA and FMS had higher mean BDNF (49.8 +/− 18.2 ng/ml) compared those without FMS (41.5 +/− 17.5; p<0.05). On multivariate analysis, the estimated means were 54.5 ng/ml (SE 2.1) and 43.5 ng/ml(SE 2.3) respectively with p<0.001 and. NGF, NT3 and NT4 were detectable in 3, 14 and 4 patients at baseline.

Conclusion: Rheumatoid arthritis disease activity and disability influences the severity of fibromyalgia. BDNF is elevated in secondary FMS associated with RA. Elevated BDNF may be contributing to FMS in RA patients.

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1104

Quality Of Life and Burden Of Ehlers-Danlos Syndrome (EDS) Type III. Marion Geoffroy[1], Christelle Guillaume[1], Amélie Servettaz[1], Violaine Laurant-Noel[1], Christine Serratrice Sr.[2], Jacques Serratrice[3], Boris Bienvenu[4] and Roland Jaussaud[1]. [1]Hôpital Robert Debré. CHU de Reims, Reims, France, [2]Foundation Hopital Saint Joseph, Marseille, France, [3]Hôpital de la Timone, Marseille, France, [4]Division of Internal Medicine, Centre Hospitalier Régional Universitaire de Caen, Côte de Nacre, Caen, France, Caen, France.

Background/Purpose: The Ehlers-Danlos syndrome (EDS) is a clinically and genetically heterogeneous group of inherited connective tissue disorders. Hypermobility type EDS is the most common type of EDS, although commonly misdiagnosed variant of EDS. It is also the most difficult type to diagnose due to the lack of specific diagnostic laboratory tests. This type is characterized by marked joint instability, mild cutaneous involvement, chronic pain, fatigue, gastrointestinal, pelvic, neurologic and cognitive dysfunctions. The burden of delayed diagnosis and misdiagnosis, the severity of symptoms may contribute to explain.

Methods: A questionnaire study was performed among 43 Hypermobility type EDS patients followed beetwen January and June 2013 in our center. Diagnosis was established on both the Villefranche and Brighton criteria. The following dimensions were assessed: fatigue (Fatigue severity scale, FFS), pain (visual analog scale VAS), anxiety (Hamilton score), depression (Beck depression inventory, BDI-II). Quality of life (QoL) was assessed through the French version of Short Form 36 (SF36).

Results: Thirty five females (81%) and 8 males (19%) were included during the study period (January to June 2013). All patients had an hypermobility assessed by a Beighton score > 5. The mean age of EDS patients was 41 years. The mean age at onset was 18 years. 84% had a fatigue score ≥ 6 (FFS) and 17% reached the maximal score of 7. Of the patients included, 43 (100%) reported having pain. The mean VAS score was 67 mm. Pain was most frequently localized in neck, shoulder, hips, and forearms, and legs. 90 % of patients reported myalgia in trunk, arms and legs. Headhache, abdominal, thoracic and pelvic pains were also frequently reported (> 50%). All the patients reported anxiety. 92 % suffered from major anxiety. Depression affected 54% of patients and a quarter presented a severe depression as depicted by the BDI-II (score ≥ 27). A marked deterioration of QoL was observed in all SF36 domains.

Conclusion: Hypermobile EDS patients are characterized by fatigue, musculoskeletal pain, anxiety and depression. All of these symptoms are major determinant of disability, which significantly influences the

quality of life. Treatment of pain and fatigue should be a prominent aspect of clinical management of EDS in association with rehabilitation therapies.

Disclosure: M. Geoffroy, None; **C. Guillaume**, None; **A. Servettaz**, None; **V. Laurant-Noel**, None; **C. Serratrice Sr.**, None; **J. Serratrice**, None; **B. Bienvenu**, None; **R. Jaussaud**, None.

1105

New and Not Improved? The Efficacy Of FMS Medications. Robert S. Katz[1], Hannah Bond[2], Lauren Kwan[2], Jessica L. Polyak[2] and Susan Shott[3]. [1]Rush Medical College, Chicago, IL, [2]Rheumatology Associates, Chicago, IL, [3]Rush University Medical Center, Chicago, IL.

Background/Purpose: A wide variety of medications are used to treat FMS, with an equally wide variety of opinions about their efficacy. We asked FMS patients which medications they had tried for treating their disease, and how effective these medications were.

Methods: 150 office patients with FMS (130 women and 20 men; mean age 51 + 12) completed a questionnaire about the FMS medications they had taken and the effectiveness of these medications (rated as 1 = not helpful, 2 = mildly helpful, 3 = moderately helpful, and 4 = very helpful). The two-sided Friedman test was used to compare pairs of medications with respect to the ratings given by patients who had tried both medications, using a 0.05 significance level.

Results: The following medications were tried by at least 40% of patients: NSAIDs (93%), prednisone (72%), Flexeril (64%), amitriptyline (64%), Norco/Vicodin (56%), Tramadol (50%), Lyrica (47%), Cymbalta (45%), and Ritalin (44%). The two least frequently tried medications were Vyvanse (9%) and nortriptyline (12%). Based on the percentage of patients who rated the medication as moderately or very helpful, the most helpful medications were Norco/Vicodin (75%), prednisone (70%), Ritalin (65%), Tizanidine (58%), NSAIDs (56%), phentermine (56%), amitriptyline (52%), Tramadol (50%), and Nuvigil/Provgil (50%). The least helpful medications were Savella (12%) and Lunesta (19%). Norco/Vicodin was significantly more helpful than Lyrica (median 4 vs. 1, $p < 0.001$), Cymbalta (median 4 vs. 1, $p < 0.001$), Flexeril (median 4 vs. 2, $p < 0.001$), Tramadol (median 4 vs. 2, $p < 0.001$), prednisone (median 4 vs. 3, $p = 0.004$), NSAIDS (median 3.5 vs. 2, $p = 0.001$), and amitriptyline (median 4 vs. 3, $p = 0.041$). Prednisone was significantly more helpful than Cymbalta (median 3 vs. 1, $p < 0.001$), Lyrica (median 3 vs. 1, $p = 0.019$), Flexeril (median 3 vs. 2, $p = 0.028$), and Tramadol (median 3 vs. 2, $p = 0.009$). Tramadol was significantly more helpful than Cymbalta (median 2 vs. 1, $p = 0.018$). Ritalin was significantly more helpful than Lyrica (median 3 vs. 1, $p = 0.008$), Cymbalta (median 3 vs. 1, $p = 0.003$), NSAIDs (median 3 vs. 2, $p = 0.028$), and Flexeril (median 3 vs. 2, $p = 0.034$). NSAIDs were significantly more helpful than Cymbalta (median 2 vs. 1, $p = 0.001$) and Lyrica (median 2 vs. 1, $p = 0.020$). Amitriptyline was significantly more helpful than Cymbalta (median 2 vs. 1, $p = 0.005$) and Lyrica (median 2 vs. 1, $p = 0.033$).

Conclusion: Older medications were significantly more helpful for treating FMS than some newer medications. However, a wide variety of FMS medications may still be needed because different patients often respond to different medications.

Disclosure: R. S. Katz, None; **H. Bond**, None; **L. Kwan**, None; **J. L. Polyak**, None; **S. Shott**, None.

1106

Effectiveness Of Interdisciplinary Program For Fibromyalgia. Dianne Whiting, Debbi Huskey, Emily Rosario and Samy Metyas. Casa Colina Centers for Rehabilitation, Pomona, CA.

Background/Purpose: Fibromyalgia (FM) affects 5 million Americans, and the prevalence is estimated to be 2– 6 percent in the general population. The symptoms associated with FM significantly affect patients' quality of life and can lead to extensive use of health care services. Fibromyalgia is a chronic, widespread pain condition accompanied by fatigue, tenderness, decrements in physical functioning, sleep disturbance, and disruptions in psychological and cognitive functioning (for example, memory problems, diminished mental clarity ("fibro fog"), mood disturbances, and lack of well-being). In this study we investigated the effectiveness of an interdisciplinary program for FM on overall pain and disability resulting from this syndrome.

Methods: The Fibromyalgia Management Program at Casa Colina Hospital is an eight-week outpatient program based on a wellness model designed to educate patients with FM in the self-management of health. Participants meet 3 times weekly and treatment includes pool therapy, education, relaxation, exercise, Yoga, and Tai Chi along with psychology and home management techniques. All patients enrolled in the outpatient FM program were asked to complete several outcomes at admission and discharge from the program, including the Revised Fibromyalgia Impact Questionnaire (FIQR), Tampa scale, and general questions about fatigue and pain. Questions were asked to compare the original onset of symptoms with the initial date of diagnosis.

Results: The study population consisted of 28 patients who completed the FM program. The mean age was 51 years with a range from 25 to 67 years. Using the FIQR, we found a significant reduction in the impact of fibromyalgia symptoms between admission and discharge. When patients were separated into two groups based on their initial FIQR scores we found that those with more severe involvement had more significant changes throughout the program when compared with patients with less involvement. The Tampa scale was used to assess fear of movement. While there was no overall significant change in movement-related fear avoidance patients did report a significant change in how they viewed the *impact* of pain throughout their body.

Conclusion: Taken together our findings support the efficacy of an interdisciplinary approach including exercise, education, cognitive behavioral therapy, and home management skills to improve outcomes in patients with FM. Specifically, we found the most significant changes in symptoms and impact of FM, resulting in improved daily life. Results from this study suggest the importance of establishing multidisciplinary treatment centers to deliver comprehensive primary care to people with Fibromyalgia.

Disclosure: D. Whiting, None; **D. Huskey**, None; **E. Rosario**, None; **S. Metyas**, None.

1107

A Randomized Trial Of a Physical Self-Management Program For Fibromyalgia Syndrome. Aline Ranzolin[1], Suélem S. Barros[2], Vanessa M. Fernandes[3], Eduardo A. S. Pimentel[3], Claudia Diniz L. Marques[1] and Angela Luzia B. Pinto Duarte[1]. [1]Hospital das Clínicas - Universidade Federal de Pernambuco, Recife, Brazil, [2]Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Pernambuco, Recife, Brazil, [3]Centro Universitário Maurício de Nassau, Recife, Brazil.

Background/Purpose: Fibromyalgia syndrome (FMS) is a painful disorder that interferes directly in the functional capacity and quality of life. Treatment advocates interventions in the physical, pharmacological, cognitive-behavioral and educational aspects. Scientific evidences show that physical exercises minimize pain, fatigue and muscle tension, improving levels of stress, anxiety and depression in individuals with FMS, when performed on a regular basis. Educational policies for self-management of symptoms are increasingly encouraged as complementary treatment, due to the chronicity of the clinical picture. This study was made to evaluate the effectiveness of a physical self-management program for FMS patients.

Methods: We conducted a single-blind, randomized trial of a physical self-management program for FMS patients compared with a control group. The physical self-management program consisted of sessions lasted 90 minutes each and took place once a week for 10 weeks, aiming to wellness and postural education and active stretching exercises, that were orientated to been done at home. The control group was only monitored through medical appointments, without any physical intervention. No drug changes were allowed during the study period. It was selected 45 FMS patients that were on stable treatment in the last month before the selection. It was excluded patients that were on physical therapy, in use of auxiliary resources gait and those who have autoimmune rheumatic diseases associated or relevant uncontrolled comorbidities. They were evaluated through the Fibromyalgia Impact Questionnaire (FIQ), the Pain Visual Analogue Scale (VAS pain) and the Sit and Reach Test (SRT). The number of analgesic tablets ingested was accounted during the study through diaries. The data were been compared through Student t test, Mann-Whitney test and Wilcoxon test and results are presented as significant differences with 95% confidence intervals.

Results: There was a loss of 11% of the sample (4 in experimental group and 1 in controls) and the study ended with 40 participants. The experimental group (n=19) had clinically important improvements in the levels of flexibility, VAS pain, FIQ total score and in the FIQ's issues Feel Good, VAS fatigue and VAS stiffness (table). The VAS depression in the control group (n=21) worsened significantly. The experimental group consumed less

analgesic tablets during the study period (p=0.046). There was no difference regarding non-refreshing sleep and anxiety.

Variables Experimental	Evaluation	Group Control	Group P Value	
Flexibility (cm)	Initial	18.25 ± 10.93	23.23 ± 7.24	p = 0.041†
	Final	25.74 ± 8.36	21.23 ± 7.49	
	P Value	**p = 0.001***	**p = 0.067***	
VAS pain	Initial	8.46 ± 1.11	7.70 ± 1.90	p = 0.067†
	Final	5.77 ± 2.65	7.27 ± 2.20	
	P Value	**p = 0.004 ‡**	**p = 0.347***	
Feel good	Initial	8.73 ± 1.78	8.44 ± 2.21	p = 0.743†
	Final	4.74 ± 2.66	8.10 ± 2.91	
	P Value	**p < 0.001***	**p = 0.782‡**	
VAS fatigue	Initial	9.11 ± 0.94	8.48 ± 2.46	p = 0.907†
	Final	7.68 ± 2.11	9.00 ± 1.92	
	P Value	**p = 0.006‡**	**p = 0.264***	
VAS stiffness	Initial	8.26 ± 2.33	7.71 ± 1.95	p = 0.245†
	Final	7.00 ± 2.49	7.95 ± 2.04	
	P Value	**p = 0.037***	**p = 0.554***	
VAS depression	Initial	8.74 ± 1.48	7.19 ± 3.46	p = 0.162†
	Final	7.53 ± 2.91	8.71 ± 2.03	
	P Value	**p = 0.083‡**	**p = 0.004‡**	
FIQ total score	Initial	79.17 ± 11.47	73.07 ± 16.22	p = 0.182*
	Final	64.46 ± 15.66	77.16 ± 12.70	
	P Value	**p = 0.001***	**p = 0.101***	

Conclusion: The physical self-management program significantly improved pain, fatigue, stiffness, total FIQ and flexibility in patients with FMS and could be an important complementary therapy, mainly, in a context of public medical assistance.

Disclosure: A. Ranzolin, None; **S. S. Barros**, None; **V. M. Fernandes**, None; **E. A. S. Pimentel**, None; **C. D. L. Marques**, None; **A. L. B. P. Duarte**, None.

1108

Methylphenidate Improves Concentration, Energy and Mood In Fibromyalgia. Robert S. Katz[1], Hannah Bond[2] and Frank Leavitt[3]. [1]Rush Medical College, Chicago, IL, [2]Rheumatology Associates, Chicago, IL, [3]Rush University Medical Center, Chicago, IL.

Background/Purpose: Central nervous system stimulants such as methylphenidate appear to have short term benefits for naming speed and cognitive functioning in fibromyalgia (FMS). Methylphenidate quickly allows patients with FMS to operate at a more normal pace in naming words and broadly improves cognitive functioning. The present study addresses the question of whether the benefits of methylphenidate extend to concentration, energy and feelings of well-being that are often found with treatment of ADHD.

Methods: Interference from pain on energy, mood and concentration was measured on a 10 point visual analogue scale, with endpoint of one indicating that pain does not interfere, and 10 indicating that pain completely interferes. The four measures were administered to 48 patients with FMS, before receiving methylphenidate and post methylphenidate. The FMS patients were female, met the new ACR criteria for FMS. Methylphenidate dosage was clinically determined and ranged from 10 to 60 mg. The median methylphenidate usage at retesting was 30 days.

Results: The mean age of the FMS sample was 48.3±12.3 years. Table 1 shows test performance at the pretest and posttest sessions. A repeated measures ANOVA showed significant reduction in pain interference on energy ($p<0.01$), concentration ($p<0.001$) and mood ($p<0.05$). The largest change occurred with concentration.

Conclusion: Methylphenidate, a primary treatment for attention deficit hyperactivity disorder (ADHD), was helpful in alleviating some of the problems patients with fibromyalgia have with concentration, energy and mood. The parallel treatment results underscore the possibility of a link between ADHD and fibromyalgia. In a previous investigation of linkage, adult symptoms of ADHD and FMS were found to co-occur more frequently than might be expected by chance. However, as a group, FMS patients satisfying criteria for ADHD in adulthood were not abnormally inattentive or disinhibited in childhood. The likelihood that ADHD in FMS has its onset in childhood is minimal. Energy, concentration and mood can be improved in fibromyalgia by the administration of methylphenidate.

Disclosure: R. S. Katz, None; **H. Bond**, None; **F. Leavitt**, None.

1109

Which Baseline Characteristics Influence The Response To Milnacipran In Patient With Fibromyalgia? Olivier Vitton[1], Olivier Vitton[1], Pierre Bunouf[2], Lilia Abtroun[3] and Frederic Bonfils[1]. [1]Pierre Fabre, Castres, France, [2]Pierre Fabre, Toulouse, France, [3]Ariana Pharma, Paris, France.

Background/Purpose: Milnacipran (MLN) has demonstrated its benefit in treating patients with fibromyalgia. Fibromyalgia is a persistent pain condition that aggregates numerous symptoms (pain, fatigue, sleep disturbance, quality of life impairment...). The aim of this study is to find patient baseline characteristics in fibromyalgia clinical trials that influence MLN treatment effect.

Methods: Two methods were used to address this problem: the first is knowledge-oriented and consisted of post-hoc analyses describing the relationships between the clinical outcome and baseline factors. The second is a data mining analysis which takes into consideration relationships between the outcome and the candidate influencing factors. Analysis was performed using KEM (Knowledge Management and Extraction) algorithm. Data were analyzed from phase 3 placebo-controlled clinical trials. In total, 75 variables including total scores, sub-scores and items of baseline scales and demography were selected as candidate influencing factors. Continuous variables were categorized into 3 categories defined according to the 33.3% and 66.6% percentage limits of values in the whole sample. Outcomes were the response on the composite criterion, improvement in both pain, and PGIC and on the two components separately. Treatment effect was measured using odds-ratio.

Results: More than 2500 patients were investigated from three clinical phase III clinical trials (FMS-031, MD-02 and GE-302). Different variables corresponding to potential patient profiles led to a significant increase in odds-ratio measuring the treatment effect versus placebo. For the 100mg/d dosage, 8 variables were identified which increase the odds-ratio beyond 2. The most three relevant variables are "unable to work due to FMS" OR=2.63 [2.15,3.19], "MFI-General Fatigue" OR=2.22 [1.81,2.72], and "FIQ-Physical functioning" OR=2.21 [1.80,2.70]. For the 200mg/d dosage, 18 such variables were identified. The most three relevant are "FIQ-Stiffness" OR=3.45 [2.78,4.30], "VAS-Pain(CRF)" OR=3.12 [2.50,3.90], and "FMS Duration" OR=2.99 [2.39,3.74].

For all the identified variables, the odds-ratio increase is coherent across the composite responder criterion and the two components Pain and PGIC. The identification of "fibromyalgia duration" as influencing factor in the exploratory KEM analysis was confirmed in a post-hoc analysis that compared the response rates in three subgroups: short, medium and long fibromyalgia duration. This analysis evidenced higher response rates and a higher odds-ratio in the "medium fibromyalgia duration" group. Furthermore, the "high fibromyalgia duration" group seemed to benefit more from the 200mg/d dosage.

Conclusion: KEM analysis allowed the identification of baseline characteristics associated with higher odd-ratios suggesting a greater treatment effect. Thus patient profiling can be very useful for clinicians to individualize drug therapy and advice. The coherence across the primary endpoint and its two components confirmed the robustness of the primary endpoint in the milnacipran fibromyalgia development program.

Disclosure: O. Vitton, Pierre Fabre, 3; **O. Vitton**, Pierre Fabre, 3; **P. Bunouf**, Pierre Fabre, 3; **L. Abtroun**, Ariana Pharma, 3; **F. Bonfils**, ¨ Pierre Fabre, 3.

ACR/ARHP Poster Session B
Imaging of Rheumatic Diseases II: Imaging in Spondyloarthritis and Osteoarthritis
Monday, October 28, 2013, 8:30 AM–4:00 PM

1110

Onychopathy: When Ultrasound Can Help The Dermatologist. Andrea Delle Sedie[1], Valentina Dini[2], Linda Carli[3], Sabrina Barbanera[2], Lucrezia Riente[1], Stefano Bombardieri[1] and Marco Romanelli[2]. [1]Rheumatology Unit, University of Pisa, Pisa, Italy, [2]Dermatology Unit, University of Pisa, Pisa, Italy, [3]GenOMeC PhD, University of Siena, Siena, Italy.

Background/Purpose: Nail disease represents a very important symptom in subjects with psoriasis and psoriatic arthritis (PsA). From a dermatologic perspective, onychopathy is a predictor for the development of arthritis while, for rheumatologist, it is associated with distal interphalangeal joint arthritis. Besides, it is included in the CASPAR classification criteria for PsA. Psoriatic onychopathy has recently become a new hot topic for ultrasound (US) in

rheumatology and a few authors have illustrated the most important findings. Nowadays, one of the main problems for dermatologists is the differential diagnosis between psoriatic onychopathy and onychomycosis or, in general, infective disease of the nail.

The aim of the study is to find possible differences in the US findings between onychopathy due to psoriasis and mycosis.

Methods: A group of patients referring to the Dermatology unit of our hospital, presenting onychopathy, was examined by US (Logiq9, General Electrics, USA), using a multi-frequency linear probe operating at 15 MHz. The nail to be assessed was decided by the dermatologist who also requested cultural examination when onychomycosis was suspected. The US examination, made by a rheumatologist who is well experienced in US and unaware of the diagnosis of the patient, was performed according to what was shown by Gutierrez *et al* (1). We also used the group of patients without an established diagnosis as self-controls, scanning at least one other nail apparently without any visible onychopathy. The final diagnosis was given by the dermatologist based on the results of the clinical examination and the laboratory test.

Results: 15 patients were studied (10 with an established diagnosis of psoriasis and 5 with a final diagnosis of mycosis). The results of the US examination are reported in Table I.

Table 1.

	US findings			
Diagnosis (N of nails)	**Conserved 3 lines appearance (yes/no)**	**Nail thickness (mm)**	**Nail matrix thickness (mm)**	**Power Doppler score (yes/no; mean value 0–3)**
Psoriasis (N=20)	11/9	0.56 ± 0.13	2.11 ± 0.20	15/5 (0.95)
Mycosis (N=8)	8/0	0.82 ± 0.19	3.65 ± 1.39	4/8 (0.625)
Controls (N=8)	8/0	0.65 ± 0.26	2.42 ± 1.36	1/5 (0.20)

Conclusion: As shown in the table, none of the patients with mycosis presented a change in the trilaminare pattern of the nail, which was thickened with respect to both the psoriasis and the "healthy" nail group. Both the mycosis and psoriasis group showed an increase of power Doppler signal with respect to the "healthy" control group. The striking difference between US findings in patients with psoriasis and mycosis could suggest that US examination of the nail might be an easy and rapid way to differentiate between nail involvement in psoriasis and mycosis.

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Utility Of An Ultrasound Enthesitis Score As a Complementary Diagnostic Tool To Detect Psoriatic Arthritis In Patients With Psoriasis. Tomas Cazenave, Christian A. Waimann, Gustavo Citera and Marcos G. Rosemffet. Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina.

Background/Purpose: To evaluate the prevalence of subclinical enthesopathy in psoriasis (Ps) patients compared with psoriatic arthritis (PsA) and healthy controls (HC), and to assess the utility of an ultrasound enthesitis score as a complementary diagnostic tool to detect PsA in patients with Ps.

Methods: We designed a cross-sectional study including patients with diagnosis of Ps (dermatologist criteria), PsA (CASPAR criteria) and HC. Each subject underwent clinical and ultrasonographic evaluation. Ultrasound evaluation was performed by two rheumatologists who were blind to clinical examination. Ten enthesal sites were evaluated: bilateral quadriceps tendon, proximal and distal patellar ligament, Achilles tendon and plantar aponeurosis. Ultrasonographic enthesopathy (UE) was defined as the presence of at least one of the following characteristics: thickening, erosion, enthesophytes and/or bursitis. The Glasgow Ultrasound Enthesitis Scoring System (GUESS) was calculated, with ranged from 0 to 36, being 36 the highest involvement. The performance of the score to discriminate between PsA and Ps was evaluated using ROC's curve. An alternative model was tested, evaluating the addition of Power Doppler (PD) assessment to the GUESS. Differences among groups were compared using Pearson's chi-squared test and Kruskal Wallis. Post hoc analysis was adjusted by Bonferroni method. P value of 0.05 was considered statistically significant.

Results: We included 51 subjects: PsA=16, Ps=15 and HC=20. Mean age was 42±13 years and 39% were female. Mean cutaneous and joint disease duration were 17±13 and 5±7 years, respectively. Half of PsA patients presented clinical enthesopathy compared with none in the other groups. A total of 510 enthesal sites were evaluated (PsA=160, Ps=150, HC=200). UE was present in 291 (57%) sites versus only 13 (3%) using clinical examination. Ps patients showed UE in 98 (65%) enthesal sites. Tendon's thickening was present in 25%, enthesophytes 43%, Bursitis 5%, Erosion 9% and Power Doppler 7%. All patients with Ps showed at least one enthesal site affected on ultrasound evaluation. None of these sites were positive on clinical examination. When comparing with PsA and HC, Ps patients showed significantly less thickning and enthesophytes than PsA, and a significantly higher frequency of enthesophytes, erosions and PD than HC. Mean GUESS score were different across the groups: PsA= 13±4, Ps=8±4, HC=3±2 ($p<0.01$). The area under the curve (AUC) for the diagnosis of PsA was 0.79 (95%CI= 0.63 to 0.95). A cutoff point >=8 showed a sensitivity and specificity of 94% and 60%, respectively [Likelihood ratio (LR) + 2.34; LR-0.1]. The addition of PD did not have a significant impact on the discriminant ability of the score (AUC 0.78, 95%CI= 0.62 to 0.95).

Conclusion: All patients with psoriasis showed subclinical enthesopathy on ultrasonographic evaluation. The GUESS showed a high sensitivity and moderate specificity to discriminate between patients with PsA and Ps. This score may be useful as a complementary diagnostic test for early detection of joint and enthesal involvement in patients with psoriasis.

Disclosure: T. Cazenave, None; **C. A. Waimann**, None; **G. Citera**, None; **M. G. Rosemffet**, None.

1112

Examining Phenotypes Of Patients With Psoriasis In The Prepare Study For Similarities Between Diagnosed Psoriatic Arthritis and Those With Signs Of Subclinical Psoriatic Arthritis Detected By Imaging. Philip J. Mease[1], Javier Coindreau[2], Lotus Mallbris[2], Annette Szumski[2] and Heather Jones[2]. [1]Swedish Medical Center and University of Washington, Seattle, WA, [2]Pfizer Inc., Collegeville, PA.

Background/Purpose: Progression of psoriatic arthritis (PsA) has traditionally been evaluated using clinical assessments. However, a strong relationship between clinical and radiological outcomes has been shown, as radiological changes often precede clinical damage detection. Our post-hoc analysis examines the characteristics of plaque psoriasis (Ps) patients without diagnosed PsA, but with imaging evidence of damage (possible early signs of PsA). The objective was to determine whether these patients have a phenotype more similar to patients diagnosed with PsA than to patients confirmed non-PsA who exhibit no evidence of damage.

Methods: In the PREPARE study, all subjects were initially seen by a dermatologist and assessed for Ps. Subjects determined to have Ps, regardless of severity, were randomized to receive one of three PsA screening questionnaires. Following questionnaire completion, patients were evaluated by rheumatologists to establish or exclude a clinical diagnosis of PsA based on the subject's medical history and physical examination. Designated site imaging assessments (magnetic resonance imaging [MRI] and ultrasound) were performed in a subset of subjects to confirm the absence or presence of abnormalities. Continuous parameters were analyzed using one-way ANOVA while categorical parameters were analyzed using chi-square tests.

Results: In these analyses, 285 patients were diagnosed with PsA and 115 were determined not to have PsA (non-PsA) by clinical assessment. Baseline demographic and disease characteristics of non-PsA patients ± imaging abnormalities were similar to one another and tended to be different to those of PsA patients. At baseline, PsA patients were significantly older, with a higher proportion of whites, higher DAS28 and had more swollen/tender joints, higher ESR, worse HAQ, longer Ps duration and worse EQ-5D than non-PsA patients either ± imaging abnormalities (Table). For most radiological measures the proportions of patients with abnormalities were similar between PsA and non-PsA groups, with the exception of dactylitis (Table). Of the imaged patients, PsA patients have a significantly greater likelihood of dactylitis than non-PsA patients (44.3% vs 9.2%; OR=7.81; P<0.0001), while the association was more muted (90.9% vs 79.1%;OR=2.65; P=0.0301) when combining all imaging abnormalities in the 'any abnormality' group.

Baseline Demographics and Disease Characteristics

Characteristic	Non-PsA + imaging result for "any abnormality" n=91	Non-PsA – imaging result for "any abnormality" n=24	PsA n=285	*P*-value†
Age, years	47.5	46.6	51.5	0.014
Race, white (%)	87.9	91.7	97.2	0.007
Duration Ps, years	16.5	17.1	21.7	0.011
DAS28	2.1	2.1	3.3	<0.001
Swollen joint count	0.03	0.08	2.7	<0.001
Tender joint count	1.5	1.2	5.0	<0.001
Erythrocyte sedimentation rate (ESR)	10.1	11.8	15.5	0.009
Health assessment questionnaire disability index (HAQ)	0.3	0.3	0.7	<0.001
EuroQol-5 dimensions utility score (EQ5D)	0.8	0.8	0.7	0.003

Radiological measure	Patients with imaging abnormalities PsA (%)	Non-PsA (%)
Any abnormality¶	90.9	79.1*
Enthesitis (Ultrasound)	70.1	61.1
Abnormality of foot joint (Ultrasound)	5.3	2.7
Abnormality of hand joint (Ultrasound)	5.3	0.9
Abnormality of sacroiliac joint (MRI)	61.3	54.0
Abnormality of spine (MRI)	50.7	45.0
Dactylitis‡ (Ultrasound)	44.3	9.2**

*P<0.05, **P<0.0001 vs patients with PsA, †Overall P-value indicates whether at least one of the three groups are statistically different.
‡*The number of subjects with ultrasound imaging of dactylitis (n=126) was smaller than other imaging studies (n=172–188) because at 2 sites dactylitis imaging was performed only in those with a suspected problem. This may have introduced some bias in the ultrasound evaluation and analyses of dactylitis.*
¶Combines the data of patients with any of the abnormalities listed in the table.

Conclusion: A higher proportion of patients diagnosed with PsA had subclinical imaging abnormalities than non-PsA patients. Radiological detection of 'any abnormality' confirmed a significant difference in the extent of joint abnormalities in diagnosed PsA patients to those with imaging detected subclinical joint damage. The baseline results indicate a phenotypic difference between PsA patients and non-PsA patients, but a lack of distinction between non-PsA patients with and without imaging detected abnormalities.

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1113

Scintigraphic Detection Of TNFα With a Radiolabeled Anti-TNFα In Patients With Active Peripheral Spondyloarthritis and Rheumatoid Arthritis. Philippe Carron[1], Bieke Lambert[2], Filip De Vos[3], Gust Verbruggen[1], Dirk Elewaut[1] and Filip van Den Bosch[1]. [1]Department of Rheumatology Ghent University Hospital, Ghent, Belgium, [2]Department of Nuclear Medicine Ghent University Hospital, Ghent, Belgium, [3]Department of Radiopharmacy Ghent University, Ghent, Belgium.

Background/Purpose: Spondyloarthritis (SpA) and rheumatoid arthritis (RA) are the most common chronic inflammatory joint diseases, with a combined prevalence close to 2%. The pathogenetic role of proinflammatory cytokines such as tumor necrosis factor alpha (TNFα) is now beyond question, with immunohistological studies showing the cytokine and its receptors to be present in inflamed synovial tissue. Nevertheless, there is a large variability in the level of TNFα expression, which may have clinical consequences, since it has been recognized that a subset of patients do not respond to TNFα antagonism. Accurate information on TNFα expression in the joints might be helpful to optimise and/or monitor the effect of TNFα blockade. Scintigraphy with 99mTc-radiolabelled anti-TNFα monoclonal antibodies may offer an exciting possibility for identifying TNF driven disease and predict anti TNF responders in SpA and RA patients in a non-invasive way.

Objectives: To evaluate the concordance between uptake of Tc99m-labeled certolizumab pegol and peripheral arthritis/dactylitis as assessed by clinical examination and ultrasound (greyscale (GS), power Doppler (PD)) in patients with active RA and peripheral SpA (pSpA).

Methods: Certolizumab pegol was conjugated with succinimylhydrazinicotinamide (S-HYNIC) and subsequently radiolabeled with Tc99m: patients were injected with 740 MBq, and whole body images and static images of hands and feet were acquired immediately following administration, after 4–6 hours and 24 hours post injection. Prior to the immunoscintigraphy, patients underwent a full rheumatological examination (68-joint count, dactylitis assessment), as well as a targeted ultrasound assessment. Ultrasound and immunoscintigraphic findings were scored semiquantitatively (0: normal, 1: mild, 2: moderate, 3: severe).

Results: Six patients were included (RA n=3, pSpA n=3). In most of the clinically involved joints of hands and feet a marked tracer uptake was visualized within minutes following injection, with the evaluation 4–6 hours post-injection, yielding the best discriminatory results. In peripheral SpA patients with dactylitis a typical scintigraphic pattern was observed with tracer uptake in both the joints and the accompanying flexor tendon. Concordance results per patient are shown in table 1. Overall, a concordance of approx. 90% was found for ultrasound and swollen joint count.

Table 1.

Patient		Concordance scintigraphy vs ultrasound PD	Concordance scintigraphy vs ultrasound GS	Concordance scintigraphy vs tender joints	Concordance scintigraphy vs swollen joints
1	p SpA	91,3%	91,3%	89,1%	91,7%
2	p SpA	100%	100%	98,4%	98,8%
3	p SpA	91,5%	91,5%	87,5%	86,6%
4	RA	80,8%	80,8%	32,3%	78,3%
5	RA	89,3%	89,3%	78,1%	85,5%
6	RA	100%	80,8%	95,2%	98,4%
Overall		92,1%	88,9%	80,1%	89,9%

Conclusion: In patients with active RA or pSpA, a high concordance rate was observed between Tc99m-labeled certolizumab pegol uptake and clinically or ultrasound detected peripheral arthritis or dactylitis (the latter with a distinct scintigraphic pattern). This technique might provide a possibility to perform 'evidence-based biological therapy' by assessing in inflamed joints/tendons the local expression of a target cytokine with a radiolabeled antibody, before using the same cold antibody therapeutically.

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Entheses Ultrasound In Patients With Ankyosing Spondylitis: A Controlled Study With Healthy Subjects. Suellen Narimatsu, Andre Rosenfeld, Germana. B. Q. Estrela, Jorge E. P. Proglhof, Rita N.V. Furtado and Jamil Natour. Universidade Federal de São Paulo, São Paulo, Brazil.

Background/Purpose: Inflammation of the entheses (enthesitis) is a characteristic finding of ankylosing spondylitis (AS). Despite the growing interest in rheumatology for musculoskeletal ultrasound (US), there are not many studies evaluating the entheses in AS through the US.

The purpose of the study are: to compare US findings of entheses between AS patients and healthy subjects; to correlate US findings with clinical, functional and inflammatory aspects in patients with AS.

Methods: We conducted a cross sectional study of 50 patients with AS and 30 healthy volunteer subjects matched for age and gender. Were evaluated by US the following entheses: brachial triceps, femoris quadriceps, proximal patellar tendon, distal patellar tendon, calcaneal tendon, and plantar fascia. The clinical evaluation of patients included visual analogue scale (VAS) for pain, swollen and global health scale, calculation of BASDAI, BASFI, BASMI, HAQ-S, ASDAS-VHS and clinical enthesitis index SPARCC (Spondyloarthritis Research Consortium of Canada Enthesitis Index). The US was performed at right and left entheses of by a radiologist expert in musculoskeletal "blind" to clinical findings and based on MASEI index (Madrid Sonographic Enthesis Index) and the analysis of its sub items (bursistis, calcification, erosion, power doppler, thicknening of tendon, structural change). For evaluation was used the Esaote MyLab60 machine equipped with a linear transducer with a frequency of 6–18 MHz.

Results: Were evaluated by US 960 entheses of total sample of 63 men (78,75%) and 17 women (21,25%). The patients had mean age of 43,44 (+ 9,91) years and healthy subjects 38,7 (+8,52) years. The mean disease duration was 11,11 (+ 6,77) years. The comparison of average MASEI total score between patient and control groups (16,32 + 11,11/ 10,70 + 5,27) was not statistically different (p = 0,519). There was a statistical difference between groups for the detection of erosion (17 patients/0 healthy; p= 0,00) and power Doppler (PD) in calcaneal entheses (6 patients/0 healthy; p= 0,053) and for erosion (7/0; p=0,037) and thickening of the plantar fascia (38/9 p = 0,002); with an odds ratio of 3,47 (p = 0,03) of belonging to AS group, according to logistic regression. There was no difference between groups for ultrasound evaluation of other entheses. Correlation of entheses US findings and clinical, functional, inflammatory aspects was weak. However, the PD of the calcaneal entheses was correlated with VAS pain (0,344 p= 0,00) and VAS swollen (0,486 p = 0,00). The VAS pain and VAS for swollen of the calcaneal entheses correlated statistically (0,653 p = 0,00).

Conclusion: At ultrasound, the entheses of the feet were the only parameters able to differentiate AS patients from healthy subjects. This difference was mainly due to bone erosion in both the calcaneal entheses, as in plantar fascia. The PD on the calcaneal entheses was the only parameter on US that correlates with clinical variables.

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Prevalence Of Structural and Inflammatory Sacroiliitis, Assessed Using Computed Tomography and MR Imaging, In Inflammatory Bowel Disease: A Retrospective Study In 78 Patients. Sophie Leclerc-Jacob[1], Guillaume Lux[1], Anne Christine Rat[1], Valérie Laurent[1], Alain Blum[1], Isabelle Chary-Valckenaere[1], Laurent Peyrin-Biroulet[1] and Damien Loeuille[2]. [1]Nancy Teaching Hospital, Nancy, France, [2]CHU Brabois, Vandoeuvre les Nancy, France.

Background/Purpose: The primary objective was to assess the prevalence of structural and inflammatory sacroiliitis on computed tomography (CT) and MRI in inflammatory bowel disease (IBD). The secondary aim was to elucidate clinico-biological factors associated with the presence of sacroiliitis in patients with IBD.

Methods: This study involved 78 patients suffering from IBD who were followed in a gastroenterology department between 2004 and 2011: 61 of them with Crohn's disease (CD) (78.2%) and 17 with ulcerative colitis (UC) (21.8%). Clinico-biological, endoscopic and imaging (CT and MRI) data were collected during patient follow-up. Structural sacroiliitis was assessed from CT exams performed according to the modified New-York criteria for structural assessement. Inflammatory sacroiliitis was assessed on axial and coronal fat suppressed injected T1-weighted sequences according to ASAS (Assessment of SpondyloArthritis international Society) criteria. Both imaging modalities were scored blindly by two independent readers (a rheumatologist and a radiologist) and the diagnosis of sacroiliitis (structural and inflammatory) was established by consensus.

Results: The prevalence of structural sacroiliitis was 14.1% (n=11) and that of inflammatory sacroiliitis 15.4% (n=12). On MRI, unilateral sacroiliitis was depicted in five cases and bilateral sacroiliitis in seven. The prevalence of sacroiliitis according to both imaging modalities was 28.2% (n=22). Sacroiliac joints (SIJ) were considered normal in 71.8% (n=56). Disease duration of IBD was significantly associated with the presence of structural sacroiliitis (p=0.01) on CT and inflammatory sacroiliitis (p=0.02) on MRI. Others factors such as gender, age, type of IBD, localization of IBD, surgery history, biological inflammation, bowel disease activity and treatment were not associated with sacroiliitis.

Conclusion: Structural or inflammatory sacroiliitis was revealed by CT or MRI in 28.2% of patients suffering from IBD. These imaging methods have a complementary role in establishing a diagnosis of sacroiliitis and contributing to an earlier diagnosis of axial spondylarthritis.

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A Prospective Evaluation Of The Diagnostic Value Of Conventional Radiography, Ultrasound and MRI In Comparison To Clinical Examination For The Assessment Of Heel and Knee Enthesitis In Patients With Peripheral Spondyloarthritis and Controls. Xenofon Baraliakos[1], Uta Kiltz[2], Frank Heldmann[1], Heiner Appel[3], Friedrich Dybowski[4], Manfred Igelmann[5], Ludwig H. Kalthoff[6], Claudia Klink[7], Dietmar MJ Krause[8], Ertan Saracbasi[1], Elmar Schmitz-Bortz[9] and Jügen Braun[1]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Ruhr-University Bochum, Herne, Germany, [3]Rheumatology and Nephrology Practice, Hamm, Germany, [4]Rheumatology Practice, Herne, Germany, [5]Private Rheumatology office, Bochum, Germany, [6]Private rheumatology office, Herne, Germany, [7]Private rheumatology office, Gladbeck, Germany, [8]Internistische und rheumatologische Gemeinschaftspraxis, Gladbeck, Germany, [9]Rheumatism Practice in Hattingen, Hattingen, Germany.

Background/Purpose: Spondyloarthritides (SpA) are characterized by inflammatory and structural changes in the axial skeleton and in peripheral joints and entheses. Imaging has an essential role in the new classification criteria for axial SpA (axSpA) but not for peripheral manifestations (pSpA). This is largely due to limited knowledge about the value of imaging to detect peripheral arthritis and enthesitis in SpA and whether it differentiates SpA from other conditions (non-SpA). We evaluated the significance of imaging procedures and their influence on treatment decision in patients with peripheral involvement of the lower limbs in pSpA vs. non-SpA.

Methods: Consecutive patients with pSpA (n=30) and non-SpA (n=30), aged <45 years presenting with a painful heel or knee were examined by a rheumatologist, blinded for the patient's diagnosis, who decided on the further treatment based on the actual clinical findings. Thereafter, several imaging procedures were performed: conventional radiographs, power-doppler ultrasound (PDUS) and magnetic resonance imaging (MRI) of the painful sites. In total 105 entheses, 71 heels and 34 knees were assessed and evaluated. Finally the treatment decisions were re-evaluated.

Results: The groups were similar in mean age (37.2±6.8 years), CRP (0.6±0.9mg/dl), NRS-pain (6.1±2.1) but symptom duration (SpA: 17.2±27.5 vs. non-SpA: 4.4±4.3 months) and HLA-B27 (67% in axSpA vs. 13% in non-SpA) differed (both n<0.005). At presentation <66% of patients were taking NSAIDs, <35% DMARDs and <20% biologics. A total of 71 heels and 34 knees were examined in both groups. There were no differences in the distribution of lesions between patients with pSpA and non-SpA. Pathologic findings were discovered most frequently using MRI of the heel (85.3% of patients), while x-rays were regarded pathologic in only 16.7% of patients (p<0.05). Bone erosions in the Achilles' insertion as assessed by PDUS occurred more frequently in pSpA than in non-SpA: 48.6 vs. 23.5% (p=0.002) and the patellar tendon at the tibial tuberosity as assessed by MRI was thicker in pSpA: 38±8mm vs. 34±5mm in non-SpA (p=0.011), while inflammatory findings were seen in similar frequencies. Based on the clinical evaluation only, a change in treatment was suggested in 47% and 57% of patients with axSpA and non-SpA, respectively. Imaging (only US and MRI) contributed to

Conclusion: In symptomatic patients with knee or heel involvement, heel erosions (assessed by PDUS) and patellar tendon thickness (assessed by MRI) helped to differentiate pSpA from non-SpA patients but active enthesitis did not. Imaging of inflammation but also of chronic changes at peripheral sites contributed in addition to the clinical findings to make treatment decisions in a limited number of patients with pSpA but not with non-SpA.

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Integrated ^{18}f-Fluoride Positron Emission Tomography and Magnetic Resonance Imaging Of The Spine – a Pilot Study and Comparison Of Signals In Patients With Axial Spondyloarthritis. Xenofon Baraliakos[1], Dr. Christian Buchbender[2], Ben Ostendorf[3], Verena Hartung, MD[4], Thorsten Poeppel, MD[4] and Juergen Braun[1]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Univ. Duesseldorf, Düsseldorf, Germany, [3]Heinrich-Heine-University, Duesseldorf, Germany, [4]University Duisburg-Essen, Duisburg, Germany.

Background/Purpose: Positron emission tomography (PET) is a high sensitive nuclear imaging technique that depicts functional processes within

the body. PET scanners detect annihilation radiation from radioactive decay of a positron-emitting radionuclide labeled to a biologically active molecule (tracer) and introduced into the body. User-defined cross-sectional images of the tracer distribution can then be reconstructed from the acquired 3D data set. ^{18}F-fluoride (^{18}F) can be used for PET as a bone-seeking agent reflecting bone perfusion and remodeling. The concentration of the tracer then represents the metabolic activity and regional bone remodeling. Recently, an integrated PET/MR device was introduced with the ability to provide simultaneously acquired images that combine morphological and metabolic information. Based on our long experience with MRIs of patients with axial spondyloarthritis (axSpA) we inaugurated a pilot study with simultaneous PET/MR in order to examine whether the addition of the PET technique may provide different and additional information in comparison to MRI alone.

Methods: Eleven axSpA patients, median age 39 years, disease duration range 0.5–10 years, mean BASDAI 5.3, most of them fulfilling the NY criteria for AS, were examined by PET/3-Tesla MRI 40 minutes after injection of a mean dose of 157 MBq of ^{18}F using a integrated whole-body PET/MR scanner (Siemens Biograph mMR®). 3T-MRIs were scored blinded to patient′s clinical characteristics by two readers (1 rheumatologist and 1 radiologist/nuclear medicine specialist) using the Berlin MRI score and also by recording inflammatory lesions on a vertebral edge (VE) level. In a second step PET/MRIs were read blindly by the same readers also based on the VE involvement of individual vertebral bodies.

Results: Acquisition of whole-spine integrated ^{18}F PET/MRI scans was successful in all patients. The resulting mean effective radiation dose per patient was 3.76 mSv. Co-registration of PET/MRI fusion images was highly accurate and allowed a precise comparison of MRI and PET findings. The mean Berlin MRI score was 6.8 (range 0 – 31). In the direct comparison of the MRI and PET signal the two readers saw consistent signals in almost 90% of the sites studied. However, there were some areas where signals differed, for example within existing syndesmophytes where the PET signal was increased but conventional MRIs showed no signal of active inflammation, or the area of sternum and lateral or posterior spinal elements such as facet joints and spinous process.

Conclusion: The new technique of integrated PET/MRI provides largely similar imaging signals as conventional MRI. However, we did observe differences between the two modalities - especially in areas with less inflammatory activity where bone metabolism seemed to be active or in areas with blurred resolution on conventional MRI. More studies are needed to answer the question whether the differences between these techniques are pathogenically relevant, whether they can be reliably reproduced and quantified, and, of course, whether they are sensitive to change. Especially the possibility that PET detects osteoblastic activity in areas where no inflammatory signal is detected with MRI seems to be of interest.

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Assessment Of Structural Damage In Patients With Ankylosing Spondylitis Using 18F-Fluoride Positron Emission Tomography-Magnetic Resonance Imaging. GeunTae Kim[1], Seung-Geun Lee[2], Seong-Ho Kim[3], Joung-Wook Lee[4] and Seung-Hoon Baek[5]. [1]Kosin University College of Medicine, Busan, South Korea, [2]Divsion of Rheumatology, Department of Internal Medicine, Pusan National University School of Medicine, Pusan National University Hospital, Busan, South Korea, [3]Division of Rheumatology, Inje University College of Medicine, Haeundae Paik Hospital, Busan, South Korea, [4]Divsion of Rheumatology, Department of Internal Medicine, Busan St. Mary's Medical Center, Busan, South Korea, [5]Divsion of Rheumatology, Department of Internal Medicine, Ilsin Christian Hospital, Busan, South Korea.

Background/Purpose: 18F-fluoride uptake represents active osteoblastic bone synthesis. We explored structural damage of patients with ankylosing spondylitis (AS) using 18F-fluoride positron emission tomography (PET)-magnetic resonance imaging (MRI).

Methods: Whole spine of 6 male AS patients was examined with 18F-fluoride PET-MRI and conventional radiography. All participants were biologics naïve patients and fulfilled modified New York criteria. All images were assessed by two independent observers blinded for clinical data who recorded the presence or absence of increased 18F-fluoride uptake lesion in PET, acute (type A) and advanced (type B) corner inflammatory lesion (CIL) in MRI and syndesmophyte in conventional radiography at the anterior vertebral corners (Figure 1). Increased 18F-fluoride uptake was defined as an uptake which is greater than the uptake in the adjacent normal vertebral body. The association of increased 18F-fluoride uptake lesion with CIL and syndesmophyte was investigated by generalized linear latent mixed models analysis (GLLMM) to adjust within-patient dependence for total numbers of vertebral corners.

Results: There were 49 type A CIL (17.8%), 7 type B CIL (2.5%) and 38 increased 18F-fluoride uptake lesion (13.8%) out of 276 vertebral corners (C2 lower to SI upper) and 30 syndesmophyte (20.8%) out of 144 vertebral corners (C2 lower to T1 upper and T12 lower to SI upper). Increased 18F-fluoride uptake lesion was significantly associated with type A CIL (OR=6.9, 95% CI=3.1–15.2, p<0.001), type B CIL (OR=10.7, 95% CI=2.1–55.1, p=0.005) and syndesmpophyte (OR=55.6, 95% CI=7.3–422.3, p<0.001).

Conclusion: Our findings suggest that increased bone synthetic activity assessed by 18F-fluoride tracer uptake in the spine of AS patients can be associated with both inflammation and pre-existing new bone formation.

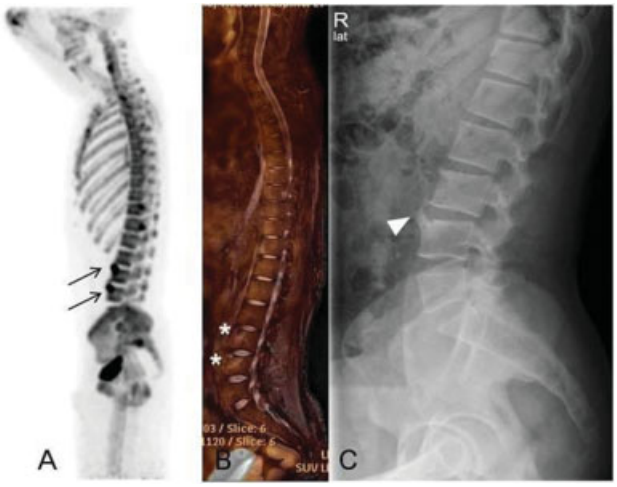

Figure 1. Forty-two-year-old male patient with ankylosing spondylitis. Increased 18F-fluoride uptake in positron emission tomography (arrows in A) and type B corner inflammatory lesion in short tau inversion recovery magnetic resonance image (asterisks in B) at L3 and 4 upper and corresponding syndesmophyte at L4 upper (arrowhead in C).

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1119

Quantification Of Inflammatory Disease Of Spine In Ankylosing Spondylitis Using Volumetric Magnetic Resonance Imaging Analysis. Ejaz Pathan[1], Adrian Lim[2], Andy Graham[3], Keshthra Satchithananda[2], Dobrina Hull[4], Sonya Abraham[5], Anshul Rastogi[6], Andrew Keat[7], Mark Hinton[8], Olga Kubassova[9], Peter C. Taylor[10] and J.V. Hajnal[11]. [1]Kennedy Institute of Rheumatology, London W6 8RF, United Kingdom, [2]Imperial College Healthcare NHS Trust, London, United Kingdom, [3]Image Analysis, London, United Kingdom, [4]The Kennedy Institute of Rheumatology, London, United Kingdom, [5]Charing Cross Hospital, Imperial college NHS trust London UK, London W6 8RF, United Kingdom, [6]Barts and the London NHS Trust, London, United Kingdom, [7]Northwick Park Hospital, Harrow, United Kingdom, [8]Image Analysis Ltd, London, United Kingdom, [9]Image Analysis Ltd., Leeds, United Kingdom, [10]University of Oxford, Oxford, United Kingdom, [11]King's College London, London, United Kingdom.

Background/Purpose: To develop methodology for quantification of spinal inflammation in AS using a volumetric MRI-based technique and to explore relationships between these findings and clinical measures of disease activity.

Methods: MRI scans were undertaken using the same scanning protocol on a 3T Philips Achieva system in 11 AS patients prior to and 12 weeks after commencing anti-TNF therapy. Scans were anonymized for patient identity and time points. They were initially scored using the Berlin method by 2 musculoskeletal radiologists (AL and KS) concurrently. Images were subsequently assessed using Dynamika software to perform volumetric analysis by 2 independent scorers (scorer 1-EP and scorer 2- AL). Areas in mm^2, volumes in mm^3 and intensity of corresponding lesions drawn by both scorers were also compared using

Bland-Altman plots. The product of volume in mm^3 and mean intensity was calculated. The volume in mm^3 of lesions was compared to total Berlin scores as well as BASDAI scores using Spearman Rank correlation. Percentage change in volume, intensity and the product of volume and intensity was also compared to percentage change in BASDAI scores.

Results: Bland-Altman plots showed good inter-observer variability for corresponding areas in mm^2, volume in mm^3 and mean intensity of lesions but compared most favourably for maximum intensity.

Correlations were observed between total volume scores and total Berlin scores, more so at baseline ($r=0.7$, $p = 0.01$ for scorer 1, $r=0.63$, $p=0.04$ for scorer 2) than at follow-up ($r=0.4$, p value $= 0.14$). No correlation was seen between volumes and BASDAI scores. However, good correlations were seen between percentage change in BASDAI and percentage change in volume in mm^3 ($r=0.8$, $p=0.002$ for scorer 1 and $r=0.6$, $p=0.04$ for scorer 2) as well as the product of volume and intensity ($r=0.7$ for both scorers, $p=0.02$ for scorer 1 and $p=0.03$ for scorer 2). A poor correlation was seen between percentage change in Berlin scores and percentage change in BASDAI ($r=0.2$, $p=0.56$).

Conclusion: Volumetric analysis of active bone oedema lesions compares well to semi-quantitative scoring using the Berlin method. Unlike semi-quantitative scoring, volumetric analysis also shows a good correlation to change in BASDAI.

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1120

Concordance Between 'a Positive MRI Of The Sacroiliac joints' Based On The Local Reading Versus a Centralised Reading: Experience From The DESIR-Cohort. Rosaline van den Berg[1], Fabrice Thévenin[2], Antoine Feydy[2], Pascal Claudepierre[3], Monique Reijnierse[1], Alain Saraux[4] and Désirée van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Paris Descartes University, Côchin Hospital, APHP, Paris, France, [3]Henri Mondor Teaching Hospital, AP-HP, Créteil, France, [4]Université Brest Occidentale, Brest, France.

Background/Purpose: Reading of MRIs of the sacroiliac joints (MRI-SI) in clinical trials is usually performed by ≥1 trained readers while in daily practice this is done by local radiologists/rheumatologists. However, this varies in cohorts and in the DEvenir des Spondylarthropathies Indifferenciées Récentes (DESIR)-cohort, MRIs-SI at inclusion were first read by the local radiologist/rheumatologist, then by central readers. The impact of reading by multiple readers in various centres as in daily practice, instead of a centralized reading, is unknown. We compared the local reading (LocR) to centralized reading (CentR) regarding the presence or absence of inflammation on MRI-SI.

Methods: The 25 participating centers included patients aged 18–50 with inflammatory back pain (IBP; ≥3 months, ≤3 years) in the DESIR-cohort (n=708). Available baseline MRIs-SI were read by local radiologists/rheumatologists with access to clinical and laboratory data, on the presence of inflammatory lesions in both SI-joints. A grade 0 corresponds to 'normal', a grade 1 to 'doubtful', and a grade 2 to 'definite inflammatory lesions'. For this analysis, a positive MRI was defined as at least one SI-joint marked grade 2. Next, 2 well-calibrated central readers independently read all MRIs-SI according to the ASAS definition[1], blinded for clinical and laboratory data. In case the readers disagreed, an experienced radiologist served as adjudicator. An MRI-SI was marked positive if 2/3 readers agreed. Agreement between the 2 central readers, between LocR and CentR and between LocR and the central readers separately was calculated (Kappa; % agreement).

Results: In this analysis patients with complete MRI-SI data (n=663) were included. Inter reader agreement between the 2 central readers is acceptable (Kappa 0.73), and the percentage agreement (87.5%) is good (table). The adjudicator scored 84/663 (12.7%) MRIs-SI because of disagreement between the 2 central readers. Comparison between CentR (2/3) and LocR shows the same levels of agreement (kappa 0.70, % agreement 86.6%; table). In 38/663 patients (5.7%), the MRI-SI was positive by LocR but negative by CentR; in 51 patients (7.7%) it was the other way around. There was no difference in agreement between LocR and CentR if MRIs-SI were scored by local rheumatologists or by local radiologists (data not shown). Comparisons of LocR versus the separate readers show very similar results (table).

		Central reader 2	
Central reader 1			
	MRI-SI+ (ASAS)	**MRI-SI+ (ASAS)**	**MRI-SI− (ASAS)**
	MRI-SI+ (ASAS)	200	56
	MRI-SI− (ASAS)	28	380
	Kappa (95% CI)/Agreement (%)	0.73 (0.67–0.78)	87.5
		Centralized reading (2/3)	
Local reading		**MRI-SI+ (ASAS)**	**MRI-SI− (ASAS)**
	MRI-SI+	185	38
	MRI-SI −	51	389
	Kappa (95% CI)/Agreement (%)	0.70 (0.65–0.76)	86.6
		Central reader 1	
Local reading		**MRI-SI+ (ASAS)**	**MRI-SI− (ASAS)**
	MRI-SI+	180	43
	MRI-SI −	76	364
	Kappa (95% CI)/Agreement (%)	0.61 (0.55–0.67)	82.1
		Central reader 2	
Local reading		**MRI-SI+ (ASAS)**	**MRI-SI− (ASAS)**
	MRI-SI+	177	46
	MRI-SI −	51	389
	Kappa (95% CI)/Agreement (%)	0.67 (0.62–0.73)	85.4

Conclusion: Both inter reader agreement between the 2 central readers and agreement between the local and centralized readings is acceptable to good. This indicates that local rheumatologists/radiologists perform as good as trained readers in identifying inflammation on MRI-SI in patients with recent onset IBP, thereby suggesting that MRI-SI is a reliable assessment in diagnosing and classifying the majority of patients with spondyloarthritis.

References:
[1]Rudwaleit ARD 2009;68:1520–7

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1121

Volatility Of The Site and Type Of Lesions In The Spine In Patients With Recent Onset Spondyloarthritis and Possible Spondyloarthritis Over a 3-Month Period. Rosaline van den Berg[1], Manouk de Hooge[1], Victoria Navarro-Compán[1], Monique Reijnierse[1], Floris van Gaalen[1], Karen Fagerli[2], Robert Landewé[3], Maikel van Oosterhout[4], Roberta Ramonda[5], Tom Huizinga[1] and Désirée van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [4]GHZ Hospital, Gouda, Netherlands, [5]University of Padova, Padova, Italy.

Background/Purpose: Inflammatory lesions on MRI of the sacroiliac joints show volatility over a short period of 3 months in patients with recent onset axial spondyloarthritis (axSpA)[1]. We investigated whether the site and/or type of lesions in the spine change over a 3-month period in patients with recent onset axSpA and possible axSpA.

Methods: 158 patients with back pain (≥3 months, ≤2 years, onset <45 years) included in the SPondyloArthritis Caught Early (SPACE)-cohort from the 5 participating centers underwent MRI of the spine (MRI-spine) at baseline and after 3 months. MRIs-spine were scored by 2 readers independently, blinded for the time sequence. Presence of corner inflammatory lesions (CIL; type A and B) and fatty lesions (FL) were scored[2,3]. Scores of both time points were compared on the vertebral unit level (VU; 23 per patient) for inflammatory lesions and on the quadrant level (4 per VU) for all lesions. Quadrants were summed (14536 in total) to study (changes in) the number, site and type of lesions. All possible changes were studied for each reader separately.

Results: On the VU level, reader 1 scored no CIL at both time points in 98/158 patients (62.0%). In 16.5% of the patients the number of inflamed VUs increased over 3 months (mean 1.7 SD 1.3; range 1–4); in 21.5% the number decreased (mean −2.1 SD 1.6; range −7 to −1). The upper 9 VUs were almost never affected. On the quadrant level, no CIL and FL were scored at both time points in 68/158 (43.7%) patients. In 18 patients, lesions (in 9 patients CIL; in 6 patients FL; in 3 patients both CIL and FL) did not change over time (mean 1.9 SD 1.7; range 1–8). In 72/158 patients (45.6%) site and type of lesions changed over time; in 18/72 purely occurrence of lesions (any type) was seen (mean 1.7 SD 0.8; range 1–3) and in 19/72 purely resolving of lesions (any type) was seen (mean −2.2 SD 1.8; range −8 to −1). Within the remaining 35/72 patients, various types of changes were seen (e.g. occurrence of CIL in a quadrant and disappearance of FL in another quadrant etc; mean number of changed quadrants 6.7 SD 5.1; range 1–22) as well as lesions that remained stable. Remarkably, more FL occurred in

quadrants without previous CIL (46 FL; in 23 patients) than in quadrants with previous CIL (14 FL; in 7 patients), and 118 FL (whether or not surrounded by CIL) resolved over time (in 48 patients) (table). The results of reader 2 are very similar to reader 1 (table).

			3 months				
	Reader 1/reader 2	No lesions	CIL type A	CIL type B	FL	CIL type A & FL	CIL type B & FL
Baseline	No lesions	14013/14024	57/46	4/4	46/54	1/2	0/2
	CIL type A	4/1	48/43	3/3	12/14	2/2	5/1
	CIL type B	12/5	4/5	3/3	2/2	0/1	1/1
	FL	53/58	5/3	2/1	157/167	4/5	0/1
	CIL type A & FL	64/50	2/2	1/0	7/10	2/9	0/0
	CIL type B & FL	1/2	1/0	2/0	8/5	3/4	7/6

FL; fatty lesion. CIL; corner inflammatory lesion

Conclusion: Almost half of the patients (45.6%) showed changes in site and/or type of lesions in the spine over a 3-month period only. Noteworthy, FL occurred more frequently de novo than in quadrants with previous CIL. Furthermore, FL can resolve over time, also when surrouneded by inflammation. The value of FLs in the spine need to be re-evaluated.

References:
[1]de Hooge ARD 2012;71(Suppl3):301 [2]Lambert J Rheumatol 2009;36 Suppl 84:3–17 [3]Østergaard J Rheumatol 2009;36 Suppl 84:18–34

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1122

How Reliable Is The Scoring Of Msasss In Clinical Practice In Centers Participating In DESIR? Comparison With The Gold Standard Central Reading. Pascal Claudepierre[1], Manouk de Hooge[2], Antoine Feydy[3], Monique Reijnierse[2], Alain Saraux[4], Maxime Dougados[5] and Désirée van der Heijde[2]. [1]Henri Mondor Teaching Hospital, AP-HP, Créteil, France, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Paris Descartes University, Côchin Hospital, APHP, Paris, France, [4]CHU de la Cavale Blanche, Brest Cedex, France, [5]Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France.

Background/Purpose: Spinal X-rays are considered as gold standard for assessing structural damage in the spine in AS, and a scoring system, the modified Stoke Ankylosing Spondylitis *Spinal* Score (mSASSS) is the preferred assessment method. In clinical studies and therapeutic trials, the mSASSS scoring process is usually done by ≥1 trained readers. In daily practice, the ability of rheumatologists and radiologists to adequately use the mSASSS without a specific training is unknown. In addition, it is not known what the impact would be in studies when using the score of multiple readers in various centres as in daily practice, instead of using a centralized scoring with a few trained readers. Therefore we want to compare the results of the mSASSS of the local reading of baseline spinal X-Rays to the centralized reading as the gold standard.

Methods: Patients aged 18–50 with recent chronic back pain (≥3 months, ≤3 years) from 25 participating centers in France were included in the DESIR (Devenir des Spondylarthropathies Indifferenciées Récentes) -cohort (n=708). All available baseline X-rays of cervical and lumbar spine were scored by the local radiologist/rheumatologist who might have access to clinical data, according to the mSASSS scoring method. In addition, 2 well-calibrated centralized readers independently scored the same X-rays, blinded for any other data. In case the centralized readers disagreed, an experienced radiologist served as adjudicator. Agreement between the 2 centralized readers, and between the local and centralized scores was calculated (Kappa; percentage agreement). To calculate the agreement between readers a cut-off of <1 for mSASSS was used. When comparing centralized readers with local readers the mSASSS of the centralized readers was combined.

Results: Patients with complete X- ray data (n=664) were included in these analyses. The large majority of patients had a normal mSASSS both scored by the central and local readers. The agreement between the 2 centralized readers was 89.3% with a kappa of 0.50 (see table). Comparing the local readings with the centralized scores there was an agreement in 72.2% of the cases with a kappa of 0.19. The local readers scored an mSASSS ≥1 in 169 cases, while this was in 119 cases if scored by central readers.

		Reader 2	
Reader 1		mSASSS≥1	mSASSS<1
	mSASSS ≥1	45	29
	mSASSS <1	42	548
	Kappa = 0.50/Agreement = 89.3%		
		Centralized score (2/3)	
Local score		mSASSS≥1	mSASSS<1
	mSASSS ≥1	52	117
	mSASSS <1	67	427
	Kappa = 0.19/Agreement = 72.2%		

Conclusion: The agreement between two trained central readers is better than between central and local readers. Local readers overestimate damage in the spine in comparison to the gold standard of central reading.

Disclosure: P. Claudepierre, None; **M. de Hooge**, None; **A. Feydy**, None; **M. Reijnierse**, None; **A. Saraux**, None; **M. Dougados**, None; **D. van der Heijde**, None.

1123

Comparison Of The Performance Of The BASRI and Msasss In Patients With Early Inflammatory Back Pain From The DESIR Cohort. Manouk de Hooge[1], Pascal Claudepierre[2], Antoine Feydy[3], Monique Reijnierse[1], Alain Saraux[4], Maxime Dougados[5] and Désirée van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Henri Mondor Teaching Hospital, AP-HP, Créteil, France, [3]Paris Descartes University, Côchin Hospital, APHP, Paris, France, [4]CHU de la Cavale Blanche, Brest Cedex, France, [5]Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France.

Background/Purpose: For assessing structural damage in AS on spinal X-rays the Bath Ankylosing Spondylitis Radiology Index (BASRI) and modified Stoke Ankylosing Spondylitis *Spinal* Score (mSASSS) scoring systems can be used. No comparison of the results of those 2 scores is available at an early stage of the disease. The purpose of this study is to present the prevalence of abnormalities based on the BASRI and mSASSS in patients with recent inflammatory back pain (IBP) and to compare these 2 scores.

Methods: Patients aged 18–50 with recent IBP (≥3 months, ≤3 years) from 25 participating centres in France were included in the DESIR (Devenir des Spondylarthropathies Indifferenciées Récentes)-cohort (n=708). All available baseline spinal X-rays (cervical and lumbar) were scored by 2 well-calibrated central readers independently, blinded for clinical data. When readers disagreed, an experienced radiologist served as adjudicator. BASRI and mSASSS were calculated from the mean of the scores of the 2 readers (and adjudicator if applicable).

Patients were classified according to the ASAS axial SpondyloArthritis (ASAS axSpA) criteria into patients fulfilling the imaging arm, either fulfilling or not fulfilling the modified New York (mNY) criteria, fulfilling the clinical arm and not fulfilling (no-axSpA patients) the criteria.

Results: Patients with complete X-ray data (n=637) were included in these analyses. Overall, 87.8% of the patients had no definite abnormalities assessed by mSASSS <2, and 88.5% by BASRI <2 (see table); those values were 88.5% and 89.0% within the ASAS axSpA patient group, respectively. A BASRI of ≥2 was scored more frequently in the imaging arm compared to the clinical arm of the ASAS criteria and the no-axSpA patient group (table). When comparing mSASSS and BASRI readings, using a cut-off of ≥2 (definite abnormalities) for both scoring methods, we found a very high percentage of agreement in all the different patient groups: range 95.4% to 98.2%.

Only in few patients syndesmophytes were found, and these were present in all patients groups (see table). More syndesmophytes were present in the cervical spine than in the lumbar spine. The number of syndesmophytes in the cervical vs the lumbar spine was 6 vs 3 in the no-axSpA group, 6 vs 1 in the clinical arm, 5 vs 1 in the imaging mNY-group, and 8 vs 1 in the imaging mNY+ group.

	ASAS axSpA, n=453			
	Imaging arm			
	mNY+ n=135	mNY− n=119	Clinical arm n=199	No-SpA, n=184
mSASSS <2	123 (91.9%)	100 (84.0%)	178 (89.4%)	158 (85.9%)
mSASSS ≥2 & <5	4 (3.0%)	8 (6.7%)	9 (4.5%)	7 (3.8%)
mSASSS ≥5 & <10	3 (2.2%)	2 (1.7%)	1 (0.5%)	0
mSASSS ≥10 & ≤15	1 (0.7%)	0	2 (1.0%)	3 (1.6%)
Total BASRI <2	117 (86.7%)	104 (87.4%)	182 (91.5%)	161 (87.5%)
Total BASRI = 2	10 (7.4%)	4 (3.4%)	7 (3.5%)	5 (2.7%)
Total BASRI = 3	2 (1.5%)	2 (1.7%)	0	1 (0.5%)
Total BASRI = 4	2 (1.5%)	0	1 (0.5%)	0
Total BASRI = 5	0	0	0	1 (0.5%)
No syndesmophytes	125 (92.6%)	105 (88.2%)	182 (91.5%)	161 (87.5%)
≥1 & <5 syndesmophytes	6 (4.4%)	3 (2.5%)	8 (4.0%)	5 (2.7%)
≥5 & <10 syndesmophytes	0	2 (1.7%)	0	2 (1.1%)
Missings	4 (3.0%)	9 (7.6%)	9 (4.5%)	16 (8.7%)

Conclusion: The agreement between mSASSS and BASRI ≥2 is very high in all patient groups. Abnormalities typical for AS such as syndesmophytes are generally infrequent in this early cohort, but if observed, syndesmophytes are more frequent in the cervical spine compared to the lumbar spine. An mSASSS and BASRI of ≥2 is more often seen in patients fulfilling the ASAS classification criteria compared to no-SpA patients.

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Lumbar Degenerative Changes In The Spondyloartritis Caught Early Cohort. F. de Bruin[1], S. ter Horst[1], Karen Fagerli[2], R. Landewe[3], M. van Oosterhout[4], J.L Bloem[5], D. van der Heijde[5] and M. Reijnierse[5]. [1]LUMC, Leiden, Netherlands, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [4]Groene Hartziekenhuis, Gouda, Netherlands, [5]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: The early diagnosis of axial spondyloarthritis (axSpA) is difficult, however new classification criteria are available, the ASAS axSpA criteria. The SPondyloArthritis Caught Early (SPACE) cohort, back pain ≥ 3 months, ≤ 2 years, onset < 45 years, was set up to diagnose SpA early. In addition to SpA associated features on MRI and conventional radiographs, degenerative changes of the spine might be clinically important. Therefore we describe the prevalence of lumbar degenerative changes in axSpA patients (ASAS+) and no-axSpA patients (ASAS-).

Methods: In 276 patients (pts) 1.5T T1 and STIR MRI and in 257 pts lateral radiography images of the lumbar spine and antero-posterior radiographs of the pelvis were available. Two readers scored for: disc degeneration (5 point scale of Pfirrmann), High intensity zone, bulging (extrusion and protrusion), herniation (central and lateral), Modic changes (3 point scale) and Schmorl's nodes on MRI and loss of disc height, facet joint osteoarthrose (FJOA), osteophytes, sclerosis, Schmorl's nodes, and sacralization on radiography. Kappa was calculated for inter rater agreement. Chi-square test was used to test for differences between pts groups.

Results: Table 1 lists the number of patients from the whole cohort with none, one or multiple lesions.

	0	Number of lesions 1	≥2
Pfirrmann*	143 (51,8%)	64 (23,2%)	69 (25%)
HIZ	86 (31,2%)	89 (32,2%)	101 (36,6%)
Extrusion	218 (79,0%)	46 (16,7%)	12 (4,3%)
Protrusion	170 (61,6%)	70 (25,4%)	37 (13,4%)
Stenosis central	274 (99,3%)	2 (0,7%)	0 ()
Stenosis lateral	262 (94,9%)	14 (5,1%)	0 ()
Modic	237 (85,9%)	35 (12,7%)	4 (1,4%)
Schmorl	111 (40,2%)	34 (12,3%)	131 (47,5%)
Loss of Disc Height	200 (66,9%)	53 (17,7%)	46 (15,4%)
FJOA	277 (92,6%)	21 (7,0%)	1 (0,3%)
Osteophytes	227 (75,9%)	49 (16,4%)	15 (5,0%)
Schmorl node	275 (92,0%)	13 (4,3%)	9 (3,0%)
Sclerosis	257 (86,0%)	34 (11,4%)	6 (2,0%)
LSTV	213 (71,2%)	86 (28,8%)	NA

On MRI, 133 pts (48%) had lower signal intensity of at least one (lumbar) intervertebral disc with or without loss of height (Pfirrmann class 3). No difference between ASAS+ (47/112, 42%) and ASAS- (86/163, 53%) pts was found (P=.078). Modic changes were seen in 39 pts (14%) and was statistically significant more present in ASAS- pts (29 vs 10, P=.038).

On X-ray, loss of disc height was found in 59 pts (23%), in 40 ASAS- pts and in 19 ASAS+ pts (P=.047). Osteophytes were present in 48 pts (19%, 13 ASAS+ and 35 ASAS-) and statistically significant more in ASAS- pts (P=.028).

Conclusion: Pts have a high prevalence of degenerative changes. Nearly half of all pts have dehydrated intervertebral discs, a smaller proportion has loss of height on both MRI and conventional images. ASAS- pts have a higher prevalence of Modic changes, loss of disc height and osteophytes than ASAS+ pts. Prevalence of Modic changes was higher than reported in literature. The high prevalence of degenerative changes in ASAS- pts might be an explanation for the back pain, although clinical correlation is required.

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Fatigue In Ankylosing Spondylitis Is Associated With The Brain Networks Of Sensory Salience and Attention. Robert Inman[1], Q. Wu[2] and Karen Davis[2]. [1]University of Toronto and Toronto Western Hospital, Toronto, ON, [2]Toronto Western Research Institute, Toronto, ON.

Background/Purpose: Fatigue is one of the cardinal features of ankylosing spondylitis (AS) and contributes substantially to the disability associated with this disease. The mechanisms underlying fatigue in AS remain poorly understood, and this has hampered the development of targeted, effective treatment for this disabling feature of AS. Thus, the current study investigated brain networks underlying fatigue.

Methods: Twenty patients with back pain secondary to AS (15M/5F; age 34.8 +/− 11.9 yr) and 20 age/sex-matched controls consented to the approved study. Patients underwent clinical assessments for AS including the Fatigue Severity Scale, Affect Intensity Measure and the McGill Pain Questionnaire. 3T MRI was performed to assess brain gray matter (GM) and white matter (WM) connectivity.

Results: The AS patients had significant fatigue that correlated with measures of their emotional strength as well as spinal mobility. Individual fatigue scores were negatively correlated with the amount of GM in areas of the dorsal and ventral attention networks, the somatosensory cortices, and caudate nucleus, but were positively correlated with GM within the executive control network and putamen (Table 1). Moreover, WM tracts connecting these brain structures (e.g., inferior fronto-occipital fasciculi, superior/inferior longitudinal fasciculi, and corticothalamic tracts) exhibited low fractional anisotropy (indicative of decreased WM tract integrity) in AS patients with high fatigue scores.

Table 1.

Fatigue Severity Score (FSS) associated cortical and subcortical regions in AS

Region	BA	MNI of peak in mm x	y	z	*T*-value	Size (voxel)	Correlation with FSS (partial r/ *P*-value)	Cortical thickness (mm) AS	HC	*P*-value
Cortical										
R S1	1	57	−14	38	−4.176	193	−0.79/$P < 0.0001$	2.4 ± 0.22	2.6 ± 0.03	0.018*
L S2	43	−53	−5	8	−3.448	168	−0.75/$P < 0.0001$	2.7 ± 0.18	3.1 ± 0.18	0.234
R M1	4	36	−14	55	−3.356	143	−0.75/$P < 0.0001$	2.6 ± 0.32	2.5 ± 0.11	0.117
L M1	4	−48	−8	49	−4.552	128	−0.81/$P < 0.0001$	3.1 ± 0.22	3.1 ± 0.06	0.122
R TPJ	41	49	−28	28	−4.745	126	−0.81/$P < 0.0001$	2.2 ± 0.18	2.5 ± 0.18	0.316
R IPL	7	40	−59	50	−3.265	121	−0.75/$P < 0.0001$	2.6 ± 0.24	2.9 ± 0.24	0.556
R SPL	7	12	−55	66	−3.152	103	−0.75/$P < 0.001$	2.8 ± 0.26	2.4 ± 0.26	0.509
R IPS	7	48	−33	41	−4.477	98	−0.77/$P < 0.0001$	2.2 ± 0.17	2.8 ± 0.17	0.097
L SMA	6	−13	5	64	3.752	153	0.8/$P < 0.0001$	3.1 ± 0.36	3.1 ± 0.04	0.749
R aPFC	9	15	51	26	3.418	112	0.79/$P < 0.0001$	2.8 ± 0.33	2.7 ± 0.09	0.792
L pMCC	6	−10	−18	48	2.536	92	0.69/$P = 0.002$	2.8 ± 0.29	2.9 ± 0.11	0.645
R al	NA	35	−6	5	4.317	90	0.79/$P < 0.0001$	3.6 ± 0.31	3.6 ± 0.08	0.613
				Subcortical				GM_{pt}	GM_{ctl}	*P*-value
THAL	NA	6	−24	2	3.009	1122	0.76/$P < 0.0001$	0.39 ± 0.04	0.39 ± 0.03	0.508
R CAUD	NA	8	14	−8	−3.029	292	−0.59/$P = 0.01$	0.66 ± 0.08	0.61 ± 0.06	0.046*
L CAUD	NA	−10	20	−6	−2.17	147	−0.51/$P = 0.031$	0.63 ± 0.10	0.59 ± 0.08	0.134
L PUT	NA	−30	−16	8	5.071	78	0.7/$P = 0.004$	0.23 ± 0.04	0.23 ± 0.03	0.608

Abbreviations: aI, anterior insula; aPFC, anterior prefrontal cortex; BA, Brodmann Area; CAUD, caudate; CT_{ctl}, cortical thickness in healthy subjects; CT_{pt}, cortical thickness in AS patients; GM_{ctl}, grey matter volume in healthy subjects; GM_{pt}, grey matter volume in AS patients; HC, healthy control; IPL, inferior parietal lobe; IPS, inferior parietal sulcus; M1, primary motor cortex; MNI, Montreal Neurological Institute; pMCC, posterior middle cingulate cortex; PUT, putamen; S1/S2, primary/secondary somatosensory cortex; SMA, supplemental motor area; SPL, superior parietal lobe; THAL, thalamus.

Conclusion: These data indicate that the fatigue in AS involves sensory salience and attention brain networks and suggests that effective therapies for fatigue in AS could target these pathways.

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Category: Imaging of Rheumatic Diseases

Keywords (at least three, no more than five): structural brain imaging, attention network, white matter, low back pain

Disclosure: R. Inman, None; **Q. Wu**, None; **K. Davis**, None.

1126

Opportunistic Computed Tomography Screening For Determining Osteoporosis In Patients With Ankylosing Spondylitis and Spine Fractures. Amanda Cagan[1], Osa Emohare[1], Robert Morgan[1], David Polly[2] and Elie Gertner[3]. [1]Regions Hospital, Saint Paul, MN, [2]University of Minnesota, Minneapolis, MN, [3]Regions Hospital and University of Minnesota Medical School, St. Paul, MN.

Background/Purpose: In advanced disease Ankylosing Spondylitis (AS) is frequently associated with a reduction in bone mineral density (BMD) which contributes to pain and predisposes to fractures. Quantifying this reduction in BMD is complicated because overgrowth of bone and loss of trabecular bone occur at the same time. Traditional methods, such as dual-energy X-ray absorptiometry (DXA), may not generate accurate estimates of BMD in AS patients. It has recently been shown that osteoporosis, osteopenia, and normal BMD can be differentiated by evaluating the L1 vertebra on abdominal Computed tomography (CT) scans. The aim of the present study was to evaluate the use of opportunistic CT screening in the diagnosis of osteporosis in patients with severe AS who had sustained vertebral fractures.

Methods: A retrospective study of patients with severe AS and bridging syndesmophytes who presented to our Level 1 trauma center with acute fractures of the spine (both high impact and low impact) and had an evaluable CT scan of the abdomen. Using a picture archiving and communication system (PACS), a region of interest (ROI) was generated to fit to the body of L1 (excluding the cortex) and a mean value for Hounsfield Units (HU) was computed. The values derived were compared against threshold values which differentiate between osteoporosis and osteopenia. For specificity of 90%, a threshold of 110 was set; for balanced sensitivity and specificity, a threshold of ≤135 HU was set, and for 90% sensitivity a threshold of ≤160 HU was set.

Results: A total of 17 AS patients fit the above criteria. Using an L1 CT-attenuation threshold of ≤135 HU balanced for sensitivity and specificity, 14/17 (82%) patients were found to have osteoporosis. Using an L1 CT-attenuation threshold of ≤160 HU to increase sensitivity, 15/17 patients (88%) were found to be osteoporotic. Even using the L1 CT-attenuation threshold of ≤110 HU to increase specificity 14/17 (82%) had osteoporosis.

Conclusion: A high proportion of AS patients who sustain fractures have osteoporosis as shown by using opportunistic CT screening. This overcomes some of the difficulties that have been encountered with the use of DXA in this unique group of patients. This simple and accessible diagnostic method saves on excess cost and exposure to radiation. It may also inform the surgeon in structuring surgical approach.

Disclosure: A. Cagan, None; **O. Emohare**, None; **R. Morgan**, None; **D. Polly**, None; **E. Gertner**, None.

1127

Semiquantitative MRI Features Of Knee Osteoarthritis Show Compartment-Specific Relationships With Quantitative Cartilage Thickness Loss: The Multicenter Osteoarthritis Study. Ali Guermazi[1], Felix Eckstein[2], Daichi Hayashi[3], Frank Roemer[3], Wolfgang Wirth[2], Tianzhong Yang[3], Jingbo Niu[3], Leena Sharma[4], Michael C. Nevitt[5], Cora E. Lewis[6], James Torner[7] and David T. Felson[3]. [1]Boston University, Boston, MA, [2]Paracelsus Medical University, Salzburg, Austria, [3]Boston University School of Medicine, Boston, MA, [4]Northwestern University, Chicago, IL, [5]University of California, San Francisco, San Francisco, CA, [6]University of Alabama, Birmingham, Birmingham, AL, [7]University of Iowa, Iowa City, Iowa City, IA.

Background/Purpose: Structural progression of knee OA has been associated with several radiographic and MRI-measured pathological features of OA, including malalignment, meniscal pathology and bone marrow changes but studies examining these risk factors generally examine one of them and not their constellation although these features coexist. To date no study has been done to assess if baseline MRI-based scores of various knee OA features predict progression of knee OA as determined by quantitative cartilage thickness measurement. We aimed to determine which semiquantitative MRI-based OA features were most predictive of subsequent cartilage thickness loss measured with quantitative MRI.

Methods: From the Multicenter OA Study subcohort, participants (one knee per person) who volunteered for a longitudinal substudy in which MRI measurement of cartilage thickness and volume were done were selected: These subjects also had conventional MRI's allowing Whole Organ MRI Score (WORMS) based scoring of cartilage lesions, bone marrow lesions (BML), meniscal pathology, effusion synovitis, and Hoffa synovitis at both time points. Progression in the medial or lateral femorotibial compartment (MFTC/LFTC) was defined as cartilage thickness loss exceeding the change observed in OAI control cohort knees (mean ± 2xSD, MFTC/LFTC: −162μm/−145μm). All MRI predictors were dichotomized into "present" (score≥2 for cartilage, ≥0 for others) or "absent". Differences in baseline scores of ipsi-compartmental predictor variables were compared between progressor and non-progressor knees by multivariable logistic regression, adjusting for age, sex, body mass index, and anatomical alignment axis (degrees). We combined MFTC and LFTC to calculate ajusted odds ratio (aOR) and 95% CI of ipsi-compartmental cartilage thickness loss across compartments, using Generalized Estimating Equations. Also, ORs and 95%CIs were calculated for MFTC and LFTC cartilage thickness loss, separately.

Results: 196 participants were included and their mean age was 59.8±6.3 years, mean BMI 29.5±4.6 kg/m^2, and 62% were women. 46 knees had radiographic knee OA at baseline. In the MFTC/LFTC, there were 35/29 progressors and 161/167 non-progressors. For analysis combining MFTC and LFTC, predictors of cartilage thickness loss were baseline cartilage lesions (aOR 2.6 [1.4–5.0]), BML (aOR 1.9 [1.1–3.3]), meniscal damage (aOR 4.5 [2.4–8.4]) and meniscal extrusion (aOR 3.3 [1.9–5.8]), all in the ipsilateral compartment, but not effusion synovitis or Hoffa synovitis. In MFTC-only analysis, MFTC progressors had higher aOR for having baseline medial meniscal damage (aOR 2.4, [95%CI 1.1–5.6]), medial meniscal extrusion (aOR 2.6 [1.1–5.8]), but not cartilage lesions, BML, effusion synovitis and Hoffa synovitis. In the LFTC-only analysis, baseline lateral cartilage lesions (aOR 3.4 [1.3–9.3]), lateral meniscal damage (aOR 13.9 [3.3–9.0]) and lateral meniscal extrusion (aOR5.0 [1.4–18.0]) predicted LFTC progression.

Conclusion: Amongst MRI features, the presence of cartilage lesions, BML, meniscal damage and extrusion in the ipsilateral FTC predict quantitatively assessed cartilage thickness loss over 30-months, but not effusion synovitis or Hoffa synovitis.

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1128

Validation Of a Rapid, Quantitative Method Of Magnetic Resonance Imaging-Detected Osteoarthritis-Related Bone Marrow Lesions In The Patellofemoral Joint. Charles Ratzlaff[1] and Jeffrey W. Duryea[2]. [1]Harvard Medical School/Brigham and Women's Hospital, Boston, MA, [2]Brigham & Women, Boston, MA.

Background/Purpose: We recently developed an efficient semi-automated measure of tibial and femoral BML volume and validated it against the Whole-Organ Magnetic Resonance Imaging Score (WORMS). Since patella-femoral (PFJ) osteoarthritis (OA) is increasingly being recognized as a cause of knee pain in OA, we have extended the method to the PFJ. The purpose of this study was to compare PFJ BML volumes with WORMS, and test the hypothesis that PFJ BML volume is associated with stair-climbing pain (but not walking or standing pain).

Methods: 115 subjects from the baseline data of the Osteoarthritis Initiative (OAI) Progression Cohort whose knees were WORMS-scored by OAI central imaging were included. Sagittal turbo spin echo fat saturated (TSE FS) (0.357 × 0.357 × 3.0 mm, TR 3200ms, TE 30ms) IW MRI were obtained on a 3T Siemens Trio MR system. A reader used software to segment subchondral BMLs in the patella and anterior femur (trochlea). The software applies a grayscale thresholding algorithm to the raw image and reader judgment is used to select, usually with 1 or 2 mouse clicks, the clinically appropriate region(s) of BML. Reliability on a random sample of 20 subjects was: ICC 0.96, and 0.97 for intra-and inter-reader respectively.

Primary outcome: segmented volume of BMLs (mm^3) in the patella and trochlear femoral compartment.

WORMS score: Comparison of PFJ BML volume was made with OAI public-release WORMS scoring for the patella and trochlea. WORMS reports BML in 4 categories based on size of BML relative to the total sub-region (0-no BML, 1–<25%, 2–25–50%, 3–>50%). Spearman's correlation and Kruskall-Wallis tests were used to assess association between the two methods.

Pain. We used the WOMAC pain sub-scale and defined the primary outcome of knee pain dichotomously as moderate to severe pain (scores 2–4) on any of the 3 weight-bearing (WB) WOMAC pain questions (pain on walking, climbing stairs, standing), acquired at the same baseline OAI visit as the MRI scans. Kruskall-Wallis test were used to assess the associations.

Results: The sample was 84% white, 52% male and were 90% K-L grade 2 and 3. Median BML volumes were progressively larger by WORMS category for patella (figure), trochlea and PFJ (all $p<0.001$) and strongly correlated (Spearman's r = 0.89, 0.74 and 0.81 respectively, all $p=0.000$). We found significant positive associations between stair-climbing pain and PFJ BML volume but not for other WOMAC WB pain items.

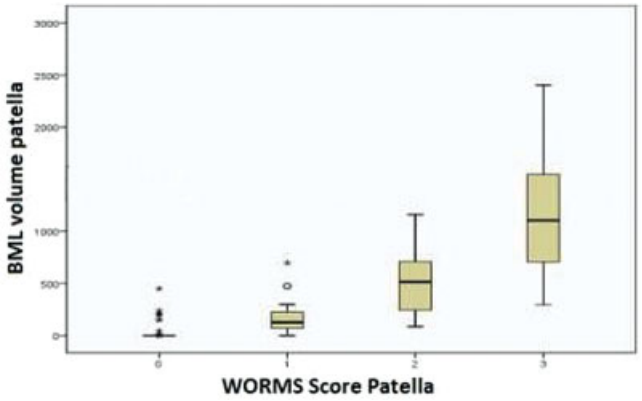

Figure. Box and whisker plots showing mean, median, lower and upper quartiles, and outliers of BML volume by WORMS scores, for patella.

BML Volume		No Stair pain (n = 58)	Stair Pain (n = 57)	p-value[1]
PFJ BML (mm3)	median	44	338	0.01
Trochlear BML (mm^3)	median	0	22	0.04
Patellar BML (mm^3)	median	0	192	0.01

Conclusion: This study reports good criterion and clinical validation of an efficient method for measuring BML in the PFJ, providing a a potentially useful tool for trials in the PFJ.

Disclosure: C. Ratzlaff, None; **J. W. Duryea**, None.

1129

Development and Validation Of a Rapid Knee Cartilage Quantification Method. Ming Zhang[1], Jeffrey B. Driban[1], Lori Lyn Price[1], Daniel Harper[1], Grace H. Lo[2], Eric Miller[3], Robert J. Ward[1] and Timothy E. McAlindon[1]. [1]Tufts Medical Center, Boston, MA, [2]Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX, [3]Tufts University, Medford, MA.

Background/Purpose: Cartilage morphometry on magnetic resonance images (MRIs) may become an acceptable outcome measure for clinical trials among patients with knee osteoarthritis (OA). However, obtaining accurate and reproducible cartilage data is burdensome. To conduct large clinical trials it will be vital to use an efficient, sensitive and reproducible method to assess cartilage morphometry. The purpose of this study was to develop and validate a rapid semi-automated method to detect cartilage loss in the medial tibiofemoral compartment.

Methods: The rapid knee cartilage quantification method was developed using 263 manually-segmented knee MRIs. We designed a pair of two dimensional, rectangular, universal coordinate systems to represent the articular surface of the distal medial femur and proximal medial tibia. Next, we projected segmented cartilage onto coordinate system and evenly selected 9 informative locations across the region most frequently denuded (Figure 1). The primary outcome is a cartilage damage index (CDI), which summates the products of cartilage thickness, cartilage length and voxel size from each informative location. To validate CDI we selected 102 subjects from Osteoarthritis Initiative with a diverse range of Kellgren-Lawrence (KL) grades (0 to 4). 3D Double-echo steady-state sagittal images were obtained on four 3-Tesla systems (0.37 mm × 0.37 mm, 0.7 mm slice thickness). One reader used customized software to measure the CDI in the medial femur and tibia from the baseline and 24-month visit. Another reader evaluated 20 subjects to establish the inter-tester reliability test.

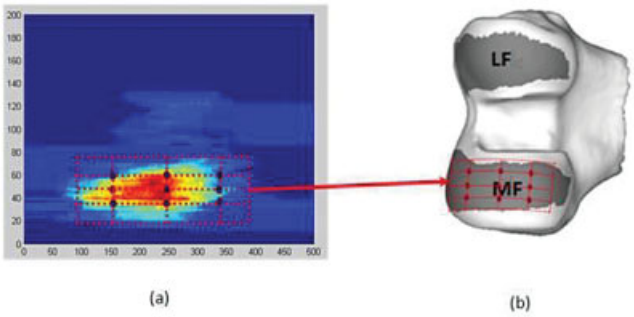

Figure 1. (a) Femur denuded projection and 9 informative locations on the coordinate system. (b) Corresponding denuded peak on the cartilage map. Note: MF = Medial Femur; LF = Lateral Femur.

Results: The average measurement time was 14 minutes per pair of knees. The intra-tester reliability (intraclass correlation coefficient ICC [3,1 model] 0.95 to 0.99) and inter-tester reliability (ICC [2,1 model] 0.85 to 0.94) were good. Knees with greater medial joint space narrowing (JSN) had lower mean CDI (i.e. greater loss, Table 1). Knees with radiographic progression (JSN grade change) had 4.5 to 22 times greater CDI loss than knees with no progression ($p < 0.0001$), Table 2.

Table 1. Cartilage damage index stratified by joint space narrowing (JSN) grade

Cartilage Measure	JSN=0 (n=43) mean	JSN=1 (n=25) mean	JSN=2 (n=26) mean	JSN=3 (n=3) mean	p-value
		Cross-sectional			
Femur CDI (Baseline)	747.95	664.55	521.57	308.95	<0.01
Tibia CDI (Baseline)	389.56	368.12	292.77	149.53	<0.01
Tibiofemoral CDI (Baseline)	1137.50	1032.70	814.34	458.48	<0.01
		Longitudinal			
Femur CDI (Change)	−2.95	−19.33	−47.15	−99.30	<0.01
Tibia CDI (Change)	−9.31	−26.25	−45.00	−43.86	<0.01
Tibiofemoral CDI (Change)	−12.26	−45.58	−92.15	−143.2	<0.01

Notes: change = follow-up minus baseline; SD = standard deviation.

Table 2. Change in cartilage damage index among knees with and without structural progression defined by change in radiographic JSN grade

Cartilage Measure	JSN change	N	Mean	SD	SRM	p-value
Femur CDI (Change)	No change	74	−3.38	47.98	−0.07	<0.0001
	Change	25	−66.17	56.76	−1.17	
Tibia CDI (Change)	No change	74	−12.85	23.38	−0.55	<0.0001
	Change	25	−55.55	39.82	−1.40	
Tibiofemoral CDI (Change)	No change	74	−16.23	56.68	−0.29	<0.0001
	Change	25	−121.70	77.17	−1.58	

Notes: JSN change, the follow-up has different JSN score with baseline; N = number of knees (the numbers were excluded JSN=3 which is the highest grade); SD = standard deviation; SRM = standard response mean.

Conclusion: This novel knee cartilage damage quantification method is rapid, reliable, and has good construct validity in the medial tibiofemoral compartment. It has utility for deployment in large epidemiological studies.

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1130

Change In Knee Osteophyte Volume By Semi-Automated Method In Knee Osteoarthritis Over Four Years Using 3T DESS 3D MRI. Michael Hakky[1], Charles Ratzlaff[2], Ali Guermazi[3], Mohamed Jarraya[4] and Jeffrey W. Duryea[5]. [1]Lahey Clinic, Burlington, MA, [2]Harvard Medical School/Brigham and Women's Hospital, Boston, MA, [3]Boston University, Boston, MA, [4]Boston University School of Medicine, Boston, MA, [5]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: The development and growth of osteophytes are considered a radiographic surrogate for osteoarthritis (OA) at the knee. Methods to determine osteophyte burden are largely semi-quantitative and subjective. Quantifying osteophyte volume could potentially provide an improved measure of change for OA trials and observational research. We have developed a software method for semi-automated osteophyte segmen-

tation on MRI. Our objective was to validate the responsiveness of this method to osteophyte volume change over four years in subjects with established knee OA according to Kellgren and Lawrence (KL) grade. We assume that OA is a progressive process, thus osteophyte burden should increase over time.

Methods: Ninety subjects (51 KL 2 and 39 KL 3) were selected from the Osteoarthritis Initiative (OAI) Progression Cohort. Double echo steady state 3D sagittal images were obtained on a 3T Siemens Trio MR system. Measurements were performed on coronal reformatted series. A reader used the software method to segment marginal osteophytes of the knee at baseline and 48-month follow up. Readings were performed paired but blinded to order of visit. The reader identified the first and last slice of the central weight bearing region and an edge detection algorithm demarcated the bone edges. The reader marked the expected normal bone contour at the base of the osteophytes (Figure 1a). The software calculated the area of the osteophyte (Figure 1b) on each slice and generated volume measurements.

The primary outcome was change in osteophyte volume (ΔV) from baseline to follow-up. Statistics used were the average change in osteophyte volume from baseline to 48 months (ΔV), the standard deviation (SD) of ΔV, the standardized response mean (SRM) ΔV/SD of ΔV, and the percentage of subjects with net increase in osteophyte burden.

Results: The average change in osteophyte volume (ΔV) was 1240 mm^3, the SD = 1557 mm^3, and the SRM was 0.80. A net increase in osteophyte volume from baseline to 48 months was observed for 83% (75/90, 40 KL 2 and 35 KL 3) of the subjects. The average reading time was approximately 10 minutes per knee.

Table 1. Responsiveness to change over 48 months

	Net Increase	Mean ΔV	SD ΔV	SRM
KL 2 + KL 3 (90)	75/90 (83%)	1240 mm^3	1557 mm^3	0.80
KL 2 (51)	40/51 (78%)	1004 mm^3	1477 mm^3	0.68
KL 3 (39)	35/39 (90%)	1549 mm^3	1624 mm^3	0.95

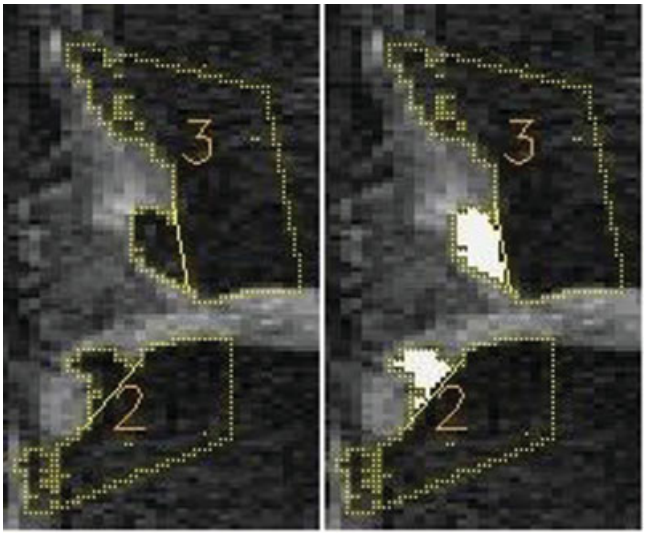

Figure 1a and b

Conclusion: The results confirm that quantitative measure of osteophyte volume can be performed efficiently and is responsive to change over time. This method has the potential be a powerful tool for monitoring longitudinal osteophyte change, and could assess a large study cohort rapidly while potentially reducing study costs and allow for evaluation of large scale trials such as the OAI.

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Disclosure: M. Hakky, None; **C. Ratzlaff**, None; **A. Guermazi**, Boston Imaging Core Lab, 1, Merck Serono, 5, Sanofi-Aventis Pharmaceutical, 5, TissueGene, 5; **M. Jarraya**, None; **J. W. Duryea**, None.

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Peri-Articular Fractal Signature Analysis and Bone Mineral Density Measure Different Aspects Of Bone: Cross-Sectional Data From The Osteoarthritis Initiative. Jeffrey B. Driban[1], Felix Liu[2], Alina O'Brien[1], Lori Lyn Price[1], Grace H. Lo[3], Michael C. Nevitt[4], Charles Eaton[5], Timothy E. McAlindon[1] and John A. Lynch[6]. [1]Tufts Medical Center, Boston, MA, [2]University of California at San Francisco, San Francisco, CA, [3]Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX, [4]University of California, San Francisco, San Francisco, CA, [5]Brown University, Providence, RI, [6]University of California-San Francisco, San Francisco, CA.

Background/Purpose: Peri-articular fractal signature analysis (FSA) and bone mineral density (paBMD) are potentially cost-effective prognostic imaging markers for osteoarthritis (OA) progression. While we know that paBMD relates to trabecular morphology, it remains unclear whether FSA, which assesses the texture of bone on radiographs, measures a similar construct of bone structure as paBMD. Understanding this association is paramount for determining if these two measurements are redundant. Therefore, we evaluated the association between FSA, paBMD, and trabecular morphology.

Methods: The sample comprised 450 participants in the Osteoarthritis Initiative (OAI) progression cohort who had weight-bearing radiographs, magnetic resonance imaging (MRI), and knee dual-energy x-ray absorptiometry (DXA) at the 48-month OAI visit. The right knee was assessed unless MRI was contraindicated. Three separate readers measured the medial proximal tibia to generate 1) paBMD on DXA, 2) fractal dimensions with FSA on digital radiographs, and 3) MRI-based apparent trabecular morphology: bone volume fraction (aBV/TV), trabecular number (aTb.Tn), spacing (aTb.Sp), and thickness (aTb.Th). Fractal dimension data in the horizontal "tension" and vertical "compression" directions were reduced into 3 piece-wise, centered linear regression from 0 to 3mm radii. We assessed univariate associations with Spearman correlations and conducted 5 robust regression models to determine the association between FSA-based data (compression and tension together; predictors) and the five other bone measures (paBMD and trabecular morphology) as outcomes. These models were adjusted for OAI clinical site.

Results: The 450 participants were 47% female, 72% radiographic knee OA in the study knee (Kellgren-Lawrence > 2), and on average 66 (SD=9) years of age with a mean body mass index of 29.6 (SD=4.7) kg/m^2. Table 1 shows that FSA-based data were not associated with paBMD. The significant associations between FSA-based data and trabecular morphology indicated that lower tension and compression gradients may be related to greater aBV/TV, aTb.Th, aTb.Tn, but lower Tb.Sp (Table 1). In the multivariate analyses we found that FSA-based compression offsets had a small relationship with paBMD (R^2 = 0.03). Furthermore, we found that lower FSA-based compression gradients were associated with greater aBV/TV (p=0.04) and aTb.Th (p=0.01) but lower aTb.Sp (p=0.01; R^2 = 0.04–0.05). Lower FSA-based tension gradients were associated with greater aTb.Th (p= 0.02) but lower aTb.Sp (p=0.04).

Cross-sectional Relationships Between Peri-articular FSA-Based Data and Other Apparent Bone Measures (n = 450 knees)

FSA-Based Data	Bone Mineral Density	Bone Volume Fraction	Trabecular Thickness	Trabecular Number	Trabecular Spacing
	r (95% CI)	r (95% CI)	r (95% CI)	r (95% CI)	r (95% CI)
Segment 1 (0 < radii ≤ 1mm)					
Compression gradient[1]	0.05 (−0.05, 0.14)	0.02 (−0.07, 0.11)	0.01 (−0.09, 0.10)	0.02 (−0.07, 0.11)	−0.01 (−0.10, 0.08)
Compression offset[2]	−0.03 (−0.12, 0.06)*	0.02 (−0.07, 0.11)	0.05 (−0.04, 0.15)	0.01 (−0.08, 0.10)	−0.01 (−0.10, 0.09)
Tension gradient[1]	−0.05 (−0.15, 0.04)	**−0.13 (−0.22, −0.04)**	−0.04 (−0.13, 0.05)	**−0.16 (−0.25, −0.07)**	**0.16 (0.06, 0.24)***
Tension offset[2]	−0.05 (−0.15, 0.04)	−0.05 (−0.14, 0.04)	−0.05 (−0.14, 0.05)	−0.05 (−0.14, 0.04)	0.05 (−0.04, 0.14)
Segment 2 (1 < radii ≤ 2mm)					
Compression gradient[1]	0.00 (−0.10, 0.09)	−0.07 (−0.16, 0.02)	−0.04 (−0.13, 0.06)	−0.08 (−0.17, 0.01)	0.07 (−0.02, 0.16)
Compression offset[2]	0.04 (−0.05, 0.13)*	0.02 (−0.07, 0.11)	0.04 (−0.05, 0.13)	0.01 (−0.08, 0.10)	−0.01 (−0.10, 0.08)
Tension gradient[1]	0.03 (−0.07, 0.12)	0.02 (−0.08, 0.11)	0.01 (−0.09, 0.10)	0.02 (−0.07, 0.11)	−0.02 (−0.11, 0.08)
Tension offset[2]	−0.01 (−0.10, 0.09)	−0.04 (−0.13, 0.05)	−0.02 (−0.11, 0.07)	−0.05 (−0.14, 0.04)	0.05 (−0.04, 0.14)
Segment 3 (2 < radii ≤ 3mm)					
Compression gradient[1]	0.01 (−0.08, 0.10)	**−0.11 (−0.20, −0.02)***	**−0.12 (−0.21, −0.03)***	**−0.10 (−0.19, −0.01)**	**0.10(0.01, 0.19)***
Compression offset[2]	0.00 (−0.10, 0.09)	−0.04 (−0.14, 0.05)	0.00 (−0.09, 0.09)	−0.06 (−0.15, 0.04)	0.06 (−0.03, 0.15)
Tension gradient[1]	0.02 (−0.07, 0.11)	−0.01 (−0.10, 0.09)	−0.09 (−0.18, 0.01)*	0.01 (−0.08, 0.10)	−0.01 (−0.11, 0.08)
Tension offset[2]	0.02 (−0.07, 0.11)	0.03 (−0.06, 0.12)	−0.06 (−0.16, 0.03)	0.04 (−0.05, 0.13)	−0.05 (−0.14, 0.05)

Note: FSA = Fractal Signature Analysis, r = Spearman rho, 95% CI = 95% confidence interval.
1 = gradients are defined as the x-coefficient in the 3 piece-wise, centered linear regressions from 0 to 3mm radii
2 = offsets are defined as the constants in the 3 piece-wise, centered linear regressions from 0 to 3mm radii
* = correlations that were significant in multivariate analyses with all of the FSA-based data included as predictors.

Conclusion: We found that lower peri-articular FSA values were not associated with paBMD but had some small associations with trabecular morphology that is typical of greater OA severity (greater aBV/TV, aTb.Th,

and aTb.N and lower aTb.Sp). This suggests that these are not redundant measures and both imaging markers warrant further evaluation.

Disclosure: J. B. Driban, None; **F. Liu**, None; **A. O'Brien**, None; **L. L. Price**, None; **G. H. Lo**, None; **M. C. Nevitt**, None; **C. Eaton**, None; **T. E. McAlindon**, NIH, 2; **J. A. Lynch**, None.

1132

Sensitivity To Change Of Radiographic Fixed-Location and Magnetic Resonance Imaging-Based Cartilage Thickness Measures In The Lateral Compartment Of Knees With Radiographic Osteoarthritis – Data From The Osteoarthritis Initiative. Wolfgang Wirth[1], Jeffrey W. Duryea[2], Michael C. Nevitt[3], Robert J. Buck[4], David Hunter[5] and Felix Eckstein[1]. [1]Paracelsus Medical University, Salzburg, Austria, [2]Brigham and Women's Hospital, Boston, MA, [3]University of California, San Francisco, San Francisco, CA, [4]StatAnswers Consulting, Minneapolis, MN, [5]Royal North Shore Hospital, St. Leonards, Australia.

Background/Purpose: Radiographic joint space width (JSW) is frequently employed to indirectly assess structural progression in the medial femorotibial compartment, but it is unclear whether assessment of the lateral compartment provides accurate results. In contrast, magnetic resonance imaging (MRI) directly delineates articular cartilage and has been employed for quantitative analyses of cartilage thickness status and progression in both the medial and the lateral compartment. In the current study, we compared the sensitivity to change between recently proposed radiographic fixed-location measures in the lateral femorotibial compartment (obtained from fixed-flexion radiography [FFR]) - vs. MRI-based cartilage thickness measures, in knees with and without lateral JSN.

Methods: One- and two-year change was assessed in one knee of 290 OAI participants with radiographic OA (210 female, age 61.8±9.1 y, BMI 29.5±4.9 kg/m^2) based on FFR and DESS (n=161) or FLASH (n=129) MRI. Of the 290 knees, 147 had definite osteophytes only and 57/78/8 had grade 1/2/3 lateral JSN. Fixed-location JSW was measured semi-automatically at 9 locations in the lateral femorotibial compartment (LFTC) between 70% (JSW(X=0.7)) and 90% (JSW(X=0.9)) of the femoral width (medial to lateral). Cartilage thickness was measured by manual segmentation in the entire LFTC and in combined external (eLFTC), central (cLFTC), and internal (iLFTC) lateral subregions. The standardized response mean (SRM=mean change/standard deviation of change) was calculated as measure of the sensitivity to change. The most sensitive MRI and FFR measures were selected for comparing the sensitivity between MRI and FFR.

Potential sample sizes for a two-arm study with an estimated treatment effect of 50 % (i.e. reduction in structural progression) was calculated using G*Power based on sensitivity results of the current study. The calculation was based on the assumption of parametric t-tests, a false positive rate of 0.05, a false negative rate of 0.2, and 15% drop-out.

Results: The greatest overall sensitivity to change in both knees without JSN and knees with lateral JSN was observed in cLFTC for MRI and in JSW(X=0.8) for FFR. In knees without JSN, the one-year SRM was relatively low in both MRI (−0.16) and FFR (−0.11). This results in required sample sizes of n=6,165 (MRI) and 11,264 (FFR). Over two years, a greater SRM was observed for both MRI (−0.30) and FFR (−0.20), reducing the required sample size to 1,626 (MRI) and 3,502 (FFR).

In knees with lateral JSN, the one-year SRM observed for MRI (−0.73) was twice that for FFR (−0.37), suggesting sample sizes of 286 (MRI) and 1048 (FFR). Over two years, the SRM for MRI was −0.86 and that for FFR was −0.64, resulting in required sample sizes of 204/364 knees, respectively.

Conclusion: The study shows that fixed location measures of lateral JSW can be used to follow structural progression in the lateral femorotibial compartment in knees with lateral JSN. However, the sensitivity to change tended to be greater for MRI than for FFR, particularly over 1 year. Treatment studies with reasonable sample sizes appear feasible when following knees with lateral JSN using MRI over one, or using FFR over two years.

Disclosure: W. Wirth, Chondrometrics GmbH, Ainring, Germany, 4, Chondrometrics GmbH, Ainring, Germany, 3; **J. W. Duryea**, None; **M. C. Nevitt**, None; **R. J. Buck**, StatAnswers Consulting, Minneapolis, MN, 4; **D. Hunter**, None; **F. Eckstein**, Chondrometrics GmbH, Ainring, Germany, 3, Chondrometrics GmbH, Ainring, Germany, 4, Abbvie, 5, MerckSerono, 5, Sanofi Aventis, 5.

1133

Sensitivity To Change Of a New Method Of Computer Measurement Of Hip Joint Space Width: Performance Of Location-Specific Measures Obtained At a 48 Month Interval. Charles Ratzlaff[1] and Jeffrey W. Duryea[2]. [1]Harvard Medical School/Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Responsive measures of radiographic joint space width (JSW) in hip osteoarthritis (OA) are a major requirement for the evaluation of treatment interventions. The primary purpose of this study was to validate a semi-automated quantitative software tool for hip JSW by measuring responsiveness at 3 different fixed locations.

Methods: We used data from the Osteoarthritis Initiative (OAI), a longitudinal cohort study of knee OA. All OAI participants had standing AP radiographs at baseline and 48 month visits using a standardized protocol.

We used a nested case-control design, and had two case definitions. First, subjects who had a total hip replacement (THR) sometime after the 48 month visit (at 60 and 72 months) and available AP pelvic films at 0 and 48 months (n=27) were selected and matched (1:1) on sex and age (2 years) to subjects without a THR and no hip pain during the study period.

Second, a larger sample of cases was selected that included all subjects who had a THR at any point after baseline and had AP pelvis films at 0 and 48 months (n=72). The *contralateral* (CL) hip from the THR was designated the case hip, and subjects were matched (1:1) as above.

Measurements of superior hip JSW were made at 3 fixed locations (10°, 30° and 50° medial to a line from the femoral head centre to the outer edge of the acetabular roof – lateral line in Figure 1) and were facilitated by software that delineated the femoral head and found the acetabular margin along each of the 3 lines. A reader used software to correct margins if needed.

Statistical analysis. Sensitivity to change was estimated by the standardized response mean for change from baseline to 48 months. Paired t-tests were used to test statistical significance between cases and controls.

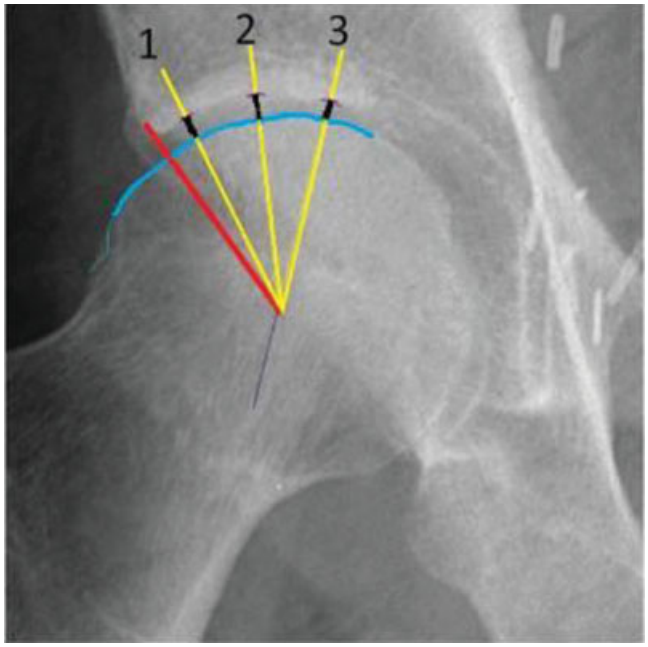
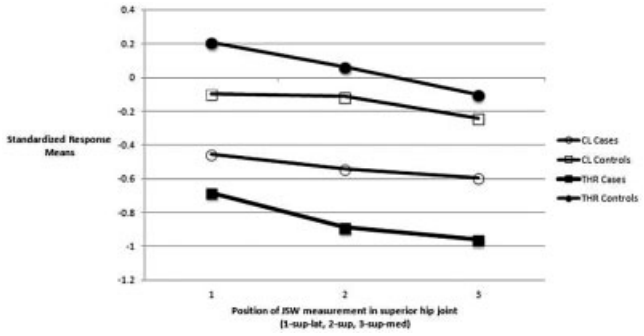


Figure 1. Example of hip JSW measurement.

Results: The overall sample was 47% male, 91% Caucasian had a mean age of 64.2 and BMI of 27.9. The results are given in Table 1 and Figure 2. Significant differences were observed between cases and controls in both case-control groups. The superior medial location (position 3) was the most responsive.

	Standardized Response Mean (baseline to 48 months)		
	Location 1 Sup-lateral (10°)	Location 2 Superior (30°)	Location 3 Sup-medial (50°)
THR Cases (n = 27)	−0.68	−0.89	−0.96
Controls (n = 27)	0.21	0.06	−0.10
p-value	0.001	0.001	0.001
Contralateral Cases (n = 72)	−0.46	−0.54	−0.59
Controls (n = 72)	−0.10	−0.11	−0.24
p-value	.002	.003	0.002



Conclusion: Location 3 (sup-med) was the most responsive in all 4 groups and warrants further study. Location specific measures of JSW are potentially an improved method to assess hip OA.

We acknowledge NIH/NIAMS R01AR056664.

Disclosure: C. Ratzlaff, None; **J. W. Duryea**, None.

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More Evidence For Breaking The 'law Of valgus': Imaging Evidence For Higher Prevalence and Volume Of Bone Marrow Lesions In The Medial Patellofemoral Joint. Charles Ratzlaff[1] and Jeffrey W. Duryea[2]. [1]Harvard Medical School/Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: We recently developed an efficient semi-automated measure of tibial and femoral BML volume and validated it against the Whole-Organ Magnetic Resonance Imaging Score (WORMS). Since patella-femoral (PFJ) osteoarthritis (OA) is increasingly being recognized as a cause of knee pain in OA, we have extended the method to the PFJ. The purpose of this study was to compare PFJ BML volumes with WORMS, and test the hypothesis that PFJ BML volume is associated with stair-climbing pain (but not walking or standing pain).

Methods: 115 subjects from the baseline data of the Osteoarthritis Initiative (OAI) Progression Cohort whose knees were WORMS-scored by OAI central imaging were included. Sagittal turbo spin echo fat saturated (TSE FS) (0.357 × 0.357 × 3.0 mm, TR 3200ms, TE 30ms) IW MRI were obtained on a 3T Siemens Trio MR system. A reader used software to segment subchondral BMLs in the patella and anterior femur (trochlea). The software applies a grayscale thresholding algorithm to the raw image and reader judgment is used to select, usually with 1 or 2 mouse clicks, the clinically appropriate region(s) of BML. Reliability on a random sample of 20 subjects was: ICC 0.96, and 0.97 for intra-and inter-reader respectively.

Primary outcome: segmented volume of BMLs (mm^3) in the patella and trochlear femoral compartment.

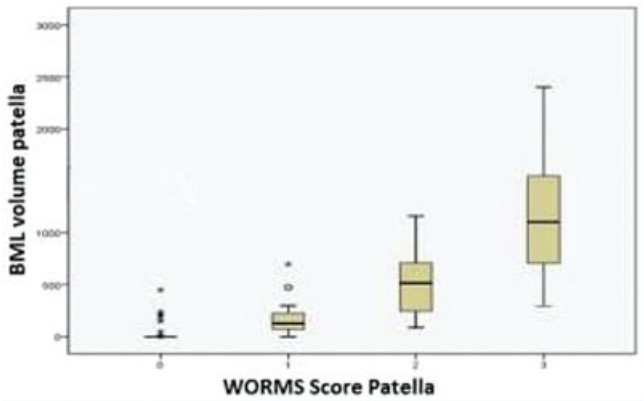

Figure. Box and whisker plots showing mean, median, lower and upper quartiles, and outliers of BML volume by WORMS scores, for patella.

BML Volume		No Stair pain (n = 58)	Stair Pain (n = 57)	p-value[1]
PFJ BML (mm^3)	median	44	338	0.01
Trochlear BML (mm^3)	median	0	22	0.04
Patellar BML (mm^3)	median	0	192	0.01

WORMS score: Comparison of PFJ BML volume was made with OAI public-release WORMS scoring for the patella and trochlea. WORMS reports BML in 4 categories based on size of BML relative to the total sub-region (0-no BML, 1-<25%, 2–25–50%, 3->50%). Spearman's correlation and Kruskall-Wallis tests were used to assess association between the two methods.

Pain. We used the WOMAC pain sub-scale and defined the primary outcome of knee pain dichotomously as moderate to severe pain (scores 2–4) on any of the 3 weight-bearing (WB) WOMAC pain questions (pain on walking, climbing stairs, standing), acquired at the same baseline OAI visit as the MRI scans. Kruskall-Wallis test were used to assess the associations.

Results: The sample was 84% white, 52% male and were 90% K-L grade 2 and 3. Median BML volumes were progressively larger by WORMS category for patella (figure), trochlea and PFJ (all $p<0.001$) and strongly correlated (Spearman's $r = 0.89$, 0.74 and 0.81 respectively, all $p=0.000$). We found significant positive associations between stair-climbing pain and PFJ BML volume but not for other WOMAC WB pain items.

Conclusion: This study reports good criterion and clinical validation of an efficient method for measuring BML in the PFJ, providing a potentially useful tool for PFJ trials.

Disclosure: C. Ratzlaff, None; **J. W. Duryea**, None.

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Synovial Fluid Vascular Endothelial Growth Factor Could Predict Progression Of Osteoarthritis According To Radiological and Ultrasonographic Findings. Sang-Heon Lee, Hae-Rim Kim and Ho-Youn Kim. Konkuk University Medical Center, Seoul, South Korea.

Background/Purpose: Vascular endothelial growth factor (VEGF) may have important contribution in the pathogenesis of knee osteoarthritis. MMP-13 is expressed by chondrocytes and synovial cells, and is thought to play a critical role in cartilage destruction. It is not certain whether VEGF correlate with the radiographic severity of knee osteoarthritis(OA). The aim of this study was to determine VEGF and MMP13 as new potential biomarkers in patients with knee OA, and their relevance for radiographic severity and ultrasonographic finding.

Methods: The study was conducted with 34 consecutive patients with clinical and radiographic evidence of knee OA with joint effusion detected clinically. The questionnaire included the duration of knee pain, 100 mm visual analog scale (VAS), and Western Ontario McMaster Universities (WOMAC) Osteoarthritis Index. All patients were examined by plain radiography on the same day as ultrasonography and arthrocetesis of knee joint were performed simultaneously. Knee radiographs were analyzed by Kellgren-Lawrence (KL) grading system. Plasma and synovial fluid (SF) VEGF and MMP 13 levels were determined by ELISA.

Results: Thirty four patients with knee OA included two men and 26 women, with a mean age of 65.5 ± 7.9 years and mean disease duration of 38.2 ± 48.9 months. Mean pain VAS was 56.8 ± 23.9 mm and total WOMAC score was 89.9 ± 42.9. Fourteen patients were categorized as grade 2 (KL 2), 16 as grade 3 (KL 3), and 4 as grade 4 (KL 4). The median value of SF VEGF were higher in KL grade 4 than those of KL grade 2 (845.0±82.3 pg/ml vs 624.6±37 pg/ml, $p=0.025$). By Spearman analysis, SF VEGF levels positively correlated with KL scores ($r=0.444$, $p=0.009$). No significant difference in SF and plasma levels of MMP-13 as well as plasma levels of VEGF were found among OA subjects with radiographic severity. We further analyzed the correlations between laboratory and ultrasonographic finding adjusted by age and BMI. The SF VEGF correlated positively with the length of the medial osteophytes ($r=0.502$, $P=0.012$), lateral osteophytes ($r=0.528$, $P=0.008$) and joint capsule distension ($r=0.423$, $p=0.048$). The SF MMP-13 did not show any correlation with ultrasonographic finding.

Conclusion: SF VEGF levels significantly increased in advanced OA according to KL scores and correlated well with ultrasonographic findings such as length of medial and lateral osteophytes and joint capsule distension.

Disclosure: S. H. Lee, None; **H. R. Kim**, None; **H. Y. Kim**, None.

1136

MR T1ρ and T2 Of Meniscus After Acute Anterior Cruciate Ligament Injuries. Elijah Abramson, Michael Hoppe, Toran MacLeod, Lorenzo Nardo, Julien Rivoire, Richard Souza, Thomas M Link, C. Benjamin Ma and Xiaojuan Li. University of California, San Francisco, San Francisco, CA.

Background/Purpose: Acute anterior cruciate ligament (ACL) injuries are high-risk factors for post-traumatic osteoarthritis. Cartilage changes in

such cases have been widely studied; however, there are fewer reports on MR quantitative evaluation of meniscus after acute ACL injuries. The goal of this study was to evaluate changes in meniscal T1ρ and T2 quantification in patients with acute ACL injuries and correlate those changes to MR clinical grading and patient-reported outcomes.

Methods: 18 control patients and 30 patients with acute ACL injuries (19 females; age = 29.9 ± 7.2 years) were studied using a 3T GE MR scanner. Injured patients were scanned post-injury and prior to ACL reconstruction (58 ± 48 days). Patients filled out the Knee Injury and Osteoarthritis Outcome Score (KOOS), a validated self-assessed questionnaire with five categories: pain, other symptoms, function in sport and recreation, function in daily living (ADL), and knee-related quality of life (QOL), on the same day of MR scan. Imaging protocol included sagittal T2-weighted 3D fast spin-echo images (CUBE) and sagittal 3D T1ρ and T2 quantification sequences. Modified whole-organ magnetic resonance imaging scores (WORMS) were determined using CUBE images. Menisci were segmented semi-automatically using CUBE images into four sub-compartments: anterior horn of the lateral/medial meniscus (AHLAT/AHMED) and the posterior horn of the lateral/medial meniscus (PHLAT/PHMED). These regions of interest (ROI) were overlaid onto T1ρ and T2 maps. Mean T1ρ and T2 values were calculated for each ROI. Paired T-tests were performed when comparing injured knees to contralateral (contra) knees; unpaired T-tests were performed when comparing injured knees to the control group; Spearman correlation coefficients were calculated between meniscal T1ρ/T2 and KOOS.

Results: Mean T2 values were significantly higher in ACL-injured knees than control group knees in the AHLAT, PHLAT, and AHMED ($P < 0.05$), but were not significant ($P = 0.06$) in the PHMED. T2 values were significantly higher in the AHLAT of ACL-injured knees than the contra knees ($P < 0.01$) but did not reach statistical significance in the PHLAT, AHMED, or PHMED ($P = 0.08$, $P = 0.11$, $P = 0.09$). ACL-injured patients with meniscal tears in the PHLAT (meniscus WORMS > 1) had significantly elevated T1ρ and T2 values ($P < 0.03$) compared to those without meniscal tears in the PHLAT. There was a significant negative correlation between KOOS and T2 ($P < 0.05$) in the PHLAT for pain, symptoms, and ADL ($\rho = -0.38, -0.48, -0.46$).

Conclusion: Quantitative MR imaging can be used to detect damage and early degeneration in meniscal matrices. This study found that acute ACL injuries led to elevated T2 values in the meniscus. We observed a significant association of meniscal degeneration to elevated T1ρ and T2 measurements in patients with acute ACL injuries in the PHLAT. There were more significantly elevated T1ρ and T2 in comparing the injured knees to control group than to contra knees. We also observed that T1ρ and T2 increased with severity of meniscal tears in acute ACL injuries. The correlation between T2 (especially in PHLAT) and KOOS suggested a relationship between meniscal damage and patient outcomes after acute injuries.

Disclosure: E. Abramson, None; **M. Hoppe**, None; **T. MacLeod**, None; **L. Nardo**, None; **J. Rivoire**, None; **R. Souza**, None; **T. M. Link**, None; **C. B. Ma**, None; **X. Li**, None.

ACR/ARHP Poster Session B
Infection Related Rheumatic Diseases
Monday, October 28, 2013, 8:30 AM–4:00 PM

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Evaluating Indeterminate Quantiferon-TB Gold In-Tube Results in Patients With Chronic Inflammatory Diseases On Immunosuppressive Therapy. Cassandra Calabrese[1], Robert A. Overman[1], Stacie Dusetzina[2] and Rula Hajj-Ali[3]. [1]Cleveland Clinic, Cleveland, OH, [2]Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Raleigh-Durham, NC, [3]Cleveland Clinic Foundation, Cleveland, OH.

Background/Purpose: The Quantiferon test (QFT) is used to for screen for tuberculosis in patients with autoinflammatory conditions (IC) prior to the use of immunosuppressant medications. Indeterminate results limit the utility of QFT and strategies are need to reduce their impact on the diagnostic progress. The aim of this study was 1) To analyze the rate of indeterminate QFT in patients with IC as compared to both the general hospital population and a healthy reference (HR) group, and 2) To analyze factors contributing to an indeterminate test result.

Methods: Adults (≥18 years) with a QFT result within the Cleveland Clinic Health System electronic medical record between 2007–2012 were included. Patients were categorized as having IC if any of the following conditions were present in the year preceding their first QFT: rheumatoid arthritis, psoriatic arthritis, systemic vasculitis, inflammatory bowel disease, inflammatory spondylarthropathy, or systemic lupus erythematous. Subjects who did not have an IC receiving their QFT at a corporate health screening center were considered the HR group of hospital employees, with all others receiving the QFT considered the general hospital population. Prevalent use of glucocorticoids (GC), biologics, or disease modifying anti-rheumatic drugs (DMARDs) or cessation within 5 days of QFT was used to evaluate the effect of these drug classes on indeterminate tests in the IC group. Binomial regression was used to estimate the risk of having an indeterminate test result, adjusting for age, gender, co-morbidities (Human immunodeficiency virus, chronic kidney disease, diabetes mellitus, chronic obstructive pulmonary disease, and asthma), and health services use in the prior year.

Results: Of the 55,132 included patients, 5.2% had inflammatory conditions and 46.6 % were employees. The mean age of patients in our sample was 40.2 years and 68.5% were female. Indeterminate tests were present in 5.3% of the IC group, 1.9% of the general hospital population, and 1.5% of the HR group. Patients with IC were 3.6 times as likely as the HR group to have indeterminate test results (adjusted risk ratio (aRR): 3.60, 95%CI: 3.00, 4.30). There was no significant difference between the general hospital population and the HR group. In adjusted models restricted to patients with IC, GC use significantly increased the likelihood of an indeterminate test (aRR:1.43, 95%CI: 1.02, 1.99) while DMARD use decreased this likelihood (aRR: 0.67, 95%CI: 0.46, 0.97) when compared to patients without medication use.

Conclusion: Patients with autoinflammatory conditions were more likely to have indeterminate QFT results as compared with a reference group of hospital employees. Among patients with IC, only prior use of GC was associated with an increase in the likelihood of having an indeterminate test result.

Disclosure: C. Calabrese, None; **R. A. Overman**, None; **S. Dusetzina**, None; **R. Hajj-Ali**, None.

1138

Tuberculin Skin Test and Booster Phenomenon In a Rheumatoid Arthritis Population. Differences Between Early and Established Disease. Lorena Perez-Barbosa[1], David Vega-Morales[2], Janett Carmen Luzmilla Riega-Torres[1], Octavio Ilizaliturri-Guerra[1] and Mario Alberto Garza-Elizondo[1]. [1]Early Arthritis Clinic, Rheumatology Service, Hospital Universitario, Monterrey, Mexico, [2]Rheumatology Service, Hospital Universitario, Monterrey, Mexico.

Background/Purpose: Tuberculosis (TB) remains a major global health problem. Chronic inflammation in Rheumatoid Arthritis (RA) and the use of immunosuppressive drugs, increase the risk of reactivation of latent TB (LTB). Although other tests are available, tuberculin skin test (TST) is widely used method which detects LTB. There are reports that the TST response is decreased in RA. TST sensitivity may be increased by a second test done 1–4 weeks after the first, referred as the "booster" phenomenon.

The purpose of our study was to evaluate the TST and booster reactivity in patients with RA divided by the time evolution.

Methods: A cross-sectional analytical study was conducted. Patients who fulfilled the RA ACR/EULAR 2010 classification were included. Five Units of PPD CT-68 were administered with the Mantoux technique. Indurations equal to or greater than 5 mm were considered positive. Patients with negative reactions were scheduled within 15 days for a booster application. We reviewed clinical records and settled a database for analysis using SPSS v. 20.

Results: We analyzed 143 patients, 126 (88.1%) were females, with a mean age of 46.9 (SD 12.8); 60 (42%) had current use of corticosteroids, with a mean dose of 7.07 mg/day (SD 3.3). One hundred patients (69.9%) had a current use of DMARDxs. The mean DAS28 was 4.5 (SD 1.9). In first TST application there were 39 patients (27.3%) with a positive test (PT). Of the negative patients, 84 (81 %) had the booster application, 9 (10.7 %) of them had a PT. On table 1 is the bivariate analysis between early RA (<52 weeks) and established RA, on table 2 for the first TST positivity ad on table 3 for the booster positivity. At the end we have a LTB prevalence of 33.6%. There was an increased prevalence on the early RA group (OR 1.3 CI 95% (1.007–1.7) $p = 0.04$).

Table 1.

	Early RA n = 83	Established RA n = 60	p	OR CI 95%
Age mean (SD)	44.07 (11.8)	50.81 (13.09)	0.002	
Female n (%)	75 (90.4)	51 (85)	0.33	
Time of evolution mean (SD)	18 (14.9)	167 (105)	0.0001	
BCG vaccination* n (%)	71 (94.7)	43 (75.4)	0.001	
BCG scar** n (%)	33 (42.3)	45 (57.7)	0.39	
Tb patient exposure* n (%)	5 (6.8)	18 (30.5)	0.0001	
First PPD n (%)	26 (31.3)	13 (21.7)	0.201	
Corticosteroid use n (%)	37 (44.6)	23 (38.3)	0.455	
Prednisone dose mg/day mean (SD)	8.02 (3.4)	5.5 (2.6)	0.005	
ESR mm/Hr mean (SD)	28.2 (15.7)	25.5 (11.7)	0.24	
DAS28 mean (SD)	4.8 (1.2)	4 (2.1)	0.017	
DMARD's use n (%)	51 (61.4)	49 (81.7)	0.009	
Booster PPD*** n (%)	7 (15.6)	2 (5.1)	0.117	
LTB**** n (%)	33 (46.5)	15 (28.8)	0.048	1.329 (1.007–1.754)

* Of 132 patients
** Of 105 patients
*** Of 84 patients
**** Of 123 patients.

Table 2.

	PPD positive n = 39	PPD negative n = 104	p	OR CI 95%
Age mean (SD)	46.9 (10.46)	46.8 (13.5)	0.98	
Female n (%)	36 (92.3)	90 (86.5)	0.342	
Time of evolution mean (SD)	78.2 (99.6)	81.8 (102.19)	0.84	
BCG vaccination* n (%)	32 (97)	82 (82.4)	0.04	1.17 (1.05–1.3)
BCG scar** n (%)	22 (88)	56 (70)	0.07	
Tb patient exposure* n (%)	6 (17.6)	17 (17.3)	0.96	
Corticosteroid use n (%)	11 (28.2)	49 (47.1)	0.041	0.599 (0.399–1.028)
Prednisone dose mg/day mean (SD)	7.27 (3.2)	7.03 (3.4)	0.833	
ESR mm/Hr mean (SD)	27.4 (13.6)	26.9 (14)	0.84	
DAS28 mean (SD)	4.5 (1.6)	4.4 (2)	0.86	
DMARD's use n (%)	25 (64.1)	75 (72.1)	0.352	
Early RA n (%)	26 (66.7)	57 (54.8)	0.201	

* Of 132 patients
** Of 105 patients.

Table 3.

	Booster positive n = 9	Booster negative n = 75	p	OR CI 95%
Age mean (SD)	49.33 (15.45)	47.3 (13–72)	0.68	
Female n (%)	9 (100)	64 (85.3)	0.264	
Time of evolution mean (SD)	31.77 (38.6)	93.53 (109.3)	0.002	
BCG vaccination* n (%)	9 (100)	57 (79.2)	0.129	
BCG scar** n (%)	3 (42.9)	43 (74.1)	0.086	
Tb patient exposure*** n (%)	1 (11.1)	13 (18.6)	0.581	
Corticosteroid use n (%)	2 (22.2)	37 (49.3)	0.123	
Prednisone dose mg/day mean (SD)	8.7 (1.7)	6.3 (2.7)	0.229	
ESR mm/Hr mean (SD)	25.6 (13.44)	28.12 (14.57)	0.632	
DAS28 mean (SD)	4.9 (1.4)	4.2 (1.4)	0.161	
DMARD's use n (%)	4 (44.4)	57 (76)	0.045	0.58 (0.279–1.227)
Early RA n (%)	7 (77.8)	38 (50.7)	0.123	

* Of 81 patients
** Of 65 patients
*** Of 79 patients

Conclusion: There are more probability to diagnose LTB in the early RA group, maybe influenced by evolution time and the corticosteroid and DMARDxs use.

Disclosure: L. Perez-Barbosa, None; **D. Vega-Morales**, None; **J. C. L. Riega-Torres**, None; **O. Ilizaliturri-Guerra**, None; **M. A. Garza-Elizondo**, None.

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Pyogenic Arthritis: Clinical and Epidemiological Features Of 101 Cases At a University Hospital. Anne Riveros-Frutos, Lourdes Mateo, Melania Martínez-Morillo, Beatriz Tejera, Samantha Rodriguez-Muguruza, Juana Sanint, Susana Holgado, Jerónima Cañellas, Xavier Tena, Alejandro Olivé and Montserrat Gímenez. Hospital Universitario Germans Trias i Pujol, Badalona, Spain.

Background/Purpose: To describe the clinical characteristics, treatment and outcome of patients diagnosed with pyogenic septic arthritis.

Methods: Design: retrospective (1984–2012). Location: University hospital. Referial area: 800,000 inhabitants. The medical records of patients with pyogenic arthritis were reviewed. Inclusion criteria: isolation of bacteria in joint fluid or blood. Patients with soft tissue infection, prosthetic, fungal and mycobacterial septic arthritis were excluded.

Results: One hundred one patients were selected: 66 males and 35 females. Mean age: 54.5 ± 21.2 years. The following risk factors were identified: alcoholism (24), cirrhosis (12), diabetes mellitus (18), chronic renal failure (17), neutropenia (6), immunosuppression (10), HIV (10), AIDS (5), parenteral drug addiction (12), cancer (6), RA (4) and microcrystalline arthritis (17). Seventeen patients had undergone joint manipulation prior to the onset of the infection: 9 arthrocentesis with corticosteroids injection, 6 arthrocentesis and 2 arthroscopies. The pattern of join involvement was monoarticular in 72 patients (71.3%): knee 38 (36.8%), and shoulder and ankle 8 (8%) respectively. Polyarticular involvement was found in 29 patients (28.7%). Fifty nine patients 58.4% had fever. Cellulitis was observed in 17 cases (17%). The mean time between onset of symptoms and diagnosis was 7.9 ± 8.2 days. Mean hospital stay was 30.4 ± 28 days. Blood cultures were positive in 40 cases (39.7%) and in 85% of them the same microorganism was isolated in joint fluid. Septic arthritis was caused by gram positive in 79%, gram negative 19% and 2% were polymicrobial. The most common were: S. aureus methicillin sensitive (45), S. aureus methicillin resistant (MRSA in 5 cases since 2008), S. agalactiae (6), S. pyogenes (3), S. pneumoniae (9), E. Coli (9), P. aeuriginosa (3), Enterobacter cloacae (2) and Salmonella (2). Acute phase reactants were increased: ESR: 89.5 ± 29.6 mm/1sth and C-reactive protein 162 ± 122 mg/dl. The mean leukocyte count of joint fluid was 65,602 ± 62477/mm3. Synovial glucose was decreased in 50% of patients. Mean duration of intravenous antibiotic therapy: 3 weeks. Thirty-four patients (33.6%) required surgical treatment. Three patients required a second arthrotomy. Complications were: septic shock (20), pneumonia (6), reflex sympathetic dystrophy (2), osteonecrosis (2), endocarditis (3), respiratory distress (1). Most of the cases evolved favorably. Fifteen cases resulted in death (15%): 8 cases had monoarticular involvement and 7, polyarticular involvement. The causative organisms were: S. Aureus (10 cases), MRSA (3 cases), Pneumococcal (1 case) and polymicrobial (1 case of S. aureus more E. Coli).

Conclusion: S. aureus is the most common pathogen isolated. Furthermore MARSA is an emerging microorganism. Hematogenous spread and polyarticular involvement are poor prognostic factors. Prolonged antibiotic therapy and surgical debridement are essential for proper healing.

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1140

Study Of The Antibody Titer By Influenza Vaccination In Rheumatoid Arthritis Patients Treated With Biologics In JAPAN. Hisato Ishikawa[1], Daihei Kida[2], Yosuke Hattori[2], Atsushi Kaneko[2] and Tomotaro Sato[2]. [1]Nagoya Medical Center, nagano, Japan, [2]Nagoya Medical Center, Nagoya, Japan.

Background/Purpose: Vaccination for influenza virus is recommended for patients with rheumatoid arthritis (RA) with underlying such as disease elderly people over the age of 65, respiratory disease, cardiovascular disease. Especially, it is believed that in general, should be vaccinated actively in patients with biologic agents. Biologic agents might suppress the immune response to influenza vaccines, but, the report is limited to the number of papers. The aim is the study to compare antibody titers changeafter influenza vaccination for rheumatoid arthritis.

Methods: 182 patients with RA of our hospital received inactive trivalent influenza vaccination. All RA patients who have been treat with methotrexate (MTX; contorol; n=48), abatacept (ABT; n=37, include the MTX combination of 18 cases), tocilizumab (TCZ; n=80, include the MTX combination of 22 cases), golimumab (GLM; n=17, include the MTX combination of 13 cases). We used commercially available inactivated trivalent influenza vaccine. Patients received a single dose of vaccine (0.5 ml). Vaccines (A/H1N1, A/H3N2, B/B-1 strains) which was used this time was a vaccine for 2012–2013 in Japan. Measuring the antibody titer prior to vaccination, again, by measuring titer one month after, examined seroprotection rates and seroconversion rate. Serum antibody titers were measured hemagglutination inhibitory assay (HI).

subcutaneously from October 2012 until January 2013. For RA patients receiving biologics, the vaccination was done on the same day as biologics infusion. Seroprotection was defined as antibody titres of ≥40. Seroconversion was defined as post vaccination antibody titres of ≥40 in patients whose pre vaccination titres were <10. Seroresponse was defined as seroconversion or 4 fold increases in antibody titres of in patients whose pre-vaccination titres were ≥10.

Results: In seroprotection rate of the type B, compared to the control, group of biologic agents was higher. But, there were no difference in the seroconversion rate in all types between control and biologics. Seroprotection rate, TCZ was higher than control in type B. In type H3N2, ABT and GLM were lower than control. Seroconversion rates, ABT tended to be lower in all types and TCZ tended to be higher in all. In type H3N2, ABT was lower than control. TCZ was higher than control in type B. This tendency is more pronounced in the Biologics group used in combination with MTX, which was the lowest antibody levels in the ABT + MTX group.

Conclusion: Treatment with anti tumour necrosis factor α (anti-TNFα) agents may impair antibody response to influenza vaccination in patients with RA and other rheumatic diseases, but the response is enough to warrant influenza vaccination for such patients. Mori et al, reported that TCZ does not hamper antibody response to influenza vaccine in RA patients and Influenza vaccination is considered effective in protecting RA patients receiving TCZ therapy with or without MTX. The results of our TCZ group did not affect the change of antibody titers as well. In ARRIVE test, Influenza vaccine seroconversion rate who patients treated with ABT, was similar to normal people. However, in our study, no significant difference, but the results were lower than the control reviews.

Disclosure: H. Ishikawa, AstraZeneca Pharma, 2; **D. Kida**, Mitsubishi Tanabe Pharma, Pfizer Japan, Eisai, Chugai Pharmaceutical, Abbvie, 2; **Y. Hattori**, None; **A. Kaneko**, Otsuka Pharmaceutical, Chugai Pharmaceutical, Eli Lilly and Company Japan, Santen Pharma, UCB Japan, Quintiles Transnational Japan, 2; **T. Sato**, Otsuka Pharmaceutical, Mitsubishi Tanabe Pharma, Chugai Pharmaceutical, Abbvie, 2.

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Response To H. Pylori Treatment and Autoantibody In Chronic Thrombocytopenia. Mitsuyo Kinjo[1] and Kensuke Nakanishi[2]. [1]Okinawa Chubu Hospital, Uruma City Okinawa, Japan, [2]Okinawa Chubu Hospital, Uruma, Japan.

Background/Purpose: Helicobacter pylori (H. pylori) infection has been linked to pathogenesis of autoimmune disease including chronic idiopathic thrombocytopenic purpura (ITP). Prior studies showed platelet counts have improved after eradication of H. pylori in some patients with ITP. To clarify the role of H. pylori in chronic thrombocytopenia and its response to treatment in association with autoantibody status.

Methods: Medical records from 2002–2012 were reviewed at Okinawa Chubu Hospital to locate patients > 18 years old with chronic ITP (platelet < 100,000/mm^{3}for > 12 months). After exclusion of acute ITP and secondary chronic thrombocytopenia, 49 patients were included. We recorded antinuclear antibody (ANA), antiphospholipid antibody (APLA) and H. pylori status. Treatment for H. pylori infection was administered to patients with positive H. pylori detected by breath test. Platelet count was monitored at least for one year after eradication of H. pylori.

Results: Median age was 44 years (range, 18–86); 39/49 subjects were female (80%). ANA or APLA was positive but H. pylori was negative in 25/49 (50%); H. pylori infection was present in 15/49 (31%), and both H. pylori and autoantibody were positive in 10/49 (20%). All patients with H. pylori infection were treated with antibiotics. Eradication failed to improve platelet counts in 10/10 cases with positive ANA or APLA. Among patients with H. pylori without autoantibodies, 3/5 responded with increased platelet counts and 2/5 did not. The overall rate of positive autoantibody in non-responders was therefore 10/12 (83%), and zero in responders.

Conclusion: Among patients with chronic ITP and H. pylori infection, refractory thrombocytopenia after eradication may identify a subset of patients with positive autoantibody. Immunological response to H. pylori may be associated with poor response rate to antibiotic treatment in patients with concomitant ITP and H. pylori infection.

Disclosure: M. Kinjo, None; **K. Nakanishi**, None.

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Distinct Pathways Of Ly6C^{hi} Monocyte Development Identified By a Novel Dual-Reporter Murine Myeloid Progenitor Cell Line. Pui Lee[1], David Sykes[2], Sarah Ameri[3], Demetrios Kalaitzidis[2], Peter A. Nigrovic[1] and Astrid Cardona[4]. [1]Boston Children's Hospital, Boston, MA, [2]Massachusetts General Hospital, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]University of Texas - San Antonio, San Antonio, MA.

Background/Purpose: Monocytes are essential to innate immunity but also propagate the inflammatory response in autoimmune arthritis and crystal arthropathies. Development of inflammatory monocytes (Ly6C^{hi} CCR2$^+$) and residential monocytes (Ly6C^{lo} CX$_3$CR1$^+$) from murine bone marrow precursor cells is an enigmatic process that involves numerous transcription factors with influence by growth factors and cytokines. Elucidation of these critical pro-inflammatory pathways is limited by the paucity of precursor cells and the need for extensive ex-vivo manipulation and cell sorting.

Methods: To develop an informative myeloid cell line, we infected bone marrow from CCR2$^{RFP/+}$ CX$_3$CR1$^{GFP/+}$ dual-reporter mice with a murine stem cell virus encoding Hoxb8 under the control of estrogen receptor. These cells remain immortalized at the myeloid precursor stage until induced by estrogen withdrawal to initiate synchronous myeloid differentiation. To identify pathways important to monocyte development, small molecule inhibitors, cytokines and growth factors were added to cell culture at specific timepoints, and key findings were confirmed in live mice.

Results: Upon cessation of Hoxb8 expression after estrogen withdrawal, our novel dual-reporter cell line spontaneously differentiated into Ly6C^{hi} CCR2$^+$ inflammatory monocytes, followed by maturation to Ly6C^{lo} CX$_3$CR1$^+$ residential monocytes. Using this cell line as a screening tool, we identified an essential role of phosphoinositide-3 kinase (PI3K) and mechanistic target of rapamycin (mTOR) in spontaneous monocyte development through a small molecule library screen. These findings were confirmed *in vivo* as mice with conditional deletion of mTOR complex 1, but not mice lacking mTOR complex 2, failed to develop Ly6C^{hi} monocytes. While macrophage colony-stimulating factor (M-CSF) was not required for spontaneous production of monocytes, the addition of exogenous M-CSF induced Ly6C^{hi} monocyte development via a PI3K/mTOR-independent pathway.

Conclusion: We describe a novel dual-reporter myeloid progenitor cell line that recapitulates the monocyte development continuum. Studies using these cells enabled identification of a previously unrecognized role of mTORC1 in normal development of inflammatory monocytes, as well as a potential "rescue" pathway of mTORC1-independent differentiation. Our work highlights the utility of this technology in studying myeloid differentiation and provides evidence for the existence of two distinct pathways of monocyte production that may be differentially employed in physiologic and inflammatory conditions.

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1143

Increased Frequency Of Pratroling Monocytes In Experimental Arthritis and Rheumatoid Arthritis Patients In Response To IL6-R Blockade. Julie Quentin[1], Jessy Presumey[2], Florence Apparailly[2], Yves-Marie Pers[3], Pascale Louis Plence[4] and Christian Jorgensen[3]. [1]Inserm U844, Montpellier, France, [2]Inserm, Montpellier, France, [3]Inserm U844, CHU saint-Eloi, Université Montpellier 1, CHU Lapeyronie, Montpellier, France, [4]INSERM U844 Montpellier, Montpellier, France.

Background/Purpose: Monocytes represent a heterogeneous circulating population of immune cells that play important roles in the inflammatory response. Two main functional subsets of human monocytes have been identified, as well as their counterparts in mouse. Increasing numbers of reports suggest that each of them exert specific roles in homeostasis and inflammation in vivo, and their involvement in pathological inflammatory responses is growing. The aim of our study was to investigate the effect of the anti-IL6R antibody therapy, in the mouse CIA model and in Rheumatoid arthritis patients, on the frequencies of monocyte sub-populations.

Methods: The CIA has been induced by immunization of DBA1 mice with bovine type II collagen. The anti-IL6R antibody (MR16-1) treatment was initiated on day 22 post-immunization using i.p. injections of 0.5mg/mouse twice a week. Blood samples were collected weekly from day 23 and the different monocyte subsets were analyzed by flow cytometry.

15 RA patients were recruited and Tocilizumab was given with approval of the French Drug Agency, in a dose of 8 mg/Kg as a 60-minute intravenous infusion every 4 weeks. For immune monitoring, blood samples from RA patients were collected just before the 1st and 4th tocilizumab infusions (8 mg/Kg).

Results: Clinical monitoring of CIA showed a stabilization of disease features from day 29 until euthanasia (D44) demonstrating that the anti-IL-6R Ab treatment was able to slowdown CIA progression and decrease disease severity when injected after the boost. We monitored the percentage of monocyte subsets and evidenced fluctuations during clinical course of the disease. The percentage of circulating inflammatory $Ly6C^{high}$ monocytes was transiently reduced on day 37 in the treated group as compared with controls, while the percentage of the non-inflammatory $Ly6C^{low}$ monocytes was significantly increased from day 30.

In parallel, we have monitored monocytes cell populations in the blood of RA patients before and during treatment with Tociluzumab and found (1) fluctuations of monocyte subsets following Tociluzumab therapy and (2) significant difference in frequencies in the various subsets before treatment between responders and non-responders and (3) a correlation between clinical benefit and increased frequency of the non-classical $CD14^{dim}CD16^{+}$ monocytes.

Conclusion: Similar to the increased frequency of the non-classical $CD14^{dim}CD16^{+}$ monocytes that we observed in the blood from RA patients under Tocilizumab therapy, an increased percentage of their mouse counterpart $Ly6C^{low}$ monocytes was observed following treatment of CIA mice with MR16-1 Ab. These data suggest new cellular mechanisms insight into clinical benefit associated with anti-IL6R-based therapy and suggest that frequency of the $CD14^{dim}CD16^{+}$ monocytes can predict clinical response to treatment.

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1144

Wnt Signaling Pathway Regulates Multi-Unconventional Differentiation and Function Of Human Dendritic Cells. Jia Wang[1], Yi Liu[2] and Yi Zhao[2]. [1]Sichuan Provincial People's Hospital, Chengdu, China, [2]West China Hospital of Sichuan University, Chengdu, China.

Background/Purpose: Dendritic cells (DCs) play a central role in regulating immune responses and govern T cell priming and polarization, mediating immunity and tolerance. Recent progress uncovered the Wnt signaling pathway is crucial for the immune balance and focuses on DCs as a direct target for their immunoregulatory role. In this study, we investigated the effect of the canonical and non-canonical Wnt signaling pathways regulate the differentiation and function of human DCs.

Methods: Human peripheral blood CD14+ monocytes were cultured for 6 days with GM-CSF/IL-4 and then treated with LPS, Wnt3a, Wnt5a, GSK-3β inhibitor (SB216763) or silencing β-catenin for 24 h. Immunophenotypic characterizations of DCs were analyzed by flow cytometry. The supernatants were collected and cytokines (IL-17, IL-23, IL-10, TNF-α, IFN-γ) were assessed. Human peripheral blood and active rheumatoid arthritis patients' synovial fluid CD3+ monocytes were isolated for mixed lymphocyte reaction. Proteins were extracted and incubated with antibodies against the total or phosphorylated forms of β-catenin, GSK-3β.

Results: Our results showed that regulating the canonical and non-canonical Wnt signaling altered the maturation status and function of already differentiated DCs. The differentiation of DCs resulted in inhibiting activity of GSK-3β and stabilizing its substrate, β-catenin. GSK-3β inhibitor induced a full maturation phenotype of DCs that expressed mostly CD14. These DCs produced low levels of IL-17, IL-23 but high level of IL-10. Consequently, these DCs have a reduced capacity to stimulate Th17 differentiation and increased Th2 and Treg differentiation. The addition of Wnt3a or Wnt5a both increased CD1a+DCs but reduced CD83, CD80, CD86, CD40 and HLA-DR expression. Wnt3a-DCs produce scant amounts of cytokines and have a reduced capacity to stimulate all T cell subsets differentiation. Wnt5a-DCs produced low level of IL-17, TNF-A while increased IL-23, IL-10 secretion and have an increased capacity to stimulate Th2 and Treg differentiation. β-catenin silencing reduced CD83 expression on LPS-induced DCs maturation and IL-10 secretion, without significant effect on capacity of DCs to stimulate T cells differentiation.

Conclusion: Wnt signaling pathway regulates multi-unconventional differentiation and function of human DCs. GSK-3β inhibitor could induce terminal differentiation DCs into unconventional phenotypic maturation of DCs with tolerogenic features. Silencing of β-catenin partly impair LPS induced maturation of DCs. Exogenous Wnt3a inhibited maturation and function of DCs while Wnt5a inhibited maturation of DCs with regulatory features.

Disclosure: J. Wang, None; **Y. Liu**, None; **Y. Zhao**, None.

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Regulation Of Plasmacytoid Dendritic Cells By Prostaglandin E2. Alice E. Wiedeman and Keith B. Elkon. University of Washington, Seattle, WA.

Background/Purpose: Plasmacytoid dendritic cells (pDCs) constitute a rare blood cell subset exquisitely attuned for production of large quantities of interferon-alpha (IFN-α), and these cells have been implicated in several autoimmune diseases. There is therefore much interest in understanding how IFN-α is regulated in pDCs. Prostaglandin E2 (PGE2) is known to have an inhibitory effect on pDCs via receptors EP2 and EP4, but the mechanism(s) underlying this inhibition is not known. The goal of this study was to elucidate the molecular pathways involved in the inhibition of IFN-α by PGE2.

Methods: Human peripheral blood mononuclear cells (PBMCs), isolated "untouched" primary pDCs, or a pDC line were cultured in the presence of lupus immune complexes (ICs) or agonists of TLR7 (Loxoribine) or TLR9 (CpG-A, ODN 2216) with or without PGE2 (1, 10, and 100 ng/mL), dibutyryl-cAMP (100 μM), or Rapamycin (10 ng/mL). At 1h, cells were harvested and fixed to slides, then stained with DAPI and fluorescently-labeled antibody against IRF7, and analyzed by confocal or fluorescence microscopy. At 20h, IFN-α, IL-6, and TNF in the supernatants were quantified by ELISA, and cells were analyzed by flow cytometry using fluorescently-labeled antibodies to identify pDCs (CD123+BDCA2+), and quantify cell death (Annexin V, propidium iodide).

Results: Lupus IC and TLR7 or 9 agonists induced IFN-α by PBMC which could be inhibited by PGE2 in a dose-dependent manner, whereas production of IL-6 and TNF were unaffected. This was also true for isolated pDC stimulated by CpG-A, and this was not due to pDC death. By confocal microscopy of primary pDCs, IRF7 translocation was increased by TLR9 agonist stimulation and significantly reduced by addition of PGE2 but not carrier control (DMSO). By fluorescence microscopy of primary pDC or the pDC line, the TLR9 agonist increased the IRF7 signal and the intensity of staining was reduced by PGE2. Because PGE2 action on pDC is believed to be via the receptors EP2 and EP4, which drive an increase in cAMP and activation of PKA in other cell types, we addressed whether dibutyryl-cAMP, a cell-permeable cAMP analog, could mimic the effects of PGE2. Indeed, dibutyryl-cAMP reduced the production of IFN-α by 56.7 ± 9.8 % ($p < 0.04$). Lastly, to determine if mTOR played a role in IFN-α regulation, we treated PBMCs with a suppressor of mTOR, Rapamyin, and found that it, too, could robustly inhibit IFN-α production (76.8 ± 5.2 %, $p < 0.004$) but not IL-6 or TNF, without inducing pDC death.

Conclusion: PGE2 is able to inhibit pDC production of IFN-α in response to both lupus IC and TLR agonist stimulation without affecting other pro-inflammatory cytokines or inducing pDC death. We show for the first time that PGE2 can inhibit pDC IRF7 protein expression and nuclear translocation. Consistent with a role for PGE2 receptors EP2 and EP4 in this inhibition, a cAMP analog could also inhibit IFN-α. Lastly, mTOR plays a significant role in IFN-α production, as treatment with its suppressor, Rapamycin, significantly inhibits IFN-α but not other pro-inflammatory cytokines IL-6 and TNF. These results are consistent with a role of PGE2 in inhibition of the mTOR pathway in pDCs, and may represent a novel target for immune modulation in type 1 IFN-associated diseases.

Disclosure: A. E. Wiedeman, None; **K. B. Elkon**, None.

1146 WITHDRAWN

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Human Dendritic Cells Produce Thymic Stromal Lymphopoietin In Response To Pattern Recognition Receptor Ligation and This Secretion Is Augmented By Endoplasmic Reticulum Stress. Matthew J Elder[1], Anthony YKC Ng[1], Steven J Webster[1], Michael J Bacon[1], JS Hill Gaston[2] and Jane C Goodall[1]. [1]University of Cambridge, Cambridge, United Kingdom, [2]University of Cambridge/Clin Med, Cambridge, United Kingdom.

Background/Purpose: Thymic stromal lymphopoietin (TSLP) is a cytokine that has an important role in inducing Th2 cell differentiation and has also been implicated as a pathogenic factor in the development of inflammatory arthritis. We have previously shown that human monocyte-derived dendritic cells (DC) secrete significant quantities of TSLP. The precise stimuli which induce TSLP secretion in DC and possible autocrine effects of TSLP production are poorly understood. Endoplasmic reticulum (ER) stress is an important signalling pathway which enables cells to adapt to increased protein synthesis. PRR and ER stress pathways are both engaged in DC following uptake of bacterial pathogens and we have previously shown that both signals synergise to enhance TSLP secretion. Our aim was to identify the key signals that induce and modulate TSLP induction.

Methods: DC were differentiated from peripheral blood monocytes, purified using positive magnetic selection, by stimulation with IL-4 and GM-CSF. Flow cytometry analysis of MoDC phenotype showed them to be $CD1c^{+}$ $CD11b^{Hi}$ $CD11c^{Hi}$ $CD14^{Lo}$ $CD86^{Lo}$ and $HLA\text{-}DR^{Hi}$. Transcriptional analysis was assayed by qRT-PCR following RNA extraction and quantified relative to HPRT; cytokine secretion was assessed by ELISA of cell supernatants.

Results: Heat killed Gram-negative bacteria including *S. typhi*, *P. aeruginosa* and *E. coli* stimulated TSLP secretion. To further examine the PRR requirements for TSLP expression we utilised the pattern recognition receptor (PRR) agonists, Peptidoglycan (TLR2 and NOD2) ultra pure LPS (TLR4) and particulate forms of β-1,3 glucan (dectin 1). These agonists stimulated TSLP mRNA transcription and protein secretion by DC, with the most potent effects induced by β-1,3 glucan (475pg/ml $+/-200$ SEM).

As expected, TSLP secretion induced by β-1,3 glucan was dependent on the dectin 1 adaptor molecule Syk. NF-κB and p38/MAPK were also shown to be essential signalling molecules for this response. Addition of IL-1 receptor antagonist substantially blocked TSLP secretion. Although TNFα was previously shown to enhance TSLP by synovial fibroblasts, neutralisation of TNFα did not reduce TSLP secretion by DC. Dectin 1 stimulation alone was sufficient to activate ER stress, as demonstrated by eIF2α phosphorylation and XBP-1 splicing. Inhibitors for the ER stress signalling molecules IRE-1α and PERK reduced TSLP secretion, suggesting that ER stress signals contribute significantly to induction of TSLP.

Conclusion: TLR2, TLR4 and Dectin 1, are important PRRs in the induction of TSLP secretion by human DC. In addition to fungal derived β-1,3 glucans, we show that bacteria can also induce significant quantities of TSLP. TSLP secretion by DC is induced following a complex integration of signals from PRRs, ER stress pathways and cytokine receptors. Since DC have previously been shown to respond to TSLP made by epithelial cells; possible autocrine effects of TSLP on DC, and their influence on T cell differentiation, warrant further exploration. Autocrine effects of TSLP would be especially relevant in primary and secondary lymphoid tissues where epithelial cells are not present, rather than in the periphery.

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Autologous Tolerogenic Dendritic Cells In Rheumatoid and Inflammatory Arthritis. Gillian Bell[1], Amy Anderson[1], Julie Diboll[1], Rachel Harry[1], Elaine McColl[1], Anne Dickinson[1], Catharien Hilkens[1] and John Isaacs[2]. [1]Newcastle University, Newcastle upon Tyne, United Kingdom, [2]National Institute for Health Research, Newcastle Biomedical Research Centre, Newcastle Hospitals Foundation Trust and Newcastle University, Newcastle Upon Tyne, United Kingdom.

Background/Purpose: Rheumatoid arthritis is a chronic autoimmune disease which results from a breakdown of immune tolerance. Current therapies include traditional DMARDs, anti-TNF, B cell depleting therapies and co-stimulation blockade. Despite their efficacious role in reducing disease activity, these therapies non-specifically suppress the immune system, with resulting risks from infection and malignancy. This has led to the development of more specific immune-modulatory therapies in order to specifically switch off the pathological immune response, inducing immune tolerance in an auto-antigen specific manner. Tolerogenic dendritic cells (tolDC) are one such autologous cellular therapy with such potential, with significantly efficacious results in animal models. We are performing a phase I study of intra-articular tolDC in inflammatory arthritis patients. Our primary and secondary objectives are to assess safety, tolerability and feasibility of treatment; exploratory objectives seek preliminary evidence of a potential therapeutic effect.

Methods: An ascending dose, randomised, controlled, un-blinded phase I study is currently underway. Three dosing cohorts are planned of 1 million, 3 million and 10 million tolDC administered arthroscopically into an inflamed knee joint following saline washout; controls will receive saline washout only. Each cohort comprises 4 patients (3 active, 1 placebo). The primary endpoint of the study is the proportion of patients experiencing adverse and serious adverse events following treatment.

Results: To date 8 subjects with inflammatory arthritis have been treated, 5 with tolDC (3 at 1 million and 2 at 3 million tolDC) and 2 controls. Manufacture of tolDC failed in a further patient. TolDC have not induced acute flares of local synovitis (defined as within 5 days of administration). Two delayed knee flares occurred between 11 and 14 days from treatment (one in a subject receiving 1 million tolDC and 1 receiving 3 million tolDC). Two patients experienced a systemic flare of their arthritis 14 days after treatment (1 in subject receiving one million tolDC and 1 in a subject receiving 3 million tolDC). There have been no knee or systemic arthritis flares in control patients. To date patient acceptability has been high but there has been no evidence of a beneficial effect of tolDC administration. There have been two infections: one wound infection at an arthroscopy port and one pneumonia.

Conclusion: In this ascending dose phase I study of intra-articular tolDC we have not seen evidence of acute toxicity. To date we have also not witnessed a beneficial effect and local inflammation has recurred following intervention. Two systemic flares were judged unrelated to therapy. Our results to date suggest that intra-articular tolDC do not induce an acute flare of inflammatory arthritis and is acceptable to patients.

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Phenotypic and Molecular Profile Of Innate Lymphoid Cells In Chronic Synovial Inflammation. Hulda S. Hreggvidsdottir[1], Maureen C. Turina[1], Troy Noordenbos[1], Marius Munneke[1], Charlotte Peters[1], Jochem Bernink[1], Jenny Mjosberg[2], Dominique L. Baeten[1] and Hergen Spits[1]. [1]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Innate lymphoid cells (ILCs) represent a novel family of effector and regulatory cells in innate immunity and tissue remodelling. The family comprises several phenotypically and functionally distinct subsets that respond rapidly upon stimulation by producing various T helper cell cytokines such as IL-22, IL-17, IFNγ, TNF, IL-13 and IL-5, of which many are shown to be important in arthritis pathogenesis. The IL-17 and IL-22 producing ILCs are of major interest as they are implicated in chronic gut inflammation. Based on the broad clinical overlap between inflammatory bowel disease and spondyloarthritis (SpA) and the clinical importance of IL-17 in SpA we hypothesize that IL-17 and IL-22 producing ILCs contribute to inflammation and remodelling in SpA synovitis. As these cells have never been described in the joint we aimed at characterising ILC in chronic inflammatory arthritis.

Methods: ILCs (lineage negative, $CD45^{+}CD127^{+}$) were analysed and sorted by flow cytometry from synovial tissue and fluid from rheumatoid arthritis (RA) and SpA patients as well as in blood from SpA patients and healthy donors. mRNA expression of sorted and expanded cells was analysed by qPCR.

Results: ILCs were identified in blood as well as in synovial tissue and fluid from both RA and SpA patients. The frequency of ILCs was higher in the inflamed joint (0,5–3,3% of the lymphocyte population) than in the peripheral blood compartment (0,1%). In the inflamed joint, the ILC3 ($CRTH2^{-}NKp44^{+}ckit^{+}$) and ILC1 ($CRTH2^{-}NKp44^{-}ckit^{-}$) populations, shown to express IL-22 and IFNγ respectively in other tissues, were present in all samples whereas the Th2 cytokine expressing ILC2s

(CRTH2$^+$) were found in low frequencies. Frequencies of ILC subpopulations varied considerably between patients and no differences could be detected between RA and SpA patients. qPCR analysis of expanded cells from the synovium revealed that ILC1s expressed *TBX21* whereas ILC3s expressed *RORC*. Accordingly, stimulated ILC3s expressed transcripts for both IL-23R and IL-22 but not IL-17. A trend towards higher frequency of total ILC and ILC3s was found in the blood of SpA patients compared to controls.

Conclusion: ILC1s and ILC3s are present in the chronically inflamed joint, are enriched compared to peripheral blood and express the key transcription factors associated with specific cytokine profiles. These data indicate that ILCs could contribute to local cytokine-driven immune alterations in SpA and RA.

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Differential Regulation Of IL-10 and Dusp1 Production By Kinases In The p38 MAPK Pathway. Deepa Hammaker, Katharyn Topolewski and G. S. Firestein. UCSD School of Medicine, La Jolla, CA.

Background/Purpose: MAPK kinases MKK3 and MKK6 regulate p38 function in inflammatory diseases like rheumatoid arthritis (RA). Targeting MKK3 or MKK6 might be superior to traditional p38 blockade because MKK-deficiency maintains p38-mediated anti-inflammatory responses. Production of IL-10 and the de-activating phosphatase Dusp1 is higher in activated MKK-deficient bone marrow-derived macrophages (BMDM) compared with p38 inhibition, especially for MKK6−/− cells. The concept that MKK6 might be the optimal target in the p38 pathway was confirmed by the observation that MKK6−/− mice have lower disease severity in collagen-induced arthritis than wild type (WT) or MKK3−/− mice (Arthritis Rheum 2012;64:2887). In this study, we explored the mechanism of protection by evaluating differential regulation of IL-10 and Dusp1 expression in MKK3−/−, MKK6−/− and p38 inhibitor-treated BMDMs.

Methods: Bone marrow isolated from WT, MKK3−/− and MKK6−/− mice was differentiated into BMDMs in vitro (n=3/group). The cells were then treated with LPS (100ng/ml) for various times. Gene expression was determined by qPCR in LPS-stimulated BMDM (4h). mRNA half life was measured in LPS-treated BMDM incubated with actinomycin D ± SB203580 (p38 inhibitor) by qPCR. De novo mRNA synthesis was quantified in BMDM treated with ethynyl-uridine ± LPS for 1h. The RNA was biotinylated using Click-iT Nascent RNA capture kit (Invitrogen). Nascent RNA was isolated with streptavidin-magnetic beads. Reverse transcription was performed using SuperScript VILO cDNA synthesis kit (Invitrogen) and IL-10 expression was measured by qPCR and presented as fold of medium-treated cells.

Results: We first determined the effect of MKK-deficiency or p38 inhibitor on the de novo synthesis of IL-10 mRNA in response to LPS. Pre-treatment of WT BMDM with p38 inhibitor significantly reduced IL-10 transcription in WT cells by 75±8% compared with control (n=3 mice/group, $p<0.0001$). Compared with WT, IL-10 induction in MKK3−/− was decreased by 60±7% ($p<0.0001$), whereas inhibition in MKK6−/− cells was minimal (16±3%, $p>0.05$). We also evaluated levels of Dusp1, a p38 phosphatase that is regulated transcriptionally by p38 and de-activates other MAPKs. Dusp1 expression was significantly reduced by 38±6% ($p=0.002$) in p38 inhibitor-treated and 46±5% ($p=0.004$) in MKK3−/− BMDM but not in MKK6−/− cells. We then measured the effect of MKK-deficiency and a p38 inhibitor on mRNA decay of IL-10. WT BMDM treated with p38 inhibitor showed a significantly higher IL-10 mRNA decay rate (t1/2 = 30 min, n=3, $p<0.005$) compared with WT control (t1/2 = 54 min). Surprisingly, IL-10 decay rates were similar in WT, MKK3−/− and MKK6−/− groups (t1/2 MKK3−/− = 45 min, MKK6−/− = 41 min), indicating that unlike p38 inhibition, MKK-deficiency does not alter IL-10 mRNA stability.

Conclusion: Suppressed expression of IL-10 and Dusp1 by MKK3-deficiency or p38 inhibition occurs primarily at the transcriptional level, but gene transcription is maintained in MKK6−/− cells. Preservation of Dusp1 expression in MKK6 deficiency permits de-activation of other MAPKs and terminates the inflammatory cascade. Together these data suggest that MKK6 is a potential therapeutic target in RA.

Disclosure: D. Hammaker, None; **K. Topolewski**, None; **G. S. Firestein**, None.

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Snapin Is Required For Functional Autophagy and Is Critical For Monocyte To Macrophage Differentiation. Bo Shi[1], Qiquan Huang[1], Robert Birkett[1], Renee E. Koessler[2], Andrea Dorfleutner[1], Christian Stehlik[1] and Richard M. Pope[3]. [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Northwestern University, Chicago, IL, [3]Northwestern Univ Med School, Chicago, IL.

Background/Purpose: Our recent data indicate that Snapin, a SNAP associated protein, is significantly increased in macrophages (MΦs) in rheumatoid arthritis (RA) synovial tissue and its expression level was correlates with inflammation. Reduction of Snapin hindered the maturation of autophagosome and phagosome, resulted in autophagosome accumulation and delayed bacterial clearance in MΦs. In this study, we further explored the mechanisms by which Snapin is involved in autophagy in MΦs as well as its role on monocyte to MΦ differentiation.

Methods: The reduction of Snapin in primary human MΦs was performed using siRNA, while in J774A mouse MΦ cell line was implemented by infection with a lentiviral vector expressing Snapin shRNA. Snapin, Lamp1 and LC3B protein levels were determined by Western blot analysis. Cell fractions enriched in lysosomes were isolated using density gradient centrifugation. Autophagosomes were purified by anti-LC3B antibody and Dyna magnetic beads. Autophagy in MΦs was detected by electron microscopy as well as by LC3B punctae determined by immunofluorescence microscopy. Human peripheral blood monocytes isolated by counter-flow elutriation were differentiated in 20% FBS plus CSF-1. Non-specific (NS), Snapin, or Beclin 1 siRNA was transfected into monocytes at Day0 and Day3 by lipofectamine. Monocyte to MΦ differentiation was measured by morphology and by the levels of differentiation markers CD163 and CD71 by flow cytometry.

Results: The forced reduction of Snapin in primary human MΦs and the murine J774A MΦ cell line resulted in increased late autophagosome vacuoles that contain partially digested organelles and other cellular material. Large sized LC3 punctae were also dramatically increased in these MΦs detected by immunofluorescence. These changes were similar to those observed by inhibition of lysosomal maturation with chloroquine but not the induction of autophagy by starvation or rapamycin. The results suggest that the reduction of Snapin blocked autophagy efflux. Snapin was abundant in lysosome-enriched cell organelles in MΦs. Snapin also co-isolated with LC3B and Lamp1 in autophagosomes which were isolated by anti-LC3B antibody from the lysosome-enriched fraction. By co-IP, Lamp1 was co-purified with Snapin employing MΦ cell lysates. These data suggest that Snapin directly interacted with Lamp1 and is necessary for the maturation of autophagosomes.

The control monocytes transfected with NS siRNA differentiated normally after 5 days into MΦs determined phenotypically and by the strong expression of both CD163 and CD71. However, monocytes transfected with Snapin or Beclin1 siRNA appeared as small round cells that loosely attached to plastic and the expression of both CD163 and CD71 was greatly reduced. These results indicate that arresting autophagy, by the reduction of Beclin1, or Snapin, suppressed monocyte to MΦ differentiation.

Conclusion: Snapin is required for the fusion of lysosomes with autophagosomes and the maturation of autophagosomes which is critical for monocyte to MΦ differentiation. These observations suggest that Snapin contributes to the pathogenesis of RA and may be a therapeutic target.

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Ligation Of TLR5 Promotes Myeloid Cell Infiltration and Differentiation Into Mature Osteoclasts In RA Patients and Experimental Arthritis. Seung-jae Kim[1], Zhenlong Chen[1], Nathan D. Chamberlain[1], Michael V. Volin[2], Suncica Volkov[1], William Swedler[1], Shiva Arami[1], Anjali Mehta[1], Nadera J. Sweiss[1] and Shiva Shahrara[1]. [1]University of Illinois at Chicago, Chicago, IL, [2]Chicago College of Osteopathic Medicine Midwestern University, Downers Grove, IL.

Background/Purpose: The aim of this study was to examine the importance of TLR5 ligation in the pathogenesis of rheumatoid arthritis (RA) and experimental arthritis.

Methods: The role of TLR5 ligation was determined on RA myeloid cell chemotaxis and osteoclast formation *in vitro*. Studies were conducted to investigate the mechanism by which TLR5 ligation promotes osteoclast

maturation in RA peripheral blood mononuclear cells (PBMC)s. Next, significance of myeloid and T cells were examined in osteoclastogenesis facilitated by TLR5 ligation. Finally, experiments were performed in collagen induced arthritis (CIA) as well as in TLR5 induced arthritis to assess the impact of joint TLR5 ligation on myeloid cell migration and osteoclast differentiation.

Results: We demonstrate that the TLR5 agonist, flagellin, is strongly chemoattractant for monocytes and can further facilitate differentiation of myeloid cells into mature osteoclasts. Consistently, RA synovial fluid induced myeloid cell infiltration and osteoclast differentiation is markedly suppressed by myeloid TLR5 blockade. We show that flagellin ligation of TLR5 promotes RA osteoclast differentiation through induction of receptor activator of nuclear factor kappa-B (RANK) on myeloid cells (by 8 fold) and its corresponding ligand, RANKL, from T cells (by 2 fold). We found that ligation of TLR5 could drive precursor myeloid cells to form fully mature osteoclasts in the absence of T cells when monocytes were cultured in the presence of suboptimal doses of M-CSF and RANKL. These results suggest that monocytes are the effector cells in TLR5 mediated osteoclastogenesis and that flagellin can facilitate osteoclast formation by increasing RANK expression and by allowing the cells to be more responsive to RANKL binding, hence lower levels of RANKL is required for this process. We next asked whether homing and differentiation of myeloid cells to mature osteoclasts are altered in acute and/or chronic arthritis driven by TLR5 ligation. We document that when CIA mice were therapeutically treated with TLR5 agonist, joint swelling was markedly greater in mice that received flagellin treatment compared to the PBS control. We also show that the F480 staining, number of TRAP+ cells and the concentration of bone erosion markers calcitonin receptor, Cathepsin K and RANKL (8–34 folds) were lower in the control ankles compared to the flagellin treated CIA joints. Since CIA ankle swelling and bone erosion were exacerbated by flagellin post onset treatment we next asked whether local injection of flagellin alone could drive joint inflammation and osteoclastogenesis. We demonstrate that ectopic TLR5 ligation elevates ankle circumference from day 0 to 2, subsequently joint inflammation plateaus until day 8, however swelling remains consistently higher than the PBS group. Corroborating with the CIA data, i.a. injection with flagellin resulted in 10 fold greater mature osteoclasts compared to the control group.

Conclusion: These novel results demonstrate for the first time that in RA as well as in acute and chronic experimental arthritis models, flagellin ligation to joint TLR5 contributes to myeloid cell infiltration and osteoclast maturation.

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Rheumatoid Arthritis Synovial Fibroblasts Lack Tolerization Of Inflammatory Cytokines and Matrix Degrading Enzymes After Repeated LPS Stimulation. Kerstin Klein[1], Renate E. Gay[1], Christoph Kolling[2], Adrian Ciurea[3], Beat A. Michel[4], Lih-Ling Lin[5], Steffen Gay[1] and Caroline Ospelt[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Schultess Clinic, Zurich, Switzerland, [3]University Hospital of Zurich, Zurich, Switzerland, [4]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [5]Pfizer, Cambridge, MA.

Background/Purpose: In macrophages, repeated stimulation of Toll-like receptor (TLR) 4 leads to adaptation of signaling pathways and epigenetic modifications resulting in a tolerant state of the cell and protecting inflamed tissues from inflammation-induced damage. We hypothesized that a lack of tolerization in rheumatoid arthritis synovial fibroblasts (RASF) significantly contributes to sustained inflammation and inflammation-induced damage seen in RA.

The objective was to investigate tolerizable and non-tolerizable effects in RASF compared to macrophages.

Methods: RASF and *in vitro* differentiated peripheral blood derived macrophages from healthy donors and RA patients were treated with LPS (100 ng/ml). 24h after the initial stimulation, cells were re-stimulated with LPS (10 ng/ml) for another 24h. Supernatants were collected from the second treatment period for ELISA and cells were harvested for isolation of RNA or protein extracts after a total treatment period of 48h. The expression of different genes, including cytokines and chemokines (IL6, CCL5, IL33, CXCL10), matrix metalloproteinases (MMP1, MMP3, MMP13), receptors (TLR2, TLR3, TLR4, MDA5, RIG1) as well as signaling molecules, activators and inhibitors of the TLR pathway (SHIP1, SOCS1, TNFAIP3, OAS1) was analyzed by quantitative Real-time PCR, Western blotting and ELISA. Nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) promoter activities in RASF were evaluated by Dual-Luciferase reporter assays after repeated stimulation with LPS (100 ng/ml, 10 ng/ml).

Results: As expected, the expression of IL6 decreased in double-stimulated (886 $\pm$ 596 pg/ml) compared to single-stimulated (2368 $\pm$ 315 pg/ml; $p<0.01$) macrophages from healthy donors (n=4) and RA patients (n=6, $p=0.06$). On the other hand, RASF (n=10) maintained their production of IL6 after repeated TLR4 stimulation and secreted 13237 $\pm$ 5764 pg/ml IL6 after a single LPS stimulation and 12421 $\pm$ 7178 pg/ml IL6 after double stimulation. A lack of tolerizable effects after LPS stimulation of RASF was also found for MMP1, MMP3, MMP13, CCL5, IL33, TLR3 and TNFAIP3. Interestingly, the known interferon-responsive genes OAS1, RIG1, MDA5 and CXCL10 were tolerizable not only in macrophages but also in RASF. RASF (n=5) secreted 531 $\pm$ 385 pg/ml CXCL10 after a single LPS stimulation and 111 $\pm$ 97 pg/ml CXCL10 after double stimulation ($p<0.05$). TLR4 mRNA was not changed in macrophages or in RASF by LPS double stimulation suggesting that a change of TLR4 expression itself was not responsible for tolerization. Reporter gene activities for NF-κB and AP-1 were similar in single and double stimulated RASF, excluding changes in signaling molecules as the underlying mechanism for tolerizable/non-tolerizable effects.

Conclusion: Based on the fact that neither TLR4 expression nor signalling pathways are altered by repeated LPS stimulation, epigenetic modifications on target gene promoters are likely to contribute to differences in tolerization between RASF and macrophages. Since many pro-inflammatory cytokines and MMPs are non-tolerizable genes in RASF, we conclude that the lack of tolerization in these cells keeps them aggressive in persistent inflammation.

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Poly(I:C)-Induced Cell Death Of Synovial Fibroblasts via an Unknown dsRNA Receptor. Jörg Hamann[1], Paul P. Tak[2] and Olga N. Karpus[1]. [1]Academic Medical Center, Amsterdam, Netherlands, [2]GlaxoSmithKline U.K. and Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands.

Background/Purpose: Rheumatoid arthritis (RA) is characterized by hyperplasia of the synovial tissue due to local proliferation of stromal and recruitment of inflammatory immune cells. Accumulation of synovial fibroblasts likely is due to an imbalance between cell proliferation, survival and death. Both cytosolic dsRNA receptors, MDA5 and RIG-I, can initiate pro-apoptotic signalling in a variety of cell types. In animal models of cancer and multiple sclerosis, treatment with dsRNA ligands causes apoptosis of effector cells and ameliorates disease. We showed that fibroblast-like synoviocytes (FLS) from RA synovial tissue are equipped with functional cytosolic dsRNA receptors. We have studied the consequences of stimulation with dsRNA on the survival of FLS.

Methods: FLS from arthritis patients were stimulated with poly(I:C) or 3pRNA complexed with fugene (FG) for intracellular uptake. Stimulation was confirmed by RT-PCR of dsRNA response genes (MDA5, RIG-I and CXCL10). Cell death of FLS after triggering of dsRNA sensors was detected by flow-cytometric analysis using annexin V/PI staining. Changes in protein expression of anti- and pro-apoptotic genes were analyzed by Western blot. Knockdown of MDA5, RIG-I and their adaptor proteins was performed using SMART pool siRNAs.

Results: dsRNA response genes, including MDA5, RIG-I and CXCL10 were similarly induced after 16 h stimulation of RA FLS with either 3pRNA or poly(I:C), complexed with FG. However, 3pRNA + FG treatment of FLS caused about 15% of cell death after 48 h, whereas poly(I:C) + FG treatment induced up to 75% cell death. Surprisingly, we did not find differences in the expression of pro- and anti-apoptotic proteins between cells stimulated with 3pRNA + FG or poly(I:C) + FG. siRNA knockdown of MDA5, a known receptor for poly(I:C), did not effect poly(I:C) + FG stimulation on dsRNA response genes, whereas knockdown of RIG-I, a known receptor for 3pRNA, completely abrogated the response to 3pRNA + FG. Knockdown of downstream adaptor proteins IPS, STING and TRIF did not have any effect on dsRNA response genes after poly(I:C) + FG stimulation.

Conclusion: Stimulation of RA FLS with artificial dsRNA poly(I:C), but not 3pRNA induced apoptosis of FLS. We confirmed that 3pRNA is recognized by the dsRNA sensor RIG-I. In contrast, intracellular recognition of poly(I:C) in FLS does not involve MDA5 and the adapter proteins IPS, STING and TRIF, suggesting the existence of a different recognition mechanism.

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1155 WITHDRAWN

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Suppression Of Immune Responses and Joint Inflammation By Myeloid-Derived Suppressor Cells In a T Cell-Dependent Mouse Model Of Rheumatoid Arthritis. Katalin Mikecz[1], Julia Kurko[1], Timea Ocsko[1], Andras Vida[1], Beata Tryniszewska[1], Tibor A. Rauch[1], Joel A. Block[1], Robert S. Katz[2], Anjali Nair[1], Carla R. Scanzello[1] and Tibor T. Glant[1]. [1]Rush University Medical Center, Chicago, IL, [2]Rush Medical College, Chicago, IL.

Background/Purpose: Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of innate immune cells with immunosuppressive properties. We previously identified MDSCs in the synovial fluid (SF) of mice with proteoglycan-induced arthritis (PGIA), a T cell-dependent model of rheumatoid arthritis (RA). Although SF MDSCs potently inhibited antigen-specific T cell proliferation in vitro, they were not available in quantities necessary for testing their in vivo suppressive activity in PGIA. Using bone marrow (BM)-derived MDSCs, expanded in culture in the presence of growth factors, we sought to determine whether these cells could exert suppression on antigen-specific responses and arthritis severity upon their transfer to syngeneic mice with PGIA. An important additional goal of this study was to identify MDSCs in the SF of human patients with RA.

Methods: As reported previously, MDSCs with strong suppressor activity were successfully expanded from murine BM in vitro in the presence of GM-CSF, G-CSF, and IL-6. We used the adoptive transfer model of PGIA, in which spleen cells from arthritic wild type donors were injected with antigen (PG) into syngeneic SCID recipients. After the clinical signs of arthritis began to develop, the SCID mice were divided into groups with similar average disease scores. The control groups received a second injection of arthritic spleen cells and PG, while the experimental groups received the same plus MDSCs. Disease severity was monitored by visual scoring. Three weeks later, spleen cells from the SCID recipients were tested for antigen (PG)-specific proliferation, and sera were assayed for anti-PG antibody titers. Human SF and blood were obtained from consenting RA patients undergoing therapeutic joint aspiration. The phenotype of SF cells was determined by flow cytometry with antibodies to human MDSC-specific markers. The ability of RA SF MDSCs to suppress T cell proliferation was tested by culturing autologous blood mononuclear cells in the presence or absence of SF cells. T cell proliferation was induced via anti-CD3/CD28 antibodies or with Mitomycin C-treated allogeneic lymphocytes.

Results: Arthritis severity in SCID mice injected with BM MDSCs were significantly lower (mean score 3.5) than in control mice injected with spleen cells only (mean score 8.25) (n=10 mice/treatment). PG-specific T-cell responses and serum IgG1 type antibodies were also significantly reduced in the BM MDSC recipient groups. Regarding the human system, both granulocytic and monocytic MDSC-like cells were identified in SF samples (n=9) from RA patients. RA SF MDSCs suppressed the proliferation of autologous blood T cells ex vivo, although the inhibitory effects were not as strong as those in the murine system. Depletion of T cells from the RA SF cell population further improved the MDSC-mediated suppression of blood T cell proliferation.

Conclusion: Murine BM-derived MDSCs effectively suppress arthritis upon injection into SCID mice developing adoptively transferred PGIA. Cells with MDSC-like phenotype and immunosuppressive activity are also present in the SF of RA patients. Our results suggest that MDSCs could represent a novel therapeutic tool in RA.

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Peptidylarginine Deiminase Inhibition Prevents Neutrophil Extracellular Trap Formation, Modulates Innate Immune Responses, and Reduces Vascular Damage In Mice. Jason S. Knight[1], Wei Luo[2], Alexander A. O'Dell[1], Wenpu Zhao[1], Venkataraman Subramanian[3], Chiao Guo[2], Robert C. Grenn[1], Paul Ryan Thompson[3], Daniel T. Eitzman[2] and Mariana J. Kaplan[1]. [1]University of Michigan Rheumatology, Ann Arbor, MI, [2]University of Michigan Cardiology, Ann Arbor, MI, [3]The Scripps Research Institute, Jupiter, FL.

Background/Purpose: Neutrophil extracellular trap (NET) formation promotes vascular damage, while stimulating interferon alpha (IFN-α) production in diseased arteries. Patients with rheumatoid arthritis and systemic lupus erythematosus have evidence of exaggerated NET formation, and suffer from a propensity toward accelerated atherosclerosis. Peptidylarginine deiminase (PAD) inhibition is a strategy that can decrease *in vivo* NET formation. We tested whether PAD inhibition can inhibit innate immune responses and reduce vascular damage in murine models of atherosclerosis.

Methods: $Apoe^{-/-}$ mice were treated for 10 weeks with daily injections of Cl-amidine, a PAD inhibitor. Innate immune responses including NET release and IFN-α production were characterized, as was anti-NET autoantibody formation. Degree of atherosclerosis and time to carotid artery thrombosis were also determined.

Results: In $Apoe^{-/-}$ mice, we found evidence of accelerated NET formation, enhanced IFN-α production in diseased arteries, and autoantibody formation to components of NETs. Further, PAD inhibition blocked NET formation, reduced atherosclerotic lesion area, and delayed time to carotid artery thrombosis in a photochemical injury model. Decreases in atherosclerosis burden were accompanied by reduced recruitment of netting neutrophils and macrophages to arteries, as well as by reduced arterial IFN-α expression.

Conclusion: A pharmacologic intervention that blocks NET formation can reduce atherosclerosis burden in murine systems. These results support a role for aberrant NET formation in the pathogenesis of atherosclerosis through modulation of innate immune responses, with implications for the accelerated atherosclerosis of rheumatoid arthritis and systemic lupus erythematosus.

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Decreased NK-Cell Numbers and Upregulation Of Markers Of Systemic Inflammation In Autoantibody –Positive Arthralgia Patients and Early Rheumatoid Arthritis Patients But Not In Autoantibody-Negative Rheumatoid Arthritis Patients. Paulina Chalan, Johan Bijzet, Kornelis S.M. van der Geest, Bart-Jan Kroesen, Annemieke M.H. Boots and Elisabeth Brouwer. University Medical Center Groningen, Groningen, Netherlands.

Background/Purpose: Identification of seropositive individuals at risk for arthritis development would open opportunities for early clinical intervention. In a recent study on seropositive arthalgia patients (SAP), 35% of the patients were found to develop RA within 12 months (van de Stadt et al, *Ann Rheum Dis* 2012). Not only autoantibodies precede clinically apparent synovitis but also serological immune features are modulated prior to the development of clinical synovitis (Rantapää-Dahlquist et al, *Ann Rheum Dis* 2007). So far, little is known on modulation of leukocyte subsets before arthritis development. Therefore, in a cross sectional study, we investigated and compared the numbers of circulating leukocyte subsets and levels of cytokines, cytokine receptors, chemokines in SAP, new-onset RA and in long-standing RA patients.

Methods: Whole blood samples obtained from 32 patients with arthralgia who were ACPA and/or RF-positive (termed seropositive arthralgia patients [SAP]), 50 early RA (39 were ACPA+ and/or RF+, 11 were ACPA- and RF-), 11 long-standing RA patients (all were ACPA+ and/or RF+) and 33 healthy controls (HC) were used to quantify the absolute numbers of leukocyte populations. Serum samples from 20 HC, 30 SAP, 21 early ACPA/RF+, 11 early ACPA/RF- RA and 8 long-standing RA patients were used to quantify systemic levels of cytokines, cytokine receptors and chemokines using Human Cytokine 25-plex Panel.

Results: Seropositive arthralgia patients showed a decrease of both the absolute number and the frequency of NK-cells compared to HC (p=0.006 and p=0.004, respectively). A similar decrease of NK-cell absolute number and frequency was observed for ACPA/RF+ early RA patients (p=0.004 and p=0.018, respectively) but not for ACPA/RF- early RA patients. The majority of systemic cytokines/cytokine receptors (IL-1β, IL-1RA, IL-2R, TNF-α, IFN-α, IL-4, IL-17, IL-2, IL-15, GM-CSF) and chemokines (MIP-

1β, IL-8, Rantes, Eotaxin, MCP-1, MIP-1α, MIG) were found to be elevated both in SAP and in early ACPA/RF+ RA compared to HC, while the levels found in ACPA/RF- RA patients were similar to HC.

Conclusion: Seropositive arthralgia patients, showed decreased numbers of circulating NK-cells and upregulation of various mediators of systemic inflammation. The same was found in ACPA/RF-positive early RA but not in ACPA/RF- negative early RA. Immune alterations found in SAP and early RA seem to be related to the presence of ACPA and or RF. In addition, marked differences in leukocytes and inflammatory markers between autoantibody- positive and –negative early RA patients suggest clear differences in disease pathogenesis between these groups.

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Exercise Suppresses Systemic Inflammation Via Inhibition Of NF-κB Activation In Monocytes. Alisa Blazek[1], Derrick Knapik[1], Lai-Chu Wu[2], Nicholas A. Young[2], Wael N. Jarjour[2] and Sudha Agarwal[2]. [1]The Ohio State University, Columbus, OH, [2]The Ohio State University Wexner Medical Center, Columbus, OH.

Background/Purpose: Inflammation is integral to joint damage and bone erosion in rheumatoid arthritis. We reported previously that physiologic levels of exercise are anti-inflammatory and suppress local inflammation of joints *in vivo*. Here, we demonstrate that the physiological levels of exercise are potent systemic biological response modifiers that block monocyte/macrophage activation.

Methods: Mice carrying a transgene containing a modified firefly luciferase cDNA whose expression is under the control of NF-κB responsive elements were used to study the regulation of NF-κB activation by exercise (treadmill walking at 8M/min). LPS (1 μg/gm body weight) was injected in the paw to trigger inflammation. The mice were treated as follows: (i) no treatment (ii) exercise alone, (iii) LPS alone, (iv) pre-exercised (Pre-Ex) for 7 days prior to LPS injection, or (v) exercised post LPS injection (Post-Ex). Activation of NF-κB was assessed following LPS injection by digitizing bioluminescent activity. Multiplex ELISA was used to assess the induction of cytokines in the serum. Human macrophages were enriched from healthy peripheral blood and subjected to Interferon-γ and LPS stimulation +/− dynamic strain (2% at 0.5 Hz) for various time intervals to assess NF-κB activation.

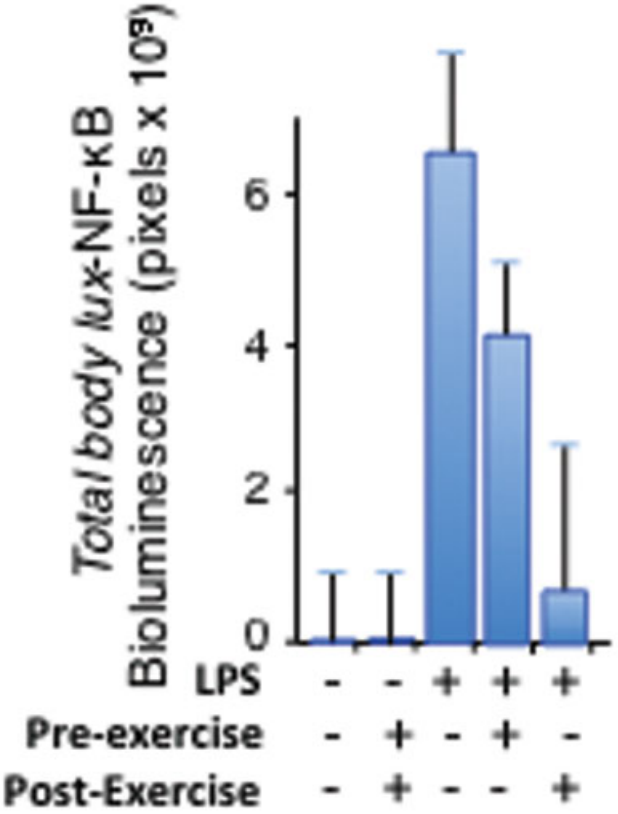

Fig. 1. Suppression of LPS induced NF-κB activation by LPS by Exercise in *NFκB-RE-luc* mice.

Results: Exercise alone did not induce significant NF-κB activation; whereas LPS injection in the right ankle provoked a robust systemic and local inflammatory response that was most severe within 2 h post-injection. Both Pre-Ex and Post-Ex mice showed a significant inhibition of LPS-induced NF-κB activation (Fig 1). As expected, the NF-κB activation was primarily in lymphatic tissue and at the site of LPS injection. Strikingly, exercise effectively suppressed LPS-induced NF-κB activation in all lymphatic tissues examined and at the site of injection. We next examined the tenacity of the effects of exercise and demonstrated that the anti-inflammatory response is transient, lasting only 24 h post-exercise. Assessment of the consequences of NF-κB inactivation by exercise (Both Pre-Ex and Post-Ex) revealed the suppression of multiple pro-inflammatory cytokines: IL-1β, TNF-α, IL-6, IL-17, IL-12 and IL-8. However, the effects of exercise were more dramatic (<90%) in Post-Ex than Pre-Ex mice. Using primary human macrophages, dynamic strain significantly suppressed NF-κB activation.

Conclusion: These findings suggest that exercise suppresses both local and systemic inflammation by inhibiting NF-κB activation in monocytes/macrophages. Importantly, these effects are transient, which supports the need for a regular exercise routine in order to achieve clinical efficacy. Our results (i) demonstrate that the signals generated by exercise are true biological response modifiers and (ii) provide the molecular basis for the actions of exercise in suppressing the inflammation observed in rheumatic diseases.

Disclosure: A. Blazek, None; **D. Knapik**, None; **L. C. Wu**, None; **N. A. Young**, None; **W. N. Jarjour**, None; **S. Agarwal**, None.

1160

Oxidative Stress As a Disease Marker and Therapeutic Target In Patients With Tumor Necrosis Factor Receptor Associated Periodic Fever Syndrome. Cornelia Cudrici[1], Ariel Bourla[1], Martin Pelletier[1], Leah Billingham[1], Amanda K. Ombrello[2], Michael Murphy[3], Daniel L. Kastner[4] and Richard M. Siegel[5]. [1]Immunoregulation Section, Autoimmunity Branch, Bethesda, MD, [2]National Human Genome Research Institute, National Institute of Health, Bethesda, MD, [3]Medical research council mitochondria biology unit Cambridge, UK, Cambridge, United Kingdom, [4]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [5]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD.

Background/Purpose: TRAPS (Tumor necrosis factors receptor associated periodic fever syndrome) is an autosomal dominant autoinflammatory disease associated with missense mutations in *TNFRSF1A* (tumor necrosis factor receptor superfamily, member 1A) gene. Our laboratory has recently demonstrated a role for mitochondrial reactive oxygen species (ROS) in triggering the hyper-responsiveness characteristic of cells from TRAPS patients. When the level of ROS generation exceeds the anti-oxidant defense capacity of the cell, oxidative damage to macromolecules including DNA ensues. We have investigated the metabolic sources of mitochondrial ROS production and levels of oxidative stress in cells from TRAPS patients, and will test the ability of MitoQ, a mitochondrial-targeted anti-oxidant to ameliorate symptoms in TRAPS patients.

Methods: Peripheral blood mononuclear cells (PBMC) from TRAPS patients and mouse embryonic fibroblasts (MEFs) from mice engineered to express TNFR1 mutations were analyzed for mitochondrial ROS production and quantification of oxidative DNA damage via the DNA adduct 8-oxo-guanine (by using flow cytometric method for detection of mitochondrial superoxide and 8-oxo-guanine). Blockers of fatty acid and glucose metabolism were used to investigate the fuels which favor ROS production and excess cytokine production in fibroblasts and myeloid cells from TRAPS patients and TNFR1 mutant mice.

Results: We previously showed that the increased inflammation in TRAPS is dependent on mitochondrial ROS rather than NADPH oxidases. Elevated levels of mitochondrial ROS were seen in cells from TRAPS patients and in mice with engineered TRAPS gene mutations. Monocytes from TRAPS patients but not from healthy donors showed significantly higher spontaneous mitochondrial ROS production. Blockade of fatty acid vs. glucose metabolism showed that fatty acid metabolism favors excess mitochondrial respiratory capacity, ROS production, and heightened expression of inflammatory cytokines after LPS treatment. Inhibition of mitochondrial ROS can reduce normal cytokine production and reverse hyperinflammatory responses in TRAPS.PBMC from TRAPS patients and MEFs from mice harboring TRAPS associated TNFR1mutation have increased levels of oxidized DNA compared controls. Inhibition of mitochondrial ROS by Mito Q can reduce normal cytokine production and reverse hyperinflammatory

responses in PBMC from TRAPS patients and MEFs from mouse with similar mutations.

Conclusion: Our data suggest that mitochondrial ROS production and 8-oxo-guanine are increased in TRAPS patients and in mice engineered to express TNFR1 mutations compared with non-inflammatory controls. Pharmacological blockade of mitochondrial ROS by mitoQ reduces inflammatory cytokine production in vitro in TRAPS patients and mice with similar TNFR1 mutations. These findings suggest that mitochondrial ROS may be a novel therapeutic target for TRAPS patients. A phase 2 clinical therapeutic trial using Mito Q for TRAPS is planned.

Disclosure: C. Cudrici, None; **A. Bourla**, None; **M. Pelletier**, None; **L. Billingham**, None; **A. K. Ombrello**, None; **M. Murphy**, Antipodean Pharmaceuticals INC, 4; **D. L. Kastner**, None; **R. M. Siegel**, None.

1161

Microrna-155 As a Proinflammatory Regulator via SHIP-1 Down-Regulation In Acute Gouty Arthritis. Hye Mi Jin[1], Young-Nan Cho[1], Seung-Jung Kee[1], Dong-Jin Park[2], Yong-Wook Park[2], Shin-Seok Lee[2] and Tae-Jong Kim[1]. [1]Chonnam National University Medical School and Hospital, Gwangju, South Korea, [2]Chonnam National University Medical School, Gwangju, South Korea.

Background/Purpose: Gout is characterised by episodes of intense joint inflammation in response to intra-articular monosodium urate monohydrate (MSU) crystals. miR-155 is crucial for the proinflammatory activation of human myeloid cells and antigen-driven inflammatory arthritis. Since, the functional role of miR-155 in gouty arthritis has not been defined. The aim of this study was to examine the role of miR-155 in pathogenesis of acute gouty arthritis.

Methods: Samples from 14 patients with gouty arthritis and 10 healthy controls (HCs) were obtained. Peripheral blood mononuclear cells (PBMCs) and synovial fluid mononuclear cells (SFMCs) were cultured *in vitro* with MSU crystals, and gene expression (human miR-155 and Src homology 2-containing inositol phosphatase, SHIP-1) were assessed by real-time PCR. THP-1 cells and human monocyte-drived macropharges were stimulated by MSU crystals and/or miR-155 transfection. Whole-cell lysates were subjected to Western blot analysis. Human TNF-α and IL-1β in cell culture supernatants were measured by Luminex. Immunohistochemistry was performed on formalin-fixed gout tissues with anti–SHIP-1 Ab. Gout peritonitis mice (Male C57BL/6J) model used to analyze expressions of miR-155, SHIP-1, and inflammatory cytokines.

Results: The samples from gouty arthritis proved to be highly enriched in miR-155, with levels of expression being higher than those found in PBMC from HC. Mir-155 was found to be strongly induced by stimulation of MSU crystals after 24 hours and their expressions gradually decreased. Stimulating with MSU crystals, the level of SHIP-1 was found to be gradually decreased in according to overexpression of mir-155. miR-155 promoted MSU-induced proinflammatory cytokine production such as TNF-α and IL-1β. Consistent with *in vitro* observations, miR-155 expression was also elevated in gout mice model. The production of inflammatory cytokines was markedly increased in MSU crystal induced peritonitis mice.

Conclusion: Our study confirmed that overexpression of miR-155 in SFMC led to down-regulation of SHIP-1 and an increase in the production of proinflammatory cytokines.

Disclosure: H. M. Jin, None; **Y. N. Cho**, None; **S. J. Kee**, None; **D. J. Park**, None; **Y. W. Park**, None; **S. S. Lee**, None; **T. J. Kim**, None.

1162

The Role Of Microrna 155 In Innate Immunity and Arthritis. Antonia Puchner, Victoria Saferding, Eliana Goncalves-Alves, Josef S. Smolen, Kurt Redlich and Stephan Blueml. Medical University of Vienna, Vienna, Austria.

Background/Purpose: MicroRNA 155 (miR155) has been demonstrated to be essential for the development of collagen induced arthritis by controlling the generation of autoreactive T and B cells. However, the contribution of miR155 in innate immune cells is not known.

Methods: We analyzed activation and cytokine production of macrophages and dendritic cells (DCs) *in vitro* and *in vivo*. We analyzed T-cells stimulatory capacity of DCs. We crossed miR155 deficient mice into hTNFtg mice and analyzed arthritis development clinically as well as histologically.

Results: MiR155 deficiency did not alter the expression of costimulatory molecules or MHCII expression after stimulation of macrophages and DCs *in vitro* and *in vivo*. We also Facs-sorted DCs after stimulation with LPS in vivo and determined the production of proinflammatory cytokines such as IL-23, IL-6 as well as TNF. We did not detect differences between wt and miR155$^{-/-}$ mice. In addition, the T cell stimulatory capacity of wt and miR155$^{-/-}$ was identical. When we analyzed hTNFtg/miR155$^{-/-}$ mice compared to wt mice, we did not detect differences in the clinical signs and symptoms of arthritis. Histologically, we even found slightly increased synovial inflammation in hTNFtg/miR155$^{-/-}$ mice compared to wt mice.

Conclusion: In contrast to the pivotal role of miR155 in autoimmunity requiring the adaptive immune system, the role of miR155 in innate immunity seems to be limited. This is emphasized by the fact that miR155 hardly influences the course of TNF-driven arthritis, which is mainly dependent on components of the innate immune system.

Disclosure: A. Puchner, None; **V. Saferding**, None; **E. Goncalves-Alves**, None; **J. S. Smolen**, None; **K. Redlich**, None; **S. Blueml**, None.

1163

The Receptor For Advanced Glycation End Products (RAGE) As a Modulator Of Inflammatory Responses and Its Contribution To Gender-Specific Effects During Arthritis. Timo Wirth[1], Christoph Kessel[1], Philipp Becker[1], Toni Weinhage[2], Nadine Nippe[2] and Dirk Foell[1]. [1]University of Muenster, Muenster, Germany, [2]University of Muenster, Münster, Germany.

Background/Purpose: The receptor for advanced glycation end products (RAGE) is a multi-ligand receptor expressed on various cells which interacts with a diverse class of ligands, e.g. 'danger signals' such as neutrophil-derived S100A12. RAGE has been implicated in the pathogenicity of various inflammatory diseases including inflammatory arthritis. However, the exact role of RAGE has not been sufficiently defined. Our recent data on S100A12-induced activation of monocytes points to a modulatory rather than pro-inflammatory function of human RAGE. To assess the role of RAGE in a more systematic way, we generated RAGE−/− mice and analyzed immune cell functions *in vitro*, followed by murine models of *staphylococcus aureus* infection (host defense), chemically induced colitis (mucosal immunity), lethal inflammatory liver injury (septic shock) and collagen induced arthritis (autoimmunity) comparing RAGE−/− and C57BL/6 wildtype (wt) mice.

Methods: Reactive oxygen species (ROS) production, phagocytosis and cytokine production of bone marrow derived monocytes were measured using flow cytometry. *Staphylococcus aureus* (*S. aureus)*infection was induced by footpad injection. Acute and chronic colitis were induced chemically by dextran sodium sulfate (DSS) solution. For the inflammatory liver injury model, mice were challenged with D-galactosamine (D-Gal) along with lipopolysaccharide (LPS). Arthritis was induced by injection of heterologous type II collagen (CII).

Results: We observed no differences of cellular immune function (ROS and cytokine production, phagocytosis) in RAGE−/− compared to wt monocytes. Male, but not female RAGE−/− mice showed more footpad swelling and bacterial dissemination in the *S. aureus* infection model. In the DSS colitis model we observed no significant differences between the two strains, whereas RAGE−/− mice were significantly protected from lethal D-Gal/LPS induced liver injury. RAGE−/− and wt mice develop arthritis at similar clinical scores and incidence with no significant differences in type II collagen autoantibody levels. However, in female animals there is a strong tendency towards aggravated disease, less remission and higher disease penetrance.

Conclusion: Overall, the contribution of RAGE seems to largely depend on the disease model and cell type studied. While no overall differences with respect to immune cell activities were observed, a striking gender-specific effect of RAGE seems to be involved in some conditions, especially in arthritis. The exact role of RAGE and its soluble form (sRAGE) during the development of arthritis and the influence of gender-specific factors is under further investigation.

Disclosure: T. Wirth, None; **C. Kessel**, None; **P. Becker**, None; **T. Weinhage**, None; **N. Nippe**, None; **D. Foell**, None.

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Both Endosomal and Surface Toll-Like Receptors Can Act As Biomarkers In Lupus. Maria Perez-Ferro, Cristina Serrano, Fredeswinda I. Romero, María J Martínez-Becerra, Jorge E Rojas, María Sanchez-Blazquez, Raquel Largo, Juan A Martínez-López, Gabriel Herrero-Beaumont and Olga Sanchez-Pernaute. Jiménez Díaz Foundation University Hospital, Madrid, Spain.

Background/Purpose: Toll-like receptors (TLR) are a major class of pathogen detectors in the cell that can trigger the innate defense and lead to activation of immunocompetent cells. Endosomal TLR have been recently associated to the pathogenesis of SLE and to the production of autoantibodies. In this study we have explored associations between TLR and disease phenotypes, which could help us understand pathogenesis and find biomarkers in specific subgroups of patients.

Methods: Thirty four patients diagnosed with lupus and 12 matched healthy controls were recruited. Patients had stable treatment during the last 4 weeks prior to recruitment. Cumulative features, and serologic markers were registered. Selena-SLEDAI and BILAG scales were employed to measure disease activity. The distribution of peripheral blood mononuclear cells (PBMC) subpopulations and their expression of TLR2, TLR4, TLR3, TLR7, and TLR9 were analyzed in patients and controls with flow cytometry. Statistics were carried out with Spearman's correlation and Mann Whitney tests for independent samples, setting significance at 95%. The relationship between dual variables was assessed with contingency tables and Fisher's exact test, setting significance at 99%.

Results: The appearance of TLR3, TLR7, and TLR9 in lymphoplasmocytoid (CD19lp) cells was higher in SLE than in healthy controls. The presence of TLR3 in CD19 cells (n = 9) was associated to active disease (p 0.006), hypocomplementemia (p 0.002), and SLEDAI and BILAG scores (p 0.018, p 0.012). SLEDAI scores were also higher in patients with TLR9 expression in CD19 cells (n= 14, p 0.044). The percentage of CD19lp cells expressing TLR3, and TLR9 increased with SLEDAI scores (rho 0.401, p 0.021; and rho 0.403, p 0.02, respectively), but not with other activity measures.

Subgroups of patients with TLR2 expression in CD3+ cells (n = 5) or in CD19+ cells (n = 6) displayed higher activity as reflected by SLEDAI (p 0.05, p 0.015) and BILAG (p 0.005, p 0.004) scores. Patients with TLR4 in CD3+ cells (n = 5) or in CD19+ cells (n = 6), showed higher SLEDAI scores (p 0.05, p 0.045), while presence of TLR4 in CD19+ and in monocytes (n = 5) were associated to higher BILAG scores (p 0.004, p 0.005). Serological markers of activity were also found more frequently in patients showing expression of TLR2 or TLR4 in PBMC. Furthermore, the appearance of TLR2 or TLR4 in CD19+ cells, CD3+ cells or monocytes was associated with renal disease and with major organ involvement. Interestingly, patients with positive past history for bacterial or viral infections more often showed TLR2 and TLR4 in CD3 and CD19+ cells, and TLR4 in monocytes (CI 99%).

Conclusion: Endosomal TLR were found significantly enhanced in patients with lupus compared to controls, and TLR3 and TLR9 expression by CDlp cells could be used as a biomarker of disease activity. However, the induction of TLR2 and TLR4 in different PBMC subsets identified a subgroup of patients with high activity, whom frequently displayed major organ involvement. Our data suggest that there could be a subgroup of patients with lupus, in whom exposure to germs could sensitize immunocompetent cells, and facilitate their activation during flares.

Disclosure: M. Perez-Ferro, None; **C. Serrano**, None; **F. I. Romero**, None; **M. J. Martínez-Becerra**, None; **J. E. Rojas**, None; **M. Sanchez-Blazquez**, None; **R. Largo**, None; **J. A. Martínez-López**, None; **G. Herrero-Beaumont**, None; **O. Sanchez-Pernaute**, None.

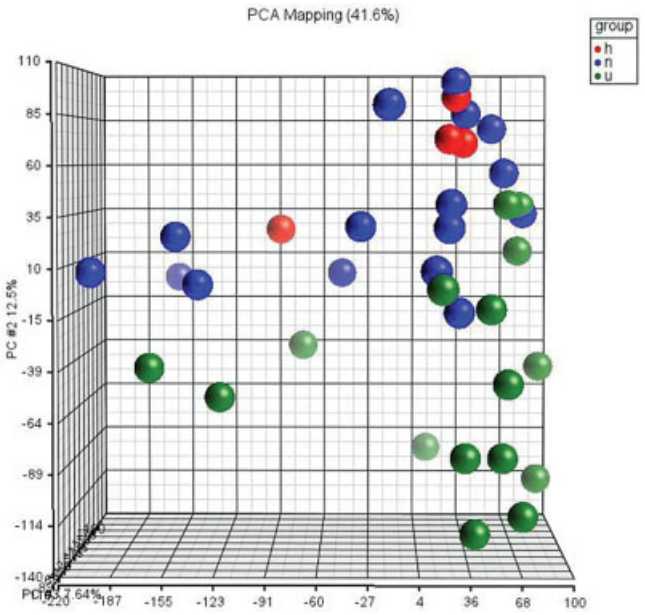
1165

Systems Approach To The Study Of the Microbiome and Inflammatory Pathways In Oral Ulcer Tissue From Patients With Active Behçet's Syndrome (BS). Cailin Sibley[1], Gulen Hatemi[2], Yusuf Yazici[3], Yin Liu[4], Steve Brooks[1], Hasan Yazici[5] and Raphaela Goldbach-Mansky[6]. [1]NIH/NIAMS, Bethesda, MD, [2]Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [3]NYU Hospital for Joint Diseases and New York University School of Medicine, New York, NY, [4]NIAMS/NIH, Bethesda, MD, [5]Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey, [6]National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD.

Background/Purpose: Behcet's syndrome (BS) exhibits features of both innate and acquired immunity. Oral ulceration is the cardinal lesion which usually precedes other manifestations. Despite the presence of clues from clinical and basic research suggesting the role of an infectious trigger in pathogenesis, a specific microorganism has not been identified. 16S rRNA sequencing provides an advantage over conventional techniques as it is quantitative and not reliant on tissue culture. This study aims to assess the microbiome in oral ulcer tissue in Turkish BS patients compared to non-lesional and healthy control mucosal tissue in parallel with pathogen recognition and pro-inflammatory cytokine pathways.

Methods: 5mm punch biopsies were obtained from ulcerated oral tissue and the contralateral unaffected side in 16 BS patients and 5 ethnically matched controls. Each sample was divided in half with16S rRNA sequencing of bacterial genomes performed in one half and mRNA-Seq performed in the other half. RNA-Seq data was probed by gene set enrichment analysis (GSEA) for the following pathways important in pathogen recognition: NOD-like receptor (NLR), Toll-like receptor (TLR), IL-1 receptor and IL-10 pathways.

Results: Bacterial sequence taxonomic representation of 16S rRNA sequencing data by Jaccard indices did not segregate 6 ulcerated, 6 unaffected and 4 normal control tissue samples on the basis of taxonomic membership. In contrast, a principal component analysis of RNA-Seq data showed the 16 ulcerated samples to cluster together with the 16 unaffected and 4 control samples clustering separately (See Figure. Green – ulcer, blue – unaffected, red – control). Of the 34,799 reads, 4595 transcripts were 2 fold or greater up-regulated in ulcerated compared to unaffected BS samples with 971 down-regulated greater than 2 fold. GSEA of NLR, TLR, IL-1 receptor and IL-10 pathways all showed enrichment in ulcerated compared to unaffected samples with normalized enrichment scores of 1.45, 1.48, 1.39 and 1.36 and nominal p-values of 0.02, 0.02, 0.11 and 0.05, respectively. These pathways did not differ between unaffected and control samples.



Conclusion: Taken together, these results show that while bacterial patterns did not differ in BS oral ulcers compared to unaffected mucosa or controls, pathways of pathogen recognition were enriched in ulcerated BS tissue. These pathways were not enriched in unaffected mucosa compared to controls. This may be due to non-bacterial triggers or may indicate an abnormal tissue response to normal flora supporting the previous contention that several microorganisms may be using a common pathway to trigger a series of events. Understanding these mechanisms is an area of active investigation.

Disclosure: C. Sibley, None; **G. Hatemi**, None; **Y. Yazici**, BMS, genentech, UCB, Abbvie, 5; **Y. Liu**, None; **S. Brooks**, None; **H. Yazici**, None; **R. Goldbach-Mansky**, None.

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Anti-Inflammatory Property Of HDL In NOD1 Ligand Induced Kawasaki Arteritis In Mice. Hajime Kono, Tamiko Yanagida, Kurumi Asako, Toshihiro Nanki, Hirotoshi Kikuchi, Akiko Okamoto, Akiko Onda and Maki Takayama. Teikyo University School of Medicine, Tokyo, Japan.

Background/Purpose: Atherosclerosis is a chronic metabolic disease of inflammatory processes. Immune cells including monocytes are recruited to the subintimal lesion of the vascular wall and store lipids to transform themselves to the foam cells. The lipid profiles in the serum are shown to be risk factors for developing atherosclerosis, such as high LDL (low density lipoprotein) or low HDL (high density lipoprotein) concentration. In addition to deliver cholesterol from vascular wall to liver, HDL is supposed to exert antiinflammatory properties which are not well characterized. We recently indentified that HDL exert an antiinflammatory property which is not ascribed to it's capacity to lower the cholesterol level of the peripheral tissue.

Objectives: To investigate the antiinflammatory function of reconstituted HDL (rHDL) in the Kawasaki arteritis murine model in vivo.

Methods: Coronary arteritis mimicking Kawasaki disease was induced by administrating 20 microgram of lipopolysaccharide followed by weekly injection of 500 microgram of the nucleotide-binding oligomerization domain 1 (NOD1) ligand FK-565 for 4 times. 2 mg of rHDL or control PBS was injected 4 times along with FK-565 administration. After a week after the last injection of FK-565 or control PBS, the severity of coronary arteritis was quantified by measuring the inflammation area surrounding the coronary arteries. The cytokine levels were determined by multiplex.

Results: The rHDL treatment reduced the inflammatory area of coronary arteries compared with the control PBS treated groups, showing statistically significance ($P=0.008$ with Student t-test, 0.29 ± 0.24 mm^2 (PBS control group) and 0.13 ± 0.07 mm^2 (rHDL group)). Serum level of IL12p40 was decreased inn mice treated with rHDL.

Conclusion: The data indicate that rHDL exert an antiinflammatory activity in the NOD1 ligand induced Kawasaki arteritis model in vivo.

Disclosure: H. Kono, None; **T. Yanagida**, None; **K. Asako**, None; **T. Nanki**, None; **H. Kikuchi**, None; **A. Okamoto**, None; **A. Onda**, None; **M. Takayama**, None.

1167

A Possible Mechanism Of NLRP3 Inflammasome Hypersensitivity In Cryopyrin-Associated Periodic Syndrome. Sayaka Ito, Chie Tagami, Yukichi Hara and Tetsuo Kubota. Tokyo Medical and Dental University, Tokyo, Japan.

Background/Purpose: NLRP3 in monocytes and other cell types plays a role in innate immunity as one of the intracellular pathogen recognition receptors, and its mutation is responsible for cryopyrin-associated periodic syndromes (CAPS). Once activated, NLRP3 forms a protein complex called the inflammasome with procaspase-1 and an adaptor protein ASC, leading to activation of caspase-1 and production of mature proinflammatory cytokine IL-1β. Some investigators have proposed a model of NLRP3-inflammasome containing CARD8, another adaptor protein, but the role of CARD8 in the NLRP3-inflammasome system remains obscure. In a previous ACR meeting, we presented some data suggesting that CARD8 normally plays a role as a negative regulator of NLRP3-inflammasome. In the assay system using HEK293 cells transiently transfected with genes for inflammasome components, CARD8 interacted with wild-type NLRP3 resulting in suppression of IL-1β secretion. In contrast, CARD8 did not interact with CAPS-associated mutant NLRP3. Current study aimed to extend the previous study to obtain more convincing data using also cells endogenously expressing components of NLRP3 inflammasome and CARD8.

Methods: HEK293 cells were transiently transfected with ASC, CARD8, procaspase-1, proIL-1β, and NLRP3. The interaction of CARD8 and NLRP3 was studied by immunoprecipitation using lysates of peripheral blood mononuclear cells (PBMCs). Human monocyte-derived macrophages (HMDMs) were obtained by culture of monocytes from peripheral blood cells with GM-CSF for 7 days. Control or specific siRNA against CARD8 was transfected to HMDMs and the knockdown efficacy was evaluated by quantitative RT-PCR. After priming with LPS, HMDMs were stimulated by ATP, and secreted IL-1β was measured by ELISA.

Results: When HEK293 cells were transfected with every inflammasome components, large amounts of IL-1β were secreted spontaneously, which was partially but significantly reduced by coexpression of CARD8. On the other hand, CARD8 did not suppress IL-1β secretion from the cells transfected with CAPS-associated mutant NLRP3 (R260W, D303N, H312P, or N477K). In immunoprecipitation experiments using resting PBMCs from healthy subjects, NLRP3 was precipitated with CARD8, but not with ASC. When PBMCs were primed with LPS followed by ATP stimulation, however, NLRP3 was precipitated with ASC instead of CARD8. By stimulating HMDMs with LPS and ATP, HMDMs secreted IL-1β, and it was further increased by CARD8 knockdown.

Conclusion: These results support our hypothesis that CARD8 normally associates with NLRP3 to prevent unnecessary activation of the inflammasome by subtle stimuli. Taken together with previous data which showed CARD8 was unable to bind to NLRP3 with CAPS-related mutation, one of the mechanisms of hypersensitivity of the NLRP3 inflammasome in CAPS patients might be the escape from CARD8 restriction.

Disclosure: S. Ito, None; **C. Tagami**, None; **Y. Hara**, None; **T. Kubota**, None.

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Innate Immune Cell Production Of Interleukin-12 Drives CpG-Induced Macrophage Activation Syndrome. Lehn K. Weaver and Edward M. Behrens. Children's Hospital of Philadelphia, Philadelphia, PA.

Background/Purpose: Hemophagocytic syndromes are caused by an uncontrolled systemic inflammatory response resulting in cytopenias, multisystem organ failure, and rapid death, often despite aggressive therapy. Macrophage activation syndrome (MAS) is one of the hemophagocytic syndromes known to complicate severe inflammatory diseases, and can be seen in patients with systemic rheumatologic conditions. Previous work describes a novel murine model utilizing repeated injection of CpG, a Toll-like Receptor 9 (TLR9) agonist, into wild-type mice to stimulate MAS. This model recapitulates the inflammatory, "cytokine storm" milieu and clinical features of MAS. TLR9, Interleukin (IL)-12 and interferon gamma are necessary for the development of MAS in this model. However, the initial cellular responses contributing to CpG-induced MAS remain elusive.

Methods: Wild-type (WT) and TLR9$^{-/-}$ bone marrow chimeras, transgenic clec4-DTR mice, and IL-12 reporter mice were treated with or without CpG, and parameters of MAS were measured. WT and TLR9$^{-/-}$ mixed *in vitro* splenocyte cultures were treated with or without CpG, and IL-12 production was measured from supernatants by ELISA and intracellular IL-12 was assessed by flow cytometry.

Results: We show that TLR9 expression within the hematopoietic compartment is necessary and sufficient for CpG-induced systemic inflammation. In contrast, TLR9 expression in radioresistant cells is not sufficient to drive CpG-mediated MAS. Surprisingly, depletion of individual innate immune cell populations does not alter the course of CpG-induced systemic inflammation including the depletion of plasmacytoid dendritic cells, cells known for their potent proinflammatory response to CpG. Using IL-12 reporter mice, IL-12 production upon CpG stimulation is shown to be redundant, as multiple innate immune cell populations produce IL-12 in this model. Finally, in contrast to *in vivo* infection models, mixed *in vitro* cultures of TLR9-deficient and TLR9-sufficient cells demonstrate that IL-12 production is intrinsic to cells capable of sensing CpG.

Conclusion: These data demonstrate that multiple innate immune cells contribute to CpG-induced immunopathology by producing IL-12. This redundancy in IL-12 production explains the inability to cure disease by targeting depletion of a single innate immune cell population. Futhermore, the ability of a cell to produce IL-12 is dependent on its ability to sense CpG through TLR9 expression. Thus, our data identify the most proximal cellular events leading to CpG-induced immunopathology providing novel insights into disease mechanisms and robust targets for the development of future therapeutic interventions in MAS.

Disclosure: L. K. Weaver, None; **E. M. Behrens**, None.

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A Novel Pro-Inflammatory Signaling Pathway Regulated By Follistatin-Like Protein 1. Yury Chaly[1], Anthony Marinov[2], Yu Fu[2], Brian Campfield[2], John Kellum[3], Bruce Hostager[1], Daniel Bushnell[2], Yudong Wang[2], Jerry Vockley[2] and Raphael Hirsch[1]. [1]University of Iowa Carver College of Medicine, Iowa City, IA, [2]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [3]University of Pittsburgh School of Medicine, Pittsburgh, PA.

Background/Purpose: Follistatin-like protein 1 (FSTL1) is a secreted glycoprotein produced mainly by cells of the mesenchymal lineage. The function of FSTL1 is still unclear, but it appears to play roles in the regulation of cell proliferation, differentiation, and organ development. We have

previously shown that FSTL1 is an important mediator in the pathogenesis of arthritis and other systemic autoimmune diseases, and that FSTL1 expression is induced in vitro by Toll-like receptor 4 signaling. The aim of the current study was to determine the molecular mechanism by which FSTL1 promotes inflammation.

Methods: The level of FSTL1 in the sera of patients with sepsis was measured by ELISA. To further test the contribution of FSTL1 to inflammatory response in vivo, we utilized a model of endotoxin shock in FSTL1 null mice recently generated in our laboratory. Serum IL-1β levels were determined by ELISA. FSTL1 binding to monocytes/macrophages and its intracellular trafficking were assessed by confocal microscopy. The expression of inflammasome components was evaluated by quantitative RT-PCR and Western blotting. To test whether FSTL1 plays a role in cellular energy production, we performed gene expression microarray analysis on ST2 stromal cells in which FSTL1 expression was knocked down using lentiviral short hairpin RNA. Enzymatic assays and in situ gel staining were used to measure the activity of mitochondrial electron transport chain complexes. ATP determination in cell lysates was performed using a colorimetric assay.

Results: We found that the sera of septic patients contained elevated levels of FSTL1 compared to healthy controls. In a mouse model of sepsis, animals deficient in FSTL-1 exhibited a significantly lower IL-1β response than did control mice. Our results indicate that FSTL1 may function to augment cellular responses to infectious organisms or various other noxious stimuli. We found that FSTL1 was able to gain access to the intracellular space of cells that do not normally express FSTL1, such as monocytes/macrophages, either via increased plasma membrane permeability or via an unidentified cell surface receptor. We found intracellular FSTL1 associated with mitochondria, where it enhanced ATP production. FSTL1 also increased NLRP3 and pro-caspase-1 expression. Together, these promote activation of the NLRP3 inflammasome and secretion of IL-1β, one of the key regulators of inflammation.

Conclusion: Here, we demonstrate that FSTL1 has the ability to enhance the responses of monocytes/macrophages to inflammatory signals. The results reveal a novel mechanism by which FSTL1 acts in inflammation. Our work suggests that the neutralization of FSTL1 activity may be useful in the treatment of various inflammatory conditions.

Disclosure: Y. Chaly, None; **A. Marinov**, University of Pittsburgh, 9; **Y. Fu**, None; **B. Campfield**, None; **J. Kellum**, None; **B. Hostager**, None; **D. Bushnell**, None; **Y. Wang**, None; **J. Vockley**, None; **R. Hirsch**, University of Pittsburgh, 9.

1170

Expression and Function Of Human Mfg-E8 In The Clearance Of Apoptotic Cells and Suppression Of Inflammation. Lucrezia Colonna, Jie An, Xizhang Sun, Nalini Agrawal, Alice Wiedeman and Keith B. Elkon. University of Washington, Seattle, WA.

Background/Purpose: Effective clearance of apoptotic cells (AC) is necessary for the maintenance of tolerance to self. MFG-E8 is one of ~20 different opsonins reported to promote AC clearance in mice. Deficiency of MFG-E8 on certain strain backgrounds promotes a lupus-like disease in mice. However, very little is known about the expression and function of MFG-E8 in humans, and its potential role in systemic lupus erythematosus (SLE). The goals of this study were to examine the expression and function of MFG-E8 in human phagocytes and its potential role in SLE.

Methods: Macrophages and dendritic cells (DC) were derived from monocytes by culture with M-CSF or GM-CSF and IL-4 respectively. MFG-E8 expression and secretion were quantified by flow cytometry (FACS) and ELISA respectively. Phagocytosis of AC was quantified by microscopy (phagocytic index) and by FACS using CFSE-labeled AC. Phagocytes were stimulated by LPS (1 ng/ml) or zymosan (50ug/ml) and cytokines quantified by ELISA.

Results: MFG-E8 expression and function was very different in human macrophages and DCs. Unlike murine thioglycollate-elicited macrophages, human macrophages did not express or secrete MFG-E8. However, when MFG-E8 was added to AC, increased cell clearance was observed in a dose responsive manner. Furthermore, specific addition of MFG-E8 to AC resulted in suppression of TNF and IL-1b in response to LPS and zymosan. In striking contrast, human DCs expressed high levels of intracellular and cell surface MFG-E8 but exogenous MFG-E8 addition to AC did not enhance DC-mediated AC uptake. Remarkably, at higher doses MFG-E8 actually exerted an inhibitory effect on AC clearance by DC.

Conclusion: These results suggest that MFG-E8 plays an important role in clearance of AC by macrophages in humans. In addition, coating of AC by MFG-E8 alone enhances the known anti-inflammatory effects of AC by further dampening the production of pro-inflammatory cytokines such as TNF and IL-1b. Surprisingly, human DC did not seem to be functionally impacted by MFG-E8 coated AC despite or, perhaps, because MFG-E8 was expressed at high concentrations on the surface of these cells. We propose that MFG-E8 plays a central role in AC clearance and dampening inflammatory responses in human macrophages. It should therefore be considered as a therapeutic to enhance AC clearance and suppress inflammation in lupus and, possibly, other autoimmune disorders.

Disclosure: L. Colonna, None; **J. An**, None; **X. Sun**, None; **N. Agrawal**, None; **A. Wiedeman**, None; **K. B. Elkon**, None.

1171

Treatment Of Psoriasis Patients With IMO-3100 Shows Improvement In Gene Expression Patterns Of Meta-Analysis Derived-3 Transcriptome and IL-17 Pathway. Mayte Suarez-Farinas[1], Jennifer Belasco[1], Tim Sullivan[2], Robert Arbeit[2] and James G. Krueger[1]. [1]The Rockefeller University, New York, NY, [2]Idera Pharmaceuticals, Inc., Cambridge, MA.

Background/Purpose: IMO-3100, an antagonist of TLRs 7 and 9, has shown significant improvement in Psoriasis Area and Severity Index (PASI) scores in a randomized, double-blind, placebo-controlled Phase 2 trial in patients with moderate-to-severe plaque psoriasis. In the Phase 2 clinical trial, 44 patients were randomized to receive 4 once-weekly injections (Days 1, 8, 15, and 22) of IMO-3100 at 0.16 or 0.32 mg/kg or placebo; 40 patients were clinically evaluable, and clinical data were presented at IID 2013. To evaluate immunological changes following treatment with IMO-3100, biopsy samples were obtained on Days 1 (lesional and normal skin) and 29 (lesional skin). Biopsy samples from six patients in the 0.16-mg/kg group with positive clinical responses and six placebo patients also were used for gene expression analysis by DNA microarray.

Methods: Meta-analysis derived (MAD)-3 transcriptome represents a gene-expression profile associated with psoriasis (PLoS ONE 7(9): e44274). The overall effect of IMO-3100 vs. placebo treatment on the psoriasis transcriptome was compared by gene set enrichment analysis (GSEA).

Results: Principal component analysis of the microarray data showed clear distinction between lesional and normal skin within the twelve patients. Analysis showed that IMO-3100-treated patients had significant improvement in MAD-3 gene profile compared to placebo-treated patients. Placebo treatment did not significantly modulate gene expression, whereas genes up-regulated in the psoriasis transcriptome were significantly ($p<10^{-16}$) improved by IMO-3100 treatment. GSEA identified strong improvements in genes regulated in keratinocytes by IL-17 and the combination of IL-17 and TNF. In addition to the DNA microarray analysis, gene expression targets were analyzed by qPCR, which showed IL-17 was downregulated in IMO-3100 treated patients with PASI improvements.

Conclusion: In summary, treatment of patients with psoriasis with IMO-3100 leads to down regulation of the IL-17 pathway, which is central to the pathogenesis of psoriasis.

Disclosure: M. Suarez-Farinas, Idera Pharmaceuticals, 2; **J. Belasco**, Idera Pharmaceuticals, Inc., 2; **T. Sullivan**, Idera Pharmaceuticals, Inc., 3; **R. Arbeit**, Idera Pharmaceuticals, Inc., 3; **J. G. Krueger**, Idera Pharmaceuticals, Inc., 2.

1172

Molecular Characterisation Of The Killer Cell Immunoglobulin-Like Receptor 3DL2 Binding To Aberrant HLA-B27 Heavy Chains In Spondyloarthritis. H. Hatano, J. Shaw, K McHugh, P. Bowness and S. Kollnberger. University of Oxford, Oxford, United Kingdom.

Background/Purpose: KIR3DL2 is a Killer cell Immunoglobulin-like Receptor which binds to HLA class I including HLA-B27 (B27) β2m-free heavy chains (FHC) and HLA-A3/A11. KIR3DL2 is comprised of 3 immunoglobulin-like domains (D0, D1 and D2) which together determine binding to HLA-class I.

We have shown that KIR3DL2 expression is enriched on a subset of CD4 T cells known as Th17 cells which produce proinflammatory mediators including IL-17 in spondyloarthritis (SpA). Indeed, we have also shown that inhibiting KIR3DL2 binding to HLA-B27 inhibits T cell production of IL-17 *in vitro*. We hypothesise that HLA-class I binding to KIR3DL2 promotes Th17 differentiation and that targeting this interaction could be therapeutically beneficial in disease. A detailed characterization of the KIR3DL2-B27 binding face could assist the development more specific molecular inhibitors of this interaction.

Methods: We developed KIR3DL2-expressing cell lines, HLA-class I tetramers and KIR3DL2Fc fusion proteins to study KIR3DL2 ligand interactions. We also developed KIR3DL2CD3ϵ expressing Jurkat T reporter cells which produce IL-2 when stimulated with HLA- class I ligands.

Results: KIR3DL2 binds more strongly to HLA-B27 free heavy chains than other HLA-class I ligands. This interaction is inhibited by B27 FHC-reactive antibodies and KIR3DL2 antibodies. The recent crystal structure of KIR3DL1 suggests that the D0 domain contacts a region that is conserved between many different HLA class I. Our results show that antibodies against the D0 domain of KIR3DL2 inhibit binding to B27.

We also studied the effect of targeted mutagenesis of potential contact amino acids in the D0 domain of KIR3DL2 shared with the D0 domain of KIR3DL1 on binding of B27 and other HLA class I. Since KIR3DL1 binds more weakly to B27 FHC than KIR3DL2, we studied the effect of mutating amino acids in KIR3DL2 close to these contact residues to the corresponding residues in KIR3DL1 on binding of B27 and other ligands.

Mutagenesis of key contact residues in the D0 domain of KIR3DL2 abolished or enhanced binding to B27 while not affecting binding to other ligands.

Conclusion: We have shown that B27 FHC binding to the immune receptor KIR3DL2 promotes the survival of IL-23 receptor expressing CD4 T cells and innate lymphocyte cell subsets. Stronger binding of B27 FHC to KIR3DL2 could promote the survival of CD4 T cells and innate lymphocytes in SpA, accounting for our observations of increased proportions of these cells in patients. A detailed characterization of the KIR3DL2-B27 binding face will assist the development of more specific molecular inhibitors of this interaction with the potential for development as novel therapeutics.

Disclosure: H. Hatano, None; **J. Shaw**, None; **K. McHugh**, None; **P. Bowness**, None; **S. Kollnberger**, None.

ACR/ARHP Poster Session B
Metabolic and Crystal Arthropathies I
Monday, October 28, 2013, 8:30 AM–4:00 PM

1173

A Clinically Significant Interaction Between Furosemide and Allopurinol: Potential Implications for Clinical Practice. Lisa K. Stamp[1], Claudia Knake[2] and Andrew Bahn[2]. [1]University of Otago, Christchurch, Christchurch, New Zealand, [2]University of Otago, Dunedin, New Zealand.

Background/Purpose: The xanthine oxidase (XO) inhibitor allopurinol is the most commonly used urate lowering therapy in gout. Allopurinol is metabolized to oxypurinol, which is responsible for most of the XO inhibition. Co-morbidities, such as hypertension, are common in gout patients and result in concomitant therapy with diuretics such as furosemide, which is known to inhibit renal urate clearance. It has been reported that patients receiving furosemide and allopurinol have higher serum urate (SU) and oxypurinol concentrations compared to patients' not receiving furosemide. The aim of this study was to identify the molecular basis for this observation.

Methods: The effect of oxypurinol and furosemide (alone and in combination) on XO activity was determined using a cell-free *in vitro* assay. HepG2 cells were incubated for 24 hours with oxypurinol (250μM), furosemide (1mM), probenecid (250μM) or a combination of oxypurinol/furosemide or probenecid/furosemide. XO protein expression was determined by Western blot analysis. *In silico* analysis revealed that miR-448 could act as a potential regulator of XO expression by binding to the 3'UTR of the XO gene. miR-448 expression was examined in the presence of oxypurinol, furosemide, probenecid or a combination by qPCR.

Results: Oxypurinol inhibited XO activity, an effect that was maintained in the presence of furosemide within the examined physiologically-relevant activity range of 1–7 mU/mL. There was a significant reduction in XO gene expression in HepG2 cells after incubation with oxypurinol. This reduction in XO gene expression was blocked by the addition of furosemide (Fig 1). Probenecid also led to a reduction in XO gene expression, but this effect was not reversed by the addition of furosemide. miR-448 showed a mirrored expression pattern to XO gene expression in the presence of oxypurinol, furosemide, probenecid or a combination. However, these results did not reach statistical significance.

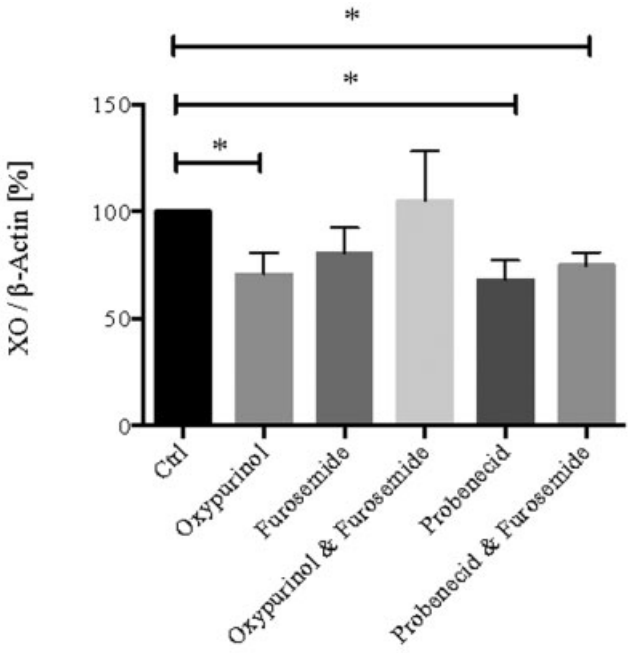


Figure 1. XO expression in HepG2 cells treated with oxypurinol (250μM), furosemide (1mM), probenecid (250μM) or a combination compared to non-treated cells (Ctrl). *$p<0.05$.

Conclusion: Oxypurinol may have effects on urate production by down-regulation of XO gene expression as well as by inhibiting XO function. Furosemide in combination with oxypurinol appears to have effects on XO expression, which may contribute to the observed increase in SU in addition to its effects on renal urate clearance. miR-448 may be a drug dependent regulator of XO expression. These effects on XO gene expression may contribute to the relative inefficiency of allopurinol in urate lowering in patients receiving furosemide. The lack of effect of probenecid, in combination with furosemide, on XO expression suggests it may be a better therapeutic option in patients receiving furosemide. Further clinical studies in patients with gout receiving different urate lowering therapies with and without furosemide are required.

Disclosure: L. K. Stamp, None; **C. Knake**, None; **A. Bahn**, None.

1174

Impact Of Bariatric Surgery On Serum Urate Targets in People With Morbid Obesity and Diabetes: A Prospective Longitudinal Study. Nicola Dalbeth[1], Peggy Chen[2], Marie White[3], Gregory Gamble[1], Caran Barratt-Boyes[2], Peter J. Gow[4] and Brandon Orr-Walker[2]. [1]University of Auckland, Auckland, New Zealand, [2]Counties Manukau District Health Board, Auckland, New Zealand, [3]CCRep, Auckland, New Zealand, [4]Middlemore Hospital, Auckland, New Zealand.

Background/Purpose: Weight loss leads to reduced serum urate (SU) in people with obesity. However, the clinical relevance of such reductions in SU are unknown. This study examined the impact of non-surgical weight loss and bariatric surgery on SU targets in people with morbid obesity and diabetes.

Methods: This was a single-centre, prospective study of 60 people with type 2 diabetes and morbid obesity (body mass index $\geq$ 35kg/m^2). Following six months of non-surgical weight loss, all participants had laparoscopic sleeve gastrectomy, with a further one year of follow-up. SU concentrations were measured at each visit throughout the study.

Results: Participants experienced mean (SD) weight loss of 5.5 (4.1) kg prior to surgery and 34.3 (11.1) kg following surgery. SU did not change following non-surgical weight loss (mean (SD) SU 6.4 (1.5) mg/dL at baseline and 6.4 (1.7) mg/dL at follow-up), but increased to 7.4 (2.5) mg/dL in the immediate post-operative period and reduced to 5.0 (1.3) mg/dL one year after surgery ($p<0.05$ for both compared to baseline) (Figure). Baseline SU, cessation of diuretics, female sex, and

change in creatinine independently predicted change in SU at the final visit. In participants without gout, SU above saturation levels (>6.8 mg/dL) were present in 19/48 (40%) at baseline and 1/48 (2%) one year after surgery ($p<0.0001$). In participants with gout, SU above therapeutic target levels (>6.0 mg/dL) were present in 10/12 (83%) at baseline and 4/12 (33%) one year after surgery ($p=0.031$). At the final study visit, 8/12 (67%) participants with gout were on no urate-lowering therapy. SU concentrations were above therapeutic target in 8/8 of these participants at baseline and 3/8 at follow-up ($p=0.004$).

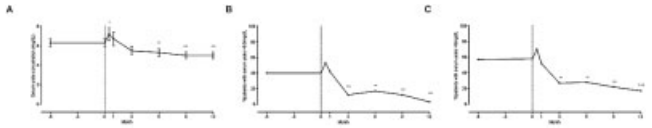


Figure. Changes in SU concentrations in the entire study group (n=60). A. Mean (95% CI) SU concentrations. B. Percentage of participants with SU above saturation levels (>6.8mg/dL). C. Percentage of participants with SU above therapeutic treatment target levels (>6mg/dL). *P<0.05, **P<0.01, ***P<0.001 compared with baseline (−6 months) values. Dashed line refers to day of surgery.

Conclusion: Clinically relevant reductions in SU occur following bariatric surgery in people with morbid obesity and diabetes. The reduction of serum urate concentrations to sub-saturation concentrations indicates that the risk of developing gout can be substantially reduced in most people following bariatric surgery. Furthermore, for those with gout, bariatric surgery allows achievement of therapeutic target serum urate concentrations and may enable cessation of urate-lowering therapy.

Disclosure: N. Dalbeth, None; **P. Chen**, None; **M. White**, None; **G. Gamble**, None; **C. Barratt-Boyes**, None; **P. J. Gow**, None; **B. Orr-Walker**, None.

1175

***ABCG2* May Influence Risk Of Gout Through Extra-Renal Metabolic Pathways: Analysis Of The Effects Of The Q141K Variant On Serum Urate Responses To a Fructose Load.** Nicola Dalbeth[1], Meaghan House[1], Gregory Gamble[1], Bregina Pool[1], Anne Horne[1], Lauren Purvis[1], Angela Stewart[1], Marilyn E. Merriman[2], Murray Cadzow[2], Amanda Phipps-Green[2] and Tony R. Merriman[2]. [1]University of Auckland, Auckland, New Zealand, [2]University of Otago, Dunedin, New Zealand.

Background/Purpose: Genetic variation in *ABCG2* is a major risk factor for hyperuricemia and gout. This gene encodes a high-capacity urate transporter expressed in the intestine, liver and renal tubule. Intake of fructose-containing beverages is also associated with development of hyperuricaemia and gout. A recent report has shown that variation in the other major genetic risk factor for gout, *SLC2A9*, influences serum urate (SU) and fractional excretion of uric acid (FEUA) responses to a fructose load. The aim of this study was to test the hypothesis that the *ABCG2* gout risk allele 141K also promotes the hyperuricemic response to fructose loading.

Methods: Healthy volunteers (n=74) provided serum and urine samples immediately before and 30, 60, 120 and 180 minutes after ingesting a 64g fructose solution. Data were analyzed based on the presence or absence of the *ABCG2* 141K gout risk allele using a mixed models approach to repeated measures.

Results: The 141K risk allele was present in 23 participants (31%). Overall, SU concentrations during the fructose load were similar in those with and without the 141K allele ($P_{SNP}=0.15$). However, the presence of the 141K risk allele was associated with a smaller increase in SU following fructose intake ($P_{SNP}<0.0001$) (Figure 1A). Those with the 141K allele also had a smaller increase in serum glucose following the fructose load ($P_{SNP}=0.002$) (Figure 1B). Higher FEUA at baseline and throughout the fructose load was observed in those with the 141K risk allele ($P_{SNP}<0.0001$). However, the change in FEUA in response to fructose was not different in those with and without the 141K risk allele ($P_{SNP}=0.39$).

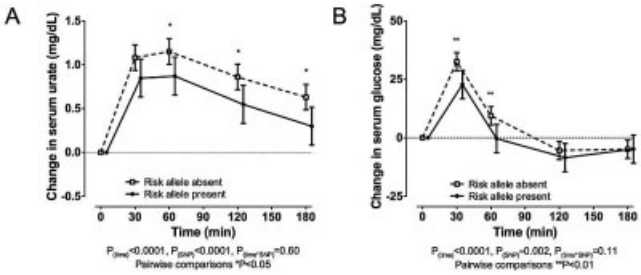


Figure 1. A. Change in SU. B. Change in serum glucose. Data are presented as mean (95% CI). Dashed line represents 141K (risk) allele absent, solid line represents 141K (risk) allele present.

Conclusion: In contrast to the predicted responses for a hyperuricemia/gout risk allele, the *ABCG2* 141K allele is associated with smaller increases in SU following a fructose load. The FEUA data provide further evidence that the *ABCG2* 141K allele does not increase hyperuricemia/gout risk through direct effects on renal tubular uric acid transport. Rather, the results suggest that *ABCG2* variants may act through extra-renal metabolic pathways, which, in turn, influence SU levels and gout risk.

Disclosure: N. Dalbeth, None; **M. House**, None; **G. Gamble**, None; **B. Pool**, None; **A. Horne**, None; **L. Purvis**, None; **A. Stewart**, None; **M. E. Merriman**, None; **M. Cadzow**, None; **A. Phipps-Green**, None; **T. R. Merriman**, None.

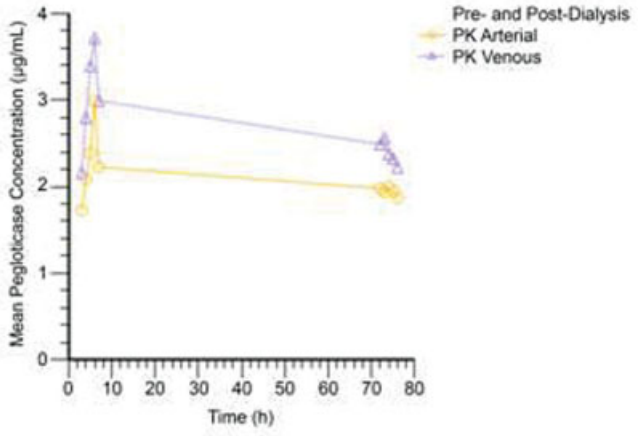
1176

Pharmacokinetics and Pharmacodynamics Of Pegloticase In Patients With End-Stage Renal Failure Receiving Hemodialysis. Anthony J. Bleyer[1], David E. Wright[2] and Alan Glicklich[3]. [1]Wake Forest University School of Medicine, Winston-Salem, NC, [2]Savient Pharmaceuticals, Inc., San Diego, CA, [3]Savient Pharmaceuticals, Inc., Bridgewater, NJ.

Background/Purpose: Among the estimated 8.3 million adults in the US with gout, approximately 40% have coexistent chronic kidney disease (CKD).[1,2] Further, the presence of gout in CKD appears to confer an increased risk for progression to end-stage renal disease (ESRD).[3] Thus, patients often proceed to dialysis with chronic gout, and some suffer from severe tophaceous gout. There has been little detailed study of the use of urate-lowering medications in the hemodialysis (HD) population. Pegloticase, a recombinant uricase conjugated to PEG, acts by converting urate to a soluble product (allantoin) that is readily excreted. Pegloticase is reserved for patients with chronic gout who are refractory to current oral urate-lowering treatments and does not require dose adjustment based on renal function. Here we present results from a Phase 1 pharmacokinetic (PK)/pharmacodynamic study of single-dose pegloticase in patients undergoing HD.

Methods: A single intravenous dose of pegloticase (8 mg) was administered over a 2-hour period to male or female (age 18–75 years) HD patients without gout (N=12), 3 hours prior to the Day 1 dialysis session; a second dialysis session was monitored on Day 4. Patients received prophylactic antihistamine and corticosteroid prior to pegloticase infusion. Blood samples were drawn predialysis and hourly over 4 hours postdialysis during the Day 1 and Day 4 sessions. The limit of detection for pegloticase was 0.6 μg/mL; all samples below this value were set to zero. Safety assessments included standard vital signs, laboratory testing, and adverse event (AE) determinations.

Results: Following a single dose of pegloticase started approximately 3 hours prior to HD, the mean C_{max} was 3.27 μg/mL (arterial) and 4.00 μg/mL (venous). Pegloticase AUC_{3-7h} was 9.86 h · μg/mL (arterial) and 12.91 h · μg/mL (venous) at the Day 1 dialysis and for the Day 4 dialysis AUC_{72-76h} was 7.93 h · μg/mL (arterial) and 9.70 h · μg/mL (venous). Mean arterial and venous pegloticase concentrations during the Day 1 and Day 4 dialysis sessions are shown in the figure. Baseline mean serum uric acid in this non-gout population was 5.98 mg/dL; by 3 hours postinfusion, serum uric acid was undetectable and remained so over the 72-hour sampling period. One patient reported an AE of headache that was possibly related to study drug.



Conclusion: In a small cohort of patients with ESRD and no evidence of gout, pegloticase concentration was not affected by a first HD session and displayed stable decline during a second HD session. Serum uric acid levels in this cohort fell to nondetectable levels 3 hours postinfusion confirming that patients with ESRD can achieve urate-lowering with pegloticase. Data presented here support the use of pegloticase in patients with chronic gout undergoing HD.

References:
1. Fuldeore et al. BMC Nephrol. 2011.
2. Zhu et al. Arthritis Rheum. 2011.
3. Yu et al. Arthritis Res Ther. 2012.

Disclosure: A. J. Bleyer, None; **D. E. Wright**, Savient Pharmaceutical, Inc, 3; **A. Glicklich**, Savient Pharmaceuticals, Inc., 3.

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Efficacy and Safety Of Canakinumab Pre-Filled Syringe Versus Triamcinolone Acetonide In Acute Gouty Arthritis Patients. Prashanth Sunkureddi[1], Edith Toth[2], Jacques P. Brown[3], Rüdiger Möricke[4], Jan Michael Nebesky[5], Gerhard Krammer[5], Aiyang Tao[6], Markus John[5] and Alan Kivitz[7]. [1]Clear Lake Rheumatology, Nassau Bay, TX, [2]Flór Francis Hospital Rheumatology Department, Kistarcsa, Hungary, [3]CHU de Québec Research Centre and Laval University, Quebec City, QC, [4]Institut für Präventive Medizin & Klinische Forschung GbR, Magdeburg, Germany, [5]Novartis Pharma AG, Basel, Switzerland, [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [7]Altoona Center for Clinical Research, Duncansville, PA.

Background/Purpose: Canakinumab (CAN), a selective, fully human, monoclonal anti-IL-1β antibody has demonstrated long-term benefits in gouty arthritis (GA) patients (pts) by targeting the inflammatory pathway through IL-1β inhibition[1]. Efficacy and safety of CAN (sc), formulated as a lyophilized (LYO) powder requiring reconstitution with water, vs triamcinolone acetonide (TA) in pts with acute GA was demonstrated in phase III trials[1]. Here, we report the efficacy and safety of CAN-PFS (pre-filled syringe) vs TA in acute GA pts.

Methods: In a 12-week, multicenter, double-blind, active controlled study, pts (≥18-'85 yrs) meeting the ACR 1977 preliminary criteria for acute GA and contraindicated, intolerant or refractory to NSAIDs and/or colchicine, with ≥3 attacks in the previous year, were randomized 1:1:1 to receive a single dose of CAN- PFS 150 mg sc or CAN- LYO 150 mg sc or TA 40 mg im and re-dosed "on demand" upon each new attack. The primary objective was to confirm superiority of CAN-PFS vs TA in reducing pain intensity in the most affected joint, measured on the 0–100 mm VAS scale, at 72h post-dose. Secondary objectives included evaluation of CAN-PFS vs TA and CAN-LYO vs PFS for the following: time to first new attack; percentage of pts with at least 1 new attack; and safety over 12 weeks.

Results: A total of 397 pts were randomized (CAN-PFS [n=133], CAN-LYO [n=132], TA [n=132]), of which 87.9% completed the study. CAN-PFS provided a statistically significant reduction in pain intensity at 72h post dose vs TA (estimated difference, −14.9mm; 95% CI: −20.6, −9.2, p<0.0001). The least square mean pain scores at 72h post-dose were comparable for both CAN formulations (PFS, 17.1mm; LYO, 19.7mm), and both were lower than that for TA (32.0mm). The percentage of pts with at least 1 new attack was lower with CAN-PFS (9.2%) vs TA (40.3%) (OR, 0.15 [95% CI: 0.07, 0.30], p<0.0001) and comparable for both CAN formulations (CAN-LYO, 9.3%) over the 12-week period. CAN-PFS treatment significantly delayed (p<0.0001) time to first new attack vs TA and both CAN formulations had similar results for this outcome. Adverse events (AEs) were observed in 43.6 % of pts in both the CAN-PFS and TA groups, and 42.9% pts in the CAN-LYO group. Serious AEs were reported in 17 pts (CAN-PFS, n=6; CAN-LYO, n=6; TA, n=5), with infections (CAN-PFS, n=2; CAN-LYO, n=3; TA, n=0) being the most common SAEs. Two patients discontinued the study: one due to non-fatal SAE in the CAN-LYO group and the other due to AE in the TA group.

Conclusion: CAN-PFS was superior to TA in relieving pain and reducing risk of new attacks, and had a safety profile similar to CAN-LYO. The safety profile was also consistent with that observed in previous CAN-LYO studies[1, 2]. Efficacy and safety of the two CAN formulations were comparable.

References:
1. Schlesinger N, et al. Ann Rheum Dis 2012; 71(11):1839–48.
2. So A, et al. Arthritis Rheum 2010; 62(10):3064–76.

Disclosure: P. Sunkureddi, Novartis, Bristol Myers Squibb, 5, Pfizer, Takeda, Bristol Myers Squibb, UCB, Amgen, Abbott, Shinogi, Savient, 8; **E. Toth**, None; **J. P. Brown**, Amgen, Bristol Myers Squibb, Eli Lilly, Novartis, Merck, Pfizer, Roche, Servier, Sanofi-Aventis, Takeda, Warner Chilcott, 2, Amgen, Eli Lilly, Merck, Warner Chilcott, Sanofi-Aventis, 5, Amgen Eli Lilly, Novartis, Merck, 8; **R. Möricke**, None; **J. M. Nebesky**, Novartis, 3; **G. Krammer**, Novartis, 1, Novartis, 3; **A. Tao**, Novartis, 3; **M. John**, Novartis, 1, Novartis, 3; **A. Kivitz**, Novartis, 2.

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Effect Of Febuxostat On Serum Urate Levels In Gout Subjects With Hyperuricemia and Moderate-To-Severe Renal Impairment: A Randomized Controlled Trial. Kenneth G. Saag[1], Michael A. Becker[2], Andrew Whelton[3], Patricia A. MacDonald[4], Yun Zhou[5] and Lhanoo Gunawardhana[5]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Chicago, Chicago, IL, [3]The Johns Hopkins University and Universal Clinical Research Center, Inc., Baltimore, MD, [4]Takeda Pharmaceuticals USA, Inc., Deerfield, IL, [5]Takeda Global Research & Development Center, Inc., Deerfield, IL.

Background/Purpose: Up to 20% of patients with hyperuricemia (serum urate [sUA] >6.8 mg/dL) and gout have moderate-to-severe renal impairment. Higher sUA (>8.5 mg/dL) may increase the risk for progressive decline in renal function. The objective of this prospective 12-m pilot study was to evaluate the effect of treatment with febuxostat (FEB) vs placebo (PLB) on urate-lowering, renal function, and general safety in gout subjects with moderate-to-severe renal impairment.

Methods: In this multicenter, double-blind, phase 2 study, subjects were randomized 1:1:1 to receive 12 m of daily treatment with either FEB 30 mg BID, FEB 40/80 mg QD (titrated from 40 to 80 mg to achieve sUA <6.0 mg/dL) or PLB. Eligible subjects fulfilled ARA criteria for gout (subjects with tophi were excluded), had sUA >7.0 mg/dL, and had an estimated glomerular filtration rate (eGFR; by MDRD) ≥15 to ≤50 mL/min (severe, eGFR ≥15 to <30 mL/min; moderate, ≥30 to ≤50 mL/min) on d −21. Endpoints at m 12 included the proportion of subjects with sUA <6.0 mg/dL (Cochran-Mantel-Haenszel test) and change from baseline (CFB) in sUA and eGFR (by ANCOVA analysis). Adverse events (AEs) were recorded throughout the study.

Results: Among 96 subjects enrolled, 80% were male with a mean sUA (SD) of 10.5 (1.70) mg/dL; 95 subjects qualified for primary efficacy analysis. At m 1 visit, 20 subjects were titrated from FEB 40 mg to 80 mg QD based on d 14 sUA. At baseline, 28%, 31%, and 53% of subjects in the FEB 30 mg BID, FEB 40/80 mg QD, and PLB groups, respectively, had severe renal impairment. The proportion of subjects with sUA <6.0 mg/dL at m 12 was significantly greater in both FEB groups compared to PLB: 69%, 45%, and 0% for FEB 30 mg BID, FEB 40/80 mg QD, and PLB, respectively (p<0.001). The CFB in sUA at m 6 and m 12 was significantly greater in both FEB groups vs PLB (**Table**). Mean (SE) baseline eGFR was 34.14 (1.46), 34.08 (1.48), and 29.31 (1.46) mL/min/1.73 m^2. Mean eGFR CFB (SE) at m 12 for FEB 30 mg BID and 40/80 mg QD (0.33 [1.17] and −0.86 [1.19] mL/min/1.73 m^2, respectively) was not significantly different from PLB (−2.05 [1.20] mL/min/1.73 m^2; p>0.1). Overall, ≥1 AE was reported by 78%, 88%, and 78% of subjects in the FEB 30mg BID, FEB 40/80 mg QD, and PLB groups, respectively. The majority of AEs were mild to moderate in intensity and not considered to be related to study treatment. Elevated serum creatinine (increase from baseline ≥0.3 mg/dL) was seen in 13/32, 16/32, and 17/32 subjects in the FEB 30mg BID, FEB 40/80 mg QD, and PLB groups, respectively.

Table. CFB in serum urate

	FEB 30 mg (N=32)	FEB 40/80 mg (N=31)	PLB (N=32)
		LS mean (SE)	
Baseline	10.36 (0.31)	10.35 (0.31)	10.72 (0.31)
CFB at m 6	−5.08 (0.30)*	−4.29 (0.31)*	0.07 (0.30)
CFB at m 12	−4.97 (0.32)*	−4.17 (0.32)*	−0.15 (0.32)

LS = least squares; SE = standard error; FEB = febuxostat; PLB = placebo; CFB = change from baseline; *p <0.001 vs PLB

Conclusion: In subjects with moderate-to-severe renal impairment, FEB urate-lowering was efficacious, with no emergent serious safety issues at 12 m. The sUA was significantly reduced in subjects receiving either regimen of FEB compared to PLB. CFB in renal function did not differ significantly between groups. Limitations include small sample size and a baseline imbalance in the distribution of subjects with severe vs moderate renal impairment across the treatment groups.

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Colchicine Use and The Risk Of Myocardial Infarction Among Gout Patients: Interim Results From a VA Retrospective Cohort Study. Daria B. Crittenden[1], Jessica N. Kimmel[1], Virginia C. Pike[1], Daniel Diaz[1], Avni Shah[1], Cilian J. White[1], Michael DeBerardine[1], Grace Kim[1], Binita Shah[2], Christopher J. Swearingen[3], Jeffrey D. Greenberg[4], Steven P. Sedlis[2], Craig T. Tenner[5], Bruce N. Cronstein[1] and Michael H. Pillinger[1]. [1]NYU School of Medicine, Division of Rheumatology, New York, NY, [2]NYU School of Medicine, Division of Cardiology, New York, NY, [3]Pediatric Biostatistics, University of Arkansas for Medical Sciences, Little Rock, AR, [4]NYU Hospital for Joint Diseases, New York, NY, [5]NYU School of Medicine, Department of Internal Medicine, New York, NY.

Background/Purpose: Gout patients are at increased cardiovascular (CV) risk. Since atherosclerosis is an inflammatory process, anti-inflammatory strategies to reduce CV risk are currently being investigated. The anti-inflammatory colchicine is commonly used in gout, and inhibits cell types implicated in atherosclerosis. Our preliminary data suggest that colchicine may reduce myocardial infarction (MI) among gout patients (Crittenden et al, J Rheum 2012). To further assess colchicine's possible effect on MI risk, we initiated a retrospective cohort study in a Veterans Affairs population and here present an interim analysis.

Methods: We identified all active NY Harbor VA patients with an ICD-9 code for gout or hyperuricemia from 2000-09. Charts were manually screened to confirm gout diagnosis (ACR criteria) and pharmacy records were used to identify subjects on daily colchicine for ≥ 30 days (colchicine group). Subjects receiving no colchicine formed the control group. We excluded patients who did not meet gout criteria, or who received PRN colchicine only. We defined colchicine lapse as any period of non-colchicine use ≥ 2 weeks after medication cessation (to account for colchicine elimination time). Primary outcome was MI (adjudicated by universal criteria) during the study period.

Results: 7819 subjects had requisite ICD-9 codes. 4486 charts have been reviewed to date; 844 patients met ACR gout criteria and 644 were enrolled. 410 subjects (64%) used colchicine (1184 person-years of active use and 682 person-years of lapse); 234 (36%) used no colchicine (1041 person-years of follow-up). Colchicine and control groups did not differ in baseline characteristics including gender (99.3 vs 97.4% male, p=0.08); age (66 vs 67 years, p=0.3); BMI (30.5 vs 30.2, p=0.7); uric acid level (8.4 vs 8.0 mg/dL, p=0.1); hypertension (80 vs 81%, p=0.9); diabetes (30 vs 30% p=1.0); hyperlipidemia (51 vs 43%, p=0.06); coronary artery disease (24 vs 26%, p= 0.6); and medication use including allopurinol (22 vs 20%, p=0.1); aspirin (30 vs 32%, p=0.7); statins (41 vs 39%, p=0.5); ACE-inhibitors (48 vs 42%, p=0.1); and beta-blockers (41 vs 34%, p=0.1). Colchicine users experienced 11 total MIs—8 occurring during lapse time (2%) and 3 during active use (0.7%). Control patients had 7 MIs (3%; active colchicine vs control p=0.04). The shortest time from last colchicine use to MI was 2 months (mean 4 months). We also compared rates of MI per person-year exposure to colchicine (0.003), control (0.007), lapse (0.012), and pooled control+lapse (0.009) periods, and observed significant differences between colchicine active use vs lapse (p=0.02), and vs lapse+control (p=0.04). Active colchicine use vs control was not statistically different (p=0.16), but is expected to reach significance if the current rates persist through the remaining data collection.

Conclusion: In this interim analysis, gout patients actively taking colchicine had a significantly reduced incidence of MI vs never-users, and significantly reduced person-year incidence rates vs lapse patients and vs a pooled group of patients not on colchicine. These data suggest that colchicine protects against MI, though probably only during active use. Evaluation of the remaining 3333 patients is ongoing.

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Rising Burden Of Gout and Poor Management Of The Disease In The United Kingdom: A Nationwide Population Study. Chang-Fu Kuo[1], Michael Doherty[2], Matthew J. Grainge[2] and Weiya Zhang[2]. [1]Chang Gung Memorial Hospital, Taipei, Taiwan, [2]University of Nottingham, Nottingham, United Kingdom.

Background/Purpose: To describe the trends of epidemiology of gout and patterns of urate-lowering treatment in the UK general population from 1997–2012.

Methods: We used the Clinical Practice Research Data-link (CPRD) to estimate the prevalence and incidence of gout and the proportion of gout patients being treated by urate-lowering therapy for each calendar year from 1997 to 2012. To determine trends of prevalence, incidence and management of gout, we used direct standardisation considering the distribution of age, sex and length of data contribution with the population structure in year 2012 as reference. Good adherence for urate-lowering treatment (ULT) was classifed as a proportion of days covers (PDC) of 80% or higher.

Results: Of 4,604,203 eligible individuals in 2012, 115,608 prevalent cases of gout were identified, giving a prevalence of 2.51% (95% CI, 2.50%–2.52%). Men had a significantly higher prevalence (4.00%; 95% CI, 3.97%–4.03%) than women (1.05%; 95% CI, 1.04%–1.06%). There were a total of 4,484,830 person-years of follow-up in this year during which 8401 incident cases of gout were identified (overall incidence 1.87 [95% CI, 1.83–1.91] per 1000 person-years). Men had a higher incidence (2.74 [95% CI, 2.67–2.81] per 1000 person-year) than women (1.05 [95% CI, 1.00–1.09) per 1000 person year). Prevalence and incidence both were significantly higher in 2012 than in 1997, with a 66.7% increase in prevalence and 25.7% increase in incidence. Among prevalent gout patients in 2012, only 44% were under medical attention (with at least one consultation with a gout diagnosis or a prescription for ULT, 31% were prescribed with ULT of which only 47% adhered to treatment. The percentage of patients under medical attention and treated by ULT remained poor from 1997 to 2012 (annual change −0.3% [95%CI −0.5%–−0.2%] and 0.1% [95%CI −0.1%–−0.3%]), while the adherence increased slightly from 10.7% to 14.6%.

Conclusion: Both prevalence and incidence of gout increased significantly in the UK in the period between 1997 and 2012. Only one-third of gout patients were given ULT and the adherence was poor. The pattern of gout management has not changed despite the rising burden of disease.

Disclosure: C. F. Kuo, None; **M. Doherty**, None; **M. J. Grainge**, None; **W. Zhang**, None.

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The Effect Of Uric Acid Lowering Therapy In Preventing Comorbidity and Acute Attack Of Gout; A Retrospective Study. Kowoon Joo[1], Won Park[1], Seong-Ryul Kwon[1], Mie-Jin Lim[1], Kyong-Hee Jung[1], Hoyeon Joo[1] and Sung-Soo Kim[2]. [1]Inha University Hospital, Incheon, South Korea, [2]Ulsan Univ College of Medicine and Gangneung Asan Hospital, Gangneung, South Korea.

Background/Purpose: We evaluated the effect of uric acid lowering therapy (ULT) in reducing the new development of comorbidities and the frequency of acute attacks in gout patients.

Methods: We retrospectively examined data of 200 patients who were diagnosed to have gout according to the American College of Rheumatology (ACR) criteria. The patients with at least 3 years of follow up during the period from January 1996 to December 2012 were divided into 2 groups; those whose mean serum uric acid level (sUA) < 6mg/dL (2012 ACR uric acid treatment target) and mean sUA °Ã 6mg/dL. Comorbidities of gout such as hypertension (HTN), type II diabetes mellitus (DM), chronic kidney disease (CKD), cardiovascular disease (CVD) and kidney stone were compared in each group at baseline and at last follow-up visit. Frequency of acute gout attacks were compared between the groups. Mann-Whitney U test and chi-square test was used to compare the variables between the 2 groups. McNemar's test was used to evaluate the treatment effects in comorbidities of gout in each group. A value of $p < 0.05$ was considered significant.

Results: Fifty-three patients were allocated to the adequately treated group (mean sUA < 6mg/dL) and 147 patients were allocated to the inadequately treated group (mean sUA °Ã 6mg/dL). Only 1 patient in the adequately treated group was woman. Patients in the adequately treated group was older (54 ± 13 years vs. 44 ± 12 years, $p<0.001$) with lower BMI (24.5 ± 4.5kg/m©÷ vs. 25.9 ± 4.5kg/m©÷, $p=0.003$) and kept higher medication possession rate (MPR) (94 ±10% vs. 61 ± 27 %, $p<0.001$) compared to the inadequately treated group. There was no difference in the duration of gout, ULT duration, tophi, family history of gout, smoking, alcohol, hypercholesterolemia between the groups. During the mean follow up period of 8 years, the yearly rate of acute attack (0.25 ± 0.39 vs. 0.47 ± 0.53, $p<0.001$) was lower in the adequately treated group compared to the inadequately treated group. New development of HTN, DM, CVD and kidney stone was lower in the adequately treated group compared to the inadequately treated group (Table 1). The frequency of CKD tended to decrease in the adequately treated group from 21 patients at baseline to 19 patients at last follow up visit.

Table 1. Comorbidities of gout according to uric acid level.

		sUA < 6mg/dL n = 53		sUA ≥ 6mg/dL n = 147	
		n(%)	p value	n(%)	p value
Hypertension	Baseline	31 (58)		33 (22)	
	Last visit	36 (68)	p = 0.063	71 (48)	p < 0.001
Diabetes mellitus	Baseline	4 (8)		9 (6)	
	Last visit	8 (15)	p = 0.125	27 (18)	p < 0.001
Chronic kidney disease[a]	Baseline	21 (40)		26 (18)	
	Last visit	19 (36)	p = 0.727	27 (18)	p = 1.000
Cardiovascular disease	Baseline	12 (23)		8 (5)	
	Last visit	15 (28)	p = 0.250	17 (12)	p = 0.004
Kidney stone	Baseline	4 (8)		5 (3)	
	Last visit	6 (11)	p = 0.500	16 (11)	p = 0.001

[a] Calculated by MDRD (modification of diet in renal disease).
CKD defined as GFR less than 60 mL/min per 1.73m^2.

Conclusion: Tight control of uric acid decreased the development of acute gout attacks and comorbidities of gout such as HTN, DM, CVD and urinary stone despite the same CVD risk factors. The renal function can be recovered by intensive ULT therapy.

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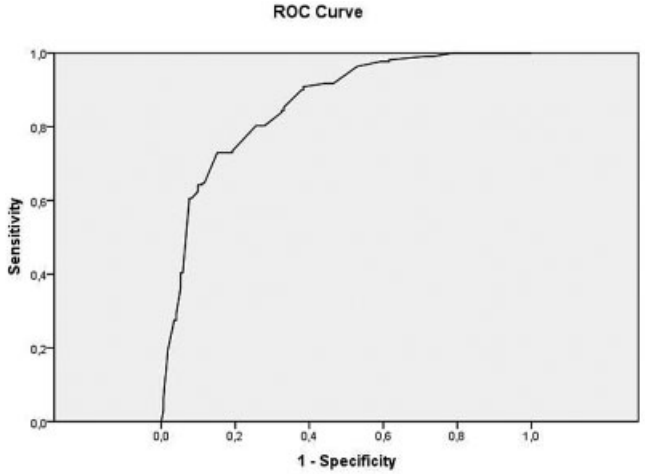
The Performance Of a Diagnostic Rule For Acute Gouty Arthritis Without Joint Fluid Analysis: a Validation Study. Laura Kienhorst[1], Hein Janssens[2], Jaap Fransen[2] and Matthijs Janssen[1]. [1]Rijnstate Hospital, Arnhem, Netherlands, [2]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.

Background/Purpose: The gold standard to diagnose gout is the identification of monosodium urate (MSU) crystals in joint fluid. In primary care gout is mostly diagnosed clinically without joint fluid analysis. However, this clinical diagnosis of gout has a positive and negative predictive value of 0.64 and 0.87, respectively.[1] To improve the clinical diagnosis of gout a diagnostic rule has been developed in a primary care population.[1] The aim of this study is to validate this diagnostic rule in a secondary care population.

Methods: In this validation study adult patients who were referred to the rheumatology department from 1 January 2011 until 8 May 2013 with signs and symptoms of monoarthritis at their first visit and who conceivably could have gout were included. The affected joint was aspirated and joint fluid analysis was performed for the presence of MSU crystals. The seven variables of the diagnostic rule (male sex, previous patient-reported arthritis attack, onset within one day, joint redness, first metatarsophalangeal joint involvement, hypertension or one or more cardiovascular diseases, and serum uric acid >0.35 mmol/L) were collected and scored without knowledge of the joint fluid analysis result. The performance of the diagnostic rule was compared to the presence of MSU crystals.

Results: 390 patients were included in this study. In 218 (56%) patients MSU crystals were found. As confirmed by the presence of MSU crystals, the prevalences of gout at the cut-off scores ≤4, >4 to <8, and ≥8 points were 6% (4 of 69), 46% (76 of 163), and 88% (138 of 157), respectively. The area under the receiver operator characteristic curve for the diagnostic rule was 0.85 (figure 1). The Hosmer-Lemeshow goodness-of-fit test showed that the difference between the expected and the observed probability was non-significant ($p=0.64$), indicating well agreement.



Conclusion: The diagnostic rule to diagnose gout without joint fluid analysis, which was developed in a primary care population, has a good performance in a secondary care population.

References:
[1]H.J.E.M. Janssens, et al. *A diagnostic rule for acute gouty arthritis in primary care without joint fluid analysis*, Arch Intern Med. 2010; 170(13):1120–6.

Disclosure: L. Kienhorst, None; **H. Janssens**, None; **J. Fransen**, None; **M. Janssen**, None.

1183

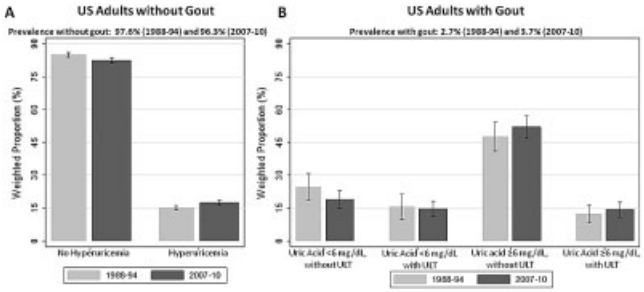
The Treatment Of Gout In Relation To The 2012 Uric Acid Target Guidelines In The US Population. Stephen Juraschek, Lara Kovell, Edgar Miller III and Allan C. Gelber. Johns Hopkins University, Baltimore, MD.

Background/Purpose: Gout is a debilitating form of arthritis mediated by elevated serum uric acid (SUA) levels. Pharmacologic interventions to prevent recurrent gout are largely focused on urate-lowering therapy (ULT). In 2012, the American College of Rheumatology (ACR) released gout

management guidelines encouraging providers to target a SUA <6 mg/dL. The proportion of US adults with gout undergoing ULT, in relation to this SUA target, is unknown. Further, while gout risk factors are well-characterized, demographic and clinical factors associated with a SUA above target have not been determined.

Methods: We examined the National Health and Examination Survey (NHANES), in the 1988–1994 and 2007–2010 survey periods. Participants <20 years or those missing data for SUA, ULT use, or gout status were excluded. Gout status was based on self-report of a physician (or health professional) diagnosis. According to the recent ACR gout treatment guidelines, a SUA above target in participants with gout was defined as a SUA ≥6.0 mg/dL in both men and women. Demographic and clinical factors associated with a SUA above target among NHANES participants with gout, were analyzed using adjusted and weighted Poisson regression.

Results: There were 15,505 NHANES participants in 1988–1994 and 10,977 in 2007–2010, among whom 443 and 514 had gout, respectively. The prevalence of gout rose from 2.7% in 1988–1994 to 3.7% in 2007–2010. In 2007–2010, the mean age was 48 years; 52% were female, 69% were white, 10% were black, and 8% were Mexican American. Notably, 66% of US adults with gout in 2007–2010 had a UA ≥6 mg/dl (**Figure**); among this hyperuricemic subgroup, 79% were not using ULT. In both time periods, higher BMI (prevalence ratio: 1.02 per 1 kg/m^2; 95% CI: 1.00, 1.03; P = 0.02) and ULT (prevalence ratio: 0.56; 95% CI: 0.45, 0.70; P <0.001) were associated with a SUA above target (**Table**). Male sex, reduced glomerular filtration rate (eGFR), low HDL cholesterol, and diuretic use were significantly associated with a SUA above target in a least one time period.



Demographic and clinical factors associated with a uric acid level above target (≥6 mg/dL) among US adults with gout.

	1988–94 (N with gout = 443)		2007–10 (N with gout = 514)	
	Prevalence Ratio (95% CI)*	*P*	Prevalence Ratio (95% CI)*	*P*
Age, per 10 yrs	1.01 (0.91, 1.11)	0.92	0.99 (0.90, 1.10)	0.91
Male	1.31 (0.95, 1.81)	0.10	1.87 (1.51, 2.30)	<0.001
Race/Ethnicity				
Non-Hispanic white	1.0 (reference)	-	1.0 (reference)	-
Non-Hispanic black	1.19 (0.97, 1.44)	0.09	0.83 (0.69, 1.01)	0.06
Mexican American	1.11 (0.78, 1.59)	0.56	0.90 (0.74, 1.11)	0.31
Body mass index per 1 kg/m^2	1.02 (1.01, 1.03)	<0.001	1.02 (1.00, 1.03)	0.02
eGFR < 60 mL/min per 1.73m^2	1.43 (1.13, 1.81)	<0.001	1.17 (1.00, 1.37)	0.06
Low HDL cholesterol	0.97 (0.77, 1.21)	0.77	1.25 (1.03, 1.51)	0.03
Urate-lowering therapy†	0.55 (0.40, 0.76)	<0.001	0.56 (0.45, 0.70)	<0.001
Diuretic medications	1.32 (1.05, 1.64)	0.02	1.20 (0.97, 1.47)	0.09

*All models were adjusted for age, sex (vs. female), race/ethnicity (vs. non-Hispanic white), body mass index, eGFR < 60 mL/min per 1.73m^2 (vs. eGFR ≥ 60 mL/min per 1.73m^2), low high density lipoprotein cholesterol (vs. elevated high density lipoprotein cholesterol), elevated total cholesterol (vs. low total cholesterol), hypertension (vs. no hypertension), diabetes (vs. no diabetes), no urate lowering therapy (vs. urate lowering therapy), diuretic use (vs. no diuretic medication use), and alcohol use (vs. never drank alcohol). Clinical factors that were not significant in either survey period (i.e.total cholesterol, hypertension, diabetes, and alcohol use)were not shown.
†Allopurinol, probenecid, sulfinpyrazone, or combination colchicine-probenecid

Conclusion: The majority of US adults with gout had a SUA above the ACR target level and were not taking ULT. This study establishes a meaningful baseline to assess the effectiveness of ACR treatment guidelines for lowering UA in coming years.

Disclosure: S. Juraschek, NIH, 2; **L. Kovell**, None; **E. Miller III**, None; **A. C. Gelber**, None.

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High Mobility Group Box 1 Plays a Role In Gouty Arthritis. Kiwon Moon[1], Jinhyun Kim[2] and Yun Jong Lee[3]. [1]Kangwon National University Hospital, Chuncheon city, Kangwon province, South Korea, [2]Chungnam National University School of Medicine, Daejeon, South Korea, [3]Seoul National University Bundang Hospital, Seongnam-si, South Korea.

Background/Purpose: High mobility group box 1 (HMGB1) is a crucial cytokine that mediated the response to infection, injury and inflammation. It is recently discovered that HMGB1 plays a role in the pathogenesis of inflammatory arthritis, such as rheumatoid arthritis. However, the role of HMGB1 in gouty arthritis has not yet determined. The purpose of the study was to investigate the role HMGB1 in gouty arthritis.

Methods: HMGB1 concentrations of the synovial fluid (SF) of gouty arthritis and osteoarthritis (OA) were measured by ELISA. Immunohistochemistry was performed in synovial tissue of gouty arthritis and OA. Double immunofluorescence staining was also performed using anti-CD55, anti-CD68, and anti-HMGB1 antibody. In vitro THP-1 cell was stimulated by monosodium urate (MSU) crystal and lipopolysaccharide (LPS). HMGB1 and IL-1β concentrations were measured by ELISA. THP-1 cell and synovial fibroblast were stimulated by IL-1β alone or in complex with HMGB1. IL-1β, IL-6, TNF-α levels were measured by ELISA, and cyclooxygenase-2 (COX-2) expression was assessed by Western blot.

Results: HMGB1 concentration was significantly higher in SF of gouty arthritis than that of OA (73.1±57.1 vs 14.8±7.3, p < 0.01). Immunohistochemistry revealed that HMGB1 was localized in the nucleus of synoviocyte in OA. However, in gouty arthritis, HMGB1 was found in the cytoplasm of synoviocyte as well as nucleus. Double immunofluorescence staining showed that HMGB1 was found in mainly synovial fibroblast in gouty arthritis. MSU crystal and LPS induced HMGB1 and IL-1β production in THP-1 cell. However, IL-1β, IL-6, TNF-α levels and COX-2 expression were not stimulated by IL-1β alone or IL-1β/HMGB1 complex in THP-1 cell. IL-1β alone enhance COX-2 expression, but IL-1β/HMGB1 complex decreased COX-2 expression in synovial fibroblast.

Conclusion: HMGB1 was highly expressed in SF and synovial tissue in gouty arthritis. MSU crystal and LPS induced HMGB-1 and IL-1β production in macrophage. Extracellular HMGB1 decreased IL-1β induced COX-2 expression in synovial fibroblast. These findings suggest that HMGB1 might plays as an anti-inflammatory mediator in gouty arthritis.

Disclosure: K. Moon, None; **J. Kim**, None; **Y. J. Lee**, None.

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More Than One-Third Of Patients Reach Serum Urate Target and Continue To Report Multiple Flares. Dinesh Khanna[1], Puja Khanna[2], Chris Storgard[3], Scott Baumgartner[4] and Robert Morlock[3]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan Medical Center, Ann Arbor, MI, [3]Ardea Bioscience, San Diego, CA, [4]Ardea Biosciences, San Diego, CA.

Background/Purpose: Gout is a common inflammatory arthritis, and its worldwide prevalence is increasing. EULAR and ACR guidelines recommend a target serum urate (sUA) ≤6 mg/dL. We describe US and EU physician, patient, and treatment characteristics in patients treated with xanthine oxidase inhibitor (XOI) therapy who achieve sUA ≤6 mg/dL yet have 2 or more physician-confirmed gout flares per year.

Methods: A large survey of more than 500 physicians across the US and EU was conducted. Data was confirmed through in-depth chart audits, which assessed diagnosis, comorbid conditions, disease severity, and laboratory results of the last 5 patients with gout that they treated. Disease severity was measured using a physician global assessment (mild, moderate, or severe), flare counts, joint damage, and presence of tophi. Type and dose of XOI, length of current treatment, compliance, physician type, and patient sociodemographic factors were identified. Comorbidities were captured using chart review and analyzed as present or absent. Descriptive and multivariate statistics described patients having 2 or more

flares per year (excluding treatment initiation flares) in patients achieving sUA ≤6 mg/dL.

Table 1. Demographics: Patients With Most Recent sUA Level ≤6 mg/dL

	≥2 Flares (n=122)	≤1 Flare (n=233)	Total (n=355)
Sex (male)	87%	79%	81%
Age (years)	60.22	58.93	59.37
Number of flares (last 12 months)*	3.11	0.43	1.35
Most recent sUA level (mg/dL)	5.20	5.16	5.18
12-month average sUA level (mg/dL)*	6.34	5.84	6.01
Tophi*	31%	19%	23%
Treated with allopurinol	72%	74%	74%
Treated with febuxostat	28%	26%	27%
Months on current urate-lowering therapy	36.78	37.19	37.05
Rheumatologist management	65%	69%	67%

*p<0.05.

Results: In total, 251 rheumatologists and 250 primary care physicians were interviewed. Of 2505 patients with gout, 82% were male and the average age was 58 (SD=12) years; 1826 (73%) patients were treated with a XOI. Of these, 811 (44%) had at least one assessment of sUA ≤6 mg/dL and 305 (38%) reported 2 or more flares in the last 12 months (Table). A backward stepwise multivariate model predicting patients classified as controlled (sUA ≤6 mg/dL) and continuing to flare (2 or more flares in the last year) found physician-reported and chart-documented coexisting comorbidities, including chronic kidney disease (OR 2.8; p<0.01), alcoholism (OR 3.6; p<0.01), and diabetes mellitus (OR 1.9; p<0.05). There was no difference by XOI or physician type. Results were similar for patients with single or multiple sUA assessments ≤6 mg/dL during the study period.

Conclusion: Less than 50% of patients treated with a XOI alone achieved sUA target. Of the patients achieving a sUA level of ≤6 mg/dL, more than one-third reported 2 or more flares in a 12-month period despite being treated with the same ULT for more than 3 years. Frequent flares and greater tophaceous burden requires treatment to an even lower urate target than 6.0 mg/dL.

Disclosure: D. Khanna, Savient, NIH, 2, University of Michigan, 3, AstraZeneca, Takeda, Savient, 5; **P. Khanna**, None; **C. Storgard**, AstraZeneca, 1, Ardea Biosciences, a wholly owned subsidiary of AstraZeneca, 3; **S. Baumgartner**, Stock options AstraZeneca, 1, Full time employment Ardea Biosciences, a wholly owned subsidiary of AstraZeneca, 3; **R. Morlock**, Employee of Ardea Biosciences, Inc, 3.

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Use Of High-Dose Allopurinol To Reach Serum Uric Acid Targets In Patients With Gout Across Multiple Countries. Jasvinder A. Singh[1], Chris Storgard[2], Scott Baumgartner[3] and Robert Morlock[2]. [1]University of Alabama, Tuscaloosa, AL, [2]Ardea Bioscience, San Diego, CA, [3]Ardea Biosciences, San Diego, CA.

Background/Purpose: Allopurinol is the most commonly used urate-lowering therapy (ULT) in the world. Although allopurinol is FDA approved for up to 800 mg/d and EMEA authorized for up to 900 mg/d, the majority of patients with gout receive ≤300 mg/d. We describe physician, patient, and treatment characteristics in patients with gout treated with allopurinol.

Methods: Data from a quantitative survey of physicians in the United States (US), France, Germany, Italy, Spain, and the United Kingdom (UK) were assessed and results confirmed through in-depth chart audits. Initial and current allopurinol doses, presence of comorbid conditions, use of anti-inflammatory prophylaxis for flare prevention, serum uric acid (sUA), physician subspecialty, and patient factors were evaluated. Data on number of patients achieving target sUA <6 mg/dL were also collected.

Results are presented as proportions or means and standard deviations (SD). Descriptive statistics and multivariable-adjusted logistic regression analyses were used to describe patients with sUA <6 mg/dL.

Results: In total, 251 rheumatologists and 250 primary care physicians were interviewed. Of 2505 patients, 1437 (57%) were treated with allopurinol.

Table 1 presents patient characteristics, treatment, and percent with sUA <6 mg/dL.

Table 1. Patients Treated with Allopurinol: Unadjusted Characteristics by Country

	France (n=146)	Germany (n=180)	Italy (n=167)	Spain (n=186)	UK (n=137)	US (n=621)
Age, years (mean±SD)	63±9.7	60±11.5	62±11.2	58±10.7	56±13.4	57±12.2
Male (n, %)	112 (77)	148 (82)	139 (83)	167 (90)	118 (86)	515 (83)
Comorbidities (n, %)						
-Hypertension	53 (36)	106 (59)	75 (45)	91 (49)	52 (38)	348 (56)
-Cardiovascular disease	26 (18)	45 (25)	42 (25)	24 (13)	30 (22)	112 (18)
-Kidney disease	12 (08)	23 (13)	23 (14)	13 (7)	34 (25)	81 (13)
-Diabetes	25 (17)	40 (22)	42 (25)	4 (13)	19 (14)	143 (23)
Allopurinol dosing (n, %)						
<300 mg/d	74 (51)	54 (30)	47 (28)	67 (36)	29 (21)	139 (22)
300 mg/d	64 (44)	117 (65)	104 (62)	108 (58)	62 (45)	361 (58)
>300 to <600 mg/d	5 (3.4)	5 (2.8)	9 (5.4)	5 (2.7)	27 (20)	86 (14)
≥600 mg/d	3 (2.1)	4 (2.2)	8 (4.8)	7 (3.8)	19 (14)	35 (5.6)
Average allopurinol dose (mean±SD)	239±97.2	261 ± 96.9	279 ± 119.0	249 ± 116.8	347 ± 168.5	303 ± 129.3
Months on allopurinol (mean±SD)	48±56.8	35 ± 42.4	39 ± 46.3	59 ± 67.9	42 ± 53.2	43 ± 53.7
% sUA ≤6 mg/dL (n, %)	57 (39)	61 (34)	62 (37)	48 (26)	92 (67)	261 (42)

Across all countries, the majority of patients were treated with ≤300 mg/d of allopurinol; ≤6.5% in France, Germany, and Spain were given >300 mg/d, whereas 10% in Italy, 19.6% in the US, and 34% in the UK achieved a dose >300 mg/d (p<0.01). Over 12 months, the number of patients achieving target sUA <6.0 mg/dL differed across the 6 countries (Spain < Germany < Italy <France <US < UK, Table 1); yet, there was no difference in achieving target sUA <6.0 mg/dL by allopurinol dose. A multivariable-adjusted model predicting use of high-dose allopurinol found patients with tophi (OR 3.53; p<0.01), coexisting alcoholism (OR 1.66; p=0.06), COPD (OR 2.01; p<0.05), and patients using smoking-cessation treatments (OR 3.53; p=0.02), and from the UK (OR 3.86; p<0.01) were more likely to be using ≥600 mg/d of allopurinol. However, only physician subspecialty [general practitioners vs rheumatologists (OR 0.56; p<0.01)], UK vs other countries (OR 3.51; p<0.01), time on therapy (OR 1.39; p=0.04), and chart-documented coexisting alcoholism (OR 0.67; p<0.05), hyperlipidemia (OR 0.74; p<0.05), hypertension (OR 1.4; p<0.05), and kidney stones (OR 0.49; p<0.05) were found to be associated with achieving sUA <6 mg/dL. After adjusting for confounding factors (age, sex, time on ULT, dose, comorbid conditions, physician type), allopurinol dose was not associated with achieving sUA <6 mg/dL.

Conclusion: Allopurinol is the most widely used ULT. Although it is approved for up to 800 mg/d in the US and 900 mg/d in the EU, the majority of patients are treated with ≤300 mg/d. On average, <50% of patients achieve sUA <6 mg/dL at any allopurinol dose.

Disclosure: J. A. Singh, Takeda and Savient, 2, Savient, Takeda, Ardea, Regeneron, Allergan, URL pharmaceuticals, and Novartis, 5; **C. Storgard**, AstraZeneca, 1, Ardea Biosciences, a wholly owned subsidiary of AstraZeneca, 3; **S. Baumgartner**, Stock options AstraZeneca, 1, Full time employment Ardea Biosciences, a wholly owned subsidiary of AstraZeneca, 3; **R. Morlock**, Employee of Ardea Biosciences, Inc, 3.

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A Large-Scale, Multicenter, Prospective, Open-Label, 6-Month Study To Evaluate The Safety Of Allopurinol Monotherapy In Patients With Gout. Michael A. Becker[1], David Fitz-Patrick[2], Chris Storgard[3], Matt Cravets[4] and Scott Baumgartner[5]. [1]University of Chicago, Chicago, IL, [2]East-West Medical Research Institute, Honolulu, HI, [3]Ardea Bioscience, San Diego, CA, [4]Ardea Biosciences, Inc., San Diego, CA, [5]Ardea Biosciences, San Diego, CA.

Background/Purpose: Documentation of the safety profile of allopurinol at doses ≥300 mg/day is important for its ongoing use as first-line monotherapy or in combination with newer agents. Current data are limited. This study examined the safety profile of allopurinol titrated as described below (ClinicalTrials.gov Identifier: NCT01391325).

Methods: Patients meeting ARA criteria for the Classification of Acute Arthritis of Primary Gout and at least 2 gout flares in the preceding year were enrolled; caregivers were encouraged but not required to titrate allopurinol doses to achieve serum urate levels (sUA) of <6.0 mg/dL. Patients receiving pretrial urate-lowering therapy other than allopurinol underwent a 7-day washout period before initiating (or re-initiating) allopurinol therapy. Regular safety assessments were made; AEs were monitored throughout the study.

Results: Of 1735 patients enrolled, 1732 received at least 1 dose of allopurinol and constituted the safety population (93% male; 75% white; mean age, 51 years; mean BMI, 34.4 kg/m^2). Baseline characteristics and comorbidity rates were similar across dosage ranges, but a higher

percentage (29.2%) of those receiving <300 mg as maximal dose had moderately impaired renal function (CrCL <60 mL/min) than those who received 300 mg (13.8%) or >300 mg (9.7%). Patients who received >300-mg maximal daily dose had more severe disease at baseline (longer gout duration, tophi, more gout flares in prior year). Maximum daily dose was <300 mg in 250 patients (14.4%), 300 mg in 1132 patients (65.4%), and >300 mg in 350 patients (20.2%). In the safety population, only 744 patients (43%) achieved sUA levels <6.0 mg/dL at their last dose.

Table. Summary of Treatment-Emergent AEs (TEAEs, Safety Population)

Category	Maximum Allopurinol Daily Dose (mg) <300 (N=250) n (%)	300 (N=1132) n (%)	<300 (N=350) n (%)	Total (N=1732) n (%)
Any TEAE	124 (49.6)	623 (55.0)	208 (59.4)	955 (55.1)
TEAE with Rheumatology Common Toxicity Criteria Grade 3 or 4	14 (5.6)	60 (5.3)	21 (6.0)	95 (5.5)
TEAE possibly related to allopurinol	38 (15.2)	107 (9.5)	40 (11.4)	185 (10.7)
TEAE possibly related to prophylaxis	32 (12.8)	110 (9.7)	41 (11.7)	183 (10.6)
Serious TEAE	8 (3.2)	35 (3.1)	9 (2.6)	52 (3.0)
TEAE with outcome of death	1 (0.4)	2 (0.2)	0	3 (0.2)
TEAE leading to allopurinol withdrawal or study discontinuation	27 (10.8)	41 (3.6)	6 (1.7)	74 (4.3)
TEAE leading to prophylaxis switch or withdrawal	27 (10.8)	56 (4.9)	11 (3.1)	94 (5.4)

No clinically meaningful changes in laboratory values, including liver function tests, occurred. Rash incidence was low overall (1.5%), and allopurinol hypersensitivity syndrome was not encountered. The discontinuation rate in patients with a maximal dose of <300 mg was 49.6% vs 19.4% in those who received >300 mg.

Conclusion: This study revealed no new safety signals with medically appropriate allopurinol doses (approximately 300 mg/day). Data inspection showed few differences in TEAEs possibly related to allopurinol. Fewer than 50% of patients achieved the target sUA of <6 mg/dL at 6 months.

Disclosure: M. A. Becker, Takeda, Savient, Ardea Biosciences, AstraZeneca, BioCryst, URL/Mutual, Metabolex, Regeneron, 5, UpToDate Inc., 7; **D. Fitz-Patrick**, Ardea Biosciences, 2; **C. Storgard**, AstraZeneca, 1, Ardea Biosciences, a wholly owned subsidiary of AstraZeneca, 3; **M. Cravets**, Full time employee of Ardea Biosciences, a wholly-owned subsidiary of AstraZeneca PLC, 3; **S. Baumgartner**, Stock options AstraZeneca, 1, Full time employment Ardea Biosciences, a wholly owned subsidiary of AstraZeneca, 3.

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An Assessment Of The Response Of Chronic, Occult, Synovial-Based Inflammation Of Gout To Serum Urate Lowering Therapy. John D. Carter[1], Michelle Patelli[1], Scott Anderson[1], Neelish Prakash[1], Robyn Aydelott[1], Ernesto Rodriguez[1], Helen E. Bateman[2], Ashley G. Sterrett[3], Joanne Valeriano-Marcet[1] and Louis R. Ricca[4]. [1]University of South Florida, Tampa, FL, [2]James A Haley VA Hospital USF, Tampa, FL, [3]JAHVA, Tampa, FL, [4]University of South Florida College of Medicine, St Petersburg, FL.

Background/Purpose: We recently demonstrated that synovitis is present in the vast majority of patients with inter-critical gout and that the severity of this synovitis did not correlate with serum urate levels[1]. The aim of this sub-study was to determine if aggressive serum urate lowering therapy can improve this chronic occult synovitis.

Methods: All patients in this sub-study had inter-critical gout and received a 3Tesla MRI with and without gadolinium of their index joint (i.e. the joint most often involved with acute attacks of gout) at their screening visit. Each subject also had a serum urate level, CRP, and creatinine obtained on the same day. If the subject had a serum urate level of ≥ 7.0mg/dL and evidence of synovial pannus (synovitis) on their MRI, they were eligible for enrollment. All subjects were treated with febuxostat with a target serum urate level of ≤ 6.0mg/dL; each subject also received colchicine prophylaxis until month 6 (corticosteroids were not permitted). At month 9, the MRI of the index joint was repeated and the severity/degree of synovial pannus (graded on a scale of 1–6 [1 best; 6 worst]) was compared to baseline. The MRI's were read by two musculoskeletal radiologists in an independent and blinded fashion. The primary endpoint was to determine if there was significant improvement in the severity of synovial pannus from baseline to month 9.

Results: 25/32 subjects enrolled in this sub-study completed the entire protocol. 20 (80%) of the participants were males (17 Caucasian, 3 African-American, 2 Hispanic, 3 other) with an average age and disease duration of 57.2 years (range 40–70) and 10.1 years (range 1–31), respectively. 20/25 (80%) index joints were the first metatarsalphalangeal joint; the average number of attacks in the index joint was 8.3 (+/− 7.1 SD) with an average of 20.6 (+/− 27.1 SD) total attacks in any joint. The average serum urate level and synovial pannus score at screening was 9.3 mg/dL (+/− 1.3 SD) and 3.66 (+/− 1.2 SD), respectively. After 9 months of treatment with febuxostat, the average serum urate level decreased significantly to 5.36 mg/dL (+/− 1.4 SD; $p<0.0001$), but there was no significant change in the severity/degree of synovial pannus with the average score being 3.42 (+/− 1.3 SD; $p=0.34$). The inter-reader agreement between the two radiologists for all of the MRIs was good (kappa=0.63). There was also no significant change in the CRP or eGFR from screening to month 9.

Conclusion: Nine months of serum urate lowering therapy significantly decreases serum urate levels but has no effect on the chronic, occult, synovial-based inflammation of gout.

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Allopurinol Dose Titration and Efficacy: A Large-Scale, 6-Month, Multicenter, Prospective Study. Scott Baumgartner[1], Hyon Choi[2], Nicola Dalbeth[3], David Fitz-Patrick[4], Matt Cravets[5] and Chris Storgard[6]. [1]Ardea Biosciences, San Diego, CA, [2]Boston University School of Medicine, Boston, MA, [3]Auckland District Health Board, Auckland, New Zealand, [4]East-West Medical Research Institute, Honolulu, HI, [5]Ardea Biosciences, Inc., San Diego, CA, [6]Ardea Bioscience, San Diego, CA.

Background/Purpose: Allopurinol is the first-line urate-lowering therapy (ULT) for most people with gout, but target serum uric acid (sUA) levels of <6.0 mg/dL (recommended by current ACR guidelines) are often not achieved with doses up to 300 mg/day. Data on allopurinol dose titration and its efficacy are limited. The aim of this international, multicenter, prospective study was to evaluate the efficacy of allopurinol dose titration in a real-world setting (ClinicalTrials.gov Identifier: NCT01391325).

Methods: Adult patients meeting ARA criteria for the Classification of Acute Arthritis of Primary Gout and at least 2 gout flares in the preceding year were enrolled in this 6-month study. Patients who had received ULT other than allopurinol before the trial underwent a 7-day washout period before initiating or re-initiating allopurinol therapy, which was prescribed according to approved product labels and/or institutional standards of care. The study protocol encouraged upward titration of the allopurinol dose to an optimal, medically appropriate dose as determined by the investigator. The main efficacy endpoint was the proportion of patients with a sUA level of <6.0 mg/dL at the end of the study.

Results: Dosing and sUA Levels

Table 1. Final Allopurinol Dose by Baseline Dose

Baseline Dose (mg/day)	Final Allopurinol Dose (mg/day) ≤100	<100–200	<200–300	>300–400	>400–500	<500–600	>600
≤100 (n=591)	**40 (6.8)**	90 (15.2)	361 (61.1)	76 (12.9)	11 (1.9)	12 (2.0)	1 (0.2)
>100–200 (n=395)	5 (1.3)	**129 (32.7)**	209 (52.9)	31 (7.8)	14 (3.5)	5 (1.3)	2 (0.5)
>200–300 (n=662)	1 (0.2)	8 (1.2)	**557 (84.1)**	55 (8.3)	19 (2.9)	14 (2.1)	8 (1.2)
>300–400 (n=62)	0 (0.0)	0 (0.0)	2 (3.2)	**34 (54.8)**	17 (27.4)	7 (11.3)	2 (3.2)
>400–500 (n=11)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	**8 (72.7)**	0 (0.0)	2 (18.2)
>500–600 (n=8)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)	0 (0.0)	**5 (62.5)**	1 (12.5)
>600 (n=3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**3 (100)**

Shading: percentage of patients in same dose category at last visit as at baseline. Those above the diagonal were at a higher dose level and those below the diagonal were at a lower dose level.

Table 2. Levels of sUA by Final Daily Allopurinol Dose

sUA Response Categories (mg/dL)	Final Allopurinol Dose (mg/day) ≤100 (n=46)	>100–200 (n=227)	>200–300 (n=1131)	>300–400 (n=197)	>400–500 (n=69)	>500–600 (n=43)	>600 (n=19)	Total (N=1732)
>6.0	6 (13.0)	77 (33.9)	485 (42.9)	111 (56.3)	40 (58.0)	19 (44.2)	6 (31.6)	744 (43.0)
>5.0	1 (2.2)	23 (10.1)	152 (13.4)	44 (22.3)	16 (23.2)	11 (25.6)	3 (15.8)	250 (14.4)
>4.0	0 (0.0)	2 (0.9)	27 (2.4)	8 (4.1)	3 (4.3)	6 (14.0)	1 (5.3)	47 (2.7)
>3.0	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	3 (0.2)

As shown, 54.1% (937 patients) finished on a higher dose than at baseline, but only 15.8% of patients exceeded 300 mg/day (Table 1). Another 44.8% finished at the same dose as baseline. At the time of the last dose, only 43.0% of all patients had achieved target sUA levels <6.0 mg/dL (Table 2). Even at

doses above 300 mg/day, approximately 46% did not reach target sUA levels of <6.0 mg/dL.

Conclusion: In this large, multinational, prospective observational study of gout, optimal allopurinol dose escalation occurred infrequently. Fewer than 50% of patients overall achieved target sUA level <6.0 mg/dL and the majority of those with a baseline dose ≥300 mg/day did not increase their dose. These data, consistent with published literature, likely reflect real-world circumstances in which a significant proportion of patients fail to reach sUA targets with allopurinol therapy as currently used.

Disclosure: S. Baumgartner, Stock options AstraZeneca, 1, Full time employment Ardea Biosciences, a wholly owned subsidiary of AstraZeneca, 3; **H. Choi**, Savient, Takeda, 2, Takeda, AstraZeneca, 5; **N. Dalbeth**, Ardea/AstraZeneca, 5; **D. Fitz-Patrick**, Ardea Biosciences, 2; **M. Cravets**, Full time employee of Ardea Biosciences, a wholly-owned subsidiary of AstraZeneca PLC, 3; **C. Storgard**, AstraZeneca, 1, Ardea Biosciences, a wholly owned subsidiary of AstraZeneca, 3.

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The Synergistic Effects Of Metabolic Syndrome Indicators and Hyperuricemia In Contributing To Cardiac Event Risk: A Cross-Sectional Examination Of The Nhanes III Data. Daniel A. Albert[1] and Sayyad Kyazimzade[2]. [1]The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH, [2]The Dartmouth Institute for Health Policy & Clinical Practice, Lebanon, NH, Lebanon, NH.

Background/Purpose: The focus of this project is to assess the contribution of hyperuricemia and gout to the risk for cardiovascular events. In a preliminary analysis we examined known characteristics of the metabolic syndrome in vascular events. Of the five metabolic syndrome indicators, hypertension, hyperglycemia, dyslipidemia, obesity and elevated triglycerides, each has been shown to increase the risk for experiencing cardiac events (heart attack or stroke). There has yet to be an investigation, however, assessing whether or not these indicators are additive or synergistic in their contribution to the risk for experiencing a cardiac event and their relationship to hyperuricemia and gout.

Methods: Using the NHANES III data set (1988–1994), we conducted a cross-sectional analysis to assess whether or not the five facets of the metabolic syndrome are additive or synergistic in contributing to the risk for experiencing a cardiac event (defined as either a heart attack or stroke). To do so, we used interaction terms in a multiple logistic regression model, controlling for age, sex, race/ethnicity, education, smoking status, exercise, gout diagnosis and serum uric acid levels. Synergy was assessed based on statistical significance of interaction term odds ratios (ORs).

Results: Among all of the interaction terms, only the interaction between all five metabolic syndrome facets was statistically significant (OR = 240.06, 95% CI: 1.73; 33,304.89, p = 0.030), indicative of a synergistic effect. All other ORs had p-values ≥ 0.060. It is important to note that both ORs for the interaction terms of four of the five indicators had p-values of 0.060 and 0.067, while all other ORs were > 0.1. In this dataset hyperuricemia and gout did contribute additional risk (Hyperuricemia OR 1.11), p-value:0.036, 95%, CI: 1.01, 2.22. Gout OR 2.20 (p-value:0.001, 95% CI: 1.39, 3.49).

Conclusion: Of the five metabolic syndrome indicators, contribution to the risk of experiencing a cardiac event is predominantly additive. Only once a patient acquires four or five of the indicators, does a synergistic relationship begin to become evident in contributing to the odds of experiencing a cardiac event. Hyperuricemia and gout contribute additional risk. Further investigation will examine the interaction between hyperuricemia, gout, and the other components of the metabolic syndrome.

Disclosure: D. A. Albert, None; **S. Kyazimzade**, None.

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Low-Dose Anakinra Is Effective For The Prophylaxis Of Acute Episodes Of Inflammation In Severe Tophaceous Gout. Fernando Perez-Ruiz[1], Ana M. Herrero-Beites[2], Monike de Miguel[3] and Joana Atxotegi[1]. [1]BioCruces Health Institute, Baracaldo, Spain, [2]Hospital de Gorliz, Gorliz, Spain, [3]Hospital Universitario Cruces, Baracaldo, Spain.

Background/Purpose: anakinra has been used off-label for the treatment of severe episodes of acute inflammation (EAIs) in gout. Only a retrospective series of 3 patients has reported the use of ankinra as prophylaxis when used in an intermittent schedule. Therefore studies are needed to explore whether a low-dose prescription of anakinra would be effective in patients with severe difficult to treat gout and a formal contraindication of other current treatments for the prophylaxis of AEIs when starting urate-lowering therapy (ULT).

Methods: an agreement between the Rheumatology and Pharmacy Divisions was approved to treat with anakinra patients with severe or recurrent EAIs and a formal contraindication for current treatments for prophylaxis (colchicine and NSAIDs) and requiring repeated doses of parenteral corticosteroids not acceptable from the clinical point of view. As a pilot study, patients with crystal-proved gout were included in a cohort for follow-up from Jul 2011 to Jan 2013. All patients were scheduled for a 6-month period of treatment: anakinra 100 mg sc once a week with additional 100 mg doses on demand during the first 3 months and only on demand 100 mg sc doses from month 3 to 6. In addition to full clinical evaluation, serum urate, hsC-reactive protein, estimated glomerular filtration (CKD_EPI), complete blood cell counts, and liver function tests were tested once a month for the first three months, and at 6-month follow-up. AEIs were evaluated using the EULAR/ACR preliminary criteria for self-referred AEIs in gout and expressed as EAIS/patient-year exposure.

Results: 11 patients with chronic tophaceous (either subcutaneous or ultrasonographic/MRI), polyarticular (> 3 joints involved), crystal-proven gout were been included in the protocol. Ten were 10 men, mean age was 60±14 years (median 61, IQ range 48–69), time from the onset of gout 8±5 years (8, 5–15), subcutaneous tophi in 9/11, chronic heart failure 4/11, CKD 3–5 in 8/11, serious AEs to NSAIDs in 9/11. Diabetes or steroid-induced hyperglycemia in 8/11. Febuxostat 80 to 120 mg/day was prescribed to 6 patients, allopurinol 50 up to 300 mg/day to 6 patients (average dose 5.2 mg/ml FG-day). One patient was on hemodialysis and one showed normal serum urate and no need for urate-lowering agents.

Results are shown in Table. In the 0–3 period, 4/11 required additional doses, and 6/11 while on demand dosing from month 3–6. A patient had an episode of heart failure (4th in the year) but was maintained on treatment, doing well 16 months after treatment. No intercurrent infection was observed in any patient. No local reaction complaint was retrieved with a weekly schedule.

*P< 0.01 vs baseline	Baseline (median, IQ range)	1st mo (100 mg qw+100 mg on demand)	2nd mo (100 mg qw+100 mg on demand)	3rd mo (100 mg qw+100 mg on demand)	6th mo (100 mg on demand)
SuA (mg/dl)	10.2 ± 2.1 (9.5, 9.1–10.3)	5.6 ± 1.4 (5.6, 5.0–6.9)*	4.6 ± 0.7 (4.6, 4.2–5.2)*	4.6 ± 1.3* (4.8, 3.6–4.9)	5.0 ± 1.1* (5.4, 4.8–5.7)
hsCRP (mg/dl)	2.05 ± 2.98 (2.4, 1.7–21.9)	1.4 ± 1.3 (0.8, 0.3–2.7)*	1.22 ± 1.52 (0.2, 0.2–2.3)*	0.39 ± 0.88* (0.1, 0.1–0.2)	0.56 ± 1.07 (0.1, 0.10–0.45)
CCR (ml/min)	67 ± 30 (62, 43–89)	65 ± 32 (63, 38–86)	69 ± 41 (67, 42–88)	78 ± 35 (78, 43–111)	74 ± 32 (65, 46–111)
EIA (per patient/ year)	13 ± 9 (10, 6–24)	-	-	2.6 ± 5.3 (0, 0–4)*	2.0 ± 2.1 (2, 0–4)*

Conclusion: this pilot study is, to our knowledge, the first to prospectively explore in pre-established doses the efficacy of low-dose anakinra for the prophylaxis of AEIs in patients with severe comorbidities and difficult to treat tophaceous gout. These encouraging results deserve further studies.

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Pharmacovigilance Update On Pegloticase For Treatment Refractory Gout: United States Clinical Experience Demonstrates The Value Of Serum Uric Acid Monitoring As a Biomarker Of Risk and Efficacy. Robert T. Keenan[1], Raymond L. Malamet[2], Tina L. Howson[2] and Kenneth M. Bahrt[2]. [1]Duke University, Durham, NC, [2]Savient Pharmaceuticals, Inc., Bridgewater, NJ.

Background/Purpose: Pegloticase was approved in the US in late 2010 for patients with chronic gout refractory to xanthine oxidase inhibitors (XOIs). The clinical development program for pegloticase used a primary endpoint based on uric acid (UA) response <6 mg/dL and 42% of treated patients were classified as "responders" (vs 0% with placebo; $P<0.001$).[1,2] Post hoc analyses revealed that UA nonresponse was associated with high titer antibodies against pegloticase resulting in increased drug clearance and risk for infusion reactions (IRs). Pegloticase treatment recommendations thus included that UA be monitored preinfusion and discontinuation considered if serum UA was >6 mg/dL (particularly with 2 consecutive levels >6 mg/dL). Postapproval safety data has provided valuable insights into UA monitoring, concomitant medication use, and risk mitigation. Here we present pharmacovigilance data with a focus on infusion-related reactions and educational efforts to prevent the use of concomitant XOIs. Concomitant XOI use can mask the loss of UA response to pegloticase and confound the use of UA as a biomarker of efficacy and IR risk. Guidance cautioning against the use of pegloticase and XOIs was distributed via a Dear Healthcare Provider (DHCP) letter and a label update.

Methods: For safety surveillance, IRs were defined as adverse events (AEs) that occurred during or within 2 hours following the end of study drug infusion and could not be reasonably attributed to another cause. The

incidence of IRs was drawn from voluntary AE reporting via MedWatch from September 2010 to March 2013 (to be updated through September 2013). All cases of IRs were evaluated for concomitant XOI use. An estimate of the total number of infusions given was based on the number of vials sold.

Results: During the postapproval period of 2.5 years, there were an estimated 12,736 vials sold and the sponsor received 91 spontaneous reports of patients with IRs (70 reports of IRs and 21 reports of possible anaphylaxis). When compared with IR rates from the clinical trials, postapproval data represents a significant reduction in IR risk of 72%. Among the 91 IRs, 78 events occurred during the infusion and 4 occurred in the 2 hours postinfusion (9 did not provide timing). The incidence of concomitant XOI use with pegloticase among patients with IRs was reduced ($P=0.0028$) after the DHCP letter and label change (table).

Concomitant Urate-Lowering Status for IRs Reported Before and After DHCP Letter	Number of IR Reports
Prior to letter (Total IR reports=31)	
Patients with IR and concomitant urate-lowering	12
Patients with IR and no concomitant urate-lowering	13
Patients with IR and unknown conmed status	6
After the letter (Total IR reports=60)	
Patients with IR and concomitant urate-lowering	5
Patients with IR and no concomitant urate-lowering	37
Patients with IR and unknown conmed status	18
Total	91

Conclusion: Given known limitations of estimating based on unsolicited AE reporting during pharmacovigilance, increasing utilization of pegloticase has been associated with a decline in the number of IRs. Educational efforts have led to significant reductions in the proportion of IRs with concomitant XOI use. Continued educational efforts regarding the need for UA monitoring with pegloticase and avoidance of concomitant XOI use should further reduce IR risk.

References:
1. Sundy et al. JAMA. 2011.
2. Becker et al. Ann Rheum Dis. 2012.

Disclosure: R. T. Keenan, Savient Pharmaceuticals, Inc., 5; **R. L. Malamet**, Savient Pharmaceuticals, Inc., 3; **T. L. Howson**, Savient Pharmaceuticals, Inc., 3; **K. M. Bahrt**, Savient Pharmaceuticals, Inc., 3.

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Target Tophus Size and Complete Response Rates In Patients Treated With Open-Label Pegloticase For Chronic Gout Refractory To Conventional Therapy. Robert T. Keenan[1], Nicola Dalbeth[2] and Herbert S. B. Baraf[3]. [1]Duke University, Durham, NC, [2]University of Auckland, Auckland, New Zealand, [3]Arthritis & Rheumatism Associates, PC, Wheaton, MD.

Background/Purpose: Pegloticase, a methoxy PEG-conjugated mammalian recombinant uricase, has been approved in the US and EU for the treatment of chronic gout refractory to xanthine oxidase inhibitors. The pegloticase development program included 2 replicate randomized placebo-controlled trials (RCTs) followed by an open-label extension (OLE) study for a maximum therapy duration of up to 3 years.[1,2] The pegloticase trials were unique in enrolling a majority of patients with baseline tophi (155/212 or 73%) and in the use of detailed digital quantitative assessment of each tophus. Here we present data on long-term treatment with pegloticase and tophus response rates as a function of tophus size.

Methods: Patients enrolled in the RCTs (n=212) were ≥18 years of age with baseline serum uric acid (UA) ≥8 mg/dL and at least 1 of the following: ≥3 self-reported gout flares in the past 18 months, ≥1 tophi, or gouty arthropathy; and contraindication to allopurinol or failure to normalize UA after ≥3 months of treatment at the maximum medically appropriate dose. Target subcutaneous tophi identified at baseline were photographed and assessed at multiple study time points using computer-assisted quantitative digital image analysis in patients receiving pegloticase (8 mg; q2wks or q4wks) or placebo in the RCTs, and pegloticase in the OLE. Complete response was defined as complete resolution of the target tophus. Tophus size was assessed at the baseline visit of the RCTs and categorized as small (<250 mm^2), medium (250–750 mm^2), or large (>750 mm^2).

Results: This tophus size analysis focused on patients receiving the approved twice-monthly pegloticase dose who entered the OLE study. These included patients treated with either q2wk pegloticase (both UA responders and nonresponders; see table for definition) or placebo in the RCTs who received q2wk pegloticase at OLE study entry. The table presents the number of tophi undergoing complete resolution for each of these subgroups by tophus size. Among patients who showed response to therapy, the majority of small and medium tophi resolved within 6–9 months of therapy. For larger tophi, 12 to 18 months of therapy resulted in complete response in over 60% of tophi.

Percentage of Target Tophi With Complete Response Over Time Based on Size Pegloticase q2wks UA Responders* in the RCTs

Study Visit	Small <250 mm^2	Medium 250–750 mm^2	Large >750 mm^2
RCT 25 weeks Total n**=37	42% (11/26)	30% (7/23)	8% (1/12)
OLE 13 weeks Total n=35	76% (19/25)	55% (12/22)	8% (1/12)
OLE 25 weeks Total n=34	84% (21/25)	67% (14/21)	18% (2/11)
OLE 53 weeks Total n=32	86% (19/22)	65% (13/20)	18% (2/11)
OLE 77 weeks Total n=32	79% (19/24)	90% (18/20)	64% (7/11)
Progressing tophi at 53 weeks Total n=32	0/22	0/20	0/11
Pegloticase q2wks UA Nonresponders* in the RCTs			
RCT 25 weeks Total n=30	6% (1/17)	16% (3/19)	6% (1/18)
OLE 13 weeks Total n=30	27% (4/15)	32% (6/19)	0/15
OLE 25 weeks Total n=18	67% (4/6)	36% (5/14)	0/11
OLE 53 weeks Total n=21	60% (6/10)	38% (6/16)	8% (1/13)
OLE 77 weeks Total n=19	60% (6/10)	27% (4/15)	8% (1/12)
Progressing tophi at 53 weeks Total n=21	0/10	6% (1/16)	23% (3/13)
Placebo → q2wks at OLE Entry			
RCT 25 weeks Total n=37	6% (1/17)	7% (2/31)	0/20
OLE 13 weeks Total n=30	44% (7/16)	26% (6/23)	0/16
OLE 25 weeks Total n=25	85% (11/13)	50% (11/22)	33% (4/12)
OLE 53 weeks Total n=21	100% (12/12)	82% (14/17)	90% (9/10)
OLE 77 weeks Total n=21	92% (11/12)	94% (16/17)	70% (7/10)
Progressing tophi at 53 weeks Total n=21	0/12	0/17	0/10

*Responders were patients who met the primary endpoint of UA reduction defined as UA <6 mg/dL for 80% of time during RCT study months 3 and 6.
**Total n is all patients in the subgroup irrespective of tophus response.

Conclusion: Many small and medium subcutaneous tophi resolved within the first 6 months of pegloticase therapy. These data show that substantial incremental benefit in tophus response for unresolved small to medium tophi can be gained with 9–12 months of therapy in UA responders. Longer periods of treatment (up to 18 months) with pegloticase were shown to resolve large tophi.

References:
1. Sundy et al. JAMA. 2011.
2. Becker et al. Ann Rheum Dis. 2012.

Disclosure: R. T. Keenan, Savient Pharmaceuticals, Inc., 5; **N. Dalbeth**, Takeda, Ardea, AstraZeneca, Novartis, Abbott, Fonterra, and Roche, 9, Fonterra, 2, Novartis, Savient, 8; **H. S. B. Baraf**, Savient, Takeda, Regeneron, and Ardea, 2, Savient, Takeda, 9, Takeda, Savient, 8.

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Enhanced IL-1β and IL-6 Production In Gout Patients Upon Stimulation With Mono Sodium Urate Crystals and Synergizing Agents Compared To Healthy Volunteers. Tania O. Crisan[1], Maartje Cleophas[1], Mihai G. Netea[1], Tim L. Jansen[1] and Leo A. Joosten[2]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Department of Medicine, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands.

Background/Purpose: Gout is an autoinflammatory disease characterized by the deposition of monosodium urate (MSU) crystals in the joints of hyperuricaemic patients and subsequent attacks of severe gouty arthritis. It is known for centuries that the MSU crystals are the necessary causative agent of gout but, in addition, it is now proven that MSU requires synergizing stimuli to induce high cytokine responses, relevant for the clinical picture of gout. Here we investigate the inflammatory response in gout patients and healthy controls upon stimulation with MSU crystals in combination with other ligands. We also investigate the effects of elevated uric acid concentrations on the pro-inflammatory cytokine production in human immune cells.

Methods: Peripheral blood mononuclear cells (PBMCs) were harvested from patients diagnosed with crystal-proven gout and from age matched healthy volunteers. Cells were stimulated for 24 hours with Pam3Cys or palmitic acid (C16) in the presence or absence of MSU crystals. In separate experiments, the cells were first treated with uric acid or left untreated for 24h

and then subjected to stimulation with Pam3Cys or LPS for another 24h. Production of IL-1beta, IL-6 was assessed using specific sandwich ELISA kits. mRNA levels were measured using quantitative real time PCR. Differences were assessed using the Mann-Whitney test and a p-value$<$0.05 was considered statistically significant.

Results: MSU crystals stimulation alone did not induce detectable levels of IL-1β or IL-6 neither in patients nor in controls, however, a significant synergy between MSU and Pam3Cys or C16 was observed. Of high importance, significantly higher levels of IL-1β and IL-6 were observed in patients compared to controls. Subsequently, when cells were pretreated with uric acid, an enhanced cytokine production was observed in cells stimulated with Pam3Cys or LPS in the presence or absence of MSU, however, uric acid alone did not induce this effect. This enhanced cytokine production correlated with higher mRNA levels observed in uric acid pre-treated cells.

Conclusion: Enhanced cytokine production was observed in cells originating from gout patients compared to controls when stimulated with MSU crystals and synergizing stimuli. Similar trends could be identified when the cells were pre-treated with high uric acid levels in vitro and then subjected to MSU crystals stimulation. These results indicate that high uric acid levels could have an effect on immune cells and facilitate higher responses upon encounter of inflammatory stimuli and this could be a mechanism for the enhanced pro-inflammatory response observed in gout patients.

Disclosure: T. O. Crisan, None; **M. Cleophas**, None; **M. G. Netea**, None; **T. L. Jansen**, None; **L. A. Joosten**, None.

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Sex Differences In Gout Evaluation and Management. Leslie R. Harrold[1], Carol Etzel[2], Allan Gibofsky[3], Joel M. Kremer[4], Michael H. Pillinger[5], Kenneth G. Saag[6], Naomi Schlesinger[7], Robert Terkeltaub[8], Vanessa Cox[2] and Jeffrey D. Greenberg[9]. [1]University of Massachusetts Medical School, Worcester, MA, [2]CORRONA, Inc, Southborough, MA, [3]Hospital for Special Surgery, New York, NY, [4]Center for Rheumatology, Albany Medical College, Albany, NY, [5]NYU School of Medicine, Division of Rheumatology, New York, NY, [6]University of Alabama at Birmingham, Birmingham, AL, [7]UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, [8]VA Medical Ctr/University of California San Diego, San Diego, CA, [9]New York Hospital for Joint Diseases, New York, NY.

Background/Purpose: Little is known regarding the evaluation, characteristics and management of women with gout. To characterize potential gender differences, we therefore compared clinical manifestations and treatment of women versus men in a nationwide sample of men and women with gout cared for by rheumatologists.

Methods: Rheumatologists participating in the Consortium of Rheumatology Researchers of North America (CORRONA) registry agreed to enroll their gout patients regardless of gender, disease severity, disease activity or medication use. All patients enrolled between 11/1/12 and 5/1/13 were included in the current study. Data was gathered at the time of enrollment from patients and their rheumatologists including demographics, gout evaluation, clinical characteristics, comorbid conditions, current treatments, and physical exam findings. Logistic regression models were created to examine the influence of sex on use of a urate-lowering drug (ULD) adjusting for patient age and duration of gout and accounting for clustering by practice site.

Results: Fifty-four rheumatologists enrolled 109 women and 414 men with gout. Women were older (71 vs. 62 years, p$<$0.001) and more commonly had a comorbid illness including hypertension (76% vs. 59%, p=0.001), diabetes (32% vs. 17%, p=0.001) and renal disease (29% vs. 14%, p$<$0.001). Women had a shorter duration of gout (6 vs. 11 years, p$<$0.001) and were less likely to have a crystal proven diagnosis (19% vs. 34%, p=0.003). While women had similar clinical features in terms of acute gout presentation (e.g., podagra, oligoarthritis, etc), and gouty arthritis (tophi, joint deformity), they were more likely to have contraindications to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) (32% vs. 21%, p=0.02) or colchicine (14% vs. 6%, p=0.01). Among those patients with 2 or more attacks per year or those with tophi, women (n=63) were less likely to be on a urate-lowering drug (ULD) as compared to men (n=233) (78% vs. 89%, p=0.02) in both unadjusted and adjusted (OR 0.42, 95% CI 0.19–0.92) analyses.

Conclusion: Compared to men, women with gout were older and less likely to have received a definitive diagnosis of gout by crystal identification. Women were more likely to have contraindications to NSAIDs and colchicine, and less likely to be receiving ULDs. Our data suggest the presence of health care disparities between women and men with gout, and that gout in women may have unique features and challenges. Further investigation is needed to ensure optimal care in women with gout.

Disclosure: L. R. Harrold, CORRONA, Inc., 5; **C. Etzel**, CORRONA, Inc., 3; **A. Gibofsky**, Abbvie, Amgen, BMS, GlaxoSmithKline, Johnson and Johnson, Pfizer Inc, Genentech, 1, Abbvie, Amgen, AstraZeneca, Celgene, Horizon, Iroko, Pfizer Inc, Genentech, 5, Abbvie, Amgen, Pfizer Inc, Genentech, 8; **J. M. Kremer**, CORRONA, Inc., 1, CORRONA, Inc., 3; **M. H. Pillinger**, Takeda Pharmaceuticals, 2, Savient Pharmaceuticals, 2; **K. G. Saag**, Takeda Pharmaceuticals, 2, Ardea, 2, Regeneron, 2, Savient Pharmaceuticals, 2, Takeda Pharmaceuticals, 5, Ardea, 5, Regeneron, 5, Savient Pharmaceuticals, 5; **N. Schlesinger**, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, Sobi, 5, Novartis Pharmaceutical Corporation; Takeda Pharmaceuticals, Savient Pharmaceuticals, 8, Novartis Pharmaceutical Corporation, Takeda Pharmaceuticals, Savient Pharmaceuticals, Sobi, 9; **R. Terkeltaub**, VA Research Service, 2, Takeda Pharmaceuticals, 5, Savient Pharmaceuticals, 5, Ardea, 5, BioCryst, 5, Novartis Pharmaceutical Corporation, 5, Regeneron, 5, Sobi, 5, Pfizer Inc, 5, Abbvie, 5; **V. Cox**, CORRONA, Inc., 3; **J. D. Greenberg**, CORRONA, Inc., 1, AstraZeneca, CORRONA, Inc., Novartis, Pfizer Inc, 5.

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Chronic Renal Injury Does Not Prevent Achievement Of Target Serum Uric Acid In Tophaceous Gout. Mireille Aujero[1], J. Steuart Richards[2], Carl A. Nunziato[3], David D. Maron[4] and Gail S. Kerr[5]. [1]Washington DC VA Medical Center and Georgetown University, Washington, DC, [2]Washington DC VA and Georgetown University, Washington, DC, [3]Howard University Hospital, Washington, DC, [4]Washington DC VA Medical Center, Washington, DC, [5]Washington DC VAMC, Georgetown and Howard University, Washington, DC.

Background/Purpose: ACR 2012 management guidelines for tophaceous gout (TG) recommend urate lowering therapies (ULT) to achieve a target serum uric acid (SUA) of $<$ 6.0 mg/dl, but in some patients, a SUA of $\leq$ 5.0 mg/dl may be appropriate. Despite new ULT, allopurinol remains the most commonly used drug. Yet, achievement of target SUA in clinical practice is subpar, with comorbidities frequently limiting optimum ULT use. We evaluated a cohort with TG and significant comorbidities to determine the applicability of recent ACR guidelines, that is, achievement of target SUA of less than 6 mg/dl and 5 mg/dl, respectively.

Methods: VA administrative data over a 3-year period was used to identify patients with gout (ICD 9 codes: 274.xx) who had at least two related outpatient visits, and BMI $>$ 28 Kg/m^2. Medical records from primary care and rheumatology clinics were filtered electronically for the prefix 'toph' and then searched manually for presence of 'tophaceous gout' or 'tophus' to identify TG subset. Demographic data, including age, race, BMI, comorbidities [hypertension (HTN), chronic renal injury (CRI) and diabetes mellitus (DM)], SUA, serum creatinine and creatinine clearance (CrCl) were extracted from Veterans Affairs Decision Support System (DSS) database. Natural Language Processing was used to extract gout behavioral modification counseling (BMC). Colchicine and allopurinol use was recorded for each patient; for allopurinol, dose and dates of therapy were obtained for patients with TG. Data were analyzed for number and percent of patients achieving target SUA $<$6 mg/dl and $\leq$ 5 mg/dl.

Results: Clinical characteristics of the 1576 eligible patients are shown in (Table). One hundred and twenty (73.2%) patients with TG were on allopurinol. SUA was evaluated at least once in 119 (99.2%) patients. Seventy-eight patients (65%) achieved target SUA $<$ 6 mg/dl at least once during follow up and 44 (36.7%) achieved SUA levels $\leq$ 5 mg/dl. Forty-two patients had CrCl $<$ 60 ml/min; 24 (57.1%) and 15 (35.7%) achieved SUA $<$ 6 mg/dl and $\leq$ 5 mg/dl, respectively. Patients with a CrCl $\geq$ 60 ml/min had mean allopurinol dose of 257.7 mg/day [54/78 (47.4%) SUA $<$ 6 mg/dl], significantly greater than patients with CrCl $<$ 30 ml/min who received a mean of 69.0 mg/day [3/6 (50%) SUA $<$ 6 mg/dl]. However, both groups had similar mean SUA levels [6.52 $\pm$ 2.1 vs. 6.03 $\pm$ 1.06 (p $<$ 0.948)], respectively. Mean allopurinol dose for patients with SUA $<$ 6 mg/dl and $\geq$ 6 mg/dl was 255.1 ($\pm$ 124.5) and 157.7 ($\pm$ 109.4) (p $<$ 0.001), respectively. There were no differences in demographics, severity of CRI, frequency of comorbidities, BMC or number of rheumatology visits between patients achieving SUA $<$ 6 mg/dl and those who remained above target values.

Table.

Characteristic	Total Population N = 1576	Tophaceous Gout N = 164	Non tophaceous gout N = 1412	P value
Age (mean and SD)	66.59 ± 11.9	65.8 ± 13.4	66.7 ± 11.8	0.36
African American (n)	502 (31.9%)	64 (39.0%)	439 (31.1%)	0.04
Caucasian (n)	83 (5.3%)	7 (4.3%)	76 (5.4%)	0.55
BMI (mean and SD)	30.75 ± 5.7	30.2 ± 5.5	30.8 ± 5.8	0.21
Cr Cl < 60	490 (31.1%)	60 (36.6%)	428 (30.3%)	0.10
Cr Cl <30 (n)	78 (4.9%)	11 (6.7%)	67 (4.7%)	0.27
Cr Cl ≥ 30 and <60 (n)	412 (26.1%)	49 (29.9%)	363 (25.7%)	0.68
Cr Cl ≥60 (n)	1086 (68.9%)	104 (63.4%)	982 (69.5%)	<0.0001
HTN	1459 (92.6%)	158 (96.3%)	1303 (92.3%)	0.06
Hyperlipidemia	820 (52.0%)	87 (53.0%)	736 (52.1%)	0.82
CVD	955 (60.6%)	106 (64.6%)	851 (60.3%)	0.27
DM	736 (46.7%)	79 (48.2%)	658 (46.6%)	0.70
Colchicine use EVER	1095 (69.5%)	152 (92.7%)	943 (66.8%)	<0.0001
Allopurinol use EVER	968 (61.4%)	141 (86.0%)	826 (58.5%)	<0.0001
Rheum visits > 1	1576 (100%)	164 (100%)	1412 (100%)	1.00
Avg # of Rheum visits 2008–2010	3.40 ± 2.7	6.14 ± 4.2	3.08 ± 2.3	0.0001
BMC	60 (3.8%)	16 (9.8%)	44 (3.1%)	<0.0001

Conclusion: Despite frequent associated comorbidities the majority of TG patients can achieve target SUA levels. In CRI, BMC and allopurinol pharmacokinetics may have significant roles in achieving SUA target.

Disclosure: M. Aujero, None; **J. S. Richards**, Ardea, 9, Savient, 9; **C. A. Nunziato**, None; **D. D. Maron**, None; **G. S. Kerr**, Saviet, 2, Savient, 9, Ardea, 9.

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Gout Medications and The Risk For Incident Coronary Heart Disease and Stroke: The Framingham Heart Study. Weiqi Wang[1], Vidula Bhole[2] and Eswar Krishnan[3]. [1]stanford university, palo alto, CA, [2]EpiSolutions Consultancy Services, Thane, India, [3]Stanford University, Palo Alto, CA.

Background/Purpose: Recent studies suggest a protective association between both urate lowering medications and colchicine and the risk for coronary heart disease. The goal of the present study was to confirm this.

Methods: We analyzed data from the Framingham heart study (FHS) spanning 20 years from 1980 to 2000, over 10 study visits (17 to 26) for gout patients only. The definition of Coronar Hert Disease (CHD) included myocardial infarction, coronary insufficiency, angina pectoris and related death. The definition of stroke included thrombotic and hemorrhagic stroke as well as transient ischemic attacks. Gout was defined by any one of: self-report, physician diagnosis, gout medication use, and radiographic changes. Hypertension was defined as systolic blood pressure >= 140 mm Hg or diastolic blood pressure >= 90 mm Hg or usage of anti-hypertensive medications. Diabetes status, BMI and total cholesterol were obtained from FHS official documents. Two types of gout medications (uric acid lowering medications and colchicine) were combined as both have been associated with beneficial cardiovascular effects in prior studies. Data were analyzed using Cox proportional hazard regression models where the dependent variable was the time to incident event and independent variables (gout medication, sex, age, BMI, hypertension, diabetes, total cholesterol) were treated as time-varying. Missing values were addressed by multiple imputations.

Results: There were 414 participants with gout included in this study, among whom 235 used gout medication before the cardiovascular event. At the baseline the proportion of men was 63.77%. Overall there were 229 incident cases of CHD and 117 incident cases for stroke during the follow up. The incidence rate per thousand person-years of CHD in the gout medication group was 24.74 and in the other group was 27.93; the incidence rates of stroke were 16.78 and 16.93, respectively. The unadjusted and age adjusted hazard ratio for gout medications were 0.88 (95% confidence interval 0.51–1.53) and 0.88 (0.51–1.53) for CHD; 0.87 (0.48–1.56) and 0.87 (0.49–1.57) for stroke. In multivariable Cox models, gout medication was associated with a hazard ratio of 0.80 (0.45–1.41) for CHD and 0.85 (0.47–1.53) for stroke. When the regressions were repeated for stroke and CHD combined, the multivariable hazard ratio was 0.81 (0.49–1.33).

Conclusion: Gout medication is associated with a beneficial effect for both incident CHD and stroke in most of our analyses. However the magnitude of the observed statistical association was small and the threshold of statistical significance was not crossed, suggesting that the real-world impact of these drugs may be negligible.

Disclosure: W. Wang, None; **V. Bhole**, None; **E. Krishnan**, Takeda, 2, takeda, 5.

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Allopurinol Dose Above Creatinine Clearance Based Dose Is Safe and Effective in Gout - Compliance, Efficacy and Safety At 2 and 3 Years. Nicole Coman-Wright[1], Peter T. Chapman[2], John L. O'Donnell[3] and Lisa K. Stamp[1]. [1]University of Otago, Christchurch, Christchurch, New Zealand, [2]Christchurch Hospital, Christchurch, New Zealand, [3]Canterbury Health Laboratories, Christchurch, New Zealand.

Background/Purpose: Gout is a common form of inflammatory arthritis caused by the crystallisation of uric acid. Sustained reduction of SU below 6mg/dl is critical for successful management of gout. Allopurinol is the most commonly used urate lowering therapy. The creatinine clearance (CrCL) based allopurinol dosing recommendations were based on a proposed relationship between allopurinol dose and allopurinol hypersensitivity syndrome. We have previously reported that target SU can be achieved at year one by titrating allopurinol dose above the CRCL based dose. The aim of this study was to determine if allopurinol was continued and if the reduction in SU was sustained during the subsequent two years.

Methods: Patients with gout receiving the CrCL based dose of allopurinol with SU >6mg/dl were recruited. The dose of allopurinol was increased until target SU (< 6mg/dl) was achieved. Patients were seen monthly for 12 months and then annually for a further 2 years. Between the annual visits, the patient's general practitioner (GP) was advised to monitor SU three monthly to ensure target SU was maintained.

Where patients were lost to follow-up after year 1 available data was collected until the 3 year time point from public and private laboratory databases and hospital records.

Results: Forty five patients were enrolled in the dose escalation study. The mean age was 59.5 years (range 27–83), 93.3% were male, and 80% were of European ancestry. Thirty-five patients completed year 1, 29 patients year 2, and 26 patients year 3. Four patients were lost to follow up, 2 experienced rashes resulting in allopurinol discontinuation, 2 were deemed too unwell to continue and 1 patient died from liver cancer. All patients who completed year 1 and 2 and 25/26 patients at year 3 were receiving allopurinol. The mean dose of allopurinol was 355.71 mg/d (150–600mg/d) at year 1, 353.5 mg/d (150–600mg/d) at year 2 and 358 mg/d (200–600mg/d) at year 3. 31/35 (88.8%) patients that completed year 1 achieved the target SU, mean 5.4mg/dl (3.9–11.3mg/dl). 24/29 (82.8%) patients that completed year 2 achieved target SU, mean 4.9mg/dl (3.2 – 7.2mg/dl). 23/26 (88.5%) patients that completed year 3 achieved target SU, mean 5.4mg/dl (3.9–10.8mg/dl). During year 2, 7/35 (20%) patients had ≥ 4 biochemistry tests including SU. At year 3, 4/35 (11.4%) patients had ≥ 4 biochemistry tests including SU. The majority of patients had been able to discontinue regular NSAIDs, colchicine or prednisone by year 3.

Conclusion: In those patients who remain compliant with allopurinol therapy, target SU can be maintained out to three years. Clinicians need to be mindful that rashes can occur even after receiving allopurinol for a prolonged period. There is poor monitoring of SU in the community. Further study is required on how frequently SU should be monitored once target is achieved and attacks have resolved.

Disclosure: N. Coman-Wright, None; **P. T. Chapman**, None; **J. L. O'Donnell**, None; **L. K. Stamp**, None.

1199

The Performance Of a Novel Scoring System In The Differential Diagnosis Between Acute Gout and Septic Arthritis. Jung-Soo Song[1], Kwang-Hoon Lee[2], Sang Tae Choi[1], Eun-Jin Kang[3] and You-Jung Ha[4]. [1]Chung-Ang University College of Medicine, Seoul, South Korea, [2]Dongguk University Ilsan Hospital, Goyang, South Korea, [3]Busan Medical Center, Busan, South Korea, [4]Yonsei University College of Medicine, Seoul, South Korea.

Background/Purpose: Recently, a novel scoring system was developed for the diagnosis of gout without joint fluid analysis (1). The performance of this scoring system in the differential diagnosis between acute gout and septic arthritis has not been validated yet. This study aimed to evaluate the diagnostic performance of this scoring system in the differential diagnosis between acute gout and septic arthritis in patients with acute monoarthritis.

Methods: The medical records of 33 patients with acute gout and 27 with septic arthritis who presented as acute monoarthritis and were diagnosed at Chung-Ang University Hospital in Seoul, South Korea and Dongguk University Hospital in Goyang, South Korea from 2007 to 2012 were reviewed. Patients with podagra were excluded. All gout patients were MSU positive and all septic arthritis patients had positive results of bacterial culture. The

diagnostic scoring system (1) gives different scores to several clinical criteria as follows: 2 to male sex, 2 to previous patient reported arthritis attack, 0.5 to onset within one day, 1 to joint redness, 2.5 to 1st MTP involvement, 1.5 to hypertension or at least one cardiovascular disease and 3.5 to serum uric acid greater than 5.88 mg/dL. The probability of gout is high when the sum of the score is ≥ 8, intermediate when between 4 and 8 and low when ≤ 4. Patients were classified to one of each probability groups according to the scores they got.

Results: Both patient groups were similar in age (55.6 ± 21.0 vs. 58.4 ± 20.2 years). However, patients with acute gouty arthritis were more likely to be male (90.9% vs. 59.2%), had shorter duration of onset (1.54 ± 1.22 vs. 2.92 ± 2.0 days, $p = 0.004$), lower levels of ESR (38.3 vs. 73.7 mm/hr, $p < 0.001$), CRP (7.8 ± 7.0 vs.13.6 ± 9.9 mg/dL, $p = 0.010$), WBC count (9,813 ± 2,122 vs. 12,502 ± 5,060/m^3, $p = 0.021$) and synovial fluid WBC count (37,295 ± 26,998 vs. 63,210 ± 41,211/m^3, $p = 0.014$) and had higher levels of serum uric acid compared to those with septic arthritis (7.88 ± 1.8 vs. 5.13 ± 1.7 mg/dL, $p < 0.001$). The sum of scores in patients with acute gout was significantly higher than those of patients with septic arthritis (7.8 ± 1.59 vs. 3.4 ± 2.3, $p < 0.001$). In 33 patients with acute gout, the numbers of patients classified to each of the 3 probability groups were 22, 11 and 0 (high, intermediate and low probability, respectively). However, in 27 septic arthritis patients, only 2 and 6 patients were relevant to high and intermediate probability groups and 19 were classified as a low probability group. The proportion of patients with high probability was significantly higher in patients with acute gout compared to those with septic arthritis (66.6% vs. 7.4%, $p < 0.001$).

Conclusion: This novel scoring system showed a good performance in distinguishing between acute gout and septic arthritis. It may be helpful to the primary care physicians.

References:

1. Janssens HJ et al. A diagnostic rule for acute gouty arthritis in primary care without joint fluid analysis Arch Intern Med. 2010;170:1120

Disclosure: J. S. Song, None; **K. H. Lee**, None; **S. T. Choi**, None; **E. J. Kang**, None; **Y. J. Ha**, None.

1200

Proportion Of Patients Achieving Serum Urate Target In a Longitudinal Veterans Administration (VA) Gout Registry: Crystal Registry. Puja Khanna[1], Andreas M. Reimold[2], Gail S. Kerr[3], J. Steuart Richards[4], Elizabeth Chang[5], Jasvinder A. Singh[6], H. Ralph Schumacher[7], Tanima Bannerjee[8] and Dinesh Khanna[9]. [1]Ann Arbor VA, Ann Arbor, MI, [2]Dallas VA and University of Texas Southwestern, Dallas, TX, [3]Washington DC VAMC, Georgetown and Howard University, Washington, DC, [4]Washington DC VAMC and Georgetown University, Washington, DC, [5]Phoenix VAHCS, Phoenix, AZ, [6]University of Alabama, Tuscaloosa, AL, [7]Department of Medicine, University of Pennsylvania and VA Medical Center, Philadelphia, PA, [8]University of Michigan, Ann Arbor, MI, [9]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI.

Background/Purpose: Gout is the most common inflammatory arthritis managed by healthcare providers at the VA Healthcare System. CRYSTAL registry is a longitudinal observational study at six VA centers across US to help understand and improve quality of care of gout. The current objective is to present data from first follow-up in patients who achieved disease control as defined by a target serum urate (sUA) of < 6 mg/dL per recommendations of the 2012 American College of Rheumatology (ACR) guidelines.

Methods: Patients who met the ACR and/or New York criteria are enrolled. At each visit, gout medications (acute and chronic) and comorbidities are reviewed. Subjects complete standardized gout-related questions on flares, interval hospitalizations, HAQ-DI, pain and severity of disease (VAS, 0–10), patient global assessment (0–10 VAS), and alcohol use. Joint exam is performed to assess disease activity and acute phase reactants, sUA, estimated glomerular filtration rate (eGFR), and complete blood counts are monitored as routine care. Data are presented as mean ± standard deviation (SD) or percentage (%). P-values of <0.05 were considered statistically significant.

Results: Of 355 enrolled in the registry, 205 (57%) had at least 1 FU visit, with average FU for 2nd visit was 8 months (range 17 days-46 months). Patients were predominantly male (96%), mean (SD) age was 67.2 (10.5) years, 34% were Caucasian and 63% were African American, and 58% had crystal proven gout. Significant improvement was seen at FU for sUA (−0.94 mg/dl, p<0.0001), patient severity scores (−1.2, p=0.002), physician severity score (−1.2, p=0.01), and HAQ-DI (−0.12, p=0.04). However, there was no significant change in number of flares between 2 visits (p=0.84). Of patients who had sUA > 6 mg/dL at baseline (N=129), 96 (74.4%) achieved the target sUA < 6 mg/dL.

Conclusion: Of gout patients who started with a sUA above 6 mg/dL at enrollment, 74% achieved sUA target of 6 mg/dL at a mean follow-up of 8 months. Further analysis will determine the predictors of sUA target in this cohort. These analyses provide a benchmark to improve quality of care for the Veterans and highlight the need for continued monitoring.

Disclosure: P. Khanna, NIH, 2; **A. M. Reimold**, None; **G. S. Kerr**, Genentech and Biogen IDEC Inc., 2, Pfizer Inc, 2, Bristol Myers Squibb, 2; **J. S. Richards**, None; **E. Chang**, None; **J. A. Singh**, Takeda, Savient, 2, Savient, Takeda, Ardea, Regeneron, Allergan, 5, URL pharmaceuicals Novartis, 5; **H. R. Schumacher**, Penn Center for Musculoskeletal Disorders, 2; **T. Bannerjee**, None; **D. Khanna**, NIH, 2, Scleroderma Foundation, 2.

ACR/ARHP Poster Session B
Miscellaneous Rheumatic and Inflammatory Diseases I: Autoinflammatory Syndromes
Monday, October 28, 2013, 8:30 AM–4:00 PM

1201

A Progress Report On An Emerging Disease: NOD2-Associated Autoinflammatory Disease. Qingping Yao. Cleveland Clinic, Cleveland, OH.

Background/Purpose: We recently reported a new disease designated as NOD2-associated autoinflammatory disease (NAID). The aim of this study was to update the progress on defining the disease.

Methods: A single tertiary medical center study and report of cases of NAID were comprehensively analyzed and summarized. The phenotypes, genotypes, and therapy of NAID were characterized based upon the author's own experience and publications with the disease.

Results: NAID does not appear very rare, and may account for approximately 1% of our Rheumatology outpatients of Cleveland Clinic. White adults of both men and women are equally affected, and NAID is largely sporadic and occasionally familial. This disease may have fever, weight loss and fatigue, and is characterized by periodic occurrence, dermatitis, inflammatory polyarthritis, distal lower extremity swelling, gastrointestinal (GI), and sicca-like symptoms. Acute phase reactants can be elevated, autoantibodies are absent, and NOD2 gene mutations (variants), mostly IVS8+158, R702W, and occasionally R703C are associated with the disease. NAID is distinct from Blau's syndrome.

Table 1. Differentiating features between NAID and Blau's syndrome

	NAID	Blau's syndrome
Age at onset	Adult	< 5 years
Fever	Several days	Rare
Serositis	Can be present	Absent
Joints	Polyarthritis, pedal swelling	Polyarthritis, granulomatous, Camptodactyly
Skin	Spongiotic dermatitis, primarily erythematous patches/plaques	Granulomatous dermatitis, mostly papulonodular and subcutaneous plaques
GI symptoms	Present 50%	Absent
Uveitis	Absent	Present
Inheritance	Mostly sporadic	Dominant
Gene mutations	NOD2: between LRR and NBD	NOD2: NBD
Therapy	GC, Sulfasalazine	NSAID, GC, Infliximab

NAID, NOD2 associated autoinflammatory disease; GI, gastrointestinal; LRR, leucin-rich repeat; NBD, nucleotide binding domain; NSAID, nonsteroidal antiinflammatory drug; GC, glucocorticoids

The pathogenesis of NAID is unclear currently; the interaction between NOD2 gene mutations and environment may play a role. Therapy for NAID should be individualized, depending on clinical manifestations. Glucocorticoids of small dose are used to successfully treat skin disease and to temporarily relieve polyarthritic symptoms. Sulfasalazine is helpful in joint, skin and GI symptoms in some cases. Biologics need to be defined. Most patients run an intermittent benign course.

Conclusion: NAID represents a polygenic autoinflammatory disorder, and it often poses diagnostic challenges, leading to superfluous workups. This report should alert physicians to the novel entity.

Disclosure: Q. Yao, None;

1202

Two Family Kindreds With Blau's Syndrome Associated With Unusual NOD2 Mutations. Qingping Yao. Cleveland Clinic, Cleveland, OH.

Background/Purpose: The aim of this study was to report families of Blau's syndrome with unusual NOD2 gene variants.

Methods: Two proband patients were seen, and their clinical phenotypes and genotypes were analyzed. Pedigree charts of both families were made.

Results: Proband A, a white 57-year-old woman, noticed painless flexion contractures of her 3rd, 4th and 5th proximal interphalangeal joints (PIPs) of both hands at age 6. She developed inflammatory polyarthritis and intermittent facial erythematous plaques/patches since age 30. As a result of cough and dyspnea, chest radiograph and computerized tomography showed multiple lung nodules without hilar adenopathy noted, and subsequent mediastinal lymph node biopsy revealed noncaseating granuloma. These symptoms markedly improved with prednisone 40 mg daily with taper. She had dry eyes on cyclosporine drops without uveitis. There were right parotid gland enlargement consistent with peiomorphic adenoma and left scanty granuloma composed of lymphocytes and mixed with debris and rare collections of histocytes. There was low grade fever. Her erythrocyte sedimentation rate (ESR), antinuclear antibodies, and blood CD4, CD8, and NK cell counts were all normal. Her blood vascular endothelial growth factor and TNFa levels were normal. A positive family history included flexion contractures of the 4th and 5thPIPs (Photographs and Pedigree chart). On examination, there was camptodactyly of the PIPs 3, 4 and 5 of both hands. Genetic testing revealed the presence of the NOD2 variant IVS8+158 in the patient, daughter and son.

Proband B, a white 50-year-old woman, developed inflammatory polyarthritis during the previous 5 months. She also had aching skin and subcutaneous nodules over her elbows, wrists and knees. She complained of mild dry eyes and mouth without parotid gland enlargement or fever; ophthalmic examination showed no evidence of uveitis. A positive family history involved flexion contractures of the 5thPIPs in several members (Pedigree chart). On examination, there were minimally tender and mobile subcutaneous nodules of 0.5 to 1.5 cm over the joints (Photograph). Her ESR and serologic testing were normal. A skin nodule biopsy showed non-necrotizing granuloma. Genetic testing revealed the presence of the NOD2 mutation R703C. These nodules resolved after 2 months of treatment with sulfasalazine.

Conclusion: Both families have autosomal dominant phenotypes of Blau's syndrome. Proband A has familial NOD2 IVS8+158, and proband B is linked to the NOD2 R703C. This study indicates that Blau's syndrome is also associated with the NOD2 variants away from the commonly reported nucleotide binding region and may present as an adult-onset disease.

Disclosure: Q. Yao, None;

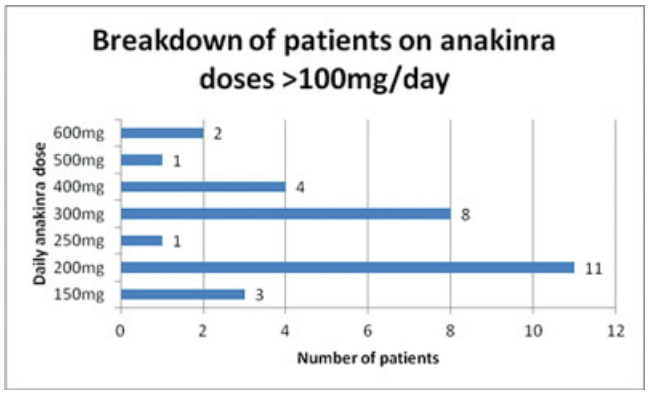
1203

An Escalating Dose Of Anakinra In Patients With Autoinflammatory Disease Is a Safe and Reasonable Therapeutic Option. Amanda K. Ombrello[1], Karyl S Barron[2], Patrycja M. Hoffmann[3], Anne Jones[3], Deborah Stone[3] and Daniel L. Kastner[3]. [1]National Human Genome Research Institute, National Institute of Health, Bethesda, MD, [2]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, [3]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD.

Background/Purpose: The autoinflammatory diseases are diseases in which there is seemingly unprovoked stimulation of the innate immune system. The enhanced release of cytokines in these diseases (TNF-α, IL-1, IL-6), enable biologic medications targeting these cytokines to be good treatment options. The IL-1 antagonist, anakinra, has been approved for use in rheumatoid arthritis and neonatal onset multisystem inflammatory disease (NOMID) but is also frequently used in other autoinflammatory diseases such as the tumor necrosis factor associated periodic syndrome (TRAPS), familial Mediterranean fever (FMF), familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome. In addition, anakinra is often used in patients with undiagnosed autoinflammatory syndromes. Although commonly effective at the approved daily dose of 100mg, there are a number of patients who continue to have frequent disease flares and documented inflammation. We have found that aggressive titration of anakinra can help to better control disease and that higher doses have not been found to have increased adverse events.

Methods: A retrospective chart review of adult patients seen in the National Institutes of Health Autoinflammatory Disease clinic was completed. Patients on daily anakinra were assessed for what dose of anakinra provided adequate disease control. Number and types of adverse events were noted.

Results: 56 patients were identified who were taking at least 100mg daily of anakinra. 26 patients were on 100mg daily. The daily dose of the remaining 30 patients is detailed in Figure 1. Comparing patients on 100mg daily with those on higher doses, local site reactions were the most common adverse event in both groups (NS). Regarding more serious adverse events, in the 100mg group there was 1 patient who developed viral meningitis and one who developed a facial abscess. In patients on greater than 100mg daily, one patient with a chronic PICC line developed Serratia bacteremia and one patient with PAPA syndrome developed a C. difficile infection after treatment with clindamycin for presumed skin infection. Inflammation was able to be suppressed in 24/26 patients (92%) and 3/3 patients who underwent organ transplantation secondary to AA amyloidosis (2 kidney and 1 liver) had viable transplants at 7, 9, and 16 years post-transplant on 300, 600, and 200mg anakinra respectively.



Conclusion: In autoinflammatory disease patients who have inadequate disease suppression on anakinra 100mg daily, an upward titration of anakinra is relatively safe and well-tolerated. Close physician supervision is needed to try and minimize adverse events. Local site reactions are the most commonly reported adverse event and the majority of patients have resolution of these reactions within one month of initiating therapy.

Disclosure: A. K. Ombrello, None; **K. S. Barron**, None; **P. M. Hoffmann**, None; **A. Jones**, None; **D. Stone**, None; **D. L. Kastner**, None.

1204

Model-Based Pharmacokinetics Of Canakinumab and Pharmacodynamics Of IL-1Beta Binding In Cryopyrin Associated Periodic Syndromes, a Step Towards Personalized Medicine. Aurélie Gautier[1], Phil Lowe[1], Andrej Skerjanec[1], Phil McKernan[1], Wenping Wang[2] and Olivier Luttringer[1]. [1]Novartis Pharma AG, Basel, Switzerland, [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ.

Background/Purpose: Cryopyrin-associated periodic syndrome (CAPS), comprises of extremely rare, inherited auto-inflammatory diseases, including the mildest form familial cold auto-inflammatory syndrome (FCAS), the more severe Muckle-Wells syndrome (MWS), and the most severe form chronic infantile neurologic cutaneous and articular syndrome/neonatal onset multisystem inflammatory disease (NOMID).[1] Canakinumab (CAN), a high-affinity fully human monoclonal antibody of the IgG1/k isotype, is designed to bind and functionally neutralize the bioactivity of interleukin 1β (IL-1β); recognized as one of the principal pro-inflammatory cytokines in CAPS.[2] The objectives of the study were: 1) to describe the pharmacokinetics (PK) of CAN and pharmacodynamics (PD) of binding IL-1β in CAPS patients; 2) to determine if PK, PD are different in 2- and 3-year-old children compared with older children and adults; and 3) to explore the impact of CAPS phenotype on the PK of CAN and PD of binding to IL-1β.

Methods: A mathematical PK-binding model was developed to describe the kinetics of CAN and binding dynamics of IL-1β patients with CAPS, other auto-inflammatory diseases and healthy volunteers. The subgroup of 7 CAPS patients who were 2 and 3 years of age at baseline was also compared with the overall CAPS population.

Results: The 7 CAPS patients did not show any difference in terms of PK. However, they showed a higher IL-1β turnover including IL-1β clearance and production. IL-1β levels were linked with age and with the severity of the CAPS phenotype. In these youngest patients, MWS and especially NOMID patients had higher concentrations of the inert CAN/IL-1β complexes after administration of CAN, indicating more cytokine in the body to be captured.

Conclusions: Correlation with clinical responses suggested that these increased levels of IL-1β may explain why younger and especially NOMID phenotype patients require escalation to higher CAN doses.[3]

References:

1. Kuemmerle-Deschner JB., et al. Arthritis ResTher 2011, 13:R34, 2. Hoffman HM, et al. Arthritis Rheum 2008; 58:2443–2452, 3. Lachmann HJ, et al. Arthritis Rheum 2012; 68 (10), S320

Disclosure: A. Gautier, Novartis Pharma AG, 3; **P. Lowe**, Novartis Pharma AG, 3, Novartis Pharma AG, 1; **A. Skerjanec**, Novartis Pharma AG, 3; **P. McKernan**, Novartis Pharma AG, 3, Novartis Pharma AG, 1; **W. Wang**, Novartis Pharmaceutical Corporation, 3; **O. Luttringer**, Novartis Pharma AG, 3, Novartis Pharma AG, 1.

1205

Effectiveness Of Canakinumab In a Cryopyrin-Associated Periodic Syndrome Cohort. A Single Center Experience. Virginia Moreira-Navarrete[1], Francisco Javier Toyos Saenz de Miera[2], Carmen Vargas Lebrón[3] and F. Navarro Sarabia[4]. [1]University Hospital Virgen Macarena, Sevilla, Spain, [2]Hospital Virgen de la Macarena, Sevilla, Spain, [3]Hospital Virgen Macarena, SEVILLA, Spain, [4]Hospital Universitario Virgen Macarena, Sevilla, Spain.

Background/Purpose: Cryopyrin-associated periodic syndrome (CAPS) comprises a group of rare, but severe, autoinflammatory diseases, characterized by urticaria, periodic fever, central nervous system inflammation, arthropathy, and increased risk of amyloidosis. In a recent trial the use of subcutaneous doses of 150 mg of canakinumab every 8 weeks was associated with complete control of clinical manifestations and laboratory parameters in patients with CAPS. The aim of this study was to verify efficacy and safety of the drug in clinical practice.

Methods: Retrospective longitudinal observational study, which included all patients diagnosed with CAPS in a tertiary hospital. Demographic and disease characteristics of all patients were collected. The decision to treat was performed by their rheumatologists. Clinical and laboratory variables at last follow-up were compared with those registered at Canakinumab treatment baseline. Percentages were obtained for qualitative variables and means with standard deviation (SD) for quantitative variables. Comparison between disease activity before and after therapy was performed with a t-student test.

Results: 10 genetically proved CAPS patients were included. 9 of them presented with the typical MWS phenotype and one of them patients with an overlapping MWS/FCAS phenotype. Seven of the patients belonged to the same family. All 10 patients were heterozygous carriers of different mutations in the NLRP3 gene: p.Thr-348-Met in exon 3, D303N in all family affected members, a deletion of bp (A) in exon 3, a mutation not described before, and finally, pR260W. Because disease activity, 50% of the patients were treated with a subcutaneous dose of 150 mg every 8 weeks of Canakinumab. Clinical and laboratory parameters of those patients are shown in Table 1. Both clinical and laboratory parameters responded quickly to that therapy. The mean decrease in CRP levels was 83.2 mg/L (SD 64.1) (p 0.04) in the levels of ESR of 40.8 mm/h (SD 24.9) (p 0,02). The mean increase in hemoglobin levels was 2.5 points (SD 2.62) (p 0.1) and the mean decrease in the platelet count was 161250 (SD 158838) (p 0.135). One of the patients is in a reduced dose schedule, receiving canakinumab every 10 weeks. No patients presented with any adverse events during follow up.

Table 1. Clinical and laboratory parameters of patient on Canakinumab Therapy.

Cases	Sex	Age	Previous Therapies	Mutation	Clinical Manifestations
1	Male	50	Colchicine Glucocorticoids Methotrexate	D303N	Arthritis Urthicaria Deafness Fever Conjunctivitis Meningitis
2	Male	35	Colchicine Glucocorticoids Methotrexate Infliximab	D303N	Arthritis Urthicaria Deafness Fever Conjunctivitis
3	Male	30	Colchicine Glucocorticoids Methotrexate	D303N	Urthicaria Deafness Fever Conjunctivitis Amiloydosis
4	Male	48	Colchicine Glucocorticoids Methotrexate Cyclosporine Etanercept	p.Thr-348-Met	Arthritis Urthicaria Deafness Fever Conjunctivitis
5	Male	53	Colchicine Glucocorticoids	pR260W	Arthritis Urthicaria Deafness Fever Conjunctivitis

Conclusion: The use of canakinumab in daily practice is associated with persistent satisfactory control of disease activity. Here 10 patients with different mutations are presented, including a not previously reported mutation.

Disclosure: V. Moreira-Navarrete, None; **F. J. Toyos Saenz de Miera**, None; **C. Vargas Lebrón**, None; **F. Navarro Sarabia**, Roche Pharmaceuticals, 2.

1206

Canakinumab Treatment Regimens In CAPS Patients. Ferdinand Hofer[1], Theresa Endres[1], Birgit Kortus-Goetze[2], Norbert Blank[3], Elisabeth Weissbarth-Riedel[4], Catharina Schuetz[5], Tilmann Kallinich[6], Karoline Krause[7], Christoph Rietschel[8], Gerd Horneff[9] and Jasmin B. Kuemmerle-Deschner[1]. [1]University Hospital Tuebingen, Tuebingen, Germany, [2]Klinikum der Philipps-Universität Marburg, Marburg, Germany, [3]University of Heidelberg, Heidelberg, Germany, [4]Universitätsklinikum Eppendorf, Hamburg, Germany, [5]Klinik für Kinder und Jugendmedizin, Universitätsklinikum Ulm, Ulm, Germany, [6]Charite, University Hospital Berlin, Berlin, Germany, [7]Dept. of Dermatology and Allergy, Allergie-Centrum-Charité, Charité – Universitätsmedizin Berlin, Germany, Berlin, Germany, [8]Clementine-Kinderhospital, Frankfurt, Germany, [9]Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany.

Background/Purpose: Canakinumab is a recombinant monoclonal fully human antibody against Interleukin-1β and approved for the treatment of CAPS in many countries including Europe and the US. Current dose recommendations are 150mg (body weight >40kg) respectively 2mg/kg body weight (15 to 40kg) every 8 weeks but yield insufficient response in some individuals, especially in children and patients with severe phenotypes1.

In this study we analyzed the response to daily practice (in contrast to trial condition) canakinumab treatment regimens in CAPS patients with focus on age, mutation and clinical presentation and the necessity and effect of dose adjustment.

Methods: An observational national multicenter study was conducted. CAPS patients were included if they received at least two doses of canakinumab. Data included information regarding demographics, treatment, clinical disease activity and inflammatory markers (including SAA, CRP, ESR, IL-6). Response to treatment was assessed using CAPS-disease activity scores, CRP and/or SAA levels.

Results: A cohort of 68 patients with CAPS was analyzed. Median age was 25.4 years (range 22 months to 73 years). When treatment was initiated, 27 patients had been younger than 18 years. The most frequent mutations were R260W, A439V, E311K, V198M, Q703K and most patients showed MWS or FCAS/MWS phenotype (3 patients with NOMID, 4 with MWS/NOMID).

The median treatment duration was 855 days (range: 28–1973 days). In 39 patients (57%) full response was sustained until the next scheduled drug application (34% (23 patients) partial remission). With standard treatment 21 patients (31%) achieved full response. In 30 patients (44%) canakinumab dose and/or application interval was increased above the standard regimen (2/3 NOMID, 3/4 MWS/NOMID).

Neither laboratory parameters nor clinical disease activity at the beginning of treatment were able to predict the necessity to adjust treatment regimen. Two serious adverse events were reported (severe infection, osteonecrosis), mild and moderate adverse events were mostly upper respiratory tract infections but almost no injection site reactions.

Conclusion: Most CAPS patients achieve full remission with canakinumab. However, almost 50% of patients, particularly children, require

dose adjustment. Full remission by dose increase was achieved without an increased rate of adverse events. Individual adjustment of therapy should be performed as needed as predictive parameters are lacking.

Disclosure: F. Hofer, None; **T. Endres**, None; **B. Kortus-Goetze**, None; **N. Blank**, None; **E. Weissbarth-Riedel**, None; **C. Schuetz**, None; **T. Kallinich**, None; **K. Krause**, None; **C. Rietschel**, None; **G. Horneff**, AbbVie, Pfizer, Roche, 2, AbbVie, Novartis, Pfizer, Roche, 8; **J. B. Kuemmerle-Deschner**, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, 5.

1207

Efficacy Of Tocilizumab In Patients With AA Amyloidosis Secondary To Familial Mediterranean Fever: A Single Centre Experience. Sedat Yilmaz, Muhammet Cinar, Ismail Simsek, Hakan Erdem and Salih Pay. Gulhane School of Medicine, Ankara, Turkey.

Background/Purpose: The most frequent underlying diseases responsible for AA amyloidosis worldwide are rheumatoid arthritis, juvenile idiopathic arthritis and ankylosing spondylitis, while familial Mediterranean fever (FMF) is responsible for almost 60% of the cases in Turkey and in countries where the FMF is prevalent. Tocilizumab (TCZ), an IL-6 antagonist, seems to be a promising agent in AA amyloidosis associated with rheumatic disorders, while there is no data regarding its use in amyloidosis due to FMF. We herein describe the short-term results of TCZ treatment in 7 patients with amyloidosis secondary to FMF.

Methods: We described a series of adult FMF patients complicated with amyloidosis and treated with TCZ (8 mg/kg once monthly) in one reference center. Diagnosis of AA amyloidosis was confirmed in the renal biopsy specimens in all patients with Congo red and immunohistochemical staining.

Results: The longest duration on the treatment with TCZ was 16 months in one patient, while 3 months in 3 patients with the shortest follow-up. At the beginning of TCZ treatment all patients had proteinuria, which was severe (>10 g/day) in 2. Following treatment with TCZ, proteinuria was normalized in one (Case with the longest duration of treatment), and considerably decreased in 5. The ameliorative effect of TCZ on proteinuria seemed to begin as early as 3 months. The renal function was normal in all but 3 patients at the beginning, and remained stable throughout the follow-up (Table 1).

Table 1. Demographic, clinical and laboratory features of study patients

Cases	Age	Diagnosis	Treatment cycles	Initial proteinuria (mg/24 hours)	Final proteinuria (mg/24 hours)	Initial creatine (mg/dl)	Final creatine (mg/dl)
1	32	FMF	16	6810	84	0,82	0.64
2	20	FMF	6	10485	3234	0,62	0,9
3	75	FMF	7	4368	901	3,21	3,05
4	45	FMF	3	1800	2300	1,32	1,44
5	38	FMF	3	5648	4935	1,62	1,79
6	33	FMF	7	11960	7714	0,67	0,68
7	23	FMF	3	29260	13801	4,06	3,63

Conclusion: To our knowledge this is the first report showing the efficacy of TCZ on renal amyloidosis secondary to FMF. While previous reports confirm the efficacy of TCZ in amyloidosis secondary to other rheumatic diseases, our findings suggest that this effect can be extended to other diseases.

Disclosure: S. Yilmaz, None; **M. Cinar**, None; **I. Simsek**, None; **H. Erdem**, None; **S. Pay**, None.

1208

Canakinumab In Patients With FMF. Serdal Ugurlu, Emire Seyahi, Gulen Hatemi, Ayse Hacioglu and Huri Ozdogan. Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey.

Background/Purpose: In a recent pilot study, it was reported that Canakinumab reduced the frequency of attacks in 9 patients with Familial Mediterranean Fever (FMF) resistant to colchicine with no apparent side effects (1). Here, we present our experience with Canakinumab in FMF patients with insufficient response to colchicine.

Methods: The charts of the patients with FMF who were on Canakinumab were evaluated retrospectively and the patients who had received 3 or more injections were asked to come to the clinic to assess the response and safety

Results: There were 19 patients with FMF (13 F/6 M) who were receiving canakinumab for various indications. Here we report 12 (8 F/4 M) who had at least 3 injections. Three patients had concomitant diseases such as psoriasis, ankylosing spondylitis and polyarteritis nodosa. The indications for canakinumab (150mg) were colchicine resistancy in 9 patients (>1 attack/month), amyloidosis in 2 and injection site reaction due to anakinra in one. The mean age of the patients was 31.25±14.51 years, while the disease duration was 22.0 ± 8.65 years. The mean colchicine dose was 2.37 ± 0.43 mg/day. The median injection number with canakinumab was 5 (range 3–10). Although injections were planned to be monthly, patients received the drug with irregular intervals due to shortage of the drug. The duration of canakinumab use was 7 ± 3.28 months. Ten of the patients had no attacks after canakinumab, while in two patients attack frequency was reduced more than 50%. In two patients with amyloidosis, proteinuria was stable in one and increased from 1.7g/d to 4.7g/d in the other. Eight of the patients who were complaining of severe myalgia, improved significantly after treatment. According to patient global assessment eleven patients reported significant improvement while only one, reported no change.

Canakinumab was tolerated well in general. None of the patients had injection site reactions. Although, the patient with psoriasis reported a flare in psoriatic plaques, the treatment was not interrupted and psoriasis was controlled eventually by local applications.

Conclusion: Canakinumab is effective in decreasing the frequency of attacks in colchicine-resistant FMF patients. In spite of the small number of patients, and short duration of follow-up, the side effect profile seems favorable. There is need for larger trials to further evaluate its long-term efficacy on amyloidosis.

References:

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Disclosure: S. Ugurlu, None; **E. Seyahi**, None; **G. Hatemi**, None; **A. Hacioglu**, None; **H. Ozdogan**, None.

1209

Starting Time Of Inflammatory Attacks In Patients With Familial Mediterranean Fever. Feyza Berktas, Nilufer Alpay Kanitez, Bahtiyar Toz, Oguz Kaan Bakkaloglu, Burak Erer and Ahmet Gul. Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey.

Background/Purpose: Familial Mediterranean fever (FMF), the most common form of the hereditary autoinflammatory diseases, is characterized by recurrent self-limiting attacks of fever and/or serositis accompanied with acute phase response. Recurrence of attacks does not show a clear periodicity, and its timing is usually unpredictable. Little is known about the factors triggering or precipitating the attacks, and some patients describe physical or emotional exertion, menstrual cycle and dietary changes as possible triggers of the attacks. In other hereditary autoinflammatory disorders, a diurnal variation for the attack was observed with a tendency to experience attacks during evening or night. Recent data suggest that expression of some genes may show a circadian rhythm and affect the immune system, especially innate immune response. In this study, we aim to collect data retrospectively from FMF patients about the starting time of their attacks.

Methods: As a pilot study, we did a questionnaire based survey in 199 consecutive adult FMF patients. All patients fulfilled the Tel-Hashomer criteria for the diagnosis of FMF, and experienced attack(s) during the last year. All patients were interviewed directly or by telephone contacts to answer the questionnaire items about their attacks. The list of questions included usual start time of attacks during the day, their attack frequency, severity and possible triggers (such as sleeplessness, hunger, tiredness, stress, diet, medications, other diseases, menstruation and cold exposure) of the attacks during the past year.

Results: All patients (n=199) agreed to participate in the study and provided answers to the questions. Their mean age was 35.7 and sixty-two (61%) were female. The most commonly reported attack triggering factors were emotional stress (61%), tiredness (57%), menstruation (42% of female patients), followed by dietary changes (18%), cold exposure (5%), sleeplessness (18%) and hunger (3%). Only 9 patients (4%) had an occupation with night shifts. In all group, 63% of the patients provided a definite answer to the question about starting time of attacks. The majority reported that of their attacks started in the evening (41.3%), and less frequently in the morning (28.6%), at night (17.4%) and in the afternoon (12.7%). There was no correlation between the start time of the attacks and triggering factors or night shifts.

Conclusion: This questionnaire-based retrospective survey suggests that starting time of FMF attacks have a tendency for evening. This information may provide some clues about circadian changes affecting the FMF-related inflammation and the threshold for attack development, after its confirmation with prospective data collection.

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1210

Epicardial Adipose Tissue and Atherosclerosis In Patients With Familial Mediterranean Fever. Adem Kucuk[1], Yalcin Solak[2], Hakan Akilli[3], Oguzhan Yildirim[3], Ibrahim Guler[4], Ramazan Ucar[5], Alpay Aribas[3], Orhan Ozbek[6], Mehmet Kayrak[3] and Recep Tunc[7]. [1]Necmettin Erbakan University, Division of Rheumatology, Konya, Turkey, [2]Karaman State Hospital, Division of Nephrology, Karaman, Turkey, [3]Necmettin Erbakan University, Division of Cardiology, Konya, Turkey, [4]Konya Research and Education Hospital, Division of Radiology, Konya, Turkey, [5]Konya Education and Research Hospital, Department ofInternal Medicine, Konya, Turkey, [6]Necmettin Erbakan University, Division of Radiology, Konya, Turkey, [7]Selçuk University, Konya, Turkey.

Background/Purpose: Familial Mediterranean Fever (FMF) is a chronic autosomal recessive hereditary disease characterized by episodic attacks of fever and inflammation of serosal and synovial membranes. Premature development of atherosclerosis has been observed in patients with chronic inflammatory diseases such as systemic lupus erythematosis and rheumatoid arthritis. The relation between epicardial adipose tissue (EAT) volume and increased inflammatory cytokines, diastolic dysfunction, myocardial ischemia and adverse clinical outcomes has been shown. We aimed to evaluate EAT as a novel marker of atherosclerosis and its relation between carotis intima media thickness (CIMT) and inflammatory markers in patients with FMF.

Methods: Seventy-nine FMF patients who had been diagnosed according to Tel-Hashomer criteria in Rheumatology outpatient clinic of a university hospital were included in the study between May 2012 and December 2012. Twenty-six age and sex matched healthy individuals were recruited as the control group. CIMT and EAT were measured and the relation between inflammatory markers were evaluated.

Results: The EAT was thicker in patients with FMF than the control group (EAT 0.47 ± 0.13 vs 0.36 ± 0.10cm, p=0.001). CIMT was also greater in patients with FMF than the control group (0.78 ± 0.2 vs 0.68 ± 0.13 mm, p=0.24). In correlation analysis, EAT was correlated with CIMT (r=0.17, p=0.1), CRP (r=0.31, p=0.005), BMI (r=0.14, p=0.16), total cholesterol (r=0.170, p=0.086), LDL (r=0.212, p=0.035) and age (r=0.188, p=0.054). CIMT was correlated with CRP (r=0.211, p=0.05), serum creatinine (r=0.224, p=0.022), total cholesterol (r=0.231, p=0.019), LDL (r=0.219, p=0.03), triglyceride (r=0.214, p=0.03), age (r=0.453, p<0.001), serum glucose (r=0.267, p=0.022) and BMI (r=0.241, p=0.013).

In multivariate linear regression model, total cholesterol level (β: 0.399, t:2.716), CRP (β: 0.150, t: 2.139) and BMI (β: 0.431, t: 2.581) were found to be independent predictors of EAT.

Table 1. Baseline characteristic of FMF patients and control subjects

	FMF Patients	Control Subjects	P value
Age (year)	38.4 ± 10	41.5 ± 9.5	0.18
BMI (kg/m^2)	26.8 ± 4.9	28.1 ± 4.2	0.20
EAT (mm)	0.47 ± 0.13	0.36 ± 0.1	**0.001**
CIMT (mm)	0.78 ± 0.2	0.68 ± 0.13	**0.02**
CRP (mg/dL)	5.5 ± 2.7	2.8 ± 1.3	**<0.001**
ESR (mm/h)	12.5 ± 1.4	5.2 ± 0.8	**0.008**
WBC (u/L)	7.5 ± 1.8	6.8 ± 1.2	0.1
Hgb (g/dL)	13.3 ± 2	14.6 ± 1.3	**0.002**
Creatinine (mg/dL)	0.7 ± 0.2	0.8 ± 0.1	0.29
ALT (u/L)	28 ± 17	25 ± 12	0.53
LDL (mg/dL)	111 ± 34	112 ± 28	0.87

Conclusion: Both EAT and CIMT were significantly greater in FMF patients than control subjects. In patients with FMF, EAT may be a novel marker of increased cardiovascular risk.

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1211

Adult Autoinflammatory Phenotypes Associated With Heterozygous MEFV Mutations: A Continuum of Familial Mediterranean Fever? Qingping Yao. Cleveland Clinic, Cleveland, OH.

Background/Purpose: Familial Mediterranean fever (FMF) is traditionally regarded as an autosomal recessive disease characterized by periodic fever, serositis, erysipelas-like erythema and good response to colchicine. The aim of this study was to analyze a cohort of adult patients with autoinflammatory phenotypes and heterozygous MEFV mutations.

Methods: A group of 8 patients were cared for by the author between 2011 and 2012, and retrospectively studied for their clinical phenotypes. Genetic testing for MEFV mutations was performed (GeneDx, MD).

Results: Eight patients consisted of 5 women, 3 men, 7 whites and 1 Arab. The mean age at disease onset was 30.5 years with only 1 patient with early-onset. All but the early-onset patient denied any family history of periodic fever syndrome. Of the 8 patients, there were 7 patients with arthritis, 6 intermittent fever, 4 abdominal pain, 3 chest pain, and 3 non erysipelas-like rash. None of the patients had proteinuria. All patients carried a single copy of heterozygous MEFV mutations, including V726A (2), K695R (2), M694V (1), E148Q (1), new mutations R329H (1) and G136V (1) (Table 1). In a study of 18 FMF early-onset patients with a single MEFV mutation, most patients reportedly presented with fever and abdominal pain with prompt response to colchicine therapy. In the current adult cohort, most patients had fever and inflammatory arthritis with poor response to colchicine. Instead, 3 of the 8 patients required treatment with prednisone in 2 cases and etanercept in 1 (R329H).

Conclusion: This study supports the presence of the clinical entity associated with a single heterozygous MEFV mutation. The adult-onset entity may be distinct from classic FMF and early-onset form. Future study to differentiate between the adult- and early-onset forms will be needed.

Disclosure: Q. Yao, None;

1212

Are Different Disease Subtypes With Distinct Clinical Expression Present In Familial Mediterranean Fever: Results Of a Cluster Analysis. Servet Akar[1], Timucin Kasifoglu[2], Dilek Solmaz[1], Sule Yasar Bilge[2], Ismail Sari[1] and Mehmet Tunca[1]. [1]Dokuz Eylul University School of Medicine, Izmir, Turkey, [2]Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkey.

Background/Purpose: Familial Mediterranean fever (FMF) is an auto-inflammatory disorder characterized by self limited attacks of fever and serositis. The disease expression may be different in different ethnic groups and patients with certain MEFV mutations may be prone to have more severe disease and a greater probability of developing amyloidosis. Recently we showed that amyloidosis is the only predictor of mortality in Turkish FMF patients, however clinical subtypes with different clinical and genetic characteristics have been never identified previously. The aim of this study was to evaluate whether there are clinical subgroups, which may have different prognosis, among FMF patients.

Methods: The cumulative clinical features of a large group of FMF patients (1168 patients, 575 female [49.2%] and mean age was 35.3 ± 12.4 years) were studied. To analyse our data and identify groups of FMF patients with similar clinical characteristics, a two-step cluster analysis using log-likelihood distance measures was performed. For clustering the FMF patients, we evaluated the following variables: gender, current age, age at symptom onset, age at diagnosis, the presence of major clinical features (fever, peritonitis, pleuritis, arthritis, erysipelas like erythema [ELE], febrile myalgia, amyloidosis), variables related with therapy (the dosage of colchicine, compliance with therapy, and the presence of attacks despite colchicine), the family history for FMF and for renal failure and the presence of M694V allele.

Results: Three distinct groups of FMF patients were identified. Cluster 1 was characterized by high prevalence of arthritis, pleuritis, ELE, and febrile myalgia. The dosage of colchicine and the frequency of amyloidosis were lower in cluster 1. Patients in cluster 2 had earlier age at symptom onset and diagnosis. Other characteristics of cluster 2 were high frequency of arthritis, amyloidosis, M694V allele and family history for FMF. This group of patients was using highest dose of colchicine. The cluster 3 was characterized by the lowest frequency of M694V allele, ELE, arthritis, protracted febrile myalgia. The colchicine resistance was

also lower in cluster 3. The mean age and age at diagnosis was the highest in cluster 3.

Table 1. Clinical and demographical findings according to the cluster analysis

	Cluster 1		Cluster 2		Cluster 3	
Current age, years (mean ± SD)	29.5 ± 11.2	↓	31.3 ± 10.2	↓	36.5 ± 12.6	↑
Age at symptom onset, years(mean ± SD)	17.9 ± 10.9	↑	10.7 ± 5.7	↓	17.5 ± 9.7	↑
Age at diagnosis, years (mean ± SD)	25.8 ± 11.7	↔	21.5 ± 9.5	↓	28.3 ± 11.7	↑
Colchicine dosage, mg (mean ± SD)	1.1 ± 0.4	↓	1.5 ± 0.4	↑	1.3 ± 0.4	↔
Peritonitis (%)	99	↔	91	↓	98	↑
Pleuritis (%)	95	↑	57	↔	60	↔
Arthritis (%)	100	↑	98	↑	13	↓
ELE (%)	99	↑	39	↔	9	↓
Protracted febrile myalgia (%)	100	↑	16	↓	3	↓
Amiloidosis	2	↓	15	↑	7	↔
To have attacks despite colchicine (%)	80	↑	60	↑	34	↓
Family history for FMF (%)	39	↓	62	↑	48	↔
Family history for renal failure (%)	5	↓	16	↔	14	↔
The frequency of M694V allele (%)	76	↔	87	↑	52	↓

Conclusion: Patients with FMF could be clustered into distinct patterns of clinical and genetic manifestations and these patterns may have different prognostic significance.

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1213

Low-Penetrance NLRP3-Variants. Theresa Endres[1], Ferdinand Hofer[1], Raphaela T. Goldbach-Mansky[2], Hal M. Hoffman[3], Norbert Blank[4], Karoline Krause[5], Christoph Rietschel[6], Gerd Horneff[7], Peter Lohse[8] and Jasmin B. Kuemmerle-Deschner[1]. [1]University Hospital Tuebingen, Tuebingen, Germany, [2]National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD, [3]University of California at San Diego, La Jolla, CA, [4]University of Heidelberg, Heidelberg, Germany, [5]Dept. of Dermatology and Allergy, Allergie-Centrum-Charité, Charité – Universitätsmedizin Berlin, Germany, Berlin, Germany, [6]Clementine-Kinderhospital, Frankfurt, Germany, [7]Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany, [8]Institut für Laboratoriumsmedizin und Humangenetik, Singen, Germany.

Background/Purpose: Cryopyrin-associated periodic syndrome (CAPS) presents as rare, autosomal dominant disease spectrum, due to mutations in the *NLRP3*-gene which lead to excessive interleukin-1 (IL-1) release.

In patients with low-penetrance NLRP3 variants, the clinical presentation varies widely. So far, a correlation with a specific phenotype could not be demonstrated.

The aim of this study was to analyze the association of the V198M, R488K, and Q703K substitutions with a specific phenotype, laboratory markers, and the response to IL-1 inhibitors anakinra, canakinumab and rilonacept.

Methods: This multi-center observational study included 45 patients (26 children and 19 adults) (study group). At baseline examination, all patients displayed some symptoms suggestive of CAPS. Genetic analysis detected one of the following NLRP3 variants: Q703K (n=19), R488K (n=6), and V198M (n=20).

Clinical presentation was recorded and inflammation markers were analyzed. Data from follow-up visits were also evaluated to assess response to IL-1 inhibitors. Results were compared to a (control) group of CAPS patients (n=28) in which disease-causing mutations had been confirmed (A439V, E311K, T348M).

Results: At baseline examination, study patients reported signs of systemic inflammation such as fever (76%), headache (73%), musculoskeletal symptoms (84%) and fatigue (78%). Other CAPS-specific features were rash (80%), conjunctivitis (44%) and sensorineural hearing loss (29%).

Compared to the control group, a history of eye impairment, hearing loss and renal involvement was significantly less frequent in the study group. However study group patients presented significantly more often with gastrointestinal symptoms such as abdominal pain (56% versus 25%, p=0.01) and gastroesophageal reflux (22% versus 0%, p=0.01). Also, a wide spectrum of concomitant diseases such as thyroid disorders (7) and neurological and psychiatric diseases were reported (epilepsy (3), Asperger syndrome (2)).

Inflammation markers were only slightly increased: ESR was elevated in 26% (9/35) and C-reactive protein (CRP) in 34% (14/41). Serum amyloid A (SAA) was raised in 36% (8/22) of the patients. Nine out of ten patients (90%) had elevated TNF-α-levels at baseline examination.

Data from follow-up visits during the first year of treatment was available from 20 patients, treated with IL1 – inhibitors. Clinical disease activity was reduced in all cases; 10 patients (50%) achieved full remission and 10 patients showed partial response to the treatment with mild disease activity and/or persistently elevated inflammation markers.

Conclusion: Heterozygous carriers of the NLRP3 variants V198M, R488K, and Q703K display distinct clinical characteristics compared to CAPS patients with confirmed disease causing mutations, including a high incidence of gastrointestinal symptoms, only slightly elevated inflammatory parameters, and a potentially inferior response to IL-1 inhibition. Also susceptibility for concomitant diseases is observed.

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1214

Resistant Or Recurrent Acute Pericarditis: A New Therapeutic Opportunity? Claire Massardier[1], Claire Dauphin[2], Romain Eschalier[2], Jean-René Lusson[2] and Martin Soubrier[3]. [1]CHU CLERMONT-FERRAND, Clermont-ferrand, Colombia, [2]CHU CLERMONT-FERRAND, Clermont-ferrand, France, [3]CHU CLERMONT-FERRAND, Clermont-Ferrand, France.

Background/Purpose: The treatment of recurrent pericarditis relies on aspirin and/or non-steroidal anti-inflammatory drugs, as well as colchicine. Corticosteroid therapy, which is offered in resistant forms, puts patients at risk of recurrence. Anakinra has shown itself to be effective in idiopathic recurrent pericarditis in childhood[1, 2].

Methods: To report case studies of two patients who responded well to anakinra.

Results: Case 1: A 60-year old obese female with insulin-dependent diabetes and hypertension who had acute pericarditis with very high inflammatory markers (CRP 337) that recurred when her treatment with aspirin was tapered.

Investigations for aetiology were unremarkable. The patient presented clinical signs of constrictive pericarditis. The ultrasound scan showed circumferential pericardial effusion with compression of the right chambers. It was assessed as 1 liter on the chest CT scan.

After four days of the standard treatment with aspirin and colchicine, which was unsuccessful, treatment with anakinra was initiated, chosen over corticosteroids due to the patient's diabetes. The patient quickly showed a favourable response. At two months, the patient is asymptomatic and no longer has pericardial effusion or signs of inflammation.

Case 2: A 52-year old female with a 7-month history of persistent recurrent pericarditis in spite of receiving a long-term standard treatment of aspirin, followed by naproxen, then IV ketoprofen, all combined with colchicine.

The clinical examination found an intermittent pericardial friction rub, echocardiography and CT found moderate pericardial effusion without compression, and inflammatory marker tests were negative (CRP<2.9 mg/l, ESR 2 mm).

Initiation of anakinra led to rapid clinical improvement, which persisted at two months, with gradual reduction of the pericardial effusion.

Conclusion: Anakinra could be a treatment for recurrent pericarditis or pericarditis with very high inflammatory markers that does not respond to the standard treatment and for which corticosteroid therapy is being considered.

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2. Picco P., et al., Arthritis & Rheumatism. 2009; 60(1):264–268

Disclosure: C. Massardier, None; **C. Dauphin**, None; **R. Eschalier**, None; **J. R. Lusson**, None; **M. Soubrier**, None.

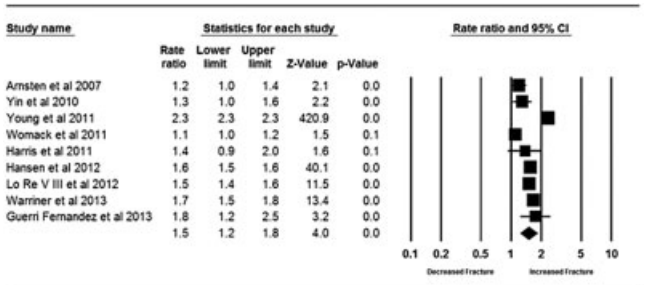
1215

Human Immunodeficiency Virus Infection and Fracture Risk-a Meta-analysis. Sian Yik Lim, Ana Marcella Rivas and Kenneth Nugent. Texas Tech University Health Sciences Center, Lubbock, TX.

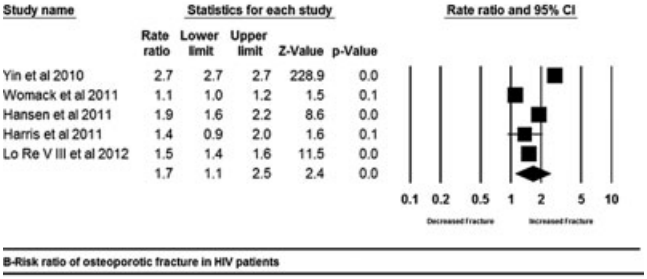
Background/Purpose: Human Immunodeficiency Virus (HIV) infection is associated with development of osteoporosis and decreased bone mineral density. However, studies have been inconclusive in whether this translates to increased fracture incidence. In our study, a meta-analysis of observational studies was performed to examine fracture rate ratio in HIV patients.

Methods: 2 independent researchers systematically searched Pub Med and Embase from earliest available online year of indexing up to March 2013 using Medical Subject Headings terms and key words pertaining to two major themes-HIV and fractures. Abstracts from the Conference on Retroviruses and Opportunistic Infections, the International Acquired Immunodeficiency Syndrome (AIDS) Society Conference on HIV Pathogenesis and Treatment, and the International AIDS Conference were also manually searched. All controlled observational studies that compared fracture incidence in HIV patients with a control group (consisting of uninfected individuals or the general population) were included. Pooled rate ratio was calculated using generic inverse variance weighting and a random effects model.

Results: Of 2050 identified publications, 9 publications (6 prospective cohort studies and 3 retrospective cohort studies) were eligible for analysis. The analysis included 169544 HIV patients with 2101 incident fractures. The pooled rate ratio for any fracture was 1.5 (95% CI 1.2–1.8), and 1.7 (95% CI 1.1–2.5) for osteoporotic fractures. For site specific fractures, the pooled rate ratio for hip, spine, and wrist/forearm fracture were 2.5 (95% CI 1.3–5.0), 1.5 (95% CI 0.8–3.0), 1.3 (95% CI 0.7–2.4). There was significant heterogeneity present among studies for main analyses and subgroup analyses. Subgroup analyses did not show significant differences regarding gender, study design, whether BMI was adjusted, and duration of follow-up. For fractures and osteoporotic fractures, both funnel plots were symmetrical and the Orwin's Fail-Safe N was 737 and 492 respectively.



A-Risk ratio of fracture in HIV patients



B-Risk ratio of osteoporotic fracture in HIV patients

Conclusion: In our meta-analysis of observational studies, HIV infection was associated with increased incidence of fracture, osteoporotic fracture, and hip fracture as compared to uninfected individuals or the general population. Because there was significant heterogeneity present in pooled estimates, and residual confounding cannot be excluded, the results have to be interpreted with caution. However, clinicians need to be aware that HIV patients may be at increased risk for fractures. Therefore, appropriate evaluation and treatment is required, especially in HIV patients with other risk factors for osteoporosis. As the HIV population ages, it is important to evaluate the timing of screening and the individual contributions of HIV, antiretroviral therapy, and traditional risk factors in the development of osteoporosis and fractures in HIV patients.

Disclosure: S. Y. Lim, None; **A. M. Rivas**, None; **K. Nugent**, None.

1216

Risk Factors Associated With Fracture Occurrence Appear to Differ Between Distal Radius, Clinical Vertebral, and Hip Fractures in Japanese Patients With Rheumatoid Arthritis: A Prospective Observational Cohort Study. Kensuke Ochi[1], Takefumi Furuya[1], Yuki Go[1], Eisuke Inoue[2], Katsunori Ikari[1], Atsuo Taniguchi[1], Hisashi Yamanaka[1] and Shigeki Momohara[1]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Patients with rheumatoid arthritis (RA) are at high risk of developing fractures. Previously, utilizing data from our Institute of Rheumatology Rheumatoid Arthritis (IORRA) cohort study, we reported clinical risk factors for clinical vertebral and any nonvertebral fractures in women [1] and men [2] and hip fractures [3] in Japanese patients with RA. However, we did not evaluate the risk factors for distal radius fractures alone, because in our previous studies, the number of distal radius fracture patients was small. In this study, we evaluated the association between potential risk factors and the occurrence of distal radius fractures and compared the risk factors for clinical vertebral, any nonvertebral, and hip fractures in Japanese patients with RA [1–3].

Methods: IORRA is a prospective observational cohort study of Japanese patients with RA at the Institute of Rheumatology, Tokyo Women's Medical University that was established in 2000. A total of 9,987 patients (82.0% female; mean age, 55.7 years) with RA were enrolled in a prospective, observational study from 2000 to 2011. Self-reported distal radius fractures were verified using patient medical records. Cox proportional hazards models were used to analyze independent contributions of various risk factors to distal radius fracture occurrence.

Results: During a mean follow-up period of 5.7 years, 139 patients reported 153 distal radius fractures. Among these patients, 85 distal radius fractures in 85 patients (6 men, 79 women) were verified by medical records. The multivariate Cox regression analyses estimated that the hazard ratios of sustaining a distal radius fracture increased by 15.27 for female gender [95% confidence interval (CI), 1.96–119.02], 1.60 for every 10 years of increased age (95% CI, 1.15–2.22), 1.11 for body mass index (BMI) (kg/m^2, 95% CI, 1.01–1.22), and 1.09 for daily prednisolone dose (mg, 95% CI, 1.01–1.18). Unlike risk factors for clinical vertebral, any nonvertebral, and hip fractures evaluated using data from this same cohort [1–3], no significant association was observed between the occurrence of distal radius fractures and Japanese health assessment questionnaire (J-HAQ) disability score (Table). A high BMI was a risk factor for distal radius fractures, whereas a low BMI was a risk factor for hip fractures [3] (Table).

Table. Risk factors for fractures in Japanese patients with RA

Risk factors \ Fractures	Clinical vertebral	Any nonvertebral	Hip	Distal radius
Advanced age	Yes [1]	Yes [1, 2]	Yes [3]	Yes
Female gender	ND	ND	NS [3]	Yes
J-HAQ disability score	Yes [1,2]	Yes [1]	Yes [3]	NS
Body mass index (BMI)	NS [1,2]	NS [1,2]	Low BMI [3]	High BMI
Daily prednisolone dose	Yes [2]	NS [2]	NS [3]	Yes
History of orthopedic surgery for RA	Yes (any) [1]	Yes (TKR) [2]	Yes (TKR) [3]	ND

ND, not determined; NS, not significant; TKR, total knee replacement

References:
1) Furuya T, et al. J Rheumatol 34: 303–310, 2007; 2) Furuya T, et al. J Bone Miner Metab 26: 499–505, 2008; 3) Furuya T et al. Osteoporos Int 24: 1257–1265, 2013

Conclusion: Female gender, advanced age, high BMI, and high daily prednisolone dose appear to be associated with the occurrence of distal radius fractures in Japanese patients with RA. Risk factors appear to be different between distal radius, clinical vertebral, any nonvertebral, and hip fractures in Japanese patients with RA.

Disclosure: K. Ochi, None; **T. Furuya**, None; **Y. Go**, None; **E. Inoue**, None; **K. Ikari**, None; **A. Taniguchi**, None; **H. Yamanaka**, Abbott, AbbVie, Asahikasei, Astellas, AstraZeneca, Bristol-Myers Squib, Chugai, Daiichi Sankyo, Eisai, GlaxoSmithKline, Janssen, Mitsubishi Tanabe, MSD, Nippon Kayaku, Pfizer, Santen, Taishotoyama, Takeda, Teijin, 2, Abbott, AbbVie, Astellas, AstraZeneca, Bristol-Myers Squib, Chugai, Daiichi Sankyo, Eisai, Mitsubishi Tanabe, Nippon Kayaku, Pfizer, Takeda, Teijin, 5, Abbott, AbbVie, Astellas, Bristol-Myers Squib, Chugai, Eisai, Mitsubishi Tanabe, Pfizer, Takeda, Teijin, 8; **S. Momohara**, None.

1217

Determination Of Vitamin D Level Prior To The Initiation Of Bisphosphonate Therapy. Chris T. Derk, Ruchika Patel, Rennie L. Rhee, Yiu Tak Leung, R. Michelle Koolaee, Shiv Sehra and Ashwini Komarla. University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Vitamin D deficiency is under-recognized and in 18–35% of patients who do not respond to bisphosphonates, concurrent use of vitamin D 1000 units daily increases bone mineral density (BMD) at the lumbar spine and femoral neck, and reduces hip and non-vertebral fractures. Recent work has shown that patients with a serum vitamin D level at 30ng/ml or above are more likely to achieve improved BMD when treated with bisphosphonates. We undertook this study to identify how many of our patients have an adequate vitamin D level prior to starting and during bisphosphonate therapy.

Methods: We identified consecutive patients at our University based rheumatology clinic as well as our Veterans Affairs (VA) rheumatology clinic who were at the time on bisphosphonate therapy and conducted a retrospective chart review. Information on age, gender, reason for bisphosphonate use, type of bisphosphonate, vitamin D levels, date levels were checked, and date of bisphosphonate prescription were obtained. Vitamin D deficiency was defined at levels <30ng/ml. A two-tailed Fisher Exact Test was used for statistical analysis of categorical variables and students t-test for continuous variables.

Results: Sixty-eight patients on bisphosphonate therapy were identified from the two clinic sites out of which 24 were from the University clinic and 44 from the VA clinic. The VA patients were more likely to be men [91% vs. 21% (p=0.0001)] and older [68.5 + 10.8 vs. 58.8 + 11.4 (p=0.0008)]. Reasons for bisphosphonate therapy included chronic steroid use (N=30), osteoporosis (N=21), osteopenia and chronic steroids (N=5), osteoporosis and chronic steroids (N=4), Paget's disease (N=3) and hypogonadism (N=1). Patients were either on zolendronate (N=13), alendronate (N=53) or risedronate (N=2). Vitamin D deficiency was identified in 47% of patients (mean vitamin D level = 22.2 ng/ml + 12.4). Vitamin D level was not checked in 29% of patients prior to initiation of bisphosphonate therapy, and when subsequently tested 21% of them were deficient. While there was no statistical significance of vitamin D deficiency between the two clinics, vitamin D level was checked more frequently prior to bisphosphonate therapy at the VA as compared to the University clinic [83.3% vs 43.5% (p =0.002)].

Conclusion: We have shown that during bisphosphonate therapy 47% of our patients can be vitamin D deficient. Vitamin D was not checked prior to initiation of bisphosphonate therapy in 29% of our patients, this being more commonly the case at our University based clinic as compared to the VA based clinic, and from these patients who were subsequently tested 21% of them were deficient. This may help explain a lack of response to bisphosphonates in many of our patients, and deserves consideration.

Disclosure: C. T. Derk, None; **R. Patel**, None; **R. L. Rhee**, None; **Y. T. Leung**, None; **R. M. Koolaee**, None; **S. Sehra**, None; **A. Komarla**, None.

1218

Incidence Of and Risk Factors For Clinical Fractures In Patients With Systemic Lupus Erythematosus and Matched Controls: A Population-Based Study In The United Kingdom. Irene Bultink[1], Nicholas Harvey[2], Arief Lalmohamed[3], Cyrus Cooper[4], Willem Lems[1], Tjeerd Van Staa[5] and Frank de Vries[6]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]MRC Lifecourse Epidemiology Unit, Southampton, United Kingdom, [3]University Medical Center Utrecht, Utrecht, Netherlands, [4]University of Oxford; Southampton General Hospital, Southampton, United Kingdom, [5]Utrecht University, Utrecht, Netherlands, [6]Care and Public Health Research Institute, Maastricht, Netherlands.

Background/Purpose: Systemic lupus erythematosus (SLE) has been associated with an increased risk of low bone mineral density and fractures. However, data on absolute fracture risk and risk factors associated with clinical fractures are very scarce. The purpose of the present study was to estimate incidence rates of clinical fractures in patients with SLE and relative risks compared with matched controls, and to evaluate risk factors associated with fractures in SLE.

Methods: We conducted a population-based cohort study using the Clinical Practice Research Datalink (from 1987 to 2012). Each SLE patient (n=4343) was matched with up to 6 controls (n=21780) by age and sex. Fracture type was stratified according to WHO definitions into osteoporotic fracture (clinical spine, hip, forearm, or humerus) and non-osteoporotic fracture. Cox proportional hazards models were used to calculate relative rates (RR) of fracture, and time interaction terms to evaluate fracture timing patterns. Incidence rates of fractures in SLE patients, stratified by age, gender, type of fracture, disease duration, and therapy variables, were compared with fracture rates in controls.

Results: Mean age was 46.7 years. Follow-up duration was 6.4 years in SLE patients and 6.6 years in matched controls. Overall, SLE patients had an increased risk of any fracture compared to controls, after adjustment for confounders (adj RR 1.22; 95% confidence interval (CI) 1.05–1.42), and the risk further increased with a longer disease duration. Glucocorticoid (GC) use in the previous six months raised the risk of any fracture (adj RR 1.27; 95% CI 1.02–1.58), but was not further increased with higher cumulative GC exposure. A similar pattern was found for osteoporotic fracture, but did not reach statistical significance (adj RR 1.23; 95% CI 0.91–1.67). Use of antimalarials was not associated with an altered fracture risk. Cerebrovascular events, seizures, and (as expected) previous osteoporotic fractures were identified as significant predictors for any and osteoporotic fractures (Table 1).

Table 1. Risk of fracture within SLE patients (n=4343), stratified according to organ damage. (reference = no risk factor)

	Any fracture		Osteoporotic fracture	
	Events	Adj RR (95% CI)*	Events	Adj RR (95% CI)*
Cognitive impairment	5	1.67 (0.68–4.08)	4	2.25 (0.82–<6.16)
Seizures	34	**2.01 (1.41–2.86)**	22	**2.81 (1.80–4.40)**
Cerebrovascular event	55	**1.49 (1.12–2.00)**	35	**1.77 (1.22–2.57)**
Renal disease	54	1.30 (0.96–1.75)	32	1.35 (0.91–2.00)
Previous osteoporotic fracture	172	**4.26 (3.49–5.18)**	95	**3.85 (2.92–5.07)**
Diabetes	21	1.39 (0.89–2.17)	11	1.33 (0.72–2.45)
Malignancy	50	1.23 (0.91–1.68)	28	1.22 (0.81–1.84)

* Adjusted for: previous fracture, use of glucocorticoids, antimalarials, calcium/vitamin D supplements, benzodiazepines, and proton pump inhibitors in the previous 6 months.

Conclusion: SLE patients in the United Kingdom have an increased risk of clinical fractures compared to age- and sex-matched controls. GC use in the previous six months and longer disease duration are important factors associated with the increased fracture risk in SLE. In addition, special attention should be paid to lupus patients with neuropsychiatric organ damage or a history of osteoporotic fractures since these subgroups of patients are at high risk of the occurrence of (subsequent) fractures.

Disclosure: I. Bultink, Servier Laboratories, 9, Merck Pharmaceuticals, 9; **N. Harvey**, Alliance for Better Bone Health, The ALR;, 2, Amgen, 2, Eli Lilly and Company, 2, Proctor and Gamble, 2, Nycomed, 2, Sanofi-Aventis Pharmaceutical, 2, Shire, 2, Servier Laboratories, 2; **A. Lalmohamed**, None; **C. Cooper**, Amgen, 5, GlaxoSmithKline, 5, Alliance for Better Bone Health, The ALR, 5, Merck Pharmaceuticals, 5, Eli Lilly and Company, 5, Pfizer Inc, 5, Novartis Pharmaceutical Corporation, 5, Servier Laboratories, 5, Medtronic, 5, Roche Pharmaceuticals, 5; **W. Lems**, Amgen, 9, Eli Lilly and Company, 9, Merck Pharmaceuticals, 9, Servier Laboratories, 9, Novartis Pharmaceutical Corporation, 9, Will Pharma, 9, Takeda, 9; **T. Van Staa**, None; **F. de Vries**, None.

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Phase 3 Fracture Trial Of Odanacatib For Osteoporosis – Baseline Characteristics and Study Design. Socrates Papapoulos[1], Henry G. Bone[2], David W. Dempster[3], John Eisman[4], Susan Greenspan[5], Michael McClung[6], Toshitaka Nakamura[7], Joseph Shih[8], Albert Leung[9], Arthur Santora[9], N. Verbruggen[10] and Antonio Lombardi[11]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Michigan Bone and Mineral Clinic, Detroit, MI, [3]Helen Hayes Hospital, West Haverstraw, NY, [4]The Garvan Institute of Medical Research, Sydney, Australia, [5]University of Pittsburgh, Pittsburgh, PA, [6]Oregon Osteoporosis Center, Portland, OR, [7]University of Occupational & Environmental Health, Kitakyushu, Japan, [8]Robert Wood Johnson Medical School, Piscataway, NJ, [9]Merck Sharp & Dohme Corp., Whitehouse Station, NJ, [10]MSD Belgium, Brussels, Belgium, [11]Merck Sharp and Dohme Corp, Whitehouse Station, NJ.

Background/Purpose: Odanacatib is a selective and reversible inhibitor of cathepsin K; a collagenase secreted by osteoclasts, and is currently being evaluated for the treatment of osteoporosis. In a Phase 2 study of postmenopausal women with low BMD, oral odanacatib 50 mg once-weekly increased

BMD progressively over 5 years by 11.9% at the lumbar spine and 9.8% at the femoral neck.

Methods: A randomized, double-blind, Phase 3 trial designed to examine osteoporotic fracture reduction and safety enrolled 16,227 postmenopausal osteoporotic women to receive odanacatib 50 mg or placebo once weekly (without regard to food). All participants also received vitamin D3 5600 IU weekly, and calcium supplements as needed. This event-driven trial was designed to be completed after 237 hip fractures had accrued, but allowed for early termination based on the results of 2 pre-planned interim analyses. The trial has three primary endpoints: morphometric vertebral fracture, non-vertebral fracture, and hip fracture. Controls are employed for elevation of the false-positive error rate due to multiple primary endpoints. Clinical fractures are adjudicated centrally via clinical history, radiology reports, and/or x-rays. Secondary endpoints include clinical vertebral fractures, BMD, height, bone turnover markers, and safety and tolerability. Collection of extensive baseline clinical information, pharmacogenomic data, archived serum and urine samples for all participants and trans-iliac bone biopsies from some participants will provide additional information.

Results: Postmenopausal women with (n=7,470) or without a prior radiographic vertebral fracture (n=8,757) were enrolled at 383 centers worldwide. At baseline they had a mean age of 73 years, were 57% Caucasian, and had mean BMD T-scores at lumbar spine −2.7, total hip −2.4, femoral neck −2.7, and trochanter −2.3.

Conclusion: This trial was designed to provide information on the efficacy and safety of once-weekly odanacatib 50 mg in reducing the risk of osteoporotic fractures in postmenopausal women with osteoporosis. A pre-planned interim analysis demonstrated anti-fracture efficacy and a favorable benefit/risk profile. Some safety findings were identified that will be followed in the pre-planned extension of the study. The trial is being extended as a placebo-controlled study with the same design for a minimum total period of observation of 5 years for each participant, in order to collect additional safety and efficacy data.

Disclosure: S. Papapoulos, Merck Sharp and Dohme Corp, 5, Merck Sharp and Dohme Corp, 8; **H. G. Bone**, Merck Sharp and Dohme Corp, 5; **D. W. Dempster**, Merck Sharp and Dohme Corp, 5; **J. Eisman**, Merck Sharp and Dohme Corp, 5; **S. Greenspan**, Merck Sharp and Dohme Corp, 5; **M. McClung**, Merck Sharp and Dohme Corp, 5, Merck Sharp and Dohme Corp, 8; **T. Nakamura**, None; **J. Shih**, None; **A. Leung**, Merck Sharp and Dohme Corp, 1, Merck Sharp and Dohme Corp, 3; **A. Santora**, Merck Sharp and Dohme Corp, 1, Merck Sharp and Dohme Corp, 3; **N. Verbruggen**, Merck Sharp and Dohme Corp, 1, Merck Sharp and Dohme Corp, 3; **A. Lombardi**, Merck Sharp and Dohme Corp, 1, Merck Sharp and Dohme Corp, 3.

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Rheumatoid Arthritis Characteristics and Fracture Risk: A Population-Based Study. Shreyasee Amin, Sherine E. Gabriel, Sara J. Achenbach, Elizabeth J. Atkinson, Terry M. Therneau and L. Joseph Melton III. Mayo Clinic, Rochester, MN.

Background/Purpose: Women and men with rheumatoid arthritis [RA] are at increased risk for a fragility fracture [fx]. To help better target those in need of fx prevention, we sought to determine which RA characteristics were associated with this increased risk for fragility fxs and specifically examined the effect of chronic glucocorticoid [GC] use.

Methods: We studied a population-based inception cohort (age ≥18 yrs), who fulfilled 1987 ACR criteria for RA between 1955–2007, and were followed until death or last available follow-up. RA characteristics (presence of rheumatoid factor [RF+], erosions, nodules, and other extra-articular manifestations), major joint surgeries, oral GC use, and all incident fxs after RA diagnosis were identified through a review of complete (inpatient and outpatient) community medical records. We studied fragility fxs, which excluded pathologic fxs and fxs resulting from severe trauma (e.g. motor vehicle accident). Chronic GC use was defined as >3 months at any dose. Using age-and sex-adjusted Andersen-Gill models, we examined the impact of RA characteristics on the subsequent risk for fxs. Most risk factors were modeled as time-dependent covariates. We performed similar analyses stratified by sex and then chronic GC use.

Results: In 1171 RA subjects, (822 women [66% RF+] and 349 men [69% RF+]; mean [± SD] age at RA diagnosis: 56 ± 16 years and 58 ± 14 years, respectively), followed for 15,195 person-years, there were 828 fragility fxs in 328 women and 253 fragility fxs in 112 men since their RA diagnosis. Over follow-up, about 1/3 of women and men each had nodules; a similar proportion developed erosions; ~12% each had other extra-articular manifestations; and 29% underwent major joint surgery. There were 424 (52%) women and 209 (60%) men who were chronic GC users; the remainder either never used GC for RA (70%) or had only limited GC exposure. We found that RF+, erosions, nodules, extra-articular manifestations, major joint surgeries and chronic GC use were all associated with an increased risk for fragility fxs (see Table). Extra-articular manifestations and major joint surgeries were associated with an increased risk for fxs regardless of GC exposure (data not shown). However, the other RA characteristics tended to be associated with increased fx risk only in chronic CG users, but not in those with no/limited GC use (data not shown).

	Hazard Ratio (95% CI) Predicting Fragility Fxs		
RA Characteristic	**All†**	**Women‡**	**Men‡**
RF+	1.4 (1.1–1.7)	1.3 (0.99–1.7)	1.8 (1.2–2.9)
Nodules*	1.6 (1.2–1.9)	1.5 (1.2–2.0)	1.7 (1.1–2.7)
Erosions*	1.4 (1.1–1.8)	1.4 (1.0–1.8)	1.3 (0.8–2.1)
Extra-articular*	1.6 (1.2–2.1)	1.4 (0.99–2.0)	2.2 (1.3–3.8)
Major joint surgery*	1.7 (1.3–2.1)	1.7 (1.3–2.2)	1.5 (0.9–2.5)
GC use >3 months*	1.9 (1.6–2.4)	2.0 (1.6–2.5)	1.7 (1.1–2.5)

† Models adjusted for age and sex; ‡Models adjusted for age
** RA characteristics modeled as time-dependent covariates*

Conclusion: RA characteristics that are often associated with greater disease severity are also associated with increased fx risk. However, only extra-articular manifestations and major joint surgeries were associated with increased fx risk regardless of chronic GC use. Although further work is required to understand their interaction on fx risk, some RA characteristics may simply be indicators of chronic GC use; on the other hand, others may either better represent greater disease activity or reflect greater frailty and/or fall risk.

Disclosure: S. Amin, None; **S. E. Gabriel**, None; **S. J. Achenbach**, None; **E. J. Atkinson**, None; **T. M. Therneau**, None; **L. J. Melton III**, None.

1221

The Effects Of Hyperthyroidism On Bone Mineral Density At Different Sites—An Observational Case-Control Study. Christopher Varley[1], Alexander Oldroyd[1] and Marwan Bukhari[2]. [1]Lancaster University, Lancaster, United Kingdom, [2]Royal Lancaster Infirmary, Lancaster, United Kingdom.

Background/Purpose: Hyperthyroidism has been described as a risk factor for poor bone health.[1, 2] The FRAX™ tool has been used to identify the ten year risk of fracture by utilising hip bone mineral density (BMD) only. If hyperthyroidism is predominantly associated with bone loss in the lumbar spine, the fracture risk in these patients may have been underestimated. No previous study has examined the differential amount of bone loss in hyperthyroidism. This study will determine the extent and site of bone loss in patients with primary hyperthyroidism compared to controls, looking at lumbar spine and femoral neck BMD.

Methods: Using a nested case-control approach, a cohort of patients referred between 2004 and 2011 for a dual-energy x-ray absorptiometry scan with hyperthyroidism as their main risk factor was identified. These were then age and gender matched with controls referred in the same time period with no indication for scanning. Sites of bone loss were ascertained by comparing the BMD in two areas (L1-L4 vertebrae and the left femoral neck) between cases and controls, using students T-test. A logistic model was then fitted to determine the odds of having a significantly reduced BMD with a diagnosis of hyperthyroidism. The fit of the model was tested using receiver operating characteristic (ROC) curves.

Results: 232 patients with current hyperthyroidism were identified, comprising 184 females (79.7%), with a mean age of 62 (SD 10.7). 232 controls were age and sex matched. Simple comparisons between cases and controls were identified using the students t-test; mean difference between L1-L4 BMD was 0.085 g/cm^2 (95% CI 0.051– 0.119) and femoral neck BMD difference was 0.057 g/cm^2(95% CI 0.031– 0.083); both had a p-value ≤0.001. The odds of having a significantly reduced BMD was found to be greater in the femoral neck, with an odds ratio of 19.4 for femoral neck BMD (95% CI 4.8–79.0) compared with 12.2 for L1-L4 BMD (95% CI 4.3–34.8). When the area under the ROC curve was calculated for both L1-L4 and femoral neck BMD, the result was a similar sensitivity and specificity, with an area under the ROC curve of 0.63 for L1-L4 BMD, and an area of 0.62 for the femoral neck.

Conclusion: Both hip BMD and lumbar spine BMD are significantly reduced in thyrotoxic patients- while BMD loss was found to be greater in the

femoral neck than in the lumbar spine, this was only marginally more. Further analysis looking at whether this risk factor has more implications on fracture risk than those used in the FRAX™ tool is needed.

References:

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Disclosure: C. Varley, None; **A. Oldroyd**, None; **M. Bukhari**, None.

1222

Analysis Of Corelation Of Bone Mineral Density Of Spine With Other Sites In Ankylosing Spondylitis As Compared To Rheumatoid Arthritis and Control Populations. Janie Bruce[1] and Vikas Majithia[2]. [1]University of Mississippi School of Medicine, Jackson, MS, [2]G.V. "Sonny" Montogomery VA Medical Center, Jackson, MS.

Background/Purpose: Bone mineral density (BMD) at the 3 central sites usually correlates with each other but the effect of disease states on this correlation is not known. Ankylosing spondylitis (AS) with spinal involvement may increase BMD at spine but not at hip. Alternatively, RA or osteoporosis may not have any effect the on it. These aspects have not been well quantified and this study aims to assess the correlation amongst patients with the three disorders.

Methods: Retrospective chart review of patients who had been seen in rheumatology clinics at VA medical center with diagnosis of AS, RA or OP and had a DEXA scan done was performed. Data including age, race, gender, BMI, BMD with T-scores was tabulated. Patients with BMD at all 3 sites-lumbar spine, hip and arm were included in analysis. Correlation amongst the amongst the T-scores at three sites was calculated using pearson coefficient.

Results: A total of 350, patient charts were reviewed. After excluding patients with missing data, 241 were included in analysis. There were 16 patients with AS (Mean age = 63 years, Average BMI= 28.81, all males), 117 patients with RA (Mean age = 63.92 years, Average BMI= 28.38, 104 males and 13 females), and 98 patients with osteoporosis (Mean age = 70.42 years, Average BMI= 25.17, 93 males and 5 females). The correlation between the total hip and femoral neck was strong in all three groups. We found moderate correlation among the t-scores between spine – total hip and forearm – total hip t-scores in both AS and RA. The correlation was poor at these 2 sites in patients with osteoporosis. The spine BMD was found to be lower than other sites in 1/16 (6.25%) of AS and 5/117 (4.3%) of RA patients as compared to 16/98 (16.4%) of patients with OP, where it was also likely to influence treatment decision. Also additional forearm testing did not yield a better result in all 3 groups. These results are summarized in the table 1.

Table 1. Correlation among BMD at 3 sites (Hip, Lumbar spine and forearm) in patients with AS, RA and OP.

Diagnosis	Site	r	r^2	p-value
Ankylosing Spondylitis (n=16)	Lumbar spine- total hip	0.5552	0.3083	0.02
	Total hip- femoral neck	0.93	0.865	<0.0001
	Forearm- total hip	0.5995	0.3594	0.01
Rheumatoid Arthritis (n=117)	Lumbar spine- total hip	0.643	0.4134	<0.0001
	Total hip- femoral neck	0.9453	0.8936	<0.0001
	Forearm- total hip	0.618	0.3819	<0.0001
Osteoporosis (n=98)	Lumbar spine- total hip	0.3429	0.1176	0.0005
	Total hip- femoral neck	0.8248	0.6802	<0.0001
	Forearm- total hip	0.3412	0.1164	0.0005

Conclusion: The results show that there was correlation among the three sites of BMD in the whole cohort and no significant difference was found among the three disorders. Having AS where spine is frequently involved did not seem to impact the correlation coefficient when compared to RA and OP patients. This suggests that spinal involvement in AS may not have any significant impact on the BMD at LS spine in majority of patients. The correlation was lowest among the patients with osteoporosis who were older than the other 2 groups and osteophyte formation may have influenced the BMD at spine. Interestingly the BMD at spine was most useful in this group impacting the treatment decisions more than other 2. The results suggest that evaluation of BMD at both spine and hip is important regardless of the underlying disorder including AS and should be done collectively. On the other hand, forearm BMD evaluation was not useful in majority.

Disclosure: J. Bruce, None; **V. Majithia**, None.

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Monitoring Osteoporosis Therapy: Can FRAX Help To Assess Success Or Failure In Achieving Treatment Goals? Yasser El Miedany[1], Ahmed Elyassaki[2], Sally Youssef[2], Annie Nasr[2], Mohammed Hegazi[3] and Ihab Ahmed[4]. [1]Medway Hospital, Gillingham, United Kingdom, [2]Ain Shams University, Cairo, Egypt, [3]Al Adan Hospital, Kuwait, Kuwait, [4]Cairo University, Cairo, Egypt.

Background/Purpose: 1. To determine whether FRAX can be used for monitoring patients receiving osteoporosis therapy and its clinical implications 2. Study the correlation between the post-treatment FRAX and the incidence of fractures.

Methods: A total of 1026 women (age ≥ 50 years) diagnosed to have osteoporosis who had baseline risk factors assessment and BMD testing were screened. All the patients were treated according to guidelines. 579 women who were adherent to the prescribed osteoporosis therapy, had FRAX probabilities calculated which were included in this study. All the patients had a follow-up DXA scan at 2 and 5-years of osteoporosis therapy. At both times, re-assessment of the risk factors was carried out and FRAX probabilities were calculated. A subgroup of patients who did not achieve an improvement in their neck of the femur BMD or who sustained a fracture in the first 2-years, had their osteoporosis therapy changed. BMD assessment and FRAX calculation were carried out 3-years after starting the new osteoporosis therapy. The patient subgroup who responded well to therapy and did not sustain a new low trauma fracture in the first 2 years, continued their therapy and had another reassessment in 3-years.

Results: During mean 5.3 years of observation, 16.9% individuals sustained incident major osteoporotic fractures, of which 48% were hip fractures. There were also 4.3 % deaths and 2.7% changed their address. 26% were excluded for non-adherence to therapy. A total of 579 women were included in this work. Femoral neck BMD strongly predicted major osteoporotic fractures and hip fractures, and this was unaffected by medication use ($P<0.05$). Assessment for major osteoporotic fractures and hip fractures showed significant negative correlation with BMD at the neck of the femur at 2-years of therapy ($R= -0.218$ and -0.445 respectively), as well as at 5-years ($R= -0.212$ and -0.220 respectively). At both 2 years and 5 years of therapy, there was significant correlation between 10-year fracture probability (both major osteoporosis and hip fractures) and the fracture incidence ($P< 0.001$). When major fracture probability was assessed with BMD, there was a significant ($P< 0.05$) difference between the responders and non-responders to osteoporosis therapy.

Conclusion: This work suggests that the FRAX tool can be used to predict fracture probability in women currently or previously treated for osteoporosis. Osteoporosis therapy does not invalidate fracture predictions and FRAX may still have value for guiding the need for continued treatment or treatment withdrawal. There are many differences between subjects in clinical trials and patients being treated in clinical practice. Thus, although defining a clinical practice patient as a "nonresponder" or "suboptimal responder" to treatment is problematic, a pragmatic approach would be to consider evaluation for contributing factors and possible changes in therapy in patients who have a statistically significant decrease in BMD, or have a fracture. Further monitoring of osteoporosis therapy, is necessary and helps the treating clinician to identify early the non-responders to therapy.

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1224

Prednisone Has No Effect On Odanacatib Pharmacokinetics In Healthy Subjects. Gene Marcantonio[1], Chengcheng Liu[1], Stefan Zajic[2], Chantal Mahon[1], David Hreniuk[1], Anish Mehta[3], Kate Mostoller[1], Denise Morris[4], Hongwei Xue[4] and S. Aubrey Stoch[1]. [1]Merck Sharp & Dohme Corp., Whitehouse Station, NJ, [2]Merck Sharp & Dohme Corp, Whitehouse Station, NJ, [3]Merck Sharp & Dohme Corp., Whitehouse Station, NJ, [4]Covance, Madison, WI.

Background/Purpose: We evaluated the effect of prednisone, a glucocorticoid believed to induce the CYP P450 enzyme, on the pharmacokinetics of odanacatib, a novel Cathepsin K inhibitor that is in development for the treatment of osteoporosis.

Methods: This was an open-label, 2-period crossover study in healthy male subjects. In Period 1, midazolam 2 mg was administered on Day −1 followed by a single oral dose of odanacatib 50 mg on Day 1. There were at least 14 days from the last pharmacokinetic sampling on Day 15 of Period 1

to the Day 1 dosing in Period 2. In Period 2, subjects were administered a single oral dose of prednisone 10 mg qd on Days 1 through 28. On Day 14 of Period 2, subjects were co-administered prednisone 10 mg and odanacatib 50 mg. On days 1 and 28 of Period 2, subjects were co-administered prednisone 10 mg and midazolam 2 mg. On Days 42 and 56 of Period 2, subjects were administered a single oral dose of midazolam 2 mg. The plasma pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, T_{max}, and apparent terminal $t_{½}$) were assessed based on blood samples that were collected at predose and various time points through 336 hours following odanacatib administration on Day 1/Period 1, as well as predose on Day 1, predose on Day 14, and various time points through 336 hours following odanacatib administration on Day 14/Period 2. Safety and tolerability were assessed by physical examination, evaluation of vital signs and electrocardiogram (ECG) measurements, and monitoring adverse experiences (AE) throughout the study.

Results: There were 15 subjects enrolled. Mean age was 31 years and a mean BMI was 25.8. The odanacatib $AUC_{0-\infty}$ GMR (90% CI) [odanacatib + prednisone/odanacatib alone] was 1.06 (0.96, 1.17). The estimated C_{max} GMR (90% CI) was 0.96 (0.84, 1.10). The median T_{max} value remained 4 hours for odanacatib alone and with co-administration of prednisone and the harmonic mean (jack-knife standard deviation) for apparent terminal $t_{½}$ was 74.6 (17.9) for odanacatib alone and 66.8 (25.1) for odanacatib + prednisone. There were no serious AEs or AEs leading to discontinuation.

Conclusion: Prednisone had no effect on odanacatib pharmacokinetics when co-administered with odanacatib.

Disclosure: G. Marcantonio, Merck Sharp Dohme Corp., 3, Merck Sharp Dohme Corp, 1; **C. Liu**, Merck Sharp Dohme Corp, 3; **S. Zajic**, Merck Pharmaceuticals, 1, Merck Pharmaceuticals, 3; **C. Mahon**, Merck Sharp Dohme Corp, 1, Merck Sharp Dohme Corp, 3; **D. Hreniuk**, Merck Human Health, 3, Merck Human Health, 3; **A. Mehta**, Merck Sharp Dohme Corp., 1, Merck Human Health, 3; **K. Mostoller**, Merck Sharp Dohme Corp., 3; **D. Morris**, Covance, 5; **H. Xue**, None; **S. A. Stoch**, Merck Sharp Dohme Corp, 1, Merck Sharp Dohme Corp, 3.

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FRAX 10-Year Fracture Risk In Women With a Fracture Of The Distal Forearm: Agreement Between Assessments With and Without Bone Mineral Density and Influence Of Measurement Side In Individual Patients. Emilie Egsmose[1], Mette Birkvig[2], Thora Buhl[2] and Ole Rintek Madsen[2]. [1]Copenhagen University Hospital Hvidovre, Copenhagen, Denmark, [2]Copenhagen University Hospital Gentofte, Copenhagen, Denmark.

Background/Purpose: The FRAX® tool has been developed by WHO to evaluate fracture (Fx) risk of patients. It is based on individual patient models that integrate the risks associated with clinical risk factors as well as bone mineral density (BMD) at the femoral neck (FN). The output is a 10-year probability of hip Fx and of a major osteoporotic Fx (clinical spine, forearm, hip or shoulder Fx). The tool allows calculation of Fx risk with and without (±) BMD. Assessment of Fx risk in the individual patient without BMD may be an advantage in the busy emergency room dealing with patients with distal forearm Fxs. Differences between Fx risk assessed ±BMD has previously been evaluated on group level, but not on the individual patient level. There is no recommendation on which side to measure BMD. The purpose was to examine the agreement between the FRAX 10-year Fx risk calculated ±BMD in patients with a recent Fx of the distal forearm. Furthermore, to examine the influence of measurement side for Fx risk assessment.

Methods: BMD of the left and right FN and of the spine was measured in 140 Danish women with a recent Fx of the distal forearm using a Lunar DXA-scanner. Only patients eligible for bilateral hip measurements were included. None of the patients were or had been on antiresorptives or anabolic treatment. Information of clinical risk factors were collected by questionnairing the patients. Using the FRAX tool for Denmark, the 10-year risk of a major Fx and of a hip Fx was calculated ±BMD with BMD from both measurement sides. Student's t-test was used for comparison of paired Fx risk assessments. The Bland-Altman method was used to examine agreement between the risk assessments. Differences between pairs of risk assessments were calculated. Agreement on the group level was expressed as the bias (mean value of individual differences) and on the individual level as the 95 % limits of agreement (LoA).

Results: Mean age, height and weight were 66±8 (range 51–85) years, 163±14 cm and 68±13 kg. Mean BMD and T-score of the left FN were 0.81±0.15 g/cm2 and −1.6±0.9 and of the spine 1.0±0.2 g/cm2 and −1.3±1.4. Fourteen (10%) patients had a parent with hip Fx, 28 (20%) were smokers, 4 (2.8%) had 3 or more alcohol units per day, 15 (11%) had conditions strongly associated with osteoporosis (predominantly early menopause), 1 (0.7%) had RA and 2 (1.4%) were on steroids. The 10-year risk of hip Fx and of a major Fx based on left hip BMD was 6.9±7.7% and 22.7±10.2%, respectively. The bias of hip Fx risk assessed without BMD was 4.2 (LoA −10.8; 19.2)% ($p < 0.0001$) and of a major Fx 5.3 (LoA −11.7; 22.3)% ($p < 0.0001$). The bias of the risk of a hip and of a major Fx assessed with the highest vs. the lowest BMD-value was −1.7 (LoA −6.1; 2.7)% ($p < 0.0001$) and −2.4 (LoA −7.4; 2.6)% ($p < 0.0001$), respectively.

Conclusion: The FRAX 10-year Fx risk calculated without BMD was averagely increased by 4–5% compared to assessment with BMD. In the individual patient, differences between risk assessments ±BMD approached 22%. Thus, Fx risk assessment without BMD should be used with caution when counselling individual patients with forearm fractures. The side of BMD measurement may also influence the risk assessment significantly, especially in individual patients.

Disclosure: E. Egsmose, None; **M. Birkvig**, None; **T. Buhl**, None; **O. R. Madsen**, None.

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Adherence With Current Osteoporosis Treatment Guidelines Among Rheumatologists Caring For Patients With Rheumatoid Arthritis Using Items From The Fracture Risk Assessment Tool Score. Jennifer Watt[1], Andrew E. Thompson[2], Nicole G. H. Le Riche[3] and Janet E. Pope[4]. [1]University of Western Ontario, London, ON, [2]St. Josephs Health Ctr, London, ON, [3]St. Joseph's Hospital, London, ON, [4]Schulich School of Medicine and Dentistry, Western University, London, ON.

Background/Purpose: To assess whether the Fracture Risk Assessment Tool (FRAX) score in patients with RA correlates with likelihood of osteoporosis (OP) prescription including drug treatment, calcium and vitamin D.

Methods: Charts of serial RA outpatients (age>40 with a calculable BMI) were reviewed to determine the 10-year risk of major osteoporotic fracture with the FRAX. Use of calcium, vitamin D, OP treatment, and a patient's BMD results were recorded. Odds ratios (OR) were calculated to determine if a higher FRAX score increased the likelihood of OP prescribing.

Results: 10-year risk of fracture was high in 92 (12.5%), moderate in 216 (29.3%), and low in 429 (58.2%). No patients had a FRAX score calculated in their records. Compared to those at low risk, patients identified as high risk were more likely to receive OP treatment (OR 16.31, 95% CI 9.45–28.13, $p<0.0001$); calcium (OR 3.89, 95% CI 2.43–6.25, $p<0.0001$); vitamin D (OR 3.46, 95% CI 2.12–5.64, $p<0.0001$); and have a BMD performed (OR 10.22, 95% CI 5.50–18.96, $p<0.0001$). Among 137 patients currently taking prednisone, 44.5% were prescribed a bisphosphonate. BMD tests were performed in 415 (56.3%), but only 228 were recorded on the specialists' charts.

Conclusion: Higher risk patients are more likely to have a BMD and receive treatment, as indicated by the clear dose response seen along the 10-year fracture risk from low to medium to high-risk groups. Although rheumatologists didn't calculate the FRAX score, they recognize important clinical risk factors included in the FRAX tool.

Disclosure: J. Watt, None; **A. E. Thompson**, None; **N. G. H. Le Riche**, None; **J. E. Pope**, None.

1227 WITHDRAWN

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Trabecular BONE Score In Rheumatoid Arthritis and Ankylosing Spondylitis and Changes During LONG TERM Treatment With TNFA Blocking Agents. Eric Toussirot[1], Laurent Mourot[2], Daniel Wendling[3], Gilles Dumoulin[4] and CIC BT[5]. [1]CIC Biotherapy 506 and Rheumatology and EA 4266 Pathogens and Inflammation, Besançon, France, [2]University of Franche Comté, Besançon, France, [3]University Hospital, Besancon, France, [4]Department of Endocrine and Metabolic Biochemistry, Besançon, France, [5]University Hospital, Besançon, France.

Background/Purpose: Inflammatory rheumatic diseases such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are associated with osteoporosis. Bone mass in RA and AS has been well evaluated by measuring areal bone mineral density (BMD) with DXA. Trabecular bone score (TBS) is a new method evaluating bone microarchitecture by assessing pixel gray-level variations in DXA images from lumbar spine.

Objectives: In a case-control study, TBS was evaluated in patients with RA or AS and healthy controls (HC) and the results were compared to lumbar spine (LS) BMD measurements. Changes in LS and hip BMD and TBS score after initiating and during long term anti-TNFa treatment were also examined in a prospective study.

Methods: In the case control study, 30 patients with RA (ACR criteria, 19 F; 12 post menopausal women; age [mean ± SD]: 56.9 ± 9.7 yrs; disease duration: 11.7 ± 8.8 yrs; 26 under low dosage corticosteroids [CTC]) and 30 patients with AS (modified NY criteria, 27 M, age 43.8 ± 13.4 yrs; disease duration: 13.0 ± 11.1 yrs; no CTC) were evaluated and compared to 50 HC (29 F, 12 post menopausal women, age: 46.6 ± 11.1 yrs). L2-L4 BMD and hip BMD were measured using DXA (Lunar GE iDXA). TBS was calculated from L2-L4 BMD images (TBS insight®, Med-Imaps).

- In the prospective study, a group of 20 patients requiring TNFa blocking agent (6 F; 12 AS, [age: 40.7 ± 16.1 yrs] and 8 RA [age 60.5 ± 9.7 yrs]; disease duration: 9.6 ± 9.8 yrs; 9 under low dose CTC) were followed for 2 years. LS BMD, hip BMD and TBS score were measured at baseline and after 6, 12 and 24 months of treatment.

Results: Case control study: RA patients had lower BMD and T score at the hip ($p < 0.005$) compared to HC. Hip T score in patients with AS was also decreased ($p = 0.02$). LS BMD did not differ between patients and HC. TBS was lower in RA and AS compared to HC: 1.242 ± 0.16 and 1.282 ± 0.13 *vs* 1.365 ± 0.14, respectively ($p= 0.005$).

- Prospective study: under anti-TNFa, LS and hip BMD at M24 increased (+ 6.3% and + 2.4% respectively), with significant changes at the spine ($p< 0.001$). In the whole group, TBS score slightly increased from baseline to M12 (1,304 ± 0.13 to 1.32 ± 0.09) without significance, then returning to initial values at M24 (1.309 ± 0.09). However, in patients with RA, TBS score decreased (baseline to M24: 1.362 ± 0.048 to 1.308 ± 0.07) ($p = 0.032$) while in patients with AS, TBS progressively increased (1.257 ± 0.15 vs 1.309 ± 0.11; NS).

Conclusion: TBS score is decreased in inflammatory rheumatic diseases, especially in RA, suggesting alterations of bone micro architecture. Long term anti TNFa treatment is associated with a positive effect on (LS) bone mass but no major changes in TBS score. Surprisingly and on the contrary of AS, TBS score decreased in RA treated by TNFa blocking agents, suggesting different influences and responses of the bone to this drug's class.

Disclosure: E. Toussirot, None; **L. Mourot**, None; **D. Wendling**, None; **G. Dumoulin**, None; **C. BT**, None.

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A Before and After Comparison Of The Effects Of Monitoring On a Quality Indicator For glucocorticoid–induced Osteoporosis In a Japanese Hospital. Yasuhiro Suyama, Mitsumasa Kishimoto, Chisun Min, Yoichiro Haji, Yuri Ohara, Ryo Rokutanda, Hisanori Shimizu, Ken-ichi Yamaguchi, Yukio Matsui and Masato Okada. St. Luke's International Hospital, Tokyo, Japan.

Background/Purpose: Glucocorticoid-induced osteoporosis (GIOP) is one of the most devastating side effects of glucocorticoid use, leading to a substantially increased risk of fracture and disability. Prevention is considered to be more critical than treatment, especially in patients with known risk factors. In rheumatology, the use of quality indicators (QI) has been receiving increasing attention; the American College of Rheumatology published recommendations in 2010 for the prevention and treatment of GIOP, recommending that patients on as low as 7.5 mg daily of prednisolone or equivalent for more than 3 months be treated with anti-osteoporosis medications. However, few studies have reported on QI implementation and interventions to improve its adherence in the clinical setting. Herein, we assess the efficacy of implementation of a QI initiative to prevent GIOP.

Methods: We reviewed records of all patients prescribed prednisolone as low as 7.5 mg daily or equivalent for more than 3 months in our institution. To evaluate adherence to population-specific preventive care for GIOP, we divided patients into 3 groups based on gender and age:, men recommended to take a vitamin D analogue (Group A); women <50 years old recommended to take a vitamin D analogue (Group B); and women ≥50 years old recommended to take a bisphosphonate with vitamin D analogue (Group C). Clinical data from 2010 to 2012 were collected to compare the proportion of patients receiving appropriate therapy in each group before and after initiation of QI monitoring, implemented in 2011. Furthermore, prescription rates of preventive therapy were assessed by department in subanalysis.

Results: We identified 1800 eligible patients (586 in Group A, 540 in Group B, and 674 in Group C) in 2010; 2125 patients (760 in Group A, 643 in Group B and 722 in Group C) in 2011; and 2446 patients (851 in Group A, 851 in Group B and 744 in Group C) in 2012. Analysis revealed significant increases of targeted anti-osteoporosis treatment per QI standards after implementation of QI monitoring. Pooled rates of compliance with recommendations improved from 46.8% in 2010 to 52.7% in 2011 and 55.21% in 2012 ($p<0.001$). Appropriate preventive therapy increased for Group A from 43.34% in 2010 to 57.50% in 2011 and 58.87% in 2012; Group B increased from 63.9% in 2010 to 66.7% in 2011 and 68.2% in 2012; and Group C increased from 36.2% in 2010 to 35.0% in 2011 and 39.5% in 2012. Subanalysis by department demonstrated QI adherance to GIOP guidelines in 2012 as follows: nephrology (81.7%), rheumatology (69.9%), gastroenterology (66.3%), dermatology (60.8%), pulmonology (54.5%), otorhinolaryngology (52.6%), endocrinology (51.5%), orthopedic surgery (41.8%), ophthalmology (31.1%), hematology (29.5%), and neurology (10.4%).

Conclusion: Implementation of a QI for GIOP significantly improves adherence to 2010 ACR GIOP guidelines for appropriate population-specific, preventive therapy. Our results also indicate that, despite institution-wide announcements of QI goals, a substantial information gap may exist between the various clinical subspecialties involved in GIOP patient care.

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Analysis Of Fracture Risk Assessment Score (FRAX) Correlation With Bone Mineral Density (BMD) In Males and Post-Menopausal Females. Vikas Majithia[1] and Khush Aujla[2]. [1]University of Mississippi Medical Center, Jackson, MS, [2]University of Mississippi School of Medicine, Jackson, MS.

Background/Purpose: Fracture Risk Assessment Tool (FRAX) is a useful clinical tool for assessment of fracture risk and a major development in evaluation of osteoporosis. Its external validity is not established. This study was done to assess how well FRAX correlates with BMD in postmenopausal females and males of White and African-American ethnicity and calculate its test characteristics in a cohort of patients undergoing BMD.

Methods: Retrospective chart review of 1026 postmenopausal women and 2 men who underwent DEXA scan performed at UMC from 2005–2009. Data regarding demographics, BMD, FRAX and other relevant variables were abstracted, tabulated and analyzed using Statistical software. standard stratification was used. Scatter plot, were calculated.

Results: In males, FRAX demonstrates a low agreement with the BMD with Kappa=0.496, Low Sensitivity and Negative Predictive Value (NPV). Agreement was low/poor (K=0.167) in African-Americans (AA). In postmenopausal females, FRAX demonstrates a moderate agreement with the BMD with Kappa=0.647, adequate Sensitivity and NPV. It had good agreement (K= 0.847) in whites and low/poor agreement (K=0.313) in African-Americans.

It had adequate/good test characteristics in whites but poor sensitivity and NPV in AA males and females. and 2 these results in detail. These highlight the lack of correlation with a gold standard bone mass measurement and raise doubts on the validity of using FRAX in males as well as in AA PM females.

Table 1. CSP.

	Normal Bone Density (T-score >−1)	Low Bone Density (T-score <−1)	Osteoporosis (T-score <−2.5)	p-value
MALES N=237	N=62	N= 114	N=61	
Mean Age (years)	**60.06**	**62.97**	**59.42**	**p-NS**
Whites	**63.48**	**65.79**	**63.53**	
African-Americans	**50.94**	**60.59**	**54.70**	
Mean BMI (Kg/m^2)	**31.53***	**27.28***	**26.03***	***p< 0.001**
Whites	**30.93**	**26.97**	**26.12**	
African-Americans	**33.15**	**27.12**	**25.92**	
FEMALES N=1026	N=229	N=552	N=245	
Mean Age (years)	**64.43**	**63.32**	**62.84**	**p-NS**
Whites	**64.23**	**63.09**	**62.63**	
African-Americans	**64.64**	**63.55**	**63.06**	
Mean BMI (Kg/m^2)	**34.69***	**28.79***	**27.39***	***p< 0.001**
Whites	**32.01**	**26.95**	**25.44**	
African-Americans	**37.37**	**30.63**	**29.34**	

Table 2. A/TC.

	Overall	Whites	African-Americans
MALES (N= 112)			
Sensitivity	54.55	78.13	21.74
Specificity	94.74	93.18	100
Positive Predictive Value (PPV)	90.91	89.29	100
Negative Predictive Value (NPV)	68.35	85.42	41.94
Agreement (Kappa)	0.496 (CI=0.335–0.658)	0.725 (CI=0.567–0.884)	0.167 (CI=0–0.439)
PM-FEMALES (N= 469)			
Sensitivity	67.75	89.61	30.76
Specificity	97.37	95.40	100
Positive Predictive Value (PPV)	96.50	95.80	100
Negative Predictive Value (NPV)	73.84	88.80	41.94
Agreement (Kappa)	0.647 (CI=0.576–0.713)	0.8467 (CI=0.785–0.908)	0.313 (CI=0.175–0.451)

Conclusion: Use of FRAX to analyze fracture risk in US males and AA postmenopausal females may not lead to valid results. FRAX analysis did not have good agreement with BMD in these populations in this analysis. The lack of agreement was significantly worse in African-Americans as compared to Whites. These results suggest the need to do further population studies in larger cohorts of these subset populations to assess its external validity.

Disclosure: V. Majithia, None; **K. Aujla**, None.

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The Quality Of Life and Resource Use Related To Hip Fractures Based On Data From The International Costs and Utilities Related To Osteoporotic Fractures Study. Moa Ivergård[1], Viktor Wintzell[1], László B Tankó[2], Victoria Barghout[2], Axel Svedbom[1], Vidmantas Alekna[3], Maria Luisa Bianchi[4], Patricia Clark[5], Manuel Díaz Curiel[6], Hans Peter Dimai[7], Mikk Jürisson[8], Olga Lesnyak[9], Eugene McCloskey[10], Kerrie M Sanders[11], Thierry Thomas[12], Fredrik Borgström[13] and John A Kanis[14]. [1]OptumInsight, Stockholm, Sweden, [2]Novartis Pharma AG, Basel, Switzerland, [3]Vilnius University, Faculty of Medicine, Vilnius, Lithuania, [4]Bone Metabolism Unit, Istituto Auxologico Italiano IRCCS, Milan, Italy, [5]Clinical Epidemiology Unit, Hospital Infantil Federico Gómez and Faculty of Medicine UNAM, Mexico City, Mexico, [6]Catedra de Enfermedades Metabolicas Óseas, Universidad Autonoma, Madrid, Spain, [7]Department of Internal Medicine, Division of Endocrinology and Metabolism, Medical University of Graz, Graz, Austria, [8]Faculty of Medicine, Tartu University, Tartu, Estonia, [9]Ural State Medical Academy, Yekaterinburg, Russia, [10]Academic Unit of Bone Metabolism, Metabolic Bone Centre, University of Sheffield, Sheffield, United Kingdom, [11]Department of Medicine, NorthWest Academic Centre, The University of Melbourne, Melbourne, Australia, [12]INSERM U1059, CHU-St-Etienne, Saint Etienne, France, [13]LIME/MMC, Karolinska Institutet, Stockholm, Sweden, [14]WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, United Kingdom.

Background/Purpose: The International Costs and Utilities Related to Osteoporotic fractures Study (ICUROS) is an ongoing 18 months prospective observational study with the objective of estimating resource use and health related quality of life (HRQoL) related to osteoporotic fractures. This study aims to describe the resource utilization for hip fractures pooled from 10 countries (Australia, Austria, Estonia, France, Italy, Lithuania, Mexico, Russia, Spain and the UK).

Methods: We studied 2,407 patients with low-energy hip fracture sustained from 2007 to 2012. For the purpose of the present study patients had to be <50 years, live in their own home prior to the fracture, and have had the first study interview within 2 weeks after fracture. Data were collected through patient interviews and review of medical records in four phases (at baseline, Month 4, 12, and 18). Key data included patient reported HRQoL (EQ-5D), and resource utilization due to the fracture. HRQoL before fracture was collected immediately after fracture. Patients with complete data at each follow-up were included in the analyses. The EQ-5D is a HRQoL instrument consisting five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with 243 possible response combinations. These health states can be translated into health utilities on a unison scale using UK population based preference values (range −0.59 to 1; 1 for full health, 0 for dead, below 0 for health states worse than dead) [1].

Results: There were 1795, 1435, 1256 patients available for analysis at the 4, 12 and 18 months follow-up, respectively. The mean age (±SD) at fracture was 77±10 years and 79% were women. Emergency or traumatology departments were the first point of contact with the healthcare system for 89% of patients. 96% of patients were hospitalized and the mean hospital length of stay due to the fracture (±SD) was 17.2±20.4 days. During the first four months after fracture, the mean number of physician, nurse and physiotherapy visits related to the fracture were estimated at 2.8±3.1, 2.4±9.6, and 8.2±13 respectively. During the same time period, 65% of patients used analgesics, 41% calcium/vitamin D, and 27% pharmacological interventions for osteoporosis. The mean utility was 0.75±0.28 before fracture, −0.13±0.37 after fracture, 0.48±0.39 at Month 4, 0.58±0.37 at Month 12, and 0.66±0.36 at Month 18 following the fracture.

Conclusion: Hip fractures were associated with severe immediate loss in HRQoL. The mean health utility was estimated at −0.13 directly after fracture, which is worse than death on the 0 (death) to 1 (full health) scale. Whereas patients gradually recovered, the mean health utility estimate of 0.66 at 18 months after fracture (compared to 0.75 prior to fracture) show that, on average, hip fractures result in substantial and persistent long-term loss in HRQoL. In addition, the mean hospital length of stay of 17.2 days suggests that hip fractures are associated with substantial costs to society.

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Disclosure: M. Ivergård, OptumInsight, 3; **V. Wintzell**, OptumInsight, 3; **L. B. Tankó**, Novartis Pharma AG, 3; **V. Barghout**, Novartis Pharma AG, 5; **A. Svedbom**, OptumInsight, 3; **V. Alekna**, ICUROS, 2; **M. L. Bianchi**, ICUROS, 2; **P. Clark**, ICUROS, 2; **M. Díaz Curiel**, ICUROS, 2; **H. P. Dimai**, ICUROS, 2; **M. Jürisson**, ICUROS, 2; **O. Lesnyak**, ICUROS, 2; **E. McCloskey**, ICUROS, 2; **K. M. Sanders**, ICUROS, 2; **T. Thomas**, ICUROS, 2; **F. Borgström**, ICUROS, 2; **J. A. Kanis**, ICUROS, 2.

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Osteoporosis In Rheumatoid Arthritis – Still a Threat In The Biologic Era? Glenn Haugeberg[1], Torhild Garen[2], Hege Sommerseth[3], Anne Prøven[3] and Knut Helgetveit[3]. [1]Hospital of Southern Norway Trust, Kristiansand, Norway, [2]Oslo University Hospital Rikshospitalet, Oslo, Norway, [3]Martina Hansens Hospital, Bærum, Norway.

Background/Purpose: Osteoporosis is a well-known extra articular manifestation in rheumatoid arthritis (RA). In RA biologic disease modifying anti rheumatic drugs (DMARDs) has been shown to be superior to synthetic DMARDs to reduce bone destruction including generalized bone loss. Our aim was primarily to study short- and long term changes in bone mineral density (BMD) at hip and lumbar spine in patients with early RA followed in the biologic treatment era.

Methods: RA patients with early disease diagnosed at an out-patient clinic between 1999 and 2001 were consecutively enrolled in the study. Demographic, disease and treatment data were collected at standard visits. Dual energy X-ray absorptiometry at hip and spine L1–4 was performed at baseline and after 2, 5 and 10 years.

Results: At baseline mean age (SD) in the 92 RA patients was 50.9 (13.3) years, symptom duration 12.4 (6.7) months, 62.0% were women, 66.3% were RF positive and 65.9%% were CCP positive. In the first 2 years ever use of biologic DMARDs was 18.5%, synthetic DMARDs 91.3% and prednisolone 62.0% whereas the figures for the subsequent 8 years were 62.6%, 51.4% and 89.2%, respectively. Baseline, mean values for 0–2 years and 2–10 years follow up was for ESR mm/hr 30 (21), 21 (12) and 13 (7), for CRP mg/dl 29 (34), 19 (15) and 8 (7), for DAS28 5.2, 4.2 and 2.9 and for MHAQ 0.68 (0.51), 0.42 (0.30) and 0.27 (0.27).

The annual rate of BMD loss in the first 2 years and in the subsequent 8 years was at femoral neck −1.00% vs. −0.56%, at total hip −0.96% vs. −0.41% and at spine L1–4 −0.42% vs. 0.00%. The corresponding figures at femoral neck, total hip and spine L1–4 were in men −0.89% vs. −0.29%, −1.01% vs. −0.07% and −0.20% vs. 0.76%, in pre-menopausal women −0.93% vs. −0.39%, −1.20% vs. −0.11% and −0.42% vs. −0.06% and in post-menopausal women −0.75% vs. −0.91%, −0.74% vs. −0.85% and −0.49% vs. −0.61%.

Conclusion: Our study adds evidence that aggressive anti-inflammatory treatment in particular with biologics reduces the rate of bone loss in RA down to a level reported in the general population.

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Strontium Ranelate Uncouples Bone Resorption From Bone Formation In Osteoporotic Patients With Or Without Clinical Risk Factors. Olivier Bruyere[1], Julien Collette[2] and Jean-Yves Reginster[1]. [1]University of Liège, Liège, Belgium, [2]Labo RIA, CHU Sart Tilman, Liege, Belgium.

Background/Purpose: Strontium ranelate has proven efficacy against vertebral and nonvertebral fractures in postmenopausal osteoporosis. We explored whether the effect of strontium ranelate on bone turnover markers is influenced by the presence of well-established risk factors for fracture (i.e. age, prevalent fractures, parental history of osteoporosis, low body mass index, and addiction to smoking).

Methods: Analysis of pooled data from two three-year randomized controlled trials (i.e. the Spinal Osteoporosis Therapeutic Intervention (SOTI) and Treatment Of Peripheral Osteoporosis (TROPOS) studies). Bone-specific alkaline phosphatase (BALP, immunoradiometric assay Tandem®-R Ostase® kit, Beckman Coulter, USA), C-terminal propeptide of type I procollagen (PICP, RIA, Orion Diagnostic) and serum C-terminal telopeptides (S-CTX, ELISA using the Serum CrossLaps® ELISA kit, Nordic Bioscience Diagnostics, Denmark) were assessed at baseline, after 3, 6, 12 24 and 36 months. Comparisons of percentage changes from baseline in strontium ranelate and placebo groups were performed with use of the Mann–Whitney test. Results were analysed on an intention-to-treat (ITT) basis.

Results: 5082 patients were included in this study (2536 receiving strontium ranelate 2 g/day and 2546 receiving a placebo). In the strontium ranelate group, the bone resorption marker S-CTX decreased compared to the placebo group at every time point (all $p<0.05$) independently of age (below or over 80 years), familial history of osteoporosis (yes/no), body mass index (below or over 25kg/m^2), or prevalent vertebral fracture (absence, 1, 2 or more). During the 2 first year of treatment, S-CTX is also decreased independently of addiction to smoking (yes/no). After 3 years of treatment the differences of S-CTX change between the placebo and the strontium ranelate groups varied between 4 and 15%, depending on the risk factor considered. In patients with family history of osteoporosis, after 3 years of follow-up, the between-group difference in S-CTX was 8.9%. In the same way, an increase in the bone formation markers PICP and BALP in women taking strontium ranelate compared to placebo was observed after 3 months and sustained during the 3 years independently of the presence of fracture risk factor in the study population (all $p<0.05$).

Conclusion: During a 3-year treatment, strontium ranelate decreases bone resorption and stimulates bone formation in postmenopausal women independently of baseline osteoporosis risk factors. This effect is independent of the disease severity as demonstrated by a significant decrease in bone resorption markers and an increase in bone forming markers in patients with, no, 1 or 2 and more prevalent fracture.

Disclosure: O. Bruyere, Servier, 2; **J. Collette**, Servier, 2; **J. Y. Reginster**, Servier, 2.

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Effects Of Biological Therapy In Bone Metabolism In Patients With Chronic Inflammatory Arthropathies. Maria Victoria Hernández, Andrea Cuervo, Pilar Peris, Ana Monegal, Raimon Sanmarti, Juan D. Cañete and Nuria Guañabens. Hospital Clínic de Barcelona. IDIBAPS. University of Barcelona, Barcelona, Spain.

Background/Purpose: The efficacy of biological agents in the treatment of chronic inflammatory arthropathies is well known, however, the effect of this therapy in bone metabolism has been scarcely evaluated. Therefore, the aims of this study were to analyze the effects of biological therapy on bone mineral density (BMD), bone turnover and the incidence of fractures in patients with chronic inflammatory arthropathies

Methods: Prospective 2-year study including patients diagnosed with chronic inflammatory arthopathies initiating or switching biological therapy in a hospital day-care unit of a Rheumatology Department. Demographic data including diagnosis and duration of the disease, current biological agent and concomitant treatment (DMARD, glucocorticoids (GC)) were evaluated in all patients as were the following determinations at baseline and at 12 and 24 months: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), calcium, phosphate, 25-hydroxyvitamin D, parathyroid hormone (PTH), bone turnover markers of formation (P1NP and bone ALP) and resorption (urinary NTX and serum CTX), bone densitometry (DXA) and spinal x-rays. Patients with chronic renal failure and/or known metabolic bone disease were excluded.

Results: Fifty-seven patients were included (84.2% female); mean age 50 ± 13.4 years; mean disease duration 14 ± 9.4 years. The diagnoses were: rheumatoid arthritis 73.7%, psoriatic arthritis 3.5%, ankylosing spondylitis 3.5%, undifferentiated spondyloarthropathy 3.5% and overlap syndrome 8.8%. 40.4% were biologic-naive patients and 59.6% switchers: 80.7% were receiving a non-anti tumour necrosis factor (TNF) agent and 19.3% a TNF antagonist; 77% received concomitant treatment with DMARDs. The number and dose of GC therapy significantly changed at two years from baseline. Thus, the number of patients on GC decreased from 73.7% to 56.1% ($p=0.018$) and the percentage of patients with a daily dose $>$ 5 mg of prednisone from 48.8% to 32.2% ($p=0.001$). Also, a significant decrease in acute serum reactants (ESR, $p=0.002$; CRP, $p=0.005$) as well as in NTX ($p=0.005$) and PTH ($p=0.03$) values was found at 24 months with a trend to an increase in lumbar BMD compared to baseline (1.105 ± 0.101 vs 1.065 ± 0.175 g/cm^2, $p=0.06$); with no changes in total hip BMD (0.828 ± 0.126 vs 0.888 ± 0.146 g/cm^2, $p=0.11$). No fragility fractures were observed in the follow-up period.

Conclusion: Patients with chronic inflammatory arthopathies receiving biological therapy show a decrease in bone resorption markers and a preservation of lumbar BMD at 2 years, a finding which may be related with the reduction in glucocorticoid dose during therapy and the outcome of the inflammatory process.

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Predictors Of Fracture In Patients With Osteopenia: Data From An Observational Cohort. Kathryn Mitchell, Peter Diggle and Marwan Bukhari. Faculty of Health and Medicine, Lancaster, United Kingdom.

Background/Purpose: The risk factors for osteoporotic fragility fractures are well documented in the literature and although they are associated with a diagnosis of established osteoporosis (T score < -2.5) it is known that the majority of fragility fractures occur in osteopenic individuals (T score between -1.0 and -2.5)[1]. It is not known whether traditional risk factors for osteoporosis convey additional fracture risk in an osteopenic population. Objectives:To identify and examine the predictors of fracture in patients with diagnosed osteopenia.

Methods: Using a nested case control approach, patients referred for a first dual energy X-ray absorptiometry (DXA) scan at a district scanner in the North West of England between 2004 and 2012 were identified and their data included in the analysis if they were found to be osteopenic at the lumbar spine and/or femoral neck. Data collected included: age at scan, gender and indication information (including history of fracture). Univariate logistic regression was used to estimate the odds of fracture in this group using traditional risk factors and subsequently multivariate logistic models were fitted to predict any fracture for using the hip and spine bone mineral density (BMD).

Results: A total of 5021 patients were diagnosed with osteopenia at the femoral neck, of whom 80.5% were female and mean age at scan was 65.1 years (standard deviation 11.8 years). 1709 of these had a history of fracture. At the lumbar spine, 3737 patients were found to be osteopenic, of whom 83.6% were female and the mean age was 64.0 years (standard deviation 12.4 years). 1300 of these had a history of fracture.

Odds ratios for risk of fracture with the presence of a classical fracture risk factor are listed in table 1. Table 2 contains the coefficients of the multivariate logistic models for fracture risk. Standardised residuals suggest good fit for both multivariatelogistic models as they lie between 2 and -2.

Table 1. Odds ratios for fracture.

	Femoral Neck	Lumbar Spine
Age (per year)	1.03 (1.02, 1.03)	1.04 (1.03, 1.04)
BMI (per unit)	1.03 (1.02, 1.05)	1.03 (1.02, 1.05)
T-score at site (per unit)	0.59 (0.51, 0.67)	0.78 (0.66, 0.91)
Female	1.18 (1.02, 1.37)	1.16 (0.96, 1.39)
Maternal Hip Fracture	1.66 (1.09, 2.55)	2.54 (1.54, 4.21)
Smoking	1.09 (0.96, 1.23)	1.15 (0.99, 1.32)
Alcohol Excess	1.37 (1.09, 1.72)	1.32 (1.01, 1.72)
Corticosteroid Therapy	0.55 (0.47, 0.64)	0.63 (0.53, 0.75)
Rheumatoid Arthritis	0.49 (0.35, 0.68)	0.56 (0.38, 0.82)
Inflammatory Bowel Disease	0.38 (0.23, 0.63)	0.42 (0.25, 0.72)
Coeliac Disease	0.33 (0.21, 0.52)	0.43 (0.27, 0.69)
Hyperthyroidism	0.89 (0.34, 2.36)	1.46 (0.54, 3.93)
Hyperparathyroidism	0.51 (0.29, 0.91)	0.52 (0.27, 1.03)

Table 2. Results of multivariate logistic modelling for both sites: the femoral neck and lumbar spine. Variables that did not significantly add to the model show NS.

Coefficients	Femoral Neck: Estimate	p-value	Lumbar Spine: Estimate	p-value
Age (per year)	0.02	<0.001	0.04	<0.001
BMI (per unit)	0.03	<0.001	0.03	<0.001
T-score at site (per unit)	−0.45	<0.001	−0.18	<0.05
Female	NS		NS	
Maternal Hip Fracture	0.57	<0.05	1.01	<0.001
Smoking	NS		0.17	<0.05
Alcohol Excess	0.43	<0.001	0.37	<0.01
Corticosteroid Therapy	−0.57	<0.001	−0.45	<0.001
Rheumatoid Arthritis	−0.63	<0.001	−0.49	<0.05
Inflammatory Bowel Disease	NS		NS	
Coeliac Disease	−0.90	<0.001	−0.57	<0.05
Hyperthyroidism	NS		NS	
Hyperparathyroidism	−0.92	<0.01	−0.83	<0.05

Conclusion: Increasing age, reducing T-score, maternal hip fracture and excessive alcohol consumption predict fracture in osteopenic individuals irrespective of site. Other classical risk factors are unreliable predictors of fracture in this cohort, some even showing protective effects. Differences exist between predictors of fracture at the two sites. Possible unmeasured confounders could predict fractures in this cohort. Further research is needed.

References:
1. Arch Intern Med. 2004 May;164(10):1108–1112.

Disclosure: K. Mitchell, None; **P. Diggle**, None; **M. Bukhari**, None.

1236

Outcomes and Costs Of Sacral Insufficiency Fractures. Shahryar Hadavi[1], Sanam Kia[1], Christian Dejaco[1], Bhaskar Dasgupta[1] and Frances Borg[2]. [1]Southend University Hospital, Westcliff-on-Sea, United Kingdom, [2]Southend University Hospital, Westcliff-on-sea, United Kingdom.

Background/Purpose: Sacral insufficiency fracture (SIF) is a poorly recognised cause of lower back pain in the elderly with significant potential morbidity. Diagnosis is often slow as the typical clinical picture is poorly recognised. SIFs are seldom seen on plain radiographs, and routine lumbar MRI rarely includes the sacrum. However they can be reliably identified on isotope bone scan.

Existing studies are small (cohorts up to 25 patients) and primarily highlight radiological findings rather than clinical outcomes. We report a cohort of 124 patients with SIF, describing patient outcomes and associated health care costs.

Objectives: 1 To describe patient outcomes following SIF.

2 To determine delays in diagnosis and length of hospital stay.

3 To estimate the financial healthcare costs of SIF.

Methods: Patients were identified retrospectively from isotope bone scans performed at Southend hospital from 2000–2012. Case notes were reviewed for clinical features, time to diagnosis, length of hospital stay, IV bisphosphonate use and mobility and functional status pre- and post-fracture. Mortality was calculated using Kaplan Meier analysis.

Results: 135 patients were identified, of which case notes for 124 patients were reviewed.

Clinical: 83.9% were female. The mean age was 79 years (range 44–96). 51.6% were inpatients at the time of diagnosis. 54.8% presented with back pain, 17.7% groin pain, 17.7% thigh pain and 20.7% buttock pain. 39.2% had preceding minor trauma. 58.9% had a previous fracture, most commonly vertebral and pubic ramus. 23/34 (67.6%) had known osteoporosis. Median time to diagnosis was 13 days (longest 345 days). The median inpatient stay was 22 days (longest 76 days).

Radiology: In 58.1%, bilateral SIF were seen on bone scan. SIF was suspected in only 37.9% of patients prior to scan. 30.6% of bone scans showed co-existing pubic rami fractures. Of 110 patients with pelvic radiographs, only 2 had sacral fractures visible on plain films.

Outcomes: Although 62.1% were fully independent and 30.6% at home with care prior to fracture, functional status fell in 32.5% and 15.8% of these patients respectively following fracture. Prior to fracture 45.3% were independently mobile and 33.3% used a stick. Similarly mobility fell in 32.1% and 41% respectively. The mean survival was 76.2 months, compared to a UK life expectancy of 118 months at 80 years of age.

Based on UK national average figures, the estimated cost per stay for inpatient bed alone is £8159 (US$12587), and the average increase in weekly cost of long-term care post SIF is £115 ($177). A single dose of intravenous bisphosphonate post-fracture was associated with a better outcome, with functional status preserved in 45/49 (91.8%) treated patients, compared to 39/65 (60%) of those untreated. The cost of a single 60mg dose of pamidronate is £55 ($84.9).

Conclusion: Our data suggest that SIF is associated with delayed diagnosis, long hospital stays, poor functional outcomes and decreased life expectancy, with large financial costs per patient. The morbidity, mortality and economic burden may be comparable to hip fracture. Intravenous bisphosphonate use post-fracture may help preserve function.

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Denosumab Leads To Significantly Greater Increases In Bone Mineral Density Than Ibandronate and Risedronate In Postmenopausal Women At High Risk For Fracture Who Were Previously Treated With An Oral Bisphosphonate. Jacques P. Brown[1], Michael A. Bolognese[2], Pei-Ran Ho[3], Jesse Hall[3], Christian Roux[4], Henry G. Bone[5], Sydney Bonnick[6], Joop van den Bergh[7], Irene Ferreira[8], Prayashi Ghelani[9], Paula Dakin[3], Rachel B. Wagman[3] and Chris Recknor[10]. [1]CHU de Québec Research Centre and Laval University, Quebec City, QC, [2]Bethesda Health Research Center, Bethesda, MD, [3]Amgen Inc., Thousand Oaks, CA, [4]Paris Descartes University, Paris, France, [5]Michigan Bone and Mineral Clinic, Detroit, MI, [6]Clinical Research Center of North Texas, Denton, TX, [7]VieCuri Medical Centre and Maastricht University, Venlo, Netherlands, [8]Amgen Inc., Cambridge, United Kingdom, [9]Ovatech Solutions, London, United Kingdom, [10]United Osteoporosis Centers, Gainesville, GA.

Background/Purpose: Low bone mineral density (BMD) is an important and modifiable risk factor for fracture in postmenopausal women with osteoporosis. Denosumab (DMAb), which has a unique mechanism of action, has demonstrated a stronger relationship between BMD increases and antifracture efficacy (new or worsening vertebral and nonvertebral fracture) than bisphosphonate (BP) therapies. There is a clinical need to treat subjects who remain at higher risk for fracture despite current BP therapy. In 2 open-label studies, DMAb significantly increased BMD and decreased bone turnover markers vs a monthly oral BP, specifically ibandronate (IBN; 150 mg, single dose once monthly) or risedronate (RIS; 75 mg on 2 consecutive days once monthly), in subjects previously treated with, though suboptimally adherent to, a BP. Here we evaluate the effects of DMAb vs a monthly oral BP (IBN and RIS) to increase BMD in a subset of subjects at higher risk for fracture.

Methods: Both studies were multicenter, randomized, open-label, parallel-group designs in which postmenopausal women ≥ 55 years were randomized 1:1 to DMAb 60 mg subcutaneously every 6 months or a BP 150 mg orally every month for 12 months. In this combined post-hoc analysis, higher-risk subjects were identified by meeting ≥ 1 risk criteria (advanced age, low BMD, prior osteoporotic fracture, high baseline sCTX-1; Table) and the BMD percentage change from baseline in total hip, femoral neck, and lumbar spine at month 12 was calculated.

Results: Subjects from these 2 studies (852 DMAb; 851 BP) had a mean (SD) age of 67 (7.4) years, and mean (SD) T-score at the total hip, femoral neck, and lumbar spine of −1.7 (0.8), −2.0 (0.7), and −2.4 (1.0), respectively. For subjects at higher risk for fracture, DMAb significantly increased BMD at 12 months compared with a BP (IBN and RIS) at the total hip (2.2% vs 0.8%, respectively), femoral neck (1.8% vs 0.3%), and lumbar spine (3.8% vs 1.4%) ($p < 0.0001$ for all; Figure). These results are consistent with the overall study population (treatment-by-risk subgroup interaction $p > 0.05$). In general, AEs and SAEs were similar between DMAb and the comparator BP group.

Table. Identification of Subjects at Higher Risk for Fracture.

	BP N = 851	DMAb N = 852	All N = 1703
Higher-risk subjects, n (%)	469 (55.1)	475 (55.8)	944 (55.4)
1. Age ≥ 75 years	150 (17.6)	160 (18.8)	310 (18.2)
2. Baseline BMD T-score ≤ −2.5 at total hip or femoral neck	250 (29.4)	245 (28.8)	495 (29.1)
3. Baseline BMD T-score ≤ −1.0 at total hip or femoral neck and with prior osteoporotic fracture	256 (30.1)	265 (31.1)	521 (30.6)
4. Baseline sCTX-1 > 0.9 ng/mL and BMD T-score ≤ −2.0 at total hip or femoral neck	17 (2.0)	10 (1.2)	27 (1.6)
Subjects remaining at risk*	319 (37.5)	319 (37.4)	638 (37.5)
Subjects with unknown risk status due to missing data	63 (7.4)	58 (6.8)	121 (7.1)

N = number of subjects randomized. *Subjects who did not meet any of the higher-risk criteria. BP = ibandronate and risedronate. DMAb = denosumab.

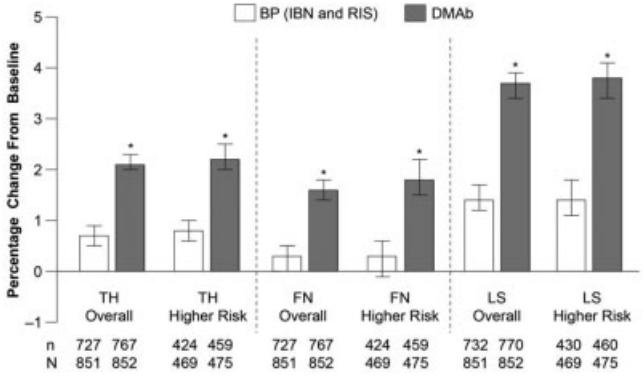

Figure. BMD Percentage Change From Baseline at Month 12.

Conclusion: For subjects previously or suboptimally treated with a BP who remain at higher risk for fracture, transitioning to DMAb led to significantly greater increases in BMD at month 12 compared with cycling to another BP. These results in higher-risk subjects are consistent with those obtained in the overall population and support DMAb as an alternative therapeutic option for women at higher risk for fracture.

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Persistence At 12 Months With Denosumab (Prolia®) In Postmenopausal Women With Osteoporosis: Interim Results From a Prospective Observational Study. Stuart L. Silverman[1], Ethel Siris[2], David L. Kendler[3], Dea Belazi[4], Jacques P. Brown[5], Deborah T. Gold[6], E. Michael Lewiecki[7], Alexandra Papaioannou[8], Christine Simonelli[9], Irene Ferreira[10], Paula Dakin[11], Suresh Siddhanti[11], Bradley Stolshek[11] and Christopher Recknor[12]. [1]Cedars-Sinai Medical Center, UCLA Center of Excellence, Beverly Hills, CA, [2]Columbia University, New York, NY, [3]University of British Columbia, Vancouver, BC, [4]AlchemiPharma LLC, Wayne, PA, [5]CHU de Québec Research Centre and Laval University, Quebec City, QC, [6]Duke University Medical Center, Durham, NC, [7]University of New Mexico School of Medicine, Albuquerque, NM, [8]McMaster University, Hamilton, ON, [9]Health East Osteoporosis Care, Woodbury, MN, [10]Amgen Inc., Cambridge, United Kingdom, [11]Amgen Inc., Thousand Oaks, CA, [12]United Osteoporosis Centers, Gainesville, GA.

Background/Purpose: Persistence with osteoporosis therapy is important for optimal reduction of fracture risk. Persistence with denosumab was >90% in a randomized clinical trial in women with low bone mineral density (BMD), but persistence in the community setting is undetermined. We are conducting a prospective observational study to evaluate persistence with denosumab in routine clinical practice in the United States (US) and Canada (CAN).

Methods: In this ongoing multicenter, single-arm study, women were enrolled within 4 weeks after the first injection of subcutaneous denosumab recommended for administration every 6 months for the treatment of osteoporosis per the local product label. Clinical sites include primary care and specialty practices. No clinical procedures, assessments, or changes to routine management of patients are required. Participants are followed for 24 months after study entry. We report results of a 12-month interim analysis. Study endpoints include persistence with denosumab at 12 months (defined as receipt of at least 2 injections no more than 6 months + 8 weeks apart); patient and physician attributes predicting persistence; and occurrence of serious adverse events (SAEs). Persistence rates are based on total patient enrollment.

Results: Enrollment was completed in April 2012 (N=935; US n=632; CAN n=303). Of 80 participating physicians (US n=54; CAN n=26), 41% in the US and 19% in CAN are rheumatologists. In the US, 76% of patients were ≥65 years of age at baseline, vs 62% in CAN. The mean (SD) Wolfe comorbidity index was 2.4 (2.0) in the US and 1.9 (1.6) in CAN. More than half of patients (53%) had osteoarthritis, 9% had rheumatoid arthritis, and 9% had other rheumatologic disorders. During the 5 years before enrollment, 92% of patients in both the US and CAN had taken a prescription osteoporosis therapy, and 59% (US 57%; CAN 62%) had used osteoporosis therapy >5 years before enrollment. Patients in the US took a mean (SD) of 8.4 (5.0) prescription medications, vs 5.7 (4.3) in CAN.

At 12 months, 82% of patients were persistent with denosumab (US, 79%; CAN 88%; Table). Several baseline factors in the US and one in CAN showed a statistically significant association with persistence (Table). Of the 118 patients (13%) who had discontinued the study at 12 months, 55 (6%) withdrew consent, 9 (1%) were lost to follow-up, 8 (1%) died, and 46 (5%) cited other reasons. SAEs were reported in 66 patients (7%); no SAEs of osteonecrosis of the jaw (ONJ), atypical femoral fracture, fracture healing complications, hypocalcemia, eczema, or hypersensitivity were reported. AEs of fracture were reported by 21 patients (2%).

Persistence at 12 Months With Denosumab

	Total N = 935	US N = 632	Canada N = 303
Persistence with denosumab (2 injections), percentage of patients	81.9%	79.3%	87.5%

Baseline factors that show statistically significant association with persistence by country

Country	Covariate	Category	Persistence	P-value
USA	Use of osteoporosis medications	Yes	83.3%	0.0040
	> 5 years before enrollment	No	73.9%	
	Lumbar spine BMD T-score	> −2.5	82.7%	0.0472
		≤ −2.5	75.9%	
	Region	Midwest	87.0%	0.143
		Northeast	83.3%	
		West	80.0%	
		South	72.2%	
	Physician gender	Female	85.2%	0.0362
		Male	77.3%	
	Marital status	Married	83.8%	0.0197
		Never married	76.9%	
		Divorced	74.5%	
Canada	Prior hip fracture	No	88.9%	0.0028
		Yes	60.0%	

Univariate analysis. The P value represents the statistical significance of the covariate when added to the univariate logistic model, with persistence as the response variable.

Conclusion: In this study of routine clinical practice, more than 80% of patients for whom denosumab was prescribed persisted on therapy at 12 months. Denosumab appears to be well tolerated; no new safety risks have been identified to date.

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The Effects Of Hyperparathyroidism On Body Mass Index and Bone Mineral Density- An Observational Case-Control Study. Chris Varley[1], Alexander Oldroyd[2] and Marwan Bukhari[3]. [1]Lancaster University, Llandudno, United Kingdom, [2]Lancaster University, Lancaster, United Kingdom, [3]Royal Lancaster Infirmary, Lancaster, United Kingdom.

Background/Purpose: Hyperparathyroidism is associated with reduced bone mineral density (BMD) and increased fracture risk. A previous study from this group has shown that bone loss in hyperparathyroidism occurs at both the lumbar spine and femoral neck.[1] The condition is also associated

with weight gain, and increased body mass index (BMI).[2] A low BMI is a risk factor for BMD loss and osteoporosis, meaning that the higher BMI of hyperparathyroid patients may play a protective role against the increased BMD loss. This study aims to determine the relationship between BMD and BMI in hyperparathyroidism.

Methods: Using a nested case-control approach, a cohort of patients referred between 2004 and 2011 for a dual-energy x-ray absorptiometry scan with hyperparathyroidism as their main risk factor was identified. These were then age and gender matched with controls referred in the same time period with no indication for scanning. The odds of having osteoporosis were compared between cases and controls using a univariate logistic model. Simple differences in BMI were ascertained using students t-test, and sites of bone loss were ascertained by comparing BMD at two sites (L1-L4 vertebrae and the left femoral neck) between cases and controls. A multivariate logistic model was fitted to determine the interaction between BMI and bone loss in patients with hyperparathyroidism.

Results: 281 patients with hyperparathyroidism were identified, with 281 age and sex matched controls. There were 233 females (83%) in each group. Both groups had a mean age of 67.4 (SD 12.2). The odd of having osteoporosis in the hyperparathyroid group was 5.08 (95% CI 3.37–7.67). BMI was found to be significantly increased in the hyperparathyroid cohort (27.9 kg/m2 v 26.2 kg/m20, mean difference of 1.612 kg/m^2 (95% CI 0.782–2.442, p≤0.001). BMD was shown to also be significantly reduced in both the lumbar spine and the femoral neck, with maximal loss in the femur; mean BMD difference was 0.0345 g/cm^2 in L1-L4 (95% CI 0.0003–0.0686, p≤0.05), and 0.0357 g/cm^2 in the femoral neck(95% CI 0.0115–0.0598, p≤0.01). In the multivariate logistic model, a significant difference in BMD only persisted in the femoral neck, with an odds ratio of 6.86 (95% CI 1.37–34.3, p≤0.05) for a lower BMD compared to an odds of 1.89 (95%CI 0.60,5.73) in the lumbar spine.

Conclusion: Hyperparathyroidism is shown to be associated with both a high BMI and an increased osteoporosis risk, with significantly reduced BMD at the femoral neck, but not the lumbar spine when adjusted for BMI. A reduced BMD in the presence of an increased BMI may be due to certain unique circumstances found in hyperparathyroidism, such as the presence of extra PTH-secreting cells in adipose tissue, or the sequestration of vitamin D in adipose tissue, which may lead to further PTH secretion and BMD loss.

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2. A Meta-Analysis. Journal of Clinical Endocrinology & Metabolism. 2005; 90(3):1525–30.

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1240

Study On The Relationship Between The Preoperative Stay and Morbimortality In Patients With Hip Fracture. Irene Martin, Maria Aparicio, Laura López-Vives, Montserrat Jordana, Antoni Coscujuela, Abelardo Montero and Carmen gomez-Vaquero. Hospital Universitari de Bellvitge, Barcelona, Spain.

Background/Purpose: Introduction: The preoperative stay (PS) in patients with hip fracture has been classically associated with the resultant morbimortality of the process. As a consequence, current clinical guidelines recommend that surgery be performed within 24 or 48 hours of the fracture event. Latest communications question these assumptions. Objectives: To analyze the factors present at the time of admission of patients with hip fracture that determine the length of PS. Analyze the relationship of the length of PS with the resultant morbimortality.

Methods: From March 1, 2009 to December 31, 2011, all patients admitted with fragility hip fracture in a university hospital were visited in a prospectively and formalized way. We collected socio-demographic, clinical and analytical data concerning the patient's status before the fracture and the complications arising during admission and follow-up at 3 months and a year. For this study, we analyzed the relationship between the length of PS, the variables present at admission [age, sex, body mass index (BMI), type of fracture, serum haemoglobin, creatinine, and calcidiol, weekday of admission, Charlson comorbidity index (CI), Pfeiffer test (PT), Barthel index (BI)], the type of surgery and the outcome variables [total stay and postoperative stay, one year mortality and worsening of the parameters of functional and cognitive status]. The variables were entered in a database and analyzed with SPSS Windows version 15.0.

Results: We included 631 patients (70% women) with a mean age of 83 ± 8 years. On admission, the mean BMI was 25.6 ± 4.5 kg/m2. The mean IC was 1.8 ± 2.0 and IB, 75 ± 29 points. The PT was normal in 54% of patients and showed mild, moderate or severe impairment in 17%, 15% and 14%, respectively. The most prevalent types of fractures were the subcapital (48%) and the intertrochanteric (39%) fractures. Regarding laboratory parameters, mean serum haemoglobin was 11.6 ± 1.9 g/dL, creatinine, 100.9 ± 77.4 mmol/L and calcidiol, 31.6 ± 22.8 nM/L. Osteosynthesis was the most commonly used surgical procedure (60%), prosthetic replacement was performed in 38% of the patients. The mean PS was 4.25 days, postoperative stay 13.4 days and total stay 17.4 days. One hundred and sixty-five patients (26%) died during the year after the fracture. None of the variables present at the time of admission or the type of surgery were related to the length of PS. A longer PS was correlated with significant higher postoperative and total stays. The length of PS was not associated with an increase in the mortality rate or with an impairment of the parameters of functional and cognitive status.

Conclusion: In this prospective series of patients with fragility hip fracture, the length of the preoperative stay is not related to the resultant morbimortality. We could not identify any factor that determines preoperative stay length. A longer preoperative stay is associated with higher postoperative and total hospital stays.

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1241

A Low Serum 25(OH) Vitamin D Level As a Risk Factor For Incidence and Severity Of Vertebral Fracture In Glucocorticoid-Induced Osteoporosis In Japan. Mari Ushikubo[1], Harumi Kuda[1], Sayaka Kubo[1], Keisuke Izumi[2], Kumiko Akiya[1] and Hisaji Oshima[1]. [1]National Tokyo Medical Center, Tokyo, Japan, [2]Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: Although levels of serum 25(OH) vitamin D (25(OH)D) have been discussed for preventing osteoporotic fractures in primary osteoporosis, an importance of the levels has not been well documented in glucocorticoid-induced osteoporosis (GIO). Also, regional differences of serum 25(OH)D levels for bone health have not been established. This study was conducted to demonstrate roles of serum 25(OH) levels for osteoporotic vertebral fractures in GIO in Japan.

Methods: A 2-year cohort study recruiting 97 patients (81 women) with collagen vascular diseases taking glucocorticoids other than rheumatoid arthritis was conducted in Tokyo, Japan. Vertebral fractures were defined from X-ray films with the semi-quantitated method (SQ, Genant 1993). Means of age, disease duration, and prednisolone dosages of subjects were 60 +/− 15 (SD), 14 +/− 12 (y), and 8.0 +/− 5.9 (mg/day), respectively. Prevalent vertebral fractures were seen in 40 patients.

Results: 1) Incident vertebral fractures were observed in 42% of the patients, and 9 patients showed more than 2 grades of the progress of fractures (DSQ≥2). 2) A mean of serum 25(OH)D levels were 18.8 +/− 6.9 pg/ml (5.9 – 36.0). Fifty five patients showed less than 20 pg/ml. 3) Patients with incident vertebral fractures showed significantly lower (p<0.04) levels of serum 25(OH)D when compared to patients with no fractures (16.9 vs 20.0 pg/ml). 4) After adjusting with known risk factors of GIO (age, predonisolone dosage, BMD, prevalent fracture, and treatments) using logistic regression analysis, a lower serum 25(OH)D level was a significant (p<0.03) risk factor (OR 1.6/5pg) for incident fractures. Patients with less than 20 pg/ml of serum 25(OH)D showed a significant higher rate (p<0.03, OR 1.2) of incident fractures than patients with more than 20. 5) A low level of serum 25(OH)D was also revealed as an independent risk factor (p<0.03, OR 3.1/5pg) for severer incident fractures (DSQ≥2).

Conclusion: It was suggested that a serum 25(OH)D level was an important factor for bone fragility in GIO in Japan.

Disclosure: M. Ushikubo, None; **H. Kuda**, None; **S. Kubo**, None; **K. Izumi**, None; **K. Akiya**, None; **H. Oshima**, None.

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A Prospective Randomized Open Label Trial To Evaluate The Effect Of Food On Vitamin D Absorption. Lucas Grisanti[1], Zeenat Ali[2], Joseph M. Grisanti[3], James Hatem[3], Mary Brennan[3], Michael Grisanti[3], Mary Margaret O'Neil[3], Linda Burns[3] and Kostas Botsoglou[4]. [1]College of Wooster, Wooster, OH, [2]Mercy Hospital of Buffalo, Buffalo, NY, [3]Buffalo Rheumatology, Orchard Park, NY, [4]Sisters Hospital, Buffalo, NY.

Background/Purpose: Vitamin D deficiency is commonplace throughout the world and is associated with a number of health related consequences. Being a fat-soluble vitamin, speculation has emerged regarding enhanced

vitamin D absorption when administered with food. Theorizing that bile salts and digestive lipases enhance vitamin D absorption, we conducted this randomized controlled clinical trial. The objective of this study was to determine if administering vitamin D with the largest meal of the day enhanced vitamin D absorption when compared to a similar group where replacement vitamin D was given following an overnight fast.

Methods: Subjects 18 years of age or greater with a low 25(OH) vitamin D level between 10 and 30 ng/mL were considered for enrollment. A total of 326 subjects were randomly assigned to a vitamin D replacement regimen that was administered either with the largest meal of the day or following an overnight fast. Four separate vitamin D replacement regimens were studied: 50,000 IU vitamin D2 once weekly, 4,000 IU vitamin D3 daily, 2,000 IU vitamin D3 daily, and 1,000 IU vitamin D daily. Results were assessed by improvement in repeat serum 25(OH) vitamin D levels obtained following 12 weeks of replacement therapy. Completers were defined as subjects who were at least 80% compliant with study medication and had a follow-up vitamin D level drawn at study completion. A total of 249 subjects completed the study.

Results: Of the 249 individuals completing the study, 118 took vitamin D with their largest meal while 131 fasted. The mean improvement in 25(OH) vitamin D levels for the "with food" group was 57% (mean baseline: 23.0, mean ending value: 36.1) with a mean raw difference of 13.2 (95% CI 11.2–15.2). Subjects in the fasting group demonstrated a mean improvement in 25(OH) vitamin D levels of 51% (mean baseline: 22.7, mean ending value: 34.2) with a mean difference of 11.5 (95% CI 9.4–13.6). While improvement in 25(OH) vitamin D levels in the entire cohort was 15% greater when administered with food, this improvement was not statistically significant ($p=0.26$) when compared to repletion following overnight fasting. Subset analysis of the four dosing regimens did demonstrate a statistically significant greater improvement in serum 25(OH) vitamin D levels when replacement was administered with food for the 4,000 IU dosing regimen ($p=0.001$). In this group the mean change when administered with food was 13.7 (CI 10.3–17.2) while the mean change when fasting was 6.9 (CI 4.6–9.1). Statistical differences were not achieved in the other three dosing regimens.

Conclusion: Administering vitamin D replacement with the largest daily meal resulted in a 15% greater improvement in serum 25(OH) vitamin D levels when compared to repletion following an overnight fast. This difference was not statistically significant. Subset analysis of various dosing regimens identified a statistically significant greater improvement when 4,000 IU of daily vitamin D was administered with the largest meal of the day. We conclude that administering vitamin D with the largest meal of the day may enhance vitamin D absorption, compared to taking it with a morning fast. The difference was modest and not statistically significant.

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1243

Osteoporosis Medication Adherence: Reasons For Stopping and Not Starting. Amy H. Warriner[1], Ryan C. Outman[1], Allison Wyman[2], Fred H. Hooven[3], Jonathan D. Adachi[4], Roland Chapurlat[5], Juliet E. Compston[6], Cyrus Cooper[7], Jeffrey R. Curtis[8], Adolfo Díez-Pérez[9], Robert Lindsay[10], Lyn March[11], Jeri W. Nieves[10] and Kenneth G. Saag[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Center for Outcomes Research, UMass Medical School, Worcester, MA, [3]University of Massachusetts, Worcester, MA, [4]McMaster University, Hamilton, ON, [5]INSERM UMR 1033 and Université de Lyon, Hôpital Edouard Herriot, Lyon, France, [6]University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom, [7]MRC Lifecourse Epidemiology Unit, Southampton, United Kingdom, [8]University of Alabama at Birmingham, Division of Clinical Immunology and Rheumatology, Birmingham, AL, [9]Hospital del Mar-IMIM, Universitat Autònoma de Barcelona, Barcelona; and RETICEF, ISCIII Madrid; Spain, Barcelona, Spain, [10]Helen Hayes, West Haverstraw, NY, [11]University of Sydney Institute of Bone and Joint Research, Royal North Shore Hospital, St Leonards, Australia.

Background/Purpose: Medication adherence with prescription osteoporosis medications is poor, with approximately half remaining adherent in the first year of treatment. Moreover, approximately one-third who are prescribed an osteoporosis medication do not fill the new prescription. Reasons for the poor initiation and persistence are multiple. The effect of the recent reports of potential long-term side effects of osteoporosis medications is unknown.

Methods: The Global Longitudinal Study of Osteoporosis in Women (GLOW) is an observational cohort through which survey data are collected annually from women aged ≥55 years old at baseline. The women were initially recruited from 17 regional sites in 10 different countries.

Results: Of 34,971 women that completed surveys in the fifth year, 3,735 were classified as osteoporosis prescription medication "stoppers" as they had been on an osteoporosis medication but stopped it in the past 2 years; whereas 175 were osteoporosis medication "non-starters" and never initiated an osteoporosis medication despite receiving a prescription from their physician. The majority (52%) of stoppers report they were instructed by their doctor to stop their medication. A large proportion also listed concerns of long-term risks associated with the medication(s) (36%) and a specific concern about effects on teeth or jaw (19%) as reasons for stopping (Table 1). For the non-starters, the majority (55%) listed possible side effects as their reason for not initiating an osteoporosis prescription medication, despite the recommendation from their physician (Table 2).

Table 1. Reasons for stopping osteoporosis medications

Reasons for Stopping	n (%)
Instructed by doctor	1947 (52)
Possible long-term risks	1327 (36)
Side effects	753 (20)
Bone density not improving	752 (20)
Taking a drug holiday, on it long enough	721 (19)
Concern about effects on teeth or jaw	693 (19)
Bone density improving	398 (11)
Efficacy (it wasn't helping)	335 (9)
Too many other medications	247 (7)
Too expensive	182 (5)
Difficult to take as directed	174 (5)
Not covered by insurance	140 (4)

Table 2. Reasons for NOT starting osteoporosis medications

Reasons for NOT taking	n (%)
Possible side effects	97 (55)
Too many other medications	31 (18)
Efficacy (would not work)	23 (13)
Too difficult to take	18 (10)
Too expensive	16 (9)
Other	72 (41)

Conclusion: Osteoporosis medication adherence is known to be poor. Our findings reflect women's concerns over possible long-term effects of these medications as a major contributor to not taking or starting these medications. However, most women that were taking medications in the past have stopped taking their osteoporosis medication per the instruction of their physician. These findings highlight increasing concerns of patients and their physicians about the safety of osteoporosis medications.

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Low Bone Mineral Density In African-American Males May Be More Prevalent Than Previously Reported and Exhibits Association With Low BMI But Not Older Age - Results Of a Retrospective Cohort Analysis. Khush Aujla[1] and Vikas Majithia[2]. [1]University of Mississippi School of Medicine, Jackson, MS, [2]University of Mississippi Medical Center, Jackson, MS.

Background/Purpose: Osteoporosis (OP) in Males is prevalent and frequently under-recognized. There are a number of known demographic factors such as age, race and BMI as well as secondary causes of low bone mineral density (BMD) i.e. osteopenia and OP. The effect of these on the prevalence of low BMD has not been well quantified. This study aims to describe the prevalence of the demographic factors and SC in men with low BMD and also assess their impact on the prevalence.

Methods: Retrospective chart review of men who underwent DEXA scan performed at UMC from 2005– 2012 was done. Data regarding BMD, demographics i.e. age, race, height, weight, BMI, secondary medical causes, medications, social factors such as smoking and alcohol use was abstracted, tabulated and analyzed using STATA software. Statistical significance was assessed using T-test and Odds ratio as appropriate.

Results: A total of 585 charts were analyzed. There were 410 whites (W), 175 African-Americans (AA). 148 patients had normal BMD. Low bone density was prevalent and seen in 437 patients (74.7%). Amongst these 143 (24.4%) had T-score < -2.5 (osteoporosis) and 294 (50.25%) had T-score > -2.5 and < -1.0 (osteopenia) BMD. The prevalence results are presented in the table with significant differences highlighted.

	NORMAL BONE DENSITY	OSTEOPOROSIS (T-Score < -2.5)	
DEMOGRAPHICS			
AGE (mean)	57.59 years	59.34 years	p-NS
AA	55.33	56.04	p-NS
Whites	62.80	62.64	p-NS
BMI (mean)	31.74	26.07*	*p<0.001
AA	33.18	26.63*	*p<0.001
Whites	30.30	25.51*	*p<0.001
SECONDARY MEDICAL DISORDERS (%)			
ANY Disorder	69.69 %	80.32 %	p=0.11
Thyroid Disorders	13.63 %	16.39 %	p-NS
Hyperparathyroidism	4.54 %	3.27 %	p-NS
Diabetes	28.78 %	16.39 %	p-NS
Asthma/COPD	6.75 %	16.1 %	*p<0.05
Rheumatoid Arthritis	10.6 %	16.66 %	p-NS
Other Connective tissue Disorders	7.57 %	13.11 %	p-NS
Malignancy	18.18 %	22.95 %	p-NS
MEDICATIONS			
Any Relevant	42.42 %	68.85 %*	*p<0.05
Steroids >5 mg	28.37 %	32.86 %	p-NS
SOCIAL FACTORS			
Smoking	15.15 %	36.06 %*	*p=0.01
Alcohol Use	0	1.63 %	–

In this cohort of patients undergoing DEXA scan, osteoporosis was seen more commonly in 53/175 AA males (30.28%) versus 90/410 white males (21.95%). These AA males were younger than whites (Mean age 56.04) as compared to whites (Mean age 62.64). There were a number of factors present with low BMD. Amongst these, low BMI seemed to be the major contributor to low bone mass in these males. Surprisingly, the patients with low BMD had no difference in the age as compared to those with normal BMD. BMI was similar in both AA and white patients. Other factors such as overall medication use, smoking and respiratory disorders were found to be significantly more prevalent than others but no racial difference was found in the prevalence of the secondary disorders.

Conclusion: The results suggest that racial differences exist in the epidemiology of male osteoporosis and these need to be assessed further. In this cohort osteoporosis was seen in a higher % of AA males as compared to white males and at a younger age but no racial differences were found in the prevalence of known risk factors. Also found was that Low BMI, smoking and overall medication use may be better associated with low BMD and potentially better predictors than older age and secondary medical disorders. Limitations of this study include its retrospective design and small sample size. Nonetheless these results highlight that the racial differences in prevalence and effect of underlying factors needs to be better quantified in population studies, so that males at risk of OP may be better identified and screened earlier. This may have significant implications on decision to consider screening for OP in males.

Disclosure: K. Aujla, None; **V. Majithia**, None.

1245

The Differential Effect Of Smoking On Bone Mineral Density At The Lumbar Spine and Neck Of Femur In Each Gender: An Observational Study. William Hedges[1], Alexander Oldroyd[2] and Marwan Bukhari[3]. [1]Royal Lancaster Infirmary, University Hospitals of Morecambe Bay NHS Foundation Trust, Lancaster, United Kingdom, [2]Lancaster University, Lancaster, United Kingdom, [3]Royal Lancaster Infirmary, Lancaster, United Kingdom.

Background/Purpose: Current smoking is a known risk factor for loss of bone mineral density (BMD), and is part of the FRAX ™ 10-year fracture risk stratification tool developed by the World Health Organisation (1).

Reduction in BMD due to smoking seems to be more in men than women, but far less data exists looking at the effects of smoking on BMD in males. The site of maximal bone loss has not been clearly identified, varying between the hip and lumbar spine in different studies in a recent review of three meta-analyses (2). There could also be a potentially confounder in abdominal aortic calcification due to atherosclerosis falsely increasing the lumbar spine BMD (3). This study aimed to establish the anatomical area of maximal BMD reduction due to smoking and to examine the differential impact in each gender.

Methods: Data was analysed from male and female patients having dual-energy X-ray absorptiometry (DEXA) assessment between 2004 and 2011. Patients were categorised as never-smoked, current smokers, and previous smokers. Student's t-test was performed to identify whether differences existed between smokers and non-smokers by gender. Logistic models, adjusting for age and body mass index (BMI) were then fitted examining the odds of a low bone density in both sites by gender. Finally the odds of being diagnosed as having osteoporosis (OP) (T score <-.25 at either spine or hip) was ascertained using logistic regression.

Results: 25,904 patients were included in the study, of which 3,136 were ex-smokers and 2,224 were current smokers. This included 3901 males (15%). Mean age at scan in the whole cohort was 62.6 years (SD12.6). Current smokers were more likely to be male 398/1826 vs 3503/20169 (17.9% vs 14.8% P <0.001). Using Student's t-test, the BMD in women was not significantly different in the lumber spine (1.06g/cm2 vs 1.05 g/cm2 p=NS) but was significantly reduced in the hip (0.84 vs 0.85 P =0.004). In men, despite the lower numbers both spine and hip BMD were significantly lower (1.08 vs 1.13 p <0.001 and 0.88 vs 0.90 p=0.02). In females, after adjustment for age at scan and BMI the odds of a low BMD in the lumbar spine were higher than the odds in the femoral neck when adjusted for age and BMI (0.54 95%CI 0.41, 0.73 vs 0.38 95%CI 0.24, 0.60 respectively) indicating more loss in the femoral neck. In men the effect was also greater in the femoral neck (OR 0.45 95%CI 0.25, 0.81 in the lumbar spine vs 0.25 95%CI 0.10 0.66 in the femoral neck). The odds of OP in female smokers was 2.13 (95%CI 1.93,2.35) and in male smokers it was 3.17 (95%CI 2.56,3.92).

Conclusion: Smoking causes significant BMD loss at both the spine and the hip but the effect appears to be more pronounced in male smokers. Abdominal aortic calcification appears to have a minor impact on assessing BMD in the lumbar spine.

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Efficacy Of a 6-Month Treatment With Strontium Ranelate 2g/Day In The Improvement Of Long Bone Fractures With Delayed-Union Or Non-Union. Jean-Marc Feron[1], Vaclav Vyskocil[2], Carlina Albanese[3], Luis Augusto Tavares Russo[4] and Jean-Denis Laredo[5]. [1]Hôpital Saint Antoine, GHU Est, AP-HP, Paris, France, [2]3. interní klinika, Všeobecná fakultní nemocnice, U Nemocnice 1, Praha2, Czech Republic, [3]Università degli studi, ROMA, Italy, [4]CCBR Brasil, Rua Mena Barreto, 33 Botofogo, 22271, Rio de Janeiro, Brazil, [5]Hopital Lariboisière, 2, rue Ambroise Paré, 75475, Paris, France.

Background/Purpose: To assess the efficacy of strontium ranelate 2g/day in the improvement of healing of peripheral fractures with delayed union or aseptic non-union.

Methods: International, phase III, open label study with a treatment duration of 6 months. Primary endpoint was the radiological status of the fracture (progress to union, union, failure to union) at 6 months (central X-ray reading), among assessable patients according to intent-to-treat principle. Other efficacy criteria included pain assessment using a Visual Analog Scale (VAS), Lower limb questionnaire, QuickDASH questionnaire (upper limb and clavicle) and quality of life (EQ-5D questionnaire).

Results: 48 patients were included (28 men and 20 women) and 44 completed the study. 4 patients withdrew the study, 3 due to non-medical reasons and 1 due to protocol deviation. Mean age at inclusion was 49.4±18.5 years. 53.7% were osteoporotic. The qualifying fracture was localised for 34 patients in the lower limb, and for 14 patients in the upper limb/clavicle. The status of the fracture at baseline was non-union* in 60.4% and delayed

union** in 39.6%. The mean duration of the qualifying fracture was 22.8+27.5 months.

40 patients were included in the intend-to-treat (ITT) population. In this population, 72.5% of the fractures had improved, with 32.5% of progress to union and 40% of union over 6 months. 18 of the 26 fractures reported as non-union fractures at baseline and 11 of the 14 fractures assessed as delayed union fractures at baseline improved to union or progress to union over 6 months.

48.7% of the patients reported a decrease of more than 50% of their pain, with a mean change in the VAS from baseline (36.9 ± 24.7 mm) to last post-baseline value over M0-M6 of −18.6 ± 3.6 mm ($p \leq 0.0001$).

There was also a positive trend in the changes in the algo-functional behaviour of the affected limb and in the patient's global quality of life as assessed with the EQ-5D questionnaire. No unexpected adverse events were reported.

Conclusion: This open label study suggests that a 6-month treatment with strontium ranelate (2g/day) improves healing of aseptic delayed or non-united fractures of the limbs or of the clavicle.

*Non-union defined as non-union for at least 6 months and no sign of radiological healing or bone reaction since at least 3 months.

**Delayed union defined as an absence of radiological full union after 6 months according to investigator's opinion.

Disclosure: J. M. Feron, Servier, 5; **V. Vyskocil**, Servier, 5; **C. Albanese**, Servier, 5; **L. A. T. Russo**, Servier, 5; **J. D. Laredo**, Servier, 5.

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Association Between Bisphosphonate Switching Behavior and Cost Outcomes In Postmenopausal United States Veterans. Joanne Lafleur[1], Scott L. DuVall[2], Jeffrey R. Curtis[3], Robert A Adler[4], Tina Willson[5], Irene Agodoa[6], Bradley Stolshek[7] and Richard E. Nelson[8]. [1]University of Utah College of Pharmacy, Salt Lake City, UT, [2]VA Salt Lake City Health Care System and University of Utah School of Medicine, Salt Lake City, UT, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Hunter Holmes McGuire VA Medical Center, Richmond, VA, [5]University of Utah, Salt Lake City, UT, [6]Amgen Inc, Thousand Oaks, CA, [7]Amgen, Inc., Thousand Oaks, CA, [8]Salt Lake City VA and University of Utah, Salt Lake City, UT.

Background/Purpose: Many bisphosphonate-treated patients discontinue therapy within the first year. Some later restart the same or a different bisphosphonate. The implications of this on total healthcare costs are unclear. In a national cohort of postmenopausal veterans, we examined the relationship between bisphosphonate switch behaviors and total healthcare costs, defined as a sum of inpatient, outpatient, and pharmacy costs from the Department of Veterans Affairs (VA) Decision Support System dataset.

Methods: We identified bisphosphonate-treated female veterans ages ≥50 in the VA healthcare system in 2003-11 who lacked an alternative indication for bisphosphonate treatment. We classified patients as "high risk" if they had a prior fracture at the hip, wrist, spine, or proximal humerus; a baseline femoral neck bone mineral density (BMD) T-score ≤-2.5; or age ≥75 and lumbar spine, total hip, or 1/3 radius BMD T-score ≤-2.5. We used generalized estimating equation regression models with a gamma distribution to estimate the percentage difference in quarterly cost associated with bisphosphonate switch behaviors, classified quarterly as non-switching, switching, discontinuing (defined as a 90-day gap from the end of the prior supply), or restarting the initial bisphosphonate after a prior discontinuation or switch. Models were stratified on risk level and adjusted for demographic characteristics, comorbid conditions, other drug exposures in the prior year, and costs in the prior year; separate models were run for high- and non-high-risk patients to assess any differences due to disease severity.

Results: 36,280 patients met all eligibility criteria, including 5,567 high-risk and 30,713 non-high-risk patients. The mean (SD) age of the cohort was 65.7 (12.5). Race was known in 87.1%; of those 85.7% were Caucasian and 10.2% were Black. Over an average follow-up time of 4.3 years, 6.9% switched, 83.8% discontinued, and 38.3% reinitiated at least once. Compared to patients who continued with their initial bisphosphonate (N=5,691), patients with change behaviors had significantly higher total healthcare costs: switchers, discontinuers, and reinitiators had 15.1%, 5.0%, and 17.2% higher costs, respectively (all p values <0.001). Findings were similar in the high- and non-high-risk strata.

Conclusion: VA patients who switched or discontinued had significantly higher quarterly total healthcare costs compared to those who continued on their initial treatment, even if they later reinitiated their original bisphosphonate. While it is not certain if higher costs are directly attributable to the switch behavior, efforts to reduce bisphosphonate change behaviors may decrease healthcare costs in this population.

Disclosure: J. Lafleur, Amgen, Genentech, Merck, 2; **S. L. DuVall**, Anolinx LLC, 2, Genentech, 2, Fa Hoffmann-La Roche Ltd, 2, Amgen, 2, Shire PLC, 2, Mylan Specialty LP, 2, Merck and Co., Inc., 2; **J. R. Curtis**, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **R. A. Adler**, Merck, Eli Lilly, Genentech, Amgen, 2, Amgen, 5; **T. Willson**, None; **I. Agodoa**, Amgen, 3, Amgen, 1; **B. Stolshek**, Amgen, 1, Amgen, 3; **R. E. Nelson**, None.

1248

Prevalence Of Vitamin D Inadequacy In European Postmenopausal Women Aged Over 80 Years. Olivier Bruyere[1], Justine Slomian[1], Charlotte Beaudart[1], Fanny Buckinx[1], Etienne Cavalier[2], Sophie Gillain[2], Jean Petermans[2] and Jean-Yves Reginster[1]. [1]University of Liège, Liège, Belgium, [2]CHU de Liege, Liege, Belgium.

Background/Purpose: Inadequate vitamin D level is associated with secondary hyperparathyroidism and increased bone turnover and bone loss, which in turn increases fracture risk. The objective of this study is to assess the prevalence of inadequate serum vitamin D levels in postmenopausal European women aged over 80 years. There are no clear international agreements on what constitutes a level of vitamin D inadequacy, but recent publications suggest that the circulating level of vitamin D should be over 75 nmol/L or at least between 50 and 75 nmol/L.

Methods: Assessment of 25-hydroxyvitamin D [25(OH)D] was performed in 8532 European postmenopausal women with osteoporosis or osteopenia of which 1984 were aged over 80 years. European countries included France, Belgium, Denmark, Italy, Poland, Hungary, United Kingdom, Spain and Germany. Two cut-offs of 25(OH)D inadequacy were fixed: < 75 nmol/L and < 50 nmol/L.

Results: Mean (SD) age of the patients was 83.4 (2.9) years, body mass index was 25.0 (4.0) kg/m^2. Level of 25(OH)D was 53.3 (26.7) nmol/L. There was a highly significant difference of 25(OH)D level across European countries ($p < 0.0001$) with the lowest level of 25(OH)D found in France [47.7 (26.4) nmol/L]. In these women aged over 80 years, the prevalence of 25(OH)D inadequacy was 88.6% and 53.4% when considering cut-offs of 75 and 50 nmol/L, respectively. In the 397 (20.0%) patients taking supplemental vitamin D with or without supplemental calcium, the mean serum 25-OH-D level was significantly higher than in the other patients (65.2 (29.2) nmol/L vs. 50.3 (25.2) nmol/L; $P < 0.001$).

Conclusion: This study indicates a high prevalence of vitamin D [25(OH)D] inadequacy in old European women. The prevalence could be even higher in some particular countries. A greater awareness of the importance of vitamin D inadequacy is needed to address this public health problem.

Disclosure: O. Bruyere, None; **J. Slomian**, None; **C. Beaudart**, None; **F. Buckinx**, None; **E. Cavalier**, None; **S. Gillain**, None; **J. Petermans**, None; **J. Y. Reginster**, None.

ACR/ARHP Poster Session B
Pain - Basic Mechanisms
Monday, October 28, 2013, 8:30 AM–4:00 PM

1249

Contrasting Pathophysiology and Behavioural Responses Associated With Osteoarthritis and An Inflammatory Arthropathy. Sanaa Zaki[1], Margaret M. Smith[1], Susan Smith[1], Mark Connor[2] and Christopher B. Little[1]. [1]University of Sydney, St Leonards, Australia, [2]Macquarie University, North Ryde, Australia.

Background/Purpose: Osteoarthritis (OA) affects more than 15% of the population, and is the major cause of disability in people over 60. There are no therapies that halt OA progression, and available symptom-modifying treatments have limited efficacy. Knowledge of OA pain-pathways is lacking, because most pre-clinical OA-pain studies use models that do not mimic human OA pathophysiology. To determine whether there are OA-pain-specific molecular mechanisms, we directly compared post-traumatic (pt)OA and inflammatory-arthritis (IA) pain pathways and how these change with time and pathology.

Methods: Forty-two male 10 wk C57BL6 mice had unilateral ptOA or sham surgery, IA or sham-IA induced. At day 0, 3, 7, 14, 28, 56, 84 and 112 mice were tested for mechanical allodynia, hind-limb weight-bearing and stride length. At each time knee joints were histologically scored for synovitis, cartilage erosion, subchondral bone (SCB) vascular invasion and sclerosis. Expression of μ-opioid-receptor (MOR), inflammatory neuropeptides (Tac1, CGRP), neuropathic marker (ATF3), and nociceptors (TRPV1, TRPV2, TRPV4, TRPA1) were quantified in ipsi- and contra-lateral lumbar dorsal-root-ganglia (DRG).

Results: IA had significantly greater synovitis and SCB vascular invasion and this corresponded to greater and persistent decrease in hind limb weight bearing, at day 3, 7, 14 and 28, and early phase (day 3–14) mechanical allodynia. In contrast, ptOA was characterized by greater SCB sclerosis and cartilage erosion at day 3, 7, 14 and 28, and osteophyte formation; with reduced stride length and late phase (day 112) mechanical allodynia, the predominant pain outcomes. Changes in DRG gene expression were similar 1–2 weeks after arthritis induction, with minor temporal differences between ptOA and IA. Increased TRPA1, CGRP and MOR were unique to late stage ptOA.

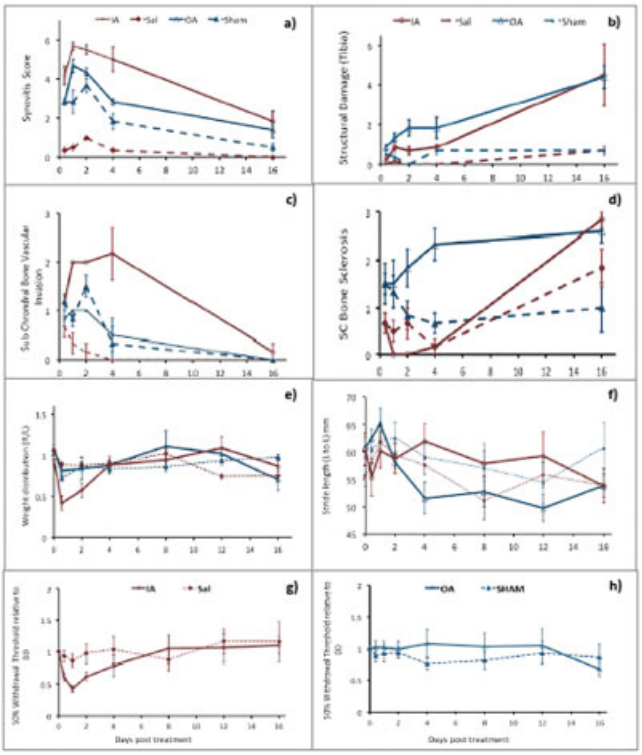


Figure 1. Temporal changes (a) synovitis, (b) Tibial structural damage—AC erosion, (c) SCB vascular invasion, and (d) SCB sclerosis in mice following unilateral ptOA or sham surgery, IA or sham-IA (SaI). Hindlimb weight distribution (R/L) (e); hindlimb stride length (L toL) (f), and mechanical allodynia [ipsilateral (g) & contralateral (h)] as measured at D3, D7, D14, D28, D56, D84 & D112 after arthritis induction. Values expressed are mean +/− S.E.

Conclusion: Our findings suggest there are temporal and model-related differences in the type of pain observed, and its mechanisms. This supports a link between particular tissue pathologies and pain, and suggests OA-specific pain mechanisms that may be therapeutic targets.

Disclosure: S. Zaki, None; **M. M. Smith**, None; **S. Smith**, None; **M. Connor**, None; **C. B. Little**, None.

1250

Serological Markers Of Structural Integrity and Inflammation Is Associated With Pain In Osteoarthritis. Anne Sofie Siebuhr[1], Lars Arendt-Nielsen[2], Thomas Navndrup Eskehave[3], Morten Asser Karsdal[1], Kristian Kjaer Petersen[2], Ole Simonsen[4] and Anne C. Bay-Jensen[1]. [1]Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, [2]Center for Sensory-Motor Interaction, Aalborg, Denmark, [3]Center for Clinical and Basic Research and C4Pain, Aalborg, Denmark, [4]Frederikshavn Hospital, Frederikshavn, Denmark.

Background/Purpose: Pain is associated with diagnosed osteoarthritis (OA), but little clinically association is found between joint integrity and the pain the individual patient experience. Peripheral and central pain mechanisms are suggested to play roles in OA-pain. Patients experiencing pain for longer periods can become sensitized; hence lesser stimulus is need for the patient to feel pain in the affected site and other remote places of the body (spreading sensitization). Biochemical markers mirroring the pathological processes in OA may aid in the linking of pain mechanisms and tissue integrity. This study investigate the link between the mechanistic, experimental pain biomarkers and serological biochemical markers of inflammation (CRPM), connective tissue turnover (C1M) and synovium (C3M) to investigate underlying causes of knee OA-pain.

Methods: A cross-sectional study of 281 participants recruited from Northern Denmark, age 42–80, with varying degrees of symptomatic knee OA (rated on a 0–100 visual analog scale, max pain for the last 24hours). Serological markers were measured in fasting serum samples: high sensitive C-reactive protein (hsCRP) and matrix metalloproteinase-mediated degradation of CRP (CRPM) and type I (C1M; connective tissue) and III collagen (C3M: synovium). Patients were divided into groups depending on sensitization; 1) sensitized, 2) moderate and 3) non-sensitized. Pressure pain thresholds (PPT) and conditioning pain modulation (CPM) were assessed from the knee, arm and leg. One-way analysis of variance with a Bonferroni post-hoc-test was used. Results are shown as mean (SD).

Results: Compared with un-sensitized patients C1M and hsCRP were higher in patients with localized knee sensitization ($p=0.047$ and $p=0.001$, respectively) and C3M and hsCRP were higher in patients with spreading sensitization ($p=0.018$ and $p=0.001$, respectively). CRPM was higher in patients with developed centralized sensitization ($p=0.006$). Interestingly, the percentage of males was higher in the non-sensitized groups and the percentage of female was higher in the sensitized groups.

	C1M	C3M	hsCRP	CRPM
PPT (knee)				
Sensitized *(N=52)*	56 (20)	19 (5.7)	2.9 (2.3)	11 (3.5)
Moderate *(N=190)*	50 (16)	19 (5.5)	2.3 (2.0)	11 (3.1)
Non-sensitized *(N=40)*	47 (14)	18 (4.3)	1.7 (1.4)	9.7 (2.7)
PPT (arm/leg)				
Sensitized *(N = 45)*	56 (18)	21 (5.7)	3.3 (2.6)	11 3.4)
Moderate *(N = 192)*	50 (16)	19 (4.9)	2.2 (1.9)	10 (3.0)
Non-sensitized *(N = 42)*	48 (14)	18 (5.1)	1.6 (1.3)	10 (3.9)
CPM (knee)				
Sensitized *(N=42)*	58 (20)	21 (6.1)	3.3 (3.6)	12 (4.2)
Moderate *(N=191)*	50 (16)	19 (4.7)	2.2 (2.0)	11 (3.0)
Non-sensitized *(N=47)*	49 (19)	19 (5.2)	2.2 (1.9)	10 (3.2)

Table 1: Values are depicted of mean (SD). PPT: Pressure pain threshold. CPM: Conditioning pain modulation. C1M, C2M, C3M and CRPM are in nmol/L and hsCRP is in mg/L. Lines between values represents statistical significance.

Conclusion: Associations between pain sensitization and serological markers of structural integrity (C1M, C3M) and inflammation (hsCRP and CRPM,) were found. These results indicate that pain in OA is highly related to inflammation and structural integrity.

Disclosure: A. S. Siebuhr, Nordic Bioscience, 3; **L. Arendt-Nielsen**, None; **T. N. Eskehave**, None; **M. A. Karsdal**, Nordic Biosciece, 1, Nordic Bioscience Diagnostic, 3; **K. K. Petersen**, None; **O. Simonsen**, None; **A. C. Bay-Jensen**, Nordic Bioscience Diagnostic, 3.

1251

Collagen Antibodies Induce Pain-Like Behavior In Mice Without Signs Of Inflammation. Gustaf Wigerblad, Katalin Sandor, Kutty Selva Nandakumar, Rikard Holmdahl and Camilla Svensson. Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Collagen Antibody Induced Arthritis (CAIA) is a mouse model of rheumatoid arthritis (RA). It is induced by injection of a cocktail of monoclonal antibodies (mAb) against collagen type II (CII) and a LPS boosting of the immune response day 5, which produces inflammation and swelling of the joints. Interestingly, in our studies aimed at characterizing pain-like behavior in the CAIA model we found that the mice displayed clear signs of nociception (pain) prior to injection of LPS and prior to the onset of inflammation. Thus, the purpose of this study was to characterize the pre-RA phase from a pain perspective and to investigate if a low-grade inflammation drives CII antibody-induced nociception.

Methods: Male B10.RIII mice were injected i.v. with either a mix of the four CII mAbs M2139, UL1, CIIC1 and CIIC2 (1 mg each, total 4 mg/mouse) or 4 mg of the respective single CII mAb and monitored for 5 days. Mice

injected with M2139 (0.5–4 mg/mouse) were followed for 21 days. LPS was not injected to any of the mice. Joint inflammation and development of arthritis were examined by visual scoring of the paws (0–60), histological examination of the ankles and assessment of mRNA levels of RA and pain-associated genes in ankle joint extracts using quantitative PCR. Pain-like behavior was assessed by measuring evoked mechanical hypersensitivity using von Frey filaments and ongoing pain by the Comprehensive Lab Animal Monitoring System.

Results: No visual signs of inflammation were observed in any of the mice days 1–4 and day 5, 3 of 14 mice showed arthritis scores <10. Histologically no signs of cell infiltration, bone erosion or cartilage destruction were observed day 5, except for the mice with arthritis scores, which had minor cell infiltration and bone erosion in the ankle joints. In contrast, all mice injected with CII mAbs, but not control mAbs, displayed a significant reduction in mechanical thresholds day 2, which remained low throughout the study and a significant decrease in ambulation, rearing and total movement during the night between day 2–3. Even though the different CII mAbs have different pathogenicity, they induced similar decreases in mechanical thresholds. To further investigate the nociceptive properties of the J1 epitope-specific M2139 CII mAb, the dose-response relationship was investigated over 21 days. Even at doses (0.5 and 1 mg) that did not induce arthritis at any time point, significant mechanical pain hypersensitivity was observed from day 5 to 21. While IL-1b, TNF, COX2, and MMP2/9/13 mRNA levels were significantly increased in joint extracts from mice with CAIA-induced joint inflammation day 15, none of these mRNAs were elevated in the CAIA mice on day 5, compared to controls.

Conclusion: As no correlation between pathogenicity of the different CII mAbs, arthritis scores, histological changes or gene expression of inflammatory factors and nociception was found, our data indicate that pre-RA pain-like behavior induced by CII antibodies are not driven by a low-grade inflammation. Thus, the current work suggests that certain RA-associated antibodies have the capacity to evoke pain through mechanisms that are uncoupled from the inflammatory process.

Disclosure: G. Wigerblad, None; **K. Sandor**, None; **K. S. Nandakumar**, None; **R. Holmdahl**, None; **C. Svensson**, None.

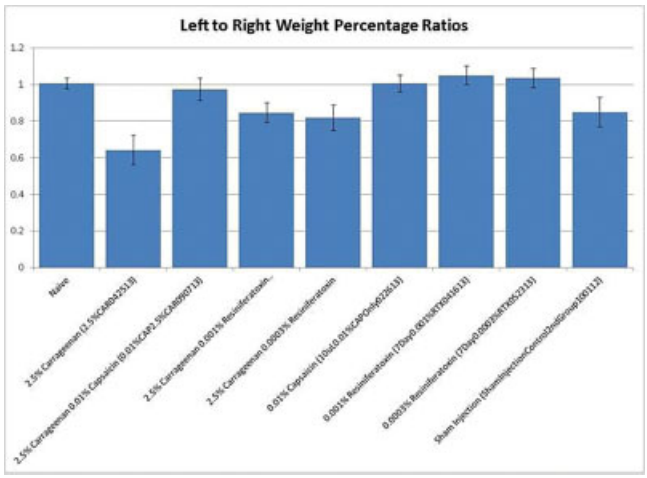
1252

The Effect of Pretreatment With Resiniferatoxin On Dynamic Weight Bearing Measures and Evoked Pain Responses in An Acute Arthritis Murine Model. Mishal Abdullah[1], Christopher W. Dorman[2], Sandra Frizelle[2], Sonia C. Funkenbusch[2], Maren L. Mahowald[3] and Hollis E. Krug[4]. [1]University of Minnesota Medical School, Minneapolis, MN, [2]Minneapolis VA Health Care System, Minneapolis, MN, [3]University of Minnesota Medical School and Minneapolis VA Health Care System, Minneapolis, MN, [4]VA Health Care System, Minneapolis, MN.

Background/Purpose: We have previously shown that activation of vanilloid receptors by intra-articular (IA) Capsaicin (CAP) injection normalizes Evoked Pain Scores (EPS) and Dynamic Weight Bearing (DWB) measures in carrageenan-induced acute inflammatory arthritis. Resiniferatoxin (RTX) is an ultrapotent CAP analogue that has a similar mechanism of action, and may have a greater efficacy on carrageenan-induced arthritis when administered intra-articularly. We hypothesized that mice with acute arthritis would have measurable changes in DWB and EPS due to joint pain, and that these changes could be prevented by pre-treating with IA RTX.

Methods: C57Bl6 mice were used for all experiments. Acute inflammatory arthritis was produced by IA injection of 10μl of 2.5% carrageenan into the left knee 3 hours prior to pain behavior testing. Two groups of mice were injected with different doses of IA RTX (10μl of 0.001% and 10μl of 0.0003%) 7 days prior to induction of arthritis. Similarly, another group of mice was injected with 10μl of 0.01% IA CAP 7 days prior to induction of arthritis. DWB was measured with a Dynamic Weight Bearing apparatus (Bioseb, Vitrolles, France). Evoked pain behavior was measured by tallying fights + vocalizations/1 min with repeated firm palpation of the knee.

Results: Arthritis pain can be clearly and reproducibly indicated by increased EPS and reduced DWB measures in the affected limb of arthritic mice. Naïve mice demonstrated low EPS scores (1.01) and equal left to right DWB ratios for weight (1.01) and time (1.00). Induction of acute arthritis by IA Carrageenan resulted in a significantly increased EPS (6.25) and a significant decrease in left to right DWB ratios for weight (0.64) and time (0.89) when compared with controls. Pretreatment with IA CAP 7 days prior to IA Carrageenan resulted in significant improvement in EPS (3.25) and near normalization of left to right DWB ratios for weight (0.975) and time (1.00). Pretreatment with the high dose and the low dose IA RTX 7 days prior to IA Carrageenan lead to significantly improved EPS (1.5 & 1.5, respectively) and left to right DWB ratios for weight (0.85 & 0.82, respectively) and time (0.99 & 0.96, respectively) when compared with the acute arthritis model. IA administration of CAP alone and RTX alone did not have a significant impact on EPS or DWB ratios after 7 days.



Conclusion: Pain can be quantitated in murine arthritis models using DWB and EPS. IA Carrageenan administration resulted in a significant increase in EPS and a significant decrease in DWB measures in the affected limb. IA RTX pretreatment in these mice clearly improved pain measures as assessed by EPS and DWB measures and these results were comparable to those previously reported for IA CAP. The potential advantages RTX may have over CAP include a possibly lower therapeutic dose and longer duration of effect. These factors represent important directions for future studies.

Disclosure: M. Abdullah, None; **C. W. Dorman**, None; **S. Frizelle**, None; **S. C. Funkenbusch**, None; **M. L. Mahowald**, None; **H. E. Krug**, None.

1253

Studies On The Relationship Between Intraplantar Carrageenan-Induced Bradykin B1 Receptor Messenger Ribonucleic Acid Expression and Oedema and Hyperalgesia In Rats: Effects Of Dexamethasone and a B1 Receptor Antagonist, BI-113823. Guy Kennett[1], Jessica Arlott[1], Phil Butler[2], Mike Comer[1], Andrew Clarkson[2], Alex Coulthard[1], Sean Lightowler[1], Rachel Upcott-Gill[2], Rebecca Upton[1], Louise Wray[2], Philipp Wabnitz[3], Sven Kühnert[3] and Simon Cruwys[3]. [1]Saretius Ltd, Reading, United Kingdom, [2]Cyprotex Ltd, Macclesfield, United Kingdom, [3]Grunenthal GmbH, Aachen, Germany.

Background/Purpose: Kinins are a group of peptides formed in plasma and tissues in response to infection, tissue trauma or inflammation (inflamm) whose actions are mediated by activation of B1 and B2 receptors (B1R and B2R). B1R are normally sparsely expressed, but can be induced by inflammatory stimuli. The current study explored the time dependence of oedema and B1 messenger ribonucleic acid (mRNA) expression in different tissues following intraplantar (ipl) carrageenan (carra) injection as well as the action of dexamethasone (dex). In a separate study, the importance of B1 mRNA induction to carra-induced oedema and hyperalgesia were explored using a novel selective bradykin B1 receptor antagonist, BI-113823.

Methods: Male rats were dosed orally with water (n=110) or dex (1 mg per kg, n=20). 1 h later at T=0, rats were given ipl injections of carra (100 μL × 1% in saline, n=60) or saline (n=70). Of the dex treated rats, half received carra. Paw volumes were measured 0, 1, 2, 4, 8 and 24 h after ipl injections. Corresponding liver, lung and paw pad samples were also collected at each timepoint (10 carra and 10 saline rats per time point) and frozen. All dex treated rats were culled after the 2 h time point.

Tissues and blood were lysed and tissues homogenised on ice. Total RNA was extracted using a MagMAX™-96 Total or Blood RNA isolation procedure and quality (260:280 ratios) and quantity assessed by spectrophotometer. Reverse transcription was performed using a high capacity RNA-to-copy deoxyribonucleic acid (cDNA) kit and 96 well Thermal Quantitative polymerase chain reaction (PCR) analysis was performed on the resultant cDNA, using TaqMan® gene expression assay kit for the target gene B1R and endogenous control (β-actin). Samples were then analysed using a real time PCR machine.

In thermal hyperalgesia and oedema studies, rats were habituated to the test room on day 1. On day 2, basal paw volumes were measured prior to compound administration. At T=-0.75 h vehicle or dex (1 mg/kg po) or B113823 (30 or 100 mg/kg po) were administered. Carra (100 μL × 1%) or saline was then injected into the right paw at T=0. Paw volume was measured at T=0, 3, 4, 6 and 24 h post-carra injection while thermal sensitivity of left and right paws was assessed at T=0, 1 and 3 h using an incident light beam.

Results: Ipl injection of carra elicited paw oedema persisting over 24h. Ipl injection of carra also induced B1R mRNA expression in paw pads which peaked between 2 and 4 hour after ipl injection but remained significant 24h later. Both oedema and B1R mRNA expression were attenuated by pretreatment with dex (1 mg per kg) when assessed 1 and or 2 h post carra. B1R mRNA in lung tissue was not increased by carra, although lowered by dex treatment. No B1R mRNA was found in either liver or blood samples. Dex also reduced thermal hyperalgesia, but BI-113823 had no effect on either oedema or thermal hyperalgesia.

Conclusion: The onset of ipl carra-induced hindpaw pad B1 mRNA induction parallels that of oedema development and both are attenuated by dex. However, the selective B1R antagonist, B113823 had no effect on oedema or thermal hyperalgesia challenging the hypothesis that the B1R might have a key role in the onset and maintenance of carra-induced inflamm and pain.

Disclosure: G. Kennett, Saretius Ltd, 4, Saretius Ltd, 3; **J. Arlott**, Saretius Ltd, 3; **P. Butler**, None; **M. Comer**, SaretiusLtd, 4, Saretius Ld, 3; **A. Clarkson**, None; **A. Coulthard**, Saretius Ltd, 3; **S. Lightowler**, Saretius Ltd, 4, Saretius Ltd, 3; **R. Upcott-Gill**, None; **R. Upton**, Saretius Ltd, 3; **L. Wray**, None; **P. Wabnitz**, None; **S. Kühnert**, None; **S. Cruwys**, None.

ACR/ARHP Poster Session B
Pediatric Rheumatology - Clinical and Therapeutic Aspects II: Pediatric Systemic Lupus Erythematosus, Pediatric Vasculitis and Pediatric Myositis
Monday, October 28, 2013, 8:30 AM–4:00 PM

1254

Prevalence Of Antinuclear Antibodies In Schoolchildren Across Puberty and Possible Relationship With Musculoskeletal Pain. A Longitudinal Study. Francesca Sperotto[1], Sara Brachi[2], Mara Seguso[1], Fabio Vittadello[1] and Francesco Zulian[1]. [1]University of Padua, Padua, Italy, [2]University of Ferrara, Ferrara, Italy.

Background/Purpose: Antinuclear antibodies (ANA) are frequently found in children with connective tissue diseases but can also be found in healthy individuals even in absence of autoimmune conditions, with a prevalence ranging from 13.3% (titer >1:80) to 5.0% (titer >1:160). Puberty is a period of important changes of the immune system, because of sexual and adenohypophyseal hormones modulation which may affect the onset of many autoimmune and connective tissue diseases. To date, a few studies have evaluated the role of ANA in healthy subjects but no one has explored their meaning and frequency across the puberty switch.

Aim of our study was to evaluate prevalence and persistence of ANA in subjects with no evident autoimmune disease followed for 3 years, and their possible relationship with chronic non-inflammatory musculoskeletal pain (MSP).

Methods: Each subject underwent a general and rheumatologic examination focusing on presence of chronic non-inflammatory MSP and including the evaluation of the pubertal stage. Chronic MSP was defined as continuous or recurrent pain lasting more than 3 months and heavily interfering with daily activities, according to the International Association for the Study of Pain. Subjects with past of present sign of any neurological, skeletal, metabolic or autoimmune conditions were excluded. Family history for autoimmune diseases in first degree relatives was also investigated. Finally, each subject underwent laboratory tests to determine the presence of ANA, ENA and anti-dsDNA, following the international guidelines. Subjects with ANA positivity (titer >1:80) and/or MSP have been re-evaluated with the same methods 3 years later.

Results: 261 subjects, aged 8–13 years, entered the study. 32 (12.3%) resulted ANA+, equally distributed as far as gender and pubertal status. None of the ANA+ subjects resulted positive at ENA or anti-dsDNA testing. A positive family history for autoimmune conditions was reported in 6.5% of the subjects.

Three years later, in the group of patients followed for MSP (no. 67) ANA-positivity significantly increased from 13.4% to 44.8% ($p<0.001$) showing a trend to involve more pre-pubertal subjects than the pubertal ones and more females than males. Particularly, ANA positivity involved more pubertal females than pubertal males (50.0% vs 28.0%). In the ANA-positive cohort (no. 28) 92.9% of subjects confirmed the ANA-positivity 3 years later and showed a significant increase of the autoantibody titer (p 0.002). The prevalence of positive family history did not significantly change during the study period. None of the ANA+ subjects resulted positive at ENA or anti-dsDNA testing. Overall, no significant association between ANA-positivity and chronic non-inflammatory MSP was found.

Conclusion: Prevalence and titer of ANA increase across puberty, especially in females, but have no relationship with MSP. This phenomenon could be explained by the complex hormonal changes of the puberty switch period. Further long-term prospective studies are needed to clarify the potential role of ANA as marker of autoimmune-rheumatic conditions, particularly in this period.

Disclosure: F. Sperotto, None; **S. Brachi**, None; **M. Seguso**, None; **F. Vittadello**, None; **F. Zulian**, None.

1255

Ovarian Dysfunction In Adult Childhood-Onset Systemic Lupus Erythematosus Patients: A Possible Role Of Methotrexate? Daniel B. Araujo[1], Lucas Yamakami[2], Eloisa Bonfá[3], Vilma S. T. Viana[3], Sandra G. Pasoto[2], Rosa M. Pereira[3], Paulo C. Serafin[2], Eduardo F. Borba[4] and Clovis A. Silva[5]. [1]Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [3]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [4]Rheumatology Division; University of São Paulo, São Paulo, Brazil, [5]University of São Paulo, São Paulo, Brazil.

Background/Purpose: Reduction of ovarian reserve has been observed in childhood-onset SLE (c-SLE) and adult SLE populations, and most of them were limited to follicle stimulating hormone (FSH) levels and few recent reports included antral follicle count (AFC) and/or anti-Müllerian hormone (AMH) levels. In addition, the contribution of diminished follicle ovarian pool using anti-corpus luteum antibodies (anti-CoL) was not available in pediatric lupus population. There are, however, no data regarding the impact of isolated methotrexate exposure and anti-CoL in ovarian reserve of adult c-SLE patients.

Methods: Fifty-seven adult c-SLE female patients and 21 healthy controls were evaluated for anti-CoL by immunoblot. Complete ovarian function was assessed on the early follicular phase of the menstrual cycle or randomly for those with sustained amenorrhea, blinded to the other parameters of ovarian function. Ovarian reserve was assessed by: FSH, luteinizing hormone (LH), estradiol, AMH and AFC in patients without hormonal contraception for at least 12 consecutive months. Demographic data, menstrual abnormalities, disease activity, damage and treatment were also studied.

Results: The median of current age was similar in adult c-SLE patients and controls (27.7. vs. 27.7 years, $p=0.414$). The median of AMH levels (1.1 vs. 1.5ng/mL, $p=0.037$) and AFC (6 vs. 16, $p<0.001$) were significantly reduced in SLE patients *versus* controls without any significant menstrual abnormalities. Anti-CoL was solely observed in SLE patients (16% vs. 0%, $p=0.103$) and not associated with demographic data, ovarian reserve parameters, disease activity/damage and treatment. Further evaluation of patients treated with cyclophosphamide revealed a higher median of FSH levels compared to SLE patients not treated with cyclophosphamide and with controls (8.8 vs. 5.7 vs. 5.6IU/L, $p=0.032$) and a lower median AMH levels (0.4 vs. 1.5 vs. 1.5ng/mL, $p=0.004$) and AFC (4.0 vs. 6.5 vs. 16IU/L, $p=0.001$). Nineteen patients were treated with methotrexate without cyclophosphamide use, and a negative correlation was observed between cumulative methotrexate dose and AMH levels ($r= -0.507$, $p=0.027$).

Conclusion: The present study demonstrated for the first time that high cumulative methotrexate dose is a possible relevant cause of subclinical ovarian dysfunction in adult c-SLE patients and confirms the deleterious effect of cyclophosphamide. These data reinforce the need of gonadal protection during immunosuppressive treatment and fertility counseling.

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1256

Depression, Anxiety and Suicidal Thoughts In a Cohort Of Pediatric Lupus and Mixed Connective Tissue Disease Patients. Andrea Knight[1], Pamela F. Weiss[2], Knashawn Morales[3] and Ron Keren[1]. [1]Children's Hospital of Philadelphia, Philadelphia, PA, [2]The Children's Hospital of Philadelphia, Philadelphia, PA, [3]University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Emerging data reveals that depression and anxiety disorders are highly prevalent in adult patients with systemic lupus erythematosus (SLE). These disorders are associated with increased healthcare utilization and poor outcomes. The prevalence of depression and anxiety disorders and their effect on children with lupus is unclear. We therefore aimed to characterize depression and anxiety in a cohort of children with SLE and the lupus-like syndrome of mixed connective tissue disease (MCTD).

Methods: The study is a cross-sectional analysis of pediatric-onset SLE and MCTD patients followed by CHOP rheumatology and nephrology. Subjects were consecutively recruited and consented at outpatient clinic visits. The presence of depression and anxiety disorders was measured by Patient Health Questionnaire 9 (PHQ-9) and the Screen for Child Anxiety Related Disorders (SCARED), using iPads and REDCap database technology. Scores of >=5 on the PHQ-9 and >=25 on the SCARED identified depression and anxiety symptoms, respectively, and educational handouts with psychiatric referral were given for subjects with positive screens. In addition, positive screens for suicide risk on the PHQ-9 were administered a suicide prevention protocol. Demographic characteristics as well as mental health history, disease duration, manifestations, medications, and activity were also measured.

Results: Forty-five patients were recruited, of which 38 had SLE and 7 had MCTD. The mean age of the study cohort was 15.6 years (SD 3.1) and 87% were female. The median PHQ-9 score was 4 (IQR 1,12) and depressive symptoms were identified in 9 patients (20%). Suicidal thoughts in the past 2 weeks were identified in 7 patients (16%), however, none required emergent psychiatric intervention. The mean SCARED score was 17.4 (SD 10.9) and anxiety symptoms were identified in 10 patients (22%).

Conclusion: Depression and anxiety symptoms, as well as recent suicidal thoughts were prevalent in the study cohort of children with pediatric lupus and MCTD, at frequencies higher than those reported in the general pediatric and adolescent population. Further investigation is needed to characterize the effects of these symptoms on clinical outcomes, quality of life and healthcare utilization.

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1257

Feasibility and Clinical Implications Of The Pediatric Automated Neuropsychological Assessment Metrics for Screening Of Childhood-Onset Neuropsychiatric Systemic Lupus Erythematosus. Patricia Vega-Fernandez[1], Natasha M. Ruth[2], Deborah M. Levy[3], Frank Zelko[4], Eyal Muscal[5], Marisa S. Klein-Gitelman[4], HaiMei Liu[6], Adam Huber[7], Jiha Lee[8], Jessica Hummel[8], Lori B. Tucker[9], Tresa Roebuck-Spencer[10] and Hermine Brunner[11]. [1]Cincinanti Children's Hospital Medical Center, Cincinnati, OH, [2]Medical University of South Carolina, Charleston, SC, [3]The Hospital for Sick Children, University of Toronto, Toronto, ON, [4]Children's Memorial Hospital, Chicago, IL, [5]Baylor College of Medicine, Houston, TX, [6]Children's Hospital of Fundan University, Shanghai, China, [7]IWK Health Centre, Halifax, NS, [8]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [9]University of British Columbia, Vancouver, BC, [10]University of Oklahoma, Norman, OK, [11]Pediatric Rheumatology Collaborative Study Group (PRCSG), Cincinnati, OH.

Background/Purpose: Neuropsychiatric disease is common in childhood-onset Systemic Lupus Erythematosus (cSLE). Signs of cNPSLE can be subtle and difficult to ascertain in daily clinical practice. Formal neuropsychological testing can be used to assess cognitive ability in SLE but can be expensive, time-consuming, and not always readily available. Automated neurocognitive computerized tests, such as the Pediatric Automated Neuropsychological Assessment Metrics (PedANAM), are convenient, require less training to administer, and cost-effective. PedANAM has shown to have good reproducibility and criterion and concurrent validity in cSLE. The *purpose* of this study is to determine 1) if the PedANAM is feasible for monitoring cognitive status in daily clinical care and 2) its relationship with disease activity indicators.

Methods: 10 subsets of the PedANAM were administered to cSLE patients (pts) recruited from 7 centers. Demographic and clinically relevant information was collected. Mean reaction time for correct responses (MNc, in msec) and accuracy (AC, % of correct responses) were measured for each subtest.

Results: Preliminary analysis of 113 of 200 expected pts was performed (mean age 15 years; White 29%, Black 32%, Asian 20%, Hispanic 14%). Most pts were in high school, 10 repeated a grade, and 19 received special services. Very low AC (<60%) scores were seen in 48 pts on at least one subtest. Only 7 pts showed low AC on 3 or more subtests. Potential reasons for the low AC scores observed were reversed key responses (1 pt) and very fast response time combined with low accuracy. The latter can be explained by either lack of effort or poor understanding of the task. Pts had the greatest difficulty (e.g. low AC) on subtests evaluating delayed and working memory (continuous performance (CPT), code substitution delayed (CDD), and matching to sample (M2S). Hispanic pts had the lowest AC especially on CPT (p=.014), M2S (p=.019), and subtest assessing associative learning (code substitution CDS, p=.019), suggesting greater illness burden. Pts with a history of a greater number of cNPSLE symptoms performed more slowly and less accurately, especially on the spatial processing (SPD) MNc and CPT AC (p's<.05). Pts with active disease measured by the SLEDAI (scores >4) were consistently slower and less accurate on all the subtests with significant differences on CDS, SPD, and simple reaction time (Fig 1). Presence of a SLEDAI-DNA binding was the only SLEDAI parameter significantly associated with PedANAM performance, especially with SPD (p=.041).

Conclusion: The PedANAM appears to be a feasible tool for the assessment of cognitive status in cSLE. Elevated disease activity scores were significantly associated with decreased PedANAM performance. The meaning of atypical low AC scores and cSLE activity needs to be investigated.

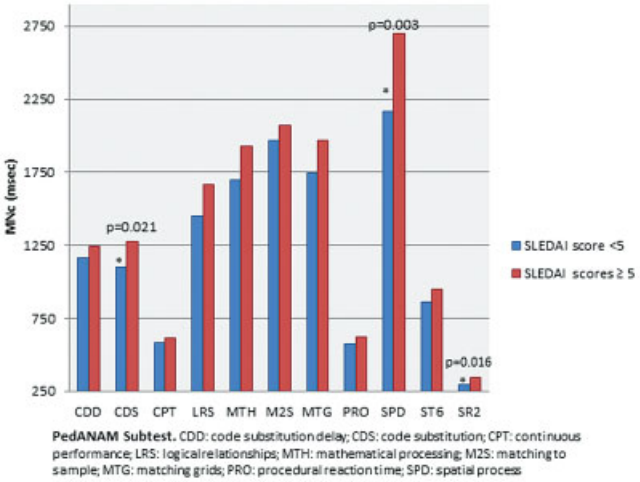

Figure 1. MNc per Subtest vs SLEDAI scores.

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Cognitive Functions In Childhood-Onset Systemic Lupus Erythematosus. Bruna Bellini[1], Cleonice de Souza[1], Mariana Postal[1], Nailu A. Sinicato[1], Paula T Fernandes[1], Roberto Marini[1] and Simone Appenzeller[2]. [1]State University of Campinas, Campinas, Brazil, [2]Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil.

Background/Purpose: To determine differences in cognitive functions in childhood-onset systemic lupus erythematosus (cSLE).

Methods: We performed a cross-sectional study including patients with age of onset of disease ≤ 18 years and controls matched for gender, age and education level. Cognitive evaluation was performed in all participants using Wechsler Intelligence Scale for children (WISC-III) and Wechsler Intelligence Scale for adults (WAIS), according to age. The subjects were divided in two groups: WISC (≤16 years and 9 months) and WAIS (>16 years and 10 months) according to the age at evaluation. Anxiety and depression were assessed by the Beck scales in all subjects. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease

Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current drug exposures. Total dose of corticosteroids and other immunosuppressant medications used since the onset of disease were calculated by data obtained by careful review of the medical charts.

Results: In the WISC group we included 35 cSLE (mean age=13.43 ± 2.10 years, range 8–17 years; mean age of disease onset of 11.23 ± 3.21; mean disease duration=2.80 ± 2.63 years) and 38 controls (mean age=12.32±2.83). In the WAIS group a total of 29 cSLE (mean age=20.34 ± 3.42 years, range 18–29; mean age of disease onset of 13.76 ± 4.08; mean disease duration=6.59 ± 4.72 years) and 35 controls (mean age 21.03±2.86) were included. cSLE patients in the WISC group had lower scores in speed processing (z-score= −0.33±1vs 0.29±1.27; $p<0.05$) and mental flexibility (zscore= −0.12±0.7vs −0.60±0.51; $p<0.05$) when compared to controls. Age at disease onset correlated with cognitive flexibility (r=0,352; p=0,038), anxiety with visuographic memory (r=0.43; p=0,016) and depression with visual perception (τ=-0,261; p=0,044). Lower scores in visual recognition and naming was observed in patients with positive anticardiolipin (p=0.022) and anti-Sm (p=0.046) antibodies. Positive lupus anticoagulant (LA) was associated with lower scores in verbal fluency (p=0.019) and motor dexterity (p=0,046).

cSLE patients in the WAIS group had significant lower scores in semantic memory (z-score −0.22±0,.80 vs 0.46±0.94), speed processing (z-score −0.02±0.78 vs 0,41±0,93) and motor dexterity (z-score=0.40±0,82 vs 0,66±0,91) when compared to controls. Lower scores of visual recognition and naming (p=0.015) and sustained attention (p=0.02) were observed in WAIS cSLE patients with anxiety. Lower temporal reasoning scores were observed in cSLE patients with positive lupus anticoagulant (p=0,013). No association of current and cummulative corticosteroid dose and other medication, disease activity, damage scores and cognitive performance in either group was observed.

Conclusion: According to age, different aspects of cognition are affected in cSLE. Overall, cSLE patients had lower scores in speed processing than controls. Mood disorders, antiphospholipid antibodies, and anti-Sm antibodies influence cognitive function in cSLE patients.

Disclosure: B. Bellini, FAPESP, 2; **C. de Souza**, FAPESP, 9; **M. Postal**, FAPESP, 9; **N. A. Sinicato**, FAPESP, 9; **P. T. Fernandes**, None; **R. Marini**, None; **S. Appenzeller**, FAPESP and CNPq, 2.

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Cognitive Dysfunction In Childhood Systemic Lupus Erythematosus: Comparison Of Different Classification Criteria. Bruna Bellini[1], Cleonice de Souza[1], Mariana Postal[1], Nailu A. Sinicato[1], Roberto Marini[1], Paula T Fernandes[1] and Simone Appenzeller[2]. [1]State University of Campinas, Campinas, Brazil, [2]Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil.

Background/Purpose: Cognitive deficits are frequently observed in systemic lupus erythematosus (SLE), in both adult and childhood (cSLE) onset. However there are several different cutoff levels to define cognitive impairment in cSLE. Objective: To determine the frequency of cognitive impairment in cSLE according to different classification criteria and to identify the relationship with clinical, immunological and treatment features of the disease.

Methods: We performed a cross-sectional study including patients with age of disease onset ≤ 18 years and controls matched for gender, age and education. We performed a battery of tests, selected from the American College of Rheumatology battery. Fifteen subtests were used to evaluate 13 cognitive functions. Cognitive dysfunction were categorized by 3 different classification criteria with different cutoff scores: criteria 1 (dysfunction=score ≤-2 SD below the standardized mean in 1 cognitive function, or scores between −1 and −2 SD below the mean in 2 or more functions); criteria 2 (dysfunction = score ≤-2 SD below the normative mean in 1 or more cognitive functions and cognitive decline = scores between −1.5 and −1.9 SD below published norms in 1 or more functions); criteria 3 (dysfunction = score ≤-1.5 SD below the normative mean). Anxiety and depression were assessed by the Beck scales. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current drug exposures. Total dose of corticosteroids and other immunosuppressant medications used since the onset of disease were calculated by data obtained by careful review of the medical charts. Statistical analysis was performed using SPSS and significance level was 5% ($p<0.05$).

Results: 64 cSLE patients (92.2% women; mean age 16.56±4.43 years; range 8–29) and 71 controls (78.9% women; mean age 16.37±5.21 years; range 8–29) were included. Active disease (SLEDAI ≥3) was identified in 28 (43.8%) cSLE patients. Following criteria 1 definition, 33 (51.6%) cSLE patients and 26 (36.6%) controls had cognitive dysfunction (p=0.08). Following criteria 2 definition 22 (34.4%) cSLE and 14 (19.7%) controls had cognitive dysfunction and 7 (10.9%) cSLE and 2 (2.8%) controls had cognitive decline (p=0.013). Applying criteria 3, 14 (21.9%) cSLE and 13 (18.3%) controls had cognitive dysfunction (p=0.61). There was no relation between cognitive impairment following any criteria and education, age of disease onset, disease duration, cumulative damage, presence of antiphospholipid, ds-DNA, Ro and Sm antibodies, chloroquine, corticosteroids and other immunosuppressive therapy.

Conclusion: Cognitive impairment is frequently observed in cSLE and in healthy age and sex matched controls. However, changes in criteria for defining cognitive dysfunction led to significant changes in frequency rates. Criteria 2 had the best discrimination between cSLE and controls in our cohort. Further studies should determine the ideal cutoff in cSLE.

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Serum S100β Is Associated With Neuropsychiatric Manifestations In Childhood-Onset Systemic Lupus Erythematosus. Aline T. Lapa[1], Mariana Postal[1], Nailu A. Sinicato[1], Bruna Bellini[1], Paula T Fernandes[1], Roberto Marini[1] and Simone Appenzeller[2]. [1]State University of Campinas, Campinas, Brazil, [2]Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil.

Background/Purpose: Involvement of the central nervous system (CNS) in systemic lupus erythematosus (SLE) is an important source of morbidity and mortality. S100β has been considered a potential biomarker that could indicate damage or dysfunction of the CNS in adult SLE patients. However there are no studies in childhood-onset SLE patients (cSLE). Objective: To investigate serum S100β protein levels in cSLE and to elucidate their association with disease activity and NP manifestations.

Methods: We included 72 SLE patients (women=67; mean age 18.21± 4.75; range 9–37) and 53 healthy (women =45; mean age 19.72±6.10; range 6–31) age and sex matched controls. Neuropsychiatric manifestations were analyzed according to the American College of Rheumatology criteria. Cognitive evaluation was performed in all participants using Wechsler Intelligence Scale for children (WISC-III) and Wechsler Intelligence Scale for adults (WAIS), according to age and validated in Portuguese. Scores lower than 2 standard deviations were considered abnormal. Mood disorders were determined through Becks Depression and Anxiety Inventory. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current drug exposures. Total dose of corticosteroids and other immunosuppressant medications used since the onset of disease were calculated by data obtained by careful review of the medical charts. Sera samples were obtained from all participants in the absence of infections at the day of clinical evaluation. S100β protein levels were measured by enzyme-linked immunosorbent assay using commercial kits from BioVendor, Inc (Czech Republic) and compared by non-parametric tests. Multivariate analysis was performed including S100β protein levels, total corticosteroid dose, disease duration, antiphospholipid antibodies, anxiety and depression.

Results: The mean S100β protein levels was significantly higher in cSLE patients [143.98 pg/mL (SD± 99.34)] when compared to controls [56.63 pg/mL (SD±44.07); $p<0.001$)]. NP manifestations were observed in 53 (73.6%) cSLE. S100β protein levels was significantly higher in NPcSLE patients (N=53; mean=161.98; SD=106.8) when compared to non-NPcSLE patients (N=19; mean=95.11; SD=52.1; $p<0.001$). Among individual NP manifestations, serum concentrations of S100β protein were significantly higher in cSLE patients with cognitive impairment (N=28; mean=186.76; SD=1022.61) when compared to cSLE patients without cognitive impairment (N=44; mean=115.37; SD=85.0; $p<0.001$). No difference of S100β levels were observed in cSLE patients with other NP manifestations, disease activity or damage. In the multivariate analysis cognitive impairment was independently associated with serum S100β levels (OR=2.69; 95%CI=1.25–5.78).

Conclusion: Serum S100β levels are significantly increased in cSLE patients with NP involvement, especially cognitive impairment, independently of otherdisease feature. S100β protein may be considered a potential biomarker for cognitive impairment in cSLE.

Disclosure: A. T. Lapa, FAPESP, 9; **M. Postal**, FAPESP, 9; **N. A. Sinicato**, FAPESP, 9; **B. Bellini**, FAPESP, 2; **P. T. Fernandes**, None; **R. Marini**, None; **S. Appenzeller**, FAPESP and CNPq, 2.

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The Usefulness Of Traditional Neurocognitive Testing and N-Methyl-D-Aspartate Receptor Antibodies In Pediatric Lupus Patients. Natasha M. Ruth[1], Mary C. Kral[2], Tamara K. Nowling[3], Stephanie Slan[1], Murray H. Passo[1] and Gary S. Gilkeson[1]. [1]Medical University of South Carolina, Charleston, SC, [2]MUSC, Charleston, SC, [3]Medical University of South Carolina and Ralph H. Johnson VA Medical Center, Charleston, SC.

Background/Purpose: In order to identify lupus patients at risk for CNS disease, and specifically, cognitive dysfunction, the ACR recommended a standard battery of tests for use in individuals with SLE. This led to the use of formal neurocognitive testing as the gold standard when measuring cognitive function in SLE. Almost all studies when measuring neurocognitive function in SLE use a standardized battery of traditional psychometric tests. These tests have been used to assess which areas of cognition are most affected in patients with SLE and also to help assess the validity of other tools that are thought to be useful in measuring cognitive function in SLE. Anti-NMDA receptor antibodies are anti-double stranded DNA antibodies that cross-react with the NMDA receptors NR2a and NR2b. The activation of the NMDA receptor is critical in learning and memory and is expressed on neurons throughout the hippocampus and cortex. To measure the prevalence of anti-NMDA receptor antibodies in pediatric patients with SLE and JIA and to assess the association between elevated anti-NMDA receptor antibodies and neurocognitive dysfunction in these populations.

Methods: Patients diagnosed with SLE prior to age of 18 were recruited. Each underwent formal neurocognitive testing. The test battery included a comprehensive assessment of cognitive domains. The patients also underwent NMDA receptor-NR-2 subunit antibody testing by ELISA.

Results: 21 pediatric lupus and 9 JIA patients were enrolled in the study. Independent samples t-tests comparing group means on the cognitive data revealed statistically significant group differences for full scale IQ ($t=-3.173$, $p<.01$), auditory working memory ($t=-2.180$, $p<.05$), single word reading skills ($t=-3.001$, $p<.01$), math calculation skills ($t=-2.805$, $p<.01$). There were trends toward significance in verbal memory ($t=-1.997$, $p=.056$), inattention [omission errors on the CPT-II] ($t=2.025$, p-.053) and reading fluency ($t=-1.968$, $p=.059$). In all cases above, the JIA group outperformed the cSLE group. There was not a significant group difference for the NMDA receptor antibody levels. There was a significant correlation between the NMDA receptor antibody level and the CPT-II reaction time ($r=.542$, $p<.01$) ie. the higher the antibody value, the slower the reaction time for all participants (including JIA patients and SLE patients).

Conclusion: Patients with SLE appear to have multiple areas of cognition that are affected as determined by traditional neurocognitive testing. NMDA receptor antibodies do not appear to correlate well with the formal testing except in the area of reaction time. Although promising in mouse models, this antibody may not prove to be a good biomarker for assessing cognition in pediatric patients with SLE.

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Comparison Of Remission Rates For Pediatric Membranous Plus Proliferative Lupus Nephritis Versus Isolated Proliferative Lupus Nephritis: An Analysis Of The Childhood Arthritis and Rheumatism Research Alliance Registry. Alexis Boneparth[1], Norman T. Ilowite[1] and The CARRA Registry Investigators[2]. [1]The Children's Hospital at Montefiore, Bronx, NY, [2]Duke Clinical Research Institute, Durham, NC.

Background/Purpose: Lupus nephritis (LN) affects many patients with pediatric systemic lupus erythematosus (pSLE) and is a significant cause of disease morbidity. Inability to achieve remission of LN is associated with worse outcomes. Data from studies of adult patients with combined proliferative plus membranous LN (P/MLN) suggests that this combined subtype may be more refractory to current treatment strategies than isolated proliferative LN (PLN). The possibility that P/MLN may represent a more difficult to treat subtype in the pediatric population has not yet been examined. We aim to assess whether remission occurs less frequently in pediatric P/MLN, compared to pediatric PLN.

Methods: CARRA Registry data was obtained for 320 subjects with pSLE (age at onset <18 years) and LN; LN was diagnosed by renal biopsy and categorized according to ISN/RPS classification criteria. Remission of proteinuria was defined as protein/creatinine ratio < 0.5. Remission of hematuria was defined as < 6 RBC/hpf on urinalysis. These cutoffs were determined by the available clinical data from the CARRA registry. Remission was assessed at the most recent CARRA registry visit gathered ≥ 6 months after diagnostic kidney biopsy. Medication exposure data, non-renal disease characteristics, and demographic data were also assessed. Comparison of these data between subjects with P/MLN and subjects with PLN was conducted.

Results: A total 184 subjects had PLN (class III or class IV) and a total of 38 subjects had M/PLN (class III+V or class IV+V). No significant difference in proportion of subjects with remission in either proteinuria or hematuria was found between groups with and without membranous disease. (See Table). Estimated GFR less than 90 ml/min/1.73m^2, indicating renal insufficiency, was found in 6.1 and 16.1% of subjects with PLN and P/MLN respectively, approaching statistical significance ($p=0.07$). Exposure rates to mycophenolate, cyclophosphamide, and rituximab were similar between groups. Patients in PLN and M/PLN groups were similar with respect to SLEDAI scores at last study visit, age of SLE onset, gender distribution, and ANA positivity. Subjects with class IV+V were significantly older at first renal biopsy compared to subjects with class IV (mean age 14.83 vs. 12.71, $p=0.005$), although this trend was not significant for comparison of subjects with class III vs. class III+V.

Table. Percentage of patients with persistent hematuria/proteinuria

Class	IV	IV + V	p	III	III + V	p	III or IV (no V)	III or IV (+V)	p
N (hem)	93	16		62	12		155	28	
hematuria	16 (17.2%)	1 (6.3%)	0.458	13 (21.0%)	2 (16.7%)	1	29 (18.7%)	3 (10.7%)	0.421
N (prot)	90	16		62	12		152	28	
proteinuria	21 (23.3%)	2 (12.5%)	0.513	14 (22.6%)	4 (33.3%)	0.47	35 (23.0%)	6 (21.4%)	1

hematuria = >5rbc/hpf
proteinuria = (pr/cr >0.5).

Conclusion: CARRA registry subjects with P/MLN and PLN have similar rates of remission for hematuria and proteinuria assessed at the last CARRA registry visit. There was a trend for the P/MLN group to have more renal insufficiency. This study was limited by its cross-sectional, retrospective design, and future longitudinal prospective studies will be useful in further assessing the relationship between renal histology findings and response of pediatric LN to treatment.

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Childhood-Onset Systemic Lupus Erythematosus In Ontario: Long Term Outcomes In a Population-Based Cohort With Universal Health Care Coverage. Deborah M. Levy[1], Nadia Gunraj[2], Janet E. Pope[3], J. Carter Thorne[4], Wesley Fidler[5], Peter B. Dent[6], Johannes Roth[7], Roberta A. Berard[8], Murray Berall[9], Astrid Guttmann[10] and Earl D. Silverman[11]. [1]The Hospital for Sick Children and University of Toronto, Toronto, ON, [2]Institute for Clinical Evaluative Sciences, Toronto, ON, [3]St. Joseph's Health Care, University of Western Ontario, London, ON, [4]Southlake Regional Health Centre, Newmarket, ON, [5]St. Joseph's Hospital, Thunder Bay, ON, [6]McMaster University, Hamilton, ON, [7]University of Ottawa, Ottawa, ON, [8]Children's Hospital of Western Ontario, London, ON, [9]Humber River Regional Hospital, Toronto, ON, [10]Institute for Clinical Evaluative Sciences, The Hospital for Sick Children and University of Toronto, Toronto, ON, [11]The Hospital for Sick Children, University of Toronto, Toronto, ON.

Background/Purpose: Little is known about the long-term morbidity and mortality of childhood-onset SLE (cSLE) after transition to adult care; however, linking clinical data to administrative databases enables study of previously unknown outcomes. Our objectives were to: i) describe differences in cSLE phenotype over time; ii) determine the mortality rate; and iii) describe health care utilization trends.

Methods: A retrospective chart review of all cSLE patients (<18 years at diagnosis) diagnosed between Jan 1, 1984 and Dec 31, 2011 and followed for ≥ 1 year was conducted after contacting all pediatric and adult rheuma-

tologists and nephrologists practicing in Ontario. Clinical data and Ontario Health Insurance Plan (OHIP) numbers were securely transferred to the Institute for Clinical Evaluative Sciences (ICES). OHIP numbers were transformed into an encrypted ICES key number (IKN) used to link the cohort to multiple administrative datasets to determine the outcomes of interest. Patients were stratified by era of diagnosis (1984–1989; 1990–2001; 2002 – 2011) because of available data on income and utilization, and to examine trends as immunosuppressive treatments changed over time. Means ± standard deviations are given unless noted.

Results: IKN linkage was successful for 620 cSLE patients in this inception cohort. The cohort was predominantly female (81%) with follow-up of 10.7 (± 7.3) years, representing 6629 person-years of disease. Age at diagnosis was 12.8 ± 3.2, which was similar across eras. Based on postal codes, patients were evenly distributed among the income quintiles; 18% were in the lowest and 13% in the highest quintile. For the whole cohort, self-reported ethnicity was White 42%, Asian 24%, Black 15%, South Asian 13%, Aboriginal 1.3% and Other 4%; however there is a larger percentage of non-white patients in the most recent era (61%), likely reflecting immigration patterns. See Table for differences in distribution of clinical features over time. There were 23 deaths for a crude mortality rate 3.7%, and standardized mortality rate of 2.8%. Six deaths (26%) occurred in the first year following cSLE diagnosis, and 14 (61%) after transfer to adult care. Physician office visits were frequent within the first year after diagnosis, with 23% requiring ≥ 20 visits, and 46% with 10 – 19 physician visits. Moreover, in the first year 43% of patients had at least one emergency room visit, 38% were hospitalized at least once, and 12% required ≥ 3 hospitalizations.

Table. Clinical Features by Era of Diagnosis (*cell size <6 suppressed)

		Era of Diagnosis			
	cSLE Cohort (N=620)	1984–1989 (N=52)	1990–2001 (N=194)	2002–2011 (N=374)	p-value
Disease Duration (y)	10.7 ± 7.3	25.7 ± 3.4	16.0 ± 3.9	5.8 ± 2.7	
Malar Rash (N, %)	485 (78)	44 (85)	155 (80)	286 (77)	0.32
Discoid Rash		<6*	12 (6)	11 (3)	0.18
Oral/Nasal Ulcers	240 (39)	24 (46)	87 (45)	129 (35)	0.03
Photosensitivity	232 (37)	26 (50)	85 (44)	121 (32)	0.004
Coombs+ Anemia	178 (29)	22 (42)	55 (28)	101 (27)	<0.001
Leukopenia	118 (19)	10 (19)	29 (15)	79 (21)	0.20
Lymphopenia	341 (55)	34 (65)	108 (56)	199 (53)	0.25
Thrombocytopenia	186 (30)	13 (25)	70 (36)	103 (28)	0.08
Arthritis	449 (72)	41 (79)	137 (70)	271 (73)	0.50
Pleuritis	96 (16)	9 (17)	39 (20)	48 (13)	0.07
Pericarditis	85 (14)	17 (33)	37 (19)	31 (8)	<0.001
Nephritis (by biopsy)	273 (44)	36 (69)	107 (55)	130 (35)	<0.001
Psychosis		<6*	13 (7)	41 (11)	0.23
Seizures		<6*	9 (5)	12 (3)	0.27
ANA	608 (98)	51 (98)	191 (99)	366 (98)	0.89
dsDNA	441 (71)	44 (85)	166 (86)	231 (62)	<0.001
ENA (Sm, Ro, La, RNP)	426 (69)	38 (73)	146 (75)	242 (65)	0.03
Antiphospholipid Abs	263 (43)	9 (17)	102 (53)	152 (41)	<0.001
Thromboembolism		<6*	16 (8)	13 (4)	0.04

Conclusion: The prevalences of autoantibodies and certain clinical manifestations such as lupus nephritis are declining in more recently diagnosed cSLE patients. These differences may reflect changes in cSLE over time, earlier diagnosis or a shifting ethnicity distribution in Ontario. For cSLE, the mortality rate is highest in the first year following diagnosis, and overall health care utilization is high.

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Evaluation Of Quality Indicators and Disease Damage In Childhood-Onset Systemic Lupus Erythematosus Patients. Julia G. Harris[1], Kristyn I. Maletta[2], Evelyn M. Kuhn[2] and Judyann C. Olson[3]. [1]Children's Hospital of Wisconsin, Milwaukee, WI, [2]National Outcomes Center, Children's Hospital of Wisconsin, Milwaukee, WI, [3]Medical College of Wisconsin, Milwaukee, WI.

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect virtually every organ system and may lead to significant morbidities. A recent publication identified quality indicators specific to childhood-onset SLE (cSLE) based on scientific evidence and expert opinion. Our study measured compliance with certain quality indicators and assessed organ-specific dysfunction in our cSLE population using a validated damage index, which will help define a baseline for which to optimize management and focus treatment to control the underlying disease and prevent adverse effects of therapy.

Methods: A retrospective chart review was performed on patients diagnosed with SLE prior to age 18 who were followed for at least one year between January 1999 and August 2012. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index was calculated to assess for chronic damage.

Results: Analysis was performed on 75 patients with mean disease duration of 4.55 years. Eighty-four percent of patients were female, 38.7% were black, 14.7% were Hispanic, and mean age of diagnosis was 13.2 years. The proportion of patients for whom care met the proposed quality indicators include: hydroxychloroquine use 94.6%, discussion of cardiovascular risk factors 17.3%, bone mineral density testing 26.7%, Vitamin D recommendation 81.3%, ophthalmologic examination 49.0%, influenza vaccination 70.3%, pneumococcal vaccination 25.3%, and meningococcal vaccination 47.2%. Disease damage was present in 41.3% of patients with average overall damage index score of 0.81. The most common entities leading to a damage score were cataracts, avascular necrosis, and diabetes. There was an association of disease damage at last follow-up with minority race ($p = 0.008$) and with presence of vitamin D recommendation ($p = 0.005$). On the contrary, there was no statistical significance relating disease damage to lupus nephritis, age at diagnosis, body mass index, hydroxychloroquine use, or discussion of cardiovascular risk factors.

Conclusion: Baseline application of proposed quality indicators in our cSLE population is varied ranging from 17.3% to 94.6%. This data is important to standardize care and target certain domains of disease management for improvement such as education and vaccination. The three most common areas of damage in our study may be related to corticosteroid use. This knowledge of organ-specific damage is important to help identify at-risk patients to optimize care and focus quality improvement efforts.

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1265

Initial Benchmarking Of The Quality Of Medical Care Of Children and Adolescents With Lupus. Ahmad I. Zaal[1], Julia G. Harris[2], Clovis A. Silva[3], Marco F. Sliva[3], Jiha Lee[1], Alexandria J. Greenler[1], Simone Appenzeller[4], Maraisa Centeville[4], HaiMei Liu[5], Joshua D. Pendl[1], Jennifer L. Huggins[1], Jessica M. Sage[1] and Hermine Brunner[1]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Children's Hospital of Wisconsin, Milwaukee, WI, [3]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [4]Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil, [5]Children's Hospital of Fundan University, Shanghai, China.

Background/Purpose: Recently, 26 quality indicators (QI) for childhood-onset systemic lupus erythematous (cSLE) have been developed based on international consensus and scientific evidence. QI are defined as minimum standards of medical care in support of optimal disease outcomes. The current level at which these QI are followed has not well documented. Hence, the objective of this study was to assess the current quality of medical care received by patients with cSLE at tertiary pediatric rheumatology centers.

Methods: Cross-sectional data pertaining to the QI were acquired via chart review and analyzed collectively in 229 cSLE patients followed at four tertiary pediatric rheumatology centers – two in United States and two in Brazil.

Results: Adherence to the QI differed by QI domain, ranging from 62 to 100%. The QI domain with the highest adherence was appropriate 'Laboratory testing at the time of diagnosis and with cSLE screening', while the recommended kidney biopsies for newly diagnosed lupus nephritis were not regularly done (Table 1). Education on medication safety and treatment with antimalarials was generally performed. Conversely, educational efforts on cardiovascular risk factors were not consistently recorded in the medical record, despite the perception of the providers that education had occurred. Likewise, transition planning was not systematically done in over 1/3 of the cSLE patients, and 18% of the patients did not have all of the recommended vaccinations. Adherence to the QI was similar across centers, supporting that the set of current QI are suitable for international use.

Table 1. Adherence to QI by Domain

Quality Indicators by Domain	Results
Lab testing at diagnosis & screening	99%
General prevention	
Vaccination against influenza & encapsulated organisms	82%
Education about sun avoidance	76%
Transition plan for adolescents	67%
Lupus nephritis (LN) and hypertension management	
Renal biopsy for newly diagnosed LN	63%
Treat proliferative nephritis with corticosteroids and immunosuppressive agent within 1 month of diagnosis	73%
Obtain kidney biopsy if patient without LN and develops proteinuria (>500 mg/day) or worsening GFR/urinary sediment	95%
Clinical assessment every 3 months if known LN	94%
Prescribe angiotensin-converting enzyme inhibitor or angiotensin receptor blockers if LN and ongoing proteinuria	90%
Consider co-management with nephrologist	63%
Medication management	
Discuss risks versus benefits of new medications	95%
Prescribe antimalarial therapy	93%
Attempt to taper unacceptably high dose of chronic steroids	71%
Laboratory surveillance for medication safety	94%
Bone Health	
Bone mineral density testing if received chronic steroids	71%
Repeat bone mineral density testing if baseline testing outside normal limits (Z score ≤ -2)	80%
Recommend calcium and vitamin D after 3 months of steroid therapy	81%
Ophthalmological surveillance	
Annual eye screening if treated with corticosteroids	74%
Annual eye screening if treated with antimalarial therapy	71%
Education on cardiovascular risk factors	
Education regarding cardiovascular risk factors with parent and patient age 13 years and older	69%
Education on lifestyle modifications	72%

Conclusion: Based on this initial benchmarking effort, the medical care of patient with cSLE at tertiary pediatric rheumatology centers is very good, although there is room for improvement. Systematic planning and documentation of patient education on lifestyle modifications seems warranted and is expected to improve the self-management skills of cSLE patients. Furthermore, increased focus on adequate vaccination of cSLE patients appears to be needed.

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1266 WITHDRAWN

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Impact Of Disease Duration On Vascular Surrogates Of Early Atherosclerosis In Childhood-Onset Systemic Lupus Erythematosus. Julie Barsalou, Timothy J. Bradley, Cameron Slorach, Lawrence W.K. Ng, Deborah M. Levy and Earl D. Silverman. The Hospital for Sick Children, University of Toronto, Toronto, ON.

Background/Purpose: Cardiovascular disease is a leading cause of morbidity and mortality in adults with systemic lupus erythematosus. Exposure to atherogenic risk factors in childhood-onset SLE (cSLE) likely leads to accelerated atherosclerosis. The aim of the study was to determine the effect of disease duration on vascular surrogates of early atherosclerosis in cSLE. We hypothesized that longer disease duration would negatively impact vascular measurements.

Methods: A cross-sectional analysis of a prospective longitudinal cSLE cohort was performed. All subjects fulfilled $\geq$ 4/11 American College of Rheumatology classification criteria for SLE. Disease activity (adjusted mean SLEDAI), disease damage (SLICC/ACR DI) and medications were recorded. Homocysteine, fasting lipid and inflammatory profiles were performed. Carotid intima-media thickness (CIMT), flow-mediated dilation (FMD) and pulse wave velocity (PWV) were measured using standardized protocols. Data from the last set of vascular studies were used. Vascular data of cSLE patients were compared to those of 138 healthy controls.

Results: One hundred and forty-nine cSLE patients participated in the study (Table). Mean disease duration at the most recent study visit was 3.5±2.6 years. Seventy-three percent of cSLE subjects had inactive disease with a SLEDAI score $\leq$2. CIMT and FMD were not worse in cSLE patients when compared to controls. PWV was slightly higher in cSLE patients. We observed a negative correlation between disease duration and FMD ($r=-0.18$, $p=0.03$) but not with CIMT or PWV. In multivariable linear regression analysis, longer disease duration was significantly associated with worse FMD ($p=0.02$). Gender, a history of lupus nephritis, inflammatory markers, the adjusted mean SLEDAI and the cumulative glucocorticoid dose did not significantly impact on vascular data.

Table. Characteristics of cSLE patients and controls.

	cSLE (n=149)	Controls (n=138)	p value
Male:female ratio	25:124	69:69	<0.001
Age at vascular test (yrs)	16.3 ± 2.4	14.4 ± 2.3	<0.001
BMI, percentile	66 ± 27	55 ± 29	0.001
SBP, percentile	52 ± 29	45 ± 27	0.04
DBP, percentile	42 ± 25	30 ± 21	<0.001
Disease duration (yrs)	3.5 ± 2.6		
Lupus nephritis, n (%)	54 (36)		
Neuropsychiatric lupus, n (%)	43 (29)		
Adjusted mean SLEDAI	3 ± 2		
SLICC/ACR DI	0		
Ever on glucocorticoid, n (%)	139 (93)		
Cumulative prednisone dose (mg/kg)	303 ± 260		
Cholesterol-total (mmol/L)	4.03 ± 1.00		
LDL-cholesterol (mmol/L)	2.13 ± 0.78		
HDL-cholesterol (mmol/L)	1.39 ± 0.41		
Triglyceride (mmol/L)	1.11 ± 0.56		
Vascular measurements*:			
CIMT (mm)	0.410 ± 0.056	0.437 ± 0.047	<0.001
FMD (% change)	9.1 ± 4.2	7.5 ± 3.1	0.003
PWV (m/s)	5.3 ± 0.9	5.1 ± 0.9	0.04

Numbers are presented as mean±SD unless otherwise specified.
*CIMT (n=148), FMD (n=142), PWV (n=146)

Conclusion: In this large single-center cSLE cohort, longer disease duration was associated with worse FMD, suggesting progressive endothelial dysfunction over time. CIMT and PWV were independent of disease duration.

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Long-Term Follow-Up Of a Pediatric Lupus Cohort: Transition Of Care and Health Related Outcomes. Susanna Felsenstein, Anusha Ramanathan, Beatriz Gonzalez and Andreas Reiff. Children's Hospital Los Angeles, Los Angeles, CA.

Background/Purpose: Transition from pediatric to adult care is a difficult process with the potential for negative impact on medical, psychological and social outcomes. In this study we assessed the social and health related outcomes of a cohort of pSLE patients transitioned to adult care.

Methods: We conducted a cross-sectional observational survey based on a telephone questionnaire of young adults with pSLE diagnosed and treated at Children's Hospital Los Angeles between 1992 and 2007. All patients met ACR criteria for SLE at diagnosis and had originally participated in a SLE genetic study prior to their transition. Outcome measures were self-reported survey responses related to transition of care, medication knowledge and adherence, employment status and disease related damage.

Results: After an average follow-up period of 5 years since transition (SD 3.7 years) 51 of the original 150 pSLE patients could be contacted of whom 41 consented to participate in the study. 2 were deceased. Median age at the time of interview was 24 years (range 18–34 years), median disease duration was 11.2 years (range 6–21 years), The patients were primarily female (90%) and Hispanic (71%). A significantly lower need for hospitalizations was seen in those patients who had been referred to the adult physician by their pediatric rheumatologist (8/18; 44%), compared to those who had no assistance in the referral process (15/19; 56%), ($p=0.04$). 38/41(93%) reported that they saw a physician regularly, 35/41 (85%) a rheumatologist. 20/41 (49%) had had an appointment with a physician within the last month, 16/41 (39%) within the last 6 months. Three patients (2 with active disease) had no regular interaction with a medical professional at all. 22/41(54%) of patients experienced difficulties with the transition process; 13/41 (31.7%) due to loss of insurance and 10/41 (24%) reported difficulties due to emotional readjustment. Patients reported taking on average 4 medications and 78% reported full compliance. Compliance did not increase with age or extent of end-organ involvement. 16/41 (39%) of patients were unemployed, and 9/16 (56%) of those reported this to be lupus-related ($p=0.01$). At the time of the interview 37/41 (90%) of patients reported symptoms with involvement of 3 or more organ systems in two thirds. Most symptoms were mild and managed as an outpatient and 34/41 (83%) felt their lupus was under good control. 9/24 (37.5%) with renal involvement at disease onset had undergone or were awaiting renal transplant and (36%) reported either new or ongoing neuropsychiatric symptoms which were associated with unemployment (10/15 vs 6/26; $p=0.009$).

Conclusion: The majority of our patients successfully transitioned from pediatric to adult rheumatologic care. However frequent challenges during transition were loss of insurance and emotional attachments to the former pediatric provider. This highlights the importance of a structured transition process by pediatric rheumatologists to their adult colleagues including preparation for the emotional readjustment and guidance for financial and insurance matters. Morbidity remains high in pSLE through adulthood, with renal and CNS manifestations as the leading cause for disease related unemployment.

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The Development Of a Mobile Application For Adolescents and Young Adults With Lupus. Natasha M. Ruth[1], Deborah M. Levy[2], Andrea Regina[3], Christy Taberner[4], Edith M. Williams[5] and Miriam Kaufman[3]. [1]Medical University of South Carolina, Charleston, SC, [2]The Hospital for Sick Children, University of Toronto, Toronto, ON, [3]The Hospital for Sick Children, Toronto, ON, [4]Mohawk College, Toronto, ON, [5]University of South Carolina, Columbia, SC.

Background/Purpose: Young adults with lupus need reliable disease-specific knowledge that includes information about lupus, the effect of lupus and lupus medication on their lives, and education about how their life choices affect their health. In order to attain autonomy and adequately manage their condition, young adults with lupus must learn effective self-management and communications skills, and build a strong, supportive social network to assist their efforts. The emergence of smartphones, devices that merge the functionalities of traditional mobile phones with computer capabilities, has created new opportunities for innovation by increasing point of care delivery of healthcare interventions. The purpose of this study was to develop a lupus application for smartphones to improve the quality of life (QOL) and ease the difficult transition to adult care for adolescents and young adults with lupus.

Methods: A team of researchers came together in Toronto, Canada in December of 2012 for a consensus conference that resulted in the development of *The Lup*. The team included two pediatric rheumatologists, one from the Medical University of South Carolina, United States and one from SickKids, Toronto, Canada. These two medical centers were chosen based on the diverse ethnic background in these regions. Information technology experts consisting of two software development students and a full-time project leader through a partnership with iDeaWORKS (Mohawk College), adolescent medicine specialists, and adolescents and young adults with lupus were also included in the consensus conference.

Results: The weekend resulted in a dynamic plan for the conceptualization, development, and implementation of *The Lup*. The app is designed to run on the iOS (Apple) operating system for iPhone, iPod Touch, and iPad with plans to eventually include Android and Windows platforms in order to reach patients that prefer these platforms. *The Lup* was conceptualized as a patient-centered tool to better understand and manage lupus. The app is equipped with tools to record demographic data and personal health information (if desired), provide medications reminders, facilitate social networking through the Lupus Foundation of America (LFA) Facebook page and Twitter feed, and provide information about lupus medications. In addition, the app includes a dynamic symptoms report/tracker and mood tracker, and will allow communication of this collected data with the health-care team. The app also includes a lupus support group locator, and multi-media peer-modeling examples using pre-existing LFA YouTube channel videos. Teens (ie users) with lupus have vetted the graphics and appearance of the app, as well as potential functionalities throughout the active development and programming process.

Conclusion: The app will be completed in August 2013. The next steps of this innovative and exciting project will evaluate the feasibility and determine preliminary estimates of effectiveness of the mobile app to improve the QOL among adolescents and young adults with lupus. *The Lup* shows promise as the first mobile app designed specifically for adolescents with lupus.

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Risk Factors For The Development Of Avascular Necrosis In Pediatric Systemic Lupus Erythematosus Patients. Reut Gurion[1], Howard Yang[2], Hong Li[3], Stephanie Frenkian[2], Kathleen A. Haines[2], Jennifer E. Weiss[2], Yukiko Kimura[2], Andrew S. Zeft[4], Angela B. Robinson[1], Suzanne C. Li[2] and for The CARRA Registry Investigators[5]. [1]Rainbow Babies and Children's Hospital/Case Medical Center, Cleveland, OH, [2]Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [3]Case Western Reserve University, Cleveland, OH, [4]The Cleveland Clinic, Cleveland, OH, [5]Duke Clinical Research Institute, Durham, NC.

Background/Purpose: Avascular necrosis (AVN) is a serious morbidity of pediatric systemic lupus erythematosus (pSLE) associated with disability, impaired quality of life, and increased cost of care. Both SLE and corticosteroid (CS) treatment have been associated with AVN but understanding of pathogenesis remains limited, and few pSLE studies have been conducted.

Methods: We conducted retrospective reviews of two pSLE cohorts, a single center site (HUMC) and from the CARRA Registry. Data from the HUMC cohort (pSLE patients seen at HUMC between 2006–2009) included disease course and manifestations, morbidity, CS treatment details, and laboratory test results at selected times. Data on HUMC pSLE AVN patients was collected from initial clinic visit until diagnosis of AVN, and on HUMC non-AVN patients from initial visit through 2009. The CARRA Registry is a prospective registry of patients with pediatric rheumatic diseases in the US that includes demographic data, disease duration and manifestations, morbidity, and some laboratory studies. Only limited disease treatment data is available from this registry. We analyzed data on the CARRA pSLE patients from 5/2010-5/2013. For the HUMC data, non-parametric two-tailed p values were calculated. For the CARRA data, t-test and Chi-square tests were performed.

Results: There were 62 pSLE subjects in HUMC cohort, of whom 7 (11.3%) had AVN. Sufficient data were available for 38 of the non-AVN subjects to use as case controls. HUMC AVN patients had an older age at onset of SLE and CS treatment, and a higher mean daily CS dose than non-AVN. The median initial and highest daily CS dose were higher for HUMC AVN than non-AVN patients, but these did not achieve statistical significance (Table). There were 849 pSLE subjects in the CARRA Registry, and AVN was reported in 38 (4.5%). Factors associated with AVN are shown in Table.

Table. Univariable analysis for both cohorts

Variable	AVN*	No AVN*	P-value
HUMC Registry	**n = 7**	**n = 38**	
Female	7 [100]	30 [78]	<0.01
Black race	2 [29]	8 [21]	NS
Age at SLE onset, yrs	16.0 (13–16)	12.5 (4–18)	<0.01
Age at onset of CS therapy, yrs	16.0 (13–17)	13.0 (4–18)	<0.01
Time to AVN, or until stopped data collection for non-AVN pSLE, mos	40.8 (8.7–109.6)	55.3 (7.5–131.6)	NS
Longest consecutive CS duration, mos	17.0 (8.7–28.5)	34.0 (0.9–88.3)	NS
Initial CS dose, mg/day	60.0 (20–80)	40.0 (5–150)	NS
Highest daily dose of CS, mg/day	80.0 (60–125)	60.0 (5–250)	NS
Mean daily CS dose, mg/day	32.8 (22.4–47.1)	19.1 (2.8–72.8)	<0.01
Highest daily dose by body weight, mg/kg/day	1.3 (0.84–1.99)	1.1 (0.10–4.23)	NS
Mean daily dose by body weight, mg/kg/day	0.48 (0.35–0.78)	0.37 (0.05–1.08)	0.05
Cumulative total dose, mg	19,373 (7,655–56,687)	18,245 (350–154,160)	NS
Number of methylprednisolone pulses	2 (0–6)	0 (0–19)	NS
CARRA Registry	**n = 38**	**n = 811**	
Age at SLE onset, yrs	13.7 (6.5–18.9)	12.8 (1.9–19.3)	0.02
Disease duration, yrs	3.4 (0.1–9.2)	2.7 (0–14.6)	0.03
Age of enrollment, yrs	18.0 (13.0–21.0)	16.1 (3.0–21.9)	<0.01
Female	33 [86.8]	664 [81.9]	NS
Black race	22 [59.5]	251 [31.6]	<0.01
Income <$50,000/yr	15 [78.9]	274 [52.8]	0.02
Insurance status	34 [89.5]	758 [96.2]	0.04
Venous or arterial thrombotic event	6 [15.8]	45 [5.6]	<0.01
Anti-Smith antibody	26 [76.5]	406 [54.5]	0.01
Anti-phospholipid antibodies	15 [42.9]	358 [49.9]	NS
Cytopenia	15 [41.7]	165 [22.4]	<0.01
BMI percentile for age > 85%, overweight	19 [50]	314 [41]	NS
BMI percentile for age = 95%, obese	10 [26.3]	171 [22.4]	NS
Current use of steroids	29 [80.6]	560 [73.2]	NS

* Median (range), n [%]

Grants: The CARRA Registry is supported by grants from NIAMS, Friends of CARRA, and the Arthritis Foundation. The CARRA Registry is supported by NIH grant RC2AR058934.

Conclusion: AVN is an uncommon but potentially devastating complication. In both cohorts, older age at SLE onset was associated with occurrence of AVN. In the CARRA Registry, longer disease duration, Black race, and presence of Smith antibodies were also associated. In the HUMC cohort, a higher mean daily CS dose was associated with AVN, while total cumulative dose, duration of treatment, and highest dose were not. Prospective studies are needed to better assess these potential risk factors and work towards improving our understanding of AVN pathogenesis.

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Longitudinal Disease Trajectory Of Juvenile Dermatomyositis. Lily Siok Hoon Lim[1], Eleanor Pullenayegum[2], Dafna Gladman[3], Earl D. Silverman[4] and Brian M. Feldman[5]. [1]University of Toronto, Toronto, ON, [2]The Hospital for Sick Children, Toronto, ON, [3]University of Toronto, Toronto Western Hospital, Toronto, ON, [4]The Hospital for Sick Children, University of Toronto, Toronto, ON, [5]Hospital for Sick Children, Toronto, ON.

Background/Purpose: 1) To determine the longitudinal disease activity trajectory of an inception cohort of Juvenile Dermatomyositis (JDM) patients, 2) To identify predictor(s) for longitudinal disease activity trajectory of JDM.

Methods: A single-center, inception cohort of juvenile dermatomyositis (JDM) patients (age of diagnosis <18 years old), recruited within 1 year of their initial presentation was studied. The patients were accrued from January 1991 to December 2010, in a JDM subspecialty clinic. Patients were evaluated at every clinic visit for disease activity with the modified Disease Activity Score (mDAS). Each individual's mDAS trajectory was plotted and compared to the whole cohort using a trellis plot. Baseline disease features– swallowing difficulty, skin ulcer, calcinosis, duration of symptoms before evaluation, age and gender– were evaluated as predictors of the longitudinal trajectory of JDM. Time-varying treatment status was also tested. Longitudinal trajectory modeling was performed with mixed random effects modeling (random slopes).

Results: Ninety-five JDM patients (33 males, 35%) were studied. The median age of onset was 7.8 ($25^{th}-75^{th}$ percentile (P): 4.9– 12.1) years. The median mDAS score at presentation was 7 ($25^{th}-75^{th}$ P: 6–9), the median skin subscale score was 3($25^{th}-75^{th}$ P:2–4), the median musculoskeletal subscale was 4 ($25^{th}-75^{th}$ P: 3–6). The median duration of follow-up was 4.6 ($25^{th}-75^{th}$ P: 2.4– 6.9) years. All patients in the cohort were treated with a standardized protocol comprising prednisone alone (before 2000) or methotrexate (MTX) and prednisone (after 2000). The disease trajectory of mDAS in this inception cohort followed a rapid reduction of activity within the first 2 years with a minor flare in disease activity beyond 2 years. Swallowing difficulty was associated with higher mDAS at diagnosis. Treatment with MTX 3 months before and baseline swallowing difficulty predicted faster improvement in mDAS trajectory.

Conclusion: Disease activity trajectory of JDM showed a general rapid reduction of mDAS followed by a small flare of disease activity beyond 2 years. Although difficulty with swallowing at presentation was associated with higher mDAS at diagnosis, it did not predict a slower rate of response of mDAS to treatment.

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Whole-Body Versus Thigh Magnetic Resonance Imaging In The Assessment Of Juvenile Dermatomyositis. Clara Malattia[1], Annalisa Madeo[2], Marta Dellepiane[1], Diliana Beleva[1], Stefania Viola[3], Alessandro Consolaro[4], Nicolino Ruperto[4] and Alberto Martini[5]. [1]Pediatria 2, Genoa, Italy, [2]Istituto G Gaslini, Pediatria II, Reumatologia, Genova, Italy, [3]Pediatria 2, Genova, Italy, [4]Istituto Giannina Gaslini, Genova, Italy, [5]Istituto Giannina Gaslini, Pediatria II, Reumatologia, Paediatric Rheumatology International Trials Organisation (PRINTO) Coordinating Center, Genoa, Italy, Genoa, Italy.

Background/Purpose: MRI is a promising tool to assess disease activity in juvenile dermatomyositis (JDM). So far all MRI JDM studies focused on the thigh musculature. Whole-body(WB)-MRI screens the entire body with the advantage to evaluate larger areas of muscles and subcutaneous tissue. Aim of the study was to compare WB-MRI and thigh-MRI (T-MRI) in the assessment of disease activity and in predicting treatment efficacy in JDM.

Methods: WB-MRI were obtained from 43 JDM patients and 43 controls. Muscle abnormalities were scored by 2 independent readers in 36 muscular groups while perifascicular and subcutaneous inflammation were assessed on 8 sites (arm, forearm, thigh and lower leg). Two different readers separately scored both thighs for muscles, subcutaneous and perifascicular oedema. WB- and T-MRI scores were compared in terms of reliability, construct validity and predictive value.

Results: WB-MRI revealed myofascial and subcutaneous inflammation of areas other than the thigh in 8 (18.6%) and 10 (23.2%) patients. Concordance between WB- and T-MRI myofascial and subcutaneous scores was moderate (rs=0.59 and rs=0.69 respectively) while the concordance for muscle inflammation was excellent (rs=0.97). Inter-reader agreement was excellent for both T- and WB-MRI scores (ICC:0.96 and 0.98). Both scores showed excellent correlations with Manual Muscle Test (rs=−0.82 for T-MRI; rs=−0.84 for WB-MRI) and Childhood Myositis Assessment Scale (rs=−0.83 for T-MRI;CMAS rs=−0.81 for WB-MRI). WB- and T-MRI muscle scores were significantly higher in JDM active patients when compared with control group (pB<0.0001 for both the scores) and inactive patients (T-MRI pB=0.0022, WB-MRI pB=0.0037). Responsiveness to change was higher for WB-MRI score (SRM=1.65) compared to that of T-MRI score (SRM=1.04). The ability of WB and T-MRI to predict treatment efficacy was tested only in patients with disease duration ' 2 months (N=21) who started treatment with prednisone alone (N=4) or in combination with methotrexate (N=15) or cyclosporine (N=2). Eleven patients (52.4%) met the PRINTO criteria for improvement at 3-months follow-up. WB-MRI muscular score (median value: 61.2) and T-MRI score (7.2) were higher in non-responders compared to responders (34.5; p=0.001 and 5; p=0.01, respectively). WB-MRI muscle score > 57 was predictive of a poor response to treatment, as evaluated by ROC curve analysis (AUC:0,9). Non-responders showed higher WB myofascial MRI score (1.5) compared to responders (0; p=0.04); no significant difference in myofascial T-MRI score and in subcutaneous involvement were found between responders and non-

responders. Seven out of 8 patients (87.5%) with diffuse homogeneous pattern of inflammation at WB-MRI were non responders; *viceversa* 10 out of 13 patients with the typical patchy distribution of muscle inflammation were responders (p=0.02).

Conclusion: WB-MRI provides a complete assessment of total inflammatory burden and was more accurate than T-MRI in identifying myofascial and subcutaneous inflammation and in predicting treatment efficacy.

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Granulomatosis With Polyangiitis In Children Is More Severe Than In Adults. A Long-Term, Single Center, Follow Up Study. Francesco Zulian[1], Grazia Minardo[1], Valeria Carraro[2], Franco Schiavon[2] and Giorgia Martini[1]. [1]University of Padua, Padua, Italy, [2]Rheumatology Clinic, University of Padova, Padova, Italy.

Background/Purpose: Granulomatosis with polyangiitis (GPA) is a rare disease in childhood. Treatment strategies and clinical approach are still mostly derived from adult GPA studies. The present study was aimed to compare onset, disease course, therapeutic approach and clinical outcome of two cohorts of children and adults affected by GPA.

Methods: The study included children and adult patients selected on the basis of complete data set and follow up of at least one year, followed at a pediatric and adult rheumatology center, over a period of 20 years (1993–2012). GPA was diagnosed according to the ACR and EULAR/PRES criteria. Clinical features, instrumental findings, laboratory parameters and therapeutic regimens of both cohorts were analyzed at diagnosis, six months later (T6) and at the last follow-up visit. Disease activity was assessed by the Birmingham Vasculitis Activity Score (BVAS) modified for GPA.

Results: Ten children with mean age at disease onset of 10.3 years (range 3–15) entered the study, 7/10 were female. Mean follow-up time was 8.4 years (range 2.5–18). Of the 23 adults 65.3% were female, mean age at onset 53 years (range 37–71) and mean follow-up 2.2 years (range 1.9–3.5). At disease onset, BVAS, clinical features and laboratory parameters of the two cohorts were not significantly different. BVAS decreased more slowly in children (p 0.002). As for internal organs involvement, renal disease was significantly higher at T6 and persisted over time in children (p 0.003). Similarly, pulmonary involvement remained elevated at T6 in children while rapidly decreased over 50% in adults (p 0.01). At the last F/U visit, eye involvement was present in 44% of children while no adult showed signs of ocular disease (p 0.004). As for the treatment strategies, immunosuppressive drugs were more widely used in children at diagnosis (p 0.06) and biological agents were used at an earlier disease stage than adults. Despite the longer follow up, all children were still on treatment at the last follow-up visit while 17% of adults were off therapy.

Conclusion: Adults and children with GPA had similar disease activity at onset. However, childhood GPA had a more severe-course due to persistent renal, pulmonary and eye involvement. Lower disease activity was obtained with a more aggressive treatment approach although no pediatric patients reached a drug-free remission.

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1274

Maternal Vitamin D, Fetal C-Reactive Protein and Brain Natriuretic Peptide Associate With The Development and Morbidity Of Cardiac Neonatal Lupus. Amit Saxena[1], Peter M. Izmirly[1], Joanne H. Reed[1], Sara Sahl[1], Deborah Friedman[2], Robert M. Clancy[1] and Jill P. Buyon[1]. [1]New York University School of Medicine, New York, NY, [2]New York Medical College, Valhalla, NY.

Background/Purpose: Women with anti-Ro antibodies face the risk of having a child with cardiac Neonatal Lupus (NL), characterized by congenital heart block and/or cardiomyopathy. Biomarkers in maternal and/or fetal blood may provide insight into pathogenesis, treatment, and risk of disease. Vitamin D has anti-fibrotic properties, and in a Swedish cohort, low maternal levels were postulated to contribute to an increase in cardiac NL cases since gestational susceptibility weeks 18–24 occurred more commonly during the winter. C-reactive protein (CRP) is known to be activated by macrophages, which have been shown to infiltrate the AV node in cardiac NL autopsy cases. Brain Natriuretic Peptide (BNP) is a predictor of cardiac disease in adults and associates with both ventricular dysfunction and cumulative damage index in Systemic Lupus Erythematosus. Troponin I is associated with myocardial damage and is elevated in autoimmune myocarditis.

Methods: Maternal and cord blood samples were obtained from the Research Registry for Neonatal Lupus. Samples were analyzed using standard laboratory assays for Vitamin D, CRP, BNP and Troponin I. Levels were then evaluated for associations with cardiac NL development, fetal echocardiographic evidence of endocardial fibroelastosis (EFE), dilated cardiomyopathy (DCM), and hydrops, as well as child's need for a pacemaker, and maternal use of fluorinated steroids (FS) at the time of blood draw.

Results: Maternal samples closest to gestational week 20 were analyzed for Vitamin D in 36 cardiac NL and 35 unaffected pregnancies. Mean vitamin D levels from affected cases were lower than unaffected pregnancies (40.8 ng/mL ± 28 vs. 53.8 ± 36, $p=0.075$). This trend became significant in comparing 9 cases with fetal EFE vs. 58 without (26.1 ng/mL ± 6.4 vs. 52.0 ± 32.3, $p=0.010$). Maternal CRP in 49 cardiac NL and 51 unaffected cases closest to week 20 did not associate with disease. Cord blood was analyzed for CRP and Troponin I in 38 affected and 52 unaffected children, and BNP in 30 affected and 42 unaffected children. Mean cord blood CRP was significantly higher in cardiac NL cases compared to unaffected children (12.9 ± 68.1 mg/L vs. 0.59 ± 1.8, $p<0.001$). In 28 affected and 32 unaffected cases where both cord blood and maternal blood from the time of delivery were available, cardiac NL was associated with higher CRP in cord blood (16.5 mg/L ± 79.3 vs. 0.39 ± 0.70, $p<0.001$), while maternal blood did not have a significant association (47.2 mg/L ± 43.8 vs. 37.2 ± 38.4, $p=0.265$). Mean cord blood BNP was higher in cardiac NL cases compared to unaffected children (237.2 ng/mL ± 412 vs. 127.9 ± 292, $p=0.04$). Troponin I in cord blood did not associate with disease. No blood tests associated with DCM, hydrops, pacemaker or FS use.

Conclusion: Maternal vitamin D levels may play a role in the development of cardiac NL. Perhaps lower values, albeit in the normal range, confer reduced "protection" from fibrosis. Increased cord blood CRP in cardiac NL cases independent of maternal levels suggests an ongoing fetal inflammatory response at the time of birth. This supports close postnatal follow up to identify worsening of disease.

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Prenatal Exposure To Fluorinated Steroids Does Not Affect Long Term Morbidity In Cardiac Neonatal Lupus. Amit Saxena[1], Peter M. Izmirly[1], Sara Sahl[1], Deborah Friedman[2] and Jill P. Buyon[1]. [1]New York University School of Medicine, New York, NY, [2]New York Medical College, Valhalla, NY.

Background/Purpose: Cardiac Neonatal Lupus (NL), characterized by inflammation and fibrosis of the conduction system, endocardium, and myocardium in anti-Ro exposed fetuses, results in significant morbidity and mortality. There is considerable debate regarding the efficacy of maternal fluorinated steroids (FS) in cardiac NL. While permanent reversal of complete block has not been reported, less advanced blocks have regressed and 6 month mortality appears decreased if fetal disease was associated with a more global cardiomyopathy. Long term information regarding the cardiac health of affected children is limited. Accordingly, substantive data on prenatal exposure to FS and outcomes are critical to decision making.

Methods: 161 individuals with cardiac NL or their mothers enrolled in the Research Registry for Neonatal Lupus responded to a questionnaire regarding current treatment with cardiac medications (beta blockers, ACE inhibitors, and/or digoxin) and overall cardiac status. Data were analyzed to determine whether fetal echocardiographic evidence of endocardial fibroelastosis (EFE), dilated cardiomyopathy (DCM) or hydrops, and the use and cumulative dosage (dexamethasone equivalent) of FS during pregnancy associated with long term morbidity.

Results: Cardiac meds were required in 3/14 (21.4%) affected children ages 0–2, 3/25 (12%) ages >2–5, 2/35 (5.7%) ages >5–10, 2/20 (10%) ages >10–15, 4/31 (12.9%) ages >15–20, and 8/36 (22.2%) >20 years. Digoxin was used by 6 individuals, ACE inhibitors by 18, Beta Blockers by 13, and

systemic hypertension was diagnosed in 3. The age ranges 0–2 and >20 years were significantly associated with taking cardiac meds ($p=0.048$). Thirty four (21.1%) had ever been told by a doctor that they had congestive heart failure, and 68 (42.2%) were told of an enlarged heart. Those with a history of an enlarged heart were significantly older at the time of the questionnaire (15.2 ± 9.75 years vs. 10.8 ± 8.03, $p=0.011$). Fetal echo evidence of EFE, DCM, or hydrops vs. 3rd degree block alone was associated with the future requirement for cardiac meds ($p=0.039$). Eighty two (50.9%) were exposed to FS in utero, with cumulative dose ranging from 12 – 693 mg of dexamethasone. Exposure to FS and cumulative dose did not associate with a decreased future need of cardiac meds, development of CHF, or an enlarged heart. The absence of an association between in utero exposure to steroids and overall cardiac well being was observed for both those children with isolated 3rd degree block and those with fetal echo documentation of EFE, DCM, or hydrops.

Conclusion: Medical therapy for cardiac NL is more frequently required shortly after birth, perhaps in order to treat the continuing primary insult which developed in utero. Increased use of cardiac meds in those over 20 and the reporting of an enlarged heart in older individuals suggests the possibility of decreased heart function as children age, perhaps due to worsening disease or the effects of long term pacing. FS exposure in utero did not associate with overall better cardiac outcomes. In those with isolated 3rd degree block, there is no long term benefit to in utero treatment with fluorinated steroids.

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Immunologic Monitoring and Infectious Complications In Pediatric Rheumatology Patients Treated With Rituximab. Alysha Taxter[1], Kathleen E. Sullivan[1] and Jon Burnham[2]. [1]The Children's Hospital of Philadelphia, Philadelphia, PA, [2]The Children's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Rituximab is an anti-CD20 monoclonal antibody increasingly used in immunologic and malignant conditions to deplete B cells. Suppression of humoral immunity after rituximab exposure may last for months or years and may increase the risk of bacterial and viral infections. The aims of this study were to characterize changes in immunoglobulin G (IgG) concentrations after rituximab exposure and determine the relation between low IgG concentrations and serious infections requiring hospitalization in children with rheumatic diseases.

Methods: This retrospective cohort study included patients in the Division of Rheumatology at our institution receiving at least one dose of rituximab therapy from 2002–2012 at our institution. Medication exposure, IgG levels, and infections requiring hospitalizations were recorded.

Results: We identified 101 patients (74% female) who received 174 rituximab courses. The median age was 15.2 years (range: 2.5–19.7 years) at initiation of rituximab therapy. More than one rituximab course was given in 41 patients with a maximum of 8 courses. The most common indications for rituximab were systemic lupus erythematosus and related conditions (n=60), inflammatory myopathies (n=17), and granulomatosis with polyangiitis (n=9). Of the 53 with baseline IgG measurements not receiving concurrent IVIG, IgG decreased by a median of 252 mg/dL ($p<0.001$) over a median of 0.63 years. IgG continued to be lower than baseline by a median of 190 mg/dL ($p<0.001$) at the last documented follow up, which was after a median of 1.5 years. Of the 51 with baseline IgG greater than 600 mg/dL, new-onset hypogammaglobulinemia was noted in five (range 307–560 mg/dL). Two patients had baseline and post-exposure IgG levels less than 600 mg/dL. In the 247.2 person years of follow up, there was a total of 31 hospitalizations for infection in 18 patients (12.5 infections per 100 person-years; 95% CI 8.1 to 16.9). The median time to first infection was 1.1 years (range: 0.1–4.2). Exposure to cyclophosphamide or more than one course of rituximab was not associated with a greater infection risk. However, IgG levels less than 400 mg/dL were associated with greater odds of infection (OR 5.7, 95% CI 1.1–28.8). Two of three patients who died of infectious complications had IgG levels less than 400 mg/dL.

Conclusion: IgG levels decreased after exposure to rituximab, but significantly low IgG levels at follow up were uncommon, particularly if levels were normal at baseline. However, infections requiring hospitalization were common in this study population. Infection rates at our institution were similar to published infection rates in clinical trials. Significant hypogammaglobulinemia was associated with a greater risk of infection and was present in two of the three children who died of infectious complications. Future research is required to define predictors of infection in rituximab recipients and strategies to reduce infection risk are urgently needed.

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A Pilot Study Of Young Adults With Juvenile Dermatomyositis With Decreased Nailfold Capillary End Row Loops: Brachial Artery Reactivity and Oxidized Lipids. Lauren M. Pachman[1], Maureen A. McMahon[2], Tamar Polonsky[3], Gabrielle A. Morgan[1], Maria Amoruso[1] and Chiang-Ching Huang[4]. [1]Ann & Robert H. Lurie Children's Hospital of Chicago Research Center, Chicago, IL, [2]UCLA David Geffen School of Medicine, Los Angeles, CA, [3]University of Chicago Medicine, Chicago, IL, [4]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Our center previously reported increased carotid intima media thickness, and lower high-density lipoprotein (HDL) levels in young or middle-age adults with a history of JDM, who were not taking medication for JDM symptoms compared to normal controls. Whether even younger adults with JDM have evidence of subclinical cardiovascular disease (CVD) is not known.

Objective: To determine whether an inception cohort of young adults with JDM have lower brachial artery reactivity (BAR) or HDL antioxidant function compared to normal controls.

Methods: After obtaining informed consent, we enrolled an inception cohort of 20 white adults, 14 F, mean age at study 21.8± 4.2 years, and mean age at JDM onset 7.6 ± 3.7 years, mean duration of untreated disease (DUD) at diagnosis 5.4 ± 4.8 months, and mean total duration of disease 14.2 ±3.9 years. JDM adults had a mean Total disease activity score (DAS) 1.9 ± 2.5, but were not taking medications for JDM symptoms. They were matched by age, race, sex and BMI with 20 healthy volunteers (mean age 23.8 ± 4.2 years). Both groups were tested for: BAR, nailfold capillary end row loop number (ERL), height and weight. To determine the antioxidant function of HDL, we measured change in fluorescence intensity caused by oxidation of dichlorfluorescein-diacetate by oxidized low density lipoprotein ±HDL. Fluorescence in the absence of HDL was normalized to 1.0. Values greater than 1.0 after the addition of HDL indicated pro-inflammatory HDL (mean HDL function in healthy controls ranges from 0.44 to 0.66).

BAR reflects endothelial function. Normal endothelial cells release nitric oxide in response to sheer stress, causing vasodilation. For BAR measurement individuals presented fasting, and lay supine in a temperature-controlled room for 10 minutes before imaging. Brachial artery diameter was measured with an 8L5 linear array transducer, 1 cm distal to the antecubital fossa. To create sheer stress, a BP cuff was inflated 50 mm Hg above the baseline BP for 4.5 min. Brachial artery diameter was then re-measured 60 seconds after cuff deflation. BAR was defined as [(post-deflation – baseline diameter)/baseline diameter] ×100%.

Results: The ERL numbers were significantly different in the JDM group, 6.35 ± 1.29 vs the controls, 7.4±0.58, p=0.003. The TNF-α −308A allele was increased in the JDM group 40% vs 15% in controls (p=0.15). Of note, the group with JDM were shorter in stature than their controls, for both JDM women, 159.7 ±8.8 cm vs 165.6 ±5.4 cm, p=0.048, and for JDM men, 172.7±3.6cm compared to controls, 181.5 ±4.6cm, p=0.0046. BAR in adults with JDM was 3.35±3.06%, and 5.22±3.07%- in normal controls (p=0.068). After adjusting for height and sex, BAR in adults with JDM was significantly decreased by 2.78 unit when compared with controls (p=0.018). There was no significant association of BAR values with the following: ERL, DUD, or DAS. The oxidized lipids did not differ between the JDM and controls.

Conclusion: The decrease in height in JDM may be a consequence of previous corticosteroid administration. The data show a marginal association of BAR in JDM, p=0.068 and a significant association with decreased BAR, p=0.018 after adjustment for height. Larger studies in young adults with JDM are needed to validate our finding.

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The Arthritis Severity and Joint Damage Locus Cia25/Pia42 Is a New Genetic Regulator of the Invasive Properties of Synovial Fibroblasts. Max Brenner, Teresina Laragione and Percio Gulko. Hosftra North Shore-LIJ School of Medicine, Manhasset, NY.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic and commonly disabling disease with a prevalence of 1% world-wide. Disease remission is rarely achieved with current treatments and little is known about the genes that control disease severity and joint damage. We have identified the arthritis severity and joint damage regulatory quantitative trait locus, *Cia25/Pia42* on rat chromosome 12, in an intercross between MHC-identical arthritis-susceptible DA and arthritis-resistant ACI rats. *Cia25/Pia42* regulates collagen-induced arthritis (CIA) and pristane-induced arthritis (PIA), two established models of RA. *Cia25/Pia42* regulates the synovial expression of IL-6, IL-1β, MMP-3 and other key mediators of arthritis pathogenesis. In this study we aimed at reducing the chromosomal interval containing the gene accounting for *Cia25/Pia42*, and to study its effect in fibroblast-like synoviocytes (FLS).

Methods: We used genotype-guided breeding to generate twelve different DA.ACI(Cia25/Pia42) subcongenic strains. These new strains were studied in the homozygous state in PIA, and their FLS studied in an *in vitro* invasion assay through Matrigel known to correlate with histologic and radiographic damage.

Results: Based on the analyses of the arthritis severity and protection in the twelve new subcongenics we were able to reduce the gene-containing interval from 23Mb to 1.7Mb. The new and reduced interval contains 34 genes. FLS from congenics had an 80% reduction in invasion, compared with DA ($p=0.02$).

Conclusion: We have significantly reduced the *Cia25/Pia42* interval towards positional cloning, and identified evidence suggesting that at least part of its effect is mediated via FLS function and invasion. The discovery of the *Cia25-Pia42* gene has the potential to generate a new target for therapy in arthritis, and a new prognostic biomarker for RA.

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Anti-IL-6 Receptor Antibody Is Effective In Arthritis Regardless Of Obesity In Mouse Model. Miho Suzuki, Hiroto Yoshida and Yoshihiro Matsumoto. Chugai Pharmaceutical Co., Ltd., Gotemba, Japan.

Background/Purpose: Compared with non-obese patients, obese patients with rheumatoid arthritis (RA) reportedly experience worsening of symptoms [Arthritis Care Res (Hoboken). 2013; 65: 78–87] and do not respond as well to TNF inhibitors [Arthritis Rheum. 2011; 63: 359–64, Arthritis Care Res (Hoboken). 2013; 65: 94–100]. However, the efficacy of IL-6 inhibition in the treatment of RA under conditions of obesity has not yet been fully examined. In this study, we investigated the response to IL-6 inhibition in an obese mouse model of collagen-induced arthritis (CIA).

Methods: 1) To prepare a model of obesity, mice were fed a high-fat diet for 5 weeks. The level of mRNA expression of macrophage marker F4/80 in hind limbs of non-collagen-immunized obese and non-obese mice was measured by real-time PCR. CIA was then induced according to a previously described method [Arthritis Rheum. 1998;41:2117–21]. We treated CIA mice with anti-IL-6 receptor antibody (anti-IL-6R) and TNF inhibitor TNFR-Fc. Clinical symptoms of arthritis were evaluated by observation and expressed as an arthritis score on a scale of 0–4 for each limb. The level of cyclooxygenase (COX)-2 mRNA expression as a parameter of inflammation was measured by real-time PCR in hind limbs of mice at the peak of arthritis. 2) The mouse macrophage cell line RAW264.7 and synovial cells from non-obese CIA mice were cultured with IL-6 or TNF-α for 24 h. After culture, to evaluate the inflammatory response, expression level of COX-2 mRNA was determined by real-time PCR.

Results: 1) We confirmed that obesity was induced by the 5-week high-fat diet (relative body weight: 125%). At this time the expression of F4/80 mRNA was higher in obese mice than in non-obese mice. Moreover, arthritis scores were relatively higher (but not significantly) in obese mice than in non-obese mice at the peak of arthritis (Day 33). Anti-IL-6R significantly inhibited the arthritis scores on Day 33 in both obese (87% inhibition) and non-obese mice (62% inhibition). On the other hand, TNFR-Fc significantly inhibited the arthritis scores on Day 33 in non-obese mice (64% inhibition) but not obese mice (54% inhibition). The expression level of COX-2 mRNA correlated well with arthritis score and was higher in obese mice than in non-obese mice on day 33. 2) Expression of COX-2 mRNA was dramatically increased by IL-6 in RAW cells and by TNF-α in synovial cells.

Conclusion: We demonstrated that there is the potential for inflammation to be increased by obesity and that the anti-arthritis effect of TNFR-Fc was reduced in obese mice, as has been shown in clinical reports. We also demonstrated that anti-IL-6R was effective in this mouse model regardless of whether the mice were obese. One reason might be that obesity promotes macrophage infiltration, and IL-6 is prominently involved in the inflammatory response of macrophages in mice. It goes without saying that it is essential for every patient to reduce excess weight not only because of its risk of exacerbating inflammation but also because of its association with risk of developing other diseases such as cardiovascular disease and diabetes. However, anti-IL-6R has the potential to be useful in the treatment of all RA patients, even those who are obese.

Disclosure: M. Suzuki, None; **H. Yoshida**, None; **Y. Matsumoto**, None.

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The Role of Sphingosine-1-Phosphate Receptor 3 Signaling in Murine Collagen-Induced Arthiritis. Hidetake Nagahara[1], Masataka Kohno[1], Ken Murakami[1], Aihiro Yamamoto[1], Takahiro Seno[1], Wataru Fujii[1], Kazuki Fujioka[1], Yuji Kukida[1], Ryo Oda[2], Hiroyoshi Fujiwara[2] and Yutaka Kawahito[1]. [1]Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, [2]Graduate School of Medical Science, Kyoto Prefectural University of Medicine, kyoto, Japan.

Background/Purpose: Sphingolipids represent a major class of lipids that are ubiquitously expressed in eukaryotic cell membranes. Through the interaction with a family of five G-protein-coupled receptors (S1P1–5), sphingosine-1-phosphate (S1P) triggers diverse cellular responses, including cytoskeletal changes, proliferation, and migration. The importance of S1P in inflammation has been extensively demonstrated. Some reports have shown that elevated S1P level and S1P1, 3 expression are detected in RA synovium, and S1P signaling via S1P1 promotes synoviocyte proliferation. It is suggested that S1P is an important inflammatory mediator in the pathogenesis of arthiritis, but the role of S1P3 in the pathogenesis of arthiritis are poorly understood. Thus, we examine the role of S1P3 receptor signaling in the development of collagen-induced arthritis (CIA) in murine.

Methods: Wild-type(WT) and S1P3-deficient($S1P3^{-/-}$) mice backcrossed more than 9 generations to DBA/1J mice were immunized with bovine type II collagen (CII), and the severity of arthritis was assessed over time. The severity was assessed using an established semiquantitative scoring system of 0–4: 0=normal, 1=mild, 2=moderate, 3=severe and 4=most severe. The cumulative score for all four paws of each mouse (the maximum score is 16) was used as the arthritis score to represent overall disease severity and progression in an animal. Mice were sacrificed on the 42nd day and their paws were fixed in 4% buffered formaldehyde. Paraffin sections of paws stained with hematoxylin and eosin (H&E) were systematically scanned in a microscope and histopathological changes were scored based on cell infiltration, cartilage destruction and bone erosion parameters.

Results: $S1P3^{-/-}$ mice showed signiflcantly lower arthritis severity score compared with WT mice ($P < 0.05$). Histopathological evaluation of paws obtained on day 42 showed marked reductions in synovial inflammation, cartilage destruction and bone erosion parameters in $S1P3^{-/-}$mice compared with WT mice ($P < 0.05$).

Conclusion: These results indicate that S1P3 receptor signaling plays an important role in the development of murine collagen-induced arthritis model. This pathway could be a therapeutic target for rheumatoid arthritis, although further investigations are required to elucidate the mechanism via S1P3 receptor signaling.

Disclosure: H. Nagahara, None; **M. Kohno**, None; **K. Murakami**, None; **A. Yamamoto**, None; **T. Seno**, None; **W. Fujii**, None; **K. Fujioka**, None; **Y. Kukida**, None; **R. Oda**, None; **H. Fujiwara**, None; **Y. Kawahito**, None.

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Inadequate Glucocorticoid Secretion in Experimental Arthritis in Rats Is Closely Linked to Impaired Mitochondria and Reduced Lipid Breakdown in the Adrenal Cortex. Christine Wolff[1], Katharina Krinner[1], Josef Schröder[2] and Rainer H. Straub[3]. [1]Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, Department of Internal Medicine I, University Hospital, Regensburg, Germany, [2]Department of Phatology, University Hospital, Regensburg, Germany, [3]Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, University Hospital of Regensburg, Regensburg, Germany.

Background/Purpose: In rheumatoid arthritis a functional deterioration of the HPA-axis in form of inadequately low secretion of glucocorticoids in relation to severity of inflammation can be detected. The reasons for this phenomenon are not known. The purpose of this study was to find possible reasons responsible for adrenal insufficiency during arthritis.

Methods: DA rats were immunized with type II collagen in incomplete Freund adjuvant to induce arthritis. Plasma corticosterone was evaluated by RIA and plasma ACTH by ELISA. Adrenal cholesterol was quantitatively studied by Sudan-III staining and scavenger receptor class BI (SR-BI, the HDL receptor) by immunohistochemistry. Fluorescent NBD-cholesterol uptake kinetics were analysed by flow cytometry. Ultrastructural morphology of adrenocortical mitochondria and lipid droplets was studied by electron microscopy.

Results: Initially increased corticosterone and ACTH levels were reduced to baseline levels in the later phase of the disease. Serum levels of corticosterone relative to IL-1β were markedly lower in arthritic than control animals (inadequacy). Cholesterol storage in adrenocortical cells and expression of SR-BI did not differ between immunized and control rats. However, number of impaired mitochondria largely increased during the course of arthritis (maximum on day 55), and this was paralleled by reduced numbers of activated cholesterol droplets (inhomogenous droplets relevant for generation of glucocorticoids). In addition, number of normal mitochondria positively correlated with serum corticosterone levels.

Conclusion: This first study on adrenal reasons for inadequate glucocorticoid secretion in arthritis demonstrated impaired mitochondria and altered cholesterol breakdown paralleled by low corticosterone levels in relation to ongoing inflammation.

Disclosure: C. Wolff, None; **K. Krinner**, None; **J. Schröder**, None; **R. H. Straub**, None.

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Effect of RC-3095, An Antagonist of Gastrin-Releasin Peptide Receptor, Regulating Synovial Fibroblasts in Experimental Arthritis. Patricia Oliveira[1], Lidiane Filippin[2], Mirian Farinon[2], Vanessa Clarimundo[2], Gilberto Schwartsmann[2] and Ricardo M. Xavier[3]. [1]Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil, [2]Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [3]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil.

Background/Purpose: The gastrin-releasing peptide (GRP) is the mammalian homologue of the bombesin (BN), and its receptor signaling is involved in several functions, including inflammatory response. Both the GRP and its receptor have been found in synovial membrane and fluid of rheumatoid arthritis patients [2]. RC-3095 is an antagonist of the GRP receptor. The objective is evaluate the role of gatrin-releasing peptide and the RC-3095, a specific antagonist of the gastrin-releasing peptide receptor, in synovial fibroblast proliferation and invasion.

Methods: Mouse DBA/1J fibroblast-like synoviocyte (FLS) were isolated from the tarsus of the hind paws of collagen-induced arthritis. FLS immunocitochemistry was performed to evaluate the presence of GRP-receptor (GRPR). FLS (2×10^4/96-wells) viability in 24 h treated with RC-3095 (concentration from 0.05 to 10 mM). FLS proliferation stimulated with Lipopolysaccharide (LPS) (1 and 10 μg/mL) or GRP (0.1, 1 and 10 mM) was performed using the MTT assay in 24 h. The invasion of FLS was assayed in a transwell system using Matrigel-coated inserts from BD (Franklin Lakes, NJ, USA) and treated with GRP (10 mM), RC-3095 (1 mM) and GRP+RC-3095 (GRP 10 mM and after 30 min RC-3095 1 mM) (n= 4 per group). Differences between experimental groups were compared by ANOVA one-way test.

Results: The immunocitochemistry confirmed the presence of GRPR on FLS. RC-3095 concentrations used were not toxic on FLS, maintaining cellular viability. The dose of 1 μM was defined for other experiments because this was the highest dose with lower cell mortality ($p<0.05$). The GRP 10 mM increased the fibroblast proliferation in 18%, while LPS 10 mM increased 15% compared to FLS unstipulated ($p<0.05$). Treatment of highly invasive DBA/1J FLS with RC-3095 (1934 ± 941 cells) significantly decreased the number of cells invading Matrigel over 24 h period in 35.3% ($p=0.003$) compared to GRP (5371 ± 418.1 cells) and non-different to FLS treated with GRP+RC-3095 (3054 ± 794.5 cells).

Conclusion: RC-3095 was able to decrease synovial fibroblasts invasion stimulated by GRP. GRP increased FLS proliferation and invasion and could be involved in the development of experimental arthritis through FLS. These findings suggest that interference with the neuropeptide GRP pathway is a potential new strategy for the treatment of arthritis.

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1283

Power Doppler Ultrasound Phenotyping of Expanding Versus Collapsed Popliteal Lymph Nodes in Murine Inflammatory Arthritis. Echoe M. Bouta[1], Yawen Ju[2], Homaira Rahimi[1], Ronald Wood[2], Lianping Xing[1] and Edward M. Schwarz[1]. [1]University of Rochester, Rochester, NY, [2]University of Rochester Medical Center, Rochester, NY.

Background/Purpose: Rheumatoid arthritis is a chronic inflammatory disease manifested by episodic flares in affected joints that are challenging to predict and treat. Longitudinal contrast enhanced-MRI (CE-MRI) of inflammatory arthritis in tumor necrosis factor-transgenic (TNF-Tg) mice has demonstrated that popliteal lymph nodes (PLN) increase in volume and contrast enhancement during the pre-arthritic "expanding" phase, and then suddenly "collapse" during knee flare. Given the potential of this biomarker of arthritic flare, we aimed to develop a cost-effective means of phenotyping PLN using ultrasound (US) imaging.

Methods: Power Doppler (PD) US was performed on TNF-Tg mice whose PLN were previously phenotyped as expanding or collapsed using CE-MRI. B-mode (Figure 1A) and PD (Figure 1B) 3D scans were used to generate 3D volume estimates (Figure 1C) to calculate the PD volume normalized to the PLN volume, or the normalized power Doppler volume (NPDV). To verify this methodology for vessels near the PLN, a mouse underwent Microfil perfusion and micro-CT to confirm the US structures were blood vessels near the PLN (Figure 1D).

Results: PD-US demonstrates that expanding PLN have a significantly higher NPDV versus collapsed PLN (0.553 ± 0.007 vs. 0.008 ± 0.003 mm^3; $p<0.05$). Moreover, we define the upper (>0.030 mm^3) and lower (<0.016 mm^3) quartile NPDVs in this cohort of mice, which serve as conservative thresholds to phenotype PLN as expanding and collapsed, respectively. To observe agreement between PD-US and CE-MRI, PLN were phenotyped as collapsed by PD-US and then underwent CE-MRI. Of the 12 PLN in the study, there was disagreement in 4 cases. However, these 4 cases presented with marked synovitis in the adjacent knee, a hallmark of arthritic flare, which occurs after PLN collapse. Therefore, we find that PD-US correctly phenotyped all of the PLN in this cohort.

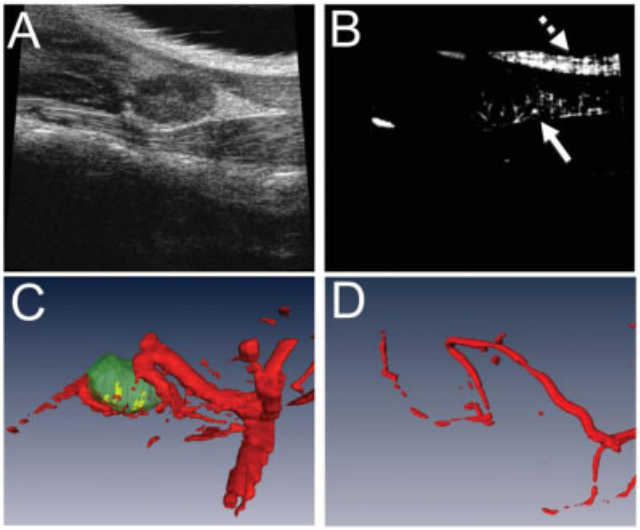

Figure 1. Quantification of NPDV using PD-US and validation with vascular micro-CT. PD-US was performed to generate the 2D images obtained using B mode (A) and PD (B) scans of the PLN. Note the artifact in the PD due to the surface of the skin (dashed arrow in B) versus the true PD signal (solid arrow in B). The PLN (green structure in C) was used to apply a mask to the total blood volume (red structures in C) to give the total PD volume within the PLN (yellow structure in C). To confirm this methodology, the mouse underwent Microfil perfusion and the micro-CT is shown (D). Note the similarities in vessel structure with decreased vessel diameter due to live *in vivo* imaging vs. perfusion.

Conclusion: We find PD-US to be more accurate for phenotyping PLN than CE-MRI. PD-US permits the PLN in the middle quartiles to be subsequently phenotyped with longitudinal scans and studied accordingly. This is a major advantage over CE-MRI phenotyping, which is too costly to utilize for this purpose. PD-US is both a safe and feasible approach and can be used to phenotype PLN as expanding versus collapsed for prospective studies.

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Nuclear Receptor 4A2 Is Differentially Expressed In Animal Models Of RA During Inflammation and Resolution. Jordan Everett[1], Fiona E. McCann[2], Andrew C. Palfreeman[2], Anita T. Shaw[3], Ellen M. Gravallese[4] and Kimberlee S. Mix[1]. [1]Loyola University New Orleans, New Orleans, LA, [2]The Kennedy Institute of Rheumatology, University of Oxford, London, United Kingdom, [3]UMass Memorial Medical Center and University of Massachusetts Medical School, Worcester, MA, [4]UMass Memorial Medical Center, Worcester, MA.

Background/Purpose: Nuclear receptor 4A2 (NR4A2/nuclear receptor related 1/Nurr1) is a constitutively active transcription factor with diverse roles in normal physiology and disease processes. NR4A2 and related receptor NR4A3 are immediate-early genes potently induced by inflammatory cytokines, growth factors, and prostaglandins in inflamed joints, suggesting that these factors may mediate chronic inflammation. NR4A2 regulates transcription of MMPs and pro-inflammatory cytokines in synoviocytes and chondrocytes, and thus may serve as a novel therapeutic target for modulating inflammatory pathways in arthritis. However, the impact of NR4A expression on the onset and progression of arthritis has not been examined. In the current study, we documented receptor expression in three different murine models of rheumatoid arthritis and correlated NR4A levels with joint inflammation and resolution.

Methods: Antigen-induced arthritis (AIA), collagen-induced arthritis (CIA), K/BxN serum transfer arthritis (STA) were studied. NR4A2 protein was detected by immunohistochemistry in knee and ankle joints from the AIA and STA models, respectively. Joint images were processed with CellSens software, and NR4A2 positivity was determined for multiple regions of the synovium and cartilage. NR4A2 and NR4A3 mRNA levels were also quantified by RT-qPCR in inflamed paws from mice with CIA. Clinical scores were recorded over the course of disease, and were correlated with protein and mRNA expression levels of the NR4A receptors.

Results: In the AIA model, NR4A2 protein levels peaked during the inflammatory phase (day 8) and declined to baseline during resolution (day 12), mirroring changes in knee swelling and histological signs of inflammation. Approximately 45% of synoviocytes and 70% of chondrocytes expressed NR4A2 protein at day 8, and receptor expression was identified in both the cytoplasm and nuclei of these cells. However, in the CIA model, NR4A2 mRNA expression remained low throughout the induction and inflammatory phases, but it was induced 2.5-fold during the resolution phase (day 10 post-onset, $p<0.05$,). In contrast, NR4A3 levels peaked during the inflammatory phase of CIA (day 5 post-onset, 2.5-fold, $p<0.05$) and correlated strongly with clinical scores (Pearson's $r = 0.98$). Interestingly, NR4A2 protein was not detected at any stage in the STA model, despite robust inflammation and evidence of joint degradation.

Conclusion: This study provides evidence for the differential regulation of NR4A receptors in response to distinct pathogenic mechanisms in models of RA. NR4A2 expression coincides with inflammation in AIA and resolution in CIA, a dichotomy that may be due to differences in the effector cytokines driving these models. Furthermore, the temporal expression patterns of NR4A3 and NR4A2 suggest that these receptors may have distinct transcriptional roles during disease progression.

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Choline Kinase: A Novel Target For Rheumatoid Arthritis. Monica Guma[1], Elsa Sanchez-Lopez[1], Alessia Lodi[2], Stefano Tiziani[2], Juan Carlos Lacal[3], Michael Karin[1] and Gary S. Firestein[1]. [1]UCSD School of Medicine, La Jolla, CA, [2]University of Texas at Austin, Austin, TX, [3]University Hospital Fundacion Jimenez Diaz, Madrid, Spain.

Background/Purpose: Choline kinase (ChoKa) is an essential enzyme for phosphatidylcholine biosynthesis and is required for cell proliferation. The enzyme has also been implicated in cancer disease progression, metastasis, and invasiveness. The unique tumor-like behavior of rheumatoid arthritis (RA) fibroblast-like synoviocytes (FLS) led us evaluate whether this pathway could play a role in inflammation and joint damage due to synovitis. Therefore, we examined the role of ChoKa in RA FLS and in murine arthritis and performed a targeted metabolomics assessment of this pathway.

Methods: ChoKa expression was evaluated by immunohistochemistry (IHC) and Western blot (WB). The metabolic profile of the choline kinase was determined by ^{1}H-MRS. FLS function using the ChoKa inhibitor MN58b (IC50=~5 nM) in medium and PDGF stimulated cells was evaluated by measuring 1) migration into a cleared area in cultured FLS monolayers; 2) proliferation using an MTT assay; and 3) protein expression by WB. Cell survival was determined in H2O2 treated cells by light microscopy. For arthritis experiments, mice were injected with K/BxN sera on day 0. MN58b (3mg/kg) was injected daily i.p. beginning on day 0 or day 4 after serum administration. Clinical arthritis scores were serially assessed. Joints were evaluated for inflammation and joint damage using histology and a semiquantitative scoring system.

Results: ChoKa mRNA and protein were highly expressed in RA synovial tissue and in cultured FLS. Its expression in FLS was increased 2–3-fold after TNF and PDGF stimulation, respectively with peak expression within 48 hours. Metabolomic studies of choline-containing compounds in cultured FLS extracts showed increased levels of phosphocholine in RA FLS compared to control FLS, confirming activation of this pathway. ChoKa regulated key FLS functions that might contribute to cartilage destruction in RA. For example, ChoKa inhibition with MN58b (5 uM) reduced proliferation by $79\pm3.2\%$ and migration by $54\pm15\%$ ($p<0.05$). ChoKa inhibition also markedly increased H2O2-induced apoptosis in FLS. Akt phosphorylation in response to PDGF as determined by WB was blocked by ChoKa inhibition. Finally, ChoKa inhibition signficantly decreased arthritis in pre-treatment protocols (day 0) as well as in established disease (day 4). For example, day 8 scores were 12 ± 1.6 and 7 ± 2.6 ($P<0.05$) for vehicle and MN58b-treated mice, respectively, when initiated on day 0; and were 6.6 ± 0.9 and 1.6 ± 2.5 ($P<0.05$) for PBS and MN58b-treated mice when initiated on day 4. Joint histology scores for vehicle and MN58b-treated mice for inflammation were 3.2 ± 0.5 and 1.25 ± 1 ($p<0.05$), bone erosion scores were 2.7 ± 0.5 and 0.25 ± 0.5 ($p<0.05$), and cartilage damage scores were 1.5 ± 1 and 1.6 ± 0.5 ($p<0.05$) respectively.

Conclusion: Careful dissection of the metabolic profile in RA FLS indicate that choline metabolism is abnormal and is similar to transformed cells. Blocking this pathway with a selective ChoKa inhibitor suppressed inflammatory arthritis in mice as well as the aggressive behavior of cultured RA FLS, including cell migration and resistance to apoptosis. These data suggest that ChoKA inhibition could be an effective strategy for arthritis.

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Anti-Inflammatory Effects Of Tyrosine-Hydroxylase(TH)-Positive Catecholamine Producing Cells In Chronic Arthritis. Zsuzsa Jenei-Lanzl[1], Silvia Capellino[2], Frieder Kees[3] and Rainer H. Straub[4]. [1]Laboratory of Experimental Rheumatology and Neuroendocrine Immunology, Regensburg, Germany, [2]2Department of Pediatrics, Division of Endocrinology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21287, USA, Baltimore, MD, [3]University of Regensburg, Regensburg, Germany, [4]Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, University Hospital of Regensburg, Regensburg, Germany.

Background/Purpose: In previous studies we have shown that inflammatory processes in experimental arthritis are strongly affected by the sympathetic nervous system (SNS): In the early acute phase SNS acts proinflammatory, whereas in the late chronic phase anti-inflammatory. At the beginning of the chronic phase, the loss of sympathetic nerve fibers in synovial tissue was reported, which is paralleled by appearance of tyrosine-hydroxylase-positive (TH+) catecholamine-producing cells. Recently, TH+ cells of rheumatoid arthritis (RA) and osteoarthritis (OA) patients have been shown to exhibit anti-inflammatory properties in vitro.

In addition, it is known that the microenvironment of inflamed joints is hypoxic and that hypoxia induces tyrosine hydroxylase (TH) *in vivo*. However, further important cofactors and inducers of this catecholamine-producing enzyme have never been studied and the role of TH+ cells in vivo is not yet known.

Methods: Synovial cells of rheumatoid arthritis (RA) and osteoarthritis (OA) patients were isolated and cultivated under normoxia or hypoxia with/without stimulating enzyme cofactors of TH and inhibitors of TH. Expression of TH, TH activity, and release of cytokines and catecholamines was analyzed. The effect of TH+-cells was tested by adoptive transfer into DBA/1 mice with collagen type II - induced arthritis (CIA). TH+-cells were generated from mesenchymal stem cells (MSC) by a defined dopaminergic factors.

Results: Hypoxia increased TH protein expression, TH enzyme activity, catecholamine synthesis, and decreased release of TNF in OA/RA synovial cells compared to normoxic conditions. This inhibitory effect on TNF was reversed by TH inhibition with alpha-methyl-para-tyrosine (αMPT). Incubation with specific TH cofactors tetrahydrobiopterin (BH_4) and iron (Fe^{2+}) increased hypoxia-induced inhibition of TNF, which was also reversed by αMPT. The success of TH+ cell generation from murine MSCs was confirmed by detetction of neuronal/dopaminergic markers. Adoptive transfer of TH+ cells reduced CIA score in mice significantly, and 6 hydroxydopamine, which depletes TH+ cells, was able to reverse this effect (Fig.1).

Conclusion: In summary, this study presents that TH-dependent catecholamine synthesis exhibits anti-inflammatory effects in human RA synovial cells in vitro, which can be augmented under hypoxic conditions. In addition, the anti-inflammatory effect of TH+ cells on experimental arthritis in mice has been presented. Using generated TH+ cells might open new avenues for cellular arthritis therapy.

Disclosure: Z. Jenei-Lanzl, None; **S. Capellino**, None; **F. Kees**, None; **R. H. Straub**, None.

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Pre-Clinical Proof-Of-Concept Of ALX-0761, a Nanobody® Neutralizing Both IL-17A and F In a Cynomolgus Monkey Collagen Induced Arthritis Model. Katrien Vanheusden[1], Laurent Detalle[1], Alex Hemeryck[1], Alain Vicari[2], Roland Grenningloh[3], Sofie Poelmans[1], Heidi Wouters[1] and Thomas Stöhr[1]. [1]Ablynx NV, Gent, Belgium, [2]Calypso Biotech, Geneva, Switzerland, [3]Merck-Serono, Darmstadt, Germany.

Background/Purpose: Interleukin (IL)-17 and Th17 cells are implicated in many auto-immune diseases, such as rheumatoid arthritis (RA), psoriasis and multiple sclerosis. Although IL-17(A) is the most characterized IL-17 family member, IL-17F may play a non-redundant role in Th17 driven diseases as it is secreted by other cell types. Therefore, a trivalent half-life extended Nanobody® ALX-0761 (MSB0010841) has been developed that neutralizes both IL-17A and IL-17F. A collagen induced arthritis model in cynomolgus monkey was used to demonstrate proof-of-concept.

Methods: Cynomolgus monkeys were immunized twice intra-dermally with bovine collagen type II to induce an arthritic disease mimicking human RA. Prophylactic ALX-0761 treatment was compared to vehicle: ALX-0761 was administered weekly for eight consecutive weeks and dosed subcutaneously at 2.8mg/kg or 10mg/kg. A tocilizumab treatment group (IV administration, 10mg/kg) was included as positive control. The preventive effect of ALX-0761 on arthritis development was evaluated by the measurement of arthritis score (AS) of the joints, general condition score, X-ray examination scores of the affected joints, C-reactive protein (CRP) concentrations and body weight. In addition, total target levels (both IL-17A and IL-17F), pharmacodynamic biomarkers, immunogenicity and drug exposure were analyzed.

Results: Immunisation with collagen type II established an arthritis-like disease in all animals. This was observed by worsening of the arthritis and general condition score and X-ray scores A and B, indicative of an increase in joint space narrowing and architectural joint destruction respectively. In addition, body weight loss and prevalence of high-CRP animals was most pronounced in the vehicle group. The levels of IL-17A and IL-17F increased during the establishment of the disease in the vehicle group, supporting a role for these cytokines in the onset and/or maintenance of the disease.

Treatment with ALX-0761 attenuated the disease symptoms when compared to the vehicle group. For the arthritis score as well as for the X-ray score B, ALX-0761 reached statistical significance. Clinical improvement was also observed based on the general condition score, X-ray score A, CRP levels and body weight, although no statistical significance was reached. Serum levels of the inflammatory cytokines IL-6, TNF-α, IL-15 and the cartilage degradation marker MMP-3 decreased in ALX-0761-treated animals, at day 28 or day 56, when compared to vehicle albeit not statistically significant. Serum IL-17A and IL-17F levels increased markedly upon first ALX-0761 administration and reached a plateau after two to three injections.

Conclusion: This model, responsive to the anti-rheumatic effect of tocilizumab proved to be at least partially dependent on IL-17 as evidenced by increased IL-17A and IL-17F levels in the vehicle group. We emphasize that ALX-0761 significantly improved the clinical endpoints, X-ray score B and the arthritis score and that promising biomarkers (IL-6, IL-15, MMP-3, TNFa) were identified to aid further clinical development.

Disclosure: K. Vanheusden, Ablynx, 3; **L. Detalle**, Ablynx, 3; **A. Hemeryck**, Ablynx, 3; **A. Vicari**, Merck Serono, 3; **R. Grenningloh**, Merck Serono, 3; **S. Poelmans**, Ablynx, 3; **H. Wouters**, Ablynx, 3; **T. Stöhr**, Ablynx, 3.

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Development Of Antibodies Specific For Carbamylated Protein Precedes Disease Onset In Mice With Collagen-Induced Arthritis. Leendert A. Trouw[1], Bisheng Liu[1], Jing Shi[1], Diahann T.S.L. Jansen[1], Martin Hegen[2], Tom W.J. Huizinga[1], Jeroen N. Stoop[1] and René E. M. Toes[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Pfizer, Cambridge, MA.

Background/Purpose: Antibodies against citrullinated proteins are a characteristic of rheumatoid arthritis (RA). Recently, we demonstrated that autoantibodies recognizing homocitrulline containing proteins are present in sera of RA patients and predict joint damage (1). Because homocitrulline is post-translationally formed by a process called carbamylation, we named these novel auto-antibodies anti-Carbamylated Protein antibodies (anti-CarP antibodies). As no information is present on the molecular mechanisms underlying the break of tolerance and hence the induction of anti-CarP-responses, therefore we analyzed their appearance in the mouse collagen-induced arthritis (CIA) model.

Methods: CIA was induced in mice by immunization with type II collagen (CII) in complete Freund's adjuvant (CFA). Arthritis severity was monitored by clinical scoring and anti-CarP levels were determined by ELISA. The specificity of the ELISA was validated using inhibition and immunoblotting assays.

Results: Anti-CarP antibodies were not detected in naïve, non-immunized mice. However they were readily detectable in mice injected with CII and CFA demonstrating arthritic scores. The ELISA results of the specificity of the antibodies for carbamylated proteins were confirmed by inhibition assays and immunoblotting. No correlation between anti-CarP antibody levels and disease severity was observed. Injection of CFA could also cause the development of anti-Carp antibodies, indicating that arthritis is not required for the emergence of anti-CarP antibodies. However, in mice with arthritic disease, the anti-CarP response was stronger and developed more rapidly. The onset of clinical symptoms of CIA was preceded by an increase of anti-CarP IgG2a levels in the serum.

Conclusion: Anti-CarP antibodies can be detected before disease onset in mice with CIA, but are not required for disease induction. Our data indicate that induction of inflammation by e.g. CFA can lead to a break of B-cell tolerance to carbamylated proteins and the emergence of anti-CarP-antibodies.

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IL-6 Is Required For Th1- and Th17-Mediated Arthritis. Alison Finnegan, Yanxia Cao and Susan Olalekan. Rush University Medical Center, Chicago, IL.

Background/Purpose: We have reported that the route of immunization in proteoglycan-induced arthritis (PGIA) determines the T helper phenotype responsible for arthritis. Intraperitoneal (i.p.) immunization induces a Th1 IFN-γ dependent arthritis whereas subcutaneous (s.c.) immunization induces a Th17 IL-17 dependent arthritis. IL-6 has been implicated in the control of leukocyte recruitment, differentiation, activation, and survival. In addition, IL-6 is involved in the differentiation of Th17 cells and in the inhibition of IFN-γ expression. In this study we examined the role of IL-6 in Th1-dependent PGIA and Th17- dependent PGIA.

Methods: Female BALB/c wild type (WT) and IL-6$^{-/-}$ littermate mice (>3 months of age) were immunized i.p. or s.c. with the G1 domain of human PG in adjuvant 3 times at 3 week intervals. Paws were examined every third day for arthritis and scored based on the intensity of erythema and swelling on a scale of 1–4. For short term in vivo T cell priming, mice were immunized and cells harvested on day 9. T cells from T cell receptor (TCR) Tg mice were transferred in WT and IL-6$^{-/-}$mice and immunized with PG in adjuvant. TCR cells were recovered 5 days later. ELISA was used to measure cytokines. Intracellular cytokines were measured by flow cytometry.

Results: In IL-6$^{-/-}$ mice, the onset and severity of arthritis was significantly reduced in both i.p. and s.c immunized mice in comparison to WT. The reduction in arthritis was associated with a reduction in IL-17 in both i.p. and s.c. immunized mice but only with reduction in IFN-γ in s.c. immunized mice. To determine the role of IL-6 in early T cell cytokine production after i.p. versus s.c immunization, we assessed IFN-γ and IL-17 in CD4+ T cells on day 9 after immunization or in TCR transfer into IL-6$^{-/-}$ mice. Despite a reduction in IFN-γ levels after arthritis induction, IFN-γ was significantly increased in s.c immunized IL-6$^{-/-}$mice in comparison to i.p. immunized mice or WT mice. IL-17 was reduced after either i.p. or s.c. immunization.

Conclusion: IL-6 is required for IL-17- and IFN-γ-dependent arthritis induced by s.c. and i.p. immunization respectively. Interestingly, despite the fact that IL-6 is known to inhibit IFN-γ, arthritis was suppressed in the IFN-γ-dependent arthritis induced by i.p. immunization. These results suggest that IL-6 effects on arthritis may be boarder than T helper cytokine responses.

Disclosure: A. Finnegan, None; **Y. Cao**, None; **S. Olalekan**, None.

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Pro-Inflammatory and Anti-Inflammatory Roles Of Interferon Regulatory Factor 5 In The Development Of Collagen-Induced Arthritis. Yoshifumi Tada, Syuichi Koarada, Rie Suematsu, Satoko Tashiro, Natsumi Nagao and Akihide Ohta. Saga University, Saga, Japan.

Background/Purpose: Interferon regulatory factor 5 (IRF5) is a transcription factor that mediates signals activated by engagement of Toll-like receptors (TLRs). IRF5 polymorphisms are associated with the risk of systemic autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis. Although it has been shown that IRF5 has crucial roles in the development of lupus in murine models, its role in arthritis has yet to be fully investigated. Therefore, the role of IRF5 in the development of murine collagen-induced arthritis (CIA) was examined.

Methods: CIA was induced in IRF5-deficient, IRF5-heterozygous, and wild-type DBA/1 mice by injecting type II collagen (CII) emulsified with CFA followed by CII with IFA 21 days later. The incidence and severity of arthritis were then evaluated, and cytokine production by spleen cells in response to CII and serum anti-CII antibody levels were determined. Wild-type mice were treated with IRF5-specific siRNA during the progression phase of CIA. For non-specific suppression, siRNA was mixed with atelocollagen and injected intravenously. For antigen-presenting cell (APC)-specific suppression, siRNA was mixed with schizophyllan, a beta-glucan that binds to dectin-1, and injected intraperitoneally.

Results: IRF5-deficient mice developed a similar degree of arthritis as wild-type mice. However, IRF5-heterozygous mice showed reduced incidence and severity of arthritis compared with wild-type or IRF5-deficient mice. The final incidence was 79%, 56%, and 75%, and the mean arthritis index was 4.8, 1.8, and 4.2, in IRF5+/+, IRF5+/−, and IRF5−/− mice, respectively. These data suggest that IRF5 has the dual effects of suppression and promotion in the development of CIA. IRF5-deficient mice showed decreased levels of anti-CII antibody, but spleen cells from IRF5-deficient mice produced higher amounts of IL-17 in response to CII. Administration of siRNA by a non-specific delivery system during the course of CIA attenuated the arthritis in wild-type mice. In contrast, treatment with siRNA by an APC-specific delivery system significantly exacerbated the CIA.

Conclusion: IRF5 has roles in anti-CII antibody production and Th17 induction, and it shows both pro- and anti-inflammatory effects in the development of CIA. IRF5 in APCs has a regulatory role in the development of CIA.

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COVA322: Overcoming Limitations Of Current Biologics In Rheumatoid Arthritis By a Novel, Bispecific Tumor-Necrosis-Factor-Alpha/Interleukin-17A (TNF/IL-17A) Inhibitor Moving Towards The Clinic. Dragan Grabulovski, Michela Silacci, Nadja Baenziger-Tobler, Wibke Lembke, Wenjuan Zha, Richard Woods, Isabella Attinger-Toller, Roger Santimaria, Susann Koenig-Friedrich, Ulrike von der Bey, Mathias Locher and Julian Bertschinger. Covagen AG, Schlieren, Switzerland.

Background/Purpose: Biologic treatment options such as TNF inhibitors have revolutionized the treatment of inflammatory diseases, such as rheumatoid arthritis (RA), psoriasis and psoriatic arthritis. However, there is still a significant unmet medical need in these diseases. In RA for example, only about half of all patients achieve an ACR50 score and many become refractory to anti-TNF treatment after a few years. Recent data suggest that full and long-lasting responses to TNF inhibitors are limited because of the activation of the pro-inflammatory T_H17/IL-17 pathway in patients. Therefore, an attractive avenue to achieve superior efficacy levels in inflammatory diseases represents dual TNF/IL-17A inhibition. In Collagen-Induced-Arthritis (CIA) animal models it was recently demonstrated that dual TNF/IL-17A inhibition resulted in significant superior activity as compared to the treatment of mice with the monospecific anti-TNF and anti-IL-17A inhibitors. We present here COVA322, a bispecific anti-TNF/IL-17A drug candidate moving towards the clinic.

Methods: Using phage display technology we have isolated Fynomers inhibiting human IL-17A. Fynomers are small binding proteins (7 kDa) derived from the human Fyn SH3 domain which can be engineered to bind to essentially any target of interest with high affinity and specificity. After genetic fusion of the anti-IL-17A Fynomer to a commercially validated anti-TNF antibody the resulting bispecific molecule COVA322 was characterized in-depth for its biophysical and *in vitro*/*in vivo* inhibition properties.

Results: COVA322 inhibited TNF and IL-17A with picomolar inhibition potencies as shown in a variety of different cell assays. Moreover, we could show that COVA322 bound and inhibited simultaneously TNF and IL-17A, as determined by simultaneous binding studies and inhibition cell assays. Importantly, COVA322 was able to inhibit both TNF and IL-17A in an acute inflammation model in mice. In addition, the fusion of the anti-IL-17A Fynomer to the fully human anti-TNF antibody did not alter the favorable biophysical properties of the antibody: First, COVA322 could be purified with very high yields (3.5 g/l in a 10 liter fermentor) from a stable CHO cell line, using standard methods as typically applied for the purification of conventional monoclonal antibodies. Second, COVA322 was monomeric and showed no signs of aggregation even after months of storage at 4 °C in PBS as determined by size exclusion chromatography.

Conclusion: These encouraging results indicate that COVA322 has highly promising biophysical properties. Through its unique mode-of-action of inhibiting simultaneously TNF and the IL-17A/A homodimer, COVA322 has game changing potential in the treatment of inflammatory diseases.

Disclosure: D. Grabulovski, Covagen AG, 3, Covagen AG, 1, Covagen AG, 4; **M. Silacci**, Covagen AG, 1, Covagen AG, 3; **N. Baenziger-Tobler**, Covagen AG, 1, Covagen AG, 3; **W. Lembke**, Covagen AG, 1, Covagen AG, 3; **W. Zha**, Covagen AG, 1, Covagen AG, 3; **R. Woods**, Covagen AG, 1, Covagen AG, 3; **I. Attinger-Toller**, Covagen AG, 1, Covagen AG, 3; **R. Santimaria**, Covagen AG, 3; **S. Koenig-Friedrich**, Covagen AG, 3; **U. von der Bey**, Covagen AG, 3; **M. Locher**, Covagen AG, 1, Covagen AG, 3; **J. Bertschinger**, Covagen AG, 1, Covagen AG, 3, Covagen AG, 4.

1292

The Spatial Energy Expenditure Configuration and Possible Applications In An Experimental Model Of Arthritis. Susanne Klatt[1] and Rainer H. Straub[2]. [1]Laboratory of Exp. Rheumatology and Neuroendocrine Immunology, University Hospital Regensburg, Regensburg, 93055, Germany, [2]Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, University Hospital of Regensburg, Regensburg, Germany.

Background/Purpose: An autoimmune response with differentiation and proliferation of immune cells and the subsequent tissue-directed inflammatory process in the symptomatic phase of the disease are very energy-demanding. As recent calculations demonstrate, the activated immune system needs approximately 20% of the basal metabolic rate.

Thus, energy regulation and cellular bioenergetics are of outstanding importance to serve a stimulated immune system. During inflammation, particularly during the chronic process of inflammation in long standing inflammatory diseases like rheumatoid arthritis, a reallocation of energy-rich fuels to the activated immune system is necessary in order to nourish the inflammatory process. Energy consumption and, thus, ATP generation can be measured by studying the consumption of oxygen.

The energy expenditure in different organs at different time points has never been investigated during immunization. We want to find out if, and how the energy expenditure in different organs changes during the course of experimental arthritis.

Methods: A new technique termed "spatial energy expenditure configuration (SEEC)" was developed to demonstrate bodily areas of high energy demand. SEEC is based on removal of tissue during the course of arthritis, and subsequent determination of oxygen consumption. For that purpose, small weighed pieces of the respective organ with a size of 4 mm are placed in 24-well multidishes with integrated oxygen sensors, which allows for non-invasive detection of oxygen consumption *in vitro*. SEEC was established in healthy control animals, arthritic animals and animals that underwent prior sympathectomy. The model of type II collagen arthritis in DBA/1 mice is used in order to develop an arthritic-specific SEEC. We determined the oxygen consumption in spleen, thymus, draining lymph nodes, liver, kidney, brain and knee joints during the course of experimental arthritis for 70 days. The values are given in μmol O_2/l/h and refer to 4 mm sized pieces as percentage of mouse weight.

Results: In draining lymph nodes of arthritic DBA/1J mice we observed a marked increase in oxygen consumption during the course of arthritis (200 %). Sympathectomy prior to immunization increases energy consumption in draining lymph nodes, which is most probably a sign of retention of leucocytes in the lymph node. C57BL/6 mice deficient for the important adipose triglyceride lipase revealed an increased oxygen consumption in the liver. This might be due to a lack of lipolysis activity, and therfore increased gluconeogenetic activity in the liver for the generation of energy rich fuels in form of glucose. ATGL-deficient arthritic animals also showed higher energy demand in lymph nodes, adrenals and gut.

Conclusion: The SEEC technique enables us to identify locations of high energy demand that are involved in the initiation and continuation of the autoimmune process in an animal model of arthritis. We identified the draining lymph nodes as target organ of the sympathetic nervous system, which will be further investigated. The technique will be applied to other chronic inflammatory disease models in order to detect further participating organs.

Disclosure: S. Klatt, None; **R. H. Straub**, None.

1293

Serum Matrix Metalloproteinase 13 As a Translational Marker For Efficacy Of Anti-Arthritic Treatments In Rat Collagen Induced Arthritis and Mouse Model Of Lipopolysaccharide-Induced Bone Resorption. Ines Glojnaric, Snjezana Cuzic, Boska Hrvacic, Vanesa Ivetic Tkalcevic, Miroslava Dominis Kramaric and Vesna Erakovic Haber. Fidelta Ltd., Zagreb, Croatia.

Background/Purpose: Matrix metalloproteinase 13 (MMP-13) is expressed by chondrocytes and synovial cells in human osteoarthritis and rheumatoid arthritis (RA) (Takaishi et al., 2008). Serum MMP-13 is increased in stages III and IV in RA and treatment with methotrexate (MTX) reduced serum concentrations of MMP-13 in RA patients (Takemura et al., 2005; Fiedorczyk et al., 2006). The aim of the study was to evaluate translational potential of serum MMP-13 as a biomarker for treatment efficacy. Therefore, we investigated effects of different anti-arthritic treatments on serum MMP-13 concentrations in correlation with severity of bone destruction in rat collagen induced arthritis (CIA). Serum MMP-13 was also used as a systemic marker of bone destruction in a mouse LPS-induced bone resorption model.

Methods: CIA was induced in male Dark Agouti rats by immunization with bovine type II collagen (days 0 and 7) and the animals were treated intraperitoneally with etanercept (10 mg/kg, 3 times per week) or orally with MTX (0.1 mg/kg once daily) starting from day 17 to day 31. Histological evaluation was performed on hind paws by scoring bone and cartilage lesion, cell infiltrate and pannus severity (scoring system ranged from 1 to 4 for all parameters). In the LPS induced bone resorption model, mice were subcutaneously injected by a single dose of 20 mg/kg LPS (*E.coli*) and treated subcutaneously with MTX (5, 0.5 and 0.05 mg/kg once daily) for 4 days. Serum MMP-13 concentration was determined in both models by ELISA (USCNK Life Science Inc., China). Serum MMP-13 concentrations were correlated with histological data on individual level.

Results: Treatment with both etanercept and MTX significantly reduced the mean serum MMP-13 concentration in rat CIA (63% and 33%, respectively). On the level of individual values, serum MMP-13 concentration correlated with individual total histological scores with $R^2=0.74$ for MTX and $R^2= 0.67$ for etanercept. The correlation with individual bone and cartilage lesion scores showed to be even better for etanercept ($R^2=0.72$ and $R^2=0.68$, respectively) while for MTX the correlations were comparable with the one obtained for individual total histological scores ($R^2=0.71$ for both). In LPS induced bone resorption model, treatment with MTX dose dependently reduced the mean serum MMP-13 concentrations: a 100% reduction at 5 mg/kg, 84% at 0.5 mg/kg and no inhibition at 0.05 mg/kg.

Conclusion: Our data showed that serum MMP-13 concentration measurement is an useful tool to assess effects of anti-arthritic therapy since it correlates with severity of bone and cartilage destruction. Furthermore, serum MMP-13 concentrations can be effectively used as marker of compound potency in a short, simple model of LPS-induced bone resorption in mice to predict efficacy of treatment in CIA. Since MMP-13 was shown to be a marker of disease activity in humans, these results strongly support its usefulness as a translational marker.

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Anti-Inflammatory Effect Of Resveratrol As a Dietary Supplement In An Antigen-Induced Arthritis Rat Model. Romina R. Riveiro-Naveira[1], Jesus Loureiro[1], Alberto Centeno-Cortés[2], Eduardo López-Peláez[2], Carlos Vaamonde-García[1], M. Noa Valcárcel-Ares[1], Francisco J. Blanco[3] and Maria J. López-Armada[1]. [1]Aging and Inflammation Research Lab, INIBIC-CHU A Coruña, A Coruña, Spain, [2]Experimental Surgery Unit, CHU A Coruña, A Coruña, Spain, [3]Osteoarticular and Aging Research Laboratory, Proteomics Unit-Associated Node to ProteoRed-ISCIII, INIBIC-CHUAC, A Coruña, Spain.

Background/Purpose: Inflammatory cells like macrophages, lymphocytes and neutrophils in hyperplasic synovial tissue have been identified as key players in the onset and development of rheumatoid arthritis (RA). Resveratrol (RSV) is a natural antioxidant with potent immunomodulatory and anti-inflammatory properties. The aim of this study was to investigate the preventive effect of dietary resveratrol and its ability to suppress inflammatory arthritis progression in an acute antigen-induced arthritis (AIA) rat model.

Methods: Six-week-old female Lewis rats were randomized into four study groups: healthy group (n=19), AIA group (n=24), RSV group (n=26) and diclofenac (DCF) group (n=17). RSV (2 mg/day) was administered daily by oral gavage as a dietary supplement beginning one month before AIA induction until sacrifice day, 48h after intraarticular injection. DCF (1,2 mg/day) was orally administered three days before AIA induction until sacrifice day. Joint swelling was assessed by measuring the mediolateral diameter of both right and left knee joints with a digital calliper. Severity of inflammation was evaluated using a blind damage scoring system (H&E). To characterize inflammatory cell infiltration and chemokine levels, CD68, CD3 and MCP-1 expression were evaluated by immunohistochemistry.

Results: On day 2 after intraarticular injection, RSV animals exhibited significant reduced knee swelling, similar to DCF group, in comparison to AIA animals (mediolateral diameter mean: RSV 7,775 mm ± 0,169, n=26; DCF 7,776 mm ± 0,253, n=17 vs. AIA 8,281 ± 0,127, n=24; $p<0,05$). Accordingly, histopatological evaluation demonstrated a reduction in synovial hyperplasia and cell infiltration in both RSV and DCF groups compared with AIA animals. CD68 and CD3 infiltrate was significantly attenuated in RSV rats synovium (0,843 ± 0,369, n=5 and 1,290 ± 0,198, n=19, respectively) compared with AIA group (CD68 3,741 ± 1,428, n=5 and CD3 2,868 ± 0,5707, n=18, $p<0,05$), similar to DCF group (CD68 1,656 ± 0,522, n=13 and CD3 1,753 ± 0,359, n=15). MCP1 levels in the synovium were significantly attenuated in RSV and DCF groups compared with AIA animals (3,167 ±

0,2649 and 2,453 ± 0,628, respectively vs. AIA 4,400 ± 0,4922, $p<0,05$).

Conclusion: The results of this study suggest that a dietary supplement with the natural antioxidant resveratrol can effectively control inflammation and could exert a protective effect against RA establishment and progression.

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Mechanisms For Fostamatinib-Induced Blood Pressure Elevation. Matthew Skinner[1], Karen Philp[1], David Lengel[2], Lucy Coverley[1], Eva Lamm Bergstroem[3], Philip Glaves[1], Helen Musgrove[1], Helen Prior[1], Martin Braddock[1], Russell Huby[1], Jon O Curwen[1], Paul Duffy[1] and Alex Harmer[1]. [1]AstraZeneca R&D Alderley Park, Macclesfield, United Kingdom, [2]AstraZeneca R&D Waltham, Waltham, MA, [3]AstraZeneca R&D Mölndal, Mölndal, Sweden.

Background/Purpose: Fostamatinib is a kinase inhibitor with activity at spleen tyrosine kinase. In clinical studies in patients with rheumatoid arthritis, fostamatinib treatment was associated with an increase in arterial blood pressure (BP). Some tyrosine kinase inhibitors are known to cause BP elevation, potentially by inhibiting vascular endothelial growth factor receptor 2 (VEGFR2). Therefore, we investigated whether there was a mechanistic link between fostamatinib-induced BP elevation and inhibition of VEGF signaling.

Methods: BP was measured in conscious rats using combined automated blood sampling and radio telemetry following oral dosing with fostamatinib. The effects of intravenous dosing of R406 (the active metabolite of fostamatinib) on BP, femoral vascular conductance and responses to acetylcholine (ACh), reactive hyperemia and VEGF were assessed in rats anesthetized with isofluorane (0.5 to 5%). The effects of R406 on contractile parameters were determined using rat isolated aorta and human resistance vessels in vitro. The effects of R406 on VEGF-stimulated nitric oxide production were determined using human microvascular endothelial cells in vitro. VEGFR2 phosphorylation was determined in mouse lung, ex vivo, following oral dosing with fostamatinib.

Results: In conscious rats, fostamatinib caused a dose-dependent increase in BP. The time course of the BP effect correlated closely with changes in R406 plasma concentration, consistent with a direct pharmacologic relationship. In anesthetized rats, infusion of R406 increased BP and decreased femoral arterial conductance. Endothelial function was not reduced, as infusion of R406 did not inhibit hyperemia- or ACh-induced vasodilatation in rats. R406 had no effect on the contraction of intact isolated vessels, suggesting the decreased arterial conductance was an indirect effect. R406 inhibited VEGF-stimulated nitric oxide production from human endothelial cells in vitro, and treatment with R406 inhibited VEGFR2 phosphorylation in vivo. R406 also inhibited VEGF-induced hypotension in anesthetized rats (see Figure).

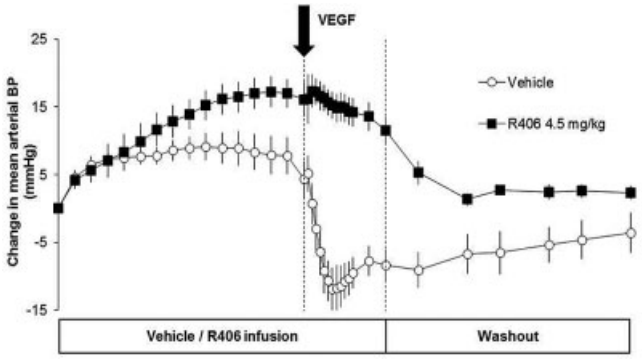

Figure. Effect of R406 on VEGF-induced vascular responses in anesthetized rats. The effects of intravenous infusion of vehicle or 4.5 mg/kg R406 on mean arterial Bp when given in conjunction with VEGF. Vehicle or R406 were administered for 20 minutes as an i.v. infusion. At 15 minutes into the infusion a bolus 55 μg/kg dose of VEGF was administered. Parameters were monitored for a further 15 minutes after the 20 minute infusion period. Data are shown as mean ± s.e.m. change from baseline, n=6 per group. Data were statistically compared via ANCOVA. The first vertical line represents the VEGF application at 15 minutes, and the second line represents the end of the R406 infusion at 20 minutes, and the start of the washout.

Conclusion: These data suggest that increased vascular resistance, potentially secondary to reduced VEGF-induced nitric oxide release from the endothelium, may contribute to BP increases observed with fostamatinib. This is consistent with the means by which other drugs that inhibit VEGF signaling elevate BP, although the contribution of other mechanisms cannot be excluded.

Disclosure: M. Skinner, AstraZeneca, 3; **K. Philp**, AstraZeneca, 1, AstraZeneca, 3; **D. Lengel**, AstraZeneca, 1, AstraZeneca, 3; **L. Coverley**, AstraZeneca, 1, AstraZeneca, 3; **E. L. Bergstroem**, AstraZeneca, 1, AstraZeneca, 3; **P. Glaves**, AstraZeneca, 1, AstraZeneca, 3; **H. Musgrove**, AstraZeneca, 1, AstraZeneca, 3; **H. Prior**, AstraZeneca, 1, AstraZeneca, 3; **M. Braddock**, AstraZeneca, 1, AstraZeneca, 3; **R. Huby**, AstraZeneca, 3, AstraZeneca, 1; **J. O. Curwen**, AstraZeneca, 1, AstraZeneca, 3; **P. Duffy**, AstraZeneca, 1, AstraZeneca, 3; **A. Harmer**, AstraZeneca, 1, AstraZeneca, 3.

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Deletion Of RBP-J In a Murine Model Of Inflammatory Arthritis Reveals Pro-Inflammatory Cytokine Expression and Immunophenotypic Differences. Soumya D. Chakravarty, Karmen Au, Lionel B. Ivashkiv and Xiaoyu Hu. Hospital for Special Surgery, New York, NY.

Background/Purpose: RBP-J, a DNA-binding protein, serves as the central transcriptional regulator of the Notch signaling pathway. Prior *in vitro* work has demonstrated that RBP-J plays a critical role in macrophage activation, polarization, and modulating pro-inflammatory cytokine expression under LPS stimulation. Others have demonstrated that TNFα can induce myeloid derived suppressor cell (MDSC; suppressors of T cell function) activity via iNOS and arginase expression, both of which are strongly dependent on RBP-J and thus implicating its role in mediating potential downstream effects of MDSCs in inflammatory arthritis. Here, we evaluated the *in vivo* effects of RBP-J's conditional deletion using the Mx1Cre system, as well as in the myeloid cell compartment only, on pro-inflammatory cytokine expression, lymphoid tissue immunocyte composition, and MDSC populations, using a K/BxN serum transfer model of inflammatory arthritis.

Methods: RBP-J$^{flox/flox}$ Mx1Cre and LysM-Cre knock-out mice with controls (n=4–5 mice per group) were used. After treatment with K/BxN serum, the clinical course of arthritis was followed by measuring total joint thickness up to 14 days, at which point the mice were sacrificed. Total joint RNA from each mouse was obtained for gene expression analyses by real-time PCR. Splenic tissue was pooled collectively from each group of mice for immunophenotyping through flow cytometry. The same was done for superficial inguinal and draining popliteal lymph node (LN) tissue, as well as bone marrow. Statistical analysis was done using the unpaired student's t-test with $p < 0.05$ considered significant.

Results: Mx1Cre deletion, but not myeloid-specific deletion, of RBP-J resulted in significantly heightened K/BxN serum-induced arthritis (up to 14 days post-induction) versus controls. Gene expression profiling of total joint tissue from RBP-J Mx1Cre deleted mice showed trends toward increased IL-12p40 expression, decreased IL-1β expression, with expression levels of IL-6, TNFα, Notch target genes, as well as bone turnover markers, being comparable. In contrast, myeloid-specific RBP-J deleted mice showed decreases in IL-12p40/IFNγ gene expression with variable expression of IL-6, TNFα, and Notch target genes. Post-arthritis induction, Mx1Cre deletion of RBP-J resulted in higher proportions of CD11b$^+$ and Ly6G$^+$ cells in splenic tissue. MDSC populations identified using various combinations of CD11b/Ly6G/Ly6C/CD115 markers in lymphoid tissue and bone marrow demonstrated a downward shift in proportions with RBP-J deletion and TNFα expression.

Conclusion: Deletion of RBP-J using the Mx1Cre system, but not myeloid-specific deletion, leads to heightened K/BxN serum-induced inflammatory arthritis. Along with selective modulation of pro-inflammatory cytokine gene expression *in vivo*, coupled with differences in myeloid cell composition and trafficking observed, including that of the MDSC population, this suggests that the stromal versus hematopoietic compartments expressing RBP-J may be contributing to these observations. Further functional studies to better characterize these conclusions are currently underway.

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Human IL-1alpha Conditional Transgenic Mice Mimic Autoinflammatory Syndromes In Human. Hiroya Kanagawa[1], Yasuo Niki[2], Yoshiaki Toyama[3] and Takeshi Miyamoto[4]. [1]Department of Orthopaedic Surgery, Keio University, Shinjuku-ku, Tokyo, Japan, [2]Department of Orthopaedic Surgery, Keio University, Tokyo, Japan, [3]Department of Orthopaedic Surgery, Keio University School of Medicine, Shinjuku, Japan, [4]Department of Orthopaedic Surgery, Keio University, Shinjuku-ku, Tokyo, Japan.

Background/Purpose: Recently, IL-1 is implicated in the pathogenesis of autoinflammatory syndrome, which characterized by rash, fever, systemic polyarthritis and neurological comorbidity. Recently, IL-1 becomes noticed now as a therapeutic target of adult onset still's disease and macrophage activation syndrome. To date, animal model of adult onset "IL-1 disease" has not been reported. Herein, we newly established IL-1alpha transgenic mice with conditional regulation of IL-1alpha overexpression, which mimicked adult onset IL-1 disease in humans. The purpose of the present study is to clarify the pathology of adult onset IL-1 disease through these mice.

Methods: Human IL-1alpha (hIL1alpha) conditional transgenic (cTg) mice were generated as loxP-neomysin resistant gene (Neo)-polyA-loxP-hIL1alpha sequence under an beta-actin promotor in a C57BL/6 background. In non-inducing condition, Neo was expressed without hIL1alpha-expression, whereas in inducing condition in the presence of Cre, Neo-polyA sequence was popped out, and hIL1alpha overexpression was induced. We crossed inducible MxCreTg mice with hIL1alphacTg to yield MxCre/hIL1alphacTg. PolyIpolyC (pI-pC) was administered to 8 week-old cTg mice to activate Mx promotor. The mice were sacrificed two weeks after pI-pC administration, and the severity of arthritis was evaluated using arthritis score, followed by a histological examination.

Results: Two weeks after pI-pC administration, hIL1alphacTg mice developed large joint arthritis in upper and lower limbs, and its incidence was 100%. Histopathologically, loss of cartilage, bony erosion, and the formation of pannus-like tissues were observed in all cTg mice. The level of transgene-derived hIL1alpha in blood was significantly elevated. The number of white blood cells and platelets were significantly elevated, in contrast, red blood cell count and hemoglobin level were decreased. The levels of IL-6, TNF, and leukemia inhibitory factor (LIF) was significantly elevated. The bone mineral density of the femur was significantly reduced. Flowcytometric analysis revealed that the proportion of Mac1+Gr1+ was significantly elevated in joint fluid and bone marrow.

Conclusion: We generated a mouse model of autoinflammatory syndrome in which systemic inflammatory arthritis was intentionally induced under a control of pI-pC administration. The incidence of large joint arthritis was 100% even in a relatively arthritis-resistant C57BL/6 background. These mice are recognized as a useful tool for better understanding of adult onset IL-1 disease.

Disclosure: H. Kanagawa, None; **Y. Niki**, None; **Y. Toyama**, None; **T. Miyamoto**, None.

1298

Statin Alleviates Rheumatoid Arthritis Progression Through Diminishing Inflammation Or Oxidative Stress-Induced Cyr61 Synthesis. Kuo Liang Hou and Sze Kwan Lin. School of Dentistry, College of Medicine National Taiwan University, Taipei, Taiwan.

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease stimulated by inflammatory mediators and oxygen species within joint space cause joint deformity and destruction. Excess amounts of Cysteine-rich protein 61 (Cyr61) will stimulate dysregulated angiogenesis, macrophage chemotaxis and cell apoptosis. Epidemiological study also suggested the connection between Cyr61 and RA development, although the pathogenesis remained unclear. In patients with autoimmune disease, genetic polymorphism was noted in their forkhead transcription factor (FoxO), a molecule responsible for DNA repair and longevity. Furthermore, a positive correlation between the degree of genetic deformity and disease severity was demonstrated. Sirtuin (SIRT) −1 is an essential co-factor of FoxO activity: interaction between SIRT1 and FoxO can resist the ROS-induced apoptosis. Concerning the connection between FoxO and RA, only a few studies have addressed the modulation of FoxO on the apoptosis of fibroblast-like synoviocyte, macrophages and T cells in RA. However, great controversy about the role of FoxO on their fate still existed. Taken together, it may be possible that FoxO may involve in RA development via its inflammation-modulating effect. Statin can attenuate inflammation, in addition to its well-known cholesterol-lowering effect. Mechanisms underlying the modulation of statin on RA progression are still unclear, since most of the investigations on the effects of statin on RA were epidemiological studies. The aims of the study were to examine the role of SIRT1/FoxO3a in Cyr61 expression in rheumatoid arthritis synovial fibroblasts (RASFs) and the influence of simvastatin on this pathway. In a model of collagen-induced arthritis (CIA), the relation between disease progression and FoxO3a/Cyr61 signaling in synovial fibroblasts (SFs) was assessed

Methods: Cyr61 and SIRT1 expressions, localization of FoxO3a in the nucleus/cytoplasm and phosphorylation/acetylation of FoxO3a were examined by immuneprecipitation and Western blotting. Promoter activity of *Cyr61* gene was evaluated by luciferase assay with or without forced expression of FoxO3a and SIRT1 by lentiviral transduction. FoxO3a/*Cyr61* promoter interaction was examined by chromatin immunoprecipitation. In CIA rats, expressions of Cyr61 and phospho-FoxO3a in SFs were examined by immunohistochemistry.

Results: In RASFs, simvastatin suppressed Cyr61 and CCL20 secretion. Simvastatin maintained Foxo3a binding to *Cyr61*promoter. SIRT1 decreased Cyr61 expression and deacetylated FoxO3a whereas simvastatin upregulated SIRT1 and SIRT1/FoxO3a binding in RASFs. In rats with CIA, simvastatin alleviated arthritis and suppressed Cyr61 expression and FoxO3a phosphorylation in SFs.

Conclusion: Cyr61 is important in RA pathogenesis and SIRT1/FoxO3a signaling is crucial to Cyr61 induction in RASFs. Simvastatin is beneficial to inflammatory arthritis by upregulating SIRT1/FoxO3a signaling in SFs. Continued study of the pathways linking sirtuins, FoxO proteins and inflammatory responses of RASFs may provide new insights into the pathophysiology of RA.

Disclosure: K. L. Hou, None; **S. K. Lin**, None.

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PTEN Controls Osteoclastogenesis and Inflammatory Bone Destruction In a TNF-Driven Model Of Arthritis. Stephan Blueml[1], Gernot Schabbauer[2], Antonia Puchner[1], Victoria Saferding[1], Emine Sahin[2], Julia Brunner[2], Tobias Lohmeyer[2], Josef S. Smolen[1] and Kurt Redlich[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University Vienna, Vienna, Austria.

Background/Purpose: Local bone destruction in inflammatory arthritides in humans such as rheumatoid arthritis is a serious health burden and the major cause of disability and severely reduced quality of life in these diseases. Damage to the bony structures is exclusively mediated by a special cell type, the osteoclast (OC). Therefore, it is important to understand factors and pathways regulating the generation of OCs under inflammatory conditions. In this study, we analyzed the impact of the PI3-Kinase/PTEN axis on OC generation and bone biology in an animal model of inflammatory bone loss.

Methods: We induced osteoclastogenesis in wt and PTEN deficient bone marrow cells and measured the generation of OCs, their resorptive capacity and induction of OC differentiation markers *in vitro*. Moreover, we analyzed mice with a monocyte/macrophage-specific deletion of PTEN (myeloid specific $PTEN^{-/-}$) by bone histomorphometry and crossed these mice into hTNFtg animals.

Results: We show that myeloid specific $PTEN^{-/-}$ mice display increased osteoclastogenesis *in vitro* and *in vivo* compared to wt mice. Loss of PTEN did not affect the generation or survival of osteoclast precursor cells. However, PTEN deficiency greatly enhanced RANKL-induced expression of the master transcription factor of osteoclastogenesis, NFATc1, resulting in markedly increased terminal differentiation of osteoclasts *in vitro*. Under non-inflammatory conditions, enhanced

osteoclastogenesis did not result in systemic bone loss *in vivo*. However, when we crossed myeloid specific PTEN$^{-/-}$ into hTNFtg mice we found significantly decreased grip strength scores in myeloid specific PTEN$^{-/-}$/hTNFtg mice compared to wt hTNFtg mice. Joint swelling scores, however, were not different between both groups. In line, myeloid specific PTEN$^{-/-}$/hTNFtg mice displayed enhanced local bone destruction as well as OC formation in the inflamed joints, whereas the extent of synovial inflammation was not different between the groups. Analysis of the synovial membranes of wt and myeloid specific PTEN$^{-/-}$ animals revealed similar relative compositions of the cellular infiltrate including neutrophil granulocytes as well as macrophages which can serve as OC precursors. This suggests that increased capacity for osteoclastogenic differentiation rather than enhanced recruitment of precursor cells is responsible for the enhanced local generation of OCs.

Conclusion: Taken together, these data demonstrate that sustained PI3-Kinase activity in myeloid cells specifically elevated the osteoclastogenic potential of these cells, leading to enhanced inflammatory local bone destruction. Therefore, targeting the PI3-Kinase pathway therapeutically may be especially useful for the prevention of structural joint damage.

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The Role Of Celastrol On Osteoclastogenesis and Bone Erosion In Collagen-Induced Arthritis. Ke Gan[1], Wenfeng Tan[2], Miaojia Zhang[2], Xiaoke Feng[3] and Lingxiao Xu[2]. [1]Nanjing University of Chinese Medicine, nanjing, China, [2]the First Affiliated Hospital of Nanjing Medical University, Nanjing, CHINA., Nanjing, China, [3]the First Affiliated Hospital of Nanjing Medical University, China, Nanjing, China.

Background/Purpose: Celastrus and its extract have been proven effective for treatment Rheumatoid arthritis (RA). Celastrol is one of bioactive component of Celastrus with a potent anti-inflammatory effect in RA therapy. However, the direct role of Celastrol on osteoclast remain unknown.

Objectives: To examine the effects of Celastrol on osteoclastogenesis in vitro and bone erosion in collagen-induced arthritis(CIA).

Methods: The roles of Celastrol on osteoclastogenesis in RAW264.7 was evaluated by tartrate-resistant acid phosphatase (TRAP) staining, Real-Time PCR and Western-blot Activity of bone resorption was tested by pit formation assay in the presence or absence of Celastrol. CIA mice were by intraperitoneal injections (IP). The effects of Celastrol bone erosion was analyzed using ELISA, Real-Time PCR, histological analysis and Micro-CT.

Results: Celastrol inhibited RANKL-induced formation of TRAP+ multinucleated cells and bone-resorbing activity in a dose-dependent manner. The osteoclast formation was completely blocked with 0.3 μM of Celastrol. Celastrol reduced the RANKL-induced expression of NFATc1, c-Jun and c-Fos and phosphorylation of NF-κB and MAPK signals in RAW264.7. In CIA mice, administration of Celastrol markedly supressed the arthritis score and reduced bone damage in the joints as demonstrated by histology and bone Micro-CT. Osteoclastic markers in the serum and joint tissues were significantly downregulated by Celastrol.

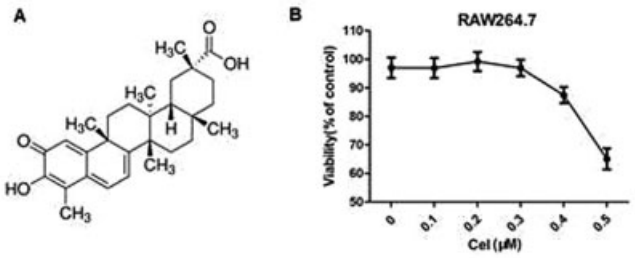

Figure 1. Cytotoxicity of Celastrol for RAW264.7 cells.

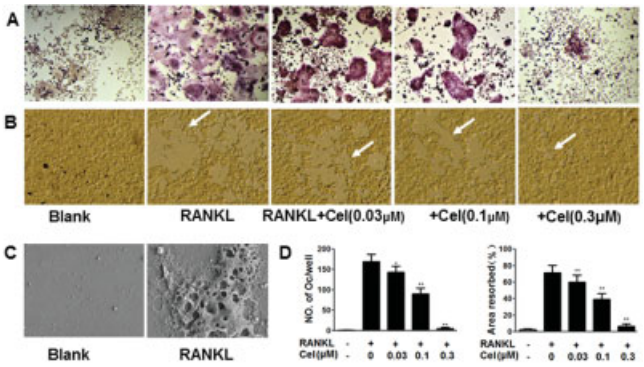

Figure 2. Effect of Celastrol for RANKL-induced osteoclast differentiation and bone resorption of RAW264.7

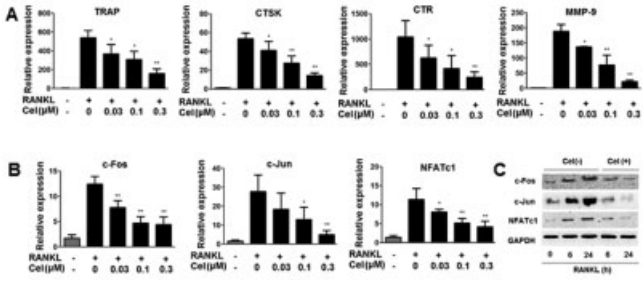

Figure 3. Effect of Celastrol on osteoclastogenic mRNA expression.

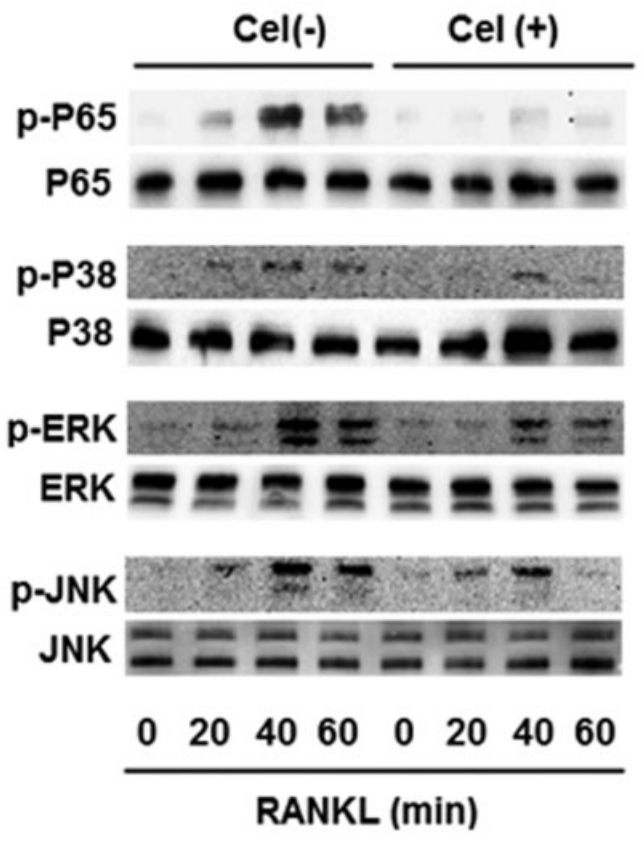

Figure 4. Effects of Celastrol on the activation of MAPKs and NF-κB p-65 in RAW264.7 cells.

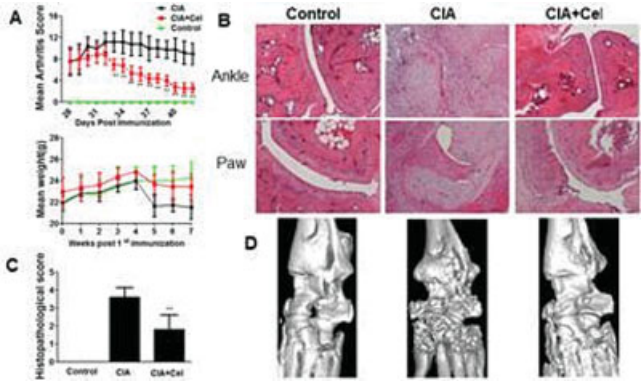

Figure 5. Effects of Celastrol on clinical evaluation and bone erosion in CIA mice.

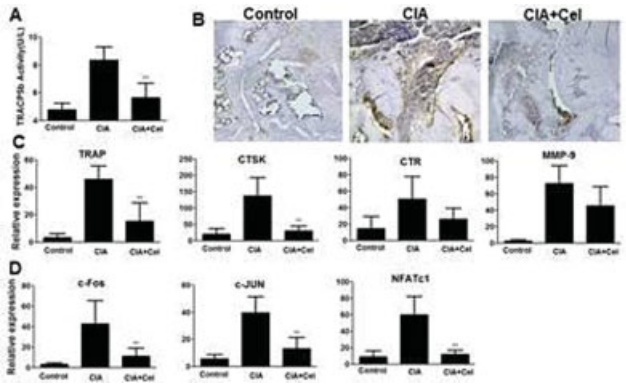

Figure 6. Effect of Celastrol on ostoclastogenic mRNA expression in CIA mice.

Conclusion: These findings suggests that Celastrol is a potent inhibitor of RANKL-induced bone resorption and has a potential therapeutic benefit in treating bone loss of rheumatoid arthritis or other bone diseases.

Disclosure: K. Gan, None; **W. Tan**, None; **M. Zhang**, None; **X. Feng**, None; **L. Xu**, None.

1301

The Tumor Necrosis Factor Stimulated Gene-6 Promoter Reporter Can Monitor The Disease Activity In Rheumatoid Arthritis. Mathijs G.A. Broeren[1], Eline A. Vermeij[1], Onno J. Arntz[2], Miranda B. Bennink[1], Emma Sterken[1], Calin Popa[2], Tim L. Jansen[2], Wim B. van den Berg[1] and Fons A.J. Van de Loo[1]. [1]Rheumatology Research and Advanced Therapeutics, Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.

Background/Purpose: An important step in the optimal personalized treatment of rheumatoid arthritis (RA) patients, is the accurate assessment of disease activity, disease progression and therapy response. The quantification of biomarkers has been proposed to monitor these processes, but no single biomarker has proven to be sufficiently reliable for this purpose. Instead of measuring the quantity of a biomarker, we focus on the biomarker promoter activity to take into account the complex interplay between stimulating and inhibiting factors.

The TNF stimulated gene 6 (TSG-6) encodes a 35-kDa secretory glycoprotein that is induced in fibroblasts, chondrocytes, synovial cells and mononuclear cells by proinflammatory cytokines. Large amounts of TSG-6 protein were found in synovial fluid of patients with RA. In this study, we set out to use the TSG-6 promoter to develop a promoter-reporter construct to monitor disease activity in RA.

Methods: Arthritis was induced in DBA1/J mice by immunization with bovine collagen-type II (CIA), or by intra-articular injection of 5 μg Streptococcal Cell Wall (SCW). Microarray experiments were performed on 15 CIA samples, 20 human end-point RA synovium samples and 6 control synovium samples. The TSG-6 promoter (−499 to +63) was cloned in a lentiviral vector (LV) encoding firefly luciferase. Murine 3T3 cells were cultured and stimulated with 1% mouse serum or 10% human serum for 6 hours. Luciferase activity was measured using BrightGlo reagent.

Results: TSG-6 was upregulated in arthritic CIA joints and expression correlated with disease severity. It was also upregulated ~6-fold in 20 human end-point RA synovium samples, compared to 6 non-arthritic synovium samples ($P=0.01$).

Subsequently, we studied the disease-inducibility of the TSG-6 promoter by developing a lentiviral construct in which the isolated TSG-6 promoter controls the expression of a luciferase reporter transgene (TSG6-luc). We infected mice with the TSG6-luc promoter reporter and induced SCW arthritis. The expression peaked at day 7 (19-fold compared to naive mice), indicating the disease-responsiveness at full blown synovitis.

Next, we transduced murine 3T3 cells with the LV TSG6-luc construct and incubated the cells with serum from mice with increasing severity of collagen induced arthritis. The response of the promoter correlated significantly with the macroscopically assessed disease severity (R^2 0.47, $P<0.0001$) and with their circulating levels of the neutrophil chemokine KC (R^2 0.31, $P=0.002$), the functional homologue of human IL-8. In addition, serum from human RA patients showed a significantly higher activation of the TSG6-luc construct, compared to serum from healthy patients ($P=0.001$).

An important characteristic of a successful reporter is a reduced signal after successful treatment. We tested this by comparing the response to serum from diseased arthritic mice to serum from mice that were successfully treated with Enbrel. Serum from Enbrel treated mice showed a significantly lower activation of the TSG-6 promoter, compared to serum from untreated mice.

Conclusion: The TSG-6 promoter reporter might be a valuable tool to monitor disease progression in RA patients.

Disclosure: M. G. A. Broeren, None; **E. A. Vermeij**, None; **O. J. Arntz**, None; **M. B. Bennink**, None; **E. Sterken**, None; **C. Popa**, None; **T. L. Jansen**, None; **W. B. van den Berg**, None; **F. A. J. Van de Loo**, None.

1302

Application of Cytostatic Agent Kinesin Eg5 Inhibitor Litronesib (KF89617) On Rat Adjuvant-Induced Arthritis and Mouse Type II Collagen-Induced Arthritis. Ichiro Miki[1] and Masako Uchii[2]. [1]Kyowa Hakko Kirin, Co., Ltd., Shizuoka, Japan, [2]Kyowa Hakko Kirin Co., Ltd., Shizuoka, Japan.

Background/Purpose: Kinesins are family of motor proteins that are involved in mitosis and intracellular transport of vesicles and organelles. The mitotic kinesin, Eg5, acts during mitosis and centrosome separation. Selective inhibitors of Eg5 would be expected to be growth inhibition of inflammatory cells and synovial cells undergoing cell division. Litronesib (KF89617, LY2523355) is a newly synthesized compound at Kyowa Hakko Kirin. Litronesib is an ATP-noncompetitive, allosteric, reversible inhibitor of Eg5 that has no observed effect on microtubule formation. Litronesib has been investigated in clinical trials for the treatment of multiple cancers by Eli Lilly and Company. Remission of rheumatoid arthritis with a mitotic inhibitor taxol in patient with breast carcinoma was reported. In this study, we investigate the anti-rheumatoid activities of Litronesib on animal models of rheumatoid arthritis.

Methods: The effect of Litronesib was tested on rat adjuvant-induced arthritis (AIA) and mouse collagen-induced arthritis (CIA). KF89617 (Litronesib) or KF88373 (L-aspartate of the racemic mixture of KF89617 and its enantiomer) was synthesized in our laboratories. Mycobacterium butyricum was intradermally injected into the right hind footpad of Lewis rats (8 weeks, female), and AIA was induced. KF88373 was intravenously administered twice a week at 2 mg/kg from the day of the immunization with the adjuvant. Type 2 collagen (CII) with Freund's complete adjuvant was intradermally injected at the base of the tail of DBA/1J mice (7 weeks, male), and CIA was induced. KF88373 at 4 mg/kg was subcutaneously administered twice a week from the day of the 2nd immunization with CII. KF89617 or KF88373 were orally administered twice a week from the day of the 2nd immunization with CII.

Results: In rat AIA, KF88373 at 2 mg/kg i.v. twice/week markedly inhibited the swelling of adjuvant-non-treated foot at 78.9% ($p<0.01$) on Day 21. The inhibitory activity of KF88373 was similar to that of MTX (0.1 mg/kg p.o. 5 times/week) on rat AIA. Inhibition of swelling of adjuvant-injected foot was 21.4% ($p<0.05$) which was less effective than that of of adjuvant-non-treated foot. Body weight loss by the induction of AIA was also improved by the treatment of KF88373 but was not by the treatment of MTX. In mouse CIA, KF88373 at 4 mg/kg s.c. twice/week markedly inhibited the arthritis score at 97.7% ($p<0.001$) on Day 35. Body weight loss by the induction of CIA was also improved by the treatment of KF88373. Effect of orally administered KF89617 was tested on CIA. KF89617 or KF88373 at 4 mg/kg p.o. twice/week, potently inhibited the arthritis score at 90.8% ($p<0.001$) or 87.1% ($p<0.01$) on Day 35, respectively. Intraperitoneal administration of Taxol (1 mg/kg i.p. twice/week) inhibited CIA score at 61.0% ($p<0.01$) which was weaker than that of KF89617. Taxol did not improve body weight loss.

Conclusion: KF89617 (Litronesib) is a newly synthesized mitotic kinesin Eg5 inihbitor. KF89617 and KF88373 markedly reduced joint inflammation on both rat AIA and mouse CIA. KF89617 and KF88373 showed pharmacological activities on various administration rute such as p.o., i.v. and s.c. The treatment of KF89617 is expected to provide a novel treatment of rheumatoid arthritis.

Disclosure: I. Miki, Kyowa Hakko Kirin, 3, Kyowa Hakko Kirin, 1; **M. Uchii**, Kyowa Hakko Kirin, 3.

ACR/ARHP Poster Session B
Rheumatoid Arthritis - Clinical Aspects II: Predictors of Disease Course in Rheumatoid Arthritis - Treatment Approaches
Monday, October 28, 2013, 8:30 AM–4:00 PM

1303

Variations In Disease Activity and Therapeutic Management Of Rheumatoid Arthritis In Different International Regions: A Comparison Of Data From The Corrona International and Corrona United States Registries. Dimitrios A. Pappas[1], Kathy Lampl[2], Joel M. Kremer[3], Sebastião C. Radominski[4], Janos Gal[5], Fredrik Nyberg[6], Anand N. Malaviya[7], Aimée Whitworth[8], Oscar Luis Rillo[9], Allan Gibofsky[10], Tatiana Popkova[11], Meilien Ho[12], Ieda Laurindo[13], George W. Reed[8], Eduardo Mario Kerzberg[14], Laura Horne[2], Roman Záhora[15], Katherine C. Saunders[8], Bernado Pons-Estel[16], Alina U. Onofrei[17] and Jeffrey D. Greenberg[18]. [1]Columbia University, New York, NY, [2]AstraZeneca R&D Wilmington, Wilmington, DE, [3]Center for Rheumatology, Albany Medical College, Albany, NY, [4]Universidade Federal do Paraná, Curitiba, Brazil, [5]County Hospital, Kecskemet, Hungary, [6]AstraZeneca R&D, Mölndal, Sweden, [7]Consultant Rheumatologist, ISIC Superspeciality Hospital, New Delhi-11007-, India, [8]CORRONA, Inc., Southborough, MA, [9]CONAART - Hospital Tornú, Buenos Aires, Argentina, [10]Hospital for Special Surgery, New York, NY, [11]Research Institute of Rheumatology -Russian Academy of Medical Science, Moscow, Russia, [12]AstraZeneca R&D Alderley Park, Macclesfield, United Kingdom, [13]Universidade de São Paulo, São Paulo, Brazil, [14]J. M. Ramos Mejía Hospital, School of Medicine, University of Buenos Aires, Buenos Aires, Argentina, [15]Revmatologická ambulance, Terezin, Czech Republic, [16]Hospital Provincial de Rosario, Rosario, Argentina, [17]University of Massachusetts Medical School, Worcester, MA, [18]NYU Hospital for Joint Diseases, New York, NY.

Background/Purpose: The CORRONA International (C.Intl) rheumatoid arthritis (RA) registry is the first multinational RA registry uniformly collecting baseline and longitudinal data. We explored variations in RA disease (dx) activity and drug utilization across regions participating in this new international registry, with the well-established CORRONA US (C.USA) RA registry.

Methods: The C.Intl registry, launched in September 2011, is a multi-center, observational registry. Adult RA patients (pts) have been enrolled from 83 rheumatology practices in 10 countries in 3 regions [Latin America (LA): Mexico, Brazil, Argentina; Eastern Europe (EEu): Poland, Czech Republic, Hungary, Romania, Russia, Ukraine; Asia (AS): India]. The only exclusion criteria are functional class IV and age >85 years old. The C.USA registry was launched in 2001 and enrolls pts from 111 rheumatology practices across the US. There are no exclusion criteria.

Both registries collect data in a similar manner on demographics, lifestyle characteristics, anthropometry, medication exposures, adverse events and comorbidities from rheumatologists and RA pts at regular clinical encounters.

We present baseline descriptive data across the regions participating in C.Intl, including variations in: RA drug utilization, dx activity and functionality. We explored differences stratified by new (≤3 years duration) versus established (3+ years) dx. We compared cross-sectional baseline C.Intl data by region with cross-sectional data from the most recent visit of pts enrolled in C.USA excluding those with functional class IV and >85 years of age. No formal statistical testing was conducted.

Results: As of March 4 2013, 5696 pts had been enrolled in C.Intl and 20,291 RA pts with a functional class <IV and age ≤85 were actively followed in C.USA.

Mean (Standard Deviation (SD)) age was highest in the US and lowest in Asia [LA 54.2 years (12.9), EEu 57.1 (12.2), AS 47.6 (11.9), US 60.3 (12.6)]. The majority of patients were women (LA: 86.7%, EEu: 83.4%, AS: 85.5%, US: 76.6%). Mean (SD) disease duration was indicative of overall established dx [LA 9.9 years (8.7), EU 9.1 (8.6), AS 6.3 (5.8), US 12 (10.1)]. The majority of pts were seropositive (LA 83.5%, EU 76.4%, AS 65.4%, US 76%).

Overall and when stratified by disease duration, dx activity was higher, but functionality, biologic drug utilization and narcotic pain medication use were lower in C.Intl regions compared to C.USA (Table 1).

Table 1*. Disease activity and therapy in RA patients with new (<=3 years) and established (>3 years) disease from international regions and from the US.

	CORRONA International-regions			
	Latin America	Eastern Europe	Asia	CORRONA US
Patients with duration ≤ 3 years				
NUMBER OF PATIENTS (N)	547	747	456	3997
Median duration (IQR)	2 (1–3)	1 (0–2)	2 (1–3)	2 (1–3)
CDAI (mean, SD)	14.8 (13.8)	20.3 (14.4)	14.6 (12.1)	12.6 (12.7)
Remission(CDAI <= 2.8)	107 (19.6%)	62 (8.3%)	66 (14.5%)	921 (23.9%)
Low (CDAI > 2.8 and <= 10)	164 (30%)	160 (21.4%)	134 (29.4%)	1236 (32%)
Moderate (CDAI > 10 and <= 22)	135 (24.7%)	233 (31.2%)	156 (34.2%)	979 (25.4%)
High (CDAI > 22)	141 (25.8%)	292 (39.1%)	100 (21.9%)	721 (18.7%)
mHAQ (mean, SD)	0.4 (0.5)	0.7 (0.6)	0.5 (0.6)	0.3 (0.4)
Main current RA treatment				
On biologic n(%)	57 (10.4%)	51 (6.8%)	4 (0.9%)	1428 (35.7%)
On DMARD(s) but not on biologics n(%)	425 (77.7%)	549 (73.5%)	408 (89.5%)	2242 (56.1%)
No DMARDs or biologics n(%)	65 (11.9%)	147 (19.7%)	44 (9.6%)	327 (8.2%)
On concomitant prednisone n(%)	257 (47%)	217 (29%)	132 (28.9%)	1073 (26.8%)
Narcotic Pain Medication n(%)	9 (1.6%)	5 (0.7%)	0 (0%)	1085 (30.4%)
NSAIDs n(%)	327 (59.8%)	331 (44.3%)	192 (42.1%)	1910 (47.8%)
Patients with duration > 3 years				
NUMBER OF PATIENTS (N)	1475	1755	691	16177
Median duration (IQR)	11 (7–17)	10 (6–16)	7 (5–11)	12 (7–20)
CDAI (mean, SD)	14.5 (13)	18.7 (14.2)	15.8 (11.6)	9.8 (10.8)
Remission(CDAI <= 2.8)	256 (17.4%)	146 (8.3%)	58 (8.4%)	4745 (29.8%)
Low (CDAI > 2.8 and <= 10)	456 (30.9%)	469 (26.7%)	208 (30.1%)	5733 (36.1%)
Moderate (CDAI > 10 and <= 22)	421 (28.5%)	558 (31.8%)	246 (35.6%)	3522 (22.2%)
High (CDAI > 22)	342 (23.2%)	582 (33.2%)	179 (25.9%)	1898 (11.9%)
mHAQ (mean, SD)	0.5 (0.6)	0.8 (0.6)	0.7 (0.6)	0.3 (0.4)
Main current RA Treatment				
On biologic n(%)	341 (23.1%)	270 (15.4%)	2 (0.3%)	9014 (55.7%)
On DMARD(s) but not on biologics n(%)	944 (64%)	1225 (69.8%)	618 (89.4%)	6158 (38.1%)
No DMARDs or biologics n(%)	190 (12.9%)	260 (14.8%)	71 (10.3%)	1005 (6.2%)
On concomitant prednisone n(%)	582 (39.5%)	471 (26.8%)	172 (24.9%)	3537 (21.9%)
Narcotic Pain Medication n(%)	38 (2.6%)	18 (1%)	7 (1%)	3368 (22.5%)
NSAIDs n(%)	884 (59.9%)	787 (44.8%)	295 (42.7%)	7818 (48.3%)

*All data are from baseline visits for CORRONA International, and cross-sectional data from the most recent visit of pts enrolled in CORRONA US.
CDAI: Clinical Disease Activity Index; mHAQ: modified Health Assessment Questionnaire; DMARDs: Disease Modifying Anti-Rheumatic Drugs; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

Conclusion: There are important regional differences in disease activity, functionality, and management of RA, which may be influenced

by variations in demographic and genetic backgrounds of pts populations, prescribing patterns of local physicians and regional differences in standard of care. The ongoing recruitment and follow-up of more patients in C.Intl will enable prospective studies of therapeutic variations and disease outcomes in different regions.

Disclosure: D. A. Pappas, Corrona, Inc., 3, Novartis Pharmaceutical Corporation, 9; **K. Lampl**, AstraZeneca, 1, AstraZeneca, 3; **J. M. Kremer**, Corrona, Inc, 1, Corrona Inc., 3; **S. C. Radominski**, Pfizer, BMS, Astra Zeneca, Amgen, Sanofi, Novartis, Celltrion, Roche, 2, Pfizer, BMS, Astra Zeneca, 5, Pfizer, BMS, Astra Zeneca, Janssen, Sanofi, GSK, 8, -Universidade Federal do Parana- Curitiba-Brzazil, 3; **J. Gal**, None; **F. Nyberg**, AstraZeneca, 1, AstraZeneca, 3; **A. N. Malaviya**, Member Advisory Board Janssen Pharma, Roche Pharma, Sanoffi Pharma, part time consultant rheumatologist at ISIC Hospital, 5; **A. Whitworth**, CORRONA, Inc., 3; **O. L. Rillo**, None; **A. Gibofsky**, AstraZeneca, 5; **T. Popkova**, GlaxoSmithKline, MSD, AstraZeneca, 8; **M. Ho**, AstraZeneca, 3; **I. Laurindo**: Abbott, Astra-Zenica, Bristol, Janssen, Pfizer, 5, Abbott, Astra-Zenica, Bristol, Janssen, Pfizer, Roche, 8; **G. W. Reed**, CORRONA, Inc., 3; **E. M. Kerzberg**, None; **L. Horne**, AstraZeneca, 3, AstraZeneca, 1; **R. Záhora**, None; **K. C. Saunders**, CORRONA Inc., 3; **B. Pons-Estel**, Abbott Laboratories, 2; **A. U. Onofrei**, UMASS Medical School, 3; **J. D. Greenberg**, Corrona, Inc., 1, Astra Zeneca, CORRONA, Novartis and Pfizer, 5.

1304

Anti-Carbamylated Antibody Positivity Is Associated With More Severe Radiological Progression In Patients With Recent Onset ACPA Negative Rheumatoid Arthritis: Results From The Norfolk Arthritis Register (NOAR). Jenny H. Humphreys[1], Suzanne M. Verstappen[1], Kimme L. Hyrich[2], Tarnya Marshall[3], Anne Barton[1], René E.M. Toes[4], Leendert A. Trouw[4] and Deborah P. Symmons[5]. [1]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Sciences Centre, Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom, [3]Norfolk and Norwich University Hospitals Trust, Norwich, United Kingdom, [4]Leiden University Medical Center, Leiden, Netherlands, [5]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academic Health Science Centre, Manchester, United Kingdom.

Background/Purpose: Autoantibodies against carbamylated proteins (anti-CarP) have been associated with more severe radiological damage in patients with rheumatoid arthritis (RA), including in a small subgroup seronegative for anti-citrullinated protein antibodies (ACPA) (1). The aims of this study were to i) validate these findings in a cohort of ACPA negative patients with early RA and ii) investigate the relationship between anti-CarP antibodies and markers of disease activity and disability cross-sectionally and over time.

Methods: The Norfolk Arthritis Register (NOAR) recruits adults with recent onset inflammatory polyarthritis (IP) (≥2 swollen joints for ≥4 weeks) from primary and secondary care in Norfolk, UK. At baseline, 5 and 10 years patients underwent a 51-tender and swollen joint count, gave a blood sample and completed a Health Assessment Questionnaire (HAQ). The 2010 ACR/EULAR classification criteria for RA were applied at baseline. X-rays of the hands and feet were performed at 5 years in all patients and at 10 years in those who were erosive at year 5. X-rays were read by two assessors using the Larsen method. ACPA and CRP measurements were performed in Manchester and anti-CarP antibodies were measured in the baseline sample in Leiden (IgG ELISA). Linear regression models tested for associations between anti-CarP antibodies and HAQ, joint counts, CRP at each assessment and Larsen score at 5 and 10 years, in ACPA negative patients with IP and those with ACPA negative RA. Multivariate models were adjusted for age, gender and disease duration.

Results: 292 patients were included in the analysis; 205 (72%) female; median age at symptom onset (IQR) 47 (36–56) years. Median symptom duration at baseline (IQR) was 26 (12–53) weeks. 87 (30%) patients were positive for anti-CarP antibodies and 161 (57%) patients satisfied the 2010 RA criteria. Anti-CarP positivity was not associated cross-sectionally with HAQ or joint counts at baseline, but there was a trend to association with CRP (table 1). X-rays were available on 240 patients at 5 years, 72 patients at 10 years. Anti-CarP positivity was associated with raised CRP at 5 years, but there was no association with Larsen score. At 10 years there was a significant association between anti-CarP antibodies and Larsen score in IP (adjusted β-coefficient 16.2, 95% CI 2.73–29.7), and RA subgroup (adjusted β-coefficient 21.2, 95% CI 3.00, 39.54).

Table 1. Association between baseline anti-CarP antibody status and outcomes at baseline, 5 and 10 years

Outcome	IP Multivariate β coefficient (95% CI)	RA Multivariate β coefficient (95% CI)
Baseline:	*n=292*†	*n=161*§
HAQ (per0.25 units)	0.06 (−0.12, 0.23)	−0.03 (−0.27, 0.21)
Tender/swollen joint count	−0.72 (−3.32, 1.88)	−2.68 (−5.75, 0.39)
CRP (mg/l)	6.76 (−0.55, 14.07)	7.55 (−2.68, 17.80)
5 year:	*n=240*	*n=129*
HAQ (per0.25 units)	0.02 (−0.17, 0.21)	−0.19 (−0.46, 0.07)
Tender/swollen joint count	−0.60 (−3.02, 1.82)	−2.37 (−5.91, 1.17)
CRP(mg/l)	*3.95 (0.89, 7.01)	*4.66 (0.96, 8.35)
Larsen score	0.52 (−2.84, 3.89)	2.61 (−2.55, 7.79)
10 year:	*n=72*	*n=36*
HAQ (per0.25 units)	0.03 (−0.19, 0.24)	−0.19 (−0.50, 0.12)
Tender/swollen joint count	−0.82 (−3.18,1.54)	−1.67 (−5.14, 1.80)
CRP(mg/l)	0.35 (−2.26, 2.95)	0.78 (−1.74, 3.30)
Larsen score	*16.22 (2.73, 29.7)	*21.2 (3.00, 39.54)

*p<0.05, † 87 anti-CarPA positive, §40 anti-CarP antibody positive

Conclusion: In a cohort of patients with ACPA negative IP and ACPA negative early RA, anti-CarP antibodies were associated with higher CRP at baseline and 5 years, and more severe radiographic disease at 10 years follow up in patients who were erosive at 5 years. Only a small proportion of patients had x-rays at 10 years, thus this association may be liable to selection bias. Nevertheless, anti-CarP antibodies may identify an important group of ACPA negative patients with poor long-term prognosis.

Reference:

(1) Shi J et al PNAS 2011; 108:17373

Disclosure: J. H. Humphreys, None; **S. M. Verstappen**, None; **K. L. Hyrich**, None; **T. Marshall**, None; **A. Barton**, None; **R. E. M. Toes**, None; **L. A. Trouw**, Janssen Biologics, 9; **D. P. Symmons**, None.

1305

Clinical Joint Involvement Is Decisive For Radiographic Progression. Miriam Gärtner[1], Farideh Alasti[1], Gabriela Supp[1], Josef S. Smolen[2] and Daniel Aletaha[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria.

Background/Purpose: Today's therapeutic targets in rheumatoid arthritis (RA) are remission or low disease activity, but it was shown that joint damage may continue to progress despite these favourable clinical states.[1;2] While progression of joint damage is related to joint swelling,[3] radiographic damage may progress even without evidence of clinical synovitis, at least in early RA.[4]

It was the aim of this study, to evaluate the frequency of radiographic progression in clinically persistently inactive joints of patients with established RA.

Methods: We included 134 RA patients (mean disease duration: 7.12±9.5yrs.) who showed a radiographic progression (increase>1) in any of the joints assessed by the Sharp van der Heijde (SvdH) score over an observational period of 3–5 years. To conform with the records of clinical joint assessment, we only considered radiographic progression in any of the 22 hand/finger joints (10 proximal interphalangeal joints, 10 metacarpophalangeal joints, 2 wrists), but excluded the feet (not assessed by the 28 joint count). Clinical data on individual joints (swelling and tenderness) from each clinical visit performed between one year prior to the baseline x-ray until the time of the x-ray endpoint were collected from the patient charts. We evaluated associations of clinical joint activity (swelling and tenderness) and radiographic progression on the individual joint level.

Results: The mean±SD time between x-rays was 3.5±0.4yrs and the mean number of clinical visits per patient was 16.2±4.6. A total of 195 (6.6%) of the 2948 evaluated joints showed progression in erosions and 343 (12.7%) worsened in joint space narrowing (JSN). Of all joints with progression in erosions, 64 (32.8%) were never swollen during the observation period (in 40 patients) and only 18 (9.2%) never showed any activity also by tenderness.

In the total patient population, progression was higher in joints with clinical swelling (during the observation period) compared to joints without

swelling (1.76±1.06 vs 1.28±0.68; p=0.01). We found a significantly higher baseline SvdH Score in patients with radiographic progression in clinically inactive joints vs. active joints (68.2±78.8 vs 42.5±51.2; p=0.022). The overall sensitivity for progression of damage of any joint activity during the observation period was 73.1% for erosion, and 73.5% for JSN. Only 25.6% of the patients showing radiographic progression in clinically inactive joints were treated with a biological during the majority (>50%) of the observation period.

Conclusion: Only 9% of joints with radiographic progression in patients with established RA show continued absences of clinical activity by both swelling and tenderness, and their degree of progression is low. Thus, structural progression without evidence of clinical activity is a negligible event on joint level. Risk factors of this are high baseline radiographic scores and absence of biological treatment, but the strongest risk factor for progression remains to be clinical joint involvement.

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Do Sustained Clinical Remission and Sustained Low Disease Activity Equally Predict Functional Status In Early Rheumatoid Arthritis?

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Background/Purpose: Sustained clinical remission (REM) is the therapeutic goal in rheumatoid arthritis (RA) but low disease activity (LDA) may be acceptable. Little is known whether sustained LDA is "as good" as sustained REM for reducing disability in early rheumatoid arthritis (ERA). Our objectives were to: (1) compare the prevalence of sustained REM and sustained LDA in ERA patients and describe any differences in core variables among the groups and; (2) determine if sustained REM and LDA are independently associated with function, measured by the health assessment questionnaire disability index (HAQ-DI).

Methods: ERA patients with at least 2 years of follow-up in the Canadian early ArThritis CoHort (CATCH) (N=833) were included in the analysis. REM/LDA was classified according to the clinical disease activity index (CDAI; ≤2.8 vs. 2.9–10) and simplified disease activity index (SDAI; ≤3.3 vs. 3.4–11). REM and LDA was defined as sustained if present for ≥ 2 consecutive visits or ≥ 6 months during the first 18 months. Linear regression models were performed with HAQ-DI score at 2 years as the outcome, and each REM or LDA definition as the independent variable, adjusted for baseline confounders.

Results: Only 77 (9%) patients achieved sustained REM by each the CDAI and SDAI definitions over the first 18 months. 426 (51%) were in sustained CDAI LDA and 333 (40%) were in sustained SDAI LDA. At baseline, there were no significant differences in demographic, clinical, laboratory or early treatment variables between patients in REM vs. LDA by either index. At follow-up, mean HAQ-DI scores for those in sustained REM ranged from 0.10 to 0.13 compared to baseline HAQ-DI (range 0.87–1.0) and scores were 0.39–0.40 at follow-up for those in sustained LDA compared to their baseline values ranging from 0.97–0.98. Overall, HAQ-DI scores were significantly lower at year 2 for those achieving sustained REM compared to sustained LDA (table). Joint counts, pain, fatigue and global health assessment were also significantly lower in the REM groups (table). Multivariable regression analyses showed that sustained CDAI REM and sustained SDAI REM were both independently associated with lower HAQ-DI than sustained LDA (p<0.001).

Table. HAQ-DI scores and differences in core variables among patients achieving sustained REM vs. LDA according to CDAI and SDAI cut-offs at year 2.

	CDAI			SDAI		
	Sustained REM	Sustained LDA	*p*	Sustained REM	Sustained LDA	*p*
TJC-28, mean ± SD	0.46 ± 1.21	1.34 ± 2.81	0.002	0.58 ± 1.84	1.42 ± 2.88	0.001
SJC-28, mean ± SD	0.58 ± 1.70	0.88 ± 2.00	0.009	0.42 ± 1.27	0.92 ± 1.97	0.002
CRP, mean ± SD mg/L	5.29 ± 8.71	5.37 ± 8.55	0.87	5.37 ± 9.08	5.34 ± 8.79	0.58
ESR, mean ± SD mm/hr	14.3 ± 12.0	15.1 ± 14.8	0.988	12.9 ± 11.7	14.9 ± 14.5	0.27
Pt-GA, mean ± SD cm (0–10 cm)	0.68 ± 1.33	2.42 ± 2.53	<0.001	0.89 ± 1.57	2.30 ± 2.45	<0.001
MD-GA, mean ± SD cm (0–10 cm)	0.36 ± 0.93	0.78 ± 1.30	<0.001	0.43 ± 1.08	0.77 ± 1.29	0.01
VAS pain, mean ± SD cm (0–10 cm)	8.60 ± 15.9	23.4 ± 24.5	<0.001	10.7 ± 18.3	22.0 ± 23.0	<0.001
VAS fatigue, mean ± SD cm (0–10 cm)	12.9 ± 21.4	26.4 ± 26.6	<0.001	15.3 ± 22.7	24.9 ± 25.1	<0.001
HAQ-DI, mean ± SD	0.10 ± 0.20	0.40 ± 0.55	<0.001	0.13 ± 0.26	0.39 ± 0.53	<0.001

Conclusion: HAQ-DI scores at year 2 are significantly lower among patients who achieve sustained REM vs. sustained LDA. This difference is greater than the minimal clinically important difference for HAQ of 0.22, suggesting there are clinically important differences in long term function based on best achieved sustained disease activity state. Further study is needed to understand what influences achieving sustained REM as opposed to sustained LDA in early RA.

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Synovial Subset–Derived Baseline Serum Biomarkers Segregate Rheumatoid Arthritis Patients Into Subgroups With Distinct Serum Protein and Clinical Characteristics.

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Background/Purpose: Rheumatoid arthritis (RA) is a heterogeneous disease. Predictive biomarkers have the potential to enhance treatment effectiveness by enabling identification of likely responders to a specific therapy.[1,2] Our previous analysis of RA synovium showed the existence of 3 large subsets characterized by gene expression signatures suggestive of lymphoid, myeloid, or fibroid biology.[3] In the present study, we demonstrated the ability of serum proteins produced by genes selected from those signatures to recapitulate the segregation of patients into these subsets.

Methods: Several protein biomarker candidates were selected based on differential gene expression in 1 RA synovial subset versus the others and on detectability in serum. Quantitative immunoassay methods were used to measure these proteins in baseline serum from 3 biologic-naive RA cohorts: Cohort 1 (cross-sectional natural history cohort, n = 197), SERENE[4] (n = 412), and TOWARD[5] (n = 526). Levels of serum proteins were also compared between Cohort 1 patients and healthy controls (n = 30). Serum protein data were used to cluster patients and proteins. Patients were clustered into a specified number of groups using Partitioning Around Medoids (PAM), whereas proteins were clustered hierarchically. Each clinical characteristic of patients in each biomarker group was compared to the respective characteristic in all other groups within the same cohort using the Wilcoxon rank-sum test of each pair.

Results: Analysis of baseline serum biomarker levels in Cohort 1 showed that MMP1, MMP3, MMP9, TIMP3, TIMP4, CXCL13, IL8, CCL2, CCL13, CXCL10, and sICAM1 were elevated compared to those in healthy controls ($p < 0.0001$). These analytes had a wide dynamic range in all RA cohorts analyzed. The patient populations within each RA cohort segregated reproducibly into 3 groups, named by the characteristics of the serum proteins in each group: Protease, Chemokine, and Low Inflammatory. The 2 inflammatory groups (Protease and Chemokine) were dominated by serum biomarkers related to lymphoid and myeloid biology, respectively (Table 1). The third group generally displayed lower levels of inflammatory proteins, CRP, and ESR and was less often rheumatoid factor positive. This group likely corresponded to the synovial fibroid subset. The clinical characteristics of each biomarker group are summarized in Table 2.

Table 1. Three Major RA Synovial Subsets and the Corresponding Serum Biomarkers

Synovial Subsets	Serum Protein Characteristics	Serum Biomarkers
Lymphoid	Inflammatory - protease	MMP1, MMP3, MMP9, TIMP3, TIMP4, CXCL13
Myeloid	Inflammatory-chemokine	IL8, CCL2, CCL13, CXCL10, sICAM1
Fibroid	Low inflammatory	Low CRP, ESR, and inflammatory biomarkers

Table 2. Clinical Characteristics of Patients in Each Biomarker Group in All Cohorts Analyzed

	Cohort 1 n = 197			SERENE n = 412			TOWARD n = 526		
Groups	Protease/ Lymphoid	Chemokine/ Myeloid	Low inflammatory	Protease/ Lymphoid	Chemokine/ Myeloid	Low inflammatory	Protease/ Lymphoid	Chemokine/ Myeloid	Low inflammatory
Population	26	39	35	34	34	32	47	35	18
CRP, mg/dL	0.8	1.7	0.4	3.1	1.2	0.7*	0.9	3.1	0.9
ESR, mm/h	39	29	21*	47	42	33*	37	52	34
SJC (66)	4	7	2*	18	18	15.5*	16	18	16
TJC (68)	20	18	12*	26	27	24	26	28	27
RF status (+), %	86	84	69	85	79	70	82	76	60
Disease duration, years	7	7	5	4.8	5.3	3.4	7.8	6.9	5.8
HAQ	1.25	1.38	1.06	1.72	1.65	1.46*	1.34	1.61	1.42

Data shown as medians.
* $p < 0.05$ in low inflammatory group versus all other groups within the same cohort by Wilcoxon rank-sum test of each pair.

Conclusion: We have identified serum biomarkers that segregate groups of patients associated with lymphoid and myeloid subtype–derived biomarkers in 3 large RA cohorts. These subpopulations of RA patients with distinct pathobiology can possibly demonstrate differential clinical response to treatments that target different inflammatory mediators. In addition, a low-inflammatory group was observed in all cohorts analyzed. This group is less likely to respond well to current biologic anti-inflammatory therapy.

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Low Accuracy Of Radiograph Reports In Identifying Patients With Rheumatoid Arthritis In The Veterans Affairs Rheumatoid Arthritis Registry. Maria P. Martes[1], Alan R. Erickson[2], Ted R. Mikuls[3] and Grant W. Cannon[4]. [1]Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [2]Omaha VA and University of Nebraska Medical Center, LaVista, NE, [3]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [4]Salt Lake City VA and University of Utah, Salt Lake City, UT.

Background/Purpose: The accurate interpretation of hand radiographs is critical in the diagnosis and management of rheumatoid arthritis (RA) patients. This project determined first, if the reading request and/or clinical history provided to the radiologist (RAD) improved the accuracy of the reported findings and second if the overall interpretation of the radiographs in the Veterans Affairs (VA) computerized patient record system (CPRS) was consistent with that of an expert reader (ER).

Methods: Bilateral hand and wrist radiographs of 302 RA patients enrolled in the Veterans Affairs Rheumatoid Arthritis (VARA) registry, a multi-center observational cohort, were assessed by an ER for the presence and/or absence of erosions (ERO) and/or joint space narrowing (JSN). RAD reports on these patients were evaluated by a blinded chart abstractor (CA) to determine if the CPRS report contained a clinical history for RA and if there was a specific request for the evaluation for ERO and/or JSN. The CA also specifically noted if a RAD reported the diagnosis of RA and/or an alternative diagnosis such as osteoarthritis (OA), mentioned ERO and/or JSN.

Results: The patients' mean age was 64±11 years, 88% were male, RA disease duration was 13±11 years, and the majority was sero-positive for rheumatoid factor (84%) and anti-CCP (80%). As noted below, 157 were reported to have abnormal findings by both CPRS RAD and ER and 38 patients were reported normal by both CPRS RAD and ER. Ten patients were reported as abnormal by CPRS RAD but were reported normal by ER and 97 were reported abnormal by ER but normal by CPRS RAD (35% overall discordance). Of the 302 reports, 27 (8.9%) were given an alternative diagnosis by the CPRS RAD, the most common being OA and Calcium pyrophosphate deposition disease (CPPD). The sensitivity, specificity, positive and negative predictive values were determined comparing the RAD to the ER as gold standard.

		Expert Reader Abnormal	Normal	TOTAL
CPRS Report	Abnormal	157	10	167
	Normal	97	38	135
TOTAL		254	48	302
Sensitivity				61.8%
Specificity				79.2%
Positive predictive value				94.0%
Negative predictive value				28.1%

A notation of 'RA' and/or a specific request for an evaluation of ERO and/or JSN in the X-ray request did not improve the accuracy of the diagnosis and/or reporting of ERO and JSN. The only factors associated with higher likelihood of CPRS RAD reporting RA was joint swelling count ($p<0.01$) and C-reactive protein level ($p<0.05$).

Conclusion: The accuracy of RAD to identify patients with RA in comparison to the ER is not enhanced in reports that provided the RAD with a clinical history and specific directions to assess for ERO and JSN. While a positive RA diagnosis by the RAD in CPRS has a high potential to be correct, the absence of this diagnosis does not possess sufficient accuracy to exclude the diagnosis of RA.

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Prognosis Of Seronegative Patients In a Large Prospective Cohort Of Patients With Early Inflammatory Arthritis. Lillian J. Barra[1], Janet E. Pope[1], Boulos Haraoui[2], Carol A. Hitchon[3], J. Carter Thorne[4], Edward C. Keystone[5], Diane Tin[4], Gilles Boire[6] and Vivian P. Bykerk[7]. [1]Schulich School of Medicine and Dentistry, Western University, London, ON, [2]Centre Hospitalier de l'Université de Montréal, Montreal, QC, [3]University of Manitoba, Winnipeg, MB, [4]Southlake Regional Health Centre, Newmarket, ON, [5]Mount Sinai Hospital, University of Toronto, Toronto, ON, [6]Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, [7]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY.

Background/Purpose: Rheumatoid Factor (RF) and anti-Cyclic Citrullinated Peptide (anti-CCP) are believed to be associated with more severe clinical outcomes; however, studies in Early Inflammatory Arthritis (EIA) have yielded conflicting results. The objective of this study is to determine the prognosis of baseline anti-CCP and RF-negative patients at 12 months follow-up in the Canadian Early Rheumatoid Arthritis cohort (CATCH).

Methods: Data were collected on patients enrolled in CATCH, a multicentre, observational, prospective inception cohort of patients with Early Inflammatory Arthritis (EIA). Treatment was based on physician discretion. IgM RF was measured and depending on the site, two different anti-CCP2 IgG (CCP) kits were used (Euroimmune™ and Inova™). Disease activity was determined using the Disease Activity Score-28 (DAS28) and remission was defined as a DAS28<2.6. Presence of erosions was determined using plain radiographs of the hands and feet. Follow-up was 12 months. Multiple logistic regression was used to account for confounders.

Results: 216/841 (26%) of patients were negative for both RF and anti-CCP2. These patients were older (57 years old) and more likely male (31%) compared to seropositive patients (51 years old and 23% male), $p<0.001$. Seronegative patients were less likely to meet 1987 ACR and 2010 ACR/EULAR criteria for RA, however, at baseline they had higher swollen joint counts (SJC) (9 vs 6), more erosive disease (32% vs. 23%) and higher DAS28 scores (5.00 vs. 4.75), $p<0.05$. Seronegative patients had shorter duration of symptoms (166 days vs. 192, $p=0.007$). The initiation of DMARDs, biologics and steroids was similar between the two groups. At 12 months follow-up, seronegative patients had greater reductions compared to seropositive patients in SJC (7 vs.4) and similar DAS28 scores (2.97 vs. 2.83); $p=0.0017$ and $p=0.3$, respectively. Accounting for confounders, seronega-

tive patients were as likely to achieve DAS28 remission as seropositive patients (OR 1.18; 95%CI: 0.70–1.99), however, they were less likely to have erosive disease at follow-up (OR 0.43; 95%CI: 0.19–0.95, p<0.04).

	Seronegative	Seropositive	p-value
Baseline:			
N	216	625	
Age, mean years (SD)	57 (15)	51 (14)	<0.0001
Male	67 (31)	145 (23.2)	0.0225
Symptom Duration, days mean (SD)	166 (87)	192 (98)	0.0007
Ever Smoker	111 (51.6)	369 (59.1)	0.055
SJC28, mean (SD)	8.8 (6.8)	6.5 (5.6)	<0.0001
TJC28, mean (SD)	9.3 (7.2)	7.1 (6)	<0.0001
ESR, mean (SD)	24.88 (22)	27.26 (22.59)	0.6513
CRP, mean (SD) (mg/L)	13.77 (18.22)	13.39 (16.94)	0.7864
Erosions	58/181 (32)	124/517 (24)	0.0335
DAS28, mean (SD)	5.00 (1.6)	4.75 (1.49)	0.0493
1987 ACR RA criteria	131 (60.7)	442 (70.7)	0.007
2010 ACR/ EULAR RA criteria	96 (44.4)	482 (77.1)	<0.0001
DMARDs	186 (86)	550 (88)	0.4567
Biologics	5 (2.4)	19 (3)	
Corticosteroids	125 (58)	319 (51.1)	0.0859
Follow-up			
N	147	474	
DAS28 Remission	80 (54)	269 (57)	0.6190
OR (95%CI)	1.18 (0.70–1.99)	Reference	0.5114
Erosive Disease	14/66 (21)	85/279 (30)	0.1350
OR (95%CI)	0.43 (0.19–0.95)		0.0366

* Values are N (%) unless otherwise indicated.
CCP=anti-cyclic Citrullinated Peptide 2, RF= Rheumatoid Factor, SJC28= Swollen Joint Count 28, TJC28= Tender Joint Count 28, ESR= Erythrocyte Sedimentation Rate, CRP= C-Reactive Protein, DAS28= Disease Activity Score 28, DMARDs= Disease Modifying Anti-Rheumatic Drugs.

Conclusion: Although seronegative EIA patients have higher disease activity at baseline compared to seropositive patients, they have a good response to treatment and are less likely to have erosive disease at follow-up.

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Evaluation Of The Japanese Patients With Rheumatoid Arthritis (RA) Of Rapid Radiographic Progression (RRP) Treated With Synthetic Disease Modifying Anti-Rheumatic Drugs (DMARDs) In Daily Practice: A Large-Scale Prospective Longitudinal Cohort Study (an interim report of Apple Survey). Akitomo Okada[1], Atsushi Kawakami[2], Takaaki Fukuda[3], Toshihiko Hidaka[4], Tomonori Ishii[5], Yukitaka Ueki[6], Takao Kodera[7], Munetoshi Nakashima[8], Yuichi Takahashi[9], Seiyo Honda[10], Yoshiro Horai[2], Tomohiro Koga[2], Mami Tamai[11], Kiyoshi Aoyagi[2], Ryu Watanabe[5], Hiroshi Okuno[12] and Katsumi Eguchi[13]. [1]Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan, [2]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Kurume University Medical Center, Kurume, Japan, [4]Zenjinkai Shimin-No-Mori-Hospital, Miyazaki, Japan, [5]Tohoku University, Sendai, Japan, [6]Sasebo Chuo Hospital, Sasebo, Japan, [7]Tohoku Kosei Nenkin Hospital, Sendai, Japan, [8]Japanese Red Cross Nagasaki Genbaku Hospital, Nagasahi, Japan, [9]Yu Family Clinic, Sendai, Japan, [10]Kurume University School of Medicene, Kurume, Japan, [11]Center for Health & Community Medicine, Nagasaki University, Nagasaki, Japan, [12]Tohoku University Hospital, Sendai, Japan, [13]Sasebo City General Hospital, Sasebo, Nagasaki, Japan.

Background/Purpose: Disease modifying anti-rheumatic drugs (DMARDs) are known to inhibit radiographic progression in patients with rheumatoid arthritis (RA). However, there has been few epidemiological report of longitudinal radiographic progression in RA patients captured in daily practice. In 26 related-centers of the Nagasaki University and Tohoku University in Japan, we are conducting a large-scale prospective study (Apple Survey) to investigate extent of radiographic progression. We have tried to assess the extent of rapid radiographic progression (RRP) in DMARDs-treated RA patients.

Methods: Nine hundred forty-two patients with RA, treated not by biologic DMARDs but by synthetic DMARDs at entry, were registered between May 09 and March 12 in this study. We have selected 742 RA patients having DAS28-ESR at entry >3.2 or apparent radiographic bone erosion and followed at least 1 year. Regarding to the RA patients treated by synthetic DMARDs without biologic DMARDs for 1 year, two hundred sixty-one patients had evaluable data at present. Patients gave their informed consent to be subjected to the protocol that was approved by the Institutional Review Board of Nagasaki University, Tohoku University and related centers. DAS28-ESR was assessed every 3 months. Radiographs of the hands and feet were taken every 6 months. The images were scored by trained readers through modified total Sharp score (mTSS). RRP was defined as yearly progression of mTSS >3.0. We have examined what variables are associated with the development of RRP at 1 year.

Results: RRP was found in 31 out of 261 patients (11.9%). Eleven variables including gender, age, disease duration at baseline, DAS28-ESR at baseline, time-integrated DAS28-ESR during 1 year, CRP at baseline (mg/dl), presence of autoantibodies (RF or ACPA), the use of MTX or non-MTX DMARDs, the use of prednisolone, HAQ at baseline, mTSS at baseline were evaluated to explore the development of RRP at 1 year. Logistic regression analysis has found that short disease duration ($p = 0.013$, 2 year decrease), high time-integrated DAS28-ESR ($p = 0.027$, 10 increase) and high mTSS at baseline ($p = 0.010$, 5 increase) are independent variables to predict the development of RRP. There was the trend of non-MTX DMARDs use ($p = 0.071$) toward RRP at 1 year.

Conclusion: Considering the development of RRP, mTSS at baseline is high and the progression of joint destruction may occur at the early-stage of RA in case of treatment without MTX. Since not high DAS28-ESR at baseline but high time-integrated DAS28-ESR is also an independent predictor toward RRP, tight disease control by treat-to-target strategy is needed in daily clinical practice.

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Aiming Simple Disease Activity Score Remission At One Year Leads To Better 3-Year Radiographic and Functional Outcomes Than aiming low Disease activity in Early Rheumatoid Arthritis Patients Treated In Routine Practice. Data From Espoir Cohort. Adeline Ruyssen-Witrand[1], Gregory Guernec[2], Delphine Nigon[3], Gabriel Tobon[4], Bénédicte Jamard[5], Anne-Christine Rat[6], Olivier Vittecoq[7], Alain G. Cantagrel[8] and Arnaud L. Constantin[1]. [1]Purpan University Hospital, Toulouse, France, [2]Inserm, Toulouse, France, [3]Purpan University Hospital, Toulouse Cedex 9, France, [4]Unit of immunology, Brest, France, [5]Toulouse University Hospital, Toulouse, France, [6]Université de Lorraine, Nancy, F-54000, France; Inserm, CIC-EC CIE6, Nancy, F-54000, France; CHU de Nancy, Clinical Epidemiology and Evaluation Department, Nancy, F-54000, France; CHU de Nancy, Rheumatology department, Nancy, France, [7]Rouen University Hospital & Inserm905, University of Rouen, Rouen Cedex, France, [8]Centre Hospitalier Universitaire de Toulouse, Toulouse, France.

Background/Purpose: The ultimate goal of Disease Modifying Anti-Rheumatic Drugs (DMARDs) treatment in early rheumatoid arthritis (RA) is to achieve remission in order to prevent structural damage and long term disability according to EULAR's recommendations. However, remission status is not always obtained and low disease activity (LDA) might be an alternative goal. Recently, an ACR/EULAR initiative recommended the use of Simple Disease Activity Score (SDAI) as a remission criterion. The aim is to assess whether obtaining SDAI remission status or LDA status at one year has a differential impact on Sharp van der Heijde Total Score (mTSS) and Health Assessment Questionnaire Disability Index (HAQ-DI) score at 3 years in early RA patients treated in routine practice.

Methods: *Patients:* 813 DMARD and corticosteroids-naïve patients with early arthritis were included in the ESPOIR cohort and were prospectively followed. Among them, 625 fulfilled the 2010 ACR/EULAR criteria for RA at baseline and had a SDAI score at one year. 496 of them had available radiographs at 3 years and 535 had available HAQ-DI score at 3 years. *Data analyzed:* Remission was defined by a SDAI $\leq$ 3.3; LDA by a 3.3 < SDAI score $\leq$ 11. Radiographs were centrally read by one rheumatologist and scored using the Sharp van der Heijde scoring method at the inclusion and 3 years. *Analysis:* comparison of mTSS and HAQ-DI scores at 3 years between patients in SDAI remission or LDA at one year using a t-test. A multivariate analysis using a linear mixed model was performed to assess the independent effect of patient SDAI status at one year on mTSS and HAQ-DI at 3 years, including age, gender, disease duration, clinical center, erosions at baseline, ACPA presence, smoking habits, DMARDs use, the delay of DMARD start, biologic agents use and glucocorticoid use as covariables. The comparison

between remission and LDA in terms of mTSS and HAQ-DI score at 3 years was obtained from the multivariate model with contrasts method.

Results: Of the 625 patients included in the study (age median=49 years [IQR:40–58], women: n=391 (79%), disease duration median=5 months [IQR:3–8] n=121 (19%) were in remission after one year and n=223 (36%) were in LDA. The mTSS mean score at 3 years was about 9.6 (SD: 9.2) in patients in remission at one year compared to 15.8 (SD:16.1) in patients with LDA (t-test: p=0.0005). The HAQ-DI mean score at 3 years was about 0.23 (SD: 0.42) in patients in remission at one year compared to 0.43 (SD:0.52) in patients with LDA (t-test: p=0.0005). After multivariate analysis, the remission status obtained after one year was independently associated with lower 3-year mTSS compared to LDA status (mean difference=−0;265, SD=0.094, p=0.005). After multivariate analysis, the remission status obtained after one year was not independently associated with HAQ-DI score at 3 years compared to LDA status (mean difference=−0;54, SD=0.59, p=0.4).

Conclusion: This study shows that aiming SDAI remission at one year leads to better radiographic and functional outcomes at 3 years compared to LDA in early RA patients treated in routine practice.

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A Multi-Biomarker Disease Activity Score Correlates With Radiographic Progression In Early Rheumatoid Arthritis: Results From a Randomized Trial. Karen Hambardzumyan[1], Rebecca Bolce[2], Scott E. Cruickshank[3], Eric H. Sasso[2], David Chernoff[2], Kristina Forslind[4], Saedis Saevarsdottir[1], Ingemar F. Petersson[5], Pierre Geborek[5], Sofia Ernestam[6] and Ronald F van Vollenhoven[1]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Crescendo Bioscience Inc., South San Francisco, CA, [3]Scott E. Cruickshank and Associates, Inc., Santa Barbara, CA, [4]Section of Rheumatology, Department of Medicine, Helsingborg General Hospital, Helsingborg, Sweden, [5]Lund University, Lund, Sweden, [6]Karolinska University Hospital, Huddinge, Sweden.

Background/Purpose: In early rheumatoid arthritis (eRA), predictors of radiographic damage would be useful for optimal targeting of therapy. It has been suggested that combining various biomarkers may improve this prediction. The multi-biomarker disease activity (MBDA, Vectra DA) score has been validated as a measurement of rheumatoid arthritis (RA) disease activity. The MBDA score ranges from 1–100 and is based on 12 serum biomarkers: VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL-40, leptin, resistin, SAA and CRP. In the SWEFOT study, 487 patients with eRA (symptom duration < 1 year) were started on methotrexate (MTX); at 3 months, responders (DAS28 < 3.2) continued MTX monotherapy and were followed in regular care, whereas non-responders were randomized to receive either triple DMARD therapy or the addition of infliximab.

The objective of this study was to assess the value of the baseline MBDA score as a predictor of radiographic progression over one year in eRA.

Methods: Analyses were performed for 235 patients from SWEFOT with baseline (BL), month 3 (n=220) and week 52 (n=235) assessments of DAS28, DAS28-CRP, CRP, MBDA score, and radiographs at BL and 1 year (using the Van der Heijde modified Sharp score [SHS]). Month 3 responders and non-responders were analyzed together. Associations between disease activity indices and radiographic progression at one year were evaluated using Wald's chi-square test. Spearman's correlation coefficients (r) were determined for the BL disease index scores versus radiographic progression (ΔSHS >5) over 1 year.

Results: For the 235 patients, mean BL values were: CRP = 3.5 mg/dl, DAS28-ESR = 5.7, and MBDA = 60. More than half of patients with low CRP (≤ 1 mg/dL) or moderate DAS28 at BL had a high BL MBDA score (>44). Baseline SHS was 4.7 (median 2.0); mean ΔSHS from BL to 1 year was 3.1 ± 6.0 (median 1.0). Baseline MBDA score correlated with ΔSHS from BL to 1 year: r = 0.271 (p<0.001); correlations of DAS28, DAS28-CRP, and CRP with ΔSHS were weaker: r = 0.063, 0.014, and 0.178, respectively (p=NS, p=NS, p=0.006). In bivariate analyses adjusting for DAS28 or CRP, MBDA had a significant additive value to prediction of radiographic progression at one year (p < 0.01). Of the 43 patients with ΔSHS > 5, 98% had a high BL MBDA score, 77% a high DAS28 (>5.1) and 49% a high CRP (>3mg/dL). Of patients with a high MBDA score at BL, 21% had SHS progression >5, versus 3% and 0% for moderate and low MBDA, respectively (p<0.04). In patients with a high MBDA score at 3 months or 1 year, 24/96 (25%) and 13/40 (33%) progressed (ΔSHS > 5) from BL to 1 year, respectively.

Conclusion: In eRA patients who were treated initially with MTX and then according to a step-up protocol, the MBDA score at baseline correlated significantly and independently from CRP or DAS28, with radiographic progression during the first year. A high MBDA score at baseline was associated with a higher risk of radiographic progression, even in patients who had a low CRP or moderate DAS28 at baseline. Conversely, for patients with low or moderate MBDA at baseline the risk of radiographic progression was small. In untreated eRA, MBDA may help identify patients at low versus high risk of radiographic progression and thereby support rational treatment choices.

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Tobacco Exposure Is Associated With Radiographic Damage In Hispanic and African American Rheumatoid Arthritis Patients. Rodolfo Perez Alamino[1], Luis R. Espinoza[2], Gail S. Kerr[3], Christopher Swearingen[4], Chunqiao Luo[4], Yusuf Yazici[5], Yvonne R. S. Sherrer[6], Edward L. Treadwell[7], Angelia D. Mosley-Williams[8], Sharon Dowell[9], Ignacio Garcia-Valladares[10], Theresa Lawrence-Ford[11], Adrian Godoy[9], Akgun Ince[12] and Cindy Flower[13]. [1]Lousiana State University and LSU Medical Center, New Orleans, LA, [2]LSU Medical Center, New Orleans, LA, [3]Washington DC VAMC and Georgetown University and Howard University Hospital, Washington, DC, [4]University of Arkansas for Medical Sciences, Little Rock, AR, [5]New York University Hospital for Joint Diseases, New York, NY, [6]Centre Rheum Immunol Arthritis, Fort Lauderdale, FL, [7]East Carolina University, Greenville, NC, [8]John Dingell VAMC, Detroit, MI, [9]Howard University, Washington, DC, [10]Guadalajara, Guadalajara, Mexico, [11]North Georgia Rheumatology Group, PC, Lawrenceville, GA, [12]Saint Louis University, St. Louis, MO, [13]University of the West Indies, Bridgetown, Barbados.

Background/Purpose: Although the etiology of rheumatoid arthritis (RA) is unknown, there are reported interactions of genetic and environmental factors. Tobacco exposure is a well-documented risk factor, both in Caucasian and African American (AA) RA cohorts for disease susceptibility and severity. Yet there are no data addressing the association of tobacco use with RA-phenotypic expression, particularly within multi-ethnic cohort, specifically Hispanic patients. We examined the association of tobacco exposure and RA phenotype in a diverse ethnic RA cohort.

Methods: Patients enrolled in EMRAC, with baseline demographics data (age, gender, tobacco use), RA disease status (severity [RF, ACPA, nodules, erosions], activity [TJC, SJC, ESR, CRP, CDAI, DAS28, RAPID3], and extra-articular manifestations) were available for analysis. Smoking status was categorized as current, former, or never use. Comparisons of RA-features with smoking status between ethnic groups were analyzed using Cochran-Mantel-Haenzel test. Any association between tobacco exposure and clinical disease activity measures and outcomes were estimated using logistic regression adjusting for race (Caucasian vs. Non-Caucasian), age and disease duration.

Results: Of 861 EMRAC patients available for analysis, the mean age was 56.3 (sd 13.5) years, and disease duration 10.2 (sd 10.1) years. 405 (47%) were Caucasians, 287 (33%) AA and 169 (20%) Hispanics. Erosions were reported in 10%, predominantly in AA (25%). Only 20% reported tobacco use (ever), and exposure was not associated with disease activity [high CDAI score: non-smokers (49%) vs. former (53%) and current smokers (62%) (p=0.253); high DAS 28 score: non-smokers (61%) vs. former (62%) and current smokers (78%) (p=0.205); high RAPID3: non-smokers (74%) vs. former (75%) and current smokers (75%) (p=0.713)] or frequency of extra-articular disease in the cohort.

Smoking ever (former or current) was associated with erosive disease, adjusting for ethnic groups (p=0.002). Smoking ever had a 144% increase in odds of having erosions compared to never smoking (OR=2.44, p=0.003), and non-Caucasians had 638% increase in odds for erosions compared to Caucasians (OR=7.38, p<0.001) in a multiple logistic regression adjusting for disease duration, age and disease activity (Table).

Table: Multiple Logistic Regression Model (Dependent Variable: Erosion)

Variables	OR (95% CI)	p
Smoking (Reference=Never)	2.44 (1.34–4.39)	0.003
Race (Reference=White)	7.38 (3.44–18.04)	<0.001
Disease duration (years)	1.05 (1.03–1.08)	<0.001
Age (years)	1.01 (1.00–1.04)	0.142
RAPID3	0.97 (0.93–1.01)	0.100

Conclusion: In a diverse ethnic RA cohort, cigarette smoking and non-Caucasian ethnicity were independently associated with higher risk of erosive disease. While further studies are developed to better understand the relationship of tobacco exposure and RA, more aggressive anti-smoking efforts and counseling, as well as more aggresive RA therapy, appears warranted in ethnic minorities with the disease.

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Synovial Ectopic Lymphoneogenesis Predicts Clinical Response To Certolizumab Pegol In Patients With Rheumatoid Arthritis. Maria Di Cicco[1], Stephen Kelly[1], Frances Humby[1], Nora Ng[1], Sabrina Dadoun[2], Rebecca Hands[1], Vidalba Rocher[1], Alessandra Nerviani[1], Michele Bombardieri[3] and Costantino Pitzalis[3]. [1]Centre for Experimental Medicine and Rheumatology, Queen Mary University of London, London, United Kingdom, [2]APHP, Pitié-Salpêtrière University Hospital, Paris, France, [3]William Harvey Research Institute, QMUL, London, United Kingdom.

Background/Purpose: Predicting response to anti-TNF alpha inhibitors (TNFi) in rheumatoid arthritis (RA) patients is challenging. Therefore there is a high need for identification of biomarkers of clinical outcome to guide therapeutical decisions. A number of studies have suggested that the differential response to TNFi may partly be explained by modulation of synovial ectopic lymphocytic aggregates (ELN) within the synovial tissue.

Certolizumab pegol is a pegylated fully humanized TNFi and at present data regarding in vivo effects on pathobiological responses within the synovial membrane of patients with RA are limited. In particular whether specific synovial pathotypes predict response to treatment is unknown.

The main aim of this study is to investigate whether the presence of synovial ELN at baseline predicts clinical response to treatment with certolizumab pegol in RA patients.

Methods: A cohort of biologic-naïve RA patients who qualified for treatment with TNFi according to NICE guidance (National Institute for Health and Clinical Excellence, http://guidance.nice.org.uk/TA186) were recruited to the study at Barts and the London Hospital. Patients underwent ultrasound guided synovial biopsy of an active joint prior to commencing therapy with certolizumab pegol. Following 3 months of therapy, response to treatment was assessed according to EULAR response criteria and a repeat ultrasound guided synovial biopsy of the same joint obtained for 20 patients.

Paraffin embedding sequentially cut sections of synovial tissue underwent routine H&E staining and immunohistochemical staining for CD20 to detect B cells. Sections were graded as either a diffuse or aggregate infiltrate as previously described [Manzo, Eur J Immunol 2005]. The study received local ethics approval.

Results: 25 patients were recruited, 72% female, median age 54 years old (IQR: 45 –59), with a median disease duration of 4 years (IQR: 2 – 8.5). Median DAS28 was 6.2 (IQR: 5.7 – 6.8), 10 pts (40%) had an erosive disease and 17 (68%) were seropositive for RF or CCP, with 16 (64%) CCP positive. ELN was found in 11 patients (44%). 18 patients (72%) responded to the drug according to EULAR response criteria (32% were good responders and 40% moderate responders). The clinical response was maintained at 48 weeks. All patients with lymphocytic aggregates had a good or moderate response, while patients with negative ELN were equally either responders (50%) or non responders (50%) [p=0,01]. 9 of the 11 patients who resulted ELN positive at baseline had a second biopsy, and 4 (44%) reversed into a ELN negative status. Univariate analysis showed that ELN was the only independent predictor of good or moderate clinical response [$p<0.05$].

Conclusion: To the authors' knowledge, this is the first time that clinical response to certolizumab pegol has been evaluated in association with synovial ELN.

Our work shows that the presence of ELN is an independent predictor of clinical response to certolizumab pegol treatment, in line with previous data observed for other TNFi [Klaasen, Arthritis & Rheum 2009], suggesting that histopathology could be considered in the future as a potential key tool to guide therapeutic decisions for RA patients.

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14-3-3η and Its Auto-Antibodies Predict Response To Anti-TNF Therapy. Walter P. Maksymowych[1] and Anthony Marotta[2]. [1]University of Alberta, Edmonton, AB, [2]Augurex Life Sciences Corp, North Vancouver, BC.

Background/Purpose: Serum 14-3-3η is an RA diagnostic marker and higher levels are associated with joint damage and more severe disease. Mechanistically, 14-3-3η upregulates factors involved in joint damage and inflammation, including TNFα. 14-3-3η's extracellular expression in RA elicits a robust, early auto-antibody response to the native protein, which may confer a protective effect. We investigated the relationship between the 14-3-3η protein as well as its auto-antibodies and response to anti-TNF therapy, in established RA.

Methods: Serum 14-3-3η protein and its auto-antibodies were measured at baseline in 99 RA patients who were refractory to either a standard DMARD or a first TNF-blocker. 14-3-3η protein was measured by ELISA and the auto-antibody levels by Meso-Scale-Discovery electrochemiluminescent platform. The changes in clinical response variables (within 15 weeks of treatment initiation) were determined and median group differences between patients who were 14-3-3η protein positive ($>$ 0.19 ng/ml) and negative or 14-3-3η auto-antibody positive ($>$ 380 U/ml) and negative were tested using the Mann-Whitney U-Test. Regression analyses were used to test whether the 14-3-3η markers were independent predictors of a good EULAR response (DAS28 $<$ 3.2, ΔDAS $>$ 1.2) or DAS remission (DAS-ESR$<$2.6) and contingency analyses for frequency distribution of biomarker positivity and response were conducted. Spearman correlations were performed to evaluate the relationship between the expression of the 14-3-3η protein and its auto-antibodies.

Results: At baseline, 88 of 99 (89%) patients were positive for 14-3-3η and 11 of 99 (11%) were positive for the 14-3-3η auto-ab. Median (IQR) and mean (SD) 14-3-3η serum levels were 2.1 (0.7 – 15.7) ng/ml and 6.6 (8.1) ng/ml with median and mean auto-ab titres being 216 (172 – 311) U/ml and 248 (103) U/ml. At 15 weeks, median ESR (29 vs. 17, $p < 0.02$) and CRP (7.3 vs. 2.9, $p < 0.03$) were significantly higher in 14-3-3η +ve patients. 14-3-3η auto-ab +ve patients achieved a significantly lower DAS (4.2 vs 4.7, $p < 0.03$), a greater change in DAS (2.3 vs 1.7, $p < 0.03$), a lower ESR (29 vs. 15, $p=0.05$), and a lower CRP (6.8 vs. 2.9, $p=0.05$) than 14-3-3η auto-ab -ve patients. Contingency analysis revealed that 14-3-3η negativity was predictive of achieving a good EULAR response with an LR of 5.0, $p<0.03$, OR=4.8 (1.3 – 18.1) and RR=3.1 (95%CI, 1.4–7.0). 14-3-3η auto-ab positivity marked a higher likelihood of achieving both a good EULAR response [LR = 5.0, $p < 0.03$, OR=0.2 (95%CI, 0.1–0.8), RR=3.1 (1.4–7.0)] and DAS remission [LR = 4.0, $p < 0.05$, OR=0.2 (0.1 – 0.9), RR=3.2 (1.4–8.5)]. The multivariate logistic regression returned both 14-3-3η and its auto-antibodies as significant independent predictors of a good EULAR response ($p<0.02$). The low Spearman correlation ($r = -0.13$, $p = 0.2$) between serum 14-3-3η and its auto-antibodies, supports their combined utility to inform therapy response.

Conclusion: RA patients who are negative for 14-3-3η and positive for its auto-antibodies are more likely to achieve a Good EULAR response and DAS remission with anti-TNF therapy.

Disclosure: W. P. Maksymowych, Augurex Life Sciences Corp, 9; **A. Marotta**, Augurex Life Sciences Corp, 3.

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MMP3 As a Predictor Identifying a Subgroup Of Rheumatoid Patients Who Are Successfully Treated With Methotrexate (MTX) Alone But Still Subject To Radiographic Progression. Shunichi Shiozawa[1], Yasushi Tanaka[2], Ryosuke Yoshihara[2], Miki Murata[2], Takashi Yamane[2], Chihiro Tanaka[2], Noriaki Yo[2] and Kazuko Shiozawa[2]. [1]Kyushu University Beppu Hospital, Beppu, Japan, [2]Kohnan Kakogawa Hospital, Kakogawa, Japan.

Background/Purpose: To discover the prognostic factor identifying a subgroup with clinical relevant radiographic progression (CRRP) and rapid radiographic progressoion (RRP) among rheumatoid patients successfully treated clinically with methotrexate (MTX) alone but still need additional biologics to halt radiographic progression, we compared the baseline data on initiation of MTX therapy and subsequent radiographic progression of patients.

Methods: Clinical, structural and functional outcomes of rheumatoid patients fulfilling the ACR diagnostic criteria who were successfully treated with MTX-alone (n=151) were evaluated using DAS28-4ESR, modified total Sharp score (mTSS) and modified health assessment of questionnaire (mHAQ), MMP-3, anti-CCP2 antibody and others for 3 yrs prospectively. To identify the predictor of CRRP (ΔTSS>3) or RRP (ΔTSS>5), baseline data were assessed in relation to radiographic progression using univariate logistic regression and Fisher's test procedures.

Results: The patients (mean: age 57.7 yrs, disease duration 4.6 yrs) were with high disease activity (mean:DAS28-4ESR 5.5, CRP 2.4mg/dL) and joint destruction (mean: ΔTSS 8.3) on initiation of MTX therapy. Clinical disease activity was significantly improved yearly from baseline to 3yrs: DAS28-4ESR from 5.5±1.2 to 3.7±1.4, %DAS28 remission from 2% to 19%, mHAQ from 0.53±0.46 to 0.18±0.31, and %mHAQ remission from 16% to 60%. After 1 yr of MTX therapy, 64/151 (42.4%) of patients were under structural remission, 45/151 (29.8%) under CRRP, and 26/151 (17.2%) under RRP: the values remained similar 48.6%, 21.5% and 12.1%, respectively at 3 yrs. When the patients who attained structural remission were compared with those classified into CRRP or RRP, baseline CRP and MMP-3 values were significantly different ($p<0.01$). According to logistic regression analysis, MMP-3 levels at baseline showed most significant association with CRRP and RRP especially after 1 yr of treatment. The cut-off value of MMP-3 was calculated to be 103.7 ng/ml by using a logistic regression receiver operating characteristics (ROC) analysis. The result showed that the patients containing MMP-3 below 103.7 ng/ml were classified not to CRRP and RRP with the sensitivity of 80.0% and 90.0%, respectively; Fisher's exact test 0.0021 and 0.0011, respectively.

Conclusion: We identified basal MMP-3 level as a predictor identifying a subgroup with CRRP and RRP among the patients who appeared successfully treated with MTX-alone but still require additional treatment with biologics to halt radiographic progression.

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Methotrexate Optimization (ie introduction during the first 3 months and with dose escalation at 6 months at least at 20mg/w or 0.3mg/kg/w) Is Associated With Better Clinical Outcomes In Daily Practice: Results From The Espoir Cohort. Cécile Gaujoux-Viala[1], Simon Paternotte[2], Bernard Combe[3], Maxime Dougados[4] and Bruno Fautrel[5]. [1]EA 2415, Montpellier I University, Nîmes University Hospital, Rheumatology Department, Nîmes, France, [2]Paris- Descartes University, Cochin hospital, Paris, France, [3]Lapeyronie Hospital, Montpellier I university, Montpellier, France, [4]Paris-Descartes University, APHP, Cochin Hospital, Paris, France, [5]Paris 6 – Pierre et Marie Curie University; AP-HP, Rheumatology, Pitié-Salpêtrière Hospital, - GRC-UPMC 08 – EEMOIS, Paris, France.

Background/Purpose: Methotrexate (MTX) is recommended as the first DMARD in rheumatoid arthritis (RA) at a weekly dose of 20–25mg in combination with folic acid supplementation. Despite its widespread use and more than two decades of experience, considerable variations exist among rheumatologists in prescribing MTX.

Objective: To describe symptomatic and structural impact of the MTX optimization in early arthritis (EA) in daily clinical practice over 2 years.

Methods:

- *Patients:* from the French cohort of EA ESPOIR (at least 2 swollen joints for less than 6 months and suspicion of RA), fulfilling the new ACR-EULAR criteria for RA at baseline, and treated by MTX as first DMARD.

- *Treatment group:* optimized MTX was defined by at least 3 months of MTX during the first 6 months and dose of initiation at least 10 mg/week with escalation at 6 months at least at 20 mg/w or 0.3mg/kg/w if DAS28>2.6.

- *Outcomes:* remissions (Boolean, SDAI and DAS28), functional stability (HAQ≤0.5 and deltaHAQ≤0.25), absence of radiographic progression (delta Sharp score <1) and absence of fast radiographic progression (delta Sharp score <1).

- *Analyses:* evaluation of the symptomatic and structural efficacy has been performed by generalized linear regression after adjustement on propensity score (by modelling the optimization of MTX by disease specific- and demographic variables obtained at baseline, using logistic regression analysis) in the group of patients receiving optimized MTX versus the ones receiving MTX without optimization.

Results: Within the first year of follow-up of 600 RA patients, 352 received MTX as first DMARD. The mean dose of MTX was 13.1 +/− 3.9 mg/week. In all, 76.1% of patients received at least 3 months of MTX during the first 6 months and 25.3% were treated initially at least by 10 mg/week with escalation at 6 months at least at 20 mg/w or 0.3mg/kg/w if DAS28>2.6; only 22.1% fulfilled the 2 criteria. MTX optimization was initiated in younger patients (45.2 years ± 12.6 vs 49.3 ± 11.3, p=0.009) with higher CRP (29.3±32.0 vs 24.4±36.7, p=0.006). After adjustment, optimized MTX was found to be more efficient in terms of remission and function than control (table).

Outcome	Optimized MTX N = 76 N (%) at m12	Non optimized MTX N=268 N (%)	Adjusted OR m0-m12 [95%CI]	Adjusted OR m12-m24 [95%CI]
Boolean remission	20 (27.4%)	25 (10.0%)	2.56 [1.22–5.37]	1.85 [0.98–3.52]
SDAI remission	23 (31.5%)	27 (10.8%)	2.35 [1.16–4.75]	2.30 [1.22–4.32]
DAS28 remission	40 (55.6%)	74 (29.6%)	2.81 [1.53–5.18]	2.72 [1.46–5.07]
Functional stability	54 (74.0%)	134 (52.6%)	3.01 [1.49–6.08]	1.93 [0.97–3.85]
Absence of radiographic progression	23 (34.9%)	81 (35.2%)	1.06 [0.56–2.01]	0.54 [0.26–1.10]
Absence of fast radiographic progression	23 (34.9%)	81 (35.2%)	0.76 [0.37–1.54]	0.44 [0.19–1.03]

* Ajusted on: SJC, CRP, ACPA or RF, Sharp score, Center, Age, Smoking, HAQ, ACR1987 criteria.

Conclusion: Optimized MTX is more efficacious on remission and function than MTX without optimization in EA in daily practice but without impact on radiographic progression over 2 years.

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Prevalence and Impact Of Soft Tissue Manifestations In Early Inflammatory Arthritis: Results From The Canadian Early Arthritis Cohort. Mihaela Popescu[1], Edith Villeneuve[2], Boulos Haraoui[3], Gilles Boire[4], Carol A. Hitchon[5], Edward C. Keystone[6], Janet E. Pope[7], J. Carter Thorne[8], Diane Tin[8] and Vivian P. Bykerk[6]. [1]University of Montreal, Montreal, QC, [2]Institut de Rhumatologie de Montréal, Montreal, QC, [3]Centre Hospitalier de l'Université de Montréal, Montreal, QC, [4]Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, [5]University of Manitoba, Winnipeg, MB, [6]Mount Sinai Hospital/University of Toronto, Toronto, ON, [7]St Joseph Health Care, London, ON, [8]Southlake Regional Health Centre, Newmarket, ON.

Background/Purpose: It is increasingly recognized that soft tissue inflammation in patients with inflammatory arthritis is frequent and might be of clinical importance. However, when therapeutic adjustments are made, the extent of soft tissue involvement is often not taken into consideration, because it is not measured objectively in disease activity indices. Our study objective was to determine the frequency of soft tissue inflammation such as tenosynovitis, enthesitis, and bursitis in a Canadian cohort of patients presenting with early inflammatory arthritis and to investigate the impact of these manifestations on disease activity, functional ability, quality of life, and self-reported outcome measures.

Methods: Soft tissue prevalence and impact was assessed at baseline in a nationwide cohort of 1509 Canadian adults who were enrolled in the Canadian Early Arthritis Cohort (CATCH) between 2007 and 2012. Disease activity, patient reported outcomes (pain and fatigue), Health Assessment Questionnaire (HAQ), and Short Form quality of life (SF-12) were collected. Soft tissue involvement was assessed by clinical examination.

Results: Our analysis included 1509 patients with a mean age of 54 years old, of whom 73% were women and the mean disease duration until diagnosis was 5.7 months. We found 290 periarticular soft tissue involvement in 222 (14.74%) patients. Periarticular involvement was found in more than one

anatomic site in only 59 (26.6) of the 222 patients and in >3 sites, in only 2 (0.9%) patients. The majority of lesions were localized to hands and wrists (56.6%) followed by feet and ankles (16.9%), elbows (11.0%), shoulders (10.4%), hips (3.4%) and knees (1.7%). There was no difference in disease activity score (DAS28), pain, fatigue, function (HAQ), or SF-12 between patients with or without soft tissue disease (Table 1).

Table 1. Comparison of patients with and without soft tissue involvement at baseline*

	Patients with soft tissue involvement (n=222)	Patients without soft tissue involvement (n=1287)	p
Pain VAS (0–100) (n=1454)	60.04 (26.83)	56.14 (28.33)	NS
Fatigue VAS (0–100) (n=1479)	52.84 (30.28)	56.3 (29.42)	NS
DAS28 (0–9.4) (n=1387)	5.04 (1.44)	5.19 (1.38)	NS
CDAI (0–76) (n=1449)	27.05 (14.04)	28.02 (1.38)	NS
SDAI (0–86) (n=1333)	28.31 (14.69)	29.55 (14.76)	NS
HAQ (0–3) (n=1484)	1.03 (0.71)	1.09 (0.69)	NS
SF-12 (physical score) (0–5) (n=1346)	3.66 (1.06)	3.55 (9.57)	NS
SF-12 (mental score) (0–5) (n=1346)	4.54 (1.58)	4.58 (1.18)	NS

* Values are presented as means and SD.

Conclusion: The clinical prevalence of soft tissue manifestations in this early inflammatory arthritis cohort was low. The presence of soft tissue involvement was not associated with differences in disease activity indices, patient self-reported symptoms, HAQ, or SF-12. In conclusion, despite the presence of periarticular soft tissue inflammation, current disease activity indices may be sufficient to guide treatment adjustments in this cohort of early inflammatory arthritis.

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Diagnostic Value Of Anti-Citrullinated Proteins Antibodies In Rheumatoid Arthritis. Claudia L. Giraldo[1], Rafael Chaparro del Moral[2], Mercedes Ciancio[3], Oscar L. Rillo[3], Emilia Saint Martin[4], Emilce Schneeberger[5], Gustavo Citera[5], Federico Zazzetti[6], Amalia Schiel[7] and Juan C. Barreira[7]. [1]Hospital General de Agudos, Buenos Aires, Argentina, [2]Hospital General de Agudos Dr. E. Tornu, Buenos Aires, Argentina, [3]Hospital General de Agudos "Dr. E. Tornú", Buenos Aires, Argentina, [4]Instituto de Rehabilitacion Psicofisica, Buenos Aires, Argentina, [5]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [6]Buenos Aires Hospital Britanico, Buenos Aires, Argentina, [7]Buenos Aires British Hospital, Buenos Aires, Argentina.

Background/Purpose: Citrulline and vimentin are some of the proteins used as antigens for anti-citrullinated proteins antibodies (ACPAs) detection for the diagnosis of rheumatoid arthritis (RA). In our country, anti-mutated citrullinated vimentin (anti-MCV) kit is 50% cheaper than the anti-cyclic citrullinated peptide (anti-CCP3) kit. The aim of our study was to evaluate the diagnostic value of anti-MCV compared to anti-CCP3 and rheumatoid factor (RF) and to explore the relationship between them and disease activity.

Methods: Consecutive patients ≥ 18 years with RA (ACR 1987 and ACR/EULAR 2010 criteria) were included. The control group consisted of 73 subjects with undifferentiated arthritis, SLE, Psoriatic Arthritis, Sjögren's Syndrome and Erosive Osteoarthritis (non RA arthritis). Anti-MCV and anti-CCP3 were determined by ELISA and RF by immunoturbidimetry. The cutoff value for the three methods was ≥ 20 IU/ml. Sensitivity (S), Specificity (E), Positive and Negative Predictive Values (PPV, NPV) and Likelihood Ratio (LR) of the RF, anti-CCP3 and anti-MCV were assessed using a two way table (Table). Binary logistic regression analyses were performed, using high disease activity (DAS28>5.1) as dependent variable. According to the RF, anti-CCP3 and anti-MCV concentrations, three groups of patients were obtained: low concentrations (under 25 percentile); intermediate concentrations (between 25 and 75 percentile) and high concentrations (above 75 percentile).The values of DAS28 for these three groups were compared by ANOVA and post-hoc tests.

Results: 234 patients were evaluated (161 RA and 73 controls). In the RA group, 85% were female, the mean age was 53 (18–91) years, the median symptoms duration was 120 months (IQR 39–180) and 31(19%) were early RA patients (<2 years). Mean DAS28 was 3.6 (±1.5); and the median HAQ 0.75 (IQR 0.25–1.25). The median of RF was 104 IU/ml (IQR 35–225); anti-CCP3 180 IU/ml (IQR 95–210) and anti-MCV 300 IU (IQR 55–1000). Higher values of DAS28 were observed in the group of patients with RF > 225 IU/ml (mean DAS28 4.3 p = 0.006) and also in patients with anti-MCV > 1000 IU (DAS28 4.2 p=0.01). There were no differences for anti-CCP3. In early RA patients, a multivariate analysis (adjusted by symptom duration) showed that anti-MCV levels were associated with high disease activity. The OR estimated for the association between high disease activity and anti-MCV ≥ 1000 IU in early RA patients was 11.8 (CI 95%1.049–132.9). There was not significant association between RF, anti- MCV nor anti-CCP3 and DAS28 > 5.1 in established RA patients.

	S	E	PPV	NPV	LR
Anti-MCV	**93.4**	**83.6**	**93**	**85**	**5.69**
Anti-CCP3	**83.7**	**84.9**	**93**	**69**	**5.54**
RF	**84.9**	**84.9**	**93**	**71**	**5.62**

Conclusion: In our study, anti-MCV compared to anti-CCP3 and RF had a higher sensitivity with equal specificity. We found increased RA activity in patients with higher titers of RF and anti-MCV.

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Categorization Of Rheumatoid Arthritis Subjects By Rheumatoid Factor and Anti-Cyclic Citrullinated Autoantibody Status Identifies Rheumatoid Arthritis Subjects With Different Characteristics. Swati Modi[1], Mariely Nieves-Plaza[1], Donald M. Jones[1], Erich R Wilkerson[1], Christine L. Amity[2], Kelly A. Reckley[3], Ilinca D. Metes[1], Jason Lyons[1], Heather Eng[4], Stephen R. Wisniewski[4] and Marc C. Levesque[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Univ of Pittsburgh, Pittsburgh, PA, [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, [4]University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA.

Background/Purpose: Rheumatoid factor (RF) and anti-citrullinated cyclic peptide (CCP) antibodies have been used to diagnose rheumatoid arthritis (RA) patients, although there is substantial heterogeneity among RA patients regarding the presence of these biomarkers. Previously, we found that RA patients grouped on the basis of RF and CCP status into 4 groups: RF+CCP+, RF+CCP-, RF-CCP+, RF-CCP- had different clinical characteristics including a higher percentage of female subjects and less use of biologics in the RF+CCP- group. Our aim was to determine whether these subgroups of RA patients had features suggestive of other overlapping connective tissue diseases.

Methods: Patients from the Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry who met the 1987 and/or 2010 ACR criteria for a diagnosis of RA were categorized based on clinical cut-offs for RF and CCP into 4 groups: RF+CCP+, RF+CCP-, RF-CCP+, RF-CCP-. We determined the association of these four RF and CCP groups with autoantibodies and inflammatory markers measured by ELISA (IL-6) or in a clinical laboratory (ANA, anti-SSA/SSB, anti-dsDNA, C3, C4, gammaglobulin and CRP). Categorical and continuous variables were analyzed using chi-square and Kruskal-Wallis tests, respectively.

Results: IL-6 levels were significantly associated with disease activity (DAS28-CRP) but only in the RF+/CCP+ and RF-/CCP- groups, while CRP levels were significantly associated with disease activity in all groups. ANA positivity was significantly different across groups (p = 0.008) (Table 1). The percentage of ANA positive subjects was highest in the RF+CCP+ group (71%) and lowest among the RF-/CCP- group (48%). There were no significant differences for the remaining laboratory characteristics, although RF+/CCP- subjects were more likely to have a low C4 level and a positive anti-SSA and/or -SSB and anti-dsDNA.

Table 1. Serological analysis

Serological Tests	RF−/CCP− (n=110)	RF+/CCP− (n=61)	RF−/CCP+ (n=33)	RF+/CCP+ (n=260)	p value
ANA (n=379)	44/92 (48%)	34/54 (63%)	18/28 (64%)	145/205 (71%)	0.008
dsDNA (n=32)	2/11 (18%)	2/5 (40%)	0/1 (0%)	3/15 (20%)	0.722
SSA (n=120)	3/22 (14%)	3/19 (16%)	0/4 (0%)	10/75 (13%)	0.942
SSB (n=113)	0/21 (0%)	2/16 (13%)	0/4 (0%)	2/72 (3%)	0.280
Low C3 (n=99)	0/30 (0%)	0/15 (0%)	0/5 (0%)	5/49 (10%)	0.963
Low C4 (n=98)	4/30 (13%)	3/15 (20%)	0/5 (0%)	5/48 (10%)	0.155
Hyper-gammaglobulinemia (n=127)	3/32 (9%)	5/18 (28%)	0/8 (0%)	21/69 (30%)	0.111

Conclusion: RF+CCP- subjects were typically ANA positive and more likely than other RF/CCP groups to be female, have low C4 levels and to have a positive anti-SSA and/or -SSB suggesting that some of these subjects may have RA and/or Sjogren's syndrome. The lower percentage of subjects in the CCP negative groups treated with biologic therapies may be due to lower levels of disease activity as seen in the RF-CCP- group and/or may be due to the presence of subjects with diseases poorly responsive to biologic therapies such as Sjogren's syndrome in the RF+/CCP- group. In summary, we believe that categorization of RA subjects by RF and CCP status may identify RA subjects with different syndromes, differential responses to therapy and different outcomes.

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Vasoactive Intestinal Peptide Serum Levels As a Marker Of Prognosis In Rheumatoid Arthritis. Rosario Garcia-Vicuña[1], Ana M. Ortiz[1], Iria Valino-Seoane[2], Amalia Lamana[1], Javier Leceta[2], Yasmina Juarranz[2], Isidoro González-Alvaro[3], Rosa P Gomariz[2] and Carmen Martinez-Mora[4]. [1]Hospital Universitario de La Princesa. IIS Princesa, Madrid, Spain, [2]School of Biology. Universidad Complutense de Madrid, Madrid, Spain, [3]Hospital Universitario de La Princesa, IIS Princesa, Madrid, Spain, [4]School of Medicine. Universidad Complutense de Madrid, Madrid, Spain.

Background/Purpose: The current shift to earlier treatment of Rheumatoid Arthritis (RA) has a major unmet need in the availability of biomarkers to identify patients requiring more intensive treatment, even in undifferentiated disease stages. Vasoactive intestinal peptide (VIP) has demonstrated physiological anti-inflammatory and immunoregulatory roles both in murine arthritis models and in "in vitro" studies with human synoviocytes and lymphocytes by decreasing the expression of proinflammatory molecules and favouring Th2 responses. In addition, low levels of VIP expression in the synovial fluid of severe forms of osteoarthritis has been described.

The aim of this work is to analyze the potential value of studying VIP serum levels (VIPs) as a prognostic biomarker in RA by longitudinal assessment of its levels in patients with early arthritis (EA).

Methods: We studied 91 patients from our prospective EA registry, in which we collect by protocol sociodemographic, clinical, laboratory, and therapeutic information. 73% were female, with age at disease onset 54 years [45–66] (median [p25-p75]), duration of disease at entry 5.4 [3.2–8.4] months and follow-up 2 to 5 years. 76% of patients met 1987 ACR classification criteria for RA after two years of follow up. VIPs were measured by ELISA (Phoenix Pharmaceutical, Karlshure, Germany) in the patients sera collected from 353 visits (3.8 visits per patient), and in 100 healthy controls. Low VIPs were considered if below the 25th percentile of the normal population. We created the variable treatment intensity (IT) as the sum of the number of days on treatment with each disease modifying anti-rheumatic drugs, including biologics. To determine the effect of independent variables on VIPs, we performed a longitudinal multivariate analysis, nested by patient and visit, through the command xtgee of Stata 12 for Windows (StataCorp LP, College Station, TX, USA).

Results: We could not detect significant differences in the VIPs between patients and controls either at their first visit (409 pg/ml [359–469] versus 403 [371–441] respectively, p = 0.915) or over the two year follow-up. Nevertheless, substantial heterogeneity in these levels was observed. Multivariate analysis aimed to deepen this VIPs heterogeneity showed differences by gender (being female beta coefficient [coef. Beta]: 0.25 ± 0.09, P = 0.007) and age of disease onset (coef. beta per year 0.003 ± 0.007, P = 0.006). In terms of disease-related variables, VIPs were lower in subjects with greater disease activity measured by DAS28 (coef. beta: −0.043 ± 0.019, P = 0.026). In addition, patients with lower VIPs at the first visit had higher disease activity at the end of follow-up (3.47 [2.83–4.37] versus 3.03 [2.16–3.77], p = 0.14) and received more intense treatment according to the variable IT (1352 [1092–1754] vs 1119 [870–1473], p = 0.22).

Conclusion: Our data suggest that VIPs may be a prognostic biomarker in RA since baseline levels are lower in patients who show a worse clinical course and increased requirements for treatment in the first two years of disease monitoring.

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Osteoprotegerin and TNF-Related Apoptosis Inducing Ligand Are Respectively Predictive Factors Of Remission and Erosion In Early Rheumatoid Arthritis Patients Included In The French Cohort Espoir. Rachel Audo[1], Laura Papon[1], Claire I. Daien[2], Cédric Lukas[2], Bernard Combe[2], Olivier Vittecoq[3], Michael Hahne[1] and Jacques Morel[2]. [1]IGMM, CNRS UMR5535, Montpellier, Montpellier, France, [2]Lapeyronie Hospital, Montpellier, France, [3]Rouen University Hospital & Inserm905, University of Rouen, Rouen Cedex, France.

Background/Purpose: TNF-Related Apoptosis Inducing Ligand (TRAIL) is a member of the TNF familly. Its soluble receptor Osteoprotegerin (OPG) also inhibits Receptor activator of nuclear factor kappa-B ligand (RANKL). We previously reported that, in a cohort of early arthritis (< 2 years), a high TRAIL/OPG ratio at baseline was associated with remission (DAS28<2.6) at 6 months, suggesting that the TRAIL/OPG ratio could be a predictive factor for remission in early arthritis.

Methods: The aim of this study was to confirm these results in the larger French cohort ESPOIR including patients with early arthritis (<6 months). Patients were assessed for clinical and biological parameters and Sharp's score at baseline (M0), 12 (M12) and 24 (M24) months. TRAIL and OPG concentrations in serum were measured at M0. We correlated these values with inflammation, disease activity and radiographic progression. We also aimed to compare TRAIL and OPG between patients with arthritis responding to ACR/EULAR 2010 criteria (RA) and those with undifferentiated arthritis (UA). Values of TRAIL and OPG were log transformed to be normalized. Correlations were performed using Pearson tests. For mean comparisons, adjustment with baseline CRP, DAS28, rheumatoid factor, BMI, steroids doses, age and sexe was performed using ANCOVA. Logistic regression was used to determine predictive value for remission (DAS28 ≤2.6) and radiographic progression (DSharp score>0).

Results: TRAIL, OPG and TRAIL/OPG at M0 were not different between patients RA (n = 641) and UA patients (n = 53). Among RA patients, OPG at M0 was significantly correlated with DAS28 (r=0.14; p=0.001), ESR (r=0.14; p=0.001) and CRP (r=0.11; p=0.007). TRAIL/OPG ratio was inversely correlated with DAS28 (r=−0.13; p=0.002), ESR (r=−0.14; p=0.002) and CRP (r=−0.15; p<0.001). TRAIL was only inversely correlated with CRP (r=−0.10; p=0.02). Patients in remission at M12 had a significantly lower concentration of M0 OPG (921±418 (n=204) vs 1014±383 pg/ml (n=342), respectively, p=0.0018). Patients in remission at M12 also tend to have a higher baseline TRAIL/OPG ratio (1.38±1.01 vs 1.17±0.59 pg/ml, p=0.051), but after adjustment, only a low M0 OPG remained significantly associated with remission at M12 (p=0.007). Logistic regression confirmed the predictive value of OPG (OR: 0.21, CI: 0.07–0.067, p=0.008). Patients with progression of Sharp score erosion at M24 have significant higher M0 TRAIL (1128±615, n=334 vs 1010±490 pg/ml, p=0.013). After adjustment, TRAIL is still significantly associated with progression of Sharp score erosion (p=0.003) and logistic regression confirmed that TRAIL is a protective factor for structural damage (OD: 0.22, CI: 0.81–0.609, p=0.003).

Conclusion: Concentrations of TRAIL and OPG could not help in distinguish UA and RA. OPG was correlated with ESR, CRP and DAS28 and TRAIL inversely correlated with CRP. In a larger cohort, this study did not confirm the predictive value of the ratio TRAIL/OPG. However, a low M0 OPG was associated with EULAR remission at M12 and is predictive of remission. A low TRAIL at baseline is associated with Sharp erosion increased at M24 and is also predictive of progression of Sharp's score erosion.

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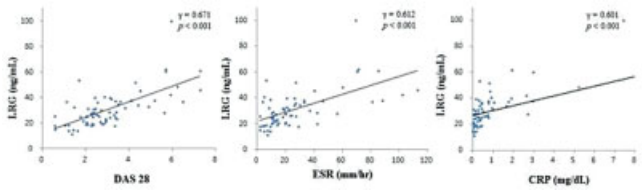
Plasma Leucine-Rich Alpha-2 Glycoprotein Is a Useful Disease Activity Biomarker In Rheumatoid Arthritis. Jung-Soo Song[1], You-Jung Ha[2], Eun-Jin Kang[3], Kwang-Hoon Lee[4], Sang-Won Lee[2], Yong-Beom Park[2], Soo-Kon Lee[2] and Sang Tae Choi[1]. [1]Chung-Ang University College of Medicine, Seoul, South Korea, [2]Yonsei University College of Medicine, Seoul, South Korea, [3]Busan Medical Center, Busan, South Korea, [4]Dongguk University Ilsan Hospital, Goyang, South Korea.

Background/Purpose: Leucine-rich α2-glycoprotein (LRG) is a plasma protein which contains leucine-rich repeats (LRRs). Though physiological functions of LRG have not been clarified yet, it has been reported that LRG could be a marker of granulocytic differentiation and its expression was up-regulated during neutrophil differentiation. LRG could show a significant increase in some inflammatory conditions, such as ulcerative colitis, in where serum LRG concentrations were well correlated with disease activity, and the expressions of LRG were increased in inflamed colonic tissues. However, the association between plasma LRG level and disease activity in RA patients remains obscure. This study aimed to investigate whether the plasma LRG level is elevated in patients with RA and its correlation with disease activity and other parameters.

Methods: Our study included 69 patients with RA and 48 age- and sex-matched healthy controls. Plasma samples were obtained from patients with RA during active and inactive disease status and from controls. We assessed the clinical characteristics and laboratory parameters including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and disease activity score 28 (DAS28). Plasma concentrations of tumor necrosis factor-α (TNF-α) and LRG were determined by enzyme-linked immunosorbent assay (ELISA).

Results: Plasma LRG concentrations were significantly elevated in RA patients compared with healthy control (30.8 $\pm$ 14.4 ng/mL vs 22.2 $\pm$ 6.1 ng/mL, $p < 0.001$). In patients with RA, plasma LRG levels were found to be correlated with DAS28, ESR, and CRP ($\gamma = 0.671$, $p < 0.001$; $\gamma = 0.612$, $p < 0.001$; and $\gamma = 0.601$, $p < 0.001$, respectively), but not with plasma TNF-α levels. Plasma LRG levels in patients with an active disease status (DAS28 >= 2.6) were significantly higher than in patients with a remission status (DAS28 < 2.6) (36.45 $\pm$ 14.36 ng/mL vs 24.63 $\pm$ 8.81 ng/mL, $p <$ 0.001).



Conclusion: Patients with RA had higher plasma LRG levels than healthy subjects, and plasma LRG concentrations were well correlated with disease activity measures. Our findings suggest that plasma LRG could play a role in the inflammatory process independently of the TNF- α, and that it may be a novel biomarker for reflecting inflammatory activity in RA patients.

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Evaluation Of The Usefulness Of Interferon-Gamma Release Assays and Tuberculin Skin Test For Detection Of Latent Mycobacterium Tuberculosis Infection In Korean Rheumatic Patients With Biologic Agents. Jae-Hoon Kim[1], Soyoung Won[2], Chan-Bum Choi[3], Yoon-Kyoung Sung[3], Gwan Gyu Song[1] and Sang-Cheol Bae[3]. [1]Korea Univ College of Med, Seoul, South Korea, [2]Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [3]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea.

Background/Purpose: The screening for and treatment of latent tuberculosis infection (LTBI) before starting biologic agents is crucial to prevent reactivation and resultant serious infection. Several national guidelines recommended to test tuberculin skin test (TST) initially and Interferon-γ Release Assay (IGRA) if TST result is indeterminate. In Korea with an intermediate tuberculosis(TB) burden, national guideline recommends use of both IGRA and TST for detection of LTBI before starting biologic therapies, and chemopreventive TB treatments are recommend in case of positive IGRA or TST results. Our study was conducted to estimate the concordance between QuantiFERON-TB Gold in tube Test (QFT-GIT) as an IGRA and TST, and to evaluate the difference in the occurrence of active TB in patients who are candidates of biologic agents who receive both QFT-GIT and TST compared with those who receive either TST or QFT-GIT alone for detection of LTBI.

Methods: A total of 959 patients who received both QFT-GIT and TST from Jan. 2004 to Dec. 2012 at Hanyang University Hospital for Rheumatic Diseases were recruited for the concordance between the 2 tests. The concordance between the 2 tests was estimated by Cohen's kappa (κ). A total of 842 patients who performed QFT-GIT or TST and used biologics from Jan. 2007 to Dec. 2012 were recruited for the usefulness of LTBI screening test. The screening test of LTBI, TB prophylaxis, TB occurrence, and clinical characteristics were examined. Among 842 patients, 260 patients received only TST, 149 patients received only QFT-GIT, and 436 patients received both QFT-GIT and TST. The occurrence of TB according to the screening method of LTBI was identified. The incidence rates of active TB were calculated as number of events per 100,000 person-years exposure.

Results: The concordance between QFT-GIT and TST was low in the whole group ($\kappa = 0.312$). A total of 5 patients developed TB after initiation of biologics according to the screening guideline of LTBI. Among them, extra-pulmonary TB occurred in 3 patients. Some patients did not comply with LTBI prophylactic strategy. TB occurred in 2 patients according to LTBI prophylactic strategy (Table). TB incidence in the group that received both QFT-GIT and TST was 151.05/100,000 person-years and that in the group that received only TST was 169.78/100,000 person-years among the patients who complied with LTBI prophylactic strategy.

Table. The incidence of TB according to LTBI prophylactic strategy

LTBI Screening	Number	LTBI Result	TB prophylaxis		Number	Occurrence of TB	Incidence rate(/100,000 person-years)
Only TST	260	Positive	120	Yes	100	233	0	0
		Negative	140	No	133		1	169.78
Only QFT-GIT	144	Positive	27	Yes	25	125	0	0
		Negative	117	No	100		0	0
TST & QFT-GIT	421	Positive/Positive	52	Yes	50	393	0	0
		Positive/Negative	67	Yes	57		0	0
		Negative/Positive	26	Yes	21		0	0
		Negative/Negative	271	No	265		1	151.05

Conclusion: The concordance between QFT-GIT and TST was low. TB did not occur in patients who received TB prophylaxis after positive results by either only TST strategy or QFT-GIT & TST strategy. TB incidence in patients who performed both QFT-GIT and TST and prophylaxis seems to be lower than that in those who performed only TST and prophylaxis. However, it was difficult to calculate the significant of this difference or superiority because the observation period was short.

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A Novel Index to Identify Interstitial Lung Disease in Rheumatoid Arthritis Patients. José Félix Restrepo[1], Inmaculada del Rincón[1], Roy W Haas[1], Daniel F Battafarano[2], Agustín Escalante[1]. [1]University of Texas Health Science Center at San Antonio; [2]San Antonio Military Medical Center, San Antonio, Texas.

Background/Purpose: Interstitial lung disease (ILD) is associated with significant morbidity and mortality in rheumatoid arthritis (RA). Diagnosis requires imaging studies or invasive procedures that are costly and may entail risk. Because of this, diagnostic procedures are only performed on patients who display symptoms or sign of the disease. A strategy to identify patients at high risk would help target those who would benefit from a diagnostic intervention. The objective of the present study is to develop an index for the identification of RA patients at high risk of ILD.

Patients and Methods: We studied patients with RA recruited from rheumatology practices. We assessed each patient for the following variables: Age, sex, joint tenderness and swelling, rales on auscultation, subcutaneous nodules, disease severity, use of methotrexate and current prednisone use, smoking status, rheumatoid factor, antibodies against cyclic citrullinated peptide (anti- CCP), and ESR. ILD was diagnosed using chest X-ray, CT scan, and/or lung biopsy. We divided the study sample into two equivalent groups using a random procedure. We used the first group as the development sample. We performed a stepwise logistic regression model using the above

variables as predictors. Using the results of the model we developed an index, which we then tested in the second group, or validation sample.

Results: The sample included 779 patients, of whom 69 had ILD, 147 had other pulmonary diseases and 563 had no lung diseases. We conducted the current analysis on 542 patients (52 with ILD, 490 without ILD) who had all the variables for the index. The variables and score in the index were as follow: male sex=2; ESR (mm/hr.) ≤ 30=0, 31–60=1,61–100=2,>100=3; anti- CCP ≤20=0, 21–60=1, 61–150=2, >150=3; rales present=2. The Index is the sum of the score for each variable. The maximum value is 10. The performance of the index in identifying patients with ILD in the development and validation sample is shown in Table.

Table. Performance of Index in 542 Patients with Rheumatoid Arthritis

Sample	Development		Validation	
Interstitial Lung Disease	**Absent**	**Present**	**Absent**	**Present**
Index ≤ 5, n (%)	212 (97)	7 (3)	224 (95)	13 (5)
Index > 5, n (%)	25 (53)	22 (47)	29 (74)	10 (26)
ROC Area		0.83		0.66

Conclusion: This novel index may be used to identify RA patients at increased risk of ILD. Patients with a score higher than 5 may benefit from additional diagnostic testing to detect ILD, while those with 5 or less are unlikely to have ILD.

Disclosure: Nothing to disclose.

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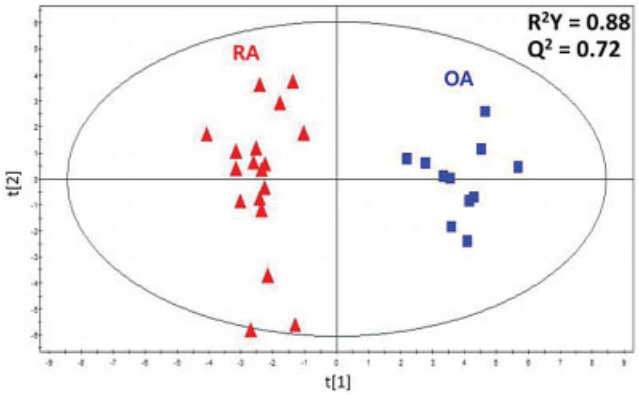
Discriminative Metabolite Profiling Of Synovial Fluid In Rheumatoid Arthritis Compared To Osteoarthritis. Jiwon Hwang[1], Joong Kyong Ahn[2], Jaejoon Lee[3], Inyoung Kim[1], Seulkee Lee[1], Chan Hong Jeon[4], Eun-Mi Koh[1] and Hoon-Suk Cha[3]. [1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Kangbuk Samsung hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [3]Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea, [4]Soonchunhyang University College of Medicine, Bucheon, South Korea.

Background/Purpose: Metabolomics is the study of unique chemical imprints that represent specific cellular processes in a cell, tissue, organ or organism. Synovial fluid in pathologic conditions reflects the diseased process and its distinctive metabolite profiles could facilitate the diagnostic ability and the understanding of disease state. The aim of this study is to investigate the metabolites of synovial fluid in patients with rheumatoid arthritis (RA) and osteoarthritis (OA) and to identify characteristic metabolites to differentiate two diseases.

Methods: Synovial fluid samples were obtained from patients with RA (n = 18, 17 females, mean age 50.3 ± 13.9 yr, disease duration 7.9 ± 6.8 yr) and OA (n = 11, 10 females, mean age 60.9 ± 8.4 yr, disease duration 2.8 ± 4.7 yr). The extracted metabolites from synovial fluid were analyzed by gas chromatography/time-of-flight mass spectrometry (GC/TOF MS). The identified metabolites from synovial fluid extracts of RA and OA were then subjected to multivariate statistical analysis by orthogonal partial least squares discriminant analysis (OPLS-DA): R^2 indicates the fitting ability of total variation and Q^2 designates the validity of discrimination. Both have range from 0 to 1, where the higher R^2 or Q^2 connotes a model with the higher predictive and discriminative value. Values of variable importance for projection (VIP) greater than 1 from OPLS-DA were used to identify potential biomarkers and the significance was defined by Welch's test with level of $p < 0.01$.

Results: Sixty-three metabolites were identified; 20 amino acids, 14 fatty acids, 10 sugars, 7 organic acids, 5 amines and 7 others. The OPLS-DA demonstrated a distinctive metabolite profile of synovial fluid between RA and OA (Figure 1), with the variation value (R^2) of 0.88 and the predictive capability value (Q^2) of 0.72. Twenty four metabolites were obtained by VIP values of greater than 1 and 17 of them were selected as specific biomarkers by Welch's t-test. Of 17 metabolites, 6 were up-regulated in RA (maltose, lignoceric acid, uracil, mannitol, pyrophosphate and phosphoric acid) and 11 in OA (lysine, tyrosine, valine, glyceric acid, alanine, asparagines, hydroxylamine, tryptophan, glycerol, glutamine and citrulline).



Conclusion: Our results demonstrated that metabolite profiling of synovial fluid clearly separates RA from OA. This study suggests that metabolomics could be a useful diagnostic tool by identifying discriminative biomarkers.

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Autoantibodies To Citrullinated Proteins Associate With Bone Destruction Marker and Are Modulated By First Anti Rheumatic Treatment In Early Rheumatoid Arthritis. Aase Haj Hensvold[1], Vijay Joshua[2], Saedis Saevarsdottir[2], Michaela Larkin[2], Lena Israelsson[2], Ferhan Qureshi[3], Per-Johan Jakobsson[2], Nadine A. Defranoux[4], Lars Klareskog[2], Vivianne Malmström[5] and Anca I Catrina[2]. [1]Rheumatology unit, Karolinska University Hospital, Karolinska Institut, Stockholm, Sweden, [2]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [3]Crescendo Bioscience, Inc., South San Francisco, CA, [4]Crescendo Bioscience Inc., South San Francisco, CA, [5]Rheumatology unit, Karolinska University Hospital, Karolinska Institutet, STockholm, Sweden, Stockholm, Sweden.

Background/Purpose: Antibodies against citrullinated proteins (especially anti citrullinated-vimentin antibodies) and high levels of RANKL have been linked to altered bone metabolism in early RA. We aimed to investigate ACPA fine specificities in relation to serum RANKL and disease activity in early-untreated RA.

Methods: 186 patients with newly diagnosed RA (patient reported symptom duration less than 1 year), naïve to disease anti modifying drug (DMARD) were started on methotrexate (MTX) monotherapy. Treatment response at 3 months was defined by EULAR response criteria. Disease activity using DAS28-ESR score, anti CCP2 antibodies (anti-CCP2 kit, Euro-Diagnostica, Malmö, Sweden), specific antibodies (Abs) against citrullinated (cit) alpha-enolase (CEP-1) aa5–21, cit vimentin aa60–75 and cit fibrinogen aa563–583 peptides (ELISA) were measured in serum samples at baseline and after 3 months. To avoid RF interference with RANKL ELISA (Biovendor Human sRANKL, Brno, Czech Republic) results, only RF negative samples (baseline and 3 month samples) were analyzed. Mann-Whitney and Wilcoxon sign tests were used to analyze differences between independent and paired variables respectively with a $p < 0.05$ being considered statistical significant.

Results: Anti-CCP2 Abs were detected in 68% (126 out of 186) of the patient sera. 54% (101 of 186) of the patients tested positive for any ACPA specificities at baseline and 46% (85 of 186) tested negative. Positive anti-CCP2 Abs titers significantly decreased from a median of 747 AU/ml (interquartile range, IRQ 2171–278) at baseline to a median of 576 (IRQ 1914–197). A significant titer decrease was similar observed for all tested ACPA specificities. Interestingly 38 % (38 out of 101) of the patients positive for any ACPA specificities at baseline become negative for at least one specific ACPA at 3 months. In contrast only 6% (5 out of 85) of the patients negative for ACPA specificities at baseline become positive at 3 months. No correlation between ACPA titers and disease activity were observed at any time point.

RANKL concentration was significant higher ($p<0.001$) in anti-CCP2+ RF- patients (n=15; median 19 ng/ml, IQR 26–12) as compared to anti-CCP2-RF- patients (n=45; median 9 ng/ml, IQR 13–5). Similar RANKL concentration was significant higher in any-ACPA specificity+ RF- patients

(n=13; median 20 ng/ml, IQR 26–15) as compared to any-ACPA specificity-RF- patients (n=47, median 9, IQR 13–6). Same differences were still detectable at 3 months but overall RANKL concentrations decreased (from a median of 11ng/ml, IQR 16–6 to a median of 9, IQR 13–6, $p<0.05$). RANKL was correlated with age ($r= -0.33$ $p= 0.01$ $n=60$).

Neither ACPA positivity, nor RANKL at baseline were discriminatory for EULAR treatment response.

Conclusion: Presence of ACPA in early-untreated RA patients is associated with increased levels of RANKL, but not disease activity and is modulated by first anti rheumatic treatment. Validation of our results in larger number of patients and investigation of potential direct effects of MTX on B cells are needed.

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Physician Global Assessment At Three Months Is Strongly Predictive Of Remission At 12 Months In Early Rheumatoid Arthritis. Results From The Canadian Early Arthritis Cohort. Tommy Choy[1], Vivian P. Bykerk[2], Gilles Boire[3], Boulos Haraoui[4], Carol A. Hitchon[5], J. Carter Thorne[6], Edward C. Keystone[7] and Janet E. Pope[8]. [1]University of Western Ontario, London, ON, [2]Hospital for Special Surgery, New York, NY, [3]Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, [4]Institut de Rhumatologie de Montréal, Montreal, QC, [5]University of Manitoba, Winnipeg, MB, [6]Southlake Regional Health Centre, Newmarket, ON, [7]Mount Sinai Hospital, University of Toronto, Toronto, ON, [8]Schulich School of Medicine and Dentistry, Western University, London, ON.

Background/Purpose: To determine predictors of 1-year remission in early rheumatoid arthritis (ERA) using baseline and 3 months data.

Methods: The Canadian Early Arthritis Cohort (CATCH) patients were included if baseline, 3 and 12 months data were available. Regression analyses for four different definitions of remission at 12 months were done to determine baseline and 3 months predictors of remission. Four remission definitions were evaluated: (1) Simplified Disease Activity Index (SDAI) score ≤ 3.3; (2) Clinical Disease Activity Index (CDAI) score ≤ 2.8; (3) 28 Joint Disease Activity Score (DAS28) score < 2.6; (4) Boolean based ACR/EULAR clinical trial definition requiring a tender joint count (TJC) ≤ 1, swollen joint count (SJC) ≤ 1, patient global assessment of disease (PTGA) ≤ 1 on a 0–10 cm scale, and C-reactive protein (CRP) ≤ 1 mg/dl using 28/28 TJC/SJC.

Results: 562 had complete data at 12 months; mean age 53.4 years, disease duration 6.2, 73% were female. The factors at baseline associated with all four remission outcomes at 12 months were age, gender, income, education, TJC, patient global assessment (PTGA), HAQ and pain. Baseline ESR was associated with DAS28 remission only. At 3 months, all four remission definitions were associated with: TJC, SJC, physician global assessment (MDGA), PTGA, HAQ, pain, ESR and CRP in univariate analyses. In the regression model, variables associated with SDAI remission were MDGA (OR 0.77, $p<0.001$), pain (OR 0.85, $p=0.004$), age (OR 0.98, $p=0.006$) and HAQ (OR 0.49, $p=0.011$); CDAI remission was associated with MDGA (OR 0.77, $p<0.001$), pain (OR 0.85, $p=0.003$), Age (OR 0.98, $p=0.015$) and CRP (OR 0.80, $p=0.031$). DAS28 remission was predicted by ESR (OR 0.95, $p<0.001$), MDGA (OR 0.76, $p<0.001$), age (OR 0.98, $p=0.001$), HAQ (OR 0.57, $p=0.006$) and male (OR 2.01, $p=0.005$), whereas Boolean remission was associated with pain (OR 0.79, $p=0.009$), age (OR 0.98, $p=0.016$), PTGA (OR 0.83, $p=0.025$), and MDGA (OR 0.86, $p=0.038$).

Conclusion: Younger age was associated with more remission. A low MDGA at 3 months was consistently associated with 1-year remission in ERA.

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Prednisone Use Associated With Worse Outcomes In Rheumatoid Arthritis Pregnancies. Prateek Chaudhary and M. E. B. Clowse. Duke University Medical Center, Durham, NC.

Background/Purpose: Prior reports suggest that disease activity in rheumatoid arthritis (RA) improves in the setting of pregnancy. However, prior studies report half of patients having moderate-severe disease activity throughout pregnancy; these are levels of activity unacceptable in our current RA treatment paradigm. The use of TNF-inhibitors remains controversial in pregnancy with many clinicians more comfortable with prednisone. The purpose of this study was to prospectively evaluate RA disease activity and medication use as predictors of pregnancy outcomes.

Methods: RA pregnancies were followed prospectively in a single clinic. An assessment of each patient was performed at all pregnancy and postpartum visits, and included demographic data and measures of disease activity, such as the physician global assessment (PGA) and 28 joint DAS-CRP. A DAS-CRP <2.6 was considered remission. Medication use was determined in collaboration between the physician and patient. Outcome measures included the presence of a miscarriage, preterm birth or preeclampsia. Non-parametric testing was used for the analysis.

Results: The 31 pregnancies in this cohort had a mean age of delivery of 32.5 years; 23 (74.2%) of mothers were Caucasian. Nine (29%) were exposed to TNF-inhibitors, while 15 (48.4%) were exposed to prednisone. 2 pregnancies (6.5%) ended in early miscarriages, neither with prednisone or TNF-inhibitor exposure and both with low RA activity. Of the 29 live births, preterm delivery occurred in 5 (17.2%) and preeclampsia in 3 (10.9%). Remission was achieved in 54% of women in the 1st trimester, 77% in the 2nd trimester, 67% in the 3rd trimester, and 61% postpartum. There was a strong correlation between DAS-CRP and PGA ($R=0.86$). Higher disease activity in the 1st trimester was associated with an increased risk of preterm birth (DAS-CRP = 5.58 preterm vs. 2.20 term, $p=0.028$; PGA= 30.0 preterm vs. 75.2 term, $p=0.019$). All pregnancies fell into one of three 1st trimester medication groups (table). Hydroxycholoroquine and sulfasalazine were evenly distributed in each group and did not appear to impact pregnancy outcomes. The patients with neither TNF-inhibitor nor prednisone exposure had a mean 1st trimester DAS-CRP of 1.63, while patients exposed to prednisone or TNF-inhibitor had a mean DAS-CRP of 3.92 or 3.19, respectively. Over half of patients (54.2%) exposed to prednisone had preterm birth and/or preeclampsia compared to 14.3% of those with TNF-inhibitor exposure.

Table. Medication group and pregnancy outcome

Medication	Mean 1st Trimester DAS-CRP	Preterm Birth	Preeclampsia	Either preterm birth or preeclampsia
No Prednisone or TNF-Inhibitor	1.63	0%	0%	0%
Prednisone	3.92	36.4%	27.3%	54.5%
TNF-Inhibitor	3.19	14.3%	0%	14.3%
p-value	0.150	0.086	0.099	0.0078

Conclusion: In the 1st trimester, high RA activity and prednisone use are both associated with an increased risk of preterm birth and/or preeclampsia. While both the prednisone and TNF-inhibitor groups had similar disease activity in the 1st trimester, prednisone use was significantly associated with a higher risk of adverse outcome. This study suggests that TNF-inhibitors may be preferable to prednisone in RA pregnancies.

Disclosure: P. Chaudhary, None; **M. E. B. Clowse**, UCB, 5.

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Mathematical Model To Predict The Early Responders In a Monocentric Cohort Of Patients With Rheumatoid Arthritis Treated By Anti TNF-Alpha. Camillo Giacomelli, Claudia Ferrari, Chiara Stagnaro, Rosaria Talarico, Arianna Consensi, Francesca Sernissi, Laura Bazzichi and Stefano Bombardieri. Rheumatology Unit, Pisa, Italy.

Background/Purpose: In the last few year the introduction of biological agents has radically changed the clinical outcome of patients with Rheumatoid Arthritis (RA). However, no single drug is able to control all patients with RA and it is known that each drug may be poorly effective in a sizable proportion of the treated patients. For these reasons the early identification of clinical responder patients would be a crucial advantage for both a clinical and

socioeconomic point of view. Recently, mathematic algorithms, based on classical clinical parameters, have been proposed to predict the clinical response to Anti TNF and DMARDs. In the present study we have applied the mathematic algorithm proposed to predict early response to anti TNF on our cohort of patients treated with antiTNF agents.

Methods: We collected the data of 96 patients followed in our unit and treated with antiTNF (Adalimumab, Etanercept, Infliximab, Golimumab and Certolizumab Pegol) from Jan 2010 to Jan 2013, with a follow up of at least 12 months. The mathematic algorithm, utilizing the following parameters: Tender Joint, Swollen Joint, Illness activity VAS by Physician and patient, Pain VAS, ESR and CRP; was applied to calculate the putative responders after one month of treatment and this value was compared with the DAS 28 at one month and after one year (yr). The patients were classified as good responders if they had a delta DAS28>1.2. In table 1 we summarized the main epidemiological and clinical data of patients under investigation.

Results: The clinical response at 1 yr was very significant for all kind of treatment. After 1 month of therapy a delta DAS 28>2.6 was recorded in 50% of all treated patients, while at one yr a delta DAS28>1.2 was found in percentage variable between 86% and 91.6% (table 1). In contrast, the mathematical model allows to predict 100% of the final responders for patients treated by Infliximab, Golimumab and Certolizumab Pegol, 93% for patients treated with Adalimumab and 90% with Etanercept, 5 false negative were registered for Etanercept and 3 false negative for Adalimumab.

Table 1.

	Certolizumab Pegol	Adalimumab	Infliximab	Etanercept	Golimumab
Number of patients	12	25	13	42	4
Age	52.63 ± 15.58	54.76 ± 15.57	58.00 ± 10.30	59.73 ± 15.32	51.21 ± 13.60
Sex	10 ♀ 2 ♂	21 ♀ 4 ♂	10 ♀ 3 ♂	35 ♀ 7 ♂	2 ♀ 2 ♂
$DAS28_{\text{at baseline}}$	5.77 ± 0.90	5.60 ± 0.89	6.46 ± 1.13	6.24 ± 0.78	5.27 ± 0.61
DAS28 at final visit	1.99 ± 0.43	2.80 ± 1.23	2.75 ± 0.74	3.14 ± 0.96	3.93 ± 0.84
% of Response Delta DAS28>1.2	91.6	86.0	91.9	88.1	89.4

Conclusion: These data indicate that in a routine clinical practice the application of a simple mathematical model is capable, at one month, to predict a good response in the majority of patients. Prospective studies are underway.

Disclosure: C. Giacomelli, None; **C. Ferrari**, None; **C. Stagnaro**, None; **R. Talarico**, None; **A. Consensi**, None; **F. Sernissi**, None; **L. Bazzichi**, None; **S. Bombardieri**, None.

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Metaflammation, PEDF and Chemerin: Potential Systemic Factors Which Link Obesity To Response To Therapy In Early Rheumatoid Arthritis. Elisa Gremese, Barbara Tolusso, Anna Laura Fedele, Maria Rita Gigante, Angela Carbonella, Silvia Canestri, Clara Di Mario and Gianfranco Ferraccioli. Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy.

Background/Purpose: Obesity *per se* is a systemic, low-grade inflammatory state and the adipose tissue is an endocrine organ that releases bioactive substances, including pro-inflammatory cytokines, like TNFα and IL6, and specific adipokines. There are only few data about early RA (ERA), suggesting that obesity associates with disease outcomes. In this work we aimed to evaluate whether the body weight, and its metabolic (PEDF) and meta-inflammatory parameters (Chemerin), could be associated with the outcomes in terms of disease remission and treatment in ERA patients (symptoms duration <12 months).

Methods: 346 ERA patients, treated according to a treat-to-target strategy, were enrolled. At each visit the ACR/EULAR core data set was registered. Baseline BMI was collected and baseline PEDF and Chemerin plasma levels were evaluated by ELISA's methods. Adipose tissue PEDF gene expression was evaluated in overweight and obese subjects (24 ERA and 6 healthy controls). Logistic regression models were applied to determine the influence of independent variables reaching a *p*value<0.25 at the univariate analysis, on the dependent variables "DAS remission at 12th month and anti-TNF therapy at 12th month".

Results: Of the 346 ERA patients (76.3% female, age 54.6±14.0 years, 32.9% very ERA, 70.2% seropositive, baseline DAS 3.6±1.1), 168 (48.6%) were normal weight, 135 (39%) overweight and 43 (12.4%) obese. BMI values correlated with baseline PEDF (r=0.33, p<0.001) and chemerin (r=0.31, p<0.001) plasma levels. Moreover, BMI values correlated with age (r=0.23, p<0.001), baseline inflammatory markers (ESR: r=0.14, p=0.009, CRP: r=0.19, p<0.001), DAS (r=0.18, p=0.001) and HAQ (r=0.17, p=0.001). PEDF relative gene expression was 1.55 times higher in ERA patients compared to healthy subjects. Overweight and obese patients reached a lower remission rate at 6 and 12 month follow-up visits (DAS remission at 6th month: 52.1% in normal, 41.2% in overweight, 28.1% in obese, p=0.03; sustained DAS remission at 12th month: 51.0% in normal, 28.8% in overweight, 34.4% in obese, p=0.004). Moreover, an higher percentage of obese and overweight ERA patients were under anti-TNF treatment after 12 months of follow-up (27.3% of obese, 30.2% of overweight, 11.4% of normal weight, p=0.003). At the multivariate analysis, the independent baseline variables associated with the risk of "not obtaining DAS remission at 12th month follow-up" were duration of symptoms >3 months (OR: 2.3 (1.0–5.3)), baseline CRP≥5.0 mg/l (OR: 2.4 (1.1–5.6)) and baseline chemerin plasma levels>99.5ng/ml (OR: 2.4 (1.1–5.6)). The independent variables associated with the probability of being in anti-TNF therapy at 12th month follow-up were age <55 years (OR: 2.70 (1.41–5.34)), baseline DAS≥3.7 (OR: 2.27 (1.19–4.34) and BMI≥25 (OR: 2.36 (1.21–4.59)).

Conclusion: In ERA patients, not only obesity, but also overweightness, are associated with worst outcomes, like higher disease activity, lower remission rates, and greater use of anti-TNF therapy. PEDF and chemerin seem to be biomarkers of metaflammation.

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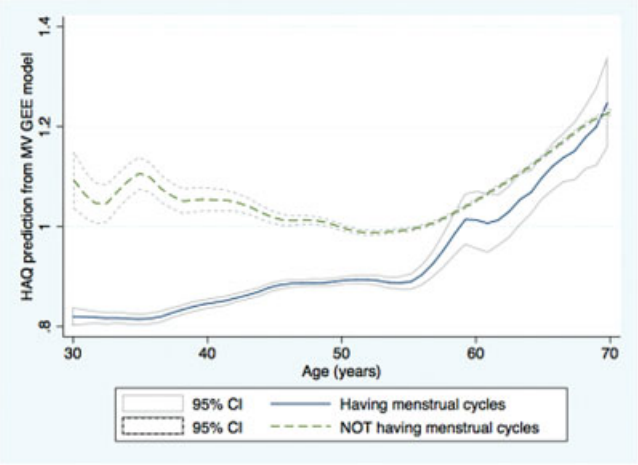
The Impact Of Menopause In Rheumatoid Arthritis Activity. Sofia Pedro[1], Eliza Chakravarty[2], Megan E. B. Clowse[3], Rebecca Schumacher[1] and Kaleb Michaud[1]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Duke University Medical Center, Durham, NC.

Background/Purpose: Factors such as menopause, hormonal replacement therapy (HRT), oral contraceptives (OC), pregnancy, and breast-feeding have been associated with the risk of developing Rheumatoid Arthritis (RA) in women. However, the effect of these factors on RA disease progression has had little investigation.

Methods: Using a large US observational cohort, the National Data Bank for Rheumatic Diseases, we investigated the impact of menopause on RA functional outcomes as measured by the Heath Assessment Questionnaire (HAQ) and HAQ annual progression rates. We excluded all women who went through menopause before RA onset. Menopausal status (1=menstruating, 0=reached menopause) was further analyzed by comparing 3 groups of women based on their menopausal status while under observation in the study: premenopausal, post-menopausal, & transitioned through menopause. Possible confounders controlled for included age, educational level, household income, use of anti-TNF agents, HRT, and OC. We used univariate and multivariate (MV) generalized estimating equations (GEE) methods with the sandwich estimator. To account for a possible non-linear relationship between age and HAQ, we used a cubic spline with 3 knots at age 40, 56, 72, and an interaction term. Best models were selected using the QIC_u criterion

Results: A total of 7,632 women were eligible between 1998 and 2012 with an average of 2.9 years in the study. Of these, 2,102 were premenopausal (28%), 618 underwent menopause (8%), and 4,912 were entirely postmenopausal (64%). Within each respective group, the mean (SD) ages were 40 (8.2), 51 (SD 6.1), and 61 (9.9) years. Our results showed that women who were still having menstrual cycles tended to have a better HAQ score by −0.33 (−0.52, −0.14) than women who stopped having menstrual cycles; these results were robust even after full adjustment for other significant factors, −0.32 (−0.51, −0.14) (see Figure). The use of OC ever in reproductive life seemed also protective for disability as well as having had a pregnancy. On the other hand, HRT did not seem to be associated with disability. HRT and pregnancy did not qualify by our criterion for the final multivariate model. Using the menopause status with the 3 groups in the full model, in comparison with pre-menopausal women, HAQ of post-menopausal women were increased by 0.51 (0.16, 0.85), and not differ for who underwent menopause, 0.038 (−0.26, 0.33). The HAQ rate of progression was −0.001 per year (−0.248, 0.117) when comparing women who reached menopause with those who didn't.



Conclusion: In this large observation study, our results suggest that higher levels of estrogen may be associated with reduced functional limitations. However, HAQ progression continued similarly post-menopause as it did pre-menopause.

Disclosure: S. Pedro, National Data Bank for Rheumatic diseases, 3; **E. Chakravarty**, None; **M. E. B. Clowse**, UCB, 5; **R. Schumacher**, National Data Bank for Rheumatic diseases, 3; **K. Michaud**, National Data Bank Bank & University of Nebraska Medical Center, 3.

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Predicted Versus Observed Radiographic Progression In a Rheumatoid Arthritis Randomized Trial. Adrian Levitsky[1], Kristina Forslind[2] and Ronald F. van Vollenhoven[1]. [1]Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), the Karolinska Institute, Stockholm, Sweden, [2]Department of Clinical Sciences, Section of Rheumatology, Skåne University Hospital, Lund, Sweden.

Background/Purpose: Radiographic progression is a key outcome in early RA. We previously developed a radiographic progression prediction method based on the patient's report of symptom duration and the radiological damage at first examination[1]. We previously included data on predicted radiological progression for a subset of patients in the SWEFOT trial. Here, we applied the analysis of predicting radiological progression (prediction of progression in early RA, or POPERA) to the full data set from this randomized trial with the aim to compare predicted versus observed radiological progression in early RA patients treated with MTX or combination therapies.

Methods: In the SWEFOT trial[2, 3], 487 patients with early RA were given MTX, and non-responders after 3–4 months (DAS28>3.2) were randomized to MTX+SSZ+HCQ ("Triple therapy") vs. MTX+infliximab ("anti-TNF"). The others continued on MTX ("MTX-responders"). Hand and foot X-rays (baseline, 1, and 2 years) were analyzed with the Sharp-van der Heijde Score (SHS). Predicted progression at 1 and 2 years was calculated as the baseline SHS divided by symptom duration in months multiplied by 12 or 24, respectively. The analysis involved intention-to-treat (ITT) patients, and, in order to allow inclusion of patients with SHS 0 at baseline in the mathematical model, all SHS values in the entire data set were increased by 1. Comparisons between observed progressions were done by non-parametric, Mann-Whitney U testing.

Results: In all three groups of patients, observed radiographic progression was reduced from predicted by 50–96%. In patients who had failed both MTX monotherapy and subsequent triple therapy, the reduction of radiographic progression was numerically the least at 12 months (40.7%). After 12 months, there were no significant between-group differences. After 24 months, progression was reduced more in the anti-TNF arm than in both the MTX and triple therapy arms.

Table I. Mean Observed Radiographic Reduction from Predicted

	MTX responders	Triple therapy ITT	Anti-TNF ITT	Triple therapy completers	Anti-TNF completers
Percent reduction at 12 months	73.9 (±5.5)	50.1 (±10.1)	72.3 (±5.6)	56.7 (±14.2)	76.5 (±4.8)
Percent reduction at 24 months	87.8* (±2.8)	87.2† (±3.1)	89.8†* (±3.1)	91.0 (±3.4)	96.0 (±1.8)

* Anti-TNF (ITT) vs. MTX: p=0.013.
† Anti-TNF (ITT) vs. Triple therapy: p=0.021.

[1]Wick et al. Ann Rheum Dis 64:134–137, 2005.
[2]Van Vollenhoven et al. Lancet 374:459–466, 009.
[3]Van Vollenhoven et al. Lancet 379:1712–1720, 2012.

Conclusion: The progression observed in patients who failed their first 2 antirheumatic therapies was 59.3% of predicted at 12 months. The overall results demonstrated significant reductions from predicted radiological progression in patient groups who were successfully treated with MTX and in those who were included in either group of the randomization. Over 24 months, anti-TNF therapy was superior to triple therapy. The POPERA method may provide valuable information on the relative radiographic efficacy of treatments for early RA.

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Sarcopenia Is Associated With Joint Damage In Rheumatoid Arthritis patients a Cross Sectional Study In a Peruvian Population. Erika Noriega[1], Rocio V. Gamboa-Cardenas[1], Manuel F. Ugarte-Gil[1], Mariela Medina-Chinchon[1], Francisco Zevallos-Miranda[1], J. Mariano Cucho-Venegas[1], Risto A. Perich-Campos[2], Jose L. Alfaro-Lozano[1], Zoila Rodriguez-Bellido[2] and Cesar A. Pastor-Asurza[2]. [1]Hospital Almenara, Lima, Peru, [2]Universidad Nacional Mayor de San Marcos, Lima, Peru.

Background/Purpose: Sarcopenia is a low-level, smoldering inflammatory state driven by cytokines and oxidative stress. In rheumatoid arthritis (RA) the relationship between sarcopenia and severity of disease as reflected by joint damage (JD) has not been established. The aim of this study was to determine the association between sarcopenia and joint damage in patients with RA.

Methods: We conducted a single center cross-sectional study. All subjects were older than 18 years at diagnosis and met the ACR criteria. We excluded patients with prosthetic or metallic elements, infections, trauma/recent surgery, cancer, hospitalized, neurological sequelae from stroke, pregnant or weight> 140 kg. Appendicular skeletal muscle mass (ASM) was measured using dual X-ray absorptiometry (DXA), sarcopenia was define as ASM/m^2 less than 5.45 kg/m^2, we assessed physical performance using the Short Physical Performance Battery (SPPB) and muscle strength of the knee and elbow flexion/extension using a digital dynamometer. A blinded investigator to sarcopenia status determined JD score according to Sharp van der Heidje method. An univariated linear regression model to determine association between sarcopenia and joint damage was applied after that, a multiple regression model, ajusted to age, disease duration, diagnosis delay, DAS28CRP, Fn-HAQ and current doses of prednisone, was performed to determine persistence of the association. Data was analyzed using SPSS v20.0.

Results: Ninety three women were evaluated, mean (SD) age was 51.56 (10.21) years, disease duration was 14.12 (8.86), and diagnostic delay was 1.73 (2.28) years, 83% were rheumatoid factor positive. Fn-HAQ score was 3.15 (1.50) and DAS28-CRP: 3.52 (1.06). The average value of ASM was 13.48 (2.63) kg/m^2. Twenty seven (29%) patients were found to be sarcopenic. Patients with sarcopenia had lower muscle strength and performance. In the multivariate linear regression model sarcopenia was independently associated with JD (β: 0.261, p: 0.031).

Conclusion: Sarcopenia was associated with JD in our female patients with RA independently of other well known risk factors for damage. Sarcopenia contributes to physical frailty, an state that distinct from functional disability, contributes indeed to adverse patient outcomes.

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The Safety and Feasibility Of a Treat-To-Target Strategy Aimed At Achieving a Simplified Disease Activity Index Of ¡Ü3.3 While Administering Entecavir In Rheumatoid Arthritis Complicated By Hepatitis B Virus. Yukitomo Urata[1], Yoshihide Nakamura[2] and Ken-ichi Furukawa[2]. [1]Seihoku Central Hospital, United Municipalities of Tsugaru, Gosyogawara, Japan, [2]Hirosaki University Graduate School of Medicine, Hirosaki, Japan.

Background/Purpose: To elucidate the safety and feasibility of a treat-to-target (T2T) strategy aimed at achieving a simplified disease activity index (SDAI) of ≤3.3 while administering entecavir (ETV) in patients with rheumatoid arthritis (RA) complicated by hepatitis B virus (HBV).

Methods: Written informed consent was obtained from patients with rheumatoid arthritis who satisfied with SDAI>3.3, alanine aminotransferase (ALT) ≤30 and unidentified HBV –DNA under medicating with ETV for HBV. The time of enrolment was set as the baseline (BL) and the time of observation two years later was set as the endpoint (EP). SDAI was measured at once every three months, and in accordance with the modified strategy of T-4 study (1), treatment was intensified with a target SDAI of ≤3.3. HBV-DNA was measured on a monthly basis from BL. SDAI, health assessment questionnaire disability index (HAQDI), and modified total Sharp score (mTSS) were measured one and two year after the enrolment. Primary, secondary and outcome measures consisted of the proportions of patients showing rate of absence of HBV-DNA reactivation (HBV-DNA>2.1 log copies/mL), clinical remission (SDAI≤3.3), normal liver function (ALT≤30), lack of radiological progression (DmTSS≤0.5), normal physical function (HAQDI=0), or comprehensive disease remission defined as the combination of clinical remission, lack of radiological progression, and normal physical function.

Results: Subjects comprised 14 patients (mean age, 61.0 ± 8.9 years; mean disease duration, 7.8 ± 7.8 years; mean SDAI, 8.7 ± 5.4; mean HAQDI, 0.2 ± 0.3; mean ALT, 21 ± 6), 8 of whom were women (57%). Among these subjects, five were carriers and 9 experienced reactivation of a resolved HBV. Treatment after the enrolment consisted of 31% of patients taking an antirheumatic drug (bucillamine, n=4;; leflunomide, n=1), 43% taking glucocorticoids (GCs) with a mean GCs dose (prednisolone equivalent of 3.4mg/day (maximum dose; 9mg/day), 57% taking methotrexate (MTX) with a mean MTX dose of 7.1 mg/week, 50% taking folic acid, and 50% taking biological drugs (etanercept, n=4; abatacept, n=2; tocilizumab, n=1). At 2 years, the rate of absence of HBV-DNA reactivation, SDAI≤3.3, ALT≤30, DmTSS≤0.5, HAQDI=0, and comprehensive disease remission were follows, 100%, 50%, 93%, 43%, 64% and 21%. ALT, SDAI, ΔmTSS and HAQDI at EP was 19 ± 7, 4.3±4.5, 0.8±2.2 and 0.2±0.3, respectively. No significant differences were observed between BL and EP for value of ALT, SDAI or HAQDI. No patient had ALT value in excess of 100 IU/L during the observation period. All of the 7patients who had HAQDI=0 at BL also had HAQDI=0 at EP.

Conclusion: T2T aimed at achieving SDAI≤3.3 is also possible safety in patients with RA complicated by HBV by performing ETV administration and appropriate HBV-DNA monitoring.

Reference:

1. Urata Y et al. Treating to target matrix metalloproteinase 3 normalisation together with disease activity score below 2.6 yields better effects than each alone in rheumatoid arthritis patients: T-4 Study. Ann Rheum Dis. 2012;71:534–40.

Disclosure: Y. Urata, None; **Y. Nakamura**, None; **K. I. Furukawa**, None.

1337

Nearly Pain Free Self-Administration Of Methotrexate Using An Investigational Auto-Injector: Results Of a Phase-2 Clinical Trial In Rheumatoid Arthritis Patients With Mild-To-Severe Functional Limitations. Alan J. Kivitz[1], David McLain[2], John Hill[3], Bruce Freundlich[4], Jonathan Jaffe[5] and Kaushik J. Dave[5]. [1]Altoona Center for Clinical Research, Duncansville, PA, [2]Rheumatology, McLain Medical Associates, PC, Birmingham, AL, [3]Avail Clinical Research, DeLand, FL, [4]University of Pennsylvania, Philadelphia, PA, [5]Antares Pharma Inc, Ewing, NJ.

Background/Purpose: Methotrexate (MTX) is the cornerstone of rheumatoid arthritis (RA) treatment. Limitations of systemic exposure of oral MTX can affect its efficacy. Subcutaneous (SC) MTX improves bioavailability, which may result in better efficacy, and tolerability. Self-administration of SC MTX via conventional vial and syringe is challenging for some patients due to injection-associated anxiety, functional limitations, injection-site adverse events (AEs), and especially pain. An investigational auto-injector that delivers SC MTX was tested with the intention of addressing these patient concerns.

Methods: 101 RA patients were enrolled in this phase 2, multi-center, open-label, single-dose, single-arm, in-clinic study to evaluate the actual human use of SC MTX administered via a developmental MTX auto-injector (MTXAI). MTX dose (10, 15, 20, 25 mg) was determined by investigators based on patient MTX regimen and disease status (controlled or uncontrolled) at time of enrollment.

Results: 99 patients were evaluable. (79.2% female, mean age 60.9 yrs. [SD± 10.1], mean disease duration 13.3 yrs. [SD± 11.0], 84.2% ACR Class II or III, 89.1% Functional Class II or III). All patients had been taking MTX for ≥3 months prior to study enrollment; 20% had used SC MTX. Safety was assessed by recording AEs and evaluating administration sites before and at 0.25, 1, 6, and 24 hours after self-administration. Administration site pain (measured on a 100-mm VAS) is summarized in the table. Mean administration site pain was 3.6 mm/100 mm [SD± 9.1] on Day 1 with a median 1.0 mm/100 mm (0–72) and a mean of 1.4 mm [SD± 3.2] with a median of 0.0 mm (0– 21) on Day 2. 93/99 pts. (94%) reported VAS scores of ≤10 on Day 1; 86/99 pts. (87%) reported scores of ≤5 on Day 1. Of 404 post-administration evaluations, 92.3% found no erythema. The remainder indicated "very slight, barely perceptible" erythema. Three patients had AEs (sick sinus syndrome, exostosis, and headache) not considered related to the study drug by the investigators. 100% of patients, including those with moderate-to-severe functional limitations in dexterity, successfully used the auto-injector.

Table. Administration site pain and erythema (Scale 0–100mm)

Administration site pain	MTX 10 mg (N=20)	MTX 15 mg (N=30)	MTX 20 mg (N=31)	MTX 25 mg (N=20)	Overall (N=101)
Day 1 (mean ± SD, median [range])	1.0 ± 1.0 1.0 (0–3)	7.6 ± 15.6 2.0 (0–72)	2.2 ± 2.9 1.0 (0–10)	2.4 ± 2.6 2.0 (0–9)	3.6 ± 9.1 1.0 (0–72)
Day 2 (mean ± SD, median [range])	1.7 ± 4.5 0.0 (0–20)	2.0 ± 4.1 0.0 (0–21)	1.0 ± 1.6 0.0 (0–7)	1.0 ± 1.2 0.5 (0–4)	1.4 ± 3.2 0.0 (0–21)

SD = standard deviation.

Conclusion: The MTXAI was well tolerated with almost no administration site pain and minimal erythema. Limitations in functional status did not affect ability to self-administer. Improving the delivery of SC MTX with this developmental, first-in-class auto-injector may increase patient tolerance of self-injection thereby improving adherence in patients with RA.

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Time To Institution Of Disease Modifying Anti-Rheumatic Drugs In Australian Patients With Early Rheumatoid Arthritis. Sharon Van Doornum[1], Joanne Tropea[2], Mark Tacey[1] and Danny Liew[1]. [1]The University of Melbourne, Melbourne, Australia, [2]Royal Melbourne Hospital, Melbourne, Australia.

Background/Purpose: Early introduction of disease-modifying anti-rheumatic drugs (DMARDs) has been shown to reduce joint destruction and long-term disability in rheumatoid arthritis (RA). Substantial and irreversible harm can occur as little as 12 weeks after onset of symptoms. Recent international studies have examined time to institution of DMARD in early RA, with median delays of between 13 and 36 weeks. The aim of the present study was to examine the time to DMARD therapy in Australian patients with early RA.

Methods: The study included patients referred to a metropolitan tertiary hospital and to 14 community-based rheumatologists in Australia. The hospital-based patients were identified retrospectively via hospital records and included patients with early RA who were first seen between January 2008 and October 2012. Medical charts were reviewed and, if necessary, the local doctor contacted for additional information. The community-based patients were recruited via the treating rheumatologists and data were collected prospectively by the rheumatologists over the period February 2012 to April 2013. Data recorded included dates of symptom onset, initial local doctor consultation, referral to rheumatologist, rheumatologist review and commencement of DMARD. Serologic status and first DMARD commenced were also noted.

Results: One hundred and thirty five patients (66% female, mean±SD age 55±16 years) were identified and contributed data. RhF and/or ACPA was positive in 66% (n=89) of patients. The median time from symptom onset to initiation of DMARD therapy was 163 days (inter-quartile range (IQR) 88–323). The median time from referral to first rheumatology appointment was 33 days (IQR 9–55) and from first rheumatology appointment to DMARD commencement was 0 days (range 0–22). The major component of the delay comprised the time from symptom onset to referral to the rheumatologist, for which the median duration was 98 days (range 51–239). Stratified analysis did not reveal any substantial differences in delays between hospital-based and community-based patients. However, among hospital-based patients, ACPA positive status resulted in more rapid commencement of DMARD therapy (median 35 vs 93 days from time of referral, p=0.014). The first DMARD commenced was methotrexate monotherapy in 61% (n=82) of patients and methotrexate combination therapy in 5% (n=7) of patients.

Conclusion: As noted in other countries, there are considerable delays in the commencement of DMARD therapy for Australian patients with early RA. A substantial component of the delay is prior to the referral of the patient by the local doctor for rheumatologist review.

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Efficacy and Safety Of Biologics Agents For Patients With Rheumatoid Arthritis and Hepatitis B Carrier. Masahiro Tada, Tatsuya Koike, Akihiro Tamori, Tadashi Okano, Yuko Sugioka, Kenji Mamoto, Kentaro Inui and Hiroaki Nakamura. Osaka City University Graduate School of Medicine, Osaka, Japan.

Background/Purpose: Biologics suppress hepatitis B virus (HBV) replication and play an important role in eradicating HBV by stimulating HBV-specific cytotoxic T-cell responses. We found that HBV reactivates or flares after biologics therapy in patients with chronic hepatitis B infection and in those with inactive hepatitis B surface antigen (HBs-Ag). The guideline, prevention of immunosuppressive-induced reactivation of HBV infection, recommend nucleoside analogs for treating patients with rheumatoid arthritis (RA) who are positive for HBs-Ag. We aimed to determine the efficacy and safety of biological therapy in patients with RA carrying hepatitis B by evaluating clinical characteristics and changes in serological and biological markers of HBV flare.

Methods: Six patients with RA who screened positive for HBs-Ag were prescribed with entecavir (ETV) under the direction of a hepatologist when HBV-DNA levels decreased to < 2.1 log copies/mL. The patients were also treated with infliximab (n = 1), etanercept (n = 2), adalimumab (n = 2) and tocilizumab (n = 1) (Table). We evaluated the disease activity score of RA (DAS28-ESR), HBV markers and genotype before starting treatment as well as changes in the amount of HBV-DNA, HBs-Ag and alanine aminotransferase (ALT).

Results: The average age, duration of RA and DAS28-ESR at baseline was 54.7 years, 10.9 years and 5.51, respectively. The minimum HBs-Ag value is 12.2 and three patients had values over >2000 before starting ETV therapy. The pre-treatment values of HBV-DNA and ALT were 4.28 log copies/mL and 20.2 U/L, respectively. Flare of HBV was not confirmed during 2.1 years the patients were treated with these agents. Hepatitis B viral DNA was undetectable in all cases at final follow-up (Table). The DAS28-ESR was 3.14 at final follow-up and disease RA activity remained low (Figure).

Table. Changes in the amount of HBs-Ag, HBV-DNA, and ALT

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age, years	56	33	58	63	64	54
HBs-Ag at baseline, mIU/mL	233.9	2000<	2000<	2000<	12.2	332
HBs-Ag at final F/U, mIU/mL	259.2	2000<	2000<	2000<	17.3	215.1
HBV DNA at baseline, log/mL	4.8	3.6	7.6	4.9	2.3	2.5
HBV DNA at final F/U, log/mL	undetectable	undetectable	undetectable	undetectable	undetectable	undetectable
ALT at baseline, U/L	13	12	58	13	8	17
ALT at final F/U, U/L	10	14	15	15	10	15
Biologics	ETN	IFX	ADA	TCZ	ETN	ADA

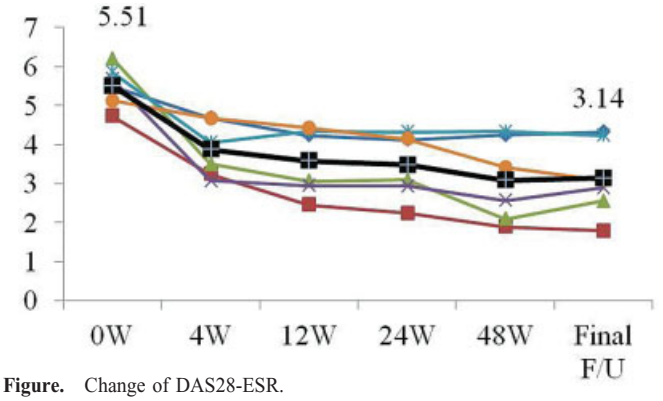

Figure. Change of DAS28-ESR.

Conclusion: Antiviral prophylaxis protected against HBV reactivation in patients with RA, indicating that biologics are relatively safe for treating such patients. Biologics could serve as a useful treatment for hepatitis B carriers who are simultaneously prescribed with nucleoside analogs under the control of a hepatologist.

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Functional Disability and Quality Of Life Are More Likely Improved In Patients With Rheumatoid Arthritis Who Achieved The New ACR/EULAR Remission Criteria Compared To DAS28 Remission In Daily Practice. Yoko Shimizu[1], Ayako Nakajima[1], Eisuke Inoue[2], Eiichi Tanaka[2], Akiko Kobayashi[1], Yohei Seto[1], Shigeki Momohara[1], Atsuo Taniguchi[1] and Hisashi Yamanaka[2]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: The new ACR/EULAR remission criteria were proposed to predict favorable outcome in patients with rheumatoid arthritis (RA).

To evaluate the functional disability and quality of life (QOL) in patients with RA who achieved the ACR/EULAR remission criteria compared to that in patients who achieved 28-joints disease activity score (DAS28) remission in 1 year in a large daily practical observational cohort, IORRA.

Methods: Patients who had moderate or high disease activity according to simplified disease activity score (SDAI) in April 2010 survey were extracted. Functional disability and QOL was assessed by the validated Japanese version of Health Assessment Questionnaire (J-HAQ) score and the European QOL-5 dimension (EQ-5D) acore, respectively. The disease activity after 1 year in each patient was assessed by SDAI and DAS28. The mean changes of progression of J-HAQ and EQ-5D scores in 1 year in each patient were calculated for the patients achieving remission criteria defined by SDAI or DAS28, respectively. The factors associated with achieving SDAI remission were evaluated by multiple regression analysis.

Results: Among a total of 5,587 patients participated in the IORRA cohort in April 2010, 1,307 (23.4%) patients had high or moderate disease activity assessed by SDAI. In these patients, 85.7 % were female, and median age was 62.2 years and RA duration was 13 years. After 1 year, 11.7% and 16.9% patients achieved SDAI remission and DAS28 remission, respectively. The progression of J-HAQ score in 1 year was −0.30 + 0.49 in patients who achieved SDAI remission and −0.05 + 0.35 in patients who didn't ($p<0.001$), whereas −0.26 + 0.47 in patients who achieved DAS28 remission and −0.05 + 0.35 in patients who didn't ($p<0.001$). The odds ratio (OR) for non-progression of functional disability by achieving SDAI remission was 2.79 (95% confidence interval (CI), 1.70–4.59), whereas that by achieving DAS28 remission was 1.96 (95% CI, 1.34–2.86). The progression of QOL score in 1 year was 0.165 + 0.162 in patients who achieved SDAI remission and 0.028 + 0.123 in who didn't ($p<0.001$), whereas 0.129 + 0.169 in patients who achieved DAS28 remission and 0.028 + 0.121 in patients who didn't ($p<0.001$). The OR for non-deterioration of QOL by achieving SDAI remission was 2.90 (95% CI 1.62–5.23), whereas that by achieving DAS28 remission was 2.11 (95% CI 1.35–3.29). The factors associated with achieving SDAI remission in 1 year were disease duration (OR 0.96, 95%CI 0.93–0.98), baseline physical function (OR 0.52, 95%CI 0.39–0.70) and biologics initiation within 6 months (OR 3.70, 95%CI 2.05–6.54).

Conclusion: Achieving SDAI remission has more impact on both better physical function and improved QOL than achieving DAS28 remission.

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Significantly Less Glucocorticoids and Better Patient-Reported Outcomes In Women With Early Inflammatory Arthritis Using Oral Contraceptives Compared To Never Users. Gisela Westhoff[1], Rainer H. Straub[2], Frank Buttgereit[3], Johanna Callhoff[4] and Angela Zink[5]. [1]German Rheumatism Research Center Berlin, Berlin, Germany, [2]Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, University Hospital of Regensburg, Regensburg, Germany, [3]Charité - Universitätsmedizin Berlin, Berlin, Germany, [4]German Rheumatism Research Center, Berlin, Germany, [5]German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany.

Background/Purpose: Data on the effects of oral contraceptives (OC) on the course of inflammatory arthritis (IA) are controversial. However, a recent analysis of data from the Norfolk Arthritis Register (NOAR) showed that the use of OC is associated with beneficial functional outcomes. We aimed at investigating the associations between OC use, need of therapies, and outcomes in women with early IA within the first year of care.

Methods: A total of 324 women with early IA (symptoms <6 months, 18 – 60 years, never having used hormone replacement therapy), were followed with respect to disease activity (CRP, ESR, S/TJC28, morning stiffness), use of DMARDs and glucocorticoids (GC) and patient-reported outcomes (PROs) according to the Rheumatoid Arthritis Impact of Disease Score (RAID 0–10), the PROFAD (0–10), the PHQ9 Depression Scale (0–27), and the Functional Scale FFbH (0–100). Use of OC was reported as never, past, or current. Outcomes by use of OC were adjusted for age, body mass index, number of natural children, and years of education using generalized linear models.

Results: At baseline, mean age was 46 ±10 years and symptoms lasted for 13 ±7 weeks. Of these women, 68% fulfilled the 2010 criteria for rheumatoid arthritis (RA), 82% were clinically diagnosed with RA at 12 months and 89% took DMARDs at that point in time. 24% had never used OC, 57% had used them in the past, and 19% used them currently. Current users were younger (36 vs. 50 yrs) and less frequently mothers than past and never users (58 vs. 80%). Independent of the time point (t0, 3, 6, 12 months), current use of OC, compared to past and never use, was not associated with biomedical measures, duration of morning stiffness or DMARD use (not shown). However, current and past OC use was associated with steadily decreasing GC use (54 and 57% at 12 months), while never users remained unaltered at 74% (P 0.016). Finally, current and past OC use was associated with significantly better outcomes in almost all considered patient-reported dimensions, such as pain, fatigue, well-being and function (Table). The effect of OC on PROs was, notably, almost the same in past and current users, although half of the past users were older than 50 years and might not have used OC for several years.

PROs at 12 months by use of oral contraceptives (means)

OC use	n	Pain*	Overall fatigue	Problems getting started	Problems to focus	Problems daily chores	Physical well being	Mental well being	Depression (PHQ90-27)	Physical function (0–100)
never	88	3.9	4.4	4.1	3.5	3.6	4.4	4.5	6.7	78.7
past	184	3.1	3.5	2.4	2.4	2.6	3.1	2.9	5.1	86.7
current	52	2.8	3.2	1.6	1.5	2.4	2.9	2.3	4.0	87.5
Total	324	3.3	3.7	2.5	2.3	2.8	3.3	3.1	5.2	85.1
P#		0.033	0.049	0.006	0.001	0.012	0.005	<0.001	0.021	0.018

* Means adjusted for age, BMI, number of children and education; #P never vs. current use.

Conclusion: Our findings confirm that women with past or current OC use have better functional outcomes without having less signs of inflammation. The specific spectrum of obviously ameliorated conditions indicates that estrogens seem to have neuro- and psycho-protective effects on many symptoms that compromise well-being in IA. It may be suggested that OC act directly at CNS cytokines rather than influencing the course of peripheral inflammation. Long-lasting programming of CNS function may explain positive effects of OC. The use of hormones should be routinely reported in studies observing IA.

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Prognosis In Espoir Rheumatoid Arthritis Cohort At 24 Months According To Remission Status At 12 Months: No Differences In Radiographic Scores According To Prior Remission Status, But Significant Differences In HAQ Scores, Highest For Boolean and RAPID3RJ1 Criteria. Isabel Castrejón[1], Maxime Dougados[2], Bernard Combe[3], Francis Guillemin[4], Bruno Fautrel[5] and Theodore Pincus[1]. [1]NYU Hospital for Joint Diseases and New York University School of Medicine, New York, NY, [2]Cochin Hospital, Paris, France, [3]CHU Lapeyronie, Montpellier, France, [4]Hopitaux de Brabois, Nancy, France, [5]APHP, Pitié-Salpêtrière University Hospital, Paris, France.

Background/Purpose: Different criteria for remission in rheumatoid arthritis (RA) have been developed from a Core Data Set of 7 measures for the DAS28, SDAI, CDAI and RAPID3 (with only patient self-report measures). An ACR/EULAR committee proposed two criteria: "Boolean," with TJC28, SJC28, CRP, PATGL all '1; and SDAI ≤3.3 *[Arthritis Rheum 2011;63:573]*. A recent report indicated that remission criteria based on RAPID3 ≤3 with ≤1 swollen joint (RAPID3RJ1) gave results similar to Boolean and SDAI criteria, but without a formal joint count to be more feasible for usual care *[J Rheumatol 2013;40:386]*. This new study analyzed 6 remission criteria to predict a good outcome for physical function and radiographic damage one year later in the ESPOIR cohort of French early arthritis patients.

Methods: ESPOIR includes patients with early arthritis who received routine care. Remission was assessed 12 months after baseline by 6 criteria: ACR/EULAR Boolean criteria; SDAI (≤3.3); CDAI (≤2.8); DAS28 (≤2.6); RAPID3 (≤3) and RAPID3RJ1 (RAPID3 ≤3 and ≤1 swollen joint). Analyses were conducted to determine status 12 months later (at 24 months) to recognize whether a patient who met each remission criteria 12 months earlier was likely or not to have a good functional outcome [stable or lower HAQ scores, and absolute score of ≤0.5 at both 12 and 24 months after baseline] or good radiographic outcome [no change in the modified Sharp/van der Heijde score from 12 to 24 months]. The proportions of good outcomes in patients who had been classified 12 months earlier as in or not in remission were compared by chi square tests and likelihood ratios.

Table. Prognosis for good HAQ physical function and radiographic outcomes at 24 months, based on 12-month remission evaluation in 656 RA patients

	Prevalence of good HAQ outcome at 24 mo			
Remission criteria	In remission at 12 mo	Not in remission at 12 mo	P (chi square)	Positive likelihood ratio
Boolean	83.1% (103/124)	50.2% (267/532)	<0.001	3.8
SDAI ≤3.3	78.6% (121/154)	49.6% (249/502)	<0.001	2.8
CDAI ≤2.8	79.1% (121/153)	49.5% (249/503)	<0.001	2.9
DAS28 ≤2.6	69.8% (190/272)	46.9% (180/384)	<0.001	1.8
RAPID3 ≤3	80.2% (170/212)	45.0% (200/444)	<0.001	3.1
RAPID3 ≤3 + SJC≤1	83.7% (134/160)	47.6% (236/496)	<0.001	4.0
	Prevalence of good radiographic outcome at 24 mo			
Remission criteria	In remission at 12 mo	Not in remission at 12 mo	P (chi square)	Positive likelihood ratio
Boolean	67.3% (74/110)	68.7% (338/492)	0.771	0.95
SDAI ≤3.3	70.4% (95/135)	67.9% (317/467)	0.583	1.09
CDAI ≤2.8	71.1% (96/135)	67.7% (316/467)	0.448	1.14
DAS28 ≤2.6	68.4% (169/247)	68.4% (243/355)	<0.994	1.00
RAPID3 ≤3	68.9% (129/187)	68.2% (283/415)	0.847	1.03
RAPID3 ≤3 + SJC≤1	69% (96/139)	68.2% (316/463)	0.856	1.03

Results: 656 patients had available data to evaluate remission; 76% were women; mean age 48 years; median baseline disease duration 5 months; 40% ACPA-positive and 44% rheumatoid factor-positive. Patients who were in remission at 12 months according to each of 6 criteria were significantly more likely to have a good functional status outcome 12 months later (24 months after baseline), ranging from 70–84%,versus 45–50% of patients not in remission. Positive likelihood ratios for having a good functional outcome were 3.8 and 4.0 for Boolean and RAPID3RJ1; 2.8–3.1 for RAPID3, CDAI and SDAI; and 1.8 for DAS28 criteria. Patients who were in remission at 12 months according to each of the 6 criteria had a similar 67–71% likelihood to have a good radiographic outcome 12 months later (24 months after baseline), similar to patients who were not in remission (Table). Similar analyses performed in subsets of patients who were RF+ and/or had baseline damage, yielded similar results.

Conclusion: A good functional outcome at 24-month follow-up was 1.8–4.0 times more likely in patients who were in remission versus not in remission 12 months after baseline; the highest likelihood ratios were seen for the Boolean and RAPID3RJ1 criteria. Radiographic outcomes at 24 months were similar, regardless of remission status 12 months earlier.

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Are There Differences Between Young and Older Onset Early Rheumatoid Arthritis and Does This Impact Outcomes? An Analysis From The Canadian Early Arthritis Cohort. Michael Arnold[1], Vivian P. Bykerk[2], Gilles Boire[3], Boulos Haraoui[4], Carol A. Hitchon[5], J. Carter Thorne[6], Edward Keystone[7] and Janet E. Pope[8]. [1]University College Dublin, Ireland, Dublin, Ireland, [2]Hospital for Special Surgery, New York, NY, [3]Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, [4]Institut de Rhumatologie de Montréal, Montreal, QC, [5]University of Manitoba, Winnipeg, MB, [6]Southlake Regional Health Centre, Newmarket, ON, [7]University of Toronto, Toronto, ON, [8]Schulich School of Medicine and Dentistry, Western University, London, ON.

Background/Purpose: To determine the impact of age on disease and remission in early rheumatoid arthritis (ERA).

Methods: Data from the Canadian Early Arthritis Cohort (CATCH) were examined at baseline, 6 and 12 months. Patients were divided into three

groups based on age. ANOVA and regression models were performed to determine the impact of age on DAS28 and remission at 12 months.

Results: 1809 patients were assessed at baseline, 442 (24.4%) 'young' (<42 years), 899 (49.7%) 'middle-aged' (^{3} 42, <64 years) and 468 (25.9%) 'old' (^{3}64 years); 72.9% were female, 63.8% met 2010 ACR/EULAR Classification Criteria for RA, symptom duration at first visit was 186.0 days, DAS28 4.9, HAQ 1.0; 25.3% had baseline erosions. A significant correlation existed between older age and less percent females, less positive RF and CCP, less meeting RA criteria, shorter symptom duration, more erosions at first visit, higher DAS28 and HAQ at baseline and 12 months, and less DAS28 remission at 12 months (all $P<0.003$). Age group did not affect the change in DAS28 and HAQ from 0–12 months. Comorbidities increased with age; more DMARDs including methotrexate and steroids and less biologics were used in older age. Age and female had a lesser chance of remission in regression model.

Conclusion: In ERA, older onset RA patients start and end their first year worse in terms of DAS28 and HAQ, with less meeting RA criteria, less remission, more DMARDs and steroids but less biologic use; however there were no differences between age groups in change in DAS28.

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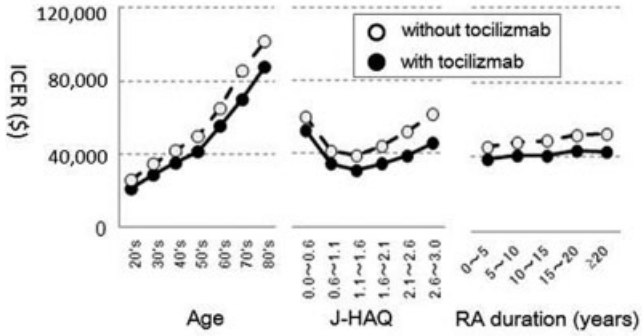
Optimal Rheumatoid Arthritis Patient Selection For Biological Treatment From Pharmacoeconomic Perspectives Based On The Institute Of Rheumatology, Rheumatoid Arthritis (IORRA) Cohort. Eiichi Tanaka[1], Eisuke Inoue[1], Yoko Shimizu[2], Akiko Kobayashi[2], Naoki Sugimoto[2], Daisuke Hoshi[2], Kumi Shidara[2], Eri Sato[2], Yohei Seto[2], Ayako Nakajima[2], Shigeki Momohara[2], Atsuo Taniguchi[2] and Hisashi Yamanaka[1]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: With the recent introduction of biological DMARDs, the economic burden of rheumatoid arthritis (RA) treatment has increased. Previous studies evaluated the cost-effectiveness of biologics, although those studies were usually conducted based on controlled clinical trials, which do not precisely reflect daily practice. From an economic point of view, it is desirable to treat patients with biologics when the cost-effectiveness is maximized, especially in daily practice. We conducted a pharmacoeconomic study to investigate the optimal timing of biologics administration to RA patients using the RA cohort database of the Institute of Rheumatology, Rheumatoid Arthritis (IORRA).

Methods: We conducted a state-transition model-based probabilistic simulation from the societal perspective. Model parameters were determined using clinical data for 421 patients from the IORRA who had failed at least one DMARD and had started either one of four biologics (adalimumab, etanercept, infliximab, and tocilizumab) or methotrexate (MTX) between April 2008 and April 2011. Patients who had not used biologics were matched using propensity scores. A hypothetical population of 10,000 patients treated with sequences of three biologics after MTX and then best supportive care (BSC) were compared to those starting MTX after BSC. The incremental cost-effective ratios (ICERs) of the biologics groups against the MTX group were estimated using base-case analysis and probabilistic sensitivity analysis. Scenario sensitivity analyses were also done for different backgrounds of the initial population classified by age, disease duration, and disability based on scores of the Japanese version of HAQ (J-HAQ). Because tocilizumab differed from TNF-blockers in mechanism and had a large decrease in price in Japan in 2012, sequences of three of four biologics and three except for tocilizumab were also considered for biologics groups.

Results: The ICERs of treatment sequences with biologics and with or without tocilizumab were $38,180 and $48,855, respectively. By probabilistic sensitivity analysis, these sequences had respective probabilities of 89.5% and 80.9% of falling below an assumed threshold of $54,000 as the societal willingness-to-pay in Japan. Scenario sensitivity analyses showed that the most influential factors on the ICER were age and J-HAQ scores. Starting biologics at a younger age had better cost-effectiveness, whereas disease duration had no effect. J-HAQ scores followed "J-curves" and the ICER was best for patients with J-HAQ scores of 1.1 to 1.6 (Figure).



Conclusion: Our results demonstrate that biological DMARDs are cost-effective for RA patients based on data from an observational cohort representing daily practice in Japan. From pharmacoeconomic perspectives, the best population for biologics use is younger RA patients with J-HAQ baseline scores between 1.1 and 1.6 and using tocilizumab as the biological DMARD.

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Retinal Vascular Calibre – a Novel Biomarker Of Inflammation and Treatment Response In Rheumatoid Arthritis. John HY Moi[1], Lauren AB Hodgson[2], Ian P Wicks[3], Tien Yin Wong[1] and Sharon Van Doornum[1]. [1]The University of Melbourne, Melbourne, Australia, [2]Centre for Eye Research Australia, Melbourne, Australia, [3]Walter & Eliza Hall Institute of Medical Research, Parkville, Australia.

Background/Purpose: Retinal vascular calibre measurement is a non-invasive tool for assessing systemic and vascular health. Widened retinal venular calibre (RVC) is associated with systemic inflammation, increased cardiovascular (CV) risk and has previously been associated with rheumatoid arthritis (RA), particularly high disease activity[1]. To date there have been no longitudinal studies assessing the effect of suppressing systemic inflammation on RVC in RA. The aims of this study were to investigate the stability of serial retinal vascular calibre measurements (RVC and retinal arteriolar calibre (RAC)) in well controlled RA and the effect of reducing systemic inflammation in RA patients requiring treatment escalation.

Methods: Two groups of patients with RA were recruited and studied concurrently. Group A included patients with moderate or high disease activity (DAS28-CRP>3.2) who required treatment escalation as standard of care. Group B had stable low disease activity (DAS28-CRP≤3.2) not requiring any alteration of medical therapy and were the control for Group A. Both groups underwent retinal photography at baseline and at weeks 6 and 24 (to assess the early and later response respectively) in Group A and at week 12 in Group B. Images were analysed by purpose designed software and a trained assessor blinded to subject identity and timing of retinal photography. Simple linear regression and paired t-tests were used to compare serial retinal vascular calibre measurements in Groups A and B respectively, with a p value <0.05 considered significant.

Results: Group A included 24 patients (71% female) with a mean (SD) age of 50.9 (18) years and a mean (SD) disease duration of 5.8 (6.4) years. Between baseline and week 6, disease activity improved signifi-

cantly (DAS28-CRP mean reduction of −2.0 (95% CI −2.5 to −1.5). This was accompanied by a significant reduction in RVC (mean difference (MD) −7.6μm; 95% CI −13.4 to −1.7μm, p=0.01), whereas RAC remained unaltered (MD −2.29μm; 95% CI −5.7 to 1.1μm, p=0.18). Week 24 data collection from Group A is ongoing. Group B included 26 patients (81% female) with a mean (SD) age of 54 (9) years and a mean (SD) disease duration of 14.5 (10.8) years. Disease activity and therapy remained unchanged between baseline and week 12 (DAS28-CRP MD −0.1, 95% CI −0.36 to 0.15, p=0.39). There was no significant change in RVC (MD 1.37μm; 95% CI −2.82 to 5.57μm, p=0.5) or RAC (MD 0.39μm; 95% CI −3.04 to 3.82μm, p=0.82) in Group B over this period.

Conclusion: This is the first study to demonstrate that suppressing inflammatory disease activity in RA reduces RVC widening as early as 6-weeks after treatment escalation. In contrast, RVC measurements were unchanged in RA with stable, low-level systemic inflammation during short-term follow-up. Taken together, these findings suggest that retinal vascular calibre measurement may be a biomarker of RA disease activity as well as CV risk and that immunosuppressive treatment may also have potential vascular benefits in RA.

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Drug Free Holiday In Patients With Rheumatoid Arthritis (RA): patients' Opinion. I.M. Markusse, G. Akdemir, T.W.J. Huizinga and C.F. Allaart. Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Clinical trials have shown that in many patients tapering and/or stopping antirheumatic medication is a realistic option. We interviewed patients to investigate their opinions, expectations and emotions with regard to tapering and discontinuing antirheumatic drugs.

Methods: 20 patients randomly identified at the rheumatology outpatient clinic were asked 12 questions through structured interviewing by two investigators (10 patients each). Interviews were sound recorded, typed out in full and screened by three assessors independently for content items. After 20 interviews, data saturation was reached.

Results: Mean (SD) age was 64.6 (15.2) years and median (minimum; maximum) disease duration was 15.0 (0.1; 40.0) years. 13 patients were female. Disease Activity Score (DAS) was ≤ 2.4 in 13 patients, even <1.6 in 8 patients, and >2.4 in 7 patients. 17 patients used antirheumatic medication at the moment of interviewing.

Six patients were of the opinion that discontinuing is a possibility for both other patients and themselves, one patient thought only tapering could be possible and five did not see this possibility. Two patients thought it could be possible for other patients, but not for themselves.

Patients' replies conveyed hope (being free from symptoms), happiness and relief (being free from drugs), fear (for a disease flare) and faith (in the decision of the rheumatologist) as feelings about tapering/discontinuing their medication. Conditions mentioned before a drug holiday might be tried were longstanding low disease activity, first tapering before stopping, intensive monitoring. Severe side effects were also a motive to stop medication.

Ten patients expected increased disease activity after stopping medication, four expected that low disease activity would be maintained, and four patients thought both could happen. Most patients expect that disease activity will decrease again after restarting medication, but they also expect that this will take (too much) time.

Conclusion: Although most patients are unaware of the option to taper and discontinue antirheumatic medication, patients express positive emotions about this option. However, they also have concerns that disease activity will flare and they expect that improvement upon restarting medication will take time. Patients' expectations and feelings should be addressed before a drug holiday is attempted.

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1347

A Multi-Biomarker Disease Activity Score For Rheumatoid Arthritis Predicts Radiographic Damage In The BeSt Study. I.M. Markusse[1], L. Dirven[1], M. van den Broek[1], K.H. Han[2], M.F. van Lieshout[3], N. Riyazi[4], R.J. Bolce[5], E.H. Sasso[5], P.J.S.M. Kerstens[6], W.F. Lems[7], T.W.J. Huizinga[1] and C.F. Allaart[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Maasstad Hospital, Rotterdam, Netherlands, [3]Spaarne Hospital, Hoofddorp, Netherlands, [4]Haga Hospital, The Hague, Netherlands, [5]Crescendo Bioscience Inc., South San Francisco, CA, [6]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [7]VU University Medical Center, Amsterdam, Netherlands.

Background/Purpose: To determine whether a multi-biomarker disease activity (MBDA) score could predict radiographic damage progression in patients with rheumatoid arthritis (RA).

Methods: The BeSt study enrolled 508 patients. Of these, 84 patients had MBDA scores at baseline and radiographs of hands and feet at baseline and 1 year later and 81 patients had MBDA scores at 1 year and radiographs at 1 year and at 2 years. Radiographs were scored by two independent blinded readers using the Sharp van der Heijde Score (SHS).

MBDA scores were calculated using a validated algorithm (Vectra® DA algorithm score) integrating the levels of 12 biomarkers, (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL-40, leptin, resistin, SAA, CRP) for assessing disease activity in patients with RA. The generated MBDA score ranges between 1 and 100, and can be categorized in low (≤ 29), moderate (>29 – 44) and high (>44) disease activity levels.

Receiver Operating Curves (ROC) were used to calculate an area under the curve (AUC) with outcome any radiographic damage progression (increase ≤ 0.5 points SHS) yes or no. Poisson regression with increase in SHS as continuous outcome was used to calculate a relative risk (RR). In all analyses MBDA scores are compared to disease activity scores (DAS) in predicting radiographic damage in the following 12 months.

Results: Baseline characteristics of patients in this analysis were similar to the entire BeSt cohort. Mean age was 53 and 75% were female. Mean Disease Activity Score (DAS) was 4.30, 62% were rheumatoid factor positive and 56% anti-citrullinated protein antibodies (ACPA) positive.

At baseline, DAS had an AUC of 0.373 (95% CI 0.248 – 0.498) and MBDA had an AUC of 0.606 (95% CI 0.482 – 0.729) on radiographic progression in the subsequent year. At one year, the AUC for DAS was 0.527 (95% 0.392 – 0.729) compared to an AUC of 0.686 (95% CI 0.564 – 0.809) for MBDA.

Poisson regression showed a RR of 1.039 for MBDA at baseline to develop radiographic progression, adjusted for DAS and ACPA, indicating a 1.47 times higher risk of radiologic progression with each 10 points MBDA increase. At 1 year, the RR of MBDA, also adjusted for DAS and ACPA, is 1.037, indicating a 1.44 times higher risk with each 10 points MBDA increase. A high baseline MBDA shows a RR of 3.7 for radiologic progression in the next year compared to low and moderate (≤ 44) baseline MBDA levels combined. At 1 year, high MBDA showed a RR of 4.6 compared to low MBDA. Moderate MBDA compared to low MBDA at 1 year does not show a significantly greater risk of radiologic progression at 2 years (Table 1).

Table 1. Poisson regression analysis with MBDA categories and progression in the subsequent 12 month period

	Risk for SHS progression, baseline to 1 year		
Baseline (N=84)	RR	95% CI	P value
MBDA ≤ 44	ref	ref	ref
MBDA > 44	3.74	1.45–9.66	0.006
At 1 year (N=81)	Risk for SHS progression, year 1 to year 2		
MBDA ≤ 29	ref	ref	ref
MBDA > 29–44	1.44	0.45–4.55	0.537
MBDA > 44	4.62	1.34–15.95	0.015

Conclusion: Adjusted for DAS and ACPA, baseline MBDA scores predicted radiographic damage progression at 1 year as well as MBDA at 1 year predicted radiographic progression at year 2 during disease course. Therefore, MBDA may be of value in future treatment strategies in RA patients.

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Initial Combination Therapy In Early Rheumatoid Arthritis: Which Patients Benefit? I.M. Markusse[1], K.H. Han[2], A.J. Peeters[3], H.K Ronday[4], P.J.S.M. Kerstens[5], T.W.J. Huizinga[1], W.F. Lems[6] and C.F. Allaart[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Maasstad Hospital, Rotterdam, Netherlands, [3]Reinier de Graaf Gasthuis, Delft, Netherlands, [4]Haga Hospital, The Hague, Netherlands, [5]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [6]VU University Medical Center, Amsterdam, Netherlands.

Background/Purpose: Initial combination therapy has proven to be effective in early rheumatoid arthritis (RA) patients. To determine which patients benefit from initial combination therapy.

Methods: In the BeSt study, 508 patients were randomized to 4 treatment strategies: 1 Sequential monotherapy 2 Step-up therapy 3 Initial combination with a tapered high dose prednisone 4 Initial combination with infliximab. For this subanalysis, groups 1 & 2 (methotrexate monotherapy) were compared to groups 3 & 4 (initial combination therapy).

Clinical assessments were performed every 3 months and radiographs of hands and feet yearly. Radiographs were assessed by 2 independent blinded readers using the Sharp van der Heijde Score (SHS).

High risk was defined as ≥ 3 of 4 features present at baseline: Swollen Joint Count ≥ 10, erosions ≥ 4, Disease Activity Score (DAS) ≥ 3.7, both rheumatoid factor and anti-citrullinated peptide autoantibodies positive.

Chi square and T-tests were used to test differences between the groups and regression analysis was performed to calculate odds ratios (OR) and risk ratios (RR).

Results: Baseline characteristics were similar among the groups. 417 of 508 patients could be categorized into high or non-high risk with available data, of which 192 were identified as having high risk for progression. At 3 months, high risk patients who started with combination therapy significantly more often than those who started with monotherapy fulfilled ACR 20 (33 vs 20%), 50 (22 vs 7%) and 70 (11 vs 2%) response criteria, and achieved more DAS-remission (DAS < 1.6) (8 vs 3%) and more functional improvement (median 0.750 vs 0.375 decrease in HAQ). At 1 year, differences in DAS-remission and ACR 20 response criteria were sustained. Also, high risk patients who started combination therapy showed significant less RRP (≥ 5 points increase in SHS) than who started with monotherapy (5 vs 14%).

Also non-high risk patients who started with combination therapy at 3 months significantly more often than who started with monotherapy met the ACR 20 (40 vs 19%), 50 (27 vs 6%) and 70 (9 vs 1%) response criteria, achieved more DAS-remission (10 vs 3%) and more functional improvement (median 0.625 vs 0.375 improvement in HAQ). At 1 year, differences remained for ACR 20 and 50 response and functional improvement. There was less RRP in non-high risk patients, without a significant difference between initial monotherapy and initial combination therapy patients (2 vs 5%). ORs and RRs are shown in table 1.

Table 1. Regression analyses: initial monotherapy was set as reference

	High risk		Non-high risk	
Logistic regression	**OR**	**95% CI**	**OR**	**95% CI**
DAS remission				
at 3 months	3.67	1.28 to 10.56	2.96	1.21 to 7.22
at 1 year	2.06	1.07 to 3.95	0.99	0.57 to 1.73
ACR20 response				
at 3 months	3.94	2.09 to 7.43	3.11	1.73 to 5.63
at 1 year	3.08	1.16 to 8.20	2.24	1.12 to 4.48
ACR50 response				
at 3 months	6.29	3.00 to 13.20	6.25	3.08 to 12.70
at 1 year	1.84	0.98 to 3.46	1.99	1.12 to 3.56
ACR70 response				
at 3 months	7.08	2.31 to 21.68	6.39	1.84 to 22.23
at 1 year	1.81	0.967 to 3.38	1.33	0.74 to 2.38
Poisson regression	**RR**	**95% CI**	**RR**	**95% CI**
RRP at 1 year	0.351	0.20 to 0.62	0.62	0.32 to 1.21
Linear regression	Beta	95% CI	Beta	95% CI
ΔHAQ				
at 3 months	−0.42	−0.61 to −0.24	−0.33	−0.51 to −0.15
at 1 year	−0.16	−0.36 to 0.04	−0.21	−0.40 to −0.01

Conclusion: High risk as well as non-high risk patients benefit from initial combination therapy. To avoid RRP, high risk patients benefit the most from combination therapy. However, taking into account the clinical outcome measurements, non-high risk patients also do benefit by achieving earlier ACR response, DAS-remission and functional improvement when starting treatment with a combination therapy.

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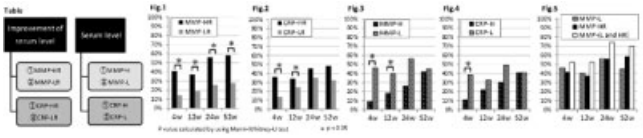
1349

High Rate Of Improvement In Serum Matrix Metalloproteinase-3 Levels At 4 Weeks Predict Remission At 52 Weeks In RA Patients With Adalimumab Therapy. Yosuke Hattori[1], Atsushi Kaneko[1], Daihei Kida[1], Hisato Ishikawa[2], Toshihisa Kojima[3] and Naoki Ishiguro[4]. [1]Nagoya Medical Center, Nagoya, Japan, [2]Nagoya Medical Center, nagano, Japan, [3]Nagoya University Hospital, Nagoya, Japan, [4]Nagoya University Graduate School of Medicine, Nagoya, Japan.

Background/Purpose: Serum MMP-3 is a specific inflammatory marker of the synovium in patients with rheumatoid arthritis (RA). Our aim in this study is to investigate whether serum MMP-3 is the predictor for remission in treatment for RA patients with biologics.

Methods: All RA patients (n=175) who underwent adalimumab (ADA) treatment in TBC (Tsurumai Biologics Communication) registry were enrolled in this study. We analyzed 107 patients in continuation with ADA therapy for 52 weeks. We divided into 2 groups based on the improvement of serum level of MMP-3 and CRP: high rate of improvement (MMP-HR group) and low rate of improvement (MMP-LR group) in serum MMP-3 levels at 4 weeks, and: high rate of improvement (CRP-HR group) and low rate of improvement (CRP-LR group) in serum CRP levels at 4 weeks. We also divided into 2 groups based on the serum level of MMP-3 and CRP: high value (MMP-H group) and low value (MMP-LR group) in serum MMP-3 levels at 4 weeks, and: high value (CRP-H group) and low value (CRP-L group) in serum CRP levels at 4 weeks (Table). We evaluated the rate of remission at 4, 12, 24, and 52 weeks in HR group and LR group.

Results: In patients continuing at 52 weeks, the rate of remission at 4, 12, 24 and 52 weeks in MMP-HR group is 41%, 37%, 56%, and 58%, and MMP-LR group is 14%, 19%, 26%, and 28% respectively. The rate of remission at 4, 12, 24 and 52 weeks in MMP-HR group is significantly higher than in MMP-LR group (Fig.1). However, the rate of remission at 24 and 52 weeks had no significance in CRP-HR group and CRP-LR group (Fig.2).The rate of remission at 4, 12, 24, and 52 weeks in MMP-H group is 9%, 18%, 26%, and 42%, and MMP-L group is 46%, 40%, 56%, and 45%. The rate of remission at 4 and 12 weeks in MMP-H group is significantly higher than in MMP-L group (Fig.3). However, the rate of remission at 4 weeks in CRP-H group is significantly higher than in CRP-L group (Fig.4). Moreover, the rate of remission at 24 and 52 weeks in MMP-(L and HR) group is very high (Fig.5). In patients continuing at 52 weeks, the best cut-off rate of improvement in MMP-3 at 4 weeks for determining remission at 52 weeks was 40% determined by ROC analysis (sensitivity: 60%, specificity: 80%, accuracy: 66%).



Conclusion: We considered that high rate of improvement in serum MMP-3 at 4 weeks can be useful for predicting the remission at 52 weeks in RA patients with ADA therapy.

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1350

Factors Influencing Selection Of Biologic Therapy and Comparative Effectiveness In Patient Reported Outcomes Among Patients With Rheumatoid Arthritis. Iris Navarro-Millan[1], Lang Chen[1], Leslie R. Harrold[2], Lisa Herrinton[3], Liyan Liu[3] and Jeffrey R. Curtis[4]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Massachusetts Medical School, Worcester, MA, [3]Kaiser Permanente, Oakland, CA, [4]University of Alabama at Birmingham, Division of Clinical Immunology and Rheumatology, Birmingham, AL.

Background/Purpose: Treatment of rheumatoid arthritis (RA) with biologics is increasingly common. A better understanding of factors that influence the selection of RA therapies and comparative effectiveness between therapies is warranted. The objectives of this study were to describe physicians' and patients' preferences in selecting specific biologics and comparing clinical response using patient reported outcomes (PROs) among RA patients started on different anti-TNF therapies.

Methods: Eligible patients for this analysis were enrollees in Kaiser Permanente Northern California. RA patients with at least 2 Kaiser visits who started a new anti-TNF therapy from 10/2010 – 8/2011 were initially eligible for participation in a longitudinal telephone survey at baseline (initiation of anti-Tumor Necrosis Factor therapy) and 6 months later. Patients' preferences in selecting their biologics were collected at baseline. PROs for effectiveness were collected both at baseline and 6 month surveys. Ordinary least squares regression evaluated the change at 6 months across PROs comparing etanercept (ETA) vs. adalimumab (ADA) initiators and controlled for multiple potential confounders.

Results: There were 384 eligible RA patients available to be contacted; 267 initially responded and 242 initiated etanercept or adalimumab and 187 completed both the baseline and 6 month follow-up telephone surveys. Mean age was 54.4 (SD ± 12.1) and 73.4% were females. A total of 56% of patients self-reported that they were involved in the selection of their specific biologic. The majority of patients (57%) preferred an injectable biologic, 22% preferred an infused biologic, and 21% had no preference. Preferences for injection biologics were mainly motivated by convenience (92%); those preferring infusion therapy were motivated by dislike or lack of self-efficacy for self-injection (15.7%). After 6 months of treatment with anti-TNF biologics, 44% of the patients reported a level of burning and stinging with injection of ≤ 4 in a scale of 0–10 with the last biologic dose, 30% experienced a level > 5 and 26% reported no burning and stinging. RAPID 3, MDHAQ and physical function via the SF12 were significantly better at 6 months without significant difference between ETA or ADA initiators (Table).

	Etanercept (N = 118)	Adalimumab (N = 69)
	All initiators	All initiators
RAPID3		
Baseline (mean, SD)	16.6 (5.7)	15.9 (5.9)
Mean difference at 6 months	−6.6 (7.1)	−3.6 (5.5)
Adjusted mean difference at 6m*	Referent	2.2 (−0.31, 4.71)*
MDHAQ		
Baseline (mean, SD)	3.6 (2.0)	3.6 (2.0)
Mean difference at 6 months	−1.3 (1.8)	−0.8 (1.6)
Adjusted mean difference at 6m*	Referent	0.5 (−0.11, 1.13)**
SF12_PCS		
Baseline (mean, SD)	30.5 (10.2)	31.2 (10.6)
Mean difference at 6 months	6.0 (12.6)	1.8 (9.5)
Adjusted mean difference at 6m*	referent	−2.2 (−6.96, 2.65)**
SF12_ MCS		
Baseline (mean, SD)	44.3 (12.8)	46.1 (13.1)
Mean difference at 6 months	5.9 (13.3)	4.8 (12.4)
Adjusted mean difference at 6m*	referent	0.05 (−4.54, 4.64)**

RAPID3 = Routine assessment of patient index data 3; MDHAQ = Multidimensional health assessment questionnaire; SF12_mcs/pcs = Short form-12 item survey mental composite scale/physical composite scale; SD = standard deviation. *Controlling for age, gender, RA duration and baseline PRO. **Data shown as Beta coefficients and 95% confidence interval.

Conclusion: Convenience, fears of self-injection and self-efficacy for self-injection were important aspects to patients when selecting an individual therapy. There were clinically small and non-significant differences in effectiveness at 6 months of etanercept versus adalimumab across several PROs.

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A Comparison Of The Clinical Effectiveness Of Treatment Strategies For Active RA Patients: Using a Prospective Biologic Registry (BIOPSY) and an RA Specific Cohort (KORONA). Yoon-Kyoung Sung[1], Soo-Kyung Cho[1], Chan-Bum Choi[1], Soyoung Won[2], So-Young Bang[3], Hoon-Suk Cha[4], Jung-Yoon Choe[5], Won Tae Chung[6], Seung-Jae Hong[7], Jae-Bum Jun[1], Hyoun Ah Kim[8], Jinseok Kim[9], Seong-Kyu Kim[5], Tae-Hwan Kim[1], Hye-Soon Lee[3], Jaejoon Lee[4], Jisoo Lee[10], Shin-Seok Lee[11], Sung Won Lee[6], Yeon-Ah Lee[7], Seong-Su Nah[12], Chang-Hee Suh[8], Dae-Hyun Yoo[1], Bo Young Yoon[13] and Sang-Cheol Bae[1]. [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [3]Hanyang University Guri Hospital, Guri, South Korea, [4]Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea, [5]Catholic University of Daegu School of Medicine, Daegu, South Korea, [6]Dong-A University Hospital, Busan, South Korea, [7]Kyung Hee University, Seoul, South Korea, [8]Ajou University Hospital, Suwon, South Korea, [9]Jeju National University Hospital, Jeju, Korea, South Korea, [10]Ewha Womans University Mokdong Hospital, Seoul, South Korea, [11]Chonnam National University Medical School and Hospital, Gwangju, South Korea, [12]Soonchunhyang University Cheonan Hospital, Cheonan, South Korea, [13]Inje University Ilsan Paik Hospital, Goyang, South Korea.

Background/Purpose: The results from RCTs may not be generalizable to clinical practice because of their inclusion and exclusion criteria. Instead, observational cohorts and registries might provide complement information for each treatment strategies in the real world. This study aimed to compare the clinical effectiveness of treatment strategies for active RA patients refractory to non-biologic DMARDs using independent biologic registry and disease specific cohort for Korean RA patients.

Methods: One year follow-up data on drug uses and clinical outcomes were compared between Korean biologics registry (BIOlogics Pharmacoepidemiologic StudY, BIOPSY) and established RA cohort (KORONA). Since all the BIOPSY patients had moderate to high disease activity (DAS28>3.2) and have started TNF inhibitors, we selected patients from KORONA with inclusion criteria at baseline: 1) DAS 28>3.2, 2) changing DMARDs within 3 months, and 3) non-biologic DMARD user. A total of 528 subjects (208 from BIOPSY and 320 from KORONA) were included in this study. Propensity score matching was used to equalize patient characteristics between TNF inhibitor user and non-biologic DMARD user groups. The one year remission rates with DAS 28 and HAQ scores were compared between two treatment strategies for active RA patients: starting TNF inhibitors vs. changing non-biologic DMARDs.

Results: Of the 208 TNF inhibitor users and 320 non-biologic DMARDs users identified from each registry and cohort, 184 patients (92 in BIOPSY and 92 in KORONA) were included in this analysis after the propensity score matching. Their baseline characteristics were comparable with age (46.5 vs. 46.6, P=0.97), female (89.1% vs. 91.3%, p=0.81), RF positivity (83.7% vs. 84.8%, p=1.0), disease duration (6.0 years vs. 5.2 years, p=0.39), DAS 28 (5.58 vs. 5.60, p=0.63) and HAQ scores (1.20 vs. 1.20, P=0.97). Remission rates after 1 year follow up with sustaining baseline treatment were 16.3% in TNF inhibitor users and 13.0% in non-biologic DMARDs users (P=0.68). For the patients with continuing initial treatment for 1 year, TNF inhibitor users had lower HAQ score than non-biologic DMARDs users (0.59 vs. 0.77, P<0.01).

Conclusion: We compared clinical effectiveness of TNF inhibitors and non-biologic DMARDs in active RA patients using independent biologics registry and RA cohort. Although the use of TNF inhibitors did not increase the one year remission rate compared to the use of non-biologic DMARDs, it decreased the one year functional disability in active RA patients.

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What Factors Lead To Achieve and Sustain Remission In Rheumatoid Arthritis Patients With Moderate To High Disease Activity? Soo-Kyung Cho[1], Yoon-Kyoung Sung[1], Jeeseon Shim[2], Chan-Bum Choi[1], Jung-Yoon Choe[3], Won Tae Chung[4], Seung-Jae Hong[5], Jae-Bum Jun[1], Tae-Hwan Kim[1], Tae-Jong Kim[6], Eun-Mi Koh[7], Jisoo Lee[8], Shin-Seok Lee[6], Sung Won Lee[4], Dae-Hyun Yoo[1] and Sang-Cheol Bae[1]. [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [3]Catholic University of Daegu School of Medicine, Daegu, South Korea, [4]Dong-A University Hospital, Busan, South Korea, [5]Kyung Hee University, Seoul, South Korea, [6]Chonnam National University Medical School and Hospital, Gwangju, South Korea, [7]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [8]Ewha Womans University Mokdong Hospital, Seoul, South Korea.

Background/Purpose: Clinical remission has now become the treatment goal in rheumatoid arthritis (RA), but it is not common in clinical practice. This study aimed to evaluate predictors for achieving remission and it's sustaining in RA patients.

Methods: A total of 709 RA patients with moderate or high disease activity at enrollment and who have data of two years annual follow-up were included in this analysis from the KORean Observational study Network for Arthritis (KORONA). Clinical remission of RA was defined as a DAS28 score less than 2.6. The prevalence of clinical remission at first follow-up visit was estimated and its predictors were identified using multivariate logistic regression analysis. Using the second follow-up data, we further divided patients who had achieved remission into two groups: sustained remission or not. We also performed multivariate logistic regression analysis to identify predictors for sustained remission.

Results: Among the patients in moderate or high disease activity (n=709), only 102 patients (14.4%) achieved remission at their first follow-up visit. Patients with remission had lower functional disability (HAQ score 0.68±0.56 vs. 0.91±0.67, P<0.01) and lower disease activity (DAS28 4.13±0.73 vs. 4.59±0.95, P<0.01) at baseline than patients who could not achieve remission. In multivariate analysis, early RA (disease duration of less than 2 years, OR 2.03, 95%CI 1.14–3.59) and moderate disease activity compared to high disease activity at baseline (OR 2.37, 95%CI 1.25–4.50) were identified as predictors for remission (See table).

Among the patients who are in remission at first visit (n=102), 45 patients (42.1%) stayed in remission while the other 57 patients (57.9%) experienced flare of their disease activity at their second follow-up. Early RA (disease duration <2 years) and moderate disease activity compared to high disease activity at baseline showed increased OR for sustained remission in multivariate logistic model, but there was no statistical significance (OR 2.61, 95%CI 0.84–8.08, OR 3.96, 95%CI 0.82–19.08, respectively).

Table. Predictors for achieving remission and sustained remission in RA patients with moderate to high disease activity

Baseline characteristic	Predictors for achieving remission univariate	Predictors for achieving remission multivariate	Predictors for sustained remission univariate	Predictors for sustained remission multivariate
Age (years)				
<40	Ref	Ref	Ref	Ref
40–49	0.62 (0.28–1.35)	0.67 (0.30–1.48)	0.96 (0.23–4.10)	1.05 (0.20–5.63)
50–59	0.85 (0.44–1.67)	1.04 (0.51–2.10)	0.58 (0.17–1.99)	0.45 (0.11–1.95)
≥60	0.70 (0.35–1.39)	0.88 (0.41–1.90)	0.38 (0.10–1.35)	0.29 (0.06–1.50)
Female	0.66 (0.36–1.21)	0.82 (0.42–1.58)	0.47 (0.15–1.44)	0.46 (0.11–1.86)
Income level				
~$9,999	Ref	Ref	Ref	Ref
$10,000~29,999	0.93 (0.55–1.56)	0.87 (0.49–1.53)	2.29 (0.84–6.23)	3.78 (0.97–14.77)
$30,000~	1.30 (0.78–2.17)	1.16 (0.64–2.12)	1.45 (0.55–3.87)	1.29 (0.33–5.05)
Disease duration				
<2 years	**1.92 (1.12–3.30)**	**2.03 (1.14–3.59)**	2.40 (0.89–6.48)	2.61 (0.84–8.08)
2≤ and <5 years	1.43 (0.83–2.45)	1.27 (0.73–2.21)	1.84 (0.67–5.03)	2.20 (0.70–6.86)
≥5 years	Ref	Ref	Ref	Ref
HAQ ≥1	**1.90 (1.21–2.98)**	1.48 (0.90–2.46)	0.65 (0.28–1.51)	0.34 (0.11–1.02)
DAS 28				
moderate	**2.77 (1.51–5.09)**	**2.37 (1.25–4.50)**	1.31 (0.40–4.31)	3.96 (0.82–19.08)
high	Ref	Ref	Ref	Ref
Biologics use	1.41 (0.71–2.81)	1.72 (0.80–3.67)	0.44 (0.11–1.76)	0.27 (0.05–1.38)
Methotrexate use	1.22 (0.66–2.28)	1.26 (0.65–2.42)	–	–
Steroid use	1.03 (0.61–1.73)	1.08 (0.62–1.86)	–	–

Conclusion: Short disease duration less than 2 years and lower disease activity are the predictors for achieving remission in RA patients with moderate to high disease activity. These factors might be associated with sustained remission.

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Remission After Twelve Month Of Treatment In The Prague Early Rheumatoid Arhritis Cohort. Herman F. Mann[1], Olga Ruzickova[1], Olga Sleglova[2], Marketa Fojtikova[3], Dana Tegzova[4], Sarka Forejtova[1] and Ladislav Senolt[4]. [1]Institute of Rheumatology, Prague, Prague, Czech Republic, [2]Institute of Rheumatology and 1st faculty of medicine, Charles University, Prague, Czech Republic, [3]Institute and Clinic of Rheumatology, Charles University, Prague 2, Czech Republic, [4]Institute of Rheumatology, Prague, Czech Republic.

Background/Purpose: Recent data have demonstrated that early treatment with disease modifying anti-rheumatic drugs (DMARDs) improves outcome in patients with Rheumatoid arthritis (RA). Early arthritis clinic (EAC) is a useful tool which allows high risk patients to bypass long waiting times for a rheumatology evaluation and thus start treatment early. We have used the data from Prague Early Rheumatoid Arthritis Clinic (PERAC)to evaluate first year treatment outcomes of patients with early RA.

Methods: Patients with symptom duration ≤6 months were reffered by their primary care physicians in accordance with published recommendations. Only patients with rheumatoid arthritis fulfilling the 2010 ACR/EULAR classification criteria or undifferentiated inflammatory arthritis which, at the time of presentation, did not fulfill classification criteria of another disease entity were included in the ERA cohort. There was no pre-specified treatment protocol in place and non-biological DMARDs were started based on the discretion of treating physician. Clinical and laboratory data were collected at pre-specified time points.

Results: 427 patients were evaluated in the PERAC between 2008 and 2012. 131 of these were included in the ERA cohort. 119 patients (91%) fulfilled RA classification criteria at baseline. 30% of newly diagnosed RA patients had normal CRP (≤0.5 mg/dl). Most patients were started on methotrexate in accordance with current guidelines. 81% of patients were initially treated by oral glucocorticoids. Data at 12 months were available for 89 patients. Mean age in this subgroup was 51 years, 67% were women, 56% were ACPA and 55% rheumatoid factor positive. Mean DAS28 score had decreased from 5.50 at baseline to 3.05 after 12 months of treatment. 40 patients (45%) were in remission based on SDAI ≤ 3.3 and 42 patients (47%) fulfilled the ACR/EULAR proposed Boolean-based definition of remission. 12 patients (13%) had to change their initial DMARD during first 12 months of treatment and only 5 patients started on methotrexate (5%) had to discontinue the drug due to side-effects during the first 12 months of treatment. 50% (4 out of 8) patients not fulfilling RA classification criteria at baseline were classified as having RA at month 12. 2 patients (2%) initially fulfilling RA classification criteria were diagnosed with another disease (paraneoplastic arthritis and systemic lupus erythematodes) at month 12.

Conclusion: Our data confirm that early RA patients have a very good clinical response to initial DMARD choice. Side effects of methotrexate leading to treatment discontinuation were rare. 2010 ACR/EULAR RA classification and provisional remission criteria are applicable in clinical practice. Appropriate refferral of patients at risk by their primary care physicians remains a problem.

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Successful Self-Administration Of Methotrexate In Rheumatoid Arthritis Patients Using a Prefilled Autoinjector Pen. Jaime Pachon[1], Alan Kivitz[2], Kay-Uwe Heuer[3] and Uwe Pichlmeier[3]. [1]Miami Research Associates, South Miami, FL, [2]Altoona Center for Clinical Research, Duncansville, PA, [3]medac GmbH, Wedel, Germany.

Background/Purpose: Methotrexate (MTX) is the most commonly used and recommended DMARD for the treatment of RA. SC administered MTX is well absorbed and appears to overcome the problems associated with oral administration, including variable absorption and saturation of the absorption mechanism with increasing doses.

The purpose of this study was to assess the usability, label comprehension, robustness, safety, and bioavailability of SC self-administration (SA) of the prefilled MTX pen containing 0.3 mL of MTX 50 mg/mL solution (medac

GmbH, Germany) in a typical population of RA patients requiring MTX treatment.

Methods: The study population consisted of 104 patients aged 16 years or older, including newly diagnosed and MTX naïve and those switching from an oral route of administration, or those already receiving an off-label SC route of administration.

The actual use study was performed at 5 sites over a 2-week period.

Visit 1 (V1) consisted of training on the use of the device followed by an actual self-injection. Training and SA were carefully documented by a 10-item questionnaire.

Visit 2 (V2) (8–10 days after V1) consisted of a written examination for assessing patient's retention of information and a panel of the following 4 scenario test case observations, including an actual self-injection: 1) Holding the needle in place for approximately 5 seconds, 2) Checking the window of pen to confirm MTX delivery, 3) Performing the skin pinch in preparation for self-administration, and 4) Proper disposal of pen following self-administration.

Ease of performance of each scenario was also judged by the patients. A subjective measures questionnaire was used to record patients' impressions, difficulties, and general comments on the device.

Bioavailability was assessed in 25 patients. Stratified by body weight categories, patients were randomly assigned to either inject MTX in the abdomen or in the upper thigh.

Results:

- After training at V1, 12 patients had questions about the MTX pen, 4 patients required assistance to perform the self-injection
- At V2, 98.1% of patients scored 80% or better on their written examination
- The successful completion rates of scenarios 1 through 4 were 96.2%, 100%, 98.1%, and 100%, respectively
- For the respective test scenarios, 91.3%, 98.1%, 99%, and 100% of patients did not require any assistance
- The mean rating of easy performance for each test case scenario was 9.8 or higher on a 1 to 10 scale with 1 being very difficult and 10 being very easy
- The subjective measures questionnaire indicated that patients felt the MTX pen was easy to use and their overall impression was favorable
- After use, all the MTX pens were intact and had reliably delivered 0.3 mL MTX
- PK analysis revealed that excessive body weight (>100 kg) significantly decreased both AUC and C_{max} of MTX when administered SC to the abdomen
- No adverse device effects, unanticipated adverse device effects, deaths, serious adverse events, or adverse events leading to study drug discontinuation were reported

Conclusion: The MTX pen was consistently and reliably used by the intended population with a high degree of effectiveness, patient satisfaction, and safety.

Disclosure: J. Pachon, Pfizer Inc, 8, Takeda, 8, UCB, 8, medac, 2; **A. Kivitz**, None; **K. U. Heuer**, medac, 3; **U. Pichlmeier**, medac, 3.

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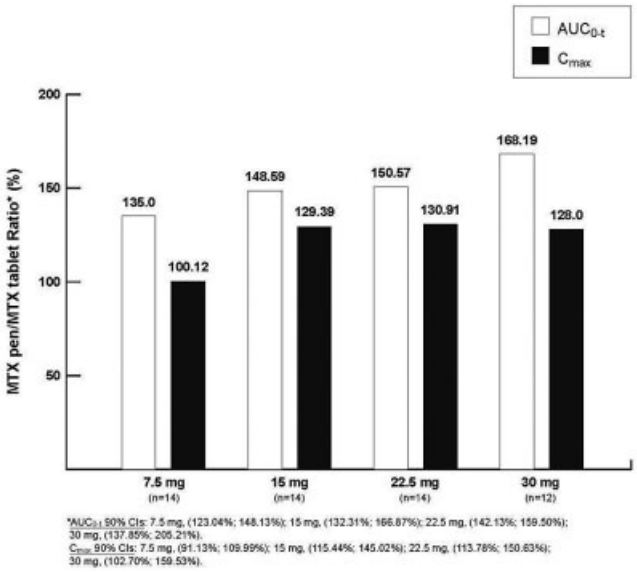
Subcutaneous Administration Of Methotrexate With a Prefilled Autoinjector Pen Results In a Higher Relative Bioavailability Compared To Oral Administration Of Methotrexate. Uwe Pichlmeier and Kay-Uwe Heuer. medac GmbH, Wedel, Germany.

Background/Purpose: Methotrexate (MTX) is commonly used in the treatment of RA, psoriasis, and psoriatic arthritis. Subcutaneously administered MTX is well absorbed and appears to overcome the problems associated with oral administration, including variable absorption and saturation of the absorption mechanism with increasing doses.

The purpose of this study was to investigate the relative bioavailability of MTX administered by subcutaneous (SC) injection with a prefilled MTX autoinjector pen (MTX pen) as compared to oral administration.

Methods: A single center, open label, randomized, 2-period, 2-sequence, single dose crossover study in 4 dose groups (7.5 mg, 15 mg, 22.5 mg, and 30 mg) with healthy subjects aged 18 to 55 years. A subject participated in only 1 of the 4 dose groups and received a single dose of the test product (MTX pen) and the reference product (methotrexate tablets, USP (Dava)). Pharmacokinetic blood samples were collected predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, and 48 h postdose.

Results: Bioavailability of MTX administered SC with the MTX pen compared with MTX tablets.



Dose	MTX pen AUC_{0-t} (h·ng/mL)	MTX tablet AUC_{0-t} (h·ng/mL)	MTX pen C_{max} (ng/mL)	MTX tablet C_{max} (ng/mL)
7.5 mg	782.73	579.79	185.99	185.77
15 mg	1594.84	1073.32	392.00	302.96
22.5 mg	2272.55	1509.34	512.71	391.64
30 mg	2824.72	1679.47	576.26	450.20

The safety results were in line with the current knowledge about the safety profile of MTX. No serious adverse events were reported after SC administration of MTX. A total of 80 adverse events were reported by 35 of the 62 subjects, of which 63 were mild and 17 were moderate events. None of these were serious. Differences in the safety profile were related to the route of administration, i.e., more GI disorders were observed after oral administration (15% vs. 28%) whereas injection site reactions were observed after administration with the MTX pen. Overall, single administrations with the MTX pen were locally well tolerated. No redness or swelling occurred, and only 2 subjects had a mild hematoma. Mild pain or burning sensation at the injection site was reported by 5 of the 59 subjects.

- AUC_{0-t} was higher after MTX pen compared to oral administration for all dose groups
- MTX pen administration resulted in a higher C_{max} compared to oral administration for all dose groups, with the exception of the lowest dose
- AUC_{0-t} ratios increased with ascending doses whereas C_{max} ratios did not increase with ascending doses

Conclusion: Administration of MTX with the MTX pen resulted in a higher relative bioavailability compared to oral administration of MTX after single doses of 7.5, 15, 22.5, and 30 mg.

Disclosure: U. Pichlmeier, medac, 3; **K. U. Heuer**, medac, 3.

1356

Disease Activity Of Rheumatoid Arthritis Is Influenced By Seasonal Change, As Analyzed Based On a Nationwide Japanese Cohort Database. Tetsuji Sawada[1], Hiroaki Mori[2], Kota Shimada[3], Haeru Hayashi[1], Koichiro Tahara[1], Jinju Nishino[4] and Shigeto Tohma[5]. [1]Tokyo Medical University, Tokyo, Japan, [2]Tokyo Meidical University, Tokyo, Japan, [3]Tokyo Metropolitan Tama Medical Center, Tokyo, Japan, [4]Nishino Clinic, Orthopedics and Rheumatology, Tokyo, Japan, [5]Sagamihara Hospital, National Hospital Organization, Sagamihara, Japan.

Background/Purpose: Previous studies have suggested that environmental factors, such as weather, humidity and seasonal change, may affect rheumatoid arthritis (RA). In the present study, we aimed to determine whether there is seasonal variation in disease activity of RA, as assessed by subjective and objective components, using a nationwide Japanese cohort

database, NinJa (National Database of Rheumatic Diseases by iR-net in Japan) in 2009, 2010 and 2011.

Methods: We analyzed data from RA patients, who were registered in NinJa and evaluated at any point during the indicated year, to evaluate seasonal effects on disease activity of RA, including tender joint count (TJC), swollen joint count (SJC), ESR, C-reactive protein (CRP), patient's assessment of pain on a visual analogue scale (pain VAS), patient's global assessment of disease activity (patient's global VAS), physician's global assessment of disease activity (physician's global VAS), DAS28, Modified Health Assessment Questionnaire (MHAQ).

Results: Univariable analysis using NinJa 2011 database revealed that pain VAS and patient's global VAS, which were subjective components of RA disease activity, as well as SJC, inflammatory markers (ESR and CRP), DAS28, mHAQ and physician's global VAS were lowest during the fall months with statistical significance, although TJC was lowest in the summer months. Furthermore, it was reproducibly demonstrated that pain VAS, patient's global VAS, DAS28 and physician's global VAS were lowest during the fall months when analyzing using Ninja 2009 and 2010 database.

Conclusion: We have clearly demonstrated that RA disease activity, as assessed both subjectively and objectively, was lowest in fall. Seasonal changes can thus affect RA, which should be taken into account when examining RA patients to better understand their symptoms.

	Spring	Summer	Fall	Winter
Number of patients	1905	628	1210	4398
TJC	2.63	1.65	2.01	2.97
SJC	2.34	2.42	1.54	1.77
ESR	29.9	27.3	26.1	32.0
CRP	0.68	0.64	0.57	0.70
pain VAS	2.71	2.84	2.25	2.76
mHAQ	0.50	0.47	0.45	0.49
patient's global VAS	2.77	3.01	2.39	2.82
DAS28	2.64	2.53	2.40	2.66
physician's global VAS	1.76	2.01	1.48	1.86

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1357

Coping Style Is An Independent Predictor For Disease Activity At Three Months In Early Arthritis Patients Initiating Therapy With Disease Modifying Anti-Rheumatic Drugs. T. Martijn Kuijper[1], Hong Xiong[1], A.E.A.M. Weel[2], A.H. Gerards[3], Jendé van Zeben[4], P.H.P. de Jong[5], Ilja Tchetverikov[6], P.B.J. de Sonnaville[7], M.V. Krugten[8], B.A. Grillet[9], Jolanda J. Luime[1] and Johanna M.W. Hazes[1]. [1]Erasmus Medical Center, Rotterdam, Netherlands, [2]Maasstad Hospital, Rotterdam, Netherlands, [3]Vlietland Hospital, Schiedam, Netherlands, [4]Sint Franciscus Gasthuis, Rotterdam, Netherlands, [5]Erasmus University Medical Center, Rotterdam, Netherlands, [6]Albert Schweitzer Ziekenhuis, Dordrecht, Netherlands, [7]Admiraal de Ruyter Ziekenhuis, Goes, Netherlands, [8]Admiraal de Ruyter Hospital, Vlissingen, Netherlands, [9]Zorgsaam Hospital, Terneuzen, Netherlands.

Background/Purpose: To explore the effect of psychosocial factors on the Disease Activity Score (DAS) and its components in early arthritis patients three months after initiating treatment with DMARDs.

Methods: Data were used from patients with recent-onset arthritis participating in a single-blinded clinical trial (Treatment in the Rotterdam Early Arthritis CoHort (tREACH))(1,2) in which three induction therapy strategies were compared: (A) combination therapy (methotrexate (MTX) + sulfasalazine + hydroxychloroquine) with glucocorticoids (GCs) intramuscularly; (B) combination therapy with an oral GC tapering scheme and (C) MTX with oral GCs similar to B.

Data were collected on demographics, clinical and psychological characteristics, including questionnaire data on coping, fatigue, depression, social support, locus of control and physical activity. The effect of baseline psychological characteristics on the DAS three months after initiation of therapy were evaluated using a multivariate linear regression model corrected for treatment arm, baseline DAS, age, sex, Rheumatoid Factor and ACPA. Separate analyses were performed for the DAS components: SJC (Swollen Joint Count), Ritchie Articular Index (RAI), ESR and patient self-report of general health (Visual Analogue Scale).

Results: 281 patients (91 men, 190 women; mean baseline DAS 3.4, median baseline HAQ 0.75) were included in the analysis. We found that passive coping with pain and higher anxiety scores at baseline were associated with higher levels of disease activity (DAS) at three months. Taking the individual components of the disease activity score at three months as an outcome, passive coping with pain was associated with higher levels of ESR, while anxiety was related to higher tender joint scores (RAI) and patient self-report of general health.

Conclusion: Our results suggest that psychological factors, especially anxiety and coping style, are associated with disease activity in early arthritis patients three months after initiation of DMARD therapy. This was not explained by baseline levels of disease activity or initial type of DMARD treatment.

Table 1. Univariate and multivariate linear regression analysis of psychological factors on disease activity (DAS) at three months.

	Univariate		Multivariate	
	β	p	β	p
Correcting factors				
Age	0.005	0.241	0.005	0.219
Sex (male)	−0.313	0.013	−0.192	0.100
DAS (baseline)	0.458	0.000	0.382	0.000
RF/ACPA positive	−0.154	0.236	−0.087	0.453
Treatment				
Arm B	−0.034	0.815	−0.080	0.541
Arm C	0.354	0.015	0.295	0.024
Psychosocial factors				
Fatigue	0.037	0.000		
Coping with pain	0.059	0.000	0.020	0.073
Depression	0.079	0.000		
Anxiety	0.076	0.000	0.049	0.002
Social support	−0.005	0.779		
Locus of control				
Internal	−0.030	0.025		
External	0.016	0.272		
Chance	−0.010	0.404		

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1358

No Differences In Patient-Reported Outcomes By Methotrexate Dose Among Early Rheumatoid Arthritis Patients Treated Concomitantly With Adalimumab: Results From The Concerto Trial. Roy M Fleischmann[1], Alan Kivitz[2], Ronald F van Vollenhoven[3], James W. Shaw[4], Stefan Florentinus[5], Piyalal M. Karunaratne[4], Hartmut Kupper[6], Maxime Dougados[7] and Gerd R Burmester[8]. [1]University of Texas Southwestern Medical Center, Dallas, TX, [2]Altoona Center for Clinical Research, Duncansville, PA, [3]Karolinska Institutet, Stockholm, Sweden, [4]AbbVie Inc., North Chicago, IL, [5]AbbVie, Rungis, France, [6]AbbVie Deutschland GmBH & Co KG, Ludwigshafen, Germany, [7]René Descartes University, Paris, France, [8]Charité-Universitätsmedizin Berlin, Free University and Humboldt University of Berlin, Berlin, Germany.

Background/Purpose: Methotrexate (MTX) in combination with the tumor necrosis factor inhibitor adalimumab (ADA) is an effective therapy for treating rheumatoid arthritis (RA), but the minimum dose of MTX in combination with ADA that can achieve an acceptable clinical response is not known.

Objectives: To evaluate different MTX doses in combination with ADA in achieving clinically meaningful improvement in patient-reported outcomes (PROs) in patients with early RA.

Methods: CONCERTO was a 26-week, phase 3, double-blind, parallel-arm study in MTX-naïve patients with active RA <1 year in duration. Patients were randomized 1:1:1:1 to open-label ADA 40 mg every other week plus blinded weekly oral MTX in a dose of 2.5, 5, 10, or 20 mg. Patients in the 20 mg arm started with 10 mg MTX with bi-weekly escalation of 2.5 mg through wk 8. PROs measured at weeks 8 and 26 included the following: Health Assessment Questionnaire Disability Index (HAQ-DI); patient global

assessment of disease activity (PGA); 36-item Short-Form Health Survey, Version 2 (SF-36v2), Physical Component Summary (PCS) and Mental Component Summary (MCS); Medical Outcomes Study Sleep Scale (MOS SS); Compliance Questionnaire Rheumatology (CQR); and Treatment Satisfaction Questionnaire for Medication (TSQM). Differences in mean changes in PROs among the 4 treatment groups were analyzed using mixed models. No adjustments for multiplicity were applied.

Results: Of the 395 patients included in the intent-to-treat population, 358 (91%) completed 26 weeks of treatment; 15, 7, 6, and 9% of pts receiving 2.5, 5, 10, or 20 mg MTX, respectively, discontinued treatment prior to completion. Clinically and statistically significant improvements from week 0 in most PROs occurred in all 4 dose groups by 8 weeks, were maintained through 26 weeks, and were similar regardless of MTX dose with no statistically significant difference between the dose groups with respect to the HAQ-DI, PCS, and MCS.

Image/graph:

Table. PRO means at wk 0 and mean changes at wks 8 and 26

	MTX Dosing Regimen											
	2.5 mg (N = 98)			5 mg (N = 99)			10 mg (N = 100)			20 mg (N = 98)		
PRO	Wk 0	ΔWk 8	ΔWk 26	Wk 0	ΔWk 8	ΔWk 26	Wk 0	ΔWk 8	ΔWk 26	Wk 0	ΔWk 8	ΔWk 26
HAQ-DI	1.5	−0.61[c]	−0.73[c]	1.6	−0.61[c]	−0.76[c]	1.6	−0.66[c]	−0.78[c]	1.6	−0.65[c]	−0.85[c]
PGA	70.5	−30.5[c]	−38.8[c]	71.7	−32.0[c]	−36.7[c]	67.6	−30.5[c]	−38.6[c]	65.5	−30.3[c]	−40.7[c]
PCS	31.2	9.1[c]	8.8[c]	31.4	7.5[c]	9.0[c]	31.1	8.4[c]	10.4[c]	31	9.5[c]	12.2[c]
MCS	37.1	7.6[c]	8.6[c]	39.4	6.6[c]	6.7[c]	39	6.1[c]	7.0[c]	39.7	6.5[c]	7.8[c]
MOS SS	48.2	−11.7[c]	−12.3[c]	48.7	−13.6[c]	−12.6[c]	48.7	−11.1[c]	−13.4[c]	50.5	−12.3[c]	−11.7[c]
CQR	80.6	1.6	1.3	80.3	1.7	−1.1	79.3	3.1[b]	2.5	80.2	2	2.1
TSQM	54.2	21.7[c]	18.9[b]	56.5	14.2[b]	11.9[a]	53	22.5[c]	22.0[c]	52.8	24.4[c]	26.2[c]

Number of randomized pts are presented. The HAQ-DI, PGA, and MOS SS were scaled such that higher values indicated worse outcomes. All other PROs were scaled such that higher values were better. Global tests of differences in mean changes among the 4 treatment groups at wks 8 and 26 were insignificant, $P > 0.05$. [a]$P < 0.05$, [b]< 0.01, [c]$P < 0.001$, mean change from Wk 0 different from 0. Wk 26 n = 83, 93, 93, and 89 for MTX doses 2.5, 5, 10, and 20 mg, respectively.

Conclusion: Patients treated with ADA in combination with MTX 2.5, 5, 10 or 20 mg per week experience similar improvements in PROs by week 8 that are maintained through 26 wks. The differences associated with MTX dose are not statistically significant and, in general, not clinically meaningful.

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Does Rheumatoid Arthritis Disease Activity Correlate With Weather Conditions? Eimear Savage[1], David McCormick[1], Stephen McDonald[1], Michael Stevenson[2], Owen Moore[3] and Andrew Cairns[4]. [1]Belfast Hospitals Trust, Musgrave Park Hospital, Belfast BT9 7JB, Northern Ireland, [2]Queens University, Belfast. School of Medicine, Dentistry and Biomedical Sciences., Belfast BT12 6BJ, Northern Ireland, [3]St. Vincent's Hospital, Melbourne, Australia, [4]Belfast Hospitals Trust, Musgrave Park Hospital, Belfast, United Kingdom.

Background/Purpose: Rheumatoid Arthritis is a common inflammatory joint condition affecting up to 1% of the Northern Ireland population. Patients often report increasing joint pain with changing weather conditions. Previous studies examining the impact of weather on pain severity have yielded contradictory results (1,2). The relationship between disease activity scores in Rheumatoid Arthritis patients and weather variance has not previously been examined.

Methods: Patients attending the Biologics Therapy Unit at the Department of Rheumatology, Musgrave Park Hospital, Belfast; with a diagnosis of Rheumatoid Arthritis and receiving injectable anti-TNF therapy (Etanercept or Adalimumab) for a period of greater than 6 months were invited to participate. A retrospective analysis of a total of 133 patients was performed. Data collected at 5 time points included tender joint count, swollen joint count, patient visual analogue score, Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), and DAS-28 (Disease Activity Score). This was correlated with maximum/minimum temperature, hours of sunshine, rainfall, relative humidity, pressure and wind-speed from a local weather station on the day of attendance. A linear regression analysis was used to determine relationship between weather components, disease activity and pain.

Results: The weather-based components were extracted after a global factor analysis using data from all time-points had revealed three weather components from the seven quantitative variables (maximum temperature, minimum temperature, hours of sunshine, mm rainfall, relative humidity, wind-speed and pressure). These seven variables were converted to z-scores. Three components indicated by the factor analysis were as follows: temperature component, sunny/dry component, wet/windy component. All components were calculated from z-scores.

Using DAS-28 as an outcome variable, when tested against weather components, it was evident that increased hours of sunshine and low humidity resulted in a lower das-28 score (p 0.001). Sunny and dry conditions ((hours of sunshine – relative humidity)/2) resulted in a DAS-28 reduction of 0.143 (95% CI −0.230, −0.057) p=0.001. Temperature component (max temperature + min temperature)/2) resulted in a DAS-28 reduction of 0.048 (95% CI −0.129, 0.032), p = 0.23. Wet and windy conditions (rainfall + wind-speed – pressure)/3) led to a das-28 increase (0.013 (95%CI −0.098, 0.123) p=0.82.

Conclusion: This study demonstrates statistically significant lower DAS-28 scores in sunny and dry conditions. A non-significant trend to higher DAS-28 scores in times of low temperature, and dull, wet and windy weather was also noted.

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1360

Evaluation Of Biomarkers Involved In Periondontal Disease Including *Porphyromonas Gingivalis* Antibodies To Predict Response To Infliximab In Rheumatoid Arthritis Patients. Mélanie Rinaudo-Gaujous[1], Pierre Miossec[2], Vincent Blasco-Baque[3], Philippe Gaudin[4], Christian Genin[1], Thierry Thomas[5], Stéphane Paul[1] and Hubert Marotte[6]. [1]Laboratory of Immunology and immunomonitoring, CIC CIE3 Inserm Vaccinology, GIMAP EA3064, Hôpital Nord, Saint-Etienne, France, [2]Immunogenomics and inflammation research unit, Lyon, France, [3]Institute of Cardiovascular and Metabolic Diseases, CHU Rangueil, Toulouse, France, [4]CHU Hôpital Sud, Grenoble Teaching Hospital, Echirolles, France, [5]INSERM U1059 and University Hospital, Saint-Etienne, France, [6]LBTO INSERM U1059 University Jean Monnet, Saint-Etienne, France.

Background/Purpose: This study evaluates biological markers of rheumatoid arthritis (RA) severity including matrix metalloproteinase 3 (MMP-3) and *Porphyromonas gingivalis (P. gingivalis)* serology during infliximab therapy and highlights predictive factors for infliximab response.

Methods: We enrolled 79 RA patients requiring infliximab therapy in this study. DAS28, anti-citrullinated protein antibodies *(*ACPA), rheumatoid factor (RF) Iga and IgM, anti-*P. gingivalis* antibodies, anti-*Prevotella intermedia* (*P. intermedia*) antibodies, and MMP-3 were monitored before and 6 months after the beginning of infliximab therapy. ACPA, RF, MMP-3 anti-*P. intermedia* antibodies, and anti-*P. gingivalis* antibodies (LPS specific and whole extract) antibodies were determined by ELISA.

Results: At baseline, ACPA titers are associated with anti-*P. gingivalis* LPS specific antibodies titers ($P<0.01$) and anti-*P. gingivalis* whole extract antibodies titers ($P<0.01$), but no association has been found between IgM RF and anti-*P. gingivalis* antibody. Conversely, anti-*P. intermedia* antibodies are not correlated with ACPA titers, but with IgM RF levels. Anti-*P. gingivalis* antibodies were not significantly correlated with clinical, biological, or destruction parameters of RA disease. At 6 months of infliximab therapy, MMP-3 levels decrease ($P<0.0001$), whereas *P. gingivalis* and anti-*P. intermedia* antibodies levels increase ($P<0.01$). DAS28 and inflammation markers (CRP and ESR) also decrease significantly during infliximab

therapy (P<0.05), as ACPA levels (P<0.001). Presence of anti-*P. gingivalis* antibodies at baseline did not influence the treatment outcome. Only high MMP-3 levels at baseline and a decreased of ACPA at 6 months were associated with infliximab efficacy (P<0.01).

Conclusion: Anti-*P. gingivalis* is associated with ACPA at baseline suggesting a role of periodontal infection in RA pathogenesis. Unlike anti-*P. gingivalis* antibodies, MMP-3 level can be a useful marker of the infliximab efficacy in RA patients as well as the evolution of ACPA during treatment.

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1361

Stringent Therapies Improve Clinical, Radiographic and Magnetic Resonance Imaging Outcome In Early-Stage Rheumatoid Arthritis Patients From Japanese Population: Longitudinal Study From Nagasaki Early Arthritis Cohort. Mami Tamai[1], Yoshikazu Nakashima[2], Junko Kita[2], Ayuko Takatani[2], Ayako Nishino[2], Takahisa Suzuki[2], Yoshiro Horai[2], Akitomo Okada[3], Shin-ya Kawashiri[2], Naoki Iwamoto[2], Kunihiro Ichinose[2], Kazuhiko Arima[2], Hideki Nakamura[2], Tomoki Origuchi[2], Masataka Uetani[2], Katsumi Eguchi[4] and Atsushi Kawakami[2]. [1]Center for Health & Community Medicine, Nagasaki University, Nagasaki, Japan, [2]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan, [4]Sasebo City General Hospital, Sasebo, Nagasaki, Japan.

Background/Purpose: Prognosis of the patients with rheumatoid arthritis (RA) nowadays is supposed to become better by treat-to-target (T2T) strategy. Osteitis determined by magnetic resonance imaging (MRI) is known as a predictor toward radiographic progression. We have tried to examine in the present study whether the change of therapeutic strategy affect the clinical, radiographic and MRI outcome of early-stage RA patients of Japanese population.

Methods: All of early-stage RA patients in the present study were recruited from Nagasaki University Early Arthritis Cohort in which the subjects received Gd-enhanced MRI of both wrist and finger joints. We have divided the periods of the Cohort into two parts. The first half includes the RA patients DMARDs treatment initiated from 2003 to 2007 (Group I: traditional therapy phase) whereas the second half includes those DMARDs treatment initiated from 2008 to 2011 (Group II: T2T phase). All of patients gave their informed consent to be subjected to the protocol that was approved by the Institutional Review Board of Nagasaki University. The good outcomes at 1 year after initiation of therapy were set as SDAI remission for clinical outcome, no radiographic progression by Genant modified Sharp score for radiographic outcome and improvement of RAMRIS osteitis score over 67% decrease or no appearance of RAMRIS osteitis for MRI outcome, respectively. We have tried to examine whether therapeutic strategies affect the outcome at 1 year in early-stage RA patients.

Results: Ninety-two patients were included. Median disease duration at entry was 3 months and there were no significant differences of patients' background between the 2 treatment groups. In T2T phase, the frequencies of MTX initiation, introduction of MTX within 1 year and the use of biologics within 1 year were significantly high as compared with traditional therapy phase. Regarding to the efficacy, the rate of SDAI remission, radiographic no progression and good outcome of MRI were significantly high at 1 year in T2T phase as compared with traditional therapy phase. Multivariate logistic regression analyses have identified; SDAI remission at 1 year is associated with T2T phase and no radiographic progression. No radiographic progression at 1 year is associated with SDAI remission and good outcome of MRI. Good outcome of MRI is associated with T2T phase and no radiographic progression. Good clinical, radiographic and MRI outcome associated each other.

Conclusion: Present data suggest that stringent therapies in early-stage RA patients improve clinical, radiographic and MRI outcome, indicating an importance of T2T in daily clinical practice.

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Isymind Significantly Reduces MTX-Induced Nausea In a Pilot Trial. Eva Ostermeier[1], Hans Ulrich Koetter[2], Hans-Peter Tony[3] and Ruth Pfister[2]. [1]University of Würzburg, Würzburg, Germany, [2]iSyMind Institut, Giessen, Germany, [3]University Hospital Würzburg, Würzburg, Germany.

Background/Purpose: MTX is the standard DMARD for treating rheumatoid arthritis and the most important partner for biological DMARDs. However MTX often induces heavy nausea accompanied by disgust and phobic fear concerning drug application leading to premature discontinuation of treatment. Therefore we analyzed the effectiveness of *Neurointrinsic Mind Modulation and Synchronization* (iSyMind), a neuropsychological method to reduce or eliminate the reported MTX side-effects in a clinical pilot study.

Methods: 4 patients with strong side-effects were screened using Visual Analog Scale (VAS; 0–100) for Intensity of Problem (IoP), Ability to Cope (AtC), Wish to Discontinue (WtD), Disgust (D), Anxiety (A). Each Patient was treated in a one-session group treatment with iSyMind 2×30 min in combination with psychoeducation concerning the development of disgust and phobia. All parameters were examined pre and post treatment and after 7, 28 and 90 days.

Results: After iSyMind treatment patients were able to receive MTX s.c. or p.o. with a highly improved tolerance. In 3 patients all 6 parameters (VAS) showed clinically significant reduction between day 1 and day 90: IoP from 91 to 24, AtC from 80 to 13, WtD from 59 to 12, D 87 from to 26, A 88 from to 26. The treatment satisfaction index via Visual Analoge Scale (0= not at all satisfied, 100 = very satisfied) at day 90 was .81. The positive effect was ongoing in 3 of 4 patients till day 90 while one patient showed a fast relapse probably because of underlying moderate depression. Due to large standard deviation, inflicted by 1 patient, the statistical significances scored between $p < .002$ and $p < .09$.

Conclusion: This pilot trial suggests that iSyMind significantly reduces MTX induced nausea, disgust and phobic fear with a response rate of about 75% enabling continuation of medication. The results indicate that the studied MTX related side-effects concerning drug application are primarily neuropsychological results of an intrinsic learning process which can be resolved. Further studies are necessary for statistical validation.

Disclosure: E. Ostermeier, None; **H. U. Koetter**, None; **H. P. Tony**, None; **R. Pfister**, None.

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Active Tuberculosis Risk With Tumor Necrosis Factor Inhibitors After Treating Latent Tuberculosis -a 7-Year Retrospective Observational Study. Minkyung Kwon, Mindong Sung, Yong-Jin Kwon, Young Goo Song, Sang-Won Lee, Min-Chan Park, Yong-Beom Park, Soo-Kon Lee and Jason Jungsik Song. Yonsei University College of Medicine, Seoul, South Korea.

Background/Purpose: Active tuberculosis (TB) risk increases during anti-tumor necrosis factor (TNF) therapy and latent TB infection (LTBI) screening is recommended in potential TNF inhibitor users. It is unclear whether anti-TNF therapy elevates active TB risk even after LTBI treatment. We sought to evaluate the risk of active TB development in LTBI-positive TNF inhibitor users following the current treatment guidelines for LTBI in South Korea, TB prevalent area.

Methods: We retrospectively studied 949 TNF inhibitor users with immune-mediated inflammatory diseases at Yonsei University Health System from 2005–2012. Long-term TNF inhibitor users who followed current national guidelines for LTBI were enrolled for analysis. We compared the incidence rate of active TB among LTBI-positive TNF inhibitor users (n=256) and LTBI-negative TNF inhibitor users (n=521) using Poisson regression.

Results: There were 256 LTBI-positive and 521 LTBI-negative TNF inhibitor users. Six LTBI-positive and five LTBI-negative TNF inhibitor users developed active TB during the 7.8-year study duration. To adjust for different TNF inhibitor exposure durations among patients, we calculated patient-years (PY) exposure rates. Active TB incidence rate was 1107 per 100,000 PY in LTBI-positive TNF inhibitor users and 490 per 100,000 PY in LTBI-negative TNF inhibitor users. Active TB risk was not elevated in LTBI-positive versus LTBI-negative TNF inhibitor users (sex- and age-adjusted incidence rate ratio, 2.2; 95% CI 0.6–7.7). The median onset of active TB in LTBI-positive TNF inhibitor users was 8.6 months (range 3.9–22.4 months) and 14.6 months in LTBI-negative TNF inhibitor users (range 9.6–18.1 months) Among the 11 TNF inhibitor users who developed

active TB, 50% of LTBI-positive TNF inhibitor users (three patients) developed active TB within 9 months while they were on isoniazid, whereas no LTBI-negative TNF inhibitor users developed active TB in the same period.

Conclusion: Risk of developing active TB in LTBI-positive TNF inhibitor users is not significantly higher than in LTBI-negative TNF inhibitor users, after receiving LTBI treatment.

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Detection of Latent Tuberculosis Infection in Rheumatologic Diseases Before Anti-TNFα Therapy: Tuberculin Skin Test Versus IFN-γ Assay. Suleyman Ozbek[1], Ismail Hanta[2], Sedat Kuleci[2], Gulsah Seydaoglu[2] and Ezgi Ozyilmaz[2]. [1]Cukurova University Faculty of Medicine, Adana, Turkey, [2]Cukurova University, Adana, Turkey.

Background/Purpose: We aimed to evaluate tuberculin skin test (TST) and interferon-gamma (IFN-γ) test results for latent tuberculosis infection (LTBI) in patients with rheumatologic diseases prior to anti-TNFα therapy.

Methods: Ninety patients were evaluated in the study at the Departments of Chest Diseases and Rheumatology for anti-TNFα therapy for their rheumatologic diseases. Tuberculin skin test was performed (Mantoux method) and peripheral blood samples were collected for IFN-γ assay (QuantiFeron TB-Gold In Tube) before the anti-TNFα therapy.

Results: Of 90 patients, TST positivity was detected in 56 (62.2%) patients, while IFN-γ positivity was detected in 34 (37.8%) patients. Among 56 TST positive patients, IFN-γ positivity was detected in 24 (42.9%) patients, and among 34 TST negative patients, IFN-γ positivity was detected in 10 (29.4%) patients. There was no significant agreement between TST and IFN-γ assay results (Kappa = 0.12, P = 0.2). Forty-three (47.8%) patients were using immunosuppressive drugs owing to their rheumatologic diseases. In this group, TST and IFN-γ positivity is significantly lower than in those who did not receive immunosuppressive treatment ($P < 0.05$).

Conclusion: We conclude that the IFN-γ assay may not be preferred to TST as a diagnostic test in patients with rheumatologic diseases prior to anti-TNFα treatment.

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1365

Incidence Of Hepatitis B Virus Reactivation In Patients With Rheumatoid Arthritis During Treatment With Biologics. Jun Nakamura[1], Takao Nagashima[1], Katsuya Nagatani[1], Taku Yoshio[2], Masahiro Iwamoto[3] and Seiji Minota[4]. [1]Jichi Medical University, Tochigi, Japan, [2]Jichi Medical University, School of Medicine, Shimotsuke-shi, Tochigi-ken, Japan, [3]Jichi Medical University, Shimotsuke, Tochigi, Japan, [4]The Safety Evaluation Committee of Actemra® for JIA, Tokyo, Japan.

Background/Purpose: Reactivation of hepatitis B virus (HBV) is very problematic in patients who are receiving biologics. Optimal precaution and management for those patients are still controversial. The aim of this study is to clarify the incidence of HBV reactivation in rheumatoid arthritis (RA) patients on biologics and to find out whether there is difference in reactivation rates among different biologics.

Methods: Retrospective observational study. HBV reactivation was defined as conversion from quantitative negativity to qualitative positivity of HBV-DNA in sera. All the patients with RA who were treated with biologics from July 2010 to December 2012 were tested for HBsAg, anti-HBs and anti-HBc. If the patients were positive for HBsAg, or negative for HBsAg but positive for anti-HBs and/or anti-HBc, ALT and AST were also retrieved from patients' records. HBsAg, anti-HBs and anti-HBc were examined using chemiluminescent immunoassay, and the levels of HBV-DNA were measured by real-time PCR (lowest detection limit was 2.1 log copies/ml). The ethics committee of our hospital approved this study.

Results: Among 247 patients received biologics, none was found positive for HBsAg. 57 patients (23.0%) were negative for HBsAg but positive for anti-HBs and/or anti-HBc. These patients were considered to have resolved HBV infection. Infliximab, etanarcept, adalimumab, tocilizumab and abatacept were used in 27, 25, 17, 18 and one, respectively; some of the patients received multiple biologics. HBV-DNA became positive in 4 patients (7.0%): 1 while on etanercept, 1 while on infliximab, and 2 while on tocilizumab. However, the levels of HBV-DNA were below the quantitative detection limits in these 4 patients. In one patient on tocilizumab, HBV-DNA levels fluctuated between positive and negative ranges for 4 months; first HBV-DNA positivity was found at 2 months after tocilizumab-use. In another case on tocilizumab, HBV-DNA was first found at 2 months after tocilizumab-use, persisted for 3 months, and disappeared thereafter. In one patient on infliximab, HBV-DNA became positive only once at 22 months after infliximab-use. In one patient on etanercept, HBV-DNA was found only once at 17 months after etanercept-use. Liver function tests were within normal ranges in all examinations from all the patients. All the patients continued treatment with the biologics and HBV-DNA became negative eventually without anti-viral treatment.

Conclusion: HBV reactivation was observed in 7.0% of RA patients with resolved HBV infection during treatment with biologics. However, HBV-DNA levels were below the quantitative detection limits and liver function tests were normal throughout. There were no differences among biologics in regards to the incidence of HBV reactivation. Anti-TNFs and anti-IL-6 receptor antibody may be used safely in RA patients with a history of HBV infection.

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Abdominal Adiposity and Body Composition In Rheumatoid Arthritis: Relation With Disease Characteristics In A Case-Control Study. Ivan Ferraz-Amaro[1], Esmeralda Delgado-Frías[1], Vanesa Hernandez-Hernandez[2], Jose Ramon Muñiz[3], Antonieta Gonzalez-Diaz[4], Angeles Gomez Rodriguez-Bethencourt[4] and Federico Diaz-Gonzalez[5]. [1]Hospital Universitario de Canarias, La Laguna, Spain, [2]Rheumatology Service, Santa Cruz de Tenerife, Spain, [3]Resonancia Magnetica IMETISA, Santa Cruz de Tenerife, Spain, [4]Servicio de Medicina Nuclear, Santa Cruz de Tenerife, Spain, [5]University of La Laguna, Hospital Universitario de Canarias, La Laguna, Spain.

Background/Purpose: To determine the relationship between measures of body composition (total body composition derived from dual energy X-ray absorptiometry and abdominal adiposity through magnetic resonance imaging) with comorbidities in rheumatoid arthritis (RA) like disease activity, radiological damage and endothelial dysfunction.

Methods: 216 subjects, 111 RA patients and 105 age and sex-matched healthy controls were included in this case-control study. Anthropometric and demographic characteristics, cardiovascular risk measurement through SCORE index, C-reactive protein (CRP), Disease Activity Score (DAS28), Health Assessment Questionnaire (HAQ), and radiological damage through Sharp index were determined. Quantification of visceral and parietal abdominal fat area was assessed using magnetic resonance imaging. Total body composition, total and regional lean mass, and fat mass and fat free mass indexes were measured by dual energy X-ray absorptiometry (DEXA). The presence of sarcopenia or overfat phenotype was established. Endothelial dysfunction was assessed through brachial artery flow-mediated dilatation sonography. Multivariate analysis was performed to define the relation of this body composition with disease characteristics.

Results: *1) Body composition.* Percentage of lean and fat mass did not differ between patients and controls. Appendicular to total lean mass (0.42 ± 0.02 vs. 0.40 ± 0.03, $p=0.00$) and appendicular to trunk lean mass (0.82 ± 0.08 vs. 0.78 ± 0.08, $p=0.00$) were significantly lower in RA patients. Parietal abdominal tissue was lower in male RA patients (19089 ± 1234 vs. 1345 ± 3930 cm^2, $p=0.02$), this difference were not reached in female patients. Presence of sarcopenia tended to be higher in RA patients (13 versus 7%, $p=0.17$) when compared to controls. Although differences in overfat were not reached between controls and patients, 44% of RA patients had a body mass index higher than 30 kg/m^2 (32% in controls, $p=0.09$) and 96% of RA patients were considered to be overfat through DEXA criteria (96% in controls). *2) Radiological damage.* Patients with a lean mass index lower that the hypothetical percentile 25 expressed higher Sharp index when compared to patients in percentile 75 or superior (22 ± 28 vs. 9.4 ± 9, $p=0.02$) and after adjusting for disease activity. Overfat phenotypes did not show associations with radiological damage. 3) *Disease activity.* Sarcopenic patients had higher CRP (3.8 [1.8–29.7] vs 2.8 [1.3–7.2] mmg/dL, $p= 0.04$) and a trend to higher

HAQ score (1.2 [0.38–1.75] vs 0.75 [0.30–1.38], p=0.18). 4) Endothelial dysfunction. Patients with 2 standard deviation of lean mass below normality expressed lower flow-mediated when compared to controls (1.9 [0–8] vs 5.4 [0–9], p=0.14).

Conclusion: Overfat and sarcopenia are present in RA patients and are related to several disease characteristics.

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Performance Of a Two-Step Latent Tuberculosis Screening Algorithm In Patients With Rheumatoid Arthritis, Psoriatic Arthritis Or Ankylosing Spondylitis Prior To Treatment With Tumor Necrosis Alpha Inhibitors: Prospective Observational Data From The Biorx.Si Registry. ŽIga Rotar[1] and Matija Tomsic[2]. [1]University Medical Centre Ljubljana, 1000 Ljubljana, Slovenia, [2]University Medical Centre Ljubjana, Ljubljana, Slovenia.

Background/Purpose: Reactivation of latent tuberculosis infection (LTBI) is of concern in patients treated with TNFi. Conversely, TB chemoprophylaxis (CP) is time consuming, delays the initiation of treatment, adds to the overall cost of treatment, and carries risk of adverse events in its own right. Since 2002 our national guidelines require following a two-step screening algorithm prior to the initiation of the first TNFi. The first step includes tuberculin skin test (TST), and a chest X-ray (CXR). If TST < 5 mm, and the radiologist finds no changes consistent with TB on CXR TNFi is prescribed. If any test is abnormal, the patient is evaluated by a pulmonologist who usually orders QuantiFERON TB Gold IT (QF) and decides whether TB CP (rifampicin/isoniazid 600/300 mg qd for 3 months) is required prior to TNFi treatment.

In February 2012 we showed that in a setting with low background annual TB incidence rate (IR; e.g. 8.4 per 10^5) following of this algorithm resulted in TB IR of 0.11 (95% CI 0.01–0.38), and 0.16 (95% CI 0.02–0.58) per 100 person years (PY) overall, and in rheumatoid arthritis (RA) patients, respectively. The costly QF and CP were required in 13.9%, and 5.2% of patients, respectively. Our aim was to revaluate the performance of this algorithm.

Methods: We cross-linked the data from the mandatory national registry of patients with rheumatic diseases treated with biologics and national TB registry to identify cases of TB in patients who were ever treated with TNFi.

Results: 1203 patients were treated with at least one TNFi for 3146.5 PY (Table 1). Flow of patients through the screening algorithm and case patient characteristics are depicted in Figure 1. QF was performed in 214/1174 (18.2%). 88/1203 (7%) patients received CP. Four cases of TB were identified; hence the incidence rates were 0.13 (95%CI 0.03–3.2), and 0.22 (95% CI 0.06–0.57) per 100 PY overall, and in RA patients, respectively. Cases of TB were only observed among RA patients. The TB IR for certolizumab vs. other TNFi prescribed for RA was 2.1 (95% CI 2.56–7.40) vs. 0.12 (95% CI 0.01–0.43) per 100 PY (p=0.016 Fisher's exact test). The first two received appropriate CP (adherence was good, isolated M. tuberculosis strains were susceptible to CP) prior to TNFi; screening was concluded after 1st, and 2nd step for the third and fourth patient, respectively. Interestingly, the third case was screened for TB again before switching to rituximab. At repeated screening two months prior to TB diagnosis the TST was 10 mm, CXR− and QF−.

Table 1.

	Rheumatoid arthritis	Ankylosing spondylitis	Psoriatic arthritis
N (%)	701 (58.3)	331 (27.5)	171 (14.2)
% female	82	34	41
Age at screening (SD)	54.9 (11.6)	45.8 (11.6)	49 (11.2)
% Glucocorticoids at screening	47.0	/	/
% ever glucocorticoids	66.2	/	/
TNFi exposure years	1792.5	950.6	403.4
% Adalimumab (ADA)	44.4	36.9	44.4
% Certolizumab (CZP)	5.3	0.0	0.3
% Etanercept (ETA)	37.4	31.1	27.2
% Golimumab (GOL)	2.3	7.1	10.9
% Infliximab (IFX)	10.7	24.9	17.2

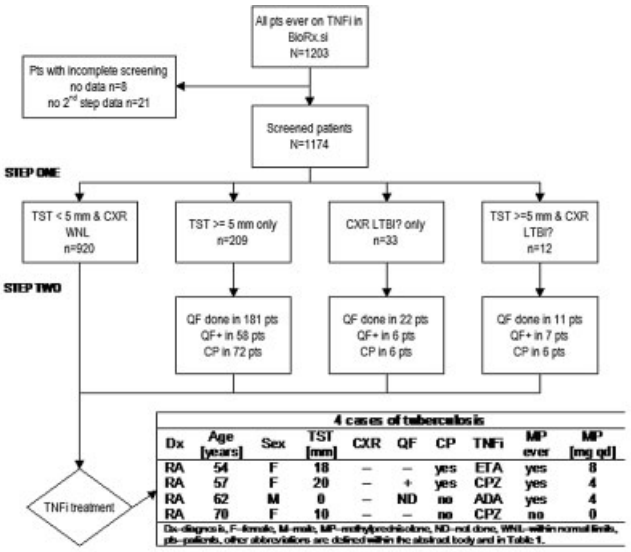

Figure 1.

Conclusion: At follow-up our two-step algorithm is still performing well. Further vigilance is warranted, especially in RA patients and those treated with CPZ.

Disclosure: Rotar, None; **M. Tomsic**, None.

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The Effect Of Vitamin D On Early Rheumatoid Arthritis: A Retrospective Cohort Analysis. Faye A H Cooles[1], Arthur G Pratt[1], Wan-Fai Ng[1], Terry J Aspray[2] and John D Isaacs[3]. [1]Newcastle University, Newcastle upon Tyne, United Kingdom, [2]The Freeman Hospital, Newcastle upon Tyne, United Kingdom, [3]National Institute for Health Research, Newcastle Biomedical Research Centre, Newcastle Hospitals Foundation Trust and Newcastle University, Newcastle Upon Tyne, United Kingdom.

Background/Purpose: There is increasing evidence that vitamin D has immunoregulatory properties in autoimmunity. In established rheumatoid arthritis (RA) there appears to be an inverse association between serum vitamin D levels and disease activity scores (DAS-28) (Rossini et al., Arthritis Res Ther, 2010; 12(6);R216) although others suggest this may be skewed by the global health visual analogue scale (GH-VAS) (Higgins et al., Clin Rheumatol, 2013 Jun; 32(6): 863–7). Given the confounding problems in established RA, such as medications or lifestyle, we wished to investigate the role of vitamin D in early RA.

Methods: We retrospectively analysed an inception cohort of patients presenting to an Early Arthritis Clinic at the Freeman Hospital, Newcastle-upon-Tyne between October 2007 - March 2009. Serum 25 hydroxy vitamin D levels (25OHD measured using the DaiSorin Liaison automated immunoassay), DAS-28, CRP, ESR, TJC (tender joint count), SJC (swollen joint count), GH-VAS and autoantibody status were measured at baseline. Diagnoses were confirmed at 1 year follow-up. Statistical analyses involved linear regression, binary logistic regression and Mann-Whitney U tests and were all performed using SPSS (statistics 19) with significance when p<0.01. Where applicable all analyses were corrected for age and sex.

Results: Of a total cohort of 453 patients, complete data was available for 344 (76%; 2:1 females:males, mean age 49 [range 16–97], median symptom duration 16 weeks [range 1–230]). No significant association was seen between serum 25OHD and GH-VAS, SJC, TJC, ESR, CRP, auto-antibodies or disease outcome in this cohort (corrected for age and sex). Amongst the 73 (21%) patients diagnosed with RA (2:1 females:males, mean age 49 [range 18–88]), associations between serum 25OHD and DAS-28, GH-VAS, SJC, TJC, ESR, CRP and autoantibody status were again not seen (corrected for age and sex). However, in those diagnosed with osteoarthritis, OA, (n=58; 3:1 females:males, mean age 55 [range 47–78]), we identified a significant inverse association between GH-VAS and serum 25OHD (p=0.006), although the other measured parameters (as above) were again non-significant (corrected for age and sex). Notably symptom duration was significantly higher in the OA group than in the RA group (median 24 versus 12 weeks; p<0.0005).

Conclusion: This is the first study to our knowledge to look at the effects of serum 25OHD in early RA. Contrary to published work in established RA, our data suggest that serum 25OHD does not impact on disease activity parameters (including GH-VAS) in early disease. We do however demonstrate a significant inverse association between GH-VAS and serum 25OHD in OA patients. The significantly prolonged symptom duration observed in this group may have permitted an association to develop between perceived health and vitamin D status, for example driven by reduced mobility/sunlight exposure. Similar factors may confound apparent associations between RA and vitamin D status in established disease. Larger scale studies are needed to validate our preliminary findings in early arthritis.

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Evaluation Of *Porphyromona Gingivalis* Serology In Rheumatoid Arthritis and Non-Rheumatoid Inflammatory Disease. Mélanie Rinaudo-Gaujous[1], Adeline Moreau[1], Vincent Blasco-Baque[2], Xavier Roblin[3], Christian Genin[1], Thierry Thomas[4], Stéphane Paul[1] and Hubert Marotte[5]. [1]Laboratory of Immunology and immunomonitoring, CIC CIE3 Inserm Vaccinology, GIMAP EA3064, Hôpital Nord, Saint-Etienne, France, [2]Institute of Cardiovascular and Metabolic Diseases, CHU Rangueil, Toulouse, France, [3]Department of gastroenterology, Hôpital Nord, Saint-Etienne, France, [4]INSERM U1059 and University Hospital, Saint-Etienne, France, [5]INSERM U1059 and University Hospital, Hôpital Nord, Saint-Etienne, France.

Background/Purpose: Periodontal disease (PD) is associated mainly with rheumatoid arthritis (RA), but recent data suggest an association with ankylosing spondylitis (AS). Role of *Porphyromonas gingivalis* (*P. gingivalis*) in RA disease is growing fast since it is the only bacteria able to citrullinate peptides and may induce autoimmune response through development of ACPA. However, few studies have reported its presence in others inflammatory diseases. The aim of this study was to evaluate immunization against two oral pathogens: *P. gingivalis* and *Prevotella intermedia* (*P. intermedia*) in patients with RA, AS, inflammatory bowel disease (IBD), and healthy subjects.

Methods: Seventy-nine RA patients, 56 AS patients, and 39 IBD patients requiring infliximab therapy enrolled in these study as well as 30 healthy controls. Anti-*P. intermedia* antibodies and anti-*P. gingivalis* LPS specific and whole extract antibodies were determined by specific ELISA. Specificity of these antibodies was evaluated by the measure of antibodies against the *Escherichia Coli (E. coli)* commensal bacterium of the intestinal tract.

Results: Anti-*P. gingivalis* antibody titers directed against LPS and/or whole extract were correlated together ($P<0.0001$) as well as antibody titers against the two oral bacteria (*P. gingivalis* and *P. intermedia*) ($P<0.0001$). By using LPS from *E. coli*, no cross reaction was observed between these two species.

Anti-*P. gingivalis* antibodies titers were higher in RA and AS patients than in healthy subjects ($P < 0.0001$) or in IBD patients ($P < 0.0001$). Moreover, there was a tendency for higher titers in RA patients than in SA patients (Fig 1A). Same results were found with anti-*P. intermedia* antibody titers which were higher in RA and AS patients than in healthy controls ($P < 0.0001$) or IBD patients ($P < 0.0001$) (Fig 1B).

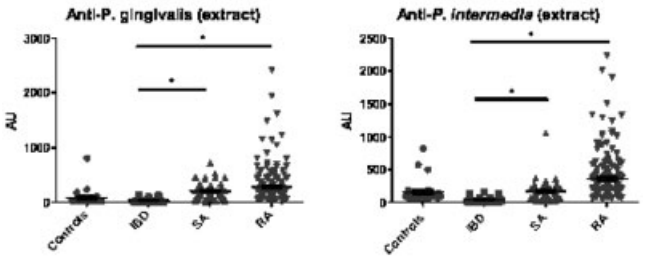

Fig 1. Evaluation of anti-*P. gingivalis* (A) and anti-*P. intermedia* (B) antibodies in RA, AS, and IBD patients and in healthy controls.

*$P < 0.0001$

Conclusion: Immunity against *P. gingivalis* and *P. intermedia* oral bacteria seems to have an important role in RA, but also in AS compared to other inflammatory disease as IBD.

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Prednisone Is a Risk Factor For Pneumocystis Jirovecii Pneumonia In Patients With Rheumatic Diseases: A Case-Control Study With 36 Cases. Wieneke van den Hombergh[1], Annelies van Ede[2], J. Fransen[3], Femke BG lamers-Karnebeek[3], Saskia Kuipers[2] and Matthijs Janssen[4]. [1]UMC st. Radboud, Nijmegen, Netherlands, [2]UMC st Radboud, Nijmegen, Netherlands, [3]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [4]Rijnstate Hospital, Arnhem, Netherlands.

Background/Purpose: Pneumocystis jirovecii is a fungal pathogen that causes pneumonia in immunocompromized hosts. Prednisone is frequently suggested as a risk factor for developing pneumocystis pneumonia (PCP) in patients with rheumatic diseases. If prednisone use is a risk factor indeed, targeted preventive measures can be taken. The aim of this study was to analyze whether prednisone is a risk factor for developing PCP in patients with rheumatic diseases.

Methods: In this case-control study all cases with a rheumatic disease who developed PCP from 2005 to 2012 in one of two clinics were included. Clinical and laboratory results were compared with controls with rheumatic disease without PCP in the same period, matched for disease duration. At least four controls were included for every PCP patient. Confounders were selected using existing literature, including concomitant medication, comorbidity and laboratory results. Logistic regression was used for analysis.

Results: Thirty-six patients with a variety of rheumatic diseases were diagnosed with PCP in the 8-year study period and 167 controls were matched to these cases. Forty-two percent of the patients with PCP required admission to the intensive care unit (ICU), and 28% died in the course of PCP. In the 6 months before PCP onset, 75% of the patients with PCP used prednisone, which was 25% for controls in the corresponding period, with an OR (95%CI) of 20 (5–85) while corrected for confounders (model 3 in the table). Especially also receiving i.v. corticosteroids (25% vs. 0,6% in the PCP group and control group, $p < 0,05$) was a risk for developing PCP, with an OR (95%CI) of 60(2–1627).

Table 1. Logistic regression models

Characteristic	OR (95% CI)	P-value
Model 1		
Use of prednisone	**23,84 (6,98–81,46)**	**0,000**
Model 2		
Use of prednisone	**26,52 (7,32–96,10)**	**0,000**
Age	1,04 (1,01–1,08)	0,024
Sex	1,05 (0,43–2,55)	0,923
Use of methotrexate	2,90 (1,19–7,03)	0,019
Model 3		
Use of prednisone	**20,18 (4,82–84,53)**	**0,000**
Age	1,04 (0,99–1,08)	0,105
Sex	0,55 (0,18–1,68)	0,295
Use of methotrexate	8,67 (2,36–31,86)	0,001
Diabetes mellitus	2,98 (0,60–14,92)	0,184
Pre-existing lung disease	3,52 (1,06–11,76)	0,041
Pneumonia	9,92 (1,78–55,45)	0,009
Leukopenia	13,96 (2,15–90,59)	0,006

OR odds ratio; use of prednisone: during 6 months prior to PCP; 95% CI: 95% confidence interval.

Conclusion: Pneumocystis jirovecii pneumonia remains a challenging infection with often severe consequences. Confirmative arguments for prednisone as a strong independent risk factor for development of PCP were found. Prophylaxis with trimethoprim-sulfamethoxazole might be considered in patients using corticosteroids, and particularly during 2 to 6 months in patients receiving high dose corticosteroids (orally or intravenously).

Disclosure: W. van den Hombergh, None; **A. van Ede**, None; **J. Fransen**, None; **F. B. lamers-Karnebeek**, None; **S. Kuipers**, None; **M. Janssen**, None.

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Tuberculosis Infection In Patients With Tumor Necrosis Factor–α Antagonists In South Korea; retrospective Analysis Using By National Health Insurance Review and Assessment Service. Jong Wook Beom[1], Eun-Jung Park[2], Jinseok Kim[2], Se Chang Park[3] and Gi Hyeon Seo[4]. [1]Medicine, Jeju National University Hospital, Jeju, South Korea, [2]Jeju National University Hospital, Jeju, South Korea, [3]Seoul National University, Seoul, South Korea, [4]Health Insurance Review and Assessment Service, Seoul, South Korea.

Background/Purpose: Tumor necrosis factor-α (TNF-α) antagonists bring new hope for treating rheumatoid arthritis (RA) over the past decade. However, the subsequent increased risk of developing tuberculosis (TB) is one of the major drawbacks in patients with TNF-α antagonists.

The aim of this study was to evaluate the overall incidence rate of TB in RA patients treated with TNF-α antagonists and compare of incidence rate according to type and duration of TNF-α antagonists, and history of treatment for latent TB infection (LTBI) in South Korea, TB-endemic area.

Methods: All RA patients treated with TNF-α antagonists registered with the National Health Insurance Review and Assessment Service (HIRA) in South Korea between January 2006 and December 2011 were included and retrospectively analyzed. The incidence of LTBI by screening test and of TB after starting TNF-α antagonists were reviewed.

Results: Total 5,853 RA patients with TNF-α antagonists were observed. Of these, 1133 (19.4 %) patients were treated with LTBI before starting TNF-α antagonists. One hundred-thirty two (2.6 %) patients developed TB during follow-up period, and the incidence rate of TB was 583.7 per 100,000 person years (PY). The incidence rate of TB in patient with infliximab revealed 1408.1 per 100,000 PY which is the highest rate, followed by adalimumab of 1211.4 per 100,000 PY and etanercept of 618.4 per 100,000 PY. Forty-five (1648.8 per 100,000 PY), 24 (1038.2 per 100,000 PY), and 63 (647.5 per 100,000 PY) cases of TB were observed during first 6 months, 7–12 months, and 13 months or more after starting TNF-α antagonists, respectively. Among the patients who developed TB, 13 (9.8 %) patients had completed treatment of LTBI. The incidence rate of TB demonstrated 477.6 per 100,000 PY and 987.7 per 100,000 PY in patients with and without history of treatment of LTBI, respectively.

Conclusion: The risk of TB infection increased in RA patients treated with infliximab, and during first 6 months with TNF-α antagonists. Relatively lower risk of TB infection were observed in patients treated with etanercept, and during 13 months and more after starting TNF-α antagonists compare to the rest of the RA patients. RA patients with TNF-α antagonists need watchful observation for TB infection, even in patients who had completed treatment of LTBI.

Disclosure: J. W. Beom, None; **E. J. Park**, None; **J. Kim**, None; **S. C. Park**, None; **G. H. Seo**, None.

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Do We Really Identify Latent Tuberculosis? Comparison Of The Performance Of Tuberculin Skin Test and Interferon Gamma Release Assay Before Biologics: A Systematic Review and Meta-Analysis. Marie Locci[1], Françoise Barchechath-Flaisler[1], Jean-Louis Leroux[1] and Cécile Gaujoux-Viala[2]. [1]Nîmes University Hospital, Rheumatology Department, Nîmes, France, [2]EA 2415, Montpellier I University, Nîmes University Hospital, Rheumatology Department, Nîmes, France.

Background/Purpose: Current guidelines mandate screening for latent tuberculosis infection prior to commencing anti-tumor necrosis factor therapy. However, many patients are already taking immunosuppressive therapy, which can affect current diagnostic tests. Due to the recent introduction of the interferon-gamma release assays (IGRA), we sought out to assess their ability to detect latent tuberculosis infections in patients before biotherapy and the impact of immunosuppressive therapy on these new tests.

Methods: MEDLINE, EMBASE and COCHRANE were searched (up to April 2013) to identify studies evaluating the performance of interferon-gamma release assays (QuantiFERON QTF, T-SPOT.TB) compared to the performance of Tuberculin Skin Test (TST) in individuals candidates for anti TNF treatment, with inflammatory bowel disease or rheumatic disease.

Results: On 533 studies, 45 studies (n= 9226 patients) were included for analysis. The agreement between IDR/IGRA was poor. Kappas between QTF and TST were calculated in 18 studies, ranging from 0.03 to 0.52: poor in 15 studies (<0.4) and moderate in 3 studies (0.4–0.6). Kappas between T-SPOT and TST were calculated in 7 studies, ranging from 0.13 to 0.40: poor in 6 studies and moderate in 1 study. Moreover, the agreement between the two IGRA was moderate. Kappas ranged from 0.28 to 0.71 in 8 studies: poor in 1 study, moderate in 5 studies and good in only 2 studies.

Immunosuppressive therapy did not significantly influence positive QTF results (pooled OR 0.86, 95% CI 0.56 – 1.33) and positive T-SPOT results (pooled OR 0.74, 95% CI 0.46 – 1.21).

Conclusion: The screening of latent tuberculosis raises concerns, especially due to the lack of agreement between IGRA. The impact of immunosuppressive therapy on IGRA was not significant.

Disclosure: M. Locci, None; **F. Barchechath-Flaisler**, None; **J. L. Leroux**, None; **C. Gaujoux-Viala**, None.

ACR/ARHP Poster Session B

Rheumatoid Arthritis - Human Etiology and Pathogenesis

Monday, October 28, 2013, 8:30 AM–4:00 PM

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Connective Tissue Growth Factor Promotes Angiogenesis Through Increased Notch-1 Signaling in Rheumatoid Arthritis. Kazuhisa Nozawa[1], Maki Fujishiro[2], Ayako Yamaguchi[1], Mikiko Kawasaki[2], Kazuhisa Iwabuchi[2], Mitsuaki Yanagida[2], Keigo Ikeda[3], Shinji Morimoto[4], Yoshinari Takasaki[5] and Iwao Sekigawa[3]. [1]Juntendo University School of Medicine, Tokyo, Japan, [2]Juntendo University Graduate School of Medicine, Chiba, Japan, [3]Juntendo University Urayasu Hospital, Tomioka, Urayasu, Chiba, Japan, [4]Juntendo University Urayasu Hospital, Tokyo, Japan, [5]Division of Rheumatology, Department of Internal Medicine, Juntendo University, Tokyo, Japan.

Background/Purpose: Increased angiogenesis has been associated with various inflammatory disease states including rheumatoid arthritis (RA), and it has been considered as one of main factors for pathogenesis of RA. Angiogenic mediators excessively released by various types of cells within the synovium possibly activate vascular endothelial cells (ECs) in RA subsequently resulting in pannus formation. A series of our previous studies has demonstrated that connective tissue growth factor (CTGF) was massively produced on synovial fibroblasts in RA. In addition, we have also demonstrated that excessive CTGF contributed to aberrant activation of osteoclasts in RA, suggesting that CTGF is an important factor for pathogenesis of RA. To extend our research project regarding CTGF function on RA pathogenesis, this study was conducted to clarify whether CTGF relates to aberrant angiogenesis of RA.

Methods: Various effects of CTGF on angiogenesis were evaluated using human umbilical vein endothelial cells (HUVECs). The efficacy of CTGF on vascularization, proliferation, and migration were evaluated by tube formation assay, BrdU assay, and boyden chamber assay respectively. Regulation of CTGF production by proinflammatory cytokines (IL-6 and TNF-a) on HUVECs was evaluated by quantitative RT-PCR and *immunoblotting.* Notch-1 activation induced by CTGF on HUVECs was evaluated by immunobolttting and IIF.

Results: CTGF had positive effects for vascularization, proliferation, and migration on HUVECs. IL-6 upregulated CTGF expression even though TNF-a oppositely downregulated CTGF expression on HUVECs. Interestingly, we found that CTGF related to not only Notch-1 production but also activation of Notch-1.

Conclusion: Our data indicated that CTGF is massively produced on not only fibroblasts but also vascular endothelial cells in synovial tissue of RA due to aberrant regulation of proinflamatory cytokines. Excessive CTGF production possibly causes aberrant angiogenesis and osteoclasts activation in synovial tissue in RA. In addition, we newly found that CTGF related to production and activation of Notch-1which has been recently postulated as important factor of angiogenesis in RA. The present study clearly demonstrated that CTGF significantly related to angiogenesis through direct or indirect mechanisms, suggesting that CTGF plays an important role for disease progression of RA. CTGF may become a new target molecule for treatment of RA.

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2. Nozawa et al. Inhibition of connective tissue growth factor ameliorates rheumatoid arthritis ina murine model. Arthritis Rheum. 2013 Feb 22. doi: 10.1002/art.37902. [Epub ahead of print]

3. Sekigawa et al. Protein biomarker analysis by mass spectrometry inpatients with rheumatoid arthritis receiving anti-tumor necrosis factor-alpha antibody therapy. *Clin Exp Rheumatol* 2008, 26:261–267.

Disclosure: K. Nozawa, None; **M. Fujishiro**, None; **A. Yamaguchi**, None; **M. Kawasaki**, None; **K. Iwabuchi**, None; **M. Yanagida**, None; **K. Ikeda**, None; **S. Morimoto**, None; **Y. Takasaki**, None; **I. Sekigawa**, None.

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NR1D1 Is a New Suppressor of Rheumatoid Arthritis Fibroblast-Like Synoviocyte Invasion. Teresina Laragione and Percio Gulko. Hosftra North Shore-LIJ School of Medicine, Manhasset, NY.

Background/Purpose: Rheumatoid arthritis (RA) is a common and chronic autoimmune disease. Arthritis severity and joint damage predict clinical outcome and the risk for disability in RA. Yet, little is known about disease severity and joint damage regulatory genes. We have previously identified a new nuclear receptor (NR) expression signature in synovial tissues that correlates with arthritis protection and development of mild and non-erosive disease. NR1D1 (Rev-erba) was the NR with the most significant difference in expression in synovial tissues, with an 8.75-fold increase in the protected rats, suggesting that increased levels and activity of NRs have a suppressive effect on disease severity and joint damage. We hypothesized that NR1D1 mediates arthritis protection at least in part via inhibition of the invasiveness of fibroblast-like synoviocytes (FLS) derived from RA patients and arthritic rats, an *in vitro* phenotype known to correlate with histologic and radiographic joint damage.

Methods: FLS were obtained from DA rats and patients with RA and used after the third passage (>95% FLS purity). Cells were treated with the NR1D1 agonist GSK4112 and studied in an *in vitro* invasion assay through Matrigel over 24 hours. qPCR was used to quantify the expression of MMPs. Confocal and immunofluorescence microscopy were used to characterize cell and actin cytoskeleton morphologic changes.

Results: Treatment of FLS from arthritic DA rats and from RA patients with the NR1D1 agonist GSK4112 reduced their invasiveness by 70% and 60%, respectively ($p<0.002$), compared with vehicle. GSK4112 treatment reduced numbers of thick actin filaments, numbers of elongated cells, and the polarized formation of lamellipodia, all actin cytoskeleton and FLS morphologic changes required for invasion. GSK4112 did not significantly affect the IL-1β-induced expression of MMP-1, MMP-2 and MMP-3 in FLS.

Conclusion: We have identified an association between increased synovial expression of NR1D1 and arthritis protection, and a new role for this gene in the regulation of FLS invasion. NR1D1 interferes actin cytoskeletal changes required for cell motility and invasion and could become a useful target for therapies aimed at preserving joint architecture and function.

Disclosure: T. Laragione, None; **P. Gulko**, None.

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Synergistic Enhancement Of Aggregated IgG-Induced Tumor Necrosis Factor α In Human Synovial Mast Cells By Interleukin 33. Hyunho Lee[1], Jun-ichi Kashiwakura[2], Masahiko Yanagisawa[1], Yuki Okamura[1], Takao Ishii[1], Masayuki Seki[1], Shu Saito[1], Yasuaki Tokuhashi[1], Chisei Ra[1] and Yoshimichi Okayama[1]. [1]Nihon University School of Medicine, Tokyo, Japan, [2]RIKEN Center for Integrateive Medical Sciences, Kanagawa, Japan.

Background/Purpose: Recent studies suggest that human synovial mast cells (MCs) are involved in the pathogenesis of rheumatoid arthritis (RA). Circulating IgG isotype autoantibodies and synovial immune complexes are detected in RA patients. Therefore a plausible pathway for the activation of synovial MCs is through IgG receptors. However, it has not been well known whether IgG receptors are expressed on human synovial MCs. The purpose of this study was to investigate which IgG receptor(s) on synovial MCs are responsible for MC activation in response to immune complexes (IC), and to evaluate the effect of IL-33, which is believed to play an important role in RA, on IC-induced synovial MC activation.

Methods: We obtained synovial tissue specimens from RA patients and osteoarthritis (OA) patients after total knee replacement surgery. Synovial MCs were enzymatically dispersed. Cultured synovium-derived MCs were generated by culturing synovial cells with stem cell factor, and receptor expression was analyzed using fluorescence-activated cell sorting and immunohistochemical techniques. Mediators released from MCs were measured using enzyme immunoassays or enzymelinked immunosorbent assays.

Results: Primary synovial MCs and cultured synovium-derived MCs obtained from both RA patients and OA patients expressed Fcϵ receptor I (FcϵRI), FcγRI, FcγRII and ST2 but not FcγRIII. Cultured synovium-derived MCs induced degranulation and the production of prostaglandin D_2 and tumor necrosis factor α (TNF-α) through FcγRI. The activation through FcγRII caused histamine release from cultured MCs but not from primary MCs. Neutralizing anti-FcγRI monoclonal antibody and anti-FcγRII monoclonal antibody significantly inhibited histamine release induced by aggregated IgG. Aggregated IgG induced TNF-α production ($\sim$330 pg/ml/1×10^6 MCs) from cultured synovium-derived MCs. Although IL-33 did not enhance aggregated IgG-triggered histamine release, IL-33 (30 ng/mL) synergistically enhanced aggregated IgG-induced TNF-α production ($\sim$5.2 fold) in cultured synovium-derived MCs.

Conclusion: With Regard to the FcR expression profile, synovial MCs from RA patients and from OA patients were similar. FcγRI was responsible for producing abundant TNF-α from synovial MCs in response to aggregated IgG. Immune complexes may activate synovial MCs through FcγRI and FcγRII. In addition, IL-33 may exacerbate IC-mediated inflammation associated with RA by abundantly producing TNF-α from synovial MCs.

Disclosure: H. Lee, None; **J. I. Kashiwakura**, None; **M. Yanagisawa**, None; **Y. Okamura**, None; **T. Ishii**, None; **M. Seki**, None; **S. Saito**, None; **Y. Tokuhashi**, None; **C. Ra**, None; **Y. Okayama**, None.

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Low Vitamin D Level Is Not Associated With Increased Incidence Of Rheumatoid Arthritis. Jonida Cote[1], Androniki Bili[1], H. Lester Kirchner[2] and Xiaoqin Tang[3]. [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Health System, Danville, PA, [3]Geisinger Center for Health Research, Danville, PA.

Background/Purpose: Vitamin D is thought to be an immunomodulator able to suppress autoimmunity in rheumatoid arthritis (RA). Some reports describe an association between low vitamin D and RA, but they had significant limitations. The objective of this study was to evaluate the association of vitamin D level with incident RA in a well characterized patient population using electronic health records (EHR).

Methods: Case-control study with data extracted from EHR in a tertiary health system, from 2001 to 2012. RA was defined as ICD-9 code 714.0 twice by a rheumatologist. Only patients with a primary care physician in the system were included. Incident RA patients (cases) were identified at one point in time and followed retrospectively with regard to vitamin D levels prior to the development of RA. Cases were matched for age and gender with 5 controls from the general non-RA population. An index date was created such that for cases it was the date of the RA diagnosis and for the controls it was the date of the RA diagnoses of the matched case. The most recent value of vitamin D to the index date was used in the analysis. Vitamin D levels were treated both as continuous and categorical; we used <30 IU as the primary cutoff, but also used <20 IU to investigate the RA association with severe vitamin D deficiency. This association was presented as the odds ratio (OR) from a conditional logistic regression model adjusting for obesity and smoking status. The study had a power of 82% to detect an OR of 1.5 between cases and controls.

Results: 270 patients with incident RA and 1341 matched controls were included in the analysis with median age 62.4 years, BMI 28.8 kg/m^{2}and vitamin D level 31 IU. There were no significant differences in median BMI and vitamin D levels between cases and controls. Smoking was significantly more prevalent in the cases than the controls. Of the RA patients, 141 (52.2%) were rheumatoid factor (RF) positive, 97 (35.9%) were RF negative, and 32 (11.9%) had unavailable RF status. The OR for the association between RA and vitamin D overall and stratified by gender is shown in Table 1. Subgroup analysis according to RF positivity is shown in Table 2.

Table 1. Association between low vitamin D level and Rheumatoid arthritis according to gender*

	All		Female		Male	
Vitamin D level	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Vitamin D (continuous)	0.996 (0.987, 1.005)	0.3652	0.996 (0.985, 1.006)	0.4014	0.997 (0.976, 1.018)	0.7693
Vitamin D <30 IU vs.≥ 30 IU	0.980 (0.745, 1.288)	0.8825	0.924 (0.682, 1.254)	0.6134	1.233 (0.649, 2.343)	0.5231
Vitamin D <20 IU vs. ≥ 20 IU	1.121 (0.801, 1.570)	0.5048	1.192 (0.825, 1.724)	0.3493	0.860 (0.362, 2.045)	0.7336

* adjusted for smoking, BMI (kg/m^2).

Table 2. Association between low vitamin D and Rheumatoid Arthritis according to Rheumatoid Factor positivity*

	RF-positive vs. controls		RF-negative vs. controls	
Vitamin D level	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Vitamin D (continuous)	0.991 (0.978, 1.005)	0.1945	0.997 (0.981, 1.013)	0.6974
Vitamin D <30 IU vs. ≥30 IU	1.062 (0.723, 1.561)	0.7594	0.810 (0.503, 1.304)	0.3854
Vitamin D <20 IU vs. ≥20 IU	1.244 (0.790, 1.961)	0.3464	0.789 (0.415, 1.502)	0.4710

* adjusted for smoking, BMI (kg/m^2); RF=rheumatoid factor.

Conclusion: Low vitamin D level was not associated with increased odds for incident RA in this patient population. Our study was powered at 80% to detect a minimum of 50% increase in the odds of low vitamin D levels.

Disclosure: J. Cote, None; **A. Bili**, None; **H. L. Kirchner**, None; **X. Tang**, None.

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Decoy Receptor 3 Regulates the Expression of Tryptophan Hydroxylase TPH1 in Rheumatoid Synovial Fibroblasts. Toshihisa Maeda[1], Yasushi Miura[2], Koji Fukuda[1], Shinya Hayashi[1] and Masahiro Kurosaka[1]. [1]Kobe University Graduate School of Medicine, Kobe, Japan, [2]Kobe University, Kobe, Japan.

Background/Purpose: Tryptophan hydroxylase (TPH) which catalyzes the hydroxylation of L-tryptophan is the rate-limiting enzyme involved in the synthesis of serotonin. TPH has two isoforms; TPH1 expresses in peripheral and central nerve system (CNS) tissues expressing serotonin, such as skin, intestine, and pineal gland, while TPH2 expresses exclusively and dominantly in CNS. Recently several studies suggested that serotonergic systems play an important role in modulating inflammatory pain and bone remodeling. We previously reported that decoy receptor 3 (DcR3), a member of TNF receptor superfamily, overexpressed in rheumatoid synovial fibroblasts (RA-FLS) stimulated with TNFα inhibits Fas-induced apoptosis. We recently reported that DcR3 induced VLA-4 expression in THP-1 macrophages to inhibit cycloheximide-induced apoptosis, and that DcR3 inhibited cell proliferation induced by TNFα or IL-1β via TL1A expressed on RA-FLS. We also reported that the concentration of DcR3 in sera and joint fluids of patients with RA was significantly higher than those with osteoarthritis (OA).

Further, by using comprehensive genetic analysis using microarrays, we newly identified TPH1 as one of the genes of which expression in RA-FLS was suppressed by DcR3.

Therefore, in this study, we investigated the expression of TPH1 in RA and OA-FLS stimulated with DcR3 and inflammatory cytokines to elucidate the involvement of TPH1 and DcR3 in the pathogenesis of RA.

Methods: *Real-time polymerase chain reaction (real-time PCR).* Primary cultured RA or OA-FLS were incubated with 1.0 μg/ml recombinant human DcR3-Fc protein or 1.0 μg/ml control IgG1 for 12 hours, or 1.0 ng/ml recombinant human TNFα or 1.0 ng/ml IL-1β for 24 hours, then the relative expression levels of TPH1 mRNA were quantified by real-time PCR.

Immunohistochemistry. Serotonin expressed in rheumatoid synovial tissues was detected by immunohistochemistry.

Results: TPH1 mRNA was expressed in both RA and OA-FLS. TPH1 mRNA expression was decreased significantly by DcR3 in RA-FLS, but not in OA-FLS. Meanwhile, TPH1 mRNA expression was significantly decreased by TNFα or IL-1β both in RA and OA-FLS. Immunohistochemistry confirmed that serotonin was present in multi-layered synovial lining cells.

Conclusion: In this study, we first revealed that TPH1 in RA-FLS was suppressed by DcR3 in a disease-specific fashion. Therefore, TPH1 in RA-FLS regulated by DcR3 may affect serotonin expression to be involved in the pathogenesis of RA, such as modulating inflammatory pain and bone remodeling. Both DcR3 and TPH1 could be a possible therapeutic target of RA.

Disclosure: T. Maeda, None; **Y. Miura**, None; **K. Fukuda**, None; **S. Hayashi**, None; **M. Kurosaka**, None.

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Associations Of Periodontitis (PD) With Established Seropositive Rheumatoid Arthritis are Independent of Smoking and Other Risk Factors. Ted R. Mikuls[1], Jeffrey Payne[2], Fang Yu[3], Geoffrey M. Thiele[3], Richard J. Reynolds[4], Grant W. Cannon[5], Jeffrey Markt[6], David McGowan[7], Gail S. Kerr[8], Robert Redman[9], Andreas M. Reimold[10], Garth Griffiths[10], Mark Beatty[2], Shawneen Gonzalez[2], Debra Bergman[6], Bartlett C. Hamilton III[11], Alan R. Erickson[12] and James R. O'Dell[6]. [1]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [2]University of Nebraska Medical Center, Lincoln, NE, [3]Univ of Nebraska Med Ctr, Omaha, NE, [4]University of Alabama at Birmingham, Birmingham, AL, [5]Salt Lake City VA and University of Utah, Salt Lake City, UT, [6]University of Nebraska Medical Center, Omaha, NE, [7]George E. Wahlen VA Medical Center, Salt Lake City, UT, [8]Washington DC VAMC, Georgetown and Howard University, Washington, DC, [9]Washington DC VA, Georgetown and Howard University, Washington, DC, [10]Dallas VA and University of Texas Southwestern, Dallas, TX, [11]University of Nebraska Medical Center and Omaha VA Medical Center, Omaha, NE, [12]Omaha VA and University of Nebraska Medical Center, LaVista, NE.

Background/Purpose: Periodontitis (PD) has been proposed as a risk factor in RA. Reports have suggested that this association may be due to confounding from smoking, sicca syndrome, impaired oral hygiene, and HLA-DRB1 alleles (increased in rare forms of PD). Recent speculation has focused on the role of P. gingivalis (Pg), an oral pathogen with the unique capacity of citrullinating protein. We sought to examine the degree to which shared risk factors might explain or confound the relationship of PD with established RA.

Methods: RA cases (N=287) and osteoarthritis controls (N=330) underwent a standardized exam with PD defined using the criteria of Machtei et al (J Periodontol, 1990). The percentage of sites with supragingival plaque served as a measure of oral hygiene. HLA-DRB1 SE containing alleles were imputed using SNPs from the extended MHC. Anti-Pg antibody to outer membrane antigen (OMA) was measured using ELISA. Subgingival plaque was assessed for the presence of Pg using PCR. Anti-cyclic citrullinated protein (aCCP) antibody and RF were measured by ELISA and nephelometry, respectively. Associations of PD with RA (and aCCP positive RA) were examined using multivariable regression.

Results: Cases and controls were similar in all demographics assessed. PD was more common in RA (35%, p = 0.022) and aCCP positive RA (n=240; 37%; p = 0.006) vs. controls (26%). There were no RA-control differences in anti-Pg or the frequency of Pg positivity by PCR. Anti-Pg antibody showed weak but statistically significant associations with both aCCP (r=0.14, p=0.022) and RF (r=0.19, p=0.001). PD was associated with increased RA disease severity based on swollen joint count (p=0.004), DAS-28-CRP (p=0.045), total Sharp score (p=0.015), aCCP (p=0.011), and RF (p<0.001) levels. Associations of PD with established aCCP positive RA were independent of all covariates examined (with similar, albeit non-significant ORs observed in never smokers). In models not shown, associations were also independent of anti-Pg and Pg PCR status.

Table. Multivariable associations of PD with RA (Odds Ratios and 95% CIs)

	Full Cohort		Analysis Limited to Never Smokers	
	All RA	**aCCP pos. RA**	**All RA**	**aCCP pos. RA**
Periodontitis	1.36 (0.89, 20.6) P = 0.153	1.59 (1.01, 2.49) P = 0.043	1.37 (0.65, 29.1) P = 0.409	1.87 (0.82, 4.25) P = 0.157
HLA-DRB1 SE pos.	3.95 (2.68, 5.83) P < 0.001	5.32 (3.44, 8.22) P < 0.001	4.71 (2.55, 8.71) P < 0.001	7.01 (3.43, 14.32) P < 0.001
Ever smoking	1.93 (1.31, 2.83) P = 0.001	1.97 (1.29, 2.99) P = 0.002	—	—

*Full models not shown; covariates included age, gender, race, BMI, diabetes, marital status, oral dryness, oral hygiene, and education; MVmodels limited to participants reporting either Caucasian or African American race/ethnicity.

Conclusion: The relationship of PD with established aCCP positive RA does not appear to be driven by the prevalence of shared risk factors such as smoking or HLA-DRB1 SE nor does this relationship appear to be dependent on evidence of Pg infection. Defining the precise role that Pg plays in early disease evolution and mechanisms linking PD with more severe RA remain important knowledge gaps for future research.

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Differential Effects Of TNF Inhibitors, Anti-IL-6 Receptor Antibody and CTLA4-Ig On Human Monocytes. Toshihiro Tono[1], Yoshiyuki Arinuma[2], Tatsuo Nagai[2], Sumiaki Tanaka[2] and Shunsei Hirohata[2]. [1]Kitasato University school of medicine, sagamihara, Japan, [2]Kitasato University School of Medicine, Sagamihara, Japan.

Background/Purpose: Biological agents inhibiting proinflammatory cytokines, especially IL-6 and TNFa, have brought a great impact in the treatment of rheumatoid arthritis (RA). In addition, CTLA4-Ig has been shown to have beneficial effects in the treatment of RA. Although several studies have disclosed the in vitro effects of biological agents on the immune competent cells, the precise mechanisms of action in RA remain unclear. On the other hand, abnormalities in monocytes have been shown to play an important role in the pathogenesis of RA. The current study was undertaken to explore the effects of etanercept, infliximab, tocilizumab and abatacept on human monocytes.

Methods: Monocytes, which were highly purified from peripheral blood from healthy donors using magnetic beads, were cultured in the presence of staphylococcal enterotoxin B (SEB) with pharmacologically attainable concentrations of various biological agents, control IgG (control for etanercept, infliximab, tocilizumab) or IgG Fc (control for abatacept). The induction of apoptosis of monocytes was evaluated by staining with annexin V and propidium iodide, followed by analysis on flow cytometry. The expression of CD80, CD86 and HLA-DR were also measured on flow cytometry. The concentrations of IL-6 and TNFα in the culture supernatants were measured using ELISA.

Results: All of etanercept, infliximab, abatacept and tocilizumab promoted apoptosis of SEB-stimulated monocytes. The induction of apoptosis of monocytes by these biological agents were reversed by addition of normal human IgG, but not by IgG F(ab)'$_2$ fragments (Figure). Of note, etanercept as well as infliximab significantly suppressed the expression of CD80, CD86 and HLA-DR on SEB-stimulated monocytes. By contrast, tocilizumab and abatacept suppressed only the expression of CD80, but neither CD86 nor HLA-DR. Finally, etanercept, infliximab, abatacept but not tocilizumab, suppressed the production of IL-6 and TNFα of SEB-stimulated monocytes.

Conclusion: These results demonstrate that all the biological agents, including TNF inhibitors, anti-IL-6 receptor antibody and CTLA4-Ig, have direct action on human monocytes, leading to the induction of apoptosis thereof, which involves interaction with Fc receptor on monocytes. Moreover, the data also indicate that these biological compounds display differential influences on various functions of monocytes, including the expression of costimulation molecules, HLA-DR and proinflammatory cytokines, depending on their interactions with different molecules on monocytes.

Disclosure: T. Tono, None; **Y. Arinuma**, None; **T. Nagai**, None; **S. Tanaka**, None; **S. Hirohata**, None.

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Histone Modifications In The Interluekin-6 Gene Promoter Region Of Rheumatoid Arthritis Synovial Fibroblasts. Takuma Tsuzuki Wada[1], Yasuto Araki[2], Kazuhiro Yokota[1], Fumihiko Miyoshi[1], Kojiro Sato[1] and Toshihide Mimura[2]. [1]Saitama Medical University, Saitama, Japan, [2]Research Center for Genomic Medicine, Saitama Medical University, Saitama, Japan.

Background/Purpose: Rheumatoid arthritis (RA) is a disease of unknown origin, which develops continuous inflammation and progressive joint destruction resulting from an autoimmune response mainly occurred in the joints. Although genetic factors in RA have been reported, another factors might be important for RA because of low concordance rate of monozygotic twins. Additionally, it is well known that environmental factors, for example smoking and infections, are involved in the pathogenesis of RA. Recently, epigenetic abnormalities in acquired chronic disorders including RA have been reported. DNA methylations, microRNAs, and histone modifications are major epigenetic abnormalities. DNA methylations and microRNAs in RA have been well characterized, however, evidences of histone modifications in RA are limited. Histone modifications are associated with gene transcriptions. In promoter regions of target genes, high-level histone acetylation and histone H3 lysine 4 trimethylation (H3K4me3) exist. One of the major pathological conditions in RA may be overproduction of interleukin (IL)-6 from RA synovial fibroblasts (SFs) stimulated by tumor necrosis factor (TNF)-alpha derived from activated macrophages. The purpose of this study is to clarify the relation of histone modifications in the IL-6 gene promoter region and IL-6 gene transcription in RASFs.

Methods: Synovial fibroblasts from the patients with RA and osteoarthritis (OA) as a control were harvested on the occasion of total knee arthroplasty in our hospital and were used for passages 4 through 8. Histone modifications (histone H3 acetylation (H3ac), H3K4me3) in the IL-6 gene promoter region were compared between RASFs and OASFs by chromatin immunoprecipitation (ChIP) assay. IL-6 mRNA and protein levels after stimulation with 10 ng/ml of TNF-alpha were detected using reverse transcription-polymerase chain reaction and enzyme-linked immunosorbent assay. Furthermore, we investigated how a treatment of histone acetyltransferase inhibitor (HATi) before stimulation with TNF-alpha had an influence on H3ac in the IL-6 gene promoter region and IL-6 mRNA in RASFs.

Results: IL-6 mRNA of RASFs were significantly increased compared with OASFs. In ChIP assay, both H3ac and H3K4me3 in the IL-6 gene promoter region of RASFs were significantly higher than those of OASFs. IL-6 mRNA and protein levels of RASFs were significantly increased more than those of OASFs after stimulation with TNF-alpha. Taken together, it is suggested that high levels of H3ac and H3K4me3 in the IL-6 gene promoter region of RASFs lead to be accessible for transcription factors to bind the region. In order to obtain more confirmed evidence of H3ac in the IL-6 gene promoter region in RASFs, we examined H3ac in the IL-6 gene promoter region and IL-6 mRNA of RASFs treated by HATi, curcumin. Both H3ac in the IL-6 promoter region and IL-6 mRNA of RASFs treated by curcumin were significantly reduced compared with those of untreated RASFs.

Conclusion: Histone modifications, especially high levels of H3ac and H3K4me3 in the IL-6 gene promoter region of RASFs, could be involved in a part of the pathogenesis in RA.

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The *ZC3HC1* rs11556924 Polymorphism Is Associated With Increased Carotid Intima-Media Thickness In Patients With Rheumatoid Arthritis. Raquel lopez Mejias[1], Fernanda Genre[2], Mercedes García-Bermúdez[3], Alfonso Corrales[4], Carlos González-Juanatey[5], J. Llorca[6], Encarnación Amigo[7], Jose A. Miranda-Filloy[8], Javier Rueda-Gotor[1], Ricardo Blanco[1], Santos Castañeda[9], Javier Martin[10] and Miguel A. Gonzalez-Gay[2]. [1]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IFIMAV, Santander, Spain., Santander, Spain, [2]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IFIMAV, Santander, Spain, [3]Instituto de Parasitologia y Biomedicina López-Neyra, IPBLN-CSIC, Granada, Spain, [4]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain, [5]Cardiology Division, Hospital Lucus Augusti, Lugo, Spain, [6]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), Santander, Spain, [7]Division of Rheumatology, Hospital Lucus Augusti, Lugo, Spain, [8]Hospital Xeral-Calde, Lugo, Spain, [9]Hospital Universitario de La Princesa, IIS Princesa, Madrid, Spain, [10]Instituto de Parasitologia y Biomedicina Lopez-Neyra (IPBLN-CSIC), Granada, Spain.

Background/Purpose: Rheumatoid arthritis (RA) is a complex polygenic disease associated with chronic inflammation, accelerated atherosclerosis and increased cardiovascular (CV) mortality. A recent meta-analysis has described the *ZC3HC1* rs11556924 polymorphism as one of the most important signals associated with coronary artery disease (CAD) in non-rheumatic Caucasian individuals. In the present study we evaluated the potential association of this gene polymorphism with subclinical atherosclerosis assessed by the evaluation of carotid intima-media thickness (cIMT) in RA patients.

Methods: For this purpose 502 RA patients from Northern Spain were recruited in this study. The *ZC3HC1* rs11556924 polymorphism was genotyped with TaqMan single-nucleotide polymorphism (SNP) genotyping assays (C__31283062_10) in a 7900 HT real-time polymerase chain reaction (PCR) system. cIMT was also assessed in these patients by carotid ultrasonography (US) technology.

Results: RA patients carrying the TT genotype had significantly higher cIMT values than those homozygous for the CC genotype (mean $\pm$ standard deviation (SD): 0.76 $\pm$ 0.18 mm and mean $\pm$ SD: 0.71 $\pm$ 0.16 mm respectively; p=0.02). Moreover, RA patients carrying the mutant allele T exhibited significantly higher cIMT values than those carrying the wild allele C (mean $\pm$ SD: 0.74 $\pm$ 0.17 mm and mean $\pm$ SD: 0.71 $\pm$ 0.17 mm

respectively; p=0.02) even after adjusting the results for sex, age at the time of US study, follow-up time and traditional CV risk factors (p=0.019) evidencing that the effect conferred by *ZC3HC1* rs11556924 polymorphism is independent of the traditional CV risk factors.

Conclusion: Our results indicate that *ZC3HC1* rs11556924 polymorphism is associated with subclinical atherosclerosis in RA.

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The 11q23.3 Genomic Region - rs964184- Is Associated With Cardiovascular Disease In Patients With Rheumatoid Arthritis. Raquel lopez Mejias[1], Fernanda Genre[2], Mercedes García-Bermúdez[3], Santos Castañeda[4], Carlos González-Juanatey[5], J. Llorca[6], Encarnación Amigo[7], Alfonso Corrales[8], Jose A. Miranda-Filloy[9], Javier Rueda-Gotor[1], Carmen Gomez vaquero[10], Luis Rodriguez Rodriguez[11], Benjamin Fernandez Gutierrez[11], Alejandro Balsa[12], Dora Pascual-Salcedo[12], Francisco Javier López-Longo[13], Patricia Carreira[14], Ricardo Blanco[1], Isidoro González-Alvaro[4], Javier Martin[15] and Miguel A. Gonzalez-Gay[2]. [1]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IFIMAV, Santander, Spain., Santander, Spain, [2]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IFIMAV, Santander, Spain, [3]Instituto de Parasitologia y Biomedicina López-Neyra, IPBLN-CSIC, Granada, Spain, [4]Hospital Universitario de La Princesa, IIS Princesa, Madrid, Spain, [5]Cardiology Division, Hospital Lucus Augusti, Lugo, Spain, [6]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), Santander, Spain, [7]Division of Rheumatology, Hospital Lucus Augusti, Lugo, Spain, [8]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain, [9]Hospital Xeral-Calde, Lugo, Spain, [10]Department of Rheumatology, Hospital Universitario Bellvitge, Barcelona, Spain, [11]Department of Rheumatology, Hospital Clínico San Carlos, Madrid, Spain, [12]La Paz University Hospital, Rheumatology, Madrid, Spain, [13]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [14]Hospital Universitario 12 de Octubre, Madrid, Spain, [15]Instituto de Parasitologia y Biomedicina Lopez-Neyra (IPBLN-CSIC), Granada, Spain.

Background/Purpose: Rheumatoid arthritis (RA) is a complex polygenic inflammatory disease associated with accelerated atherosclerosis and high risk of cardiovascular (CV) disease. A recent meta-analysis has described the rs964184 polymorphism as one of the most important signals associated with coronary artery disease, increased LDL-cholesterol and decreased HDL-cholesterol levels in non-rheumatic Caucasian individuals. In the present study we assessed the potential association of this gene polymorphism with CV disease in RA.

Methods: 2160 Spanish patients with RA were genotyped for the rs964184 polymorphism. Three hundred and eighty-four (17.7%) of them had experienced CV events. The rs964184 polymorphism was genotyped with TaqMan single-nucleotide polymorphism (SNP) genotyping assays (C___8907629_10) in a 7900 HT real-time polymerase chain reaction (PCR) system.

Results: Sex (men), age at RA diagnosis and most traditional CV risk factors (diabetes mellitus, dyslipidemia and smoking habit) were associated with increased risk of CV events ($p<0.05$ in all the cases). Interestingly, when RA patients were stratified according to the presence or absence of CV disease after adjusting for sex, age at RA diagnosis, and traditional CV risk factors, we observed that RA patients carrying the rs964184 GG genotype had significantly higher risk of CV events than those with CC genotype (HR = 2.91, 95% CI: 1.36 – 6.26, p = 0.006).

Conclusion: Our results indicate that rs964184 polymorphism is associated with CV disease in RA.

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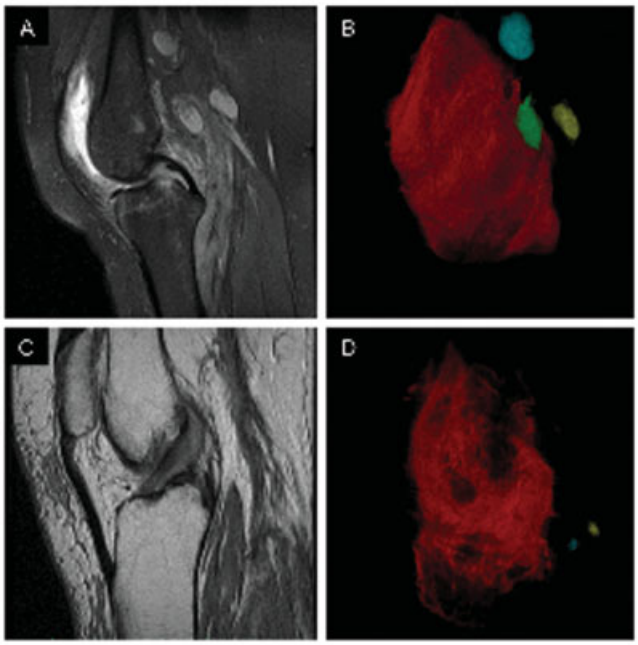
Validation Of Popliteal Lymph Node Phenotype and Bin Expansion As Biomarkers Of Rheumatoid Arthritis Knee Flare. Homaira Rahimi[1], Ronald Wood[2], Igor Kuzin[1], Wakenda Tyler[1], Gregory Dieudonne[1], Stephen Kates[2], Christopher T. Ritchlin[1] and Edward M. Schwarz[1]. [1]University of Rochester, Rochester, NY, [2]University of Rochester Medical Center, Rochester, NY.

Background/Purpose: Factors precipitating joint flare in rheumatoid arthritis (RA) patients are poorly understood. Contrast enhanced (CE) MRI studies in murine models have identified popliteal lymph node (PLN) phenotypes that correlate with arthritic flare in the adjacent knee defined by a sudden increase in synovial volume and focal erosions. Prior to flare, the PLN expands in size and CE due to increased lymph volume and accumulation of $CD23^{+}CD21^{hi}CD1d^{hi}$ B cells (Bin). Arthritic flare following PLN collapse is characterized by decreased CE and translocation of Bin to the paracortical sinuses with loss of efferent lymphatic drainage. To validate lymphatic biomarkers in RA, we performed pilot studies to demonstrate the feasibility of detecting expanding and collapsed PLN via CE-MRI. We analyzed PLN from RA patients undergoing total knee replacement or amputation for ischemic limbs in patients without RA.

Methods: RA patients experiencing knee flare had a 3T CE-MRI prior to initiation of biologic therapy. PLN and synovial volumes were measured with Amira. PLN from RA patients and amputees were harvested, cells were stained and examined by flow cytometry.

Results: MRI and 3D volume rendering of a representative flaring knee from early vs. long-standing RA (Fig. 1) show evidence of expanding PLN (n=3; 3.57, 1.23, 2.2 cm^3) adjacent to highly vascular synovitis (203.40 cm^3). In contrast, knee flare in long-standing RA (>30yrs) presents with collapsed PLN (n=2; 0.24, 0.16 cm^3) adjacent to pannus (159.88 cm^3) that contains both bright (vascular) and dark (necrotic) regions on MRI. Flow cytometry confirmed large numbers of Bin-like cells ($CD23^{hi}CD21^{hi}$) in RA vs. non-RA PLN. Clinical endpoints measured by disease activity score (25% improvement) and C-reactive protein levels (40% decrease) preliminarily show a correlation between effective therapy and CE-MRI changes.



Conclusion: We present evidence that similar to murine inflammatory arthritis, knee flare in RA is modulated by altered dynamics of draining lymph nodes and lymphatic vessels. We found that the flare in early arthritis is characterized by extensive joint inflammation that appears to exceed the capacity of expanded lymphatics. In contrast, knee flare in long-standing arthritis is associated with loss of lymphatic drainage, which in mice, is caused by loss of the lymphatic pulse and clogging of efferent lymphatics by Bin cells. Additional studies are warranted to demonstrate the reliability of these findings of knee flare in early vs. chronic RA. Figure 1. Representative images of MRI and corresponding 3D rendering from RA patients with knee flare shows inflamed synovium with bright PLN in the T2 fat-suppressed MRI

(A) and uniform inflammatory tissue and large PLN (B) in early RA. In contrast, note the marked focal erosions in the proton density weighted MRI (C) and patchy synovium with collapsed PLN (D) in long-standing RA.

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Estimation Of The Effect Of Denosumab On Bone Loss From The Results Of The 12-Month Phase II Study In Patients With Rheumatoid Arthritis (RA) On Background Methotrexate (MTX). Yoshiya Tanaka[1], Tsutomu Takeuchi[2], Naoki Ishiguro[3], Hisashi Yamanaka[4], Toshiyuki Yoneda[5], Harry K. Genant[6] and Désiréé van der Heijde[7]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Keio University, Tokyo, Japan, [3]Nagoya Univeristy Graduate School of Medicine, Nagoya, Japan, [4]Tokyo Women's Medical University, Tokyo, Japan, [5]Indiana University School of Medicine, Indianapolis, IN, [6]University of California, San Francisco, CCBR-Synarc, Newark, Tiburon, CA, [7]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: RANKL is an essential factor for osteoclast differentiation and activation. Denosumab, a fully human monoclonal IgG_2 antibody, is a potent inhibitor of RANKL and osteoclastgenesis. In this study, the pathological effect of denosumab was investigated with efficacy on bone turnover and structural damage in Japanese patients with RA receiving MTX.

Methods: The 12-month, multicenter, randomized, double-blind, placebo-controlled, phase II study included 4 treatment groups; denosumab 60 mg every 6 mos (Q6M), 3 mos (Q3M), or 2 mos (Q2M) or placebo. Daily supplements of vitamin D (≥400 IU) and calcium (≥600 mg) were taken concomitantly in all groups. Bone mineral density (BMD) of the lumbar spine (L1 to L4) and total hip (including the femoral neck) were measured by dual energy X-ray absorptiometry at 0, 6 and 12 mos. Serum CTX-I and P1NP, and urinary CTX-II were collected at 0, 1, 2, 3, 4, 6 and 12 mos. Bisphosphonates treatment was prohibited throughout the study.

Results: Of the 350 pts enrolled, 346 pts received treatment and 35 pts were discontinued; placebo n=6; Q6M, n=8; Q3M, n=13; and Q2M, n=8. Demographic and clinical characteristics were comparable between groups (Table 1).

Table 1. Demographic and clinical characteristics of enrolled pts

		Denosumab 60mg			
	Placebo (N = 88)	Q6M (N = 85)	Q3M (N = 82)	Q2M (N = 85)	All (N = 340)
Female, n (%)	76 (86.4)	65 (76.5)	59 (72.0)	66 (77.6)	266 (78.2)
Age, mean (SD), years	57.0 (10.6)	54.4 (10.6)	52.0 (11.7)	54.6 (10.5)	54.5 (10.9)
Disease duration, mean (SD), years	2.3 (1.3)	2.2 (1.3)	2.3 (1.3)	2.3 (1.4)	2.3 (1.3)
Osteoporosis, n (%)	23 (26.1)	12 (14.1)	10 (12.2)	12 (14.1)	57 (16.8)
Glucocorticoid use, n (%)	37 (42.0)	36 (42.4)	37 (45.1)	37 (43.5)	147 (43.2)

Significant increases of BMD in lumbar spine and total hip at month 12 were demonstrated in the RA pts treated with denosumab, including the pts with concomitant glucocorticoid use (Table 2).

Table 2. Difference between denosumab and placebo in percent change from baseline in lumbar spine (L1–L4) and total hip BMD at month 12

	Denosumab 60mg		
Percent change difference from placebo	Q6M (N = 78)	Q3M (N = 72)	Q2M (N = 79)
Lumbar spine (L1–L4)			
Least squares means (SE)[a]	4.62 (0.47)	5.35 (0.48)	6.30 (0.47)
95% confidence interval[a]	3.70, 5.53	4.41, 6.29	5.38, 7.23
P-value[a]	<0.0001	<0.0001	<0.0001
Total hip			
Least squares means (SE)[a]	3.32 (0.38)	3.28 (0.38)	3.51 (0.38)
95% confidence interval[a]	2.58, 4.06	2.53, 4.04	2.77, 4.26
P-value[a]	<0.0001	<0.0001	<0.0001

a: Based on repeated measures model adjusting for treatment, visit, baseline BMD, randomized strata (4 strata from the combination of baseline glucocorticoid use and baseline rheumatoid factor) and treatment-by-visit interaction.

Markers of bone resorption and bone formation, CTX-I and P1NP, respectively, were decreased by denosumab treatment. These results correspond with significant increases in BMD and suppression of progression of RA in patients treated with denosumab for 12 mos. Denosumab treatment rapidly reduced CTX-II with sustained levels in a dose dependent manner (Figure 1).

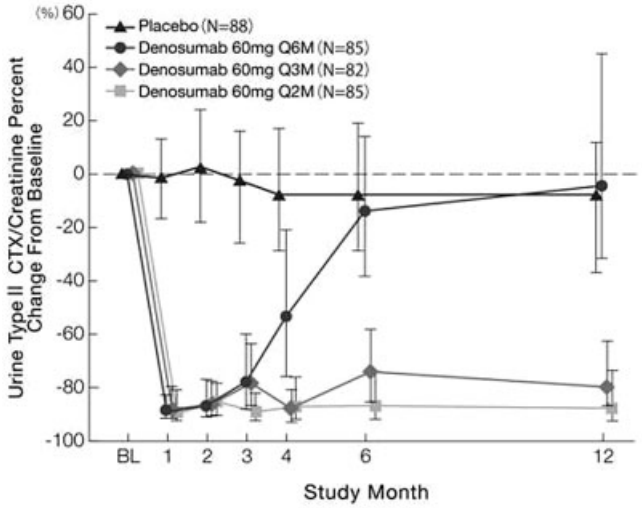

Figure 1. Percent change from baseline for CTX-II/creatinine

Conclusion: Significant increases in BMD were observed after 12-mo denosumab treatment in comparison to placebo in patients with RA regardless of glucocorticoid use. Denosumab inhibits the activation and survival of osteoclasts, which leads to the reduced bone turnover and reduction of bone resorption. Furthermore, suppression was evident in marker of cartilage metabolism, CTX-II, suggesting an effect of denosumab on cartilage turnover.

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A Study Of Natural Killer Cell Subfractions In Abatacept Therapy For Rheumatoid Arthritis. Masao Sato[1], Masao Takemura[1], Ryuki Shinohe[1], Yasuko Yamamoto[2] and Kuniaki Saito[2]. [1]Gifu University, Gifu, Japan, [2]Kyoto University, Kyoto, Japan.

Background/Purpose: Inflammatory cytokines and cell-mediated immunity function of mainly lymphocytes are complicatedly involved in disease onset of rheumatoid arthritis (RA). Recently, together with biologicals such as tumor necrosis factor-alpha (TNF-α) inhibitor and interleukin-6 (IL-6) inhibitor, which block the signal transduction into cells via cytokine, T-cell costimulatory modulator (Abatacept, ABT), which uses mechanism of cytotoxic T-Lymphocyte Antigen 4 (CTLA4) as cell auxiliary signal molecule that frequently develops on the membrane with activated T lymphocytes, has been used to treat RA. In this study, we examined the impact of treatment with ABT on a subfraction of natural killer (NK) cells (CD57) in peripheral blood.

Methods: The subjects were 32 RA patients treated with ABT (6 men and 26 women; aged 39 to 81 years, mean 62). The duration of disease was 10.0 ± 7.9 years (1 to 30 years). Eight, 14, and 10 patients had stage II, III, and IV RA, respectively. Of these, 16 biological-naïve patients and 16 patients who had received other biologicals were included. Blood samples were collected before each administration at 0 week (before treatment), and at 4, 12, 24, and 52 weeks. The changes in CD8+/CD57, CD8+/CD11b+, and CD4+/CD25+, which were demonstrated by double-staining with fluorescein isothiocyanate and phycoerythrin, were assessed by flow cytometry.

Results: Lymphocyte subset (%) according to the stage at the induction of ABT was as follows (mean ± SE). For CD8+/CD11b+, 13.2 ± 1.8, 15.7 ± 2.2, and 22.0 ± 3.1 in patients with stage II, III, and IV, respectively. For CD8+/CD57+, 12.9 ± 1.9, 18.0 ± 3.1, and 19.5 ± 3.9 in patients with stage II, III, and IV, respectively; higher values were observed in patients with advanced stage, although there was no statistically significant difference among the stages. For CD8+/CD57+, 26.9 ± 2.9, 25.4 ± 2.5, and 26.3 ± 3.1 in the patients with stage II, III, and IV, respectively; there was no substantial difference among the stages. The change between the value before treatment with ABT and that at the 52nd week was as follows: for CD8+/CD11b+, 16.7 ± 1.6 and 12.1 ± 1.1, $p < 0.02$; for CD8+/CD57+, 16.9 ± 1.9 and 10.2 ± 1.1, $p < 0.004$; both values were significantly decreased after 52 weeks. For CD4+/CD25+, 26.4 ± 1.6 and 28.1 ± 1.6; although the value increased at 52 week, there was no significant difference. However, CD4+/CD25+high cells were decreased gradually until the 52nd week in the biological-naïve patients, but were increased from the 12th week after administration in patients receiving ABT switched from other biologicals.

Conclusion: In this study, CD8+/CD57 and CD8+/CD11b+ before treatment tended to be higher as the stage of RA advanced. This tendency was maintained after 52 weeks. The values were decreased for 52 weeks in each patient. The proportion of D8+/CD57 and CD8+/CD11b may reflect the therapeutic effect of ABT. It is not known whether the changes in CD4+/CD25+high cells observed in the patients receiving ABT switched from other biologicals indicated cell activation or showed the dynamics of auto-regulatory cells such as regulatory T cells.

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Intracellular Concentration Of Methotrexate Is Influenced By Polymorphisms Of Gamma-Glutamyl Hydrolase Gene In Japanese Patients With Rheumatoid Arthritis. Tatsuhiro Yamamoto, Mai Kawazoe, Emiko Shindo, Natsuki Fujio, Kotaro Shikano, Kanako Kitahara, Sei Muraoka, Makoto Kaburaki, Nahoko Tanaka, Kaichi Kaneko, Natsuko Kusunoki, Yoshie Kusunoki, Kenji Takagi, Tomoko Hasunuma, Hirahito Endo and Shinichi Kawai. School of Medicine, Faculty of Medicine, Toho University, Tokyo, Japan.

Background/Purpose: Methotrexate (MTX) is an anchor drug for treatment of rheumatoid arthritis (RA). Appropriate effective and/or tolerable doses of weekly pulse MTX therapy vary widely among RA patients, especially in different countries. MTX is intracellularly converted to polyglutamate compounds (MTX-PGs) being active forms by several transporters and enzymes. Although genetic polymorphisms of enzymes such as dihydrofolate reductase and methylenetetrahydrofolate reductase have been studied in patients with malignant lymphoma, relationships between the genetic conditions of these enzymes and intracellular MTX-PGs or also clinical responses in RA patients were not cleared yet. We then investigated genetic polymorphisms of solute carrier family 19 member 1 (SLC19A1), a transporter protein of MTX into cells, and gamma-glutamyl hydrolase (GGH), an enzyme that has the capacity to cleave gamma-glutamyl bonds from MTX-PGs.

Methods: Two hundred and seventy-three RA patients (Mean±SD; 58.3±9.8 y.o.) undergoing stable oral doses of weekly pulse MTX (8.9±2.6 mg/week) for at least more than 3 months were inclued in this study. MTX-PGs concentration in red blood cells (RBCs) was measured by TDX analyzer (Abbott, IL) after extraction and purification from RBCs. The polymerase chain reaction-restriction fragment length polymorphism assay was applied to determine the genotypes of *SLC19A1* and *GGH*.

Results: Mean concentration of MTX-PGs in RBCs of 273 patients was 108±12 nmol/L. Mean concentration in the patient group receiving different doses of MTX was increased in a dose-dependent manner, however, individual MTX-PGs concentration was widely distributed among patients. MTX-PGs concentration was then devided by weekly MTX dose to exclude the influence of doses. The adjusted MTX-PGs values revealed a tendency of constant levels among the different dose groups. Results of minor allele frequencies of *SLC19A1* and *GGH* in our Japanese RA patients were shown in the Table. Adjusted MTX-PGs (11.70±6.70 nmol/L/mg) in patients with at least either one of 3 *GGH* variants (−401C>T, −354G>T, or 16T>C) was significantly ($p<0.03$) increased, when compared to that (9.88±6.24 nmol/L/mg) in patients with wild types of these genes. Adjusted MTX-PGs in patients with other *SLC19A1* and/or *GGH* gene variants was not changed from that in patients with wild types of these genes.

Table 1. Minor allele frequencies of *SLC19A1* and *GGH* genes in our Japanese RA patients

SNPs		No. of rs	Minor Allele Frequency
SLC19A1	80G > A	rs1051266	0.698/0.302
GGH	−401C > T	rs3758149	0.799/0.201
	−354G > T	rs719235	0.892/0.108
	16T > C	rs1800909	0.850/0.150
	452C > T	rs11545078	0.952/0.048
	14269G > A	rs12681874	0.638/0.362

Conclusion: GGH may play an important role in regulation of the intracelluler MTX-PGs. Since intracellular MTX-PGs level is known as a surrogate marker of the efficacies and/or adverse responses of MTX, measurement of the *GGH* polymorphisms may predict clinical responses to MTX therapy.

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Reversing Vascular Dysfunction In Rheumatoid Arthritis: Peroxisome Proliferator-Activated Receptor Gamma Agonist Therapy Improves Augmentation Index But Not Endothelial Function. Michelle J. Ormseth, Aihua Bian, Annette M. Oeser, Andrew Cunningham, Ayumi Shintani, S. Bobo Tanner and C. Michael Stein. Vanderbilt Medical Center, Nashville, TN.

Background/Purpose: Rheumatoid arthritis (RA) is associated with insulin resistance and increased cardiovascular (CV) risk. Impaired vascular function, including arterial stiffness and endothelial dysfunction, is associated with insulin resistance and is an important CV risk factor. Pioglitazone, a thiazolidinedione PPAR-γ agonist insulin sensitizing drug, decreased CV risk in diabetes, but little is known about its CV effects in RA. We examined the hypothesis that treatment with pioglitazone would improve vascular function in RA patients.

Methods: We performed a 20-week, single center, randomized, double-blind, placebo-controlled, cross-over study. Patients with RA (n=34) and moderate disease activity on stable disease modifying anti-rheumatic drug therapy were randomized to drug sequence, receiving either pioglitazone 45mg daily or matching placebo for 8 weeks separated by a 4-week washout period and the alternative treatment for 8 weeks. We measured change in augmentation index, aortic pulse wave velocity, reactive hyperemia index, and blood pressure. High sensitivity C-reactive protein (CRP), and the homeostatic model assessment of insulin resistance (HOMA) were also measured. Intention-to-treat analysis and linear mixed-effects models were used to determine the treatment effect of pioglitazone.

Results: Pioglitazone reduced augmentation index by −4.7% units (95% CI, −7.9, −1.5% units) P=0.004 and diastolic blood pressure by −3.0 mmHg (−5.7, −0.2 mmHg) P=0.03, but did not significantly change aortic pulse wave velocity (P=0.33), reactive hyperemia index (P=0.46) or systolic blood pressure (P=0.45). The improvement in augmentation index and diastolic blood pressure were not mediated by pioglitazone's effect on insulin resistance (HOMA) or inflammation (CRP).

Conclusion: Pioglitazone improves some indices of vascular function, including augmentation index and diastolic blood pressure in patients with RA.

Disclosure: M. J. Ormseth, None; **A. Bian**, None; **A. M. Oeser**, None; **A. Cunningham**, None; **A. Shintani**, None; **S. B. Tanner**, None; **C. M. Stein**, NIH, 2.

1388

Multiplex Cytokine Analyses In Patients With Rheumatoid Arthritis Require Use Of Agents Blocking Heterophilic Antibody Activity. Peter Olsson[1], Elke Theander[1], Ulf Bergström[1], Stefan Jovinge[2], Lennart Jacobsson[1] and Carl Turesson[1]. [1]Lund University, Malmö, Sweden, [2]Lund University, Lund, Sweden.

Background/Purpose: Rheumatoid factor (RF) and other circulating heterophilic antibodies have been shown to interfere with antibody-based immunoassays, in particular with multiplex protein detection platforms. Previous studies have suggested that available blocking agents reduce such erroneous signal amplifications. The purpose of the present study was to develop a protocol for multiplex cytokine analyses using standardized blocking procedures in patients with rheumatoid arthritis (RA), and to test this protocol in samples derived from patients with active RA who were started on adalimumab therapy.

Methods: Analyses of cytokines in peripheral blood samples was performed using a custom made 12-plex kit (Bioplex®, Bio-Rad). Samples were obtained from patients with known high levels of serum RF, as well as from healthy controls. Based on the literature (Todd et al. Arthritis Rheum 2011; 63: 894–903), various concentrations of Heteroblock®, an agent that is known to block heterophilic binding activity, were added. In controls, including sera from healthy controls spiked with a cytokine mix (Bio-Rad), the results were stable regardless of the concentration of Heteroblock®. The optimal blocking concentration was determined based on analyses of patients with high levels of RF.

Furthermore, we investigated cytokine levels in 14 patients with active RA [11 females; mean age 63.7 years; median RA duration 9.0 years; 78 % RF positive; mean DAS28: 5.6], who were started on treatment with adalimumab 40 mg subcutaneously every two weeks. In the present pilot study, data on interleukin (IL)-6, IL-7 and IL-8 are reported.

Results: In patients with RA and high RF levels, there was a major effect on the measured signal from adding the blocking agent, with some differences across analytes and across individuals. In analyses using multiple concentrations of Heteroblock®, a higher optimal concentration than previously described was found and used in subsequent investigations.

In the 14 patients treated with adalimumab, the median impact of blocking on the estimated cytokine concentration was 39 % of the unblocked value for IL-6, 13 % for IL-7 and 9 % for IL-8. In analyses of baseline samples from patients in the adalimumab study with no blocking agent added, there was no significant correlation between IL-6 and CRP ($r=0.19$; $p=0.51$). By contrast, in baseline samples exposed to optimal concentration of the blocking agent, there was a significant correlation between IL-6 and CRP ($r=0.65$; $p=0.01$). The decrease in IL-6 from baseline to three months after adalimumab initiation correlated with the decreases in ESR ($r=0.89$; $p=0.02$) and CRP ($r=0.77$; $p=0.07$), with a similar trend for DAS28 ($r=0.32$; NS). IL-7 and IL-8 did not correlate with disease severity parameters.

Conclusion: These results support the concept that agents blocking heterophilic antibody activity should be used and systematically evaluated in immunoassays involving multiplex protein detection platforms. In analyses using optimized concentrations of the blocking agent, IL-6 levels correlated with baseline markers of inflammation, and changes of IL-6 correlated with clinically important measures of reduced inflammation in patients treated with adalimumab.

Disclosure: P. Olsson, None; **E. Theander**, None; **U. Bergström**, None; **S. Jovinge**, None; **L. Jacobsson**, Abbvie, 5; **C. Turesson**, Abbvie, 2, Abbvie, 5.

1389

Serum 14-3-3η Precedes and Independently Predicts The Development Of RA. Dirkjan van Schaardenburg[1], Reetinder Dhaliwal[1], Walter P. Maksymowych[2] and Anthony Marotta[3]. [1]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [2]University of Alberta, Edmonton, AB, [3]Augurex Life Sciences Corp, North Vancouver, BC.

Background/Purpose: We have previously reported on a risk prediction rule for the development of rheumatoid arthritis (RA) in 374 seropositive (RF and/or ACPA) arthralgia patients, incorporating such variables as a first degree relative with RA, alcohol consumption and ACPA status. Serum 14-3-3η is a new marker that complements ACPA/RF in the diagnosis of RA. In this study, we investigated whether 14-3-3η is present in the serum of subjects prior to the onset of RA and whether its expression is useful as a predictor of RA development.

Methods: Serum 14-3-3η protein levels at study entry were measured in 40 seropositive arthralgia subjects, selected on the basis of twenty (20) subjects developing RA within 4 years from study entry, and the other half not. 14-3-3η positivity was defined as >0.19 ng/ml. Twenty-eight (28) of the 40 subjects were ACPA positive, 26 were RF positive, and 16 were positive for both markers. Contingency and logistic regression analyses were performed to determine if 14-3-3η positivity was independently associated with RA development and whether titres of ACPA, 14-3-3η and RF could strengthen its prediction.

Results: Eleven (11) of the 40 subjects were seropositive for the 14-3-3η protein, 9 (82%) of which developed RA, and of the 29 who were 14-3-3η negative, 18 (62%) did not develop RA. Similar to our findings in the larger cohort, ACPA positivity was associated with the development of RA with a Likelihood Ratio (LR) of 17.3, $p < 0.01$ while RF positivity was not. Contingency analysis revealed that 14-3-3η positivity was an independent predictor of RA development delivering an LR of 6.5, $p = 0.01$, an Odds Ratio (OR) of 7.4 $p < 0.01$ (95%CI, 1.3 – 40.6) and a Relative Risk (RR) of 2.2 (95%CI, 1.3 – 3.7). Consistent with previously published findings, median ACPA levels were significantly higher in 14-3-3η positive versus 14-3-3η negative subjects [312 IU/ml (IQR, 155 – 1403) versus 113 IU/ml (IQR, 1 – 735), $p = 0.05$]. RF titres did not differ significantly between these two groups. The predictive value of 14-3-3η positivity was strengthened through the addition of actual 14-3-3η titres yielding an OR of 17.1, $p < 0.009$ (95%CI, 1.9 – 660.2). Since ACPA titres were also significantly different between 14-3-3η positive and negative subjects, adding the actual ACPA titres to the model further strengthened the predictive power of 14-3-3η positivity delivering an OR of 21.5, $p < 0.008$ (95%CI, 2.0 – 981.2).

Conclusion: 14-3-3η expression precedes the onset of RA and its presence is strongly associated with the development of RA. The predictive power of positive 14-3-3η status was further strengthened by the addition of 14-3-3η and ACPA titres to the model. A larger study is underway to investigate 14-3-3η as a diagnostic biomarker to screen seropositive arthralgia patients for the risk of developing RA.

Disclosure: D. van Schaardenburg, Augurex Life Sciences Corp, 2; **R. Dhaliwal**, None; **W. P. Maksymowych**, Augurex Life Sciences Corp, 9; **A. Marotta**, Augurex Life Sciences Corp, 3.

1390

Chaperonin Protein 14-3-3n (eta) In Rheumatoid Arthritis and Arthritogenic Viral Infections. Stanley J. Naides, Olga S Zhukov, Rania W Abolhosn and Joanna M Popov. Quest Diagnostics Nichols Institute, San Juan Capistrano, CA.

Background/Purpose: The 14-3-3 proteins are ubiquitously-expressed intracellular chaperonins. Expression of the η (eta) isoform is restricted to synovial and CNS tissues. Extracellular 14-3-3η induces proinflammatory MAPK and NFkB cascades in THP-1 cells *in vitro*. Extracellular 14-3-3η has been proposed as a novel biomarker for joint damage in rheumatoid arthritis (RA) and psoriatic arthritis, with serum elevation occurring in early RA. 14-3-3η positivity may add diagnostic sensitivity to laboratory RA markers such as rheumatoid factor (RF) and citrullinated cyclic peptide antibody (CCP). However, 14-3-3η expression in arthritogenic viral infection has not been studied. The aim of this study was to determine the frequency of elevated 14-3-3η in patients with RA and in those with HCV, acute EBV, or acute B19 infections.

Methods: We developed a quantitative 14-3-3η sandwich ELISA and verified the reference range using 134 serum specimens from healthy donors (67 males, 67 females; ages 18–65). 14-3-3η was measured in de-identified residual clinical specimens originally submitted for routine RA or infectious disease diagnostic testing.

Results: The 14-3-3η 95th-percentile reference range was defined as <0.2 ng/mL and the reportable range was <0.2 to >20.0 ng/mL. Six healthy subjects (4%) had elevated 14-3-3η levels; 2 of them were weakly RF positive. RF+/CCP+ subjects had the highest frequency of elevated 14-3-3η (56%) and the highest 14-3-3η median level (Table). Frequency of elevated 14-3-3η was lower in the RF+/CCP- and virus-infected groups. None of the RF-/CCP+ subjects had elevated 14-3-3η, but the number of subjects was small (n=10). The frequency of elevated 14-3-3η in the RF-/CCP- group was 5%. Of 23 subjects with elevated 14-3-3η in the HCV group, 1 was RF+/CCP+, 13 RF+/CCP-, and 9 RF-/CCP-. Of 6 subjects with elevated 14-3-3η in the EBV group, 1 was RF+/CCP+, 2 RF+/CCP-, and 3 RF-/CCP+. All 5 subjects with elevated 14-3-3η in the B19 group were RF-/CCP-.

Subject Group	n	Number with Elevated 14-3-3η (%)	Median Abnormal 14-3-3η Value (Interquartile Range) (ng/mL)
Healthy	134	6 (4%)	1.19 (0.66–4.61)
RF+/CCP+	43	24 (56%)	4.37 (0.66–8.24)
RF+/CCP-	131	20 (15%)	0.73 (0.39–1.15)
RF-/CCP+	10	0 (0%)	NA
RF-/CCP-	305	14 (5%)	0.54 (0.33–0.73)
HCV (RIBA)+	162	23 (14%)	0.46 (0.29–1.21)
EBV VCA IgM+	101	17 (17%)	0.44 (0.33–1.54)
B19 IgM+	34	5 (15%)	0.26 (0.20–0.72)

Conclusion: 14-3-3η elevation was most frequent among patients with RF+/CCP+ results (consistent with an RA diagnosis). The data suggest that RA and some HCV, EBV, and parvovirus B19 infections may share pathogenetic mechanisms characterized by synovial release of 14-3-3η. Of note, the median abnormal 14-3-3η level was higher in the RF+/CCP+ group than in the virus-infected groups. This suggest less synovitis in viral arthritis than in RA, consistent with clinical observations.

Disclosure: S. J. Naides, Quest Diagnostics, 3; **O. S. Zhukov**, Quest Diagnostics, 3; **R. W. Abolhosn**, Quest Diagnostics, 3; **J. M. Popov**, Quest Diagnostics, 3.

1391

Transporters As Drug Gateway Into The Cell For Specific Targeting Of Tyrosine Kinase Signaling Pathway In Rheumatoid Arthritis. Saliha Harrach[1], Christian Schmidt-Lauber[1], Bayram Edemir[2], Eberhard Schlatter[1], Thomas Pap[1], Giuliano Ciarimboli[1] and Jessica Bertrand[1]. [1]University Hospital Münster, Münster, Germany, [2]University Hospital Münster, Muenster, Germany.

Background/Purpose: Tyrosine kinase inhibitors (TKI) are effective in treating malignant disorders and were suggested to also have an impact on non-malignant diseases such as rheumatoid arthritis (RA). To exert their effect hydrophilic TKI are actively accumulated in target cells by membrane transporters, a process which is known to govern drug efficiency. This study aims to evaluate the importance of this process for TKI delivery in inflammatory diseases and its pathology induced regulation at the example of the treatment of RA with the SRC kinase inhibitor Saracatinib (AZD0530). Since Saracatinib is an organic cation and fibroblasts are major players in RA-development, we focused on its interaction with transporters for organic cations (OCTs) in human RA synovial fibroblasts (hRASF).

Methods: Saracatinib transport was investigated in OCT-transfected HEK293 cells and hRASF by HPLC detection of Saracatinib accumulation. The anti-proliferative effect of Saracatinib on PDGF stimulated hRASF was quantified by cell counting. Saracatinib transport under disease-relevant conditions like an altered pH milieu, following stimulation with TNF-α and in the presence of specific transporter inhibitors was quantified by HPLC. Gene expression analysis for OCTs with and without TNF-α was performed using quantitative RT-PCR.

Results: Saracatinib demonstrated concentration dependent inhibition of hRASF cell proliferation at sub-micromolar levels. In transfection experiments, hOCTN1 (organic cation transporter, novel, type 1) showed the highest apparent affinity (IC50 = 72 nM) for Saracatinib among the OCTs. Experiments quantifying the Saracatinib uptake in the presence of specific inhibitors identified hOCTN1 as mediator of the uptake in hRASF. This uptake was significantly reduced by an acidic extracellular pH as present in the inflamed joints of patients with rheumatoid arthritis. The stimulation with TNF-α enhanced Saracatinib uptake in hRASF by increasing hOCTN1-mRNA expression.

Conclusion: The uptake of Saracatinib in hRASF via hOCTN1 is regulated by the pH and RA associated pro-inflammatory cytokines. pH alterations and cytokine levels (TNF-α) as present in RA enhance the effective Saracatinib concentration in hRASF. Our results suggest that investigating transporter mediated drug processing is important for developing intracellularly acting drugs used in inflammatory diseases (supported by IMF of the Medical Faculty Münster, BE121009).

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1392

The Expression Of Proto-Oncogene Survivin Splicing Variant 2B In Synovial Tissues and Blood From Patients With Rheumatoid Arthritis. Sho Mokuda[1], Tatsuhiko Miyazaki[2], Junya Masumoto[2], Masamoto Kanno[3] and Kiyoshi Takasugi[4]. [1]Center for Rheumatic Diseases, Dohgo Spa Hospital, Matsuyama, Japan, [2]Ehime University Graduate School of Medicine, Toon, Japan, [3]Graduate School of Biomedical Sciences, Hiroshima University, Hirosima, Japan, [4]Dohgo Spa Hospital, Matsuyama, Japan.

Background/Purpose: It has been reported that serum survivin level was an independent risk factor for predicting joint destruction in early rheumatoid arthritis (RA). The proto-oncogene *BIRC5* generates alternative splicing variants, including wild-type (WT) survivin, survivin 2B, survivin delta-Ex3, survivin 3B and survivin 2-alpha. We herein examined which variants of survivin were expressed in the synovial tissues and blood samples of patients with RA and osteoarthritis (OA).

Methods: We observed the expression of survivin splicing variants in synovial tissues by the real-time PCR and immunohistochemistry (IHC) analyses, and serum survivin 2B was measured with enzyme-linked immunosorbent assay (ELISA). Moreover, to determine the effects of survivin splicing variants in fibroblasts, cell viability and chemosensitivity of an anti-metabolite were evaluated by overexpression experiments in a fibroblast model with the MTS and LDH assays.

Results: We found that three types of splicing variant (WT survivin, survivin 2B and survivin delta-Ex3) were expressed in RA and OA synovial tissues by RT-PCR, and the WT survivin and survivin 2B mRNA expression levels in RA synovial tissues were higher than those in OA patients by real-time PCR (6 RA cases vs. 6 OA cases) ($p=0.010$ and 0.016, respectively). On the other hand, there was no significant difference in the survivin delta-Ex3 expression levels between the RA and OA synovial tissues ($p=0.150$) (Figure 1). In the IHC analyses, survivin delta-Ex3 was expressed in both RA and OA synovial tissues, while survivin 2B was strongly expressed in RA tissues and hardly expressed in OA tissues. In addition, the serum survivin 2B levels of RA patients were higher than those of OA patients and healthy controls (40 RA cases vs. 16 OA + controls cases) (mean 17.9 μg/ml vs. 6.1 μg/ml, $p=0.019$). Furthermore, double staining by IHC revealed that survivin and CD55 merged, so survivin was mainly expressed in synovial fibroblasts. Transfection experiments revealed that survivin delta-Ex3-overexpressing fibroblasts were fast-growing and their sensitivity to anti-metabolites was elevated compared with that of fibroblasts transfected with a vector plasmid. On the other hand, survivin 2B-overexpressing fibroblasts were fast-growing, but their sensitivity to anti-metabolites was not elevated compared with that of fibroblasts transfected with a vector plasmid.

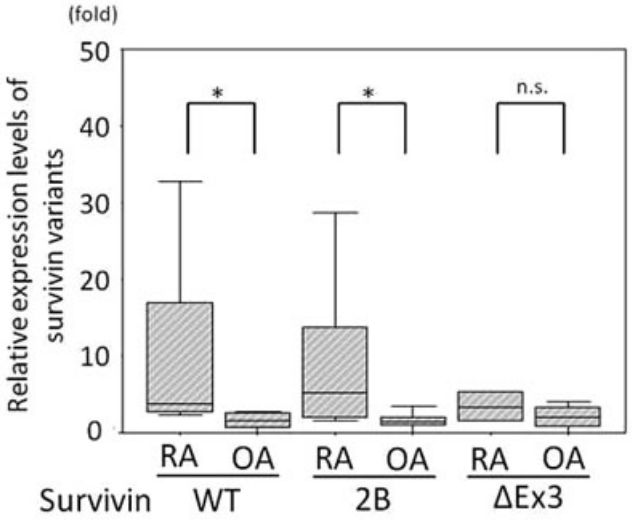

Figure 1. Relative expression levels of survivin splicing variants in synovial tissues from RA and OA. Results were presented relative to expression of the housekeeping gene Hprt. * Mann-whitney U test, $p<0.05$.

Conclusion: The expression of survivin 2B in synovial tissue and serum samples was a specific biomarker of RA. In addition, survivin

2B-expressing fibroblasts were associated with proliferation and resistance to an anti-metabolite. Therefore, survivin 2B is a RA-specific molecule and might contribute to the rheumatoid synovial hyperplasia.

Disclosure: S. Mokuda, None; **T. Miyazaki**, None; **J. Masumoto**, None; **M. Kanno**, None; **K. Takasugi**, None.

1393

Survivin But Not Fms-Like Tyrosine Kinase Ligand Is Up-Regulated Before Onset Of Rheumatoid Arthritis. Mikael Brink[1], Maria Bokarewa[2], Malin Erlandsson[2] and Solbritt Rantapää Dahlqvist[3]. [1]Umeå University, Umea, Sweden, [2]Göteborgs University, Göteborg, Sweden, [3]Umeå University Hospital, Umeå, Sweden.

Background/Purpose: Presence of antibodies against citrullinated peptides (anti-CCP2) and increased levels of cytokines and chemokines precedes the development of rheumatoid arthritis (RA) by several years. Recently, the proteins survivin and Fms-like tyrosine kinase 3 ligand (Flt3L) have been associated with RA and RA associated joint damage. The objective with this study was to investigate the potential of survivin and Flt3L as predictors of RA and their relationships to cytokines and anti-CCP antibodies in blood samples from individuals before onset of symptoms of RA.

Methods: This study includes 47 individuals sampled before onset of symptoms of RA (median 2.5 years (IQR 1.1–5.6) and 155 population controls matched for sex and age, all donors to the Medical Biobank of Northern Sweden. 36 of the pre-symptomatic individuals were also sampled at the time of RA diagnose (ACR criteria 1987). Levels of survivin and Flt3L were measured using sandwich ELISAs (both, R&D Systems, Minneapolis, MN). Anti-CCP antibodies was analyzed using ELISA (Euro-Diagnostica AB, Malmö, Sweden) and 29 cytokines, and chemokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, eotaxin, IL-1Ra, bFGF, G-CSF, GM-CSF, IFNγ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGFBB, TNFα, VEGF, Mig, MIF and IL-2Rα by multiplex detection (Bio-Rad, Hercules, CA). The cut-off levels were for survivin 450 pg/mL, and for Flt3L 130 pg/mL.

Results: The levels of survivin were increased in the pre-symptomatic individuals compared with the controls ($p=0.003$) whilst the levels of Flt3-ligand ($p=0.21$) were similar. The frequency of survivin in the pre-symptomatic individuals was increased compared with controls (36.2 vs. 14.2% $p=0.001$). The odds ratio (OR) for predicting disease development in individuals with survivin levels above cut-off was 3.4 (95%CI 1.6–7.2). The frequencies of survivin and Flt3L were increased in RA patients compared with controls (both, $p<0.0001$. OR12.1 [95%CI, 5.3–27.6] and OR11.0 [3.9–30.9], respectively). Anti-CCP positive pre-diseased individuals and RA-patients had significantly higher concentrations of survivin compared with those being negative. After correction for the number of comparisons, IL-1β, GM-CSF in pre-symptomatic individuals was correlated with survivin and IL-1α, IL-10, eotaxin and TNF-α was correlated with Flt3L, while IL-2, IL-9 and IL12 was correlated with both survivin and Flt3L in the pre-symptomatic individuals.

Conclusion: The proto-oncogene survivin was increased in individuals before onset of symptoms of RA and it was related to cytokines suggesting its role in the events preceding development of the disease.

Disclosure: M. Brink, None; **M. Bokarewa**, None; **M. Erlandsson**, None; **S. Rantapää Dahlqvist**, None.

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Self Reported Dental Symptoms Do Not Predict Periodontal Status In Patients With Rheumatoid Arthritis. Gurpal Buttar, Anastasia Zelekis-Cholakis, Robert Schroth, Hani S. El-Gabalawy, Christine A. Peschken and Carol A. Hitchon. University of Manitoba, Winnipeg, MB.

Background/Purpose: Periodontal disease (PD) and inflammatory arthritis (IA) share features of inflammation and bone loss and are linked in epidemiologic studies. Severe PD may be one environmental trigger for the development of seropositive rheumatoid arthritis. We evaluated the prevalence of periodontal disease in patients with inflammatory arthritis and determined the validity of self-reported dental symptoms and hygiene habits for periodontal disease.

Methods: Sixty one patients with IA (mean age 50.3 ($\pm$11.1) years; rheumatoid arthritis n=47 or undifferentiated arthritis n= 14) answered questions about their periodontal symptoms (bleeding gums, metallic taste, halitosis, xerostomia, loose teeth, pain with food impaction) and dental habits (frequency of brushing, flossing and dental visits), functional status (modified health assessment questionnaire mHAQ), co-morbid medical conditions, and smoking history. All were examined by a periodontist using the periodontal screening and recording index (PSR) a validated screening tool which records the presence of bleeding on probing, calculus, and defective restorative margins at six points per tooth in six segments of the mouth. The highest score in each sextant was recorded. Patients were classified as periodontically healthy, gingivitis, mild, moderate or severe periodontitis based on the PSR. Associations between dental exam findings, arthritis severity and symptoms, arthritis serology (CCP2, RF) and dental symptoms and habits and the validity of the self-reported dental questionnaire were tested. Percentages or means(SD) are reported.

Results: No patients were periodontically healthy; 23 gingivitis, 14 mild periodontitis, 16 moderate periodontitis and 3 severe periodontitis, 5 edentulous. The mean PSR score was 2 (0.5). Patients were seropositive (RF 67%, CCP2 67%) with moderate disease activity (DAS28CRP(3var) 2.69($\pm$1.05) and function (mHAQ 0.4($\pm$0.41) despite 95% taking DMARDs, 49% combination DMARDs and 36% biologics. There was no correlation between the PSR score and disease activity (DAS28CRP(3var), functional status (mHAQ), arthritis duration or age at the time of the dental exam. There were no robust associations between PSR and RF, CCP2, or diabetes, a known risk for PD. Increased total pack years of smoking was moderately associated with worse periodontal health ($p=0.05$). The majority (28/42) rated their overall oral health as very good or good. The sensitivity for self-reported responses of "sometimes" "often" or "always" for moderate or severe PD based on the PSR was greatest for reporting bleeding gums (72%), metallic taste (89%) loose teeth (95%) and pain on food impaction (84%). However, the sensitivity of these questions for moderate or severe PD was poor (32%, 5%, 21% and11% respectively).

Conclusion: Periodontal disease is common in patients with inflammatory arthritis but does not correlate with severity or activity of arthritis. Self-reported dental symptoms have reasonable specificity but poor sensitivity for detecting significant periodontal disease thus a formal periodontal examination should be part of arthritis care. Periodontal disease may play a more important role in the pathogenesis of imminent or very early arthritis.

Disclosure: G. Buttar, None; **A. Zelekis-Cholakis**, None; **R. Schroth**, None; **H. S. El-Gabalawy**, None; **C. A. Peschken**, None; **C. A. Hitchon**, None.

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CXCL13 Is Elevated In Early and In Established Seropositive Rheumatoid Arthritis and Correlates With Rheumatoid Factor Levels. Jonathan D. Jones[1], B. JoNell Hamilton[1], Greg Challener[1], Artur Fernandes[2], Pierre Cossette[2], Patrick Liang[2], Ariel Masetto[2], HA Menard[3], Nathalie Carrier[2], Gilles Boire[2] and William Rigby[1]. [1]Geisel School of Medicine at Dartmouth, Lebanon, NH, [2]Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, [3]McGill University, Montréal, QC.

Background/Purpose: CXCL13 is a B cell chemokine whose expression has been reported to be elevated in serum and synovium from patients with rheumatoid arthritis (RA). Synovial production of CXCL13 has been associated with lymphoid aggregates and germinal center formation. We analyzed the relationship of serum CXCL13 levels to several clinical and serologic parameters, using both established and early RA cohorts.

Methods: Patients with established RA were recruited from the rheumatology clinic at Dartmouth-Hitchcock Medical Center. Serum CXCL13, Rheumatoid Factor (RF) levels, anti-citrullinated peptide antibody (ACPA) and total IgG were measured by ELISA. Seropositivity (positive for RF, ACPA, or both) and highly sensitive C-Reactive Protein (hsCRP) were determined by the clinical lab. HLA-DR status was obtained previously in RA patients from this cohort. A confirmatory analysis was performed using seropositive and seronegative samples from early RA patients from the Canadian Early Undifferentiated PolyArthritis (EUPA) Cohort. Statistical analysis was performed using STATA software, with t-test and linear regression utilized to evaluate relationships between variables.

Results: In the cross-sectional Dartmouth Cohort (n=193), log-transformed CXCL13 levels strongly correlated with seropositivity (Figure 1A, $p=0.0002$). Among the seropositive patients, several interesting patterns emerged. Linear regression of log-transformed CXCL13 plotted against RF levels was highly significant ($p<0.0001$). Tertile analysis demonstrated the strong association of high CXCL13 levels with RF titers (Figure 1B, $p<0.0001$). A weaker relationship was seen between CXCL13 levels and ACPA titers ($p=0.02$). A relationship between CXCL13 and total IgG was also observed ($p=0.0009$), but not with age, gender, shared epitope or hsCRP. Analysis of the Canadian EUPA Cohort (n=339) confirmed the strong

relationship between CXCL13 and seropositivity ($p<0.0001$), as well as serum RF titer ($p<0.0001$). No relationship with ACPA or serum IgG levels was seen in this cohort. Moreover, no relationship was seen with age, gender, shared epitope status, DAS28-CRP or the presence of erosions. In contrast to DAS28-CRP, there was a weak association between CXCL13 levels and hsCRP ($p=0.05$).

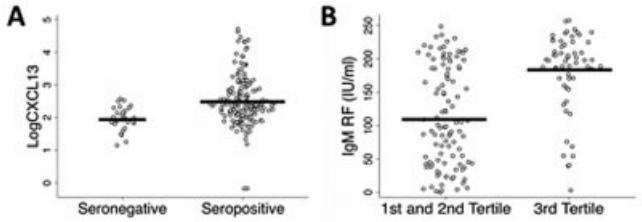

Figure 1. Serum CXCL13 levels correlate with seropositivity and rheumatoid factor (RF) status. **A,** Seropositive patients exhibit marked elevation of serum CXCL13 (n=193, $p=0.0002$) in an established RA cohort. **B,** Tertile analysis of CXCL13 in seropositive patients reveals that IgM RF has a strong relationship with the highest CXCL13 tertile ($p<0.0001$). Identical patterns were seen in the Canadian EUPA Cohort.

Conclusion: Using both established and early RA cohorts, marked elevations of serum CXCL13 levels resided nearly completely within the seropositive population. Within this seropositive RA subset, CXCL13 elevations exhibited a surprisingly strong relationship with RF. The association of CXCL13 levels with either clinical (age, gender, DAS28-CRP, erosions) or serologic (ACPA, IgG) parameters was either much weaker or absent. These results suggest that serum CXCL13 levels not only identify differences in the pathophysiology of seronegative RA, but also may define a subset of seropositive RA patients.

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Survivin–positivity Increases Risk For RA and Has a Strong Additive Effect On The Shared Epitope Alleles and Antibodies To Citrullinated Peptides In Patients Of The Malaysian Epidemiological Investigation Of Rheumatoid Arthritis (MyEIRA) Study Group. Chun Lai Too[1], Shahnaz Murad[2], Malin Erlandsson[3], Heselynn Hussein[4], Wahinuddin Sulaiman[5], Jasbir Singh Dhaliwal[1] and Maria Bokarewa[6]. [1]Institute for Medical Research, Allergy and Immunology Research Center, Jalan Pahang, Kuala Lumpur, Malaysia, [2]Institute for Medical Research, Jalan Pahang, Kuala Lumpur, Malaysia, [3]Göteborgs University, Göteborg, Sweden, [4]Putrajaya Hospital, Putrajaya, Malaysia, [5]Tengku Bainun Hospital, Ipoh, Perak, Malaysia, [6]University of Gothenburg, Gothenburg, Sweden.

Background/Purpose: The human leukocyte antigen (HLA)-DRB1 with alleles that contain common amino acid motif QKRAA termed shared epitope (SE) confer the major locus of genetic susceptibility to rheumatoid arthritis (RA). Molecular basis of tolerance loss marked by autoantibody production remains to be resolved. The aim of this study was to analyse an association between survivin, oncoprotein recently reported to be associated with early bone damage and poor therapy response, HLA-DRB1 SE alleles and antibodies to citrullinated peptides (ACPA) in Malaysian patients.

Methods: 1233 RA patients and 1566 age, sex and ethnically matched healthy controls of the Malaysian Epidemiological Investigation of rheumatoid arthritis (MyEIRA) study group were included in the study. The levels of survivin, ACPA and rheumatoid factor were measured by specific and standardized ELISAs. HLA-DRB1 genotyping was performed by the PCR-SSO method. Among the HLA-DRB1 alleles, DRB1*01, DRB1*0401, DRB1*0404, DRB1*0405, DRB1*0408, DRB1*0410, and DRB1*10 were defined as SE alleles. The odds ratio (OR[95%CI]) and relative risk (RR) of developing ACPA-positive and ACPA-negative RA was calculated for survivin and the presence of any SE allele. Potential interaction between survivin and HLA-DRB1 SE alleles was also calculated.

Results: The prevalence of survivin-positivity among RA patients was 50.7%, compared to 5.4% in healthy controls ($p=2.66E-164$) with a significantly higher prevalence in the Indian ethnic population compared to the Malay and Chinese ($p<0.0001$). Survivin-positivity was associated with an increased risk of developing ACPA-positive RA (OR 33.5[25.8–43.6]) and ACPA-negative RA (OR 5.3[3.9–7.2]), both $p<0.0001$. The survivin-positivity was associated with SE-alleles in 23.6% of RA patients and the majority of patients combining survivin and SE (91%) were also ACPA–positive. The combination of survivin-positivity and SE increased the risk of ACPA-positive RA 19 folds.

Conclusion: The survivin-positivity increases risk of the development of ACPA-positive and ACPA-negative RA. Combination of survivin-positivity, SE and APCA has a strong additive effect for the risk of RA in the population from Malaysia.

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1397

Changes In MMP In Fibroblast-Like Synoviocytes Following Adipogenesis. Satoshi Yamasaki, Kazuhiko Kumagai, Kouji Endo, Takaki Nojima and Eiji Sugiyama. Hiroshima University Hospital, Hiroshima, Japan.

Background/Purpose: Fibroblast-like synovial cells (FLS) play important roles in the disease progression of RA. FLS produce cytokines and chemokines that contribute to chronic inflammation of RA-affected joints. They also secrete matrix metalloproteinases (MMPs) that cause degradation of joint tissues, including bone and cartilages, which leads to severe structural destruction of inflamed joints. We previously reported that the production of IL-6, a cytokine that contributes to the progression of RA, by FLS is reduced by adipogenesis induction. Therefore, we predict that induction of FLS adipogenesis could be a new therapeutic strategy to treat RA. Our objective in this study was to examine whether MMPs production in FLS could be altered by adipogenesis induction.

Methods: FLS were isolated from the synovial tissues by enzymatic digestion. MSC were purchased from Lonza (Walkersville, USA). Adipogenesis of FLS was carried out by using the MSC adipogenic differentiation medium BulletKit (Lonza), according to the manufacturer's instructions. The mRNA expression levels of MMPs and tissue inhibitors of metalloproteinases (TIMPs) were evaluated by DNA array (SurePrint G3 Human GE 8×60K Microarray, Agilent Technologies) by using two-colour detection mode. Production of MMP and TIMP proteins in FLS culture supernatant was evaluated by Human MMP Antibody Array (RayBiotech, Inc., Norcross, USA) and confirmed by ELISA (MMP1, MMP2, and MMP3 purchased from Abcam).

Results: After adipogenesis induction, transcripts unique to adipocytes (e.g., lipoprotein lipase 4, fatty acid-binding protein 5, fatty acid-binding protein 4, aquaporin 7, perilipin 2, adiponectin, and peroxisome proliferator-activated receptor γ) were clearly induced in FLS, which confirms that adipogenesis was properly induced. Expressions of MMP-1, -2, and -11 transcripts were decreased in FLS following adipogenesis. Conversely, expression of MMP-3 and -25 transcripts was increased by FLS adipogenesis. Consistent with these results, antibody array studies demonstrated that MMP-1 protein production was reduced in FLS culture medium following adipogenesis, whereas MMP-3 protein production increased. Supernatant concentrations of MMP-1 and -2 from FLS obtained from 4 different RA patients were reduced after adipogenesis. The mRNA and protein expression of TIMP-4, a MMP-2 inhibitor, were induced by FLS adipogenesis.

Conclusion: Our data demonstrate that MMP-1 and -2 production was inhibited in FLS by adipogenesis induction. If the FLS in pannus were to differentiate into adipocytes with reduced IL-6 and MMPs, the adipocytes would be a more physiological component that would produce fewer pathogenic molecules in the joint. Specifically, the strategy of inducing adipogenesis in FLS may restore both the levels of the harmless cytokine and protease production as well as fat-rich tissue deposition in the affected joint as seen in a normal joint. Further studies are required to include "adipogenesis-induction therapy" in the treatment of RA.

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1398

Comparison Of Atherogenicity Of Plasma From Patients With Rheumatoid Arthritis and Psoriatic Arthritis. Beenish Hafiz, Iryna Voloshyna, Michael J. Littlefield, Steven E. Carsons, Elise Belilos, Kristina Belostocki, Lois A. Bonetti, Gary C. Rosenblum and Allison B. Reiss. Winthrop University Hospital, Mineola, NY.

Background/Purpose: Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are immune mediated inflammatory disorders linked to increased risk of cardiovascular disease (CVD), mostly due to accelerated atherosclerosis. An imbalance between cholesterol inflow and outflow leads to lipid overload

and is one mechanism for initiation of atherosclerosis. This study examines the effect of RA and PsA plasma compared to healthy control (HC) plasma on expression of genes responsible for cellular cholesterol efflux and influx by exposing naïve THP-1 human macrophages to RA, PsA and HC plasma. In addition, cytokine levels were measured in RA, PsA and HC.

Methods: THP-1 differentiated macrophages (10^6 cells/ml, phorbol dibutyrate, 100nM, 48h), were incubated (37°C, 5% $C0_2$, 18h) in RPMI 1640 media in the presence of 10% plasma from the following subjects: 1) 22 RA, 2) 21 HC age and sex-matched to the RA group, 3) 8 PsA, 4) 8 HC age matched to the PsA group. The study was performed under a Winthrop University Hospital IRB-approved protocol. Cytokine levels were evaluated by ELISA. Cholesterol transport protein mRNA was quantified by real-time RT-PCR using specific primers for each gene.

Results: 10% RA plasma increased macrophage expression of cholesterol influx genes (scavenger receptors CD36 and LOX-1). CD36 mRNA increased by 134.45±38.56% ($P<0.001$) and LOX-1 by 68.9±12.45% ($P<0.001$) above cells exposed to HC plasma (set at 100%). SR-A1 expression did not different in RA vs. HC. Expression of cholesterol efflux genes (ATP binding cassette transporter (ABC)A1, ABCG1 and 27-hydroxylase) was suppressed in macrophages treated with RA plasma vs. HC plasma. Mean ABCA1 mRNA expression decreased to 55.29±10.23% ($P<0.001$) compared to cells treated with HC plasma. ABCG1 mRNA fell to 73.65±9.67% ($P<0.05$) upon exposure to RA plasma vs. HC plasma. 27-Hydroxylase mRNA in THP-1 macrophages in the presence of RA plasma was diminished to 26.5±8.56% ($P<0.01$). In contrast, 10 % PsA plasma did not alter message level of the cholesterol influx or efflux proteins compared to HC (Figure). Pro-inflammatory cytokines were significantly higher in RA plasma compared to HC plasma: IL-6 (4.66±0.44 pg/ml vs. 1.71±0.045 pg/ml, $P<0.01$), TNF-α (4.34±0.40 ng/ml vs. 1.30±0.22 ng/ml, $P<0.001$) and IFN-γ (171.2±125.5 pg/ml vs. 9.54±0.7 pg/ml, $P<0.001$), respectively. In contrast, PsA plasma did not show significant elevations in IFN-γ, TNF-α or IL-6.

Conclusion: RA plasma but not PsA plasma induced a pro-atherogenic profile of genes responsible for cholesterol infux and efflux. This may be due to the significantly greater elevation of inflammatory cytokines, notably IFN-γ (which is known to alter cellular cholesterol flux in a pro-atherogenic manner) demonstrated in the RA plasma samples. A lack of significant effect on cholesterol transport gene expression by PsA plasma is consistent with less CVD risk in PsA compared to RA.

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1399

Citrullinated Proteoglycan (Aggrecan) Present In Human Cartilage Is Recognized By Serum Antibodies From Rheumatoid Arthritis Patients. Timea Ocsko[1], Beata Tryniszewska[1], Andras Vida[1], Janos Gal[2], Gyorgyi Soos[2], Zoltan Szekanecz[3], Tibor A. Rauch[1], Joshua Jacobs[1], Tibor T. Glant[1] and Katalin Mikecz[1]. [1]Rush University Medical Center, Chicago, IL, [2]Bacs-Kiskun County Hospital, Kecskemet, Hungary, [3]University of Debrecen Medical and Health Sciences Center, Debrecen, Hungary.

Background/Purpose: Citrullination is a post-translational protein modification, where arginine (Arg) is converted to citrulline (Cit) by peptidyl arginine deiminases (PADI). The presence of anti-citrullinated protein antibodies (ACPA) in serum is highly specific for rheumatoid arthritis (RA). Some of these ACPA may recognize citrullinated cartilage components such as type II collagen (CII) or the proteoglycan (PG) aggrecan in the RA joints afflicted with inflammation. The major goals of this study were (1) to determine whether a citrullinated form of cartilage PG is present in normal or diseased human cartilage, and (2) to identify citrullinated PG (CitPG)-specific serum antibodies (Abs) in $ACPA^+$ RA patients.

Methods: PG from cartilage of normal human joints was extracted with 4M GuHCl and purified by CsCl gradient ultracentrifugation. Crude extracts were also prepared from osteoarthritic (OA) and RA cartilage specimens obtained from joint replacement surgery. Serum ACPA concentrations in RA patients were measured using anti-MCV (Orgentec) and anti-CCP3 (Inova) kits. RA serum samples with high ACPA titers were reacted with both purified PG and crude cartilage extracts in dot blots and Western blots. The PG specificity of reactions was verified using monoclonal Ab G18 to the G1 domain of human PG. Recombinant G1 domain of PG and purified human CII, both citrullinated in vitro with PADI4, were used for the measurement of CitPG- and CitCII-specific serum Abs, respectively, by ELISA. CitPG was visualized in frozen sections of human cartilage specimens by immunohistochemistry.

Results: While there was a strong correlation between anti-MCV and anti-CCP3 titers, the correlation was weaker between anti-CitPG and anti-CCP3 Ab levels in the 68 $ACPA^+$ RA serum samples tested. ELISA assays, using CitPG and CitCII as a capture antigens, showed that 66% of the $ACPA^+$ sera reacted with CitPG, 46% with CitCII, and 41% with both CitPG and CitCII. When we compared sera from healthy subjects and OA patients with the 'calibrator' serum standards supplied with the anti-CCP3 kits, only the anti-$CCP3^+$ calibrator sera gave a positive reaction with CitPG. Comparison of matched cartilage and serum samples from OA patients demonstrated the presence of CitPG in ~60% of OA cartilage extracts, while CCP3- or CitPG-specific Abs could not be detected in any of their serum samples. On the other hand, all cartilage specimens from RA patients contained CitPG, and 92% of the serum samples from the same RA donors were positive for both anti-CCP3 and anti-CitPG Abs. Western blot of fragmented cartilage PG showed that the G1 domain contained an abundance of citrullinated epitopes. In cartilage tissue sections, CitPG was predominantly localized intracellularly and in the pericellular matrix of chondrocytes.

Conclusion: PG (especially the Arg-rich G1 domain) in both normal and diseased cartilage is subjected to citrullination in vivo, likely by PADI in chondrocytes. While a significant proportion of normal, OA, and RA cartilage specimens contains CitPG, only sera from RA patients seem to recognize it. There is a significant overlap between anti-CitPG Abs and other ACPA, including anti-CCP3, anti-MCV, and anti-CitCII Abs in RA.

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1400

Dipeptidyl Peptidase IV (DPP-IV, CD26) Levels In Patients With Rheumatoid Arthritis Treated With Biologic Therapies and Correlation With The Activity Of The Disease. José M. Pego-Reigosa[1], Oscar Cordero[2], Tania López-González[2], Coral Mouriño-Rodríguez[3], Bruno Aspe[4], Juan Viñuela-Roldán[5], Rubén Varela-Calviño[6], Cristina Calviño[6], Marina Rodríguez-López[4], Iñigo Hernández-Rodríguez[4] and Víctor del Campo-Pérez[4]. [1]Instituto de Investigación Biomédica de Vigo (IBIV), Vigo, Spain, [2]Universidade de Santiago de Compostela, Santiago de Compostela, Spain, [3]Meixoeiro Hospital, Vigo, Spain, [4]University Hospital Complex of Vigo, Vigo, Spain, [5]University Hospital Complex of Santiago, Santiago de Compostela, Spain, [6]Faculty of Pharmacy, University of Santiago de Compostela, Santiago de Compostela, Spain.

Background/Purpose: Dipeptidyl peptidase IV (DPP-IV, CD26), a protease cleaving N-terminal X-Pro dipeptides from selected proteins including chemokines is expressed both as a soluble form and on the surface of various immune and non-immune cells. In rheumatoid arthritis (RA), low DPP-IV/sCD26 activity has been shown in serum and synovial fluid, with restoration of normal levels of activity in patients treated with anti-TNF-alfa therapy. The objective of our study was to study DPP-IV/sCD26 in RA patients and its correlation with disease activity and the different therapies received.

Methods: Patients diagnosed with RA according the 1987 ACR classification criteria for RA were included. The degree of RA activity was evaluated by using DAS 28, acute-phase reactants and hemoglobin levels. Data about all the medications and their doses were collected.

Expression levels of CD26 on white blood cells were evaluated by flow cytometry analysis and the serum levels of the enzyme DPP-IV by ELISA. All laboratory tests were performed blindly. An institutional review board approved this study. All patients gave written informed consent.

To evaluate the correlation among clinical and serological variables, bivariate analysis was performed (SPSS 16.0).

Results: Sixty-eight patients were recruited: 75% woman, median age (IR): 57.1 years (18.6), median disease duration (IR): 9.8 years (14.0). Regarding the RA activity variables, median DAS28, ESR, CRP and Hemoglobin (IR) were: 3.4 (1.7), 30.5 (31), 4.1 (10) and 13.3 (2.2), respectively.

There were not significant differences in the percentages of CD26 expressing T helper subsets in RA patients treated vs. non-treated with biologics. However, we found a statistically significant raise in the levels of cell surface CD26 expression (mean of fluorescence intensity, MFI) in the T helper effector/memory CD45RO+ CD26+ or CD26high subset in patients on biologic therapy compared with those without biologic therapy ($p = 0.03$).

Overall, the levels of cell surface CD26 expression measured by MFI in the T helper effector/memory CD45RO+ CD26+ correlated significantly

with the activity of the disease measured by DAS28 score (Pearson's CC: 0.4, p = 0.001).

Conclusion: Higher levels of plasma membrane CD26 (measured by MIF) may be related with the decreased circulating sCD26 levels in RA, and these levels correlates with the disease activity. Patients on biologic therapies showed increased levels of plasma membrane CD26 in a similar way to the restoration of circulating levels of CD26 associated with anti-TNF-alfa therapy described in the literature. These changes may be also related with the number of Th17 cells, which express high levels of CD26, this hypothesis being under study. Thus, different therapies may influence distinctly the CD26-mediated regulation of the chemotactic SDF-1/CXCR4 axis of inflammation.

Reference:

Mavropoulos JC, Cuchacovich M, Llanos C, et al. Anti-tumor necrosis factor-alpha therapy augments dipeptidyl peptidase IV activity and decreases autoantibodies to GRP78/BIP and phosphoglucose isomerase in patients with rheumatoid arthritis. J Rheumatol 2005;32:2116–24.

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1401

Reduced Oral Glucose Tolerance Is Associated With a Lower Risk Of Rheumatoid Arthritis. Carl Turesson, Ulf Bergström, Mitra Pikwer, Jan-Åke Nilsson and Lennart Jacobsson. Lund University, Malmö, Sweden.

Background/Purpose: Studies have demonstrated a negative association between high body mass index (BMI) and development of rheumatoid arthritis (RA) in men, and a neutral or positive association in women. This may reflect effects of body fat distribution and related metabolic pathways on the risk of RA. The purpose of the present study was to investigate the impact of oral glucose tolerance on the risk of future development of RA.

Methods: Between 1974 and 1992, subjects (n=33346; 22444 men and 10902 women) from a defined catchment area were included in a Preventive Medicine Program (PMP). Information on life style factors was obtained using a self-administered questionnaire. A standard oral glucose tolerance test (OGTT) was performed after an overnight fast. From this population, we identified individuals who developed RA after inclusion by linking the PMP register to the local community based RA register and to local and national patient administrative databases. In a structured review of the medical records, patients were classified according to the 1987 American College of Rheumatology criteria for RA. Four controls for each validated case, matched for sex, year of birth and year of screening, who were alive and free of RA when the index person was diagnosed with RA, were selected from the PMP register. The impact of the 2-hour OGTT glucose level on the risk of RA was examined in conditional logistic regression models.

Results: Two hundred and ninety patients [151 men and 139 women; median time from inclusion to RA diagnosis 12 years (interquartile range 8–18, range 1–28); mean age at diagnosis 60 years] were diagnosed with RA and fulfilled the ACR criteria after inclusion in the PMP. An OGTT was performed in 177 cases (104 men, 73 women) and 708 controls (413 men, 295 women). Fasting glucose levels were similar in cases and controls (mean 4.91 vs 4.90 mmol/l). Cases with a diagnosis of RA during the follow-up had lower 2-hour OGTT glucose levels at baseline compared to controls [mean 5.58; standard deviation (SD) 1.76 vs. 6.03 (SD 1.77) mmol/l; OR 0.72 per SD; 95 % confidence interval (CI) 0.58–0.89)]. Impaired glucose tolerance (2-hour OGTT glucose level ≥ 7.8 mmol/l) was less frequent in pre-RA cases compared to controls (9.0 % vs. 15.1 %; p=0.04). The association between lower 2-hour OGTT glucose levels and subsequent development of RA remained significant in separate multivariate analyses adjusted for smoking (p=0.01) or socio-economic status (p=0.04). In analyses stratified by sex, the estimated impact of 2-hour OGTT glucose was similar in men (OR 0.71 per SD; 95 % CI 0.54–0.92) and women (OR 0.73 per SD; 95 % CI 0.51–1.05). Two-hour OGTT glucose levels were correlated with BMI in men (r=0.22; p<0.001) and, to a lesser extent, in women (r=0.13; p=0.02). In analysis adjusted for BMI, a lower 2-hour glucose level remained a significant predictor for RA in men (OR 0.75 per SD; 95 % CI 0.50–0.98).

Conclusion: A reduced oral glucose tolerance was associated with a lower risk of RA. Taken together with the known impact of fat distribution on glucose tolerance, and previous observations of sex-specific effects of BMI on the risk of RA, this suggests that mechanisms related to abdominal or visceral fat may protect against RA.

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1402

Regulatory B10 CELLS ARE Decreased In Patients With Rheumatoid Arthritis and Inversely Correlated With Disease Activity. Claire I. Daien[1], Sarah Gailhac[2], Thibault Mura[3], Bernard Combe[1], Michael Hahne[4] and Jacques Morel[1]. [1]Lapeyronie Hospital, Montpellier, France, [2]CNRS, Montpellier, France, [3]Hopital Gui De Chauliac, Montpellier, France, [4]IGMM, CNRS UMR5535, Montpellier, Montpellier, France.

Background/Purpose: Regulatory IL-10 producing B cells (B10) have been shown to prevent and cure collagen-induced arthritis in mice. In human, very little is known about B10 cells in rheumatoid arthritis (RA). Several B cell subsets such as CD24hiCD38hi, CD24hiCD27+ and CD5+ B cells were suggested to be precursors of B10 cells. In the present study, we aimed to analyze these B cell subsets and B10 cells in RA patients and healthy controls. We also compared the ability of these different B cell subsets to produce IL-10.

Methods: B10 cells were generated from PBMCs stimulated for 24 hours with CpG and 4 hours with PMA and ionomycine. Intra-cellular B cell IL-10 was assessed by cytometry. Thirty-one controls + 99 RA patients were included for B cell subsets and 21 controls + 66 RA patients for B10 cell assessment. To study the ability of the different B cell subsets to produce IL-10, we sorted them using cytometry before activation.

Results: After multiple adjustments, CD24hiCD38hi, CD24hiCD27+ and CD5+ B cell levels were found to be similar in patients with RA and in controls. CD24hiCD27+ levels were higher in patient with active disease than in patient with DAS28≤3.2 whereas other subsets were not different between the two groups. Levels of B10 cells were lower in patients with RA, especially in RA with disease duration under 5 years than controls. B10 cells inversely correlated with DAS28. It was more pronounced in RA≤5 years where B10 cells also inversely correlated with CRP levels. Moreover, B10 cells inversely correlated with rheumatoid factor and anti-citrullinated peptide antibody levels. CD24hiCD27+ B cells were found to be the main producers of IL-10 when taking into account their percentage in peripheral blood. However, all B cell subsets were able to produce more or less IL-10 after stimulation.

Conclusion: B cell ability to produce IL-10 was altered in RA and this impairment influenced disease activity, biological inflammation and autoantibody levels, especially in patients with RA≤5 years. This strongly suggests a role of B10 cells in RA initiation.

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1403

Protein Tyrosine Phosphatase Non-Receptor Type 2 (PTPN2) Is Expressed In a TNF-Dependent Manner In RA Synovial Tissues. Borbala Aradi[1], Masaru Kato[1], Mária Filková[2], Stephanie Kasper[3], Kerstin Klein[1], Michael Bader[1], Michael Scharl[3], Beat A Michel[4], Renate E Gay[1], Edit I Buzas[5], Steffen Gay[1] and Astrid Jüngel[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Institute of Rheumatology and Department of Rheumatology of the First Faculty of Medicine, Charles University in Prague, Czech Republic, Prague, Czech Republic, [3]Division of Gastroenterology and Hepatology, University Hospital Zürich and Zürich Center for Integrative Human Physiology, Zurich, Switzerland, [4]Rheumatology, University Hospital Zurich, Switzerland, Zurich, Switzerland, [5]Department of Genetics, Cell- and Immunobiology, Budapest, Hungary.

Background/Purpose: Protein Tyrosine Phosphatase Non-receptor Type 2 (PTPN2) is a protein phosphatase that has been associated with the development of autoimmune diseases in GWA studies. Here we analyse its contribution to inflammation in RA before and after anti-TNFα therapy.

Methods: Immunohistochemistry was used to detect PTPN2 in synovial tissues from patients with osteoarthritis (OA) and RA with and without

anti-TNF treatment. The mRNA expression of PTPN2 was measured in synovial tissues using real-time PCR. RASF and OASF were stimulated with TNFα for short (10 ng/ml, 24 h) or long term (10 ng/ml, in 7 days), TNFα and IL1-β (1 ng/ml, 24 h), LPS (100 μg/ml, 24 h), and hypoxia (1%, 24 h). The levels of PTPN2 transcripts and protein were measured with real-time PCR or Western blotting. PTPN2 was silenced with three silencing RNAs. Commercially available ELISA was used to measure IL-6 and IL-8 production. TRAIL (20 ng/ml, 24h) was used to induce apoptosis. Apoptotic cells were detected by flow cytometry, using AnnexinV staining. Thapsigargin-induced (5μM, 24 h) autophagy was measured by Western blot using antibodies against LC3B-I and LC3B-II.

Results: Levels of PTPN2 expression were higher in the lining and sublining layers of RA compared to OA synovial tissues (OA n=11, RA n=30, 1.75-fold, $p<0.001$). This was also confirmed with real-time PCR on mRNA level (2.0 fold, RA tissue n=4, OA tissue n=5). Most interestingly, in synovial tissues from patients who were treated with anti-TNFα, 30% less PTPN2 staining could be detected by immunohistochemistry than in patients without anti-TNFα treatment (n=8, $p<0.05$). In synovial fibroblasts, the constitutive expression of PTPN2 was higher in RASF compared to OASF on mRNA (1.6 fold, $p<0.01$, n=10–16) and on the protein level (2.0 fold, $p<0.05$, n=3–7). The transcript levels of PTPN2 could be upregulated after stimulation with TNFα (3.1 fold, $p<0.05$, n=4), TNFα and IL-1β (2.3 fold, n=5), LPS (1.9 fold, n=5) and hypoxia (1.3 fold, n=3). The upregulation after stimulation with TNFα could also be confirmed on the protein level (1.7 fold, $p<0.05$, n=7). Moreover, PTPN2 protein expression was further increased after long term stimulation with TNFα (2.4 fold, n=3). Next, the function of PTPN2 was studied in synovial fibroblasts. Using siRNAs, PTPN2 was silenced by 80%. PTPN2 silenced cells produced more IL-6 (2.1 fold, n=4) than scrambled control cells, whereas levels of IL-8 did not change. TRAIL-induced apoptosis was increased by 37 % (n=5) and TG induced autophagy was decreased by 20% (n=5) after PTPN2 silencing.

Conclusion: We show here for the first time that PTPN2 is expressed in a TNF-dependent manner in RA synovial tissues. PTPN2 counter regulates the expression of the inflammatory cytokine IL-6 and regulates apoptosis and autophagy in RASF.

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1404

Effects Of Smoking On Joint Physiology In Men and Mice. Caroline Ospelt[1], Giovanni Camici[2], Anna Engler[1], Christoph Kolling[3], Renate E. Gay[1], Beat A. Michel[4] and Steffen Gay[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Institute of Physiology, University of Zurich, Zurich, Switzerland, [3]Schultess Clinic, Zurich, Switzerland, [4]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland.

Background/Purpose: Smoking is a major risk factor for the development of anti-citrullinated protein antibodies positive rheumatoid arthritis (RA) in individuals who carry shared epitope alleles. The molecular mechanisms that confer this risk are however not clarified up to now. Even more it is not clear whether smoking can affect joint physiology directly or via indirect immune mechanisms that cross-react with joint structures. We analyzed synovial tissues of human smokers and of mice exposed to cigarette smoke as well as in vitro stimulated RA synovial fibroblasts (SF) to find effects of smoking on joint physiology.

Methods: Synovial tissues were obtained from smoking (n=5) and non smoking (n=6) RA patients undergoing joint replacement surgery and from mice exposed to cigarette smoke (n=6) or room air (n=8) or) in a whole body exposure chamber for 3 weeks. RASFs were incubated with 5% cigarette smoke extract (CSE) (n=7). Changes in gene expression were detected using whole genome microarrays and verified with Real-time PCR and immunoblotting.

Results: Gene expression analysis and functional classification showed that CSE treatment in vitro leads to a broad activation of the chaperone and heat shock protein system. This finding could be confirmed *in vivo*, where we found a significant increase in the expression of the HSP40 family members, DnaJB4 (1.8 fold) and DnaJC6 (2.2 fold) in synovial tissues of human smokers as well as in mice exposed to cigarette smoke (DnaJB4 2.2 fold, DnaJC6 2.7 fold). Furthermore, in human synovial tissues, but not in mice, smokers had 3.5 fold higher levels of Hsp70 and 3.2 fold higher levels of HspB8 similar to what was seen in *in vitro* stimulations.

The list of CSE altered genes also contained a ligand of the activating immune receptor NKG2D. This ligand, MICB, together with other ligands of this receptor namely MICA, ULBP2 and ULBP3 was significantly increased after CSE *in vitro*. MICA (2.6 fold) and MICB (2.1 fold) were also significantly higher in synovial tissues of smokers compared to non-smokers. In addition the mouse homologue of these ligands, H60 was 2.9 fold higher expressed in joints of smoke exposed mice.

Conclusion: Our results clearly show that systemic effects of cigarette smoke include changes in joints. Since synovial fluid is passively filtrated from the blood, it is feasible to assume that cigarette smoke components in the blood can reach the synovial fluid and influence local tissue physiology. Therefore smoking can increase the risk to develop RA by locally changing gene expression in the synovium.

Disclosure: C. Ospelt, None; **G. Camici**, None; **A. Engler**, None; **C. Kolling**, None; **R. E. Gay**, None; **B. A. Michel**, None; **S. Gay**, None.

1405

Expression Of High Mobility Group Protein B1 and Its Receptors In Heart Of Patients With Coronary Artery Disease With and Without Inflammatory Rheumatic Disease: A Biopsy Study. Mei Zong[1], Ivana Hollan[2], Huiyuan Xiao[3], Cecilia Grundtman[4], Eva Lindroos[5], Helena E. Harris[6], Knut MIkkelsen[7], Stein E. Rynning[7], Sven M. Almdahl[8] and Ingrid E. Lundberg[1]. [1]Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, [2]Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway, [3]University of Oxford, Oxford, United Kingdom, [4]Innsbruck Medical University, Innsbruck, Austria, [5]Rheumatology Unit, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden., Stockholm, Sweden, [6]Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden, [7]Feiring Heart Clinic, Feiring, Norway, [8]University Hospital of North Norway, Tromsø, Norway.

Background/Purpose: Patients with inflammatory rheumatic diseases (IRD) have increased risk of morbidity and mortality in coronary artery disease (CAD) compared to the general population. High mobility group protein B1 (HMGB1) is an alarmin that can drive the pathogenesis of IRD when it is released from nuclei. Recently it was also shown that HMGB1 can mediate myocardial dysfunction in rat. In this study, we aimed to investigate whether and how HMGB1 and its signal-mediated receptors are expressed in heart muscle tissues of humans with CAD with or without IRD.

Methods: We examined myocardial specimens from the right atria (1.5×2.0mm) taken during coronary artery bypass grafting from 18 patients with CAD included in Feiring Heart Biopsy Study between 2001 and 2004. Among them, 10 patients had an IRD (IRD group) and 8 patients were without IRD (control group). The IRD group comprised of 5 patients with rheumatoid arthritis, 2 with polymyalgia rheumatica, 1 with psoriasis arthritis, 1 with temporal arteritis and 1 patient with ankylosing spondylitis. The heart samples were snap-frozen and stored at −80°C until they were cryostat-sectioned and stained by immunohistochemistry using the antibodies specific for HMGB1 and its three most well-known receptors: Toll-like receptor (TLR) 2, TLR4 and receptor for advanced glycation end products (RAGE). The cytosol HMGB1 staining was described as weak (+) and strong (++) which was scored without knowing the identity of the patients.

Results: In the control group, HMGB1 was localized to the nuclei of cardiomyocytes in 7 out of 8 patients, while in one patient it was also detected in the cytoplasm weakly (+). In contrast, in the IRD group, HMGB1 was strongly expressed in the cytosol of the cardiomyocytes in 6 out of 10 patients (++), and weakly expressed in cytosol in the remaining 4 patients (+). For the receptors, RAGE and TLR4 displayed a general expression in the cardiomyocytes mainly localized to the cytosol, while TLR2 was detectable in the cytosol of occasional cardiomyocytes.

Conclusion: HMGB1 and its receptors are expressed in the cardiomyocytes of patients with CAD. However, the HMGB1-signalling pathways may get a "better" chance to be activated in the patients with IRD as HMGB1 was detected with a more pronounced extranuclear staining pattern compared to the non-IRD patients. Therefore, targeting HMGB1 therapy in the future may protect the patients with IRD from developing severe cardiovascular diseases.

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1406

The Scaffold Protein p62 Is Involved In NF-κB Signaling, Caspase-3 Dependent and -Independent Cell Death and Autophagy In Rheumatoid Arthritis Synovial Fibroblasts. Masaru Kato[1], Caroline Ospelt[1], Christoph Kolling[2], Beat A. Michel[3], Renate E. Gay[4], Steffen Gay[4] and Kerstin Klein[1]. [1]University Hospital Zurich, Zurich, Switzerland, [2]Schultess Clinic, Zurich, Switzerland, [3]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [4]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland.

Background/Purpose: Sequestosome 1 (p62/SQSTM1) is a multifunctional ubiquitin-binding protein implicated in selective autophagy, cell signaling pathways and regulation of cell death. Recently, we described a functional role of p62 in the formation of poly-ubiquitinated protein aggregates and non-apoptotic cell death associated with autophagy in rheumatoid arthritis synovial fibroblasts (RASF). Here we investigated the role of p62 in the activation of apoptosis and nuclear factor-κB (NF-κB) activity in RASF.

Methods: The expression of p62 in synovial tissues from RA and osteoarthritis (OA) patients was verified by immunohistochemistry using antibodies against p62. RASF were incubated with and without TNF-α (10 ng/ml), IL-1β (1 ng/ml) and IL-6 (50 ng/ml) in presence or absence of soluble IL-6 receptor (30 ng/ml) for 24 hours and p62 expression was evaluated by quantitative Real-time PCR and immunoblotting. RASF were transfected with siRNA targeting p62 and knockdown was verified by immunoblotting. To induce cell death, RASF were treated with TRAIL (100 ng/ml) in presence or absence of a pan-caspase inhibitor (20 μM Z-VAD) for 24 hours. Apoptosis was evaluated by flow cytometry using annexin V/propidium iodide staining and a caspase-3 activity assay (NucView 488, Biotium). RASF were transfected with reporter-gene vectors containing NF-κB response elements and control vectors (GAPDH). NF-κB activity was measured by Dual-Luciferase reporter assays.

Results: The expression of p62 was restricted to the lining layer of synovial tissues and was increased in synovial tissues from RA patients (n=30) compared to OA patients (n= 9, p=0.01). Interestingly, the expression of p62 in RA patients treated with anti-TNF agents (n=14) was similar to the p62 expression observed in OA patients and was decreased compared to patients treated with non-biologics (n=9, p = 0.006) or patients treated with tocilizumab (n=4, p=0.008) or abatacept (n=3, p=0.02). Consistently, p62 mRNA (n=4, p=0.02) and protein (n=5, p=0.002) were induced in RASF by TNF-α, but not by IL-1β or by IL-6 stimulation even in the presence of soluble IL-6 receptor. p62 knockdown in RASF promoted TRAIL-induced cell death (n=6, p=0.02) that was accompanied by caspase-3 activation and was inhibited by a pan-caspase inhibitor. Furthermore, p62 knockdown strongly suppressed basal NF-κB activity (68.0 ± 10.6% reduction, n = 3, p = 0.008) in RASF.

Conclusion: Our data indicate that the scaffold protein p62 is involved in the regulation of multiple pathways in RASF, including NF-κB signaling, as well as the induction of caspase-3 dependent and -independent cell death and autophagy. p62 is positively regulated by TNF-α and plays a protective role against apoptosis in RA.

Disclosure: M. Kato, EURO-TEAM, IMI-BT Cure, IAR, 2; **C. Ospelt**, EURO-TEAM, IMI-BT Cure, IAR, 2; **C. Kolling**, EURO-TEAM, IMI-BT Cure, IAR, 2; **B. A. Michel**, None; **R. E. Gay**, EURO-TEAM, IMI BTCure, IAR Epalinges, 2; **S. Gay**, None; **K. Klein**, EURO-TEAM, IMI-BT Cure, IAR, 2.

1407

High Serum Cholesterol Predicts Rheumatoid Arthritis In Women. Carl Turesson, Ulf Bergström, Mitra Pikwer, Jan-Åke Nilsson and Lennart Jacobsson. Lund University, Malmö, Sweden.

Background/Purpose: Patients with active rheumatoid arthritis (RA) tend to have low cholesterol levels due to effects of inflammation on lipid metabolism. However, several prospective studies have indicated that a high serum cholesterol may be associated with increased risk of of RA. Metabolic pathways in the development of RA may be affected by hormonal factors, and have a different impact in men and women. The purpose of this study was to examine sex-specific effects of total serum cholesterol on the future risk of RA.

Methods: Between 1974 and 1992, subjects (n=33346; 22444 men and 10902 women) from a defined catchment area were included in a Preventive Medicine Program (PMP). Information on life style factors was obtained using a self-administered questionnaire. Blood samples were taken in the morning, after an overnight fast. Serum cholesterol was immediately assessed by an enzymatic method routinely used by the local hospital laboratory. From this population, we identified individuals who developed RA after inclusion by linking the PMP register to the local community based RA register and to local and national patient administrative databases. In a structured review of the medical records, patients were classified according to the 1987 American College of Rheumatology criteria for RA. Four controls for each validated case, matched for sex, year of birth and year of screening, who were alive and free of RA when the index person was diagnosed with RA, were selected from the PMP register. The impact of serum cholesterol on the risk of RA was examined in conditional logistic regression models, stratified by sex.

Results: Two hundred and ninety patients [151 men and 139 women; median time from inclusion to RA diagnosis 12 years (interquartile range 8–18, range 1–28); mean age at diagnosis 60 years] were diagnosed with RA and fulfilled the ACR criteria after inclusion in the PMP. There was no difference in cholesterol levels between men who subsequently developed RA and controls (mean 5.66 vs. 5.64 mmol/l). By contrast, women with a diagnosis of RA during the follow-up had higher cholesterol levels at baseline compared to controls [mean 6.04; standard deviation (SD) 1.16 vs. 5.71 (SD 1.11) mmol/l; OR 1.54 per SD; 95 % confidence interval (CI) 1.22–1.94)]. A higher cholesterol was predictive of RF positive RA (OR 1.45 per SD; 95 % CI 1.08–1.94) as well as RF negative RA (1.85 per SD; 95 % CI 1.22–2.80) in women. The association between higher cholesterol and subsequent development of RA in women remained significant in separate multivariate analyses adjusted for smoking (p=0.001) or early menopause (at age <46 vs. ≥ 46 years) (p=0.01). The association with future RA was statistically significant among those included 1–12 years before RA diagnosis (OR 1.36 per SD; 95 % CI 1.02–1.80) as well as among those included 13–28 years before RA diagnosis (OR 1.94 per SD; 95 % CI 1.30–2.87).

Conclusion: A higher serum cholesterol was associated with increased risk of RA in women, but not in men. This suggests that sex-specific exposures modify the impact of lipids on the risk of RA. The strong association with higher cholesterol among women surveyed long before RA diagnosis implicates early metabolic pathways in the etiology of RA.

Disclosure: C. Turesson, None; **U. Bergström**, None; **M. Pikwer**, None; **J. Nilsson**, None; **L. Jacobsson**, None.

1408

High Body Mass Index Is Associated With a Reduced Long Term Risk Of Rheumatoid Arthritis In Men. Carl Turesson, Ulf Bergström, Mitra Pikwer, Jan-Åke Nilsson and Lennart Jacobsson. Lund University, Malmö, Sweden.

Background/Purpose: There are diverging results on the relation between body mass index (BMI) and risk of rheumatoid arthritis (RA). From a previous nested case-control study, based on a population based health survey performed in 1974–1992, we reported a reduced risk of RA in men with high BMI, whereas BMI did not affect RA development in women. The purpose of the present study was to investigate the impact of BMI on the risk of RA in a later population based survey performed in the same area.

Methods: Between 1991 and 1996, 30447 subjects (12121 men; 18326 women) were included. Height and weight were measured, and alcohol exposure was assessed using a diary, completed during 7 consecutive days, and classified as low/moderate/high intake. From this population, we identified individuals who developed RA after inclusion by linkage to 4 different RA registers. In a structured review of the medical records, patients were classified according to the 1987 American College of Rheumatology criteria for RA. Four controls for each validated case, matched for sex, year of birth and year of screening, who were alive and free of RA when the index person was diagnosed with RA, were selected from the health survey database. The impact of BMI on the risk of RA was examined in conditional logistic regression models, stratified by sex. Models including alcohol use were restricted to individuals classified as adequate reporters of total energy intake based on previous studies, and adjusted for total energy intake.

Results: A total of 172 patients (36 men/136 women, mean age at RA diagnosis 63 years) were diagnosed with RA after inclusion in the health survey. The median time from inclusion to RA diagnosis was 5 years (range 1–13). Seventy-nine cases (24 men/55 women) had been included in the previous survey. There was no difference in BMI between women who subsequently developed RA and controls [mean 25.9; standard deviation (SD) 4.9 vs. 25.6 (SD 4.4) kg/m^2; odds ratio (OR) for RA development 1.09 per SD; 95 % confidence interval (CI) 0.88–1.35]. By contrast, men with a diagnosis of RA during the follow-up had a lower BMI at baseline compared to controls [mean 24.6 (SD 3.1) vs. 26.5 (SD 3.5) kg/m^2; OR 0.47 per SD (95

% CI 0.29–0.76)]. The negative association between BMI and RA development in men remained significant in separate models adjusted for smoking (p=0.007) and level of formal education (p=0.034), and adjustment for alcohol intake did not lead to major change in the estimated effect of BMI (OR 0.57; 95 % CI 0.30–1.09). Similar adjustments had no significant impact in women. For pre-RA cases who participated in both surveys, the mean time between BMI measurements was 12.4 years in men and 8.7 years in women. Among these subjects, there was on average a slight decrease in BMI in men (mean change −0.06 kg/m^2 per year; 95 % CI −0.27 to 0.15) and a slight increase in women (mean change 0.14 kg/m^2 per year; 95 % CI −0.25 to 0.53).

Conclusion: BMI was negatively associated with future RA development in men. This pattern did not appear to be explained by differences in smoking, education or alcohol use. There were no major changes in BMI over time in cases who later developed RA. Hormonal factors related to adipose tissue may reduce the long term risk of RA in men.

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ACR/ARHP Poster Session B
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy II
Monday, October 28, 2013, 8:30 AM–4:00 PM

1409

Long-Term Impact of Delaying Combination Therapy With Adalimumab Plus Methotrexate By 2 Years in Patients With Early Rheumatoid Arthritis: Final 10-Year Results of the Premier Trial. Edward C. Keystone[1], Ferdinand C. Breedveld[2], Désiréé van der Heijde[2], Robert Landewe[3], Stefan Florentinus[4], Udayasankar Arulmani[5], Shufang Liu[5], Hartmut Kupper[6] and Arthur Kavanaugh[7]. [1]University of Toronto, Toronto, ON, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Academic Medical Center, Amsterdam, Netherlands, [4]AbbVie, Rungis, France, [5]AbbVie Inc., North Chicago, IL, [6]AbbVie Deutschland GmbH & Co KG, Ludwigshafen, Germany, [7]University of California San Diego, San Diego, CA.

Background/Purpose: The PREMIER trial demonstrated the superiority of initial adalimumab (ADA)+MTX vs the individual monotherapies in MTX-naïve patients (pts) with early, aggressive rheumatoid arthritis (RA). The purpose of this study was to assess long-term outcomes in pts treated with ADA, with or without MTX, for up to 10 years (yrs).

Methods: Pts completing the 2yr blinded study were eligible to receive open-label (OL) ADA for up to an additional 8 yrs; MTX could be added at the investigator's discretion. This *post hoc* analysis evaluated data as observed (ie, no imputation for missing data); results are summarized overall and by initial treatment arm. DAS28(CRP) and HAQ-DI were used to assess clinical and functional outcomes, respectively. Radiographic progression (change from baseline in mTSS) was assessed in 10yr completers with radiographic data available at baseline and yr 10. Adverse events (E) of interest were summarized for pts receiving ≥1 ADA dose and presented as E/100-pt yrs (PY).

Results: Of the 799 pts randomized, 497 (62%) entered the OL extension; 250 (31%) maintained OL ADA±MTX through yr 10. MTX co-therapy was (re)initiated in 261 pts (53%) during the OL extension. Overall, pts completing 10 yrs of therapy continued to demonstrate effective disease control (mean DAS28=2.4; mean HAQ-DI=0.6; mean ΔmTSS=7.8). Although the addition of OL ADA±MTX to the initial MTX and ADA arms at yr 2 led to increases in the proportions achieving DAS28(CRP) <2.6 and HAQ-DI <0.5 over time, differences between initial treatment arms persisted through yr 10 (**Table**). Further, ΔmTSS remained significantly lower over time in the initial ADA+MTX arm compared with the 2 monotherapy arms (ΔmTSS = 4.0, 11.0, and 8.8 at yr 10 for the initial ADA+MTX, MTX, and ADA arms, respectively; both P <0.05), despite OL ADA±MTX slowing progression comparably in each of the arms (both P>0.05). No new safety signals arose following 3708 PY of ADA exposure (N=697 pts): serious infections = 2.6 E/100-PY; TB =0.2 E/100-PY; malignancy (other than NMSC) SIR (95% CI) =0.89 (0.62, 1.26). There were 23 deaths during this 10yr study, resulting in an SMR (95% CI) of 0.72 (0.49, 1.02).

Parameter	ADA+MTX → OL ADA±MTX	MTX → OL ADA±MTX	ADA→ OL ADA±MTX
DAS28(CRP) <2.6, n/N (%)			
Yr 2[a]	131/198 (66)	64/167 (38)	69/160 (43)
Yr 10	59/78 (76)	41/73 (56)	50/81 (62)
HAQ-DI <0.5, n/N (%)			
Yr 2[a]	130/199 (65)	88/167 (53)	74/160 (46)
Yr 10	54/85 (64)	42/77 (55)	45/85 (53)
ΔmTSS ≤0.5, n/N (%)			
Yr 2[a]	61/85 (72)	33/77 (43)	39/84 (46)
Yr 10	31/86 (36)	24/77 (31)	22/85 (26)
DAS28(CRP) <2.6 + HAQ-DI <0.5 + ΔmTSS ≤0.5[b], n/N (%)			
Yr 2[a]	29/85 (34)	10/77 (13)	12/84 (14)
Yr 10	17/86 (20)	5/77 (7)	6/85 (7)

[a]End of double-blind period.
[b]NRI was used to replace missing DAS28(CRP) or HAQ-DI values.

Conclusion: ADA±MTX maintained effective disease control for up to 10 yrs in pts with early, aggressive RA. Of the pts who continued in the study, those who initiated ADA+MTX combination therapy retained better outcomes through 10 yrs than pts who began treatment with MTX or ADA monotherapy.

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1410

Tocilizumab Improves Left Ventricular Mass and Cardiac Output in Patients With Rheumatoid Arthritis. A Cohort Study. Kensuke Kume[1], Kanzo Amano[1], Susumu Yamada[1], Toshikatsu Kanazawa[2], Hiroshi Komori[2], Hiroyuki Ohta[3], Kuniki Amano[4] and Noriko Kuwaba[5]. [1]Hiroshima Clinic, Hiroshima, Japan, [2]Hiroshima Clinic, Hiroshima, Japan, [3]Hiroshima Clinic, Hiroshima, Japan, [4]Sky Clinic, Hiroshima, Japan, [5]Sanki Clinical Link, Hiroshima, Japan.

Background/Purpose: Rheumatologists need to develop primary prevention strategies for cardiovascular disease (CVD) in rheumatoid arthritis (RA) patients. We reported tocilizumab (TCZ) improved arterial stiffness as well as etanercept and adalimumab. RA is associated with an increased **left**ventricular mass index (LVMI), a strong marker of cardiovascular mortality. There is no evidence that TCZ effects on left ventricular (LV) morphology and function. To study the effect of TCZ plus methotrexate (MTX) on LV morphology and function in MTX resistant active RA patients, in a cohort study design.

Methods: RA patients were eligible if they had active disease despite treatment with MTX. All patients have no steroids, and no previous history of CVD. Consecutive 34 patients with moderate to severe active RA patients (DAS28>3.2) despite MTX were received TCZ plus MTX. LV morphology and function was assessed with cardio-MRI at baseline and 24 weeks follow-up. Cardiovascular risk factors and clinical data were collected at regular visits.

Results: 31 patients completed 24 weeks. Left ventricular mass index (LVMI) was attenuated significantly by TCZ (week 0-week24, −19.8±6.9 g/m^2; p=0.0002). Cardiac output (CO) was attenuated significantly by TCZ (week 0-week24,-0.99 ± 1.4l/min). DAS28 and CRP improved significantly by TCZ (week 0-week24; DAS28: −2.35±0.85; CRP: 24.3±7.2 mg/l) (p<0.05). Surprisingly, the change of disease activity (DAS 28 and CRP) is no correlation with the change of LVMI or CO in this study. Observationally, 6 cases significantly improved right ventricular mass as well as left ventricular mass (20 % improved right ventricular mass index from baseline).

Conclusion: TCZ improved LVMI and CO in active RA despite MTX. TCZ improves LVMI and CO independently of its effects on disease activity. TCZ might be improved right ventricular mass. Interleukin (IL) 6 might be an important role of LV hypertrophy. TCZ, anti- Interleukin (IL) 6 receptor antibody, may prevent cardiovascular morbidity and mortality in RA.

References:

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2) Etanercept normalises left ventricular mass in patients with rheumatoid arthritis. Claire Immediato Daïen et al. Annals of the rheumatic diseases. 2013 Jun; 72(6); 881–7. doi: 10.1136/annrheumdis-2012–201489.

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1411

The Peroxisome Proliferator Activated Receptor-gamma pioglitazone Decreases Cardiovascular Risk and Disease Activity In Patients With Rheumatoid arthritis. Wendy Marder[1], Shokoufeh Khalatbari[2], James D. Myles[3], Rita Hench[1], Susan Lustig[1], Srilakshmi Yalavarthi[4], Aishwarya Parameswaran[1], Robert Brook[2] and Mariana J. Kaplan[4]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan at Ann Arbor, Ann Arbor, MI, [3]Michigan Institute for Clinical and Health Research, University of Michigan, Ann Arbor, MI, [4]University of Michigan Rheumatology, Ann Arbor, MI.

Background/Purpose: Rheumatoid arthritis (RA) is associated with heightened mortality due to atherosclerotic cardiovascular disease (CVD). Inflammatory pathways in RA negatively affect vascular physiology and promote metabolic disturbances that contribute to CVD. We hypothesized that the peroxisome proliferator activated receptor-γ (PPAR-γ) pioglitazone could promote potent vasculoprotective and anti-inflammatory effects in RA, thereby decreasing CV risk and RA disease activity.

Methods: 143 non-diabetic adult RA patients (76.2% female, age 55.2 $\pm$ 12.1 (mean +SD) on stable RA standard of care treatment were enrolled in a randomized, double- blind placebo controlled crossover trial of 45 mg daily pioglitazone versus placebo, with a 3 month duration/arm with a 2 month-washout period. Brachial artery flow mediated dilatation (FMD), nitroglycerin mediated dilatation (NMD), pulse wave velocity of the aorta (PWV), microvascular endothelial function (reactive hyperemia index [RHI]) and circulating biomarkers of inflammation, insulin resistance and atherosclerosis risk were quantified. RA disease activity was assessed with the 28 Joint-Disease Activity Scale-C-reactive protein (DAS28-CRP) and the SF-36 quality of life questionnaire.

Results: When added to standard of care RA treatment, pioglitazone significantly decreased pulse wave velocity (i.e., aortic stiffness) ($p=0.01$), while FMD and RHI remained unchanged when compared to treatment with placebo. Further, pioglitazone significantly reduced RA disease activity ($p=0.02$) and CRP levels ($p=0.001$), while improving lipid profiles. The drug was well tolerated.

Conclusion: Addition of pioglitazone to RA standard of care significantly improves aortic elasticity and decreases inflammation and disease activity with minimal safety issues.

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1412

Use Of a Biologic Marker For An Integrated Pharmacodynamic and Clinical Analysis To Inform Further Clinical Development, Including Dose Selection For The Phase 2b Trial - *Treat 2b* - Of Tregalizumab In Rheumatoid Arthritis. Eva Dokoupilova[1], Slawomir Jeka[2], Jiri Vencovsky[3], Janusz Badurski[4], Klaas Prins[5], Vibeke Strand[6], Edward C. Keystone[7], Ronald F van Vollenhoven[8], Jurgen Wollenhaupt[9], Andrea Wartenberg-Demand[10], Gabriele Niemann[10], Ahmed Abufarag[10], Silke Aigner[10], Sibylle Kaiser[10], Faiza Rharbaoui[10], Niklas Czeloth[10], Ralf Wolter[10], Benjamin Dälken[10] and Thorsten Holzkämper[10]. [1]Medical Plus s.r.o, Uherske Hradiste, Czech Republic, [2]Clinic of Rheumatology and Connective Tissue Diseases University Hospital No 2 in Bydgoszcz Collegium Medicum UMK in Torun, Bydgoszcz, Poland, [3]Institute of Rheumatology, Department of Clinical and Experimental Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [4]Center of Osteoporosis and Osteo-articular Diseases, Bialystock, Poland, [5]qPharmetra, Nijmegen, Netherlands, [6]Stanford University, Portola Valley, CA, [7]Mount Sinai Hospital, University of Toronto, Toronto, ON, [8]Karolinska Institutet, Stockholm, Sweden, [9]Schoen-Klinik Hamburg-Eilbek Teaching Hospital of the University of Hamburg, Hamburg, Germany, [10]Biotest AG, Dreieich, Germany.

Background/Purpose: In patients with rheumatoid arthritis (RA) reduced numbers and functional impairment of regulatory T cells (Tregs) have been observed. Tregalizumab is a humanized, agonistic monoclonal antibody which binds to a unique epitope of CD4, and induces Treg-specific activation and suppresses CD4 and CD8 effector cell proliferation and activity *in vitro*. Phase 2a randomized controlled RA trials of monotherapy (Study 962) and in combination with methotrexate (MTX) (Study 971) indicated efficacy in RA patients at SC doses of $\geq$25 mg with most pronounced effects on tender and swollen joint counts.

A biomarker was developed to monitor biologic response in humans. An integrated pharmacokinetic-pharmacodynamic (PK-PD) model was utilized to better characterize the optimal doses of tregalizumab for further investigation.

Methods: In the Phase 2b trial 979, MTX inadequate responders (MTX-IR) were randomized to tregalizumab 25, 50, 75 mg, or placebo SC weekly (in combination with stable MTX) for 12 weeks with 12 weeks' follow-up. The primary endpoint was ACR20 response at week 13 (1 week post treatment); SDAI, CDAI, PK-PD, and safety were also evaluated.

The integrated model utilized biomarker and clinical data from all completed RCTs and healthy volunteer studies of tregalizumab, together with interim data from the ongoing Study 979. This model was able to describe the relationship between SC tregalizumab doses and biologic responses. The model was then used to predict the dose-response relationship and to inform dose selection for the planned Phase 2b trial TREAT 2b (Study 986).

Results: The interim clinical analysis of Study 979 in 112 patients indicated efficacy vs. placebo (ACR20/50/70 responses at Week 13). The most pronounced effects were seen for tender and swollen joint counts. In Study 979 tregalizumab was well tolerated with no major safety findings, no CD4 cell depletion was observed.

PK-PD modeling demonstrated a significant correlation between dose, biomarker data, and clinical efficacy. Moreover, the model showed that maximal biologic response had not yet been attained with weekly doses up to 75 mg, predicting greater biologic response and better clinical efficacy with higher doses exceeding 75 mg, approaching a plateau at 200 mg weekly.

Conclusion: Interim efficacy and safety data from the Phase 2b Study 979, combined with data from previous RCTs, indicated the feasibility and tolerability of this therapeutic approach. The integrated PK-PD model confirmed the rationale for testing higher doses of tregalizumab up to 200 mg SC weekly in combination with MTX. Therefore, in the Phase 2b multicenter RCT (TREAT 2b – Study 986) 304 MTX-IR patients will receive tregalizumab 25 mg, 100 mg, 200 mg, or placebo SC weekly for 24 weeks, followed by an extension phase of 24 weeks. The available data support further development of tregalizumab.

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1413

Long-Term Safety and Efficacy Of Certolizumab Pegol In Combination With Methotrexate In The Treatment Of Rheumatoid Arthritis: 5-Year Results From a 52-Week Randomized Controlled Trial and Open-Label Extension Study. Edward Keystone[1], Robert Landewé[2], Ronald van Vollenhoven[3], Bernard Combe[4], Vibeke Strand[5], Philip J. Mease[6], Laura Shaughnessy[7], Brenda VanLunen[7] and Désirée van der Heijde[8]. [1]University of Toronto, Toronto, ON, [2]Academic Medical Center Amsterdam & Atrium Medical Center, Heerlen, Netherlands, [3]The Karolinska Institute, Stockholm, Sweden, [4]Montpellier University Hospital, Montpellier, France, [5]Stanford University, Palo Alto, CA, [6]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA, [7]UCB Pharma, Raleigh, NC, [8]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: In the RAPID1 randomized controlled trial (RCT; NCT00152386),[1] certolizumab pegol (CZP) every 2 weeks (Q2W) plus MTX over 52 weeks (wks) provided rapid improvements in signs and symptoms and inhibition of radiographic damage in patients (pts) with active rheumatoid

arthritis (RA). In this publication we examine the safety and efficacy of CZP plus MTX over 5 yrs in RA.

Methods: Eligible pts were treated in the open-label extension (OLE) to RAPID1 (NCT00175877) with CZP 400mg Q2W, reduced to 200mg Q2W after ≥6 months, plus MTX.[2] Primary objective of the OLE was to monitor safety; secondary objective was to assess efficacy. Combined safety data from RCT and OLE are presented to Wk334 (6.4 yrs) for all pts receiving ≥1 dose of CZP in RCT or OLE (Safety population, N=958). ACR20/50/70, DAS28(ESR) and HAQ-DI are reported to Wk256 (4.9 yrs) for CZP pts who completed the 52-wk RCT (CZP Completers, N=508) and for all pts randomized to CZP 400mg or 200mg in RCT (ITT population, N=783). Change from baseline in modified Total Sharp Score (mTSS) and % of pts with radiographic non-progression (defined as a change in mTSS from RCT baseline of ≤0.5) are reported to Wk148 (2.8 yrs) for CZP Completers. Missing categorical data were imputed by modified non-responder imputation, continuous data by last observation carried forward, and radiographic data by linear extrapolation. Kaplan-Meier analysis was used to estimate pt retention.

Results: Overall event rate per 100 pt-yrs (ER) of AEs was 290.4 and SAEs was 20.3 (serious infections=5.9; total exposure [including 84-day safety follow-up period]: 3,732 pt-yrs). The most common AEs (MedDRA preferred terms) were urinary tract infection (ER=7.9), nasopharyngitis (ER=7.3) and upper respiratory tract infection (ER=7.3). 177 pts (18.5%) experienced an AE leading to withdrawal (incidence rate per 100 pt-yrs [IR]=4.8). 21 (2.2%) experienced an AE leading to death (IR=0.6) (including 5 malignancies, 5 cardiac disorders, 3 infections). ACR20/50/70 response rates for CZP Completers and ITT population were maintained to Wk256 (74.4%/57.3%/39.6% and 59.0%/43.7%/28.8%, respectively), as were DAS28(ESR) remission rates (25.2% and 20.3%), improvements in DAS28(ESR) (mean values: 3.43 and 3.83; mean change from baseline: −3.49 and −3.08) and HAQ-DI (mean values: 0.90 and 1.00; mean change from baseline: −0.77 and −0.66). The rate of radiographic progression in CZP-treated pts was not observed to change over time (mean change in mTSS from RCT baseline to Wk52: 0.27, from RCT baseline to Wk148: 0.77; proportion of pts achieving radiographic non-progression at Wk52: 76.5%, Wk148: 68.9%).

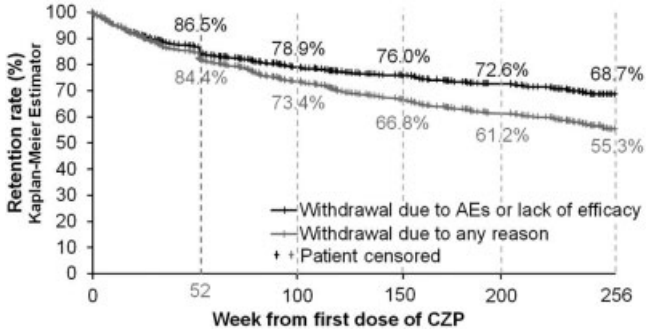

Figure. Kaplan-Meier estimators of pt retention to Wk256 (ITT Population).

Conclusion: CZP plus MTX provided a favorable risk-benefit profile over 5 yrs of treatment in pts with active RA. No new safety signals were identified.

Reference:

1. Keystone E. Arthritis Rheum 2008;58(11):3319–3329; 2. Keystone E. Rheumatology 2012;51(9):1628–1638

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Final 5-Year Safety and Efficacy Results Of a Phase 3, Randomized Placebo-Controlled Trial Of Golimumab In Patients With Active Rheumatoid Arthritis Despite Prior Treatment With Methotrexate.

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Background/Purpose: The safety and efficacy of subcutaneous golimumab (GLM)+/−MTX has been evaluated through 2yrs in a phase 3 trial (GO-FORWARD) of pts with active rheumatoid arthritis (RA) despite MTX therapy. Final safety and efficacy results through 5yrs are reported.

Methods: Pts in GO-FORWARD were randomized to placebo (PBO)+MTX, GLM 100mg+PBO, GLM 50mg+MTX, or GLM 100mg +MTX q4w. PBO+MTX pts crossed over to GLM+MTX at wks 16 (blinded early escape) or 24 (crossover). Pts continued treatment at wk52 (start of long-term extension). After the last pt completed wk52 and unblinding occurred, MTX and corticosteroid use could be adjusted, and a one-time GLM dose increase (50 à100mg) or decrease (100 à50mg) was permitted based on investigator judgment. The last GLM injection was at wk252. Observed efficacy results (ACR20/50/70, DAS28-CRP, HAQ-DI, radiographic) by randomized treatment group and cumulative safety data are reported through wks 256 and 268, respectively.

Results: A total of 444 pts were randomized; 313 pts continued treatment through wk252, and 131 pts withdrew (64 for AE, 25 for lack of efficacy, 1 protocol violation, 6 lost to follow-up, 32 for other reasons, 3 deaths). 301 completed the safety follow-up through wk268. Efficacy results are presented in the table. At wk256, 76.0% of all pts had an ACR20, 89.5% had a DAS28-CRP EULAR response, and 68.5% had improvement in HAQ-DI ≥0.25. Changes from baseline in mean total vdH-S scores were small; 54% of pts randomized to GLM+MTX had no radiographic progression (DvdH-S ≤0). The most common AEs were upper respiratory tract infection (32.9%), nasopharyngitis (17.1%), and bronchitis (17.1%); 9.2% of pts had an injection-site reaction. Through wk268, 172/434 pts (39.6%) had an SAE; 14.1% of pts discontinued study agent due to AEs. The rates of serious infections, malignancies, and death were 11.5%, 6.2%, and 1.8%, respectively. Of 429 pts with available samples, 33 (7.7%) were positive for antibodies to GLM.

Table. Efficacy results at wk256

Efficacy at wk256	PBO+MTX[a]	GLM100mg+ PBO[b]	GLM 50mg +MTX[b]	GLM 100mg +MTX[b]	Total
ACR20	69/91 (75.8%)	71/93 (76.3%)	57/74 (77.0%)	44/59 (74.6%)	241/317 (76.0%)
ACR50	43/91 (47.3%)	48/93 (51.6%)	40/74 (54.1%)	28/59 (47.5%)	159/317 (50.2%)
ACR70	21/91 (23.1%)	27/93 (29.0%)	28/74 (37.8%)	15/59 (25.4%)	91/317 (28.7%)
DAS28-CRP EULAR Response	81/90 (90.0%)	83/92 (90.2%)	65/73 (89.0%)	52/59 (88.1%)	281/314 (89.5%)
DAS28-CRP Remission (<2.6)	38/90 (42.2%)	41/92 (44.6%)	35/73 (47.9%)	27/59 (45.8%)	141/314 (44.9%)
SDAI ≤3.3	25/90 (27.8%)	21/92 (22.8%)	20/73 (27.4%)	17/60 (28.3%)	83/315 (26.3%)
DAS28-CRP ≤3.2	56/90 (62.2%)	59/92 (64.1%)	46/73 (63.0%)	38/60 (63.3%)	199/315 (63.2%)
HAQ-DI improvement ≥0.25	61/91 (67.0%)	59/93 (63.4%)	55/74 (74.3%)	42/59 (71.2%)	217/317 (68.5%)
Radiographic results at wk256.					
Estimated annual progression rate at baseline[c]	5.3 ± 7.8	5.6 ± 8.9	4.7 ± 6.9	5.4 ± 13.7	5.3 ± 9.3
Mean ± SD annual rate of progression through 5yrs[d]	0.7 ± 2.0	1.0 ± 2.3	0.3 ± 1.2	0.7 ± 2.2	0.7 ± 2.0
Mean ± SD change in vdH-S score	3.2 ± 9.2	4.6 ± 10.9	1.7 ± 6.1	3.3 ± 10.2	3.3 ± 9.4
Change in vdH-S score ≤0	52/95 (54.7%)	43/99 (43.4%)	47/79 (59.5%)	30/65 (46.2%)	172/338 (50.9%)

[a]Pts switched to GLM at wk16 or 24. [b]After wk52 pts could receive GLM50 mg or 100mg, and MTX could be added/adjusted. [c] vdH-S score divided by the disease duration per pt. [d]Change in vdH-S score divided by GLM treatment duration per pt.

Conclusion: The retention rate was high (70.5%), and improvements in signs/symptoms of RA and in physical function with GLM+MTX therapy were maintained long-term. Radiographic progression appeared controlled with small changes in mean vdH-S scores observed through 5yrs. The long-term safety of GLM is consistent with other anti-TNFα agents.

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Safety and Effectiveness Of Abatacept In 3985 Japanese Patients With Rheumatoid Arthritis; Japan All-Cases Post-Marketing Surveillance.

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Background/Purpose: A large-scale post-marketing surveillance (PMS) has been implemented to evaluate the safety and effectiveness on the use of intravenous abatacept (ABT) in Japanese patients with rheumatoid arthritis (RA) as per approval condition.

Methods: This observational study has registered all of the patients intended to be treated with ABT in Japan after its start of marketing in September 2010. Patients were prospectively monitored for adverse events (AEs) for 24 weeks. Disease Activity Score 28-CRP (DAS28-CRP) was calculated at baseline, Weeks 4, 12 and 24 of treatment.

Results: Of 4256 patients treated with ABT between September 2010 and June 2011, the safety and effectiveness were analyzed in 3985 and 3094 patients, respectively. Most of the patients from the safety population had established RA. Their mean age was 61.3 years and mean RA duration was 10.3 years. About 70% of patients had received biologic drug(s) prior to ABT. Methotrexate (MTX) and corticosteroid were used concomitantly in 67.0% and 63.3% of patients, respectively. Adverse drug reactions (ADRs) and serious ADRs occurred in 15.4% and 2.5% of patients, respectively. ADRs in ≥0.5% of patients included upper respiratory tract inflammation (1.2%), herpes zoster (1.0%), bronchitis (0.9%), stomatitis (0.9%), nasopharyngitis (0.9%), abnormal hepatic function tests (0.8%), pyrexia (0.6%), and rash (0.6%). Infections occurred in 5.9%; pneumonia in 28 patients (0.7%), *Pneumocystis jirovecii* pneumonia in 4 patients (0.1%), tuberculosis in 1 patient (0.03%) and atypical mycobacterial infection in 2 patients (0.05%). Serious infections were reported in 1.0% of patients. ABT was tolerated even in patients who had prior biologics use, there was no statistical difference of the incidence of ADRs or serious ADRs between biologic-naïve and -experienced patients. The incidence of ADRs was numerically lower, although not statistically, in patients using MTX than in patients not using MTX. Multivariate logistic regression analyses showed that age >65 years, body weight <40 kg, hepatic comorbidities, history/presence of respiratory disorders, history of allergies, prior use of tocilizumab, and concomitant use of prednisolone >5 mg/day were risk factors for infections. DAS28-CRP decreased from 4.47 at baseline to 3.25 at Week 24, with significant reductions from baseline as early as Week 4 ($P < 0.001$). The decrease in DAS28-CRP was significantly greater in the biologic-naïve group than in the biologic-experienced group ($P < 0.001$). The mean change in DAS28-CRP from baseline to Week 24 in patients not using MTX (–1.10) was almost same as in patients using MTX (–1.27), although with a statistical difference ($P = 0.003$). In the biologic-naïve group, the reduction in DAS28-CRP at Week 24 was not statistically different between patients using MTX and not using MTX.

Conclusion: This large-scale PMS program showed that ABT was well tolerated with no new safety concerns and significantly reduced signs and symptoms of Japanese patients with RA treated in real-world settings.

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Safety and Efficacy Of Subcutaneous Golimumab In Chinese Patients With Active Rheumatoid Arthritis Despite MTX Therapy: Results From a Randomized, Placebo-Controlled, Phase 3 Trial.

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Background/Purpose: Assess safety and efficacy of GLM+MTX over 1yr in a multicenter, randomized, placebo (PBO)-controlled study of Chinese pts with active RA despite MTX therapy.

Methods: 264 pts were randomized (1:1) to subcutaneous PBO+MTX (Group1) or GLM 50mg+MTX (Group2) q4wks. All pts received stable doses of oral MTX (7.5–20mg/wk). Group1 pts with inadequate treatment response entered blinded early escape to GLM 50mg+MTX at wk16. All remaining Group1 pts switched to GLM 50mg+MTX at wk24. Blinding to randomization assignment was maintained through wk 56. The last GLM injection was at wk48; the last efficacy assessment was wk52. The primary endpoint was ACR20 at wk14. Efficacy assessments included DAS28-CRP, HAQ-DI, SF-36 PCS and MCS, and FACIT-Fatigue scores. Adverse events (AEs) were monitored through wk56.

Results: Baseline demographics and disease characteristics were generally similar between the groups; median age was 49 yrs and 81.1% of pts were female. 23 (8.7%) pts discontinued treatment through wk56. Efficacy results are shown in the table. At wk14, 15.9% of Group1 pts and 40.9% of Group2 pts had ACR20 response ($p<0.001$). At wk24, Group2 pts had significantly greater improvements in DAS28-CRP, SF-36 PCS and MCS scores, and FACIT-fatigue score. A greater proportion of Group2 pts had HAQ-DI improvement ≥0.25 vs. Group1. The responses to GLM+MTX therapy were maintained through wk52 in Group2; after switching to GLM, Group1 pts also achieved rapid improvement. Through wk16, 23.5% of Group1 pts and 26.7% of Group2 pts reported AEs (infections were the most common); 0.8% and 1.5% reported serious AEs. Through wk56, 130/259 (50.2%) of GLM+MTX-treated pts had an AE, and 11/259 (4.2%) had an SAE. 3 serious infections (pneumonia, lung infection, respiratory tract infection) and 1 death (acute myocardial infarction) occurred in GLM+MTX-treated pts. No malignancies or opportunistic infections were reported. Only 1 pt had an injection site reaction (mild pain).Of the 251 GLM+MTX-treated pts with available samples, 6 (2.4%) were positive for antibodies to GLM through wk52.

Table. Efficacy results through week 52

	PBO+MTX/GLM 50 mg+MTX (n = 132)	GLM 50 mg +MTX (n = 132)
Wk24		
ACR20	21 (15.9%)	56 (42.4%)**
DAS28-CRP, Mean±SD change from baseline	−0.2 ± 1.5	−1.2 ± 1.3**
HAQ-DI improvement ≥ 0.25	39 (29.5%)	65 (49.2%)*
SF-36 PCS, Mean±SD change from baseline	−0.88 ± 6.92	4.30 ± 7.05**
SF-36 MCS, Mean±SD change from baseline	−2.68 ± 12.07	2.23 ± 10.59**
FACIT-F, Mean±SD change from baseline[a]	−2.2 ± 11.2	3.4 ± 9.4**
Wk52		
ACR20	75 (56.8%)	92 (69.7%)
DAS28-CRP, Mean±SD change from baseline	−2.0 ± 1.4	−2.2 ± 1.4
HAQ-DI improvement ≥ 0.25	65 (49.2%)	87 (65.9%)
SF-36 PCS, Mean±SD change from baseline	3.6 ± 7.1	6.8 ± 8.9
SF-36 MCS, Mean±SD change from baseline	0.2 ± 9.8	3.9 ± 11.0

* $p = 0.001$, ** $p < 0.001$
[a] No assessments past wk24.

Conclusion: Among Chinese pts with RA, GLM+MTX-treated pts had significantly greater improvements in RA signs/symptoms vs. PBO+MTX-treated pts through wk24, and responses were maintained through wk52. GLM+MTX was well tolerated and no unexpected safety events occurred through wk56. In Chinese pts, GLM+MTX demonstrated efficacy and acceptable safety similar to that in a global population in the GO-FORWARD trial.

Disclosure: Z. Li, Janssen Research & Development, LLC., 9; **F. Zhang**, Janssen Research & Development, LLC., 9; **J. Kay**, Abbott Laboratories, 2, Ardea Biosciences, 2, Eli Lilly and Company, 2, Fidia Farmacutici, SpA, 2, Pfizer Inc, 2, Roche Laboratories, 2, sanofi-aventis, 2, Amgen Inc., 5, Baxter Healthcare Corporation, 5, Bristol-Myers Squibb Company, 5, Celgene Corp., 5, fourteen22 Inc., 5, Genentech Inc., 5, Hospira, Inc., 5, Horizon Pharma, Inc., 5, Janssen Biotech, Inc., 5, medac pharma Inc., 5, PanGenetics, B.V., 5, Pfizer Inc., 5, Roche Laboratories, Inc., 5, Savient Pharmaceuticals, Inc., 5, Sun Pharmaceutical Industries Ltd., 5, UCB, Inc., 5; **K. Fei**, Janssen Research & Development, LLC., 3; **C. Han**, Janssen Global Services, LLC., 3; **Y. Zhuang**, Janssen Research & Development, LLC., 3; **Z. Wu**, Janssen Research & Development, LLC., 3; **E. C. Hsia**, Janssen Research & Develpment, LLC., 3.

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Lack Of Correlation Between Golimumab Exposure and Selected Safety Events Following Intravenous Or Subcutaneous Administration In An Integrated Analysis Of Phase 3 Data Of Patients With Rheumatoid Arthritis, Psoriatic Arthritis, Or Ankylosing Spondylitis.

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Background/Purpose: For anti-TNFα agents, infections and malignancies are key safety concerns. It is unknown whether safety events are driven by peak (C_{max}), trough (C_{min}), average (C_{avg}) concentrations or by total systemic exposure (AUC). This PK/safety analysis was performed by pooling data from Phase 3 IV/SC golimumab (GLM) studies to investigate if there is any relationship between PK exposure and the occurrence of infections, serious infections, SAEs and malignancies after treatment with IV or SC GLM in pts with RA, PsA, or AS.

Methods: Seven Phase 3 GLM rheumatology studies (2 IV/5 SC) were included to leverage data from a large number of pts over a wide range of dosing regimens. Dosing regimens ranged from 2 mg/kg q8w to 4 mg/kg every q12w (IV studies) and 50 mg q4w to 100 mg q4w (SC studies) and included GLM as monotherapy and in combination with MTX/other nonbiologic DMARDs. Established population PK models of SC & IV GLM were used to generate empirical Bayesian estimates of steady-state GLM PK exposure metrics (C_{max}, C_{avg}, C_{min} and Cumulative AUC) for individual pts using actual dosing records. Infections, serious infections and SAEs were evaluated through ~1yr after initial GLM exposure. Malignancies were evaluated through the latest data cut for the IV program (Aug 15, 2012) and through wk 160 in the SC studies to leverage as much data available as possible due to lower incidence of malignancies compared to infections and SAEs. A total of 2486 pts were included in the PK/safety dataset. For infections, serious infections and SAEs, 2 analyses were performed: (1) a quartile analysis where the proportion of pts with these events were assessed by 4 PK quartile subgroups and (2) the distribution of PK exposure vs. number of occurrences. For malignancies, the distribution of PK exposure vs. the occurrence of malignancies was plotted.

Results: From the quartile analyses of the pooled SC & IV data, as systemic exposures to GLM increased there was no trend of increasing infections, serious infections or SAEs regardless of the distribution of the number of safety events for all PK exposure metrics. When comparing SC to IV data for serious infections, there was also no trend of increasing serious infections with higher exposures. From the distribution plots of the combined IV & SC data, it was observed that for C_{avg}, C_{max}, and AUC, the ranges of exposures across categories of having 0, 1, or >1 infections were similar, while for SAEs and serious infections, higher rates of infections trended to occur in pts having lower exposures. A trend toward the observation of higher systemic exposure to GLM correlating with more safety events was not observed, contrary to what might be expected. From the distribution plots for malignancies, no difference was observed in the PK exposure for pts who had no malignancies vs. pts who had malignancies.

Conclusion: No correlation of the occurrence of infections, serious infections, and SAEs with GLM C_{max}, C_{avg}, C_{min} and Cumulative AUC was observed over 1yr of treatment with SC or IV GLM. There was also no correlation of PK GLM exposure with malignancy occurrences up to 3yrs of treatment. The data suggest that the GLM IV and SC dosing regimens evaluated in these studies have similar safety profiles.

Disclosure: J. H. Leu, Janssen Research & Development, LLC., 3; **A. Beutler**, Janssen Research & Development, LLC., 3; **A. M. Mendelsohn**, Janssen Research & Development, LLC., 3; **S. Liao**, Janssen Research & Development, LLC., 5, Johnson & Johnson, 1; **H. M. Davis**, Janssen Research & Development, LLC., 3; **H. Zhou**, Janssen Research & Development, LLC., 3; **Z. Xu**, Janssen Research & Development, LLC., 3.

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Effects Of Smoking Status On Response To Treatment With Tofacitinib In Patients With Rheumatoid Arthritis.

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Background/Purpose: Cigarette smoking is a known risk factor for developing rheumatoid arthritis (RA).[1] Several recent observational studies suggest that cigarette smoking may be associated with a poor response to treatment with methotrexate (MTX) and TNF inhibitors (TNFi).[2,3] Tofacitinib is a novel, oral Janus kinase inhibitor for the treatment of RA. Analyses investigated the effects of smoking on the response to tofacitinib treatment in patients (pts) with RA enrolled in the Phase (P) 3 program.

Methods: Data from five P3 studies of tofacitinib as monotherapy (ORAL Solo, NCT00814307) or in combination with MTX or other nonbiologic disease-modifying anti-rheumatic drugs (DMARDs) (ORAL Scan, NCT00847613 [1 year data]; ORAL Sync, NCT00856544; ORAL Standard, NCT00853385; ORAL Step, NCT00960440) in DMARD-inadequate responder pts were pooled and analyzed by smoking status at baseline (BL) for pts treated with tofacitinib 5 mg twice daily (BID), 10 mg BID and placebo (PBO). ORAL Standard included an adalimumab (40 mg Q2W; ADA) arm; data from the small subgroup of this population are presented for completeness.

Results: Of the 3315 pts included in the analysis, 1143 (34.5%) reported to be smoking or an ex-smoker ("ever" smokers) at BL. There were greater proportions of males (non-smokers 8.8%, ever smokers 30.7%) and white pts (non-smokers 52.9%, ever smokers 80.2%) among ever smokers; other BL demographics and disease characteristics were similar for non-smokers and ever smokers (age, BMI, RF status, anti-CCP status, DAS28-4(ESR) and HAQ-DI). A history of ever smoking at BL was associated with a higher probability of previous treatment failures with TNFi (non-smokers 19.0%, ever smokers 31.0%) for tofacitinib and PBO arms; a smaller proportion of ADA pts had previous exposure to TNFi regardless of smoking history (<10%). Significant and similar treatment differences for tofacitinib vs PBO for efficacy parameters at Month 3 were seen regardless of smoking status at BL (Table; significance declared as $p \leq 0.05$, 2-sided testing, no adjustment for multiple comparisons). Correlations calculated between smoking duration as of BL and Month 3 continuous efficacy measures (e.g. change from BL in Patient Global Assessment) indicated that smoking duration was generally uncorrelated with efficacy. No consistent differences across efficacy measures were observed between pts that never smoked, were ex-smokers or currently smoked at BL.

Table. Efficacy parameters at Month 3

	Non-smokers (N = 2041)				Ever smokers* (N = 1070)			
	PBO	Adalimumab 40 mg Q2W	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	PBO	Adalimumab 40 mg Q2W	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID
ACR 20, % (n/N)	25.5 (106/415)	55.9*** (71/127)	58.1*** (458/788)	63.4*** (498/785)	28.1 (71/253)	56.9** (41/72)	52.1*** (209/401)	60.6*** (245/404)
ACR 50, % (n/N)	8.9 (37/415)	22.1** (28/127)	29.6*** (233/788)	33.3*** (261/785)	9.1 (23/253)	26.4* (19/72)	29.4*** (118/401)	33.7*** (136/404)
ACR 70, % (n/N)	2.7 (11/415)	7.9* (10/127)	11.4*** (90/788)	15.4*** (121/785)	2.8 (7/253)	9.7 (7/72)	12.0*** (48/401)	16.8*** (68/404)
Change from BL in HAQ-DI, mean (N, SE)	−0.14 (382, 0.03)	−0.37** (123, 0.06)	−0.44*** (748, 0.03)	−0.50*** (758, 0.03)	−0.19 (236, 0.04)	−0.43* (67, 0.08)	−0.41*** (380, 0.04)	−0.56*** (371, 0.04)
Change from BL in DAS28-4 (ESR), mean (N, SE)	−0.80 (344, 0.1)	−1.7*** (108, 0.1)	−1.8*** (660, 0.1)	−2.0*** (663, 0.1)	−0.9 (218, 0.1)	−2.1*** (59, 0.2)	−1.9*** (354, 0.1)	−2.2*** (343, 0.1)
Change from BL in Patient Global Assessment, mean (N, SE)	−7.9 (383, 1.4)	−18.5*** (123, 2.42)	−21.7*** (749, 1.2)	−25.1*** (755, 1.2)	−10.8 (234, 1.9)	−25.7*** (67, 3.4)	−23.9*** (378, 1.7)	−28.9*** (370, 1.7)
Change from BL in Physician Global Assessment, mean (N, SE)	−15.2 (382, 1.2)	−25.9*** (122, 2.1)	−28.3*** (744, 1.0)	−31.2*** (756, 1.0)	−19.2 (234, 1.7)	−31.1** (67, 3.1)	−29.3*** (374, 1.5)	−33.1*** (367, 1.5)

Rates vs PBO using normal approximation to the binomial using the five P3 studies as strata; changes from BL vs PBO using a longitudinal, mixed-effect linear model including all visits to account for repeated measures of the pts; the five P3 studies, BL values and randomized treatment as terms in the model
*P < 0.05, **P < 0.001, ***P < 0.0001 vs PBO; *Pts reported to be smoking or an ex-smoker at the BL assessment; BID, twice daily; BL, baseline; Q2W, every two weeks; SE, standard error

Conclusion: This pooled analysis from five P3 trials indicates that pts receiving tofacitinib achieved a significant response vs PBO, regardless of smoking status at BL. Further research is required to examine the effect of smoking on response to tofacitinib over the long-term.

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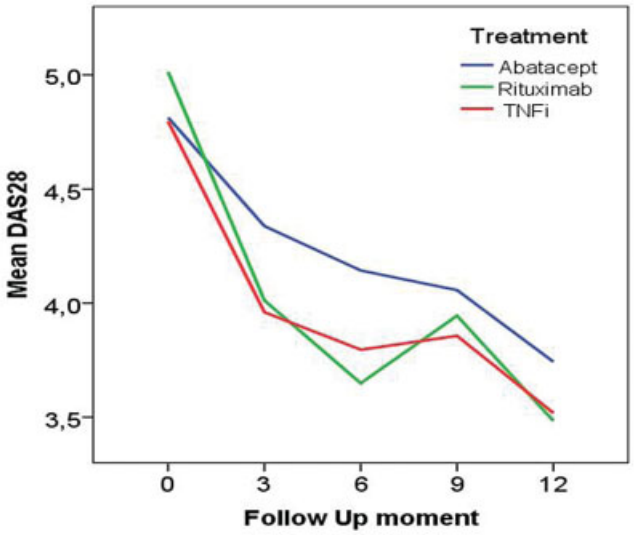
Mode Of Action Change Not Necessary After Failing The First Tumor-necrosisfactor Inhibitor: Preliminary Results Of a Randomized Controlled Trial. Sofie H.M. Manders[1], Wietske Kievit[1], Herman L.M. Brus[2], Hein J. Bernelot Moens[3], Andre Hartkamp[4], Reinhard Bos[5], Elisabeth Brouwer[6], Henk Visser[7], Harald E. Vonkeman[8], Rene Westhovens[9], Mart A.F.J. van de Laar[8] and Piet LCM Van Riel[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]TweeSteden Ziekenhuis, Tilburg, Netherlands, [3]Ziekenhuisgroep Twente, Almelo, Netherlands, [4]Jeroen Bosch Hospital, 's-Hertogenbosch, Netherlands, [5]Medical Center Leeuwarden, Leeuwarden, Netherlands, [6]University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [7]Rijnstate, Arnhem, Netherlands, [8]Medisch Spectrum Twente & University of Twente, Enschede, Netherlands, [9]University Hospital KU Leuven, Leuven, Belgium.

Background/Purpose: The best treatment option after a patient has failed a first TNFi is still unknown. Therefore the objective of this randomized open label study is to compare the effectiveness of abatacept, rituximab or another TNFi after failing a first TNFi, with the DAS28 as outcome measure, in patients with Rheumatoid Arthritis.

Methods: The inclusion criteria for this pragmatic randomized trial within the DREAM cohort were: failing a first TNFi, a DAS28 > 3.2, not treated before with abatacept or rituximab and no contraindications. Patients were randomized to abatacept, rituximab or TNFi treatment. The DAS28 was compared between the three groups with ANOVA, 6 and 12 month after randomization.

Results: 143 patients were randomized into one of the treatments (mean age 56.5 yrs, 76.5% female, median disease duration 5.85 yrs, 63.6% rheumatoid factor positive, mean DAS28 of 4.9). The mean DAS28 (+95% Confidence Interval) after 6 and 12 months respectively was 4.1 (3.7–4.6) and 3.7 (3.2–4.2) for abatacept, 3.6 (3.2–4.1) and 3.5 (3.0–3.9) for rituximab and 3.8 (3.3–4.3) and 3.5 (2.9–4.1) for TNFi, see figure. These were not statistically significant. Remission (DAS28<2.6) was attained in 10.7% and 12.0% in the abatacept group, 24.3% and 27.3% in the rituximab group and 12.9% and 24.1% in the TNFi group at 6 and 12 month respectively.



Conclusion: The data do not reveal a significant difference in effectiveness, measured with the DAS28, between the three different biological. Therefore other reasons than DAS28 status at 6 and 12 months might play a more important role in the choice of a second biological like long term stability of response, side effects, costs or patients preferences for route of administration of treatments.

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1420

Induction Therapy With Adalimumab On Top Of An Aggressive Treat-To-Target Strategy With Methotrexate and Intraarticular Corticosteroid Reduces Radiographic Erosive Progression In Early Rheumatoid Arthritis, Even After Withdrawal Of Adalimumab. Results Of a 2-Year Trial (OPERA). Kim Hørslev-Petersen[1], Lykke Midtbøll Ørnbjerg[2], Merete L. Hetland[3], Peter Junker[4], Jan Pødenphant[5], Torkell Ellingsen[6], Palle Ahlqvist[7], Hanne M. Lindegaard[8], Asta Linauskas[9], Annette Schlemmer[10], Mette Y. Dam[11], Ib Hansen[12], Tine Lottenburger[7], Anette Jørgensen[11], Sophine B. Krintel[2], Johnny Raun[1], Christian G. Ammitzbøll[11], Julia Johansen[2], Mikkel Østergaard[13] and Kristian Stengaard-Pedersen[11]. [1]University of Southern Denmark, Graasten, Denmark, [2]Copenhagen University and Glostrup Hospital, Copenhagen, Denmark, [3]DANBIO, Center for Rheumatology and Spine Diseases, Glostrup Univ Hospital, Glostrup, Denmark, [4]University of Southern Denmark, Odense, Denmark, [5]Copenhagen University at Gentofte, Hellerup, Denmark, [6]Silkeborg Regional Hospital, Silkeborg, Denmark, [7]University of Southern Denmark, Vejle, Denmark, [8]Odense University Hospital, Odense, Denmark, [9]Vendsyssel Hospital, Hjørring, Denmark, [10]Aalborg University Hospital, Aalborg, Denmark, [11]Arhus University Hospital, Aarhus, Denmark, [12]Viborg Hospital, Viborg, Denmark, [13]Copenhagen University Hospital Glostrup, Copenhagen, Denmark.

Background/Purpose: In a randomized double-blind, placebo-controlled 2-year investigator-initiated trial of patients with early rheumatoid arthritis[1] (RA) we aimed to investigate if additional adalimumab (ADA) for 1 year on top of an aggressive treat-to-target strategy with methotrexate (MTX) and intraarticular (i.a.) corticosteroid reduces structural damage progression assessed by conventional radiography.

Methods: DMARD naïve early RA patients (n=180) were randomized 1:1 to receive i.a. triamcinolone (40 mg/ml) in any swollen joint and MTX (20 mg/wk) for two years in combination with placebo-ADA (MTX+PLA) or MTX+ADA (40 mg eow) during the first year. Oral glucocorticoid was not allowed. After 1 year, PLA/ADA was withdrawn. During year 2, in both treatment arms, ADA (40 mg eow) was only (re)initiated in patients with recurrence of active disease (DAS28CRP>3.2). Radiographic changes in hands, wrists and feet (Joint Space Narrowing (JSN), Erosion (ES) and Total Sharp Score (TSS)) were evaluated at baseline, 1 and 2 years.

Results: Baseline characteristics were similar in the MTX+PLA and MTX+ADA groups: DAS28CRP 5.6 vs. 5.5, p=0.53. After 2 years the

median MTX dose in the MTX+PLA/MTX+ADA group was 20/20 mg/wk, p=0.33, and the cumulated i.a. triamcinolone dose 8/6 ml, p=0.15. During the 2nd year biologics were initiated in 15%/17%, p=0.97. The 1- and 2-year remission rates (DAS28CRP<2.6) in the MTX+PLA/MTX+ADA group were 49%/74% (p=0.0001) and 69%/66% (p=0.79), respectively. ADA reduced erosive progression (ΔES) throughout the study (table). The percentage of patients with erosive disease increased in the MTX+PLA/MTX+ADA group with 12%/2% during year 1 and remained unchanged during year 2. The annual erosive progression (ΔES) and the percentage of patients who progressed were lower in the MTX+ADA group in year 1 (p=0.02/p=0.04) and also in year 2, after ADA withdrawal (p=0.005/p=0.04). After 2 years total ES was borderline lower in the MTX+ADA group (p=0.06). ΔTSS was lower in the ADA+MTX group than in the PLA+MTX group in year 1 (mean 0.27 vs. 1.64, p<0.009) but not in year 2 (0.78 vs. 0.99, p=0.46).

	MTX+ 1stYR PLACEBO	MTX+ 1stYR ADA	P	MTX+ 1stYR PLACEBO	MTX+ 1stYR ADA	P	MTX+ 1stYR PLACEBO	MTX+ 1stYR ADA	P
	Baseline			Year1			Year2		
ES	1[0;12]/ 2.23(4.23)	1[0;8.7]/ 1.92(3.56)	0.87	1[0;15]/ 3.23(5.09)	1[0;6]/ 2.06(3.49)	0.17	1[0;18]/ 4.02(6.19)	1[0;10]/ 2.15(3.77)	0.06
JSN	1[0;9.4]/ 2.26(3.24)	2[0;8.8]/ 2.33(2.88)	0.53	2[0;9.5]/ 2.74(3.43)	2[0;7]/ 2.38(2.78)	0.69	2[0;9.6]/ 2.97(3.86)	2[0;10.8]/ 3.06(3.66)	0.80
TSS	2[0;21]/ 4.48(6.68)	3[0;14.3]/ 4.28(5.06)	0.32	4[0;22.6]/ 5.94(7.37)	4[0;14.2]/ 4.46(5.10)	0.39	4[0;28]/ 6.97 (8.61)	3[0;17.4]/ 5.23(6.03)	0.36
ES≥1	52 %	54 %	0.94	66 %	56 %	0.24	66 %	56 %	0.21
JSN≥1	57 %	62 %	0.69	63 %	61 %	0.97	66 %	67 %	0.96
TSS≥1	72 %	80 %	0.28	78 %	79 %	1.00	80 %	84 %	0.66
	Year 0–1			Year 1–2			Year 0–2		
ΔES	0[−2;7.5]/ 1.13(3.08)	0[−2;2]/ 0.12(1.37)	**0.02**	0[−1;4.6]/ 0.76(2.14)	0[−1.8; 2.8]/ 0.09(1.52)	**0.005**	0[−2;8]/ 1.90(4.68)	0[−2;2]/ 0.21(1.49)	**0.008**
ΔJSN	0[−2;3.7]/ 0.52(1.71)	0[−2;2]/ 0.15(1.34)	0.08	0[−2;3]/ 0.22(1.56)	0[−0.8;3]/ 0.68(2.31)	0.13	0[−2;5.7]/ 0.74(2.16)	0[−2;5]/ 0.84(2.65)	0.86
ΔTSS	0[−2;8]/ 1.64(3.88)	0[−2.8;3]/ 0.27(2.01)	**0.009**	0[−1.6;5.6]/ 0.99(2.71)	0[−2;5]/ 0.78(2.72)	0.46	0[−2.8; 10.8]/ 2.63(5.67)	0[−2.8;7.8]/ 1.05(3.07)	0.12
ΔES≥1	41 %	24 %	**0.04**	36 %	21 %	**0.04**	45 %	28 %	**0.03**
DJSN ≥1	28 %	16 %	0.12	20 %	27 %	0.36	29 %	29 %	1.00
ΔTSS≥1	48 %	33 %	0.07	39 %	40 %	1.00	49 %	46 %	0.81

Erosion (ES), Joint Space Narrowing (JSN) and Total Sharp (TSS) scores at baseline, year 1 and 2; and Δ scores 0–1, 1–2 and 0–2 years. Values are median [5%; 95% percentiles]/mean(SD) or percentage. P values are based on Mann-Whitney or Pearson's chi-square tests. Analysis was by intention-to-treat. ITT with last observation carried forward and completer analyses gave similar results (not shown).

Conclusion: Despite very limited radiographic progression following an aggressive treat-to-target therapeutic strategy applying methotrexate and i.a. glucocorticoid injections into swollen joints during 2 years, radiographic erosive progression was significantly reduced by adding induction therapy with adalimumab during the 1st year. The effect of adalimumab persisted even after its withdrawal.

Reference:

[1]Hørslev-Petersen K et al. Ann Rheum Dis Online First 7 mar 2013

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1421

Treatment Responses and Their Predictors Of Abatacept In Biologic naïve Patients With Rheumatoid Arthritis; Data Form Abroad Study.

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Background/Purpose: The identification of predictors of good response to biologic therapy is needed in the perspective of personalized medicine. To determine the predicting factors of efficacy of abatacept (ABT) in biologic naïve rheumatoid arthritis (RA) patients, we conducted the ABROAD study (Abatacept Research Outcomes as a first-line biological Agent in the real worlD) in collaboration with 46 institutions in Japan.

Methods: Patients received 500mg of ABT for patients weighted less than 60kg or 750mg for patients with more than 60kg with or without methotrexate (MTX) for 24 weeks. We measured SDAI, DAS28-CRP (DAS), CRP levels at week 0, 4, and 24 after treatment. To evaluate the response to abatacept, we used validated response definitions (50/70/85% improvement) for the simplified disease activity indices (SDAI), which are correlated with ACR (20/50/70 improvement) response and influenced with radiographic progression and function (Aletaha D, et al. Ann Rheum Dis. 71:1190-6, 2012). Predictors of good SDAI response were identified by using univariate followed by multivariate logistic regression analysis.

Results: We examined 179 RA patients with moderate and high disease activity (SDAI >11, female = 85.5 %, mean age = 62.4 years old, mean disease duration =7.9 years, mean dosage of MTX: 7.5 ± 2.6mg/week). SDAI remission (<3.3) at 24 week was achieved in 13% of our patients. SDAI 50%, 70%, and 85% improvement rate at week 24 were 71%, 39%, 16%, respectively. In univariate analyses, very high-positive ACPA (equal or more than 22 times of the ULN, ≧99 U/mL) at baseline was significantly associated with SDAI 50% improvement at week 24 (OR = 3.390, 95% CI = 1,434-8.0, p = 0.005). Short disease duration (< 1 year) was significantly associated with SDAI 85% improvement (OR = 3.191, 95% CI = 1.262–8.072, p = 0.014). In multivariate analyses, very high-positive ACPA, short disease duration (<1 year), 70% improvement of CRP at week 4 were significantly associated with SDAI response.

ACPA titer at baseline influences on SDAI response.

1. Patients with short disease duration (<1 year)

	SDAI 50% improvement (24wk)	SDAI 70% improvement (24wk)	SDAI 85% improvement (24wk)
ACPA< 4.5	25.0%	0.0%	0.0%
ACPA< 99	50.0%	12.5%	12.5%
ACPA ≧ 99	85.7%	71.4%	50.0%

2. Patients with CRP 70 % improvement (at week 4)

	SDAI 50% improvement (24wk)	SDAI 70% improvement (24wk)	SDAI 85% improvement (24wk)
ACPA < 4.5	44.4%	33.3%	0.0%
ACPA < 99	58.6%	37.9%	13.8%
ACPA ≧ 99	95.0%	65.0%	30.0%

Conclusion: In this large biologic naïve observational cohort of RA patients treated with ABT, we suggest that very high-positive ACPA at baseline, short disease duration and CRP improvement at week 4, may be predictors for good response to ABT.

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1422

Efficacy and Safety Of a Novel Disease-Modifying Antirheumatic Drug, Iguratimod, As Add-On Therapy For Patients With Rheumatoid Arthritis.

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Background/Purpose: Iguratimod is a newly-developed disease-modifying antirheumatic drug (DMARD) that was approved in Japan in September 2012. It has been reported to suppress tumor necrosis factor-alpha-induced production of interleukin (IL)-6, IL-8, and monocyte chemoattractant protein 1 via inhibition of nuclear factor kappa B activation in cultured human synovial cells and human acute monocytic leukemia cells. It can also reduce

immunoglobulin production by acting directly on human B lymphocytes. A double-blind, placebo-controlled study of iguratimod in Japanese patients with rheumatoid arthritis (RA) revealed that it achieved a 20% improvement based on the American College of Rheumatology criteria (ACR20), being almost equivalent to the effect of salazosulfapyridine. In the present study, we examined the efficacy and safety of iguratimod as add-on therapy for patients with RA who had shown inadequate responses to previous therapy.

Methods: Patients with a diagnosis of RA according to the 2010 ACR/EULAR criteria who had been unresponsive to previous therapy, and who had been prescribed iguratimod as add-on therapy at Niigata Rheumatic Center between September 2012 and Feburary 2013 were enrolled. Details of the patients' background factors, clinical parameters and laboratory findings, including C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), matrix metalloprotease-3 (MMP-3), rheumatoid factor (RF), Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate (DAS28-4[ESR]), Disease Activity Score for 28-joint counts based on the C-reactive protein (DAS28-4[CRP]), clinical disease activity index (CDAI) and simplified disease activity index (SDAI) were obtained from their medical records retrospectively. The efficacy of iguratimod was evaluated at week 12.

Results: Twenty-six patients (5 males, 21 females) participated in this study. They had a mean age of 65.6 ±12.4 years and a mean disease duration of 7.5±8.3 years. Patients were treated with corticosteroids and/or DMARDs as monotherapy or in combination (corticosteroids 20 cases, salazosulfapyridine 18 cases, methotrexate 10 cases, bucillamine 5 cases, tacrolimus 5 cases, tocilizumab 1 case), together with iguratimod. Clinical parameters of disease activity at the baseline had improved 12 weeks later as follows: ESR, 29.9±25.9 mm/h to 25.8±21.5 mm/h (p = 0.33); CRP, 2.44±3.46 mg/dL to 1.27±1.64 mg/dL (p = 0.11); MMP-3, 257.7±160.0 ng/mL to 207.5±128.0 ng/mL (p = 0.17); RF, 141.3±168.7 U/mL to 97.6±121.0 IU/mL (p = 0.011); DAS28-4[ESR], 4.36 ± 3.46 to 3.75 ± 1.00 (p=0.053); DAS28-4[CRP], 3.96±1.28 to 3.27±0.94 (p= 0.02); SDAI, 18.9±13.6 to 13.3±6.2 (p= 0.062); CDAI, 17.0±10.6 to 12.0±5.5 (p= 0.042). Among these 26 patients, 5 discontinued taking iguratimod because of nausea in 2, skin rash in 1, brain hemorrhage in 1, and pulmonary hemorrhage in 1 who was receiving warfarin.

Conclusion: Iguratimod is effective as add-on therapy in RA patients who have shown inadequate responses to previous therapy, although caution is necessary regarding hemorrhagic tendency in patients receiving warfarin, which was cautioned by Ministry of Health, Labour and Welfare of Japan.

Disclosure: D. Kobayashi, None; **S. Ito**, None; **A. Murasawa**, None; **I. Narita**, None; **K. Nakazono**, None.

1423

The Influence Of Body Mass Index On The Efficacy Of Tumor Necrosis Factor Blocking Therapy For Rheumatoid Arthritis. Ingrid M. Visman[1], Inge A.M. van den Oever[1], Charlotte L. M. Krieckaert[1], Gertjan Wolbink[1] and Michael T. Nurmohamed[2]. [1]Jan van Breemen Research Institute Reade, Amsterdam, Netherlands, [2]VU University Medical Center & Jan van Breemen Research Institute, Amsterdam, Netherlands.

Background/Purpose: The impact of Body mass Index (BMI) on efficacy of TNF blocking therapy is an important question, as adipose tissue appears to have an immunomodulating effect (Tilg et al 2006), and may adversely impact treatment response in patients receiving TNF blocking therapy (Gremese et al 2013). The aim of this study is to ascertain the impact of BMI on the efficacy of TNF blocking therapy with either adalimumab or etanercept for the treatment of RA.

Methods: At the outpatient clinic in Amsterdam, the Netherlands, 853 consecutive RA patients were included who started with TNF blocking therapy adalimumab (411) or etanercept (442), and of whom baseline BMI and follow-up data for at least 16 weeks was available. Adalimumab was dosed at 40 mg fortnightly and etanercept at 50 mg weekly for all patients, regardless of body weight.

Results: The average BMI was 26.0 (SD: 5.2, range 14–50). The baseline DAS was high at 4.9 (SD: 1.3). Mean age was 54 years (SD: 13) and 682 (80%) were female. Median disease duration was 7 years (IQR: 3–16). Median follow-up was 2.1 years (IQR 0.7–4.4 years), 2337 patient years total. Nearly half (407, 48%) of patients were of healthy weight according to the WHO criteria (BMI 18.5–25), 257 (30%) of the patients were overweight, and another 168 (20%) were obese (BMI of 25–30, and >30 respectively). Few patients (21, 2%) were underweight (BMI<18.5). Overall, the patients with healthy weight responded best to TNF blocking therapy, followed by the overweight and the underweight groups. The group who performed worst was the obese group (see Figure 1). After one year the overweight group had a significantly higher DAS (28 joints) than the normal weight group (3.0 (1.3) vs. 2.6 (1.2), p= 0.005), and the obese group did significantly worse than either (3.4 (1.4), p=0.000 (vs. normal) and 0.026 (vs. overweight)). The DAS at one year of the underweight group did not differ significantly from any other weight group. When comparing the individual components of the DAS for obese vs. normal weight RA patients, both tender joint score and BSE were elevated at baseline and 52 weeks, and patient global assessment was only significantly higher at 52 weeks for the obese group. Swollen joint score was not significantly different at baseline or 52 weeks.

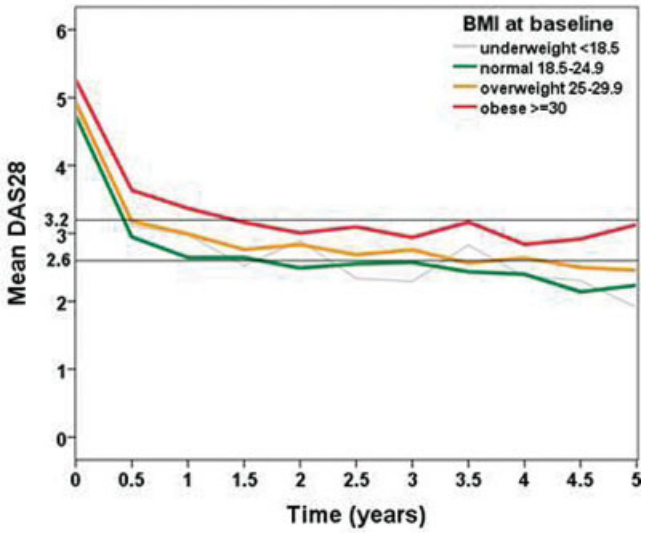

Figure 1. Mean DAS over time.

Conclusion: Our findings support the hypothesis that adipose tissue has an impact on treatment outcome of TNF-blockers in RA. This is important as it may have implications for other immune-mediated inflammatory conditions treated with TNF blocking therapy.

In addition, as adalimumab and etanercept are given in a standard dose, regardless of body weight, it may be that for obese patients a better response could be achieved with an increased dose. This could be an important avenue for further study, and eventually leading to better treatment outcomes of obese RA patients.

Disclosure: I. M. Visman, None; **I. A. M. van den Oever**, None; **C. L. M. Krieckaert**, None; **G. Wolbink**, None; **M. T. Nurmohamed**, None.

1424

Persistence On Single Disease Modifying Anti-Rheumatic Drug Therapy In US Veterans With Rheumatoid Arthritis Is Extremely Rare. Jonathan Kruger[1], Ted R. Mikuls[2] and Grant W. Cannon[1]. [1]Salt Lake City VA and University of Utah, Salt Lake City, UT, [2]Omaha VA and University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: A limited number of rheumatoid arthritis (RA) patients are managed with a single disease-modifying anti-rheumatic drug (DMARD). Previous studies have suggested that DMARD naïve patients could potentially have a sustained clinical response to single DMARD therapy. However, little information has been available regarding the persistence of single agent therapy. This investigation determined the prevalence and clinical characteristics of US veterans with RA treated with a single DMARD in comparison to patients receiving multiple DMARDs alone or in combination.

Methods: Using the multi-centered observational Veterans Affairs Rheumatoid Arthritis (VARA) registry and VA pharmacy databases, US veterans receiving DMARDs and with ≥3 years of RA were identified. Patients were classified as persistent single DMARD (PS-DMARD), current single DMARDs (CS-DMARD), or combination/complex DMARD (ComCX-DMARD) groups. PS-DMARD patients were persistently treated with a single DMARD since diagnosis. CS-DMARD had received only a single DMARD for the past 12 months of observation but previously received one or more prior DMARDs as either mono-therapy or in combination. ComCX-DMARD patients received more than one DMARD within the prior

12 months of observation. The clinical characteristics, laboratory values and clinical outcomes in these three groups were compared.

Results: There were 966 VARA with ≥ 3 years RA disease duration who had received DMARDs with55 (6%) PS-DMARD, 280 (29%) CS-DMARD and 631 (65%) ComCx-DMARD. The most commonly used DMARD in the PS-DMARD group was methotrexate (75%). However, while methotrexate was still the most dominant agent in the CS-DMARD group, the use of other agents increased, especially anti-TNF agents. PS-DMARD patients were older at onset, more likely to be seronegative, had fewer nodules and had less radiologic evidence for RA. There was not a clear difference in disease duration, smoking status, and genotype in comparison of the three groups.

	PS-DMARD N=55	CS-DMARD N=280	ComCX-DMARD N=631	p-value
Age at diagnosis	57±16	52±14	51±14	0.01
Age at VARA enrollment	68±11	66±11	63±11	0.01
Disease duration (years)	15±13	18±12	17±11	0.06
Gender (male)	52 (95%)	257 (92%)	572 (91%)	0.25
Smoking status				
Never	15 (27%)	62 (22%)	137 (22%)	0.36
Former	28 (51%)	154 (55%)	315 (50%)	
Current	12 (22%)	64 (23%)	179 (28%)	
Education level (years)	13±2.5	13±2.6	13±2.7	0.85
Rheumatoid Factor (pos)	35(64%)	212 (76%)	516 (82%)	0.01
Anti-CCP (pos)	32 (58%)	209 (75%)	489 (77%)	0.01
Rheumatoid nodules (pos)	17 (31%)	151 (54%)	342 (54%)	0.01
Radiographic changes of RA	34 (62%)	206 (74%)	448 (71%)	0.18
Shared Epitope				
2 copies	12 (22%)	58 (21%)	141 (23%)	0.86
1 copy	25 (46%)	142 (53%)	303 (49%)	
Negative	17 (31%)	70 (26%)	171 (28%)	
Most recent DAS28 Score	2.8±1.1	3.4±1.4	3.7±1.5	0.01
Current DMARD Rx				
MTX	41(75%)	93 (33%)	Complex DMARDs–not applicable	
Hydroxychloroquine	7 (13%)	53 (19%)		
Sulfasalazine	3 (5%)	24 (9%)		
Leflunomide	1 (2%)	31 (11%)		
Anti-TNF	3 (2%)	55 (20%)		
Other DMARDs	0	14 (5) (1%)		

Conclusion: Persistent single DMARD therapy was very rare after three years of therapy (approximately 6%) and current single DMARD therapy uncommon (approximately 28%) in this cross-sectional analysis of US veterans. Persistent single DMARD therapy was associated with older age at RA diagnosis and VARA enrollment, lower rates of sero-positive status, fewer rheumatoid nodules, and lower DAS28 scores at the most recent VARA evaluation. While CS-DMARD and ComCX-DMARD patients were very similar in presentation, no clear association was seen in smoking, gender, radiographic changes or in genotypes between all groups. These data suggest that most RA patients will require multiple DMARDs and/or a combination of concurrent DMARDs for management of their disease while persistent single DMARD therapy is very rare.

Disclosure: J. Kruger, None; **T. R. Mikuls**, None; **G. W. Cannon**, None.

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Discontinuation Of Tumor Necrosis Factor Inhibitors In Rheumatoid Arthritis Patients In Low Disease Activity: Persistent Benefits. Arthur Kavanaugh[1], Susan J. Lee[2], Daniel H. Solomon[3], Jeffrey D. Greenberg[4], Joel M. Kremer[5], Lilian Soto[6], Carol J. Etzel[7] and George W. Reed[8]. [1]University of California, San Diego, La Jolla, CA, [2]University of California San Diego, La Jolla, CA, [3]Harvard Medical School, Brigham and Women's Hospital, Division of Rheumatology, Division of Pharmacoepidemiology, Boston, MA, [4]NYU Hospital for Joint Diseases, New York, NY, [5]Center for Rheumatology, Albany Medical College, Albany, NY, [6]University of California San Diego, San Diego, CA, [7]CORRONA, Inc., Houston, TX, [8]CORRONA, Inc., Worcester, MA.

Background/Purpose: A key question is whether biologic agents can be stopped but clinical benefit maintained for rheumatoid arthritis (RA) patients (pts) in remission or low disease activity (LDA). Potential benefits include lower costs, reduced safety concerns, and conforming with pt preference. To date, this has been addressed in a few clinical trials, using heterogeneous methods (1). We sought to determine the time course for persistent clinical benefit among RA pts in LDA (CDAI ≤ 10) who discontinued their first TNF Inhibitor (TNFi).

Methods: We assessed RA pts from the CORRONA registry. End of Benefit (EOB) was defined as: a) having CDAI>10 at any followup b) initiation of another biologic or DMARD, or c) adding or increasing prednisone. Pts with no EOB event were censored at their last recorded CORRONA visit. Kaplan-Meier method was used to estimate median time to EOB and proportion remaining 'with benefit' at 6 month intervals from 6 to 36 months after drug discontinuation. Cox proportional hazard models were assessed to identify factors related to EOB. Factors that were significant at the 20% level in univariable modeling were evaluated in a multivariable models, adjusting for age, gender, race, smoking, and BMI.

Results: Among 35,656 RA pts, we identified 717 who had: a) discontinued their 1st TNFi while in CORRONA, b) did not add another biologic or DMARD, c) were in LDA at the time TNFi discontinuation, and d) had ≥ 1 followup visit: 301 of these pts had initiated their first TNFi while in CORRONA. At discontinuation, pts had median RA duration of 8 yrs, mean CDAI of 4.3 ± 0.11. 41.8% used TNFi as monotherapy. 601/717 (83.8%) patients had an EOB event and 116 (16.8%) were censored. Kaplan-Meier estimates for the proportion of patients remaining with benefit (percentage, 95%CI) were: 6 mos - 98.7 (97.6–99.3), 12 mos - 73.4 (70.0–76.5), 18 mos - 55.6 (52.8–59.2), 24 mos 42.2 (38.6–46.0), 36 mos 27.6 (24.2–31.0)(Figure). Time course was similar among the 301 pts initiating their 1st TNFi within CORRONA.

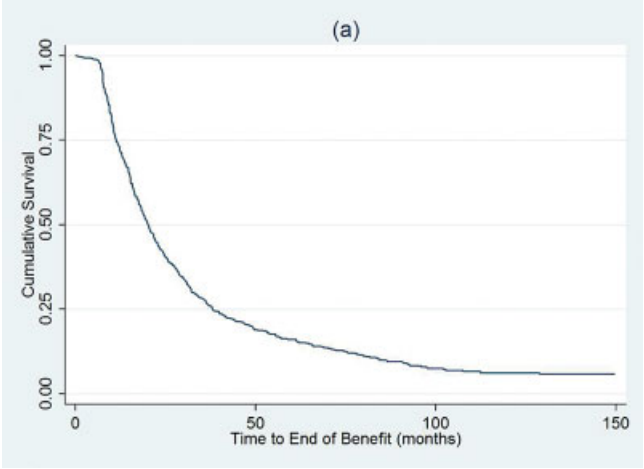

Fig 1. Kaplan-Meier Curve for Time to End of Benefit (in months)

Factors predictive of EOB in univariate analysis included higher CDAI, pt pain score, and HAQ at discontinuation, as well as smoking, higher BMI, and positive RF/ACPA. In multivariate analysis, the 1st 3 factors remained significant with a HR for EOB with CDAI of 1.28 (1.08–1.5 95%CI). Among pts initiating their 1st TNFi within CORRONA, slower responders (time to LDA while on TNF>4 months) did worse than faster responders (HR 1.54 [1.17–2.04 CI]). Of note, RA disease duration did not affect time to EOB.

Conclusion: These data show that discontinuation of a first course of TNFi may be associated with persistent benefit, and that patient characteristics at TNFi discontinuation may help predict persistent benefit.

Reference:

1. Yoshida K et al. Ann Rheum Dis Epub 30 May 2013.

Disclosure: A. Kavanaugh, AbbVie, Inc., 2, Amgen, 2, Janssen Pharmaceutica Product, L.P., 2, UCB, 2; **S. J. Lee**, None; **D. H. Solomon**, Amgen, Lilly, CORRONA, 2, UpToDate, 7, Pfizer, Novartis, Lilly, BMS, 6; **J. D. Greenberg**, Corrona Inc., 1, Corrona, Inc, 5, AstraZeneca, 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5; **J. M. Kremer**, Corrona, Inc, 1, Corrona Inc., 3; **L. Soto**, None; **C. J. Etzel**, Corrona Inc., 3; **G. W. Reed**, Corrona, Inc, 3.

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Inhibition Of Spermidine/Spermine N1-Acetyltransferase Activity – a New Therapeutical Concept In Rheumatoid Arthritis. Emmanuel Karouzakis[1], Astrid Jungel[1], Beat A. Michel[2], Renate E. Gay[1], Steffen Gay[1] and Michel Neidhart[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland.

Background/Purpose: Spermine/spermidine N1-acetyltransferase (SSAT1) and polyamine modulating factor 1 (PMF1) are increased in rheumatoid arthritis synovial fibroblasts (RASF). Since PMF1 regulates the expression of SSAT1, we hypothesized that changes in PMF1 promoter DNA

methylation favor the expression of SSAT1 that causes an excessive consumption of S-adenosylmethionine (SAM) in RASF. The second objective was to decrease the activity of SSAT1 and to evaluate the effect of this treatment - alone or in combination with a supplement of SAM on DNA methylation and behavior of RASF.

Methods: Synovial fibroblasts were isolated from patients with RA or osteoarthritis (OA). Promoter methylation of PMF1 was determined by pyrosequencing. The fibroblasts were treated for 2 weeks with 40 mM diminazene aceturate (DA), an inhibitor of SSAT1. DNA 5-methylcytosine content, SSAT1, adenosylmethionine decarboxylase (AMD), PMF1, DNA methyltransferase 1 (DNMT-1), CXCL12, integrin b1 and CD44 were measured by flow cytometry. Cell adhesion to fibronectin was tested. Levels of matrix metalloproteinases (MMP-1 and -3) were measured in cell culture supernatant. The SCID-mouse model of RA allowed monitoring the invasiveness of RASF.

Results: Compared with OASF (n = 6), RASF (n= 12) expressed more SSAT1, AMD and PMF1: 240+57%, 169+38% and 196+20%. However, PMF1 promoter methylation was unchanged. DA, like siRNA against SSAT1, decreased the expression of AMD in RASF (by 33±5%; $p<0.001$). DA increased the DNA 5-methylcytosine content (by 150±12%; $p<0.05$), increased the expression of DNMT-1 (303±70%; $p<0.001$), decreased the expression of activation markers (CXCL12: 42±7%; Integrin β1: 29±2%, $p<0.001$) and MMP1 (9±2%, $p<0.05$) and altered the adhesion of RASF to fibronectin (Control: 100±17, DA: 72±13%; $p<0.001$). DA was more efficient in RASF with higher levels of SSAT1. The combination of DA plus SAM increased most efficiently DNMT-1 (523±110%; $p<0.001$), than DA or SAM alone. In addition, it further decreased CXCL12 and integrin b1 expression, as well as MMP-1 levels (by 48±5%, 58±5% and 24±6%; $p<0.001$), but not of MMP-3. Most interestingly, the combination DA and SAM reduced the invasiveness of RASF in the SCID mouse model of RA by 70%.

Conclusion: The use of DA alone or in combination with SAM/L-methionine might introduce a new therapeutic concept in RA.

Disclosure: E. Karouzakis, Novartis foundation, IMI-BTCure, IAR, EURO-TEAM, 2; **A. Jungel**, IMI-BTCure, IAR, 2; **B. A. Michel**, None; **R. E. Gay**, EURO-TEAM, IMI BTCure, IAR Epalinges, 2; **S. Gay**, EURO-TEAM, IMI BTCure, IAR Epalinges, 2; **M. Neidhart**, Novartis foundation, IMI-BTCure, EURO-TEAM, IAR, 2.

1427

Discovery and Characterization Of ABT-122, An Anti-TNF/IL-17 DVD-Ig™ Molecule As a Potential Therapeutic Candidate For Rheumatoid Arthritis. Chung-Ming Hsieh[1], Carolyn Cuff[1], Edit Tarcsa[2] and Margaret Hugunin[2]. [1]AbbVie Pharmaceuticals, Worcester, MA, [2]AbbVie Bioresearch Center, Worcester, MA.

Background/Purpose: Rheumatoid arthritis (RA) is a serious autoimmune disease that significantly impacts patients' quality of life. Several approved biologic drugs targeting tumor necrosis factor (TNF) and other immune targets are efficacious treatments for RA, and newer drug candidates, including antibodies to interleukin-17 (IL-17), are at various stages of clinical development. Previous and current studies have demonstrated that in a preclinical mouse model of arthritis treatment with antibodies to TNF and IL-17 is significantly more efficacious than treatment with either antibody alone. We therefore generated a novel bispecific dual variable domain immunoglobulin (DVD-Ig™) molecule to both TNF and IL-17 as a potential drug candidate for RA.

Methods: An *in vitro* PROfusion™ mRNA display technology was used to screen for fully human antibodies against human IL-17. The identified IL-17 antibodies were further engineered to improve affinity. We inserted the variable domain of several affinity-matured IL-17 antibodies between an available anti-TNF variable domain and the human IgG1/κ constant region to obtain a panel of novel DVD-Ig" molecules. These DVD-Ig™ molecules differ from each other in the anti-IL-17 variable domains and the peptide linkers (lengths and sequences) connecting the two variable domains. We characterized the DVD-Ig™ activities by ELISA, surface plasmon resonance, and cell-based potency assays. To demonstrate the activities of these DVD-Ig™ molecules *in vivo*, we studied the pharmacokinetic profiles of the top three candidates in rat. The *in vivo* pharmacologic activity was assessed in mouse models by inhibition of recombinant human TNF-*D*gal-induced lethality and recombinant human IL-17-induced KC production.

Results: Fully human antibodies with sub-nM affinity to human IL-17 were selected from human antibody libraries. Their affinities were enhanced by molecular engineering to low pM range. The affinity-matured IL-17 antibodies were combined with an antibody to TNF into a panel of DVD-Ig™ molecules, and screened for optimal activities in antigen binding and neutralization assays. Three drug candidates with strong affinities and potencies (K_D and IC_{50} in the low pM range) were selected for further characterization. In rat pharmacokinetic studies these DVD-Ig™ molecules had 9 to 13 day circulating half-lives upon intravenous injection. In acute mouse models *in vivo*, these DVD-Ig™ molecules also demonstrated potent inhibition of human TNF and IL-17 activity. The DVD-Ig™ molecule with the best affinity and potency, as well as the longest half-life in rat was designated ABT-122 for further development.

Conclusion: ABT-122 is a novel DVD-Ig™ molecule that is engineered to have high affinity and neutralizing potency to both human TNF and IL-17 cytokines. Based on the combined efficacy in a preclinical mouse arthritis model, the demonstrated efficacy of TNF-targeted therapy in RA patients, and encouraging response to IL-17 antibodies in RA clinical trials, we will be evaluating the efficacy and safety profile of the anti-TNF/IL-17 DVD-Ig™ molecule in human RA clinical trials.

Disclosure: C. M. Hsieh, AbbVie, 3, AbbVie, 1; **C. Cuff**, AbbVie, 3, AbbVie, 1; **E. Tarcsa**, AbbVie, 3, AbbVie, 1; **M. Hugunin**, Abbvie, 3, Abbvie, 1.

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The Safety and Efficacy Of Tocilizumab Subcutaneous In Combination With Traditional Dmards In Patients With Moderate To Severe Rheumatoid Arthritis Up To 48 Weeks (BREVACTA). Alan Kivitz[1], Ewa Olech[2], Michael A. Borofsky[3], Beatriz M. Zazueta[4], Federico Navarro-Sarabia[5], Sebastião C. Radominski[6], Joan T. Merrill[7], Chris Wells[8], Sunethra Wimalasundera[8], Wendy Douglass[8] and Janet E. Pope[9]. [1]Altoona Center for Clinical Research, Duncansville, PA, [2]University of Nevada School of Medicine, Las Vegas, NV, [3]Clinical Research Center of Reading, Reading, PA, [4]Centro de Investigacion en Enfermedades Reumaticas, Mexicali, Mexico, [5]Hospital Virgen Macarena, Serv. de Reumatología, Sevilla, Spain, [6]Universidade Federal do Paraná, Curitiba, Brazil, [7]Oklahoma Medical Research Foundation, Oklahoma City, OK, [8]Roche, Welwyn Garden City, United Kingdom, [9]St Joseph Health Centre, London, ON.

Background/Purpose: The BREVACTA study assessed the efficacy and safety of subcutaneous tocilizumab (TCZ-SC) in pts with moderate to severe RA who had an inadequate response to ≥ 1 DMARD (21% had failed an antiTNF). The primary objective of the study was to assess efficacy and safety up to week 24; as reported previously, superiority over placebo was demonstrated, with a safety profile comparable to intravenous TCZ (TCZ IV). Here we report the longer-term efficacy and safety data for TCZ SC administration to Week 48.

Methods: This phase 3, randomized, multicenter, parallel-arm study included a 24 week double-blind, PBO controlled period followed by open label treatment for 72 weeks and 8 weeks of safety follow up. Pts were randomized 2:1 to receive TCZ SC 162 mg every 2 weeks (q2w) or PBO SC q2w via a pre-filled syringe (PFS), in combination with stable doses of pre-study DMARD(s). Escape therapy with TCZ SC qw (PFS) was available from week 12. At week 24, pts remaining on q2w therapy in both arms were re-randomized 1:1 to receive open-label TCZ SC q2w via PFS or Autoinjector Pen. The data presented here focuses on pts who received TCZ SC from baseline to week 48, regardless of injection device used. Efficacy was assessed to week 48. Safety was assessed to 29 October 2012 (when all pts had reached ≥ week 48) using AE reports and laboratory data.

Results: 437 pts were randomized at baseline to receive TCZ SC q2w, with 334 (76%) re-randomized at week 24 to continue to receive TCZ SC q2w in the open-label phase. Efficacy was maintained to week 48, with the proportion of pts with ACR20/50/70 responses, in clinical remission (DAS28 < 2.6) and with a clinically meaningful improvement in physical function (change from baseline in HAQ-DI ≥ 0.3) remaining stable or improving from week 24 to 48 (table). Mean reduction in radiographic progression of structural joint damage (measured as change in modified Total Sharp Score, mTSS) was also maintained from week 24 to 48. The rates of AEs and SAEs, including serious infections, remained stable or decreased between weeks 24 and 48. The most common AEs were infections, particularly respiratory ones. No anaphylaxis or medically confirmed serious hypersensitivity occured. The most common injection site reactions were erythema, pain and pruritis. Ten pts developed antiTCZ antibodies postbaseline, but did not experience loss of efficacy or clinically significant or serious hypersensitivity. A total of 21 pts withdrew from TCZ SC due to AEs, most commonly due to infections or elevated liver enzymes. Six pts died up to the week 48 cut-off.

	TCZ SC q2w 24 weeks	TCZ SC q2w 48 weeks
Patient disposition (ITT population)		
Randomized, n	437	–
Re-randomized at week 24, n (%)	334 (76)	–
Withdrew from TCZ SC q2w regimen, n (%)	26 (6)	46 (11)
Received escape therapy with TCZ SC qw regimen[a], n (%)	71 (16)	77 (18)
Withdrew from escape therapy, n (%)	2 (<1)	3 (<1)
Completed treatment period[b], n (%)	340 (78)	314 (72)
Efficacy (ITT population)		
N	437	437
ACR20, %	61	62
ACR50, %	40	45
ACR70, %	20	26
DAS28 < 2.6, %	32	45
Decrease in HAQ-DI ≥ 0.3 from baseline, %	58	62
Change in modified Total Sharp Score (mTSS) from baseline[c], mean±SD	0.62 ± 2.692	0.64 ± 3.266
Safety (safety population[d])		
N	437	437
Patient years of exposure	182.68	393.53
Total AEs, n	803	1472
Rate of AEs per 100 patient years	439.56	374.05
Total SAEs, n	25	51
Rate of SAEs per 100 patient years	13.68	12.96
Total serious infections, n	12	15
Rate of serious infections per 100 patient years	6.57	3.81
Clinically significant hypersensitivity reactions[e], n	2	3
Rate of clinically significant hypersensitivity reactions per 100 patient years[e]	1.09	0.76
Injection site reactions[f], n	57	97
Rate of injection site reactions per 100 patient years[f]	31.20	24.65
Confirmation assay positive anti-TCZ antibodies, n	7	10
Withdrawals due to AEs, n	9	21
Deaths, n	3	6

[a] Escape therapy with weekly open-label TCZ SC 162 mg was offered from week 12 to 48 to pts with less than 20% improvement from baseline in both their tender and swollen joint count, and from week 48 onwards to pts with less than 70% improvement in both their tender and swollen joint count. Escape pts were not rerandomized to PFS or AI at week 24, and remained on TCZ SC qw using the PFS for the remainder of the study. The number of pts who received escape therapy includes pts who subsequently withdrew from escape therapy.
[b] Number of pts who completed the TCZ SC q2w regimen to week 24 and week 48, excluding pts who withdrew or received escape therapy with TCZ SC qw.
[c] Mean change in mTSS at week 24 was 0.62 ± 2.692 for TCZ SC vs 1.23 ± 2.816 for placebo (P = 0.0149), and at week 48 was 0.64 ± 3.266 for TCZ SC vs. 1.48 ± 3.804 for pts who switched from placebo to TCZ SC at week 24.
[d] 29 Oct 2012 was the clinical cut-off for week 48.At this time point, the majority of pts had received TCZ SC for longer than 48 weeks.
[e] Events that occurred during or within 24 hours of an injection (excluding ISRs) that were not deemed unrelated to treatment and led to withdrawal.
[f] AEs occurring at the site of a SC injection as recorded by the investigator.

Conclusion: TCZ SC demonstrated long term efficacy, including sustained ACR response rates and reduced progression of joint damage over 48 weeks. There was no change in the AE profile for TCZ SC compared with earlier evaluations. TCZ SC is an effective treatment in RA, and will offer an alternative route of administration and the possibility of self-administration for pts.

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Adiponectin Levels Are Increased After Tocilizumab Therapy Among Adults With Rheumatoid Arthritis: Results From The Measure Study.

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Background/Purpose: Cardiovascular disease (CVD) is the leading cause of death in patients (pts) with rheumatoid arthritis (RA). Adiponectin has been shown to have anti-inflammatory and atheroprotective effects on the vasculature, with higher levels associated with improved insulin sensitivity, lower triglyceride levels, and less atherosclerosis. The effect of tocilizumab (TCZ) on adiponectin level has not been studied. The purpose of this study was to explore the change in adiponectin level associated with treatment with TCZ and response to treatment.

Methods: Pts from the MEASURE study (moderate to severe RA with inadequate response to methotrexate [MTX]) who received randomized treatment with either TCZ 8 mg/kg or placebo (PBO) plus MTX were examined if they had fasting adiponectin samples at baseline and week 24. Demographics, RA disease parameters, CVD risk factors, and laboratory assessments of fasting lipids and leptin were assessed at baseline and after 24 weeks of treatment. Within-group change was examined using paired *t*-tests. All association analyses were conducted using linear regression, adjusted for age and sex.

Results: Baseline and week 24 adiponectin samples were available for 108/132 pts, with equal allocation to TCZ + MTX and PBO + MTX. Median (IQR) age was 56 (49–63) years, and median (IQR) body mass index (BMI) was 29 (26–33) kg/m^2. Median (IQR) baseline fasting adiponectin level was 11.2 (7.5–17.7) mg/mL. Baseline characteristics did not significantly differ according to treatment allocation. At baseline, older and female pts were more likely to have higher adiponectin levels, whereas those with higher BMI and/or diabetes were more likely to have lower adiponectin levels. Baseline inflammatory disease activity (DAS28 and C-reactive protein) was not significantly associated with baseline adiponectin. Pts treated with TCZ + MTX had a significant increase in adiponectin by an average of +10% (Table). There was no change in adiponectin among the PBO + MTX group (mean change [95% CI]: 0.25 [–0.54, 1.28]). There was no significant change in leptin or BMI in the TCZ + MTX group. No baseline variables showed significant association with change in adiponectin; however, among pts treated with TCZ + MTX, higher increase in adiponectin level was associated with greater increase in total cholesterol level (β=1.00; p<0.05) and larger improvement in disease activity (β for association for DAS28ESR=–0.67; p<0.05). Increasing adiponectin levels paralleled increases in both LDL and HDL levels and increases in proatherogenic (ApoB) and anti-atherogenic (ApoA-1) apolipoproteins (Table).

Table. Baseline, Week 24, and Change From Baseline in Variables for Patients Treated With TCZ (n = 54)

Variable	Baseline Value Median (IQR)	Week 24 Value Median (IQR)	Mean Change (95% CI)
Adiponectin, μg/mL	11.8 (8.3, 17.4)	13 (7.3, 17.8)	0.85 (0.01, 1.93)*
BMI, kg/m^2	29.3 (25.5, 32.8)	28.9 (26.2, 33.2)	0.25 (–0.1, 0.47)
Leptin, ng/mL	23.5 (11.3, 39.6)	28.8 (14.4, 44.7)	1.6 (–2.7, 4.5)
Total cholesterol, mmol/L	5 (4.19, 5.87)	5.7 (4.78, 6.34)	0.67 (0.45, 0.89)*
LDL-P, mg/dL	1108 (924, 1372)	1343 (1020, 1568)	119 (77, 227)*
HDL-P, mg/dL	30.8 (26.6, 33.7)	34.5 (30.4, 39.5)	4.6 (3.2, 5.8)*
ApoB, mg/dL	0.94 (0.78, 1.15)	1.07 (0.91, 1.36)	0.16 (0.11, 0.22)*
ApoA-1, mg/dL	1.23 (1.06, 1.47)	1.46 (1.18, 1.59)	0.18 (0.09, 0.2)*
DAS28	6.74 (5.9, 7.28)	3.15 (1.93, 4.46)	–3.2 (–3.8, –2.8)*

*Paired *t*-test showed statistically significant change.

Conclusion: Adiponectin is increased with TCZ treatment in RA pts, with higher increases observed in pts with greater degrees of RA disease activity suppression. Future studies should confirm whether TCZ increases adiponectin level and, if so, whether adiponectin change predicts CVD risk change with TCZ.

Disclosure: H. Mirjafari, Roche Pharmaceuticals, 3; **M. Klearman**, Genentech and Biogen IDEC Inc., 3; **J. Wang**, Roche Pharmaceuticals, 3; **N. Sattar**, Roche Pharmaceuticals, 5, Roche Pharmaceuticals, 8; **J. T. Giles**, Genentech and Biogen IDEC Inc., 5.

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Safety and Efficacy Of Subcutaneous Tocilizumab Monotherapy In a Long-Term Extension Study In Japanese Rheumatoid Arthritis Patients.

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Background/Purpose: Tocilizumab (TCZ) blocks interleukin-6-receptor signaling and is an effective rheumatoid arthritis (RA) therapy. The MUSASHI[1] and SUMMACTA[2] studies showed the efficacy and safety of TCZ 162 mg subcutaneous injection (TCZ-SC) to be comparable to those of TCZ 8 mg/kg intravenous infusion (TCZ-IV). Here we assess the long-term

(108-wk) safety and efficacy of TCZ-SC monotherapy in Japanese RA patients (pts).

Methods: This long-term, open-label study followed a 24-wk double-blind, non-inferiority study (MUSASHI study). Pts completing the MUSASHI study were administered 162 mg TCZ-SC every 2nd wk for 84 wks without concomitant DMARDs. Depending on disease activity of individual pts, adjustment of administration interval within a 1- to 3-wk range was allowed after Wk 36.

Results: 346 pts received TCZ for a total exposure of 639.0 pt-yrs. At last observation (Wk 108), 278 pts remained. Most withdrawals were due to AEs (10.3%, 36/346) and insufficient therapeutic response (4.9%, 17/346). AEs occurred at 498.3 events/100 pt-yrs (E/100PY); most common were infections and infestations (138.3 E/100PY). SAEs occurred at 16.9 E/100PY; most common were infections and infestations (5.3 E/100PY). There was 1 death from gastric cancer and disseminated intravascular coagulation. Incidence of malignancy was 0.8 E/100PY. There were no serious anaphylactic events during the TCZ-SC dosing period. The incidence rate of injection site reaction was 13.2% (44/333) in patients who were administered TCZ-SC. The severity of all injection site reactions was mild and tolerable.

ACR20, 50, and 70 response rates increased slightly with continuous TCZ-SC treatment. At Wk 24, ACR20, 50, and 70 response rates were 84.8% (274/323), 65.9% (213/323), and 39.9% (129/323); and at Wk 108, they were 92.5% (258/279), 80.6% (225/279), and 61.6% (172/279). DAS28 and CDAI remission rates at Wk 48 were 64.7% (202/312) and 27.6% (86/312); at Wk 108 they were 79.6% (222/279) and 47.7% (133/279). TCZ administration interval was shortened in 24 pts due to insufficient response; in those pts, DAS28(SD) improved from 4.63(1.56) at before shortening to 2.39(1.14) at 12 wks after shortening. Administration interval was extended in 26 pts due to sufficient response; in 61.5% of those pts, disease activity remained low during the study period with the interval extended.

Table. Events per 100 pt-yrs in TCZ-SC and TCZ-IV[3]

	TCZ-SC pooled *N*=346	TCZ-IV pooled[3] *N*=601
Total exposure (pt-years)	639.0	2188
AEs (E/100PY)	498.3	465.1
Infections and infestations	138.3	129.2
Investigations	86.4	100.9
SAEs (E/100PY)	16.9	23.1
Serious infections	5.3	6.2
Malignancies	0.8	0.8
Deaths	0.2	0.2

Conclusion: The incidence rates of SAEs, serious infections, malignancies, and deaths with TCZ-SC were comparable to those of TCZ-IV pooled data[3] in Japanese RA pts, suggesting that the long-term safety profile of TCZ-SC is not different from established TCZ-IV. Efficacy remained stable with long-term exposure to TCZ-SC. TCZ-SC is a tolerable and useful treatment option for RA.

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Disclosure: A. Ogata, Chugai, 5.

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Algorithms Using Genome-Wide SNP Analysis For Prediction Of Efficacy and Adverse Events Of Abatacept Using Two Population Samples From Multiple Medical Cohorts. Tsukasa Matsubara[1], Satoru Koyano[2], Keiko Funahashi[2], Takako Miura[1], Kosuke Okuda[1], Takeshi Nakamura[1], Mitsuyoshi Iwahashi[3], Tomomi Tsuru[4], Shoichi Uchimura[5], Shigeru Honjo[6], Akira Sagawa[7], Takeo Sakurai[8], Hiroaki Matsuno[9], Tomomaro Izumihara[10], Eisuke Shono[11], Kou Katayama[12], Toyomitsu Tsuchida[13] and Motohiro Oribe[14]. [1]Matsubara Mayflower Hospital, Kato, Japan, [2]Research Institute of Joint Diseases, Kobe, Japan, [3]Higashi-Hiroshima Memorial Hospital, Higashi-hiroshima, Japan, [4]PS Clinic, Fukuoka, Japan, [5]Kanzaki Municipal General Hospital, Kanzaki, Japan, [6]Honjo Rheumatism Clinic, Takaoka, Japan, [7]Sagawa Akira Rheumatology Clinic, Sapporo, Japan, [8]Inoue Hospital, Takasaki, Japan, [9]Matsuno Clinic for Rheumatic Diseases, Toyama, Japan, [10]Izumihara Rheumatic and Medical Clinic, Kagoshima, Japan, [11]Shono Rheumatology Clinic, Fukuoka, Japan, [12]Katayama Orthopedic Rheumatology Clinic, Asahikawa, Japan, [13]Tsuchida Clinic, Chiba, Japan, [14]Oribe Rheumatism and Internal Medicine Clinic, Oita, Japan.

Background/Purpose: Abatacept (ABT), a CTLA4-Ig fusion protein agent targeted to T-cells, is a relatively new biological agent for RA treatment in Japan. However, there is no method for prediction of responders, non-responders, or adverse events which can occur during treatment. We established SNP algorithms for prediction of responsiveness, remission and adverse events in ABT-treated patients by using multiple medical cohorts.

Methods: The first population sample included 46 RA patients treated with ABT and the second, 52 patients; a total of 98 patients from 13 hospitals in different regions of Japan. Efficacy was assessed by DAS28 (CRP) at 48 weeks after the initiation of treatment. Any adverse events that may have been related to ABT administration and observed at 48 weeks of this long-term administration and during phase II were considered to be side effects. Genome-wide SNP genotyping was performed by Illumina HumanHap 300K chip technology. Case-controlled analyses between 302,814 SNPs and responsiveness, remission or occurrence of adverse events were examined by Fisher's exact test. We selected 10 SNPs associated with ABT-responsiveness, remission, and adverse events which were common in both analyses of the first and second populations ($p < 0.05$). We scored the relationship between each SNP and responsiveness, the estimated total score of 10 SNPs (estimated scoring in each SNP was as follows: homo allele in the majority in responders: +1 point, hetero allele: 0 points, and homo allele in the majority of non-responders: -1 point), and then examined relationships between responders and non-responders, remission and non-remission, and occurrence of adverse events, plus or minus, and the total score.

Results: Accuracy ((true positive+true negative)/total), specificity (true negative/(false positive+true negative)), and sensitivity (true positive/(true positive+false negative)) of the algorithm for responsiveness of abatacept ranged from 87–92%. For remission, accuracy, specificity and sensitivity of the algorithm ranged from 81–87%. For adverse events, accuracy, specificity and sensitivity of the algorithm ranged from 83–96%. It is therefore suggested that the SNP algorithms can predict responders and adverse events prior to the initiation of treatment with abatacept.

Conclusion: These highly accurate algorithms using SNP analysis may be useful in the prediction of responsiveness and adverse events before treatment with abatacept, and in this way can contribute to future tailor-made treatment with biologic agents.

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The Rate Of Serious Infections Remains Stable In Patients With Multiple Retreatments In Real life: Data From The "Auto Immunity and Rituximab" (AIR) Registry. Jacques-Eric Gottenberg[1], Philippe Ravaud[2], Patrice Cacoub Sr.[3], Thomas Bardin[4], Alain G. Cantagrel[5], Bernard Combe[6], Maxime Dougados[7], Rene-Marc Flipo[8], Bertrand Godeau[9], Loic Guillevin[10], Xavier Le Loet[11], Eric Hachulla[12], Thierry Schaeverbeke[13], Jean Sibilia[14], Isabelle Pane[15], Gabriel Baron[16] and Xavier Mariette[17]. [1]Strasbourg University Hospital, Strasbourg, France, [2]Hopital Hotel Dieu, Paris Descartes University, Paris, France, [3]CHU Pitié-Salpêtrière, Paris, France, [4]Hôpital Lariboisière, Paris, France, [5]Purpan University Hospital, Toulouse Cedex 9, France, [6]Lapeyronie Hospital, Montpellier, France, [7]Paris-Descartes University, APHP, Cochin Hospital, Paris, France, [8]Hopital R Salengro CHRU, Lille, France, [9]University of Paris, AP-HP, Hôpital Mondor Créteil, Creteil, France, [10]Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, [11]CHU of ROUEN, Rouen, France, [12]Claude Huriez University Hospital, Lille, France, [13]Groupe Hospitalier Pellegrin, Bordeaux, France, [14]CHU Hautepierre, Strasbourg, France, [15]Hotel Dieu University Hospital Paris, Paris, France, [16]Groupe Hospitalier Bichat-Claude Bernard, Paris, France, [17]Bicêtre University Hospital, Paris, France.

Background/Purpose: Serious infections in patients with rheumatoid arthritis (RA) treated with rituximab (RTX) are slightly more frequent in common practice than in clinical trials. Morevover, retreatment with multiple cycles might result in hypogammaglobulinemia, which is associated with an increased risk of serious infections. We therefore addressed this issue in the "Auto Immunity and Rituximab" (AIR) registry.

Methods: The AIR registry is an independent multicenter prospective 7-year registry promoted by the French Society of Rheumatology. Serious adverse events are validated by copy charts by the coordinators of the registry. Serious infections are defined as infections which required hospitalization,

intravenous antibiotics or resulted in death. All serious infections occurring in the 12 months following a RTX infusion are considered to occur on RTX therapy.

Results: 1985 patients with RA have been included. Baseline characteristics of the patients are the following: mean age: 58 years, women: 79%, disease duration: 19 years, RF-positivity: 79.5%, anti-CCP positivity: 72,6%, number of previous synthetic DMARDs: 3, 22% of patients without prior anti-TNF, 13% of patients with history of cancer, 34.7% of patients with previous serious or recurrent infections, 65.8% of patients treated with a concomitant synthetic DMARD, 77.2% with corticosteroids (mean dose: 12 mg/d), DAS28 at initiation of RTX: 5.6. 1977 patients have already had at least 1 follow-up visit, with a mean follow-up of 3 years (5865 patient/years).

- Retreatment with RTX: 70.6% of patients with RA were retreated (at least 2 cycles of RTX): ≥2 cycles: 1405 patients; ≥3 cycles: 1043 patients; ≥4 cycles: 763 patients; ≥5 cycles: 532 patients; ≥6 cycles: 330 patients).

- Safety: 95 deaths, 81 cancers, and 281 serious infections occurred. 961 patients (48.4%) discontinued RTX (initiation of a new biological, death, or no infusion in the 18 months preceding last follow-up visit) including 557 patients for inefficacy, 100 for adverse events (including 91 for a serious infection, 32.4% of the patients with serious infections), and 294 patients for other reasons. 96 serious infections occurred after the 1st cycle (4.8% of patients), 69 after the 2d cycle (4.9%), 38 after the 3d (3.6%), 32 after the 4th (4.2%), 20 after the 5th (3.8%), 8 after the 6th (2.4%), respectively, resulting in RTX discontinuation in 36 (37.5% of the serious infections occurring after 1stcycle), 28 (40.5%), 11 (28.9%), 10 (31.2%), 3 (15.0%), 2 (25.0%), after cycle 1 to 6, respectively.

Conclusion: In common practice, the proportion of patients with serious infections remains stable over cycles of RTX despite the increasing risk of hypogammaglobulinemia. It could be partly related to the depletion of the more susceptible patients with time. However, approximately two thirds of patients who experienced a serious infection did not discontinue RTX. Analysis of the contribution of the improvement of disease activity and decrease of corticosteroid dosage to this stable risk of serious infections, is currently ongoing.

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Lack Of Early Clinical Response To Treatment With Baricitinib Predicts Low Probability Of Achieving Long Term DAS28-ESR Low Disease Activity Or Remission In Patients With Rheumatoid Arthritis. Edward Keystone[1], Mark C. Genovese[2], Peter Taylor[3], Baojin Zhu[4], Scott D. Beattie[4], Stephanie de Bono[4], Terence Rooney[4], Douglas E. Schlichting[4] and William Macias[4]. [1]University of Toronto, Toronto, ON, [2]Stanford University Medical Center, Palo Alto, CA, [3]University of Oxford, Oxford, United Kingdom, [4]Eli Lilly and Company, Indianapolis, IN.

Background/Purpose: Baricitinib, an oral inhibitor of JAK1 and JAK2 activity, was investigated as treatment for patients with moderately to severely active RA despite use of conventional disease modifying anti-rheumatic drugs (Phase 2b Study JADA; NCT01185353). Compared to placebo, baricitinib (4 mg or 8 mg once daily (QD)) improved signs, symptoms, and physical function through 12 weeks of treatment with statistically significant effects observed as early as Week 2 of the study. Beneficial responses to baricitinib were maintained or improved through Week 24[1]. The objective of this post-hoc analysis was to determine whether early clinical response to baricitinib at Week 4 for the combined 4 and 8-mg dose groups predicted low disease activity (LDA) or remission at Week 12 and 24.

Methods: In Study JADA, 301 patients were randomized 2:1:1:1:1 to receive placebo or 1, 2, 4, or 8 mg baricitinib QD for 12 weeks, respectively, with the 2, 4, and 8-mg doses continued for an additional 12 weeks. Early clinical response was assessed by a variety of measures including DAS28-ESR (DAS-ESR). Week 12 and 24 outcomes were also assessed by a variety of measures including DAS-ESR LDA (DAS-ESR ≤3.2) or remission (DAS-ESR < 2.6). The association between improvements in clinical response at Week 4 for the combined 4/8-mg dose group (n=97) and Week 12 and 24 outcomes was evaluated based on observed data.

Results: Compared to placebo, baricitinib treatment was associated with rapid decrease in DAS-ESR observed as early as Week 2 ($p<0.001$ for both 4 and 8-mg dose groups). DAS-ESR LDA and remission rates were similar at Week 12 and Week 24 (35.1% and 35.2% for LDA; 21.6% and 24.2% for remission, respectively) for the combined 4/8-mg dose group. In 16.5% of patients, the decrease in DAS-ESR was <0.6 at Week 4. Among these patients, only 6.3% and 7.1% achieved DAS-ESR LDA at Week 12 and 24, respectively. No patients achieved remission at either time point. Among the 83.5% of patients whose DAS-ESR improved by ≥0.6 at Week 4, 40.7% and 40.3% achieved DAS-ESR LDA and 25.9% and 28.6% achieved DAS-ESR remission at Weeks 12 and 24, respectively (Table). Larger decreases in DAS-ESR at Week 4 were associated with a higher percentage of patients achieving LDA or remission at Weeks 12 and 24.

Low Disease Activity and Remission After 12 and 24 Weeks of 4 or 8 mg Baricitinib Treatment

Change in DAS-ESR from Baseline to Week 4	LDA (DAS28-ESR ≤ 3.2)		Remission (DAS28-ESR < 2.6)	
	Week 12	Week 24	Week 12	Week 24
	% (Number) of Patients Achieving Clinical Outcome of Interest			
<0.6	6.3% (1/16)	7.1% (1/14)	0% (0/16)	0% (0/14)
<0.8	8.7% (2/23)	14.3% (3/21)	0% (0/23)	4.8% (1/21)
<1.0	9.4% (3/32)	16.7% (5/30)	0% (0/32)	6.7% (2/30)
<1.2	8.3% (3/36)	17.6% (6/34)	0% (0/36)	5.9% (2/34)
	% (Number) of Patients Achieving Clinical Outcome of Interest			
≥0.6	40.7% (33/81)	40.3% (31/77)	25.9% (21/81)	28.6% (22/77)
≥0.8	43.2% (32/74)	41.4% (29/70)	28.4% (21/74)	30.0% (21/70)
≥1.0	47.7% (31/65)	44.3% (27/61)	32.3% (21/65)	32.8% (20/61)
≥1.2	50.8% (31/61)	45.6% (26/57)	34.4% (21/61)	35.1% (20/57)

Conclusion: Baricitinib treatment was associated with a rapid decrease in DAS-ESR with stable DAS-ESR LDA and remission rates observed as early as Week 12 with persistence of benefit through Week 24. A <0.6 decrease in DAS-ESR after 4 weeks of baricitinib treatment was associated with a very low percentage of patients achieving LDA or remission at either Week 12 or Week 24. Larger decreases in DAS-ESR at Week 4 were associated with improved clinical responses. If replicated in Phase 3 studies, a lack of early response to baricitinib may be useful in tailoring therapy to individual patients.

Reference:

1. M Genovese et al Arthritis and Rheumatism. 2012;64(10(supp)):S1049.

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Assessing Janus Kinase inhibitor's Place In Therapy In Established Rheumatoid Arthritis Patients – From a Simplified Indirect Comparison Versus Tumor Necrosis Factor Inhibitors To a Bayesian Probability Of Response – The Value Of Transparency. Michael P. Ingham[1], Paul Song[2], Shannon Cartier[3], Karin Lawson-Remer[2] and Erin Murray[2]. [1]Janssen Scientific Affairs, LLC, Horsham, PA, [2]Doctor Evidence LLC, Santa Monica, CA, [3]Optum, Eden Prairie, MN.

Background/Purpose: Bayesian style network meta-analyses and mixed treatment comparisons help address potential bias from effect modifying trial covariates within indirect comparisons and are theoretically easier to incorporate into decision making, but are not commonly used today by providers when making treatment decisions. Health care reform is paving the way for potentially easier access to tools like this, however quick interpretation still requires as simple an indirect comparison as is reliable, with a preference for greater transparency. From provider perspective, compare tumor necrosis factor inhibitors (TNFi) to Janus kinase inhibitor tofacitinib (TOFA) in

established RA patients when used with non-biologic disease modifiers (DMARDs).

Methods: A systematic review focused on randomized controlled trials (RCTs) with unsatisfactory response to prior DMARD, placebo comparator, active treatment with add-on DMARD, lowest labeled dose and 24-week ACR20 endpoint. Outcomes were extracted double-blind and analysed using a payer validated simulation tool. Indirect comparisons followed ISPOR taskforce on good research practices. ACR20 response was also analyzed within a Bayesian framework, estimating the percentage of time TNF inhibitors had a greater response than tofacitinib. Results presented as relative risks (RR) with confidence intervals where appropriate. Probabilities did not include statistical analyses. Each trial result versus placebo was graphically presented, for transparency, and rank ordered based on relative risk (RR) versus placebo.

Results: Eight TNFi and three TOFA RCTs were identified that reported ACR20 results at 24 weeks. Trials differed primarily in placebo response and intent-to-treat (ITT) reporting methodology. Based on published ITT evidence, it was not possible to extract ACR50 and ACR70 scores for all TOFA trials. For ACR20, six of eight TNFi trials had RR values larger than combined TOFA 5mg results. The indirect RR (and confidence interval) of TNFi versus TOFA for ACR20 was 1.48 (1.02 to 2.14). I^2heterogeneity values were zero for TOFA trial data, and were $>$ 85% for TNFi trials. The probability the risk difference (RD) $>$ 0 from the Bayesian analysis was 85.4% and 80.6% when unadjusted and adjusted for baseline risk respectively. RR $>$ 1.0 and RD$>$0 favor TNFi. DAS Remission and HAQ-DI results were not significantly different TNFi versus TOFA. Results may be sensitive to trials included and time point selected.

Conclusion: Visual inspection of original trial results and the multiple traditional meta-analyses helped identify how and why TNFi compares favorably to TOFA on the most common trial primary outcome (ACR20). Simple indirect comparisons demonstrate analyses of relative treatment effects available to providers, based on published evidence and with access to simulation tools. Supplementing with easily interpretable and adjustable probability of response versus placebo analysis, allows for a more transparent discussion on place in therapy of new treatments. Based on this analysis, time point and outcome, TNFi are likely to be more effective than TOFA more often, when considering biologics used concomitantly with DMARDs.

Disclosure: M. P. Ingham, Janssen Scientific Affairs, LLC, 3; **P. Song**, Janssen Scientific Affairs, LLC, 5; **S. Cartier**, Janssen Scientific Affairs, LLC, 5; **K. Lawson-Remer**, Janssen Scientific Affairs, LLC, 5; **E. Murray**, Janssen Scientific Affairs, LLC, 5.

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Effectiveness Of TNF-á Inhibitor Therapy Does Not Differ Between Elderly and Younger Patients With Rheumatoid Arthritis: Results From The Corrona Registry.

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Background/Purpose: Biologics have revolutionized the therapy and prognosis of patients (pts) with Rheumatoid Arthritis (RA). Studies evaluating whether the effectiveness of TNF-α inhibitor (TNFi) therapy varies by age group are lacking. The present analysis compares the effectiveness of TNFi treatment between older and younger pts with RA.

Methods: Data were obtained from the Consortium of Rheumatology Researchers of North America (CORRONA) registry. We identified RA pts having at least moderate disease activity (CDAI $\geq$10) who initiated their first TNFi and had a follow up visit 6 months (4–9 months) later. We subsequently compared the odds of achieving low disease activity (LDA), as measured by CDAI, in older ($\geq$65 years old) vs younger (18–64 years old) pts. Non-response was imputed for pts who discontinued the TNFi and switched to another biologic prior to the 6 month follow up visit. The actual 6 months disease activity was used if TNFi was stopped without switching to a different biologic.

Multivariate models (MV) compared the odds of achieving LDA between older and younger pts. Propensity scores (PS) were used to evaluate the probability of pts to belong in the elderly group and were used to fit MV models in two ways: a) After excluding pts in the non overlapping regions of the PS distribution, we adjusted for variables still not balanced after trimming. b) Using the PS to 1:1 match older to younger TNFi initiators we adjusted only for disease duration.

Results: 1415 biologic naïve TNFi initiations were identified: 377 of them were $\geq$ 65 years old and 1038 pts were $<$ 65 years old. Baseline characteristics in older versus (vs) younger group: 72.4% vs 77.1% women, 88.3% vs 81.7% Caucasian, 74.2% vs 70.2% seropositive. Mean $\pm$ SD age was 72.4$\pm$6.1 vs 50.8$\pm$9.6 years, RA disease duration 10.9$\pm$10.8 vs 6.1$\pm$7.6 years; CDAI: 25.7$\pm$ 10.8 vs 26.3$\pm$12.8 in older vs younger pts respectively. 82.2% of older pts received the TNFi in combination with non-biologic DMARDs vs 85.4% in the younger group. 72 (19.10%) older pts discontinued the TNFi during the follow up period and 10 of them (2.65%) switched to different biologic vs 180 (17.34%) and 50 pts (4.82%) respectively in the younger group.

After trimming pts in non-overlapping regions of PS, 365 pts remained in the older and 1021 in the younger group. After PS 1:1 matching, 326 pts remained in each group. Table 1 shows the results of unadjusted and adjusted comparisons in the odds of achieving LDA in older and younger pts.

Table 1.

Treatment	Odds Ratios	[95% CI]	p-value
	Unadjusted Results		
Younger patients (N=1038)	1 (referent)		
Older patients (N=377)	0.98	0.76–1.26	0.874
	Adjusted Results after trimming of patients on non-overlapping Propensity Score* distributions**		
Younger patients (N=1021)	1 (referent)		
Older patients (N=365)	0.89	0.67–1.17	0.387
	Adjusted Results after Propensity Score* 1:1 matching***		
Younger patients (N=326)	1 (referent)		
Older patients (N=326)	0.91	0.65–1.27	0.575

* Propensity score variables: gender, functional class, subcutaneous nodules, baseline CDAI, baseline mHAQ score, BMI, smoking status, history of cardiovascular disease, and history of malignancy.
** Adjusted for: gender, functional class, subcutaneous nodules, baseline mHAQ, baseline CDAI, BMI, history of cardiovascular disease, history of malignancy, and smoking status.
*** Adjusted for: duration of Rheumatoid Arthritis.

Conclusion: The effectiveness of TNFi therapy does not differ between older and younger pts with RA based on the current analysis. This suggests that treatment decisions for those with RA should not be based on age considerations alone.

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Early Changes In a Multi-Biomarker Disease Activity Score After Starting Adalimumab Treatment Predict Change In MRI Inflammation At 6 Months.

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Background/Purpose: A multi-biomarker disease activity (MBDA) score has been validated as a measure of disease activity in rheumatoid arthritis. This study aimed to see if baseline MBDA score and early treatment-induced changes in MDBA score predict magnetic resonance imaging (MRI) inflammation and joint damage at week 26 and 52 in patients initiating anti-TNF therapy in an investigator-initiated trial (HURRAH trial, NCT00696059).

Methods: Fifty-two RA patients with active disease despite conventional DMARD therapy were included. All started adalimumab 40 mg s.c. eow at baseline and continued on methotrexate. MRI of the wrist and MCP joints of one hand was obtained at baseline, week 26 and 52, and OMERACT RAMRIS scores were assigned. Blood tests were drawn at baseline, week 2, 6, 12, 26, 39 and 52 for measurement of 12 serum biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL-40, leptin, resistin, SAA, CRP) used to generate a Vectra® DA algorithm score. Associations between MBDA score, DAS28-CRP and changes in MRI inflammation and joint damage at week 26 and 52 were tested using Spearman's rank correlations. We did not control for multiple testing in this post-hoc analysis.

Results: Of the 52 patients, 67% were women, 79% IgM rheumatoid factor positive. At baseline, age was median 61 years (range 19–86), disease duration 7 years (0–36), DAS28-CRP 4.9 (2.9–7.4), HAQ 1.125 (0–2.125), MRI synovitis score 15 (3–21), MRI bone marrow oedema score 7 (0–42), MRI erosion score 16 (3–155), MBDA score 63 (15–89).

At week 26 MBDA score was statistically significantly correlated with MRI synovitis (rho = 0.42, p=0.016), but not with MRI bone marrow edema (rho = 0.32, p=0.06). At baseline and week 52 no statistically significant correlations between MBDA score and MRI inflammation were found.

MBDA score at week 2 and 6 and percent change in MBDA score at week 6 predicted changes in MRI synovitis score at week 26. In similar analyses at week 52, no statistically significant associations were found. A borderline significant (p = 0.07) correlation was observed between percent change in MBDA score at week 6 and change in MRI erosion score at week 26.

In all 15 patients with clinical remission (DAS28-CRP<2.6), subclinical inflammation could be detected at 6 months by MRI (all had synovitis, 9 had bone marrow edema). Of these 15 patients only 2 (13%) were grouped as in MBDA remission (≤25), 7 (44%) in MBDA moderate disease activity (30–44) and 6 (40%) in MBDA high disease activity (>44). 4 patients had MRI erosive progression above the smallest detectable difference (change in score ≥3) at week 52, none of these were in clinical or MBDA remission at week 26.

	Change in MRI synovits score from baselineto week 26			Change in MRI bone marrow edema score from baselineto week 26			Change in MRI erosion score from baselineto week 26		
	N	rho	P-value	N	rho	P-value	N	rho	P-value
Baseline MBDA	36	0.28	0.10	36	0.06	0.73	38	0.08	0.62
MDBA at week 6	34	0.49	0.033	34	0.10	0.58	36	0.28	0.10
Change in MBDA score at week 6	34	0.30	0.09	34	0.15	0.41	36	0.23	0.17
Percent change in MBDA score at week 6	34	0.44	0.009	34	0.15	0.41	36	0.31	0.06
Baseline DAS28-CRP	36	0.37	0.025	36	0.17	0.31	38	−0.00	0.99
DAS28-CRP at week 6	33	0.15	0.40	34	0.32	0.06	35	0.02	0.91
Change in DAS28-CRP score at week 6	33	−0.10	0.59	34	0.19	0.28	35	0.09	0.61
Percent change in DAS28-CRP score at week 6	33	−0.06	0.73	34	0.28	0.10	35	0.11	0.54

Conclusion: MDBA score at week 2 and 6 and percent change in MBDA score at week 6 was predictive of MRI synovitis at week 26, but not at week 52. This study encourages further investigation of MBDA as en early marker of treatment response and risk of erosive progression in patients with RA.

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Clinical and Radiographic Outcomes At Two Years and The Effect Of Tocilizumab Discontinuation Following Sustained Remission In The Second Year Of The ACT-RAY Study. Thomas W.J. Huizinga[1], Philip G. Conaghan[2], Emilio Martin-Mola[3], Georg Schett[4], Howard Amital[5], Ricardo M. Xavier[6], Orrin Troum[7], Maher Aassi[8], Corrado Bernasconi[8] and Maxime Dougados[9]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [3]Hospital Universitario La Paz, Madrid, Spain, [4]University of Erlangen-Nuremberg, Erlangen, Germany, [5]Sheba Medical Center, Tel-Hashomer, Tel-Aviv University, Tel-hashomer, Israel, [6]Faculdade de Medicina, Universidade Federal do Rio Grande do Sul - Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, [7]University of Southern California School of Medicine, Santa Monica, CA, [8]F. Hoffmann-La Roche Ltd, Basel, Switzerland, [9]Cochin Hospital, Paris, France.

Background/Purpose: 24- and 52- week data from ACT-RAY comparing an add-on strategy (tocilizumab [TCZ] + methotrexate [MTX]) with a switch strategy (TCZ + placebo [PBO]) in MTX-IR pts have been previously reported, demonstrating relevant clinical and radiographic benefit without clinically meaningful between-arm differences for most endpoints. During year 2, the study included a step-down strategy with the goal of achieving drug free remission (discontinuation of study drugs with DAS28 <2.6). The objective here is to further assess the efficacy and safety of TCZ-based treatment strategies and to determine the ability to discontinue study drugs in year 2 after sustained clinical remission (DAS28 <2.6 at 2 consecutive visits 12 weeks apart).

Methods: ACT-RAY is a phase 3b trial. Pts on stable doses of MTX were randomized to either add TCZ 8 mg/kg IV every 4 weeks (q4w; add-on) or switch to TCZ 8 mg/kg IV with oral PBO (switch). Utilizing a treat to target (T2T) approach, OL DMARDs other than MTX were added from week 24 usually if DAS28 was >3.2, while maintaining MTX/PBO blinding. In year 2, if sustained clinical remission was achieved, first TCZ and then OL DMARDs and MTX/PBO were discontinued. In case of flare, the last effective treatment or TCZ with blinded MTX/PBO was restarted.

Results: Pt baseline (BL) data were similar between treatment arms (mean disease duration 8.2 y, BL DAS28 6.4) except for higher Genant-Sharp Scores (GSS) in the switch group (41.2 vs 36.9 for add-on pts). 76% of 556 randomized pts (277 add-on and 276 switch) completed year 2. Reasons for withdrawal included lack of efficacy (1.8% add-on, 4.7% switch) and adverse events (AEs; 9.7% add-on, 11.2% switch, including 3 and 6 deaths, respectively). Of pts entering into year 2,~50% discontinued TCZ after achieving sustained remission, and 86% of these pts experienced flare before the end of year 2 (flares can still occur in year 3). For pts who restarted TCZ and had a DAS28 assessment (n = 164), mean DAS28 at flare was 4.46. The effects of restarting TCZ were rapid with mean DAS28 dropping to 2.99, 2.18 and 2.02 within 4, 12 and 20 weeks, respectively. See table for additional results. Despite many pts stopping TCZ for some period, radiographic progression was minimal in both arms (table). Safety was consistent with previous findings. SAEs and serious infections per 100 PY were 11.9 and 4.2, respectively, for the add-on and 14.6 and 3.8, respectively, for the switch arm. In pts with normal BL values, ALT elevations >3× ULN were observed in 13.5% of add-on and 4.9% of switch pts.

Table. Week 104 Efficacy Results

Clinical Parameter	Add-on N = 277[1]	Switch N = 276[1]	*P*value
TCZ discontinuation after achieving sustained remission[2], %	53%	47%	0.13
Pts achieving study drug-free remission[2,3], %	5.1%	1.8%	0.037
Flares[2,4], %	85%	87%	0.075
Median time to flare (days)[5]/Mean DAS28-ESR at flare	113/4.4	79/4.4	0.075/0.22
Mean DAS28-ESR 12 weeks after TCZ restart/% with DAS28-ESR<2.6[6]	2.22/76%	2.13/74%	–
DAS28-ESR, mean change ± SEM from baseline[7,8]	−3.5±0.14	−3.6±0.14	0.43
GSS, mean change ± SEM from baseline[8]	0.35±0.35	0.95±0.32	0.036
Pts without radiographic progression[9], %	94%	91%	0.14

[1]Ns for ITT population only. See additional footnotes for analysis-specific ns. [2] Kaplan-Meier estimates (for TCZ discontinuation and drug-free remission based on the 85% of ITT pts eligible for step-down phase). Further flares and drug-free remissions may still occur. [3] First TCZ, then OL DMARDs and then MTX/PBO were stopped if remission was maintained. Does not consider steroids. [4] Definition of flare was at the investigator's discretion. [5] *P* value from a Log-Rank test. [6] N = 73 (add-on) and 68 (switch). [7] N = 218 (add-on) and 192 (switch). [8] Estimates and *P* values adjusted for region, baseline DAS28 (DAS28 change)/baseline GSS (GSS change). Baseline GSS scores from reading campaign 2. [9] No progression defined as change from baseline GSS ≤2.1 (smallest detectable change for reading campaign 2); N = 214 (add-on) and 202 (switch): pts with a Week 104 reading; *P* value from a Cochran-Mantel-Haenszel test stratified by baseline GSS quartile and DAS28 ≤ or >5.5.

Conclusion: Previous clinical improvements were largely maintained in year 2 of ACT-RAY. Year 2 results suggest that T2T strategies can be successfully utilized in MTX-IR pts (whether or not currently on MTX) to achieve sustained remission. However, stopping TCZ in this established RA pt population was associated with a high flare risk. Pts who restarted TCZ achieved improvements in DAS28.

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Comparative Effectiveness Of Rituximab Vs. Subsequent Anti-Tumor Necrosis Factor In Patients With Rheumatoid Arthritis With Prior Exposure To TNFi. Leslie R. Harrold[1], George W. Reed[2], Robert P. Magner[1], Ashwini Shewade[3], Ani John[3], Jeffrey D. Greenberg[4] and Joel M. Kremer[5]. [1]University of Massachusetts Medical School, Worcester, MA, [2]CORRONA, Inc., Southborough, MA, [3]Genentech Inc., South San Francisco, CA, [4]NYU Hospital for Joint Diseases, New York, NY, [5]Albany Medical College and The Center for Rheumatology, Albany, NY.

Background/Purpose: In patients (pts) who have failed 1 or more TNF-α inhibitors (TNFi), there is little data to guide clinical decision making in terms of changing mechanism of action or prescribing another TNFi. The objective of this study was to examine the comparative effectiveness of rituximab (RTX) versus a subsequent TNFi in RA pts with prior TNFi exposure using data from the Consortium of Rheumatology Researchers of North America (CORRONA), a multi-center observational registry within the United States.

Methods: Using CORRONA data spanning from 10/8/2001 through 10/31/2012, we identified RTX-naïve RA pts with prior TNFi use who were initiating RTX or a subsequent TNFi, had a 1-year follow-up visit and had Clinical Disease Activity Index (CDAI) measurements at baseline and 1-year follow-up. A propensity score (PS) for TNFi vs. RTX was estimated using baseline clinical characteristics. The PS distributions were trimmed to exclude pts who fell outside the region of common support ($n = 2$). Effectiveness outcomes at 1 year included achievement of low disease activity (LDA, CDAI $\leq$ 10), achievement of modified ACR (mACR) 20/50/70 and decrease in mHAQ of 0.25. Nonresponse was imputed for pts who switched biologics. A sensitivity analysis using stratified matching by 1 vs. $\geq$ 2 prior TNFi and matching by PS was performed. Multivariable regression models adjusted for baseline parameters with a standardized difference > 0.1, baseline CDAI, steroid use, number of prior TNFi (1 vs. $\geq$ 2), and concomitant MTX use.

Results: 265 RTX pts and 737 TNFi pts met the inclusion criteria for the analysis. At baseline, both groups were mostly female (79–81%) with a mean age of 56–58 years, mean CDAI of 25.2–27.3 and mean mHAQ of 0.64–0.78. RTX pts had longer duration of disease (15 vs 11 years), greater prior use of $\geq$ 2 TNFi's (63% vs 27%) and greater prior use of non-TNF biologics (41% vs 13%) compared with TNFi pts. Results of comparative effectiveness analyses are presented in Table 1. In the PS-trimmed population, RTX treatment was estimated to be associated with a 35–66% increased likelihood of response compared with TNFi treatment, however this was only significant for mACR20, mACR50 and mHAQ. In the TNFi-stratified matched and PS-matched population, RTX treatment was associated with a significantly increased likelihood of achieving LDA compared with TNFi treatment (OR 1.54 [95% CI: 1.01 to 2.35]). During the 1-year follow-up, 16.2% of RTX pts and 29.4% of TNFi pts switched biologics.

Table 1. Effectiveness Outcomes by Treatment Regimen and Adjusted Odds Ratios (OR)

	RTX responders	TNFi responders	Adjusted OR (95% CI)[a]
LDA (CDAI $\leq$ 10), %	34.3	33.7	1.35 (0.95, 1.91)
mACR20, %	36.6	28.7	1.66 (1.17, 2.36)
mACR50, %	21.1	17.4	1.53 (1.01, 2.30)
mACR70, %	10.2	8.8	1.59 (0.92, 2.76)
mHAQ, %	33.2	24.2	1.46 (1.01, 2.12)

[a]Adjusted for demographics, RA characteristics, baseline disease activity, comorbidity and medication use (past and current).

Conclusion: In a population of RA pts with prior exposure to TNFi, RTX initiators had longer duration of active disease and had more prior biologic use compared with TNFi initiators. Across measures of disease activity and function, there was an estimated 35–66% increased likelihood of response in pts treated with RTX compared with those treated with TNFi. Fewer RTX pts than TNFi pts were switched to another biologic over the 1-year follow-up period.

Disclosure: L. R. Harrold, CORRONA, 2; **G. W. Reed**, CORRONA, 3; **R. P. Magner**, University of Massachusetts Medical School, 3; **A. Shewade**, Genentech, Inc., 3; **A. John**, Genentech, Inc., 3; **J. D. Greenberg**, CORRONA, 1, CORRONA, AstraZeneca, Novartis, Pfizer, 5; **J. M. Kremer**, CORRONA, 1, CORRONA, 3.

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Safety, Pharmacokinetics, and Pharmacodynamics Of SAN-300, a Novel Monoclonal Antibody Against Very Late Antigen-1: Results Of a Phase 1 Study In Healthy Volunteers and Patients With Active Rheumatoid Arthritis. Charles Inderjeeth[1], Andrew Redfern[1], Michael Huang[2], Yun Hardiman[2], Theresa Grant[2], Lawrence C. Fritz[2], David Fuller[3], David Haughey[4] and Mark C. Totoritis[2]. [1]Linear Clinical Research Ltd, Perth, Australia, [2]Santarus, Inc., San Diego, CA, [3]INC Research, Inc., New South Wales, Australia, [4]ICON Development Solutions, Whitesboro, NY.

Background/Purpose: Very late antigen-1 (VLA-1; $\alpha 1\beta 1$ integrin), a cell adhesion molecule expressed on activated lymphocytes and monocytes/macrophages, binds extracellular matrix molecules and facilitates migration, proliferation, and retention of these cells at sites of inflammation. Inhibition of VLA-1 by antibody blockade or genetic ablation is associated with decreased disease severity in animal models of acute and chronic inflammation, including models of rheumatoid arthritis (RA). This Phase 1, escalating single-dose study evaluated safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of intravenous (IV) and subcutaneous (SC) administration of SAN-300, an anti-VLA-1 antibody, in healthy subjects and patients with active RA.

Methods: In a randomized, placebo-controlled design, 66 healthy subjects received single IV or SC SAN-300 administrations (0.03–2.0 mg/kg IV; 2.0–6.0 mg/kg SC; N=45) or placebo (N=21). Two patients with active RA received SAN-300 2.0 mg/kg IV (N=1) or placebo (N=1). Serum SAN-300 concentrations, VLA-1 receptor occupancy (RO), and safety were assessed through Day 29. American College of Rheumatology (ACR) response criteria and Disease Activity Score 28 based on CRP (DAS28-CRP) were assessed in patients with active RA.

Results: Serum SAN-300 concentrations were undetectable in most subjects at low doses (0.03–0.3 mg/kg IV). In subjects receiving SAN-300 0.6–2.0 mg/kg IV or 2.0–6.0 mg/kg SC, a nonlinear pharmacokinetic profile was observed. Essentially complete VLA-1 RO ($\geq$ 90%) was noted at doses above 0.8 mg/kg IV and 2.0 mg/kg SC, with durable RO ($>$ 50%) observed through Day 8 for SAN-300 2.0 mg/kg SC and Day 15 for SAN-300 4.0–6.0 mg/kg SC. SAN-300 was generally well tolerated. No severe/serious infections were reported. Most adverse events (AEs) were mild or moderate in intensity. The most common AEs upon IV administration were mild or moderate headaches and infusion reactions. Infusion reactions occurred with 0.8–2.0 mg/kg IV; all events improved by 72 h. Among subjects receiving SAN-300 SC, headaches and mild injection-site reactions were most common. Transient, mild to moderate decreases in absolute neutrophil counts (1.1–1.9 $\times$ 10^9/L; normal: 1.9–8.0 $\times$ 10^9/L) were observed, mostly at higher doses. All cases resolved without sequelae. The single patient with active RA who received SAN-300 2.0 mg/kg IV met ACR50 at Days 15 and 29 and achieved a good response per EULAR criteria based on DAS28-CRP at Day 15 (-1.66; absolute score 2.31), and a moderate response at Day 29 (-0.92; 3.05). The placebo patient did not meet criteria for ACR20 or DAS28-CRP response at any time point.

Conclusion: In this first-in-human study, SAN-300, an antibody against novel therapeutic target VLA-1, showed nonlinear pharmacokinetics. However, durable saturation of VLA-1 was observed following IV or SC administration. SAN-300 was generally well tolerated, with the SC formulation mitigating the occurrence of mild or moderate infusion reactions seen at higher IV doses. Given favorable tolerability, encouraging RO, and ease of administration, the SC route of administration warrants investigation in future multiple-dose studies in patients with active RA.

Disclosure: C. Inderjeeth, Linear Clinical Research Ltd, 5; **A. Redfern**, Linear Clinical Research Ltd, 3; **M. Huang**, Santarus, Inc., 1, Santarus, Inc., 3; **Y. Hardiman**, Santarus, Inc., 1, Santarus, Inc., 3; **T. Grant**, Santarus, Inc., 3, Santarus, Inc., 1; **L. C. Fritz**, Santarus Inc., 1, Santarus, Inc., 5; **D. Fuller**, INC Research, 3; **D. Haughey**, ICON Development Solutions, 3; **M. C. Totoritis**, Santarus, Inc., 1, Santarus, Inc., 3.

1440

Effects Of Tocilizumab On Serum Cytokines In Rheumatoid Arthritis With An Inadequate Response To Disease-Modifying Antirheumatic Drugs. Sang Jin Lee[1], Kyung Rok Kim[2], Sang Hyun Joo[2], Jae Myung Lee[2], In Ah Choi[2], Joo Youn Lee[1], Hyun Jung Yoo[1], Eun Young Lee[2], Eun Bong Lee[3], Won Park[4], Sung Hwan Park[5], Seung-Cheol Shim[6], Dae-Hyun Yoo[7], Han Joo Baek[8], Hyun Ah Kim[9], Soo Kon Lee[10], Yun Jong Lee[3], Young Eun Park[11], Hoon-Suk Cha[12] and Yeong Wook Song[2]. [1]Department of molecular medicine and biophamaceutical sciences, Seoul National University, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul National University, Seoul, South Korea, [3]Rheumatology, Seoul National University, Seoul, South Korea, [4]Inha University Hospital, Incheon, South Korea, [5]Rheumatology, The Catholic University, Seoul, South Korea, [6]Rheumatology, Eulji University, Daejeon, South Korea, [7]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [8]Rheumatology, Gachon University, Incheon, South Korea, [9]Hallym university, Kyunggi, South Korea, [10]Yonsei University College of Medicine, Seoul, South Korea, [11]Rheumatology, Pusan Nationl University, Pusan, South Korea, [12]Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea.

Background/Purpose: The objective of this study was to investigate the effects of tocilizumab on serum cytokines in rheumatoid arthritis (RA) patients with an inadequate response to disease-modifying antirheumatic drugs (DMARDs).

Methods: We collected sera from tocilizumab study (CWP-TCZ301), a 24-weeks, randomized, double–blinded trial of tocilizumab in RA patients with an inadequate response to disease-modifying antirheumatic drugs (DMARDs). Serum cytokine levels (tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-17, IL-21, IL-23 and IL-33) were determined by luminex multiplex analysis at baseline and after treatment (4, 12 and 24 weeks). Therapeutic response was evaluated by American College of Rheumatology 20% improvement (ACR 20) in tocilizumab (n=47) and DMARDs group (n=48) after 24 weeks.

Results: Serum levels of IL-17, IL-21, IL-23 and IL-33 were significantly higher in RA patients than in healthy controls (all $p<0.05$). Early withdrawal patients from the study were excluded in the evaluation. In tocilizumab group, 29 patients were ACR 20 responders and 11 patients were non-responders after 24 weeks of treatment. Baseline serum levels of IL-17 were significantly lower in responders than in non-responders (mean ± SEM, 3.21 ± 1.74 pg/mL vs 15.89 ± 8.27 pg/mL, $p<0.05$). However IL-17 level did not significantly change during tocilizumab treatment irrespective of ACR 20 responsiveness. Levels of IL-21, IL-23 and IL-33 were not significantly different at baseline in responders and non-responders. However they were significantly decreased at 4, 12, 24 weeks in responders ($p<0.005$, respectively), but not in the non-responders. Levels of IL-6, TNF-α were not significantly different at baseline and did not significantly change during tocilizumab treatment. In DMARDs group, 8 patients were ACR 20 responders after 24 weeks of treatment. These patients' baseline serum levels of IL-17 were significantly lower than those of DMARDs non-responders (n=35) (0.46 ± 0.46 pg/mL vs 4.40 ± 2.47 pg/mL, $p=0.001$). Levels of IL-21, IL-23 and IL-33 were not significantly different at baseline and did not significantly change during DMARDs treatment irrespective of ACR 20 responsiveness.

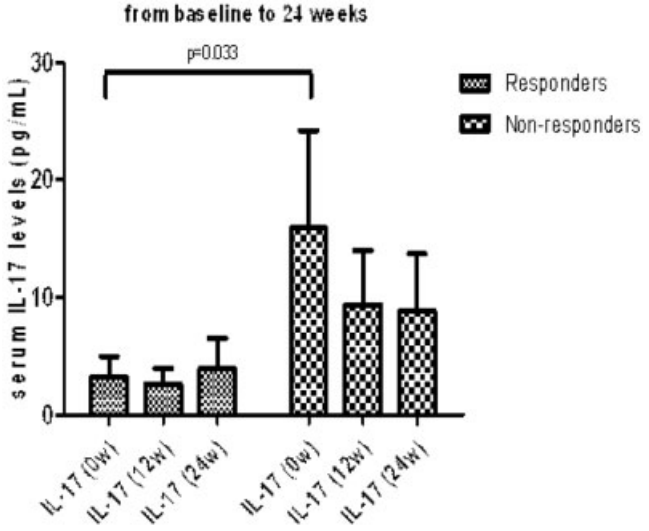

Figure 1. After tocilizumab infusion, the change in serum cytokine levels in ACR 20 responders and non-responders from baseline to 24 weeks

Conclusion: Baseline serum levels of IL-17 were lower in ACR 20 responders after tocilizumab therapy in RA. Serum levels of IL-21, IL-23 and IL-33 were significantly decreased during tocilizumab therapy in ACR 20 responders compared to non-responders.

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Predictive Factors Of Response To Tocilizumab In Patients With Active Rheumatoid Arthritis. Maria Victoria Hernández[1], Javier Narvaez[2], Raimon Sanmarti[3], Delia Reina[4], Cesar Diaz-Torne[5], Berta Magallares[5], Arturo Rodriguez de la Serna[5], José María Llobet[5], Hector Corominas[4] and Joan Miquel Nolla[6]. [1]Hospital Clínic of Barcelona. IDIBAPS. University of Barcelona, Barcelona, Spain, [2]Hospital Universitario de Bellvitge, Barcelona, Spain, [3]Hospital Clínic of Barcelona, Barcelona, Spain, [4]Hospital de Sant Joan Despí Moisès Broggi, Barcelona, Spain, [5]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [6]Hospital Universitari de Bellvitge, Barcelona, Spain.

Background/Purpose: To analyze the efficacy and identify predictors of response to tocilizumab (TCZ) in patients with rheumatoid arthritis (RA).

Methods: A multicenter ambispective observational study in 126 patients with active RA treated with TCZ. The variables associated to achieve the therapeutic goal (remission of the disease defined as a DAS28 < 2.6) at 3 and 6 months were identified by a logistic regression model by using the backward approach. SAS 9.3 was used for the management and statistical analysis.

Results: Patients' demographic and clinical characteristics are shown in table 1, as well as the response rates at 3 and 6 months of treatment. TCZ was administered as the first biologic in 33 out of 126 patients, while in the remaining 93 was used after inadequate response or intolerance to > 1 biological therapies (mean 2.18 ± 1.1, range 1–6). Forty-three patients (35%) received TCZ as monotherapy. In the multivariate analysis, the predictive factors that increase the likelihood of clinical remission (DAS28-ESR < 2.6) at 3 months were baseline ESR > 30 mm/h (OR: 19.07, 95% CI: 2.7– 133.7) and the presence of extra-articular manifestations of the disease (OR: 15.5, 95% CI: 2.3– 102.3). The factors that decreased it were of haemoglobin (OR: 0.53, 95% CI: 0.32– 0.91), baseline DAS28-ESR (OR: 0.30, 95% CI: 0.15–0.64) and the number of previous DMARDs and biological therapies used (OR: 0.42, 95% CI: 0.22– 0.78). The only significant factor that reduced the possibility of clinical remission (DAS28-ESR < 2.6) at 6 months was the baseline DAS28-ESR (OR: 0.55, 95% CI: 0.35– 0.88). No relationship was found in the decrease of the neutrophils count or in the positivity of rheumatoid factor/ACPA.

Table 1.

Number of patients	126
Age: (mean ± SD), years	57 ± 13
Gender: (female/male)	108/18
Disease duration: median (range), years	10 (1–41)
Presence of rheumatoid factor/ ACPA	72%/67%
Erosive disease	70%
Systemic extra-articular manifestations	33%
Number of previous DMARDs: (mean ± SD)	2.53 ± 1.4 (1–7)
Baseline DAS28-ESR: (mean ± SD)	5.5 ±1.08
Response rates at 3 and 6 months of treatment	31%/40%
Remission by DAS28-ESR (< 2.6)	48%/64%
Low activity by DAS28-ESR (< 3.2)	25%/31%
Remission by SDAI(< 3.3)	69%/76%
Low activity by SDAI(< 11)	48%/63%
Good EULAR response	15% /16%

Remission by ACR/EULAR criteria.

Conclusion: The high inflammatory activity of the disease (measured by haemoglobin, ESR and DAS28), as well as the presence of extra-articular manifestations and the previous DMARDs and biological therapies may help in the selection of the best candidates for treatment with tocilizumab.

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1442

Three-Year Drug Survival and Effectiveness Of Abatacept and Tocilizumab In Patients with Rheumatoid Arthritis Treated In Routine Care. Results From The Nationwide Danish Danbio Registry. HCB Leffers[1], Mikkel Østergaard[2], Bente Glintborg[3], Niels Steen Krogh[4], Ulrik Tarp[5], Tove Lorenzen[6], Annette Hansen[7], Lene Dreyer[8] and Merete L. Hetland[2]. [1]Department of Rheumatology, Frederiksberg Hospital, Frderiksberg, Denmark, [2]Copenhagen University Hospital Glostrup, Copenhagen, Denmark, [3]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Glostrup Hospital, Glostrup, Denmark, [4]ZiteLab ApS, Copenhagen, Denmark, [5]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [6]Department of Rheumatology, Region Hospital Silkeborg, Silkeborg, Denmark, [7]Department of Rheumatology, Gentofte University Hospital, Copenhagen, Denmark, [8]Copenhagen University Hospital at Gentofte, Copenhagen, Denmark.

Background/Purpose: Treatment with abatacept and tocilizumab has been shown to be efficacious in rheumatoid arthritis (RA) patients refractory to tumor necrosis factor inhibitor (TNFi). However, reports on long term effectiveness in clinical practice are scarce. In this extension of previously published 48-week data[1], we aimed to describe three-year drug survival and clinical response in RA patients treated with abatacept or tocilizumab in routine care, based on data from the nationwide Danish DANBIO registry.

Methods: In the DANBIO registry we identified 341 RA patients treated with abatacept and 790 RA patients treated with tocilizumab. The clinical effectiveness was assessed by drug survival and by changes since baseline in DAS28 and EULAR response rates after 48, 96 and 144 weeks. No imputation of missing values was done. No direct comparison of the 2 drugs was made.

Results: Of the patients receiving abatacept or tocilizumab, respectively, 20%/25% (abatacept/tocilizumab) were male, median (interquartile range, IQR) age 55(47–64)/58(47–66) years, disease duration 4 (1–11)/4 (1–12) years and number of previous biological drugs 3 (2–4)/2 (2–3), >90%>/90% of patients, had previously received ≥1 TNFi.

After 48, 96 and 144 weeks, the drug adherence to abatacept was 47%, 35% and 28% and to tocilizumab it was 61%, 54% and 47% (figure).

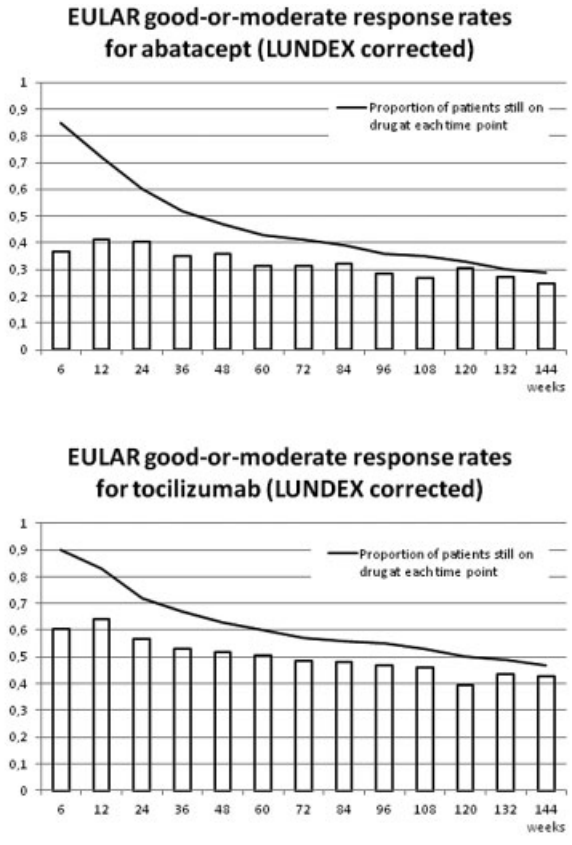

Figure 1. Proportion of patients starting on abatacept or tocilizumab in clinical practice achieving EULAR good-or-moderate response (bars) (LUNDEX corrected).

Median DAS28 at baseline, week 48, week 96 and week 144 in the abatacept group was 5.1, 3.3, 2.8 and 2.7 respectively, and 5.1, 2.6, 2.6 and 2.2 in the tocilizumab group.

At week 48, 96 and 144, the remission rates were 26%, 41% and 48% for abatacept and 47%, 45% and 63% for tocilizumab. Rates of good-or-moderate EULAR response at week 48, 96 and 144 was 76%, 79% and 85% for abatacept and 82%, 85% and 91% for tocilizumab. Response rates after correction for proportion of patients still on drug (LUNDEX values[2]) are presented in figure 1.

Conclusion: In this study of RA patients whereof >90% were previous TNFi failures, 28% of patients who started abatacept and 47% who started tocilizumab still received the drug after 144 weeks. Good-or-moderate EULAR response was seen in the majority (85%-91%) of patients who still received the drugs after 144 weeks, reflecting that almost all patients with poor response was withdrawn from therapy. Due to the non-randomised study design, no direct comparison of the drugs was made.

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Disclosure: H. Leffers, None; **M. Østergaard**, Abbott, Pfizer, Centocor, 2, Abbott Pfizer, Merck, Roche, UCB, 5, Abbott, Pfizer, Merck, BMS, UCB, Mundipharma, 8; **B. Glintborg**, None; **N. S. Krogh**, None; **U. Tarp**, None; **T. Lorenzen**, Phizer, Roche, 6; **A. Hansen**, UCB, ABBVIE and MSD, 5; **L. Dreyer**, None; **M. L. Hetland**, Roche Pharmaceuticals, 5, Abbott, BMS, MSD, Pfizer, UCB, 8.

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Is The Risk Of Tumor Necrosis Factor Inhibitor-Induced Lupus The Same With Monoclonal Antibodies and Soluble Receptor? A Case/Non-Case Study In a Nationwide Pharmacovigilance Database. Guillaume Moulis[1], Agnès Sommet[2], Maryse Lapeyre-Mestre[2] and Jean-Louis Montastruc[2]. [1]Toulouse University Hospital, Clinical Pharmacology Department, University of Toulouse, UMR INSERM-UPS 1027, Toulouse, France, [2]Toulouse University Hospital, INSERM U1027, University of Toulouse, France, Toulouse, France.

Background/Purpose: Albeit lupus occurring on each TNFi have been reported, no epidemiological study has been conducted to assess the link between lupus onset and each TNFi drug. Indeed, the risk may differ because of different structural properties. Moreover, there are reports of infliximab-induced lupus without positive rechallenge with etanercept, and etanercept seems beneficial in systemic lupus erythematosus patients with arthritis and seritis. The aim of this study was to describe the cases of TNFi-related lupus reported in the French PharmacoVigilance Database (FPVD), and to assess the putative association with each TNFi.

Methods: All spontaneous reports of TNFi-related lupus recorded in the FPVD between January 2000 and December 2012 were described. We conducted disproportionality analyses (case/non-case method) to assess the link between lupus and exposure to TNFi. Cases were all reports of lupus recorded during the study period. Non-cases were all other reports recorded during the same period. Exposure to TNFi was searched in cases and non-cases. Reporting odds ratios (ROR) were calculated to assess the association. We used exposure to isoniazid (well-known as lupus inducer) as positive control and acetaminophen as negative one. Sensitivity analyses were performed to test for event-related competition bias (removing reports of infections from the model) and for drug-related competition bias restricting to the marketing period of each TNFi and withdrawing well-known lupus-inducers. These were identified from the Chang and Gershwin list (J Autoimmunity 2010), updated through MEDLINE search until 2012 to detect new signals (comparative studies or ≥3 reports).

Results: During the study period, 309 671 spontaneous reports were colligated in the FPVD, of which 5213 (1.68%) involved TNFi. Among these TNFi reports, 39 were lupus in 37 patients: 25 involved infliximab, 9 adalimumab, and 5 etanercept. Male:female sex-ratio was 0.1 and mean age was 44.9 ± 14.4 years. Seventeen patients were treated for rheumatoid arthritis, 15 for inflammatory bowel disease, 4 for ankylosing spondylitis. Median delay from TNFi introduction to lupus onset was 11 months (range: 1–84 months). Cutaneous and rheumatologic involvements were the more frequent. Antinuclear autoantibody were positive in all the patients with this data reported (n=35). Anti-DNA antibodies were positive in 21/27 patients (77.8%). Improvement was observed after TNFi withdrawal (data available for half of the reports). Association between TNFi exposure and lupus was significant for all TNF-alpha antagonists pooled together (ROR=7.72, 95%CI [5.50–10.83]) and for isoniazid (3.5 [1.44–8.49])

but not with acetaminophen (0.28 [0.12–0.63]). It was similar for infliximab (10.97 [7.27–16.56]) and adalimumab (9.03 [4.64–17.58]) but was only 4.02 [1.66–9.75] for etanercept. Sensitivity analyses lead to similar results.

Conclusion: Albeit confidence intervals slightly overlap probably because of lack of power, the association of etanercept and lupus occurrence is estimated the half of the association with monoclonal antibodies in all analyses. Etanercept should be preferred patients who experienced lupus while exposed to monoclonal antibody TNFi.

Disclosure: G. Moulis, None; **A. Sommet**, None; **M. Lapeyre-Mestre**, None; **J. L. Montastruc**, None.

1444

Immunogenicity Induced By Tumor Necrosis Factor Antagonists In Chronic Inflammatory Arthropathies: Retrospective Study In Clinical Practice Conditions. Jose Inciarte-Mundo[1], Maria Victoria Hernández[2], Sonia Cabrera[3], Virginia Ruiz-Esquide[4], Julio Ramirez[1], Juan D. Cañete[2], Jordi Yague[5] and Raimon Sanmarti[1]. [1]Hospital Clínic of Barcelona, Barcelona, Spain, [2]Hospital Clínic of Barcelona. IDIBAPS. University of Barcelona, Barcelona, Spain, [3]Hospital Clínic, Barcelona, Spain, [4]Hospital Clinic, Barcelona, Spain, [5]Hospital Clínic/IDIBAPS, Barcelona, Spain.

Background/Purpose: Biological therapy has proved efficacious in various chronic inflammatory arthropathies but, in practice, clinical efficacy is reduced in some patients, suggesting drug-induced immunogenicity as a possible mechanism. Our objective was to analyze the development of tumor necrosis factor (TNF) antagonist antibodies (AB) and serum drug levels in patients with loss of treatment or adverse events in clinical practice.

Methods: Descriptive, retrospective study of patients attended by a tertiary hospital rheumatology department between February 2012 and May 2013, who were on active TNF antagonist treatment and suffered loss of efficacy or adverse treatment effects. Patients were included according to clinical judgment. We measured antidrug AB and serum drug levels using an ELISA immunoassay (Promonitor®). Only patients on infliximab (IFX), etanercept (ETN) or adalimumab (ADA) were analyzed. All blood samples were obtained in the 24 h before the next scheduled dose of treatment. Only patients with positive AB were finally analyzed. The following variables were collected: demographic variables; diagnosis and disease duration; previous and current treatment; reason for the analysis; antidrug AB and serum drug levels; and, the clinical decision.

Results: Seventy patients were included; 67% female; mean age 51±14 years. The main diagnoses were: rheumatoid arthritis (RA) (54.3%); ankylosing spondylitis (AS) (20%); psoriatic arthritis (PsA) (10%); and miscellaneous (MISC) (15.7%), which included, among others, Behçet disease, undifferentiated spondyloarthropathy and juvenile idiopathic arthritis. The reason for the analysis was: loss of efficacy in 47% of patients, adverse events in 47%, and partial response in 6%. Seventeen patients (24.3%) developed antidrug AB:11 anti-ADA and 6 anti-IFX, representing 36.6% and 40%, respectively, of study patients on these treatments. Antidrug AB were found directly in 14/17 patients and by a dissociation method in the remaining 3 patients. In 15 patients, serum drug levels were undetectable and in 2 cases (1 ADA and 1 IFX), both analyzed by the dissociation method, suboptimal (suboptimal level ADA: 0.04–0.80 ng/ml and IFX: 0.05–1.50 ng/ml). Diagnoses were: 8 RA; 4 AS; 2 PsA; and 3 MISC. Eight of 17 patients received concomitant synthetic DMARDs (4 leflunomide, 2 methotrexate, 1 sulphasalazine and 1 mycophenolate). The remaining 9 received biological therapy in monotherapy. Nine out of 17 had previously received another biological agent (7 anti-TNF and 2 non anti-TNF), which was discontinued due to inefficacy or adverse events. After development of antidrug AB, 15 patients were withdrawn from current biological therapy: 12 were switched to another anti-TNF agent and 3 to a non anti-TNF drug with a good response. Of the remaining two patients, one was lost to follow up and the other is still receiving the same treatment with methotrexate added with a good response.

Conclusion: In this study, 24.3% of patients with loss of efficacy or adverse events to TNF antagonists developed antidrug AB, which were only observed in patients receiving monoclonal antibodies.

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GEMS Audit: An Evaluation Of Routine Use Of Subcutaneous Methotrexate In Rheumatoid Arthritis. Esme Roads[1], Scot Buchan[2] and Charles Li[1]. [1]Royal Surrey County Hospital, Guildford, United Kingdom, [2]Strategen Ltd, Basingstoke, United Kingdom.

Background/Purpose: Methotrexate (MTX) forms the backbone of treatment for the majority of patients with rheumatoid arthritis (RA), and is advocated in most guidelines.[i],[ii],[iii] Existing studies imply in as many as 21% of new patients oral MTX is either ineffective or not tolerated.[iv],[v] In our clinical practice these patients are routinely prescribed subcutaneous (SC) MTX, which has demonstrated improved efficacy and tolerability over the oral formulation.[vi],[vii]To identify outcomes of patients prescribed SCMTX, a retrospective audit was undertaken.

Methods: All RA patients who had received SCMTX at the Royal Surrey County Hospital, Guildford were identified from medical records. Demographic data, reason for switch from oral to SCMTX, continuation rates, eventual requirement of biologic therapy and disease activity scores (DAS) were recorded. Data presented represents audit analysis to date.

Results: We are presenting the first 102 RA patients who switched from oral MTX to SCMTX therapy. Average age of diagnosis was 50 years and 78% of patients were female. Mean duration of oral therapy was 8.8 years, at a mean weekly dose of 20.3 mg. Patients were switched from oral to SCMTX due to lack of efficacy (46%) or tolerability issues (27%). 43% of all patients were on at least two DMARDS and 12% were on three. Patients switching to SCMTX were given a mean weekly dose of 20.49 mg at initiation. The average duration of SCMTX therapy by time of analyis was 2.8 years. 87 patients thereafter remain on SCMTX either alone or in combination with other disease modifying antirheumatic drugs (DMARDs); treatment of 15 (14.7%) required escalation of therapy to include a biologic due to aggressive disease. Continuation rates for SCMTX were 94% at 1 year and 82% at 2 years, with only 8% of patients progressing to a biologic during the two years. In patients who required a biologic and SCMTX the continuation rate was 93% at 1 year and 92% at 2 years. DAS assessments were made over differing time periods, a subset of which was analysed and showed continued DAS improvement over time and a rise in significant improvement (ΔDAS28 >1.2) and remission rates (DAS <2.6).

Conclusion: The GEMS audit has confirmed efficacy and tolerability of SCMTX in patients after failing oral MTX either due to inefficacy or toxicity with high continuation rates and maintenance of disease activity control either with or without biologic therapy. These results further support our routine practice of switch of route of administration of MTX prior to the use of biologics without compromising patient care.

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The Efficacy Of Etanercept In Combination With Methotrexate In Moderate To Severe Rheumatoid Arthritis Is Not Dependent On The Dosage Of Methotrexate. T.W.J. Huizinga[1], Fiona Brock[2], Urs Kerkmann[3] and Gaia Gallo[3]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Quanticate, Hitchin, Hertfordshire, United Kingdom, [3]Pfizer Europe, Rome, Italy.

Background/Purpose: Anti-TNF therapy in combination with a synthetic DMARD such as methotrexate (MTX) has been extensively shown to be superior to MTX and anti-TNF therapy as monotherapy, and is recommended in patients with rheumatoid arthritis (RA) who failed to reach treatment target, remission or low disease activity (LDA), in particular when poor prognostic markers are present.[1] When combined with anti-TNF therapy, MTX is usually administered in doses ranging from 7.5 to 25 mg/week. In patients who develop intolerable side effects to MTX during combination therapy, MTX may be discontinued or its dosage reduced. In clinical studies, the anti-TNF agent etanercept (ETN) has demonstrated sustained efficacy after MTX withdrawal in patients with moderate to severe RA,[2] but ETN efficacy across different dosages of concomitant MTX has not been investigated in early to established active RA patients. Based on data pooled from two historic ETN trials (TEMPO[3] and COMET[4]), we evaluated the impact of MTX dosage on clinical, functional, and quality of life (QoL) outcomes in RA patients after 24 months of treatment.

Methods: Patients with active RA in the ETN+MTX combination treatment arms of the TEMPO[2] and COMET[3]studies were stratified into three

subgroups based on the MTX dosage at 24 months, having MTX monotherapy groups as control: low dose (L), <10 mg/week; medium dose (M), 10–17.5 mg/week; and high dose (H), >17.5 mg/week. Data from these patient subgroups were included in descriptive summaries of demographic and disease characteristics at baseline; the following outcomes at 24 months were also evaluated for each subgroup: DAS28 LDA and remission; ACR20, 50 and 70 responses; and changes from baseline in DAS28, HAQ-DI, and EQ-5D-VAS.

Results: At baseline, patients in the ETN+MTX arm (n=276; L=73, M=155, H=48), had a mean age of 51.1, 51.7, and 51.7; weight of 69.6 and 70.2, and 75.0 kg; and female gender in 75%, 75% and 69% for the L, M and H dose groups, respectively. Patients in the MTX arm (n=218; L=39, M=117, H=62) had a mean age of 56.1, 50.7, and 51.8; weight of 67.6 and 71.1, and 70.4 kg; and female gender in 79%, 80% and 81% for the L, M and H dose groups, respectively. Responses to ETN+MTX combination therapy at 24 months were consistently high across MTX dosage groups, with very similar rates of LDA/remission (Table). Improvements in DAS28, HAQ-DI, and EQ-5D were also not dependent on MTX dosage in the combination treatment arm; poorer responses and less improvement were observed in the high MTX dose subgroup.

Table. Clinical, functional, QoL outcomes by MTX dosage in patients in the ETN+MTX and MTX arms across TEMPO and COMET studies[3,4]

	ETN+MTX Arm (n=276)			MTX Arm (n=218)		
	Low MTX Dose	Medium MTX Dose	High MTX Dose	Low MTX Dose	Medium MTX Dose	High MTX Dose
% patients achieving endpoint at 24 months (n/N)						
DAS28 LDA/Remission	68 (48/71)	69 (103/149)	70 (30/43)	53 (19/36)	41 (43/106)	57 (29/51)
ACR20	93 (68/73)	92 (141/153)	89 (39/44)	87 (34/39)	81 (91/112)	63 (34/54)
ACR50	79 (58/73)	78 (120/153)	73 (32/44)	64 (25/39)	55 (62/112)	46 (25/54)
ACR70	56 (41/73)	59 (91/153)	57 (25/44)	36 (14/39)	33 (37/112)	26 (14/54)
Change from baseline to 24 months, mean (SD)						
DAS28	−3.8 (1.2)	−4.0 (1.2)	−4.1 (1.5)	−3.2 (1.3)	−3.2 (1.5)	−2.8 (1.7)
HAQ-DI	−1.1 (0.8)	−1.1 (0.6)	−1.2 (0.8)	−0.9 (0.7)	−0.9 (0.6)	−0.9 (0.7)
EQ-5D VAS	35.6 (28.7)	38.0 (26.0)	32.5 (26.7)	34.1 (25.9)	35.3 (27.5)	19.7 (26.4)

DAS28 LDA, Disease Activity Score based on 28-joint count low disease activity (defined as DAS28 ≤3.2); ACR20/50/70, American College of Rheumatology 20%, 50%,and 70% improvement; HAQ-DI, Health Assessment Questionnaire-Disability Index; EQ-5D VAS, EuroQol-5 total index visual analog scale.

Conclusion: At 24 months, etanercept plus MTX showed similar efficacy outcomes regardless of MTX dosage in patients with RA who participated in the TEMPO[2] and COMET[3]trials.

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Success Rate Of 5-Or-More-Week Extended-Interval Therapy With Tocilizumab In Rheumatoid Arthritis Patients In Routine Practice.

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Background/Purpose: Tocilizumab retreatment is effective and well tolerated in patients with rheumatoid arthritis whose disease activity flared after stopping the therapy. Therefore, reducing tocilizumab dose intensity by extending intervals is worthwhile. However, feasibility of entended-interval (≧5 weeks) therapy with tocilizumab for rheumatoid arthritis patients in routine practice is not well known.

Methods: We studied rheumatoid arthritis (RA) patients who used tocilizumab in the Cohort of Arthritis Biologic Users at Kameda Institute (CABUKI) registry from Jan/2003 to Mar/2013. Inclusion criteria were tocilizumab users age 18 years or older and DAS28-ESR <3.2 at the start of interval extension. We studied the success rate of interval extension and baseline factors at the beginning of extended intervals that predicts successful interval extension. We defined interval extension as tocilizumab administration at intervals 5 weeks or longer. The success rate was calculated at 24 weeks. The failure to maintain the extended intervals was defined as experiencing moderate or high disease activity or requiring intensification of DMARDs or glucocorticoids during follow up periods. Analyses were conducted using Fisher's exact test, Mann-Whitney U test, and log rank test.

Results: Among 54 patients who received tocilizumab, 22 patients underwent interval extension. Of 21 patients who were followed for 24 weeks, 13(61.9%) patients were still on extended intervals successfully, but 8(38.1%) patients had failed. Baseline characteristics of interval extension success group and failure group were mean age 58.8 years/61.4 years (P=0.77), female 76.9%/75%(P=1.00), disease duration 6.2 years/12.5 years (P=0.09), RF positive 76.9%/100%(p=0.26), anti-CCP positive 85%/100%(p=0.52), mean DAS28-ESR 1.76/1.86(p=0.70), mean modified HAQ 0.15/0.57(p=0.20) and radiographic erosion 53.8%/87.5%(p=0.17). In the successful interval extension group, disease duration was shorter, mean modified HAQ was smaller, and the number of non-radiographic erosion was smaller than failure group.

Conclusion: Among tocilizumab users in routine practice who underwent extended-interval administration of tocilizumab, 61.9% successfully maintained low disease activity at 24 weeks without shortening of intervals or dose intensification of non-biologic treatment. Interval extension is a feasible treatment strategy in RA patients treated with tocilizumab in routine practice.

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Drug Retention Rates Of Biologic Monotherapies For Patients With Rheumatoid Arthritis In Daily Clinical Practice; Using Multicenter Registry In Japan.

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Background/Purpose: In general, drug retention rate reflects the effectiveness and tolerability of the drug. In Japan, six biological agents have been approved for the treatment of rheumatoid arthritis (RA). There is few data comparing the retention rates between biological monotherapies for RA patients in daily clinical practice. The purpose of this study is to compare the drug retention rates of three biological monotherapies with different target molecules, etanercept (ETN), tocilizumab (TCZ), abatacept (ABT).

Methods: We collected the data from the patients who started monotherapies with ETN, TCZ, ABT as first-biologics since 2008 and registered in the multicenter, large cohort of RA patients (Tsurumai Biologics Communication Registry; TBCR). We surveyed the following information: demographic data, disease activity (DAS28-CRP) at the baseline of each biological treatment. Drug retention rates were calculated by the Kaplan-Meier analysis and compared using the log-rank test among groups. We investigated drug retention rates for discontinuation due to insufficient effectiveness and adverse events.

Results: We analyzed 279 patients of 2072 patients registered in TBCR until March 2011 (141 patients in the ETN group, 63 patients in the TCZ group, 75 patients in the ABT group). The mean follow up time was 25.7 months. Table shows baseline characteristics of the groups (Table). The patients in the ABT group were older compared with other groups. Cumulative incidence rate for discontinuation due to insufficient effectiveness was significantly lower in the TCZ group (p=0.019, Fig.1A). Cumulative incidence rate for discontinuation due to adverse events was significantly lower in the ABT group (p=0.007, Fig. 1B).

Table. Baseline characteristics of the groups

Variables	ETN (n=141)	TCZ (n=63)	ABT (n=75)	*P* value
Age (mean ± SD)	58.2 ± 15.0	57.7 ± 13.8	67.7 ± 11.2	<0.001
Women (%)	81.2	82.1	72.0	n.s.
Disease duration (years)	12.8 ± 11.6	10.6 ± 10.5	10.0 ± 10.5	n.s.
Disease duration ≤2 years (%)	12.8	20.0	26.9	0.041
Steinbrocker's Stage (%)				
I	10.7	22/6	13.3	n.s.
II	16.0	18.9	22.7	
III	31.3	22.6	32.0	
IV	42.0	35.8	32.0	
Steinbrocker's Class (%)				
I	15.8	24.5	4.0	<0.001
II	33.8	32.1	46.7	
III	33.8	24.5	45.3	
IV	16.6	18.9	4.0	
PSL use (%)	68.8	50.9	41.9	<0.001
PSL dosage (mg/day)	4.9 ± 1.8	4.5 ± 2.2	5.4 ± 3.4	n.s.
DAS28-CRP	4.60 ± 0.98	4.73 ± 1.45	4.29 ± 1.52	n.s.

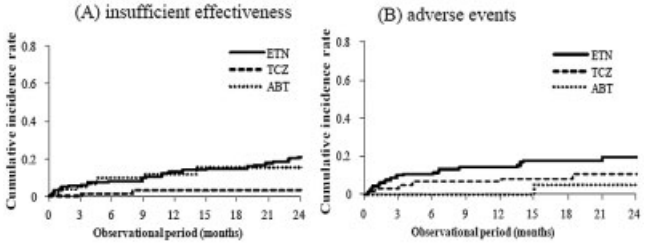

Figure 1.

Conclusion: We demonstrated that TCZ monotherapy had a lower discontinuation rate due to insufficient efficacy and that ABT monotherapy had a lower discontinuation rate due to adverse events.

Disclosure: H. Matsubara, None; **T. Kojima**, None; **M. Hayashi**, None; **N. Ishiguro**, Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, BMS, Eisai, Janssen, Kaken and Pfizer, 2, Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, BMS, Eisai, Janssen, Kaken, Pfizer, Taisho-Toyama and Otsuka, 8.

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Comparison Of Effects Of Standard- and Low-Dose Etanercept On Inflammatory Synovitis In Rheumatoid Arthritis Patients As Assessed By Ultrasonography. Kenji Mamoto, Tatsuya Koike, Tadashi Okano, Yuko Sugioka, Masahiro Tada, Kentaro Inui and Hiroaki Nakamura. Osaka City University Graduate School of Medicine, Osaka, Japan.

Background/Purpose: The presence of synovitis has been recognized as one of the most important predictive factors of subsequent structural damage in patients with rheumatoid arthritis (RA). We previously reported that the effects of low-dose etanercept (ETN) (25 mg/week) were not inferior to the effects of standard-dose ETN (50 mg/week) clinically, but in terms of the radiographic non-progression rate, the effects of low-dose ETN were inferior to the effects of standard-dose ETN in the PRECEPT study. It was considered that low-dose ETN may not be able to suppress inflammatory synovitis. The aim of this study was to compare ultrasonographic inflammatory synovitis between patients using standard- and low-dose ETN for RA.

Methods: Patients with RA receiving standard- and low-dose ETN underwent musculoskeletal ultrasonography (US) at 34 synovial sites (30 joints) in the following joints: bilateral first to fifth metacarpopharangeal (MCP) joints (dorsal recess), first interpharangeal (IP) and second to fifth proximal interpharangeal (PIP) (dorsal recess) joints, the wrists (dorsal radial, dorsal median, and dorsal ulnar) and second to fifth metatarsopharangeal (MTP) (dorsal recess) joints. The GS (Gray scale) and power PD (Power Doppler) signals were scored in each joint using a semiquantitative scale from 0 to 3. The GSUS and PDUS scores were compared with the sums of scores obtained for the 34 synovial sites and the maximum score between two groups.

Results: We analyzed 31 and 21 patients who received standard- and low-dose ETN, respectively. The overall comparison showed no significant differences between groups. However, when we analyzed patients in remission and low disease activity, the PDUS score and maximum PD score were significantly higher in the low-dose ETN group. In particular, the PDUS score in wrist were significantly higher in the low-dose ETN group. But, GSUS score showed no significant difference between two groups (Table 1).

Table 1. Clinical and demographic characteristics in patients in remission and low disease activity of DAS28-ESR

	ETN 25mg(n=11)	ETN 50mg(n=15)	
Age (years old)	62.33	59.48	NS
Disease duration (years)	11.54	16.76	NS
Duration of ETN use (years)	3.06	3.59	NS
Female (%)	72.73	100.0	NS
RF positive (%)	55.56	73.33	NS
ACPA positive (%)	66.67	91.67	NS
DAS28-ESR	2.62	2.30	NS
ESR (mm/hour)	12.55	19.27	NS
CRP (mg/dl)	0.18	0.14	NS
MMP-3 (ng/ml)	62.10	50.80	NS
mHAQ	0.29	0.23	NS
mTSS	142.44	158.93	NS
Total GSUS score	17.0	13.8	NS
Total PDUS score	7.91	4.20	P<0.05
Total PDUS score in finger	1.55	0.60	NS
Total PDUS score in wrist	5.82	3.33	P<0.01
Total PDUS score in foot	0.55	0.29	NS
Maximum PDUS score	1.73	1.13	P<0.01

Conclusion: Low-dose ETN is not inferior to standard-dose ETN in terms of effects on clinical assessment. However, in terms of ultrasonographic inflammatory synovitis, the effects of low-dose ETN may be inferior to the effects of standard-dose ETN. We consider that synovitis may not be suppressed sufficiently, and therefore joint destruction may progress, in RA patients receiving low-dose ETN.

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Safety Of Resuming The Tumor Necrosis Factor Antagonists Therapy In Patients Who Developed Tuberculosis After Use Of Tumor Necrosis Factor Antagonists. Seokchan Hong[1], You Jae Kim[1], Bon San Koo[1], Kyung joo Ahn[2], Wook Jang Seo[3], Yong-Gil Kim[1], Chang-Keun Lee[1] and Bin Yoo[1]. [1]University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [2]KEPCO medical center, Seoul, South Korea, [3]Seoul Veterans Hospital, Seoul, South Korea.

Background/Purpose: Tuberculosis is one of the most serious adverse events related to tumor necrosis factor (TNF) antagonists in inflammatory diseases. However, there is no consensus on the current treatment guidelines about resuming TNF blockers after development of active tuberculosis infection (TI). Our objective was to analyze the optimal time-point for resuming the TNF antagonist with no relapse of TI.

Methods: Retrospective study has included 683 patients from June 2003 to December 2012 (362 ankylosing spondylitis; 307 rheumatoid arthritis; 10 psoriatic arthritis; 4 Behcet's disease), who have started TNF blockers at a single tertiary hospital. Data on cases of active TI during biologics were collected and the outcomes of resuming TNF blockers were evaluated.

Results: Of the 683 patients, 15 (2.1%) patients (6 female, mean age 47.4 ± 17.5 years) were diagnosed with active tuberculosis during anti-TNF treatment. Diagnoses were: 10 ankylosing spondylitis; 4 rheumatoid arthritis; 1 Behcet's disease. Tuberculosis was detected in one patient by routine CXR and in others by the development of symptoms such as fever. The type of tuberculosis infection was: pulmonary in 7 patients; gastrointestinal in 3; lymph nodes in 2; disseminated in 1, miliary in 1, pericardium in 1. The TNF blocker used at TI diagnoses was; 4 etanercept, 4 adalimumab,

and 7 infliximab. The mean duration of anti-TNF treatment before development of TB was 26.7± 28.1 months. Anti-TNF treatment was reinitiated in 6 (40%) patients; 4 patients during under treatment of TI treatment (mean TI treatment of 1.5 ± 1.0 months) and 2 patients after completion of TI treatment. Four patients reinitiated with the same agents, whereas 2 patients started with another TNF blocker. All six patients successfully completed anti-tuberculosis treatment and showed good responses. The outcomes in patients after reinitiation of anti-TNF treatment were favorable that no patients had a relapse of TI after a mean follow-up duration of 28 ± 18.1 months.

Conclusion: Active tuberculosis infection in relation to TNF antagonist may be safe for resuming the therapy even before completion of TI treatment. Our results may suggest that it is possible to restart TNF blockers if patients were treated concomitantly with adequate anti-tuberculosis treatment.

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Comparison Of Clinical Characteristics Of Patients With Rheumatoid Arthritis Receiving Their First Biologic and Biologic-Naïve Patients Considered Biologic-Suitable In The United States. Siva Narayanan[1], Yao Lu[2], Richard Hutchings[2] and Amanda Baskett[2]. [1]Ipsos Healthcare, Columbia, MD, [2]Ipsos Healthcare, London, United Kingdom.

Background/Purpose: Data on clinical status of biologic-naïve Rheumatoid Arthritis (RA) patients who are considered suitable for biologic therapy (by their physicians) is lacking. We assessed clinical characteristics of RA patients who are considered suitable for biologic therapy (by their physicians) in comparison to those currently treated with 1st line biologics in the United States (US).

Methods: A retrospective chart review study of RA patients was conducted among physicians (primarily rheumatologists) in hospitals/private practices to collect de-identified data on patients who were either recently treated with a biologic as part of usual care or considered suitable for biologic treatment. Physicians from the US were screened for duration of practice (3–30 yrs) and patient volume (incl. >2RA biologic patients/week) and recruited from a large panel to be geographically representative. Eligible patient charts (>6 biologic patients, > 2 biologic-suitable (and yet biologic-naïve) patients per physician judgment) were randomly selected from a sample of prospective patients visiting each center/practice during the screening period. Physicians abstracted patient diagnosis, treatment patterns/dynamics and patient symptomatology/disease status. This retrospective de-identified data collection method met the criteria for IRB exemption under federal regulation 45 CFR 46.101(b)(4).

Results: Seven hundred and twenty six eligible RA patient charts were abstracted; 378 (52%) patients were on their first biologic and 175 (24%) patients have never experienced biologic but were considered suitable for one. Mean age was: 1st line-52.8yrs, biologic-suitable-51.5yrs; Female: 1st line-73%, biologic-suitable-76%. Disease severity at diagnosis and current disease severity (both per physician judgment) (mild:moderate:severe) were: 1st line – 6%:74%:14% and 67%:29%:3%, biologic-suitable – 11%,74%, 10% and 25%:66%:9% respectively. Current drug class usage differed between the two groups (1st line/biologic-suitable): non-biological DMARD (57%/88%), steroids (19%/36%), NSAIDs-COX2 inhibitors (6%/10%), NSAIDs- non-COX2 inhibitors (14%/22%), and analgesics (11%/12%). Key lab measures documented were (1st line/biologic suitable): ESR (24.2/40.0 mm/h) and CRP (2.5mg/5.6 dl). Current ACR scores were (1st line/biologic-suitable): no response (2%/19%), ACR20 (12%/36%), ACR50 (18%/15%), ACR70 (20%/5%), ACR90 (26%/1%). Among patients with available data, current HAQ (1st line–0.7, biologic-suitable–1.1), DAS28 (1st line–2.5, biologic-suitable – 4.1), 100mmVAS (1st line – 2.3, biologic-suitable – 4.6), Swollen Joint Count (1st line – 2.0, biologic-suitable – 5.9) and Tender Joint Count (1st line – 2.8, biologic-suitable – 7.0) differed between the patient groups.

Conclusion: Compared to the patients currently treated with 1st line biologic, RA biologic-naïve but suitable patients (per physician judgment) had relatively higher disease burden. Reasons for non-initiation of biologic treatment among 'biologic-suitable' patients warrant further investigation to alleviate disease burden.

Disclosure: S. Narayanan, Ipsos Healthcare, 3; **Y. Lu**, Ipsos Healthcare, 3; **R. Hutchings**, Ipsos Healthcare, 3; **A. Baskett**, Ipsos Healthcare, 3.

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An Early Economic Evaluation Of Personalized Treatment With Rituximab By Prediction Of Effectiveness Using The Interferon Type I Signature In Rheumatoid Arthritis. Sandhya C. Nair[1], P.M.J. Welsing[1], Saskia Vosslamber[2], A.E. Voskuyl[2], M. T. Nurmohamed[3], J.W.J. Bijlsma[1], Floris Lafeber[4] and Cornelis L. Verweij[2]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands, [3]VU University Medical Center/Jan van Bremen Research Institute, Amsterdam, Netherlands, [4]UMC Utrecht, Utrecht, Netherlands.

Background/Purpose: Tailoring therapy to individual patients, for instance by predicting its effectiveness has become increasingly important especially with chronic use of expensive biological DMARDs. To evaluate the cost effectiveness of a personalized approach to biological treatment of rheumatoid arthritis RA) patients indicated for rituximab (RTX) using interferon (IFN) type I response genes as prediction tool.

Methods: 26 consecutive patients diagnosed according to 1987 ACR criteria from the VU University Medical Center and READE starting RTX were followed. Baseline IFN type I response genes expression level was used as a biomarker for response to RTX using an optimal cut-off (1). The Positive Predictive Values (PPV) for good and moderate EULAR response were used to simulate the response using a personalized approach, assuming that the response in patients not selected for the RTX therapy was equal to the average response to treatment (biological) in the population. Using a patient level Markov model, response was extrapolated to disease activity (DAS28), functional disability (HAQ), direct and productivity costs and Quality Adjusted Life Years (QALYs) over 5 years using external data. The Incremental Cost Effectiveness Ratio (ICER) comparing the personalized approach to (observed) usual care was calculated from a societal and health care perspective. Although RTX treatment is less costly than other biologicals no differences in drug cost were assumed and testing costs were assumed € 50 per patient. All the analyses were performed probabilistically and a sensitivity analysis was also performed.

Results: 50% were moderate responders and 50% were non-responders (no good responders). Twenty-nine percent decreased more than 1.2 points on the DAS28. Using the selected IFN cut-off, 35% of patients were selected for treatment and the PPV (for moderate response) was 100%. On average € 236 (2.5 – 97.5 percentile range −6,083 to 5,557) were saved and 0.03 QALYs (−0.08 to 0.15) were gained leading to an ICER of €−8099 per QALY gained. In 37% of simulations the personalized approach was found to be cheaper and more effective, in 32% more expensive and more effective, in 16% less expensive and less effective and in 15% more expensive and less effective. Due to the limited data on prediction using IFN so far and the resulting uncertainty the probability of costs-effectiveness did not increase to more than 70%. Using a healthcare perspective the results were less positive with a mean ICER of € 1920 per QALY gained (represents extra costs and QALY, which is within the often mentioned limit of € 20,000/QALY). Decreasing the effectiveness of alternative biological therapy with 10% resulted in a lower probability of cost-effectiveness but average results still indicated cost saving and QALY gain.

Conclusion: Although results are still uncertain due to the limited clinical data, the use of the IFN type I response genes for personalized biologic treatment seems very promising and should continue to be studied in patients indicated for RTX treatment to obtain more precise estimates of cost-effectiveness results.

References:

1.Raterman et al., Arth. Res. Ther. 2011.

Disclosure: S. C. Nair, None; **P. M. J. Welsing**, None; **S. Vosslamber**, None; **A. E. Voskuyl**, None; **M. T. Nurmohamed**, None; **J. W. J. Bijlsma**, None; **F. Lafeber**, None; **C. L. Verweij**, None.

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Repeated High Or Low Multi-Biomarker Disease Activity (VECTRA® DA Algorithm) Scores Associated With Radiographic Outcomes In Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor Inhibitors. Shintaro Hirata[1], Wanying Li[2], Nadine A. Defranoux[2], Rebecca Bolce[2], Eric H. Sasso[2], Satoshi Kubo[1], Shunsuke Fukuyo[1], Kentaro Hanami[1], Kunihiro Yamaoka[1], Kazuyoshi Saito[1] and Yoshiya Tanaka[1]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Crescendo Bioscience Inc., South San Francisco, CA.

Background/Purpose: A novel multi-biomarker disease activity (MBDA) score that is based on the serum concentrations of 12 biomarkers has

been shown to correlate with clinical disease activity in patients with rheumatoid arthritis (RA) including patients treated with TNF inhibitors (TNFi). The purpose of this study is to explore the role of MBDA to predict radiographic progression in RA patients treated with TNFi.

Methods: The study was conducted at UOEH, Kitakyushu, Japan, on 141 patients who had received TNFi: adalimumab (ADA), etanercept (ETN) and infliximab (IFX), for at least 1 year. X-rays were taken at baseline (BL) and week 52 of treatment and change (Δ) in modified total Sharp score (mTSS) over 1 year was determined. Clinical disease activity, serum biomarkers were assessed at BL and week 52 in all 141 patients and at week 24 in a subset of 83 patients. Concentrations of VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL-40, leptin, resistin, SAA and CRP were measured using a multiplex immunoassay and the MBDA score (1–100) was calculated using the validated Vectra DA algorithm. Correlations between ΔmTSS and disease activity measures (MBDA, DAS28-ESR, CRP) were examined using Spearman correlation. The association between ΔmTSS and maintenance ofhigh/low MBDA score was assessed in the subset of 83 patients with clinical and biomarker data at all 3 time points (BL, week 24 and week 52) using Fisher's exact test.

Results: At baseline, patients had mean (±SD) values of DAS28-ESR 5.7 (±1.1), MBDA score 61 (±18), disease duration 103 (±121) months, and mTSS 68 (±103). In the overall group of 141 patients, 102 (72%) patients had a ΔmTSS ≤0.5 (non-progressors) and 12 (9%) had a ΔmTSS >3 (clinically relevant radiographic progression) by week 52. ΔmTSS correlated with the yearly average of both DAS28-ESR ($r = 0.26$, $p = 0.002$) and MBDA score ($r = 0.33$, $p < 0.001$). Among the 12 patients with ΔmTSS >3 by week 52, 7 were EULAR good responders and, 8 had a high MBDA score >44.

In the subset of 83 patients with clinical and biomarker data at BL, week 24 and week 52, 10 (12%) patients had ΔmTSS >3. ΔmTSS from BL to week 52 correlated with the MBDA score DAS28-ESR and CRP at week 24 and with ΔMBDA score from BL to week 24 ($p < 0.05$). Patients with high MBDA scores >44 for at least 2 of any of the 3 visits had a greater risk of radiographic progression (ΔmTSS >3; OR =14.9, $p = 0.002$). Patients with a low MBDA score ≤29 for at least 2 of any of the 3 visits had a higher likelihood to be non-progressors (ΔmTSS ≤0.5; OR =13.9, $p = 0.002$). A logistics regression model showed that low MBDA score ≤29 at week 24 had additive association with non-progression (ΔmTSS ≤0.5) above low DAS28-ESR at week 24 ($p = 0.007$).

Conclusion: In patients with RA treated over one year with TNFi, repeated low MBDA scores were associated with no radiographic progression while repeated high MBDA scores were associated with clinically relevant radiographic progression. Disease activity at 24 weeks post-treatment and change in MBDA score from BL to 24 weeks correlated with radiographic progression at 1 year. At week 24, low MBDA score had additive association with good radiographic outcome above low DAS28-ESR alone.

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The Effects Of The Spleen Tyrosine Kinase Inhibitor Fostamatinib On Ambulatory Blood Pressure In Patients With Active Rheumatoid Arthritis – Results Of The Oskira Ambulatory Blood Pressure Monitoring Trial.

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Background/Purpose: Fostamatinib (Fosta) is a spleen tyrosine kinase (SYK) inhibitor in clinical trials in patients (pts) with rheumatoid arthritis (RA). Previous clinical studies showed blood pressure (BP) elevation with Fosta treatment using clinical measurements. As 24-hour ambulatory BP monitoring (ABPM) improves the sensitivity of detecting BP changes over the dosing period, OSKIRA-ABPM was developed as a randomized, placebo-controlled clinical trial to assess the effects of Fosta 100 mg twice daily (bid), taken on a background of a disease-modifying antirheumatic agent on ambulatory systolic BP (SBP) in pts with active RA.

Methods: After a screening visit and a 4-wk run-in period, pts were randomized to receive Fosta 100mg bid or placebo (PBO) bid for 4 weeks (wks), followed by a 1-wk washout of study drug. The ABPM was obtained at baseline and Wk 4; clinic BP was assessed at scheduled clinic visits; and home BP during 4 × 1 week periods, including 1 wk pre-randomization and the washout period. The primary safety endpoint was change from baseline in 24-hour mean SBP on Fosta vs PBO. Changes from baseline in 24-hour diastolic BP (DBP), BP assessed by clinic and home measurements, as well as the persistence and/or reversibility of any effect in BP after discontinuation of Fosta treatment were secondary endpoints.

Results: Of 135 randomized pts, 68 received Fosta and 67 received PBO, with balanced characteristics at baseline. There were 2 discontinuations in each group due to adverse events (1 in each group due to high BP), and 2 further discontinuations in the Fosta group that were non-adverse event related. Nine pts in the Fosta group vs 1 in the PBO group received newly prescribed and/or dose increase of existing antihypertensive medication after randomization. Compared to placebo, Fosta increased the 24-hour mean SBP by 2.9 mmHg (95% CI, 0.4–5.5; $p = 0.023$) and the 24-hour mean DBP by 3.5 mmHg (95% CI, 2.0–5.0; $p < 0.001$). There was no impact of Fosta on the circadian variation of BP. Individual changes of >5 mmHg in 24-hour mean SBP were seen in approx. 47% vs 27% of pts, and in 24-hour mean DBP in 41% vs 13% of pts in the Fosta and PBO groups, respectively. Individual changes of >10 mmHg in 24-hour mean SBP were seen in approx. 22% vs 12% of patients in the Fosta and PBO groups, respectively. Pts randomized to Fosta who were treated with antihypertensives or with steroids at baseline had numerically higher BP increases from baseline compared to those without. Baseline treatment with nonsteroidal anti-inflammatory drugs did not affect the BP response to Fosta. The magnitudes of clinic- and home-measured BP changes were similar to that of the ABPM-derived values. No effect on heart rate was observed by any measurement method. The effect of Fosta on clinic BP was seen at Wk 1 and plateaued thereafter. After treatment discontinuation, mean values of BP returned to baseline levels.

Conclusion: Fosta induced small but significant elevations in ambulatory BP in pts with active RA. Most elevations were <10 mmHg in individual pts and these elevations resolved with discontinuation of Fosta by 1 wk. In addition, there were no alterations to the circadian pattern of BP and there were no changes in heart rate.

Disclosure: G. Kitas, Pfizer Inc, 2, AstraZeneca, BMS, Abbott, 5; **G. Abreu**, AstraZeneca, 3, AstraZeneca, 1; **K. Jedrychowicz-Rosiak**, None; **J. Miller**, AstraZeneca, 9; **R. Nakov**, AstraZeneca, 3; **S. Panfilov**, AstraZeneca, 3; **J. Vencovsky**, None; **M. Wang**, AstraZeneca, 3; **M. Weinblatt**, Rigel, AstraZeneca, 5; **W. White**, AstraZeneca, 5.

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Comparison Of Serum Matrix Metalloproteinase-3 Levels In Rheumatoid Arthritis After Treatment With Adalimumub Or Abatacept For 24 Weeks.

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Background/Purpose: MMP-3 is an enzyme produced by synoviocytes, and is a marker of synovitis that gives a more direct indication of actual joint destruction than either C-reactive protein (CRP)in patients with rheumatoid arthritis (RA). Our aim in this study is to investigate the impact of the trend of MMP-3 and CRP during the treatment Adalimumub (ADA) and Abatacept (ABT) in the early stage of RA patients.

Methods: Among 548 patients with active RA (DAS28-CRP≥2.7) who were recruited in TBC (Tsurumai Biologics Communication) registry, 303 patients were received ADA (40mg subcutaneously every other week) and 245 patients were received ABT therapy (500mg for<60 kg; 750 mg for 60 kg-100 kg; and 1 gram for>100 kg infusion at week 0, 2, 4 and every 4 weeks). DAS28-CRP remission (DAS28-CRP<2.3) rates at 24 weeks were 34.7% (73/210) for ADA therapy and 19.4% (39/201) for ABT therapy. We analyzed 112 patients who had DAS28-CRP remission at 24 weeks, consisting of 73 patients in ADA group and 39 patients in ABT group respectively. We compared the change in serum MMP-3 and CRP levels from first administration to 24 weeks between the two groups.

Results: While there was significant baseline difference in age, methotrexate (MTX) use and dose between the two groups, there was no significant baseline difference in serum MMP-3 and CRP levels between the two groups (Table). Serum MMP-3 and CRP levels decreased promptly at 4 weeks. The change in

serum MMP-3 levels at 4, 12, and 24 weeks was greater in the ADA group than in the ABT group (Fig. 1-a). However, the change in CRP levels at 4, 12, and 24 weeks had no deference between the two groups (Fig. 1-b). The % change in serum MMP-3 levels at 12, and 24 weeks was significantly greater in the ADA group than in the ABT group (Fig. 2-a). The % change in serum CRP levels at 4 weeks was significantly greater in the ADA group than in the ABT group. However, there was no difference in the % change in CRP levels at 12, and 24 weeks between the two groups (Fig. 2-b).

Table Demographics and baseline clinical characteristics

	ADA (N =73)	ABT (N =39)	*P value*	
Age (years)	54 ±15	67 ±10	<0.01	b
Female, *n* (%)	61 (84%)	32 (82%)	0.84	c
Duration of disease (years)	13 ±13	11 ±13	0.28	b
Stage (Ⅰ.Ⅱ/Ⅲ.Ⅳ %)	41/59	44/56	–	
Class (1.2/3.4 %)	77/23	59/41	–	
Previous biologics, *n* (%)	14 (19%)	10 (26%)	0.58	a
Prednisone use, *n* (%)	43 (59%)	23 (59%)	0.99	c
Prednisone dose (mg/day)	4.2 ±2.4	4.4 ±2.1	0.41	b
Methotrexate use, *n* (%)	68 (93%)	18 (46%)	<0.01	a
Methotrexate dose (mg/week)	8.2 ±2.6	7.0 ±2.8	<0.05	b
DAS28-CRP	4.1 ±0.9	4.3 ±1.2	0.62	b
Tender joint count, 0-28 joints	5.3 ±4.3	5.2 ±4.2	0.82	b
Swollen joint count, 0-28 joints	5.4 ±3.8	5.6 ±5.3	0.61	b
Patient's global assessment	48 ±24	46 ±28	0.46	b
CRP (mg/dl)	2.1 ±2.0	2.5 ±3.3	0.75	b
MMP-3 (ng/mL)	253 ±210	226 ±140	0.95	b

Values are given as the mean ± standard deviation (SD) unless stated otherwise.
P value calculated by using (a) $\chi 2$ test or (b)Mann-Whitney-U test or (c)Fisher's exact test.
C-reactive protein (CRP), DAS28 Disease Activity Score in 28 joints (DAS28-CRP)

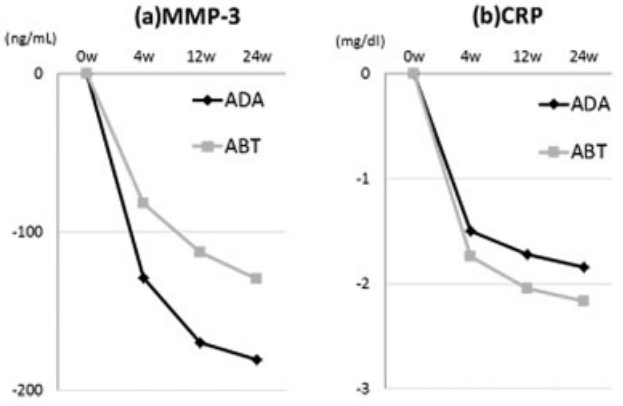

Fig. 1. Change in serum (a) MMP-3 and (b) CRP levels.

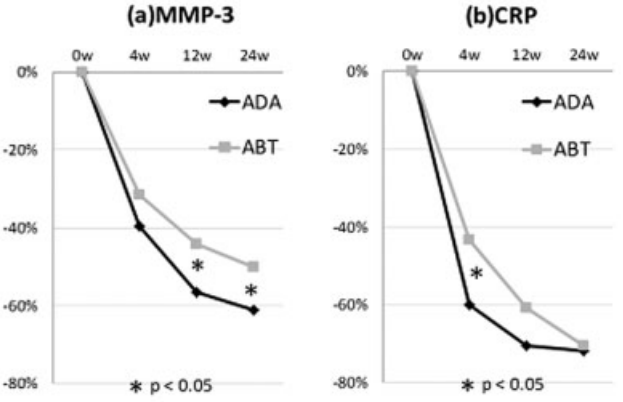

Fig. 2. Change in serum (a) MMP-3 and (b) CRP levels.

Conclusion: ADA showed improvements in serum MMP-3 levels from an early stage in 24 weeks in a comparison with ABT. ADA can suppress synovitis and therefore the progression of joint destruction by strongly inhibiting MMP-3 when it is administered from an early stage.

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Golimumab Levels, Anti-Drug Antibodies and Clinical Response In Rheumatoid Arthritis Patients At 28 Week Of Follow-Up.

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Background/Purpose: Low drug levels of anti-Tumor Necrosis Factor (TNF) therapies are related to poorer response in patients with rheumatoid arthritis (RA). Furthermore, anti-drug antibodies (ADA) against several TNF-inhibitors have been described and are associated with lower drug levels and therefore with lower response rates in RA.

Objectives: To study the relation between clinical response, golimumab levels and ADA in RA patients treated with golimumab.

Methods: Prospective observational cohort study of 38 consecutive RA patients treated with golimumab 50 mg subcutaneously (SC) once every month in the Netherlands (n=36) and Spain (n=2), monitored during 28 weeks of follow-up. Golimumab levels and ADA titres were determined retrospectively using an enzyme linked immunosorbent assay and an Antigen Binding Test (ABT), respectively, designed by Sanquin Research, Amsterdam. Response was defined according to the European League Against Rheumatism (EULAR) response criteria. The last observation was carried forward for patients who dropped out before week 28.

Results: At baseline, most patients had an active disease (median DAS28 (IQR) 4.5 (3.1–5.5)), 24 patients used concomitant methotrexate (median mg/week (IQR)) (11.3 (0–25)) and 18 used prednisone (median mg/day (IQR)) (7.5 (5–10)). Fourteen patients had used 1 prior biological (anti-TNF) and 10 patients had used 2 or more prior biologicals (anti-TNF and/or another). At 28 weeks, 10 patients were good, 9 were moderate and 19 were EULAR non-responders. In total, 16 patients dropped-out before week 28; 11 due to inefficacy and 5 due to adverse events.

Median golimumab level at 28 weeks of treatment (μg/mL) (IQR) was 0.8 (0.3–1.9) and varied from undetectable to 3.6μg/mL. Median golimumab levels were lower in non-responder (0.4 (0.2–1.5)) vs. moderate (1.0 (0.2–1.9)) and good responders (1.6 (0.7–2.4)) at 28 weeks of treatment, although this difference was not statistically significant (p=0.08). In 2 patients high ADA titres (between 303 and 1510 AU/mL) were detectable at week 16 which resulted in undetectable golimumab levels. In 1 other patient ADA were detectable (36.8 AU/mL) at week 4 which resulted in a low level of golimumab (0.35 μg/mL). All 3 patients were EULAR non-responder and golimumab was discontinued before 28 weeks of treatment due to inefficacy according to the treating rheumatologist.

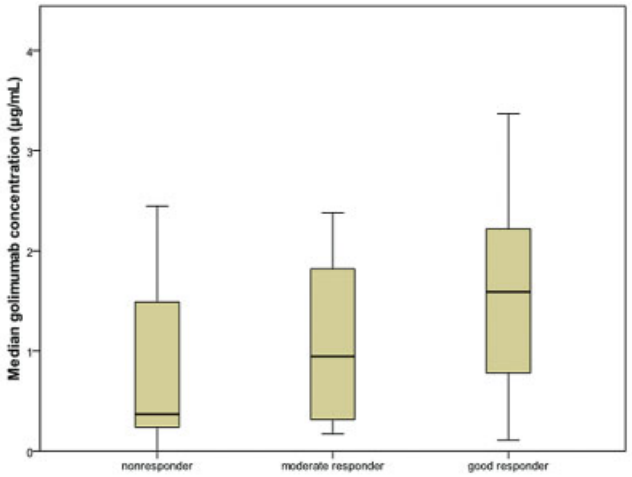

Figure. Median golimumab levels (μg/mL) (last observation carried forward) for EULAR good, moderate and non-responders at 28 weeks of treatment (p=0.08).

Conclusion: In our study of 38 RA patients, golimumab levels were lower in EULAR non-responders compared to moderate and good responders at 28 weeks of treatment. In 3 patients ADA were detectable which resulted in undetectable golimumab levels in two and low golimumab levels in one patient. All ADA positive patients dropped-out before 28 weeks of treatment due to inefficacy.

Disclosure: E. L. Kneepkens, None; **D. pascual-Salcedo**, None; **C. Plasencia**, None; **C. L. M. Krieckaert**, None; **D. van der Kleij**, None; **M. T. Nurmohamed**, Abbott Immunology Pharmaceuticals, 2, Roche Pharmaceuticals, 2, Pfizer Inc, 2, Abbott Immunology Pharmaceuticals, 5, Roche Pharmaceuticals, 5, Pfizer Inc, 5, MSD, 5, UCB, 5, SOBI, 5, BMS, 5, Abbott Immunology Pharmaceuticals, 8, Roche Pharmaceuticals, 8, Pfizer Inc, 8; **M. T. lópez-Casla**, None; **T. Rispens**, None; **G. Wolbink**, Pfizer Inc, 2, Pfizer Inc, 8, Amgen, 8.

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Inhibitory Effect Of Abatacept On Joint Damage In Rheumatoid Arthritis Patients With Or Without Concomitant Methotrexate: A Retrospective Multicenter Analysis Of 12 Months Of Abatacept Treatment In Routine Clinical Practice. Isao Matsushita, Hiraku Motomura, Eiko Seki and Tomoatsu Kimura. Faculty of Medicine, University of Toyama, Toyama, Japan.

Background/Purpose: Abatacept is approved for use with or without methotrexate (MTX). The purpose of this study was to clarify the inhibitory effect of abatacept on joint damage and its clinical efficacy in rheumatoid arthritis (RA) patients with or without concomitant MTX in routine clinical practice.

Methods: A retrospective multicenter study was conducted. Patients with RA who underwent abatacept treatment for 52 weeks were analyzed.

Results: Forty eight chronologically consecutive patients in the hospitals (4 males, 44 women, mean age of 62.8 years old, mean disease duration of 12.0 years, mean DAS28-CRP of 4.0, rate of MTX use of 56.3%) with active RA who started abatacept therapy were analyzed. All patients fulfilled the ACR 1987 revised criteria. Five patients were withdrawn during 1 year due to insufficient efficacy. The retention rates at 1 year of patients with or without concomitant MTX were 88.9% and 90.5%, respectively. At week 52, 37% and 35% of patients with or without concomitant MTX achieved clinical remission, respectively. There was no significant difference in achievement of remission by the concomitant use of MTX. The ΔmTSS decreased significantly from 9.44 at baseline to 0.86 at week 52. Rates of the structural remission [ΔmTSS: 0.5 or below] was achieved in patients with and without concomitant MTX were 58.3% and 68.4%, respectively. Thus, the radiographic changes were not significantly affected by the concomitant use of MTX.

Conclusion: Abatacept showed good clinical and radiographic effects for RA patients with or without concomitant MTX in routine clinical practice.

Disclosure: I. Matsushita, Bristol-Myers Squibb, 9; **H. Motomura**, None; **E. Seki**, None; **T. Kimura**, Bristol-Myers Squibb, 9.

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Rates Of Switching and Healthcare Costs Associated With Switching Biologic Disease-Modifying Antirheumatic Drugs In a Commercial Population: Evidence From Real-World Observational Studies. A Nadkarni[1], F Lobo[1] and T Juday[2]. [1]Bristol-Myers Squibb, Princeton, NJ, [2]Bristol-Myers Squibb, Plainsboro, NJ.

Background/Purpose: Several biologic disease-modifying antirheumatic drugs (bDMARDs) are approved for the treatment of moderate-to-severe RA. Switching between bDMARD therapies is common in real-world settings, and may have an impact on healthcare costs. This analysis evaluated bDMARD switching and associated healthcare costs in patients with RA across two commercially insured populations in the US.

Methods: Two retrospective cohort studies of adult patients with RA who initiated a bDMARD were conducted using US commercial insurance claims databases. Patients were categorized into first- and second-line bDMARD cohorts. The first-line bDMARD cohort included patients who newly initiated a bDMARD (adalimumab, etanercept, infliximab, or abatacept). The second-line bDMARD cohort included patients who initiated a second bDMARD. Patients in both first- and second-line bDMARD cohorts were required to have continuous eligibility 6 months before (pre-index) and 12 months after (post-index) initiation of first- or second-line bDMARD treatment. Patients in both cohorts were categorized into switchers and non-switchers. Switchers had a claim for a different bDMARD within a 200% gap in days supply for the index bDMARD. Non-switchers stayed on their index bDMARD in the post-index period. Switch rates were compared for each bDMARD. Patients who discontinued their index bDMARD and did not switch in the post-index period were excluded from the analyses. Rates of bDMARD switching, and pre- and post-index healthcare costs for switchers and non-switchers were examined.

Results: The first- and second-line bDMARD cohorts included 10,281 and 2354 patients, respectively, in Study 1, and 6320 and 1297 patients, respectively, in Study 2. In both studies, rates of switching for the first- and second-line bDMARD cohorts were lower for abatacept compared with adalimumab, etanercept, and infliximab (Table 1). Pre- and post-index healthcare costs in both studies were higher for first- and second-line bDMARD switchers compared with non-switchers (Table 2).

Table 1.

	Proportion of first-line bDMARD cohort who switched bDMARD during post-index period		Proportion of second-line bDMARD cohort who switched bDMARD during post-index period	
Index bDMARD	**Study 1**	**Study 2**	**Study 1**	**Study 2**
Adalimumab	8.9%	10.5%*	15.2%	19.1%*
Etanercept	8.5%	9.5%	13.3%	17.4%
Infliximab	5.2%	10.3%	13.5%	22.7%*
Abatacept	2.0%	6.5%	7.4%	12.6%

* $p<0.05$ vs abatacept.

Table 2.

	First-line bDMARD switchers versus non-switchers		Second-line bDMARD switchers versus non-switchers	
	Study 1	**Study 2**	**Study 1**	**Study 2**
Pre-index monthly healthcare costs	$1025 vs $796*	$2417 vs $2081*	$2173 vs $1856*	$3705 vs $3719
Post-index monthly healthcare costs	$3759 vs $2343*	$6081 vs $4415*	$3956 vs $2616*	$8376 vs $5625*

*$p<0.05$.

Conclusion: Patients on first- or second-line abatacept switched less frequently than patients on other bDMARDs. Post-index monthly healthcare costs were higher for first- and second-line bDMARD switchers versus non-switchers, suggesting there may be an economic benefit to using abatacept as the first- or second-line bDMARD in patients with moderate-to-severe RA.

Disclosure: A. Nadkarni, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1; **F. Lobo**, Bristol-Myers Squibb, 3; **T. Juday**, Bristol-Myers Squibb, 3.

1459

Multiple Cytokine Profiling Predicts The Effectiveness Of Switching Biologics In Rheumatoid Arthritis. Kensuke Koyama, Katsunori Ikari, Atsuo Taniguchi, Shigeki Momohara and Hisashi Yamanaka. Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: There is some rheumatoid arthritis (RA) patients with poor responses to certain biologics which requires switching to another biologics. However, there is no solid evidence to support such switching of biologics. We examined cytokine profiles for these patients to identify effective switching of biologics.

Methods: IORRA cohort is a hospital-based large observational cohort of Japanese RA patients. Clinical information and laboratory data are collected biannually. The patients who had switched biologics were chosen from the cohort. Serum levels of various cytokines (TNF alpha, IL-6, IL-17A, IL-1 beta, IL-8, MCP-1, TNF R1, TNF R2) before switching biologics were measured by using multiplex cytokine array system. Multiple regression model were used to examine following variables (objective variable: delta DAS28, explaining variable: previous DAS28, various cytokines) in several switching patterns. Statistical significant was established at $p < 0.05$.

Results: Eighty seven patients were identified as first TNF alpha antibody failure (infliximab: 50, etanercept: 21, adalimumab: 16). Thirty patients switched from one anti-TNF alpha antibody to another anti-TNF alpha agent, 36 switched to an anti-IL-6 antibody. Delta DAS28 (Post DAS28-Pre DAS28) set up in accordance with regression coefficient is

shown Figure 1 **(NO GRAPHIC AVAILABLE)**. Constant term, IL-17A and IL-1 beta was identified as significant regression coefficients in switching from one anti-TNF antibody to another anti-TNF alpha agent group. Pre DAS28 was only extracted as significant regression coefficients in switching from one anti-TNF antibody to an anti-IL-6 antibody group. Pre DAS28, TNF alpha, IL-8, MCP-1, TNFR1 and TNFR2 were chosen in concordance with EULAR good and moderate response cases in this group. It was impossible to examine the patients switching from etanercept because of the small number.

Conclusion: Our results suggest that cytokine profile maybe an effective way of predicting of possible switching from one biologic to another. Inefficient biologics switching may expose patients to further unnecessary joint destruction and cost.

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1460

10 Years Of Treat-To-Target Therapy In Rheumatoid Arthritis Patients (the BeSt study): Clinical and Radiological Outcomes. I.M. Markusse[1], G. Akdemir[1], M. van den Broek[1], L. Dirven[1], R.J. Goekoop[2], K.H. Han[3], M. van Oosterhout[4], P.J.S.M. Kerstens[5], W.F. Lems[6], T.W.J. Huizinga[1] and C.F. Allaart[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Haga Hospital, The Hague, Netherlands, [3]Maasstad Hospital, Rotterdam, Netherlands, [4]Groene Hart Hospital, Gouda, Netherlands, [5]Jan van Breemen Research Institute Reade, Amsterdam, Netherlands, [6]VU University Medical Center, Amsterdam, Netherlands.

Background/Purpose: Long term studies with treat-to-target therapy are essential to guide treatment strategies. We report on a study that compared clinical and radiological outcomes of four treatment strategies in early rheumatoid arthritis (RA) patients after ten years of treat-to-target therapy.

Methods: The BeSt (Dutch acronym for Treatment Strategies) study enrolled 508 patients with recent onset RA. Patients were randomized to 1 of 4 treatment strategies: 1 sequential monotherapy, 2 step-up therapy, 3 initial combination therapy with prednisone, 4 initial combination therapy with infliximab. Treatment adjustments were made based on 3-monthly disease activity scores (DAS) measurements (DAS $>$ 2.4: next treatment step; DAS $\leq$ 2.4 for $\geq$ 6 months: taper to maintenance dose, next if DAS $<$ 1.6 for $\geq$ 6 months: stop last Disease-Modifying AntiRheumatic Drug). Functional ability (Health Assessment Questionnaire, HAQ) was analyzed with a linear mixed model (LMM) with time, treatment and time $\times$ treatment as independent variables. Annual radiographs were scored in one session by two independent and blinded readers (IM and GA) using the Sharp van der Heijde Score (SHS).

Results: Baseline characteristics in all groups were comparable (over all groups mean DAS 4.4, mean HAQ 1.4). 200 of 508 (39%) have dropped out of the study. Of them, 6 returned for the final visit. Thus, in total 314 patients (62%) completed 10 years follow-up.

Mean age of completers was 61 years and 68% were female. Mean (SD) DAS was 1.6 (0.8) and mean HAQ (SD) was 0.6 (0.6), comparable among the groups. 82% had a DAS $\leq$ 2.4, 53% had a DAS $<$ 1.6 (DAS-remission), 15% were in drug free remission (DFR) with a mean (median) duration of 52 (58) months. After 10 years, 39% were still on the initial treatment step. Toxicity was similar in all groups. In table 1, outcomes per treatment strategy are shown.

	Group 1 n=126	Group 2 n=121	Group 3 n=133	Group 4 n=128	p-value
Clinical Outcomes					
DAS, mean ± SD *	1.7 ± 0.7	1.7 ± 0.8	1.5 ± 0.8	1.6 ± 0.8	0.333
HAQ, mean ± SD *	0.6 ± 0.6	0.7 ± 0.6	0.5 ± 0.5	0.6 ± 0.6	0.121
DAS ≤ 2.44, n (%) *	61 (85)	43 (71)	59 (84)	75 (84)	0.102
DAS < 1.6, n (%) *	36 (50)	28 (46)	40 (57)	50 (56)	0.507
Drug free remission, n (%) *	11 (14)	11 (15)	12 (15)	13 (13)	0.604
Still on initial treatment step, n (%) *	21 (28)	13 (19)	33 (43)	52 (59)	<0.001 □
Current use of infliximab, n (%) *	14 (18)	7 (10)	9 (12)	22 (24)	0.080
Drop out, n (%)	50 (40)	53 (44)	55 (41)	36 (28)	0.163
SAE, total n	124	97	126	126	0.665
Patients with SAE, n (%)	60 (48)	50 (41)	61 (46)	63 (49)	0.630
SHS progression					
Year 0–10, median (IQR)*	2.0 (0.0–11.0)	2.5 (0.0–13.5)	3.0 (0.3–11.3)	1.5 (0.0–6.0)	0.390
Patients with ΔSHS > 5, n (%)*	24 (38)	23 (42)	27 (42)	21 (27)	0.190
Patients with ΔSHS > 10, n (%)*	16 (25)	16 (29)	18 (28)	12 (15)	0.196

* Completers analysis; □ Group 1 and 2 vs 4: $p < 0.001$, group 3 vs group 4 $p < 0.05$, group 2 vs group 3 $p < 0.05$

Across groups, the initial functional improvement is maintained after 10 years of follow-up. Over time patients in group 4 have a significantly lower HAQ than patients in group 2 (0.52 versus 0.70, p= 0.03, other comparisons between groups non-significant).

After 10 years follow up there was no longer a significant difference in radiographic damage progression between groups, and progression was low in all groups. In patients with longstanding DFR mean SHS progression was 0.21 (median (IQR) 0.0 (0.0, 0.0)) per person year. Patients in longstanding DAS-remission (defined as mean DAS $<$ 1.6 during year 5 to 10) had a mean SHS progression of 0.56 per year (median (IQR) 0.0 (0.0, 2.0)).

Conclusion: Ten years follow up in the BeSt study shows the benefit of continued treat-to-target therapy, steering at low disease activity. Of 508 patients, 62% completed follow up. After initial improvement no decline in function occurred. 53% of completers were in DAS remission, and 15% in prolonged drug free remission. Radiologic damage progression was low and no longer different between groups.

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1461

Corticosteroid Use In Rheumatoid Arthritis Patients On Infliximab: Treatment Implications Based On A REAL-WORLD Canadian Population. Boulos Haraoui[1], Algis V Jovaisas[2], William G. Bensen[3], Rafat Y. Faraawi[4], John T. Kelsall[5], Sanjay Dixit[6], Emmanouil Rampakakis[7], John S. Sampalis[7], Francois Nantel[8], Susan M. Otawa[8], Allen J. Lehman[8] and May Shawi[8]. [1]Centre Hospitalier de l'Université de Montréal, Montreal, QC, [2]University of Ottawa, Ottawa, ON, [3]St. Joseph's Hospital and McMaster University, Hamilton, ON, [4]Rheumatologist, KW Musculoskeletal Research Inc., Kitchener, ON, [5]Mary Pack Arthritis Centre, Vancouver, Vancouver, BC, [6]McMaster University, Burlington, ON, [7]JSS Medical Research, St-Laurent, QC, [8]Janssen Canada Inc, Toronto, ON.

Background/Purpose: The Canadian Rheumatology Association[1] recommends that addition of corticosteroids (CS) should be considered only for the shortest period possible in rheumatoid arthritis (RA) patients treated with a traditional or biologic DMARD based on the patient's clinical status. The objective is to examine the effect of chronic systemic CS treatment at different doses on the incidence of infections in RA patients treated with IFX in a real-life setting. The impact of CS use on the sustainability of remission was also assessed.

Methods: BioTRAC is an ongoing, Canadian, prospective, registry of rheumatology patients initiating treatment with IFX or golimumab as first biologics or after having been treated with a biologic for less than 6 mos. RA patients treated with IFX who were enrolled between 2002 and 2012 were included. Cox regression was used to examine the time-dependent association between systemic CS dose (no CS, ≤5 mg, >5 mg) and the incidence of first infection, while adjusting for possible confounders, and to assess the sustainability of remission.

Results: 838 RA patients were included in the analyses. Mean (SD) age of the patient cohort was 56.6 (13.5) yrs and mean (SD) duration since diagnosis was 10.5 (9.8) yrs. At initiation of treatment, 38.2% of patients

were treated with a systemic CS. After a mean (SE) follow-up of 51.3 (1.7) mos, 310 infections were reported for 19.7% of patients (19.6/100 PYs). Among these, the majority (90.0%) were non-serious infections. Multivariate survival analysis using Cox regression showed that, upon adjusting for enrolment period, age, disease duration, number of steroid administrations, and HAQ-DI, the hazard ratio (HR) (95%CI) for acquiring an infection was 2.48 (1.24–4.98) in patients treated with high dose (>5 mg) CS compared to patients not receiving CS. Treatment with low dose CS was also associated with an increased hazard for infection (HR (95%CI) = 2.12 (0.97–4.66)) which did not reach statistical significance. Consistent with previous studies, increased HAQ-DI (HR (95%CI) = 1.51 (1.15–1.92)) and disease duration (HR (95%CI) = 1.01 (1.00–1.03)) were also identified as significant predictors. CS use was continued in 15% of cases despite the achievement of remission (DAS28-CRP: 15.2%; CDAI: 15.7%). Survival analysis did not show a significant positive effect of steroid use on sustainability of remission [HRDAS28-CRP (95%CI) = 1.40 (0.95–2.06); HRCDAI (95%CI) = 1.19(0.75–1.88)].

Conclusion: Treatment with systemic CS was associated with an increased hazard ratio for acquiring an infection upon adjusting for possible confounders. Despite the achievement of remission, steroid use was continued in 15% of cases without having an impact on sustainability of remission. We show that treatment with systemic CS is an independent predictor of infection in patients treated with anti-TNF agents and suggest that the use of concomitant medications should be considered in the interpretation of safety data.

References:
1. J Rheumatol 2012;39;1559–1582.

Disclosure: B. Haraoui, None; **A. V. Jovaisas**, None; **W. G. Bensen**, None; **R. Y. Faraawi**, None; **J. T. Kelsall**, None; **S. Dixit**, None; **E. Rampakakis**, None; **J. S. Sampalis**, None; **F. Nantel**, None; **S. M. Otawa**, Janssen Canada, 3; **A. J. Lehman**, Janssen Canada, 3; **M. Shawi**, Janssen Canada, 3.

1462

Unmasking The Tolerability Of Methotrexate In Patients With Rheumatoid and Psoriatic Arthritis: A Retrospective Review Of Discontinuation From a Large UK Cohort. Andra Negoescu[1], Elena Nikiphorou[2], Anshuman P. Malaviya[2], Andrew Badcock[2], John D. Fitzpatrick[2], Calum T. Goudie[2] and Andrew J. Ostor[2]. [1]Rheumatology Research Unit, Addenbrooke's Hospital, Cambridge, United Kingdom, [2]Addenbrooke's Hospital, Cambridge, United Kingdom.

Background/Purpose: Due to its efficacy and perceived safety, methotrexate (MTX) has become the foundation disease-modifying drug for rheumatoid (RA) and psoriatic arthritis (PsA) however its tolerability has not been a focus of research. The objective of our study therefore was to analyse this by identifying RA and PsA patients in whom MTX was discontinued and to determine the reasons for this. We were specifically interested in how long patients remained on MTX prior to withdrawal.

Methods: A retrospective review of our institutions electronic database was undertaken to identify all RA and PsA patients who had been prescribed MTX. Patients who had discontinued MTX were then identified from both the electronic and paper-based records and the reasons for this were categorised. The duration of MTX treatment was then assessed in those who had stopped treatment due to intolerability.

Results: 762 RA and 193 PsA patients had received MTX. In those the DMARD had been stopped in 260 (34%) RA patients and 71 (36%) PsA patients with intolerability cited as the most common reasons for this (60% and 63% in RA and PsA respectively). Haematological abnormalities (leukopenia and thrombocytopenia) were reported more frequently in RA (11.5% vs 6.8% $p<0.05$) and liver enzyme abnormalities more common in PsA (27% vs 12%; $p<0.05$). The most common symptoms resulting in MTX withdrawal were nausea, shortness of breath, feeling generally unwell, headache and fatigue. Other reasons for stopping MTX included: ineffectiveness, planned pregnancy, lifestyle choice and disease remission. The median duration of MTX treatment was 10 months in both groups, mean duration 21 and 18.6 months in RA and PsA groups respectively (Range: 0.25 – 122.25 months for RA, 1.00–79.25 months for PsA). The mode was at 3 months for RA and 1 month for PsA. See figure 1 for duration of MTX treatment.

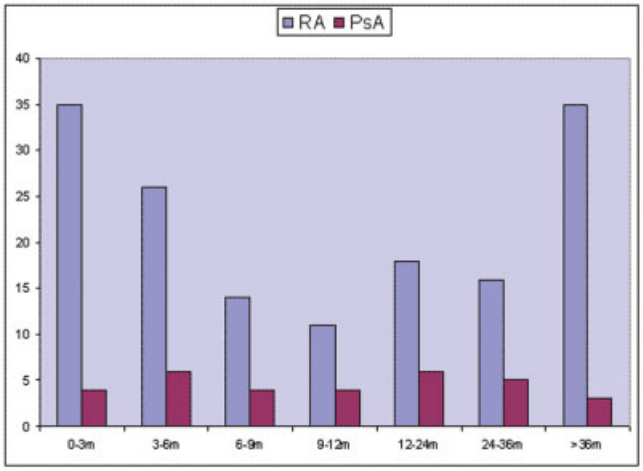

Fig 1. Duration of MTX therapy in patients who stopped treatment due to side effects

Conclusion: Overall one third of patients with RA and PsA stop MTX most commonly due to poor tolerability. In the context of chronic disease the median duration of treatment is short (10 months). Clinicians need to be aware of the frequency of MTX intolerability, and that this may occur early in the treatment cycle, and to alter therapy accordingly to optimise outcomes.

Disclosure: A. Negoescu, None; **E. Nikiphorou**, None; **A. P. Malaviya**, None; **A. Badcock**, None; **J. D. Fitzpatrick**, None; **C. T. Goudie**, None; **A. J. Ostor**, None.

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Dietary Impact On Treatment Results Of Methotrexate In Patients With Rheumatoid Arthritis. Cecilia Lourdudoss[1], Alicja Wolk[2], Camilla Bengtsson[3], Lena Nise[4], Lars Alfredsson[3] and Ronald van Vollenhoven[5]. [1]Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), Karolinska institutet, Stockholm, Sweden, [2]Institute of Environmental Medicine (IMM), Karolinska institutet, Stockholm, Sweden, [3]Karolinska Institutet, Stockholm, Sweden, [4]Karolinska institutet, Stockholm, Sweden, [5]Unit for Clinical Research Therapy. Inflammatory Diseases (ClinTrid), Karolinska Institute, Stockholm, Sweden.

Background/Purpose: Some specific diets have been shown to ameliorate rheumatoid arthritis (RA). However, there is generally a lack of studies on any possible dietary impact on the efficacy of anti-rheumatic therapies such as methotrexate. We hypothesized that some dietary nutrients may affect the treatment response. Thus, the aim of this study was to investigate dietary impact on treatment results of methotrexate (MTX) in patients with RA.

Methods: We used data from the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study as well as from the Swedish Rheumatology Quality (SRQ) register. In EIRA, data on dietary intake at baseline were collected using a previously validated dietary questionnaire. DAS28 values at baseline and at 3 months were obtained from the SRQ and used to calculate EULAR responses.

Statistical analysis was performed using IBM SPSS Statistics 20 and included independent samples t-tests and ANOVA.

Results: This study included 293 RA patients from the EIRA study who started treatment with MTX. 70.6% were females. Mean age was 52.7 years. Most patients were RF positive (63.3%) and ACPA positive (70.0%). In 55.4%, MTX was combined with glucocorticoids (GC). At baseline, 59.3% had high disease activity and 36.4% had moderate disease activity.

Mean DAS28 scores decreased significantly from 5.4 (±1.2SD) at baseline to 3.4 (±1.3SD) at 3 months ($p<0.001$).

After 3 months of MTX treatment, 45.1% of patients had a good EULAR response. Average daily folate intake was 326.9μg in good responders and 318.5μg in moderate/non-responders (not significant). In contrast, the daily intake of long-chain fatty acid C22:5 was higher in good responders versus moderate/non-responders (0.069±0.035 vs. 0.058±0.032, $p=0.011$). In patients who were not on GC at baseline,

good responders had significantly higher vitamin D intake compared to moderate/non-responders (6.58±3.45 vs. 5.01±2.33, p=0.004). Associations were also found between therapeutic response and the intake of other fatty acids and of niacin and selenium in different subsets of patients (table).

		Good response		Moderate/Non-response		
Patient subset	**Nutrient**	**N**	**Mean ± SD**	**N**	**Mean ± SD**	**p value**
Total study sample	Fatty acid C22:5 (g)	119	0.07 ± 0.3	151	0.06 ± 0.03	0.011
Overweight/Obese	Fatty acid C20:4 (g)	57	0.12 ± 0.05	80	0.10 ± 0.05	0.034
Ex smoker	Polyunsaturated fatty acids (g)	46	11.32 ± 4.92	49	9.44 ± 3.64	0.036
Ex smoker	Niacin (mg)	46	17.89 ± 5.71	49	15.58 ± 4.89	0.036
No GC at baseline	Total fat (g)	39	76.21 ± 29.18	85	63.01 ± 27.71	0.017
No GC at baseline	Monounsaturated fatty acids (g)	39	25.73 ± 9.77	85	21.13 ± 8.99	0.011
No GC at baseline	Selenium (μg)	39	36.49 ± 16.37	85	29.85 ± 12.15	0.013
No GC at baseline	Vitamin D (μg)	39	6.58 ± 3.45	85	5.01 ± 2.33	0.004

Conclusion: In early RA, the therapeutic response to MTX at 3 months might be linked to several nutrients. Perhaps surprisingly, daily folate intake did not influence the response to MTX. In contrast, higher intake of C22:5 in the whole cohort, and the intake of various other nutrients, including higher vitamin D, in specific subsets of patients were significantly related to better clinical responses. In conclusion, dietary habits may affect treatment results.

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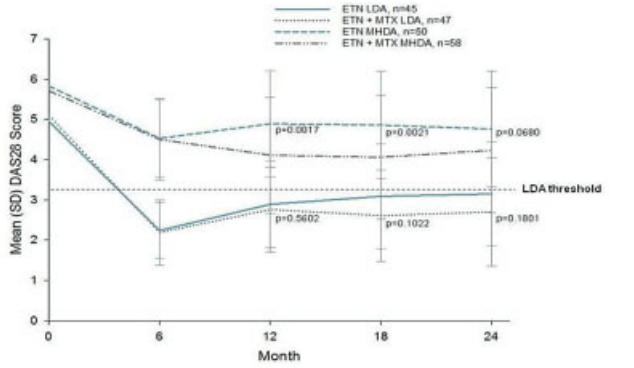
1464

Clinical and Radiographic Outcomes With Etanercept and Etanercept and Methotrexate In Patients With Rheumatoid Arthritis: Two-Year Results From The Canadian Methotrexate and Etanercept Outcome Study (CAMEO). Boulos Haraoui[1], J. Carter Thorne[2], Edward C. Keystone[3], Melanie Poulin-Costello[4], Eric Trottier[5], Andrew Vieira[4] and Janet E. Pope[6]. [1]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [2]Southlake Regional Health Centre, Newmarket, ON, [3]Mount Sinai Hospital/University of Toronto, Toronto, ON, [4]Amgen Canada Inc., Mississauga, ON, [5]Amgen Canada, Mississauga, ON, [6]St Joseph Health Care, London, ON.

Background/Purpose: Data from the CAMEO study demonstrated that patients with rheumatoid arthritis (RA) who achieved low disease activity (LDA) after 6 months of combination therapy of etanercept (ETN) and methotrexate (MTX) had similar clinical outcomes at 12 months whether they continued ETN+MTX or stopped MTX at 6 months. Yet response was reduced when MTX was withdrawn in patients with moderate or high disease activity (MHDA). Clinical and radiographic data for up to 24 months from the CAMEO study are presented.

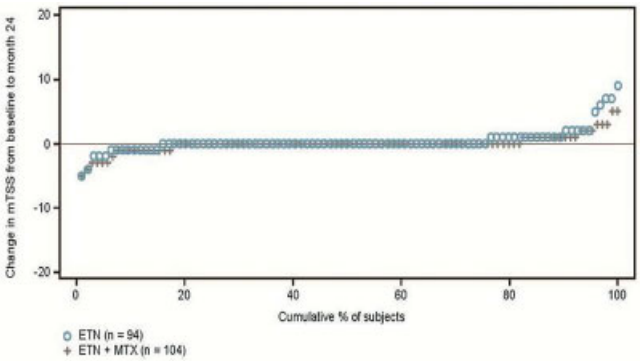
Methods: TNF-inhibitor naïve patients with active RA (defined as ≥3 swollen joints and a Disease Activity Score [DAS28] ≥3.2) despite treatment with MTX (≥15 mg/week, or 10 mg/week if intolerant) for >12 weeks were treated with ETN (50 mg/week SC) and MTX for 6 months. Patients were then randomized (1:1) to switch to ETN monotherapy or to continue ETN+MTX for an additional 18 months. DAS28 was assessed at baseline and at 6, 12, 18, and 24 months/early termination (24m/ET), and X-rays of the hands and feet were taken at baseline and at 12 and (24m/ET).

Results: A total of 258 patients enrolled, and 205 were randomized to either begin ETN monotherapy (n=98) or to continue ETN+MTX treatment (n=107). Seventy-six percent were females with a mean age of 54.7±12.5 years, disease duration of 8.9±8.4 years, and baseline DAS28 score of 5.4±1.1. Overall, patients who reached LDA at month 6 maintained LDA at (24m/ET) whether they were treated with ETN or ETN+MTX; those with MHDA treated with ETN monotherapy had worsening of disease activity, while those treated with ETN+MTX had a sustained response (Figure 1). Radiographic progression between patients treated with ETN or ETN+MTX was similar at 24 months (Figure 2). The proportion of patients with LDA showing no radiographic progression was similar between the ETN and ETN+MTX at both 12 (88% vs. 85%) and (24m/ET) (86% vs. 87%). However, fewer patients with MHDA receiving ETN monotherapy had no radiographic progression compared with ETN+MTX at 12 (68% vs. 81%) and (24m/ET) (64% vs. 76%).



*p-values comparing ETN with ETN+MTX were analyzed using an ANOVA, with terms for treatment, reimbursement type, and disease duration.

Figure 1. Comparisons[a] of mean (SD) DAS28 scores from 6-month randomization to 24m/ET, stratified by disease status at month 6.



*End-of-study assessments are used for patients who prematurely terminated before 24 months

Figure 2. Cumulative change from baseline to month 24[a] in Total Sharp Scores (N=198).

Conclusion: These data clarify the role of long term combination of ETN+MTX in maintaining optimal disease control. For patients who achieve LDA by 6 months, ETN monotherapy provides an effective clinical and radiological alternative to combination therapy for up to 24 months. However, patients with MHDA may need to continue combination therapy, as clinical response may be reduced when MTX is withdrawn.

Disclosure: B. Haraoui, Amgen, 5, Abbott Laboratories, 5, Bristol-Myers Squibb, 5, Merck Pharmaceuticals, 5, Pfizer Inc, 5, Roche Pharmaceuticals, 5, UCB, 5; **J. C. Thorne**, Amgen, 5, Pfizer Inc, 5, Abbott Laboratories, 5, Bristol-Myers Squibb, 5, Centocor, Inc., 5, Merck Pharmaceuticals, 5, Roche Pharmaceuticals, 5, UCB, 5; **E. C. Keystone**, Abbott Laboratories, 5, Amgen, 5, AstraZeneca, 5, Bristol-Myers Squibb, 5, Centocor, Inc., 5, Hoffmann-La Roche, Inc., 5, Genzyme Corporation, 5, Merck Pharmaceuticals, 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5, UCB, 5, Genentech and Biogen IDEC Inc., 5, Nycomed, 5; **M. Poulin-Costello**, Amgen, 3; **E. Trottier**, Amgen, 3; **A. Vieira**, Amgen, 3; **J. E. Pope**, Amgen, 2, Pfizer Inc, 2.

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Adherence To The Recommended Dosing Regimen Of Abatacept In The Real-World Setting In The Action Study: Is There a Dose-Creep In Overweight Patients? H Nüβlein[1], R Alten[2], M Galeazzi[3], H M Lorenz[4], D Boumpas[5], M T Nurmohamed[6], W G Bensen[7], G R Burmester[8], H-H Peter[9], F Rainer[10], K Pavelka[11], M Chartier[12], C Poncet[13], C Rauch[14] and M Le Bars[15]. [1]University Erlangen, Nürnberg, Germany, [2]Schlosspark-Klinik, University Medicine Berlin, Berlin, Germany, [3]University of Siena, Siena, Italy, [4]University Hospital Heidelberg, Heidelberg, Germany, [5]Panepistimio Kritis, Rethymnon, Greece, [6]VU University Medical Center/Jan van Breeman Research Institute, Amsterdam, Netherlands, [7]St. Joseph's Hospital/McMaster University, Hamilton, ON, [8]Charité-Universitätsmedizin, Berlin, Germany, [9]University Medical Center Freiburg, Freiburg, Germany, [10]Hospital Barmherzige Brueder, Graz, Austria, [11]Institute of Rheumatology, Prague, Czech Republic, [12]Chiltern International, Neuilly, France, [13]Docs International, Sèvres, France, [14]Bristol-Myers Squibb, Munich, Germany, [15]Bristol-Myers Squibb, Rueil Malmaison, France.

Background/Purpose: Reduced efficacy for achieving DAS28 <2.6 has been observed for anti-TNF agents in obese patients following 12 months of

therapy. The odds ratio (95% confidence interval) was 2.43 (1.21, 4.88; p=0.01) with initial body mass index [BMI] 20–30 kg/m^2 versus >30 kg/m^2,[1] which in theory could induce dose increases to maintain efficacy. Here we explore adherence to abatacept over 6 months in patients categorized according to BMI.

Methods: ACTION is an ongoing, 2-year, international, non-interventional, prospective cohort of patients with RA treated with IV abatacept. All patients on abatacept treatment for ≥6 months, and with data available for infusion (at initiation and at 6 months) and BMI (at initiation), were considered in this analysis. BMI calculated at abatacept initiation categorized patients into normal (<25 kg/m^2), overweight (25–<30 kg/m^2) or obese (≥30 kg/m^2) subgroups. Within each BMI category, adherence to treatment was assessed in patients who received appropriate dosage by body weight at initiation. Increase in dose and frequency of administration was assessed over 6 months.

Results: An even distribution of patients was observed across the BMI subgroups at abatacept initiation in the overall population (<25 kg/m^2: 399/1048 [38.1%]; 25–<30 kg/m^2: 363/1048 [34.6%]; ≥30 kg/m^2: 286/1048 [27.3%]). Baseline disease characteristics were similar across BMI subgroups, except auto-antibody status, with fewer obese seropositive patients: rheumatoid factor-positive, <25 kg/m^2: 228/315 (72.4%); 25–<30 kg/m^2: 220/293 (75.1%); ≥30 kg/m^2: 132/232 (56.9%); anti-cyclic citrullinated peptide-positive, <25 kg/m^2: 152/213 (71.4%); 25–<30 kg/m^2: 138/204 (67.6%); ≥30 kg/m^2: 87/153 (56.9%). Overall, 737/1048 (70.3%) patients with BMI data available received abatacept for ≥6 months and had infusion data available at initiation and at 6 months. A large proportion of patients received appropriate dosage regardless of BMI: at initiation (<25 kg/m^2: 236/290 [81.4%]; 25–<30 kg/m^2: 224/245 [92.2%]; ≥30 kg/m^2: 182/202 [91.0%]). Adherence over 6 months in patients receiving appropriate dosage at initiation is presented in the table.

	<25 kg/m^2 (n=236)	25–<30 kg/m^2 (n=224)	≥30 kg/m^2 (n=182)
Appropriate dosage at 6 months*	203/215 (94.4%)	197/200 (98.5%)	154/161 (95.7%)
Dose increase over 6 months*	11/215 (5.1%)	2/200 (1.0%)	4/161 (2.5%)
7–9 infusions received**	203/236 (86.0%)	199/224 (88.8%)	150/182 (82.4%)
1 additional infusion received	6/236 (2.5%)	3/224 (1.3%)	2/182 (1.1%)
Increase in dose or in frequency	17/236 (7.2%)	5/224 (2.2%)	6/182 (3.3%)

*Some patients had missing data for dose reported at 6 months; **Corresponding to a ratio of actual to recommended infusions within range of 80–120%
No patient received more than 1 additional infusion. No patient had both a dose increase and an increase in frequency of administration over 6 months.

Conclusion: Analysis of adherence to the recommended dosing regimen of IV abatacept in the ACTION study showed that a large proportion of patients had good adherence at initiation, regardless of BMI. Few patients had an increase in dosage or frequency of administration over 6 months and nobody had both. Overall, there was no evidence for dose creep in overweight and obese patients treated with IV abatacept over 6 months in routine clinical practice.

References:
1. Gremese E, et al. *Arthritis Care Res* 2013;**65:**94–100.

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Survival On Treatment Of The Second Line Biologic Therapy: Switch Or Swap Strategy? Ennio G. Favalli[1], Martina Biggioggero[1], Antonio Marchesoni[2] and Pier Luigi Meroni[3]. [1]Chair and Division of Rheumatology, Gaetano Pini Institute, University of Milan, Milan, Italy, Milan, Italy, [2]UOC Day Hospital Rheumatology, Gaetano Pini Institute, Milan, Italy, Milano, Italy, [3]Division of Rheumatology, Gaetano Pini Institute, Milan, Italy, Milan, Italy.

Background/Purpose: The strategy for the choice of the second biologic agent after the failure of the first TNF inhibitor is still an unclear aspect in the treatment of rheumatoid arthritis (RA). The aim of the study is to evaluate in a real-life setting the survival on treatment of the second biologic agent in anti-TNF non-responders, comparing patients treated with a second anti-TNF (switch strategy) with patient treated with a different mechanism of action (abatacept, rituximab, or tocilizumab; swap strategy).

Methods: We extracted data from a local registry that includes all RA patients treated with biologic therapies between October 1999 and December 2012 in our Rheumatology Unit. We limited our analysis to the period after the first biologic agent other than anti-TNF became available (January 2007-December 2012), in order to minimise differences in exposure among biologics. Patients who stopped a first course TNF inhibitor and started a second line biotherapy since January 2007 were included in the analysis. The rate of drug discontinuation in both subgroups were retrospectively estimated by Kaplan-Meier analysis and compared by log-rank (Mantel-Cox) test.

Results: Between 1999 and 2012, 641 patients were treated with etanercept (n=192), infliximab (n=221), adalimumab (n=192), golimumab (n=14), or certolizumab pegol (n=22) as first line biotherapy. Since January 2007, 183 of these patients discontinued the TNF blocker because of inefficacy (56%) or safety (44%) issues and switched to a second anti-TNF (n=107) or swapped to abatacept (n=21), rituximab (n=40), or tocilizumab (n=15). The drug survival was significantly greater in swap than in switch subgroup (p=0.0009). This difference was confirmed after the stratification of both subgroups according to cause of first anti-TNF discontinuation (inefficacy, p=0.03; safety, p=0.01). No significant differences emerged comparing the retention rate of abatacept, rituximab, and tocilizumab (p=0.2).

Conclusion: In a set of clinical practice, the choice of a second biologic agent with different mechanism of action seems to be a better strategy to treat anti-TNF non-responders, irrespective of the cause of TNF blocker discontinuation.

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Adalimumab In Combination With High and Low Dose-Methotrexate In Rheumatoid Arthritis Patients With Inadequate Response To Methotrexate: Pharmacokinetic Results From The Musica Study. Ghada Ahmed[1], Sandra L Goss[1], Cheri E Klein[1], Neelufar Mozaffarian[2], Gurjit S. Kaeley[3] and Walid Awni[1]. [1]AbbVie Inc., North Chicago, IL, [2]Eli Lilly, San Diego, CA, [3]University of Florida, Jacksonville, FL.

Background/Purpose: Rheumatoid arthritis (RA) patients with inadequate response to methotrexate (MTX) may be initiated on combination therapy with anti-TNF agents such as adalimumab. However, it is not known whether MTX doses can be reduced when adalimumab is added. Also, little is known about the disposition of intracellular MTX polyglutamates (PG). This is important because MTX PGs are thought to account for the anti-inflammatory effect of MTX in RA.

Methods: MUSICA was a 24-wk, phase 4, prospective parallel-arm study in patients with moderately to severely active RA and an inadequate response to stable, high dose MTX (≥15 mg/wk for at least 12 wks prior to Screening). Eligible subjects were randomized 1:1 to blinded oral MTX at 20 mg/wk ("high dose") or 7.5 mg/wk ("low dose"). All patients also began open-label adalimumab 40 mg SC every other week. Blood samples were collected prior to dosing at Baseline and every 4 wks to measure adalimumab and anti-adalimumab antibody (AAA) in serum (using validated ELISA assays) and MTX PG 1 to 5 levels in erythrocytes using a validated LC-MS method. A patient was considered AAA+ if he/she had at least one serum sample with AAA level > 20 ng/mL that was confirmed by a confirmatory assay and was collected within 30 days after an adalimumab dose.

Results: Steady-state (SS) adalimumab trough levels were attained by Week 16. At Week 24, mean adalimumab trough concentrations were 8.98 μg/mL (n=155) and 7.46 μg/mL (n=154) in the high and low MTX dose groups, respectively. Overall, 11/309 patients (3.6%) were classified as AAA+ at week 24. The percentages of subjects with at least one AAA+ sample in the high and low MTX dose groups were 1.9% and 5.2%, respectively. For both MTX dose groups, new SS total MTX PG levels appeared to be reached by week 20–24. At week 24, mean total MTX PG1–5 concentrations were 130.30 nM and 60.43 nM for the high and low MTX dose groups, respectively. MTX PG1–2 (short-chain PG) were more prevalent in those treated with low MTX dose (64% of total PG) than high MTX dose (37.5% of total PG). MTX PG4–5 (long-chain PG) were however more prevalent in those treated with high MTX dose (22% of total PG) than low

MTX dose (5% of total PG). Compared to the low dose group, high dose MTX resulted in a less-than-dose-proportional increase in MTX PG1–2 (mean SS levels of PG1+2 were 47.6 nM and 38.6 nM in the high and low MTX dose, respectively), a dose-proportional increase in MTX PG3 (mean SS levels of PG3 were 54.4 nM and 18.8 nM in the high and low MTX dose, respectively), and a more-than-dose-proportional increase in MTX PG4–5 (mean SS levels of PG4+5 were 28.3 nM and 3.03 nM in the high and low MTX dose, respectively).

Conclusion: In RA patients with incomplete response to MTX, slightly higher mean adalimumab serum levels were achieved when combined with high than low MTX dose. A new SS for total MTX PG appeared to be reached by week 20–24. Short-chain PGs were more prevalent in the low MTX dose than high MTX dose; while long-chain PGs were more prevalent in the high MTX dose than low MTX dose. High dose MTX resulted in a less-than-dose-proportional increase in MTX PG1–2, a dose-proportional increase in MTX PG3, and a more-than-dose-proportional increase in MTX PG4–5 compared to the low MTX dose.

Disclosure: G. Ahmed, AbbVie, 1, AbbVie, 3; **S. L. Goss**, AbbVie, 1, AbbVie, 3; **C. E. Klein**, AbbVie, 1, AbbVie, 3; **N. Mozaffarian**, AbbVie, 1, AbbVie, 9, Eli Lilly and Company, 3; **G. S. Kaeley**, AbbVie, 5; **W. Awni**, AbbVie, 1, AbbVie, 3.

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Reasons For Discontinuation Of Biologic Agents In Rheumatoid Arthritis Patients. Eric Elkin[1], Martin J. Bergman[2], Tripthi Kamath[3], Sarika Ogale[3], Adam Turpcu[3], Kristin King[4], Jae Oh[4], Monarch Shah[1] and Max I. Hamburger[5]. [1]ICON Clinical Research, San Francisco, CA, [2]Taylor Hospital, Ridley Park, PA, [3]Genentech, South San Francisco, CA, [4]ICON Late Phase and Outcomes Research, San Francisco, CA, [5]Rheumatology Associates, Melville, NY.

Background/Purpose:

Results: from randomized controlled trials indicate that about one-third of rheumatoid arthritis (RA) patients initially treated with anti-TNF agents do not respond, show a sub-optimal response, lose response, or develop adverse events (Kwoh et al 2002). Patients who discontinue their first biologic DMARD therapy might need to switch to a second or subsequent biologic DMARD treatment. The objective of this analysis is to describe reasons for discontinuation of their first anti-TNF for the treatment of RA and subsequently discontinuing either a second anti-TNF or biologic DMARDs with other mechanisms of action (oMOA).

Methods: An observational, non-interventional, retrospective chart review study was conducted in 8 centers in the United States from February to September 2012. Patient charts were eligible if the patient's first biologic DMARD was a anti-TNF; they were 18 years or older at time of the second DMARD; and they were prescribed the second and/or third biologic DMARD during the period July 1, 2006 and October 1, 2011. The proportion of patients stating each reason for treatment discontinuation are described for patients discontinuing anti-TNF vs. oMOA as their second and/or third biologic DMARD.

Results: A total of 176 charts were abstracted for patients who discontinued a anti-TNF as their first biologic DMARD and received a second biologic DMARD. Second biologic DMARD treatments were another anti-TNF for 122 patients and treatments with oMOA for 54 patients. At time of chart abstraction 108 patients had discontinued the second DMARD. Of these, 98 then received a third biologic DMARD (36 anti-TNF and 62 with oMOA) with 43 of these patients discontinuing the third biologic DMARD. Reasons for discontinuation are shown in the table:

	Reasons for discontinuation of Biologic DMARDs				
		Second biologic		Third biologic	
	First anti-TNF (n=176)	anti-TNF (n=122)	oMOA (n=54)	anti-TNF (n=36)	oMOA (n=62)
Discontinued, n (%)	176 (100)	87 (71.3)	21 (38.9)	21 (58.3)	22 (35.5)
Reason, n (%)*					
Lack of initial efficacy	40 (22.7)	35 (40.2)	4 (19.0)	10 (47.6)	12 (54.5)
Failure to maintain response (disease flare)	82 (46.6)	27 (31.0)	7 (33.3)	2 (9.5)	6 (27.3)
Safety/tolerance	30 (17.0)	18 (20.7)	3 (14.3)	4 (19.0)	1 (4.5)
Patient doing well	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patient or physician preference	1 (0.6)	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)
Cost, insurance, or formulary	13 (7.4)	1 (1.1)	3 (14.3)	1 (4.8)	2 (9.1)
Other or not reported	13 (7.4)	7 (8.0)	3 (14.3)	4 (19.1)	1 (4.5)

*Among those who discontinued

Conclusion: The most common reasons for discontinuation of the first anti-TNF agent were efficacy related (69.3%). A numerically greater proportion of patients receiving anti-TNF as their second biologic discontinued due to lack of initial efficacy compared with those that received second biologic with other mechanism of action. In addition, safety/tolerance was a more common reason for discontinuation among those receiving anti-TNF than those receiving treatment with other mechanisms of action.

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Therapeutic Strategy In Patients With Rheumatoid Arthritis and Insufficient Response To a 1st Anti-TNF: Results of the Multicenter Randomized Controlled "ROC" Trial. Jacques-Eric Gottenberg[1], Olivier Brocq[2], Aleth Perdriger[3], Slim Lassoued[4], Jean-Marie Berthelot[5], Daniel Wendling[6], Liana E. euller-Ziegler[7], Martin Soubrier[8], Christophe Richez[9], Bruno Fautrel[10], Arnaud L. Constantin[11], Xavier Mariette[12], Jacques Morel[13], Melanie Gilson[14], Grégoire Cormier[15], Jean Hugues Salmon[16], Stephanie Rist[17], Frédéric Liote[18], Hubert Marotte[19], Christine Bonnet[20], Christian Marcelli[21], Jeremie Sellam[22], Olivier Meyer[23], Elisabeth Solau-Gervais[24], Sandrine Guis[25], Jean-Marc Ziza[26], Charles Zarnitsky[27], Isabelle Valckenaere[28], Olivier Vittecoq[29], Alain Saraux[30], Yves-Marie Pers[31], Martine Gayraud[32], Gilles Bolla[33], Pascal Claudepierre[34], Marc Ardizzone[35], Emmanuelle Dernis[36], Maxime A. Breban[37], Olivier Fain[38], Jean-Charles Balblanc[39], Ouafaa Aberkane[1], Marion Vazel[1], Christelle Back[1], Elodie Perrodeau[40], Philippe Ravaud[41] and Jean Sibilia[42]. [1]Strasbourg University Hospital, Strasbourg, France, [2]Hospital of Princesse Grâce de Monaco, Monaco, France, [3]Hôpital Sud, Rennes, France, [4]Cahors Hospital, Cahors, France, [5]Nantes University Hospital, Nantes, France, [6]University Hospital, Besancon, France, [7]L Archet Hospital (University), Nice CEDEX 3, France, [8]CHU CLERMONT-FERRAND, Clermont-Ferrand, France, [9]Pellegrin Hospital, Bordeaux, France, [10]UPMC-Paris 6 University, Paris, France, [11]Purpan University Hospital, Toulouse, France, [12]Bicêtre University Hospital, Le Kremlin Bicetre, France, [13]Montpellier University Hospital, Montpellier, France, [14]CH Grenoble Hopital Sud, Grenoble, France, [15]CHD Les Oudairies, LA ROCHE SUR YON, France, [16]Reims Hospital, Reims, France, [17]Orleans Hospital, Orleans, France, [18]Hôpital Lariboisière, Paris, France, [19]INSERM U1059 and University Hospital, Hôpital Nord, Saint-Etienne, France, [20]CHU Dupuytren Limoges, Limoges, France, [21]Rheumatology Department, Caen University Hospital, CAEN, France, [22]Hopital Saint-Antoine, Pierre et Marie Curie University Paris 6, AP-HP, 75012, France, [23]Hopital Bichat, Paris, France, [24]Poitiers University Hospital, Poitiers, France, [25]Aix Marseille Univ; AP-HM, Marseille, France, [26]Croix Saint Simon Hospital, Paris, France, [27]CH du Havre, Le Havre, France, [28]Nancy University Hospital, Nancy, France, [29]RouenUniversity Hospital, Rouen, France, [30]CHU de la Cavale Blanche, Brest Cedex, France, [31]CHU Lapeyronie, Montpellier, France, [32]Institut Montsouris, Paris, France, [33]Cannes Hospital, Cannes, France, [34]Henri Mondor Teaching Hospital, AP-HP, Créteil, France, [35]Mulhouse Hospital, Mulhouse, France, [36]Le Mans Hospital, Le Mans, France, [37]Ambroise Paré Hospital (AP-HP), and Versailles Saint Quentin en Yvelines University, Boulogne-Billancourt, France, [38]Internal Medicine, Jean Verdier Hospital, Bondy, France, [39]Centre Hospitalier Général de Belfort, Belfort, France, [40]Epidemiology, Hotel Dieu, Paris, France, [41]Hopital Hotel Dieu, Paris Descartes University, Paris, France, [42]CHU Hautepierre, Strasbourg, France.

Background/Purpose: TNF inhibitors often represent the 1st biologic prescribed to patients with rheumatoid arthritis (RA). Approximately one third of patients fail to respond. However, therapeutic strategy in patients with insufficient response to a 1stanti-TNF is not codified.

Methods: The "Rotation of anti-TNF Or Change of class of biologic" (ROC) trial (NCT01000441) is a pragmatic open multicenter randomized controlled trial comparing the initiation of a second anti-TNF or of another class of biologic in patients with inadequate response to a first anti-TNF. Patients were randomly assigned in one of the two groups according to a computer generated randomization list using a block design with variable blocks sizes and a stratification on center. The choice of the second anti-TNF (adalimumab, certolizumab, etanercept, infliximab) or of the other biologic abatacept, rituximab or tocilizumab) remained at the appreciation of the clinician. Inclusion criteria were: RA according to ACR criteria, insufficient response to 1 anti-TNF, DAS28 equal or greater than 3.2. Primary outcome criteria was EULAR response at 6 months.

Results: Another class of biologic and a second anti-TNF were respectively initiated in 146 patients (abatacept: 35, rituximab: 41, tocilizumab: 70) and in 145 patients (adalimumab: 57; certolizumab: 23; etanercept: 53; infliximab: 8). Baseline characteristics are summarized in Table 1. EULAR response at 6 months was observed in 74.4% of patients (good: 41.8%/ moderate response: 32.6%) treated with another class of biologic versus 65.7% (27.1%/38.6%) of those treated with a 2d anti-TNF (OR 1.6 (CI95% [0.9; 3.0], p = 0.1). EULAR good/moderate responses at 6 months were

28.1/34.4%, 28.2/35.9%, 55.7/30.0%, 27.3/43.6%, 31.8/31.8%, 26.9/38.5%, and 12.5/25.0% in patients treated with abatacept, rituximab and tocilizumab, adalimumab, certolizumab, etanercept and infliximab, respectively. Low disease activity (LDA) was observed in 47.1% of patients who changed of class of biologic vs 33.6% of patients who had a 2d anti-TNF, and DAS28-ESR remission was observed in 29.0 and 20.4% of patients, respectively.

Conclusion: The ROC trial first demonstrates the efficacy of a second biologic in more than 2 thirds of TNF-IR patients. At 6 months, the proportion of responders between patients who changed of class of biologic and those who had a second anti-TNF was overall similar. EULAR good response, LDA, DAS remission appeared higher in patients who changed of class of biologic compared to those who had a second anti-TNF. Analyses of clinical efficacy of each biologic, changes in synthetic DMARDs and corticosteroids, biologic retention rate and radiographic progression at 1 year are ongoing.

Table 1. Baseline characteristics of patients

	Other class of biologic abatacept, rituximab, tocilizumab, n=146	2d anti-TNF adalimumab, certolizumab, etanercept, infliximab, n= 145
Age/female sex	58.2 (11.1)/82.2%	55.9 (13.1)/ 84.1%
Disease duration	10 [4;17.8]	10.5[4;19.2]
RF+/anti-CCP+	84.6/83.3%	77.1/80.0%
Ever smokers	18.5%	19.3%
Duration since 1st anti-TNF discontinuation, days	17[6–56]	16[7–50.5]
Concomitant corticosteroids	54.8%	51.0%
Synthetic DMARD	76.7%	76.6%
TJC	8[4;12]	6[3;10]
SJC	5[3;8]	4[3;7]
Patient's activity VAS	6.2(1.9)	6.3(1.7)
ESR	27[11;50]	22[10;46]
DAS28-ESR	5.2(1.2)	5(1.1)
HAQ	1.3(0.6)	1.3(0.6)

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Anti-Tumour Necrosis Factor Alpha Therapy Reduces Platelet Reactivity and Is Associated With Improved Insulin Sensitivity In Patients With Inflammatory Arthritis. Paul A. MacMullan[1], Anne M. Madigan[2], Laura J. Durcan[3], Karl Egan[1], Paola M. Bagaglia[2], Dermot Kenny[4] and Geraldine M. McCarthy[2]. [1]RCSI, Dublin, Ireland, [2]Mater Misericordiae University Hospital, Dublin 7, Ireland, [3]Mater Misercordiae University Hospital, Dublin 7, Ireland, [4]RCSI, Dublin 2, Ireland.

Background/Purpose: Patients with inflammatory arthritis (IA) die prematurely from cardiovascular disease (CVD). The increased CVD risk is not fully explained by traditional risk factors, but is strongly associated with inflammation and is significantly reduced in those who respond to anti-TNF therapy. Platelets also play a crucial role in the pathogenesis of atherothrombotic events. We have previously shown enhanced platelet reactivity in patients with active IA compared to those in remission. Therefore we prospectively assessed the influence of improved disease control with anti-TNF therapy on platelet function, LDL cholesterol, and insulin metabolism in patients with IA.

Methods: Patients with an established diagnosis of IA (rheumatoid, psoriatic, seronegative spondyloarthropathy) and who were due to commence anti-TNF therapy were recruited. Patients with a history of cardiovascular disease (CVD), diabetes mellitus, or receiving anti-platelet therapy were excluded. Demographic data, traditional CVD risk factors and medication use were recorded. Patients were evaluated on 2 separate occasions, before commencing an anti-TNF agent (adalimumab, etanercept, certolizumab, infliximab) and again after 4 months of treatment. Disease activity assessment was comprised of serological markers (ESR, CRP,fibrinogen), patient measures (VASDA),evaluator global assessment, and the DAS-28 score. Patients were classified as responders by reduction of at least 1 disease category in DAS-28 or >50% improvement in VASDA, where applicable. Samples of fasting LDL, glucose, and insulin were obtained. Insulin resistance was assessed using the HOMA-IR method. Platelet responses to multiple concentrations of arachidonic acid, collagen, epinephrine, thrombin receptor activating peptide (TRAP), and ADP were measured simultaneously using a modification of light transmission aggregometry, and log dose-response curves were calculated.

Results: Data from 19 patients were analysed (n=15 responders [mean DAS 28 scores pre and post-treatment, 5.1 vs 3.18, $p<0.01$], n=4 non-responders (mean DAS-28 scores pre and post-treatment, 4.51 v 4.55]). Post-treatment platelet responses to ADP were significantly reduced in responders only (EC50 1.97 vs 1.17, $p<0.001$, while in non-responders, pre and post treatment values were similar (EC50 1.89 vs 1.94). Also, there were no differences in pre/post treatment platelet responses to any of the other agonists for either group. Responders also demonstrated reduced insulin resistance (mean [95%CI] HOMA-IR 1.995 [1.4–2.58] vs 1.19 [0.86–1.52] pre and post treatment, $p<0.01$) compared to non-responders (mean HOMA-IR 1.9 vs 2.05, pre and post treatment, respectively), while mean LDL values were similar across all subjects.

Conclusion: These data are a prospective demonstration of decreased platelet reactivity and improved insulin sensitivity in patients with active IA who respond to anti-TNF therapy, and may represent potential mechanisms by which anti-TNF therapy reduces CVD events in this high risk population.

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Tofacitinib For Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Maria A. Lopez-Olivo[1], Maria E. Suarez-Almazor[2] and Mahesh Bavineni[3]. [1]University of Texas. M.D Anderson Cancer Center, Houston, TX, [2]University of Texas MD Anderson Cancer Center, Houston, TX, [3]Louisiana State University Lafayette, Lafayette, LA.

Background/Purpose: Tofacitinib was developed as a small molecule inhibitor of the Janus kinase (JAK) pathways that are central to the maintenance of the inflammatory state in rheumatoid arthritis.

Methods: To evaluate the efficacy and safety of tofacitinib, we conducted a comprehensive search in the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, CINAHL, EMBASE, Web of Science, International Pharmaceutical Abstracts (IPA) database and Biological abstracts from inception through February 2013. We included any randomized controlled trial comparing tofacitinib alone or in combination with any DMARD versus placebo or other traditional or biologic DMARDs for the treatment of patients with rheumatoid arthritis. Study selection, data collection and risk of bias assessment were performed by two independent reviewers. We performed a meta-analysis when there was more than one study reporting in the percent of patients achieving an ACR50 response, clinical remission (DAS <2.6), discontinuations due to adverse events and serious adverse events.

Results: Out of 310 citations, 10 RCTs met our inclusion criteria. Most studies compared more than two doses of tofacitinib, for our review we only evaluated the recommended dose of 5 mg twice daily. Greater percentage of patients in the tofacitinib group achieved an ACR 50 response and clinical remission compared to control (placebo + MTX) at 6–24 weeks (RR 3.4 95% CI 2.3, 5.0 and 3.1 95% CI 1.4, 6.7, respectively). There were no differences between groups in the rate of discontinuations. Serious adverse events were less likely to occur in the tofacitinib group 0.10 (95% CI 0.02, 0.55) at 12–24 weeks. When compared tofacitinib with adalimumab, similar rates of ACR50 response, discontinuations due to adverse events and serious adverse events were observed between groups.

Conclusion: Tofacitinib had better efficacy responses compared to placebo at 6–24 weeks and rates of serious adverse events or discontinuations were similar between groups. Tofacitinib had also similar effects compared to adalimumab. Tofacitinib can be considered an additional therapeutic option with different mechanisms of action to treat patients with moderate to severe disease.

Disclosure: M. A. Lopez-Olivo, None; **M. E. Suarez-Almazor**, None; **M. Bavineni**, None.

1472

Discontinuation Rates Of Tocilizumab Therapy In Rheumatoid Arthritis Patients In a Nonacademic Clinical Setting. Jaishree Manohar[1] and Charles H. Pritchard[2]. [1]Drexel University College of Medicine, Sarasota, FL, [2]Drexel University College of Medicine, Willow Grove, PA.

Background/Purpose: Tocilizumab(TCZ) and other biologics are expensive and switching between them is difficult. The goal of this retrospective chart analysis is to identify the discontinuation rate of TCZ therapy in patients who have rheumatoid arthritis and to identify characteristics of patients who are able to continue TCZ in nonacademic settings.

Methods: We conducted a review of all patients who received TCZ therapy in our office. Patients were excluded if they were part of the initial TCZ studies, had missing records, left the practice or treated for conditions other than rheumatoid arthritis. All other patients were included. The primary endpoint was the rate of discontinuation of TCZ. The secondary endpoint was to identify the differences in characteristics of patients who discontinued versus continued TCZ therapy.

Results: 104 charts were reviewed and 26 excluded. 59.6% (62/104, 95%CI 50%-69%) of all patients on TCZ therapy discontinued the medication. The most common reasons for discontinuation were ineffectiveness and adverse events. Table 1 describes the characteristics of patients who continued and those who discontinued TCZ use. A higher percentage of patients were on methotrexate in the group who continued TCZ (42.9%) as compared to the group who discontinued TCZ (24.2%, p=0.0242). Prednisone dosage after TCZ use was statistically significant between those who discontinued TCZ and those who continued TCZ, 9.10mg and 4.65mg respectively with a p value of 0.016. In patients who continued TCZ and those who discontinued TCZ HAQ scores (0.929 and 1.237, p=0.009), ESR levels (4.81 and 11.14, p=0.027) and CRP levels (0.18 and 1.15, p= 0.002) after TCZ therapy were statistically different.

Table 1. Characteristics of patients who continued and discontinued Tocilizumab

	Continued Tocilizumab (N=42)	Discontinued Tocilizumab (N=62)	P value
Female gender	40.5% (34)	59.5% (50)	0.97
Male gender	40% (8)	60% (12)	0.97
Age	58.98	60.23	0.62
Duration of disease (years)	2.87	3.09	0.164
Rheumatoid Factor positive	44.4% (16)	55.6% (20)	0.784
RheumatoidFactor negative	41.5% (22)	58.5% (31)	0.784
Anti-CCP positive	43.8% (14)	56.3% (18)	0.86
Anti-CCP negative	41.8% (23)	58.2% (32)	0.86
HAQ score prior to tocilizumab (mean)	1.045	1.281	0.126
HAQ score after tocilizumab use (mean)	0.929	1.278	0.009
ESR prior to tocilizumab use (mean)	23.91	20.03	0.433
ESR after tocilizumab use (mean)	4.81	11.14	0.027
CRP prior to tocilizumab use (mean)	1.96	5.04	0.064
CRP after tocilizumab use (mean)	0.18	1.15	0.002
Methotrexate prior to tocilizumab use (mean)	15mg	13.67mg	0.23
Methotrexate use (%) prior to tocilizumab	42.9%	24.2%	0.024
Methotrexate after tocilizumab use (mean)	14.38mg	14.11mg	0.43
Prednisone dosage prior to tocilizumab use (mean)	9.94mg	7.97mg	0.14
Prednisone dosage after tocilizumab use (mean)	4.65mg	9.10mg	0.016
Number of prior biologics used	2.21	2.45	0.26

HAQ health assessment questions, ESR erythrocyte sedimentation rate, CRP c-reactive protein

Conclusion: We found a higher rate of discontinuation compared to those reported in literature. TCZ discontinuation rates in clinical registries from Japan and Denmark were 30.4–42%[1–2]. The higher rate of discontinuation of TCZ in our study could be because of different clinical practices in nonacademic setting in the USA. We found that patients who continued TCZ therapy did show improvement in HAQ scores, ESR and CRP levels that were statistically different from patients who discontinued TCZ therapy. HAQ scores, ESR and CRP levels may be important predictors of response to TCZ therapy.

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1473

Anti-Tumor Necrosis Factor α Therapy (Etanercept) Plus Methotrexate Lowers Serum Amyloid A Levels To a Greater Extent Than Triple Oral Disease Modifying Anti-Rheumatic Drug Therapy In Early Rheumatoid Arthritis Subjects. Ilinca D. Metes[1], Douglas W. Chew[1], Aarat M. Patel[1], G.K. Balasubramani[2], S. Louis Bridges Jr.[3], Jeffrey R. Curtis[3], Stephen R. Wisniewski[2], Larry W. Moreland[1] and Marc C. Levesque[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, [3]University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Amyloidosis is often due to an underlying inflammatory disorder, such as rheumatoid arthritis (RA), with organ deposition of serum amyloid A (SAA). Oral disease modifying anti-rheumatic drugs (DMARDs) and biologics can ameliorate RA, reduce SAA levels and improve amyloidosis. Anti-tumor necrosis factor α (TNF) therapy has yielded remarkable benefits in case studies of patients with amyloidosis, and studies suggest TNF regulates SAA production. Our aim was to determine if RA patients treated with the TNF antagonist, etanercept, have greater reductions in SAA levels than RA patients treated solely with oral DMARD therapies.

Methods: Samples were analyzed from RA subjects (n = 755) enrolled in the Treatment of Early RA (TEAR) study, a randomized, double-blind trial. In the TEAR trial, early RA subjects with less than 2 years of disease duration were randomized to either combination etanercept (ETN)/methotrexate (MTX) therapy (n = 244), MTX/hydrochloroquine/sulfasalazine (triple oral) therapy (n = 132) or MTX monotherapy (n = 379). MTX monotherapy subjects with a DAS28-ESR > 3.2 after 6 months of treatment were stepped up to either ETN/MTX (n = 205) or triple oral therapy (n = 93). Serum samples and clinical data were collected when treatment was initiated and at 24, 48 and 102 week follow-up visits. The results from the TEAR trial indicated that there were equal reductions in disease activity in all arms of the study after two years of treatment. A mixed effects model was used to determine whether ETN/MTX treatment compared to triple oral therapy differentially lowered SAA levels. In addition to treatment, fixed effects in the model included time, baseline SAA levels, treatment*time and DAS28-ESR.

Results: There were no baseline differences in age, SAA level, CRP level, RF status, or disease duration between the different treatment arms of the TEAR trial. Overall, there were significant differences in SAA levels by both visit (p=0.0197) and treatment arm (p=0.0130). SAA levels were lower by an average of 66 ranks following treatment with ETN/MTX compared to triple oral therapy. Similar results were found for serum CRP levels by visit (p=0.0254) and by treatment (p < 0.0001), with an even more pronounced mean difference than SAA levels; serum CRP levels were lower by an average of 144 ranks following treatment with ETN/MTX compared to triple oral therapy.

Conclusion: RA subjects treated with ETN plus MTX had a greater reduction in SAA levels than subjects treated with oral DMARD therapy, even after correcting for disease activity. While the TEAR trial was not designed to study amyloidosis, our analysis suggests that RA patients with amyloidosis may derive greater benefit from treatment with TNF antagonists than oral DMARDs in clinical situations where both treatments lower disease activity to the same extent. Interestingly, the differential effect of ETN plus MTX compared to triple oral DMARDs on SAA levels may be less pronounced than the differential effects of ETN plus compared to triple oral DMARDs on CRP levels. The latter may be important when considering use of SAA versus CRP levels as biomarkers for disease activity during treatment with TNF antagonists.

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1474 WITHDRAWN

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Subcutaneous Delivery Of Methotrexate Is Associated With Improved Treatment Survival Compared To Oral Administration For The Initial Treatment Of Patients With Early Rheumatoid Arthritis. Glen S. Hazlewood[1], J. Carter Thorne[2], Janet E. Pope[3], Juan Xiong[4], Gilles Boire[5], Boulos Haraoui[6], Carol A. Hitchon[7], Edward C. Keystone[8], Diane Tin[2] and Vivian P. Bykerk[9]. [1]University of Calgary, Calgary, AB, [2]Southlake Regional Health Centre, Newmarket, ON, [3]St Joseph Health Care, London, ON, [4]Mount Sinai Hospital, Toronto, ON, [5]Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, [6]Institut de Rhumatologie de Montréal, Montreal, QC, [7]University of Manitoba, Winnipeg, MB, [8]Mount Sinai Hospital/University of Toronto, Toronto, ON, [9]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY.

Background/Purpose: To determine the comparative survival of initial treatment with subcutaneous (sc) methotrexate (MTX) versus oral MTX for patients with early rheumatoid arthritis (ERA) in routine care. Previous work had demonstrated sc MTX was associated with improved DAS28 scores over the first year.

Methods: Patients with early rheumatoid arthritis (ERA) initiating methotrexate therapy were included from the Canadian Early Arthritis Cohort (CATCH), a multicenter, prospective cohort study of patients with ERA. In CATCH patients are treated at the discretion of the rheumatologist and followed every 3 months over the first year according to a standardized protocol. For this study, all patients had an age >16 years, a diagnosis of RA by 2010 criteria, symptom duration < 1 year, used MTX within 3 months of study entry and were MTX-naive or minimally exposed to MTX. We compared the survival between sc and oral administration over the first year. Treatment failure was defined as either a change in route of MTX or addition/switch of any DMARDs other than glucocorticoids. A Cox-Proportional Hazards model was used to adjust for important potential confounders: age, gender, comorbidities, smoking, education, symptom duration, serological status, erosions, baseline DAS28, functional status (HAQ-DI), mean starting dose of MTX (over first 3 months of treatment) and other concurrent DMARDs or corticosteroids.

Results: 674 patients were included (418 oral MTX, 256 sc MTX); mean age 53, 72% female, mean symptom duration 5.2 months, mean baseline DAS-28 5.5. Patients treated with sc MTX were less likely to receive other DMARDs (56% vs. 71%, $p<0.01$), and had a higher mean starting dose of MTX (23 mg vs. 17 mg, $p<0.01$). Other characteristics were similar between groups. Unadjusted Kaplan-Meier curves showed significantly improved survival with sc MTX (figure 1, log-rank $p<0.001$). After adjusting for confounders the association remained significant (Hazard ratio (HR) for treatment failure: 0.58 (95%CI: 0.37–0.92, p=0.02). Older age (HR: 0.98 (95%CI: 0.97–0.99) per year of age) and the use of other DMARDs in combination (HR: 0.53 (0.35–0.81)) were also associated with improved survival. The starting dose of MTX (HR: 0.98 (0.94–1.02)) and all other covariates demonstrated no significant association.

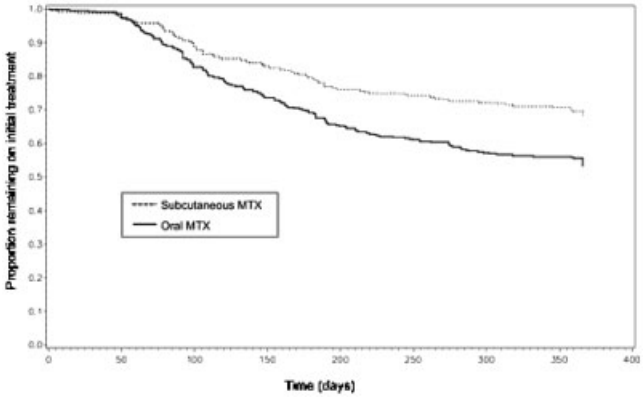

Figure 1. Kaplan-Meier curve comparing unadjusted survival of initial treatment with sc versus oral MTX for patients with early rheumatoid arthritis

Conclusion: Subcutaneous MTX is associated with improved survival over oral MTX for initial treatment in patients with early rheumatoid arthritis. This is not a randomized trial so other confounding could have occurred.

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Effectiveness Of Etanercept In Elderly Patients With Rheumatoid Arthritis: A Single Center Retrospective Study. Arthur N. Lau[1], Alpesh Shah[2], Melissa Deamude[3], Cynthia Mech[3], Robert Bensen[2] and William G. Bensen[4]. [1]McMaster University, Hamilton, ON, [2]Rheumatology Health Team, Dr. Bensen's Rheumatology Clinic, Hamilton, ON, [3]Rheumatology Health Team, St. Joseph's Hospital Hamilton, Hamilton, ON, [4]St. Joseph's Hospital and McMaster University, Hamilton, ON.

Background/Purpose: Biological drugs have dramatically improved the prognosis of rheumatoid arthritis (RA), especially in those with early disease. These patientsare often in younger age with fewer co-morbidities. Recent Canadian data suggests the highest incidence and prevalence of RA is in the 55–85 year old age group, often with associated co-morbidities, poly-pharmacy, and often longstanding disease. The purpose of this real world retrospective effectiveness study is to evaluate effectiveness, safety and durability of etanercept initiated in patients over the age of 65 (inclusive).

Methods: This study is a retrospective analysis of all elderly RA patients, started on etanercept for at least 3 months, between Jan 2004 and Dec 2011 at a single center in Hamilton, Canada. Information was collected on demographic variables, previous and ongoing DMARDs/steroids, swollen joint counts (SJC), tender joint counts (TJC), etanercept treatment details, reason for treatment discontinuation and any reported adverse event. Efficacy was evaluated by the change in swollen and tender joint counts over a period of time after etanercept treatment. Treatment effectiveness assessed by calculating the overall drug-survival.

Results: A total of 72 patients from the study period of January 2004 to December 2011 were included in the analysis. A total of 71% of the patients were female, with a mean age of 73.0 ± 5.35 years, and 73.3% were rheumatoid factor positive. 42.6% of patients had a disease duration less than 10 years. The median drug survival was 42 months, with 60% and 50% patients respectively were still on etanercept in the age group of 65–75 and more than 75 years at the end of the study period. Significant improvement in the mean SJC (*p-value* < 0.001) from baseline (8.45 ± 4.81) to treatment at 3 months (4.56 ± 3.92), at 13 months (2.56 ± 2.84) and 23 months (1.85 ± 2.06) was observed. Similar efficacy was observed in patients between age group of 65–80 and over 80 years. Patients with early as well as longstanding RA showed similar sustained improvement in disease activity over time. Concomitant use of DMARDs (methotrexate and leflunomide) reduced significantly (*p-value*< 0.05) after treatment with etanercept. Common reported adverse events were injection site reaction (2.77%), lung infection (6.94%), URTI (4.16%), UTI (8.33%) and other infections (12.5%).

Conclusion: As the demographics of RA changes, knowledge about RA care in the elderly population will be crucial. In this real world effectiveness study assessing RA patients over age 65, our results suggest that etanercept is an effective therapy despite the advanced age, and often long disease duration. There were also no unexpected safety concerns.

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A Novel Method Predicting Good Response Using Only Background Clinical Data In RA Patients Treated With Infliximab. Fumihiko Miyoshi[1], Kyoko Honne[2], Seiji Minota[3], Masato Okada[4], Noriyoshi Ogawa[5] and Toshihide Mimura[6]. [1]Saitama Medical University, Saitama, Japan, [2]Jichi Medical University, Shimotsuke, Tochigi, Japan, [3]Jichi Medical University, Shimotsuke, Tochigi, Japan, [4]St. Luke's International Hospital, Tokyo, Japan, [5]Hamamatsu University School of Medicine, Hamamatsu, Japan, [6]Research Center for Genomic Medicine, Saitama Medical University, Saitama, Japan.

Background/Purpose: Treatment using biologics is widely used for rheumatoid arthritis (RA) in these days. Prediction of the clinical response to biologics prior to the administration is important mainly because of their price, efficacy and adverse events. Several methods for predicting the response to biologics have been reported, however, it is hard to know if they are applicable for the real-world patients. The aim of the present study was to generate a novel method for predicting the clinical response to infliximab, using machine-learning algorithm with only clinical data obtained before treatment in real-world RA patients.

Methods: We obtained about 40 components of the clinical examinations from 141 patients with RA (Group-1) before infliximab (IFX) treatment at the Saitama Medical University Hospital and Jichi Medical University Hospital. Patients fulfilling the 1987 revised ACR classification criteria were assessed for overall disease activity using DAS28-CRP before IFX treatment and after 12 weeks and were divided into two groups (responder group and non-responder group) according to EULAR response criteria. These data were used for training. To determine the best machine-learning algorithm and the best clinical parameter set, 50 algorithms in the WEKA software package, which consisted of a collection of machine-learning algorithms for data mining tasks, were compared using the training data. As a criterion for selecting combinations of algorithm and parameter set, the accuracy of prediction was required over 95%. However, the predictive accuracies were lower, mainly in the 70–80%. Therefore, we developed the technique to weight each clinical parameter in the training data, and could generate the high-versatility prediction score over 90 %. Next, the selected combination methods were applied to other clinical data which were obtained from 38 patients with RA (Group-2) before IFX treatment at St. Luke's International Hospital and Hamamatsu Medical University Hospital. Finally, the best prediction method was selected from the combinations of algorithm and parameter set.

Results: The combination of Multilayer Perception algorithm (neural network) and 9 clinical parameters shows the best accuracy performance, compared to the others. This prediction method could completely reproduce (100% accuracy) the result of training data (Group-1). This method was applied to the clinical data of other hospitals (Group-2) and could predict the good or moderate response to IFX with 92% accuracy. The positive prediction value of this method was 93.5%, while the negative value was 85.7%.

Conclusion: We have developed a novel method for predicting the clinical response to IFX, using Multilayer Perceptron algorithm with 9 clinical parameters of RA patients before treatment. This method has predicted the clinical response of IFX on different groups of RA patients with 92% accuracy. We believe that our method for predicting the response to IFX in real-world RA patients has advantages over the other methods in several points including easy usability, cost-effectiveness and accuracy.

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The Prevalence Of Biological Monotherapy Among Rheumatoid Arthritis Patients In Denmark: Results From The Danish Nationwide Danbio Registry. Tanja Schjoedt Joergensen[1], Lars-Erik Kristensen[2], Tove Lorenzen[3], Jørgen Jensen[4], Lida Zanjani[5], Toke Laursen[6], Sheraz Butt[7], Mette Y. Dam[8], Hanne M. Lindegaard[9], Jakob Espesen[10], Oliver Hendricks[11], Prabhat Kumar[12], Anita Kincses[13], Line H. Larsen[14], Marlene Andersen[15], Esben K. Næser[16], Dorte V. Jensen[17], Jolanta Grydehøj[18], Barbara Unger[19], Ninna Dufour[20], Vibeke N. Sørensen[21], Sara Vildhøj[22], Inger Marie J. Hansen[23], Johnny Raun[24] and Merete Hetland[25]. [1]The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen F, Denmark, [2]Department of Clinical Sciences, Section of Rheymatology, University Hospital of Skåne, Lund, Sweden, [3]Department of Rheumatology, Region Hospital Silkeborg, Silkeborg, Denmark, [4]Department of Rheumatology, Køge, Denmark, [5]Department of Rheumatology, Glostrup, Denmark, [6]Department of Rheumatology, Gentofte, Denmark, [7]Department of Rheumatology, Frederiksberg, Denmark, [8]Department of Rheumatology, Aarhus, Denmark, [9]Department of Rheumatology, Odense, Denmark, [10]Department of Rheumatology, Vejle, Denmark, [11]Department of Rheumatology, Gråsten, Denmark, [12]Department of Rheumatology, Esbjerg, Denmark, [13]Department of Rheumatology, Copenhagen, Denmark, [14]Department of Rheumatology, Aalborg, Denmark, [15]Department of Rheumatology, Hjørring, Denmark, [16]Department of Rheumatology, Silkeborg, Denmark, [17]Department of Rheumatology, Rønne, Denmark, [18]Department of Rheumatology, Viborg, Denmark, [19]Department of Rheumatology, Horsens, Denmark, [20]Department of Rheumatology, Helsingør, Denmark, [21]Department of Rheumatology, Randers, Denmark, [22]Department of Rheumatology, Holstebro, Denmark, [23]Department of Rheumatology, Svendborg, Denmark, [24]Department of Rheumatology, Fredericia, Denmark, [25]The Danish Rheumatologic Database (DANBIO), Glostrup Hospital., Copenhagen, Denmark.

Background/Purpose: It is estimated that between 10 and 30% of rheumatoid arthritis (RA) patients are methotrexate (MTX)-intolerant and discontinuation is common in clinical practice. For RA patients' requiring biological treatment and not tolerating MTX, the options are either combination therapy with other disease-modifying antirheumatic drugs (DMARDs) or biological monotherapy. In Denmark it is mandatory to register the patients in the national database, DANBIO. The objective of the present study was to elucidate the prevalence of Danish RA patients currently on biological monotherapy.

Methods: All RA patients, treated with biologics, that were registered in DANBIO, as receiving biological treatment as monotherapy during the period May 1st 2011 to April 30th 2013 were eligible for inclusion. All files of individual patients were reviewed for inconsistence with the treatment registration in DANBIO. Results are presented as descriptive statistics, with no adjustments or statistical models applied.

Results: Twenty-one of 25 Danish rheumatology departments participated in the study. In total 4,744 RA patients were registered in DANBIO as being in biological treatment, of which 4,151 (87.5%, Figure) were treated in the participating departments. Of these, 1,000 (24.1%) were registered as receiving biological monotherapy. 225 (22.5%) of the 1000 were excluded after file review due to use of concomitant conventional DMARDs not registered in DANBIO, leaving 775 (18.7%) in verified currently biological monotherapy. Etanercept, adalimumab, tocilizumab and rituximab were the biological drugs that most often were given in monotherapy (Table).

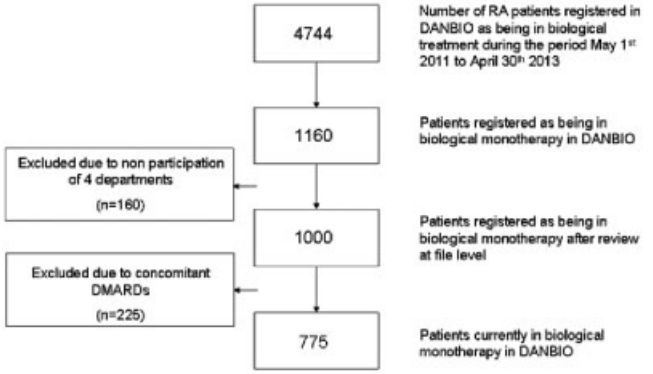

Figure 1. Flow diagram

Table. The distribution of various biologics

	Numbers treated (N=775)	% of total
Abatacept	17	2.2
Adalimumab	165	21.3
Anakinra	3	0.4
Certolizumab	26	3.4
Etanercept	284	36.6
Golimumab	21	2.7
Infliximab	48	6.2
Rituximab	92	11.9
Tocilizumab	119	15.3

Conclusion: In Denmark, 18.7% of biological treatments for RA are prescribed as monotherapy, i.e. without concomitant DMARDS. Monotherapy is prevalent across all biologics, while with a preponderance with adalimumab, etanercept, and tocilizumab, all three having the indication monotherapy.

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Relationship Between physicians' Decision To Use Concomitant Glucocorticoid and Remission During Treatment With Tocilizumab In Patients With Background Of Limited Dose Of MTX. Toshihisa Kojima[1], Nobunori Takahashi[1], Koji Funahashi[1], Shuji Asai[1], Masahiro Hanabayashi[1], Shinya Hirabara[1], Nobuyuki Asai[2] and Naoki Ishiguro[2]. [1]Nagoya University Hospital, Nagoya, Japan, [2]Nagoya Univeristy Graduate School of Medicine, Nagoya, Japan.

Background/Purpose: Now, predictive factors at baseline for the good outcome of treatment with biologics are very important not to waste time to treatment goal "remission". It is still arguable how to use glucocorticoid (GC) in treatment strategy of rheumatoid arthritis (RA). Another critical question would be whether MTX is even needed for better clinical outcomes during TCZ treatment in clinical settings with a variety of baseline characteristics, including previous use of other biologics. The aims of this study are 1) to identify the predictive factors at baseline and 2) to clarify the meaning of concomitant use of GC as well as MTX to achieve the remission in treatment with tocilizumab (TCZ), especially with background of limited dose of MTX(≤8mg/week).

Methods: This study included 240 RA patients who received TCZ in the multicenter study group (Tsurumai Biologics Communication Registry; TBCR, 2176 cases treated with biologics were registered until 2011). We explored the differences in baseline characteristics by concomitant use of GC. We also determined the predictive baseline factors for remission (DAS28) at week 52 using multivariate logistic regression analysis.

Results: In Japan, dose of MTX is limited up to 8mg/week until 2011. Baseline characteristics: median (IQR); Age 60 ys (51–67), Disease duration 8.1 ys (3.7–14.5), DAS28-ESR 5.6 (4.8–6.5), MTX dose 8mg(6–8), concomitant MTX 48.8 %, concomitant PSL 67.5 %, previous use of biologics 67.9 %. Remission rate (DAS28) at 52 weeks in our study was 42.9 %. Patients with concomitant GC at baseline had significant higher disease activity (DAS28; 5.8 vs 5.3, p=0.01) and rate of previous biologics use (74.1 % vs 55.1 %, p=0.003), and marginally higher rate of concomitant MTX (53.1% vs 39.7%, p=0.053), compared to patients with no concomitant GC, respectively. The multivariate logistic regression analysis showed predictive factors for remission in patients with high DAS28(≥5.6) at week 52 were follows: no previous use of biologics [OR3.15 (1.20–8.58)], and concomitant MTX [OR3.04(1.23–8.03)] and no concomitant GC[OR3.48 (1.36–9.29)]. Interestingly, that in the patients with low DAS28(<5.6) was only no concomitant GC [OR2.81 (1.21–6.82)]. MTX plays critical roles on RA treatment. However, approximately one-third of RA patients receive monotherapy without MTX due to MTX-induced adverse events. Therefore, the information with treatment background of limited dose of MTX should be important for clinical practice. Decision of prolonged concomitant GC was based on physicians' clinical observation during treatment before initiation of TCZ. This bias could be critical predictive factor not to achieve better outcome.

Conclusion: Remission rate at week 52 in TCZ treatment was predictable by baseline factors in daily practice. In patients with high disease activity, concomitant MTX could be important for achievement of remission with TCZ. Physicians' decision for concomitant use of GC in practice was strongly associated with not-achievement of remission during TCZ treatment with background of limited dose of MTX.

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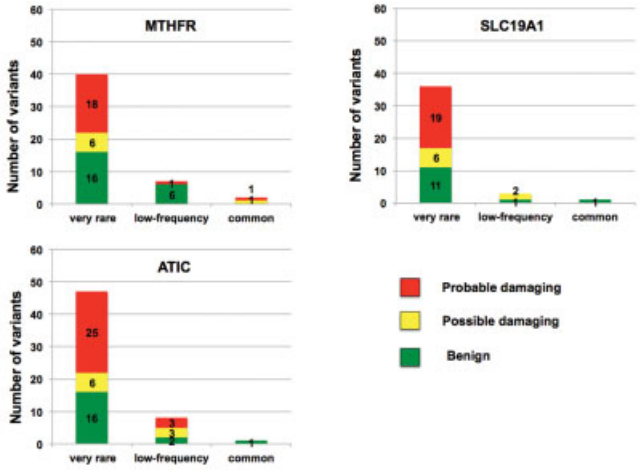
1480

Prevalance Of Rare Variants In Methotrexate Pathway Genes: Implications From The National Heart Lung Blood Institute (NHLBI) Exome Sequencing Project. Fardina Malik. Alton Memorial Hospital, Alton, IL.

Background/Purpose: Inter-individual variation to methotrexate (MTX) therapy in patients with rheumatoid arthritis (RA) is attributed at least in part to the presence of genetic variation in methotrexate pathway genes. However, the majority of the candidate-gene association studies published to date have focused on the effect of common allelic variants on drug efficacy and toxicity. Prevalence of rare variants in methotrexate pathway genes remains largely unknown.

Methods: Variants in 3 major MTX pathway genes (Methylenetetrahydrofolate reductase (MTHFR), solute carrier family 19 member 1 (SLC19A1), and 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase (ATIC)) were queried using data from NHLBI Exome sequencing project (ESP) which provides high-coverage (average>100x), high quality data for 6,503 individuals of white and black ethnicity (http://evs.gs.washington.edu/EVS/) [accessed in June, 2013, data release ESP6500SI-V2]. Variants were categorized based on their function as well as minor allele frequency: common (>5%), low frequency (0.1–5%), and very rare (<0.1%). Polyphen2 scores were utilized to assess possible impact of aminoacid substitutions on protein structure and function.

Results: Overall, 272 exomic variants were present in MTHFR, SLC19A1, and ATIC genes. Majority of these variants were missense (n=145, 53.3%), followed by coding/synonymous (n=96, 35.3%), utr (n=17, 6.3%), and splice-nonsense-frameshift (n=14, 5.1%) mutations. Only 9 (3.3%) variants were common (MAF>5%), compared to 40 variants with low frequency, and 223 variants with very rare frequency (MAF <0.1%). Overall, 143 variants (52.5%) were private mutations, that is distinct to an individual. Analysis of missense variants accurately identified known common variants of MTHFR pathway including MTHFR 677C>T, MTHFR 1298A>C, SLC19A1 80G>A, and ATIC 347 C>G SNPs. Polyphen2 scoring suggested that 62.1% of missense mutations were potentially damaging to protein structure (Figure).



Conclusion: Exome sequencing data suggests that nearly 1.6% of population carry a potentially pathologic variant in any of the 3 major MTX pathway genes. As the technology and cost of the sequencing platforms improve, exome and/or whole-genome sequencing could potentially improve outcomes in patients with RA on MTX therapy.

Disclosure: F. Malik, None;

1481

Negative Effect Of Glucocorticoids Persistence Therapy On Porosity In Rheumatoid Arthritis Patients Treated With TNFα Blockers. Hubert Marotte[1], Sara Djemouai[2], Béatrice Pallot-Prades[2], Hervé Locrelle[3] and Thierry Thomas[4]. [1]LBTO INSERM U1059 University Jean Monnet, Saint-Etienne, France, [2]University Hospital, Saint-Etienne, France, [3]INSERM U1059 and University Hospital, Hôpital Nord, Saint-Etienne, France, [4]INSERM U1059 and University Hospital, Saint-Etienne, France.

Background/Purpose: Rheumatoid arthritis is the most common joint inflammatory disease associated with an increased risk of bone fractures. The standard of therapeutic strategy is to achieve remission of the disease, which may require a combination of treatment including anti-TNFa therapy and long-term glucocorticoids (GC). While the former has already shown a beneficial effect on bone loss in RA patients, use of GC has two paradoxical effects: it can effectively reduce arthritis and inflammation-induced bone loss while it can also impair bone remodelling balance which results in bone loss. Moreover, GC-induced bone fragility may occur rapidly suggesting deleterious effects on the cortical envelope together with reduced trabecular bone volume. The objective of this study was to assess the effects of GC persistence in RA patients with TNFa blockers on cortical porosity.

Methods: In this pilot study, we selected a group of RA patients in the mid-age range, excluding those below 18 and above 65 years old, with neither concomitant bone disease nor endocrinopathy, to avoid any alteration of bone status unrelated to RA. We enrolled 6 RA patients requiring anti-TNFa therapy because of a methotrexate non-responding disease.

Porosity was assessed by High Resolution Peripheral Quantitative Computerized Tomography (HRpQCT) on radius at the diaphysis site before, 6 and 12 months after introducing anti-TNFa therapy. At the same time, bone mineral density (BMD) was assessed at the radial distal site.

Results: These 8 RA patients (4 men and 4 women) shared the usual characteristic of RA patients with a median age of 49.5 years (range: 35.8–62.4), median disease duration of 3 years (1–11), and a median DAS28 of 4.8 (3.9–6.1) with elevated biological inflammation (ESR: 25 mm/hr (9–68) and CRP at 27.1 mg/L (3–68). Rheumatoid factor and ACPA were present in 71%. Four of the 8 RA patients received GC therapy at the inclusion.

While BMD remained stable under treatment, we observed an increasing of cortical porosity between baseline and 12 month ($P<0.05$). Doses of GC therapy during the 6 last months correlated with the increasing of porosity in the same time ($P=0.042$; $R=0.653$), whereas we observe no correlation during the 6 first months ($P=0.34$; $R=0.122$).

Conclusion: Despite the small sample size of this pilot study, the strong difference between the 2 periods infers that the anti-inflammatory effects of GC participate to the beneficial effects of therapy on bone while persistence of GC on the long term contribute to bone damage with increasing cortical porosity.

Disclosure: H. Marotte, None; **S. Djemouai**, None; **B. Pallot-Prades**, None; **H. Locrelle**, None; **T. Thomas**, None.

1482

Survival Of Biological Treatment In Chronic Inflammatory Arthritis: A Preliminary Analysis Of 13 Years Of Follow Up In Clinical Practice. Gabriela Ávila[1], Sara Marsal[1], Arnald Alonso[1], Carolina Diaz[2], Estefanía Quesada-Masachs[2], María López-Lasanta[1] and Isabel Acosta[1]. [1]Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [2]University Hospital Vall d'Hebron, Barcelona, Spain.

Background/Purpose: The wide use of biological therapies (BTs) has largely modified the therapeutic approach in Chronic Inflammatory Arthritis (CIA). These relatively new drugs have different molecular structure, pharmacokinetic properties and their survival in clinical practice is not well established. The aim of the present study was to analyze the survival of different biological therapies in patients with CIA (i.e. rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA)) and to compare this survival between the three diseases in clinical practice.

Methods: The present study is a retrospective and observational study of patients with CIA treated with BT from December 1999 to December 2012, followed in a university hospital. A large number of epidemiological and clinical data were analyzed (i.e. gender, age, disease diagnosis, date of diagnosis and several variables related to the treatment). Phase I of the study was focused in the analysis of the relationship between clinical (i.e. RF, ACPA, presence of erosions and previous biological therapies) and epidemiologic variables, with the survival curves and treatment discontinuation rate (DR) in RA patients. In Phase II, we compared the survival curves between AS and PsA with RA. Multivariate analysis was used to adjust for potential confounder factors.

Statistical analysis was performed using the R statistical software. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. Cox regression analysis was used to detect the rate of discontinuation and to evaluate the effect of different covariates

Results: 300 CIA clinical records were analyzed and data from 291 CIA patients were finally included (RA n=221, AS n=39, PsA n=31). In these 291 patients, a total of 614 BTs were identified (RA n=488, AS n=69, PsA n=57). In Phase I we found that etanercept showed a significant difference in DR ($P=9.08e-5$) when it was compared with other BTs (HR= 0.63 [95% CI, 0.49–0.79). The number of previous BTs (*P*-Value = 2.24 E-0.3) and previous DMARDs (*P*-Value=3.14 E-0.6) were significant variables in DR.

When DR and survival curves were compared between the three CIA we did not find differences in the survival curves in PsA patients compared to RA patients. However, we found a highly significant difference in AS patients compared to the RA patients (*P*- Value= 5.85E-0.5), showing a lower DR (HR= 0.49 [95% CI, 0.35–0.70]).

Conclusion: In our series of patients with chronic inflammatory arthritis treated with biological therapies, we found that etanercept is the treatment with the highest survival in rheumatoid arthritis patients. We also found that ankylosing spondylitis is the chronic arthritis where biological therapies have the longest survival.

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Physician and Patient Characteristics Associated With The Decision To Treat Rheumatoid Arthritis Patients With Biologic Monotherapy In Usual Care Settings. Mariely Nieves-Plaza[1], Heather Eng[2], Ilinca D. Metes[3], Ashwini Shewede[4], Stephen R. Wisniewski[2], Ani John[4] and Marc C. Levesque[3]. [1]Univeristy of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, [3]University of Pittsburgh, Pittsburgh, PA, [4]Genentech Inc., South San Francisco, CA.

Background/Purpose: Approximately 30% of rheumatoid arthritis (RA) patients treated with a biologic, receive the biologic as monotherapy i.e. without concomitant oral disease modifying anti-rheumatic drugs (DMARDs). The purpose of this study was to compare the characteristics of RA subjects treated with biologic monotherapy versus RA subjects treated with biologic therapy combined with oral DMARDs (combo therapy).

Methods: We used data from a longitudinal registry (Rheumatoid Arthritis Comparative Effectiveness Research (RACER)) based at the University of Pittsburgh that includes 1,029 RA subjects with 5,886 usual care clinic visits. We compared the demographic, disease activity, physician and prior treatment characteristics of RA subjects who initiated a biologic therapy since RACER's inception ($n = 473$ subjects with 602 biologic initiations). Using variables with $p < 0.05$ in bivariate analyses, we developed a multivariable random-intercept logistic regression model that accounted for between subject correlations.

Results: Among 602 biologic initiations from Feb 2010 to May 2013, 31.2% of biologic therapy was monotherapy. Individual physicians ($n = 19$) varied widely with a range of prescribed monotherapy from 10% to 55%. In bivariate analyses, monotherapy compared to combo therapy was associated with longer disease duration (16.4 vs. 13.3 years, $p=0.04$), higher alanine aminotransferase (ALT) (29.4 vs. 25.5 U/L, $p = 0.02$), aspartate aminotransferase (AST) (27.1 vs. 22.7 U/L, $p = 0.02$) and alkaline phosphatase (ALP) (85.8 vs. 79.0 U/L, $p < 0.01$), and lower physician visual analogue scale (VAS) scores of global health (2.9 vs. 3.5, $p = 0.02$). As expected, no immediate prior therapy ($p = 0.003$) and previous use of monotherapy ($p = 0.001$) were associated with monotherapy use, whereas previous use of combo therapy was associated with lower use of monotherapy ($p = 0.05$). In multivariable analyses, after adjustment for AST and ALT levels and disease duration, the odds of monotherapy treatment increased 6% per unit increase in ALP level (OR [95% CI]; 1.06 [1.01, 1.11]) and decreased 40% per unit increase in physician VAS (0.60 [0.40, 0.89]).

Conclusion: Liver enzyme elevations and the physician's global health VAS were the strongest predictors of monotherapy use. The presence of liver disease is typically a contraindication to the use of methotrexate and leflunomide and this likely explains the liver enzyme association. Although liver enzyme elevations were associated with use of biologic monotherapy, other comorbidities, as measured by Charlson scores, were not associated with biologic monotherapy use. Surprisingly, our analysis did not find associations of biologic monotherapy use with composite disease activity measures (DAS28, CDAI and RAPID3) or their individual components, except for the physician's global health VAS; worse physician global health assessments were associated with more use of combo therapy. Coupled with the wide variation in physician monotherapy prescribing habits, this suggests that besides liver enzyme elevations, physician characteristics may strongly influence use of biologic monotherapy and will be the focus of future analyses.

Disclosure: M. Nieves-Plaza, Genentech and Biogen IDEC Inc., 2; **H. Eng**, Genentech and Biogen IDEC Inc., 2; **I. D. Metes**, Genentech and Biogen IDEC Inc., 2; **A. Shewede**, Genentech and Biogen IDEC Inc., 3; **S. R. Wisniewski**, Genentech and Biogen IDEC Inc., 2; **A. John**, Genentech, 3; **M. C. Levesque**, Genentech and Biogen IDEC Inc., 2, Genentech and Biogen IDEC Inc., 5.

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Treatment With The Glucagon-Like Peptide-1 Analogue Liraglutide Is Associated With Amelioration Of Disease Activity In a Prospective Cohort Study Of Patients With Inflammatory Arthritis. Catherine Sullivan[1], Gadintshware Gaoatswe[2], James Gibney[3], Marie Louise Healy[4], Michele Doran[5], David Kane[1], Donal O'Shea[2] and Ronan Mullan[1]. [1]Department of Rheumatology, Tallaght Hospital, TCD, Dublin 24, Ireland, [2]Obesity Immunology Group, Education and Research Centre, St Vincent's University Hospital, UCD, Dublin 4, Ireland, [3]Department of Endocrinology, Tallaght Hospital, TCD, Dublin 24, Ireland, [4]Department of Endocrinology, St James Hospital, TCD, Dublin 8, Ireland, [5]St James's Hospital, Dublin, Ireland.

Background/Purpose: Glucagon-like peptide-1 (GLP-1) analogues such as liraglutide, which are used for the treatment of type 2 diabetes (T2DM), mimic the action of endogenous incretin hormones through both enhancing post-prandial pancreatic glucose-dependent insulin release and promoting

early satiety. Recent evidence indicates novel anti-inflammatory effects of GLP-1 analogues, including the amelioration of TNF inflammatory responses on human endothelial cells, and reduction in monocyte TLR2, TLR4 and TNF expression following treatment with GLP-1 analogues for T2DM. We have previously shown decreased inflammatory activity of invariant Natural Killer T (iNKT), modulation of monocyte cytokine secretion and amelioration of skin psoriasis in a cohort of patients with concomitant psoriasis and T2DM. Here we investigate a role for liraglutide in the amelioration of inflammatory arthritis disease activity in a cohort of patients undergoing liraglutide treatment for concomitant T2DM.

Methods: Following institutional ethics committee approval, patients with T2DM and a concomitant diagnosis of either rheumatoid arthritis (n=11) or psoriatic arthritis (n=4) were recruited from rheumatology out patient clinics and commenced on the GLP-1 analogue, liraglutide 1.2mg s/c od. No changes were made to patient Disease Modifying Anti Rheumatic or biological drug therapies for the duration of the study. DAS28 scores, weight, HbA1C, were recorded at baseline and weeks 6, 12 and 24. DAS28 outcomes were defined by EULAR good, or moderate vs non-responders. Results expressed as Mean + SE.

Results: Patients had active arthritis (DAS28 4.38 + 0.4) and inadequate glycaemic control Hba1C (55 + 5.1) at baseline. Following liraglutide therapy 9 patients achieved DAS28 response (DAS28 = 4.2 + 0.8 pre, 2.7 + 0.5 post) vs 6 non-responders (DAS28 = 4.7 + 0.8 pre, 5.0 + 2.7 post). Significant weight loss was seen in DAS28 responders (94 + 5 pre, 90.6 + 5.2kg, p=0.008) but not non-responders (93.8 + 3.3kg pre, 95 + 2.8kg post, p = 0.79). A significant fall in HbA1C was seen in DAS28 responders (60.5 + 6.3 pre vs 45.5 + 2.1 post, p = 0.012) but not non-responders (47.1+9.5 pre vs 39.4+13, p=0.144). A significant fall in SJC28 was seen in DAS28 responders (3.3 + 0.9 pre vs 1.2 + 0.6, p = 0.027) but not non-responders (4.2 + 2.8 pre vs 4.8 + 3.2, p = 0.66). Weight loss following liraglutide was also significantly associated with achieving a DAS28 response by Chi Square analysis (p = 0.044). No significant differences were observed in baseline levels of DAS28, weight, HbA1C, SJC, ESR or CRP analysed according to subsequent DAS28 response grouping.

Conclusion: In a cohort of patients with both inflammatory arthritis and T2DM, clinical efficacy of the GLP-1 analogue liraglutide in reducing HbA1C and inducing weight loss was significantly associated with a concomitant reduction in inflammatory arthritis clinical disease activity by EULAR DAS28 response criteria. Further studies investigating common pathways of inflammation between these diseases may lead to novel therapeutic stretegies in the treatment of inflammatory arthritis.

Disclosure: C. Sullivan, None; **G. Gaoatswe**, None; **J. Gibney**, None; **M. L. Healy**, None; **M. Doran**, None; **D. Kane**, None; **D. O'Shea**, None; **R. Mullan**, None.

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RNA Transcripts From Peripheral Blood Mononuclear Cells As Predictors Of Clinical Responsiveness In Rheumatoid Arthritis Subjects Treated With Abatacept. Matthew Henkel[1], Fang Du[2], Donald M. Jones[2], Erich R Wilkerson[2], William Horne[2], Jay K. Kolls[3], Marc C. Levesque[2] and Mandy McGeachy[1]. [1]Univeristy of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA, [3]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA.

Background/Purpose: Biologics, including abatacept (CTLA4Ig), improve outcomes for many RA patients. However, approximately 40–50% of RA patients fail to respond to abatacept, and there are currently no biomarkers that predict responsiveness. Analysis of a defined panel of peripheral blood mononuclear cell (PBMC) gene transcripts is a non-invasive and technically feasible approach for routine clinical use to predict abatacept responsiveness. Advances in transcriptome profiling techniques (RNA-Seq) now allow high-throughput "deep-sequencing" of relatively small amounts of input RNA. Direct detection of transcripts by RNA-Seq offers several advantages over conventional microarrays: high sensitivity, low background signal, high dynamic range and accuracy of transcript quantification and high reproducibility.

Methods: We analyzed RNA samples derived from PBMC from 6 subjects treated with abatacept ± oral DMARDs and ± prednisone who were enrolled in the Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry at the University of Pittsburgh. Five of 6 subjects were anti-CCP positive and all 6 RA subjects had active disease at baseline (mean DAS28-CRP ± SD; 4.4 ± 0.7) despite recent TNF inhibitor therapy. Based on DAS28-CRP scores at baseline and at 6 months after abatacept initiation, 3 of the RA subjects were deemed responders (DDAS28-CRP = −1.3 ± 1.0) and 3 non-responders (DDAS28 = 0.1 ± 0.8). PBMC RNA samples from the 6 RA subjects were analyzed by RNA-Seq prior to receiving abatacept and approximately 2 months (6 to 10 weeks) after abatacept initiation. We identified genes that differed at baseline between abatacept responders and non-responders, and for responders and non-responders, genes that changed between baseline and 2 months by ≥ 1.3 fold with $p < 0.05$ (t test).

Results: There was relatively little overlap between responders and non-responders when analyzing RNA transcript changes from baseline to 2 months (< 10 transcripts). A substantially larger proportion of transcripts were significantly altered (increased or decreased) from baseline to 2 months in responders (6339 transcripts) compared to non-responders (117 transcripts). We analyzed expression of genes related to T and B cell function, analyzing baseline predictors of response (different at baseline between responder and non-responder groups) and 2 month predictors of response (different at 2 months versus baseline). We found that PBMC RNA transcripts for IgG isotypes and IL-17 were good 2-month predictors of a 6-month clinical response, but baseline levels of these transcripts did not predict efficacy. In contrast, IL6R transcripts were a good baseline predictor of efficacy but did not change from baseline to 2 months.

Conclusion: These data support the sensitivity of RNA-Seq as an assay for responses to biologic therapies in PBMC from RA patients. These RNA-Seq results, with only three subjects per group demonstrate the great potential of this technique to elucidate both mechanistic and biomarker-related pathways altered in PBMC by therapy. Future studies will validate these results in prospectively collected samples and expand these analyses to other biologic therapies.

Disclosure: M. Henkel, None; **F. Du**, None; **D. M. Jones**, Genentech and Biogen IDEC Inc., 2; **E. R. Wilkerson**, Genentech and Biogen IDEC Inc., 2; **W. Horne**, None; **J. K. Kolls**, None; **M. C. Levesque**, Genentech and Biogen IDEC Inc., 2, Genentech and Biogen IDEC Inc., 5; **M. McGeachy**, None.

ACR/ARHP Poster Session B
Sjögren's Syndrome: Pathogenesis
Monday, October 28, 2013, 8:30 AM–4:00 PM

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High Resolution HLA Analysis In Primary and Secondary Sjögren's Syndrome. Gabriela Hernandez-Molina[1], Jose Manuel Rodriguez-Perez[2], Nancy Martínez-Rodríguez[2], Guadualupe Lima[1], Gilberto Vargas-Alarcon[2] and Jorge Sanchez-Guerrero[3]. [1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubirán, Mexico City, Mexico, [2]Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico, [3]Mount Sinai Hospital, University Health Network, Toronto, ON.

Background/Purpose: The Class II HLA-DR and HLA-DQ alleles have been associated with primary Sjögren's Syndrome (SS) susceptibility. The aim of this study was to explore and compare the distribution of HLA-A, B, DRB1 and DQB1 alleles in patients with primary SS, secondary SS and patients with Connective Tissue Disease (CTD) without (w/o) SS.

Methods: Patients were drawn from a previous study where 50 pSS and 300 CTD patients were randomly selected from our total population of over 5000 patients, and tested for the presence of SS according to the AECG criteria. For the present study we included 28 patients with pSS, 30 patients with sSS and 96 patients with CTD w/o SS with available DNA samples. HLA-A, B, DRB1 and DQB1 were typed by standard PCR-sequencing based typing method. Serum samples were also examined for anti-Ro/SSA and anti-La/SSB antibodies by ELISA. We used the chi-square analysis or the Fisher's exact test and the software EPIINFO.

Results: Overall the alleles A*68:01 (a.f. 0.086 vs. a.f 0.02) and DRB1*1406 (a.f. 0.10 vs a.f. 0.008) were associated with SS (OR 4.43 95% C.I. 1.35–14.48, p= 0.007 and OR 14 95% C.I. 1.68–116, p=0.001, respectively). Patients with pSS had a significant higher prevalence of DRB1*1406 than sSS and CTD w/o SS patients (a.f 0.11, a.f 0.09 and a.f 0.008, respectively, OR 16 95% C.I. 1.59–390 p=0.001). Patients with sSS had a higher frequency of the allele A*03:36 when compared with CTD w/o SS patients (a.f. 0.067 vs. a.f 0.005, OR 13.64 95% C.I., 1.40–327, p=0.01). Then we analyzed the patients according to the positivity to anti-Ro/SSA or anti-La/SSB positivity regardless of SS status. Anti-Ro/SSA positive patients had more frequently the allele B*51:01 (a.f. 0.100 vs. a.f. 0.011, OR 10.11 95% C.I. 1–09-245.99, p=0.02) and DRB1*03:01 (a.f. 0.10 vs. a.f 0.027, OR 4.26 95% C.I. 1.01–18.89, p=0.029). The DRB1*03:01 allele was also more prevalent among patients with anti-La/SSB antibodies (a.f. 0.13 vs. a.f. 0.03, OR 4.26 95% C.I.0.93–18.70 p=0.043), as well as the A*01:01 allele (a.f. 0.20 vs. a.f. 0.05, OR 4.75 95% C.I. 1.32–16.92, p=0.003). When we

analyzed by generic HLA, we also found an association with DQB1*02 (a.f. 0.23 vs a.f. 0.06, OR 4.16 95% CI 1.32–12.93, p=0.003) and DQB1*04 (a.f. 0.43 vs a.f. 0.07, OR 4.04 95% C.I. 1.63–9.99, p=0.005) and the presence of anti-Ro/SSA antibody.

Conclusion: DRB1*1406 identified patients with both SS varieties whereas B*51:01 and DRB1*03:01 patients with anti-Ro/SSA positivity.

Disclosure: G. Hernandez-Molina, None; **J. M. Rodriguez-Perez**, None; **N. Martínez-Rodríguez**, None; **G. Lima**, None; **G. Vargas-Alarcon**, None; **J. Sanchez-Guerrero**, None.

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Gene Expression Profile According To Systemic Disease Activity In Primary Sjögren's Syndrome: Results From The Assessment Of Systemic Signs and Evolution Of Primary Sjögren's Syndrome (ASSESS) Cohort. Nawal Rahal[1], Nicolas Cagnard[2], Ghada Alsaleh[3], Raphaèle Seror[4], Corinne Miceli-Richard[5], Joelle Benessiano[6], Philippe Dieude[7], Jean Jacques Dubost[8], Anne-Laure Fauchais[9], Vincent Goeb[10], Eric Hachulla[11], Pierre-Yves Hatron[12], C. Larroche[13], Véronique le Guern[14], Jacques Morel[15], Aleth Perdriger[16], Xavier Puechal[17], Stephanie Rist[18], Alain Saraux[19], Damien Sene[20], Jean Sibilia[21], Olivier Vittecoq[22], Philippe Ravaud[23], Xavier Mariette[24] and Jacques-Eric Gottenberg[21]. [1]Strasbourg University Hospital, STRASBOURG, France, [2]Institut Cochin, 75014 Paris, France, [3]Univerity of Strasbourg, STRASBOURG, France, [4]Bicetre university hospital, LE Kremlin-Bicetre, France, [5]Université Paris-Sud 11, Bicêtre Hospital, Kremlin Bicêtre, France, [6]Rheumatology, Paris Unervisity Hospital BICHAT, Paris, France, [7]Rheumatology departement & INSERM U699, Paris Diderot university, APHP, Bichat hospital, Paris, France, [8]CHU G.-Montpied, Clermont-Ferrand, France, [9]Department of Internal Medicine A, Dupuytren Hospital, Limoges University Hospital, Limoges, France, [10]Amiens University Hospital, Amiens, France, [11]Internal Medicine, Lille CEDEX, France, [12]Claude Huriez University Hospital, Lille, France, [13]Hospital University Bobigny, bobigny, France, [14]Cochin Hospital, Paris, France, [15]Montpellier University Hospital, Montpellier, France, [16]Hôpital Sud, Rennes, France, [17]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, Paris, France, [18]Orleans Hospital, Orleans, France, [19]CHU de la Cavale Blanche, Brest Cedex, France, [20]Hopital Lariboisière, Paris, France, [21]Strasbourg University Hospital, Strasbourg, France, [22]Rouen University Hospital & Inserm905, University of Rouen, Rouen Cedex, France, [23]Hopital Hotel Dieu, Paris Descartes University, Paris, France, [24]Bicêtre University Hospital, Le Kremlin Bicetre, France.

Background/Purpose: In primary Sjögren's syndrome (pSS), the pathogenesis of systemic complications remains unclear. Only few gene expression studies were performed and concerned a limited number of patients, without any systemic complications. We therefore analyzed the gene profile of patients according to the international validated systemic disease activity score, the ESSDAI.

Methods: The ASSESS cohort, a multicenter 5-year prospective cohort, has been set up to identify predictive biomarkers of systemic complications in pSS. We selected 45 patients with high, moderate, or low systemic disease activity according to the ESSDAI. ARN extraction was performed from whole blood and was hybridized to Agilent 8×60K microarrays.

Results: 41 patients were women, median age was 61 (25–80) years and median disease duration was 7 years. Median ESSDAI was 6 (0–31), 28 patients had at least one active domain and 18 patients had 2 or more active domains of the ESSDAI. The 45 patients were separated into 3 groups according to the ESSDAI: high (H) (ESSDAI≥15, n= 16), moderate (M) (5<ESSDAI ≤14, n= 8), and low (L) (0≤ESSDAI≤5, n= 21) activity.

16 patients were treated with corticosteroids (2 in L, 3 in M, 11 in H; median dose: 5 mg/day (2–20 mg)), 14 with hydroxychloroquine (6/1/6 in L/M/H, respectively), and 6 with another immunosuppressant. Compared to patients in the L group, patients in the M group had 201 differentially expressed genes (DEG) and patients in the H group had 586 DEG. Most of the DEG belonged to various immune pathways involved in antigen presentation. The expression of BLK and EBF-1, 2 genes involved in B-cell activation and genetic predisposition to pSS, were significantly upregulated in H vs L patients. 79 interferon-regulated genes were differentially expressed, including 39 up- and 40 downregulated, in H vs L patients. In addition, the gene expression profile of distinct systemic involvements only weakly overlapped. Thus, patients with articular involvement (n=5) had 400 DEG compared to those without, patients with lung involvement (n=9) had 305 DEG and patients with peripheral nervous system involvement (PNS, n=9) had 314 DEG. Only 11 genes were common between the list of DEG in articular and lung involvement, 10 were common between lung and PNS and 2 genes were common to the 3 lists.

Conclusion: We identified different gene expression profiles according to the level of the ESDDAI and the nature of systemic involvement. Interestingly, systemic disease activity was not tightly associated with an interferon signature. This might be related to the study of peripheral blood, the effect of hydroxychloroquine and other immunosuppressants, or might suggest that systemic disease activity is not specifically driven by interferons in pSS.

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RNA-Sequencing Identifies Novel Differentially Expressed Coding and Non-Coding Transcripts In Sjögren's Syndrome. Indra Adrianto[1], Mikhail G. Dozmorov[1], Graham B. Wiley[1], John A. Ice[1], He Li[2], Jennifer A. Kelly[1], Astrid Rasmussen[1], Donald U. Stone[2], Juan-Manuel Anaya[3], Barbara M. Segal[4], Nelson L. Rhodus[5], Lida Radfar[2], John B. Harley[6], Judith A. James[7], Courtney G. Montgomery[1], R. Hal Scofield[8], Patrick M. Gaffney[1], Jonathan D. Wren[1], Kathy L. Sivils[1] and Christopher J. Lessard[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [3]School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia, [4]Hennepin County Medical Center, Minneapolis, MN, [5]University of Minnesota, Minneapolis, MN, [6]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [7]Oklahoma Medical Research Foundation and University of Oklahoma Health Sciences Center, Oklahoma City, OK, [8]US Department of Veterans Affairs Medical Center, Oklahoma City, OK.

Background/Purpose: Sjögren's syndrome (SS) is a common, clinically heterogeneous autoimmune disease characterized by exocrine gland dysfunction that involves both innate and adaptive immune responses. SS etiology is complex, with environmental, genetic, and genomic factors contributing. Of the many genetic associations reported in complex diseases, >80% map to non-protein coding DNA sequences; however, many reside in regions shown to be transcriptionally active. We used RNA-seq to identify differentially expressed (DE) protein-coding (~3% of the genome) and non-coding transcripts in 57 SS cases and 37 healthy controls.

Methods: RNA samples were isolated from whole blood and prepared for sequencing using the NuGEN Encore kit and sequenced using the Illumina HiSeq 2000. Raw FASTQ files were aligned to the human genome using TOPHAT. DE transcripts were determined using DESeq with a false discovery rate q-value of 0.05 and a fold change of >2.

Results: After the alignment, the reads were summarized for 55,076 transcripts across the human genome annotated by Ensembl. A total of 2614 DE transcripts were identified. Of the protein-coding regions, SRP14 was the most statistically DE locus in the case-control analysis (q=2.03×10E–20, FC=2.32). Two other DE protein-coding transcripts of interest were identified: UQCRB (q=1.94×10E-19, FC=2.86) and ATP5I (q=1.88×10E-18, FC=2.34). Biological functions of these genes are unclear. Among the 408 DE non-protein coding transcripts, we observed DE of a long non-coding RNA (lncRNA) at 2p25.1 (q=3.69×10E-5, FC=2.55). lncRNAs are important regulators of the human genome with diverse functions; however, most have yet to be characterized. Bioinformatics evaluation in the 2p25.1 region showed transcription factor binding sites and transcription of lncRNA sequences using immunologically relevant cell lines. To formulate functional hypotheses for the lncRNA at 2p25.1, we evaluated co-expression patterns with protein coding sequences and identified T cell activation and development as the most likely pathways influenced. When evaluating the difference in anti-Ro status, we found the FC increased to 2.85 in anti-Ro(+)patients and decreased to FC=2.24 when anti-Ro(-), indicating a possible relationship to antibody status.

Conclusion: In this SS RNA-seq study, we identified multiple candidate loci and, for the first time, DE lncRNA regions in SS. Although the function of the lncRNAs identified in this study are unknown, many others have been described to function as scaffolds, decoys, signals, and guides for various

proteins by conferring nucleotide sequence specificity not possible by motifs alone. Future studies in SS are warranted to elucidate the functional consequences of these lncRNA.

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Comparative Study Of The Transcriptome Of Minor Salivary Gland Of Sjögren's Syndrome Patients Versus Healthy Controls Based On RNA-Seq. Alessia Gallo[1], Shih-Ing Jang[2], Stamatina Danielides[2], Ana Paola Cotrim[2] and Ilias Alevizos[3]. [1]NIDCR, Bethesda, MD, [2]NIH, Bethesda, MD, [3]NIDCR/NIH #10 1N110, Bethesda, MD.

Background/Purpose: Primary Sjögren's syndrome (pSS) is a complex autoimmune disease characterized by a progressive hypofunction of the salivary and lachrymal glands. In order to better understand the pathways potentially involved in the outcome and progression of the disease, we used the latest RNA-Seq technique to characterize the transcriptome of the human salivary gland. Sjögren's syndrome patients' salivary gland and compare it to healthy controls.

Methods: Total RNA was isolated from minor salivary glands stored in RNAlater from healthy volunteers and a primary Sjögren's syndrome patient. The amount and the quality of the RNA was assessed by different system (Nanodrop, Qubit and Bioanalyzer). 2 mg of total RNA were depleted of the ribosomal RNA, fragmented, retro-transcribed and amplified according to the library construction protocols for the Ion Torrent sequencer of Life Technologies. The library quality and enrichment was assessed by Bioanalyzer and Qubit. The libraries obtained were then loaded in the Ion PI chip and ran on the Ion Torrent semiconductor sequencer, system based on the standard pyrosequencing chemistry. The data generated were then aligned to the human sequence databases (hg19) and analyzed with Partek Suite.

Results: The average size library was 160 bp, and the final number of aligned sequences to the human genome database was 2.84E+07 (Healthy Volunteers) and 1.36E+07 (pSS patients). These genome-matched reads were then analyzed with Partek Suite and a list of 43.000 mRNAs was screened in order to find expression differences. Preliminary analysis identified several genes differentially expressed in pSS versus controls. Functional analysis identified both well established in autoimmunity and novel pathways that might play a role in Sjogren's syndrome biogenesis, such as cytokine-cytokine receptor interactions. Analysis of mRNA splicing also identified significant and unexpected differences between pSS and healthy controls.

Conclusion: This is the first known effort for comparison of the transcriptome of Sjögren's Syndrome patients' salivary glands versus healthy controls. Using the latest RNA-Seq technique we were able to identify important pathway and genes differentially expressed that could shed light to the mechanism of salivary gland hypofunction in pSS.

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Discovery and Validation Of Novel Micrornas In Minor Salivary Glands Of Sjögren's Syndrome Patients. Alessia Gallo[1], Mayank Tandon[1], Stamatina Danielides[2], Ana Paola Cotrim[2] and Ilias Alevizos[3]. [1]NIDCR, Bethesda, MD, [2]NIH, Bethesda, MD, [3]NIDCR/NIH #10 1N110, Bethesda, MD.

Background/Purpose: Sjögren's syndrome is a complex autoimmune disease of the salivary gland with an unknown etiology, so a thorough characterization of the transcriptome would facilitate our understanding of the disease. We used ultra-deep sequencing of small RNAs of human salivary glands to identify and discover novel miRNA sequences that may play a role in the disease and validated the presence of those novel miRNAs in other human tissues.

Methods: Total RNA was isolated from minor salivary glands of healthy volunteers and patients with either high or low salivary flow. The sequencing was performed on the SOLiD platform (Applied Biosystems), using their Small RNA Expression Kit protocol, which selectively enriches small RNAs (< 300 bp). These sequencing reads were mapped to three different databases, and if reads matched to any of the databases were removed. The unmapped sequences were subsequently examined for other characteristics of microRNA, such as the loop formation of the premicroRNA, with the web-based algorithm miRanalyzer. The novel sequences that possessed the characteristics of microRNAs were subsequently validated with custom desgined TaqMan probes, in several human tissue (bladder, brain, lung, ovary, kidney, adipose tissue, spleen, colon, placenta, thymus, liver and testes total RNA) and a new cohort of minor salivary gland RNA from healthy volunteer and Sjögren's syndrome patients).

Results: There were 121,148 (patient – high flow), 52,568 (patient – low flow), and 174,482 (Healthy Volunteer) unique reads that matched to the human genome. These genome-matched reads generated a total of 222 predicted mature miRNAs. Following the selection process, we identified 44 candidates. Of these candidates, 16 had variable expression among the different human tissues and some of them were differentially expressed between Sjogren's syndrome and healthy control salivary glands.

Conclusion: Sequencing small RNAs in the salivary glands has not been extensively and systematically performed. Our work not only identified novel microRNAs, but also identified differentially expressed microRNAs between healthy controls and Sjögren's syndrome patients

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Histone Deacetylase 1 But Not 2 Is Highly Expressed In The Lymphocyte Foci In The Labial Glands Of Patients With Sjogren's Syndrome. Juan Guo and Wei Zhou. Peking University First Hospital, Beijing, China.

Background/Purpose: Sjogren's syndrome (SS) is an autoimmune disease with abnormally infiltrating lymphocytes in exocrine glands expressing Th1 cytokines and increased incidence of lymphoma. Histone deacetylases (HDACs) regulate the state of acetylation of histones and many other intracellular proteins, and their role in the pathogenesis of malignancies has been established. HDAC1 and 2 may also affect the balance of Th1 and Th2 immune response. The aim of this study is to investigate whether HDAC1 and 2 are abnormally expressed in the salivary glands of SS.

Methods: Labial gland biopsies were performed in 55 patients, among them 25 were diagnosed as SS. The expression of HDAC1 and 2 were investigated by immunohistochemistry and immunofluorescence (IF). The HDACs expression level was semi-quatatvely analyzed by counting the number of positively stained cells in randomly chosen microscopic fields. The difference of HDAC expression level in different locus was analyzed by t test.

Results: HDAC1 was highly expressed in the infiltrating lymphocytic foci in the labial glands of patients with SS. The proportion of HDAC1+ cells in lymphocytic foci was higher than that in interstitium (0.66 ± 0.24 vs 0.26 ± 0.08, $p<0.01$). Concerning the expression of HDAC1 in lymphocytes outside the foci, the number of HDAC1+ cells in the interstitium of labial glands was higher in SS patients than that in non-SS patients (21 ± 11/hpf vs 11 ± 6/hpf, $p<0.05$). IF showed that HDAC1 was mainly expressed in CD4+ T cells. HDAC2 was not detected in the labial glands comparing positive control staining of tonsil tissue. The expression level of HDAC1 was not associated with the IgG level and presence of autoantibodies in patients with SS.

Conclusion: The expression of HDAC1 is elevated in the lymphocytic foci in SS and may be involved in its pathogenesis. Thus, inhibiting HDAC1 specifically is a potential therapeutic strategy of SS that is worthy of further investigation.

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Increased Expression Of Interleukin 33 In Sera and Salivary Gland From Patients With Sjögren Syndrome. Seung Min Jung[1], Young Sun Suh[1], Jung Hee Koh[1], Jae Ho Lee[1], Jennifer Lee[1], Soo Young Lee[2], Ji Hyeon Ju[1], Kyung-Su Park[1], Dae Chul Jeong[1], Sung Hwan Park[1] and Seung-Ki Kwok[1]. [1]The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea, [2]The Catholic University of Korea, Incheon St. Mary's Hospital, Incheon, South Korea.

Background/Purpose: Interleukin 33 (IL-33), a member of IL-1 superfamily, exerts pro-inflammatory effect by binding with ST2 expressed on many cell types. Recently, the association of IL-33 with autoimmune disease has been increasingly reported. The aim of this study is to identify the

expression of IL-33 and ST2 in sera and salivary gland tissues from patients with Sjögren syndrome (SS).

Methods: Serum level of IL-33 and expression of IL-33 in salivary gland were assessed in patients with and without SS by ELISA and immunohistochemistry, respectively. Difference in expression of ST2 between patients with and without SS was compared by mRNA level and ST2 positive cells in peripheral blood mononuclear cell (PBMC) from each group. The source of IL-33 in salivary gland of patients with SS was investigated using confocal microscopy system after staining with cytokeratin antibody, CD31 antibody and IL-33 antibody. Additionally, we examined mRNA expression of IL-33 from salivary gland cell line (human head and neck squamous cell carcinoma A253 cell) after stimulation with pro-inflammatory cytokines.

Results: Serum IL-33 level was significantly higher in SS group than that of control group ($p=0.004$). Immunohistochemistry of salivary gland also revealed increased expression of IL-33 in SS group. However, the level of ST2 mRNA in PBMC was lower in SS group than control group, although statistically not significant ($p=0.093$). Consistently, the proportion of ST2 positive cells in PBMC was smaller in SS patients ($p=0.004$). We demonstrated the expression of IL-33 in epithelial and endothelial cells from salivary gland of patients with SS. The expression of IL-33 mRNA in A253 cell was considerably increased after stimulation with interferon gamma.

Conclusion: Our result shows that IL-33 is involved in the pathogenesis of SS. Further research would suggest a new therapeutic approach associated with IL-33/ST2 pathway in SS.

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Lesional Intereukin-21 Expression Correlates With Functional Germinal Center Formation and T Follicular Helper Cell Infiltration In The Salivary Glands Of Sjogren's Syndrome. William Murray-Brown[1], Cristina Croia[1], Nurhan Sutcliffe[2], Anwar Tappuni[3], Costantino Pitzalis[1] and Michele Bombardieri[1]. [1]William Harvey Research Institute, QMUL, London, United Kingdom, [2]Queen Mary University of London, London, United Kingdom, [3]Institute of Dentistry, Queen Mary University of London, London, United Kingdom.

Background/Purpose: IL-21 is a pro-inflammatory cytokine that plays a key role in the activation and differentiation of B cells. B cells infiltrate the salivary glands (SG) of Sjögren's syndrome (SS), an autoimmune disease characterized by immune infiltration in the lacrimal and salivary glands leading to exocrine dysfunction. In SS SG, B cells are often organized as functional ectopic germinal centers (GC) and are pivotal in SS pathogenesis. Follicular helper T cells (Tfh) abundantly express IL-21 and contribute to GC B cell affinity maturation via induction of AID, somatic hypermutation and class switching. Here we aimed to investigate IL-21 expression in SS SG and its correlation with key regulators of GC responses and markers of B cell differentiation. Finally, we aimed to assess the relationship between IL-21, infiltrating Tfh cells and the development of functional ectopic GC.

Methods: IL-21 and IL-21R mRNA expression was assessed by Taqman PCR in 28 labial SG of patients with SS and 37 with non-specific chronic sialadenitis (NSCS). Expression levels were correlated with genes regulating ectopic GC formation such as CXCL13 and Ltb and B cell function such as BAFF, AID, Pax5 and Blimp1. In addition, GC formation in the SG was assessed by IHC for B/T cell segregation and follicular dendritic cell (FDC) networks. Finally, Tfh cells infiltration in the SG was assessed by IF for CD3/CD45RO/ICOS and PD1.

Results: SG of SS patients displayed higher expression of IL-21 and IL-21R mRNA compared to NSCS (mean fold increase$\pm$SEM 38 ± 12 vs 5 ± 4, $p=0.02$ for IL-21 and 59 ± 13 vs 12 ± 2, $p=0.01$). In SS, IL-21 mRNA strictly correlated with the levels of CXCL13 (Spearman's $r=0.697$, $p<0.0001$) and Ltb ($r=0.478$, $p<0.001$) which were closely associated with the formation of CD21L+ ectopic GC. Furthermore, IL-21 expression was associated with functional B cell activation as shown by its correlation with AID ($r=0.540$, $p<0.0001$) and Pax5 ($r=0.456$, $p<0.002$). Finally, a subset of CD45RO/ICOS/PD1+ T cells highly resembling Tfh were observed in the presence of ectopic GC characterised by FDC networks but not in FDC- or NSCS SG.

Conclusion: Here we show that IL-21 expression is significantly increased in the SG of SS patients and strongly correlates with ectopic GC formation, functional B cell activation and accumulation of Tfh. These data strongly implicate IL-21 and Tfh cells in the development and maintenance of functional ectopic GC in the SG and could represent novel therapeutic targets in SS.

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DNA Methylation In Six Cell and Tissue Types In Sjögren's Syndrome Reveals Distinct Patterns Across Samples and Clustering Based On Disease Status. Alice Baker[1], Diana Quach[1], Hong L. Quach[1], Emon Elboudwarej[1], Lisa F. Barcellos[1] and Lindsey A. Criswell[2]. [1]University of California, Berkeley, Berkeley, CA, [2]University of California, San Francisco, Rosalind Russell Medical Research Center for Arthritis, San Francisco, CA.

Background/Purpose: Sjögren's Syndrome (SS) is a chronic, multisystem autoimmune disease characterized by progressive destruction of the exocrine glands, with subsequent mucosal and conjunctival dryness. Increasing evidence supports a role for DNA methylation status in autoimmune disease risk and severity. Our goal was to characterize methylation profiles in SS subjects and healthy controls across multiple cell and tissue types to identify similarities and differences relevant to disease status and pathogenesis.

Methods: We generated genome-wide DNA methylation profiles using Illumina HumanMethylation450 BeadChips in minor salivary gland biopsy tissue, fresh and banked peripheral blood mononuclear cells (PBMC), CD14+ monocytes, CD19+ B cells, and CD4+ T cells in ten participants (five cases and five controls) from the Sjögren's International Collaborative Clinical Alliance (SICCA; http://sicca.ucsf.edu/; N01 DE32636) repository. Sorting of freshly collected blood samples was performed using MACS® technology. DNA yields for all cell and tissue types were high; all samples were background subtracted and normalized with beta-mixture quantile dilation (BMIQ). After removing SNPS and sites with beta-value detection p-values <0.05, 473,864 CpGs remained in our final data set.

Results: Methylation of individual CpG sites was stable across the six cell types for ~240,000 CpGs (variance<0.001); however, variance was less than 0.0001 for ~94,000 CpGs and exceeded 0.10 for ~900 CpGs. Mean methylation was calculated within each cell and tissue type for all CpGs in the final data set. Mean methylation was moderately to highly correlated between all cell and tissue types in cases, controls, and in a combined data set (r^2: 0.82 – 0.99) with the lowest correlation between salivary gland tissue and CD14+ monocytes and the highest correlation between fresh and banked PBMCs. Methylation levels within 16 putative SS genes were similar between cases and controls. However, median levels of methylation in individual CpGs within *IL10* and *TNFSF4* were 12% and 26% decreased in CD14+ T cells, and CD19+ B cells in cases compared to controls, respectively. Median levels of methylation in individual CpGs within *TNFAIP3* and *KLHL24* were hyper-methylated by 10%, 27%, and 19% in CD4+ T cells, CD19+ B cells and gland tissue biopsy samples in cases compared to controls, respectively. Data visualization of methylation profiles using Multi-Dimensional Scaling applied to several different subsets of CpG revealed distinct separation between cell types in addition to separation based on SS case status. The greatest separation by case status was visible in CD19+ B cells and salivary gland tissue samples.

Conclusion: Our results emphasize the cell and tissue specificity of DNA methylation in addition to differences in methylation based on case status for some cell types. Additional research, including studies of gene expression for regions associated with disease risk or severity, will be required to fully define the role of DNA methylation in SS.

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Endosomal TLR Triggering Of B Cells In Sjögren's Syndrome Induces Increased Plasma Cells Differentiation, Ig Class Switch and Immunoglobulin Production. Marie Wahren-Herlenius[1], Susanna Brauner[1], Marika Kvarnström[1], Lasse Folkersen[1], Sabrina Görgen[1], Christina Trollmo[2], Vivianne Malmström[3] and Gunnel Nordmark[4]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Karolinska Institutet, Stochkolm, Sweden, [3]Rheumatology unit, Karolinska University Hospital, Karolinska Institutet, STockholm, Sweden, Stockholm, Sweden, [4]Uppsala University, Uppsala, Sweden.

Background/Purpose: Patients with primary Sjögren's syndrome have B cell disturbances resulting in hypergammaglobulinemia and autoantibody

production. Most patients are not treated by immunomodulatory drugs, enabling studies of an unmanipulated human autoreactive immune system. In this study we used the novel approach of employing vaccination as a tool to analyze immune responses *in vivo*.

Methods: Patients with Sjögren's syndrome receiving no treatment and healthy controls were vaccinated twice against the H1N1 influenza, and monitored by multiple sampling.

Results: Surprisingly, patients developed higher titers of IgG H1N1 antibodies, increased total IgG and increased autoantibody levels in response to vaccination. In addition, an expansion of CD138+ plasmablasts was observed, and up-regulation of several B cell promoting cytokines, including IL-10, IL-6 and IL-7. To dissect the B cell hyperreactivity, immunoglobulin class switch was induced *in vitro* in CD19+IgD+ B cells from patients and controls. Significantly more plasmablasts and higher titers of IgM and IgG were observed in TLR9 stimulated Sjögren-patient derived cultures in vitro. Similar results were obtained by TLR7 stimulation, but not by a-CD40 or BAFF that induce class switch through other pathways. The importance of the endosomal TLR pathway in plasma cell differentiation and immunoglobulin production was further demonstrated by analyzing B cells from patients treated with the drug chloroquine, which targets the endosome. In these patients, no differences were observed in class switch and plasma cell differentiation compared to healthy individuals. This observation was further confirmed by *in vitro* treatment of IgD+ B cells with chloroquine which significantly inhibited class switch and plasma cell differentiation.

Conclusion: In conclusion, we demonstrate for the first time that B cell activation via endosomal TLRs leads to enhanced plasma cell differentiation and class-switch in patients with Sjögren's syndrome, explaining the induction of hypergammaglobulinemia in Sjögren's syndrome patients.

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Hypofunction In Intact Cell Lobules Reflect Salivary Flow Rates In Sjogren's Patients. Leyla Y Teos[1], Bill Swaim[2], Ana Paola Cotrim[1], Margaret Grisius[1], Lolita Bebris[3], Indu Ambudkar[4], Gabor G. Illei[5] and Ilias Alevizos[6]. [1]NIH, Bethesda, MD, [2]NIH/NIDCR, Bethesda, MD, [3]NIDCR/NIH, Bethesda, MD, [4]NIDCR, Bethesda, MD, [5]MedImmune, LLC, Gaithersburg, MD, [6]NIDCR/NIH #10 1N110, Bethesda, MD.

Background/Purpose: Neurotransmitter stimulation of fluid secretion in salivary glands is regulated by increases in intracellular calcium concentration. The increase in cytosolic calcium triggers ion channel activities, leading to the secretion of fluid. The latter can be detected as a decrease in cell volume. Patients with primary Sjögren's syndrome (pSS) display dry mouth conditions due to low salivary flow. We hypothesized that alterations in calcium signaling in acinar cells could account for the salivary gland dysfunction seen in pSS.

Methods: The standard salivary gland cell preparation used for studying acinar function is obtained by enzymatic digestion of the gland. This procedure results in considerable loss of tissue and alterations in cellular integrity. Moreover, healthy cells could be selected in the digestion process. We have therefore developed a non-enzymatically dispersed tissue preparation in combination with confocal microscopy, to assess the functional status of minor salivary glands from Sjögren's syndrome patients. We measured agonist-stimulated cytosolic calcium changes as well as cell volume changes by loading the salivary gland cluster-preparations with the calcium indicator, Fluo-2 AM, or cell-volume indicator, calcein. In addition we have examined the morphological characteristics of the glands.

Results: Cell clusters showed well preserved acinar and ductal morphology and displayed dose-dependent response to stimulation by carbachol, both in terms of cytosolic calcium, where intracellular calcium increase and cell volume decreases. Cells from patients with poor flow displayed attenuation of agonist-stimulated cytosolic calcium and volume changes. Additionally, decreases in cell volume predicted salivary flow rates.

Conclusion: We have developed a reproducible system to utilize non-enzymatically dispersed tissue preparations and examine with confocal microscopy the functional status of minor salivary glands. This system allows the exploration of mechanism(s) underlying the decrease in salivary gland function in each individual patient pertaining to the decrease in calcium mobilization. More specifically, this method will allow for the determination of whether the defect is at the level of intracellular calcium release or calcium entry and will also allow for the screening of therapeutic compounds in a personalized way. First, by identifying the secretory deficiencies of each individual pSS patient, and second testing which compounds might be more effective in treating salivary gland hypofunction.

Disclosure: L. Y. Teos, None; **B. Swaim**, None; **A. P. Cotrim**, None; **M. Grisius**, None; **L. Bebris**, None; **I. Ambudkar**, None; **G. G. Illei**, AstraZeneca, 1, MedImmune, 3; **I. Alevizos**, None.

1499

Detection Of $CD4^+CD25^{low}GITR^+$ T Lymphocytes In Sjogren's Syndrome-Interstitial Lung Disease. Wu Zhenbiao[1] and Chen Lina[2]. [1]First Affiliated Hospital, Fourth Military Medical University, Xi'An, China, [2]First Affiliated Hospital, Fourth Military Medical University, Xi'an, China.

Background/Purpose: $CD4^+CD25^{low}GITR^+$ T lymphocytes expressing FoxP3 and showing regulatory function have been recently described in healthy donors (HD). The objective of this study was to determine whether $CD4^+CD25^{low}GITR^+$ T lymphocytes are detected in peripheral blood (PB) and broncho-alveolar lavage (BAL), to investigate their in patients with interstitial lung disease (ILD) secondary to primary Sjogren's syndrome (pSS).

Methods: $CD4^+CD25^{low}GITR^+$ cells circulating in PB and BAL of patients with pSS-ILD were isolated by MACS technique, and their phenotype was studied by flow cytometry and real-time PCR, and their function was studied by in vitro co-culture. $CD4^+CD25^{low}GITR^+$ cells infiltrating salivary glands (SGs) were revealed by immunohistochemistry.

Results: Nineteen patients with idiopathic pulmonary fibrosis (IPF) and 13 patents with pSS-ILD were enrolled in the study. Ten healthy donors were concluded in the study, too. Results indicated that conventional $CD4^+CD25^{high}$ regulatory T cells (Tregs) are decreased, whereas $CD4^+CD25^{low}GITR^+$ cells are expanded in the PB of pSS-ILD as compared with HD and IPF. Phenotypic analysis demonstrated that $CD4^+CD25^{low}GITR^+$ cells display Treg markers, including FoxP3, TGF-β and IL-10, and functional experiments demonstrated that they exert a strong inhibitory activity against autologous effector cells. The number of $CD4^+CD25^{low}GITR^+$ cells infiltrating in the SG were positively correlated with the inflammatory infiltrating of $CD4^+CD25^{low}GITR^+$ cells in BAL.

Conclusion: The present data demonstrate that $CD4^+CD25^{low}GITR^+$ cells are detectable in PB and BAL of pSS-ILD patients. These cells, displaying Treg phenotype and function, are present in SG inflamed tissues and are in accordance with that infiltrating in BAL.

Disclosure: W. Zhenbiao, None; **C. Lina**, None.

1500

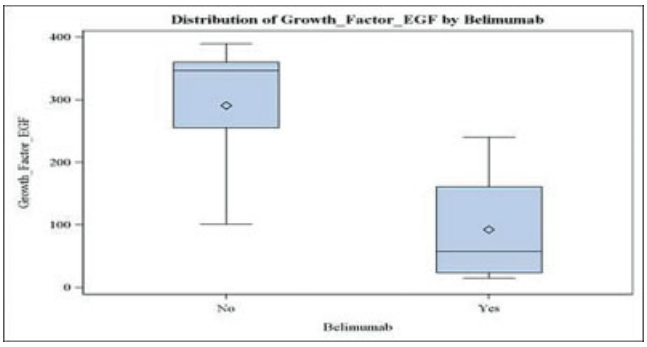
Use Of B Lymphocyte Stimulator Inhibitor Belimumab May Be Associated With a Decrease In the Serum Concentration Of Endothelial Growth Factor In Patients With Primary Sjögren's Syndrome. Slavica Bobic[1], Sabeeda Kadavath[1], Linda Gerber[2], Ekaterini Zapantis[1] and Petros V. Efthimiou[3]. [1]Lincoln Medical and Mental Health Center, New York, NY, [2]Weill Cornell Medical College, New York, NY, [3]LM&MHC/Weill Cornell MC, New York, NY.

Background/Purpose: Primary Sjögren's Syndrome (pSjS) is a systemic autoimmune inflammatory disease that primarily affects the lacrimal and salivary glands and is associated with B cell hyper-reactivity and elevated serum concentrations of Blys. Belimumab is approved for the treatment of Systemic Lupus Erythematosus, where B cell mediated inflammation is commonly seen. In this retrospective study, we examined the off-label use of belimumab in a small cohort of pSjS with systemic manifestations. We analyzed clinical endpoints based on questionnaires and patient reported outcomes (PROs) as well as multiple serum biomarkers, individually measured as part of a multi-biomarker disease activity assay (MBDA), used predominantly in RA. Vectra DA is a cumulative score based on the serum concentrations of 12 serum proteins (biomarkers); although the score has been validated for use in RA, several components of the test have been implicated in the pathogenesis of SjS.

Methods: A retrospective chart review study was conducted at a teaching hospital and nine patients diagnosed with pSjS were identified, as defined by the American-European group consensus criteria. The patient's age ranged from 26 to 73 (mean: 51). All patients studied (1 male, 8 females) had confirmatory minor salivary gland biopsy (focal score>1), 3/9 (33%) were African American and 6/9 (67%) Hispanic. Of the 9 patients studied, 4 were also treated with monthly belimumab infusions (10 mg/kg), as an add-on

treatment to address predominantly extra-glandular manifestation, such as arthritis and fatigue, for approximately 60 weeks. Vectra was done for all patients and clinical improvement was assessed by RAPID-3 and FACIT-F scores during the course of the treatment. Individual biomarker concentrations were compared in the 2 groups using the Wilcoxon Exact test.

Results: The results for EGF biomarker suggest that there is a statistically significant difference between the underlying distributions of the EGF scores of control group and the EGF scores of Belimumab group ($p = 0.03$, $r = -0.71$). The patients on Belimumab had numerically lower serum concentrations of VCAM-1, VEGF-a, IL-6, MMP-3, YKL-40, Leptin, Resistin, SSA, and CRP biomarkers and higher concentrations of the TNF-RI and MMP-1 biomarkers compared to the control group, although the difference did not reach statistical significance. Vectra-DA scores for the belimumab group (mean: 38) and the control group (mean: 31.5) were similar in both groups and were not affected by treatment. Clinical endpoints, such as the RAPID-3 and FACIT scores, did not show a difference between the two groups.



Conclusion: In our pSjS cohort, treatment with Belimumab was associated with significantly lower EGF concentrations, albeit no apparent extra-glandular clinical improvement. Controlled studies and development of more specific disease activity measures are needed.

Disclosure: S. Bobic, None; **S. Kadavath**, None; **L. Gerber**, None; **E. Zapantis**, None; **P. V. Efthimiou**, None.

1501

Umbilical Cord Mesenchymal Stem Cells Inhibit The Generation Of T Follicular Helper Cell In Sjogren's Syndrome. Rui Liu, Min Zhou, Dinglei Su, Xia Li and Lingyun Sun. Department of Rheumatology and Immunology, the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China.

Background/Purpose: The immune suppressive properties of mesenchymal stem cells (MSC) have garnered increasing attention over past decades. Human umbilical cord-derived MSC (UC-MSC) share similar immunosuppressive functions as bone marrow-derived MSC (BM-MSC). Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by extra-glandular abnormalities and overproduction of antibodies. Previous studies showed that MSC transplantation were effective both in an animal model and SS patients. However, the underlining mechanism remains largely unknown. The aim of this study is to investigate whether UC-MSC might suppress the generation of T follicular helper (Tfh) cells in SS.

Methods: The percentages of CXCR5+PD-1+CD4+ cells were analyzed by flow cytometry in peripheral blood mononuclear cells (PBMC) from SS patients and healthy controls. The correlation between frequencies of Tfh cells and levels of total IgG, anti-Ro/SSA and anti-La/SSB in SS patients were assessed. PBMC of SS patients in the presence or absence of PHA were cultured with UC-MSC supernatant or UC-MSC at a ratio of 1 to 1, 1 to 10 or 1 to 100 in a cell-to-cell contact or transwell system for 3 days. CD4+ naïve T cells were isolated from SS PBMC and then co-cultured with or without UC-MSC under Tfh-skewing condition for 2 days (for RT-PCR) or 4 days (for FACS). CD4+ T cells were isolated from SS PBMC and labeled with carboxyfluorescein diacetate succinimidyl ester (CFSE) and then co-cultured with or without UC-MSC in the presence of anti-CD3/CD28 for 4 days. The percentages of CXCR5+PD-1+CD4+ T cells were tested by flow cytometry.

Results: We showed that the circulating percentage of CXCR5+PD-1+CD4+ cells in SS patients were significantly higher than in healthy controls, and positively correlated with levels of anti-La/SSB but not with total IgG or anti-Ro/SSA. UC-MSC inhibited the generation of Tfh cells in PHA-stimulated PBMC dose-dependently in vitro. The differentiation and proliferation of Tfh cells were blocked by UC-MSC significantly and this suppression was mediated by UC-MSC-secreted soluble factors. RT-PCR showed that UC-MSC suppression of Tfh cells was dependent on indoleamine 2, 3-dioxygenase (IDO). Furthermore, UC-MSC supernatant was also able to inhibit the generation of Tfh cells in SS.

Conclusion: These results suggest that Tfh cells may play a pathogenic role in SS. UC-MSC inhibition of Tfh cells may be a potential mechanism for the therapeutic effect of MSC in SS.

Disclosure: R. Liu, None; **M. Zhou**, None; **D. Su**, None; **X. Li**, None; **L. Sun**, None.

1502

Antibodies To Anti-Type -3 Muscarinic Acetylcholine Receptor Are Highly Prevalent To Rabbits Immunized With 4-Hydroxy-2-Noneal-Modified and 60-Kda Ro. Valerie Harris[1], Biji T. Kurien[2], R. Hal Scofield[3], Timothy Gross[3] and Mary Girton[3]. [1]University of Oklahoma Health Science Center, Oklahoma City, OK, [2]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: In Sjörgen's Syndrome, an autoimmune disease, the lacrimal and salivary glands are the primarily affected glands. Previous studies have proposed autoantibodies that target type-3 muscarinic acetylcholine receptors (M3R) found in salivary and lacrimal glands as a clinical marker for SS. In this study, we hypothesize that rabbits and mice immunized with 4-hydroxy-2-noneal (HNE)-modified or unmodified 60-kDa Ro will have increased levels of circulating anti-M3R and anti-Ro antibodies mirroring some of the symptoms of Sjörgen's Syndrome.

Methods: In the first experiment, two rabbits were immunized multiple times with 500μg of 10mM of HNE-modified Ro60 and two rabbits were immunized with 500μg unmodified Ro60. In the second experiment, 50 mice, ten mice from five different strains (SJL/J, DBA, BALB/c, C57BL/6, and PL/J) were immunized subsequent times with 50μg of Ro60 peptide. In the third experiment, fifty mice were in immunized with unmodified Ro60, or low (.4mM), moderate (2mM), or high (10mM)-HNE modified Ro60. ELISA analysis was used to detect the presence of antibodies specific to Ro60, HNE-modified Ro60, and the second extracellular loop (amino acids 213–228) or the third extracellular loop (amino acids 514–527) of the type-3 muscarinic acetylcholine receptor using the serial bleeds from the immunized rabbits and mice.

Results: Immunization with HNE-modified Ro60 or unmodified Ro60 abrogates tolerance to autoimmunity. Rabbits immunized with unmodified Ro60 showed in an induction of antibodies to Ro60 and the second loop (213–228) of M3R, but not 514–527. Conversely, rabbits immunized with HNE-modified Ro60 had suppressed levels of antibodies to either variant of the M3R peptide, but showed a rapid response after immunization with increased levels of anti-Ro60 and anti-HNE Ro60 antibodies. The five strains of mice immunized with HNE-modified Ro60 or unmodified Ro60, as well as, the mice immunized with various concentrations of HNE-modified Ro60 had negligible levels of antibodies directed toward M3R, but both experimental groups showed an induction in anti-Ro60 antibodies.

Conclusion: We previously published data showing that the rabbits and mice immunized with unmodified or HNE-modified Ro60 developed anti-Ro antibodies, as commonly seen in circulation of SS patients. Add to that, this data which shows increasing levels of anti-M3R antibodies in rabbits immunized with Ro60, but not mice. Taken together this data suggests that second extracellular loop of the type-3 muscarinic receptor is a target in the lacrimal and salivary glands during SS autoimmunity progression in rabbits.

Disclosure: V. Harris, None; **B. T. Kurien**, None; **R. H. Scofield**, None; **T. Gross**, None; **M. Girton**, None.

1503

The Suppressive Ability Of Altered Peptide Ligands To M3R Reactive T Cells In M3R Induced Autoimmune Sialadenitis. Hiromitsu Asashima[1], Hiroto Tsuboi[2], Naomi Matsuo[1], Chihiro Hagiya[1], Tomoya Hirota[2], Mana Iizuka[1], Yuya Kondo[2], Isao Matsumoto[2] and Takayuki Sumida[2]. [1]Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [2]University of Tsukuba, Tsukuba, Japan.

Background/Purpose: Previous studies have shown that Rag1$^{-/-}$ mice transferred with splenocytes of M3 muscarinic acetylcoline receptor

$(M3R)^{-/-}$ mice immunized with M3R peptides mixture (three N-terminal regions; N1, N2, N3, and three extracellular loops; 1st, 2nd, 3rd) ($M3R^{-/-}$<Mix>→$Rag1^{-/-}$) developed sialadenitis like Sjögren's syndrome (M3R induced autoimmune sialadenitis; MIS). Besides, altered peptide ligands (APLs), the peptides with substitutions in amino acid residues at T-cell receptor contact sites, are reported to regulate the activation of T cells. To develop antigen-specific therapy, we tried to clarify the T cell epitopes of M3R reactive T cells in MIS and also to evaluate the antagonistic APLs.

Methods: 1) Splenocytes of $M3R^{-/-}$ mice immunized with M3R peptides mixture were cultured with each M3R peptide. The cytokines (IFN-g, IL-17, and Il-4) production was measured by ELISA. Similarly, the splenocytes of $M3R^{-/-}$ mice immunized with each N1 and 1st peptide, which was the candidate for the T cell epitopes, and the combination of N1 and 1st peptides were cultured and evaluated.

2) The splenocytes of $M3R^{-/-}$ mice, immunized with N1 alone, 1st alone, the combination of N1 and 1st peptides, or PBS as control were transferred into $Rag1^{-/-}$ mice (each $M3R^{-/-}$<N1>→$Rag1^{-/-}$, $M3R^{-/-}$<1st>→$Rag1^{-/-}$, $M3R^{-/-}$<N1+1st>→$Rag1^{-/-}$, and $M3R^{-/-}$<PBS>→$Rag1^{-/-}$). On day 45 after transfer, the salivary glands of $Rag1^{-/-}$ mice were pathologically examined.

3) APLs of each N1 and 1s peptide were designed.

4) CD4+ and CD11c+ cells were isolated from $M3R^{-/-}$ mice immunized with each N1 and 1st peptide. Each APL was loaded to CD11c+ cells pre-cultured with each suboptimal concentration (N1: 1.5 μM, 1st: 4.5 μM) of N1 and 1st peptide. Afterward, CD4+ T cells were added and cytokines (IFN-g and IL-17) production was measured by ELISA.

Results: 1) Splenocytes immunized with M3R peptide mixture produced IL-17 and IFN-g against N1 and 1st peptide. IL-4 production could not be detected. Splenocytes immunized with N1 and 1st peptide produced IL-17 and IFN-g, but not IL-4, against each corresponding peptide.

2) $M3R^{-/-}$<N1>→$Rag1^{-/-}$, $M3R^{-/-}$<1st>→$Rag1^{-/-}$, and $M3R^{-/-}$<N1+1st>→$Rag1^{-/-}$ developed sialoadenitis. The majority of infiltrating cells in salivary glands were $CD4^+$ T cells, only few with $CD8^+$ T cells and $B220^+$ B cells. The focus scores of these mice (1.0±0.3 in $M3R^{-/-}$<N1+1st>→$Rag1^{-/-}$, 1.3±0.3 in $M3R^{-/-}$<N1>→$Rag1^{-/-}$, and 0.7±0.3 in $M3R^{-/-}$<1st>→$Rag1^{-/-}$) were significantly higher than that of control mice (0.1±0.2 in $M3R^{-/-}$<PBS>→$Rag1^{-/-}$) ($p<0.05$).

3) Seven APLs of N1 peptide (N1-APL 1–7) and eight APLs of 1st peptide (1st-APL 1–8) were designed.

4) N1-APL5 (AA15 N→T), N1-APL6 (AA15 N→C) and N1-APL7 (AA15 N→S) suppressed the production of IFN-g (N1-APL5 38.8±11.6 pg/mL, N1-APL6 54.9±16.5 pg/mL, N1-APL7 38.0±15.7 pg/mL, control 363.6±65.1 pg/mL). 1st-APL8 (AA140 A→M) suppressed both IL-17 and IFN-g production (IL-17: 1st-APL8 403.4±14.1 pg/mL, control 720.3±49.0 pg/mL. IFN-g: 1st-APL8 185.4±1.6 pg/mL, control 268.8±94.8 pg/mL).

Conclusion: The major T cell epitopes in MIS might be both N1 terminal region and 1st extracellular loops of M3R. N1-APL5, 6, 7 and 1st-APL8 were the candidate for antagonistic APLs, which might have a possibility to suppress MIS *in vivo*.

Disclosure: H. Asashima, None; **H. Tsuboi**, None; **N. Matsuo**, None; **C. Hagiya**, None; **T. Hirota**, None; **M. Iizuka**, None; **Y. Kondo**, None; **I. Matsumoto**, None; **T. Sumida**, None.

1504

Anti-Inflammation Effect Of Peroxisome Proliferator-Activated Receptor-γ (PPAR-γ) In Non-Obese Diabetic Mice With Sjogren's Syndrome. Bei Xu[1] and Xiaomei Li[2]. [1]The third Affiliated Hospital of Anhui Medical University, The First Hospital of Hefei, Hefei, China, [2]Anhui Medical University Affiliated Provincial Hospital, Hefei, Anhui, China.

Background/Purpose: To investigate the anti-inflammation effect of peroxisome proliferator-activated receptor-γ (PPAR-γ) in non-obese diabetic mice (NOD mice) with sjogren's syndrome

Methods: Twenty 8-weeks-old female NOD mice were randomly divided into 2 groups. rosiglitazone and normal saline were administered in PPAR-γ group and control group respectively. At the age of 12 weeks and 15 weeks, we killed one mouse in PPAR-γ group and control group respectively, and the others were sacrificed at the age of 17 weeks. Blood were obtained by cardiac puncture, and salivary glands were resected. The histopathological change was examined by H&E staining. The level of IL-1β, IL-4, IL-6 and TNF-α in serum were measured by ELISA. Real-time PCR was used to evaluate the mRNA expression level of IL-1β, IL-4, IL-6 and TNF-α in MSG

Results: Compared with the control group, the mice in PPAR-γ group showed that: At histopathological change was significantly ameliorated; At the age of 17 weeks, IL-6 [(25.86±7.32) pg/ml vs (37.41±11.34) pg/ml] and TNF-α [(56.88±22.19) pg/ml vs (78.61±20.76) pg/ml] were expressed significantly lower and IL-4 [(25.76±12.65) pg/ml vs (12.11±3.70) pg/ml] was expressed significantly higher in serum ($P<0.05$); The expression of TNF-α was significantly decreased and the expression of IL-4 was significantly increased in MSG ($P<0.05$).

Conclusion: PPAR-γ can ameliorate Sjogren's syndrome on NOD mice effectively. The mechanism may be related to reduce Th1 cytokines, and promote the direction of Th1/Th2 balance into Th2.

Disclosure: B. Xu, None; **X. Li**, None.

ACR/ARHP Poster Session B
Spondylarthropathies and Psoriatic Arthritis: Clinical Aspects and Treatment II
Monday, October 28, 2013, 8:30 AM–4:00 PM

1505

Evaluation Of a Case Ascertainment Tool For Ankylosing Spondylitis and Axial Spondylarthritis Among All Referrals To General Rheumatology Clinics. Eswar Krishnan[1], Michael H. Weisman[2], Atul A. Deodhar[3], Linjun Chen[1] and Lianne S. Gensler[4]. [1]Stanford University, Palo Alto, CA, [2]Cedars-Sinai Medical Center, Los Angeles, CA, [3]Oregon Health & Science University, Portland, OR, [4]University of California, San Francisco, San Francisco, CA.

Background/Purpose: Several strategies for distinguishing Ankylosing Spondylitis (AS) and Axial Spondylarthritis (axSpA) from other conditions have been proposed but have only been studied in the context of chronic back pain. Prior strategies have not been evaluated in the context of an unselected rheumatologic population where the prevalence is lower and/or in older age groups. This study evaluates a psychometrically distinct patient questionnaire in an unselected population that includes patients without back pain and those with fibromyalgia.

Methods: The study comprised of 490 consecutive, unselected new patients referred to 4 academic rheumatology outpatient clinics in the period 2011–12. Patients completed a questionnaire prior to clinical evaluation. Inability to obtain informed consent in the English language was the only exclusion criterion. Patients were followed for 6 months from the baseline visit. Protocol specified gold standard for AS and axSpA diagnosis was the rheumatologist assessment (blinded to the results of the questionnaire) based on the history, physical examination, radiographs, and laboratory testing and appropriate work up. Questionnaire summary scores were converted to Z-scores.

Results: The mean (range) age of the study population was 48 (18–91) years; 74% were women. Of the 490 patients 102 tested positive by the questionnaire using original cut off values and 22 received a rheumatologist diagnosis of AS (prevalence 4.4%) and 36 were diagnosed with axSpA (prevalence =7.4%). Results of ROC analyses are shown in Table 1. The areas under the curve for AS and axSpA for patients with and without back pain were 0.74, 0.67, 0.84,0.75 respectively

Table 1. Receiver Operator Curve Analysis for patients with AS and axSpA with and without back pain

	AS		Axial SpA	
Z-score cut off	**Sen**	**Spec**	**Sen**	**Spec**
All patients				
>=−1	95	18	86	17
>=0	86	41	72	41
>=1	36	91	39	90
Patients with Back pain				
>=−1	95	31	89	31
>=0	85	70	69	71
>=1	40	91	38	91

Sen: Sensitivity (%); Spec:Specificity (%).

Conclusion: With adjustments to the score cut-offs, the evaluated patient questionnaire may be used either as a sensitive screening tool or as a specific diagnostic aid in assessing AS and axSpA in non-selected patient populations.

Disclosure: E. Krishnan, UCB Pharmaceuticals, 2; **M. H. Weisman**, UCB Pharmaceuticals, 9; **A. A. Deodhar**, UCB Pharmaceuticals, 9; **L. Chen**, UCB Pharmaceuticals, 9; **L. S. Gensler**, UCB Pharmaceuticals, 9.

1506

Total Hip Replacement Outcomes in Ankylosing Spondylitis. Susan M. Goodman, Rebecca Zhu, Wei-Ti Huang, Mark P. Figgie, Michael Alexiades and Lisa A. Mandl. Hospital for Special Surgery, New York, NY.

Background/Purpose: Historically, outcomes for total hip replacement (THR) in ankylosing spondylitis (AS) patients were poor, but contemporary outcomes are not well described. We analyzed two-year THR outcomes in a cohort of AS patients compared with osteoarthritis (OA) controls.

Methods: A case- control study was performed using data from a high volume single institution THR registry. AS were identified by ICD-9 code and confirmed by chart review. AS cases were matched 4:1 by age, bilateral, primary or revision procedure, and date of surgery, and availability of 2 year data, after excluding potential controls with ICD-9 codes for other rheumatic disease or fracture. Self-report quality of life and administrative data were obtained pre-operatively and at 2-years. Pain, function, and quality of life scores were compared between groups using standard statistical methods.

Results: 30 eligible AS THR cases were identified between 5/2007 and 10/2010: 21 primary, 2 bilateral, and 7 revisions. Mean age was 52.7 years, (SD 16); more AS were male (80% vs 45%; p-value$<$0.001). AS had worse baseline ASA class (ASA Class$\geq$3: 40% vs 9%; p-value$<$0.001). 2-year self-report data were available on 63% of AS cases. AS had worse pre-operative WOMAC pain (46.1 vs 54.8; p-value=0.05) and WOMAC function (43.5 vs 53.7; p-value=0.04) compared to OA controls but had similar excellent outcomes at 2 years: WOMAC pain (90.6 vs 92.8; p-value=0.5) and WOMAC function (85.4 vs 90.4; p-value=0.18). AS were as likely as controls to have a clinically meaningful improvement (Δ WOMAC $>$10) in pain (87% vs 93%; p-value=0.4) and function (100% vs 90%; p-value=0.2) and were no more likely to have a poor outcome (WOMAC $<$ 60) for pain (89% vs 93%; p-value=0.4) or function (89% vs 93%; p-value=0.5). AS without 2-year data had significantly worse pre-op WOMAC function than AS with data (30.9 vs 44.1; p-value=0.04). However, neither AS nor OA without 2-year data had clinically meaningful differences in pre-op pain scores compared with those with data (AS:45 vs 40; p-value=0.31; OA:53.6 vs. 50.5; p-value$<$0.001). AS SF-12 was lower at baseline (31.3 vs. 36.1; p-value=0.01) and remained clinically significantly worse at 2 years (41.5 vs 50.2; p-value$<$0.001). Scores on the HSS Expectations Survey were high for both AS and OA (77.5 vs 83.3; p-value=0.24), and both were very/somewhat satisfied with their 2-year outcomes (100% vs 96%; p-value=0.4).

Table 1. Total Hip Replacement

	AS (n=30)	OA (n=132)	P-value
Age (SD)	52.7 (16.2)	53.2 (14.6)	0.88
Male, n (%)	24 (80%)	59 (45%)	**<0.001**
WOMAC Baseline Pain (SD)	46.1 (19.3)	54.8 (19.3)	**0.05**
WOMAC 2 year Pain (SD)	90.6 (14.1)	92.8 (12.9)	0.5
WOMAC Baseline Function (SD)	43.5 (22.4)	53.7 (20.4)	**0.04**
WOMAC 2 year Function (SD)	85.4 (17.1)	90.4 (14.4)	0.18
Δ WOMAC $>$ 10, Pain, n (%)	13 (87%)	110 (93%)	0.36
Δ WOMAC $>$ 10, Function, n (%)	13 (100%)	96 (90%)	0.23
Poor outcome @ 2 year, WOMAC Pain $\leq$60, n (%)	2 (11%)	7 (6%)	0.4
Poor outcome @ 2 year, WOMAC Function $\leq$60, n (%)	2 (11%)	8 (7%)	0.52
SF-12 PCS Baseline (SD)	31.3 (8.4)	36.1 (8.1)	**0.015**
SF-12 PCS 2 year (SD)	41.5 (11.0)	50.2 (9.8)	**<0.001**
Expectation Score (SD)	77.5 (17.7)	83.3 (18.1)	0.24
Baseline ASA class, n (%)			**<0.001**
Class 1 or 2	18 (60%)	119 (91%)	
Class 3	12 (40%)	12 (9%)	
Satisfaction at 2 years, Overall, n (%)			
Very Satisfied	14 (78%)	102 (86%)	0.42
Somewhat Satisfied	4 (22%)	12 (10%)	
Neither Satisfied nor Dissatisfied	0 (0%)	2 (2%)	
Somewhat Dissatisfied	0 (0%)	0 (0%)	
Very Dissatisfied	0 (0%)	3 (3%)	

Conclusion: AS patients achieve similar levels of pain relief at 2-years compared with OA controls. These data may overestimate 2-year function in AS, but the majority have significant improvement. Despite having worse pre-operative health status than matched OA controls, THR is an effective treatment for end stage hip arthritis in AS. However, lower 2-year SF-12 PCS scores suggest that some limitations due to health status persist. These data can be used to ensure AS patients have accurate expectations of THR.

Disclosure: S. M. Goodman, None; **R. Zhu**, None; **W. T. Huang**, None; **M. P. Figgie**, Mekanika, 1, Ethicon, 2; **M. Alexiades**, None; **L. A. Mandl**, Boehringer Ingelheim, 2.

1507

Infection Risk in Ankylosing Spondylitis: Results From a Longitudinal Observational Cohort. Dinny Wallis[1], Arane Thavaneswaran[2], Nigil Haroon[1], Renise Ayearst[2] and Robert D. Inman[1]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Long term data on infection risk in ankylosing spondylitis (AS) are sparse and derived mainly from RCTs. Anti-TNF therapy is increasingly used in AS, with infection being the most important adverse event. In rheumatoid arthritis (RA), serious infections are common adverse events of anti-TNF therapy with an incidence of 4–10 per 100 patient-years (pys). We aimed to investigate the frequency of infections in AS and to identify factors predisposing to infection.

Methods: Data were extracted from a longitudinal observational database for patients meeting Assessment of SpondyloArthritis international Society (ASAS) criteria for axial SpA. Infection rates were calculated and multivariate analysis using a GEE model was performed to investigate the association of independent variables with infection.

Results: 440 patients (73% male) were included in the analysis. 259 infections (23 serious, defined as requiring IV antibiotics or hospitalization) occurred during 1712 pys of follow-up. 80% were bacterial and 15% were viral. The most common site of infection was lung, followed by skin, genitourinary tract, upper respiratory tract, sinus and gastrointestinal tract. Ninety percent of infections were treated with antibiotics, of which 10% required intravenous antibiotics.

The overall rate [95% CI] of any infection was 15 [13, 17]/100 pys and the serious infection rate was 1.3 [0.9, 2.0]/100 pys. Of the 264 patients prescribed a biologic drug during a total follow up time of 684 pys on biologic therapy, 127 infections (10 serious) were recorded in 101 patients. The rate of any infection while on a biologic drug was 19 [16, 22]/100 pys and the serious infection rate was 1.5 [0.7, 3.0]/100 pys. Of the 186 patients never prescribed a biologic drug during a total follow up time of 651 pys, 91 infections (12 serious) were recorded in 71 patients. The rate of any infection was 14 [11, 17]/100 pys and the serious infection rate was 1.8 [1.0, 3.0]/100 pys. There was no significant difference in the rates for patients on biologic drugs compared to patients never on biologic drugs for any infection (p=0.78) or serious infection (p=0.19).

In the univariate analysis, DMARD use and glucocorticoid use were associated with an increased risk of infection. In the multivariate analysis, only DMARD use remained significant (OR 1.76 [1.12, 2.76], p$<$0.01). However, the number of patients on DMARDs was small (n=31). Biologic use, age, disease duration, smoking status, BASFI, BASDAI, comorbidity score and hospitalizations were not associated with an increased risk of infection.

Conclusion: Biologic therapy in this longitudinal AS cohort was not associated with an increased risk of infection, while DMARD use appeared to confer risk of infection. However, most infections were not serious and the serious infection rate was much lower than previously reported in RA. Our findings represent a "real-world" experience which includes AS patients with comorbidities which often exclude them from RCTs. The apparent lower rate of infection in patients with AS compared to RA may reflect several factors: the younger age and lower frequency of comorbidities in AS, differing immunogenetic mechanisms in the respective diseases, and differences in treatment.

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1508

How Well Are The Assessment Of Spondyloarthritis International Society (ASAS)/Outcome Measures In Rheumatology (OMERACT) Core Outcome Sets For Ankylosing Spondylitis Implemented In Randomized Clinical Trials? A Systematic Literature Review. Wilson Bautista-Molano[1], Victoria Navarro-Compán[1], Robert Landewé[2] and Désirée van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Academic Medical Center, Amsterdam, Netherlands.

Background/Purpose: The Assessment of SpondyloArthritis international Society (ASAS) has selected a core set of variables to include as

standardized endpoints in clinical trials and clinical practice. These core sets received endorsement by OMERACT and specific measurement instruments to assess each of these domains have been chosen. The implementation of the ASAS/OMERACT core sets, though, has so far not been evaluated. The purpose of this systematic literature review, therefore, was to compare the usage of domains and instruments of the core-sets before and after the original publication.

To investigate how well the ASAS/OMERACT core sets for the outcome of ankylosing spondylitis (AS) have been implemented in randomized controlled trials (RCTs) testing pharmacological and non-pharmacological interventions.

Methods: A systematic literature search was performed in electronic databases looking for RCTs in patients with AS. Domains of outcome, and instruments belonging to them, for disease controlling antirheumatic therapy (DC-ART) and symptom modifying antirheumatic drugs (SMARD) were extracted.

Results are reported for clinical trials published before (control trials) in comparison to those published 2 years after the publication of the core set (1 April 2001, implementation trials).

Results: One hundred eight articles reporting results from 91 RCTs, and together including 11.174 patients, fulfilled the selection criteria for this project, and were included in the analysis. Forty-seven RCTs were considered 'control trials' and 44 were considered 'implementation trials'. NSAID and conventional non-biological DMARD therapies were more often tested in the 'control'—than in the 'implementation trials'. Biological DMARDs and physical therapy were more often tested in the 'implementation trials'. The domains 'physical function', 'pain', 'stiffness', 'peripheral joint/entheses', 'acute phase reactants' and 'fatigue', as well as the instruments 'BASFI', 'BASMI', 'CRP' and 'spine radiograph' were more frequently addressed in the 'implementation trials' (Table 1).

Table 1. Usage of ASAS/OMERACT DCART Core Domains and instruments in trials evaluating interventions with DMARD, biologic or corticosteroids

Assessment	Control trials before 2001 (%)	Implementation trials after 2001 (%)	p value
Physical function	**41.7**	**100**	**<0.001**
BASFI	8.3	100	<0.001
Dougados FI	33.3	4.5	0.02
HAQ	8.3	13.6	0.6
Pain	**91.7**	**100**	**0.2**
Night	33.3	45.5	0.5
Global	91.7	100	0.2
Spinal mobility	**91.7**	**86.4**	**0.6**
BASMI	0	54.5	0.001
Spinal stiffness	**91.7**	**100**	**0.2**
Patient global assessment	**66.7**	**81.8**	**0.3**
Peripheral joint/entheses	**33.3**	**100**	**<0.001**
Joint count	33.3	45.5	0.5
MASES	0	9.1	0.3
Berlin	0	4.5	0.4
Acute phase reactants	**83.3**	**95.5**	**0.2**
CRP	58.3	90.9	0.03
ESR	83.3	59.1	0.2
Spine radiograph	**0**	**27.3**	**0.046**
mSASSS	0	18.2	0.1
BASRI	0	13.6	0.2
Fatigue	**0**	**100**	**<0.001**

Conclusion: This systematic literature review suggests that the implementation of ASAS/OMERACT core set has been partly successful. The definition and dissemination of the core set measures for clinical trials in AS has indeed resulted in an improved usage of the endorsed domains and instruments.

References:

1. van der Heijde D. *J Rheumatol* 1999;26:951–4
2. Sieper J. *Ann Rheum Dis* 2009;68 (Suppl 2):ii1–44

Disclosure: W. Bautista-Molano, None; **V. Navarro-Compán**, None; **R. Landewé**, None; **D. van der Heijde**, None.

1509

Immunogenicity, Adalimumab Levels and Clinical Response In Ankylosing Spondylitis Patients During 24 Weeks Of Follow-Up. Eva L. Kneepkens[1], James C. Wei[2], Michael T. Nurmohamed[1], Kai-Jieh Yeo[2], CY Chen[2], Irene E. van der Horst-Bruinsma[3], Desiree van der Kleij[4], Theo Rispens[5], Gertjan Wolbink[5] and Charlotte L. M. Krieckaert[1]. [1]Jan van Breemen Research Institute Reade, Amsterdam, Netherlands, [2]Chung Shan Med Univ Hospital, Taichung, Taiwan, [3]VU University Medical Center, Amsterdam, Netherlands, [4]Sanquin Diagnostic Services, Amsterdam, Netherlands, [5]Sanquin Research, Amsterdam, Netherlands.

Background/Purpose: Immunogenicity influences adalimumab levels and therefore clinical response in patients with rheumatic diseases.

Objectives: To study the relation between clinical response, adalimumab levels and anti-drug antibodies (ADA) in ankylosing spondylitis (AS) patients.

Methods: Prospective observational cohort study of 115 consecutive AS patients treated with adalimumab in the Netherlands (n=85) and Taiwan (n=30), monitored during a maximum of 24 weeks. Adalimumab levels and ADA titres were determined retrospectively using an enzyme linked immunosorbent assay (ELISA) and an Antigen Binding Test (ABT), respectively, designed by Sanquin Research, Amsterdam. Response to adalimumab treatment was defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) response (50% improvement or an absolute improvement of 2 points on a BASDAI, scale 0–10) and disease activity was measured using the AS Disease Activity Score, including CRP (ASDAS).

Results: Of 115 patients 78 (67.8%) were male and 95 (82.6%) were HLA-B27 positive. At baseline median BASDAI (IQR) was 6.4 (4.5–7.6) and mean ASDAS (SD) was 3.5 (1.0). After 24 weeks of follow-up 49 (42.6%) patients were BASDAI responders (last observation carried forward). Mean ASDAS (SD) for responders was 1.5 (1.0) vs. 2.6 (1.0) for non-responders ($p<0.001$). Nine patients dropped out: 8 patients due to treatment failure or adverse events and 1 due to loss of follow-up. Thirty-one (27.0%) patients had detectable ADA. Median ESR levels (mm/hour) were significantly different between patients with or without ADA (respectively, 35.5(13.0–52.5) vs.19.0 (7.0–34.0), $p=0.008$). After 24 weeks, median adalimumab level (mg/L) (IQR) was significantly higher for ADA negative than for ADA positive patients (12,7 (8.2–18.0) vs. 1.2 (0.0–2.0), $p<0.001$). At 24 weeks the percentage of detectable ADA was higher in patients from Taiwan 12 (40.0%) vs. Dutch patients, 19 (22.4%) ($p=0.06$). General estimate equation analysis demonstrated a significant association between adalimumab levels and ASDAS ($p=0.02$; RC −1.1; 95% CI −2.0 to −0.2). For BASDAI response no significant association with adalimumab levels was found. Eleven (9.6%) patients had no detectable adalimumab levels and high detectable ADA titres (>100 AU/mL). In these patients CRP and ESR remained elevated, although BASDAI decreased during 24 weeks of follow-up.

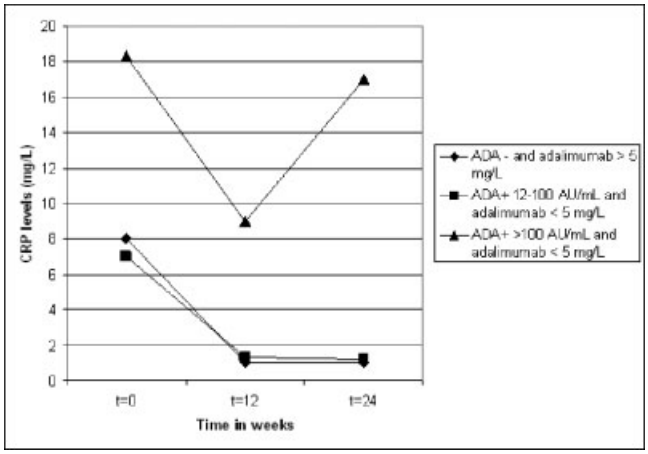

Fig 1. Median CRP levels (mg/L) for AS patients divided in 3 groups: no detectable ADA *titres with normal drug levels (> 5 mg/L); intermediate detectable ADA titres with low drug levels (< 5 mg/L) and high detectable ADA titres with low drug levels (< 5 mg/L) during 24 weeks of follow-up.*

Conclusion: Adalimumab levels are related to clinical response in AS patients and are influenced by ADA detectable with an ABT. Therefore therapeutic drug monitoring should be investigated further as a possible tool to optimise treatment.

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1510

Disease Activity In Male Smokers Has A >10-Fold Amplified Effect On Radiographic Damage In Comparison With Female NON-Smokers In Ankylosing Spondylitis. Sofia Ramiro[1], A.M. van Tubergen[2], Robert Landewé[3], Carmen Stolwijk[2], Maxime Dougados[4], Filip Van den Bosch[5] and Désirée van der Heijde[6]. [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Maastricht University Medical Center, Maastricht, Netherlands, [3]Academic Medical Center Amsterdam & Atrium Medical Center, Heerlen, Netherlands, [4]Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France, [5]Gent University Hospital, Gent, Belgium, [6]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: We have shown that disease activity has an effect on radiographic progression over the long-term and that gender and symptom duration are effect modifiers. Smoking has been shown to predict radiographic progression. We sought to investigate whether smoking influenced this longitudinal relationship between disease activity and radiographic damage

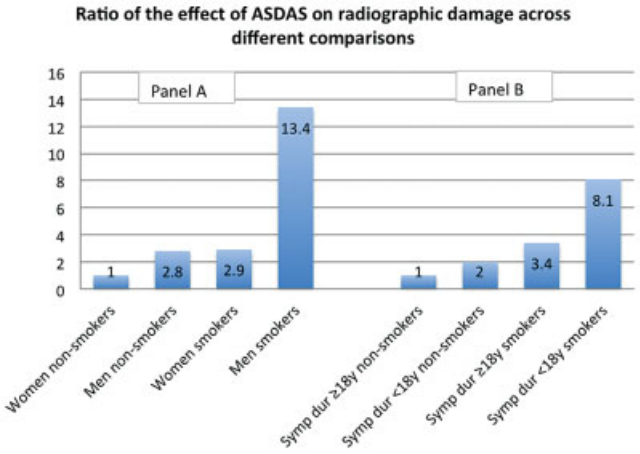
Methods: Patients from the Outcome in AS International Study (OASIS) were followed-up for 12 years, with biannual clinical and radiographic assessments. Two readers independently scored the x-rays according to the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) and scores were averaged. Disease activity was assessed by the ASDAS-CRP. The relationship between ASDAS and radiographic damage was investigated using generalized estimating equations, with auto-regressive (i.e. adjusted for the 2-year previous mSASSS) models with a 2-year time-lag. Interactions were tested with baseline smoking status and if significant, analyses were repeated in strata.

Results: A total of 127 patients were included (71% males, mean (SD) age 41(12) years, mean symptom duration 18(11) years and 82% HLA-B27 positive). Smoking status modified the relationship between disease activity and radiographic damage significantly ($p<0.001$), and this effect extended to other strata: males ($p=0.002$) and patients with shorter symptom duration (<18y) ($p=0.009$); Overall, an increase in one ASDAS-unit led to an increase in 0.72 mSASSS-units per 2 years. In smokers, this value reached 1.94 mSASSS-units and in male smokers 2.15 mSASSS-units (Table). Comparing the magnitude of the effect of ASDAS on mSASSS in smokers vs non-smokers, smokers had a 5.5 fold amplified effect, whereas male smokers had a 13.4 fold amplified effect compared to female non-smokers. Smokers with short symptom duration had a 8.1-fold amplified effect compared to non-smokers with long symptom duration (Figure).

Table. Longitudinal relationship between ASDAS and radiographic damage in different strata

Stratification for	Effect analyzed	Multivariable regression models (auto-regressive and time-lagged) μ(95%CI)*
Smoking status	– ASDAS in non-smokers (n = 78)	0.35 (0.04; 0.65)
	– ASDAS in smokers (n = 49)	1.94 (1.00; 2.87)
Smoking status & gender	– ASDAS in women, non-smokers (n = 29)	0.16 (−0.13; 0.44)
	– ASDAS in women, smokers (n = 9)	0.47 (−0.12; 1.06)
	– ASDAS in men, non-smokers (n = 49)	0.44 (0.02; 0.86)
	– ASDAS in men, smokers (n = 40)	2.15 (1.01; 3.30)
Smoking status & symptom duration	– ASDAS in symptom duration <18y, non-smokers (n = 39)	0.52 (0.24; 0.80)
	– ASDAS in symptom duration <18y, smokers (n = 31)	2.11 (0.86; 3.36)
	– ASDAS in symptom duration >=18y, non-smokers (n = 35)	0.26 (−0.18; 0.70)
	– ASDAS in symptom duration >=18y, smokers (n = 13)	0.88 (0.15; 1.62)

* Results refer to different multivariable models. De μ indicates the progression in mSASSS per unit increase in ASDAS



Conclusion: Smoking amplifies the effect of disease activity on radiographic damage (5-fold). This effect is further amplified in male smokers (13.4-fold) in comparison with female non-smokers.

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1511

What Impairs Balance In Ankylosing Spondylitis? Posture Or Disease Activity? Osman Hakan Gunduz, Emel Ece Ozcan, Esra Giray and Ilker Yagci. Marmara University School of Medicine, Istanbul, Turkey.

Background/Purpose: To compare ankylosing spondylitis (AS) patients and healthy individuals in terms of posture and balance and to identify the factors affecting balance among patients with AS.

Methods: Thirty AS patients (13 women and 17 men) admitted to our outpatient clinic and 33 healthy volunteers (15 women, 18 men) as the control group were included. Both groups were evaluated in terms of balance via Neurocom Balance Master System with weight bearing squat, standing on firm and foam bases when eyes open and closed, walking across, tandem walk, and step and quick turn tests. Postural assessment parameters were tragus-wall distance, Modified Schober test and chest expansion measurements. Pain and disease activity were evaluated with Visual Analog Scale (VAS) for pain level (0–10 cm), and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), respectively.

Results: The mean age of AS and control group were 41.7±7.6 and 41.3±7 years, respectively. There was no significant difference in terms of age, height and body mass index between AS and control groups. Mean disease duration in the AS group was 8.6±8.4 years with a mean BASDAI of 4.7±2.6. Mean VAS for pain, tragus-wall distance, and Modified Schober test were 5.9±2.1 cm, 17.7±5.6 cm and 18.6±2.8 cm in the patient group. Parametric tests were analyzed with independent t-test. AS patients had significantly greater step width ($p=0.024$). Step length ($p=0.011$), walking speed at walk across test ($p=0.002$), and tandem walk test ($p=0.015$) were significantly decreased among AS patients when compared to healthy volunteers.

In AS group, duration of disease was only correlated to step width at tandem walk test ($r=0.443$, $p=0.014$). Modified Schober was negatively correlated to tandem walk step width ($r=-0.418$, $p=0.022$), sway velocity on foam base when eyes open ($r=-0,473$, $p=0.008$), and closed ($r=-0.558$, $p=0.001$). Tragus wall distance was positively correlated to tandem walk step width ($r=0.433$, $p=0.017$). Neither BASDAI nor VAS was correlated to sway velocity on foam base when eyes open and closed, walk across speed, step width, step length, and tandem walk step width.

Conclusion: Walking speed and step length were significantly impaired in AS patients. As Modified Schober test measurement decreases, sway velocity on foam base and step width at tandem walk increase. Tragus wall distance lengthening results in increased step width at tandem walk. To sum up, forward head posture and limited spine flexibility are suggested to be the main causes of balance disorders in AS. Postural changes have more effect on balance than disease activity. Poor posture leads to impaired balance and AS patients adopt compensatory strategies, such as increasing their step width and decreasing their speed, to maintain their balance.

Disclosure: O. H. Gunduz, None; **E. E. Ozcan**, None; **E. Giray**, None; **I. Yagci**, None.

1512

Smoking and Its Relationship With Clinical, Radiological and Functional Status In Patients With Ankylosing Spondylitis. Fernando Andres Sommerfleck, Emilce Edith Schneeberger, Natalia Zamora, Luis Alejandro Cayetti and Gustavo Citera. Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina.

Background/Purpose: In recent years, smoking has been reported as an environmental risk factor that influence the course of certain diseases such as psoriasis, ulcerative colitis and spondyloarthritis (SpA), especially ankylosing spondylitis (AS). Our objective was to investigate the possible effect of smoking on disease activity, functional capacity, quality of life and radiographic damage in patients with AS.

Methods: Consecutive patients ≥ 18 yrs old with AS (ASAS 2009 criteria) were included. We recorded demographic data, age at onset of symptoms, duration of disease, disease-related symptoms, comorbidities and toxic habits (specifically about current or past smoking and number of packs/year (p/y)). Clinical and therapeutic aspects of the disease were collected prospectively in our AS outpatient clinic. Specific questionnaires to determine disease activity (BASDAI), functional capacity (BASFI), quality of life (ASQoL), metrology (BASMI) were performed every 6 months. Cervical, lumbar and pelvic X-rays were performed yearly and read by a single, blinded observer, according to BASRI. Comparison of categorical variables was assessed by Chi 2 or Fisher exact test and continuous variables by T test and ANOVA. Pearson correlation, multiple linear and logistic regression, were used in the analysis.

Results: We studied 147 patients, 111 (75.5%) were male, with a median age of 46 years (IQR 32–56) and a median of disease development of 16 years (IQR 8–25). Fifty one (34.7%) patients had axial commitment and 96 (65.3%) mixed. Medium (IQR) for: BASDAI 4.5 (2.5–6.4), BASFI 4.3 (1.6–6.7), BASMI 4.3 (2.7–6), ASQoL 8 (4–11), BASRI 8.5 (6–12.7) and mSASSS 23 (7 –50.7), respectively. Comorbidities frequency was 130/147 (91.5%) and 17 (11.6%) patients had one or more hip replacements. Smoking was observed in 66 (44.9%) patients (50% were past-smokers), the median pack year was 13.5 (IQR 5–32). In univariate analysis, smoking was associated with worse functional capacity (BASFI 4.9 in smokers vs. non-smokers 3.7, $p = 0.01$) and higher frequency of comorbidities (98.5% in smokers vs. nonsmokers 80.2%, $p < .01$). The association of smoking and worse functional capacity remained as an associated variable in multiple regression analysis after adjusting for disease duration and the presence of comorbidities. (OR: 1.82 95% CI 1.08–3.07).

Conclusion: Smoking adversely affects the functional capacity of our patients with AS. We did not observed that smoking has had a major impact in quality of life, metrology or radiographic damage in our cohort of patients with AS.

Disclosure: F. A. Sommerfleck, None; **E. E. Schneeberger**, None; **N. Zamora**, None; **L. A. Cayetti**, None; **G. Citera**, None.

1513

Human Leukocyte Antigen Tag Single Nucleotide Polymorphisms in Turkish Population: Polymerase Chain Reaction Restriction Fragment Length Polymorphism May Not Be Appropriate Genotyping Method For These Single Nucleotide Polymorphisms Due To Presence Of Complicating Polymorphism. Servet Akar[1], Yusuf Ziya Igci[2], Ismail Sari[1], Elif Pala[2], Esra Geyik[2], Dilek Solmaz[1], Pinar Cetin[1], Mehmet Nedim Tas[1] and Nurullah Akkoc[1]. [1]Dokuz Eylul University School of Medicine, Izmir, Turkey, [2]Gaziantep University School of Medicine, Gaziantep, Turkey.

Background/Purpose: Ankylosing spondylitis (AS) is strongly associated with HLA-B27. Although AS and HLA-B27 interaction is one of the best known disease associations, accurate HLA-B27 typing is technically challenging. Previously MHC tag single nucleotide polymorphisms (SNPs) rs4349859 and rs13202464 were shown to be able to identify HLA-B27 in European and Asian AS patients. Recently SNP rs116488201 was found to tag HLA-B27 allele in both European and Asian populations. Therefore the objective of our study was to evaluate the performance of HLA-B27 tag SNPs by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP).

Methods: We genotyped three SNPs (rs116488202, rs13202464 and rs4349859) by using PCR-RFLP. The primers were designed using Primer3 algorithm via primer-BLAST interface. PCR products were digested by using *NlaIII*, *BmrI*, and *TaqαI* restriction endonuclease enzymes. All suspicious and randomly selected samples' results were also verified by using DNA sequence analysis in order to prevent misleading results. HLA-B27 analysis for patient group was performed by using commercially used SSP-typing kit.

Results: In total 207 patients (72% male, mean age 42.3 ± 10.8 years and 146 [71%] was HLA-B27 positive) with AS according to the modified NY criteria and 32 healthy controls (78%male, mean age 52.7 ± 10.8 years and 2 [6%] was HLA-B27 positive) were included in the study. The effect alleles of SNPs rs116488202 (T) and rs4349859 (A) showed a high specificity for HLA-B27 since we did not identified T and A alleles in HLA-B27 negative subjects. However all the SNPs were quite polymorphic in HLA-B27 positives. For the SNPs rs13202464 and rs4349859, our experimental design worked well. However, there is another SNP (rs141774149) in the neighborhood of rs116488202 in which the altered sequence is also recognized by *BmrI* restriction enzyme (Figure 1). *BmrI* enzyme has the ACTGGG (5/4) recognition sequence which complicates the SNP analysis in that region. By using only *BmrI* enzyme digestion method, T allele carrying samples (TT or CT) cannot be exactly discriminated. Then, we decided to make DNA sequence analysis for all samples in order to prevent misleading results.

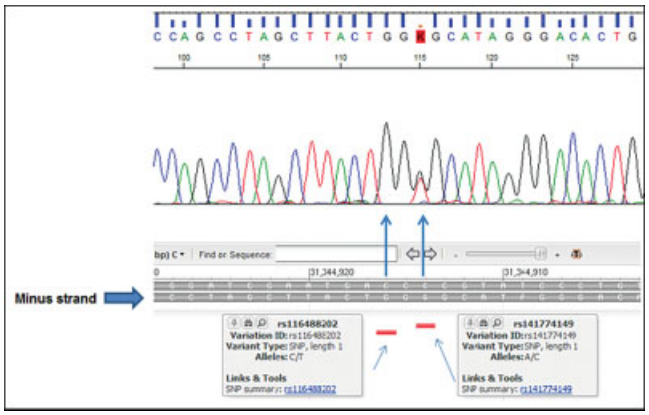

Figure 1. Sequence analysis of an example patient

Conclusion: This study shows that PCR-RFLP may not be appropriate method for genotyping the reported tag SNPsfor HLA-B27. The difficulties we experienced in this study took root from the highly variable sequences in HLA region involving the PCR primer design, PCR optimization, and RFLP analysis. Alternative consequences should be taken into account by the researchers who design and plan to conduct research concerning those variable sequences.

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1514

Drug Survival In Patients Receiving Golimumab Treatment 2010–2013. Results From The Swedish Rheumatology Quality Register. Saedis Saevarsdottir[1], Michele Santacatterina[2], Leszek Stawiarz[3], Carl Turesson[4], Helena Forsblad[5], Lennart T.H. Jacobsson[6] and Staffan Lindblad[7]. [1]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [2]Biostatistics Core Facility, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [3]Dept. of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden, [4]Lund University, Malmö, Sweden, [5]Dept of Rheumatology & Inflammation Research, Institute of Medicine, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [6]Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [7]Dept. of Learning, Informatics, Management and Ethics; Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Golimumab is a TNF inhibiting biological drug that was approved in Sweden in 2010 for the treatment of Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA) and Ankylosing Spondylitis (AS). In observational studies, the 24-month adhesion to therapy of TNF inhibitors in bio-naïve patients has ranged from about 50–70% in RA, 55–70% in PsA and 65–70% in AS. The aim of the current study was to evaluate cumulative survival probability of golimumab in clinical practice for these patient groups, as well as in patients registered with other spondyloarthritidies (SpA).

Methods: Data were retrieved for all patients initiating golimumab treatment from 2010 until April 30th2013 from the nationwide Swedish Rheumatology Quality register (SRQ), which hosts the register on biological

treatments, ARTIS (Anti Rheumatic Treatment in Sweden). Survival analysis (Kaplan Meier) was performed with right censoring and log-rank test of equality across strata.

Results: In total, 1681 patients had initiated golimumab treatment during the study period. Of those, 678 (40%) had RA, 364 (22%) had PsA, and 240 (14%) had AS, while 194 (12%) were registered as SpA and 205 (12%) had other diagnoses. The proportions of women in RA/PsA/AS/SpA patient groups were 80%/50%/28%/52%, respectively; and their median age at baseline was 58/50/45/43 years. In patients with RA/PsA/AS/SpA, the proportions receiving golimumab as the first biological treatment were 47%/45%/41%/37%; and the proportions receiving concurrent disease-modifying anti-rheumatic drugs (DMARDs) were 70%/58%/22%/38%.

Table 1. Cumulative survival probability (% (N)) of golimumab treatment for the four main diagnoses, stratified by previous exposure to biological treatment.

Diagnosis	Number of previous biologicals	Baseline	6	12	18	24
RA	**Bio-naive**	100 (318)	78 (206)	65 (138)	59 (111)	56 (77)
	1–2	100 (263)	74 (162)	60 (97)	54 (65)	52 (46)
	3+	100 (97)	66 (56)	45 (33)	42 (24)	32 (14)
PsA	**Bio-naive**	100 (163)	83 (107)	69 (70)	59 (47)	56 (31)
	1–2	100 (150)	79 (89)	62 (51)	55 (33)	51 (20)
	3+	100 (51)	71 (32)	59 (21)	53 (15)	53 (7)
AS	**Bio-naive**	100 (98)	81 (66)	77 (47)	68 (32)	65 (14)
	1–2	100 (118)	80 (79)	70 (54)	59 (31)	57 (22)
	3+	100 (24)	74 (16)	45 (9)	40 (7)	40 (6)
SpA	**Bio-naive**	100 (72)	83 (46)	73 (33)	60 (19)	60 (15)
	1–2	100 (94)	76 (61)	61 (36)	51 (24)	49 (15)
	3+	100 (28)	61 (13)	55 (8)	47 (4)	47 (2)

Cumulative survival probability of golimumab treatment is shown in Table 1, stratified by previous exposure to biological treatment. In RA patients, there was a statistically significant difference in survival probability between bio-naïve patients and those patients who had received 1–2 or 3+ biological drugs before golimumab ($p=0.0018$), a similar trend was observed in patients with AS ($p=0.069$), but interestingly, not in patients with PsoA ($p=0.6$). The number of individuals who had received 3+ biological drugs before golimumab was limited in all patient groups.

Conclusion: In this large nationwide rheumatology register, drug survival in patients receiving golimumab treatment was generally higher in bio-naïve patients compared to patients previously treated with biological drugs. The 24-month adhesion rates in clinical practice appear to be comparable to other TNF inhibitors, whereas further studies are necessary to evaluate the long term performance of golimumab.

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1515

Influence Of Taking Structural Lesions Into Account In Addition To Inflammatory Lesions On MRI Of The Sacroiliac Joints On The Classification Of Patients With Possible Axial Spondyloarthritis. Rosaline van den Berg[1], Manouk de Hooge[1], Floris van Gaalen[1], Victoria Navarro-Compán[1], Monique Reijnierse[1], Karen Fagerli[2], Robert Landewé[3], Maikel van Oosterhout[4], Roberta Ramonda[5], Tom Huizinga[1] and Désirée van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [4]GHZ Hospital, Gouda, Netherlands, [5]University of Padova, Padova, Italy.

Background/Purpose: The ASAS definition of a positive MRI of the sacroiliac joints (MRI-SI+) for the classification of axial spondyloarthritis (axSpA) patients includes inflammatory lesions only[1,2]. The role of structural lesions on MRI-SI in classifying patients is unclear[1]. We explored the potential role of structural lesions on MRI-SI in classifying axSpA patients.

Methods: Patients with back pain (≥3 months, ≤2 years, onset <45 years) from the 5 centers in the SPondyloArthritis Caught Early (SPACE)-cohort were included. Patients underwent MRI-SI. MRI were scored by 3 well-calibrated readers independently for ankylosis, sclerosis, erosions, and fatty lesions (FL) (T1-weighted images; STIR viewed simultaneously). Erosions, sclerosis and FL were defined according to the MORPHO definition[3] (≥1 lesion on ≥2 consecutive slices or ≥2 lesion on 1 slice). Ankylosis was defined as ≥1 lesion on ≥1 slice. Lesions were considered present if 2/3 readers agreed. MRI was considered positive for several (combinations of) structural lesions (MRI-SI-s+) using cut-offs based on the acceptance of ≤5% false-positives in patients without SpA. Patients are considered as possible axSpA if not fulfilling the ASAS axSpA criteria[3], but if ≥1 specific SpA-feature (LR+ >6) or ≥2 less specific SpA-features (LR+ <6) are present[4]. We classified possible axSpA patients using MRI-SI-s+ instead of MRI-SI+ and calculated the LR product with LR+ 9.0 for MRI-SI-s+ as if MRI-SI+[4]. Based on the LR product the probability of having axSpA was calculated[4].

Results: Only possible axSpA patients with MRI-SI data were included (n=116). Depending on the used MRI-SI-s+ definition, 1% (ankylosis ≥1) to 6% (erosions ≥2 or FL ≥2) of the possible axSpA patients could be classified as axSpA (table). Combining the various definitions of MRI-SI-s+ results in 14 additional patients (12.1%) classified as axSpA (5 patients with probability ≥80%); 5 patients fulfilled 4 of the proposed MRI-SI-s+ definitions. In patients with a high number of SpA-features, using MRI-SI-s+ to calculate the LR product results in a probability ≥80%, making an axSpA diagnosis very likely. However, in patients with only 1 or a few SpA-features, the probability remains <80%.

ASAS axSpA+ in possible axSpA patients if structural lesions are added	Possible axSpA n=116	Mean (range) no. SpA-features	Probability ≥80%	Probability 50–79%	Probability 20–49%	Probability <20%
Ankylosis ≥1	1 (0.9%)	1 (1)	–	–	–	1
Fatty lesions ≥2	7 (6.0%)	2.3 (1–4)	3	1	1	2
Erosion ≥2	7 (6.0%)	2.1 (2–3)	3	1	2	1
Sclerosis ≥1	1 (0.9%)	1 (1)	–	–	–	1
Any structural lesions ≥5	5 (4.3%)	2.4 (1–3)	2	2	–	1
Any structural lesions (except ankylosis) ≥5	4 (3.4%)	2.8 (2–3)	2	2	–	–
Fatty lesions and/or erosions ≥5	4 (3.4%)	2.8 (2–3)	2	2	–	–

Conclusion: These explorative data point out that structural lesions on MRI of the SI joints might play a role in classifying possible axSpA patients. However, only few additional patients are classified as axSpA with a high probability while the same number of patients with a low probability would (falsely) be classified if structural lesions would be added to the definition of a positive MRI. Further studies are needed to define the best type/combination and cut-off of structural lesions.

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1516

Safety and Efficacy Of Etanercept In Early Non-Radiographic Axial Spondyloarthritis: A Randomized, Double-Blind, Placebo-Controlled Trial At 24 Weeks. Maxime Dougados[1], Désirée van der Heijde[2], Joachim Sieper[3], Jügen Braun[4], Walter P. Maksymowych[5], Gustavo Citera[6], James Cheng-Chung Wei[7], Jan Lenaerts[8], Ronald Pedersen[9], Randi Bonin[9], Ehab Y. Mahgoub[9], Bonnie Vlahos[9] and Jack Bukowski[9]. [1]Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Charité Universitätsmedizin Berlin, Berlin, Germany, [4]Rheumazentrum Ruhrgebiet, Herne, Germany, [5]University of Alberta, Edmonton, AB, [6]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [7]Chung Shan Medical University Hospital, Taichung, Taiwan, [8]Reuma Instituut, Hasselt, Belgium, [9]Pfizer Inc, Collegeville, PA.

Background/Purpose: Limited data are available on the efficacy of anti-TNF agents in non-radiographic axial spondyloarthritis (nr-axSpA). The objective of this analysis is to compare the efficacy and safety of etanercept (ETN) vs placebo after 12 weeks of double-blind treatment and an additional 12 weeks of open-label ETN treatment in patients with nr-axSpA who had an insufficient response to NSAIDs.

Methods: Enrolled patients satisfied ASAS criteria for axSpA, had been exhibiting symptoms between 3 months–5 years, failed ≥2 NSAIDs (including current one), and a BASDAI score ≥4 despite current NSAID use. Patients were blinded and randomized to ETN 50 mg weekly (QW) or placebo and continued NSAIDs for 12 weeks followed by open-label ETN 50 mg QW for an additional 12 weeks (weeks 12–24). Efficacy outcomes were assessed at week 12 and 24 and safety monitored throughout the study. Analyses used ANCOVA models with baseline score, treatment, region and sacroiliac joints status at baseline (MRI) as variables. LOCF imputation was used for missing data.

Results: 215 patients were randomized and included in the mITT population (ETN=106; placebo=109); mean age at baseline was 32 years (range, 18–49 years); 61% were male; and mean disease duration was 2.4 years (range, 0–16.0 years; median, 2.3 years). At week 12, 208 patients (ETN=102; placebo=106) enrolled in the open-label phase. ASAS40 at 12 weeks was achieved by a significantly greater proportion of patients receiving ETN vs placebo (32.4% vs 15.7%, respectively; $P=0.006$). At week 12, there were substantial differences in clinical outcomes between the ETN and placebo groups, but the differences largely disappeared when placebo patients were treated with ETN in the open-label phase (table). As compared to week 12, an increased proportion of patients achieved all efficacy outcomes at week 24, after the switch to open label ETN. The percentages of patients (safety population) with any adverse events were 57% (63/111) vs 46% (52/113) at week 12 and 34% (35/102) vs 50% (53/106) at week 24 in the ETN vs placebo groups, respectively.

Table. Effects of ETN versus placebo in patients with nr-axSpA (mITT, LOCF[a])

	Week 12 (double-blind period)		Week 24 (open-label period)	
	ETN 50 mg + NSAID (n=106)	Placebo + NSAID (n=109)	ETN 50 mg + NSAID/ETN 50 mg + NSAID (n=102)	Placebo + NSAID/ETN 50 mg + NSAID (n=106)
Parameter, n/N (%)				
ASAS20[b]	53/105 (50.5)	41/108 (38.0)	66/102 (64.7)	75/105 (71.4)
ASAS40[b]	34/105 (32.4)[c]	17/108 (15.7)	45/102 (44.1)	54/105 (51.4)
ASAS 5/6[b]	33/103 (32.0)[c]	10/106 (9.4)	40/99 (40.4)	43/104 (41.4)
ASAS partial remission[b]	27/105 (25.7)[c]	13/109 (11.9)	32/102 (31.4)	46/106 (43.4)
ASDAS inactive disease	42/105 (40.0)[c]	19/109 (17.4)	48/102 (47.1)	62/106 (58.5)
Mean Change from Baseline (95%CI)				
ASDAS-CRP	−1.1 (−1.3, −0.9)[d]	−0.5 (−0.7, −0.3)[d]	−1.5 (−1.7, −1.3)	−1.6 (−1.8, −1.4)
BASDAI	−2.0 (−2.5, −1.4)[d]	−1.3 (−1.8, −0.8)[d]	−2.9 (−3.3, −2.4)	−3.3 (−3.7, −2.9)
BASFI	−1.4 (−1.9, −0.9)[d]	−0.8 (−1.3, −0.4)[d]	−1.9 (−2.3, −1.4)	−1.8 (−2.2, −1.4)
BASMI	−0.3 (−0.6, −0.0)[d]	−0.3 (−0.5, 0.0)	−0.5 (−0.7, −0.2)	−0.3 (−0.5, −0.1)
BAS-G total	−1.9 (−2.4, −1.3)[d]	−1.4 (−1.9, −0.9)[d]	−2.8 (−3.3, −2.3)	−2.89 (−3.3, −2.5)

[a]Patients were not carried forward into the open-label period if they dropped out during the double-blind period. [b]Modified ASAS criteria (2009) European Medicines Agency, available at: http://www.ema.europa.eu. [c]P<0.05 vs placebo, CMH chi-square test. [d]P<0.05 within treatment group from baseline.

Conclusion: In this population of patients with early, active nr-axSpA who had an inadequate response to ≥2 NSAIDs, etanercept was more effective than placebo during the first 12 weeks. Clinical outcomes were similar after all patients were treated with ETN (weeks 12–24). No new safety signals were reported.

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Different Imaging Abnormalities Suggestive Of Spondyloarthritis Are Present In Early Axial Spondyloarthritis. Data From The DESIR Cohort. Anna Moltó[1], Simon Paternotte[2], Désirée van der Heijde[3], Pascal Claudepierre[4], Martin Rudwaleit[5] and Maxime Dougados[1]. [1]Paris- Descartes University, Paris, France, [2]Paris- Descartes University, Cochin hospital, Paris, France, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Paris-Est University; LIC EA4393; APHP, Henri Mondor Hospital, Creteil, France, [5]Endokrinologikum Berlin, Berlin, Germany.

Background/Purpose: Patients can fulfil the ASAS (Assessment of SpondyloArthritiS) sets of criteria with either objective evidence of sacroiliac joint damage (X-Ray) or inflammation (MRI) ("imaging" arm) or without such imaging abnormalities in B27 patients ("clinical" arm). Currently, there is still a debate regarding the imaging abnormalities permitting to classify a patient as fulfilling the imaging arm. The aim of the study was to evaluate different imaging abnormalities (*e.g.*inflammatory and chronic changes at the sacroiliac joint (SIJ) and spine level) as of potential interest for classification.

Methods: Prospective, multi-centre, observational study. 708 patients with early inflammatory back pain suggestive of spondyloarthritis were included in the DESIR cohort. Data collected: demographics, items of the ASAS criteria, disease activity, severity, quality of life. Inflammatory and chronic changes evaluated using either X-rays or MRI at both the SIJ and spine level by the radiologist/rheumatologist of the participating center. Statistical analysis: patients fulfilling the ASAS criteria were split in two groups (imaging vs. clinical) and within the clinical arm, with regard to the presence of CRP abnormality (e.g. >6mg/L). The other imaging abnormalities suggestive of SpA (e.g. MRI chronic changes of the SIJ, MRI inflammatory and chronic changes at the spine level, and the presence of at least 1 syndesmophyte at the cervical or lumbar level) present in each of the groups were depicted.

Results: 476 (69.8%) of the 708 included patients fulfilled the ASAS criteria, either the imaging (296 (60.1%)) or the clinical (190 (39.9%)) arms. Imaging findings different than the ones of the "imaging" definition of the ASAS criteria were observed (MRI-SIJ chronic changes (53.5% vs. 4.3%), MRI-Spine inflammatory changes (35.0% vs. 12.3%), MRI-spine chronic changes (11.9% vs. 6.4%) and X-ray-syndesmophytes (13.6% vs. 7.0%) in the imaging versus clinical arm, respectively.

The table summarizes the different imaging abnormalities observed.

	ASAS axSpA criteria				
	Imaging			Clinical	
	X-ray+/ MRI+ (132)	X-ray+/ MRI− (55)	X-ray−/ MRI+ (99)	X-ray−/ MRI− Abnormal CRP (33)	X-ray−/ MRI− Normal CRP (154)
MRI SIJ structural changes	93 (70.5%)	27 (54.0%)	33 (33.3%)	3 (9.1%)	5 (3.3%)
MRI Spine inflammatory lesions	55 (42.3%)	9 (18.0%)	36 (36.7%)	7 (21.2%)	16 (10.5%)
MRI Spine structural lesions	20 (15.4%)	5 (10.0%)	9 (9.3%)	2 (6.1%)	10 (6.5%)
X-ray spine	17 (12.9%)	14 (25.5%)	8 (8.1%)	3 (9.1%)	10 (6.5%)

MRI chronic changes of the SIJ were, as expected, more frequently observed in the subgroup of patients with X-ray damage of the SIJ. MRI inflammatory changes of the spine were more frequently observed in presence of other markers of inflammation. In the subgroups of patients without imaging abnormalities but abnormal CRP as much as 9.1% of patients presented with definite X-ray damage of the spine.

Conclusion: This study shows that different imaging abnormalities suggestive of SpA (*e.g.* MRI chronic changes of the SIJ) are present in early SpA, but need to be confirmed by central reading. Descriptive studies of these abnormalities in healthy controls are necessary to confirm (or not) whether these findings might be may be considered for classification in the imaging arm of the ASAS criteria.

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Prevalence Of Spondylarthritis In Individuals Needing To Purchase An Orthopedic Mattress Because Of Chronic Back Pain. Ahmet Eftal Yucel, Muzeyyen Temel, Muhtesem Agildere and Mustafa Agah Tekindal. Baskent University Faculty of Medicine, Ankara, Turkey.

Background/Purpose: We hypothesize that the real prevalence of spondylarthritis (SpA) is much higher than reported in the literature. In this study, we aimed to investigate the presence of SpA in individuals who needed to purchase an orthopedic mattress because of their chronic back pain, and to emphasize the importance of determining the main underlying reason for these complaints.

Methods: Two hundred adults aged< 45 years who had purchased an orthopedic mattress because of chronic back pain were called by phone and asked 3 screening questions in order to identify whether their back pain was inflammatory. The questions were about the presence of (1) non-traumatic pain, swelling and stiffness in any joints, (2) lower back pain or back stiffness on awakening which lasted over a period of at least 3 months and which improved with exercise, (3) heel pain more powerful in the morning which lasted over a period of at least 3 months and which

improved with activity. Of 200 individuals, 105 gave positive answers to one or more of the screening questions and 80 individuals [42 women (52.5%), mean age 36.3 ± 6.3] who agreed to clinical evaluation were included in the study. In all evaluated individuals, comparative sacroiliac radiography was taken for the screening of sacroiliitis and lateral radiographies of both feet were taken for the screening of enthesitis. Peripheral blood samples were taken for ESR and serum CRP levels. Patients with suspected sacroiliitis upon direct radiography were examined with sacroiliac MRI. In order to diagnose SpA, the European Spondyloarthritides Study Group (ESSG) criteria were applied.

Results: Among 80 subjects, 65 (81.3%) were diagnosed with SpA, and among these 65 patients, we diagnosed 48 (73.9%) with undifferentiated SpA, 14 (21.5%) with ankylosing spondylitis and 3 (4.6%) with psoriatic arthritis. Thirty seven of 80 subjects (46.3%) were found to have sacroiliitis at different stages and 42 (52.5%) had enthesitis (epin calcanei and/or Achilles enthesopathy) by radiography. ESR and CRP levels were similar in individuals with or without SpA.

Conclusion: We diagnosed SpA in a remarkable percentage of the individuals who were in the need of an orthopedic mattress due to a complaint of chronic back pain. For this reason, we suggest that evaluation of those individuals for SpA will be helpful for early diagnosis, treatment and improvement in the quality of life of the patients. We also think that is important to create awareness about SpA in the general population so that patients will seek out medical diagnosis and treatment instead of transient and inadequate remedies like a new mattress for their back pain.

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Meeting The ACR 2010 Fibromyalgia Criteria Worsens Disease Activity and Quality Of Life In Patients With Axial Spondyloarthritis Treated With Infliximab. Mathieu Verdet[1], Clément Guillou[2], Julien Michaud[1], Christopher Banse[1], Sandra Desouches[1], Gilles Avenel[1], Quentin Bréhier[3], Aurélia Bisson-Vaivre[1], Sophie Pouplin[1] and Olivier Vittecoq[4]. [1]Rouen University Hospital, Rouen, France, [2]Inserm 905 & Institute for Biomedical Research, University of Rouen, Rouen, France, [3]Le Havre Hospital, Le Havre, France, [4]Department of Rheumatology, Rouen University Hospital & Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen Cedex, France.

Background/Purpose: Managing axial spondyloarthritis (aSpA) may be difficult because sometimes patients are not good responder to anti-TNF. We made the hypothesis that in certain patients, high disease activity could be due to associated fibromyalgia (FM). Indeed, some patients describe more widespread pain and more associated symptoms than others. The objective of this study was to analyse differences between aSpA patients (ASAS 2009) according to their meeting of the ACR 2010 FM criteria.

Methods: It was a prospective transversal observational study. 51 patients with aSpA satisfying the ASAS 2009 criteria were included during one year. All patients were treated with infliximab. Every patient filled once an auto-questionnaire with items of ACR 2010 FM criteria, Visual Analog Scale (VAS) for pain and global disease activity (GDA), BASDAI, BASFI, FIQ, HAQ, FACIT-13, SF-36 and First Score. We collected items of BASMI, numbers of tender joint (TJ), swollen joint, MASES score and number of Yunus tender points. Erythrocyte Sediment Rate (ESR) and C-reactive protein (CRP) levels and ASDAS score were collected.

Results: Twenty-four patients (47%) met the FM ACR 2010 criteria (FM+). No difference between FM+ and FM- patients for age at inclusion, age at beginning of aSpA, number of infusion and interval between infusions of infliximab. Female proportion was higher in FM+ group (NS) (70% vs 48%; p=0.1). Compared to FM- patients, FM+ patients had higher TJ number (6.4 ± 7.6 vs 1.7 ± 3.5 p<0.0001), MASES (7.67 ± 3.88 vs 2.8 ± 4.08 p<0.0001), Yunus points number (8.75 ± 5.45 vs 3.19 ± 4.11; p<0.0001), Pain VAS (6.19 ± 1.88 vs 3.56 ± 2.74; p=0.0006), GDA VAS (6.25 ± 2.04 vs 3.39 ± 2.36; p<0.0001). BASMI, ESR and CRP levels did not differ between the groups. ASDAS-CRP was higher in FM+ patients (3.05 ± 0.85 vs 1.89 ± 0.66; p<0.0001). BASFI (56.1 ± 26.8 vs 31.5 ± 24.22 p=0.0012), FIQ (63.03 ± 16.25 vs 30.21 ± 17.7, p<0.0001), FACIT-13 (17.49 ± 6.45 vs 33.39 ± 11.44), mental SF-36 (33.19 ± 17.94 vs 62.77 ± 21.9, p<0.0001), physical SF-36 (29.89 ± 16.09 vs 55.05 ± 22.39, p<0.0001) and First score (4.70 ± 1.12 vs 2.41 ± 1.85, p<0.0001) were more severe in FM+ patients.

When we analysed by which arm of the ASAS 2009 criteria, patients were diagnosed with aSpA, we showed that 11% of FM- patients were diagnosed only by the HLAB27 arm compared to 37.5% in FM+ patients (p=0.046).

Conclusion: Patients with axial SpA (ASAS 2009) that fulfilled the FM ACR 2010 criteria were more severe in terms of pain, fatigue, quality of life, mental and physical function and SpA disease activity.

When disease activity is high, despite anti-TNF treatment, assessment of FM ACR 2010 criteria status should be useful to understand the reasons for lack of efficacy.

In a context of FM ACR 2010 criteria fulfilling, when SpA disease activity is high, physicians should consider diagnosis revision if only HLAB27 arm of ASAS 2009 aSpA criteria has been used to make the diagnosis.

A longitudinal study could be interesting in order to assess the benefit of anti-TNF in aSpa patients that also fulfils the FM ACR 2010 criteria before treatment introduction.

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1520

Reduction Of Disease Burden On Workplace and Household Productivity In Axial Spondyloarthritis, Including Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis, Over 48 Weeks Of Treatment With Certolizumab Pegol. Désirée M. van der Heijde[1], Jürgen Braun[2], Martin Rudwaleit[3], Oana Purcaru[4] and Arthur Kavanaugh[5]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, [3]Endokrinologikum Berlin, Berlin, Germany, [4]UCB Pharma, Brussels, Belgium, [5]University of California San Diego, San Diego, CA.

Background/Purpose: Axial spondyloarthritis (axSpA) includes both ankylosing spondylitis (AS, meeting modified New York criteria) and axSpA with no sacroiliitis on X-ray (non-radiographic axSpA, nr-axSpA). AS significantly affects work productivity[1] but data is limited for the impact of nr-axSpA on productivity. Previous results show improvements in workplace and household productivity with certolizumab pegol (CZP) vs placebo (PBO) up to Week (Wk) 24 in the RAPID-axSpA study.[2] This report estimates the economic burden of axSpA, AS and nr-axSpA, and examines long-term effects of CZP on productivity outcomes up to Wk48.

Methods: The ongoing RAPID-axSpA trial (NCT01087762) is double-blind and PBO-controlled to Wk24 and dose-blind to Wk48.[3] Patients (pts) had active axSpA according to ASAS criteria,[4] including both AS and nr-axSpA pts. Pts originally randomized to CZP (200mg Q2W or 400mg Q4W, following 400mg loading dose at Wks 0, 2, 4) continued on their assigned dose in dose-blind phase; PBO pts entering dose-blind phase were re-randomized to CZP loading dose followed by CZP 200mg Q2W or CZP 400mg Q4W. The arthritis-specific Work Productivity Survey (WPS),[5] administered Q4W from baseline (BL), assessed the impact of axSpA on workplace and household productivity in the full analysis set (FAS). Disease burden was evaluated at study BL. WPS responses (LOCF imputation) in both CZP groups are summarized descriptively over 48 wks.

Results: BL disease activity was similar for AS and nr-axSpA pts but symptom duration varied (median 9.1 vs 5.5 yrs, respectively). At BL, 69.2% of axSpA pts, 67.4% AS and 71.4% nr-axSpA were employed outside the home. More AS vs nr-axSpA pts were unable to work due to spondyloarthritis (15.7% vs 8.2%). High burden of axSpA on workplace and household productivity was reported at BL, with higher burden in nr-axSpA vs AS (Table). At BL, axSpA pts reported >1 wk of paid work (mean 7.2 days), ~2 wks of household duties (mean 13.3 days), and mean 4.4 days of social activities affected over previous month. Employed pts in both CZP groups reported reductions in workplace absenteeism and presenteeism to Wk24, with further improvements to Wk48 (Table). CZP groups reported continued improvements in household productivity up to Wk48 (Table). Similar improvements were observed in AS and nr-axSpA (Table).

Table. Workplace and household productivity over 48 wks in the RAPID-axSpA trial (FAS population [a])

	axSpA		AS		nr-axSpA	
WPS responses, mean	CZP 200mg Q2W n = 111	CZP 400mg Q4W n = 107	CZP 200 mg Q2W n = 65	CZP 400mg Q4W n = 56	CZP 200mg Q2W n = 46	CZP 400mg Q4W n = 51
Productivity at workplace (employed subjects)						
Work days missed due to arthritis per month [b]						
BL	2.3	1.4	2.4	1.0	2.2	1.9
Wk24	1.1	0.6	1.1	0.3	1.2	0.8
Wk48	0.4	0.1	0.5	0.2	0.1	0.1
Days with work productivity reduced by ≥50% due to arthritis per month [b,c]						
BL	5.8	4.7	5.4	3.8	6.5	5.6
Wk24	2.4	2.7	3.1	1.7	1.2	3.8
Wk48	1.0	1.6	1.5	1.4	0.2	1.8
Level of arthritis interference with work productivity (0–10 scale) [b,d]						
BL	4.5	4.6	4.7	4.3	4.1	4.8
Wk24	2.2	2.0	2.3	1.8	2.0	2.2
Wk48	1.3	1.5	1.7	1.4	0.6	1.6
Household productivity and social participation (all subjects)						
Household work days missed due to arthritis per month						
BL	5.8	4.7	5.2	4.4	6.7	5.0
Wk24	2.3	2.2	2.2	1.8	2.5	2.6
Wk48	1.7	1.7	1.8	1.9	1.6	1.4
Household work days with productivity reduced by ≥50% due to arthritis per month [c]						
BL	7.9	7.0	7.2	6.7	9.0	7.3
Wk24	3.5	3.0	3.1	2.9	4.0	3.2
Wk48	1.9	1.7	2.2	1.6	1.5	1.7
Level of arthritis interference with household productivity (0–10 scale) [d]						
BL	5.0	4.6	5.0	4.7	5.0	4.4
Wk24	2.4	2.2	2.6	2.2	2.3	2.2
Wk48	2.1	1.7	2.2	1.8	2.0	1.6
Days missed family/ social/leisure activities due to arthritis per month						
BL	4.4	3.6	4.0	2.7	4.9	4.7
Wk24	1.1	1.9	1.0	1.8	1.3	1.9
Wk48	0.7	1.0	1.0	0.4	0.5	1.6

[a] FAS; all patients who received ≥1 dose of study medication and had a valid baseline and post-baseline measurement for ASAS20; [b] Based only on employed pts at the specific visit; pts employed at BL (CZP 200mg Q2W/CZP 400 mg Q4W): axSpA (77/80), AS (48/41), nr-axSpA (29/39); [c] Does not include work days missed counted in the previous question; [d] 0–10 scale, 0 = no interference 10 = complete interference.

Conclusion: At BL, similarly high burden of disease on workplace and household productivity was seen in AS and nr-axSpA pts that could lead to a large financial burden for pts and society. This analysis indicates that CZP continued to improve workplace and household productivity in axSpA pts over 48 wks. Similar CZP improvements over time were observed in AS and nr-axSpA.

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1521

Latent Tuberculosis Screening and Treatment In Ankylosing Spondylitis Patients Eligible For Anti-TNF Therapy In Endemic Area. Renata Miossi, Karina Rossi Bonfiglioli, Carla G.S. Saad, Ana Cristina Ribeiro, Julio C. B. Moraes and Eloisa Bonfá. Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: Anti-TNF agents have emerged as an important treatment for rheumatic diseases, particularly for ankylosing spondylitis (AS). Screening and treatment of latent tuberculosis infection (LTBI) is essential before the use of these drugs. However, current recommendationsfor this screening and treatment and their efficacy are still not well established in endemic regions. The purpose of the present study is to evaluate, in an endemic area, the efficacy of LTBI screening and treatment in AS patients under anti-TNF.

Methods: One hundred and ten AS patients eligible for anti-TNF agents were initially screened for LTBI by tuberculin skin test (TST), chest X-ray and history of contact. Patients were regularly followed at 1–3 months interval, from June 2004 to January 2013.

Results: LTBI screening was positive in 48 (43.6%) patients. TST positivity accounted for majority of LTBI diagnosis (46; 95.2%): 39 (81.2%) solely positive TST, 6 (12.5%) with positive TST and history of contact, 1 (2.1%) with positive TST and abnormal chest X-ray and 2 (4.2%) with isolated history of contact. These patients received at least 1 month isoniazid before starting anti-TNF treatment and all of them completed 6 months of isoniazid treatment. Two patients developed TB in spite of LTBI treatment: one was a medical doctor with proven exposure to TB after 8 months receiving adalimumab, and the other became symptomatic right after the second dose of adalimumab, and probably had active TB that was misdiagnosed as LTBI. Sixty seven (60.9%) patients were treated with one anti-TNF, 33 (30%) with two and 10 (9.1%) with three (86 infliximab, 49 adalimumab and 75 etanercept). Thirty three (30%) patients were under prednisone, mean dose 10.6 mg/day. No difference was observed in TST positivity rate in this group comparing with the patients without this drug (48.5% vs. 39%, p=0.40). TST was repeated in 9/64 (14%) patients initially screened negative in case of prolonged discontinuation and reintroduction of biologic treatment (n=2) or clinical tuberculosis (TB) suspicion (n=7). In the latter group, TST conversion was observed in 3 patients diagnosed with active pulmonary TB. Median duration of anti-TNF treatment (2 adalimumab e 1 infliximab) in these three patients before the diagnosis of TB was 1.8 (0.6 – 3.5) years.

Conclusion: Our study provides evidence that TBLI screening and treatment is also efficient for endemic areas. In addition, we report that new exposure accounts for nearly all cases of TB infection and further demonstrate that symptom guided TST repetition is very effective for TB diagnosis during anti-TNF therapy in high TB incidence region.

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1522

Remission In Spondyloarthritis: ASDAS and Basdai Thresholds From a Prospective Real Life Study. Marie Godfrin-Valnet[1], Marc Puyraveau[2] and Daniel Wendling[1]. [1]Minjoz University Hospital, Besancon, France, [2]CHU, Besançon, France.

Background/Purpose: Remission is the current target of management of chronic rheumatic diseases. Whereas in rheumatoid arthritis remission criteria have been recently proposed, in spondyloarthritis, no activity score allows a clear definition for remission. SpA activity is evaluated with the BASDAI score (Bath Ankylosing Spondylitis Disease Activity Index) and more recently with the ASDAS (Ankylosing Spondylitis Disease Activity Score). Thresholds for the ASAS score have been proposed to classify disease activity (inactive, moderate, active, very active), but no remission threshold was defined.

The aim of this study was to evaluate a threshold for remission in SpA patients.

Methods: In this prospective study, a questionnaire answering the question: "do you consider the disease in remission at the present time ?" was filled by the patient with Spa (according to ASAS classification criteria) and the rheumatologist. Data allowing BASDAI, ASDAS-CRP and ASDAS-ESR calculation were collected, and PASS (Patient Acceptable Symptomatic State) was also assessed with a specific question at the same time. Thresholds

were defined by building ROC curves for remission according to the patient's and to the rheumatologist's opinion.

Results: One hundred and fifty patients were prospectively included, 67.3 % men, mean age 43.2 ± 11.5 years. HLA-B27 was positive in 84.5 % of the patients; SpA was axial in 81.7 %. Mean CRP was 8.6 ± 13.5 mg/l, and mean ESR 17.4 ± 16 mm/hour. PASS was considered by 56.6% of the patients. For disease activity, 47.3 % of the patients had a BASDAI score less than 4/10, and 19.2 % an ASDAS-CRP score less than 1.3 (inactive disease) (19.4 % for the ASDAS-ESR score). The thresholds of activity scores for remission defines by ROC curves are reported in table:

Threshold of activity score (ROC curves)	Remission «patient» N: 41/128	Remission «physician» N: 49/143	PASS in case of remission «patient» N: 41/128
ASDAS-CRP	≤ 1.6	≤ 1.8	≤ 2.2
95 % CI	0.67–0.84	0.82–0.94	0.82–099
Sensibility %	62.2	75.6	93.3
Spécificity %	86.3	91	100
ASDAS-ESR	≤ 1.7	≤ 2	≤ 2.4
95 % CI	0.71–0,.87	0.76–0. 90	0.76–0.9
Sensibility %	63.9	75.6	71.4
Spécificity %	87	82.2	81.6
BASDAI	≤ 3.6	≤ 3.6	≤ 4.1
95 % CI	0.71–0.86	0.81–0.93	0.80–0.90
Sensibility %	75.6	83.7	75.7
Spécificity %	75.9	79.4	85

Conclusion: This is the first study tempting to define in a large series of patients in real life a threshold for remission in SpA with an ASDAS –CRP less than 1.6. These results corresponding to the patients reported definition are somewhat different from those endorsed by the ASAS classifying SpA as inactive for a threshold less than 1.3. These differences may be related to different study methods: randomized controlled studies, thresholds evaluated by experts at one hand, and real life situation, thresholds evaluated by the patients at the other hand. However, our results are coherent since the remission threshold is lower than PASS, but raise the question of the definition of remission in SpA.

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1523

Presence Of Peripheral Arthritis Delays Spinal Radiographic Progression In Ankylosing Spondylitis: Observation Study Of Korean Spondyloarthropathy Registry (OSKAR) Over 5 Years. Tae-Jong Kim[1], Seunghun Lee[2], Kyung-Bin Joo[3], Dong-Jin Park[4], Yong-Wook Park[4], Shin-Seok Lee[4] and Tae-Hwan Kim[5]. [1]Chonnam National University Medical School and Hospital, Gwangju, South Korea, [2]Hanyang University College of Medicine, Seoul, South Korea, [3]Hanynag University, Seoul, South Korea, [4]Chonnam National University Medical School, Gwangju, South Korea, [5]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea.

Background/Purpose: The most unique feature in ankylosing spondylitis (AS) is subchondral eburnation and syndesmophytes, possibly leading to ankylosis and spinal fusion. So far a clear relationship between spinal bone formation and peripheral arthritis in patients with AS has not been established. The aim of this study was to determine whether presence of peripheral arthritis can affect the progression of structural damage in patients with AS.

Methods: A total of 915 patients with AS from the Observation Study of Korean spondyloArthropathy Registry (OSKAR) cohort were enrolled for this analysis. We used a two-step approach to explore the relationships between the peripheral arthritis and the progression of spinal structural damage in AS. First, all OSKAR data were analyzed in relation to the history of peripheral arthritis on cross-sectional survey. Second, we analyzed the radiographic spinal progression over 5 years according to the presence or absence of peripheral arthritis. The modified Stoke AS Spinal Score (mSASSS) were examined by two experienced radiologists to validate the results. The collection of the clinical parameters was conducted to investigate the associations between clinical factors and the radiographic progression.

Results: The agreement between the two readers regarding mSASSS was very good: ICC coefficient 0.75 (95% CI 0.61–0.82) and 0.71 (95% CI 0.58–0.82) at each time. On cross-sectional survey, in spite of adjusting for multiple comparisons by Bonferroni correction, the patients with history of peripheral arthritis had fewer mSASSS unit than those without history of peripheral arthritis (19.56±1.06 vs 22.67±0.81, p=0.005). In a analysis over 5 years, the mean progression of mSASSS in patients with peripheral arthritis was 3.26±0.58 units, while that of mSASSS in patients without peripheral arthritis was 4.97±0.44 units (p=0.024).

Conclusion: The patients with the peripheral arthritis had slower radiographic spinal damage progression than those without peripheral arthritis.

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1524

Lower Etanercept Levels Are Associated With High Disease Activity In Ankylosing Spondylitis Patients At 24 Weeks Of Follow-Up. Eva L. Kneepkens[1], Charlotte L. M. Krieckaert[1], Desiree van der Kleij[2], Michael T. Nurmohamed[1], Irene E. van der Horst-Bruinsma[3], Theo Rispens[4] and Gertjan Wolbink[4]. [1]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [2]Sanquin Diagnostic Services, Amsterdam, Netherlands, [3]VU University Medical Center, Amsterdam, Netherlands, [4]Sanquin Research, Amsterdam, Netherlands.

Background/Purpose: Etanercept levels are associated with clinical response in rheumatoid arthritis, however, in a small group of 53 patients with ankylosing spondylitis (AS) this association was not found.[1]

Objectives: To investigate the relationship between etanercept levels and clinical response in a large cohort of AS patients.

Methods: Prospective observational cohort study of 170 consecutive AS patients treated with etanercept 50 mg SC once a week, monitored during 24 weeks of follow-up. Clinical measurements and trough serum samples were obtained at all visits. Etanercept trough levels were determined retrospectively using an enzyme linked immunosorbent assay (ELISA) designed by Sanquin Research, Amsterdam. Response to etanercept treatment was defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) response (50% improvement or an absolute improvement of 2 points on a BASDAI, scale 0–10) and disease activity was measured using AS Disease Activity Score, including CRP (ASDAS).

Results: Of 170 patients, 122 (71.8%) were male and 130 (82.8%) were HLA-B27 positive. At baseline median BASDAI was 6.0 (IQR 4.8–7.1) and mean ASDAS was 3.5 (SD 1.0). After 24 weeks 98 (57.6%) patients were BASDAI responder (last observation carried forward), mean ASDAS (SD) for responders was 1.6 (0.9) vs. 2.4 (0.9) for non-responders (p<0.001). Of 170 patients 19 dropped out: 16 (84.2%) due to treatment failure or adverse events and 3 (15.8%) due to other reasons. At 24 weeks of treatment etanercept levels were significantly higher in patients with inactive to moderate disease activity (ASDAS <2.1, median (IQR) 3.7 (2.5–5.5)) compared to patients with high to very high disease activity (ASDAS ≥2.1, (median (IQR) 2.3 (1.2–3.7)) (p=0.01). When patients were categorized into quartiles according to the height of etanercept levels at 24 weeks, the lowest quartile (etanercept level < 1.8 mg/L) comprised 35.1% of all patients with ASDAS ≥2.1. The highest quartile (etanercept level > 5.0 mg/L) comprised 33.8% of all patients with ASDAS <2.1 (fig. 1). There were no significant differences at baseline between patients from the lowest quartile compared to patients from the highest quartile.

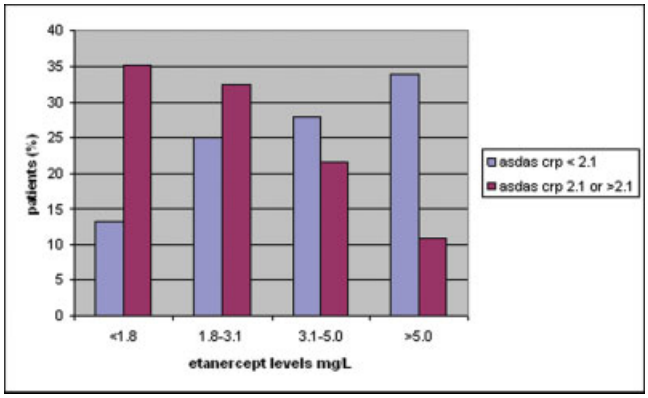

Figure 1. Percentage of patients with ASDAS <2.1 and ≥2.1 stratified according to the height of *etanercept levels. Each group contains 25% of all patients.*

Conclusion: Lower etanercept levels in AS are associated with higher disease activity at 24 weeks of treatment.

[1]de Vries MK et al. ARD 2009

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1525

Measurement Of Lateral Spinal Flexion and Schober Is Sufficient To Be Informed About Spinal Mobility In Patients With Ankylosing Spondylitis: 12-Year OASIS Results. Sofia Ramiro[1], Robert Landewé[2], Désirée van der Heijde[3], Carmen Stolwijk[4], Maxime Dougados[5], Filip Van den Bosch[6] and A.M. van Tubergen[4]. [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center Amsterdam & Atrium Medical Center, Heerlen, Netherlands, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Maastricht University Medical Center, Maastricht, Netherlands, [5]Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France, [6]Gent University Hospital, Gent, Belgium.

Background/Purpose: We have shown that spinal mobility gets impaired in a fixed order in ankylosing spondylitis (AS), with the highest impairment in lumbar spine. We sought to investigate whether assessing few measures could capture full information on impairment in spinal mobility, which would be useful for clinical practice.

Methods: Patients from the Outcome in AS International Study (OASIS) were followed-up for 12 years in which spinal mobility was regularly measured (see Table). From a previous study in normal subjects (1), percentile curves (2.5th to 97.5th) were obtained for each of the spinal mobility measures (SMMs) (Figure). We added 4 parallel curves representing z-scores of 2.5, 3, 3.5 and 4 respectively (helplines a to d) to be able to plot impaired measures. Each of the SMMs was defined as impaired if the measurement fell below help-line a (first cutoff below normal subjects). The number of observations and of patients using baseline observation only with at least one SMM impaired was calculated. Of those, the proportion of observations or of patients, respectively, with each of the SMMs impaired was calculated. Furthermore, we investigated in how many cases would impairment in spinal mobility be missed if only a fixed number of SMMs was assessed.

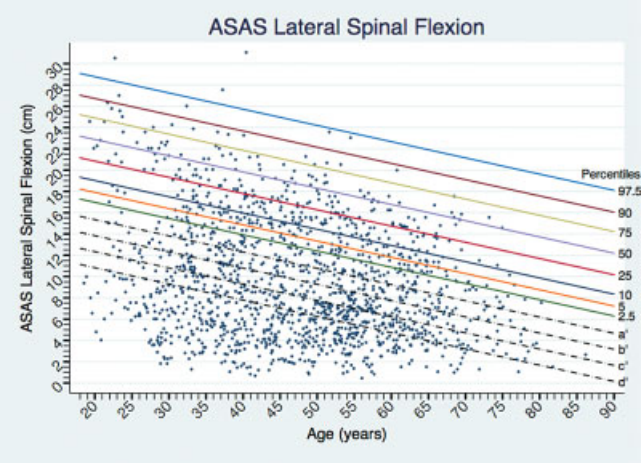

Figure. Lateral spinal flexion in function of age and with the percentile curves and help-lines derived from normal subjects

Results: A total of 216 patients were included (70% males, mean (SD) age 44(13) years, mean symptom duration 21(12) years and 85% HLA-B27 positive). Impairment in spinal mobility was present in 1111 (78%) out of 1422 observations and in 161 (79%) out of the 203 patients with a complete baseline assessment. From the observations (and also patients) with at least one impaired SMM, in 83% (86% of the patients) lateral spinal flexion (LSF) was impaired, followed by Schober in 63% of them (58% of the patients). In one quarter of the observations, 1 SMM was impaired, in 32% 2 SMMs and in 18% 3 SMMs. At a patient-level, 1 SMM was impaired in 30% of the patients, 2 SMMs in 33% and 3 SMMs in 17%. If only LSF was measured, 17% of the observations (14% of the patients) with impairment in SMM would be missed. If additionally Schober was also measured, only 9% of the observations (and also of patients) would be missed (Table).

Table. Impairment of each of the spinal mobility measures in patients with AS in measurements with at least one SMM impaired

	Observation-level n (%) (N = 1111)	Patient-level (baseline assessment) n (%) (N = 161)
Impairment in each of the spinal mobility measures		
Lateral spinal flexion	919 (83)	138 (86)
Schober	696 (63)	94 (58)
Tragus-to-wall distance	490 (44)	62 (39)
Cervical rotation	349 (31)	44 (27)
Intermalleolar distance	207 (19)	27 (17)
Chest expansion	139 (13)	17 (11)
Impairment in spinal mobility missed if only the following measurements are performed		
Lateral spinal flexion	192 (17)	23 (14)
Lateral spinal flexion+ Schober	103 (9)	14 (9)
Lateral spinal flexion+ Schober+ tragus-to-wall distance	44 (4)	7 (4)
Lateral spinal flexion+ Schober+ tragus-to-wall distance+ cervical rotation	14 (1)	1 (1)
Lateral spinal flexion+ Schober+ tragus-to-wall distance+ cervical rotation+ intermalleolar distance	3 (0)	1 (1)

Conclusion: Impairment in spinal mobility can be investigated by assessing only 2 SMMs. We hereby recommend that measurement of LSF and Schober is sufficient to be informed about impairment in spinal mobility in patients with AS. Only if these are impaired it is important to assess additional measures.

Reference:

(1) Ramiro et al. A&R 64(12):4173–4174

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1526

Stable Clinical and MRI Response In Patients With Early Axial Spondyloarthritis After 3 Years Of Continuous Treatment With Etanercept, Data Of The Esther Trial. In-Ho Song[1], Kay-Geert A. Hermann[2], Hildrun Haibel[1], Christian Althoff[3], Denis Poddubnyy[4], Joachim Listing[5], Anja Weiss[6], Ekkehard Lange[7], Bruce Freundlich[8], Martin Rudwaleit[9] and Joachim Sieper[4]. [1]Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany, [2]Charité Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany, [3]Charite Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany, [4]Charité Universitätsmedizin Berlin, Berlin, Germany, [5]German Rheumatism Research Center, Berlin, Germany, [6]German Rheumatism Research Centre, Berlin, Germany, [7]Pfizer Pharma AG, Berlin, Germany, [8]University of Pennsylvania, Philadelphia, PA, [9]Endokrinologikum Berlin, Berlin, Germany.

Background/Purpose: In patients with early axial spondyloarthritis (SpA) with a disease duration of < 5 years and evidence of active inflammation on whole-body magnetic resonance imaging (wb-MRI) in the spine and/or sacroiliac joints (SIJ) at baseline [1] the long-term efficacy of etanercept (ETN) was assessed over three years.

Methods: In the previously reported ESTHER trial axial SpA patients were treated with ETN (n= 40) versus sulfasalazine (SSZ) (n= 36) in the first year [1]. All patients who were not in remission at week 48 (n=48) were either continuously treated with ETN, or sulfasalazine treatment was switched to ETN treatment. We analysed the clinical and MRI response in he pooled data set of patients who were continously treated with ETN for 3 consecutive years. Data were analysed as observed.

Results: In the pooled group of patients treated continously over 3 years with ETN (n= 60) the BASDAI decreased from 5.7 (standard deviation 1.3) to 2.0 (1.5), the ASDAS from 3.4 (0.8) to 1.2 (0.7). Also mean values for MRI spine and sacroiliac joint scores showed a significant decrease (table 1). ASAS partial remission after three years of ETA was reached by 43%, ASDAS inactive disease by 60% (table 1).

Table 1. Long-term efficacy over 3 years in patients with early axial spondyloarthritis treated with etanercept. Data at baseline (BL), after one year of treatment with etanercept, after two years and after three years of treatment with etanercept.

	ETN, Baseline	Data after one year of treatment with ETN	Data after two years of treatment with ETN	Data after three years of treatment with ETN
BASDAI (0–10)	5.7 (1.3)	2.5 (2.0)	2.1 (1.8)	2.0 (1.5)
BASFI (0–10)	4.4 (2.1)	2.0 (2.0)	1.6 (1.7)	1.4 (1.3)
ASDAS (0–…)	3.4 (0.8)	1.6 (0.8)	1.4 (0.9)	1.2 (0.7)
CRP (mg/l)	10.5 (13.6)	3.5 (4.6)	3.6 (5.5)	2.9 (5.5)
MRI Spine Score (−69)	1.6 (3.4)	NA	0.7 (1.4)	0.9 (1.8)
MRI SI-joint Score (−24)	4.6 (6.3)	NA	3.5 (6.1)	3.3 (6.0)
ASAS40, %	NA	68.4%	67.4%	75.0%
ASAS PR, %	NA	35.1%	53.5%	42.5%
ASDAS inactive disease, %	NA	38.9%	53.7%	60.0%
BASDAI50, %	NA	64.9%	65.1%	72.5%

Data shown as mean values (standard deviation) unless otherwise stated. Abbreviations: ETN: etanercept; ASAS PR: ASAS partial remission; NA: not applicable; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; ASAS: Assessment of SpondyloArthritis international Society; MRI: magnetic resonance imaging; SI-joint: sacroiliac joint.

Conclusion: There was a constant and sustained clinical response in patients with early axial SpA patients treated with ETN over 3 years. The response in this early axial SpA cohort seems to be better compared to established AS cohorts with a longer disease duration (> 10 years) where BASDAI50 response rates of 47% after 3 years of infliximab treatment [3] and ASAS40 and ASAS partial remission rates of 49% and 27%, respectively after 4 years of etanercept treatment [4] were reported.

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1527

Routine Assessment Of Patient Index Data 3 Scores Correlate Well With Bath Ankylosing Spondylitis Disease Activity Index In The Assessment Of Disease Activity and Monitoring Progression Of Ankylosing Spondylitis. Abhijeet Danve[1], Kiana Vakil-Gilani[1], Anusha Reddy[1], Annan Sheffield[2], Alexis Dinno[2] and Atul Deodhar[1]. [1]Oregon Health and Science University, Portland, OR, [2]Portland State University, Portland, OR.

Background/Purpose: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a composite tool unique to measure disease activity in ankylosing spondylitis (AS) just as Disease Activity Score 28 (DAS28) is for rheumatoid arthritis (RA). Routine Assessment of Patient Index Data 3 (RAPID3) is another composite tool that measures physical function, pain and patient global assessment in various rheumatic diseases. It correlates well with DAS28 in RA. If RAPID3 can also be used to assess disease activity in AS it may save time and costs in busy practices. Objectives of this study were to analyze the association between BASDAI and RAPID3 in patients with AS, and to obtain a cut-off value for RAPID3 which correlates with BASDAI of 4 (indicative of high disease activity).

Methods: An electronic medical record search identified 157 patients with AS at our university who were followed between 2007 to 2012. Of these, 113 patients had BASDAI and RAPID3 measured at each visit (intervals ranged from 1 to 57 months). Nonparametric receiver operating characteristic (ROC) determined a cut-off of RAPID3 best correlating with BASDAI ≥ 4. RAPID3 captures both pain and function, but BASDAI measures predominantly pain without function, so multiple linear regression modeled BASDAI with RAPID3 and RAPID3^2 while controlling for visit number. Individual BASDAI and RAPID3 scores and summaries were plotted and compared over time.

Results: Of 113 patients, 75 (66%) were male and 38 (34%) were female, age averaged 44.3 (SD: 13.7), disease duration averaged 8.4 years (SD 9), 77 (61%) had more than one visit, and 36 (39%) had only one. At baseline BASDAI and RAPID3 averaged 4.17 and 3.79 respectively. BASDAI was explained by RAPID3 ($b = 1.218$; s.e. $= 0.110$, $p < 0.001$), RAPID3^2 ($b = -0.045$; s.e. $= 0.014$, $p = 0.002$), and visit number ($b = -0.141$; s.e. $= 0.038$, $p < 0.001$) with adjusted $R^2 = 0.691$. RAPID3 cut-off was 3.33 for 82.4% correct classification, 87.5% sensitivity and 78.8% specificity.

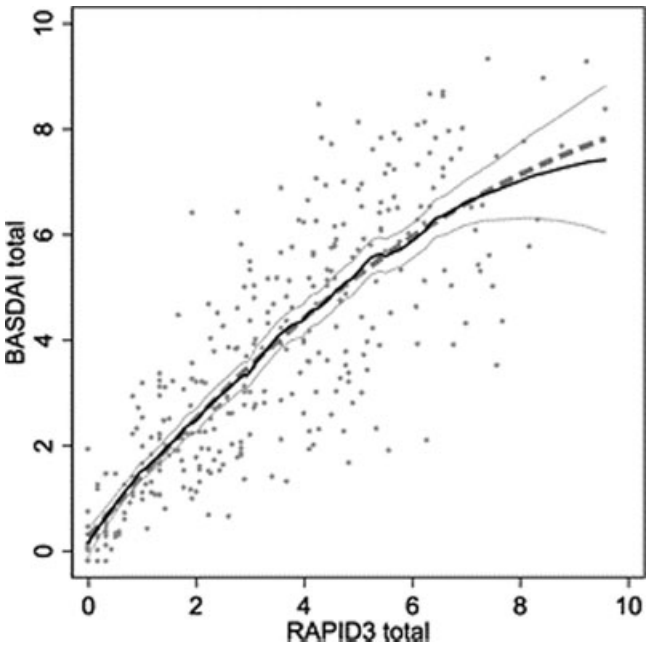

Figure 1. Nonparametric regression of BASDAI on RAPID3 (black with 95% CI in gray) controlling for visit number suggested we model BASDAI as a quadratic function of RAPID3 (thick dashed).

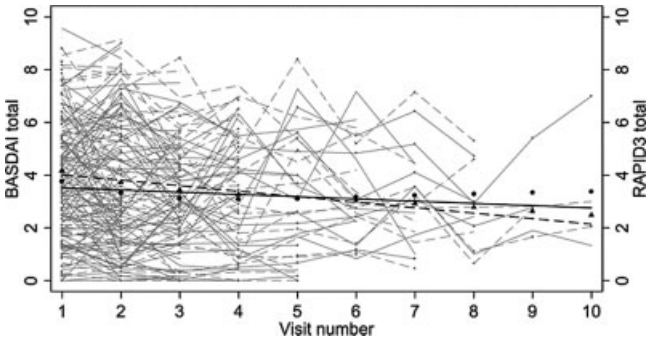

Figure 2. Individual BASDAI (thin dash) and RAPID3 (thin solid); regressions of BASDAI (thick dash) and RAPID3 (thick solid); locally weighted estimate BASDAI (▲) and RAPID3 (■).

Conclusion: RAPID3 correlates well with BASDAI, and along with pain, it provides additional information about patient function. Since it also correlates with measures of disease activity in RA and other rheumatic diseases, RAPID3 could be an attractive measure to be used in busy rheumatology practices.

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Patient-Tailored Dose Reduction Of Tumor Necrosis Factor-Alpha Blocking Agents In Ankylosing Spondylitis Patients With Stable Low Disease Activity. Suzanne Arends[1], Eveline van der Veer[1], Fleur B.S. Kamps[1], Monique Efde[2], Martha K. Leijsma[1], Hendrika Bootsma[1], Elisabeth Brouwer[1] and Anneke Spoorenberg[2]. [1]University Medical Center Groningen, Groningen, Netherlands, [2]Medical Center Leeuwarden, Leeuwarden, Netherlands.

Background/Purpose: Tumor necrosis factor-alpha (TNF-α) blocking agents are very effective in controlling inflammation and improving clinical assessments in patients with ankylosing spondylitis (AS). In view of the high costs and possible side effects, our aim was to investigate whether dose reduction of TNF-α blocking agents is possible without loss of effectiveness in AS patients in daily clinical practice.

Methods: Patients included in the Groningen Leeuwarden AS (GLAS) cohort, fulfilling the modified New York criteria for AS, with active disease (Bath AS disease activity index (BASDAI)≥4) before start of anti-TNF-α treatment and stable (≥6 months) low disease activity (BASDAI<4) on conventional dose regime, who started with dose reduction were studied. The dose reduction was patient-tailored and consisted of either lowering the dose or extending the interval between doses. For each specific TNF-α blocking agent, a fixed dose reduction schedule was used and evaluated at each follow up visit and, if necessary, adjusted in response to disease activity, side effects and co-morbidity, Data concerning medication dose, reasons for changing medication dose, and disease activity were collected after 6, 12, 18, and 24 months of dose reduction.

Results: Between November 2005 and January 2011, 49 AS patients with stable low disease activity started with dose reduction of infliximab (n=8), etanercept (n=35), or adalimumab (n=6). 88% of these patients were male, mean age was 46 years (SD±12), and mean duration of symptoms was 20 years (SD±10). Mean BASDAI was 1.8 (SD±1.1) at start of dose reduction, coming from 6.2 (SD±1.2) just before start of anti-TNF-α treatment.

In total, 71%, 54%, 47%, and 42% of the patients maintained on dose reduction after 6, 12, 18 and 24 months, respectively. The mean dose reduction was 37% (SD±11). Disease activity remained low (BASDAI<4) in 86% of the patients who continued dose reduction at 24 months (Table 1).

Of all 25 patients who did not continue dose reduction, 23 (92%) returned to the conventional dose regime and 2 (8%) patients stopped TNF-α blocking therapy (1 adverse events, 1 inefficacy due to antibody formation).

Table 1. Disease activity in AS patients who maintained dose reduction

	6 months	12 months	18 months	24 months
Patients still on dose reduction	35/49	25/46	21/45	18/43
	71%	54%	47%	42%
BASDAI <4	88%	83%	89%	86%

Conclusion: In this observational cohort, long-term dose reduction of TNF-α blocking agents was successful preserving stable low disease activity in a substantial number of AS patients.

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Patients With Imaging Abnormalities Of The Sacroiliac Joints Are More Likely To Respond To TNF Alpha Inhibitors In Early Axial Spondyloarthritis. Data From The DESIR Cohort. Anna Moltó[1], Simon Paternotte[2], Pascal Claudepierre[3] and Maxime Dougados[1]. [1]Paris- Descartes University, Paris, France, [2]Paris- Descartes University, Cochin hospital, Paris, France, [3]Paris-Est University; LIC EA4393; APHP, Henri Mondor Hospital, Creteil, France.

Background/Purpose: Efficacy of TNF alpha inhibitors (TNFi) has been clearly established in patients with axial SpondyloArthritis (ax-SpA), but its effectiveness and adherence with regard to specific patient characteristics remains to be evaluated in patients with early disease. The aim of the study was to evaluate the effectiveness of TNFi in a cohort of patients with inflammatory back pain (IBP) suggestive of ax-SpA. Secondary objectives were to estimate the retention rate of TNFi after 2 years of follow-up and the baseline predictors of such retention rate.

Methods: Observational prospective multi-centre study, with 708 patients with early IBP (< 3 years duration) suggestive of ax-SpA. Data included: demographics and disease characteristics of the first two years of follow-up. Statistical analysis: Effectiveness: patients receiving TNFi were matched with patients not receiving TNFi (but receiving usual care) at a 1:1 ratio according to a propensity-score. The primary endpoint of the study was ASAS40, assessed here at the last available visit still on treatment. Exploratory subgroup analyses evaluated the potential interactions existing between baseline characteristics and the treatment effect (p<0.10). Retention rate was estimated for all TNFi using a survival-data analysis by Kaplan-Meier. Cox analyses were performed to identify potential predisposing factors of such retention rate.

Results:

1. Treatment effect: 203 patients (28.7%) received at least one TNFi during follow-up; data for the assessment of the primary endpoint was available in 197 patients (97.0%) receiving TNFi, that were matched according to a propensity score to 197 patients receiving any other usual care. An ASAS40 response at the last available visit (74±30.9 weeks after initiation of TNFi) was achieved in 62 (31.8%) patients receiving TNFi treatment vs. 31 (16.0%) patients receiving usual care (OR = 2.45 [1.50 – 3.99], p=0,004).
2. Exploratory subgroup analyses detected that patients with X-ray sacroiliitis (OR=9.12 [3.22–25.80] and OR=1.32[0.73–2.41], for X-ray sacroiliitis yes/no, p=0.002), MRI sacroiliitis (OR=5.10 [2.28–11.41] and OR=1.32[0.68–2.56] for MRI sacroiliitis yes/no, p=0.011) and fulfilling the imaging arm (OR=5.34 [2.51–11.33] and OR=0.78 [0.32–1.89] for the imaging and clinical arms, respectively, p=0.001) were more likely to achieve an ASAS40 response with TNFi, compared to usual care. No significant interaction was detected between CRP abnormality and treatment effect.
3. Retention rate: Of the 203 patients included, Kaplan-Meier estimates of the proportion of patients still on TNFi over time were 75.2% [69.0–81.3] and 41.2% [33.2–49.1], at 6 and 24 months after initiation, respectively. HLA B27 presence (HR=0.66[0.44–0.99], p=0.044) and X-ray sacroiliitis at baseline (HR=0.48 [0.30–0.78], p=0.003) were associated with a prolonged continuation of the TNFi over time.

Conclusion: In daily practice, use of TNFi was frequent in active early ax-SpA, whatever the subgroup of the ASAS criteria the patients were fulfilling. However patients with imaging abnormalities were more likely to achieve a TNFi response compared to usual care.

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Vitamin D Deficiency Is Associated With a More Active and Severe Disease In Early Axial Spondyloarthritis: Data From The DESIR Cohort. Ihsane Hmamouchi[1], Simon Paternotte[2], Didier Borderie[3] and Maxime Dougados[4]. [1]Paris Descartes University, Cochin Hospital, Paris, France, [2]Paris- Descartes University, Cochin hospital, Paris, France, [3]Paris Descartes UNiversity, Pris, France, [4]Paris-Descartes University, APHP, Cochin Hospital, Paris, France.

Background/Purpose: Objectives

a) to describe the vitamin D status b) to assess the relationship between vitamin D status and disease activity/severity and c) to estimate the relationship between vitamin D status and comorbidities in an early axial spondyloarthritis (SpA).

Methods: Patients: 708 patients with early inflammatory back pain suggestive of spondyloarthritis have been included in the DESIR cohort. This analysis was restricted to the patients fulfilling at least one set of criteria for the diagnosis of SpA (e.g. Amor, ESSG or ASAS criteria).

Study design: prospective, multi-centre, observational study.

Data collected: 25OHvitD was measured on baseline frozen stored plasma. Radiological and densitometric variables were collected at baseline as well as the cardiovascular risk factors (high-density lipoprotein (HDL) cholesterol, abdominal obesity, triglycerides, blood pressure and fasting glucose) whereas clinical variables (BASDAI, BASFI, BASMI, ASDAS) were collected at each 6 month interval visits during the 2 years follow-up.

Data analysis: The 25OHvitD insufficiency threshold was defined by the Vitamin D first quartile. Correlations between this insufficiency and the other variables were done using uni- and multivariate analysis.

Results: A total of 653 patients fulfilling at least one of the criteria for SpA were analysed. A 25OHvitD insufficiency was defined by a value below: 13.29 ng/ml. Such insufficiency was more pronounced in winter (37.1% vs. 9.2%) and in non Caucasian patients (50.8% vs. 22.6%).

After adjusting for season and ethnicity, baseline 25OHvitD remained significantly associated with baseline radiological sacroilitis (1.71 [1.13 – 2.57]), baseline ASDAS crp (1.20 [0.99 – 1.46]), and mean BASMI during the 2 years of follow up (1.46 [0.99 – 2.15]). There was no statistically significant correlation between baseline vitamin D levels and bone densitometry or cardiovascular risk factors.

Conclusion: These results indicate that high disease activity and severity in early axial SpA is associated with low vitamin D. Further longitudinal studies are required to evaluate the interest of Vit D supplementation on the long term outcome of the disease.

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Agreement Between Disease Activity States and Improvement Scores As Defined by Bath Ankylosing Spondylitis Disease Activity Index and Ankylosing Spondylitis Disease Activity Score Cut-Off Values. Dilek Solmaz[1], Pinar Cetin[1], Ismail Sari[1], Merih Birlik[2], Servet Akar[1], Fatos Onen[1] and Nurullah Akkoc[1]. [1]Dokuz Eylul University School of Medicine, Izmir, Turkey, [2]Dokuz Eylul University School of Medicine, izmir, Turkey.

Background/Purpose: BASDAI has been extensively used to assess disease activity in ankylosing spondylitis (AS) BASDAI score ≥4 represent high disease activity and has been suggested as an eligibility criterion for initiation of anti-TNF therapy. ASDAS is a new composite clinical tool to assess disease activity in AS. ASDAS values of 2.1 and 3.5 have been selected as cut-off values to define high and very high disease activity, respectively and ASDAS ≥ 2.1 has been proposed as a suitable cut-off for eligibility for anti-TNF therapy The aim of this study was to estimate the corresponding BASDAI and ASDAS cut-off values for initiation of anti-TNF therapy and to assess the agreement between disease activity states defined by BASDAI and ASDAS values.

Methods: Patients with complete baseline data for ASDAS based on CRP and BASDAI were included. Mean ASDAS and BASDAI values were compared by Spearman correlation. Receiver operating characteristic (ROC) curves were constructed to determine the cut-off value of ASDAS that correspond to BASDAI score of 4 and to asses the cut-off value of BASDAI that correspond to ASDAS values of 2.1 and 3.5 Each cut-off point was calculated on the basis of the best trade-off values between sensitivity and specificity. The Kappa statistic was used to test the agreement between the disease activity states according to ASDAS and BASDAI, as well as the agreement between the clinical improvement as assessed by the two instruments (for patients with available data).

Results: 396 patients (291 M; 44 ±12.0) were identified with complete data at baseline Mean disease duration was 9.4 ± 8.2.Mean BASDAI, and ASDAS scores were 3.6 ± 2.3 and 2.9 ± 1.1 There was good correlation between ASDAS and BASDAI when tested by Spearman ($p<0.001$; $r=0.9$). The best trade-off ASDAS value corresponding to BASDAI score of 4 was 2.9 (80% sensitivity and 77% specificity; AUC: 0.88) whereas the best trade-off BASDAI values corresponding to ASDAS≥2.1 and ≥3.5 were 2.4 (84% sensitivity and 83% specificity; AUC: 0.90) and 3.7 (89% sensitivity and 69% specificity; AUC: 0.87), respectively. Similar cut-off values were obtained for different gender and age groups(≤40/>40 years).Overall percent agreement of BASDAI≥4with ASDAS≥2.1 and ASDAS≥ 3.5were 67 and 76%, with κ valuesof 0.39 and 0.48, respectively. There was a moderate agreement between both the major clinical response measured by BASDAI50 and that by ΔASDAS≥2 ($\kappa=0.441$) and the minimal clinical improvement as measured by ΔBASDAI≥ 2and ΔASDAS≥1.1 ($\kappa=0.545$).

Table 1. Agreement between BASDAI≥4and high and very high disease activity states according to ASDAS

		ASDAS				
		<2.1	≥2.1	>3.5	≥3.5	Total
BASDAI	<4	99	129	211	17	228
	≥4	1	167	78	90	168
	Total	100	296	289	107	396

Conclusion: The ASDAS value that corresponds to the recommended BASDAI cut-off ≥4 for initiation of anti-TNF therapy is higher than the recommended ASDAS threshold of ≥ 2.1. Agreement between high disease activity states as defined by BASDAI and that by ASDAS is only fair, whereas agreement between clinical response as measured by BASDAI and that by ASDAS seems to be better.

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Anti-Tumor Necrosis Fator Therapy Is Associated With Resolution Of Erosion In The Sacroiliac Joints Of Patients With Spondyloarthritis. Susanne Juhl Pedersen[1], Stephanie Wichuk[2], Praveena Chiowchanwisawakit[3], Robert GW Lambert[2] and Walter P. Maksymowych[2]. [1]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [2]University of Alberta, Edmonton, AB, [3]Mahidol University, Bangkok, Thailand.

Background/Purpose: Radiography of the sacroiliac joints (SIJ) in spondyloarthritis (SpA) is a valuable diagnostic tool but is unreliable and unresponsive for assessment of treatment effects. There is an unmet need for imaging tools to assess the potential disease-modifying effects of therapeutic agents early in SpA when disease is still confined to the SIJ. There has been limited assessment of MRI-based scores for structural lesions in the SIJ, which indicate that scoring fat metaplasia may discriminate between therapies. But the significance of this for structural damage is unclear. The SPARCC MRI SIJ Structural Score (SSS) assesses a broader spectrum of structural lesions and its potential to discriminate between therapies requires evaluation.

Methods: The SSS method assesses fat metaplasia (FAT), erosion (ER), backfill (BF), and ankylosis (ANK) according to standardized and validated definitions (Morpho). It scores 5 consecutive coronal slices anteriorly through the cartilaginous portion of the joint from the transitional slice, defined as the first slice in the cartilaginous portion that has a visible portion of the ligamentous joint. Lesions are scored dichotomously (present/absent) in SIJ quadrants (fat, erosion) or halves (backfill, ankylosis) using a direct online data entry system based on schematics of the SIJ. Scoring ranges are: FAT (0–40), ER (0–40), BF (0–20), ANK (0–20). After a calibration exercise, two readers independently scored 147 pairs of scans conducted at baseline and 2 years from a prospective cohort of patients with SpA who received either standard (n=69) or anti-TNF (n=78) therapies. Baseline status and change scores were assessed by intraclass correlation coefficient (ICC3,1), and smallest detectable change (SDC) was calculated using ANOVA and expressed as an absolute value and as a percentage of the maximum score. Discrimination was assessed using Guyatt's effect size and treatment group differences using the Mann-Whitney test.

Results: Baseline clinical characteristics were similar except for significantly higher CRP and BASDAI in the anti-TNF treated group. Baseline SSS ANK and BF scores were also significantly higher in the anti-TNF treated group ($p=0.014$ and 0.022, respectively). The number (%) of patients with new and resolved erosions at 2 years was 6 (7.6%) and 32 (40.5%) in the anti-TNF group versus 16 (23.5%) and 21 (30.9%) in the standard group ($\chi^2=7.4$, $p=0.02$). Significantly greater increase in SSS Fat and decrease in SSS ER scores was evident in the anti-TNF treated group (Table).

	Baseline ICC [95%CI]	Change ICC [95%CI]	SDC (% maximum range)	Mean BL Score (SD)		Mean change score (SD)		Guyatt's ES	P value
				Anti-TNF	Standard	Anti-TNF	Standard		
FAT	0.72 [0.47–0.84]	0.40 [0.25–0.53]	3.4 (8.5%)	3.6 (5.1)	4.0 (6.6)	0.7 (2.2)	0.2 (1.5)	0.46	0.017
BACKFILL	0.48 [0.24–0.64]	0.49 [0.35–0.61]	4.2 (21.2%)	3.7 (4.5)	2.2 (3.1)	0.1 (2.9)	0.4 (1.9)	0.03	NS
EROSION	0.56 [0.30–0.72]	0.51 [0.38–0.62]	4.7 (11.7%)	2.7 (3.2)	3.6 (4.4)	−1.5 (2.8)	−0.5 (2.7)	0.55	0.017
ANKYLOSIS	0.97 [0.96–0.98]	0.63 [0.52–0.72]	2.1 (10.6%)	7.3 (8.5)	4.1 (7.0)	0.4 (1.6)	0.3 (1.2)	0.33	NS

Conclusion: The SPARCC SSS method for assessment of structural lesions has discriminative capacity in demonstrating significantly greater reduction in erosion in patients receiving anti-TNF.

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Work Outcome In Patients With Ankylosing Spondylitis: 12-Year Results From OASIS. Jose Dionisio Castillo-Ortiz[1], Sofia Ramiro[2], R. Landewe[3], D. van der Heijde[4], Maxime Dougados[5], Filip van Den Bosch[6] and Annelies Boonen[7]. [1]Unidad de Investigacion en Enfermedades Cronico-Degenerativas, Guadalajara, Mexico, [2]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [3]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands, [4]Leiden University Medical Center, Leiden, Netherlands, [5]Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France, [6]Department of Rheumatology Ghent University Hospital, Ghent, Belgium, [7]Maastricht University Medical Center, Maastricht, Netherlands.

Background/Purpose: Almost all studies on the impact of Ankylosing Spondylitis (AS) on the employment status or work disability (WD), the far majority of these studies are cross-sectional analyses and none compared work outcome over time with the general population. We aimed at quantifying the long-term impact of AS on participation in labour force over 12 years in a prospective cohort study, at identifying predictors of an adverse work outcome (AWO) and at comparing the incidence of WD over time with the general population.

Methods: Work related information and clinical characteristics were obtained from patients followed in the Outcome in AS International Study (OASIS) during 12 years. Patients who were at risk of having an AWO at any time were included in the analysis (i.e. those working, either at baseline or

starting/resuming work later). AWO was defined as WD or a reduction in the number of working hours. Survival analysis was used to investigate AWO. With Cox regression, first baseline and secondly time-varying predictors (with 2-year time-lag) were identified; the latter adjusted for 2 time dependent variables (change in social security system and market availability of anti-TNF). Incidence rate for WD over 12 years among Dutch patients was compared with the general population using indirect standardization.

Results: Of the 215 (of 216) patients in OASIS cohort with baseline data on work status, 139 (65%) were at risk for AWO (mean age 38(SD 10) years, 75 % male, 81% HLA-B27 positive, mean disease duration 9 (SD 7) years), of whom 11% (n=15) were not working at baseline but resumed work over time. Thirty one of 139 patients (22%) experienced AWO; 12 (39%) became full-work disabled (full-WD), 5 (16%) partial work disabled (partial-WD) and 14 (45%) reduced working hours. For a total 1404, person years, Kaplan Meier analysis revealed a 2.2% of annual rate of AWO. Multivariable Cox analysis showed that higher baseline BASFI (HR 1.3; 95% CI 1.01–1.4) and Dutch origin (HR 3.6; 95% CI 1.3–10.0) predicted long-term AOW. In the time-lagged prediction analysis, higher BASFI (HR 1.3; 95%CI 1.1–1.5) and Dutch origin (HR 3.0; 95% CI 1.2–8.2) significantly predicted AWO over time. Of 130 Dutch patients in working age, 9% (n=12) became WD over 12 years. Among Dutch patients the incidence rate of WD over 12 years was 2.9 (95% CI 1.2; 4.6) and 1.2 (95% CI −0.4; 2.9) times higher compared with the general population, for males and females, respectively.

Conclusion: Even in AS patients with already long disease duration, the disease continues to have a negative impact on work outcome. Self-reported physical function (BASFI) and system characteristics, but not job-type, disease activity or structural damage consistently influence AWO.

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Safety and Efficacy Of Golimumab, a Human Anti-Tumor Necrosis Factor Monoclonal Antibody Injected Subcutaneously Every 4 Weeks, In Chinese Patients With Active Ankylosing Spondylitis: 1-Year Results Of a Phase 3, Randomized, Placebo-Controlled Study. Chunde Bao[1], Feng Huang[2], Muhammad Asim Khan[3], Kaiyin Fei[4], Zhong Wu[4], Yanli Zhuang[4], Timothy A. Gathany[5], Chenglong Han[5] and Elizabeth C. Hsia[6]. [1]Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, [2]Chinese PLA General Hospital, Beijing, China, [3]Case Western Reserve University Hospital, Cleveland, OH, [4]Janssen Research & Development, LLC., Spring House, PA, [5]Janssen Global Services, LLC., Malvern, PA, [6]Janssen Research & Development, LLC./U of Penn, Spring House/Philadelphia, PA.

Background/Purpose: A multicenter, randomized, placebo (PBO)-controlled study of golimumab (GLM) was performed in Chinese pts with ankylosing spondylitis (AS). To assess efficacy and safety of golimumab (GLM) through wk56 in Chinese patients with active AS.

Methods: Chinese pts aged >18yrs with a diagnosis of active AS (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] >4, and a visual analogue scale [VAS] for total back pain >4, each on a scale of 0–10cm) for >3 months prior to screening were eligible for the study. Pts with prior exposure to anti-TNF agents and those with complete ankylosis of the spine were excluded. 213 pts were randomized (1:1) to q4wk subcutaneous (SC) injections of PBO from wks 0 to 20, followed by GLM 50mg from wks 24 to 48 (Group1, n=105) or GLM 50mg from wks 0 to 48 (Group2, n=108). Group1 pts with <20% improvement from baseline in both total back pain and morning stiffness at wk16 were switched to SC GLM 50mg SC q4wks in a blinded fashion (early escape). At wk 24, all remaining PBO pts in Group1 crossed over to SC GLM 50mg q4wks. The primary endpoint for efficacy was the proportion of patients who achieved ASAS20 response (^{3} 20% improvement in the ASsessment in AS [ASAS] criteria) at wk14. Major secondary endpoints included ASAS20 response at wk24,changes from baseline at wk14 in Bath AS Functional Index (BASFI) and Bath AS Metrology Index (BASMI). Other efficacy assessments included health-related quality of life (SF-36 PCS and MCS scores), and sleep (Jenkins Sleep Evaluation Questionnaire, JSEQ) measures. Antibodies to GLM were evaluated at wk52. The last GLM injection was at wk48; final efficacy assessments were at wk52. Safety was monitored through wk56.

Results: Baseline demographics were comparable in the 2 groups; median age was 29yrs, median weight of 62.0kg, and 83.1% were males. ASAS20 at wk14 was achieved by 49.1% of pts in Group2 vs. 24.8% in Group1 (p<0.001). GLM treatment also elicited a significantly better response than PBO in other efficacy parameters assessed, including ASAS20 response at wk24 (50.0% vs. 22.9%; p<0.001) and mean improvements in BASFI (−1.26 vs. 0.113; p< 0.001) and BASMI (−0.42 vs. −0.19; p=0.021) scores at wk14 and SF-36 PCS and MCS and JSEQ at wk14 and wk24. These improvements in clinical symptoms, physical function, range of motion, as well as significant improvements in SF-36 MCS and PCS were further enhanced through the final efficacy assessment at wk52. Through wk16, 31.4% and 30.6% of pts had adverse events (AEs) in Groups1 and 2, respectively. Through wk56, 41.2% of GLM-treated patients reported AEs, and 2.8% reported serious AEs. Through wk56, infections were reported in 20.9% of all GLM-treated pts. One SAE of tuberculosis pleurisy was reported, and the pt recovered. No opportunistic infections or deaths were reported. Antibodies to GLM were not detected in GLM-treated patients through wk52.

Conclusion: GLM significantly reduced AS symptoms/signs and functional limitations and improved health-related quality of life in Chinese pts with active AS. Treatment with GLM was well tolerated and without unexpected safety concerns.

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1535

Phenotype Of Patients and Impact Of The Disease In Early Spondyloarthritis Are Similar Regardless The Arm Of The Assessment In Spondyloarthritis International Society Criteria ("imaging" or "clinical") Fulfilled By The Patients. Data From The DESIR Cohort. Anna Molto[1], Simon Paternotte[2], Désirée van der Heijde[3], Pascal Claudepierre[4], Martin Rudwaleit[5] and Maxime Dougados[1]. [1]Paris-Descartes University, APHP, Cochin Hospital, Paris, France, [2]Paris- Descartes University, Cochin hospital, Paris, France, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Henri Mondor Teaching Hospital, AP-HP, Créteil, France, [5]Endokrinologikum Berlin, Berlin, Germany.

Background/Purpose: Patients can fulfil the ASAS (Assessment of SpondyloArthritiS) sets of criteria with either objective evidence of sacroiliac joint damage (X-Ray) or inflammation (MRI): ("imaging" arm) or without such imaging abnormalities in B27 patients ("clinical" arm). The clinical arm is not well recognized by the medical community and the health care systems. The aim of this study was to compare the phenotype but also the impact of the disease on the daily life of the patients with regard to the 2 different arms (e.g. "imaging" versus "clinical") of early spondyloarthritis patients.

Methods: Study design: prospective, multi-centre, observational study. Patients: 708 patients with early inflammatory back pain suggestive of spondyloarthritis have been included in the DESIR cohort. Data collected: demographics, items of the ASAS criteria, disease activity, severity. Statistical analysis: The patients fulfilling the ASAS criteria were split in two groups regarding the presence of imaging (X-ray or MRI) abnormalities of the sacroiliac joints (e.g. imaging arm), and within the clinical arm, with regard to the presence of CRP abnormality (e.g. >6mg/L).

Results: Of the 708 recruited patients, lack of missing data permitted to classify 682 patients according to the ASAS criteria: 206 (30.2%) did not fulfill them; of the 476 (69.8%) remaining patients, 296 (60.1%) and 190 (39.9%) fulfilled the imaging and clinical arm respectively. Comparison in the patients (age, gender, B27 positivity) and disease (clinical presentation, activity and severity) characteristics fulfilling the two arms of the ASAS criteria for axial SpA showed no differences between both groups except in terms of age, gender and CRP: younger patients, more males and higher CRP values in the "imaging" arm. The multiple logistic regression analysis (by including all variables with a p<0.20 in univariated analyses) confirmed the positive association of male gender (OR 1.70 [1.12 – 2.58]) and ASDAS-CRP (OR 2.44 [1.73 – 3.44]) with the "imaging" arm.

Conclusion: This study suggests that despite some differences (e.g. gender, inflammation) the impact of the disease on daily activities were similar in both arms (e.g. imaging vs. clinical) and therefore therapeutical strategies and access to care in disabled patients should be identical regardless the arm of the ASAS criteria they are fulfilling.

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1536

Do Patients With Ankylosing Spondylitis Have An Excess Prevalence Of Chronic Widespread PAIN?: Results From The Scotland and Ireland Registry For Ankylosing Spondylitis (SIRAS) and The Musician Study. Fabiola Azeni[1], Marcus Beasley[2], Linda E. Dean[2], Gareth T Jones[2], Jane Gibson[3], Piercarlo Sarzi-Puttini[4] and Gary J. Macfarlane on behalf of SIRAS and MUSICIAN study investigators[2]. [1]Rheumatology Unit, L.Sacco University Hospital, Milan, Italy, [2]University of Aberdeen, Aberdeen, United Kingdom, [3]Fife Rheumatic Diseases Unit, Kircaldy, United Kingdom, [4]Rheumatology Unit, L. Sacco University Hospital, Milan, Italy.

Background/Purpose: To determine whether there is an excess prevalence of chronic widespread body pain (CWP) in patients with Ankylosing spondylitis (AS).

Methods: Patients were participants in the Scotland and Ireland Registry for Ankyolsing Spondylitis (SIRAS), an ongoing study of patients attending secondary care in Scotland who had received a clinical diagnosis of AS. The study collected information on clinical features, including extra-spinal manifestations, BASDAI and BASFI from medical records, and patient-reported data by self-completion questionnaires (including fatigue measured by the Chalder Fatigue Scale (CFS)). Information on CWP was collected by four-view body manikins and required to satisfy the definition used in the ACR 1990 criteria for FM (ACR-CWP) – i.e. chronic pain (>3 months) in 2 contralateral body quadrants, plus axial pain. We believed the reporting of CWP among AS patients would be strongly influenced by spinal disease and, thus, would be difficult to interpret. Therefore, we evaluated the total number of painful body regions reported (up to a maximum of 30) and used an alternative definition for CWP (aCWP) requiring chronic pain in 2 contralateral body quadrants, but excluding pain in the axial skeleton and/or the buttocks. Population data on the prevalence of CWP (using the same definitions) was from the MUSICIAN study, a large two-centre UK population-based study of pain in adults. Prevalence of aCWP was calculated in AS patients and reported as a standardised prevalence ratio (SPR). Relationships with reporting aCWP in the AS population were evaluated by logistic regression and expressed as odds ratios (OR) with 95% Confidence Intervals (95%CI).

Results: The analysis involved 547 AS patients in SIRAS (71% male; median age 52yrs) and a population sample of 14,680 persons from the MUSICIAN study. The majority of the AS patients (89% of those tested) were HLA B27 positive, 81% had documented sacroiliitis, 34% had peripheral joint involvement and 29% had a history of uveitis. 24% had ever been prescribed anti-TNF drugs. The prevalence of ACR-CWP among AS patients was 55.0% The number of non-spine body regions in which pain was reported was significantly higher in AS patients (median=5) than the general population (median=2) (Mann-Whitney $p<0.001$). The prevalence of aCWP was 53.4% and the SPR in AS patients using this alternative definition was (284; 95%CI 260–307). Prevalence of aCWP was higher among women than men (OR: 1.56; 95%CI: 1.07–2.27), and amongst those of lower education (school vs university education 1.89; 1.14–3.14); those unemployed due to ill-health (5.11; 2.57–10.17, vs those in paid employment); and those with a BASDAI or BASFI score ≥4 (3.94; 2.38–6.49, and 3.75; 2.24–6.25, respectively). Similarly, high levels of fatigue (CFS >4) (2.86, 2.01–4.08) and past or current use of anti-TNF agents (1.63; 1.07–2.49) were also associated with aCWP.

Conclusion: The age and sex adjusted prevalence of CWP (using a modified definition more suited to AS patients) was almost three times higher in AS patients than in the general population, and was related to both individual and clinical factors. The identification of such symptoms in AS patients is challenging but important for management.

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Primary & Subsequent Orthopedic Surgeries More Common In Juvenile *Vs.* Adult-Onset Ankylosing Spondylitis. Deepak R. Jadon[1], Ramani Arumugam[1], Gavin Shaddick[2], Alison L Nightingale[2], Athimalaipet V Ramanan[3] and Raj Sengupta[1]. [1]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [2]University of Bath, Bath, United Kingdom, [3]University of Bristol Hospital Trust, Bristol, United Kingdom.

Background/Purpose: Patients experiencing ankylosing spondylitis (AS) symptoms [2]16 years-of-age are classified as juvenile-onset AS (JoAS), whilst those ≥17 years adult-onset AS (AoAS). We compared JoAS and AoAS cases with respect to proceeding to orthopedic surgery, date and type of surgery, and revisions.

Methods: A cross-sectional observational cohort study was conducted of all AS patients attending a secondary care rheumatology hospital since 1970.

The following were recorded: sex, age at symptom onset, age at diagnosis, *HLA-B27* genotype status, smoking history, peripheral arthritis, psoriasis, uveitis, enthesitis, inflammatory bowel disease, family history of spondyloarthropathy (SpA), and AS-related orthopedic surgery.

Univariate analyses used t-tests and Fisher's exact tests for continuous and categorical variables, respectively. Multivariate analyses were performed using logistic regression with variable selection based on stepwise selection.

Results: 143 JoAS were compared with 411 AoAS patients. At assessment, JoAS were slightly younger than AoAS cases (mean difference 2.9 years), and had slightly longer disease duration since diagnosis (26.0 *vs.*19.3 years). No statistically significant differences were found between the two groups in terms of sex distribution, *HLA-B27* positivity, psoriasis, enthesitis or uveitis.

JoAS cases (n=29/143) were more likely to have had AS-related surgery than AoAS cases (n=29/411) even after adjusting for longer time since diagnosis (p=0.017).

Direct comparisons were then made of JoAS and AoAS cases proceeding to surgery (*Table 1*). No significant difference was found in the disease durations of JoAS and AoAS surgical cases to first surgery (diagnosis to first surgery, p=0.458; or symptom onset to first surgery, p=0.724).

The likelihood of second surgery (of any type) in AoAS cases was significantly less than for JoAS cases (adjusted analysis: OR 0.277; 95% CI 0.078–0.980; p=0.047).

Considering the likelihood of having a second surgery in the AS surgical cohort, smoking (OR 6.559 for ever having smoked *vs.* never smoked; p=0.097) and *HLA-B27* positivity (OR 1.002; p=0.054) were significant predictors.

Considering the likelihood of having a hip procedure (arthroplasty or resurfacing), family history of SpA (OR 0.999; p=0.05) and age of symptom onset (OR 0.997; p=0.09) were significant predictors.

Most AoAS cases had their hip arthroplasty by 20 years disease duration (n=22), thereafter the procedure was infrequent (n=2 of 36 potential native hips).

Table 1.

	SURGERY																
	1st		2nd		3rd		4th		5th		6th		7th		8th		ROW
PROCEDURE	JoAS	AoAS	JoAS	AoAS	JoAS	AoAS	JoAS	AoAS	JoAS	AoAS	JoAS	AoAS	JoAS	AoAS	JoAS	AoAS	TOTALS
Hip arthroplasty	19	20	13	13	3	0	0	0	0	0	0	0	0	0	0	0	68
Hip resurfacing	7	3	3	2	1	0	0	0	0	0	0	0	0	0	0	0	16
Knee replacement	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Knee arthroscopy	1	1	4	0	0	0	1	0	0	0	0	0	0	0	0	0	7
Lumbar laminectomy	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Lumbar osteotomy	1	2	0	0	0	0	0	1	0	0	0	0	0	0	0	0	4
Spinal fusion	0	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	3
Wrist fusion	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Tendon surgery	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Hip revision	0	0	2	1	8	5	5	2	4	2	4	0	1	0	1	0	35
ACL repair	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Shoulder hemiarthroplasty	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
COLUMN TOTALS	29	29	23	17	12	6	7	3	5	2	4	0	1	0	1	0	
COLUMN TOTALS	58		40		18		10		7		4		1		1		139

Conclusion: This is the largest reported study of detailed AS-related orthopedic surgery data comparing JoAS with AoAS cases. JoAS cases were more likely to proceed to surgery, and have had a second surgery, even after adjusting for a longer disease duration. Smoking and *HLA-B27* positivity were predictors of a second surgery; age of symptom onset and family history of SpA were predictors of hip surgery.

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The Age At Onset Of Symptoms Influence The Clinical Expression Of The Disease In Patients With Ankylosing Spondylitis. Natalia Zamora, Emilce Edith Schneeberger, Luis Alejandro Cayetti, Fernando Sommerfleck and Gustavo Citera. Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina.

Background/Purpose: The onset of symptoms before 10 years and after 40 years is uncommon in patients with ankylosing spondylitis (AS). Some authors have found specific characteristics in patients with late-onset AS. Objective: To evaluate demographic and clinical characteristics in patients with conventional and late onset AS.

Methods: Consecutive patients with AS (ASAS 2009 criteria) were included. Age at onset of symptoms, demographic and clinical characteristics were recollected. Presence of comorbidities, as well as specific questionnaires to determine disease activity (BASDAI), functional capacity (BASFI), quality of life (ASQoL) and metrology (BASMI) were assessed. Cervical, lumbar and pelvic X-rays were performed yearly and read by a single, blinded observer, according to BASRI. Descriptive statistics was used, the study population was dichotomized into two age groups in terms of symptom's onset: ≤ 40 years and > 40 years. Categorical variables were compared by Chi2 or Fisher exact test and continued variables by T test and ANOVA. Logistic regression analysis using the two age groups as dependent variable was performed to determine associations and to adjust for covariates.

Results: A total of 147 patients were included, 111 (75.5%) were male, with a median age of 46 years (IQR 32–56), median age of onset of symptoms 25 years (IQR 16–23) and median disease duration of 16 years (IQR 8–25). 18 (12.2%) patients had associated psoriasis, 18 were juvenile onset AS, 8 had inflammatory bowel disease associated (IBD), 5 were undifferentiated and the rest 98 (66.7%) had pure AS. 127 (86.4%) of patients had started the disease ≤ 40 years and 20 (13.6%) > 40 years. The group of patients with late onset AS were most often women [11 (45%) vs 27 (21%)], and patients with early onset had longer disease duration 19.4 vs 11.4 yrs p=0.01. After adjusting for these variables, patients in group > 40 showed a higher frequency of psoriasis (45% vs 11.3%), higher disease activity (BASDAI: 5.9 vs 4.4), worse functional capacity (BASFI:5.6 vs 4.1), and quality of life (ASQoL:11.4 vs. 7.2), but less radiological damage (BASRI:6.75 vs 9.27), p values <0.05 for all comparisons.

Conclusion: Patients with late onset AS are more frequently women with psoriasis and have worse indices of disease activity, functional capacity and quality of life. The presence of less radiological damage in this group deserves further investigation.

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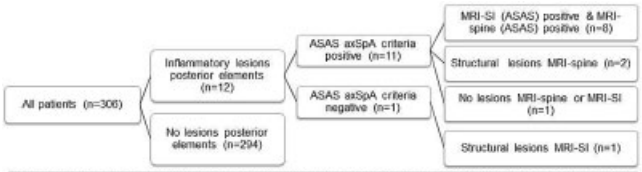
1539

Inflammation In The Posterior Elements Of The Spine Is Infrequent In Patients With Recent Onset Axial Spondyloarthritis, Especially If No Inflammation In The Vertebral Bodies Is Observed. Rosaline van den Berg[1], Manouk de Hooge[1], Monique Reijnierse[1], Victoria Navarro-Compán[1], Karen Fagerli[2], Maureen Turina[3], Maikel van Oosterhout[4], Roberta Ramonda[5], Floris van Gaalen[1], Tom Huizinga[1] and Désirée van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [4]GHZ Hospital, Gouda, Netherlands, [5]University of Padova, Padova, Italy.

Background/Purpose: There is evidence that in almost all patients with longstanding and active ankylosing spondylitis (AS) inflammatory lesions in the posterior elements are as frequent as in the anterior spine[1]. Therefore, it was argued that assessment of posterior structures should be embedded in routine diagnostic MRI assessment of the spine in patients with established AS or suspected of having AS[1]. However, little is known about the prevalence of lesions in the posterior elements in patients with recent onset axial spondyloartritis (axSpA). We investigated the prevalence of inflammatory lesions in the posterior elements in patients with and without inflammation in the vertebral bodies in patients with recent onset axSpA and patients with possible axSpA.

Methods: Patients with back pain (≥3 months, ≤2 years, onset <45 years) visiting the rheumatology outpatient clinics of the five participating centers were included in the SPondyloArthritis Caught Early (SPACE)-cohort (n=345). During the diagnostic work-up, all patients underwent MRI of the spine (MRI-spine). MRIs-spine were scored by 3 independent readers according to the ASAS consensus definition[2] and the Canada-Denmark score[3,4], including assessment of posterior elements[1]. The ASAS consensus definition states that evidence of anterior/posterior spondylitis in ≥3 sites is highly suggestive of axSpA. Therefore, we used a cut-off of ≥3 inflammatory lesions to mark an MRI-spine positive. Definite lesions were considered present if 2/3 readers agreed on it.

Results: Only patients with complete MRI-spine data were included in this analysis (n=306), of which 126 patients fulfilled the ASAS axSpA criteria[5]. In total, only 12/306 patients (3.9%) had inflammatory lesions in the posterior elements; 8 of them (66.7%) fulfilled the ASAS axSpA criteria (imaging-arm) and had also a positive MRI-spine. The remaining 4 patients (33.3%) had lesions in the posterior elements but no inflammatory lesions in the vertebral bodies, yet two out of four had signs of structural lesions (≥3 fatty lesions). Three out of these four patients fulfilled the ASAS axSpA criteria via the clinical-arm. The remaining patient had signs of structural lesions in the SI-joints (MRI) plus 3 other SpA-features (inflammatory back pain, good response to NSAIDs and elevated CRP and ESR) and has a clinical diagnosis of SpA by the rheumatologist.



Flow chart of the patients with inflammatory lesions in the posterior elements. Structural lesions on MRI-spine defined as ≥3 fatty lesions. Structural lesions on MRI-SI defined as ≥5 structural lesions (fatty lesions, erosions, sclerosis and/or ankylosis).

Conclusion: The prevalence of inflammatory lesions in the posterior elements in the SPACE-cohort is low, suggesting that assessment of inflammatory lesions in the posterior elements in addition to the vertebral bodies gives only limited extra information in patients with recent onset axSpA and possible axSpA.

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Sustained Clinical Remission In Patients With Non-Radiographic Axial Spondyloarthritis After Two Years Of Adalimumab Treatment. Joachim Sieper[1], Dominique L. Baeten[2], Filip Van den Bosch[3], Suchitrita S. Rathmann[4], Jaclyn K. Anderson[5] and Aileen L. Pangan[4]. [1]Charité Universitätsmedizin Berlin, Campus Benjamin-Franklin, Berlin, Germany, [2]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [3]Gent University Hospital, Gent, Belgium, [4]AbbVie Inc., North Chicago, IL, [5]AbbVie, North Chicago, IL.

Background/Purpose: Adalimumab (ADA) is currently approved in the EU for the treatment of severe non-radiographic axial spondyloarthritis (nr-axSpA), in patients (pts) with an elevated CRP and/or positive MRI who have had an inadequate response to, or are intolerant to NSAIDs. Short-term and 1 year (yr) remission data have been previously reported for the ABILITY-1 trial. The objective of this analysis was to determine drug survival and durability of clinical remission at yr 2 among pts with nr-axSpA.

Methods: ABILITY-1 is an ongoing phase 3, double blind (DB), randomized, controlled trial in pts with nr-axSpA who had an inadequate response, intolerance, or contraindication to NSAIDs. A 12-wk DB period of ADA 40 mg every other week (eow) or placebo (PBO) was followed by an open-label (OL) extension phase in which pts could receive OL ADA 40 mg eow for up to an additional 144 wks. This *post hoc* analysis evaluated the wk 104 efficacy and safety of ADA in the MRI+/CRP+ nr-axSpA subpopulation, defined as pts who had a positive baseline (BL) MRI (SPARCC score ≥2 for either the SI joints or spine) or an elevated CRP at BL. Clinical remission was defined by ASDAS inactive disease (ASDAS ID, ASDAS <1.3) or by ASAS partial remission (ASAS PR). Sustained remission was defined as achieving clinical remission at wks 52, 80, and 104. Clinical responses were summarized by observed case analysis. Safety was assessed in terms of adverse events (AE).

Results: 142 (69 ADA, 73 PBO) of the total efficacy population (N=185) were in the MRI+/CRP+ subpopulation; 107 (75%) had data available for wk 104 analysis. The table lists clinical response and sustained remission rates for the MRI+/CRP+ subpopulation. Sustained remission rates were similar between pts with symptom duration <5 vs. ≥5 years (sustained ASDAS ID 38% vs. 31%; sustained ASAS PR 26% vs. 29%). Among pts exposed to ADA during the study (356.2 patient-yrs [PY] of exposure) there were 8

serious infections (2.2/100 PY, including 1 case of disseminated TB), 1 case of lupus-like syndrome, and 2 deaths (suicide and cardiopulmonary failure due to opiate toxicity). No malignancies or demyelinating diseases have been reported.

Table. Clinical Responses in MRI+/CRP+ Subpopulation (Completers Analysis)[a]

	Week 104 (N=107) (%)	Sustained Remission at Weeks 52, 80 and 104 (%)
ASAS20	82	–
ASAS40	66	–
BASDAI50	69	–
ASDAS inactive disease	49[b]	35[d]
ASAS partial remission	44[c]	28[e]

[a]Data as observed. [b]N=105, [c]N=104; [d]N=101 and [e]N=102 pts with available data at wks 52, 80 and 104.

Conclusion: Almost half of the pts who remained on long-term ADA therapy in ABILITY-1 were in remission at wk 104, the majority of whom were also in this state of remission at wks 52 and 80. Long-term safety data are comparable to the known AE rates with ADA in other rheumatology indications.

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Spinal Mobility Gets Impaired In a Fixed Order In Patients With Ankylosing Spondylitis: 12-Year OASIS Results. Sofia Ramiro[1], Robert Landewé[2], Désirée van der Heijde[3], Carmen Stolwijk[4], Maxime Dougados[5], Filip Van den Bosch[6] and A.M. van Tubergen[4]. [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center Amsterdam & Atrium Medical Center, Heerlen, Netherlands, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Maastricht University Medical Center, Maastricht, Netherlands, [5]Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France, [6]Gent University Hospital, Gent, Belgium.

Background/Purpose: Spinal mobility is impaired in patients with ankylosing spondylitis (AS) compared to normal subjects. However, the extent of impairment and the relative contribution of different measures are unknown. We investigated which spinal mobility measures are most frequently impaired in patients with AS and whether a hierarchy for the impairment of the measures could be established.

Methods: Patients from the Outcome in AS International Study (OASIS) were followed-up for up to 12 years in which spinal mobility was regularly measured (measures detailed in Table). From a previous study in normal subjects (1), percentile curves (2.5th to 97.5th) were obtained for each of the spinal mobility measures (Figure). We added 4 parallel curves representing z-scores of 2.5, 3, 3.5 and 4 respectively (helplines a to d) to be able to plot impaired measures. For every observation, and taking patient's age into account, each of the spinal mobility measures was defined as impaired if the measurement fell below each of the cutoffs (2.5th percentile and each of the 4 helplines). The proportion of observations and also of patients (using baseline observation) in which each of the spinal mobility measures was impaired according to each of the cutoffs was calculated. Analyses were repeated in strata according to gender, symptom duration (median and tertiles) and baseline number of syndemophytes (0 vs ≥1 and <5 vs≥5).

Results: A total of 216 patients were included (70% males, mean (SD) age 44(13) years, mean symptom duration 21(12) years and 85% HLA-B27 positive). Lateral spinal flexion (LSF) was always the most frequently impaired measure, sequentially followed by Schober's, tragus-to-wall, cervical rotation, intermalleolar distance (IMD) and chest expansion (CE) (Table). This order was strikingly similar at both the observation-level and the patient-level (baseline observations only) as well as for all cutoffs (with the only exception being the 2.5th percentile, for which CE was slightly more impaired than IMD). Even with stratifications did this hierarchy in general persist.

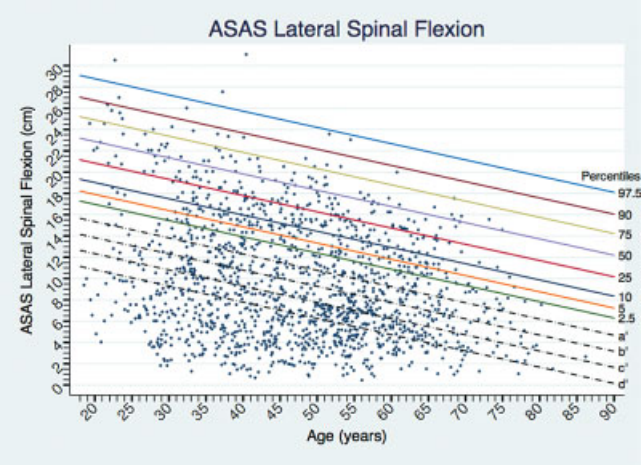

Figure. Lateral spinal flexion in function of age and with the percentile curves and help-lines derived from the normal subjects measurements.

Table. Impairment of each of the spinal mobility measures in patients with AS compared to cutoffs derived from mobility in normal subjects

	Below 2.5th percentile n (%)	Below Helpline a n (%)	Below Helpline b n (%)	Below Helpline c n (%)	Below Helpline d n (%)	Total number of observations (N)
OBSERVATION LEVEL (ALL OBSERVATIONS)						
ASAS Lateral Spinal Flexion (cm)	1052 (73)	933 (64)	818 (57)	673 (47)	321 (22)	1447
10-cm Schober's test (cm)	906 (58)	745 (48)	609 (39)	480 (31)	294 (19)	1551
Tragus-to-wall distance (cm)	679 (44)	532 (34)	363 (23)	*	*	1550
Cervical rotation (degrees)	486 (31)	382 (25)	300 (19)	236 (15)	187 (12)	1555
Intermalleolar distance (cm)	343 (22)	220 (14)	161 (10)	97 (6)	62 (4)	1543
Chest expansion (cm)	412 (27)	151 (10)	37 (2)	5 (0)	1 (0)	1548

*Not possible to derive these values due to mathematical characteristics of the equation for the percentile curves for tragus-to-wall distance.

Reference:

(1) Ramiro et al. Arthritis & Rheumatism 64(12):4173–4174

Conclusion: LSF and Schober's are the most frequently impaired mobility measures in AS, reflecting an earlier involvement of lumbar spine in spinal mobility impairment, followed by the involvement of the thoracic and cervical spine. This fixed order of involvement of the spine persists across different patient groups.

Disclosure: S. Ramiro, None; **R. Landewé**, None; **D. van der Heijde**, None; **C. Stolwijk**, None; **M. Dougados**, None; **F. Van den Bosch**, None; **A. M. van Tubergen**, None.

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Regular Exercise Is Associated With Better Functional Outcomes In Ankylosing Spondylitis. Lianne S. Gensler[1], John D. Reveille[2], MinJae Lee[3], Mohammad Rahbar[3], Manouchehr Ardjomand-Hessabi[4], Matthew A. Brown[5], Michael H. Weisman[6] and Michael M. Ward[7]. [1]University of California, San Francisco, San Francisco, CA, [2]University of Texas Health Science Center at Houston, Houston, TX, [3]The University of Texas Health Science Center at Houston, Houston, TX, [4]The University of Texas, Health Science Center at Houston, Houston, TX, [5]University of Queensland Diamantina Institute, Brisbane, Australia, [6]Cedars-Sinai Med Ctr, Los Angeles, CA, [7]NIAMS/NIH, Bethesda, MD.

Background/Purpose: Exercise and physical therapy are the cornerstones of non-pharmacologic therapy in Ankylosing Spondylitis. The long-term association of exercise on function has not been evaluated. The

purpose of this study was to assess the role of regular exercise in longitudinal functional outcomes in AS patients.

Methods: This is a prospective cohort of 611 AS patients, meeting the modified New York criteria followed up to 4 years. We collected demographic, clinical and self-reported outcomes every 6 months. Exercise data were also collected every visit, including how many days per week patients exercised. Regular exercise was defined as greater than or equal to 3 times per week. Functional outcomes were assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI). Using mixed models, we assessed univariable associations between independent variables and functional outcome (BASFI) that accounted for correlation of repeated measures over time. Potential confounding and effect modifications were examined and addressed while developing a final longitudinal multivariable model.

Results: There were 611 patients included with a mean age of 41.1 years (SD= 13.6). The cohort comprised 71% males and 76% of patients were white. Mean Disease duration was 17.6 years (SD=13.5). Table 1 shows the univariable associations between BASFI and each independent variable from the longitudinal models. After adjusting for potential confounders, including age, gender, education level, employment status, race, past AS-related joint surgery, occupation, smoking, TNF inhibitor use, disease activity by the Bath Ankylosing Spondylitis Activity Index (BASDAI), disease damage by the baseline modified Stoke Ankylosing Spondylitis Spine Score (mSASSS), depression by the Center for Epidemiologic Studies Depression Scale (CES-D), and past joint involvement, the effect of regular exercise on BASFI remained significant ($p < 0.0001$) over time. Figure 1 shows the adjusted means of BASFI by exercise group over time.

Table 1. Univariable Association between BASFI and other variables

	Mean BASFI										
	Baseline		Year 1		Year 2		Year 3		Year 4		*p*-
Variables	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	value*
Exercise ≥ 3 per week	28.7	37.0	25.9	32.6	24.9	31.0	26.7	30.3	29.5	33.0	<.0001
Age older than 40	38.1	27.2	33.9	23.3	32.8	22.6	33.5	22.6	36.1	23.3	<.0001
Sex (Male)	32.3	32.8	28.7	28.0	27.9	27.1	28.1	28.3	30.2	33.1	0.90
Race/Ethnicity subgroups (White)	31.3	36.0	28.0	30.0	27.5	28.2	28.0	28.9	31.2	29.7	0.28
Smoked more than 100 cigarettes	37.9	28.6	33.8	24.7	32.2	24.3	30.6	26.1	32.3	29.7	0.001
Past surgery (Yes)	50.9	30.2	45.0	26.6	43.8	25.8	39.4	26.9	48.5	28.9	<.0001
Occupation (higher physical activity)	38.9	30.8	33.1	27.6	31.5	27.3	30.6	27.9	26.3	31.9	0.02
Past affected joint											
Upper extremity joints	38.7	24.6	33.6	21.8	33.2	20.4	33.7	20.8	39.2	20.5	<.0001
Lower extremity joints	34.3	25.3	29.6	24.1	28.2	25.3	28.9	25.2	32.6	24.3	<.0001
Total BASDAI ≥ 40	48.8	18.3	51.0	16.9	51.8	17.0	46.8	17.4	50.2	16.0	<.0001
Baseline mSASSS > 5	38.8	24.8	34.8	20.6	32.8	19.7	33.1	21.5	34.9	23.4	<.0001
Total CES-D score > 8	39.0	21.5	38.6	18.5	38.4	16.8	37.0	19.6	42.3	18.6	<.0001
TNF inhibitor use	35.2	30.3	30.1	26.5	29.1	26.3	29.5	26.2	27.0	29.5	<.0001

*p-value for exercise group (Exercise ≥3 per week vs. <3 per week)

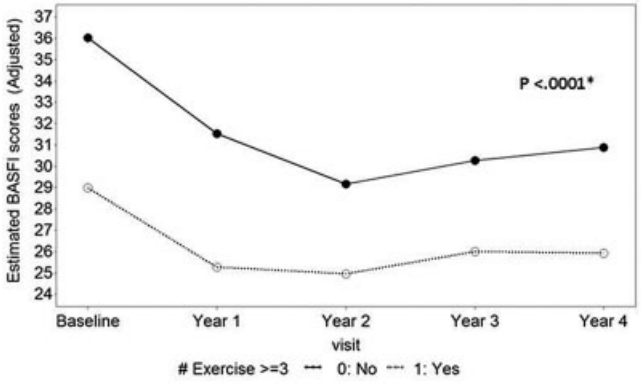

Figure 1. Longitudinal Association of Regular Exercise with Function from the multivariable longitudinal model

Conclusion: AS patients that exercise regularly (≥ 3 times per week) have significantly better function than those that do not.

Disclosure: L. S. Gensler, None; **J. D. Reveille**, None; **M. Lee**, None; **M. Rahbar**, None; **M. Ardjomand-Hessabi**, None; **M. A. Brown**, None; **M. H. Weisman**, None; **M. M. Ward**, None.

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Patients With Ankylosing Spondylitis Are Substantially Undertreated For Hypertension and Hypercholesterolemia. Sjoerd C. Heslinga[1], Inge A.M. van den Oever[2], Alper M. van Sijl[2], Irene E. Van der Horst-Bruinsma[1] and Michael. T. Nurmohamed[2]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands.

Background/Purpose: Patients with ankylosing spondylitis (AS) have a decreased life expectancy due to an increased cardiovascular (CV) risk. The general inflammatory process is held responsible together with an increased prevalence of traditional risk factors such as hypertension and hypercholesterolemia. We investigated the prevalence of these CV risk factors in AS patients and whether these are treated according to the present guidelines.

Methods: We evaluated CV risk factors in all patients (n=290) eligible for treatment with TNF inhibitors. All patients fulfilled the New York 1984 criteria for AS. Hypertension was defined as systolic blood pressure (SBP) >140 mmHg and/or diastolic blood pressure (DBP) >90 mmHg. Overweight was defined as body mass index (BMI) >25 kg/m^2. Hypercholesterolemia was defined as LDL> 2.5 mmol/L. The 10- year estimated cardiovascular risk was calculated with the Dutch multidisciplinary guideline for cardiovascular risk management. It is expressed as the risk percentage (%) for cardiovascular events in the next ten years.

Results: More than 40% of patients smoked at baseline compared to 27% in the general Dutch population. Overweight was present in 144 (50%) of patients compared to 26% in the general Dutch population. Of 187 patients the cardiovascular risk could be calculated. Hundred sixty-four patients (88%) had low cardiovascular risk (<10%). Twenty-three patients (12%) had a medium or high cardiovascular risk (>10%). Eleven of these patients (48%) were treated with either antihypertensive agents or statins. In addition, four patients had SBP >180 mmHg, of which two were on antihypertensive agents and four patients had a total cholesterol/HDL ratio of >8, of which one was treated with statins.

Fifty-one out of 270 patients (19%) were on antihypertensive medication on baseline, of which 15 (29.4%) were inadequately treated as they still had higher BPs than treatment targets. Twenty-six out of 270 patients (10%) were on statin treatment, of which 9 (35%) were inadequately treated as they still had higher LDL levels than recommended (>2.5 mmol/L).

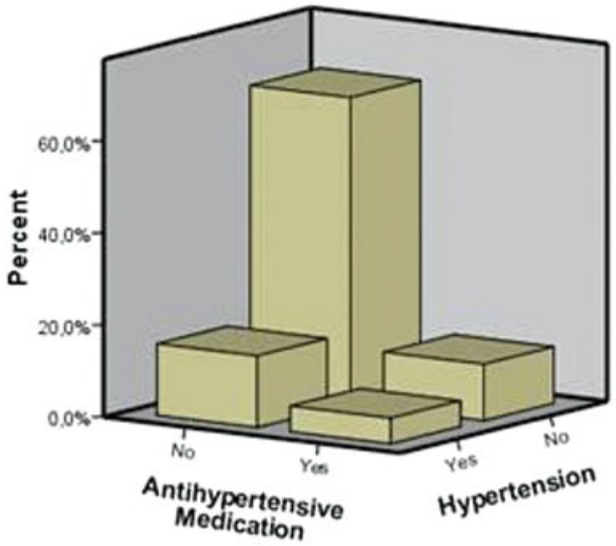

Figure 1. Treatment of AS patients with antihypertensive medication.

Conclusion: One in five AS patients were treated for hypertension and one in ten for hypercholesterolemia. Of these patients approximately one third did not reach the treatment targets. Over half of AS patients with medium to high cardiovascular risk were not treated at all. Obviously, there is an impressive under treatment of cardiovascular risk factors in AS. Hence, more attention for screening as well as proper management of cardiovascular risk factors in patients with AS is urgently needed to lower the cardiovascular risk.

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Good Agreement Between The Ankylosing Spondylitis Disease Activity Scores Based On C-Reactive Protein and Erythrocyte Sedimentation Rate. Dilek Solmaz[1], Pinar Cetin[1], Ismail Sari[1], Merih Birlik[2], Servet Akar[1], Fatos Onen[1] and Nurullah Akkoc[1]. [1]Dokuz Eylul University School of Medicine, Izmir, Turkey, [2]Dokuz Eylul University School of Medicine, izmir, Turkey.

Background/Purpose: Recently, ASDAS has been developed as a disease activity measuring tool for ankylosing spondylitis (AS), using a similar methodology to that used for the development of the Disease Activity Score (DAS) in rheumatoid arthritis. Two versions of ASDAS have been proposed, one based on CRP (preferred) and the other based on ESR (alternative).In the light of recent reports showing substantial difference between the two versions of DAS28, it is of interest to assess the agreement between the two ASDAS versions at individual level. Our aim is to assess the agreement between the ESR and CRP-based ASDAS scores in AS patients.

Methods: Data were obtained from the local clinical database which contains slightly over 500 AS patients. Patients with full data at baseline were included in this analysis. Mean ASDAS-CRP and ASDAS-ESR values were compared by Spearman correlation and scatter plot with linear regression analysis. Bland-Altman analysis and kappa statistics were used to assess the agreement between the two ASDAS definitions in the whole group as well as in different gender and age groups.

Results: 396 patients (291 M; 44 ±12.0 years) were identified with complete data at baseline for this analysis. Mean (±SD) disease duration was 9.4 (±8.2) years. Mean (±SD) BASDAI, BASFI and BASMI scores were 3.5 (±2.2), 2.9 (±2.6), 3.9 (±1.9), respectively. HLA B27 was positive in 65% of the patients of whom 83.7% were using NSAIDs and 20.7% were using TNF inhibitors. Mean (±SD) ASDAS scores, based on CRP and ESR were 2.9 (± 1.1), and 2.8 (± 1.0), respectively. There was a strong correlation between the two definitions by Spearman's correlation test ($r=0.9$, $p<0.001$) and linear regression analysis ($R^2=0.82$, $p<0.001$). The agreement was good for both genders and all age groups with weighted kappa values ranging from 0.680 to 0.876 (Table 1). Similar number of patients was classified into the defined categories of disease activity with ASDAS-CRP and ASDAS-ESR (Table 2). Bland-Altman analysis showed excellent agreement between the two scores (ASDAS-CRP – ASDAS-ESR) with a mean difference (bias) of −0.0 ± 0.48 (95% CI −0.04, −0.047). Upper and lower limits of agreement were 0.95 (95% CI 0.87, 1.03) and −0.95 (95% CI −1.03, −0.87), respectively. Mean difference was 0.20 ± 0.49 in females and −0.10 ± 0.44 in males.

Table 1. The correlation and agreement between ASDAS-CRP and ASDAS-ESR values in different gender and age groups

Patient group	Mean ASDAS-CRP	Mean ASDAS-ESR	Spearman correlation coeficient r	Spearman correlation coeficient P	Agreement rate	Kappa value	Weighted kappa value
Females (n=104)	2.8 ± 1.1	3.1 ± 1.0	0.906	<0.001	64.4%	0.455	0.680
Males (n=292)	2.9 ± 1.1	2.7 ± 1.0	0.923	<0.001	73.6%	0.618	0.803
≤40 years old (n=163)	3.0 ± 1.1	2.9 ± 1.0	0.918	<0.001	69.7%	0.549	0.790
41–60 years old (n=193)	2.7 ± 1.1	2.8 ± 1.0	0.888	<0.001	70.5%	0.561	0.740
≥61 years old (n=40)	3.0 ± 1.2	3.0 ± 1.0	0.954	<0.001	74.4%	0.672	0.876
Overall (n=396)	2.9 ± 1.1	2.8 ± 1.0	0.906	<0.001	70.0%	0.567	0.760

Table 2. Agreement between ASDAS-CRP and ASDAS-ESR on the classification of the patients into different categories of disease activity

		ASDAS CRP <1.3	1.3–2.0	2.1–3.5	>3.5	Total
ASDAS ESR	<1.3	13	5	2	0	20
	1.3–2.0	17	40	19	0	76
	2.1–3.5	6	19	137	25	187
	>3.5	0	0	22	91	113
	Total	36	64	180	116	396

Conclusion: The results suggest a good agreement between ASDAS-ESR and ASDAS-CRP for both genders and all age groups.

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1545

Serum Periostin: a New Marker Of Local Bone Formation In Early Inflammatory Back Pain: results From The DESIR Cohort. Karine Briot[1], Simon Paternotte[1], Didier Borderie[2], Corinne Miceli-Richard[3], Maxime Dougados[1] and Christian Roux[1]. [1]Paris Descartes University, Paris, France, [2]Paris Descartes UNiversity, Pris, France, [3]Université Paris-Sud 11, Bicêtre Hospital, Kremlin Bicêtre, France.

Background/Purpose: Periostin is a secreted, homodimeric protein that is synthesized by mesenchymal cells of the periosteum, which is involved in osteoblast homeostasis of the periosteum and could be one of the mediators of local bone formation in response to mechanical stress and/or inflammation. Our hypothesis is that periostin could be involved in the syndesmophyte formation in spondyloarthritis. The objective was to assess the relationships between serum periostin levels, bone formation regulators (sclerostin, Dickkof-1 (DKK-1)) and presence of syndesmophyte, in a cohort of early inflammatory back pain (IBP) suggestive of axial spondyloarthritis.

Methods: The DESIR cohort is a prospective, multicenter French cohort of patients with early IBP (Calin or Berlin criteria) (>3 months and <3 years of duration) suggestive of axial SpA, including 708 patients. All SpA patients were naive of any TNF blocker at inclusion in the study. Serum periostin levels were assessed at baseline in the whole cohort by sandwich enzyme-linked immunosorbent assay (ELISA) (Nordic Biosite, Sweden). Demographic characteristics, disease activity parameters, bone mineral density measurements were assessed at baseline and 2 years. DKK-1 and SOST serum levels (by sandwich ELISA), radiographs and MRI of axial skeleton (spine and sacroiliac joints) were performed at baseline. Correlations between serum periostin levels with baseline and 2 year variables were tested.

Results: Serum periostin was available in 701 patients (mean age 33.7±8.6 years, 46.2% of males). Mean (±SD) serum level of periostin was 396.5±461.4 pg/mL. Levels were higher in men (431.5±486.5 pg/mL) than in women (366.4 ±113.7 pg/mL) and decreased with age. Patients with at least one syndesmophyte at baseline had a lowest level of serum periostin than patients without syndesmophytes (222.4 ±286.5 ng/ml vs 412.89 ±471.3 ng/ml, respectively, $p=0.021$). There was a significant correlation between serum periostin levels and baseline sclerostin levels ($r=-0.09$; $p=0.02$) and baseline DKK-1 levels ($r=-0.12$; $p=0.002$). Serum periostin levels were weakly correlated with 2-year changes in disease activity parameters: CRP ($p=-0.1$; 0.027), ESR ($r=-0.14$; $p=0.002$), BASDAI ($r=-0.12$; $p=0.003$) and ASDAS CRP ($r=-0.18$; $p=\leq 0.0001$). We did not find any difference between patients with and without the presence of bone marrow oedema on MRI. Serum periostin was not correlated with low BMD ($Z\leq -2$ at at least one site) and was not a predictor of significant bone loss (decreased in BMD ≥0.03g/cm at at least one site).

Conclusion: This study conducted in a large cohort of patients with early axial SpA shows that low serum level of periostin is associated with local bone formation. Periostin is correlated to serum sclerostin and DKK-1 levels and parameters of inflammation. Relationship between serum periostin and formation of new syndesmophyte will be studied using the 2-year centralized analysis of X-rays and MRI.

Disclosure: K. Briot, None; **S. Paternotte**, None; **D. Borderie**, None; **C. Miceli-Richard**, None; **M. Dougados**, None; **C. Roux**, None.

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Patient-Reported Outcomes of Etanercept in Early Non-Radiographic Axial Spondyloarthritis: A 12-Week, Randomized, Double-Blind, Placebo-Controlled Trial. Maxime Dougados[1], Wen-Chan Tsai[2], Diego Luis Saaibi[3], Randi Bonin[4], Jack Bukowski[4], Ronald Pedersen[4], Bonnie Vlahos[5] and Sameer Kotak[6]. [1]Paris-Descartes University, APHP, Cochin Hospital, Paris, France, [2]Chung-Ho Memorial Hospital, Kaohsiung, 807, Taiwan, [3]MEDICITY S.A.S, Bucaramanga, Santander 681001, Colombia, [4]Pfizer Inc, Collegeville, PA, [5]Pfizer Inc., Collegeville, PA, [6]Pfizer Inc., New York, NY.

Background/Purpose: Limited data are available on the efficacy of anti-TNF agents in non-radiographic axial spondyloarthritis (nr-axSpA). This analysis compares the impact of etanercept (ETN) vs placebo (PBO) on patient-reported outcomes (PROs), after 12 weeks of double-blind treatment in patients (pts) with nr-axSpA who had an insufficient response to NSAIDs.

Methods: Enrolled pts satisfied ASAS criteria for axSpA, had symptom duration of 3 months-5 years and a BASDAI score ≥4 despite current NSAID use. Pts were randomized to ETN 50 mg weekly or PBO with concomitant background NSAIDs. The primary clinical endpoint was ASAS40 at week

12. PROs included BASDAI, BASFI, BAS-G, Work Productivity and Activity Index-Ankylosing Spondylitis (WPAI-AS), Multidimensional Fatigue Inventory (MFI), Nocturnal back pain VAS, total back pain VAS, subject assessment of disease activity (SGA), Short Form (SF-36), Medical Outcomes Study (MOS)-Sleep, Patient Acceptable Symptom State (PASS), Minimal Clinically Important Improvement (MCII), EuroQol (EQ)-5D and Hospital Anxiety and Depression Screening (HADS). ANCOVA models were used with baseline score, treatment, region and SI status as variables. LOCF was used for missing data.

Results: At baseline, MFI general scores (14.7, 15.0 [ETN, PBO]), EQ-5D utility scores (0.52, 0.57), EQ-5D VAS scores (56.5, 56.4) and MOS Sleep Index II scores (45.5, 48.1) were worse than population norms (6.6–8.0[1], 0.86[2], 82.5[3] and 25.8[4], respectively). By week 12, more pts achieved ASAS40 with ETN50 than PBO (32% vs. 16%, P=0.006).[5] By week 12 significant improvements favoring ETN50 vs. PBO were seen in stiffness, joint pain, ease of standing from an armless chair, ease of physically demanding and full-day activities, looking over the shoulder, reaching up high, putting on socks and SGA ($p<0.05$ for all, Table). Mean WPAI presenteeism, SF-36 bodily pain and MOS-sleep quantity favored ETN50 ($P<0.05$), as did the proportion of pts with MCII ($p=0.0458$). Non-significant improvements for ETN50 vs. PBO were seen in bending forward from the waist, WPAI, MFI, MOS-Sleep Problems Index I and II, HADS, EQ-5D and SF-36 total scores ($P>0.05$ for all).

Table. Improvements from baseline to week 12 in PROs (observed cases), adjusted mean change (95% CI)

	ETN50 + NSAID (n=106)	PBO + NSAID (n=109)
BASDAI PRO		
Duration of morning stiffness	−2.05 (−2.67, −1.44)†	−0.84 (−1.43, −0.25)†
Severity of morning stiffness	−2.30 (−3.01, −1.60)†	−1.39 (−2.06, −0.72)†
Severity of pain in the neck/back/hip	−2.46 (−3.19, −1.74)†	−1.48 (−2.17, −0.80)†
Severity of pain in joints other than neck/back/hip	−1.37 (−2.06, −0.69)*	−0.69 (−1.34, −0.03)*
BASFI		
Ease of bending forward from the waist	−1.26 (−1.85, −0.67)	−0.72 (−1.28, −0.16)
Ease of standing from an armless chair	−1.80 (−2.37, −1.22)†	−0.95 (−1.50, −0.40)†
Ease of doing a full day of activities	−2.16 (−2.75, −1.56)†	−1.13 (−1.70, −0.56)†
Ease of looking over your shoulder	−1.48 (−2.06, −0.90)*	−0.85 (−1.40, −0.29)*
Ease of physically demanding activities	−1.65 (−2.24, −1.06)†	−0.81 (−1.37, −0.25)†
Ease of reaching up high	−0.60 (−1.15, −0.06)*	−0.06 (−0.58, 0.46)*
Ease of putting on socks	−1.08 (−1.64, −0.51)*	−0.51 (−1.05, 0.03)*
BAS−G total	−1.88 (−2.44, −1.33)*	−1.29 (−1.82, −0.77)*
BAS−G (since last week)	−2.00 (−2.66, −1.34)*	−1.20 (−1.83, −0.57)*
Nocturnal back pain VAS	−2.00 (−2.75, −1.26)†	−0.93 (−1.63, −0.22)†
Total back pain VAS	−2.00 (−2.67, −1.33)†	−1.03 (−1.67, −0.40)†
Average back pain VAS	−2.01 (−2.70, −1.32)†	−0.98 (−1.64, −0.32)†
Subject assessment of disease activity	−2.12 (−2.76, −1.47)†	−1.19 (−1.81, −0.58)†

*P <0.05 for ETN50 vs. PBO at week 12; †P<0.01 for ETN50 vs. PBO at week 12.

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Conclusion: The data show substantial improvements in PRO measures for disease specific and functional domains such as BASDAI, BASFI, BAS-G, and pain, but limited improvement on general PRO measures such as sleep, fatigue and general health. Short disease duration, a short placebo-controlled period, and a wide range of PRO scores at baseline may have influenced relative improvements.

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1547

How The Delay In Diagnosis Impacts On The Clinical, Functional and Radiographic Status Of Patients With Ankylosing Spondylitis. Is There a Window Of Opportunity?

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Background/Purpose: The delay in diagnosis has deleterious effects in patients with Rheumatoid Arthritis. This fact has not been fully investigated in patients with Ankylosing Spondylitis (AS). Objective: To determine the influence of the delay in the diagnosis, over the clinical, functional and radiographic status in patients with AS.

Methods: Consecutive patients ≥ 18 yrs old with AS (ASAS 2009 criteria) were included. Demographic, clinical and therapeutic aspects of the disease were collected prospectively in our AS outpatient clinic. Specific questionnaires to determine disease activity (BASDAI), functional capacity (BASFI), quality of life (ASQoL), metrology (BASMI) are performed every 6 months. Cervical, lumbar and pelvic X-rays are performed yearly and read by a single, blinded observer, according to BASRI. Delay in diagnosis was assessed as a continuous variable and expressed as median (IQR), but also patients were divided in 3 groups according to the delay in diagnosis. Group 1: ≤ 3 yrs, Group 2: > 3 ≤ 10 yrs, and Group 3: ≥ 10 yrs. Differences were assessed by ANOVA, Chi Square test and multiple regression analysis adjusting for confounders and propensity scores. Dichotomous dependent variable was set using extreme categories (G1 vs. G3).

Results: 147 patients were included, 111 (75.5%) were male, median age 46 yrs (IQR 18–35). Median time delay for the diagnosis was 5 yrs (IQR 2–13). 62 patients (42.4%) belong to group 1 (≤ 3 yrs), 36 (24.5%) to group 2, and 49 (33.3%) to group 3. Patients with juvenile onset were less frequently observed in group 1 (16.7%) as compared to other groups ($p=0.01$). Patients in G1, were significantly older at the time of diagnosis as compared to the other groups (30 yrs, 23 yrs and 22 yrs respectively, $p=0.02$). Presence of tarsitis was more frequent in G1 (58% vs. 25% $p=0.01$). Gender, comorbidities, NSAID, DMARD and biologic treatment were comparable between groups. After a median follow-up time of 12 years and after adjusting for disease duration, BASDAI, BASFI, ASQoL, and BASMI were comparable between groups. There was only a tendency, not reaching statistical significance of a greater BASRI in group 3.

Conclusion: We did not observed that the delay in diagnosis has had a major impact in functional capacity, quality of life or radiographic damage in our cohort of patients with AS.

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1548

Effect Of TNF Inhibitors On Bone Mineral Density In Patients With Ankylosing Spondylitis- a Systematic Review and Meta-Analysis.

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Background/Purpose: Patients with ankylosing spondylitis (AS) are susceptible to osteoporosis (OP) and have high fracture risk. Currently, no specific strategies are established to treat OP in these patients. TNF inhibitors are now increasingly used for treating AS. If TNF inhibitors are shown to prevent or reverse bone loss, use of bisphosphonates can be avoided. We did a systematic review and meta-analysis to study the effect of TNF inhibitors on spine and hip BMD in patients with AS.

Methods: Two authors searched MEDLINE, EMBASE & Cochrane databases, reviewed abstracts, and extracted data. A third author resolved discrepancies. Eligible studies had at least 70% of subjects satisfying Modified New York AS criteria and a minimum follow-up of 1 year. Case reports and studies on children and adolescents were excluded. The quality of the studies was assessed by Newcastle–Ottawa Quality Assessment Scale. Primary outcomes (BMD at spine, hip & femoral neck) were analyzed at 1 and 2 years. BMD was expressed as the percent change from baseline. Publication bias was assessed by Funnel plots. Statistical heterogeneity was assessed using Q statistic. The overall summary estimate was determined using the random effects model, which was weighted by the inverse variance of the effect size.

Results: Our search was narrowed down to 8 studies (7 observational studies and 1 RCT). BMD data available from 470 patients were included in the meta-analysis. Most subjects were males and their proportion varied from 70–92%. Mean age at enrolment ranged from 36–48 years, and mean disease duration was 9–17 years. Bisphosphonate use was negligible. Little data was available on intake of calcium and vitamin D. The use of TNF inhibitors led to significant improvement in spine and total hip BMD after 1 and 2 years when compared to baseline (Table 1). Femoral neck BMD remained stable at 1 year. The BMD gain was also significant in those treated with TNF inhibitors when compared to controls. In the RCT (TNF inhibitors vs. placebo), the gain in BMD was significantly higher in those treated with TNF inhibitors for 2 years versus those treated with placebo for the first 6 months.

Table 1. Summary estimates of the effect of TNF inhibitors on BMD in patients with AS

Duration of follow up (Years)	Lumbar spine Mean difference, % (95% CI)	Total hip Mean difference, % (95% CI)	Femoral neck Mean difference, % (95% CI)
1 year	5.1 (4.0–6.1)	1.8 (1.0–2.5)	0.73 (−0.8–2.2)
2 years	8.6 (6.8–10.3)	2.5 (1.9–3.0)	Insufficient data

Conclusion: Treatment with TNF inhibitors is associated with improvement in spine and hip BMD in patients with AS. More studies of longer duration and larger sample sizes are needed to better understand the effect of TNF inhibitors on fracture risk.

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1549

Prevalence Of Syndesmophytes In Patients With Chronic Back Pain Suspected Of Axial Spondyloarthritis (axSpA) Not Fulfilling The Modified New York (mNY) Criteria. Manouk de Hooge[1], Rosaline van den Berg[1], Floris van Gaalen[1], Monique Reijnierse[1], Victoria Navarro-Compán[1], Karen Fagerli[2], Maureen C. Turina[3], Maikel van Oosterhout[4], Roberta Ramonda[5], Tom Huizinga[1] and Désiréé van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [4]GHZ Hospital, Gouda, Netherlands, [5]University of Padova, Padova, Italy.

Background/Purpose: The mNY criteria[1], which indicate sacroiliitis of at least grade 2 bilaterally or grade 3 or 4 unilaterally, are used to classify patients as Ankylosing Spondylitis (AS). However, little is known about the occurrence of syndesmophytes in the spine in the absence of radiographic sacroiliitis. Therefore we want to investigate if syndesmophytes are prevalent in patients with chronic back pain suspected of axSpA who are not fulfilling the mNY criteria and if syndesmophytes should be included in criteria to define patients as having radiographic axSpA.

Methods: Patients with back pain (≥3 months, ≤2 years, onset ≤45 years) recruited from the 5 participating centres across Europe were included in the SPondyloArthritis Caught Early (SPACE)-cohort. All patients underwent conventional radiographs of the cervical and lumbar spine and sacroiliac (SI)-joints (X-spine and X-SI, respectively). X-spine was scored on the presence or absence of ≥1 syndesmophytes, X-SI was scored according to the mNY[1]. X-rays were scored independently by 3 well-calibrated readers. Lesions on x-ray were considered present if 2/3 readers agreed.

Results: All patients with both X-spine and X-SI data available (n=302) were used for comparison. There were 26 patients (8.6%) fulfilling the mNY criteria and 7 patients (2.3%) with ≥1 syndesmophytes present in the spine. None of those 7 patients showed radiographic sacroiliitis nor active lesions on MRI of the SI joints. Two patients fulfil the ASAS axSpA criteria and 5 patients had SpA features without fulfilling the ASAS axSpA criteria. In table 1 the number and location of syndesmophytes and SpA features are presented. Most patients (n=5) had 1 syndesmophyte. The two patients with >1 syndesmophytes did not fulfil the ASAS axSpA criteria. All patients had syndesmophytes located solely in the cervical part of the spine. None of the patients had psoriasis. Only 2/302 (0.7%) patients would be considered as having signs of radiographic axSpA if syndesmophytes (in absence of radiographic sacroiliitis) would be considered a sign of radiographic involvement.

There were 2 patients (*italic* in table) in whom corresponding syndesmophytes on the MRI of the spine were scored by both readers.

No. of synd.	Location of synd.	No. of SpA features	SpA features	ASAS axSpA criteria
1	cervical	2	IBP+ESR	no
1	cervical	2	IBP+NSAIDs	no
1	cervical	4	IBP+NSAIDs+HLA-B27+pos. fam. hist.	yes
1	cervical	4	IBP+NSAIDs+HLA-B27+pos. fam. hist.	yes
1	*cervical*	*7*	*IBP+NSAIDs+heel pain+dact.+IBD+ ESR+peripheral arthritis*	*no*
2	cervical	2	IBP+NSAIDs	no
3	*cervical*	*1*	*HLA-B27*	*no*

IBP; inflammatory back pain, ESR; elevated erythrocyte sedimentation *rate* and/or C-reactive protein, NSAIDs; good response to non-steroidal anti-inflammatory drugs, HLA-B27; Human Leukocyte Antigen B27, pos. fam. hist.; positive family history, dact; dactylitis, IBD; inflammatory bowel disease.

Conclusion: In this population, syndesmophytes in patients without sacroiliitis on radiographs and MRI are infrequent and solely located in the cervical spine. Indicating that syndesmophytes are not informative in classifying patients as having radiographic axSpA in early disease.

Reference:
[1]van der Linden S A&R 984;27:361–8

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1550

Validation Of The Ankylosing Spondylitis Disease Activity Score and Effectiveness Of Infliximab In The Treatment Of Ankylosing Spondylitis Over 4 Years: The Canadian Experience. Proton Rahman[1], Denis Choquette[2], Majed M. Khraishi[3], William G. Bensen[4], Saeed A. Shaikh[5], Dalton E. Sholter[6], Maqbool K. Sheriff[7], Emmanouil Rampakakis[8], John S. Sampalis[8], Francois Nantel[9], Susan M. Otawa[9], Allen J. Lehman[9] and May Shawi[9]. [1]Memorial University, St. Johns, NF, [2]Institut de Rhumatologie de Montréal, Montreal, QC, [3]MD, Memorial University of Newfoundland, Nexus Clinical Research, St Johns, NF, [4]St. Joseph's Hospital and McMaster University, Hamilton, ON, [5]McMaster University, St Catharines, ON, [6]Rheumatology Associates, Edmonton, AB, [7]Nanaimo Regional General Hospital, Nanaimo, BC, [8]JSS Medical Research, St-Laurent, QC, [9]Janssen Canada Inc, Toronto, ON.

Background/Purpose: The efficacy of anti-TNF in the management of Ankylosing Spondylitis (AS) has been demonstrated in numerous controlled clinical trials. The objective of this study is to assess in Canadian routine clinical practice the 4-year outcomes in patients with AS treated with infliximab (IFX) and the performance of Ankylosing Spondylitis Disease Activity Score (ASDAS), a new disease activity measure in AS.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, AS, or PsA with infliximab or golimumab as first biologics or after having been treated with a biologic for less than six months. People with AS treated with infliximab who were enrolled between 2005 and 2012 were included in this analysis. Descriptive statistics were produced for clinical outcome measures and patient reported outcomes at baseline and follow-up assessments over four years. Within-group changes were assessed for statistical significance with the paired-samples Student's t-test. The correlation of ASDAS with BASDAI and BASFI was assessed with the Pearson correlation coefficient. The correlation of these measures with MDGA was assessed with the Spearman's rho.

Results: A total of 230 AS patients who had at least one follow-up assessment were included in this analysis, with a mean (SD) age of 45.7 (11.5) years and mean (SD) disease duration since diagnosis of 10.0 (10.1) years. Among these, 167, 116, 74, and 38 had a 12-, 24-, 36-, and 48-month assessment, respectively. At the time of enrollment in the registry, mean (SD) patient parameters were: C-reactive protein (CRP) = 16.9 (20.2) mg/dL, erythrocyte sedimentation rate (ESR) = 25.8 (20.2) mm/hr, morning stiffness = 74.6 (40.2), health assessment questionnaire (HAQ-DI) = 1.20 (0.61), physician global assessment of disease activity (MDGA) = 6.6 (1.9), BASDAI = 6.4 (2.1), BASFI = 6.1 (2.5), and ASDAS = 3.8 (1.0). By 6 months of treatment significant improvements ($P<0.01$) were observed in all clinical and patient outcome parameters studied, which were sustained or further enhanced over 48 months of treatment.

Similar significant changes were observed in ASDAS, BASDAI, and BASFI over time providing evidence of construct validity and sensitivity to change. A strong positive linear correlation between ASDAS and BASDAI ($r=0.85$; $P<0.001$) and BASFI ($r=0.76$; $P<0.001$) was observed. The correlation of MDGA was strong with ASDAS ($rho=0.73$; $P<0.001$) and BASDAI ($rho=0.70$; $P<0.001$) and moderate with BASFI ($rho=0.64$; $P<0.001$).

By 12, 24, 36, and 48 months 66%/72%/77%/75% achieved Clinically Important Improvement in ASDAS ($\Delta \geq 1.1$) and 37%/49%/47%/50%, achieved ASDAS Major Improvement ($\Delta \geq 2.0$), respectively. The proportion of patients with very high disease activity (ASDAS > 3.5) decreased from 62.4% at baseline to 6.9% at 48 months.

Conclusion: The results of this Canadian, longitudinal, real-world observational study demonstrate that treatment with infliximab over four

years is effective in reducing symptom severity and improving outcomes in patients with AS. Furthermore, the data from this registry confirm the validity and sensitivity to change of the ASDAS score in a real-world AS cohort.

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The Minimum Clinically Important Improvement and Patient Acceptable Symptom State In Basdai and BASFI For Patients With Ankylosing Spondylitis. Milla Kviatkovsky[1], Sofia Ramiro[2], Robert Landewé[2], Florence Tubach[3], Maxime Dougados[4] and D. van der Heijde[5]. [1]Nova Southeastern University, Miami, FL, [2]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [3]Universite Paris Diderot, Paris, France, [4]Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France, [5]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: The minimum clinically important improvement (MCII) and patient acceptable symptom state (PASS) are clinically relevant measures that report the patient response and condition. We aimed at estimating the MCII and PASS cut-off values for BASDAI and BASFI in patients with Ankylosing Spondylitis (AS).

Methods: A multinational study including patients with AS receiving NSAIDs for 4-weeks has been used to define PASS and MCII, by using external anchor questions for patient global assessment for BASDAI and functional impairment for BASFI. For PASS, patients were asked to consider the ways AS has affected them during the last 48 hours and if this would be an acceptable state for the rest of their life. Patients who answered "acceptable" met criteria for PASS analysis. For MCII, patients were asked to compare how they felt in the past 48 hours to the start of the study. Secondly, if they felt improved, to consider how important the improvement was. Those reporting moderate or slightly important improvement met criteria for MCII analysis. Subgroup analysis was performed for gender, age, baseline BASDAI and BASFI scores, disease duration, HLA-B27 status and presence/history of SpA extra-articular manifestations. Continuous variables were stratified according to the median value. For MCII in BASDAI, a separate analysis was done on patients with a baseline BASDAI≥4 to represent patients recommended to receive treatment in clinical practice. The 75th percentile approach was used to establish cut-off values.

Results: 283 patients with AS (76% males, 64% HLA-B27 positive, mean (SD) age: 43(14) years and mean disease duration: 13(10) years) were included. Mean baseline BASDAI and BASFI values were 5.0 and 4.6 respectively. Cut-off values for PASS values were 4.1 for BASDAI and 3.8 for BASFI (Table 1). The MCII cut-off was an absolute change of 0.7 BASDAI and 0.4 in BASFI. Subgroup analyses revealed differences between groups if stratified for age, disease duration and baseline value, with differences larger for PASS than MCII. For the sub-analysis of the patient group with a baseline BASDAI score ≥4, the MCII was 1.1 in BASDAI and 0.6 in BASFI for absolute change.

Table 1. MCII/PASS for BASDAI and BASFI with Subgroup Analysis

	BASDAI				BASFI			
	PASS		MCII		PASS		MCII	
	N	Value (95% CI)	N	Value (95% CI)	N	Value (95% CI)	N	Value (95% CI)
Overall Cut Off Values	176	4.1 (3.8, 4.4)	113	0.7 (0.4, 1.0)	165	3.8 (3.5, 4.1)	95	0.4 (0.2, 0.6)
Stratified Analysis								
Women	40	4.2 (3.5, 4.8)	27	0.5 (0.0, 1.0)	34	3.5 (2.7, 4.3)	25	0.5 (0.0, 0.9)
Men	136	4.1 (3.8, 4.4)	87	0.7 (0.4, 1.0)	130	3.8 (3.5, 4.1)	70	0.4 (0.1, 0.7)
HLA B27 Positive	121	4.1 (3.8, 4.4)	75	0.6 (0.3, 0.9)	117	3.8 (3.4, 4.2)	57	0.4 (0.1,0.7)
HLA B27 Negative	28	4.1 (3.5, 4.7)	15	0.5 (0.0, 1.3)	23	3.5 (3.4,4.2)	16	0.7 (0.0, 1.4)
Age ≤41.4 years	79	4.0 (3.6, 4.4)	53	0.7 (0.3, 1.1)	74	2.9 (2.5, 3.3)	49	0.4 (0.0, 0.8)
Age > 41.4 years	91	4.2 (3.8, 4.6)	60	0.5 (0.1, 0.9)	85	4.8 (4.3, 5.3)	46	0.5 (0.2, 0.8)
Disease Duration≤11yrs	82	3.5 (3.1, 3.9)	52	0.8 (0.4,1.2)	83	3.2 (2.8, 3.6)	51	0.5 (0.2, .8)
Disease duration >11 yrs	89	4.4 (4.1, 4.7)	56	0.5 (0.2, .8)	78	4.5 (4.1, 4.9)	39	0.4 (0.0, .8)
Baseline score <median[a,b]	101	3.1 (2.8, 3.4)	50	0.5 (0.2, 0.8)	102	2.9 (2.7, 3.1)	50	0.3 (0.1, .5)
Baseline score≥median[a,b]	76	4.8 (4.4, 5.2)	64	1.2 (0.8, 1.6)	64	5.8 (5.2, 6.4)	50	0.6 (.2,1.0)
Patients with Baseline BASDAI ≥ 4								
Cut Off Values	115	4.5 (4.2, 4.8)	88	**1.1 (0.8, 1.4)**	103	4.6 (4.2, 5.0)	**73**	**0.6 (0.3, 0.9)**

[a]: median Baseline BASDAI = 4.9 [b]: median baseline BASFI = 4.6

Conclusion: PASS for both BASDAI and BASFI are highly variable based on important patient characteristics such as age, disease duration and baseline value. Frequently the PASS value is even higher than the recommended cut-off for start of treatment. Therefore, no uniform PASS can be proposed and this makes this instrument less useful. This applies similarly to the MCII but to a lesser extent. As MCII will mostly be applied in patients who start with new treatment (and a BASDAI ≥4), we recommend a cut-off value for MCII of 1.1 for BASDAI and 0.6 for BASFI.

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Effective Prevention Of New Osteitis On Magnetic Resonance Imaging In Patients With Early Axial Spondyloarthritis During 3 Years Of Continous Treatment With Etanercept - Data Of The Esther Trial. In-Ho Song[1], Kay-Geert A. Hermann[2], Hildrun Haibel[3], Christian Althoff[4], Denis Poddubnyy[3], Joachim Listing[5], Anja Weiss[6], Ekkehard Lange[7], Bruce Freundlich[8], Martin Rudwaleit[9] and Joachim Sieper[10]. [1]Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany, [2]Charité Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany, [3]Charité Universitätsmedizin Berlin, Berlin, Germany, [4]Charite Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany, [5]German Rheumatism Research Center, Berlin, Germany, [6]German Rheumatism Research Centre, Berlin, Germany, [7]Pfizer Pharma AG, Berlin, Germany, [8]University of Pennsylvania, Philadelphia, PA, [9]Endokrinologikum Berlin, Berlin, Germany, [10]Charité Universitätsmedizin Berlin, Campus Benjamin-Franklin, Berlin, Germany.

Background/Purpose: In patients with early axial spondyloarthritis (SpA) with a disease duration of < 5 years and evidence of active inflammation on whole-body magnetic resonance imaging (wb-MRI) in the spine and/or sacroiliac (SI-) joints at baseline [1] we assessed the degree of fluctuation of active inflammation (bone marrow edema/ osteitis) on MRI during treatment with 3 consecutive years with etanercept (ETN).

Methods: In the previously reported ESTHER trial axial SpA patients were treated with ETN (n= 40) versus sulfasalazine (SSZ) (n= 36) in the first year [1]. All patients who were not in remission at week 48 (n=48) were either continuously treated with ETN, or sulfasalazine treatment was switched to ETN treatment. Wb-MRIs of those 40 patients who reached the end of year 4 were scored for active inflammation (osteitis) in the SI-joint quadrants and spine vertebral units (VUs). We here analysed MRI data in terms of osteitis in the pooled data set of 40 patients who were continously treated with ETN for 3 consecutive years. Data were analysed as observed. Scoring was performed by two radiologists, blinded for treatment arm and MRI time point. For this analysis, the presence or absence of osteitis were only counted if both scorers agreed.

Results: At baseline there were 136 SI-joint quadrants with osteitis (according to both scorers). At year 2 osteitis disappeared in 50% of quadrants (68/136), at year 3 osteitis disappeared in 41% (56/136) of quadrants and osteitis disappeared at both year 2 and 3 in 32% (44/136).

In the spine at baseline 37 vertebral units (VUs) showed osteitis. Of these at year 2 osteitis disappeared in 65% (24/37), at year 3 in 57% (21/37) and in both year 2 and 3 in 51% (19/37).

Of the SI-joint quadrants which did not show osteitis (according to both scorers) at baseline (n= 131) the rate of new development of osteitis was 4% (5/131) at year 2; 7% (9/131) at year 3 and only 1.5% (2/131) at both year 2 and 3.

Of the spine vertebral units which did not show osteitis at baseline (n= 843) the rate of new development of osteitis was 0.8% (7/843) at year 2; 1.3% (11/843) at year 3 and 0.4% both at year 2 and 3.

The mean osteitis spine score (range 0–69) decreased from 1.6 (standard deviation 3.4) at baseline to 0.7 (1.4) at year 2 and 0.9 (1.8) at year 2. The mean SI-joint score (range 0–24) decreased from 6.8 (6.1) at baseline to 2.0 (2.2) at year 2 and 2.2 (2.5) at year 3.

Conclusion: There was a consistently effective suppression of osteitis on MRI in patients with early axial SpA and only a very low rate of new onset of osteitis during 3 years of continous treatment with etanercept. Whether this also prevents the occurrence of bone proliferation has to be proven by longer follow-ups.

Reference:

1. Song I.-H. Ann Rheum Dis. 2011;70 (4):590–596.

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Responsiveness Of Health Related Quality Of Life Questionnaires To Treatment With Anti-TNF Therapy In Psoriatic Arthritis. Zahi Touma, Arane Thavaneswaran, Vinod Chandran and Dafna D. Gladman. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Patient-reported outcomes (PRO) on Health Related Quality of Life (HRQoL) are increasingly used to assess responsiveness after treatment. This study aimed to determine the ability of different PRO to asses responsiveness in psoriatic arthritis (PsA) after the initiation of anti-TNF therapy.

Methods: A retrospective analysis was conducted on all PsA patients followed at the PsA clinic who had started and continued anti-TNF therapy and had at least 1 year of follow up.

PRO questionnaires administered at baseline and follow up visits included: patient global assessment (PGA) [very good, good, fair, poor and very poor], Short-Form 36 (SF-36), Health Assessment Questionnaire (HAQ), Functional Assessment of Chronic Illness Therapy (FACIT), Fatigue Severity Scale (FSS), EuroQol-5D (EQ-5D) and Dermatology Life Quality Index (DLQI). PGA after treatment was used as an external anchor to group the patients as: Improved, same or worse.

Ceiling and floor effects were checked at baseline and follow up visits. Distribution-based methods (effect size [ES], standardized response mean [SRM], Guyatt's responsiveness statistic [GRS]) and anchor-based methods (Spearman correlation of the change scores of PRO) were used to assess responsiveness.

A priori hypothesis was that moderate to large responsiveness scores would be observed for the patients who improved or worsened.

Results: 223 patients with active PsA (62% male and 90% Caucasian) were identified. Disease duration at baseline visit was 12.9 (9.2). At follow up visit, 70 patients improved, 126 remained the same and 27 worsened based on PGA.

Ceiling effect: 1) At baseline, a ceiling effect was identified for HAQ, and 3 domains of SF-36 (Role Physical, Social Functioning and Role Emotional) and 2) At follow up, a ceiling effect was identified for HAQ, 4 domains of SF-36 (Physical Functioning, Role Physical, Social Functioning and Role Emotional) and DLQI.

Floor effect: At baseline and follow up, a floor effect was identified for 2 domains of SF-36 (Role Physical and Role Emotional).

In particular SF-36, FACIT, DLQI and FSS indicated moderate to large responsiveness in the patients who improved and worsened (SRM 0.51–1.07 and Guyatt 0.64–3.06). A small SRM (0.25) was observed for HAQ in patients who improved. HAQ and FACIT were not responsive for patients who worsened.

At follow up, strong correlation was observed between the change scores: 1) Δ FACIT and Δ FSS ($r = -0.82$, $p = 0.007$) in patients who improved and 2) Δ FACIT and Δ HAQ ($r = -0.91$, $p = 0.004$) and Δ EQ-5D and Δ SF-36 MCS (0.80, $p = 0.02$) in patients who worsened.

Conclusion: SF-36 and DLQI are responsive questionnaires able to capture improvement and worsening in response to treatment based on patient judgment.

HAQ is extremely nonresponsive and EQ-5D was the worst responsive compared to the other questionnaires. FACIT was responsive and superior to FSS for measuring fatigue in patients who improved on biologics but not for measuring worsening. A larger sample size is needed to decide on the exclusion of either FACIT or FSS.

Disclosure: Z. Touma, None; **A. Thavaneswaran**, None; **V. Chandran**, None; **D. D. Gladman**, None.

1554

Real-World Effectiveness Of Infliximab In The Treatment Of Psoriatic Arthritis Over 12 Months: The Canadian Experience. Proton Rahman[1], Majed M. Khraishi[2], William Bensen[3], John T. Kelsall[4], Brian D. Hanna[5], Craig Watts[6], Emmanouil Rampakakis[7], John S. Sampalis[7], May Shawi[8], Susan M. Otawa[8] and Allen J. Lehman[8]. [1]Memorial University, St. Johns, NF, [2]MD, Memorial University of Newfoundland, Nexus Clinical Research, St Johns, NF, [3]St. Joseph's Hospital and McMaster University, Hamilton, ON, [4]Mary Pack Arthritis Centre, Vancouver, Vancouver, BC, [5]McMaster University, Ontario, Kitchener, ON, [6]McGill University and Montreal General Hospital, Sainte-Anne-de-Bellevue, QC, [7]JSS Medical Research, St-Laurent, QC, [8]Janssen Canada Inc, Toronto, ON.

Background/Purpose: The efficacy of anti-TNF in the management of psoriatic arthritis (PsA) has been demonstrated in numerous controlled clinical trials. Longitudinal observational studies assessing the real-world effectiveness of anti-TNF agents are essential in order to demonstrate the true benefits. The objective of this study was to assess in Canadian routine clinical practice the 12-month outcomes in patients with PsA treated with infliximab.

Methods: Biologic Treatment Registry Across Canada (BioTRAC) is an ongoing, prospective registry of patients initiating treatment for RA, AS, or PsA with infliximab or golimumab as first biologics or after having been treated with a biologic for less than six months. People with PsA treated with infliximab who were enrolled between 2005 and 2012 were included in this analysis. Descriptive statistics were produced for clinical outcome measures and patient reported outcomes at baseline and six or twelve months of treatment. Within-group changes were assessed for statistical significance with the paired-samples Student's t-test.

Results: A total of 92 PsA patients were included in the analysis. Mean (SD) age of the patient cohort was 48.7 (9.9) years and mean (SD) duration since diagnosis was 6.8 (9.1) years. The majority of patients were male (52.2%). Upon six months of treatment, statistically significant ($P<0.05$) and clinical meaningful improvements were observed in all parameters analyzed, which were sustained over 12 months of treatment. Mean (SD) patient parameters at baseline and 12 months of treatment were: PASI: 3.3 (5.6) vs. 1.3 (2.2), $P=0.009$; DAS28-CRP: 4.0 (1.3) vs. 2.8 (1.3), $P=0.002$; C-reactive protein (CRP): 13.0 (18.9) vs. 8.2 (12.5) mg/L, $P=0.196$; erythrocyte sedimentation rate (ESR): 21.4 (22.7) vs. 12.9 (15.4) mm/hr, $P=0.171$; morning stiffness: 58.1 (45.3) vs. 40.0 (43.1) min, $P=0.020$; tender joint count (TJC28): 5.9 (5.3) vs. 3.0 (4.7), $P=0.001$; swollen joint count (SJC28): 4.0 (3.8) vs. 1.9 (3.7), $P=0.001$; health assessment questionnaire (HAQ-DI): 1.15 (0.66) vs. 0.86 (0.77), $P=0.001$; patient global assessment of disease activity (PtGA): 5.0 (2.8) vs. 3.5 (2.9) cm, $P=0.005$; physician global assessment of disease activity (MDGA): 5.8 (2.2) cm vs. 2.6 (2.3), $P<0.001$; pain: 46.4 (25.6) vs. 33.1 (28.5) mm, $P=0.013$.

Conclusion: The results of this Canadian longitudinal observational study have shown that a significant burden of illness is observed at initiation of infliximab in PsA patients in routine clinical practice. Treatment with infliximab was effective in reducing symptom severity and improving outcomes in patients with PsA over 12 months.

Disclosure: P. Rahman, Amgen, Abbott, BMS, Merck, Pfizer, Janssen, Hoffman-La Roche, UCB, Novartis, Sanofi-Aventis, 5, Amgen, Abbott, BMS, Merck, Pfizer, Janssen, Hoffman-La Roche, UCB, Novartis, Sanofi-Aventis, 9; **M. M. Khraishi**, Hoffman-La Roche Canada, Amgen and Pfizer Canada, and Abbott Canada., 2; **W. Bensen**, None; **J. T. Kelsall**, None; **B. D. Hanna**, None; **C. Watts**, None; **E. Rampakakis**, None; **J. S. Sampalis**, None; **M. Shawi**, Janssen Canada, 3; **S. M. Otawa**, Janssen Canada, 3; **A. J. Lehman**, Janssen Canada, 3.

1555

Anti-TNF Drug Survival In Psoriatic Arthritis Patients Treated In Ordinary Clinical Practice. Glenn Haugeberg[1], Andreas P. Diamantopoulos[1], Agnete Gulati[2], Mari Hoff[3] and Arthur Kavanaugh[4]. [1]Hospital of Southern Norway Trust, Kristiansand, Norway, [2]St. Olavs Hospital, Trondheim, Norway, [3]St Olavs Hospital, Trondheim, Norway, [4]University of California San Diego, San Diego, CA.

Background/Purpose: The use of TNF-inhibitors in psoriatic arthritis (PsA) has been shown to improve clinical and radiographic outcome in randomized controlled trials (RCT) and shown to be well tolerated with a rather low rate of drop outs. However, patients in RCT may not be representative of patients followed in ordinary clinical practice. The aim was to assess drug survival of TNF-inhibitor treatment in patients with PsA treated in an ordinary rheumatology clinic in Norway.

Methods: The PsA patients were recruited from an ordinary rheumatology clinic in Norway. All PsA patients in this clinic are monitored and outcome measures and drug data is registered in a clinical hospital computer database. In the database termination and/or change of therapy had been registered. A survival analysis (Kaplan-Meyer) was performed and survival time for sequential therapeutic regimens were compared by Wilcoxon test. Anonymised data was analyzed using SPSS.

Results: We identified 148 patients with PsA who started treatment with their first TNF-inhibitor (from 2002 through 31.12.2012). During the first year of therapy 52 (35%) of these patients stopped treatment. 54 patients started their second and 22 patients started their third or more TNF-inhibitor, and within the first year 33 (61%) and 12 (55%), respectively, stopped treatment. The rate of patients who stopped treatment was highest in the beginning and lover during follow up. This was also seen for the second and $\geq 3^{rd}$ TNF

inhibitor. Overall drug survival was significantly higher for the first TNF-inhibitor compared to the second drug ($p<0.001$). The median survival time for the first, second and subsequent drug was 24, 7, and 9 months.

Conclusion: In an ordinary clinic setting, patients with PsA have a significantly reduced drug survival for the subsequent TNF-inhibitor if they fail on the first drug. For each drug, the first year of treatment had the highest termination rate.

Disclosure: G. Haugeberg, None; **A. P. Diamantopoulos**, None; **A. Gulati**, None; **M. Hoff**, None; **A. Kavanaugh**, None.

1556

Paradoxical Psoriasis: Experience Of a Biological Therapy Monographic Unit. Maria Luz Garcia Vivar[1], Silvia Perez Barrio[2], EVA Galindez Agirregoikoa[3], Catalina Gomez Arango[4], Jose Francisco Garcia Llorente[5], Rosa Izu Belloso[6], Esther Ruiz Lucea[5], Ignacio Torre Salaberri[7] and Jesus Maria Careaga Alzaga[8]. [1]Rheumatology department, Basurto University Hospital., BILBAO, Spain, [2]Dermatology Department. Basurto University Hospital, BILBAO, Spain, [3]Rheumatology Department. Basurto University Hospital, BILBAO, Spain, [4]Rheumatology Department, Basurto University Hospital, Bilbao, Spain, [5]Rheumatology Department, Basurto University Hospital, BILBAO, Spain, [6]Dermatology Department. Basurto University Hospital. Bilbao, BILBAO, Spain, [7]Rheumatology Department. Basurto University Hospital, Bilbao, Spain, [8]Dermatology department. Basurto University Hospital, BILBAO, Spain.

Background/Purpose: Anti TNF therapy's efficacy in controlling cutaneous psoriasis has widely been proven, but development of paradoxical psoriasis (PPs) as a side effect can occur. We define psoriasis as a paradoxical effect when it appears as new onset or as a different type of psoriatic lesion; some authors also include worsening of previous psoriasis, when it is clearly related with the treatment.

Methods: We reviewed the medical records from the 371 patients visited in the biological therapy monographic unit and from 150 pateients visited in the psoriatic arthropathy multidisciplinar clinic during 2011 and 2012. We selected 13 patients with suspected paradoxical psoriasis and we analyze clinical data, characteristics and severity of skin lesion, and the change in treatment required to control skin lesion.

Results: From the 13 selected patients, two presented flares of their skin lesions related to the underlying diagnosis of PsA with severe cutaneous disease prior to biological treatment. Therefore, 11 patients fulfilled the previously exposed criteria for PPs; six female and 5 male, mean aged 47 years (from 34 to 78). 7 patients had had no previous psoriatic lesions: 5 were diagnosed with ankylosing spondylitis (one negative HLA B27), one with rheumatoid arthritis and one with juvenile idiopathic arthritis (an adult patient). The remaining 4 patients were mixed forms of PsA, 3 of them had positive HLA B27.

The treatment involved was adalimumab in 7 patients, infliximab in two patients, and etanercept in the remaining two. PPs appeared between 2 and 38 months from the start of the biological therapy (mean 9 months), in 8 patients during the first year of the treatment.

PPs in two patients consisted of desquamative annular lesions that were confirmed by skin biopsy procedure. 7 patients had palmoplantar pustulosis, 4 presented skinfold psoriasis, 4 had scalp lesions, and 6 plaque psoriasis. 7 presented a mixture of different types of cutaneous psoriatic lesions.

The injury was considered mild in 4 cases managed with topical corticosteroid treatment, and moderate to severe in six patients that had to discontinue biologic therapy. Another one needed tapering of the dose of etanercept from 50 to 25 mgs per week. After discontinuation, 4 patients needed a new biological drug (three antiTNF and one ustekinumab), with no cutaneous complication. Skin evolution was satisfactory to improvement in all cases, with practical resolution in two.

Conclusion: Paradoxical psoriasis is a rare complication appearing in less than 3% of our patients under biological therapy. Although it can occur in patients with any diagnosis and receiving any kind of antiTNF drug, we find it more frequently in those patients with spondyloarthropaties during the first year of treatment with monoclonal antibodies. It may be an important and disabling side effect, but withdrawal of the biological drug is not always needed. Switching to another antiTNF when needed seems also a safe therapeutic decision with satisfactory outcomes.

Disclosure: M. L. Garcia Vivar, None; **S. Perez Barrio**, None; **E. Galindez Agirregoikoa**, None; **C. Gomez Arango**, None; **J. F. Garcia Llorente**, None; **R. Izu Belloso**, None; **E. Ruiz Lucea**, None; **I. Torre Salaberri**, None; **J. M. Careaga Alzaga**, None.

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Assessing The Real Life Impact Of Psoriatic Arthritis On Disability, Quality Of Life, and Provider Satisfaction. M. Elaine Husni[1], Daniel Duch[2] and Neil J. Korman[3]. [1]Cleveland Clinic Foundation, Cleveland, OH, [2]Curatio CME Institute, Exton, PA, [3]University Hospitals Dermatolo, Cleveland, OH.

Background/Purpose: Despite the availability of more targeted therapies for psoriatic arthritis (PsA), an assessment of the impact these have had on patient well-being has not recently been undertaken. We investigated a real world perspective on patient disability, quality of life (QoL), and patient encounters with various health care providers (HCP).

Methods: A cross sectional analysis of data were derived from a 52-question survey on the effect of PsA on the QoL, daily activities, work, patient satisfaction with treatment and physician care was included. The survey was distributed by the National Psoriasis Foundation (NPF) to its members with a prior diagnosis of PsA by a HCP. The survey was developed using validated questionnaires (PDRQ-9, PASE and HAQ20) and also collected information on PsA disease severity and treatment.

Results: 773 survey responses were collected after distribution to 9,336 NPF members (6.7% response rate); 144 responses were removed due to incomplete data. Based on the epidemiologic features of PsA from the medical literature, this survey of 629 PsA patients was representative of other patients with this disease in the US (margin of error, 3.9%)The average age at diagnosis was 41.7±13 years. Comorbidities, PASE and HAQ20 scores for patients in the survey were consistent with those reported in the medical literature. The average HAQ20 disability index score, 0.98±0.66 (Maximum score = 3, highest level of disability) reflects a moderate to severe level of disability. Higher HAQ20 and PASE scores were associated with higher disability, pain and worse overall status. Overall (scale of 0 –very well to 100 –very poor), patients averaged 43.6±28.2 with females statistically worse than males. A majority of patients (61.7%) reported that they were unable to work some days due to their health. A mean of 66.6±104.5 work days (median 15) were missed in the last year; 89.4% of days missed resulted from joint/pain problems.

The most common HCP was a rheumatologist (35.5%; n=223); the proportion of patients treated only by a dermatologist or only by a PCP was 12% (n=76) for each. The PDRQ-9 satisfaction rating for a rheumatologist (36.8) was 22% higher ($P\leq0.001$) than the rating for a PCP (30.1) but not different from dermatologists (33.7). Several patient factors appear correlated with these differences, including the number of prescription drugs and psoriasis severity scores.

Patients rated satisfaction with their treatment on a 5-point scale (1=Very Unsatisfied, 5=Very Satisfied). Etanercept had the highest satisfaction rating and cyclosporine A was lowest. Ratings for the 5 most frequently used treatments reported were:

Etanercept (n=138): 3.93±1.33; very satisfied (VS): 50%
Adalimumab (n=144): 3.48±1.52; VS: 37%
Methotrexate (n=204): 3.45±1.43; VS: 30%
Infliximab (n=51): 3.12±1.58; VS: 26%
Sulfasalazine (n=46): 2.50±1.63; VS: 17%
cyclosporine A (n=19): 2.32±1.46; VS: 6%

Conclusion: Survey results suggest that PsA may be a very aggressive disease and that despite new targeted treatments, many patients are still not doing too well. Limitations do exist with survey methodology however, results may be used to improve patient outcomes and generate critical measures for further study such as provider satisfaction.

Disclosure: M. E. Husni, National Psoriasis Foundation, 2, Arthritis National Research Foundation, 2; **D. Duch**, None; **N. J. Korman**, None.

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Drug Trends In Psoriatic Arthritis. Arane Thavaneswaran[1], Gideon Kalman-Lamb[1], Teneille Loo[2], Vinod Chandran[1] and Dafna Gladman[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Toronto, Toronto, ON.

Background/Purpose: Psoriatic arthritis (PsA) is now recognized as a potentially severe form of arthritis which requires aggressive medical therapy. The aim of this study was to determine trends in drug usage among patients with PsA followed longitudinally.

Methods: 1229 patients with PsA were included from an observational cohort from 1978 to 2013. Descriptive statistics at baseline were conducted to characterize the study population. Comparisons of medication use by decade

(1970–1980, 1980–1990, 1990–2000, 2000–2010, 2010 onwards) were made for NSAIDS (Non-steroidal anti-inflammatory drugs), DMARDs (Disease Modifying Anti-Rheumatic Drugs) and Biologics were conducted frequencies and trend tests.

Results: Demographics at baseline: 56% males with mean (s.d.) age of 44 (13.1) years, disease duration 6.8 (8.2) years, PASI of 5.9 (8.1), active joint count of 11.0 (9.9), and 57% with radiographic damage [modified Steinbrocker score 12.7 (25.2)]. Medication use at baseline: 79% of the patients on NSAIDs, 51% on DMARDs and 7% on Biologics. Over follow-up 89% of the patients took NSAIDs with the highest frequency of use on Indomethacin (43%), Naproxen (40%) and Diclofenac (30%). Of the 75% treated with DMARDs, mostly Methotrexate (MTX) 54% orally and 26% parenterally), sulfasalazine (26%) Leflunomide (14%). 29% were on biologics, most commonly Etanercept (20%) adalimumab 9% and golimumab 4%. There was a clear trend towards decreased NSAID use (p-value<0.0001) but increased DMARD and Biologics use by decade (<0.0001) (Table 1 & 2).

Table 1. Frequency of Medication Use at Baseline by Decade

	DECADE					
MEDICATION	1970–1980	1980–1990	1990–2000	2000–2010	2010 & on	p-value
NSAIDs	41 (71.9%)	240 (87.0%)	214 (84.6%)	375 (73.7%)	40 (66.7%)	<0.0001
DMARDs	25 (45.6%)	118 (42.8%)	129 (52.0%)	276 (54.2%)	35 (55.6%)	0.12
BIOLOGICs	0 (0%)	1 (0.4%)	0 (0%)	55 (11.3%)	16 (25.4%)	<0.0001

Table 2. Combination of Medication use by Decade

	DECADE					
MEDICATION	1970's	1980's	1990's	2000's	2010's	p-value
None	12 (21.1%)	27 (9.5%)	27 (10.6%)	80 (15.5%)	8 (12.7%)	0.27
NSAIDs only	19 (33.3%)	140 (49.1%)	98 (38.6%)	146 (28.3%)	14 (22.2%)	<0.0001
DMARDs +/− NSAIDs	26 (45.6%)	117 (41.1%)	129 (50.8%)	235 (45.5%)	25 (39.7%)	0.73
BLGs +/−DMARDs +/− NSAIDs	0 (0%)	1 (0.4%)	0 (0%)	55 (10.7%)	16 (25.4%)	<0.0001

Conclusion: Medication use over the past four decades shows reduced NSAID use but increased DMARD and Biologics use as the severity of PsA was recognized.

Disclosure: A. Thavaneswaran, None; **G. Kalman-Lamb**, None; **T. Loo**, None; **V. Chandran**, None; **D. Gladman**, None.

ACR/ARHP Poster Session B
Systemic Lupus Erythematosus - Clinical Aspects II: Central Nervous System Manifestations, Therapeutics
Monday, October 28, 2013, 8:30 AM–4:00 PM

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Cyclophosphamide and Rituximab Combination Treatment For Severe Systemic Lupus erythematosus is Effective and Well Tolerated. Ali Shahzad[1], Farheen Jafri[2], Bisharah Rizvi[2], Xiongce Zhao[3], Meryl Waldman[3] and Sarfaraz A. Hasni[4]. [1]NIAMS/NIH, Bethesda, MD, [2]R-Research, Hamilton, NJ, [3]NIDDK/NIH, Bethesda, MD, [4]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD.

Background/Purpose: Systemic lupus erythematosus (SLE) is often complicated by resistance or partial response to initial immunosuppressive regimen and flares after initial response. Optimal management of these patients is unclear due to lack of scientific evidence. There is limited data suggesting that the combination of cyclophosphamide (CYC) and rituximab (RTX) may have efficacy in recurrent and treatment resistant lupus. We present our experience with intravenous (IV) CYC plus RTX combination and its comparison to CYC only therapy.

Methods: Data from SLE patients who were treated with IV CYC monotherapy only or IV CYC and RTX combination from 2000–2013 was retrospectively reviewed. Patient's demographic information, SLE duration, SLE manifestations, co-morbidities, relevant labs, response to therapy and post-treatment infections were recorded every month for the first 6 post –treatment months and then every 3 months up to 60 months (if available) or until last data entry. Patients with incomplete data or insufficient follow-up(less than 6 months post-treatment) were not included. IV CYC monotherapy was given according to the NIH standard protocol for the treatment of lupus nephritis. IV CYC and RTX combination therapy regimen consisted of simultaneous administration of IV CYC and 2 doses of RTX 1000 mg given 15 days apart. Combination regimen was prescribed based on clinician's discretion most commonly for recalcitrant or recurrent flares of lupus nephritis(LN). Predetermined definitions (based on published literature) were used to record flares (renal vs. non-renal) and response (complete, partial or no response). Statistical analysis was done using SAS software (SAS Inc., Cary, NC).

Results: A total of 43 SLE pts. with adequate follow up were identified: 31 (72%) received CYC; 12 (28%) received CYC plus RTX. Indications for combination treatment were partial response or recurrent LN (10/12), CNS lupus(1/12) and treatment resistant extra-renal SLE(1/12). Most (75%) patients treated with CYC and RTX combo were previously treated with IV CYC, most commonly for lupus nephritis. There was no difference in overall survival between CYC only and CYC and RTX combo groups. In patients receiving combo treatment, median duration of follow –up was 36 months (6–50 months) prior to combo treatment and 21 months (6–60 months) after receiving the combo treatment. In the 12 patients who received CYC plus RTX, number of flares before receiving CYC and RTX combo was significantly higher= 38(Renal flares=26; non-renal flares=12) as compared to after receiving combo=13(Renal=3; non-renal=10). There was no significant increase in bacterial, viral or fungal infections after receiving combo therapy.

Conclusion: CYC and RTX combination regimen may have efficacy in reducing renal and non-renal lupus flares. This does not appear to be associated with increased risk of infections. Long term sequelae if any, of this regimen is not known. Our study has inherent limitations due to its retrospective nature and small sample size. Based on these preliminary results we are planning a clinical trial studying the efficacy and tolerability of CYC/RTX combination in patients with recurrent severe SLE.

Disclosure: A. Shahzad, None; **F. Jafri**, None; **B. Rizvi**, None; **X. Zhao**, None; **M. Waldman**, None; **S. A. Hasni**, None.

1560

Clinical Characterization Of Anti-CCP+Ve Systemic Lupus Erythematosus Patients. Samera Vaseer[1] and Eliza Chakravarty[2]. [1]University Of Oklahoma, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: SLE is a heterogeneous autoimmune disease characterized by the presence of autoantibodies and manifestations of numerous organ systems. One of the most common SLE manifestations is inflammatory arthritis, often indistinguishable from rheumatoid arthritis in early stages when other manifestations are not present. Antibodies directed against citrullinated peptides (anti-CCP) were initially thought to be highly specific for RA (specificity estimated at 98%). The prevalence and role of anti-CCP antibodies has not been well characterized in SLE patients.

The purpose of this study is to estimate the prevalence of anti-CCP antibodies among SLE patients and to identify unique characteristics of CCP+ve SLE patients in comparison to CCP -ve SLE patients in a case control fashion.

Methods: The Oklahoma Lupus Cohort is a prospective longitudinal observational cohort. Participants provide written informed consent to participate, and have clinical data as well as peripheral blood specimens collected during routine clinical care. Serologies are obtained on all participants.

SLE patients with positive anti-CCP antibodies were identified and their demographic, clinical, and serological characteristics were compiled through chart review. In order to identify features that are unique to CCP+ SLE, we identified 2–3 controls, CCP- SLE patients matched for age and gender, to each CCP+ case.

Results: Of the total 227 SLE patients with known CCP serologies, 26 (11.5%) were found to be anti-CCP positive (>20 IU). Mean anti-CCP value was 90. Cases were separated into high positive anti CCP group (>60) and low to moderate positive anti-CCP group (<60). 60% were current or former smokers in the high positive group. Ethnic distribution was as follows; Caucasian 60%, African American10%, Native American 20%, and 10% Hispanic.

Majority of CCP+ SLE patients had clinical features similar to CCP negative group with high frequency of sicca symptoms 80% vs. 49% in controls. Inflammatory arthritis, Raynauds, cutaneous manifestations and mucosal ulcers were also frequent, though similar to the control group. The prevalence of renal disease and CNS disease in the CCP+ SLE patients was similar to that reported in the literature.

Aside from ANA, the most prevalent autoantibodies among CCP+SLE patients were anti-Ro/SSA (50%), and RNP (40%). RF was seen in 40% of high CCP+ group compared to 15% in control group.

Conclusion: Anti CCP positive SLE subjects have a high frequency of arthritis and sicca symptoms. CCP+SLE patients share many common SLE autoantibodies with CCP- patients with high prevalence of anti Ro, RNP and RF among this group.

Disclosure: S. Vaseer, None; **E. Chakravarty**, None.

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Treat-To-Target In Systemic Lupus Erythematosus: Report From the T2T/SLE Working Party. Ronald F. van Vollenhoven[1], Marta Mosca[2], George Bertsias[3], Annegret Kuhn[4], Kirsten Lerstrøm[5], Josef S. Smolen[6], David A. Isenberg[7], Matthias Schneider[8] and the T2T/SLE Working Party[9]. [1]Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), the Karolinska Institute, Stockholm, Sweden, [2]Rheumatology Unit, Internal Medicine, University of Pisa, Pisa, Italy, [3]University of Crete, Iraklion, Greece, [4]University of Münster, Münster, Germany, [5]Lupus Europe, Farum, Denmark, [6]Medical University of Vienna, Vienna, Austria, [7]University College London, London, United Kingdom, [8]Heinrich-Heine-University, Duesseldorf, Germany, [9]the Karolinska Institute, Stockholm, Sweden.

Background/Purpose: The principle of treating-to-target has been applied successfully to many diseases outside rheumatology and more recently to rheumatoid arthritis. Identifying appropriate therapeutic targets and pursuing these systematically has led to improved care for patients with these diseases and useful guidance for health care providers and administrators. Thus, an initiative to evaluate possible therapeutic targets and develop treat-to-target guidance was believed to be of benefit in SLE as well. An expert panel was convened for this purpose.

Methods: Thirty-four specialists in rheumatology, nephrology, dermatology and/or clinical immunology and a patient representative contributed to this initiative. The majority convened on three occasions. Twelve topics of critical importance for this endeavor were identified and a systematic literature review (SLR) was performed on these topics. The results of the SLR were condensed and reformulated as recommendations, discussed, modified, and voted upon. The finalized bullet points were analyzed for degree of agreement among the panel (strength of recommendation, SoR). The Oxford Center level of evidence (LoE, corresponding to the research questions, not shown) and grade of recommendation (GoR) were determined for each recommendation.

Results: The twelve systematic literature searches and their summaries led to eleven recommendations (Table). LoE and GoR of the recommendations were variable but agreement was >0.9 in each case. An extensive research agenda was identified, and four overarching principles were also agreed upon.

Table.

Overarching Principles	GoR (A–C)	SoR (0–10)
I. The management of SLE should be based on shared decisions between the informed patient and her/his physician(s)		9.48
II. Treatment of SLE should aim at ensuring long-term survival, preventing organ damage, and optimizing health-related quality-of-life, by controlling disease activity and minimizing comorbidities and drug toxicity		9.90
III. The management of SLE requires an understanding of its many aspects and manifestations, which may have to be targeted in a multidisciplinary manner		9.42
IV. Patients with SLE need regular long-term monitoring and review and/or adjustment of therapy		9.81
Recommendations		
1. The treatment target of SLE should be remission of systemic symptoms and organ manifestations or, where remission cannot be reached, the lowest possible disease activity, measured by a validated lupus activity index and/or by organ-specific markers	C(SLE)/A(LN)	9.52
2. Prevention of flares (especially severe flares) is a realistic target in SLE and should be a therapeutic goal.	B(SLE)/A(LN)	9.32
3. It is not recommended that the treatment in clinically asymptomatic patients be escalated based solely on stable or persistent serological activity.	B	9.03
4. Since damage predicts subsequent damage and death, prevention of damage accrual should be a major therapeutic goal in SLE.	A	9.71
5. Factors negatively influencing health-related quality of life (HRQOL), such as fatigue, pain, and depression should be addressed in addition to control of disease activity and prevention of damage.	B	9.03
6. Early recognition and treatment of renal involvement in lupus patients is strongly recommended.	B	9.87
7. For lupus nephritis, following induction therapy, at least 3 years of immunosuppressive maintenance treatment is recommended to optimize outcomes.	A	9.13
8. Lupus maintenance treatment should aim for the lowest glucocorticoid dosage needed to control disease, and if possible glucocorticoids should be withdrawn completely.	B	9.58
9. Prevention and treatment of anti-phospholipid antibody syndrome (APS)-related morbidity should be a therapeutic goal in SLE, but therapeutic recommendations do not differ from those in primary APS.	C	9.52
10. Irrespective of the use of other treatments, serious consideration should be given to the use of antimalarials.	B	9.35
11. Relevant therapies adjunctive to any immunomodulation should be considered to control comorbidity in SLE patients.	C	9.55

Conclusion: Treat-to-target-in-SLE (T2T/SLE) recommendations were developed by a large panel of multi-specialty experts and a patient representative. Although LoE and GoR were variable, agreement was excellent. Prominent features of these recommendations are targeting remission, preventing damage, and improving quality of life. It is anticipated that "treating-to-target" can and will be applicable to the care of patients with SLE.

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Elevated Serum B-Cell Activating Factor (BAFF/BlyS) Characterises Disease Relapse Following Rituximab In Systemic Lupus Erythematosus. Lucy M. Carter, David A. Isenberg and Michael R. Ehrenstein. University College London, London, United Kingdom.

Background/Purpose: Numerous reports suggest that B cell depletion therapy (BCDT) using rituximab is effective in patients with systemic lupus erythematosus (SLE). However, two major trials did not confirm these results. We, and others, have shown that the characteristics and kinetics of repopulating B cells are associated with different clinical responses to BCDT. B cell activating factor/B Lymphocyte Stimulator (BAFF/BLyS) is a key mediator of B cell survival and self-tolerance, which is over-expressed in many patients with SLE. The present study examines changes in serum BAFF at disease flares and remission following BCDT and repopulation of peripheral B cells, and assesses the relationship between serum BAFF, B cell number and autoantibody levels according to treatment outcome.

Methods: 35 patients with SLE, treated with one or more cycles of BCDT using rituximab, cyclophosphamide and methylprednisilone, had stored serum samples available for analysis. Patients were followed up until disease flare, further BCDT or for a minimum of 18 months following BCDT. Anti-dsDNA levels, immunoglobulins and CD19+ counts were recorded during follow up. Clinical disease was assessed using the BILAG index. Serum BAFF was measured during disease flare prior to BCDT and at subsequent relapse or remission, using a human BAFF ELISA.

Results: Following initial BCDT, 10 patients remained in remission for the duration of follow up. Twenty-five patients went on to relapse, of which 22 were treated with further BCDT. BAFF levels were positively correlated with B cell numbers ($R = 0.65$, $p < 0.05$) and serum IgG ($R = 0.56$, $p < 0.01$) prior to BCDT, but did not predict subsequent treatment outcome or time to repopulation following rituximab ($p > 0.05$). However, serum BAFF after BCDT and subsequent B cell repopulation was significantly higher at disease relapse compared to levels in patients who remained in remission ($p < 0.01$) but also compared with the disease flare prior to BCDT ($p < 0.05$).

Following BCDT serum BAFF was inversely correlated with B cell numbers at disease flare ($R = -0.44$, $p < 0.05$), with flare at lower B cell numbers associated with the highest BAFF levels. Changes in serum BAFF during relapse or remission strongly correlated with change in anti-dsDNA antibody levels ($R = 0.62$, $p < 0.001$).

Conclusion: The present data suggest a significant role for BAFF in driving disease flare after B-cell repopulation following BCDT. In some patients sequential BCDT promoted ever increasing BAFF levels accompanied by rising anti-DNA antibodies and flare even at low B-cell numbers. Therefore, our data justifies the judicious use of BAFF blockade in a subgroup of lupus patients after BCDT.

Disclosure: L. M. Carter, None; **D. A. Isenberg**, None; **M. R. Ehrenstein**, None.

1563 WITHDRAWN

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Efficacy Of Influenza Vaccination Is Strongly Decreased In Systemic Lupus Erythematosus: A Meta-Analysis Of Literature Data. Laurent Arnaud[1], Alexis Mathian[1], Hervé Devilliers[2], Du Boutin-LE Thi Huong[1], Ahlem Chaib[1], Fleur Cohen-Aubart[1], Julien Haroche[1], Miguel Hié[1], Makoto Miyara[1] and Zahir Amoura[1]. [1]Hôpital Pitié-Salpêtrière, AP-HP, UPMC Univ Paris 06 & French National Reference Center For Systemic Lupus and Antiphospholipid Syndrome, Paris, France, [2]Internal medicine and systemic disease unit, Dijon University Hospital, Dijon, France.

Background/Purpose: Several studies suggest that the efficacy of influenza vaccination may be decreased in systemic lupus erythematosus (SLE). We performed a meta-analysis to assess systematically the immunogenicity of influenza vaccination in SLE, comparatively to healthy subjects.

Methods: All studies published until February 2013, comparing the immunogenicity of influenza vaccination in SLE comparatively to healthy subjects were identified from the MEDLINE, Cochrane and EMBASE databases and included in our meta-analysis. The immunogenicity was evaluated using the proportion of subjects with influenza antibody titers ≥1:40 (seroprotection rate) and the proportion of subjects with either a prevaccination hemagglutination-inhibiting titer <1:10 and a postvaccination titer ≥1:40 or a prevaccination titer ≥1:10 and an increase in the titer by a factor of 4 or more (seroconversion rate). Pooled effect estimates were obtained using a random-effects model.

Results: Of 146 citations retrieved, 16 primary studies including 1010 SLE patients and 578 healthy controls met inclusion criteria. Pooled analysis revealed significantly decreased immunogenicity of H1N1 influenza vaccine in SLE patients compared to healthy controls for both seroprotection rates (Odd Ratio, OR: 0.34 [95% confidence interval, 95%CI: 0.21 – 0.55]) and seroconversion rates (OR: 0.34 [95%CI: 0.21 – 0.56]) with significant statistical heterogeneity for seroconversion ($T^2 = 0.37$; $p = 0.01$; $I^2 = 0.54$). Our meta-analysis also reveals significantly decreased seroprotection rates with H3N2 (OR: 0.34 [95%CI: 0.18 – 0.66]) and B (OR: 0.40 [95%CI: 0.22 – 0.73]) influenza vaccines and non-significantly decreased seroconversion rates for H3N2 (OR: 0.55 [95%CI: 0.21 – 1.45]) and B (OR: 0.44 [95%CI: 0.19 – 1.01]) influenza vaccines. Subgroup analyses considering only SLE patients without corticosteroids and immunosuppressors (n=209) revealed non significantly decreased seroprotection rate (OR: 0.60 [95%CI: 0.35 – 1.01]) and decreased seroconversion rate (OR: 0.64 [95%CI: 0.42 – 0.98]) compared with healthy controls (n=226).

Conclusion: Our meta-analysis demonstrates significantly decreased immunogenicity of influenza vaccines in SLE compared to healthy patients. Subgroup analysis suggests that decreased immunogenicity may be independent of immunosuppressive treatments. Specific vaccination schemes, such as the use of a second injection or the use of adjuvanted vaccines-, should be evaluated in SLE patients.

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RNA-Sequencing Confirms Clinical Safety Of Herpes Zoster Vaccine. Christopher J. Lessard, Indra Adrianto, Joel M. Guthridge, John A. Ice, Graham B. Wiley, Stuart B. Glenn, Judith A. James, Joan T. Merrill, Patrick M. Gaffney, Courtney G. Montgomery, Kathy L. Sivils and Eliza Chakravarty. Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: SLE patients have increased risk of Herpes Zoster (HZ). A live-attenuated vaccine is available for healthy persons > 50 years old, but its safety in immunocompromised individuals is unknown. Two areas of possible concern regard the development of vaccine-induced HZ, and increased disease activity following stimulation from an immunogenic vaccine. We sought to evaluate gene expression profiles between SLE patients and healthy controls after VZV vaccination to identify any potential increase in immune system activation or impaired viral control in SLE patients.

Methods: We performed a pilot open-label study of HZ vaccine in 10 SLE patients with low disease activity and 10 healthy, matched controls. Safety outcomes included vaccine-induced HZ or flare of underlying SLE following vaccination. Whole-blood RNA was collected in Tempus tubes to study early changes in immune related pathways at baseline and 2 weeks post-vaccination in a subset of 5 matched pairs of SLE patients and controls. RNA-sequencing was done using an Illumina HiSeq 2000 with the resulting FASTQ files aligned to the human genome using STAR. DEseq was used to determine differential expression with the threshold of $P<0.01$ and fold change (FC) >2 or <0.5.

Results: No subjects developed vaccine-induced HZ during the 12 weeks of the study. SLE patients had quiescent disease at baseline, and no clinical flares were noted. When comparing the baseline samples of the SLE cases to the healthy controls, we identified 107 differentially expressed genes including several that are known to be type I interferon (T1IFN)-inducible (OAS1, OAS2, OAS3, MX1, IFIH1, IFIT2, IFIT3, among others). These genes mapped to pathways involved in response to virus ($P=8.08\times10E{-}20$), immune response ($P=1.15\times10E{-}16$), and T1IFN-mediated signaling pathway ($P=7.17\times10E{-}16$), among others. The analysis of the 14-day post-vaccination visits between SLE case and healthy controls yielded only 37 differently expressed genes. Although some of the same T1IFN-inducible genes were differently expressed (e.g. OAS3, MX1, IFIT2, IFIH1), we observed a statistically significant reduction in the number of T1IFN-inducible genes between the baseline and the post vaccination analyses ($P=0.005$). Moreover, a statistically significant reduction was observed in the FC between the differentially expressed genes that overlapped between the baseline and post-vaccination analyses ($P=8.34\times0E{-}7$). No evidence of HZ viral gene expression was detected in either the cases or controls.

Conclusion: In this pilot study of quiescent SLE patients, HZ vaccine did not lead to clinical flares, nor increased evidence of systemic inflammation or autoimmunity. HZ viremia was not detected. At baseline, differences in gene expression between SLE patients and controls were consistent with other studies of SLE. Changes observed in expression profiles 14 days post-vaccination suggests that the controls have responded to the vaccine and have become more similar to the SLE cases. Future studies with larger samples sizes are needed to determine true flare rates and gage any differences in immune response to vaccine in those patients for whom vaccine might be associated with flare.

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Consensus Definition and Preliminary Validation Of a Low Disease Activity State In Systemic Lupus Erythematosus. Eric F. Morand[1], Kate Franklyn[1], Chak S. Lau[2], Sandra V. Navarra[3], Worawit Louthrenoo[4], Aisha Lateef[5], Laniyati Hamijoyo[6], Singgih Wahono[7], Shun-Le Chen[8], Jinou Ou[9], Alberta Y. Hoi[1] and Mandana Nikpour[10]. [1]Monash University, Melbourne, Australia, [2]Queen Mary Hospital, Hong Kong, Hong Kong, [3]University of Santo Tomas Hospital, Manila, Philippines, [4]Faculty of Medicine, Chiang Mai, Thailand, [5]National University of Singapore, Singapore, Singapore, [6]Hasan Sadikin Hospital, Bandung, Indonesia, [7]Universitas Brawijaya, Malang, Indonesia, [8]Shanghai Jiao Tong University School of Medicine, Shanghai, China, [9]3rd Hospital of Sun Yat-san University, Guang Zhou, China, [10]University of Melbourne, Fitzroy, Australia.

Background/Purpose: The definitions of low disease activity state (LDAS) and remission as desirable treatment goals in rheumatoid arthritis have been widely applied in research and clinical practice. In SLE, the measurement of active disease is problematic, and while a definition of remission has been published it was met by <2% of patients (Urowitz, 2007).

A definition of 'lupus low disease activity state' (LLDAS) could, once validated, be applied as a novel outcome measure in observational and interventional studies. We sought to define LLDAS using consensus methodology, and to perform preliminary validation of LLDAS using prospective data from an SLE cohort.

Methods: We defined LLDAS conceptually as 'a state which, if sustained, is associated with a low likelihood of adverse outcome', considering both disease activity and medication safety. A panel of experts from Hong Kong, China, Philippines, Thailand, Singapore, Indonesia and Australia individually generated items for potential inclusion in a definition of LLDAS. Using the Delphi method, these items were scored on a 5-point scale and then reduced. Six experts participated in the first round of Delphi, and items with a mean score > 3 were retained. Eleven experts then participated in a consensus meeting using the nominal group technique, and in a second round of Delphi, in which items with a mean score > 4 were retained. The frequency of attainment of LLDAS and its ability to predict accrual of irreversible organ damage (measured using the SDI) was determined in a longitudinally followed cohort of patients with SLE, using logistic regression.

Results: Fifty-six 'unique' items were initially generated, in two domains: (i) disease activity, and (ii) medication use. Following two rounds of Delphi and a nominal group discussion, unanimous agreement on a definition of LLDAS was reached. The final list of five items defining LLDAS comprised:

1. SLEDAI-2K ≤ 4, with no SLEDAI activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, hemolytic anemia, fever) and no gastrointestinal activity);
2. No *new* features of lupus disease activity compared to the previous assessment;
3. SELENA-SLEDAI physician global assessment (PGA, scale 0–3) ≤ 1;
4. Current prednisolone (or equivalent) dose $\leq$ 7.5 mg daily; and
5. Well-tolerated standard maintenance doses of immunosuppressive drugs and/or approved biologic agents, excluding investigational drugs.

Among 192 patients with SLE followed for a median duration of 3.37 years, LLDAS was achieved on at least one occasion by 72%. The median cumulative duration of LLDAS was 245 days. Patients in whom the cumulative duration of LLDAS was greater than 245 days had significantly less accrual of organ damage during follow up than patients in whom the cumulative LLDAS duration was less than 245 days (SDI (mean$\pm$SD) 1.01$\pm$1.4 v.1.6$\pm$1.9, Mann-Whitney p=0.023, Odds Ratio=0.8, 95% CI: 0.66–0.97, p=0.025).

Conclusion: We have generated a definition of LLDAS and shown that LLDAS is a predictor of organ damage in SLE. This definition of LLDAS requires further validation, against outcomes including organ damage and death, in a large prospective multicenter cohort. LLDAS may serve as a treatment target in SLE clinical practice and research.

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Desensitization To Trimethoprim/Sulfamethoxazole In Systemic Lupus Erythematosus Patients: A Retrospective Cohort Study. Yasuhiro Suyama[1], Mitsumasa Kishimoto[1], Hiroto Nakano[2], Chisun Min[1], Yoichiro Haji[1], Ryo Rokutanda[1], Yuri Ohara[1], Hisanori Shimizu[1], Ken-ichi Yamaguchi[1], Yukio Matsui[1], Kazuo Matsui[2] and Masato Okada[1]. [1]St. Luke's International Hospital, Tokyo, Japan, [2]Kameda Medical Center, Kamogawa, Japan.

Background/Purpose: A high incidence of trimethoprin-sulfamethoxazole (TMP/SMX) hypersensitivity is reported in patients with systemic lupus erythematosus (SLE), and reactions are often severe. Desensitization protocol is widely used for patients who have experienced minor reactions, but is contraindicated in patients with a history of severe drug eruption or hepatitis. We evaluated the safety and efficacy of TMP/SMX desensitization in patients with SLE who had not been previously exposed to TMP/SMX. Specific autoantibody profiles were also assessed as potential risk factors for TMP/SMX hypersensitivity.

Methods: Data from 56 SLE patients who received glucocorticoids and prophylactic TMP/SMX, with or without immunosuppressive agents, from 1997 to May 2013 were retrospectively analyzed. We evaluated 32 SLE patients prescribed a standard prophylactic dose of TMP/SMX (routine care group) and the results were compared with 24 SLE patients given oral TMP/SMX desensitization prophylaxis(desensitization group). We also assessed risk factors for allergic reactions using patients' demographic and laboratory data including specific antibody status. T-test and $\chi 2$ test were performed to analyze the data.

Results: The incidence of TMP/SMX hypersensitivity reactions in the routine care group was 43.8% (14/32) versus 12.5% (3/24) in the desensitization group ($p = 0.041$). The medication was discontinued in all patients who experienced clinical hypersensitivity reactions including high fever, severe drug eruption, and hepatitis; symptoms in the desensitization group appeared milder and never required hospitalization. In the routine care group, there was a higher rate of anti-Ro/SS antibody positivity in patients who experienced hypersensitivity reactions (46.2% in patients with hypersensitivity reactions vs 5.6% in patients with no reaction; $p = 0.008$); no association was found with other specific antibodies. Finally, when only anti-Ro/SS-A antibody positive patients were included in the analysis, there were significantly fewer hypersensitivity reactions in the desensitization group (18.2%) than the routine care group (85.7%) ($p = 0.013$).

Conclusion: We confirmed the high incidence of TMP/SMX hypersensitivity in patients with SLE, especially in whom anti-Ro/SS-A antibody is present. Administration of TMP/SMX per desensitization protocol appears to be effective in decreasing the incidence and severity of hypersensitivity reactions.

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A Comparative Study For High Prevalence Of A Positive Family History Of Systemic LUPUS Erythematosus In Juvenile-Onset Systemic LUPUS Erythematosus Versus Adult-Onset Disease. Maumer Durrani, Shirish Sangle, Natasha Jordan and David P. D'Cruz. Louise Coote Lupus Unit, St Thomas' Hospital, London, United Kingdom.

Background/Purpose: The pathogenesis of SLE is complex and poorly understood. Infectious triggers, immunological abnormalities, environmental factors and genetic background play a combined role in disease development. A genetic contribution to SLE has been evident from familial clustering of cases with a monozygotic twin concordance rate of 30–40%. Juvenile-onset SLE doesn't necessarily present identically to adults as described by some investigators suggesting that disease might be more severe in juvenile-onset patients at presentation. We compared family history of SLE, immunology, severity of organ involvement and differences between medications used in both groups.

Methods: Clinical and demographic data was collected on 25 juvenile-onset SLE patients and compared with 65 patients with adult-onset disease. Adult data was collected randomly from our SLE clinics. All patients met the American College of Rheumatology (ACR) classification criteria for SLE. Juvenile-onset was defined as those who were diagnosed with SLE before16 years of age. Data collected included ethnicity, family history of SLE/autoimmune disease, autoantibody profile, lupus-related disease manifestations and medications used.

Results: 36% of juvenile-onset SLE patients have a positive family history of SLE as opposed to 12% of adult-onset disease patients (p=0.011). Family history of other autoimmune conditions such as rheumatoid arthritis, hypothyroidism did not differ significantly between the two groups. In juvenile-onset patients 21(84%) were female and 4 (16%) male. Mean age of disease onset was 13 years (range 10–16 years). 13 (52%) were Afro-Caribbean, 7(28%) Caucasian, 4 (16%) Asian and 1 (4%) was of mixed ethnic origin. In adult-onset disease, 60 (92%) were female and 5 (7%) male. Mean age of disease onset was 29 years (17–50 years). 29 (44%) were Afro-Caribbean, 13 (20%) Asian, 21(32%) Caucasian and 2 (3%) were of mixed ethnicity. 18(72%) patients of juvenile-onset SLE patients had lupus nephritis, 3(12%) had interstitial lung disease, 4(16%) had APS. Only 1(4%) patient had AIHA. 43(66.1%) patients of adult-onset SLE patients had lupus nephritis, 5(7.69%) were diagnosed with interstitial lung disease. 12(18.4%) patients had APS and 4(6.1%) had either AIHA or thrombocytopenia.

Autoantibody Profile	Juvenile-onset SLE (n=25)	Adult-onset SLE (n=65)
ANA	23 (92%)	64 (98%)
Anti-dsDNA	18 (72%)	32 (49%)
Anti-Ro (SSA)	9 (36%)	24 (36%)
Anti-La (SSB)	3 (13%)	7 (10%)
Anti-Sm	7 (31%)	16 (32%)
Anti-RNP	10 (40%)	24 (36%)
Anti-cardiolipin	13 (52%)	19 (29%)
Lupus anticoagulant	8 (32%)	16 (24%)
Anti-C1q	11/17 (65%)	19/30 (63%)
Medications		
Prednisolone	21 (84%)	53 (81%)
Hydroxychloroquine	18 (72%)	54 (84%)
Mepacrine	1 (4%)	5 (7%)
Mycophenolate mofetil	17 (68%)	32 (49%)
Azathioprine	5 (20%)	19 (29%)
Methotrexate	1 (4%)	(3%)
Cyclophosphamide	5 (20%)	10 (15%)
Rituximab	6 (24%)	7 (10%)
Plasmapheresis	2 (8%)	0
Intravenous immunoglobulin	1 (4%)	0

Conclusion: A family history of SLE was significantly more common in juvenile-onset SLE than in adult-onset disease. Frequencies of lupus nephritis and anti-dsDNA antibody positivity were higher in juvenile-onset SLE which may reflect a more severe clinical phenotype. The majority of juvenile-onset SLE patients in our cohort were of African ancestries, who are known to have worse clinical outcomes. Medications and clinical interventions such as mycophenolate mofetil, cyclophosphamide, rituximab were more frequently used in juvenile-onset SLE patients, which supports the likelihood of more severe and difficult to manage disease in this subset of patients.

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The Accuracy Of The ICD-9 Code 710.0 To Identify a Cohort Of SLE Patients From The Electronic Medical Record. Arshad Mustafa[1], Jennifer Cai[1], Teresa Bosler[1], Nancy J. Olsen[2] and David R. Karp[1]. [1]UT Southwestern Medical Center, Dallas, TX, [2]Penn State MS Hershey Medical Center, Hershey, PA.

Background/Purpose: The electronic medical record (EMR) is increasingly used as a primary source of retrospective research data from large 'virtual cohorts' of patients. The accuracy of EMR data is not guaranteed. Importantly, when performing case-control studies, the cases and controls may be imperfectly defined by EMR data, particularly for syndromic conditions such as SLE. This study was undertaken to ascertain the accuracy of EMR diagnoses of SLE made by specialists at an academic medical center.

Methods: Cases of specialist-diagnosed SLE were defined as individuals who had billing diagnoses using the ICD-9 CM code 710.0 applied by a faculty rheumatologist, nephrologist, or dermatologist two or more times in a twelve month period. These patients' EMR were reviewed by a single rheumatologist trained in SLE diagnosis and 10% of these charts were independently reviewed by a second rheumatologist for verification. Each patient's EMR was categorized for its support for the diagnosis of SLE using both the 1997 ACR and 2012 SLICC criteria. "Certain" diagnoses had >4 criteria found in the chart; "Likely" diagnoses had <4 criteria but had serology findings specific for SLE (anti-DNA or anti-Sm) and 1 typical clinical feature (e.g., malar rash, arthritis, cytopenia); "Possible" diagnoses had >1 criterion suggesting SLE and no better explanation given in the chart; "Unlikely" diagnoses included a positive ANA and no other findings, or a single clinical finding with temporally inconsistent serology; "Not SLE" diagnoses were documented if another diagnosis for their condition was firmly established.

Results: From a database of almost 4 million patient records, a total of 139 outpatient charts meeting the definition of specialist-diagnosed SLE were identified. 99 (71.2%) were felt to have Certain lupus; 19 (13.7%) were Likely; 14 (10%) were Possible; 4 (2.8%) were Unlikely; 3 (2.1%) were Not SLE. Combining the Certain patients (who meet classification criteria) and the Likely patients who might have 'early' or 'incomplete' lupus, or may only lack proper documentation for SLE, the positive predictive value of repeated ICD-9 710.0 codes is approximately 85%. Conversely, about 15% of patients who carry diagnoses of SLE lack sufficient, easily accessible data in their EMR to support that finding. SLE features that had significantly different prevalence between the Certain/Likely and Possible/Unlikely/Not groups were both lupus-specific: anti-DNA (55.9% vs 19.0%, $p=0.002$), anti-Sm (30.5% vs 0%, $p=0.002$), and nephritis (51.7% vs 0%, $p<0.0001$), as well as non-specific: hypocomplementemia (57.6% vs 9.5%, $p<0.0001$) and lymphopenia (71.2% vs 28.6%, $p=0.0003$).

Conclusion: This study underscores the challenges of using ICD-9 billing codes to identify research cohorts from EMR data. Even specialist physicians persistently label patients incorrectly while their notes and data do not support the lupus diagnosis. Surprisingly, lymphopenia, an inexpensive and widely obtained laboratory parameter, differentiates patients who truly have lupus from patients incorrectly labeled with the disease, and can be used to develop "decision support" features in the EMR to assist with the diagnosis of SLE.

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Maintenance Therapy With Taclorimus and Mizoribine Pulse In SLE. Hiroshi Kajiyama, Daisuke Ikuma, Muneo Ota, Yuki Shimada, Kazuhiro Yokota, Yasuto Araki, Kojiro Sato, Yu F. Asanuma, Yuji Akiyama and Toshihide Mimura. Saitama Medical University, Saitama, Japan.

Background/Purpose: It was reported in 2008 that multitarget therapy, consisting of taclorimus (TAC), mycophenolate mofetil (MMF) and glucocorticoid, is effictive and safe in induction therapy of active lupus nephritis. However, its efficacy and safety in maintenance therapy of SLE is not clarified yet. Mizoribine (MZR), an immunosuppressive drug targeting inosine monophosphate dehydrogenase, inhibits de novo pathway for purine synthesis as MMF. Recently, multitarget therapy consisting of TAC, MZR and glucocorticoid has been reported to be effective and safe in maintenance therapy, although the mode of MZR administration widely varies. Intermittent MZR pulse therapy (300mg single dose, once to four times per week) gives higher rise of peak blood concentration to suppress lymphocyte function than low dose daily therapy (50mg three times per day, total 150mg per day). It remains to be elucidated, if intermittent MZR pulse therapy is effective and safe in SLE maintenance therapy.

Methods: Eleven SLE patients (2 males, 9 females) were treated with multitarget therapy with TAC and MZR pulse after the induction therapy. Demographic data, laboratory data (serum dsDNA antibody and serum CH50) and daily prednisolone (PSL) dose and SLE disease activity index (SLEDAI) score were documented at three different time points, first and second add-on of immunosuppressant and recent by medical record review. Average duration is 8.9 ± 12.0 months between the first add-on and the second add-on, and 6.0 ± 4.3 months between the second add-on and recent. Statistical analysis (Kruskal-Wallis test) was done using Prism version 5.0d. Adverse effects and the number of relapse were also documented. Each value was described as mean $\pm$ standard deviation.

Results: Seven of 11 patients presented lupus nephritis. Three of these seven patients treated with methylprednisolone pulse therapy as induction therapy. After induction therapy, TAC in 10 patients and MZR in one patient were started at first add-on, and MZR in 10 patients and TAC in one patient were further added at second add-on. Serum CH50 level significantly increased (first add-on:31.4 ± 11.8 U/mL, second add-on:37.7 ± 11.8 U/mL, recent:46.5 ± 12.7 U/mL, $P=0.00252$). The mean values of SLEDAI score and serum dsDNA antibody level improved, although they did not reach statistical significance (SLEDAI first add-on:4.0 ± 2.8, second add-on: 2.9 ± 1.9, recent:1.8 ± 1.4, $P=0.1095$, dsDNA first add-on:42.9 ± 54.4, second add-on:20.0 ± 11.2, recent:14.3 ± 5.8, $P=0.3$). Daily oral prednisolone dose was significantly reduced (first add-on:26.9 ± 13.7, second add-on:16.7 ± 6.1, recent:10.4 ± 5.0, $P=0.0012$). There was only one patient with relapse during multitarget maintenance therapy, although he treated with methylprednisolone pulse for nephritis in induction therapy. No patients had major adverse effects, resulting in the interruption of the multitarget maintenance therapy. There were three minor adverse events such as transient increase of serum creatinine level and herpes zoster in three patients.

Conclusion: Multitarget maintenance therapy with TAC and MZR pulse is safe and effective enough to reduce daily steroid dose and to minimize relapse without major adverse effects in Japanese patients with SLE.

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Efficacy Of Tacrolimus Combination Therapy During The Maintenance Phase Of Systemic Lupus Erythematosus. Kumiko Ohtsuka, Yusuke Miwa, Nao Oguro, Yoko Miura, Sho Ishii, Shinya Seki, Hidekazu Furuya, Ryo Yanai, Ryo Takahashi, Kuninobu Wakabayashi, Nobuyuki Yajima and Tsuyoshi Kasama. Showa University School of Med, Shinagawa-ku Tokyo, Japan.

Background/Purpose: In Japan, a placebo-controlled clinical trial was undertaken to investigate the efficacy and safety of tacrolimus (TAC) for lupus nephritis. Based on the results obtained, administration of TAC at an oral dose of 3 mg/day was effective for the treatment of lupus nephritis.

Objective: The aim of this study was to prospectively evaluate the efficacy and safety of TAC combination therapy during the maintenance phase of systemic lupus erythematosus (SLE).

Methods: From 2009 to 2012, 38 patients were examined over a 1-year study period. If manifestations of mild active SLE, such as arthritis, skin eruptions, or asymptomatic nephritis, worsened and/or decreasing titers of serum complement (C3c) were observed, TAC combination therapy (from 1 mg to 5 mg once daily) was administered (that is, TAC was added to the patient's existing treating regimen, and the dosage of prednisolone (PSL) was decreased). Scores on the SLE Disease Activity Index (SLEDAI), PSL dosage, and serum levels of C3c, anti-dsDNA titers, and proteinuria were examined.

Results: Thirty-eight patients responded to TAC combination therapy. 1) The PSL dose was reduced from 11.7 ± 5.6 to 8.2 ± 4.2 mg/day ($P<0.001$). 2) The serum concentration of C3c increased from 74.7 ± 21.9 to 86.4 ± 17.8 mg/dl ($P=0.006$). 3) Titers of anti-dsDNA antibodies decreased from 39.6 ± 68.0 to 24.8 ± 49.1 U/ml ($P<0.001$). 4) Scores on the SLEDAI improved from 6.2 ± 3.7 to 2.6 ± 2.3 ($P<0.001$). In particular, the following symptoms improved on the SLEDAI: headache (from 7 patients to 1 patient), arthritis (from 3 patients to 0 patients), rash (from 6 patients to 2 patients), alopecia (from 5 patients to 0 patients), mucosal ulcers (from 2 patients to 0 patients), and fever (from 5 patients to 1 patient). Although proteinuria decreased from 0.31 ± 0.70 to 0.31 ± 0.85 g/g of Cr, the difference was not significant ($P=0.47$). In contrast, 8 patients did not respond and/or had worsening SLE and 2 patients discontinued treatment as a result of an adverse effect: muscle cramp or rhabdomyolysis. No patients experienced complications with adverse effects of abnormal urinalysis, and none progressed to renal failure or became candidates for dialysis.

Conclusion: TAC combination therapy therefore is a useful alternative treatment for SLE.

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High Type I Interferon In Systemic Lupus Erythematosus Plasma Predicts Future Renal Disease. Kyriakos A. Kirou, Mikhail Olferiev, Elzbieta E. Jacek, Mari Lliguicota, Margaret Robotham, Wei-Ti Huang, Elena Gkrouzman and Mary K. Crow. Hospital for Special Surgery, New York, NY.

Background/Purpose: Type I interferon (IFN-I) is elevated in many patients with SLE and is associated with more severe disease. However, the relationship between elevated levels of IFN-I and disease activity over time has not been defined. We evaluated the biological activity of IFN-I retrospectively in SLE plasma samples collected longitudinally from 60 SLE patients. The IFN-I activity in plasma was determined based on the response of the WISH cell line, which is sensitive to IFN-I stimulation and has a minimum detection level of 6 IU/ml.

Methods: Plasma samples as well as clinical and laboratory data were collected longitudinally. On average, 9 visits (range: 2–20 visits) per patient or 568 data points were collected. WISH cells were stimulated with either recombinant IFN-I standard, healthy donor or SLE plasma for 5 hours. The response of WISH cells was measured by quantitative PCR (qPCR) using interferon response gene IFIT1 as the target and HPRT1 as the reference gene. Patients were divided into two groups based on either low or high IFN-I activity at study initiation. Based on the collected data we built statistical models (linear mixed effect model and generalized linear model) using the level of plasma IFN-I activity at the first patient visit as a predictor of future clinical and laboratory outcomes.

Results: SLE patients with high IFN-I plasma activity at study initiation showed increased IFN-I plasma activity during follow up visits ($p<0.01$). Among the laboratory parameters, the same patients had significant decreases in peripheral blood complement component 3 levels ($p<0.03$), white blood cell count ($p<0.04$), absolute lymphocyte count ($p<0.01$) and had higher erythrocyte sedimentation rate ($p<0.02$) and double stranded DNA titers ($p<0.02$). Patients with high plasma IFN-I activity during the first visit were prone to overall greater disease activity during the study as measured by SLEDAI ($p<0.02$) or BILAG ($p<0.05$). Strikingly, SLE patients with high IFN-I activity in plasma at study initiation were more likely (1.0 versus 0.4 incident per year $p<0,001$) to demonstrate renal BILAG activity.

Conclusion: Lupus nephritis is the most common severe manifestation of SLE and confers an increased risk of death and end-stage renal disease. In this study, we observed that IFN-I activity in SLE plasma could predict future disease activity, particularly involving the kidney. Furthermore, patients with higher plasma IFN-I activity at study initiation maintained elevated levels at future visits. Measurement of IFN-I activity in plasma of SLE patients may help identify patients at high risk for lupus nephritis and thus serve as an important disease monitoring biomarker.

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1573

Longer Duration Of B Cell Depletion In Patients With Systemic Lupus Erythematosus Is Associated With a Better Outcome. Sofia Dias[1], Veronica Rodriguez[2], Hanh Nguyen[3], Charis Pericleous[4] and David A. Isenberg[4]. [1]Hospital de Santa Maria, Lisbon, Portugal, [2]Hospital Regional Universitario Carlos Haya, Malaga, Spain, [3]University College of London Hospital, london, United Kingdom, [4]University College London, London, United Kingdom.

Background/Purpose: We were alerted to the possibility of very long term B cell depletion (BCD) in Systemic Lupus Erythematosus (SLE) by a patient treated with rituximab in 2001 whose CD19 counts remain $<0.001\times 10^9$/L 12 years later. The duration of B cell depletion is variable between SLE patients. Because most relapses occur after the return of B cells, our purpose was to analyse clinical and serological features and outcome in patients considering the duration of B cell depletion.

Methods: We analysed our lupus cohort retrospectively to identify those BCD treated patients. We collected data noting the time to return of the B cells, clinical and serological features and classic British Isles Lupus Assessment Group (BILAG) scores and baseline, 6 months and 12 months after the treatment. Logistic regression analysis was made using SPSS Statistics Data Editor software.

Results: A total of 190 courses of BCD in 101 patients in whom we had full serological and clinical data prior to December 2012 were considered.

Among the 101 patients, 94 were female and ethnicities included 40 Caucasian, 28 Afro-Caribbean, 23 Asian, 7 Oriental and 3 others.

57 patients had more than 1 treatment. One patient and one of the infusions of another patient were excluded because of incomplete BCD after the treatment.

32.1% repopulated between 6 to 9 months and 28.6% repopulated after 12 months (figure 1). Two groups were analysed based on the time to repopulation at a defined threshold of 12 months. We included infusions for which the patients had not repopulated but were depleted for at least 12 months. We excluded the infusions for which a follow up was less than 12 months and for which the patients remained depleted. 144 treatments were analysed. 41.7% (group 1) repopulated in less than 12 months and 58.3% (group 2) were depleted for at least 12 months.

An association with longer time to repopulate and lymphopenia ($p=0.008$) at any point in the course of the patient's disease was noted. Inverse association with alopecia ($p=0.033$) and oral ulcers ($p=0.039$) was also noted. No association was found between serological features such as the presence of anti-dsDNA or anti-Sm antibodies or low complement.

The cohort's mean classic BILAG numerical score at baseline was 13.44 (SD=7.55). Group 2 was associated with a higher BILAG score at baseline ($p=0.026$). At 6 months group 2 patients had lower numerical BILAG score ($p=0.002$); at 12 months the same tendency was observed but with no statistical significance. Likewise, there was an association between group 2 patients and no BILAG As nor Bs at 6 months ($p=0.012$). Also a decrease of the BILAG score at 6 months ($p=0.012$) and 12 months ($p=0.012$) in these

patients was noted.

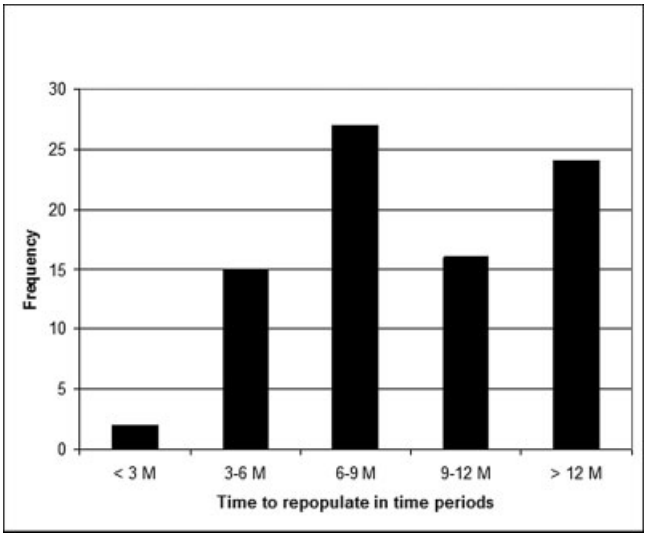

Figure 1. Time to repopulate in time periods.

Conclusion: Despite higher disease activity at baseline, as measured by classic BILAG, patients who were B cell depleted for longer showed some differences in clinical features and, most importantly, had a better outcome at 6 and 12 months.

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1574

Favorable Clinical Response To Belimumab At Three Months. Anca Askanase[1], Arthi Reddy[1], Jill P. Buyon[2], Andrew G. Franks Jr.[3], Richard A. Furie[4], Diane L. Kamen[5], Susan Manzi[6], Michelle Petri[7], Rosalind Ramsey-Goldman[8], Chung-E Tseng[2], Ronald F. van Vollenhoven[9] and Daniel J. Wallace[10]. [1]New York University School of Medicine, New York, NY, [2]NYU School of Medicine, New York, NY, [3]New York University, New York, NY, [4]The Feinstein Institute for Medical Research and North Shore-Long Island Jewish Health System, Lake Success, NY, [5]Medical University of South Carolina, Charleston, SC, [6]West Penn Allegheny Health System, Pittsburgh, PA, [7]Johns Hopkins University School of Medicine, Baltimore, MD, [8]Northwestern University Feinberg School of Medicine, Chicago, IL, [9]The Karolinska Institute, Stockholm, Sweden, [10]Cedars-Sinai Medical Center, Los Angeles, CA.

Background/Purpose: Belimumab (Benlysta) is a human monoclonal antibody that inhibits soluble B-Lymphocyte Stimulator and improves SLE disease activity. This study was initiated to evaluate the use and efficacy of Belimumab in academic SLE clinical practices.

Methods: An invitation to participate was sent to 16 physicians experienced in SLE Phase III clinical trials. All agreeing to participate completed a one page questionnaire for each patient (pt) prescribed Belimumab. Information collected included: demographics (age, gender, race/ethnicity), SLE data (duration of disease, SELENA-SLEDAI, clinical manifestation(s) targeted, background medications), and Belimumab information (start date, clinical response, side effects). Clinical response was defined as the investigator's impression of a ≥50% improvement in the initial manifestation being treated and no worsening in other organ systems.

Results: Of 16 invitations sent, nine investigators participated. Questionnaires on 151 treated pts were returned. The mean age was 43.1±11.8 years. 92.1% were female, 69.7% White, 21.2% Black, 6.1% Asian, and 4.5% Hispanic. The average SLE disease duration was 12.9±8.4 years. 3 pts (2.4%) were ANA negative. Concomitant medications included: antimalarials in 71.5%, immunosuppressants in 72.2% (Azathioprine 21.9%, Mycophenolate Mofetil 37.1%, Methotrexate 13.2%), and prednisone in 70.9% (mean dose of 12.3±11.3, 38.3% on ≥10 mg). Only 2.6% of pts were not on any background SLE medications. 12 pts (7.9%) were on anti-malarials alone. The dominant clinical manifestations driving treatment were arthritis in 73.5%, rash in 51.0%, and serositis in 17.2%. Other SLE manifestations were renal 12.0%, hematological 14.6%, and inability to taper steroids 20.5%. 70.2% of pts had ≥2 active manifestations. Data on 115 pts on Benlysta for at least 3 months (mos.) were available for analysis. Of those, 55 (47.8%) clinically responded by 3 mos. with marked improvement in arthritis and/or rash. Similarly, of the 79 pts on Benlysta for at least 6 mos., 46 (58.2%) clinically responded with improvements in arthritis, rash and/or nephritis. Clinical response for each of the SLE manifestations was also evaluated. At 3 mos., 36 of 61 (59.0%) pts with arthritis clinically responded with marked improvement and at 6 mos., 24 of 50 (48.0%). For rash, 19 of 57 (33.3%) pts responded at three mos. and 20 of 40 (50.0%) at six mos. Interestingly, of the 5 pts with renal involvement for whom follow up data are available, 4 of 5 (80.0%) improved at 3 mos. and 2 of 3 at 6 mos. Data on blacks shows a similar pattern of improvement. At 3 mos., 13 of 17 (76.5%) improved and at 6 mos., 13 of 16 (81.2%). Of the 20 (13.2%) pts overall in whom Benlysta was discontinued, 3 had CNS lupus, 1 MI, 3 losses of insurance, 3 infections, 3 infusion reactions, 1 severe arthritis flare, 1 stroke-like symptoms, 1 worsening neuropsychiatric condition, 1 worsening myositis, 1 elective surgery, and 2 no clinical response.

Conclusion: These early data support the use of Benlysta across all ethnic groups and efficacy similar to that reported in the Phase III trials. While the numbers are limited, black pts showed an improvement at 3 mos. Relevant to physician and pt decision-making, improvement was observed within 3 mos.

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Identification Of Novel Distinct Autoantigen Clusters Reflecting The Heterogeneity Of Systemic Lupus Erythematosus. Petra Budde[1], Angelika Lueking[1], Stefan Vordenbäumen[2], Heike Göhler[1], Martin Gamer[1], Klaus Marquardt[1], Anna Telaar[1], Daniel Chamrad[1], Carmen Theek[1], Peter Schulz-Knappe[1] and Matthias Schneider[2]. [1]Protagen AG, Dortmund, Germany, [2]Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany.

Background/Purpose: Diagnosis of systemic lupus erythematosus (SLE) is based on a combination of clinical findings and laboratory evidence such as anti-nuclear autoantibodies (ANA), anti-Smith and anti-double stranded DNA (dsDNA) antibodies. However, no biomarker individually displays sufficient performance to diagnose SLE, to predict the disease course or to allow the identification of patient sub-groups. This lack of specific biomarkers also affects clinical development of new SLE therapeutics. Luminex bead-based antigen arrays were employed to characterize in-depth the autoantibody reactivity of SLE as a source to develop improved diagnostic and patient stratification tests for SLE.

Methods: To characterize the autoantigen repertoire in patients with SLE, we performed a large-scale screen of 5,885 recombinant human antigens using the bead-based Luminex xMAP technology. The autoantibody signature of 130 SLE patients was compared against healthy controls (n=350) and samples from patients with other autoimmune diseases including early rheumatoid arthritis (n=75), systemic sclerosis (n=100) and ankylosing spondylitis (n=100). Autoantigens with significant autoantibody response were selected to develop biomarker panels with improved sensitivity and specificity. Spearman's rank correlation of the top 50 SLE antigens was computed to identify novel autoantigen clusters.

Results: The first analysis included the comparison of autoantigen profiles of SLE patients with healthy controls and active disease samples. This led to the identification of 15 novel autoantigens (adjusted p-value<0.05, 1.5 fold increase). To further improve the sensitivity and specificity of single antigens to diagnose SLE, combinatory antigen panels were defined using 26 biomarkers providing appropriate statistical characteristics. Sequential addition and different combinations of new antigens to a panel of known SLE antigens resulted in a stepwise improvement of the classification performance yielding an AUC of 0.94. In the second analysis the new antigens were applied to capture clusters formed by subsets of antigens across different samples. At first, the seven known SLE antigens (Ro52/SS-A, Ro60/SS-A, ribosomal P0, P1, P2, and SmB/B′protein) were subjected to hierarchical cluster analysis and identified two major antigen clusters in SLE patients. Then, a combination of 50 known and new SLE markers was used to test if the new antigens provide independent information to allow further sub-classification of SLE samples based on autoantigen signatures. Seven different antigen clusters were identified offering a new tool for characterizing SLE sub-groups.

Conclusion: Comprehensive profiling of SLE sera enabled the in-depth characterization of the autoantigen repertoire of SLE patients. The combination of established and new antigens significantly increased the sensitivity to diagnose SLE. Based on their autoreactivity profile SLE sub-groups were revealed. However, further studies are needed to link specific antigen clusters to clinical profiles.

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Type I Interferon-Mediated Skewing Of The Serotonin Synthesis In Systemic Lupus Erythematosus Is Associated To Cardiovascular Disease. Christian Lood[1], Helena Tydén[1], Birgitta Gullstrand[1], Cecilia Klint[2], Christina Wenglén[2], Christoffer T. Nielsen[3], Niels H. H. Heegaard[4], Andreas Jönsen[1] and Anders A. Bengtsson[1]. [1]Lund University, Lund, Sweden, [2]Ana-Mar AB, Lund, Sweden, [3]Statens Serum Institut, Copenhagen S, Denmark, [4]Statens Serum Institut, Copenhagen, Denmark.

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease characterized by increased expression of type I interferons (IFNs). Indoleamine 2,3-dioxygenase (IDO), a type I IFN-regulated protein, limits the conversion of tryptophan to serotonin in favor of kynurenine. Serotonin has been implicated in development of cardiovascular disease in the general population, but its role in SLE, a disease characterized with markedly increased cardiovascular morbidity and mortality, is not known. The aim of this study was to investigate if SLE patients had a type I IFN-mediated dysregulation of the serotonin production and whether or not this was associated to cardiovascular disease.

Methods: Serotonin was measured in serum from patients with SLE (n=148) and healthy volunteers (n=79) with ELISA and intracellularly in platelets using flow cytometry and related to cardiovascular disease adjusted for traditional risk factors. Tryptophan and kynurenine were measured by liquid chromatography.

Results: SLE patients had decreased serum and platelet levels of serotonin as compared to healthy volunteers. The serum levels were associated to type I IFNs, compatible with IFN-mediated skewing of the tryptophan metabolism. Serum serotonin levels were inversely associated to disease severity and cardiovascular disease in SLE patients, independently of traditional cardiovascular risk factors.

Conclusion: We suggest that the serotonin system is dysregulated in SLE due to increased type I IFN production. Furthermore, the serum level of serotonin is identified as a novel risk factor for cardiovascular disease in SLE, independently of traditional cardiovascular risk factors.

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Comparison Of Clinical and Serological Manifestations Among Juvenile-, Adult-, and Late-Onset Systemic Lupus Erythematosus Patients In Korea. Dong-Jin Park[1], Ji-Hyoun Kang[1], Kyung-Eun Lee[1], Jeong-Won Lee[1], Lihui Wen[1], Tae-Jong Kim[2], Yong-Wook Park[1] and Shin-Seok Lee[1]. [1]Chonnam National University Medical School, Gwangju, South Korea, [2]Chonnam National University Medical School and Hospital, Gwangju, South Korea.

Background/Purpose: Up to 30–40% of patients with systemic lupus erythematosus (SLE) experience their onset prior to adulthood or at over 50 years of age. Patients with juvenile-onset SLE (JSLE) frequently present with severe organ involvement and higher disease activity at the onset of disease. In contrast, patients with late-onset SLE (LSLE) tend to show more insidious onset and mild initial clinical manifestations. However, few studies have investigated differences in clinical manifestations with disease onset in Asian lupus patients. Thus, we investigated whether SLE patients could be distinguished based on the time of disease onset and, if so, whether the groups differed in their clinical and laboratory features in ethnically homogeneous Korean patients.

Methods: We enrolled 201 SLE patients (mean age 34.1±12.7, 184 women) with available clinical data at the time of onset of SLE from the lupus cohort at Chonnam National University Hospital. Sociodemographic, clinical, and laboratory data, including autoantibodies, and concomitant diseases were found at the time of diagnosis of SLE by reviewing the patient charts. We divided SLE patients according to age at SLE diagnosis into three groups: JSLE (diagnosed at ≤ 18 years), adult-onset SLE (ASLE, diagnosed at 19–50 years), and LSLE (diagnosed at > 50 years), and compared baseline demographic, clinical, and relevant laboratory findings. Data were analyzed using the chi-squared test for categorical variables and one-way ANOVA test for continuous variables.

Results: Of the 210 patients, 27 (14.4%), 149 (74.1 %), and 25 (12.4 %) were JSLE, ASLE, and LSLE patients, respectively. Fever, oral ulcer, nephritis, anemia, and thrombocytopenia were more common in JSLE patients than ASLE or LSLE patients ($p < 0.05$, $p < 0.05$, $p = 0.001$, $p < 0.05$, and $p < 0.05$, respectively). On the other hand, Sjögren's syndrome was found more frequently in LSLE patients than JSLE or ASLE patients ($p < 0.05$). SLEDAI-2000 scores at the onset of SLE were 14.6±7.1 in JSLE, 11.1±6.1 in ASLE, and 6.6±2.7 in LSLE, and disease activity was significantly higher in JSLE patients than in ASLE or LSLE patients ($p < 0.001$). Anti-dsDNA and anti-nucleosome antibodies were found more frequently in JSLE patients and less frequently in LSLE patients ($p < 0.05$, $p = 0.005$) and decreased complement levels (C3, C4, and CH50) were more common in JSLE patients and less common in LSLE patients ($p < 0.001$, $p < 0.001$, and $p < 0.05$, respectively).

Conclusion: Our results showed that SLE patients present with different clinical and serological manifestations according to age at disease onset. JSLE patients have severe disease activity and more frequent renal involvement and LSLE patients have mild disease activity, more commonly accompanied by Sjögren's syndrome, at disease onset.

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Decreased Sensitivity Of a Commercial Anti-dsDNA Assay In Patients With Moderately To Severely Active Systemic Lupus Erythematosus. Munther A. Khamashta[1], Gabor G. Illei[2], Stephen Yoo[2], Liangwei Wang[2] and Warren Greth[2]. [1]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [2]MedImmune, LLC, Gaithersburg, MD.

Background/Purpose: Anti-dsDNA autoantibodies are highly specific for SLE. Anti-dsDNA positivity is an important eligibility criterion in many SLE studies, and decreases in anti-dsDNA levels are a measure of clinical improvement. Various anti-dsDNA assays have similar performance characteristics in distinguishing SLE patients from controls and those with other diseases. Previous studies have shown that the performance characteristics may change when testing active vs inactive SLE patients. The performance characteristics of a commercially available multilyte assay to the Farr radioimmunoassay (considered a gold standard of anti-dsDNA testing) were compared in adults with active moderate to severe SLE.

Methods: Subjects included adults with moderate-severe active SLE (92% female, median disease duration 6.3 years, mean SLEDAI 2K: 11.3) in an ongoing international, multi-center, double-blind, randomized, placebo-controlled trial. Anti-dsDNA levels were determined by both the Farr radioimmunoassay and the AtheNA Multi-Lyte® ANA-II Plus Test System (AMLII) in the 409/431 randomized subjects who were included in this analysis. Both assays were performed according to manufacturers' instructions in Clinical Laboratory Improvement Amendments (CLIA) certified laboratories. The sensitivity and specificity of the recommended cutoff values for positive (>120) and indeterminate (>100) AMLII assay were assessed using the recommended values for positive (>10) and indeterminate (>5) and cutoffs of the Farr assay. Alternative optimal cutoff values of AMLII for different Farr values were determined by ROC analysis.

Results: Using the recommended cutoff values for positivity, 24% of the patients were anti-dsDNA positive by the AMLII compared to 66% by the Farr assay. When compared to the Farr assay, the recommended cutoff values for AMLII had high specificity but low sensitivity, leading to an unacceptably low concordance with the gold standard of anti-dsDNA testing in this population. Using the optimal cutoff values determined by ROC analysis identified ≥28 (the lower limit of quantifiable detection) as the optimal cutoff for AMLII, which significantly improved the performance of the AMLII (Table).

	Positive		Indeterminate or positive	
Farr cutoff			≥10	≥5
Recommended	AMLII cutoff ≥120	ROC determined ≥28	Recommended ≥100	ROC determined ≥28
ROC AUC	0.84		0.79	
Sensitivity	36%	78%	33%	68%
Specificity	99%	82%	97%	87%
Concordance	57%	79%	45%	72%

ROC: receiver operator curve; AUC: area under the curve. An AUC ≥0.8 represents good diagnostic accuracy

Conclusion: The optimal cutoff value in a population with a high pretest likelihood of anti-dsDNA positivity should be confirmed for any non-gold standard assay if it is being considered to replace a gold standard, such as the Farr assay. Misclassification of a large proportion of subjects with active moderate to severe SLE who are anti-dsDNA positive by the Farr assay as anti-dsDNA negative may lead to unnecessary exclusion of otherwise eligible subjects from clinical trials and may reduce the likelihood of demonstrating a change in the SLEDAI component of composite endpoints in SLE trials.

Disclosure: M. A. Khamashta, MedImmune, 9; **G. G. Illei**, AstraZeneca, 1, MedImmune, 3; **S. Yoo**, AstraZeneca, 1, MedImmune, 3; **L. Wang**, AstraZeneca, 1, MedImmune, 3; **W. Greth**, AstraZeneca, 1, MedImmune, 3.

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Novel Risk Factors For Thrombotic Thrombocytopenic Purpura In Systemic Lupus Erythematosus patients. Javier Merayo-Chalico, Diana Gómez-Martín, Roberta Demichelis-Gómez, Sandra Rajme-Lopez, Luis Aparicio-Vera and Jorge Alcocer-Varela. Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, Mexico city, Mexico.

Background/Purpose: Thrombotic thrombocytopenic purpura (TTP) is an uncommon disease characterized by thrombocytopenia and microangiopathic hemolytic anemia and, in some cases, fever, neurologic and/or renal abnormalities. The mortality rate is high despite appropriate diagnosis and treatment. Presence of TTP in SLE is rare (< 2.5%) and diagnosis can be difficult between this two pathologies; sometimes, this results in delayed/suboptimal treatment with higher mortality. The aim of this study was to identify novel risk factors for TTP in SLE and to address the epidemiological profile in this subset of patients.

Methods: We performed a retrospective, case-control study which included patients admitted between January 1994 and March 2013. Three different study groups were included as follows: Cases: TTP/SLE (A) and Controls: non-autoimmune TTP (B) and SLE without TTP (C). TTP was diagnosed by the presence of at least microangiopathic hemolytic anemia, thrombocytopenia < 100,000 cells/μl and high LDH levels. Variables that were measured included: demographic variables, SLEDAI score, clinical and laboratorial parameters (complete blood count, hemolytic parameters and serological tests), treatment, length of hospital stay and mortality. Differences between groups were analyzed by Student t test or U Mann-Whitney. Association between variables was assessed by OR (CI 95%). Multivariate analysis was performed by binary logistic regression model.

Results: Ninety one patients were included: 23 in group A, 22 in group B and 46 in group C. Variables that were associated to TTP diagnosis in SLE patients in comparison to non autoimmune TTP were: lymphopenia (≤1000 cells/μl) (OR 11.5, CI 95% 2.82–47.35), severe anemia (≤7g/dl) (OR 4.9, CI 95% 1.03–7.32) and age (≤30 years) (OR 2.87, CI 95% 1.25–6.55), which remained significantly associated after multivariate analysis. Moreover, after comparing SLE patients with and without TTP, the variables that were related to TTP diagnosis included: severe thrombocytopenia (≤50,000 cells/μl) (OR 17.8, CI 95% 4.66–68.08), severe anemia (OR 8.07 CI 95% 2.33–27.9), history of hematological activity (OR 3.25 CI 95% 1.12–9.39), history of persistent thrombocytopenia (OR 3.21 CI 95% 1.002–10.31), positive antiphospholipid antibody profile (OR 3.11 CI 95% 1.083–8.93) and history of thrombosis (OR 1.20, CI 95% 1.048–1.37). After the multivariate analysis, variables that remained significant were severe anemia (OR 8.9, CI 95% 1.81–43.8) and severe thrombocytopenia (OR 5.71, CI95% 1.5–21.7). Interestingly, we did not find differences in mortality between patients with TTP associated to SLE and non autoimmune TTP.

Conclusion: Patients with TTP associated with SLE are younger than non-autoimmune TTP. Severe anemia, severe thrombocytopenia and lymphopenia are independent risk factors for TTP in SLE. These findings might lead to early diagnosis and treatment as well as lower mortality.

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Drug-Resistant Bloodstream Infections In Systemic Lupus Erythematosus Patients: A Clinical Perspective. Ana Barrera-Vargas, Diana Gómez-Martín, Alfredo Ponce de León and Jorge Alcocer-Varela. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

Background/Purpose: Infections are an important cause of mortality and morbidity in Systemic Lupus Erythematosus (SLE) patients. Different risk factors have been described for the development of infections in SLE, such as immunosuppressive therapy, intrinsic immune system dysfunction, disease activity, and lymphopenia. However, there is no current data on the potential risk factors for drug-resistant bacteria (DRB) in SLE. Bloodstream infections (BI) are common in SLE patients and are associated with increased mortality. An inadequate empirical antibiotic coverage in BI has been associated to higher mortality rates. Moreover, antibiotic resistance has become more prevalent, and it is important to define which patients require broad-spectrum antibiotics (BSA) initially. The aim of this study was to identify risk factors that influence the development of DBR in SLE, in order to determine which patients might benefit from an initial BSA coverage.

Methods: A retrospective, case-control study was performed. All patients fulfilled at least four ACR 1997 criteria for SLE and had an episode of BI between 2001 and 2012. Cases were defined as patients who had BI caused by DRB (*P. aeruginosa*, methicillin-resistant *S.aureus* or extended-spectrum β-lactalamase-producing *E. coli*), while patients in the control group had BI by susceptible strains of *S. aureus* or *E. coli*. Groups were age and gender matched. The variables that were measured included: disease activity, SLEDAI, anti-dsDNA antibodies, C3 and C4 levels, leukocyte and lymphocyte count in the three months prior and at the time of the infection; comorbidities; use of antibiotics or hospitalization in the previous three months; immunosuppressive treatment in the previous year and at the moment of the infection. Differences between groups were analyzed by Student t test or U Mann-Whitney test. Association between variables was assessed by OR (CI 95%). Multivariate analysis was performed by binary logistic regression model.

Results: Forty four patients were included in each group. 93% were female, with ages between 16 and 73. Variables associated with drug-resistant BI were the following: a history of CNS activity (OR 2.66, CI 95% 1.15–6.17); hematological activity (OR 2.11, CI 95% 1.07–4.14), immunosuppressive treatment (OR 1.24, CI 95% 1.02–1.5) and prednisone dose ≥ 20 mg/d at the time of the infection (OR 5.11, CI 95% 2–12.6); low C3 levels previous to infection (OR 2.71, CI 95% 1.25–5.9); and antibiotic use (OR 2.18, CI 95% 1.43–3.32) or hospitalization in the previous 3 months (OR 2.9, CI 95% 1.61–5.2). In the multivariate analysis, variables that remained significant were: low C3 previous to infection (OR 2.83, CI 95% 1.11–7.18), previous hospitalization (OR 2.18, CI 95% 1.21–3.95), and prednisone dose at the time of infection (OR 1.058, CI 95% 1.027–1.089).

Conclusion: Low C3 levels, a recent hospitalization and prednisone dose at the time of infection are risk factors for developing BI caused by DRB in SLE patients. Patients with these characteristics may benefit from initial BSA coverage.

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Lipid Lowering Medication Use Is Associated With Reduced Muscle Strength In Systemic Lupus Erythematosus. James S. Andrews[1] and Patricia P. Katz[2]. [1]University of California San Francisco, San Francisco, CA, [2]University of California, San Francisco, San Francisco, CA.

Background/Purpose: Premature atherosclerotic coronary artery disease is a major source of morbidity for women with systemic lupus erythematosus (SLE). Lipid lowering medications (LLM) are among the most commonly prescribed medications used to reduce cardiovascular risk. However, LLM use may be complicated by muscle symptoms, including weakness. This study examines the relationship between LLM use and muscle strength in women with SLE.

Methods: Subjects were participants in a longitudinal cohort with documented SLE. All measures were collected during an in-person research visit among a subset of the cohort. Only women were included in the analysis. LLM use was assessed by asking participants, "Do you have or are you being treated for high cholesterol? If yes, are you taking any prescription medicines for it?" Which specific LLM participants were taking was not assessed. Lower extremity muscle strength was assessed by knee torque and chair-stand time. A Biodex® unit was used to measure peak torques of knee extension and flexion at 150 degrees/second adjusted for body weight. Chair-stand time was measured as the time to complete 5 chair-stands from a standard chair without using one's arms. Mean knee torque and chair-stand time were compared between participants taking and not taking a LLM using Student's t-test. Regression analyses controlling for age, SLE duration, prednisone use, and SLE disease activity measured with the Systemic Lupus Activity Questionnaire (SLAQ) modeled the effect of LLM use on lower extremity muscle strength and chair stand time.

Results: Twenty-nine of 137 women (21%) reported taking a LLM. Mean age was 48 (±12) years; duration of SLE was 16 (±9) years. Women taking a LLM, compared to women not taking a LLM, had significantly lower strength on knee extension (mean peak torque 19 [±13] vs 29 [±15] foot-pounds, p=0.001) and on knee flexion (mean peak torque 14 [±9] vs 21 [±11] foot-pounds, p=0.002). Mean chair-stand time was greater for women taking a LLM than women not taking a LLM: 23 (±9) and 18 (±8) seconds (p=0.004). The results did not substantively change after adjusting for the effect of age, SLE duration, prednisone use, and SLAQ score.

Conclusion: Women with SLE who take a LLM, compared to women who do not, demonstrated decreased muscle strength on two objective assessments of lower extremity strength. Additional studies are needed to further characterize the association between LLM use and reduced muscle strength among women with SLE.

Disclosure: J. S. Andrews, None; **P. P. Katz**, None.

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The Accrual Of Damage In Corticosteroid-Naïve Patients With Systemic Lupus Erythematosus. Barry J. Sheane, Dominique Ibanez, Dafna D. Gladman and Murray B. Urowitz. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Despite improved survival rates in systemic lupus erythematosus (SLE) over the last 4 decades, organ damage and associated morbidity continues over time. Corticosteroids (CS) contribute to this accrual of damage. Due to the reliance on CS in the treatment of SLE there is a paucity of data on the disease characteristics of those that remain CS-naïve.

We hypothesized that CS-naïve patients with SLE accrue less damage and at a slower rate than CS-exposed patients, and that initiation of antimalarial medication (AM) soon after diagnosis may reduce exposure to CS over time.

Methods: Patients with SLE attending a large lupus clinic with 3 years or more of follow-up from inception, in the absence of damage (as per the SLICC Damage Index (SDI)) or exposure to CS at the inception visit, were included in the analysis. Two groups were identified from this cohort: those who remained CS-naïve up to their last visit at the Clinic and those who were exposed to CS at any point during follow-up. Differences in the rate of exposure to AM, rate of organ damage accrual (SDI ≥ 1) and disease activity at inception (SLEDAI-2K) and over time (adjusted mean SLEDAI (AMS) were examined. Organ-specific damage at the last Clinic visit was sub-classified as: 'definitely steroid-related' (e.g. osteonecrosis), 'possibly steroid-related' (e.g. myocardial infarction), and 'unrelated to steroid' (e.g. chronic kidney disease). A generalized linear model with repeated measures was used to assess the increase in damage over fifteen years in the two groups.

Results: From 209 patients fulfilling inclusion criteria, 84 remained CS-naïve from inception to the last recorded visit, while 125 were exposed to CS at some point during the disease course. Mean disease duration at first exposure to CS was 3.8 ± 5.5 years. Gender, race and age (37 ± 14.2 years in the CS-naïve group vs 35.1 ± 13.5 years in the CS-exposed (p=0.33)) were similar between the 2 groups at diagnosis. Baseline SLEDAI-2K was lower in the CS-naïve group (5.48 ± 3.53) compared with the CS-exposed (8.12 ± 5.93; p<0.0001). The AMS at all time points up to 10 years after diagnosis was significantly greater in the CS-exposed group. In the CS-naïve group, 35.7% developed damage during their disease course compared to 60.8% of the CS-exposed (p=0.0004). Mean SDI was significantly greater 1 year after diagnosis in the CS-exposed compared to the CS-naïve (0.14 ± 0.43 vs 0.02 ± 0.15, p=0.008) and at bi-annual intervals up to 15 years (1.52 ± 1.59 vs 0.54 ± 0.75, p<0.0001). On average, CS-naïve patients accrued damage at the rate of 0.05 per year compared to 0.10 per year in the CS-exposed patients (p=0.003). The increase in damage over 15 years 'definitely' and 'possibly' CS-related was significantly greater in the CS-exposed compared with the CS-naïve (p=0.009 and 0.024, respectively), but not in damage 'unrelated to CS' (p=0.3). Within the first year from inception, 51% of the CS-naïve and 61% of the CS-exposed groups were prescribed AM (p=0.17).

Conclusion: One third of CS-naïve SLE patients accrue damage over time, yet develop less damage and at a slower rate than those exposed to CS. Disease activity is lower in those naïve of CS, while early initiation of AM does not reduce exposure to CS.

Disclosure: B. J. Sheane, None; **D. Ibanez**, None; **D. D. Gladman**, None; **M. B. Urowitz**, None.

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Serositis In Systemic Lupus Erythematosus: Prevalence, Recurrence, Treatment and Outcome. Mansour Somaily, Dafna D. Gladman, Dominique Ibanez and Murray B. Urowitz. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Serositis is one of the ACR classification criteria for SLE. Its incidence is variable in studies varying from 12 to 60%.

The aim of this study is to determine the prevalence of serositis, its recurrence, management and complications in a large longitudinal cohort study.

Methods: Patients studied were seen in a long term single center observational cohort study. Pleurisy and pericarditis were diagnosed according to SLEDAI-2K Disease Activity Index criteria, which require objective measures to classify the serositis.

Demographic and clinical data collected at the time of serositis onset included age, gender, age at diagnosis, disease duration, medication used, damage index and SLEDAI assessment. Patients were divided into two groups: 1) patients with no recurrence and 2) those with recurrence. Those patients who had serositis features for more than six months despite appropriate treatment were considered to have refractory disease. Recovery was defined as resolution of pain attributed to the serositis. Descriptive statistics were used.

Results: 214 patients out of 1678 patients in the cohort (12.8%), had serositis during their disease course. This group was made up of 83% Female, 67% Caucasian, 14% Black, 8% Asian and 10% Other. Age at SLE diagnosis was 33 ± 12 years. At onset of serositis, disease duration was 4.6 ± 6.1 years; SLEDAI-2K (excluding serositis items) was 11.3 ± 9.7 and 61 (36%) patients had some damage.

174 patients had no recurrence and 40 patients (18.7%)had recurrence – 31 patients had 2 episodes, 5 patients had 3 episodes and 4 patients had 4 episodes. 12 (0.7%) patients had complications including pleural fibrosis and thickening and pericardial thickening.

202 (94.4%) patients went on to complete recovery and 12 (5.6%) were refractory. Average time to recovery was 8.6 ± 9.6 weeks. Refractory patients had serositis for an average of 1.2 ± 0.5 year.

Excluding refractory patients and comparing patients with recurrence to those without recurrence, there was no difference in sex, age at SLE diagnosis, age and disease duration at serositis onset, SLEDAI-2K or percent of patients with damage. More patients with recurrences had steroids and immunosuppressives compared to the non-recurrence group (100% vs 89% for steroids p=0.05; 36% vs 11% for immunosuppressives, p=0.0002).

Conclusion: Serositis occurs in 12.8% of our patients as defined by SLEDAI-2K. They responded well to corticosteroid but approximately 1 in 5 had a recurrence. Refractory disease is rare. There were no predictive variables for recurrence.

Disclosure: M. Somaily, None; **D. D. Gladman**, None; **D. Ibanez**, None; **M. B. Urowitz**, None.

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Clinical Correlates Of Chronic Isolated Thrombocytopenia In Patients With Systemic Lupus Erythematosus. Amanda J. Steiman, Dafna D. Gladman and Murray B. Urowitz. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Past studies have revealed disparity in the clinical significance of thrombocytopenia in systemic lupus erythematosus (SLE), ranging from a benign and incidental finding in some to a life-threatening manifestation, associated with severe disease and a high mortality rate in

others. Some patients evolve to a state of chronic isolated thrombocytopenia (CIT), the clinical significance of which is unknown. It is thus unclear whether this isolated finding warrants prompt, reactive therapy, or whether these patients may be monitored, free from immunosuppressive therapies and their associated toxicities, without risk of worsening disease activity. Thus the purpose of this study was to investigate the clinical correlates of CIT in a large cohort of SLE patients.

Methods: Patients with CIT were identified from the Lupus Clinic database. CIT was defined as at least two consecutive visits, ≤18 months apart, with SLE Disease Activity Index 2000 (SLEDAI-2K) score of 1 from platelets < 100, irrespective of pharmacotherapy. Any divergence from this score ended the thrombocytopenic period. Descriptive statistics were used.

Results: 16/1678 (1%) patients had CIT, occurring over 42 discrete episodes, and spanning 147 visits. The mean duration of a thrombocytopenic episode was 10.9 months, and the mean cumulative duration of isolated thrombocytopenia per patient was 28.6 months. Mean time to first CIT episode from clinic entry was 8.6 years (range 4 months – 31 years). Platelet counts during these periods ranged from 15 – 99, and were associated with antiphospholipid antibody positivity in 6/16 (37.5%). Fifteen patients (93.8%) were known to have thrombocytopenia as an SLE manifestation, associated with other signs/symptom of activity, earlier in their disease course; in the remaining patient it correlated with the introduction of an herbal remedy. There were no clinically significant episodes of bleeding in any of the patients over the visits studied, but critically low counts (≤20) were managed by increasing immunosuppression. Thrombocytopenia was associated with pregnancy in 3/42 (7.1%) of the episodes. Eleven patients (68.8%) were taking steroids at low doses, and six patients (37.5%) each were taking antimalarials or immunosuppressives during the CIT episodes. At times, these therapies overlapped. Four patients (25%) required none of these therapies for the duration of their CIT episodes. Prior to or after a CIT episode, patients were serologically and clinically quiescence in 14/78 (17.9%) instances, had active serology with or without thrombocytopenia in 34/78 (43.6%) instances, and were clinically active in 27/78 (34.6%) instances; there were more than 18 months between visits in three instances.

Conclusion: CIT is a rare event that can occur anytime in the SLE disease course and is usually associated with treatment with low dose steroids and/or immunosuppressives. Patients with this manifestation require close clinical monitoring and cannot be considered to be in remission.

Disclosure: A. J. Steiman, None; **D. D. Gladman**, None; **M. B. Urowitz**, None.

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Corticosteroid Use Across 52 Weeks Of Belimumab Therapy In Patients With Systemic Lupus Erythematosus: Combined Analyses From The BLISS Trials. Ronald F. van Vollenhoven[1], Michelle Petri[2], Daniel J. Wallace[3], David Roth[4], Charles T. Molta[4], Anne Hammer[5], Tom Tang[5] and April Thompson[5]. [1]The Karolinska Institute, Stockholm, Sweden, [2]Johns Hopkins University School of Medicine, Baltimore, MD, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]GlaxoSmithKline, King of Prussia, PA, [5]GlaxoSmithKline, Research Triangle Park, NC.

Background/Purpose: Patients with systemic lupus erythematosus (SLE) frequently receive corticosteroids (CS) as standard therapy. We examined the effects of belimumab on CS dose across 52 weeks of treatment in two randomized, controlled trials.

Methods: Data from BLISS-52 (NCT00424476) and BLISS-76 (NCT00410384) were pooled (GSK 200317). Patients treated with CS at baseline and randomized to receive belimumab 10 mg/kg plus standard therapy or placebo (standard therapy) were compared. A conservative steroid taper was imposed by each protocol. The primary endpoint was the cumulative change from baseline (average dose over the prior 7 days) in CS dose (prednisone or equivalent) through week 52. Rank analysis of covariance (ANCOVA) was applied. Cumulative dose reductions and increases, and change from baseline in average daily CS dose were examined. Adverse events (AE) were summarized.

Results: At baseline, 966 (Total N=1125, 86%) subjects received CS therapy: 478 belimumab 10 mg/kg, 488 placebo. Most subjects were female (n=910, 94%); mean age was 37.1 (11.5 SD) years, mean SELENA SLEDAI score was 9.8 (3.8 SD) and mean CS dose (prednisone or equivalent) was 12.5 (8.2 SD) mg/day. Baseline parameters for subjects treated with CS were similar between treatment groups. The mean of all cumulative decreases in CS dose was 741 mg for belimumab 10 mg/kg and 542 mg for placebo (p=0.017). The mean of all cumulative increases in CS dose was 1272 mg for belimumab and 1458 mg for placebo (p<0.001). The mean cumulative change from baseline in CS dose was 531 mg for belimumab compared with 916 mg for placebo (p <0.001). The mean change from baseline in average daily CS dose was 1.46 mg for belimumab and 2.51 mg for placebo (p <0.001). The most commonly reported AE among those subjects receiving CS at baseline was headache for both belimumab and placebo groups.

Conclusion: Although there was an increase in total CS dose in both arms over the duration of the trial, this increase was significantly smaller in patients who received belimumab 10 mg/kg plus standard therapy compared with standard therapy alone after one year of treatment. Adverse events for patients treated with CS were comparable among treatment groups.

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Defining Hand Arthritis In Systemic Lupus Erythematosus, From An Ultrasound, Magnetic Resonance Imaging and Antibody Status Perspective. Elisabeth M.A Ball[1], Arthur Grey[2], Ai Lyn Tan[3], Eiji Fukuba[4], Gunter Steiner[5], Dennis McGonagle[3], Aubrey Bell[2] and Madeleine Rooney[6]. [1]Queens' University/Musgrave Park Hospital, Belfast, United Kingdom, [2]Musgrave Park Hospital, Belfast, United Kingdom, [3]University of Leeds, Leeds, United Kingdom, [4]Shimane University, Izuma, Japan, [5]Medical University of Vienna, Vienna, Austria, [6]Queens University Belfast, Belfast, United Kingdom.

Background/Purpose: Musculoskeletal involvement in systemic lupus erythematosus (SLE) is common but poorly characterised with only a few Magnetic Resonance Imaging (MRI) or ultrasound (US) studies to date published in lupus arthritis. Erosive disease in SLE associated with rheumatoid factor (RF) or anti-CCP antibody (ACPA) is often referred to as '*rhupus'* to indicate a mixture of the character of RA and lupus. This study used MRI and US to investigate a cohort of hand and wrist SLE disease in comparison to RA and in respect to autoantibody status.

Methods: 50 SLE patients (median (IQR) disease duration 15.5 (9,20) yrs) with joint symptoms and /or objective arthritis, and 40 RA patients (median disease duration 15 (5,23) yrs) had a detailed US scan (Greyscale (GS) and Power Doppler (PD)) of dominant hand and wrist as per standardised protocols. 34 of these SLE patients and 15 RA patients also had a contrast enhanced MRI of their hand which was scored according to the OMERACT RAMRIS system. Extended antibody analysis (which included the anti-RA33 antibody and ACPA) was performed.

Results: There were no normal MRI examinations in the SLE group; 85% of MCP joints in lupus patients showed at least Grade 1 synovitis, compared to 76.7% of all RA MCP joints. *All SLE* wrist joints showed at least Grade 1 synovitis. 61.8% of those SLE patients had MRI determined MCP joint erosion compared to 100% of RA patients. 93.3% had at least one erosion at the wrist with erosions in 45% of the total number (n = 240) of SLE carpal bones. The prevalence of extensor tenosynovitis on MRI at the wrist was greater in the SLE group (20.3%), than in the rheumatoid group (10.7%) (p = 0.05).

Anti-RA33 titres correlated with SLE disease activity (SELENA SLEDAI) scores (p = 0.03) but in addition there was a strong negative correlation with total MRI MCP and total PIP bone oedema (p = 0.013 and p = 0.019 respectively). Only five SLE patients fulfilled the criteria for *'rhupus'* in that they had a positive ACPA or RF in the presence of erosive disease.

There was good correlation of MRI synovitis scores at the MCP joints with MCP ultrasound GS and PD (p = 0.003 and p < 0.001 respectively). There was excellent correlation of MRI and US wrist extensor tenosynovitis scores (p < 0.003).

Patient No.	ACPA	RF	Anti-RA33 (titre)	Total MCP erosion score on MRI (range 0–50)	Total Wrist erosion score on MRI (range 0–100)	Total Extensor Tenosynovitis score on Ultrasound (range 0–18)	Total MCP Bone Oedema (range 0–12)
89	+	−	−(10.2)	24	7	3	0
45	+	−	−(8.4)	0	1	3	0
59	+	−	−(9.5)	22	10	2	6
2	−	+	−(6.8)	n/a	n/a	0	0
3	−	+	−(3.2)	33	7	0	19
6	−	−	+(28)	0	1	0	0
16	−	−	+(52)	2	5	0	0
33	−	−	+(82)	3	1	0	0
37	−	−	+(316)	2	8	0	0
39	−	−	+(96.2)	0	4	0	0
41	−	−	+(83.7)	n/a	n/a	0	n/a
42	−	−	+(78.5)	n/a	n/a	0	n/a
67	−	−	+(40)	14	12	3	0

'+', positive antibody test, '−' negative antibody test, n/a, non-applicable as patient did not have an MRI scan.

Conclusion: This is the largest study to date using MRI in lupus arthritis and the first study to combine US and MRI in the assessment of SLE patients. We have shown that erosive lupus arthritis is independent of RF or ACPA status, challenging the use of the term *'Rhupus'* as the only manifestation of erosive arthritis in SLE. The negative association of bone oedema with anti-RA33 titres would suggest that those patients who have high titres are less likely to have more aggressive arthritis. This association with a more favourable outcome has been reported before in RA but has not yet been studied in relation to lupus arthritis.

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Continuous Variables Of Treatment Interventions In Patients Diagnosed With Systemic Lupus Erythematosus Among Commercially and Medicaid Insured Populations In The U.S. Hong Kan[1], Saurabh Nagar[1], Jeetvan Patel[1], Anna Oh[2], Daniel J. Wallace[3] and Charles T. Molta[4]. [1]GlaxoSmithKline, Research Triangle Park, NC, [2]University of California San Francisco, San Francisco, CA, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]GlaxoSmithKline, Philadelphia, PA.

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple organs including the heart, lungs, kidneys, joints, and the nervous system. Standard therapies for SLE include corticosteroids, antimalarial agents, non-steroidal anti-inflammatory drugs, cytotoxic agents, and immunosuppressive/ immunodulatory agents, some of which can be associated with significant toxicity. The objective of this study is to describe how SLE treatment evolves over time in newly diagnosed SLE patients in the U.S.

Methods: This retrospective, observational cohort study (HO-13–13054) followed incident SLE patients' treatment for 5 years in the Truven commercial and Medicaid claims database. The earliest date of a medical claim with a diagnosis of SLE (710.0x) from Jan 1, 2004 to Dec 31, 2009 was defined as the index date. Patients were required to be ≥ 18 years old at index date, had continuous medical and pharmacy benefits for 24 months prior to index date without SLE diagnosis and 12 months after index date with ≥ 1 SLE-related inpatient claim or ≥ 2 office or emergency room visits with an SLE diagnosis at least 30 days apart. At least one SLE diagnosis on or during 12 months after index date must be made by a rheumatologist, dermatologist, nephrologist, or neurologist.

Results: 4,036 commercially insured incident SLE patients (mean age: 46.9 years; female: 88.8%; mean Charlson comorbidity index (CCI): 1.01; mean follow up: 1,289 (SD: 645) days) and 234 incident patients with Medicaid coverage (mean age: 42.5 years; female: 94.0%; mean CCI: 1.80; mean follow up: 1,389 (SD: 767) days; white: 18.4%, black: 59.4%, Hispanic 1.3%, other: 20.9%) were identified. The number of patients in both cohorts declined over time due to insurance change or death. The proportion of patients with ≥ 1 prescriptions of SLE therapies decreased over 5 years after diagnosis (Table). In the first year after diagnosis, corticosteroid treatment rate was 48.1% and 62.8%, antimalarial treatment rate was 53.4% and 57.3%, and immune suppressive treatment rate was 22.2% and 25.6% in commercially insured and Medicaid insured patients, respectively. Biologic use in the two cohorts was no more than 1.5% throughout the period.

Table. Proportion of Patients with SLE Treatment Over Time in Commercially Insured and Medicaid Incident SLE Patients

	% with ≥ 1 prescriptions, commercially insured SLE patients (%)					% with ≥ 1 prescriptions, Medicaid SLE patients (%)				
Year after SLE diagnosis	1 N=4,036	2 N=4,029	3 N=3,149	4 N=2,144	5 N=1,311	1 N=234	2 N=234	3 N=161	4 N=120	5 N=98
Corticosteroids	48.1	35.3	26.4	22.3	19.2	62.8	44.4	31.1	27.5	20.4
Antimalarials	53.4	42.9	31.7	26.0	22.0	57.3	39.3	29.8	20.0	19.4
Immune suppressives	22.2	19.2	13.9	11.7	10.5	25.6	21.4	17.4	12.5	12.2
Anti-TNFs (including adalimumab, certolizumab, etanercept, golimumab and infliximab)	1.5	1.5	1.2	1.0	0.9	0.4	0.0	0.0	0.0	0.0
Other Biologics (including abatacept, tocilizumab and rituximab)	0.0	0.2	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0

Conclusion: Over a 5 year period, SLE patients were treated with less antimalarials, immune suppressive regimens, and targeted therapies than reported in tertiary lupus cohorts. This could reflect poor adherence, inability to afford medication, milder disease, or practitioner unfamiliarity with prescribing agents other than corticosteroids. The decrease in prescriptions over time might relate to response to treatment, lapses in physician or patient education, or exit of more severe patients from the cohorts. Further study is needed to explore the implications of treatment options upon outcomes.

Disclosure: H. Kan, GlaxoSmithKline, 3; **S. Nagar**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **J. Patel**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **A. Oh**, None; **D. J. Wallace**, Abbott Immunology Pharmaceuticals, 5, Abbott Immunology Pharmaceuticals, 8, GlaxoSmithKline, 5, GlaxoSmithKline, 8, Pfizer Inc, 5, Amgen, 5, UCB, 5; **C. T. Molta**, GlaxoSmithKline, 3, GlaxoSmithKline, 1.

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Poor Adherence To Medications For Systemic Lupus Erythematosus Among U.S. Medicaid Beneficiaries. Jinoos Yazdany[1], Jun Liu[2], Graciela S. Alarcon[3], Karen H. Costenbader[4] and Candace H. Feldman[5]. [1]University of California, San Francisco, San Francisco, CA, [2]Brigham and Women's Hospital, Boston, Massachusetts, Boston, CA, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [5]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Immunosuppressive and anti-malarial drugs are the cornerstones oftreatment for patients with systemic lupus erythematosus (SLE) and have beenshown to improve outcomes, including reduced disease activity, damage andmortality. We examined adherenceto treatment with these medications in a nationwide study of Medicaidbeneficiaries with SLE.

Methods: We used U.S. Medicaid Analytic eXtract (MAX) datafrom 2000–2006 containing person-level files on Medicaid eligibility, utilization and payments. Weidentified patients meeting a validated administrative SLE definition, who hadreceived either an immunosuppressive (oral cyclophosphamide, mycophenolatemofetil, mycophenolic acid, azathioprine, leflunomide, methotrexate, ortacrolimus) or anti-malarial (hydroxychloroquine) drug through an outpatientpharmacy over the period of observation. Pharmacy claims were used to assess adherence to drugs by calculating amedication possession ratio (MPR), defined as the proportion of days covered bythe total days' supply dispensed after the first claim for each drug. We observed each patient over a fixedinterval of 180 days to ensure all patients were studied for the same timeinterval. Data were stratified bysociodemographic characteristics and geographic region and we used Fisher'sexact test to compare MPRs between groups. In addition, we examined the percentage of patientsconsidered adherent, defined as having a MPR greater than or equal to 80%.

Results: 23,187 patients with SLE were taking at least oneimmunosuppressive or anti-malarial drug. Mean age was 38 years (SD 12) and 94% were female. The sample was diverse (40% Black, 34%White, 16% Hispanic, 5% Asian, 5% Other, and 1% Native). Most resided in the U.S. South (36% vs.18% Midwest, 23% Northeast, 22% West). MPRs ranged from 31.1% for tacrolimus to56.9% for hydroxychloroquine (Table). Across all medications, Blacks had loweradherence compared to Whites. Formany medications, Asians had higher adherence than Whites. For example, for hydroxychloroquine, the MPR was significantly higher among Asians (63, SD 27), and lower in Blacks(53, SD 29), Hispanics (57, SD 28), and Native populations (56, SD 26) comparedto Whites (59, SD 31; $p<0.0001$ for group comparisons). MPRs were lowest for patients residingin the Midwest, and highest for those in the Northeast ($p<0.01$ acrossdrugs). A minority of patients had

MPRs greater than or equal to 80% (range 14%for tacrolimus to 40% for mycophenolate mofetil; Table).

Table. Adherence to Commonly Used Medications for Systemic Lupus Erythematosus in a Nationwide Study of U.S. Medicaid Beneficiaries.

Oral Drug	Population Taking Medication, n	Average Medication Possession Ratio (MPR*), SD	Population with MPR greater than or equal to 80%, %
Hydroxychloroquine	23,187	56.9 (30)	31
Azathioprine	6,137	56.5 (30)	31
Methotrexate	5,278	53.1 (31)	27
Mycophenolate mofetil	3,954	56.1 (30)	40
Cyclosporine	1,185	42.9 (31)	20
Tacrolimus	1,020	31.1 (31)	14
Cyclophosphamide	778	41.2 (33)	20
Leflunomide	989	54.4 (31)	29

*Proportion of days covered by the total days' supply dispensed over a 180-day period after the initial drug claim.

Conclusion: Ourstudy demonstrates poor adherence to all classes of medications used to treatSLE among Medicaid beneficiaries. Although adherence was low across all racial/ethnic groupsand regions examined, it was particularly low among Blacks, Hispanics andNative populations, as well as for those residing in the Midwest. These findings suggest that a majorityof Medicaid beneficiaries may be at risk for inadequate clinical responsebecause of poor adherence.

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Obesity and Vascular Factors May Play a Role In Persistent Depression Among Individuals With Systemic Lupus Erythematosus. Patricia P. Katz[1], Chris Tonner[1], Laura Trupin[1], Edward H. Yelin[2] and Jinoos Yazdany[1]. [1]University of California, San Francisco, San Francisco, CA, [2]UC San Francisco, San Francisco, CA.

Background/Purpose: Depression is commonly reported in systemic lupus erythematosus (SLE), yet information is lacking about long-term patterns of depression. In particular, because depression is thought to arise at least partially from disease-specfiic sources, information regarding predictors of persistent depression is needed. We examined a longitudinal SLE cohort to identify factors that predicted persistent depression vs. remission.

Methods: Data derive from the UCSF Lupus Outcomes Study (LOS), in which participants with confirmed SLE are interviewed by phone annually. During each interview, the Center for Epidemiologic Studies Depression scale (CESD) is administered. We defined depression using a lupus-specific cut-point of 20 (1). Individuals who were depressed by this criterion at the initial interview were followed through subsequent interview waves. Those whose CESD score remained ≥ 17 (within 0.5 SD of the cut-point) were classified as having persistent depression. Those whose CESD score dropped below 17 were classified as remitting. We then used bivariate and multivariate analyses to define baseline factors associated with persistent depression. Variables examined were sociodemographics (age, sex, education, income), SLE duration, self-rated disease activity (on 0–10 scale), history of cardiovascular events (previous MI or stroke), history of other vascular events (e.g., DVT, PE, or other clot), obesity based on body mass index (BMI≥30), current smoking, and current reported use of antidepressants. Analyses controlled for the number of interviews contributed by each individuals. Individuals who were interviewed at least three times were included in the analysis.

Results: Of 1008 individuals in the analysis sample, 340 were depressed at their initial interview. Among these, 135 (40%) remained depressed through all remaining observations. Factors significantly associated with persistent depression in bivariate analyses were: low education, income below poverty, higher self-rated disease activity, current smoking, history of vascular events other than MI or stroke, obesity, and current use of depression medication (Table). In multivariate analyses, low education, history of other vascular events, obesity, and current use of depression medication were independently associated with persistent depression.

Table. Factors associated with persistent depression in bivariate and multivariate analyses

	Bivariate analyses		Multivariate analysis†
	Remission (n = 205)	Persistent depression (n = 135)	OR (95% CI)
Sociodemographic			
Age (mean±SD)	45 ± 13 yrs	47 ± 10 yrs	1.01 (0.98, 1.03)
Female	94%	94%	1.52 (0.44, 5.30)
Education ≤ high school	18%	36%*	**2.16 (1.17, 3.99)**
Income below poverty	17%	32%*	1.60 (0.84, 3.05)
Health characteristics			
SLE duration (mean±SD)	12 ± 10 yrs	12 ± 10 yrs	0.98 (0.94, 1.02)
SLE disease activity (mean±SD)	5 ± 3	6 ± 3*	1.07 (0.97, 1.18)
Current smoking	8%	20%*	1.37 (0.60, 3.14)
History of MI or stroke	10%	14%	1.63 (0.73, 3.66)
History of other vascular event	15%	27%*	**2.25 (1.14, 4.43)**
Obese (BMI ≥ 30)	27%	42%*	**1.87 (1.07, 3.26)**
Taking antidepressants	42%	48%*	**2.02 (1.12, 3.66)**

* p<.01.
† Multivariate model included all variables shown plus number of interviews contributed.

Conclusion: Forty percent of women who met the depression criterion initially were persistently depressed. Results suggest that obesity and vascular factors may play a role in persistent depression in SLE, and that such depression may be resistant to treatment. Further study is needed to identify mechanisms for those associations.

(1) Julian L, et al. Using the CES-D to screen for depression in SLE. *Arthritis Care Res* 2011; 63:884–890

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1590

A CD8 T Cell-IFN-γ-IDO Axis Is Required For Mesenchymal Stem Cell Suppression Of Human SLE. Dandan Wang, Lin Lu, Xuebing Feng, Xia Li and Lingyun Sun. Department of Rheumatology and Immunology, the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China.

Background/Purpose: Stem cell-based regenerative medicine is a promising approach in tissue reconstruction. Mesenchymal stem cells (MSC) show therapeutic effects on human autoimmune diseases including systemic lupus erythematosus (SLE), but the underlying mechanisms remain largely unknown.

Methods: The effects on inhibiting T cell proliferation by allogenic umbilical cord derived MSC were determined. Then MSC functional molecules were examined by real-time PCR under the stimulation of peripheral blood mononuclear cells (PBMC) from healthy controls and SLE patients, respectively. CD4+ and CD8+T cell were purified by microbeads to stimulate MSC, respectively, to determine IDO expression as well as supernatant cytokines, to further get to know which cell subset(s) or which molecule(s) involved in MSC mediated T cell proliferation inhibition. Meanwhile, the possible signaling pathways were assessed. Moreover, we analyzed the correlation between baseline serum cytokines and clinical response of MSC transplantation (MSCT).

Results: UC MSC efficiently inhibited T cell proliferation in both healthy controls and lupus patients, with a more inhibitory effect in lupus T cell. *In vitro* activated lupus PBMC significantly induced MSC to secret TGF-β1, IDO, HGF and IL-6, with a more than 200-fold increase of IDO. The addition of IDO inhibitor could almost completely abrogate MSC mediated T cell proliferation inhibition. Moreover, we found that lupus peripheral CD8+T cell markedly stimulated MSC to secret IDO and supernatant IFN-γ significant increased. The addition of anti-IFN-γ monoclonal antibody could inhibit IDO activity and similarly abrogate inhibition of T cell proliferation by MSC. We further found that lupus CD8+T cell secreted predominant intracellular IFN-γ compared to CD4+T cell or compared to healthy CD8+ or CD4+T cell subsets. Furthermore, in the presence of lupus CD8+T cell, IFNGR/JAK/STATs signaling pathways were activated, then to induce MSC to secret IDO and upregulate IDO activity. However, bone marrow MSC from lupus patients are less response to allogenic CD8+T cell or recombinant IFN-γ stimulation and produce far less IDO, consequently fail to efficiently inhibit

T cell proliferation. In the last, clinical analysis showed that lupus patients had significant higher proportion and absolute number of CD3+CD4-CD8+T cell than healthy controls, and serum IFN-γ markedly increased. Predominant IFN-γ in lupus patients was mainly secreted by CD8+T cell. Baseline serum IFN-γ as well as CD8+T cell levels were significant higher in good responders than in poor responders who underwent UC MSC transplantation.

Conclusion: We uncovered a previously unrecognized CD8+T cell-IFN-γ-IDO axis that mediates the immunotherapy by allogenic MSC in lupus patients.

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1591

Efficacy and Safety Of Atacicept For Prevention Of Flares In Subjects With Moderate To Severe Systemic Lupus Erythematosus (SLE). David Wofsy[1], David A. Isenberg[2], Daiana Licu[3], Yong Li[4], Claudia Pena Rossi[3] and Caroline Gordon[5]. [1]University of California San Francisco and NIAID Autoimmunity Centers of Excellence, San Francisco, CA, [2]University College London, London, United Kingdom, [3]Merck Serono S.A., Geneva, Switzerland, [4]EMD Serono, Rockland, MA, [5]University of Birmingham, Birmingham, United Kingdom.

Background/Purpose: Atacicept is a fusion protein that inhibits B-cell stimulation factors BLyS and APRIL. Levels of BLyS and APRIL are elevated in patients with SLE. We report on the efficacy and safety of atacicept in preventing new flares of SLE during 52 weeks on treatment and 24 weeks of safety follow-up in the APRIL-SLE trial.

Methods: Subjects with active SLE (≥1 BILAG A and/or B) were treated with a corticosteroid taper for 10 weeks. Subjects reaching BILAG C or D were randomized 1:1:1 to receive placebo or atacicept 75 or 150 mg twice weekly for 4 weeks, then weekly for 48 weeks. The primary outcome measure was percent of subjects experiencing a flare, defined as a new BILAG A or B, during the 52-week treatment period. Subjects were also followed during a 24-week follow-up period.

Results: 461 subjects were randomized (placebo, n=157; atacicept 75 mg, n=159; atacicept 150 mg, n=145). The primary endpoint was not met in the atacicept 75 mg arm (flare rate 57.9% vs 54.1% among controls; OR 1.15, p=0.54). Treatment was discontinued in the 150 mg arm after enrollment of 145 subjects due to two fatal pulmonary infections (pneumococcus and leptospirosis). The flare rate in the 150 mg arm was 36.6% vs 54.1% in the placebo arm (OR 0.48, p=0.002). Time to first new flare was significantly longer in the 150 mg arm vs placebo (HR 0.62, p=0.02). Improvements were seen with atacicept 75 mg and 150 mg in SF-36 physical and mental summary scores exceeding the minimal clinically important difference (MCID=2.5) at Week 52 (atacicept 75 mg=3.14, 2.64; 150 mg=4.26, 3.46; placebo=2.00, 1.33). Adverse events (AEs) due to infection were similarly distributed in the placebo and treatment arms during treatment and during the 24-week follow-up period (Table). Serious AE (SAE) rates, and SAE rates due to infection, were also similar in the placebo, 75 mg, and 150 mg groups (5.8%, 7.0%, and 5.6%, respectively) throughout the treatment and follow-up period. There were no deaths during the follow-up period.

Table. Proportion of subjects experiencing at least one adverse event (safety population)

	Placebo (n=154)		Atacicept 75 mg (n=157)		Atacicept 150 mg (n=144)	
	Week 52	(24-week follow-up)	Week 52	24-week follow-up	Week 52	24-week follow-up
Adverse events*	117 (76.0)	48 (31.2)	130 (82.8)	59 (37.6)	116 (80.6)	50 (34.7)
Serious adverse events*	21 (13.6)	9 (5.8)	23 (14.6)	11 (7.0)	20 (13.9)	8 (5.6)
Infections*	80 (51.9)	27 (17.5)	93 (59.2)	32 (20.4)	79 (54.9)	28 (19.4)
Serious infections*	7 (4.5)	4 (2.6)	6 (3.8)	7 (4.5)	10 (6.9)	2 (1.4)

*All data are n (%).

Conclusion: The primary endpoint was not met in the atacicept 75 mg arm compared with placebo. Two fatal infections in the 150 mg arm caused sufficient concern to terminate this arm prematurely. *Ad-hoc* analysis of those subjects who had received 150 mg atacicept (either by reaching 52 weeks or by withdrawing during the 52-week treatment period) showed a reduced risk of SLE flares, and increased time to flare. Clinically meaningful improvements in quality of life were observed in both atacicept arms compared to controls. Total SAEs were similar between groups. Fewer subjects in all groups experienced AEs during the 24-week follow-up period than during the 52-week treatment period. Taken together, these findings show signals suggestive of risk as well as efficacy for atacicept. Future studies will be needed to further clarify the balance between risk and benefit and to identify subsets of subjects in whom the benefits may outweigh the risks.

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"Lupus Headache": Results From a Prospective, International, Inception Cohort Study. John G. Hanly[1], Murray B. Urowitz[2], Aidan o'Keeffe[3], Caroline Gordon[4], Sang-Cheol Bae[5], Jorge Sanchez-Guerrero[6], Juanita Romero-Diaz[7], Ann E. Clarke[8], Sasha Bernatsky[9], Daniel J. Wallace[10], E.M. Ginzler[11], David A. Isenberg[12], Anisur Rahman[12], Joan T. Merrill[13], Michelle A. Petri[14], Paul R. Fortin[15], D. D. Gladman[16], Barri J. Fessler[17], Graciela S. Alarcon[17], Ian N. Bruce[18], Mary Anne Dooley[19], Kristjan Steinsson[20], Munther A. Khamashta[21], Rosalind Ramsey-Goldman[22], Susan Manzi[23], Gunnar K. Sturfelt[24], Ola Nived[25], Asad A. Zoma[26], R. F. van Vollenhoven[27], Manuel Ramos-Casals[28], Cynthia Aranow[29], Meggan Mackay[30], Guillermo Ruiz-Irastorza[31], Kenneth C. Kalunian[32], S. Sam Lim[33], Murat Inanc[34], Diane L. Kamen[35], Christine Peschken[36], Søren Jacobsen[37], Chris Theriault[38], Kara Thompson[1] and Vernon Farewell[39]. [1]Dalhousie University and Capital Health, Halifax, NS, [2]University of Toronto, Toronto Western Hospital, Toronto, ON, [3]MRC Biostatistics Unit, Institute of Public Health, University Forvie Site, Cambridge, United Kingdom, [4]University of Birmingham, Birmingham, United Kingdom, [5]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [6]Mount Sinai Hospital, University Health Network, Toronto, ON, [7]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [8]McGill University Health Center, Montreal, QC, [9]Research Institute of the McGill University Health Ctre, Montreal, QC, [10]Cedars-Sinai Medical Center, Los Angeles, CA, [11]SUNY-Downstate Medical Center, Brooklyn, NY, [12]University College London, London, United Kingdom, [13]Oklahoma Medical Research Foundation, Oklahoma City, OK, [14]Johns Hopkins University School of Medicine, Baltimore, MD, [15]Centre de Recherche du Chu de Québec et Université Laval, Quebec City, QC, [16]Toronto Western Hospital and University of Toronto, Toronto, ON, [17]University of Alabama at Birmingham, Birmingham, AL, [18]Arthritis Research UK Epidemiology Unit and NIHR Manchester Musculoskeletal Biomedical Research Unit, The University of Manchester, Manchester, United Kingdom, [19]University of North Carolina at Chapel Hill, Chapel Hill, NC, [20]Landspital Univ Hospital, Reykjavik, Iceland, [21]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [22]Northwestern University Feinberg School of Medicine, Chicago, IL, [23]West Penn Allegheny Health System, Pittsburgh, PA, [24]Lund University, Lund, Sweden, [25]Rheumatology, Lund, Sweden, [26]Hairmyres Hospital, East Kilbride, United Kingdom, [27]The Karolinska Institute, Stockholm, Sweden, [28]Hospital Clínic, Barcelona, Spain, [29]The Feinstein Institute, Manhasset, NY, [30]Feinstein Institute for Medical Research, Manhasset, NY, [31]Hospital de Cruces, UPV/EHU, Barakaldo, Spain, Bizkaia, Spain, [32]UCSD School of Medicine, La Jolla, CA, [33]Emory University, Atlanta, GA, [34]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [35]Medical University of South Carolina, Charleston, SC, [36]University of Manitoba, Winnipeg, MB, [37]Department of Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [38]Capital Health, Halifax, NS, [39]MRC Biostatistics Unit, Cambridge, United Kingdom.

Background/Purpose: "Lupus headache" is controversial and is included in validated measures of global SLE disease activity. We examined the frequency and characteristics of "lupus headache" in a large, prospective, inception cohort of SLE patients and the association with global disease activity and health related quality of life.

Methods: An international network of 30 academic medical centers enrolled patients within 15 months of SLE diagnosis. Annual assessments were performed for 19 neuropsychiatric (NP) syndromes as per the ACR case definitions. This included 5 types of headache using the International Headache Society (IHS) criteria. Additional data were demographic and clinical variables, SLE global disease activity (SLEDAI-2K), which includes "lupus headache" as a standalone variable, SLICC/ACR damage index (SDI) and self-report mental (MCS) and physical (PCS) component summary scores of the SF-36. Statistical analysis used linear regression models with generalized estimating equations to account for within patient correlation.

Results: Of the 1732 enrolled patients 89% were female. Race/ethnicity was Caucasian (48%), African (16%), Asian (16%), Hispanic (16%) and other (4%). At enrollment the mean (±SD) age was 34.6±13.4 years, disease duration was 5.6±4.8 months and followup was 3.8±3.1 years. Twenty-six (1.5%) patients had "lupus headache" at 27 (0.36%) of 7523 assessments. Concurrent classification using the IHS headache case definitions were: migraine (13), tension headaches (8), intractable non-specific headaches (5), cluster headaches (1) and intracranial hypertension (1). Two patients had 2 types of headache and in 5 (18.5%) of 27 assessments there were concurrent NP events. "Lupus headache" was reported at both enrollment (n=14) and follow-up (n=13) assessments, in patients from all racial/ethnic groups in 15 of 30 (50%) sites located in 8 of 11 countries (USA, Canada, UK, Spain, South Korea, Mexico, Sweden and Iceland). The estimated mean (±SE) SLEDAI-2K scores, without including "lupus headache" variable, for visits with no headache (n=6019), a non-lupus headache (n=1330) and both a non-lupus and "lupus headache" (n=27) were 3.8±0.08, 3.6±0.18 and 7.2±1.40 respectively (p=0.034). Concurrent SF-36 MCS scores were 47.8±0.28, 42.6±0.56 and 39.4±2.41 (p<0.001) and PCS scores were 42.6±0.30, 38.1±0.53 and 32.4±1.76 (p<0.001). SLEDAI-2K scores, without including "lupus headache" variable, for patients with and without "lupus headache" were 7.2±1.40 vs 3.7±0.08 (p=0.035). In 5/26 (19.2%) patients "lupus headache" was the sole contributor to the SLEDAI-2K score. Concurrent SF-36 MCS and PCS scores for patients with and without "lupus headache" were 39.4±2.41 vs 46.8±0.27 (p=0.002) and 32.4±1.76 vs 41.7±0.28 (p<0.001) respectively.

Conclusion: "Lupus headache", although infrequent, was associated with higher global disease activity and a lower HRQoL. It was not reproducibly aligned with a uniform IHS classification of headache (e.g. intractable headache). The lack of consistency in diagnosing "lupus headache", even by experienced clinicians, indicates a need to better define "lupus headache" and to reach consensus on whether it is truly a standalone manifestation of NPSLE.

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Blood-Brain Barrier Damages and Intrathecal Synthesis Of Anti-NMDA Receptor NR2 Antibodies In Diffuse Psychiatric/Neuropsychological Syndromes In Systemic Lupus Erythematosus. Shunsei Hirohata[1], Yoshiyuki Arinuma[1] and Taku Yoshio[2]. [1]Kitasato University School of Medicine, Sagamihara, Japan, [2]Jichi Medical University, School of Medicine, Shimotsuke-shi, Tochigi-ken, Japan.

Background/Purpose: Neuropsychiatricmanifestations in SLE are difficult complication that may cause substantialimpairment of quality of life as well as disability. Among a variety of neuropsychiatric manifestations in SLE, acute confusional state (ACS) in diffusepsychiatric/neuropsychological syndromes (diffuse NP-SLE) is the most seriousone. Recent studies have demonstrated that cerebrospinal fluid (CSF) anti-NMDAreceptor NR2 antibodies (anti-NR2) are associated with diffuse NP-SLE, especially ACS. However, the precise mechanism of elevation of CSF anti-NR2remains uncertain. There are 2 mechanisms for the elevation of CSF IgG, including transudation through the damaged blood-brain barrier and intrathecalsynthesis. The current studies therefore examined the blood-brain barrierfunction and intrathecal synthesis of anti-NR2 in NP-SLE.

Methods: Pairedserumand CSFsamples were obtained from 85 SLE patients whosatisfied the 1982 ACR revised criteria when they showed activeneuropsychiatric manifestations (59 patients with diffuse NP-SLE and 26patients with neurologic syndromes [focal NP-SLE]) as well as from 26 control patients with non-inflammatory neurologicaldiseases. IgG anti-NR2 were measured by ELISAusing synthetic peptide containing the extracellular ligand-binding domain ofNR2. Albumin was also quantitated by ELISA. Blood-brain barrier function andintrathecal synthesis of anti-NR2 were evaluated by Q albumin (CSF albumin x1,000/serum albumin) and by CSF anti-NR2 index ([CSF anti-NR2 × serumalbumin]/[serum anti-NR2 × CSF albumin]), respectively.

Results: CSF anti-NR2levels were significantly elevated in diffuse NP-SLE compared with those infocal NP-SLE or in control patients. Q albumin as well as CSF anti-NR2 indexwas also significantly elevated in diffuse NP-SLE compared with those incontrol patients. CSF anti-NR2 levels and Q albumin were significantly higherin ACS than in non-ACS diffuse NP-SLE (cognitive disorder, mood disorder, anxiety disorder and psychosis), whereas there was no significant difference inCSF anti-NR2 index between both groups (Figure). Finally, CSF anti-NR2 levelswere significantly correlated with Q albumin (r=0.3628, p=0.0083), but not withserum anti-NR2 (r=0.0366, p=0.7807) in patients with diffuse NP-SLE.

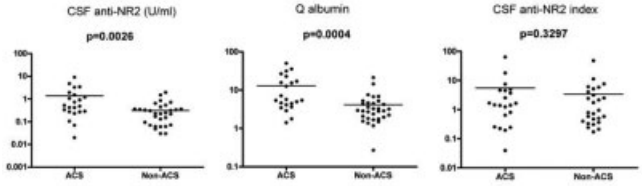

Figure. CSFanti-NR2 levels, Q albumin and CSF anti-NR2 index in patients withacute confusional state and in those with non-acute confusional state ofdiffuse NPSLE

Conclusion: Theseresults demonstrate that CSF anti-NR2 were elevated by both transudationthrough the damaged blood-brain barrier and intrathecal synthesis. Moreover, thedata indicate that the severity of the damages of blood-brain barrier, whichallows transudation of higher concentrations anti-NR2 into the central nervoussystem, play a crucial role in the development of ACS, a more serious form of diffuseNP-SLE.

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Cognitive Dysfunction, Depression and Anti N-Methyl-D-Aspartate Receptor Antibodies and Anti- Ribosomal P In Systemic Lupus Erythematosus Patients In Argentina. Graciela Gómez, Judith Sarano, Maria de los Angeles Gargiulo, María Victoria Collado, Lorena Suarez, Daniel Fadel, Alexandra Panopulos and Marina Khoury. Instituto de Investigaciones Medicas Alfredo Lanari, Buenos Aires, Argentina.

Background/Purpose: Cognitive dysfunction (CD) and depression (D) are common manifestations of neuropsychiatric systemic lupus erythematosus (SLE) and they have been linked to antibodies (abs) like ribosomal P (anti-P), phospholipids and to the NR2 subunit of human N-Methyl-D-Aspartate receptor (anti NR2-NMDAR). The aim of the study was to describe the frequency of neurocognitive dysfunction and depression in patients with SLE and to assess their association with anti-NR2, anti-P and anticardiolipins (aCL) abs.

Methods: Patients who fulfilled the ACR classification SLE criteria were recruited in this cross-sectional study. Demographic and clinical information was obtained during the interview. Anti NR2-NMDAR isotype IgG was determined by commercial ELISA (Cis Biotech, Inc), cut off value=2ng/ml, anti-DNAds, aCL IgG/IgM by ELISA, anti-P by Lineal Immunoassay. Psychiatric evaluation, DSM IV, A-HAM and Depression Beck scales were applied. The ACR tests were applied to evaluate CD.Cognition was assessed in 4 domains:(1) attention, (2) memory, (3) executive skills and (4) language. Individual tests were: Trail Making Test Part A (1) and Part B (2), Digit symbol (2), Clock Drawing Test (2), SPAN (2), Rey-Osterrieth Complex figure test (3), Rey Auditory Verbal learning test (3), immediate and delayed logical memory(3), semantic Fluency (4). Z-scores (representing standard deviations [SD] from the tests standardization sample mean) were generated for each test. Overall mean z-scores were then determined for each subject in each of the four domains, method used by Diamond (A&R 2006).CD was defined as a mean z score worse than −1.0 in at least one domain. Statistical analyses: data are presented as mean ±SD and percentages. Fisher exact test for categorical variables. Alpha=0.05.

Results: 50 SLE patients, mean age 46±13 yrs, female 96%, white 76%, *mestizos* 20%, disease duration 18±12 yrs, SLEDAI ≤ 4 66%, SLICC ≤ 1 68%. Antibodies to NR2 52% (7/26 strong positive), anti-P 12%, aCL IgG 18%, aCL IgM 20%.Global CD 82%,depression 56% and anxiety 56%. Analyzing by groups (table 1) no significant differences with age (p=0,30) or disease duration(p=0,76) were observed.

	Without CD and D n= 3 (6%)	Only CD n=19 (38%)	With CD and D n=22 (44%)	Only D n=6 (12%)	p value
NR2-NMDA (n=7)	0	3	1	3	0,056
anti-P (n=6)	0	1	3	2	0,26
a-CL Ig G (n=9)	0	2	7	0	0,21
a-CL Ig M(n=10)	0	3	7	0	0,30

Conclusion: We found cognitive dysfunction and depression in our patients with SLE. Although the differences among the groups were not statistically significant, there was higher frequency of anti NR2 in depression and higher frequency of aCL and anti-P in cognitive dysfunction. These antibodies did not appear in patients without depression or cognitive impairment. No association was found between CD and NR2 abs, perhaps due to abs levels that may fluctuate over time or to methodological differences in abs assay detection. These findings would requiere a great number of patients to assess the possible association between these antibodies and these manifestations of neuropsychatric SLE.

Disclosure: G. Gómez, None; **J. Sarano**, None; **M. D. L. A. Gargiulo**, None; **M. V. Collado**, None; **L. Suarez**, None; **D. Fadel**, None; **A. Panopulos**, None; **M. Khoury**, None.

1595

Electroclinical Correlates and Outcome Of Status Epilepticus In Systemic Lupus Erythematosus. Jamal Mikdashi[1], Tricia Ting[2] and Allan Krumholz[3]. [1]University of Maryland School of Medicine, Baltimore, MD, [2]University of Maryland. School of Medicine, Baltimore, MD, [3]University fo Maryland school of Medicine, Baltimore, MD.

Background/Purpose: Predictors of seizures and epilepsy in systemic lupus erythematosus (SLE) patients are well described but descriptions of status epilepticus (SE) have thus far been limited to isolated case reports. The purpose of this study is to determine the electro-clinical characteristics as potential predictors of long-term outcome of SE in SLE.

Methods: This is an observational study of consecutive SLE patients with SE, enrolled out of the Maryland Lupus cohort that consists of 1138 SLE patients. Demographic, clinical features, laboratory data, brain magnetic resonance imaging (MRI) studies and video electroencephalography (EEG) were examined during SE event. Outcome was determined at 12 months following SE event. Seizure not related to SLE were excluded.

Results: In this SLE population, 78 (6.9%) of all patients had seizures related to SLE, and of these 7 (9.0%) had SE. At the SE events, patients [mean age 21.4 years, 72 % women, 72 % African American, and a mean duration of SLE of 6.5 years] presented with cutaneous vasculitis (57%), arthritis (43 %), psychosis (29 %), nephritis (14 %) and ischemic stroke (14 %). Convulsive SE was observed in 6 patients (3 generalized, 3 complex partial with secondary generalized) and non-convulsive SE in 1. Prolonged electrographic seizure activity (1–3 days) with continuous slowing and multifocal spikes in the bifornatal and temporal regions, associated with refractory complex partial and generalized seizures were observed in 5 patients. EEG seizures resolved abruptly in 2 patients. In addition to immunotherapy, multiple anti-epileptic drugs were needed to control SE in all patients.

All SE patients had a symptomatic structural lesion with probable etiologic significance with increased T2/FLAIR hyperintensity in the front-temporal and posterior cortex, and hypointense lesions in the regions of the amygdyla –hippocampal complex, thalamus and basal ganglia areas. Restricted weighted sequence images demonstrated restricted diffusion in the corresponding cortical regions of the frontal and temporal lobes in two patients. Two patients had normal initial brain MRI, but abnormal lesions were identified using functional FDG-PET scanning.

A favorable clinical and EEG response was recognized in all SLE patients with SE, with improvement in consciousness and survival. Recurrent seizure events were observed in 3 patients following the SE event, while recurrent SE events were observed in one patient who developed mesial temporal sclerosis overtime. Poor functional and cognitive outcome observed in 3 (43 %) patients, was associated with prolonged SE event, presence of cortical and subcortical structural lesions on brain MRI that correlated with the recorded EEG abnormality. No mortality among the SE patients was observed.

Conclusion: Overall, SLE patients with SE seem to have a favorable clinical outcome. Patients with prolonged SE events with a greater cortical-subcortical lesion burden on brain MRI have poor physical and cognitive function on long-term outcome. Identifying the pathogenic role of specific SLE related autoantibodies/cytokines in relation to brain structural lesions of SLE patients with SE is needed.

Disclosure: J. Mikdashi, None; **T. Ting**, None; **A. Krumholz**, None.

1596

Relationship Between IgG Anti-NR2 Glutamate Receptor Antibodies and Depressive/Anxiety Symptoms In Patients With Systemic Lupus Erythematosus. Chi Chiu Mok[1], Kar Li Chan[1] and Betty Diamond[2]. [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Feinstein Institute for Medical Research, Manhasset, NY.

Background/Purpose: To study the relationship between anti-NR2 glutamate receptor antibodies (anti-NR2) and depressive/anxiety symptoms in patients with systemic lupus erythematosus (SLE).

Methods: Consecutive Chinese patients who fulfilled >=4 ACR criteria for SLE were recruited. Depressive/anxiety symptoms were assessed by the validated Chinese version of the Hospital Anxiety and Depression scale (HADS) (0–21 points). Serum samples were taken at 10am in the morning for the assay of anti-NR2 antibodies (in-house ELISA using peptide adsorbed to plate and serum diluted 1:100, developed with an anti-human IgG antibody). Disease activity of patients recruited was assessed by SLEDAI and physicians' global assessment (PGA), whereas organ damage since SLE diagnosis was assessed by the ACR/SLICC damage index (SDI). Correlation among anti-NR2 titer, age, sex, HADS-depression score, HADS-anxiety score, SLEDAI, PGA and SDI in various systems was studied by linear regression models.

Results: 285 SLE patients were studied (95% women; age 38.9±12.6 years; SLE duration 9.0±7.0 years). At the time of study, 57 (20%) patients had clinically active SLE (SLEDAI>5); and 106 (37%) patients had organ damage (SDI score>=1). The mean SLEDAI was 3.9±4.6 and the mean PGA was 0.36±0.66. Forty-four (15%) patients had HADS-anxiety score of >10 and 28 (9.8%) of patients had HADS-depression score of >10. Anti-NR2 antibodies were present in 154 (54%) patients, defined as titers of greater than the mean+2SD (standard deviation) of healthy controls. Strongly positive values of anti-NR2 (defined as mean+4SD of controls) were found in 90 (32%) patients. Linear regression revealed that anti-NR2 reactivity correlated with SLEDAI score (Beta 0.25; $p<0.001$), PGA score (Beta 0.31; $p<0.001$), mean SLEDAI in the preceding 12 months (Beta 0.18; $p=0.003$), C3 level (Beta −0.25; $p<0.001$), HADS-depression score (Beta 0.14; $p=0.022$) and HADS-anxiety score (Beta 0.14; $p=0.023$), adjusted for age and sex. There was no relationship between anti-NR2 titers and anti-dsDNA titer, total SDI damage score (Beta 0.09; $p=0.14$), neuropsychiatric damage (Beta 0.06; $p=0.32$) or SDI scores in other systems.

Conclusion: Anti-NR2 antibodies are prevalent in patients with SLE. Anti-NR2 reactivity correlated with disease activity and depressive/anxiety symptoms in SLE patients.

Disclosure: C. C. Mok, Pfizer Inc, 8, GlaxoSmithKline, 8, Mundipharma Pte Ltd, 9; **K. L. Chan**, None; **B. Diamond**, None.

1597

Autonomic Dysfunction In Systemic Lupus Erythematosus Patients With Previous Neuropsychiatric Involvement. Yang Gao, Sheung Wei Li, Lai Heung Chau, Chak Sing Lau and Mo Yin Mok. University of Hong Kong, Hong Kong, Hong Kong.

Background/Purpose: Autonomic dysfunction has increasingly been described to be associated with central nervous system (CNS) disorders and has been attributed to damage of the central autonomic network. In this study, we examined autonomic function among systemic lupus erythematosus (SLE) patients with previous neuropsychiatric involvement (NPSLE) compared to those without NPSLE.

Methods: SLE patients with previous CNS involvement including seizure, acute confusion state and stroke (NPSLE), age-, sex- and disease duration- matched SLE patients (non-NPSLE) and age- and sex- matched healthy subjects were evaluated by standardized tests on sympathetic and parasympathetic functions of the cardiovascular system. Symptoms of autonomic dysfunction were screened by questionnaire.

Results: 96.0% of NPSLE and non-NPSLE patients reported one or more autonomic symptoms (24/25 for both groups) compared with 37.5% (6/16) of healthy subjects ($p<0.001$). Patients with NPSLE had more complaints over urinary frequency (48% vs. 20%, $p=0.04$) and incomplete voiding (48% vs. 12%, $p=0.005$) than non-NPSLE patients. They had significantly lower heart rate response to standing compared with healthy controls (1.12±0.12 vs. 1.26±0.11, $p=0.003$ by post hoc Tukey's test) but not with non-NPSLE patients (1.17±0.11, $p=0.44$). NPSLE patients also had significantly smaller heart rate variation during deep breathing compared with non-NPSLE patients (13.1±5.3 vs. 19.5±6.1 bpm, $p=0.01$ by post hoc Tukey's test). Linear

regression analysis showed NPSLE as predictive factor for smaller heart rate variability during deep breathing (p=0.02) after adjustment for age. However, NPSLE was not found to have more autonomic dysfunction than non-NPSLE patients when Ewing's criteria were applied.

Conclusion: NPSLE patients were found to have smaller heart rate variation during deep breathing compared with non-NPSLE patients but the frequency of autonomic dysfunction was similar in both groups.

Disclosure: Y. Gao, None; **S. W. Li**, None; **L. H. Chau**, None; **C. S. Lau**, None; **M. Y. Mok**, None.

1598

Cognitive Dysfunction, a Non-Inflammatory Neuropsychiatric Syndrome In Systemic Lypus Erythematosus. Juanita Romero-Díaz[1], Alí Duarte-García[2], Sandra Juarez-Arellano[3], Alba Cicero-Casarrubias[1], Hilda Fragoso-Loyo[4], Luis Llorente[5] and Jorge Sánchez-Guerrero[6]. [1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Tufts Medical Center, Boston, MA, [3]Instituto Nacional de Ciencias Medicas y Nutricion S.Z., Mexico city, Mexico, [4]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, Mexico, [5]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubirán, Mexico City, Mexico, [6]Mount Sinai Hospital and University Health Network, Toronto Canada, Toronto, ON.

Background/Purpose: Cognitive dysfunction (CD) affects 15 – 60% of SLE patients; nevertheless, its pathogenesis and predisposing factors are unknown.

Objective: To identify factors associated with CD in SLE, focusing on clinical manifestations, neuropsychiatric syndromes (NPSLE), disease activity, inflammation, treatment, and co-morbidities.

Methods: Patients and methods: A random sample of 100 ambulatory patients from a prospective cohort of SLE of recent-onset (<12 months) at enrollment, participated. At entry into the cohort, patients have a standardized medical history with emphasis in atherosclerosis and NPSLE, physical examination, and laboratory tests (chemical analyses, lipids, homocystein, hsCRP, autoantibodies, complement, etc.). Every 3–6 months, patients are seen for medical care, and disease activity (SLEDAI-2K), medications use/dose are assessed. Every year, information is up-dated; including damage accrual (SLICC-DI), co-morbidities, cardiovascular risk-factors, NPSLE, and a blood sample is drawn. Clinical information is stored in a database containing demographic, anthropometric, lifestyle habits, medical family history, obstetric variables, and lupus information. Two rheumatologists perform all assessments.

At screening for CD, participants were assessed using: Trail Making test, Digit Span, California Verbal Learning test, Rey-Osterrieth complex figure test, the Stroop Color-Word test, WAIS III letter-number sequencing, Animal naming test, Controlled Oral Word association, WAIS-R/III digit symbol substitution test, Grooved pegboard test, and WAIS-R/III similarities. Tests were grouped in 7 cognitive domains: memory, attention/executive function, visuospatial, motor, psycho-motor speed, language, and problem solving. An expert neuropsychologist applied and graded the cognitive tests. Cognitive Dysfunction was defined as at least −2 SD in 2 or more cognitive domains. A nested analysis of autoantibodies, cytokines and chemokines in serum and cerebrospinal fluid (CSF) was conducted among 10 patients with moderate/severe CD and 30 patients without CD.

Results: At enrolment into the cohort, mean age of patients was 25.9 (8.2) years, and SLE duration 5.3 (3.7) months. At screening for CD, mean age was 32.6 years, 93% females, SLE duration 6.2 years. CD was diagnosed in 16 (16%) patients, since age 24 years and from 1.2 years of diagnosis. Patients with CD had lower education 9 vs.12 years (p=0.006), higher BMI 26.7 vs. 24.3 (p=0.03), tested positive of IgG aCL antibodies (50% vs. 18%, p=0.009), and were older (35 vs. 31 years, p=0.09). They had had other NPSLE more often (50% vs. 27%, p=n.s.) and their median number was higher (2.5 vs. 1, p=0.04). No difference was observed in other variables including disease activity, anti-dsDNA antibodies, C3, C4, or treatment.

No difference in autoantibodies, cytokines and chemokines was observed in serum and CSF in the nested analysis, except for higher levels of MCP-1 in CSF (886.1 vs. 515.8, pg/mL, p=0.04) among patients with CD.

Conclusion: Cognitive dysfunction is a non-inflammatory NPSLE syndrome. Lower education, higher BMI, presence of IgG aCL antibodies, and previous NPSLE syndromes influence its onset.

Disclosure: J. Romero-Díaz, None; **A. Duarte-García**, None; **S. Juarez-Arellano**, None; **A. Cicero-Casarrubias**, None; **H. Fragoso-Loyo**, None; **L. Llorente**, None; **J. Sánchez-Guerrero**, None.

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High Proportion Of Intrathecal Ro52 SSA Antibodies In Neuropsychiatric Lupus Patients – Relations To Neuropsychiatric Manifestations. Johanna Estelius, Liisa Hopia, Vijole Dzikaite-Ottosson, Magnus LA. Andersson, Elisabet Svenungsson and Jon Lampa. Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Neuropsychiatric (NP) manifestations in Systemic Lupus Erythematosus (SLE) are often associated with significant impact on quality of life and work capability. The underlying mechanisms behind NPSLE are still largely unknown. Here, we aimed to investigate the associations between the occurrence of Ro52 SSA autoantibodies and manifestations of NPSLE.

Methods: Presence or absence of SSA antibodies were detected with a non-quantitative in-house Ro52 ELISA in serum and cerebrospinal fluid (CSF) samples from a cohort of unselected SLE patients displaying neuropsychiatric features, collected between 2005 and 2011. Sensitivity of the assay was tested against confirmed Ro52 negative and positive individuals in serum. All SSA serum negative patients were also SSA negative in CSF indicating specificity of the assay. Blood brain barrier (BBB) permeability was calculated with the serum/CSF albumin ratio, and a ratio < 5.7 – 9 (age related) was considered to associate with an intact BBB.

Results: 55 NPSLE patients (mean age 50, 93% women) with paired serum and CSF samples were included in the analysis. Out of these, 40% (n=22) tested positive for SSA in serum. 64% (n=14) of SSA serum positive patients were also SSA positive in CSF (double positive), leaving 8 patients SSA positive in serum only (single positive). The distribution of major clinical NP manifestations in the total group of NPSLE patients was as follows (overlapping data): seizures 27% (n=15), headache 46% (n=25), cognitive dysfunction 31% (n=17), mood disorder or depression 11% (n=6) and stroke 11% (n=6). In the SSA double positive group this distribution was 29% (seizures), 29% (headache), 57% (cognitive dysfunction), 29% (mood disorder or depression) and 7% (stroke) respectively. There was a tendency that double positive patients had higher frequency of cognitive dysfunction than the other groups (57% (double positive) vs. 25% (single positive) and 31% (total)), however, this did not reach statistical significance. No clear differences were found between the groups concerning the other NP manifestations, distribution of ACR SLE criteria, age, disease duration, presence of brain lesions, cortisone treatment or smoking.

Conclusion: Presence of serum SSA autoantibodies in 40% of the NPSLE patients is in line with previous reports; however, our finding of high prevalence of double serum- and CSF SSA positivity in NPSLE patients was unexpected and indicates either facilitated passage over the BBB or intrathecal production of these autoantibodies. Our assay did not allow quantitative comparisons, but patients with confirmed intact BBB showed similar relation in SSA serum vs. CSF positivity, thus excluding BBB breakage as a main factor for detection of intrathecal SSA in this context. Moreover, intrathecal SSA tended to associate with cognitive dysfunction. Altogether, our results indicate the possibility of SSA antibodies interacting with cerebral functions, which may be in line with previous reports showing that other lupus-associated autoantibodies, i.e. anti-dsDNA antibodies, may cross react with neuronal N-metyl-D-aspartat (NMDA) receptors affecting neuron function and viability.

Disclosure: J. Estelius, None; **L. Hopia**, None; **V. Dzikaite-Ottosson**, None; **M. L. Andersson**, None; **E. Svenungsson**, None; **J. Lampa**, None.

1600

Anti-Ribosomal P Protein Antibodies Exacerbate Long-Term Prognosis In Patients With Diffuse Neuropsychiatric/Neuropsychological Syndromes In Systemic Lupus Erythematous. Yoshiyuki Arinuma[1], Hirotoshi Kikuchi[2], Eisuke Ogawa[1], Tatsuhiko Wada[1], Tatsuo Nagai[1], Sumiaki Tanaka[1] and Shunsei Hirohata[1]. [1]Kitasato University School of Medicine, Sagamihara, Japan, [2]Teikyo University School of Medicine, Tokyo, Japan.

Background/Purpose: Systemic lupus erythematous (SLE) is a chronic inflammatory disease characterized by the expression of a variety of autoantibodies. Although the comprehensive survival from the disease has been improved in recent decades, neuropsychiatric manifestations in SLE (NPSLE) still remain one of the difficult complication. However, the factors that influence the long-term mortality in patients with NPSLE, especially diffuse neuropsychiatric/neuropsychological syndromes (diffuse NPSLE), have not been fully elucidated. Anti-ribosomal P protein antibodies (anti-P) are detected in 12–16% of patients with SLE, and have been shown to be

associated with diffuse NPSLE. The aim of this study is to clarify the effects of various autoantibodies, including anti-P, on the overall mortality in patients with diffuse NPSLE.

Methods: Fifty-eight patients with diffuse NPSLE (9 males and 49 females, ages 38.6 ± 17.0 years [mean ± SD]) who had been admitted to Kitasato University Hospital and to Teikyo University Hospital from 1992 to 2012 were exhaustively collected for the study. The medical charts were reviewed for various clinical parameters. The relationship of various serum autoantibodies with overall mortality was analyzed.

Results: Of 58 patients, 12 patients [20.7%] died during the observation periods (2322 ± 2250 days [mean ± SD]) including 6 patients from SLE itself, 5 patients from infections and 1 patient from aortic aneurysm. The 5-year, 10-year and 15-year mortality rates based on the Kaplan-Meier method were 17.9%, 22.0% and 30.7%, respectively. The overall mortality was neither correlated with age nor with the duration of SLE at the onset of diffuse NPSLE. Among various autoantibodies in the sera, the presence of anti-P, but not that of anti-DNA, anti-Sm or anti-cardiolipin (CL) antibodies, at the onset of diffuse NPSLE, significantly increased the hazard ratio for death of the patients (p=0.0447). Moreover, on the Kaplan-Meier analysis, the survival rate was lower in patients with positive anti-P than those with negative anti-P at the onset (p=0.0711).

Table. Logistic regression analysis of effects of various autoantibodies on the death in patients with diffuse NPSLE

autoantibodies	HR	95% CI	p	n
anti-DNA	0.923	0.244–3.616	0.906	57
anti-Sm	0.785	0.204–3.107	0.722	54
anti-CL	1.333	0.171–7.405	0.754	43
anti-P	4.909	1.0954–26.729	0.0447	47

HR = hazard ratio. CI = confidence interval.

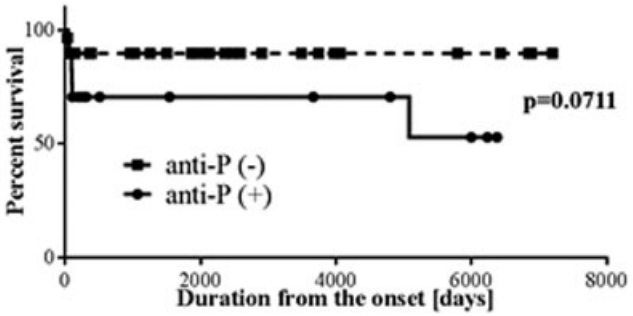

Figure. The effect of anti-P on the survival in patients with diffuse NPSLE.

Conclusion: These results indicate that the presence of anti-P in the sera is a significant risk factor for the poor prognosis of diffuse NPSLE.

Disclosure: Y. Arinuma, None; **H. Kikuchi**, None; **E. Ogawa**, None; **T. Wada**, None; **T. Nagai**, None; **S. Tanaka**, None; **S. Hirohata**, None.

1601

The Presence Of IgG-Immune Complexes In The Cerebrospinal Fluids Is Associated With Central Neurocychiatric Manifestatin But Not With Intrathecal Production Of Proimmflammatory Cytokines/Chemokines Such as Interferon-α In Systemic Lupus Erythematosus. Taku Yoshio[1], Hiroshi Okamoto[2], Kazuhiro Kurasawa[3], Yoshiaki Dei[4], Shunsei Hirohata[5] and Seiji Minota[6]. [1]Jichi Medical University, School of Medicine, Shimotsuke-shi, Tochigi-ken, Japan, [2]Minami-Otsuka Clinic, Tokyo, Japan, [3]Dokkyo Medical University, Mibu-machi, Shimotsuga-gun, Tochigi-ken, Japan, [4]Saiseikai Utsunomiya Hospital, Utsunomiya-shi, Tochigi-ken, Japan, [5]Kitasato University School of Medicine, Sagamihara, Japan, [6]Jichi Medical University, Shimotsuke, Tochigi, Japan.

Background/Purpose: IgG-Immune complexes (IC) formed by CSF autoantibodies in patients with neuropsychiatric syndromes of systemic lupus erythematosus (NPSLE) has reported to stimulate the production of interferon (IFN)-α, IL-8, IP-10, MCP-1 in a bioassay containing plasmacytoid dendritic cells and a source of antigens. The pathological roles of these cytokines/chemokines in the CSF has been reported in patients with NPSLE. These results suggest that IgG-IC in the CSF may have pathogenic roles in central NPSLE.

We investigated whether IgG-IC are present in the CSF of patients with central NPSLE and correlated with cytokines/chemokines such as IFN-a levels in the CSF.

Methods: 50 SLE patients, of whom the CSF samples were obtained, were enrolled. Of 50 SLE patients, 29 had central NPSLE and the reminder 21 did not have central NPSLE. The levels of IgG-IC in the CSF samples were measured by ELISA kits. The levels of IL-6, IL-8, IP-10, MCP-1, and G-CSF in the CSF samples were measured by Bio-Plex Pro Assays. IFN-α in the CSF samples were measured by ELISA kits. Antiribosomal P protein antibody (anti-P) titers in the CSF samples were measured by ELISA using recombinant ribosomal P0 protein as the antigen.

Results: CSF IgG-IC levels in 29 patients with central NPSLE were significantly higher than in 21 patients without central NPSLE (mean ± SD, median [range]; 3.75 ± 4.80 μg/ml, 1.28 [0.09 – 18] vs. 1.01 ± 1.40 μg/ml, 0.49 [0.09 – 6.38]; p = 0.047). The CSF levels of IL-6, IL-8, IP-10, MCP-1, and G-CSF and CSF anti-P titers in 29 patients with central NPSLE were significantly higher than those in 21 patients without central NPSLE, respectively (275.1 ± 595.9 pg/ml, 17.4 [1.9 – 2882.2] vs. 11.6 ± 12.8 pg/ml, 5.0 [1.3 – 45.2]; p = 0.007, 482.5 ± 1697.6 pg/ml, 99.2 [17.7 – 9233.7] vs. 58.5 ± 81.2 pg/ml, 31.0 [6.3 – 366.8]; p = 0.004, 8988.0 ± 15406.2 pg/ml, 3248.2 [228.7 – 76941.5] vs. 2988.3 ± 4126.9 pg/ml, 1137.8 [427.6 – 15765.1]; p = 0.034, 555.7 ± 481.0 pg/ml, 387.6 [35.6 – 2008.5] vs. 284.3 ± 161.5 pg/ml, 265.1 [55.6 – 664.6]; p = 0.021, 71.5 ± 156.0 pg/ml, 33.4 [0.81 – 779.4] vs. 15.5 ± 24.8 pg/ml, 3.9 [0 – 102.7]; p = 0.009 and 6.90 ± 9.36 CSFU/ml, 2.6 [0 – 31.0] vs. 3.75 ± 9.25 CSFU/ml, 0.95 [0.14 – 41.3]; p = 0.021). Unexpectedly, CSF IFN-α levels in patients with central NPSLE were not significantly higher than in patients without central NPSLE (13.1 ± 58.9 pg/ml, 0 [0 – 314.0] vs. 0.17 ± 0.75 pg/ml, 0 [0 – 3.4]; p = 0.565). Discriminant analysis showed the most significant association between IgG-IC levels in the CSF and the presence of central NPSLE (P = 0.02). However, CSF IgG-IC levels in these patients were not significantly correlated with CSF levels of any of the studied cytokines/chemokines. The significant positive association between CSF IgG-IC levels and CSF anti-P titers was not observed in these patients.

Conclusion: The intrathecal IgG-IC might have important roles in the pathogenesis of central NPSLE. But the intrathecal IgG-IC was not associated with the intrathecal production of cytokines/chemokines studied in this study.

Disclosure: T. Yoshio, None; **H. Okamoto**, None; **K. Kurasawa**, None; **Y. Dei**, None; **S. Hirohata**, None; **S. Minota**, None.

1602

Autoantibodies, Cytokines and Chemokines In Serum and Cerebrospinal Fluid Of SLE Patients With Cognitive Dysfunction. Hilda Fragoso-Loyo[1], Alí Duarte-García[2], Sandra Juárez-Arellano[3], Alba Cicero-Casarrubias[4], Juanita Romero-Díaz[4], Luis LLorente-Peters[1] and Jorge Sánchez-Guerrero[5]. [1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, Mexico, [2]Tufts Medical Center, Boston, MA, [3]Instituto Nacional de Ciencias Medicas y Nutricion S.Z., Mexico city, Mexico, [4]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [5]Mount Sinai Hospital and University Health Network, Toronto Canada, Toronto, ON.

Background/Purpose: The nature and pathogenesis and cognitive dysfunction (CD) in patients with SLE is unkown. To determine the presence and levels of autoantibodies, cytokines and chemokines in serum and cerebrospinal fluid (CSF) of SLE patients with CD.

Methods: 40 patients participating in a larger study of CD in SLE were analyzed. All patients are active members in a prospective cohort of SLE of recent-onset at enrollment. At entry into the cohort, patients have a standardized medical history, and laboratory tests. Every 3–6 months, patients are seen for medical care, and disease activity (SLEDAI-2K), medications use/dose are assessed. Every year, information is up-dated; including damage accrual (SLICC-DI), co-morbidities, cardiovascular risk-factors, NPSLE, and a blood sample is drawn. All patients were screened for CD using: Trail Making test, Digit Span, California Verbal Learning test, Rey-Osterrieth complex figure test, the Stroop Color-Word test, WAIS III letter-number sequencing, Animal naming test, Controlled Oral Word association, WAIS-R/III digit symbol substitution test, Grooved pegboard test, and WAIS-R/III similarities. Tests were grouped in 7 cognitive domains: memory, attention/executive function, visuospatial, motor, psycho-motor speed, language, and problem solving. Cognitive Dysfunction was defined as at least −2 SD in 2 or more cognitive domains.

In all patients a blood and CSF sample were drawn and the following autoantibodies were measured: NMDA, nucleosomes, ribosomal-P, ds-DNA, b_2-glycoprotein-I IgG and IgM, anticardiolipin IgG and IgM. Cytokines [Interferon-alpha(IFN- a), Interleukin-6 (IL-6)] and chemokines [monocyte chemoattractant protein-1 (MCP-1), gamma interferon inducible protein-10 (IP-10), Interleukin-8 (IL-8), and CCL-19] were analyzed by luminometry. Results are expressed as pg/mL.

Results: CD was diagnosed in 10 patients. Patients with CD had median age of 33 years (24 – 57), disease duration 7.0 years, and SLEDAI-2K score 5 (0 – 14) at CD assessment and did not differ from patients without CD.

No difference in autoantibodies, cytokines and chemokines was observed in serum between patients with and without CD.

In CSF, no difference in the levels of autoantibodies and cytokines was observed; however, MCP-1 was significantly higher among patients with CD [886.1 (374.9 – 1439.7) vs. 515.8 (3.2 – 1958.2) pg/mL, p=0.04]. No difference was observed with other chemokines.

Conclusion: The levels of autoantibodies, cytokines, and chemokines in serum and CSF do not differ between patients with or without CD. Although the levels of MCP-1 in CSF were higher in patients with CD, they do not reach the levels observed in inflammatory NPSLE manifestations. These results support that CD is a non-inflammatory NPSLE manifestation.

Disclosure: H. Fragoso-Loyo, None; **A. Duarte-García**, None; **S. Juárez-Arellano**, None; **A. Cicero-Casarrubias**, None; **J. Romero-Díaz**, None; **L. LLorente-Peters**, None; **J. Sánchez-Guerrero**, GlaxoSmithKline, 5, Bristol-Myers Squibb, 5, Biogen Idec, 5, Genentech and Biogen IDEC Inc., 5.

1603

Sustained Reductions In Circulating B Cell Populations and Immunoglobulin G Levels With Long-Term Belimumab Treatment In Patients With Systemic Lupus Erythematosus. Herbert Struemper[1], William Freimuth[2], Christi Kleoudis[3], Thi-Sau Migone[4], David Roth[3] and William Stohl[5]. [1]GlaxoSmithKline, Research Triangle Park, NC, [2]Human Genome Sciences, Inc., Rockville, MD, [3]GlaxoSmithKline, King of Prussia, PA, [4]Igenica, Burlingame, CA, [5]University of Southern California Keck School of Medicine, Los Angeles, CA.

Background/Purpose: Belimumab treatment in autoantibody-positive systemic lupus erythematosus (SLE) patients for up to 76 weeks results in sustained reduction in several circulating B cell subsets, including naïve and activated B cells, as well as in serum immunoglobulin (Ig) levels. The purpose of the present analysis was to examine long-term changes in B cell subsets and IgG beyond 76 weeks through 172 weeks of continued belimumab treatment.

Methods: B cell, B cell subset and IgG data were collected in the Phase 3 Study BLISS-76 (NCT00410384; N=819) and in its US extension study (NCT00724867; N=268). All B cell subsets were measured at baseline, Weeks 8, 24, 52, 76, 100, 124, 148 and 172. Subjects randomized to 1 mg/kg or 10 mg/kg cohorts in BLISS-76 received bi-weekly doses of belimumab for the first month followed by dosing every 4 weeks thereafter. Placebo subjects, who chose to enter the extension study, received 10 mg/kg belimumab every 4 weeks starting at Week 76. Subjects in all cohorts received standard of care SLE agents (eg. corticosteroids, immunosuppressants, and/or antimalarials).

Results: Most B cell subsets in peripheral blood showed a rapid initial decline over the first 24 weeks followed by a comparatively slower decline or sustained suppression. Memory B cells were an exception and roughly doubled by Week 8, followed by a slow and sustained decline through Week 172. Beyond 76 weeks of treatment, B cell reductions either stabilized (naïve and plasma B cells), or continued to gradually decrease (CD19+ /CD20+ B cells, memory cells, plasmacytoid B cells) leading to net reductions of about 80–90% for naïve, activated, and plasmacytoid B cells, 70–75% for CD19+/CD20+ B cells and 50–60% for plasma cells after 172 weeks of continued belimumab dosing. Over 172 weeks, a 20–30% reduction in IgG levels was observed. Only 1 completer (10 mg/kg) experienced a shift from no to Grade 3 hypogammaglobulinemia (HGG; <400 mg/dL). Of all belimumab treated subjects, 3 subjects (0.5%) experienced a Grade 3/4 HGG shift. Development of Grade 3/4 HGG was not associated with severe infections.

Results for 1 and 10 mg/kg groups in the timing and magnitude of the response were similar for most measures. Results for placebo patients, who received 10 mg/kg at Week 76, confirmed the response patterns observed for patients who received belimumab at Week 0.

Response in Week 172 completers:

Response parameter	Median % change from baseline (N) Placebo → 10 mg/kg	1 mg/kg	10 mg/kg
$CD20^+$ B cells	−69.3 (57)	−74.3 (63)	−72.2 (46)
$CD19^+$ B cells	−69.2 (65)	−70.6 (68)	−72.2 (51)
$CD20^+/CD27^+$ memory B cells	−16.7 (57)	−35.6 (63)	−37.7 (46)
$CD20^+/CD27^-$ naïve B Cells	−79.4 (57)	−79.7 (63)	−81.6 (46)
$CD20^+/CD69^+$ activated B cells	−90.8 (68)	−89.9 (80)	−85.5 (54)
$CD20^+/CD138^+$ plasmacytoid B cells	−88.6 (61)	−89.8 (70)	−87.9 (50)
$CD20^-/CD138^+$ plasma B cells	−64.1 (61)	−47.2 (70)	−57.9 (51)
IgG	−19.6 (65)	−23.4 (69)	−26.2 (53)

Conclusion: Treatment of SLE patients with belimumab for 172 weeks results in substantial, but subtotal, declines in circulating B cell subsets. These declines are associated with a modest decline in IgG levels and do not appear to be associated with development of severe infections.

Disclosure: H. Struemper, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **W. Freimuth**, Human Genome Sciences, Inc., 1, Human Genome Sciences, Inc., 3; **C. Kleoudis**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **T. S. Migone**, Igenica, 1, Igenica, 3; **D. Roth**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **W. Stohl**, Pfizer Inc, 2, GlaxoSmithKline, 2, Xencor, 2, Eli Lilly and Company, 5, Novartis Pharmaceutical Corporation, 5.

1604

Effects Of Chronic Treatment With Blisibimod, An Inhibitor Of B Cell Activating Factor, On Renal and Inflammation Biomarkers In Patients With Systemic Lupus Erythematosus: Observations From The Placebo-Controlled Pearl-SC and Open-Label Extension Studies. Richard A. Furie[1], Matthew Thomas[2], Alvina Chu[3], Renee S. Martin[3], Colin Hislop[3] and Morton A. Scheinberg[4]. [1]The Feinstein Institute for Medical Research and North Shore-Long Island Jewish Health System, Lake Success, NY, [2]Health and Research Centre, Trivandrum, Kerala, India, [3]Anthera Pharmaceuticals Inc, Hayward, CA, [4]Rheumatology Hospital Abreu Sodre Pesquisa Clínica, São Paulo, Brazil.

Background/Purpose: To evaluate the effects of subcutaneously-administered blisibimod on renal and inflammation biomarkers in patients with SLE during the phase 2b clinical trial PEARL-SC (NCT01162681) and the ensuing open-label extension (OLE) study (NCT01305746).

Methods: 547 patients with serologically-active SLE and SELENA SLEDAI ≥6 were randomized to receive placebo or blisibimod. Per SELENA-SLEDAI definitions, 76 subjects (13.9%) had renal involvement at baseline. In the PEARL-SC study, subjects received blinded study drug for up to 52 weeks (with a median of 37 weeks) or until the last subject completed 6 months of therapy. A total of 382 subjects enrolled in the OLE study and received blisibimod. Here we report the effects of blisibimod in subjects who initiated blisibimod therapy in the PEARL study (N=277), evaluating changes on renal and inflammation biomarkers in the combined PEARL and OLE studies through March 2013. In addition, we report blisibimod effects on renal biomarkers in 2 renal subgroups defined as (i) baseline proteinuria equivalent ≥0.5 g/24hr (determined from random spot urinary protein:creatinine ratio, N=41), or (ii) baseline proteinuria equivalent to ≥1g/24hr (N=25).

Results: Compared with baseline, decreases in proteinuria were observed with blisibimod from Week 12 through Week 52 in the subgroup of subjects with proteinuria equivalent ≥1 g/24hr at enrollment (Figure 1A). Similarly decreases in proteinuria were observed in subjects with proteinuria equivalent ≥0.5 g/24hr through Week 44. When compared with response in the patients randomized to receive placebo in PEARL-SC, there was a tendency toward greater decreases in mean GFR in the patients receiving placebo compared with blisibimod at Week 24 in both renal subgroups, eg mean ΔGFR =1.4 and −3.0 mL/min [N=36,37], for blisibimod and placebo respectively in the ≥0.5 g/24hr subgroup.

Consistent with a durable pharmacological effect, decreases in anti-double-stranded DNA (dsDNA) antibodies, and increases in complement C3 and C4 compared with baseline were observed through 52 weeks of blisibmod therapy (Figure 1B, C and D).

Blisibimod was safe and well-tolerated at all dose levels with no meaningful imbalances in serious adverse events or infections between blisibimod and placebo in the PEARL-SC study, and continued to be well-tolerated through the OLE study.

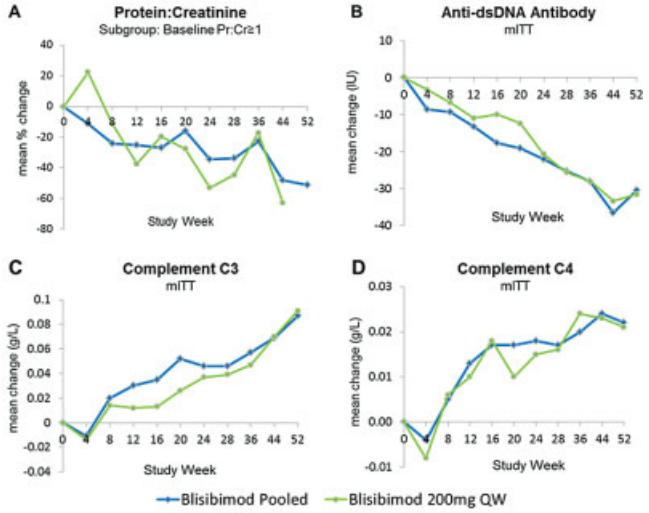

Figure 1. Effect of Blisibimod on Proteinuria and SLE biomarkers.

Conclusion: These data demonstrate that blisibimod induces pharmacological effects on proteinuria and SLE biomarkers that are consistent with BAFF-mediated inhibition of B cells and plasma cells, without adversely impacting the risk of infection in patients with SLE. These data support further evaluation of blisibimod in patients with SLE and other B cell-mediated diseases.

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1605

Post-Marketing Experience With Belimumab In U.S. Lupus Centers: Data From The Lupus Clinical Trials Consortium, Inc. (LCTC) National Patient Registry. Jinoos Yazdany[1], Doruk Erkan[2], Jorge sanchez-Guerrero[3], Bevra H. Hahn[4], Alana B. Levine[2], Galina Marder[5], W. Joseph McCune[6] and Ellen M. Ginzler[7]. [1]University of California, San Francisco, San Francisco, CA, [2]Hospital for Special Surgery, New York, NY, [3]Mount Sinai Hospital and University Health Network, Toronto Canada, Toronto, ON, [4]UCLA David Geffen School of Medicine, Los Angeles, CA, [5]North Shore Long Island Health System, Great Neck, NY, [6]University of Michigan, Ann Arbor, MI, [7]SUNY-Downstate Medical Center, Brooklyn, NY.

Background/Purpose: Much of the published experience with belimumab in lupus patients has derived from clinical trials. We examined the non-sponsored experience with belimumab in routine clinical practice among 15 U.S. lupus centers participating in a national patient registry, the Lupus Clinical Trials Consortium, Inc. (LCTC).

Methods: The LCTC registry consists of consecutively enrolled adults with SLE from U.S. centers, each contributing approximately 100 patients. Patients who received at least one belimumab infusion after enrollment in the registry between March 2011, the date of FDA approval, and April 2013 were analyzed. We investigated clinical characteristics, indications for belimumab, and reasons for discontinuation. We calculated changes in SELENA-SLEDAI, physician global assessment, glucocorticoid dose, and serological parameters between baseline and follow-up at 6 months and 1 year for those maintained on the drug.

Results: Among 1189 patients followed for 27,469 months (mean 23.2 months), 68 patients started belimumab (5.7%). Mean treatment duration was 13.2 months (SD 6.7). Three centers started no patients on the drug, and the remaining started between 1–5 patients. In the 68 treated patients, mean age was 39.1 years (SD 12), 94% were female, 41% Caucasian, 47% Black and 12% Hispanic. Mean disease duration was 10.7 years (SD 8). Mean SELENA-SLEDAI at drug initiation was 4.4 (SD 4.3, range 0–22). 30 patients (44%) had a positive dsDNA upon starting belimumab and 15 (22%) had low complements. The mean physician global assessment was 1.4 on a scale of 0–3 (SD 0.7). 56 patients (82%) were on glucocorticoids, with a mean prednisone dose of 14.6 mg (SD 23). 27% received azathioprine, 31% mycophenolate mofetil, 15% methotrexate, and 75% an anti-malarial. The most common reasons for belimumab initiation were arthritis (52%), mucocutaneous disease (19%), and serositis (8%). 12 patients received the drug solely for maintenance, and 4 solely for steroid-sparing. After 898 person-months of follow-up, 18 patients discontinued belimumab (4 for adverse events/intolerability, 3 lack of efficacy, 3 no longer needed it, 3 patient preference, and 1 for insurance reasons). Response at 6 months and 1 year for those maintained on belimumab is shown in the Table.

Table. Serological and lupus progression characteristics at treatment initiation, 6 months, and 12 months following belimumab administration among 68 patients.

	Belimumab initiation	Six month follow-up	One year follow-up
N	**68**	**58**	**44**
Mean SELENA-SLEDAI (N)	**68**	**58**	**44**
Mean ± SD	4.40±4.32	3.09±3.41*	2.30±2.79**
Mean physician global assessment (N)	**62**	**51**	**37**
Mean ± SD	1.35±0.67	0.91±0.71*	0.78±0.72**
Prednisone equivalent dose (N)	**55**	**45**	**33**
Mean ± SD	17.8±23.7	14.4±15.6	16.0±27.9
C3 (N)**	**64**	**54**	**40**
Mean ± SD	22.8±28.5	23.7±32.2	31.5±42.2*
Low (%)	60 (93.8)	49 (90.7)	34 (94.4)
Returned to normal from prior 6 months	–	2/47 (4.3)	2/36 (5.6)
C4 (N)**	**63**	**54**	**41**
Mean ± SD	7.1±9.2	7.6±11.5	9.1±13.8
Low (%)	51 (81.0)	45 (83.3)	32 (94.1)
Returned to normal from prior 6 months	–	1/39 (2.6)	2/34 (5.9)
Anti ds-DNA (N)**	**62**	**41**	**26**
Positive (%)	30 (48.4)	22 (53.7)	13 (50.0)
Became negative from last follow-up (%)	–	1/20 (5.0)	1/12 (8.3)

P values are two-tailed and represent results of paired t-tests.
* $p < 0.05$, ** $p < 0.01$,
**C3, C4, and anti-dsDNA results reflect available data collected +/−3 months of each time point examined.
Note: Because the components of the British Isles Lupus Assessment Group Index (BILAG) was not collected, the BILAG it is not presented here and the SLE responder Index or SRI could not be calculated

Conclusion: Since the approval of belimumab, 5.7% of patients enrolled in the LCTC registry have received the drug in routine clinical practice. Utilization was similar across centers; the primary indications were arthritis and mucocutaneous disease. After 6 and 12 months, there were statistically significant improvements in SELENA- SLEDAI and physician global assessment. There was no statistically significant steroid-sparing effect. 65% of patients remained on belimumab by one year.

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1606

Overview Of The Safety Of Epratuzumab In Systemic Lupus Erythematosus. Daniel J. Wallace[1], Josep Ordi-Ros[2], C. Michael Neuwelt[3], Kenneth Kalunian[4], Michelle A. Petri[5], Slawomir Jeka[6], Ronald F. van Vollenhoven[7], Brian Kilgallen[8], Sabine Bongardt[9], Caroline Gordon[10] and Vibeke Strand[11]. [1]Cedars-Sinai Medical Center, Los Angeles, CA, [2]Vall De Hebron General Hospt, Barcelona, Spain, [3]East Bay Rheumatology Research Institute, San Leandro, CA, [4]UCSD School of Medicine, La Jolla, CA, [5]Johns Hopkins University School of Medicine, Baltimore, MD, [6]2nd University Hospital in Bydgoszcz Medical College of Nicolaus Copernicus University, Bydgoszcz, Poland, [7]The Karolinska Institute, Stockholm, Sweden, [8]UCB Pharma, Raleigh, NC, [9]UCB Pharma, Brussels, Belgium, [10]University of Birmingham, Birmingham, United Kingdom, [11]Stanford University, Palo Alto, CA.

Background/Purpose: The efficacy and safety of epratuzumab, a monoclonal antibody targeting CD22, has been evaluated in patients with moderate-to-severe systemic lupus erythematosus (SLE). A pooled analysis of epratuzumab adverse event (AE) data from open-label extension (OLE) studies in SLE is provided.

Methods: AE data were pooled from 2 completed OLE pilot studies (015 and SL0002 [NCT00113971]), and 4 completed and on-going long-term OLE studies (SL0006 [NCT00383513], EMBLEM™ OLE [NCT00660881],

SL0012 [NCT01408576] and SL0027 [NCT01534403]. Data are presented for epratuzumab at a total monthly dose of 2400 mg (dose used in Phase III studies). These analyses are presented as event rates (AEs/100 patient-years [pt-yrs]) and as the proportion of pts experiencing each AE. Malignancies classified as serious AEs are reported.

Results: As of 15 April 2013 in OLE studies, 488 pts with moderate-to-severe SLE had received a total of 726 pt-yrs of exposure to epratuzumab. The overall rate of AEs, serious AEs (SAEs) and infusion reactions per 100 pt-years was 457.6, 21.1 and 23.1 respectively (Table). 40 patients (8.2%) withdrew due to AEs. The most common AEs (≥10% incidence for all epratuzumab dose group) were upper respiratory tract infection (17.0%), urinary tract infection (13.9%) and headache (12.3%). The most common SAEs (≥3 pts) were worsening of SLE (1.8%), cholelithiasis (0.6%), pneumonia (0.6%), sepsis (0.6%), depression (0.6%) and dyspnea (0.6%). The most common serious infections were pneumonia and sepsis (0.6 and 0.4 per 100 pt-yrs respectively). Malignancies were reported in 3 pts; 1 CNS lymphoma, 1 squamous cell CA and 1 patient experienced basal cell CA, breast CA and lip neoplasm. There were 6 deaths; 5 with known causes: bilateral lobal pneumonia, pneumonia/septic shock/acute respiratory failure, chronic heart failure, polydrug overdose, stroke. In 1 case cause was unknown.

Table. Overall summary of AEs with epratuzumab in OLE studies

	Epratuzumab (total monthly dose of 2400 mg) n=488
Total treatment exposure, pt-years	726.0
Any AE, rate per 100 pt-years	457.6
Any AE, n (%)	322 (66.0)
AE leading to discontinuation, n (%)	40 (8.2)
SAEs, rate per 100 pt-years	21.1
SAE, n (%)	91 (18.6)
Serious infectious events, rate per 100 pt-years	4.0
Serious infectious events, n (%)	24 (4.9)
Infusion reactions, rate per 100 pt-years	23.1
Infusion reactions, n (%)	53 (10.0)

Conclusion: Epratuzumab at a total monthly dose of 2400 mg was well tolerated. These data, based on >700 pt-years of exposure, support the ongoing development of epratuzumab for treatment of SLE.

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1607

Two Year Follow-Up On Biologics Use In 13 Centers- Data From The International Registry For Biologics In Systemic Lupus Erythematosus. Ronald F. van Vollenhoven[1], Melinda Mild[2], Søren Jacobsen[3], S. Bernatsky[4], Daniel J. Wallace[5], Sang-Cheol Bae[6], Manuel Ramos-Casals[7], Francisco J. García-Hernández[8], R. Ramsey-Goldman[9], Andrea Doria[10], Marta Mosca[11], Michelle A. Petri[12], M Ayala-Gutiérrez[13], J.G. Hanley[14] and for The SLICC group[15]. [1]Unit for Clinical Therapy Research, Inflammatory Diseases (CliniTRID), the Karolinska Institute, Stockholm, Sweden, [2]Karolinska Institutet, Stockholm, Sweden, [3]Department of Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [4]McGill UHC/RVH, Montreal, QC, [5]Cedars-Sinai Medical Center, Los Angeles, CA, [6]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [7]Hospital Clínic, Barcelona, Spain, [8]Hospital Virgen del Rocío, Sevilla, Spain, [9]Northwestern University Feinberg School of Medicine, Chicago, IL, [10]University of Padova, Padova, Italy, [11]Rheumatology Unit, University of Pisa, Pisa, Italy, [12]Johns Hopkins University School of Medicine, Baltimore, MD, [13]Hospital Carlos Haya, Malaga, Spain, [14]Division of Rheumatology, Halifax, NS, [15]Department of Medicine, the Karolinska Institute, Stockholm, Sweden.

Background/Purpose: Only one biologic agent has been approved for use in SLE, but some are used off-label in various settings. To obtain systematic information regarding this, members of the SLICC group initiated the International Registry for Biologics in SLE (IRBIS). The entire registry contains data from 28 centers. Here, data are presented from 13 centers for which two-year follow-up was available on patients for whom a biologic was initiated in 2010–2011. The purpose with this study was to analyse the use of biologics in SLE, and assess the results achieved over the first two years after initiation.

Methods: IRBIS investigators provided retrospective data on all patients treated with a biologic for SLE at their center in 2010–2011. Standardized case report forms were used to collect demographic, disease-specific and treatment data at the time of biologic initiation and at yearly follow-ups.

Results: In the entire cohort, 455 patients were treated with rituximab (84%), belimumab (10%), epratuzumab (5%), and anti-tumor necrosis factor agents (abatacept, etanercept and adalimumab, each <1%). The major organ manifestations leading to biologic treatment were lupus nephritis (LN, 44%), hematological (17%), musculoskeletal (16%), skin disease (10%), CNS (4%) and other (9%). Reasons for choosing the biologic were disease-control (73%), steroid-sparing (5%) or both (23%). At biologic initiation mean disease duration (±SD) was 9.5±7.9 years, and mean age was 42.2±12.5. Most patients (91%) were female. Prior to biologic treatment, most patients (91%) had been treated with one or more immunosuppressives (ISs). Just over half (57%) had used 1–2 ISs, 21% had used three, and 13% had used 4–6 ISs.

At two-year follow-up (n=120), SLE disease activity (SLEDAI) and corticosteroid (CS) dose were significantly lower versus baseline (SLEDAI: 9.4±5.3 to 3.1±2.5; CS dose: 10.7±13.9 to 4.8±5.9 mg; mean±SD paired analyses, p<0.0001 for both comparisons). SLICC damage-index remained unchanged.

At baseline, concomitant CS was used in 91% of patients compared to 61% at follow-up. There were six deaths, none attributed to the biologic. In almost half of patients (48%) there was at least one adverse event reported over the indicated follow-up period, of which 5% were attributed to the biologic agent. Serious adverse events included 6 infections, 4 opportunistic infections, posterior reversible encephalopathy syndrome (3), allergic reactions (4).

Conclusion: Rituximab was the biologic used most commonly in this international cohort of patients who were started on biologics in 2010–2011. Biologics were used for a range of SLE manifestations. At two-year follow-up both lupus activity and concomitant corticosteroid dosage had decreased significantly and corticosteroids had been discontinued in 30% of patients.

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1608

A Phase I Single-Dose Crossover Study To Evaluate The Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Clinical Efficacy Of AMG 811 (anti-IFN-gamma) In Subjects With Discoid Lupus Erythematosus. Victoria P. Werth[1], David Fiorentino[2], Stanley B. Cohen[3], David Fivenson[4], Chris Hansen[5], Steve Zoog[6], Greg Arnold[6], Christine Wang[6], Michael Boedigheimer[6], Andrew Welcher[6], James Chung[6], Barbara Sullivan[6] and David A. Martin[7]. [1]Philadelphia Veterans Affairs Medical Center, Philadelphia, PA, [2]Stanford University School of Medicine, Redwood City, CA, [3]Metroplex Clinical Research Center, Dallas, TX, [4]David Fivenson, MD, Dermatology, PLLC, Ann Arbor, MI, [5]University of Utah School of Medicine, Salt Lake City, UT, [6]Amgen, Thousand Oaks, CA, [7]Amgen, Seattle, WA.

Background/Purpose: Discoid Lupus Erythematosus (DLE) is the most common form of chronic cutaneous LE (CCLE) and develops in up to a quarter of SLE patients. DLE inflammation typically involves hair follicles and the epidermis leading to scaring, atrophy, telangiectasias and/or dyspigmentation. Patients with DLE have an IFN signature in the blood and the skin, and the level of gene expression correlates with cutaneous disease activity. Skin biopsies of DLE lesions show elevated mRNA levels of interferon gamma and provide rationale for a therapeutic trial of AMG 811, a human IgG1 monoclonal antibody that selectively neutralizes human IFN-g.

Methods: This multi-center, randomized, double-blind, placebo-controlled, two-period, crossover study in which 16 subjects with DLE received AMG 811 and placebo in one of two sequences [ie, AMG 811 followed by placebo (n=9) on day 85 or placebo followed by AMG 811 on day 85 (n=7)]. The primary objectives were to evaluate the safety, tolerability and immunogenicity of a single subcutaneous (SC) dose of AMG 811. Secondary objectives focused on the single-dose pharmacokinetic (PK) profile of AMG 811 and changes from baseline in the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) score following a single SC dose of either AMG 811 or placebo. Adverse events, safety laboratory tests and disease activity were assessed. Serum AMG 811 concentrations were measured by ELISA, and anti-AMG 811 antibodies were measured by an immunoassay. Skin biopsies were obtained from lesional and non-lesional areas pre-dose and from lesional areas on day 15 and 57. T cell and macrophage infiltrate in the skin was quantitated by laser scanning cytometry. Whole blood and skin RNA and serum proteins were analyzed by microarray and ELISA, respectively.

Results: During the study all but one DLE subject (9/9 AMG 811 and 6/7 placebo) experienced treatment-emergent adverse events. AMG 811 displayed linear pharmacokinetics and no immunogenicity to AMG 811 was observed. Changes in the CLASI scores were similar between subjects that received AMG 811 and placebo over the first 85 days, and there was no beneficial effect on disease activity seen in placebo subjects receiving AMG 811 on day 85. IFN-g modulated genes were elevated in both blood and lesional skin, indicating the presence of an interferon signature. In blood AMG 811 led to a dose dependent modulation of the expression of genes previously shown to be modulated by AMG 811 in subjects with SLE. Histopathology and RNA transcript analysis revealed substantial intra- and inter-subject heterogeneity between skin biopsies from DLE subjects at baseline and following AMG 811 treatment. The number of CD3+ T cells and CD68+ macrophages were elevated in the lesional skin compared to non-lesional and there was no apparent reduction following AMG 811.

Conclusion: AMG 811 demonstrated acceptable safety and favorable PK profiles in this single dose study of DLE subjects but there was no apparent clinical benefit. Evidence of a pharmacodynamic effect in the blood (e.g. inhibition of IFN-g) was apparent; however, heterogeneity in skin samples prevented definitive conclusions about the effects of AMG 811 in diseased skin.

Disclosure: V. P. Werth, Medimmune, 9; **D. Fiorentino**, None; **S. B. Cohen**, Abbott, Amgen, Astellas, BMS, Merck, Lilly, Pfizer, UCB, 5; **D. Fivenson**, None; **C. Hansen**, None; **S. Zoog**, Amgen, 3; **G. Arnold**, Amgen, 3; **C. Wang**, Amgen, 3; **M. Boedigheimer**, Amgen, 3; **A. Welcher**, Amgen, 3; **J. Chung**, Amgen, 1, Amgen, 3; **B. Sullivan**, Amgen, 3; **D. A. Martin**, Amgen, 3.

1609

AMG 811 (anti-IFN-gamma) Treatment Leads To a Reduction In The Whole Blood IFN-Signature and Serum CXCL10 In Subjects With Systemic Lupus Erythematosus: Results Of Two Phase I Studies. David A. Martin[1], Andrew Welcher[2], Michael Boedigheimer[2], Zahir Amoura[3], Alan Kivitz[4], Jill P. Buyon[5], Jorge Sanchez-Guerrero[6], Juanita Romero-Diaz[7], Alla Rudinskaya[8], Kevin M. Latinis[9], S Cohen[10], Cynthia Aranow[11], Mike Damore[2], Winnie Sohn[2], Kit Chiu[2], Christine Wang[2], Naren Chirmule[2], Barbara Sullivan[2] and James Chung[2]. [1]Amgen, Seattle, WA, [2]Amgen, Thousand Oaks, CA, [3]CHU Pitié-Salpêtrière, Paris, France, [4]Altoona Center for Clinical Research, Duncansville, PA, [5]NYU School of Medicine, New York, NY, [6]Mount Sinai Hospital, University Health Network, Toronto, ON, [7]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [8]Danbury Hospital, Danbury, CT, [9]Latinis Rheumatology, Leawood, KS, [10]Metroplex Clinical Research Center, Dallas, TX, [11]The Feinstein Institute, Manhasset, NY.

Background/Purpose: Interferon-gamma (IFN-g) is a major pro-inflammatory cytokine that modulates the function of several important populations of immune cells including B cells, T cells, and macrophages. Several lines of evidence from animal models and in humans suggest increased levels of Type I and/or Type II IFN are associated with inflammatory disorders including systemic lupus erythematosus (SLE). Although some information is available on the effect of blocking Type I IFNs from human trials in SLE, little is known about the role of Type II. AMG 811 is a human IgG1 monoclonal antibody that selectively targets and neutralizes human IFN- g. The safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and multiple dose administration of AMG 811 was assessed in SLE subjects. The studies were not powered to assess efficacy.

Methods: Mild, stable SLE subjects were administered AMG 811 or placebo in single (SD) (n=26) or multiple doses (MD) (n=28) ranging from 2 mg to 180 mg SC or 60 mg IV. Adverse events, laboratory tests and disease activity were assessed. Serum AMG 811 concentrations were measured using an enzyme-linked immunosorbent assay, and anti-AMG 811 antibodies were measured using an immunoassay. Whole blood immunophenotyping parameters were measured by flow cytometry. Whole blood RNA and serum proteins were analyzed pre- and post-dosing by microarray and ELISA, respectively.

Results: In the SD cohorts there were no withdrawals due to adverse events and few adverse events were reported by more than a single subject receiving either AMG 811 or placebo. In the MD cohorts the number of subjects reporting treatment emergent adverse events was similar between placebo (7/8) and AMG 811 (18/20). AMG 811 displayed linear pharmacokinetics and properties consistent with a typical IgG1 antibody. Immunogenicity to AMG 811 was low in both SD (1/18) and MD (none observed) cohorts. There were no detectable changes in expression of MHC I or II on circulating immune cells following AMG 811 treatment. AMG 811 led to a dose dependent and reversible modulation of the expression of many genes associated with IFN-g signaling and that are differentially expressed in lupus patients. The list of impacted genes and the magnitude of modulation following AMG 811 treatment in SLE subjects suggests that the lupus 'interferon signature' is not solely derived from Type 1 IFNs. Levels of several serum proteins were elevated at baseline relative to healthy individuals, including CXCL10 (IP-10), which has been associated with increased disease activity and to correlate with future SLE flare. Treatment with AMG 811 led to dose-related and reversible reduction in CXCL10 in both single- and multiple-dose settings.

Conclusion: AMG 811 demonstrated acceptable safety and favorable PK profiles in single and multiple dose studies in mild SLE subjects. AMG 811 administration impacted IFN-associated gene expression. AMG 811 reduced serum CXCL10 levels in a dose and concentration dependent manner. No impact of AMG 811 on disease activity was observed in these mild, stable SLE patients. These data support further evaluation of AMG 811 as a therapeutic for SLE, including subjects with active lupus nephritis.

Disclosure: D. A. Martin, Amgen, 3; **A. Welcher**, Amgen, 3; **M. Boedigheimer**, Amgen, 3; **Z. Amoura**, None; **A. Kivitz**, AbbVie, Amgen, AstraZeneca, BMS, Celgene, Genentech, Janssen, Pfizer, UCB, 2, BMS, Genentech, UCB, 5, BMS, 8; **J. P. Buyon**, None; **J. Sanchez-Guerrero**, GlaxoSmithKline, 5, Bristol-Myers Squibb, 5, Genentech and Biogen IDEC Inc., 5; **J. Romero-Diaz**, None; **A. Rudinskaya**, None; **K. M. Latinis**, Human Genome Sciences, Inc., 8, Genentech and Biogen IDEC Inc., 8, GlaxoSmithKline, 8; **S. Cohen**, Amgen, Biogen Idec, Bristol-Myers Squibb, Centocor, Genentech, Johnson Johnson, Pfizer, Merck, Roche, 2; **C. Aranow**, GlaxoSmithKline, 2, Amgen, 5, Bristol-Myers Squibb, 5, Human Genome Sciences, Inc., 2, GlaxoSmith-Kline, 5, Pfizer Inc, 2, Eli Lilly and Company, 2, UCB, 2, Dynavax, 2, Genentech and Biogen IDEC Inc., 2; **M. Damore**, Amgen, 3; **W. Sohn**, Amgen, 3; **K. Chiu**, Amgen, 3; **C. Wang**, Amgen, 3; **N. Chirmule**, Amgen, 3; **B. Sullivan**, Amgen, 3; **J. Chung**, Amgen, 1, Amgen, 3.

1610

Lymphoablation Including B Cell Depletion and Autologous Hematopoietic Stem Cell Transplantation Leads To Long Remissions In Treatment-Resistant Systemic Lupus Erythematosus Patients. Sarfaraz A. Hasni[1], Gabor G. Illei[2], Nikolay P. Nikolov[3], Francis Hakim[4], Susan Leitman[4], James E. Balow[5], Howard A. Austin[6], Juan Gea-Banacloche[4], Unsong Oh[7], Paulo Muraro[8], Claude Sportes[9], Peter E. Lipsky[10], Ronald Gress[9], Steve Pavletic[9] and Amrie Grammer[10]. [1]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [2]NIDCR/NIH, Bethesda, MD, [3]NIDCR, NIH, Bethesda, MD, [4]NCI, NIH, Bethesda, MD, [5]National Institutes of Health, Bethesda, MD, [6]NIDDK/NIH, Bethesda, MD, [7]NINDS, NIH, Bethesda, MD, [8]NINDS/NIH, Bethesda, MD, [9]NCI/NIH, Bethesda, MD, [10]NIAMS/NIH, Bethesda, MD.

Background/Purpose: Over the past two decades, approximately 200 patients with severe systemic lupus erythematosus(SLE) have received autologous hematopoietic stem cell transplants (autoHSCT). More than half of these patients achieved clinical remission, but the duration of clinical benefit is variable and not well defined. We report long term clinical outcomes of eight refractory SLE patients in whom B cell depletion was combined with a reduced intensity T cell lymphoablative conditioning regimen before autoHSCT.

Methods: Eight patients were enrolled with active SLE despite prior treatment with IV cyclophosphamide (CYC): 2 had transverse myelitis, 1 retinal vasculitis and 5 WHO Class IV nephritis. Stem cell mobilization consisted of 2,000 mg/m^2 CYC, 750 mg/m^2 rituximab (RTX) and G-CSF.

The conditioning regimen consisting of 750 mg/m^2 RTX, 4.8 g/m^2 CYC and 120 mg/m^2 fludarabine was followed by CD34+ selected stem cell infusion and G-CSF.

All immunosuppressive medications and hydroxychloroquine were discontinued at the start of mobilization and steroids were rapidly tapered off after the transplant. Clinical response was evaluated by organ specific response criteria. Disease activity indices (SLEDAI and SLAM) were used to assess overall lupus activity. The primary endpoint was complete response (CR) at 24 months defined as no lupus activity and no treatment for lupus (including HCQ and steroids).

Immune depletion and reconstitution was followed by multiparameter flow cytometry.

Results: Of the 8 patients, there were 2 early infectious deaths (one from diffuse alveolar damage associated with coronavirus infection, one from mycobacterial meningoencephalitis) at 6 and 5 months post autoHSCT, respectively in subjects with no signs of active SLE. Four patients have had no disease activity in the 7 years of follow up and continue to have SLEDAI of 0 since 3 months after auto-HSCT. Two patients had lupus flares (at 6 and 18 months post-HSCT) which was subsequently well controlled requiring only modest doses of immunosuppressive medications (one on prednisone <10 mg/day and one on daily azathioprine). Six patients had no evidence of serological disease activity post autoHSCT, whereas one early response patient and one patient who flared at 6 months continued to have positive ANA and anti-SSA antibody with negative anti-ds-DNA antibody.

In responding patients, autoHSCT resulted in a loss of memory B cells and plasma B cells and recovery of naïve T and B cell populations in the first year after transplant. Notably, in contrast, the patient who flared at 6 months had an early reappearance of circulating plasma cells that preceded the flare.

Conclusion: The novel regimen that included B cell depletion, modified immunoablation and autoHSCT resulted in sustained medication free remission in one half of the refractory SLE patients and a marked reduction in disease activity in another quarter. There were 2 (25%) deaths from infection, although these patients had no evidence of active SLE at the time of death. Whereas long term remission of SLE activity appears possible with this approach, additional studies are required to assess risk: benefit ratio and the appropriate patient population to treat.

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1611

Off-Label Use Of Rituximab For Systemic Lupus Erythematosus in Europe: Limited Use Mostly In Refractory Patients. Ronald F. van Vollenhoven[1], Melinda Mild[2], Andrea Doria[3], T. Dörner[4], Gianfranco Ferraccioli[5], Frederic Houssiau[6], T.W.J. Huizinga[7], David A. Isenberg[8], László Kovács[9], Guillermo Ruiz-Irastorza[10], Danilo Squatrito[11], Alexandre Voskuyl[12], Marta Mosca[13], G D Sebastiani[14], Murat Inanç[15], Gabriella Szücs[16], Søren Jacobsen[17], A. Castro[18] and for The IRBIS-EMA group[19]. [1]Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), the Karolinska Institute, Stockholm, Sweden, [2]Karolinska Institutet, Stockholm, Sweden, [3]University of Padova, Padova, Italy, [4]Charité University Medicine Berlin, Berlin, Germany, [5]Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy, [6]Université catholique de Louvain, Brussels, Belgium, [7]Leiden University Medical Center, Leiden, Netherlands, [8]University College London, London, United Kingdom, [9]University of Szeged, Szeged, Hungary, [10]Hospital de Cruces, UPV/EHU, Barakaldo, Spain, Bizkaia, Spain, [11]Careggi Hospital- Florence, Florence, Italy, [12]VU University Medical Center, Amsterdam, Netherlands, [13]Rheumatology Unit, University of Pisa, Pisa, Italy, [14]Rheumatology Unit, San Camillo-Forlanini Hospital, Rome, Rome, Italy, [15]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [16]University of Debrecen Medical and Health Sciences Center, Debrecen, Hungary, [17]Department of Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [18]Hospital Universitari de Reus, Spain, Reus, Spain, [19]ClinTRID, Department of Medicine, Karolinska Institute, Stockholm, Sweden.

Background/Purpose: Rituximab (Rituxan, Mabthera; RTX) has not been approved for use in SLE, but uncontrolled observations have suggested efficacy in some patients and the medication can be used off-label in many European countries. We previously reported that based on data from the IRBIS registry and additional data from investigators, between 0.5 and 1.3% of European patients with SLE have been treated, off-label, with RTX. The objective for this study was to compare characteristics of SLE patients treated off-label with RTX to those of SLE patients treated with conventional, non-biological immunosuppressives (ISs) at the same specialty centers.

Methods: Investigators participating in the International Registry for Biologics in SLE (IRBIS), which was initiated by the SLICC group, provided the data for this study. Data previously submitted to the IRBIS registry by 28 centers in 11 European countries were complemented with additional clinical information from the participating sites. Comparator patients had been started on any conventional IS but were not necessarily naïve for this.

Results: 175 patients were analyzed; 103 were treated off-label with RTX and 72 with a conventional IS. The most frequently used ISs were mycophenolate mofetil (43%) and azathioprine (33%). For both groups, about 90% were female, 90% were Caucasians and 85% were non-smokers. Organ manifestations leading to treatment with RTX were lupus nephritis in 58%, hematological lupus in 16%, musculoskeletal manifestations in 11%, skin disease in 6%, CNS lupus in 7%, and other manifestations in 7%. For patients started on conventional ISs the corresponding percentages were 53%, 11%, 22%, 6%, 7%, and 6%. These distributions were not statistically different. Reason for treatment initiation with RTX was mainly disease control while steroid sparing was frequently the main reason for conventional ISs. At treatment initiation mean disease duration ($\pm$SD) was 9.1$\pm$7.0 for RTX-treated patients and 4.1$\pm$6.6 for patients on ISs ($p<0.0001$) and mean ages were 41.2$\pm$12.5 and 36.1$\pm$11.3, respectively ($p=0.007$). There were significant differences between the groups for SLEDAI scores (12.2$\pm$7.0 vs. 9.4$\pm$7.0; $p=0.001$) and SLICC damage index (1.6$\pm$3.4 vs. 0.57$\pm$1.0, $p=0.014$).

Conclusion: Both RTX and conventional ISs are mostly used for lupus nephritis, and no other specific organ manifestation was more likely to be treated with RTX. However, patients started on RTX were somewhat older, had significantly longer disease duration, higher disease activity and more damage compared to patients started on conventional ISs only. These data support the view that RTX is used for selected patients with later-stage, more severe SLE.

Disclosure: R. F. van Vollenhoven, AbbVie, BMS, GSK, Merck, Pfizer, Roche, UCB, 2, AbbVie, AstraZeneca, Biotest, BMS, GSK, Lilly, Merck, Pfizer, Roche, UCB, Vertex, 5; **M. Mild**, None; **A. Doria**, None; **T. Dörner**, None; **G. Ferraccioli**, None; **F. Houssiau**, UCB Pharma, 2, UCB Pharma, 5; **T. W. J. Huizinga**, TWJ Huizinga has received lecture fees/consultancy fees from Merck, UCB, Bristol Myers Squibb, Biotest AG, Pfizer, Novartis, Roche, Sanofi-Aventis, Abbott, Crescendo Bioscience, Nycomed, Boeringher, Takeda, and Eli Lilly, 5; **D. A. Isenberg**, I have consulted for a number of companiews including GSK, Roche, UCB and teva. I arrange for the payments offered to go a local arthritis charity., 5; **L. Kovács**, None; **G. Ruiz-Irastorza**, None; **D. Squatrito**, None; **A. Voskuyl**, None; **M. Mosca**, None; **G. D. Sebastiani**, None; **M. Inanç**, None; **G. Szücs**, None; **S. Jacobsen**, None; **A. Castro**, None; **F. T. IRBIS-EMA group**, None.

1612

Rituximab For Treatment Of Refractory Auto-Immune Hepatitis. Chadi Rakieh, Edward M. Vital, Paul Emery and Michael Martin. Division of Rheumatic and Musculoskeletal Disease, Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, LTHT, Leeds, United Kingdom, Leeds, United Kingdom.

Background/Purpose: Auto-immune hepatitis (AIH), also known as lupoid hepatitis, is a chronic progressive disease of unknown aetiology. First-line therapy consists of corticosteroids alone or in combination with azathioprine. Cyclophosphamide, mycophenolate mofetil (MMF), and tacrolimus have also been used but some patients do not respond or experience toxicity. Rituximab is effective in other connective tissue diseases. The aim of this study was to evaluate the efficacy and safety of rituximab in patients with refractory AIH.

Methods: We conducted a prospective open-label single centre trial in patients with seropositive biopsy-proven AIH resistant to conventional therapy including high dose corticosteroids and multiple immunosuppressants. Two infusions of rituximab 1000 mg two weeks apart were given, each preceded by 100mg methylprednisolone. Response was assessed at month 3 using biochemical parameters including alanine transaminase (ALT), bilirubin, and immunoglobulin G (IgG). B cell subsets were enumerated using highly sensitive flow cytometry with a lower limit of detection. Repeat cycles were given if the disease flared up with rising liver enzymes.

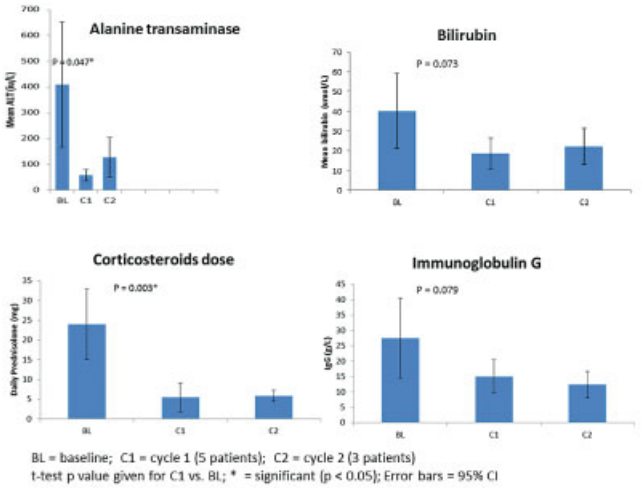
Results: Between November 2007 and January 2013, 5 patients (3 females) with refractory AIH were treated with rituximab. Mean age was 25 years. Median follow-up duration was 26 months. All patients were positive for antinuclear antibody (ANA), 3 for anti-smooth muscle antibody (SMA), and 3 for anti-double stranded DNA. All of the patients achieved good response with marked improvements in clinical symptoms and laboratory

abnormalities. Significant reductions were observed in the mean values of ALT and daily prednisolone dose after cycle 1 with trends to improvement in other parameters. Three patients to date required another cycle of rituximab after 18, 20, and 60 months and maintained good response. All patients exhibited B cell depletion by conventional flow cytometry (0.01×10^9 cells/L), although complete B-cell depletion ($<0.0001 \times 10^9$cells/L) was seen in just 3 of the 8 cycles given; this did not appear to impact on the therapeutic outcome. One serious adverse event possibly related to treatment was observed; a patient, who had previously suffered from inflammatory bowel disease, developed a large bowel perforation six weeks after starting rituximab and stopping tacrolimus.

Biochemical outcomes and prednisolone dose before and after rituximab

Outcomes Means (SD)	Baseline N = 5	Cycle 1: month 3 N = 5	t-test p value vs. baseline	Cycle 2: month 1 N = 3
ALT (iu/L)	409 (273)	53 (23)	0.047*	128 (95)
Bilirubin (μmol/L)	40 (21)	18.6 (9)	0.073	22.6 (13)
IgG (g/L)	28 (13)	15 (5.4)	0.079	12.4 (2.5)
Albumin (g/L)	35.2 (8)	39.8 (4.4)	0.294	40 (1.7)
Prednisolone (mg/day)	24 (8.9)	5.5 (3.7)	0.003*	5.8 (1.5)
CRP (mg/L)	15.8 (18)	4 (5.5)	0.200	6.6 (11.5)

SD = standard deviation; ALT = alanine transaminase; CRP = C-reactive protein; IgG = immunoglobulin G; * = si?????????



BL = baseline; C1 = cycle 1 (5 patients); C2 = cycle 2 (3 patients)
t-test p value given for C1 vs. BL; * = significant (p < 0.05); Error bars = 95% CI

Disclosure: C. Rakieh, None; **E. M. Vital**, None; **P. Emery**, None; **M. Martin**, None.

1613

Anti-Malarial Drugs (hydroxychloroquine and quinacrine) Decrease The Production Of Interferon-Alfa Initiated By TLR-9 Agonist. Ou Jin[1], Xi Zhang[2], Qiuxia Li[3], Lingkai Fang[3], Hongyue Huang[3], Chengcheng Hou[3], Zetao Liao[4], Qiujing Wei[3], Zhiming Lin[1], Dongfang Lin[3] and Jieruo Gu[5]. [1]third affiliated hospital of Sun Yat-sen Universtiy, Guangzhou, China, [2]The Affiliated Third Hospital of Sun Yat-san University, Guangzhou, China, [3]The Affiliated Third Hospital of Sun Yat-san University, Rheumatology, Guangzhou, China, [4]THIRD AFFILIATED HOSPITAL OF SUN YAT-SEN UNIVERSIT, Guangzhou, China, [5]Third Affiliated Hospital of Sun Yat-sen University, GuangZhou, China.

Background/Purpose: Toll-like receptor 9 (TLR-9) plays an important role in initiating innate immunity. The recognition of self DNA fragments by TLR-9 may results in the production of interferon-α, a central cytokine in the pathogenesis of Systemic lupus erythematosus (SLE). Anti-malarial drugs such as hydroxychloroquine (HCQ) and quinacrine (Qn) are commonly used in the treatment of SLE. Some studies imply that anti-malarial drugs may influence TLR pathway, though detail mechanisms are still under study. In this study, we want to evaluate the influence of anti-malarial drugs (HCQ and Qn) on the initiation of IFN-α production through TLR-9 pathway, combinded with or without glucocorticoid.

Methods: Freshly isolated PBMCs of healthy donors were stimulated with the TLR-9 agonist CpG oligodeoxynucleotides (CpG-A ODN)-2216, then incubated with different kinds of anti-malarial drugs (HCQ and Qn or both) and/or different doses of glucocorticoid (hydrocortisone: 10^{-6}M (low dose), 10^{-5}M (median dose), 10^{-4}M (high dose), 10^{-3}M (pulse dose)). The changes in the expression of IFN-α were detected by real time PCR.

Results: (1). Hydroxychloroquine or quinacrine alone or combined together significantly inhibited the production of IFN-α initiated by ODN 2216 (Qn (p=0.047), HCQ (p=0.047), Qn and HCQ (p=0.046)). (2). When combined with low (10^{-6}M), median (10^{-5}M), or high (10^{-4}M) dose of hydrocortisone, HCQ or Qn or both significantly revised the elevation of IFN-α caused by ODN 2216 ((low dose: Qn (p=0.017), HCQ (p=0.017), Qn & HCQ (p=0.017), median dose: Qn (p=0.034), HCQ (p=0.032), Qn & HCQ (p=0.036), high dose: Qn (p=0.028), HCQ (p=0.024), Qn & HCQ (p=0.028)), which cannot be decreased by glucocorticoid (each p>0.05). (3). When combined with pulse dose (10^{-3}M) hydrocortisone which could promote the expression of IFN-α to some extent, anti-malarial drugs (HCQ, Qn alone or both) could not significantly down-regulate the expression of IFN-α stimulated by ODN 2216.

Conclusion: (1). Anti-malarial drugs hamper the production of IFN-α by TLR-9 recognition of nucleotides (ODN 2216), which is the critical cytokine in the pathogenesis of lupus. (2). The combination with anti-malarial drugs (HCQ, Qn alone or both) seem to be a good choice to help low, median, high dose glucocorticoid to achieve a better disease control by inhibiting IFN-α, which cannot be decreased by glucocorticoid. (3). When combined with pulse dose glucocorticoid, anti-malarial drugs (HCQ, Qn alone or both) could not down-regulate the expression of IFN-α stimulated by TLR-9 agonist.

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1614

Hydroxychloroquine Reverse The Elevation Of Interferon-Alfa Initiated By TLR-9 Agonist Which Irresponsive To Glucocorticoid. Ou Jin[1], Xi Zhang[2], Lingkai Fang[3], Qiuxia Li[3], Hongyue Huang[3], Zhiming Lin[1], Zetao Liao[4], Dongfang Lin[3], Chengcheng Hou[3] and Jieruo Gu[5]. [1]third affiliated hospital of Sun Yat-sen Universtiy, Guangzhou, China, [2]The Affiliated Third Hospital of Sun Yat-san University, Guangzhou, China, [3]The Affiliated Third Hospital of Sun Yat-san University, Rheumatology, Guangzhou, China, [4]THIRD AFFILIATED HOSPITAL OF SUN YAT-SEN UNIVERSIT, Guangzhou, China, [5]Third Affiliated Hospital of Sun Yat-sen University, GuangZhou, China.

Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by chronic stimulation of the innate immune system by endogenous nucleic acids through toll-like receptors (TLRs) pathway, which results in the elevation of interferon-alfa (IFN-α). Though glucocorticoid have been widely used to treat autoimmune diseases for their strong anti-inflammatory effects, a recent research has found that TLRs recognition of self nucleic acids hampers the effects of glucocorticoid in lupus. Hydroxychloroquine has been reported to block the TLRs. We want to evaluate whether hydroxychloroquine and/or glucocorticoid influence the production of IFN-α stimulated by TLR-9 agonist in human peripheral blood mononuclear cells (PBMCs). Moreover, we want to explore whether hydroxychloroquine influences the expression of signal proteins in the TLR-9 pathway.

Methods: Freshly isolated PBMCs of healthy donors were stimulated with the TLR-9 agonist, CpG oligodeoxynucleotides (CpG-A ODN)-2216, then treated with hydroxychloroquine and/or different doses of glucocorticoid (hydrocortisone: low dose (10^{-6}M), median dose (10^{-5}M), high dose (10^{-4}M), pulse dose (10^{-3}M)). The changes in the expression of IFN-α and signal proteins (TLR7, TLR9, MyD88, AP-1, IKK-α, NF-κB) in PBMCs were detected by real time PCR.

Results: (1) Hydroxychloroquine significantly reversed the elevation of IFN-α caused by ODN 2216 (p=0.005), and in low dose (p=0.017), median dose (p=0.01) and high dose (p<0.001) of glucocorticoid, while could not significantly down-regulate the expression of IFN-α stimulated by ODN 2216 in pulse dose of glucocorticoid (p=0.05). (2) Hydroxychloroquine had no effects on the expression of TLR7, TLR9, MyD88, AP-1, IKK-α and NF-κB in PBMCs stimulated by ODN 2216. (3) Pluse dose of glucocorticoid could increase the production of IFN-α stimulated by ODN 2216 to some extent. (4) Pluse dose of glucocorticoid could significantly elevate the expression of TLR9 (p=0.016), IKK-α (P=0.025) and NF-κB (P<0.001) in the TLR pathway.

Conclusion: (1) Hydroxychloroquine hampers the critical pathogenesis of SLE that the IFN-α expression elevates in PBMCs through TLR-9 recognition of nucleotides, which is irresponsive to glucocorticoid alone. This result suggests that combination with hydroxychloroquine may help glucocorticoid to achieve a better disease control. (2) Hydroxychloroquine does not significantly influence signal proteins (TLR7, TLR9 MyD88, AP-1, IKK-α and NF-κB) in the TLR pathway, which implies its weak influence in innate immunity. (3) The side-effects of pluse dose glucocorticoid in the elevation of IFN-α may related to the elevated expression of TLR9, IKK-α and NF-κB in PBMCs stimulated by ODN 2216.

Disclosure: O. Jin, None; **X. Zhang**, None; **L. Fang**, None; **Q. Li**, None; **H. Huang**, None; **Z. Lin**, None; **Z. Liao**, None; **D. Lin**, None; **C. Hou**, None; **J. Gu**, None.

ACR/ARHP Poster Session B
Systemic Lupus Erythematosus - Human Etiology and Pathogenesis: Genetics and Genomics
Monday, October 28, 2013, 8:30 AM–4:00 PM

1615

Type I Interferons As a Serum Biomarker Of Subclinical Atherosclerosis In Pediatric Systemic Lupus Erythematosus Patients.
Smriti Mohan[1], Julie Barsalou[2], Timothy J. Bradley[2], Cameron Slorach[2], Lawrence Ng[3], Deborah M. Levy[4], Earl D. Silverman[2] and Mariana J. Kaplan[5]. [1]University of Michigan, Ann Arbor, MI, [2]The Hospital for Sick Children, University of Toronto, Toronto, ON, [3]The Hospital for Sick Children, Toronto, ON, [4]The Hospital for Sick Children and University of Toronto, Toronto, ON, [5]University of Michigan Rheumatology, Ann Arbor, MI.

Background/Purpose: Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disorder with a marked increase in cardiovascular (CV) morbidity and mortality due to premature atherosclerosis, distinct from what is predicted by the Framingham risk equation alone. This risk may be increased in pediatric-onset SLE (pSLE) due to the younger age of disease onset, greater disease severity, and longer disease burden seen in pSLE. Type I interferon (IFN) levels are elevated in SLE and have been shown to play a prominent role in premature vascular damage in adult patients and in animal models of SLE. We hypothesized that serum type I IFN activity may also be an independent predictor of subclinical atherosclerosis and endothelial dysfunction in pSLE.

Methods: A cross-sectional analysis of a pSLE cohort was performed. The following markers of subclinical atherosclerosis and endothelial dysfunction were measured in 132 pSLE patients and 138 healthy controls using standardized protocols: carotid intima-media thickness (CIMT), flow-mediated dilatation (FMD) of the brachial artery, and aortic pulse wave velocity (PWV). Serum samples from the pSLE patients were assayed to quantify type I IFN serum activity, using a previously validated bioassay in which HeLa cells were incubated in the presence of pSLE or age- and gender-matched healthy control sera. HeLa RNA was then isolated and real-time quantitative PCR was performed to quantify the expression of 5 type I IFN-inducible genes (*MX1, C1orf-29, IFIT1, PRKR*, and *IFI44*) and the housekeeping gene *HPRT1*. Principal component analysis was used to establish the association between individual type I IFN-inducible genes and markers of subclinical atherosclerosis and endothelial dysfunction.

Results: Females accounted for 89% of pSLE patients; mean age was 14.8 $\pm$ 2.7 years. Disease duration at time of vascular tests was 2.1 $\pm$ 2.1 years, with a wide range spanning 2 months to 13.25 years. Mean CIMT was 0.41 $\pm$ 0.05 mm, mean FMD was 8.2% $\pm$ 3.94%, and mean aortic PWV was 5.45 $\pm$ 1.0 m/s. These results did not differ from the healthy control population. Four type I IFN-inducible genes were found to be significantly elevated in pSLE patients when compared with controls: *MX1* (8-fold higher), *C1orf-29* (3-fold higher), *PRKR* (2-fold higher), *and IFI44* (2-fold higher). There was no correlation between type I IFN serum activity and markers of subclinical atherosclerosis and endothelial dysfunction in pSLE patients.

Conclusion: Serum type I IFN activity is increased in pSLE patients, but we found no association between serum type I IFN activity and markers of subclinical atherosclerosis and endothelial dysfunction in pSLE. These results are in contrast to the association which has been shown in adult SLE patients. Further study including longitudinal assessments is needed to evaluate if change in type I IFN activity over the duration of disease predicts progression of atherosclerosis and/or development of CV events in pSLE.

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Interferon Regulatory Factors 3 and 5 As Key Elements Of The Interferon Signature On Plasmacytoid Dendritic Cells From Systemic Lupus Erythematosus Patients.
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Background/Purpose: Plasmacytoid dendritic cells (pDC) are considered the main source of type-I interferon (IFN-I). The interferon signature has been widely associated to systemic lupus erythematosus (SLE). Among these over-expressed genes, interferon regulatory factors (IRF) have been proposed as key regulators of the increased IFN-I production in SLE patients and murine models. Many genetic association studies have found association between many IRF-5 polymorphisms with increased susceptibility to SLE in different ethnic groups, however these studies have been done with total mononuclear cells, which may not reflect specific DC alterations. The aim of the present study was to address the expression of IRF-3 and 5 on different DC subsets from SLE patients, as well as their association to IFN-I production.

Methods: In this work we included 35 patients with SLE (20 with SLEDAI=0, 15 with SLEDAI>6) according to the classification criteria of the American College of Rheumatology as well as 35 healthy age and gender matched controls. Peripheral blood mononuclear cells were isolated by density gradient. Monocytes were purified by positive selection with magnetic beads. mDC were generated by culturing monocytes for 6 days in presence of GM-CSF, IL-4 and for 2 additional days in presence of LPS to induce maturation. The expression of CD80, CD86, HLA-DR, CD40 was evaluated by flow cytometry. IRF3 and IRF5 expression was assessed by qPCR, flow cytometry and western blot in mDC and pDC from peripheral blood and monocyte derived DC. IFN-I serum levels were measured by ELISA. Data were analyzed by the Student t test. In all cases, an informed consent was obtained, and the ethics committee approved this study.

Results: We found increased expression of IRF-3(4331.6$\pm$794 vs 2400.8$\pm$225.9, p=0.038) and 5 (2724.6$\pm$335.9 vs 1785$\pm$115.2, p=0.031) by flow cytometry (mean fluorescence intensity) on pDCs from SLE patients vs healthy controls. This finding was associated to increased IFN-I serum levels in SLE patients vs healthy controls (160.2$\pm$21 vs 106.1$\pm$14, p=0.036). We found as well that monocyte derived DC from SLE patients showed decreased levels of CD40 after maturation with LPS. However no other differences were observed on the other DC phenotype markers. Interestingly, differences between IRF-3 and 5 expression were restricted to pDC subset. Moreover, these findings were present regardless of disease activity.

Conclusion: Our findings suggest that increased levels of IFN-I in SLE patients are associated to increased expression of IRF-3 and 5, which is restricted to pDC subset. Furthermore, the abnormal expression of these factors might be an intrinsic defect in SLE, since it is present regardless of disease activity.

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Toll-Like Receptor 3 Plays a Role In Loss Of Tolerance To The Ro/SSA Auto-Antigen In Systemic Lupus Erythematosus. Julie Ducreux[1], Christine Galant[1], Julie Verbeeck[1], Pierre Coulie[2], Benoît Van den Eynde[2], Frédéric A. Houssiau[1] and Bernard Lauwerys[1]. [1]Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium, [2]Institut de Duve, Université catholique de Louvain, Brussels, Belgium.

Background/Purpose: Toll-like Receptor (TLR)7 and TLR9 play a role in the pathogenesis of systemic lupus erythematosus (SLE) by inducing Interferon (IFN)-α and IFN-induced genes expression. However, recent data indicate that other agonists inside the type I IFN system could be involved in the pathogenesis of the disease. In the present study, we described the presence of IFN-β in cutaneous lesions of patients with SLE, an observation that led us to investigate the role of TLR3 in the disease.

Methods: IFN-β evaluation in SLE skin biopsies versus controls was performed by immunohistochemistry. The variations in the genomic sequence of the *TLR3* gene were first explored in a population of Western-European SLE patients versus age- and gender-matched healthy controls, using 8 Tag SNP from the HapMap database. In addition, the distribution of *TLR3 rs3775291* alleles and genotypes were assessed in two independent populations of Western- and Southern-European SLE patients (n = 197 and 282, respectively) and controls (n = 262 and 291, respectively). Functional experiments were performed on peripheral blood mononuclear cells (PBMC) and monocyte-derived dendritic cells (moDC) generated from PBMC of healthy individuals categorized according to their *TLR3 rs3775291* genotype. Anti-Ro/SSA- specific T cells were derived from PBMC of healthy individuals by repeated stimulations with autologous Ro/SSA-pulsed moDC.

Results: We found a positive IFN-β immunostaining in skin lesions of SLE patients, compared to controls. This result prompted us to evaluate the potential role of TLR3 in the pathogenesis of the disease. Out of the 8 *TLR3* Tag SNP, 2 are significantly associated with SLE in Western-European anti-Ro/SSA antibody (Ab)-positive patients. None of these intronic SNP have a functional impact. However, one of them is in linkage disequilibrium with *rs3775291*, a SNP that encodes an amino-acid substitution in the ligand-binding pocket of TLR3. We found a positive association between *rs3775291* and susceptibility to SLE in patients with anti-Ro/SSA Ab, in two independent populations of SLE patients and controls. We confirmed that the rs3775291 major allele, which is enriched in anti-Ro/SSA Ab-positive patients, is associated with increased TLR3 responses to stimulation. In addition, moDC from individuals homozygous for the susceptibility *TLR3 rs3775291* allele are more susceptible to UV-induced apoptosis, thereby resulting in the release of larger amounts of the Ro/SSA autoantigen in response to UV irradiation. UV exposure of dendritic cells from individuals homozygous for the susceptibility *TLR3 rs3775291* allele also results in higher interleukin-6 secretion, and cell surface expression of MHC II molecules and CD86. Finally, we found that UV exposure of Ro/SSA-pulsed moDC from individuals homozygous for the susceptibility *TLR3 rs3775291* allele leads to a higher activation of auto-reactive autologous CD4+ T cells.

Conclusion: *rs3775291*, a functional SNP in the *TLR3* gene, is associated with susceptibility to SLE in anti-Ro/SSA Ab-positive patients, and facilitates loss of tolerance to the Ro/SSA auto-antigen through increased maturation of moDC after UV exposure.

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Chromatin Binding In SLE Patients Correlates With The Intensity Of Apoptotic Binding By 9G4+ B Cells. Asiya Seema Chida[1], Quan-Zhen Li[2], Chandra Mohan[2], Youliang Wang[1], Scott Jenks[3], Louise Hartson[1] and Ignacio Sanz[4]. [1]Emory University Medical Center, Atlanta, GA, [2]University of Texas Southwestern Medical Center, Dallas, TX, [3]Emory University School of Medicine, Atlanta, GA, [4]Emory University, Atlanta, GA.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a multi-organ autoimmune disease characterised by production of autoantibodies to multiple nuclear antigens, some of which are highly specific for SLE including anti-ds DNA, anti-Smith and anti-nucleosome antibodies. IgG antibodies expressing the 9G4 idiotype, encoded by the framework-1 hydrophobic patch (HP) of VH4–34, are specifically expanded in SLE and provide a unique model to understand the participation of different autoantigens in the pathogenesis of this disease. 9G4 autoreactivity may be directed against different lupus antigens and accounts for a significant fraction of anti-apoptotic cell binding (APCB), of lupus serum. Here we sought to understand the contribution of anti-nucleosome reactivity to APCB.

Methods: A panel of 9G4+ monoclonal antibodies was generated from IgD-CD27+ memory cells of SLE patients. APCB was determined by flow cytometry. Positive and negative binders for Apoptotic binding were tested for anti-Chromatin reactivity by ELISA. Three representative antibodies with strong APCB activity were also tested against a glomerular proteome antigen microarray.

Results: Our preliminary data demonstrate a strong correlation of apoptotic binding with chromatin by ELISA. Out of 37 9G4+ monoclonals tested 10 were positive for apoptotic binding and out of these 10, 9 were positive for chromatin ($p=<0.001$; fisher exact test). Glomerular microarray analysis identified reactivity with Chromatin, histones H2A, H2B, H3 and H4 in different patterns for the individual antibodies. This assay also identified interesting patterns of polyreactivity against of other lupus antigens including Riboprotein P1, but not P0 or P2, U1-RNP and Sm. Of note, these patterns reflected the reactivity of the patients serum. Levels of reactivity against chromatin, H2A, H2B, H3, and U1-Sn-RNP-68 correlated with disease activity.

Conclusion: SLE-specific 9G4 antibodies recognize nucleosomal antigens (chromatin and individual histones) and may be polyreactive against components of the snRNP complex. Both these types of antigens are expressed at high density on apoptotic cells which are highly immunogenic sources of self-antigens in SLE at least in part due to deficient clearance. Detailed structural, antigenic and functional studies of our mAbs should shed significant light into the triggering of these autoimmune responses and the role of different antigens in the shaping and selection of the autoimmune B cell memory compartment. Determination of 9G4 antibodies against apoptotic cells and/or nucleosomal antigens might provide a useful test for the diagnosis and monitorization of SLE.

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***In Vitro* Assessments Of Mesenchymal Stem Cells From Lupus Patients To Predict Suppressive Function *In Vivo*.** Erin Collins[1], Fei Gu[2] and Gary S. Gilkeson[1]. [1]Medical University of South Carolina, Charleston, SC, [2]Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston, SC.

Background/Purpose: Broad immune suppression by mesenchymal stem cells (MSCs) make them an attractive candidate as a cell therapy for autoimmune diseases, such as systemic lupus erythematosus (SLE). MSCs can be derived from various sources and vary slightly depending on the source of origin. Currently the source of MSCs that will be most effective in ameliorating SLE is unknown. Moreover, *in vivo* studies have suggested that lupus derived MSCs are not as effective as MSCs from non-diseased sources. In this study we assess the suppressive capabilities of MSCs from different sources *in vitro*.

Methods: To determine the suppressive efficacy of human MSCs we harvested MSCs from healthy donor umbilical cords, bone marrow, and lupus patient bone marrow (n=3–4 of each). Peripheral blood mononuclear cells (PBMCs) were isolated from healthy individuals and used immediately for cell culture. PBMCs were labeled with CFSE for detection of suppression. PBMCs (5×10^5) were then stimulated with 1μg/ml αCD3/CD28 and co-cultured with varying dilutions of MSCs. Co-cultures were incubated for 72 hours before cells were collected for flow cytometry and qPCR analysis. MSC activation was assessed by stimulating 1×10^5 MSCs with varying concentrations of IFNγ and incubating for 24 hours. Expression of MSC activation/suppressive markers was assessed by qPCR.

Results: In comparison to MSCs from healthy donors, lupus MSCs were able to suppress PBMCs equally well. Only a modest decrease in suppression was seen when lupus MSCs were diluted 1:40 (MSC:PBMC), when compared to healthy MSCs. We next examined the expression of markers that are important for suppressive MSCs. Our data showed increased expression of IDO1, CFH, TGFβ and IL6 in lupus MSCs compared to healthy MSCs during PBMC co-culture. To determine whether lupus MSCs were more readily activated for suppression, we activated the various MSCs with graded doses of IFNγ. We found that IDO1 and CFH were upregulated in a dose dependant manner similarly in both lupus and healthy MSCs. However, lupus MSCS had higher expression of IL6, TGFB and T cell attractant chemokines (CXCL9 and CXCL10) when compared to healthy MSCs.

Conclusion: Our results indicate that lupus MSCs are equally as suppressive as healthy MSCs *in vitro*. Additionally, certain standard suppressive markers are up regulated in lupus MSCs. Although our *in vitro* assessments do not show that lupus MSCs are defective, these results do not correlate with *in vivo* studies showing reduced capacity of lupus MSCs to mediate disease. Moreover, our studies suggest that different *in vitro* evaluations need to be utilized to determine *in vivo* effectiveness of MSCs.

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Characterization Of a Jamaican Lupus Cohort: Proinflammatory Biomarkers and Disease Activity. Rohan Willis[1], Monica Smikle[2], Karel de Ceulaer[3] and Silvia S. Pierangeli[1]. [1]University of Texas Medical Branch, Galveston, TX, [2]University of the West Indies, Kgn 7, Jamaica, [3]University of the West Indies, KIngston, Jamaica.

Background/Purpose: Systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) are related systemic autoimmune diseases associated with proinflammatory prothrombotic biomarkers/cytokine (PPM) and antiphospholipid antibodies (aPL). Reports also suggest that low 25-hydroxy vitamin D (25OH-VD) levels are associated with disease activity in SLE. There is an increased prevalence and severity of SLE in Black and Afro-Caribbean patients (pts) but few data highlighting 25OH-VD and PPM levels in this population. We sought to determine which cytokines and oxidative stress markers are elevated in a unique population of Jamaican (JA) SLE pts.

Methods: A total of 47 patients (mean age 43.3 ± 11.9yrs) satisfied ACR classification criteria for definite or incomplete SLE; the BILAG index was used to measure disease activity. Two groups of controls served as comparison for PPM. ELISAs were used to measure anti-dsDNA, aPL (anticardiolipin (aCL), anti-β_2-glycoproteinI (aβ_2GPI) and APhL®), 25OH-VD, IgG anti-oxLDL/β_2GPI antibodies (IgG aOXLβ-Ab) and oxLDL/β2GPI antigen-complex (OXLβ-Ag). Interferon (IFN)-α, Interleukin (IL)1b, IL6, IL8, inducible protein (IP)10, tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF), and soluble CD40 ligand (sCD40L) levels were determined by the MILLIPLEXMAP human cytokine/chemokine assay in the serum of patients and controls. Pearson's correlation and the Kruskal-Wallis test were used to evaluate PPM levels in SLE patients and controls.

Results: A third of patients (14/47,29.8%) had at least one positive aPL and 5/47 (10.6%) had isolated IgA anti-β2GPI positivity. Most PPM were significantly elevated in SLE patients vs controls (Table 1). Only 6.4% (3/47) patients had positive IgG aOXLβ Ab levels but all of these patients had extremely elevated aPL. IgG aOXLβ Ab was significantly correlated with IgG aCL (r0.854, $p<0.001$), IgG APHL (r0.940, $p<0.001$) and IgG aβ_2GPI (r0.978, $p<0.001$) while OXLβ-Ag was associated with IgA aβ2GPI (r.316, $p=0.031$). Disease activity was significantly correlated with both dsDNA (r0.341, $p=0.020$) and IP10 (r0.362, $p=0.013$) and these 2 markers were also correlated (r0.490, $p<0.001$). Most patients (34/47, 72.3%) had below normal 25OH-VD levels and patients with 25OH-VD deficiency had higher mean IFN-α levels compared to those with normal levels (49.9 vs 3.6 pg/ml, $p=0.05$).

Table 1. Proinflammatory markers in SLE patients vs controls

Marker	JA SLE patients median	Controls median	P value
IL6 (pg/mL)	1.7	0.0	<0.001
IL1β (pg/mL)	0.0	0.0	0.108
TNFα (pg/mL)	7.1	0.0	<0.001
IP10 (pg/mL)	226.7	96.2	<0.001
sCD40L (pg/mL)	232.3	16.4	<0.001
IFNα (pg/mL)	4.5	0.0	0.162
VEGF (pg/mL)	154.6	88.3	0.031
OXLβ Ag (U/mL)	14.5	2.8	<0.001

Conclusion: Jamaican SLE patients have a high rate of aPL positivity, particularly IgA anti-β_2GPI, associated with oxidative stress markers and this may be an underlying reason for the increased prevalence of severe disease in Afro-Caribbean patients. IFN-inducible cytokines appeared to drive disease activity on the background of dsDNA activity, which is unsurprising. IFN activity was also associated with low 25OH-VD.

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T Helper 17 Cells and Interferon Type I: Partners In Crime In SLE? Odilia B.J. Corneth, Zana Brkic, Cornelia G. van Helden-Meeuwsen, Radboud J.E.M. Dolhain, Naomi I. Maria, Sandra M.J. Paulissen, Nadine Davelaar, Jan Piet van Hamburg, Paul L. Van Daele, Virgil A. Dalm, Martin van Hagen, Marjan A. Versnel and Erik Lubberts. Erasmus Medical Center, Rotterdam, Netherlands.

Background/Purpose: A hallmark of systemic autoimmune diseases, such as systemic lupus erythematotsus (SLE), is the increased expression of interferon (IFN) type I inducible genes, the so-called IFN type I signature. Recently, a novel T helper 17 subset (Th17 cells), which produces IL-17A, IL-17F, and IL-22, has also been implicated in autoimmune diseases. We investigated a possible link between these two pro-inflammatory immune pathways in SLE.

Methods: 25 SLE patients and 15 healthy controls (HC) were included. SLE patients were divided into an IFN type I signature negative (n=9) and positive (n=16) group as assessed by mRNA expression of IFN type I inducible genes. Peripheral expression of Th17 cytokines IL-17A, IL-17F and IL-22 by CD4+CCR6+ memory T cells was measured by flow cytometry and compared between IFN type I signature positive and negative patients and HC.

Results: Increased fraction of IL-17A and IL-17A/IL-17F double producing CCR6+ cells was found in IFN type I positive patients compared with IFN type I negative patients and HC. The expression of IL-17A and IL-17F within CCR6+ cells correlated significantly with IFN scores. In addition, we found a significant correlation between BAFF and IL-21 producing CCR6+ cells.

Conclusion: Here we show for the first time a correlation between IFN type I activation and expression of the Th17 cytokines in SLE patients. These data give new insight into the pathogenesis of SLE with possible implications for treatment.

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Deep-Sequencing Reveals Class-Specific Urinary Micrornas In Human Lupus Nephritis. Beatrice Goilav[1], Iddo Z. Ben-Dov[2], Irene Blanco[3], Olivier Loudig[3], Dawn M. Wahezi[4] and Chaim Putterman[3]. [1]Children's Hospital at Montefiore, Bronx, NY, [2]The Rockefeller University, New York, NY, [3]Albert Einstein College of Medicine, Bronx, NY, [4]Children's Hospital Montefiore, Bronx, NY.

Background/Purpose: Lupus nephritis (LN), particularly, ISN/RPS class IV LN, is associated with significant morbidity and mortality. microRNAs (miRs) are small, non-coding RNAs that regulate translation. Previous studies report changes in miR expression in kidney tissue, urine and PBMCs that correlate with LN disease activity. However, LN class-specific miRs have not been previously described.

Using deep-sequencing, we aimed to identify class-specific miRs in urine from adult and pediatric patients with biopsy-proven LN.

Methods: Cell-free urine from adult (n=25) and pediatric (n=8) female patients with ISN/RPS class III, IV (proliferative) and class V LN were obtained at time of active disease and during remission. Total RNA was used to prepare small RNA cDNA libraries for sequencing. Multiplexing through sample-specific 3' adapters was applied to limit batch effects and cost. Sequence reads were mapped to the human genome and small RNA databases. miRs were quantified by relative read abundance. qRT-PCR was used for quantitative validation.

Results: We had specimens from adult patients with distinct class III, IV, and V LN and pediatric patients with class III and IV. Samples from pediatric patients with class V LN were mixed with another class LN. We obtained reproducible miR profiles. In a paired-sample analysis we compared miR abundance in adult and pediatric active vs inactive LN, proliferative vs non-proliferative LN, class IV vs class III LN, active class III vs inactive class III LN, active class IV vs inactive class IV LN, and adult active class V vs inactive class V LN. In this analysis, we found significant changes in miR-324, -320, -200c (adult), -375 (pediatric), -200c, -30a, and -671*, respectively. All changes had a p value of <0.001, except for miR-30a ($p=0.0011$). Changes in miR abundance ranged from −11.8-log fold change to 11.3-log fold change.

Conclusion: In this study, we detected significant changes in miR abundance related to specific LN classes. Given that the prognosis of class IV LN is significantly worse than that of class III, identifying miRs that are associated with class IV LN is an important step in biomarker discovery of this particular aggressive form of LN. Identification of target genes of these miRs may open a venue for the discovery of new pathogenic pathways in this devastating disease.

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Differential Methylation Of Interferon-Related Genes Is Associated With Anti-dsDNA Autoantibody Production In Systemic Lupus Erythematosus. Sharon A. Chung[1], Joanne Nititham[2], Kimberly E. Taylor[1], Emon Elboudwarej[3], Hong L. Quach[3], Lisa F. Barcellos[3] and Lindsey A. Criswell[2]. [1]University of California, San Francisco, San Francisco, CA, [2]University of California, San Francisco, Rosalind Russell Medical Research Center for Arthritis, San Francisco, CA, [3]University of California, Berkeley, Berkeley, CA.

Background/Purpose: DNA methylation studies in systemic lupus erythematosus (SLE) have shown that SLE patients have less methylation in genes regulating the immune response compared to unaffected individuals. We conducted this study to determine if differences in methylation are associated with specific SLE manifestations, and focused on anti-dsDNA autoantibody production since it indicates more severe disease.

Methods: Genomic DNA from peripheral blood leukocytes was isolated from 326 women with SLE of European descent who never smoked. Approximately 48% of the SLE cases were anti-dsDNA autoantibody positive. Using the Illumina HumanMethylation450 Beadchip, the methylation status of 484,740 CpG sites across the genome was characterized in all SLE cases. For analysis, the cases were divided into discovery (n=186) and replication datasets (n=140). Wilcoxon rank sum tests were used to identify sites whose methylation status showed evidence of association with anti-dsDNA autoantibody production. Significantly associated sites in the discovery dataset were examined for association in the replication dataset. Linear and logistic regression was used to adjust for estimated leukocyte cell proportions, age, disease duration, batch effects, and population substructure (assessed by principal component analysis of previously generated genotype data).

Results: Statistically significant associations between anti-dsDNA autoantibody production and methylation status were identified for 18 sites using the discovery dataset ($p<1.0E–07$ with Bonferroni correction) and were replicated ($p<0.0028$, corrected for 18 sites). All associated sites were less methylated in anti-dsDNA positive SLE cases compared to anti-dsDNA negative SLE cases. These 18 sites represent 12 genes, and the most significantly associated sites were in *IFIT1*, *MX1*, and *RSAD2*. For the top 3 associated sites, the adjusted mean difference in methylation between anti-dsDNA positive and negative SLE cases and the adjusted odds ratio for anti-dsDNA autoantibody production if a subject's methylation level was below the median are presented in Table 1. Of note, 7 of 12 associated genes identified are either interferon inducible or involved in the interferon signaling pathway, including the 3 genes shown in Table 1.

Table 1. The top 3 methylation sites associated with anti-dsDNA autoantibody production.

Site	Gene	Adjusted mean difference in methylation[1] (95% CI)	p	Adjusted OR for anti-dsDNA autoantibody[2] (95% CI)	p
cg05696877	*IFI44L*	−15% (−19% to −11%)	9.8E–13	7.2 (4.0–13.1)	5.4E–11
cg21549285	*MX1*	−18% (−23% to −13%)	1.7E–12	6.5 (3.6–11.9)	4.1E–10
cg10959651	*RSAD2*	−4.8% (−6.2% to −3.5%)	7.7E–12	7.2 (4.0–12.8)	4.2E–11

[1] difference < 0 indicates that methylation levels were lower in the anti-dsDNA positive group
[2] OR for anti-dsDNA autoantibody if a subject's methylation level was below the median

Conclusion: This study suggests that differential methylation is associated with specific SLE manifestations in addition to disease susceptibility. Among SLE cases, additional hypomethylation of interferon-related and other genes is associated with anti-dsDNA autoantibody production. Thus, the extent of hypomethylation for critical genes may influence disease severity in SLE.

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Lupus Risk Alleles With High Ethnic Variability Worldwide Are Associated With Renal Disease In Hispanic Patients. Belinda Waltman[1], Kimberly E. Taylor[2], Joanne Nititham[2] and Lindsey A. Criswell[2]. [1]University of California, San Francisco, San Francisco, CA, [2]University of California, San Francisco, Rosalind Russell Medical Research Center for Arthritis, San Francisco, CA.

Background/Purpose: Systemic lupus erythematosus (SLE) disproportionately affects minority patients. Non-European ancestry is associated with more severe disease, and conversely, European ancestry is associated with a lower risk of developing renal disease in SLE. Large genetic studies have identified 58 single nucleotide polymorphisms (SNPs) that influence risk of SLE. Separately, the Human Genome Diversity Project (HGDP) has characterized the allele frequency of 650,000 SNPs in 938 people from 53 different populations worldwide. We hypothesized that SLE SNPs with the greatest allele frequency differences across populations compared to Europeans could identify risk alleles that are associated with severe disease manifestations.

Methods: We analyzed the frequency distribution of the 58 SLE SNPs across populations in the HGDP database grouped into 6 geographic regions; 50 SNPs or proxies had available data. For each SNP, we determined the maximum absolute difference (max diff) in mean frequency between each region and Europe. SNPs were selected whose max diff was greater than 4 standard deviations of the distribution of intra-European frequencies. We tested these SNPs in our multiethnic cohort of 1588 SLE patients for severe disease outcomes (renal disease by ACR renal criterion, severe renal disease including severe forms of lupus nephritis on biopsy or end-stage renal disease, and production of double-stranded DNA antibodies) stratified by ethnicity: Caucasian, African American, Hispanic, and Asians. Logistic regression was performed for these 3 outcomes, adjusting for disease duration and gender.

Results: The max diff approach identified 19 SNPs; 13 had been genotyped in our SLE collection. Analysis identified a strong association between renal disease and Hispanic ethnicity: the number of these 13 risk alleles cumulatively increased the risk of renal disease among Hispanic patients (OR=1.2 per allele, p=0.006). Three of the 13 SNPs were individually associated ($p \leq 0.05$) with renal disease or severe renal disease. The strongest single allele associations were rs2205960/TNFSF4 (OR=2.2, p=0.0014 for renal disease), rs2736340/BLK (OR 2.1, p=0.006 for severe renal disease and OR 1.6, p=0.05 for renal disease) and rs9888739/ITGAM (OR 1.8, p=0.04 for renal disease). In HGDP data, the Central/South American region was the first or second greatest max diff compared to Europeans for these alleles.

Conclusion: Using worldwide genetic ancestry data, we identified SLE risk SNPs with high allele frequency variability across populations, postulating that these variants might influence severe disease phenotypes. Indeed, in a multiethnic SLE cohort, these 13 SNPs cumulatively increased the risk of renal disease in Hispanics, and 3 of these 13 alleles were individually associated with renal disease outcomes. This approach may be useful for identifying genetic variants that influence disease severity in SLE.

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Prolactin-Induced Interferon Regulatory Factor 1 Activation and Histone H4 Hyperacetylation In Monomac-6 Cells Correlating With Changes Seen In Monocytes From Systemic Lupus Erythematosus Patients. Yiu Tak Leung[1], Lihua Shi[2], Kelly Maurer[2], Li Song[2], Michelle Petri[3] and Kate Sullivan[2]. [1]University of Pennsylvania, Philadelphia, PA, [2]The Children's Hospital of Philadelphia, Philadelphia, PA, [3]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Epigenetic changes have been described in systemic lupus erythematosus (SLE) and offer a potential explanation for the chronicity of disease and missing heritability. Therapies targeting the epigenome will require a greater understanding of the cellular pathways regulating the epigenetic changes. We previously found a global increase in histone H4 acetylation (H4ac) in monocytes of SLE patients as compared to controls using tiling arrays. Transcription factor motif analysis found 63% of genes with increased H4ac had potential interferon regulatory factor (IRF) 1 binding sites within the 5kb upstream region. IRF1 is highly inducible by prolactin, a hormone implicated in the pathogenesis of SLE: hyperprolactinemia has been reported in 15–33% of SLE patients as compared to 0.4–3% of controls. Prolactin upregulation of IRF1 can lead to H4ac in Nb2 T cells, representing

a potential pathological pathway in SLE. Prolactin-induced IRF1 activation in MonoMac-6 (MM6) cells was examined, with the aim to identify IRF1 interactions with specific histone acetyltransferases (HATs) and histone deacetylases (HDAC) leading to pathological H4ac in SLE.

Methods: Flow cytometry for acetylated H4 lysines: K5, K8, K12, K16 were run on the Accuri C6 with isotype controls. H4ac was defined in monocytes from 20 controls and 24 SLE patients, as well as in unstimulated and prolactin-stimulated MM6 cells. Real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR) evaluated HAT/HDAC expression in monocytes from 10 SLE patients and 4 controls. IRF1 activation by prolactin in MM6 cells was studied by immunofluorescence microscopy and western blot analysis.

Results: Flow cytometry data found significantly increased H4K5, H4K8, H4K12, and H4K16 acetylation ($p = 0.03, 0.01, 0.004, 0.02$) in SLE monocytes compared to controls. H4K5 and H4K16 acetylation were also increased in MM6 cells stimulated by prolactin concentrations comparable to pregnancy (200 ng/mL) and prolactinoma levels (2000 ng/mL).

Immunofluorescence microscopy showed translocation of IRF1 from the cytoplasm to the nucleus in prolactin-stimulated MM6 cells by 1 hr, demonstrating IRF1 activation. This was supported by western blots of MM6 nuclear extracts showing IRF1 increase at 1–2 hrs of prolactin stimulation.

Potential mechanisms were examined. qRT-PCR studies of HAT/HDAC expression patterns found decreased HDAC3 and HDAC11 expression in SLE monocytes ($p = 0.19$ and 0.16). HDAC3 deacetylates all H4 lysine acetyl groups, preferentially H4K5 and H4K12. PCAF, a HAT that places H4K5, H4K8, and H4K16 acetylation marks, had significantly ($p = 0.001$) higher expression in SLE monocytes than in controls. IRF1 was overexpressed and H4ac at target genes defined by ChIP assays. Overexpression led to increased H4ac at known IRF1 targets.

Conclusion: These data demonstrate that prolactin stimulation of monocytes induces IRF1 activation and a pattern of acetylated H4 that corresponds to the changes seen in monocytes of SLE patients. This helps to explain the known association of prolactinomas with SLE. The identification of candidate HATs that associate with IRF1 in the context of prolactin stimulation may provide for potential therapeutic targets in SLE.

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Genetic Alterations In Abnormal Neutrophils Isolated From Human Systemic Lupus Erythematosus Patients. Namrata Singh[1], Kayla Martin[1], Mariana J. Kaplan[2], Philip L. Cohen[3] and Michael F. Denny[1]. [1]Temple University, Philadelphia, PA, [2]University of Michigan Rheumatology, Ann Arbor, MI, [3]Temple University School of Medicine, Philadelphia, PA.

Background/Purpose: Human SLE patients have an abnormal population of neutrophils called low density granulocytes (LDGs). LDGs express the surface markers of mature neutrophils, yet their nuclear morphology resembles an immature cell. A similar discrepancy in maturation status is observed in myelodysplasias, suggesting a disruption in neutrophil development in the LDGs. Because disruption of neutrophil development is frequently associated with genomic alterations, we compared genomic DNA isolated from autologous pairs of LDGs and normal-density neutrophils for genetic changes.

Methods: Somatic alterations were detected by cytogenetic microarray analysis of genomic DNA from LDGs and neutrophils from 13 female SLE patients, as well as neutrophil samples from 9 healthy female donors. Autologous pairs of SLE LDGs and neutrophils were processed and analyzed together to minimize variability. Variations present in both samples are consistent with inheritance, while alterations found exclusively in the LDG sample suggest somatic alterations. While copy number alterations are associated with repair of DNA strand breaks, a different type of genomic alteration is associated with defects in the correction of DNA replication errors. Microsatellite instability (MSI) is a characteristic of replication error-prone cells. MSI was assessed at 6 mononucleotide markers.

Results: Control neutrophils had an average of 7.76 chromosomal alterations per genome, similar to the average of the SLE neutrophils value of 8.77 alterations per genome, in contrast, the autologous SLE LDGs had 18.77 alterations per genome. The increased frequency of copy number alterations was comprised of both an elevation in the number of deletions and duplications. Copy number alterations were prevalent in 6 of the 13 patients and occurred preferentially on certain chromosomes with the majority of the alterations restricted to the × chromosome, and chromosomes 19, 17, and 8. These elevations in copy number alterations were accompanied with an increase in large genome-wide losses of heterozygosity in these same SLE patients. The enhanced level of copy number alterations and losses of heterozygosity are consistent with DNA strand break repair in LDGs. Microsatellite instability (MSI) was also detected in the LDGs of three patients, suggesting impaired correction of replication errors. Two patients displayed MSI in greater than one marker, and one patient had MSI and increased copy number alterations. No correlations between genomic instability or MSI and immunosuppressive drugs, disease activity or disease manifestations were apparent.

Conclusion: LDGs had elevated levels of genetic alterations consistent with accumulated genetic damage or genomic instability. Copy number alterations were more prevalent on certain chromosomes and restricted to discrete chromosomal intervals, suggesting an increased propensity for damage within these intervals and/or that these alterations confer a selective advantage. The pro-inflammatory environment in SLE patients may promote accumulation of these genetic alterations, alternatively a genetic predisposition toward impaired mechanisms of DNA repair may facilitate the apparent genomic instability in the LDGs.

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1627

Typing TREX1 Gene In Patients With Systemic Lupus Erythematosus. Micaela Fredi[1], Marika Bianchi[2], Laura Andreoli[3], Gaetano Grieco[2], Ivana Olivieri[4], Simona Orcesi[4], Elisa Fazzi[5], Cristina Cereda[2] and Angela Tincani[3]. [1]Rheumatology Chair, University of Brescia and Pavia, Brescia, Italy, [2]Laboratory of Experimental Neurobiology, C. Mondino National Institute of Neurology Foundation, Pavia, Italy, [3]Rheumatology Unit, University of Brescia, Brescia, Italy, [4]Child Neurology and Psychiatry Unit C. Mondino National Institute of Neurology Foundation, Pavia, Italy, [5]Child Neurology and Psychiatry Unit, Mother-Child Department, Civil Hospital, University of Brescia, Brescia, Italy.

Background/Purpose: An increased expression of type I interferon regulated genes (IFN signature) has been reported in patients (pts) with Systemic Lupus Erythematosus (SLE) and it is involved in the pathogenesis of the disease. Raised level of IFN-α in the cerebral spinal fluid are found in pts with Aicardi-Goutières syndrome (AGS), a rare genetic encephalopathy characterized by calcification of basal ganglia, abnormalities in white matter and chronic cerebrospinal fluid lymphocytosis. One of AGS-causing mutations is located in the Trex1 gene chromosome3. Subsequent studies demonstrated that up to 2% of pts with SLE had pathogenic mutations in Trex1. The enzymatic function of TREX1protein is still not clear, but 3′ Repair exonuclease (Trex1) is the most abundant mammalian 3′->5′ DNA exonuclease with specificity for ssDNA. The loss or reduction of Trex1 activity may result in the accumulation of double-stranded DNA degradation intermediates that could trigger autoimmune activation. A recent study (1) described significant associations between a risk haplotype made by common single nucleotide polymorphisms (SNPs) of Trex1 and closely linked ATRIP gene in European SLE pts with neurologic manifestations, especially seizures.

Methods: 51 SLE pts were screened for Trex1 gene. Genomic DNA was extracted by automatic extraction and stored at −20°C. Trex1 gene was amplified and automatically sequenced (Genetic Analyzer 3130xl, Applied Biosystems). Each fragment was sequenced on both strands. Alignments were viewed using Sequencher 4.8. PolyPhen2 pathogenicity prediction software was used to determine possible pathogenic significance of the not previously described mutation. NM_033629.2 (isoform b-short isoform) was used to report novel variation. Clinical and serological data were collected from clinical charts.

Results: A novel heterozygous variant (NP_338599.1 p.Asp130Asn) was identified in one patient affected by SLE. Trex1 missense variation was classified as probably damaging by PolyPhen2 (score 1/1). This change was absent in 150 control samples sequenced. We also reported mutations of SNP rs11797 in 33 pts and the rs3135944 variation in only 1 patient. We searched for clinical or serological differences among pts with the wildtype rs11797 and the pts with the mutations. No significant associations were found. We reported a high prevalence of neuroSLE manifestations in pts who had rs11797 mutations: among the 8 pts who had clinical features of neuroSLE, 1 was homozygous for the major allele, 2 had heterozygous mutations for these SNP and 5 had homozygous mutations. The distribution of mutations of rs11797 were similar between pts and controls, but the homozygous mutations of rs11797 was significantly more frequent in the pts with neuroSLE than in the controls (p=0,00013;OR=11,5).

Conclusion: Although we analyzed a small number of SLE patients, we found a probably novel pathogenic variation (1,96% of pts) of TREX1. Homozygous mutations of rs11797 was significant more frequent in SLE patients with neurologic manifestations than in controls.

(1)Namjou B, Kothari P.H, Kelly J.A. et al. Evaluation of the TREX1 gene in a large multi-ancestral lupus cohort; Genes Immun. 2011;12(4):270–9

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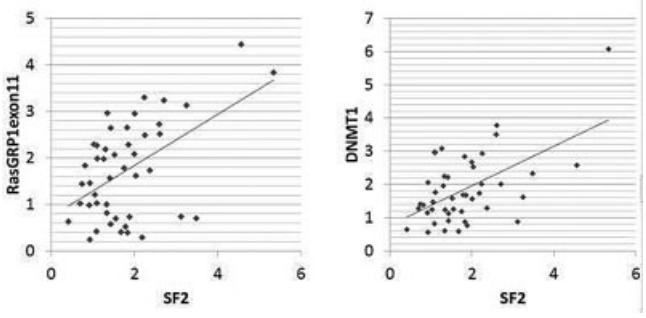
Decreased Levels Of Splicing Factor 2/Alternative Splicing Factor (SF2/ASF) Correlate With Lower Transcript Levels Of The RasGRP1 Normal Isoform In Lupus T Cells. Takashi Kurita[1], Shinsuke Yasuda[1], Vaishali R. Moulton[2], Michihito Kono[1], Hideyuki Koide[1], Kenji Oku[1], Toshiyuki Bohgaki[1], Olga Amengual[1], Tetsuya Horita[1], George C. Tsokos[2] and Tatsuya Atsumi[1]. [1]Hokkaido University Graduate School of Medicine, Sapporo, Japan, [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

Background/Purpose: Down-regulation of MAP kinase pathway has been recognized in T cells from patients with SLE that results in hypomethylation of DNA. RasGRP1 is an intracellular signaling protein highly expressed in T cells and activates the Ras signaling pathway downstream of TCR engagement. RasGRP1 deficient mice develop late-onset lymphoproliferative autoimmune syndrome. Previously we reported that defective (alternatively spliced) RasGRP1 transcripts correlate with lower levels of RasGRP1 protein in SLE T cells (Yasuda S et.al. J Immunol 2007). Splicing factor 2/Alternative Splicing factor (SF2/ASF) is a member of the serine arginine family of splicing proteins that binds pre-mRNA to regulate alternative splicing. For instance, SF2/ASF binds to the 3'UTR of CD3 zeta and enables normal splicing of this signaling protein. (Moulton V et.al. J Biol Chem. 2010). The purpose of this study is to determine the relationship between aberrant splicing of RasGRP1 and SF2/ASF expression in SLE T cells.

Methods: Forty-five SLE patients and eighteen healthy subjects were included in this study. T cells were collected from peripheral blood of each subject and RNA was isolated. Expression levels of SF2/ASF, normally spliced RasGRP1 and DNMT1 transcripts were assessed by real time quantitative PCR. RNA electrophoretic mobility shift assays (EMSA) and immunoprecipitations (IP) were performed to confirm the direct binding of SF2 to RasGRP1 pre-mRNA. RasGRP1 exon11 RNA oligonucleotides end-labeled with biotin and recombinant SF2/ASF phosphate mimic were used in these experiments.

Results: Expression levels of SF2/ASF transcripts were significantly lower in SLE patients compared with healthy subjects ($p=0.001$, t-test). In patients with SLE, expression levels of SF2/ASF correlated with those of normally spliced RasGRP1 and DNMT1 ($r=0.517$, $p=0.023$ [RasGRP1]; $r=0.557$, $p=0.013$ [DNMT1], Figure). EMSA and IP studies suggested that SF2/ASF binds directly to RasGRP1 exon 11 RNA.



Conclusion: SF2/ASF binds to RasGRP1 mRNA and controls its expression. Low SF2/ASF levels in SLE T cells correlate with the expression levels of RasGRP1 and DNMT1. We propose that SF2/ASF regulates the alternative splicing of important genes in SLE T cells including RasGRP1 and CD3 zeta.

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Functional Effect Of NR1H3 (LXRA) Promoter Polymorphisms In Korean Patients With Systemic Lupus Erythematosus. Ja-Young Jeon[1], Hyoun-Ah Kim[1], Ju-Yang Jung[1] and Chang-Hee Suh[2]. [1]Ajou University School of Medicine, Suwon, South Korea, [2]Ajou University Hospital, Suwon, South Korea.

Background/Purpose: Liver × receptor alpha (LXRA, NR1H3) and beta (LXRB, NR1H2) can influence macrophage biology by modulation of lipid metabolism and by effects on innate immunity. The recent studies have reported that LXRs are involved in regulation of inflammation and immune responses. In our previous data, we have identified five polymorphisms (−1851 T>C, −1830 T>C, −1003 G>A, −840 C>A and −115 G>A) including one novel SNPs (−1003 G>A) in the *NR1H3* gene. Especially, the −1830 T>C promoter polymorphism was significantly different in genotype analysis and clinical manifestations. This study evaluated the functional effect of the *NR1H3* promoter polymorphism on systemic lupus erythematosus.

Methods: The promoter activity was analyzed by luciferase reporter assay in Hep3B cells and COS-7 cells. To investigate the effects of the stimulation, we used a functional assay of transcriptional activity and B cell proliferation assay with lipopolysaccharide, GW3965 and T0901317. The mRNA expression of *NR1H3* gene according to the genotype was analyzed by RT-PCR and quantitative real-time PCR. To investigate whether the genetic polymorphism changed a transcription factor binding, we performed an electrophoretic mobility shift assay (EMSA).

Results: Luciferase activity of the constructs containing −1830 C was lower than that of the constructs containing −1830 T ($p=0.009$). Moreover, promoter activity of the −1830 C was less enhanced compared to that of the −1830 T in GW3965 and T0901317 treated cells ($p=0.034$ and $p<0.001$, respectively). Proliferation of −1830 TC type was increased compared to that of −1830 TT type in basal, GW3965 and T0901317 treated B cells from SLE patients ($p=0.011$, $p=0.040$ and $p=0.017$, respectively). The −1830 TC type B cells displayed lower *NR1H3* mRNA expression level than the −1830 TT type B cells in both SLE and NC. Moreover, *NR1H3* expression level significantly different between genotypes in real-time PCR. In both SLE and NC, the −1830 TC type was an approximately 1.8-fold decrease than the −1830 TT type. EMSA using nuclear extracts prepared from Hep3B cells revealed a specific band with the −1830 T probe, but not with the −1830 C probe. We performed a competition assay using GATA-3 probes, and found that the shifted band corresponding to the −1830 T probe was completely competed for by the unlabeled GATA-3 probe. The −1830 T specific band was also competed by anti-GATA-3 antibodies but not supershifted.

Conclusion: These results suggest that the *NR1H3* gene −1830 T>C promoter polymorphism may be involved in regulation of *NR1H3* expression.

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Association Of TREM-Like Transcript-1 With Systemic Lupus Erythematosus. Yerania Rodríguez-Navedo[1], Karina Vilá -Rivera[1], Mariely Nieves-Plaza[2], Martha Ricaurte[3], A. Valance Washington[3] and Luis M. Vilá[1]. [1]University of Puerto Rico Medical Sciences Campus, San Juan, PR, [2]University of Pittsburgh, Pittsburgh, PA, [3]University of Puerto Rico, Río Piedras Campus, San Juan, PR.

Background/Purpose: Recent studies suggest that a platelet α-granule protein named TREM-like transcript-1 (TLT-1) is a key molecule in modulating the inflammatory response. TLT-1 has been proposed to be an inhibitor of the inflammatory gene activator TREM-1 and its soluble ligand, thus preventing overactivation of the immune cellular response and sustained inflammation. TLT-1 plasma levels are markedly elevated in infectious disorders such as sepsis and dengue to counterbalance the inflammatory response. The role of TLT-1 in systemic lupus erythematosus (SLE) is unknown. Thus, the aims of this study were to assess TLT-1 plasma levels in SLE patients and healthy individuals, and to determine the factors associated with TLT-1 levels among SLE patients.

Methods: A cross-sectional, case-control study was performed in 46 SLE patients (per American College of Rheumatology [ACR] criteria) and 28 healthy individuals. Data on demographic parameters, clinical manifestations (ACR and non ACR lupus manifestations), disease activity (as per the Systemic Lupus Activity Measure [SLAM]), health-related quality of life (using the Lupus Patient Reported Outcome [LupusPRO] questionnaire), comorbidities, pharmacologic treatment, and damage accrual (as per the Systemic Lupus International Collaborating Clinics/ ACR Damage Index)

were gathered. Plasma TLT-1 levels were measured by ELISA. Student's t test (or Wilcoxon signed-rank test, as appropriate) and Pearson's correlation coefficient test were used for statistical analysis.

Results: The mean (standard deviation [SD]) age for SLE patients and healthy individuals was 45.5 (11.8) and 37.3 (12.1) years respectively; 93% of SLE patients and controls were females. The mean disease duration (SD) of SLE patients was 10.7 (4.1) years. SLE patients had lower mean (SD) levels of plasma TLT-1 than controls (9.0 [7.2] vs. 18.6 [22.3] ng/ml, p=0.008). A negative correlation was observed between TLT-1 levels and the SLAM (r = −0.278, p 0.064) and some domains of LupusPRO (lupus symptoms [r = −0.388, p = 0.055], cognition [r = −0.442, p = 0.027], physical health [r = −0.382, p = 0.060], desires/goals [r = −0.435, p = 0.030]). SLE patients receiving corticosteroid treatment had higher mean (SD) levels of TLT-1 than those not taking corticosteroids (11.1 [8.8] vs. 6.9 [4.6] ng/ml, p = 0.014).

Conclusion: Plasma levels of TLT-1 were lower in SLE patients compared to healthy individuals. Among SLE patients a negative correlation was observed for disease activity and some domains of the LupusPRO. Given that TLT-1 has anti-inflammatory properties, deficiency of this protein could have an important role in the pathogenesis of SLE.

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Transcription Activation-Like Effector Nuclease-Mediated Enhancer Knockout Influences *TNFAIP3* Gene Expression and Mimics a Functional Phenotype Associated With Systemic Lupus Erythematosus. Shaofeng Wang[1], Feng Wen[1], Bo He[2] and Patrick M. Gaffney[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]The University of Oklahoma Health Sciences Center, Oklahoma City, OK.

Background/Purpose: Emerging technologies for precise, targeted genome editing provide new opportunities for the functional elucidation of causal genetic variants and genomic elements without the confounding effects of correlated variants. Transcription Activation-Like Effector Nucleases (TALENs) represents an efficient tool to mediate site-specific genome modification in human cell lines. Previously, we described the influence of systemic lupus erythematosus (SLE)-associated functional variants (rs148314165, rs200820567; collectively referred to as TT>A) on *TNFAIP3* gene expression. The TT>A variants, which lie 42-kbs downstream of the *TNFAIP3* promoter, are located in a putative enhancer and were recently proposed as causal variants responsible for genetic association of SLE in the region of *TNFAIP3*. In this study, we generated a TT>A enhancer knockout in human cell lines to further characterize the role of the enhancer in regulating *TNFAIP3* gene expression.

Methods: The genomic DNA sequence surrounding the TT>A enhancer was scanned for potential TALEN target sites using TALEN Targeter 2.0. A modified TALEN Golden Gate assembly system was then used to generate RVD repeat arrays, which were then subcloned into the expression vectors pCS2TAL3DD and pCS2TAL3RR. TALENs were expressed in HEK293T cells by transient transfection, and single-cell clones were isolated. Targeted cell clones were selected based on high-resolution melt analysis of PCR amplicons from each cell clone. Sanger sequencing was performed to determine the sequence of the targeted allele. Protein expression of A20 and mRNA expression of *TNFAIP3* were determined by Western blot and RT-qPCR assay, respectively. Chromatin conformation capture (3C) assay was performed to determine the interaction frequency between the TT>A enhancer and the *TNFAIP3* promoter.

Results: We assembled RVD repeat arrays targeting the TT>A enhancer, generated TALEN constructs, and expressed TALENs in HEK293T cells. Using high-resolution melt analysis, we identified an engineered HEK293T cell that carries a 26-bp deletion at the TT>A enhancer, which leads to alteration of NF-κB binding sites predicted using the UniProbe database. Assessing the effect of the mutant TT>A enhancer on the expression of *TNFAIP3* at the protein and transcript level, we demonstrated low-level expression of *TNFAIP3* mRNA and A20 protein in the mutant cell line. Follow up allele-specific 3C assay with the engineered cells demonstrated significantly fewer interactions with the *TNFAIP3* promoter as a result of the mutant allele. This is consistent with the naturally occurring SLE-associated TT>A polymorphism, in which the risk allele reduces gene expression of *TNFAIP3*.

Conclusion: The SLE-associated TT>A enhancer plays an important role in regulating gene expression of *TNFAIP3*. By generating an engineered TT>A enhancer mutant HEK293T cell line, we have characterized the influences of the mutated enhancer on *TNFAIP3* gene expression. These results suggest that TALEN-mediated genome editing has potential to be used for the identification and characterization of complex disease-associated causal variants.

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Identification Of a Novel Systemic Lupus Erythematosus Risk Locus Between FCHSD2 and P2RY2 In Koreans. Christopher J. Lessard[1], Satria Sajuthi[2], So-Young Bang[3], Hye-Soon Lee[3], Young Mo Kang[4], Chang-Hee Suh[5], Won Tae Chung[6], Soo-Kon Lee[7], Jung-Yoon Choe[8], Seung-Cheol Shim[9], Shin-Seok Lee[10], Ji Hee Oh[11], Young Jin Kim[12], Jong-Young Lee[12], Bok-Ghee Han[12], Patrick M. Gaffney[1], Timothy J. Vyse for SLEGEN[13], John B. Harley[14], Carl D. Langefeld[2], Sang-Cheol Bae[15], Kathy L. Sivils[16] and Betty P. Tsao[17]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Wake Forest School of Medicine, Winston-Salem, NC, [3]Hanyang University Guri Hospital, Guri, South Korea, [4]Kyungpook National University School of Medicine, Daegu, South Korea, [5]Ajou University Hospital, Suwon, South Korea, [6]Dong-A University Hospital, Busan, South Korea, [7]Yonsei University College of Medicine, Seoul, South Korea, [8]Catholic University of Daegu School of Medicine, Daegu, South Korea, [9]Daejeon Rheumatoid & Degenerative Arthritis Center, Chungnam National University Hospital, Daejeon, South Korea, [10]Chonnam National University Medical School and Hospital, Gwangju, South Korea, [11]Center for Genome Science, Korea National Institute of Health, Osong, South Korea, [12]Korea National Institute of Health, Osong, South Korea, [13]King's College London, Guy's Hospital, London, United Kingdom, [14]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [15]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [16]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [17]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA.

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic, heterogeneous autoimmune disorder characterized by inflammation, loss of tolerance to self-antigens, and dysregulated interferon responses. Although >40 loci have been associated with SLE, a substantial portion of the genetic risk has not been explained. Previous work has shown that the genetic architecture and associated loci differ among ancestral populations. In this study, we performed a genome-wide association scan to identify genes associated with SLE in Korean subjects.

Methods: Genotyping was performed using Illumina OMNI-express arrays with ~700,000 variants. Standard best practice quality control measures were applied for Hardy-Weinberg proportions, missing and differential missing genotypes data, genetic outliers determined by principal component (PC) analysis. Only SNPs with minor allele frequencies >1% are reported. After quality control filtering, a total of 1174 Korean SLE cases and 4248 population controls were available for analysis. SNP-SLE association was tested using logistic regression model adjusting for PC. Inference is the additive genetic model unless there was significant (P<0.05) departure from additivity, then dominant additive and recessive examined. Bioinformatic analysis was done using HaploReg ver. 2.0.

Results: Ten regions outside the HLA exceeded the genome-wide significance threshold of P<5×10E–8. Of these, 9 regions replicated previously identified SLE risk loci: *TNFSF4, STAT1-STAT4, TNFAIP3, IKZF1, HIP1, IRF5, BLK, WDFY4, and ETS1*. The novel associated locus was between *FCHSD2* and *P2RY2* on 11q14. (rs11235667, P=1×10E–8, odds ratio = 0.59, 95% CI= 0.50–0.71). No additional SNP was significant after adjusting for rs11235667 via logistic regression. Bioinformatics analysis reported that rs11235667 is a strong enhancer in B lymphoblastoid cell lines. Chromatin immunoprecipitation followed by sequencing experiments done by the ENCODE project found POL2 and YY1 proteins cross-linked to this region. Moreover, sequence prediction methods indicate that rs11235667 can alter the binding motif for the FOXa family of transcription factors.

Conclusion: We have identified a novel association in the region of *FCHSD2-P2RY2* and confirmed associations with 9 previously-associated SLE regions outside the HLA in Korean subjects. Although *FCHSD2* (FCH and double SH3 domains 2) has no known function, variants in this region are associated with Crohn's disease in Japanese subjects. P2RY2 (purinergic receptor P2Y, G-protein coupled, 2) is known to be involved in cell proliferation, apoptosis, and inflammation. In rheumatoid synoviocytes, IL-6

has been shown to increase the expression of *P2RY2*. Ongoing studies are seeking to replicate the *FCHSD2-P2RY2* association in additional samples.

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Sub-Phenotype Mapping In Systemic Lupus Erythematosus Identifies Multiple Novel Loci Associated With Circulating Interferon Alpha. Silvia Kariuki[1], Yogita Ghodke[2], Jessica M. Dorschner[2], Beverly Chrabot[1], Jennifer A. Kelly[3], Betty P. Tsao[4], Robert P. Kimberly[5], Marta E. Alarcon-Riquelme[6], Chaim O. Jacob[7], Lindsey A. Criswell[8], Kathy L. Sivils[3], Carl D. Langefeld[9], John B. Harley[10], Andrew D. Skol[1] and Timothy B. Niewold[2]. [1]University of Chicago, Chicago, IL, [2]Mayo Clinic, Rochester, MN, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [5]University of Alabama at Birmingham, Birmingham, AL, [6]Oklahoma Medical Research Foundation, Center for Genomics and Oncological Research Pfizer-University of Granada-Junta de Andalucia, Oklahoma City, OK, [7]University of Southern California Keck School of Medicine, Los Angeles, CA, [8]University of California, San Francisco, Rosalind Russell Medical Research Center for Arthritis, San Francisco, CA, [9]Wake Forest University Health Sciences, Winston-Salem, NC, [10]Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a phenotypically heterogeneous complex disease. Our previous work has documented significant genetic heterogeneity, with some well-validated risk factors demonstrating strong sub-group effects. Approximately 50% of patients have high circulating levels of interferon alpha (IFN-α), and many lines of investigation support IFN-α as a heritable and primary causal factor in human SLE. This study aims to genetically map the serum IFN-α trait in SLE patients, allowing for novel genetic discovery in this heterogeneous disease.

Methods: GWAS data were obtained from 450 European ancestry SLE cases who were genotyped as part of the Systemic Lupus Erythematosus Genetics (SLEGEN) study. Genotypes were generated on the Illumina Infinium HumanHap 300 genotyping platform, and principal component analysis was used to correct for population stratification. Sera were obtained from each of these subjects, and IFN-α activity was measured using a sensitive and specific reporter cell assay. Associations between genome-wide SNP markers and serum IFN-α were detected using logistic regression conditioned on the principal components to control for structure. IFN-α activity was studied as a categorical trait. Patients with IFN-α levels 2SD above the mean of healthy controls were designated as high IFN-α, and the remainder as low IFN-α.

Results: Top novel associated loci in the GWAS screen include multiple SNPs in the C7orf57, PRKG1, ANKRD44, and PNP loci. Interestingly, three of the 5 top SNPs are missense SNPs. Strong association signals were also detected in chromosomes 12 and 14. Genome-wide imputation using SNPs from the 1000 Genomes Project did not yield additional significant association signals beyond those identified by the directly genotyped SNPs.

Conclusion: These novel loci have not been previously associated with SLE in case-control analyses. This supports the concept that studying pathogenic subgroups within the complex disease SLE will be important in our efforts to fully map disease susceptibility. These loci could provide novel therapeutic targets in the IFN-α pathway and assist in personalizing therapy in this disease.

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Genome-Wide Transcriptional Profiling Of Isolated Immune Cell Populations From SLE Patients With Different Ancestral Backgrounds. Shruti Sharma[1], Zhongbo Jin[2], Elizabeth Rosenzweig[1], Swapna Rao[1], Kichul Ko[1] and Timothy B. Niewold[2]. [1]University of Chicago, Chicago, IL, [2]Mayo Clinic, Rochester, MN.

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex multi-system autoimmune disease of uncertain etiology. Different ancestral backgrounds demonstrate different clinical manifestations and autoantibody profiles. Whole blood gene expression studies in SLE have demonstrated a prominent type I interferon (IFN) signature. Presumably different cell types will exhibit different patterns of gene expression, and in this study we sorted major immune cell populations from PBMC and examined genome-wide transcription patterns in cell subsets and in different ancestral backgrounds.

Methods: Peripheral blood was collected from 21 African-American (AA) and 21 European-American (EA) SLE patients, 5 AA controls, and 5 EA controls. $CD4^+$ T-cells, $CD8^+$ T-cells, monocytes and B cells were purified by flow sorting. Each cell population from each subject was run on an Illumina HumanHT-12 V4 expression BeadChip array. The raw data were filtered to exclude the non-detected genes. Quantile normalization and Log2 transformation were applied prior to between-group comparisons. Differentially expressed genes (DEGs) were determined by comparing cases and controls of the same ancestral background, and then DEG lists were compared between cell types and between ancestral backgrounds. Because IFN-related gene expression differed between cell types, we also developed a novel metric to encompass IFN-induced gene expression more globally and comprehensively than pathway analyses, generating a quantitative metric.

Results: While we observed approximately 1000 DEGs in each cell type that was isolated, the overlap in DEG lists between different cell types was very modest (<1%), supporting the idea that different transcripts are upregulated in different cell types. Typically between 5 to 10% of DEGs were shared when comparing the same cell type in different ancestral backgrounds (for ex. CD20 AA vs. CD20 EA). Interestingly, gene expression profiles different cell types from the same subject exhibited individualized patterns on unsupervised hierarchical clustering, supporting some cell-type independent inter-individual variations. Quantitative measurement of global IFN-induced gene expression revealed that AA subjects demonstrated more concordance across all studied cell types in IFN-induced gene expression. In EA subjects, a subset of patients demonstrated increased IFN-induced gene expression in all lymphocyte populations but not monocytes, and another subgroup demonstrated IFN-induced gene expression in monocytes and B-cells but not in CD4 or CD8 T-cells.

Conclusion: We find fascinating differences in gene expression between different immune cell populations and between ancestral backgrounds in SLE patients. It seems that the IFN signature is relatively diverse, affecting different cell populations in different ways, and behaving differently in EA vs. AA patients. These data may impact efforts to target this pathway therapeutically.

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Identification Of Novel Genetic Associations Within Major Histocompatibility Complex (MHC) Class I and Class II In Systemic Lupus Erythematosus (SLE) Patients: An Examination Of Epitopes Of Early Autoimmunity. Gerard Dumancas[1], Chee Paul Lin[1], Indra Adrianto[1], Jennifer A. Kelly[1], Stuart B. Glenn[1], Jourdan Anderson[1], John B. Harley[2], Timothy J. Vyse[3], Robert P. Kimberly[4], Marta E. Alarcon-Riquelme[5], Carl D. Langefeld[6], Betty P. Tsao[7], Lindsey A. Criswell[8], Chaim O. Jacob[9], Patrick M. Gaffney[1], Kathy Sivils[1], Judith A. James[1] and Courtney Montgomery[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Divisions of Genetics and Molecular Medicine and Immunology, King's College London, London, United Kingdom, [4]University of Alabama at Birmingham, Birmingham, AL, [5]Oklahoma Medical Research Foundation, Center for Genomics and Oncological Research Pfizer-University of Granada-Junta de Andalucia, Oklahoma City, OK, [6]Wake Forest University Health Sciences, Winston-Salem, NC, [7]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [8]University of California, San Francisco, Rosalind Russell Medical Research Center for Arthritis, San Francisco, CA, [9]University of Southern California Keck School of Medicine, Los Angeles, CA.

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by autoantibody production, multiple organ involvement, strong genetic predisposition and specifically, to be associated with Class II alleles within the Major Histocompatibility Complex (MHC). Immunochemistry studies have shown that specific antibodies often occur years before clinical diagnosis and accrue new specificities through preclinical and clinical phases of SLE. More specifically, specific epitopes appear to

be unique to SLE patients early in the course of disease evolution, even compared to other rheumatic diseases. The goal of our study was to better characterize the role of the genes within the MHC by assessing genetic association between antibodies to early epitopes of SmB', SmD1 and 60kD Ro (termed here GMR, GRx4 and Ro169, respectively) in 703 SLE European-American (EA) and 557 African American (AA) SLE cases. We also assessed genetic association with autoantibodies directed against the parent lupus autoantigens, Sm and 60kD Ro, in both races.

Methods: Standardized ELISA assays tested serum samples for binding of SmB': amino acid sequence PPPGMRPP (GMR); SmD1: Glycine Arginine repeat sequence (GRx4); 60kD Ro: amino acids 169–180 (Ro169). Levels of anti-Sm and anti-Ro60 were determined by Bio-Rad Bioplex2200 ANA testing. All data are semi-quantitative and only measured in SLE patients. This is in contrast to previous studies, which assessed genetic association of the dichotomous trait, positive versus negative by immunodiffusion asays.

We evaluated $>$ 50,000 SNPs within the MHC in both EA and AA samples. SNP data were collected from Affymetrix Genome-Wide Human SNP Array 5.0, Illumina iSelect Infinium II, and Immunochip and imputed with IMPUTE2. Quality control included removing of SNPs with call rate $<$90%, minor allele frequency $<$0.01 and Hardy-Weinberg proportion tests $P < 0.001$.

Results: Autoantibodies against the GRx4) yielded a novel association within the Class I region, with the most significant SNP near TRIM40/TRIM15 in EAs ($P < 5 \times 10^{-7}$) and near TRIM39 in AAs ($P < 5 \times 10^{-5}$). The Ro169 was also strongly associated in EAs at this location ($P < 5 \times 10^{-5}$). Autoantibodies against the GMR showed no association with Class I genes but was significant for Class II ($P < 5 \times 10^{-4}$, nearest DQB1) in the same race. Both Sm and 60kd Ro autoantibody responses were also significantly associated within the Class I region ($P < 5 \times 10^{-5}$ and $P < 5 \times 10^{-4}$, respectively) in the EAs. 60kD Ro was also highly significant ($P < 5 \times 10^{-8}$) within the Class II region at DRB1, DQB1 and DQA1 in EAs. Further conditional analysis showed the driving effect to be within HLA-DQA1. The AA sample was significant for DQB1 and DQA1 ($P < 5 \times 10^{-6}$) for the 60kD Ro epitope.

Conclusion: Our genetic study of the MHC region identified novel association between autoantibody responses against some of the earliest epitopes of lupus, their parent proteins and Class I variants. We further confirmed and more specifically characterized association between Class II variants and 60kd Ro. These findings and other investigations into the genetic mechanisms underlying early lupus autoimmunity will give significant insight into disease etiology.

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Pro-Inflammatory HDL and Subclinical Atherosclerosis Are Associated With Altered Expression Of Epigenetic and Oxidative Stress-Related Gene Transcripts In SLE. Brian Skaggs, Bevra H. Hahn, Jennifer M. Grossman, Elaine Lourenco, Isao Matsuura, Lori Sahakian and Maureen A. McMahon. UCLA David Geffen School of Medicine, Los Angeles, CA.

Background/Purpose: Premature atherosclerosis is widely recognized as a significant co-morbid condition of systemic lupus erythematosus (SLE), but exact mechanisms are unknown. Although traditional cardiovascular risk factors correlate with subclinical atherosclerosis in cohort studies, they are unable to fully account for the increased risk. Longer SLE duration correlates with higher risk for cross-sectional and longitudinal progression of atherosclerosis, suggesting that chronic inflammation and/or oxidative stress could be SLE-specific factors contributing to accelerated atherosclerosis. Plasma pro-oxidant, pro-inflammatory HDL (piHDL) is also closely linked to presence and progression of plaque in SLE and can abnormally activate monocytes, the major immune cell type involved in atherosclerosis. Recent data have linked oxidative stress to epigenetic aberrations in non-autoimmune subjects with atherosclerosis, and we wanted to examine whether these mechanisms could partially explain the risk of premature atherosclerosis in SLE.

Methods: Patients were recruited from a pre-existing cohort to study atherosclerosis in SLE. Carotid ultrasound was performed to determine the presence or absence of subclinical atherosclerosis (plaque). HDL status was determined by a fluorometric assay examining oxidation of human LDL in the presence of patient HDL. RNA was isolated from freshly isolated primary monocytes from 51 SLE patients subdivided into three groups: a) plaque+piHDL+ (LPP, n=15), b) plaque-piHDL+ (LPN, n=18), and c) plaque-piHDL- (LNN, n=18). Whole-genome monocyte expression analysis was performed using Affymetrix Human U133+2.0 chips. dChip software (Li lab, Harvard) was utilized to determine differentially expressed transcripts between the three groups. Clustering was performed and graphed using Cluster and TreeView (Eisen lab, UC Berkeley). Confirmation of significantly altered transcript levels was determined using quantitative PCR.

Results: Expression of 385 genes was significantly altered between the LPP and LNN groups (fold change $\geq$1.2 or ≤ -1.2, $p \leq 0.05$, false discovery rate 6.8%). The majority of the differentially-expressed genes were downregulated in LPP (vs. LNN). A large proportion of genes were involved in histone acetylation, DNA methylation, and oxidative stress (14% of the total; $<$5% expected). Multiple methyltransferases (MT) were downregulated in LPP subjects, including DNMT1. The presence of piHDL correlates with lower MT, acetyltransferase, and oxidative stress transcripts, as many of the same transcripts were downregulated in the LPN group (vs. LNN). Conversely, the antioxidants peroxiredoxin2 (PRDX2) and superoxide dismutase 2 (SOD2) were upregulated in LPN and LPP groups versus LNN. Unsupervised clustering placed almost all samples into their piHDL/plaque subgroups.

Conclusion: The presence of piHDL correlates with dysregulation of multiple epigenetic and oxidative stress-related transcripts in circulating monocytes of SLE patients. Further epigenetic and biochemical experiments will determine the role of lipid and protein oxidation in the initiation of premature atherosclerosis in SLE.

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IKZF1 Modulates PP2Ac Expression Through An Intronic Binding Site. Kamalpreet Nagpal[1], Katsue S. Watanabe[2] and George C. Tsokos[1]. [1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [2]Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan.

Background/Purpose: Protein phosphatase 2A (PP2A) is a highly conserved and ubiquitous serine/threonine phosphatase. We have previously shown that mRNA and protein, as well as the activity of the catalytic subunit (PP2Ac) of PP2A are increased in T-cells of SLE patients as compared to healthy controls. This increased expression and activity of PP2A plays a central role in the molecular pathogenesis of SLE, including reduced production of the cytokine IL-2. Although the control of PP2Ac expression has been the focus of many studies, many aspects of its regulation still remain poorly understood. In this study, we identify the transcription factor Ikaros (*IKZF1*) as a novel regulator of PP2Ac expression.

Methods: CD3 (+)ve T-cells from healthy individuals were transfected with Ikaros expression plasmid using AMAXA nucleoporation. RNA and protein were isolated and Real-Time PCR and western blotting were used to analyze gene expression. Biotinylated oligos spanning the putative Ikaros binding site or a non-specific control oligo were used in pull-down assays followed by western blotting with Ikaros specific antibody to examine the binding of Ikaors. EMSA with Jurkat cells nuclear protein extract and radio-labeled oligos was used to confirm this binding. Binding of endogenous Ikaros to the PP2Ac intron region was validated by ChIP using a commercially available kit.

Results: An online *in-silico* transcription factor search identified the transcription factor Ikaros as having a binding site in the first intron of *PPP2AC* gene. To examine this binding, biotinylated oligos spanning this region in the intron were used in a pull-down assay with nuclear proteins extracted from Jurkat cells. As compared to the control oligo, the specific oligo exhibited significant binding to Ikaros. EMSA with radio-labeled oligos as well as ChIP assays in primary T-cells further validated the binding of Ikaros to this region. Exogenous expression of Ikaros in T-cells led to diminished PP2Ac expression. Conversely, siRNA enabled knockdown of Ikaros enhanced the expression of PP2Ac, suggesting that Ikaros acts as a

suppressor of PP2Ac gene expression. We also attempt to delineate the mechanism of Ikaros mediated PP2Ac gene suppression. We report that Ikaros recruits the histone deacetylase HDAC1 as well as DNA methyltransferase DNMT1 to this intronic site, thus mediating epigenetic alterations leading to reduced gene expression.

Conclusion: We show for the first time that the transcription factor Ikaros can regulate the gene expression of PP2Ac by binding to a site in the first intron. Ikaros seems to mediate this suppression by modulating chromatin modifications at this site. Our study thus identifies a novel means of control of PP2A, a critical molecule involved in lupus pathogenesis.

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Concurrent Autoimmune Disease and Autoantibodies In a Large, Multi-Racial Cohort Of First Degree Blood Relatives Of SLE Patients. Julie M. Robertson[1], Benjamin F. Bruner[2], Rufei Lu[1], Joel M. Guthridge[1], John B. Harley[3] and Judith A. James[4]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Harding University, Searcy, AR, [3]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Oklahoma Medical Research Foundation and University of Oklahoma Health Sciences Center, Oklahoma City, OK.

Background/Purpose: First degree relatives (FDRs) of SLE patients have an increased risk of developing autoantibodies and/or autoimmune disorders. Between 20% and 40% of FDRs develop autoimmune diseases. FDRs with a family history of SLE have 6 fold higher risk of developing SLE and a 4 fold higher risk for developing a non-SLE autoimmune disease. Previous studies have estimated that about 30% of FDRs develop anti-nuclear antibodies (ANA). This study is the first to examine the prevalence of autoimmune disease and autoantibody development in a large, multi-racial group of FDRs of lupus patients.

Methods: Clinical and demographic (age, sex, and self-reported race) information from individuals in the Lupus Family Registry and Repository was obtained for 1,092 FDRs of SLE patients, including information regarding diagnosed autoimmune disorders and symptoms of clinical autoimmune rheumatic diseases by connective tissue disease screening questionnaire (CSQ). Serum samples from European-American (EA, n=680), African-American (AA, n=264), and Hispanic (Hisp, n=148) individuals were examined for 13 common autoimmune rheumatic disease autoantibodies using a multiplexed bead-based assay. Autoantibody prevalence and association with non-SLE rheumatic disease and non-rheumatic disease was evaluated using Fisher's exact tests and Kruskal-Wallis tests for continuous data.

Results: Among the 403 families included in the study, 134 reported autoimmune disease in FDRs (33%). In the 1092 FDRs, 172 (15.8%) reported a rheumatic autoimmune disease while 65 (5.96%) reported a non-rheumatic autoimmune disease. The most common autoimmune disease reported was rheumatoid arthritis (RA, n= 83, 7.6% of FDR). No ethnic differences were observed in the development of non-lupus autoimmune disorders in FDRs. ANA positivity was detected in 34.3% EA, 37.1% AA, and 32.4% Hisp FDRs out of all FDRs tested. Anti-Sm/nRNP antibodies were more prevalent in African-American FDRs with a rheumatic autoimmune disease ($p<0.05$) compared to EA and Hisp individuals with rheumatic autoimmune disease. Anti-nRNP A antibodies are significantly increased in EA FDRs with a rheumatic autoimmune disease compared to a EA FDRs with a non-rheumatic autoimmune disease or no autoimmune disease. Anti-chromatin, Sm, Sm/nRNP, and 60kD Ro antibodies trend towards being increased in AA FDRs with a non-lupus rheumatic autoimmune disease compared to AA individuals with a non-rheumatic autoimmune disease or no autoimmune disease. In Hisp FDRs, antibodies against chromatin, nRNP A, and 60kd Ro are significantly more prevalent ($p<0.05$) in Hisp FDRs with.

Conclusion: First degree blood relatives of SLE patients have an increased risk for developing autoimmune disease and autoantibodies. In this large, multi-racial cohort, 21.7% of the FDRs report a non-SLE autoimmune disease and about 30% have detectible ANA. Racial differences in autoantibody prevalence are observed in FDRs of lupus patients with autoantibodies against chromatin, 60kD Ro, and Sm/nRNP being the most common autoantibody specificities.

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GWAS In Hispanic and Latin American Individuals Enriched For Amerindian Ancestry Identifies a New Locus Associated With Systemic Lupus Erythematosus. Marta Eugenia Alarcon Riquelme[1], Julie T. Ziegler[2], Mary E. Comeau[3], Elena Sanchez[4], Bernado Pons-Estel[5], Eduardo Acevedo[6], Jorge Mariano Cucho[6], Ignacio Garcia de la Torre[7], Mario H. Cardiel[8], Pedro Miranda[9], Luis Cattogio[10], Marco Maradiaga[11], Jorge Esquivel-Valerio[12], Jose F Moctezuma[13], Mercedes Garcia[14], Guillermo Berbotto[15], Alejandra Babini[16], Hugo Scherbarth[17], Sergio Toloza[18], Judith A James[1], Teresa Tusie-Luna[19], John B Harley[20], Raphael Zidovetski[21], Carl Langefeldt[2] and Chaim O. Jacob[22]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Wake Forest School of Medicine, Winston-Salem, NC, [3]Wake Forest University Health Sciences, Winston-Salem, NC, [4]King's College London, London, United Kingdom, [5]Hospital Provincial de Rosario, Rosario, Argentina, [6]Hospital Nacional Guillermo Almenara Irigoyen, Lima, Peru, [7]Hospital General de Occidente, Zapopan, Mexico, [8]Hospital General, Morelia, Mexico, [9]Universidad de Chile and Centro de Estudios Reumatologicos, Santiago de Chile, Chile, [10]Hospital Italiano, Buenos Aires, Argentina, [11]Hospital General de Culiacán, Culiacan, Sinaloa, Mexico, [12]Hospital Universitario Dr. José Eleuterio González, Universidad Autonoma de Nuevo León, Nuevo Leon, Mexico, [13]Hospital General de Mexico, Mexico, Mexico, [14]Hospital San Martin, La Plata, Argentina, [15]Hospital Eva Peron, Granadero Baigorria, Argentina, [16]Hospital Privado de Cordoba, Cordoba, Argentina, [17]H.I.G.A. Oscar E. Alende, Mar del Plata, Argentina, [18]Hospital San Juan Bautista, Catamarca, Argentina, [19]Instituto de Investigaciones Biomédicas de la Universidad Nacional Autónoma de México, and Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, Mexico, [20]Childrens Hospital, Cincinnati, OH, [21]University of Southern California, Los Angeles, CA, [22]University of Southern California Keck School of Medicine, Los Angeles, CA.

Background/Purpose: Systemic lupus erythematosus (SLE), a chronic autoimmune disease with a strong genetic component, exhibits a 9:1 female to male ratio and disproportionate impact on individuals of admixed ancestries in the Americas. We performed a genome-wide association scan on individuals from Latin America and the United States enriched for Amerindian while admixed with European ancestry.

Methods: A total of 4516 individuals were genotyped, 2906 for the Illumina Human Quadv1 (OMNI1) and data from1610 out-of-study controls for the OMNI2.5 Bead array was obtained yielding, 996,672 SNPs for final analysis (580,483 SNP were on both BeadArrays). After quality control filters were applied, a total of 3710 individuals were kept for genetic association analysis. The final inflation factor was 1.00 using the 2 first principal components (PC). Principal component analysis revealed 2 differentiated populations that corresponded to a South American (individuals from Argentina, Chile and Peru; $N = 875$), and a North American group composed of individuals from Mexico, and Hispanics and Native Americans from the United States ($N = 2835$). SNP-SLE association was tested using logistic regression model adjusting for PC. Results for the additive model are reported.

Results: One novel genetic association was identified in chromosome 10, between *INA*, *USMG5* and *PDCD11* (rs4917385, $P_{value} = 7.48 \times 10^{-8}$, min FDR p-value=0.00099, OR=0.75, CI=0.67–0.84). Several known lupus susceptibility loci were replicated. Overall, the strongest effect was that of *TNPO3-IRF5* locus, followed by the HLA class II region. Regions previously associated in Europeans that were associated for the first time in individuals with enriched Amerindian ancestry were *TNFSF4*, *NCF2*, *NMNAT2*, *JAZF1*, *FAM167A-BLK*, and *PTTG1-MiR146a*. Regions previously associated in Asians and associated for the first time in individuals with enriched Amerindian ancestry were *SLC15A4* and *WDFY4*.

Conclusion: We identify a new locus for SLE in chromosome 10. Our data show the major importance of genes outside the HLA in the susceptibility for lupus in this population and provide support for loci previously found in Asians and Europeans.

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Methotrexate Treatment Affects Effector, But Not Regulatory T Cells in Juvenile Idiopathic Arthritis. Maja Bulatovic Calasan, S.J. Vastert, Rianne C. Scholman, Frederik Verweij, Mark Klein, Nico M. Wulffraat, Berent J. Prakken and Femke van Wijk. University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: The balance between regulatory (Treg) and effector T cells (Teff) is crucial for immune regulation in juvenile idiopathic arthritis (JIA). How methotrexate (MTX), the cornerstone treatment in JIA, influences this balance *in vivo* is poorly elucidated. The aim of this study was to investigate quantitative and qualitative effects of MTX on Treg and Teff in JIA patients during MTX treatment.

Methods: Peripheral blood samples were obtained from JIA patients at MTX start and 3 and 6 months thereafter. Treg numbers and phenotype were determined by flow cytometry and suppressive function in allogeneic suppression assays. Teff proliferation upon stimulation with anti-CD3, activation status and intracellular cytokine production were determined by flow cytometry. Effector cell responsiveness to suppression was investigated in autologous suppression assays. Effector cell cytokines in supernatants of proliferation and suppression assays and in plasma were measured by cytokine multiplex assay.

Results: MTX treatment in JIA did not affect Treg phenotype and function. Instead, MTX treatment enhanced, rather than diminished, $CD4^+$ and $CD8^+$ T cell proliferation of JIA patients after 6 months of therapy, independent of clinical response. Effector cells during MTX treatment were equally responsive to Treg-mediated suppression. MTX treatment did not attenuate Teff activation status and their capacity to produce IL-13, IL-17, TNFα and IFNγ. Similarly to Teff proliferation, plasma IFNγ concentrations after 6 months were increased.

Conclusion: This study provides a novel insight that MTX treatment in JIA does not attenuate Teff function but conversely, enhances T cell proliferation and IFNγ plasma concentrations in JIA patients.

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Bispecific Antibodies For Redirection Of Human Regulatory T Cells To Surface-Inducible Autoantigen La/SS-B. Stefanie Koristka[1], Marc Cartellieri[1], Claudia Arndt[1], Anja Feldmann[1], Irene Michalk[1], Claudia C. Bippes[1], Nicole Berndt[1], Anne Hermsdorf[1], Slava Stamova[1], Biji T. Kurien[2], Robert Hal Scofield[3], A. Darise Farris[4], Judith A. James[5], Holger Bartsch[1] and Michael Bachmann[1]. [1]Carl Gustav Carus TU-Dresden, Dresden, Germany, [2]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [3]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation; Department of Medicine, University of Oklahoma Health Sciences Center; US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [4]Oklahoma Medical Research Foun, Oklahoma City, OK, [5]Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: Adoptive transfer of regulatory T cells (Tregs) represents a promising strategy for treatment of auto- and alloimmunity. However, it is difficult to obtain therapeutically relevant numbers of antigen-specific Tregs. Bispecific antibodies (bsAb) are promising tools for a target-specific redirection of polyclonal Tregs. BsAb are composed of two different antigen binding moieties facilitating the cross-linkage of two different cell types. E.g. T cells redirected by bsAb to tumor cells result in an eradication of tumor cell as shown in various *in vitro, in vivo* and first clinical trials. Recently, we reported that bsAb can also be used for redirection of Tregs leading to the search of potential target structures in inflamed tissues. Many pathological immune-mediated conditions, e.g. autoimmune diseases, graft rejection or GvHD are associated with massive cell death. Recently, we established a cell culture system allowing us to unequevocally show that the nuclear autoantigen La is released from dying cells and tightly binds to neighbouring living intact cells. Therefore, we wanted to learn if La can be used as inducible surface target for redirection of subpopulations of T cells including Teff and Tregs via bsAbs.

Methods: In order to induce cell death, cultured human cells were irradiated with UV. After irradiation human cells were cocultured with untreated murine cells. Human La released and bound to the surface of co-cultured murine cells was stained with three different anti-human La specific mabs (SW5, 5B9, 7B6). These mabs recognize well defined epitopes either in the N- (SW5, 5B9) or C-terminus (7B6) of La. Alternatively, recombinant human La was added to cultured human cells. Cell surface bound La was used for redirection of sorted Tregs via two novel bispecific anti-CD3-anti-La abs. The effects of sorted redirected Tregs on activation, cytokine release, killing efficacy, and proliferation of immune effector T cells were estimated by FACS.

Results: Two novel fully humanized bsAb targeting La and the CD3 complex of T cells were established and their capability to redirect Teff and Tregs to surface bound La was tested. Both CD4+ and CD8+ Teff redirected to surface bound La resulted in an efficient killing of target cells while highly enriched sorted Tregs were not able to mediate cytotoxicity. In contrast, the cross-linkage of Tregs with La-decorated target cells resulted in activation of both freshly isolated and expanded human Tregs. Moreover, such bsAb-activated Tregs displayed a potent suppressive capacity and negatively influenced proliferation, expansion and cytokine production of autologous CD4+ and CD8+ Teff cells.

Conclusion: Our results indicate that La released and tightly bound to the surface of living cells are accessible for abs and can therefore be used as inducible surface target for redirecting of T cell (sub)populations via bsAb. While redirected effector T cells mediate cell death Tregs can attenuate Teff cell-mediated inflammatory immune responses and tissue destruction and may therefore be useful for a site-specific recruitment of Tregs into inflamed tissues for the treatment of GvHD, autoimmunity or transplant rejection.

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CD25+CD39+ Regulatory T Cells Are Enriched At The Site Of Inflammation Of Patients With Rheumatoid Arthritis and Impaired In Suppressing IL-17A Secretion. Jessica Herrath[1], Karine Chemin[2], Inka Albrecht[1], Anca Catrina[2] and Vivianne Malmström[3]. [1]Karolinska University Hospital, Department of Medicine, Solna, Unit of Rheumatology, Stockholm, Sweden, [2]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Regulatory T cells (Tregs) are important for the maintenance of self-tolerance and are implicated in the origin of autoimmunity. Despite enrichment of Tregs in joints of rheumatoid arthritis (RA) patients, local inflammation persists and becomes chronic. Recently, CD39 expression has been described on FOXP3+ Tregs and suggested to be a novel mechanism of Treg suppression by producing anti-inflammatory adenosine together with CD73. Interestingly the capacity of CD39+ Treg to suppress Th17 responses is impaired in multiple sclerosis. Whether this defect is a general feature found in autoimmune diseases is currently unknown. In this study, we first aimed to better characterize the CD39+ Treg compartment in blood and synovial fluids from RA patients. We then further addressed their capacity in suppressing T effector cell responses, especially Th17 responses.

Methods: Multi-parameter flow cytometry was used to assess the *ex vivo* frequencies of FOXP3+CD39+ and FOXP3+CD39- Tregs in blood of healthy controls (n=11) and RA patients (n=15) as well as at the site of inflammation of RA (n=15) and spondylarthropathy patients (n=10). In addition, the differential suppressive capacity of synovial CD39+ and CD39- Tregs was investigated by conventional co-culture systems (n=6). Proliferation and cytokine secretion was measured by thymidine incorporation and luminex, respectively.

Results: FOXP3+CD39+ Tregs were enriched at the site of inflammation ($p=0.0007$) whereas synovial FOXP3+CD73+ Tregs were reduced compared to the circulation ($p<0.001$). The same pattern for CD39 and CD73 expression was also seen for the total population of synovial CD4+ T cells, ($p<0.0001$). Furthermore, synovial CD25+CD39+ Tregs were able to suppress proliferation of T effector cells ($p=0.0313$) in contrast to their CD39- counterparts that proliferated instead ($p=0.026$). Finally, cytokine suppression was exerted by the CD25+CD39+ Treg subset (and not by CD39-) for many cytokines but not for IL-17A.

Conclusion: Our data suggest that FOXP3+CD39- and FOXP3+ CD39+ Tregs are distinct subsets with different functions as exemplified by synovial CD39- T cells that proliferate *in vitro* and secrete pro-inflammatory cytokines instead of suppressing them. CD39- Tregs could represent plastic Tregs that converted to IL-17 producers under inflammatory conditions. Furthermore, we demonstrate that, in synovial fluid, CD39+ Treg are impaired in suppressing IL-17A secretion, a cytokine that may contribute to disease pathogenesis. This finding could partly explain why accumulation of Tregs is seen at the site of inflammation without facilitating remission.

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***Ex Vivo* Suppression Of RA Effector T Cells (Teff) By Mapc Media Is Synergistic With Treg.** Gali Malul[1], David Soler[2], Donald D. Anthony[3], Hillard M. Lazarus[2], Nicholas Lehman[4], Thomas McCormick[2], Julia M. Sugalski[5], Anthony E. Ting[4] and Nora G. Singer[6]. [1]MetroHealth Medical Center, Cleveland, OH, [2]Case Medical Center, Cleveland, OH, [3]Case Western Reserve University, Cleveland VA Medical Center, University Hospitals of Cleveland, Cleveland, OH, [4]Athersys, Inc., Cleveland, OH, [5]Case Western Reserve University, Cleveland, OH, [6]Director, Division of Rheumatology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH.

Background/Purpose: Use of mesenchymal/multipotent stem cells (MSCs/MAPCs) is an emerging immune modulatory therapeutic strategy promising for a number of human diseases. Multipotent adult progenitor cells (MAPC) are adherent cells isolated from adult bone marrow and have strong anti-inflammatory and immunomodulatory properties. MultiStem®, a cGMP manufactured MAPC product, is in Phase II clinical use for treatment of ischemic strokeand ulcerative colitis. We are interested in treating new onset Rheumatoid Arthritis (RA) patients with MAPC to induce immune regulation and tolerance. In the present study our goal was to demonstrate the potential for of MAPC-based therapy in new onset RA. To that end, we characterized the effect of MAPC conditioned media on RA effector T-cell (Teff) and T-regulatory (Treg) function *ex vivo*. We hypothesized that Treg function and number might improve following treatment with MAPC conditioned media. We evaluated RA Teff function in the presence of cytokine stimulated conditioned media (CCM) that was generated following co-culture with MAPC.

Methods: Active sero-positive RA subjects (RF+ or CCP+) with DAS28 scores varying from 4.5–5.8 were recruited. Teff and Treg were obtained (flow sorted) from seropositive RA patients off therapy, and 6 weeks after start of therapy with methotrexate. Treg were CD4+CD25^{hi} cells and Teff were CD4+CD25 ^{low}. To measure the effect of conditioned MAPC media and Treg on Teff responses, suppression assays were performed; RA and healthy donor (HD) Teff were incubated with CCM with or without Treg and proliferation was measured at 5– 6 days by dye dilution method and flow cytometry. The dilution of CCM to growth media (GM) ranged from a high of 7/8 to a low of 1/8 (GM is media prior to addition of cytokines or culture with MAPC).

Results: Cytokine stimulated MAPC conditioned media (CCM) alone suppressed Teff proliferation in a dose dependent fashion. Maximal suppression by CCM was observed with 7/8 CCM/GM and ranged from 48 to 80% (median 57%) suppression. Treg also suppressed Teff in a dose dependent fashion; 50% suppression of Teff proliferation was observed with Treg (no CCM) at a Treg:Teff ratio of 1:1. Combining Tregs (1:1 Treg:Teff) and CCM (CCM:GM 1:1) led to 86% suppression of Teff. Dose dependent suppression was observed with varying Treg numbers and/or CCM dilution. The possibility that Treg proliferation occurred was excluded by stimulating Treg alone with beads, and measuring proliferation as described for Teff.

Conclusion: Potent suppression of RA Teff by combining MAPC conditioned media and Treg is demonstrated. This strongly suggests that MAPC will offer therapeutic value in RA and may act in synergy with Treg. To what extent MAPC therapeutic effects *in vivo* are mediated by increases in Treg number and/or function is an open question. Studies testing MAPC therapeutically in RA should be accompanied by studies to understand mechanism.

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1644 WITHDRAWN

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Circulating CD4+CD161+ T Lymphocytes Are Increased In Seropositive Arthralgia Patients But Decreased In Patients With Newly Diagnosed Rheumatoid Arthritis. Paulina Chalan, Bart-Jan Kroesen, Kornelis S.M. van der Geest, Minke G. Huitema, Wayel H. Abdulahad, Elisabeth Brouwer and Annemieke M.H. Boots. University Medical Center Groningen, Groningen, Netherlands.

Background/Purpose: Improved understanding of the immune events discriminating between seropositive arthralgia and clinical synovitis is of key importance in rheumatology research. Ample evidence suggests a role for Th17 cells in rheumatoid arthritis (RA). We hypothesized that CD4+CD161+ T-cells representing Th17 lineage cells may be modulated prior to or after development of clinical synovitis. Therefore, in a cross-sectional study, we investigated the occurrence of CD4+CD161+ T-cells in seropositive arthralgia patients who are at risk for developing RA and in newly diagnosed RA patients. In a prospective study, we evaluated the effect of methotrexate treatment on circulating CD4+CD161+ T-cells. Next, we assessed if these cells can be detected at the level of the RA joints.

Methods: Whole blood from healthy controls (n=20), ACPA and/or RF seropositive arthralgia patients (n=26) and newly diagnosed, DMARD-free RA patients (n=35), was analyzed by flow-cytometry using anti-CD4, -CD8, -CD45RO, -CCR7, -CD161 fluorochrome-conjugated antibodies. Next, CD4+CD161+ T-cells were prospectively assessed in 26 and 12 RA patients at 3 and 6 months after MTX treatment, respectively. Paired samples (peripheral blood and synovial fluid, n=11) and enzyme-digested synovial tissue cells (n=4) from late-stage RA patients were analyzed for the same markers. T-cell cytokine production potency (IL-17, IFNγ and TNFα) was assessed in peripheral blood mononuclear cells and in synovial fluid mononuclear cells.

Results: Precursor Th17 lineage cells were found to be increased in seropositive arthralgia patients. In contrast, circulating CD161+CD4+ T-cells were decreased in newly diagnosed RA patients. The decrease in CD4+CD161+ T-cells correlated inversely with C-reactive protein ($r = -0,43$ and $p = 0.02$) and with the swollen joint count 66 ($r = -0,41$ and $p = 0.03$). Methotrexate treatment led to normalization of CD4+CD161+ T-cells and reduced disease activity. CD4+CD161+ T cells were readily detected in synovial tissue from both early and late stage rheumatoid arthritis. In addition, synovial fluid was found to be enriched for CD4+CD161+ T-cells compared to blood. Late stage synovial fluid CD4+CD161+ T-cells showed skewing towards the Th1 phenotype as evidenced by increased IFN-γ expression.

Conclusion: The changes in peripheral numbers of CD4+CD161+ T-cells in seropositive arthralgia and early RA and the enrichment of these cells at the level of the joint predict a role for CD4+CD161+ T-cells in the early immune events leading to clinical synovitis. Our findings may add to the development of RA prediction models and provide opportunities for early intervention.

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Alterations In Circulating T Follicular Helper Cells and T Regulatory Cells In Autoimmune Rheumatic Diseases Treated With B Cell Depletion Therapy: Rituximab. Pamela M.K Lutalo[1], Yuan Zhao[1], Lee Meng Choong[2], Shirish Sangle[2], Jo Spencer[1] and David P. D'Cruz[2]. [1]Peter Gorer Department of Immunobiology, School of Medicine, King's College London, London, United Kingdom, [2]Louise Coote Lupus Unit, St Thomas' Hospital, London, United Kingdom.

Background/Purpose: Granulomatosis with polyangiitis (GPA) and systemic lupus erythematosus (SLE) are autoimmune rheumatic diseases which develop due to failure of immune self-tolerance. T follicular helper cells have been linked with autoimmunity, where they are thought to reduce B cell survival threshold. In contrast, T regulatory cells can suppress autoimmune responses.

Hypothesis:GPA and SLE patients have low T regulatory (T_{REG}) cell frequencies and high circulating T follicular helper (cT_{FH}) cell frequencies during severe, active disease. B cell depletion therapy may correct disease-associated changes of cT_{FH} and T_{REG} frequencies in treatment responsive patients.

Methods: A longitudinal study of GPA and SLE patients treated with rituximab, an anti-CD20 monoclonal antibody.

Fluorochrome labelled antibody cell staining (FACS) flow cytometry of peripheral blood mononuclear cells was analysed for $CD4^+$ $CD25^{high}CD127^{low}$ T_{REG} cells, $CD3^+CD4^+CXCR5^{high}PD1^{high}$ cT_{FH} cells and B lymphocyte subsets pre-rituximab and at 1 month, 3 months and 6-months post-rituximab.

The Birmingham Vasculitis Activity Score (BVAS) and SELENA-SLEDAI score were used to measure disease activity in GPA and SLE patients.

Statistical analysis was done using GraphPad Prism 5.

Results: Mean age of GPA patients 47 years (25–67), SLE patients 38years (18–64) and healthy controls (HC) 44 years (23–65).

cT_{FH}%$CD4^+$ lymphocytes in HC mean=0.24%, GPA pre-rituximab=0.68% [p=0.02] and SLE pre-rituximab=0.69% [p=0.0001]. GPA 3-months post-rituximab mean cT_{FH}=0.24% [p=0.02], GPA 6-months post-rituximab mean=0.42% [p=0.01] compared to GPA pre-rituximab. SLE 3-months post-rituximab mean cT_{FH}=0.34% [p=0.006], SLE 6-months post-rituximab mean cT_{FH}=0.39% [p=0.09] compared to SLE pre-rituximab.

T_{REG}%$CD4^+$ lymphocytes in HC mean=8.42%, GPA pre-rituximab=5.06% [p=0.001] and SLE pre-rituximab=8.25% [p=0.95].GPA 3-months post-rituximab mean T_{REG}=7.96% [p=0.04], GPA 6-months post-rituximab mean=6.74% [p=0.1] compared to GPA pre-rituximab. SLE 3-months post-rituximab mean T_{REG}=12.15% [p=0.03], SLE 6-months post-rituximab mean T_{REG}=9.68% [p=0.04] compared to SLE pre-rituximab.

GPA pre-rituximab mean BVAS=16, 3-months post-rituximab=3 [$p < 0.0001$] and 6-months post-rituximab=7 [p=0.06]. BVAS shows a positive correlation with cT_{FH} cell frequencies r=0.51 [p=0.004] and negative correlation with T_{REG}cell frequencies r=−0.45 [p=0.01].

Mean SELENA-SLEDAI score pre-rituximab=14, 3-months post-rituximab=4 [p<0.0001] and 6-months post-rituximab=3 [p=0.0003].

SELENA-SLEDAI scores show a positive correlation with cT_{FH} cell frequencies r=0.50 [p=0.005] and negative correlation with T_{REG}cell frequencies r=−0.51 [p=0.004].

Conclusion: The frequencies of cT_{FH} are higher in severe, active GPA and SLE compared to health, whilst the frequencies of T_{REG} are only lower in GPA compared to health. cT_{FH} and T_{REG}frequencies were similar to those in healthy controls following successful treatment with rituximab.

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An Altered Frequency Of Circulating Follicullar T Helper Cell Counterparts and Their Subsets Is Associated With Increased Circulating Plasmablasts In Seropositive RA Patients. Irene Arroyo-Villa[1], M. Belén Bautista-Caro[1], Alejandro Balsa[1], Pilar Aguado[1], Alejandro Villalba[1], Chamaida Plasencia[1], Amaya Puig-Kröger[2], Emilio Martín-Mola[1] and Maria Eugenia Miranda-Carus[1]. [1]Hospital La Paz-IdiPaz, Madrid, Spain, [2]Hospital Gregorio Marañon, Madrid, Spain.

Background/Purpose: Follicular T helper (Tfh) cells, a CD4 T helper subset localized in lymphoid organs, help B cell differentiation and function. Circulating CD4 T cells expressing CXCR5 together with ICOS and/or PD-1 are considered as counterparts of Tfh, can function as B cell helpers, and can be subdivided into three subpopulations based on the expression of CCR6 and/or CXCR3: CXCR5+CXCR3+CCR6- (Tfh-Th1), CXCR5+CXCR3-CCR6+ (Tfh-Th17) and CXCR5+CXCR3-CCR6- (Tfh-Th2). Only Tfh-Th17 and Tfh-Th2, as opposed to Tfh-Th1, seem to display functional properties of Tfh cells. An altered proportion of these subpopulations has been associated with autoimmune diseases. Terefore, our objective was to study the frequency of circulating Tfh and Tfh cell subsets together with the frequency of circulating plasmablasts (CD19+CD20-CD27+CD38high B cells) in patients with Rheumatoid Arthritis (RA).

Methods: Peripheral blood was drawn from healthy controls (n=27) and RA patients (n=27). After isolation by Ficoll- Hypaque gradient, PBMCs were stained with antibodies to CD3, CD4, CXCR5, ICOS, PD-1, CCR6, CXCR3, CD19, CD20, CD27, and CD38, and examined by flow cytometry. The percentages of CXCR5+CXCR3+CCR6- (Tfh-Th1), CXCR5+CXCR3- CCR6+ (Tfh-Th17) and CXCR5+CXCR3-CCR6- (Tfh/Th2) cells were calculated after gating for CD3, CD4 and CXCR5+. The percentage of CD20-CD38high cells was calculated after gating for CD19+ and CD27+.

Results: The frequency of circulating CXCR5+ cells gated for CD4+ T cells was not different among the studied groups. In contrast, RA patients demonstrated an increased frequency of CD4+CXCR5+ICOS+PD-1+ cells. Furthermore, in RA patients, the frequency of Tfh-Th1 cells was significantly decreased and the frequency of Tfh-Th17 and Tfh-Th2 cells was significantly increased as compared with controls. Subsequently, the ratio (Tfh-Th17+Tfh-Th2)/Tfh-Th1 was increased in RA patients. When examining seropositive (RF+ and/or ACPA+) and seronegative RA patients (RF- and ACPA-) separately, it was evident that the above described alterations were only apparent in seropositive RA. That is, seropositive but not seronegative RA patients demonstrate a higher proportion of Tfh subsets bearing a phenotype associated with B cell helping capacity. At the same time, the frequency of circulating plasmablasts was increased in seropositive but not in seronegative RA. Interestingly, there was a significantly positive correlation between the percentage of circulating plasmablasts and the frequency of CXCR5+ICOS+PD-1+CD4+ T cells. In addition, the frequency of circulating plasmablasts showed a positive correlation with the ratio (Tfh-Th17+Tfh-Th2)/Tfh-Th1.

Conclusion: Seropositive, but not seronegative RA patients, demonstrate an increased frequency of circulating Tfh counterparts (CXCR5+ICOS+PD-1+CD4+ T cells) and altered proportions of circulating Tfh subpopulations, with overrepresentation of subsets bearing a phenotype associated with B cell helping capacity. At the same time, an increased proportion of circulating plasmablasts is apparent in seropositive RA patients.

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PD-$1^+$$CD45RB^{lo}122^{lo}$ Autoantibody-Inducing CD4 T Cells (*ai*CD4 T cells) As a Key In The Pathogenesis Of Systemic Lupus Erythematosus (SLE). Yumi Miyazaki, Ken Tsumiyama and Shunichi Shiozawa. Kyushu University Beppu Hospital, Beppu, Japan.

Background/Purpose: We found that systemic lupus erythematosus (SLE) was induced experimentally by repeatedly immunizing the mice normally not prone to autoimmune diseases by any exogenous antigen so far examined (Tsumiyama K. *et al.* PLoS ONE 4(12):e8382, 2009). We have then proposed a novel 'self-organized criticality theory' that takes place when host's immune system is overstimulated by repeated exposure to antigen to levels that surpass the immune system's stability limit, i.e., self-organized criticality. The autoreactive lymphocyte clones, which we name autoantibody-inducing CD4 T cells (*ai*CD4 T cells), are newly generated *via de novo* T cell receptor (TCR) revision from thymus-passed non-autoreactive clones at peripheral lymphoid organs. They not only stimulated B cells to generate varieties of autoantibodies but also helped final differentiation of CD8 T cell into cytotoxic T lymphocyte (CTL) *via* antigen cross-presentation to induce tissue injuries identical to SLE. We further showed that the transfer of $CD45RB^{lo}122^{lo}$ CD4 T cell of repeatedly-immunized mice could did induce autoantibodies in the naïve recipients, indicating that *ai*CD4 T cell seemed to belong to $CD45RB^{lo}122^{lo}$ CD4 T subpopulation. To identify the phenotype of *ai*CD4 T cell in more detail, we here performed microarray analysis and cell transfer assay to show that *ai*CD4 T cell belongs to PD-1^+ $CD45RB^{lo}122^{lo}$CD4 subpopulation.

Methods: BALB/c mice were repeatedly immunized with ovalbumin (OVA). To investigate gene expression profiles of *ai*CD4 T cell, we performed microarray analysis (Whole Mouse Genome Microarray; Agilent Technologies) of $CD45RB^{lo}122^{lo}$ CD4 T cell after immunization 12x with OVA. We also studied protein expression on $CD45RB^{lo}122^{lo}$ CD4 T cell by flow cytometric analysis. $CD45RB^{lo}122^{lo}$CD4 T cells were isolated additionally referring to PD-1 expression, and these fractionated cells were adoptively transferred into naïve recipients. Autoantibodies in sera of recipient mice were measured 2 weeks after cell transfer.

Results: Upon repeated immunization 12x with OVA, varieties of autoantibodies including RF, anti-Sm and anti-dsDNA antibodies were generated. Under microarray analysis, we compared the gene expression profile between $CD45RB^{lo}122^{lo}$ CD4 T cell and the rest of CD4 T cell subsets after immunization 12x with OVA. We found that gene expression of programmed cell death 1 (PD-1) was increased x2 in the $CD45RB^{lo}122^{lo}$ CD4 subset. Simultaneously, surface expression of PD-1 protein was also significantly increased in this subset: The PD-1^+ cell was concentrated up to 25.2 ± 6.3% in $CD45RB^{lo}122^{lo}$ CD4 T subset versus 7.5 ± 2.4% in $CD45RB^{hi}$ and/or $CD122^{hi}$ CD4 T subset ($P < 0.001$). Adoptive cell transfer from 12x immunized mice showed that RF and anti-dsDNA antibody in the transferred

recipients with PD-1^{+}CD45RB^{lo}122^{lo} CD4 T cell were 36.3 ± 336.0 U/ml and 0.5 ± 0.007 AU, whereas those with PD-1^{-}CD45RB^{lo}122^{lo} CD4 T cell were 12.6 ± 2.9 U/ml and 0.4 ± 0.002 AU, respectively ($P < 0.05$ and $P < 0.05$). These results indicated that PD-1^{+}CD45RB^{lo}122^{lo}CD4 T cells were capable of inducing autoantibodies in the naïve recipients.

Conclusion: The *ai*CD4 T cell that induces SLE belongs to a PD-1^{+}CD45RB^{lo}122^{lo} CD4 subpopulation.

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Assessment Of Cytomegalovirus-Specific T Cell Responses Upon Initiation Of Immunosuppression In Patients Suffering From Rheumatic Diseases As Novel Approach For Functional Immune Monitoring. Emmanuelle Le Bras[1], Sandra Weigand[2], Ludwig Deml[3], Dagmar Halbritter[4], Boris P. Ehrenstein[2], Wolfgang Hartung[2] and Martin Fleck[1]. [1]University Medical Center of Regensburg, Regensburg 93053, Germany, [2]Asklepios Clinic Bad Abbach, Bad Abbach, Germany, [3]Lophius Biosciences GmbH, Regensburg 93053, Germany, [4]University Medical Center of Regensburg, 93042 Regensburg, Germany.

Background/Purpose: The management of immunosuppressive therapies is challenging, as physicians are confronted with difficulties to keep the balance between immunosuppression on one hand and raised risk of infection on the other hand. Currently, there is no standardized immune monitoring established helping to guide immunosuppression. Therefore, CMV-specific T cell responses were analyzed before and after initiation of immunosuppression in patients with newly diagnosed rheumatic diseases to assess the immune network in a functional fashion.

Methods: PBMC were isolated from treatment naive patients and at different time points following initiation of immunosuppression using a ficoll-separation protocol, and stimulated utilizing a novel urea-activated-CMV-tegument phosphoprotein 65 (pp65, T-Track® CMV, Lophius Biosciences, Germany). Protein specific T cell responses were analyzed and quantitated by ELISPOT detecting IFN-γ secreting cells. In addition, FACS-analyses have been performed simultaneously to observe phenotypic changes in PBMC subpopulations utilizing characteristic surface markers.

Results: 23 treatment naive patients suffering from newly diagnosed rheumatic diseases were included in this study (RA: 11, PMR: 7, SpA: 3, connective tissue diseases: 3). In total, 14 of the 23 patients (60,8%) had a positive IgG-CMV-serology and were further analyzed. A CMVpp65-specific T cell response could be observed in 5 of these 14 CMV-positive patients (35,7%) allowing for monitoring of the T cell function. There was a decrease of more than 80% of IFN-γ secreting cells 8–19 days (mean 10,6; SD ± 4,7) following initiation of immunosuppression (cumulative glucocorticoid dosage median: 405 mg) in 4 (80%) of these patients demonstrating substantial impairment of the specific immune response leading to a diminished T cell function. In contrast, no or only a minimal decrease in IFN-γ secreting cells could be observed in 1 (20%) patient despite immunosuppressive therapy. Phenotypic analyses revealed an increase (mean +26%) of the effector-memory CD4+-T-cell population in all patients, as well as a rise (mean +22%) of the central memory CD4+-T-cells. Moreover, there was a decrease of CD8+-T cells (mean −23,7%) as well as NK cells (mean −46%), whereas a substantial increase (mean +70%) could be observed in the memory B-cell subpopulation. From the CMV-positive patients, 8 could be followed-up. Clinically relevant infections occurred in 3 patients. 2 of these patients presented with an impaired pp65 specific T cell response already before initiation of immunosuppression, whereas a dramatic decrease of −86% in IFN-γ secreting cells could be observed in one patient 12 weeks following initiation of immunosuppression, who developed a respiratory infection.

Conclusion: The present results demonstrate a substantially impaired function of the specific immune system in a subgroup of patients following initiation of immunosuppression. We propose that these patients have a higher risk for infection and that utilization of the novel Elispot-assay based on urea-activated CMV-pp65 has the potential to guide immunosuppression as a valuable tool for functional immunmonitoring.

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The Route Of T Cell Priming Determines The Requirement For IL-23 In The Development Of Arthritis. Alison Finnegan, Yanxia Cao and Susan Olalekan. Rush University Medical Center, Chicago, IL.

Background/Purpose: Rheumatoid arthritis is a very heterogeneous disease and distinct molecular mechanisms may underlie the disease process. IL-23 is an important cytokine for the expansion of Th17 cells and in the development of a number of autoimmune diseases. IL-23 is a heterodimeric cytokine composed of p19 and p40 subunits. IL-12, an important cytokine for differentiation of Th1 cells, is composed of p40 and p35. We have reported in proteoglycan-induced arthritis (PGIA) that the route of antigen exposure, intraperitoneal (i.p.) versus subcutaneous (s.c.), determines the Th1/Th17 phenotype respectively of the T cells involved in arthritis. In this study, we assess the contribution of IL-23 to the development of PGIA induced by i.p. or s.c. immunization.

Methods: Wild type (WT), p19$^{-/-}$ and p40$^{-/-}$ female BALB/c mice (>3 months of age) were immunized i.p. or s.c. with 50 ug recombinant G1 domain of human PG in adjuvant dimethydioctadecy ammonium bromide (DDA) 3 times at 3-week intervals. Paws were examined every third day for arthritis assessed based on the intensity of erythema and swelling on a score of 1–4. ELISA measured cytokines from CD4^{+}T cells and spleen cells re-stimulated in vitro with PG. T cell intracellarular cytokines were assessed by flow cytometry.

Results: In p19$^{-/-}$ mice, arthritis severity was significantly reduced in s.c. immunized mice, but only mildly reduced in i.p. immunized mice. In p40$^{-/-}$ mice, arthritis was significantly reduced in both i.p. and s.c. immunized mice. Levels of IL-17 were suppressed in splenocytes and inguinal lymph nodes (LN) from p19$^{-/-}$ mice either s.c. or i.p. immunization. However, IFN-γ levels were reduced only in p19$^{-/-}$ mice after s.c. immunization. To determine if suppression of IFN-γ was an early event after T cell priming we assess splenocyte responses early after immunization on day 9, IFN-γ was not suppressed in p19$^{-/-}$ mice. In p40$^{-/-}$ mice, IFN-γ and IL-17 responses were reduced after id or i.p. immunization.

Conclusion: The present results demonstrate that IL-23 plays a critical role in the development of arthritis after s.c. immunization and a minor role after i.p. immunization. Since p40 is a shared subunit of IL-12 and IL-23 reduction in arthritis after i.p. or s.c. follows the requirement of IL-12 in Th1 responses after i.p. immunization and the requirement for IL-23 in Th17 responses after s.c. immunization. These data suggest that activation of T cells in different compartments or routes of antigen exposure could affect the dominance of a Th1 versus a Th17 response.

Disclosure: A. Finnegan, None; **Y. Cao**, None; **S. Olalekan**, None.

1651 WITHDRAWN

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Autophagy May Contribute To Glucocorticoid Resistance In Patients With Myositis By Maintaining T Lymphocytes Homeostasis In The Muscles. Mei Zong[1], John Jörholt[2], Julia Winter[2], Eva Lindroos[3], Helena E. Harris[2] and Ingrid E. Lundberg[1]. [1]Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, [2]Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology Unit, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden., Stockholm, Sweden.

Background/Purpose: Infiltrating T cells is a typical histopathologic feature in muscles of patients with myositis and these cells are also believed to play important roles in the disease development. In contrast to macrophages which can be reduced after glucocorticoid (GC) treatment, T cells often persist after treatment. The explanation for these persisting T cells after treatment even with high doses of GC is still unclear. Autophagy helps cells to survive under variable cellular stresses. In this context the effects of endogenous, cytosolic high mobility group box 1 (HMGB1) protein is of interest as HMGB1 can induce autophagy by binding Beclin1 (an upstream protein initiating autophagy) and thereby contribute to cell survival. In this study, we investigated whether autophagy initiated by HMGB1-Beclin1 binding can contribute to T cell survival in the muscles of patients with myositis, and whether this homeostasis of T cells can contribute to the GC resistance.

Methods: Muscle biopsies were obtained from poly- and dermatomyositis patients with no or limited clinical response to GC and from patients with good response to GC. Biopsies were investigated by immunohistochemistry for macrophages (CD163, CD68), T cells (CD3), HMGB1 and Beclin1. Computer image analysis was performed for each marker. Co-localization of HMGB1, Beclin1 and T cells was done by consecutive section staining and was confirmed by double fluorescence staining.

Results: Both HMGB1 and Beclin1 expression was detected in muscle tissue of patients with myositis; furthermore, the expression co-localized to the infiltrating T cells as demonstrated by consecutive section staining and double fluorescence staining. Moreover, the expression of HMGB1 and Beclin1 correlated strongly ($p=0.002$, $R=0.8$). In five patients who were good responders, the number of T cells in the muscles was decreased after treatment, and simultaneously the HMGB1 and Beclin1 expression was decreased. Analyses are ongoing on the non-responders. According to our hypothesis in these patients T cells will not be reduced after treatment and HMGB1 and Beclin1 expression will maintain at high levels too.

Conclusion: Markers of autophagy are present in the invading T cells in muscle tissue of myositis patients. Autophagy initiated by HMGB1-Beclin1 binding may contribute to T cell survival in the muscles of patients with myositis. And this homeostasis in T cells could be a factor that contributes to the GC resistance.

Disclosure: M. Zong, None; **J. Jörholt**, None; **J. Winter**, None; **E. Lindroos**, None; **H. E. Harris**, None; **I. E. Lundberg**, BMS, 2, Novartis Pharmaceutical Corporation, 5.

1653

Rheumatoid Arthritis Synovial IL-21+CD4+ T Cells Specifically Induce Matrix Metalloproteinase Production By Fibroblast-Like Synoviocytes. Maria C. Lebre[1], Pedro L. Vieira[2], Saïda Aarrass[1], Thomas Newsom-Davis[2], Paul Peter Tak[3] and Gavin R. Screaton[2]. [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Imperial College London, London, United Kingdom, [3]Academic Medical Center/University of Amsterdam, Department of Clinical Immunology and Rheumatology & GlaxoSmith-Kline, Amsterdam, Netherlands.

Background/Purpose: IL-21 is a cytokine produced by activated CD4+ T cells and T follicular helper cells (TFh) that has been implicated in several autoimmune diseases including rheumatoid arthritis (RA). IL-21 regulates antibody production by B cells and induces osteoclastogenesis, mechanisms that contribute to rheumatoid arthritis (RA) pathology. Importantly, IL-21R blockade ameliorates arthritis in mice. Here we investigated the functional characteristics of synovial CD4+IL-21+ T cells in RA.

Methods: Matched peripheral blood (PB) and synovial fluid (SF) from 13 RA and 6 psoriatic arthritis (PsA) patients, and PB of 17 healthy control (HC) subjects were stimulated with PMA/Ionomycin/brefeldin A and intracellular cytokine production assessed by FACS. STAT3-dependent IL-21 production by SF CD4+ T cells was investigated by using a STAT3 specific inhibitor (WP1066). The effects of IL-21 were evaluated on cytokine and matrix metalloproteinase (MMP) release by RA synovial biopsies. In addition, the capacity of sorted RA SF IL-21+ or IL-21-CD4+ T cells in mediator release by fibroblast-like synoviocytes (FLS) was evaluated in co-cultures. IL-21, IL-6 and MMP-1 and MMP-3 concentrations were assessed by ELISA.

Results: The frequency of both SF IL-21+CD4+ or IL-21+TNF-a+CD4+ T cells in RA was significantly higher compared to PsA ($p=0.0140$ and $p=0.0038$, respectively). STAT3-specific inhibitor blocked significantly the production of IL-21 by SF CD4+ T cells. Synovial IL-21+CD4+ T cells did not phenotypically fit the TFh cell paradigm in that they did not co-express CXCR5 and ICOS. The levels of SF IL-21 were associated with CRP, MMP-1 and MMP-3. Related to this, IL-21 selectively induced MMP-1 and MMP-3 secretion by RA synovial biopsies. Sorted SF IL-21+CD4+ T cells induced specifically the release of MMP-1 and MMP-3 by FLS compared to medium (both $p<0.0001$) or IL-21-CD4+ T cells ($p=0.0035$ and $p=0.0088$, respectively). This induction was specific since the capacity of IL-21+ and IL-21- CD4+ T cells to induce IL-6 production by FLS was similar.

Conclusion: The results of this study support the notion that RA IL-21-producing CD4 T cells are involved in promoting joint destruction by inducing MMP release and might be a therapeutic target in RA.

Disclosure: M. C. Lebre, None; **P. L. Vieira**, None; **S. Aarrass**, None; **T. Newsom-Davis**, None; **P. P. Tak**, None; **G. R. Screaton**, None.

1654

Characterization Of T Cell Phenotype and Function In a Double Transgenic (Collagen-Specific TCR /HLA-DR1) Humanized Model Of Arthritis. Seunghyun Kim[1], Bo Tang[2], Sarah Hammond[1], DL Cullins[1], David Brand[3], EF Rosloniec[1], John M. Stuart[4], Arnold E. Postlethwaite[1], AH Kang[1] and Linda Myers[1]. [1]University of Tennessee Health Science Center, Memphis, TN, [2]St. Jude Children's Research Hospital, Memphis, TN, [3]VA Medical Center, Memphis, TN, [4]VA Medical Center, University of Tennessee Health Science Center, Memphis, TN.

Background/Purpose: T cells orchestrate joint inflammation in rheumatoid arthritis (RA), yet they are difficult to study due to the small numbers of antigen-specific cells. The goal of this study was to characterize the phenotypic and functional changes that occur in autoimmune T cells following the induction of pathological events in a humanized model of arthritis.

Methods: We developed a double transgenic mouse containing both the HLA-DR1 transgene and an HLA-DR1-restricted CII (263–273)-specific TCR in order to more closely mimic the human immune responses that occur in RA.

Results: *In vitro*, CII-specific T cells demonstrated an increased ability to proliferate in response to the CII immunodominant peptide and the cells altered their phenotype to become predominately $CD62L^{low}$ and $CD44^{high}$ "activated" T cells. Functionally, the CII-specific T cells produced increased levels of Th1, Th2, and Th17-type cytokines in comparison to controls from HLA-DR1 single transgenic animals, when challenged with CII peptide. Following immunization with CII/CFA, these mice develop an accelerated arthritis compared to single transgenic HLA-DR1 mice. Histology confirmed that the double transgenic mice had greater pannus formation and cartilage destruction when compared to arthritic DR1 mice. On the other hand, when the mice were treated orally with the analog peptide A12, the arthritis was significantly suppressed, despite the fact that >90% of the CD4+ T cells express the TCR Tg. In the A12-treated mice, IL-2, IFN-γ, and IL-17 production dropped and high levels of IL-10 and IL-4 were produced.

Conclusion: These data suggest that the model will be useful to study T cell directed therapies as well as the mechanisms of autoimmune diseases.

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HLA-B27 and KIR3DL2 Interactions Promote The Differentiation and Survival Of Proinflammatory T Cells In Spondyloarthritis. A. Ridley, I. Wong-Baeza, H. Hatano, J. Shaw, H. Al-Mossawi, P. Bowness and S. Kollnberger. University of Oxford, Oxford, United Kingdom.

Background/Purpose: T helper 17 (Th17) cells are a subset of pro-inflammatory CD4+ T cells implicated in a number of inflammatory arthritides including the Spondyloarthritides (SpAs). Ankylosing Spondylitis (AS), the commonest spondyloarthropathy, is genetically associated with HLA-B27 (B27) and IL-23 receptor polymorphisms, however the link remains unexplained. We have previously shown KIR3DL2+ CD4+ T cells are expanded in the peripheral blood of individuals with AS. In addition to classically folded heterotrimers, HLA-B27 can form β2m-free homodimers (B272). B272, as well as free heavy chains, are able to interact with KIR3DL2. The aim of this study was to investigate whether KIR3DL2 expression was induced by activation of CD4+ T cells and to investigate the consequence of co-culturing HLA-B272-expressing cells with KIR3DL2+ CD4+ T cells.

Methods: Production of cytokines by PMA/ionomycin stimulated-peripheral blood mononuclear cells (PBMCs) was investigated by intracellular cytokine staining (ICS). KIR3DL2 expression by PMA/ionomycin stimulated-naïve CD4+ T cells was investigated by flow cytometry (FACS). Expression of Bcl-2, RORC and T-bet by naïve CD4+ T cells was investigated using qPCR after co-culture with SEB stimulated-HLA-B272-expressing cells, or control HLA-expressing cells.

Results: KIR3DL2+ CD4+ T cells from AS patients are enriched for production of IL-17 ($p<0.0001$, $n=16$) and IL-17/IFNγ ($p=0.002$, $n=8$), as compared to KIR3DL2- CD4+ T cells. KIR3DL2+ CD4+ T cells from AS patients produce more IL-17 than KIR3DL2+ CD4+ T cells from HLA-B27- healthy controls ($p=0.013$). Naïve CD4+ T cells express KIR3DL2

de novo by FACS after activation (p=0.02, n=3). Co-culture of naïve CD4+ T cells with HLA-B272-expressing cells further increased KIR3DL2 expression and increased expression of the anti-apoptotic molecule Bcl-2. Time-dependant alterations in RORC and T-bet expression were observed.

Conclusion: Expression of KIR3DL2 on naïve CD4+ T cells can be induced by activation. Co-culture of naïve CD4+ T cells with HLA-B272-expressing cells preferentially promotes the survival of KIR3DL2+ CD4+ T cells and promotes a Th17 (and Th1) transcriptional profile. SpA KIR3DL2+ CD4+ T cells are enriched for production of IL-17 and for dual production of IL-17 and IFNγ, consistent with the theory that AS is a Th17 or a Th17/1 driven disease.

Disclosure: A. Ridley, None; **I. Wong-Baeza**, None; **H. Hatano**, None; **J. Shaw**, None; **H. Al-Mossawi**, None; **P. Bowness**, None; **S. Kollnberger**, None.

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Interferon Type I and T Helper 17: A Dangerous Liaison In Primary Sjögren's Syndrome? Zana Brkic, Sandra M.J. Paulissen, Cornelia G. van Helden-Meeuwsen, Naomi I. Maria, Odilia B.J. Corneth, Nadine Davelaar, Jan Piet van Hamburg, Paul L. Van Daele, Virgil A. Dalm, Martin van Hagen, Erik Lubberts and Marjan A. Versnel. Erasmus Medical Center, Rotterdam, Netherlands.

Background/Purpose: The T helper 17 (Th17) cell subset, which produces IL-17A, IL-17F, IL-22 and IL-21, has been implicated in the pathogenesis of primary Sjögren's syndrome (pSS). The aim of this study was to elucidate a possible link between the Th17 system and another key-player in the pathogenesis of pSS− Interferon (IFN) type I.

Methods: IFN type I signature was assessed by mRNA expression of IFN type I inducible genes. Th cell populations were analyzed by flow cytometry in peripheral blood of 12 pSS patients positive (IFN+) and 12 patients negative (IFN-) for the IFN type I signature and 12 healthy controls (HC). Cytokine expression by memory Th cells (CD4+ CD45RO+) cells and memory CCR6+ Th cells (CD4+CD45RO+ CCR6+) cells was assessed.

Results: Th17 (defined as CD4+CD45RO+CCR6+CCR4+CXCR3-CCR10-) and Treg cell percentages were significantly increased in IFN+ patients compared with IFN- patients and HC. This was accompanied by a significant decrease in Th1 cells in IFN+ patients compared to HC. IL-22 and IL-21 production by memory Th cells and memory CCR6+ cells was higher in IFN+ patients. Interestingly, Th17 cell percentage was significantly correlated with presence of anti-SSA antibodies, hypergammagloblulinemia and elevated expression of monocyte B cell activating factor (BAFF), all three previously found in IFN type I signature positive patients.

Conclusion: Here we show for the first time a relation between two key players of pSS pathogenesis − IFN type I and the Th17 pathway. This study brings new insights in the pathogenesis of pSS, having possible implications for future treatment.

Disclosure: Z. Brkic, None; **S. M. J. Paulissen**, None; **C. G. van Helden-Meeuwsen**, None; **N. I. Maria**, None; **O. B. J. Corneth**, None; **N. Davelaar**, None; **J. P. van Hamburg**, None; **P. L. Van Daele**, None; **V. A. Dalm**, None; **M. van Hagen**, None; **E. Lubberts**, None; **M. A. Versnel**, None.

ACR/ARHP Poster Session B
Vasculitis II

Monday, October 28, 2013, 8:30 AM–4:00 PM

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Enothelin-1 Plays a Role In The Pathogenesis Of Reversible Cerebral Vasoconstriction Syndrome. Tariq Hammad[1], Leonard H. Calabrese[1], Ken Uchino[2], Seby John[2], Mark Stillman[2], Stewart Tepper[2], Colin O'Rourke[1], Allison Janocha[1], Serpil Erzurum[1] and Rula Hajj-Ali[2]. [1]Cleveland Clinic, Cleveland, OH, [2]Cleveland Clinic Foundation, Cleveland, OH.

Background/Purpose: Cerebral vasoconstriction is thought to be the underlying pathogenetic mechanism of Reversible Cerebral Vasoconstriction Syndromes (RCVS). However, mediators of the syndrome at molecular levels have not been elucidated. We aim in this proposal to assess the role of Endothelin-1 (E-1), a potent vasoconstrictor, in the pathogenesis of RCVS.

Methods: Seven patients with RCVS, recruited from the Cleveland Clinic prospective RCVS registry were included. Five peripheral blood samples were collected during the cerebral vasoconstrictive acute attack (group 1) and four samples after complete resolution of the vascular abnormalities and resolution of the symptoms (group 2). Further, E-1 levels were measured from 10 healthy controls of similar races and genders, who were then matched to group 1 using a one-to-one Greedy matching algorithm based on age. Plasma E-1 levels were measured using Quantikine Endothelin-1 enzyme-linked immunosorbent assay kit (from R& D Systems) according to the user manual. Average E-1 levels for patients was compared to the average E-1 levels for matched healthy patients using mixed effects modeling to account for matched group clustering.

Results: During the acute vasoconstrictive attack, average plasma E-1 level differs significantly between the patients and the healthy controls (p = 0.002). Mean plasma E-1 levels for RCVS patients (group 1) was estimated to be about 1.2 pg/ml (95% CI 0.6 pg/ml – 1.7 pg/ml) higher as compared to the healthy controls. Paired samples from the same patients (during the acute attack and after resolution) were available from two patients (4 samples). In these patients, there was a trend for plasma E-1 level to decline to the average level of healthy controls (2.7 to 1.6 and 2.8 to 1.2) when comparing acute attack to the resolution phase levels. Average plasma E-1 levels of all patients in group 2 (the resolution phase, n=4) was 1.41pg/ml similar to the average plasma healthy control group.

Conclusion: Plasma Endothelin-1 (E-1) levels are significantly elevated in RCVS patients during the vasoconstrictive acute attack as compared to healthy controls, with a trend to decline after resolution of the vasoconstriction. These results suggest a potential role of E-1 in the pathogenesis of RCVS.

Disclosure: T. Hammad, None; **L. H. Calabrese**, None; **K. Uchino**, None; **S. John**, None; **M. Stillman**, None; **S. Tepper**, None; **C. O'Rourke**, None; **A. Janocha**, None; **S. Erzurum**, None; **R. Hajj-Ali**, None.

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Vessel Wall Characteristics Using High Resolution Magnetic Resonance Imaging In Reversible Cerebral Vasoconstriction Syndrome and Central Nervous System vasculitis. Rula Hajj-Ali[1], Seby John[1], Tariq Hammad[2], Emmanuel Obusez[2], Ken Uchino[1], Stephen Jones[2], Ferdinand Hui[3], Russell Cerejo[2] and Leonard H. Calabrese[2]. [1]Cleveland Clinic Foundation, Cleveland, OH, [2]Cleveland Clinic, Cleveland, OH, [3]Cleveland Clinic, Cleveland, OH.

Background/Purpose: Distinguishing between reversible cerebral vasoconstriction syndrome (RCVS) and central nervous system (CNS) vasculitis is often a diagnostic dilemma. High-resolution-3-Tesla Magnetic Resonance Imaging with contrast (HR-MRI) is a non-invasive method which has an added value to the vascular imaging by defining the intracranial vessel wall characteristics (enhancement and thickening). We have explored the utility of HR-MRI in distinguishing RCVS from CNS vasculitis.

Methods: A retrospective analysis of all patients with a diagnosis of RCVS or CNS vasculitis that underwent HR-MRI at our institution was performed. Inclusion criteria for RCVS included acute thunderclap headache with no aneurysmal subarachnoid hemorrhage, normal cerebrospinal fluid and reversible multifocal intracranial vessel stenosis. The CNS vasculitis group included patients with primary CNS vasculitis diagnosed according to the Calabrese criteria, and one patient with Varicella Zoster CNS vasculitis. Images were reviewed by two radiologists, Demographics, clinical presentation, laboratory testing, imaging studies and outcomes were collected.

Results: Twenty-six patients met inclusion criteria with 13 patients in each group. Median age was 52 and 42 in the RCVS and the vasculitis groups respectively. Females represented the majority in the RCVS groups 85 % (11/13) and only 15% (2/13) in the vasculitis group. In the RCVS group 77% (10/13) had wall thickening, only 31 % (4/13) had minimal wall enhancement. In the vasculitis group 92% (12/13) had vessel wall enhancement as well as wall thickening.

Conclusion: Findings of enhancement of the intracranial vessel wall by HR-MRI occurred mainly in the CNS vasculitis group as compared to the RCVS group. The enhancement in RCVS group was very minimal. HR-MRI may be a useful tool in differentiating RCVS from CNS vasculitis, in the acute presentation. Further studies with larger number of cases are needed to confirm the utility of HR-MRI in the diagnosis of cerebral arteriopathies.

Disclosure: R. Hajj-Ali, None; **S. John**, None; **T. Hammad**, None; **E. Obusez**, None; **K. Uchino**, None; **S. Jones**, None; **F. Hui**, None; **R. Cerejo**, None; **L. H. Calabrese**, BMS Genentec Jansen Pfizer Sanofi Horizon, 5.

1659

Systematic Review Of Amyloid Beta-Related Angiitis: A Treatable Cause Of Vasculitis Affecting Central Nervous System. Abhijeet Danve and Atul Deodhar. Oregon Health and Science University, Portland, OR.

Background/Purpose: Amyloid β-related angiitis (ABRA) is a rare type of Central Nervous System Vasculitis (CNSV), which complicates Cerebral Amyloid Angiopathy (CAA). Data about clinical features, management and outcomes of ABRA are scant. It is important to differentiate this treatable disease from primary CNSV and other irreversible neurological disorders.

Methods: We searched the OVID Medline database for relevant articles between 1946 to 2012 using the key words "Cerebral amyloid angiopathy", "vasculitis" "inflammatory CAA" "Amyloid Beta-Related Angiitis". Data from major case series and reviews as well as individual case reports was extracted. We found total 98 patients who were reported in the literature. Two case reports were in other languages and data was unavailable for 2 other patients. Demographics, clinical features, lab and imaging findings, treatment and follow up was extracted for 94 patients and is summarized descriptively.

Results: Patients with mean age of 67 years presented acutely (54%) or subacutely (46%) with cognitive or behavioral changes of variable severity (71%), focal deficits (51%), seizures (36%) and headache (35%). More than 2 features were present in 77%. Prior malignancy was reported in 10 patients and associated autoimmune disease (e.g. autoimmune thyroiditis, autoimmune hepatitis, RA and pernicious anemia) in 11. ESR and CRP were elevated in 14 /47 (29.7%); 70% patients (12/17) had ApoE genotype e4/e4 CSF showed elevated protein in 71% (42/59) and lymphocytic pleocytosis in 44% (26/ 59) and abnormalities normalized after treatment in 2/2 patients. Brain MRI was abnormal in 97.4 % (75/77) and typically showed asymmetrical bilateral white matter hyperintensity on T2W and FLAIR (88%), cortical microbleeds in 87% (21/24) on SWI and minimally enhancing mass like lesions (26%). Post treatment MRI showed improvement in 38/47 (80%) patients. Brain biopsy confirmed diagnosis in 97.8% (92/94) patients which showed transmural inflammation with deposition of A β-amyloid in vessels in 80% and pervasculitis in 20% patients. Of 73 patients who received corticosteroids 78% showed either partial or complete clinical improvement. Cyclophosphamide (34%), azathioprine (6.6%), methotrexate (2%) and mycophenolate (2%) were also used successfully in conjunction with steroids. Relapse occurred in 26% of 57 patients, either after reduction or cessation of therapy and responded well after retreatment.

Study	Scolding et al	Kinnecom et al	Salvarani et al	Chung et al	Others	Total
No of patients	34	14	8	16	22	94
Age	67.3 (43–82)*	63.2 (45–79)*	63 (42–84)*	69 (46–83)**	67.6 (52–87)*	65.2 (42–87)*
Sex (M/F)	17/17	9/5	6/2	7/9	11/11	50/44
Clinical features	29/34	9/12	6/8	9/16	13/22	66/92 (71%)
CB change	8/34	7/12	0/8	7/16	12/22	34/92 (36%)
Seizures	15/34	1/12	7/8	9/16	15/22	47/92 (51%)
Focal deficits	12/34	6/12	4/8	7/16	4/22	33/92 (35%)
Headache						
ApoE e4/e4	NA	10/13	NA	NA	2/4	12/17 (70%)
CSF	11/18	4/5	7/8	8/11	12/17	42/59 (71%)
Elevated proteins	8/18	1/5	5/8	5/11	7/17	26/59 (44%)
Pleocytosis	12/21	NA	NA	1/1	3/3	16/16(100%)
Oligoclonal bands						
Repeat CSF						
MRI	13/20	12/12	6/8	14/14	21/21	66/75(88%)
White matter changes#	4	6/7	NA	4/4	11/13	21/24(87%)
Microbleed on SWI/GEI	7/10	NA	5/8	5/9	6/11	23/38 (60%)
Enhancement	4/5	10/12	4/6	6/9	13/15	37/47 (79%)
Improvement with Rx						
Pathology Vasculitis or perivasculitis	34/34	14/14	8/8	16/16	19/20‡‡	91/92 (99%)
Response to therapy	12/20	10/12	6/8	10/12	19/20	57/72 (79%)
Relapse	NA	3/12	2/8	NA	3/14∞	8/34 (23%)

*Mean (range) age **Median (range) age
Hyperintesnsities on T2W or FLAIR
SWI Susceptibility weighted imaging
CB- Cognitive behavioral
‡‡ 2 patients were treated presumptively
∞ As per the information wherever it was reported

Conclusion: ABRA is a rare, but treatable cause of progressive dementia and neurological dysfunction in elderly and should be considered in the differential diagnosis of rapid onset neurological disease. It has characteristic MRI findings and responds well to steroids and immunosuppressants.

Disclosure: A. Danve, None; **A. Deodhar**, AbbVie, Merck-Sharp-Dohme, Pfizer and UCB, 5, AbbVie, Merck-Sharp-Dohme, Pfizer and UCB, 8, AbbVie, Amgen, Novartis, UCB, 2.

1660

Primary Central Nervous System Vasculitis: Treatment and Course. Carlo Salvarani[1], Robert D. Brown Jr.[2], Teresa J. H. Christianson[2], John Huston III[2], Kenneth Calamia[3], Caterina Giannini[2] and Gene G. Hunder[2]. [1]Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy, [2]Mayo Clinic, Rochester, MN, [3]Mayo Clinic, Jacksonville, FL.

Background/Purpose: To determine the response to therapy and long-term outcome of PCNSV we reviewed all cases of PCNSV seen over a 29-year period.

Methods: The cohort included 163 consecutive patients diagnosed with PCNSV at Mayo Clinic Rochester over a 29-year period (1983 through 2011). The diagnosis was based on findings of brain or spinal cord biopsy, cerebral angiography, or both. Biopsy specimens were reviewed by a neuropathologist and angiograms by a neuroradiologist. Information about clinical findings, laboratory, radiologic imaging, type of, duration of, and response to treatment, number of relapses, functional status at followup, and cause of death were completed for all cases.

Results: In 75 patients, glucocorticoids (GCs) were the only initial therapeutic agents. In 66 intravenous pulse GC doses (median: 5 pulses of methylprednisolone [1 gm/pulse]) were administered before oral GCs were started. The median initial oral prednisone dose was 60 mg/day. The median duration of prednisone therapy was 10 months, and 75% were treated for 19 months or less. In 69 patients cyclophosphamide (CYC) (49 had daily oral doses, 23 had intermittent intravenous pulses) and prednisone were the only initial treatment. The median initial dose of oral CYC was 150 mg/day and the median duration of therapy was 7 months. The median dose of intravenous pulse CYC was 1 gm/month. Other initial treatments included CYC alone (2) azathioprine (median initial dose 100 mg/day) and GCs (6), mycophenolate mophetil and GCs (3), rituximab and GCs (1), plasma-exchange, CYC and GC therapy (2), and infliximab (1). Four patients received no specific therapy. In the 75 treated with GCs only, a favorable response was observed in 83%. In those with CYC plus GCs, 76% responded favorably. 44 patients had relapses that led to a change in therapy. The frequency of relapses were significantly lower in the patients treated with CYC compared to those treated with GCs alone (18% vs 39%, $p = 0.006$). The median follow-up duration of the 163 patients was 12 months (range: 0–13.7 years). Age- and sex-adjusted survival of the patients with PCNSV was significantly reduced compared to the estimated survival of the US white population ($p < 0.001$). 25 patients died during follow-up. The cause of death was cerebral infarction in 10 patients. Univariate Cox proportional hazards model was used to assess survival and findings at diagnosis: older age at diagnosis (HZ 1.4) and cerebral infarction at MRI (HZ 4.4) were associated with poor survival, while gadolinium enhanced cerebral lesions or meninges at MRI (HZ 0.20) with better survival. Univariate logistic regression analysis was used to assess association of findings at diagnosis with Rankin score outcomes. Older age (HZ 1.4) and MRI evidence of cerebral infarction (HZ 3.7) at presentation were associated with a high disability score at last

follow-up (Rankin score of 4–6), while patients with gadolinium enhanced cerebral lesions or meninges had lower disability at follow-up (HR 0.35).

Conclusion: Most patients with PCNSV showed a favorable response to therapy. Recognition of findings at diagnosis associated with poor outcomes may aid decisions regarding initial therapy.

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The Spectrum of childhood Inflammatory Brain Diseases; An Increasingly Recognised Field. Marinka Twilt[1], Eyal Muscal[2], Tania Cellucci[3], Pavla Dolezalova[4], Rob Forsyth[5], Susan Kim[6], David A. Cabral[7], Johannes Roth[8], Adam Kirton[9], Rolando Cimaz[10], Jasmin Kummerle-Deschner[11], Annet van Royen-Kerkhof[12], Jürgen Brunner[13], Gaelle Chedeville[14], Jordi Anton[15], Angela Robinson[16], Mary Toth[17], Tilmann Kallinich[18], Claudia Bracaglia[19], Alexis Boneparth[20], Shehla Sheikh[1] and Susanne M. Benseler[21]. [1]The Hospital for Sick Children, Toronto, ON, [2]Baylor College of Medicine, Houston, TX, [3]Hamilton Health Sciences, McMaster, Hamilton, ON, [4]First Faculty of Medicine and General Faculty Hospital, Prague, Czech Republic, [5]Newcastle upon Tyne's NHS foundation Trust, Newcastle upon Tyne, United Kingdom, [6]Children's Hospital Boston, Boston, MA, [7]BC Children's Hospital, Vancouver, BC, [8]University of Ottawa, Ottawa, ON, [9]Alberta Children's Hospital, Calgary, AB, [10]A. Meyer Children's Hospital, Florence, Italy, [11]University Childrens Clinic Tuebingen, Tuebingen, Germany, [12]Wilhelmina Children's Hospital, Utrecht, Netherlands, [13]University Children's Hospital, Innsbruck, Austria, [14]Montreal Children's Hospital, Montreal, QC, [15]Hospital Sant Joan de Deu, Barcelona, Spain, [16]University Hospital, Rainbow babies & Children's Hospital, Cleveland, OH, [17]Akron Children's Hospital, Akron, OH, [18]Charite, University Hospital Berlin, Berlin, Germany, [19]Division of Rheumatology, Department of Pediatric Medicine, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, [20]The Children's Hospital at Montefiore, Bronx, NY, [21]Hospital for Sick Children, Toronto, ON.

Background/Purpose: Childhood Inflammatory Brain diseases are potentially life-threatening diseases leading to severe neurological deficits if not treated. The spectrum of childhood inflammatory brain diseases is rapidly expanding, and recent evidence shows the presence of inflammatory markers in previously thought to be vasculopathies, such as Moyamoya. We reviewed all pediatric patients enrolled in the international BrainWorks database.

Methods: All pediatric patients enrolled through a BrainWorks center were identified in the BrainWorks database. Patients were eligible for inclusion if predetermined information at the baseline visit was available. This included, information on demographic information, such as age at diagnosis and gender, diagnosis at enrollment, clinical, laboratory, neuroradiology and if applicable brain biopsy.

Results: In total 370 (190 boys, 180 girls) children were enrolled in BrainWorks with complete dataset at baseline. The mean age at diagnosis was 9.33 years (boys 9.67 years, girls 9.07 years). The diagnosis included were; Non-progressive large vessel CNS vasculitis n=108 (68 boys, 40 girls, mean age 8.15 years), Small vessel CNS vasculitis n = 76 (26 boys, 50 girls, mean age 11 years), Progressive large vessel CNS vasculitis n=25 (17 boys, 8 girls, mean age 10.3 years), NMDAR-encephalitis n=42 (15 boys, 27 girls, mean age 9.9 years), secondary CNS vasculitis due to underlying systemic disease n=33 (16 boys, 17 girls), and Moyamoya n=33 (18 boys, 15 girls). Other diagnosis included CNS vasculitis due to infection n=20, ADEM n=5, MS n=2, Rasmussen n=2, and other vasculopathies/vasculitis (n-21).

Focal deficits at presentation were more commonly seen in patients with large vessel CNS vasculitis and infantile Moyamoya, while diffuse deficits were seen more in children with small vessel CNS vasculitis and NMDAR encephalitis. Seizures were seen in all inflammatory brain diseases, but were more frequently present in NMDAR encephalitis and small vessel CNS vasculitis (80% and 61%) compared to the large vessel CNS vasculitis subtypes and Moyamoya.

Conclusion: Childhood inflammatory Brain diseases encompasses many different diagnosis. The most frequent diagnosis are the different subtypes of childhood CNS vasculitis, however NMDAR encephalitis and Moyamoya are increasingly recognized and diagnosed.

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Developing Guideline for Polymyalgia Rheumatica: Prioritisation of Outcome Measures – Perspective of Patients, General Practitioners and Rheumatologists. Yogesh Singh[1], Christian Dejaco[2], Sarah Mackie[3], Daniel Ching[4], Artur Bachta[5], Ajesh Maharaj[6], Alexandre Wagner[7], Manuela Lima[8], David Jayne[9], Kevin Barraclough[10], Christian D Mallen[11], Stephen P. Merry[12], Jane Hollywood[13], Madeline Whitlock[14], Kate Gilbert[15], Pamela Hildreth[15], Jennifer Nott[15], Hannah Padbury[15], Jean Miller[15], Lorna Neill[15], David Tronnier[16], Pablo Perel[17], Andrew Hutchings[18], Dario Camellino[19], Steven E. Carsons[20], William Docken[21], Christina Duftner[22], Andy Abril[23], Robert F. Spiera[24], Colin T. Pease[25], Andreas P. Diamantopoulos[26], Frank Buttgereit[27], Peter V. Balint[28], Elisabeth Nordborg[29], Lina Bianconi[30], Billy Fashanu[14], Shunsuke Mori[31], Víctor M. Martínez-Taboada[32], Maria C. Cid[33], Wolfgang A. Schmidt[34], Marco A. Cimmino[35], Michael Schirmer[36], Carlo Salvarani[37], Eric L. Matteson[12] and Bhaskar Dasgupta[38]. [1]Southend university hospital, Westcliff-on-sea, United Kingdom, [2]Southend University Hospital, Westcliff-on-sea, United Kingdom, [3]University of Leeds, Leeds, United Kingdom, [4]Timaru Hospital, Timaru, New Zealand, [5]Military Medical Institute, Warsaw, Poland, [6]Prince Mshiyeni Memorial Hospital, Durban, South Africa, [7]Universidade Federal de São Paulo, Sao Paulo, Brazil, [8]Universidade dos Açores, Azores, Portugal, [9]Addenbrookes Hospital University of Cambridge, Cambridge, United Kingdom, [10]Hoyland House General Practice, Painswick, United Kingdom, [11]University of Keele, Keele, United Kingdom, [12]Mayo Clinic, Rochester, MN, [13]Southend Hospital, Southend, United Kingdom, [14]Southend University Hospital, Southend, United Kingdom, [15]PMRGCAUK, Southend, United Kingdom, [16]patients' representative, Rochester, MN, [17]London School of Hygiene & Tropical Medicine, London, United Kingdom, [18]London School of Hygiene and Tropical Medicine, London, United Kingdom, [19]Clinica Reumatologica, Genova, Italy, [20]Winthrop University Hospital, Mineola, NY, [21]Brigham Orth & Arthritis Center, Chestnut Hill, MA, [22]Hopital Kufstein, Kufstein, Austria, [23]Mayo Clinic, Jacksonville, FL, [24]Hospital for Special Surgery, New York, NY, [25]Leeds Teaching Hospitals NHS Trust, Harrogate, United Kingdom, [26]Hospital of Southern Norway Trust, Kristiansand, Norway, [27]Charité - Universitätsmedizin Berlin, Berlin, Germany, [28]National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, [29]Sahlgenska University Hospital, Goteborg, Sweden, [30]Ambulatorio Medicina Generale, Bibbiano, Italy, [31]NHO Kumamoto Saishunsou National Hospital, Kumamoto, Japan, [32]Hospital Universitario Marqués de Valdecilla. IFIMAV., Santander, Spain, [33]Hospital Clínic. University of Barcelona. IDIBAPS, Barcelona, Spain, [34]Med Ctr Rheumatology Berlin Buch, Immanuel Krankenhaus Berlin, Berlin, Germany, [35]University of Genoa, Genova, Italy, [36]Innsbruck Medical University, Innsbruck, Austria, [37]Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy, [38]Southend University Hospital, Essex, United Kingdom.

Background/Purpose: To explore similarities and differences between rheumatologists (rheum), general practitioners (GP) and patients (pt) regarding the relevance of outcome parameters in polymyalgia rheumatica (PMR).

Methods: This study was part of the ACR/EULAR project for the development of guidelines for PMR. A candidate list of outcome parameters was identified by literature review and input from the guideline development group (GDG) involving rheum, GP and pt. The candidate item list contained 119 outcome measures including symptoms, physical examination findings, laboratory parameters, imaging, composite outcome measures, drug related adverse effects, functional status, quality of life and PMR related complications. A survey-based grading of the candidate outcomes was performed using SurveyMonkey®. We invited 43 rheum (15 with a special interest in PMR), 87 GP (all UK) and 43 pt (all UK) to rate each item based on its relative importance for clinical decisions on a 1–9 point scale (1–3 not important, 4–6 important, but not critical and 7–9 critical). We excluded the rating of a group if >33% of responders marked an item with "don't know".

Results: Thirty-eight rheum (88%; 100% of those with special interest in PMR), 15 (17%) GP and 41 (95%) pt responded. Only 6 (5.0%) parameters were deemed as critical (score ≥7) by all groups [remission, relapse, duration of glucocorticoid (GC) therapy, discontinuation of GC therapy, development of GCA, osteoporosis].

General symptoms such as fatigue, malaise, sleep disturbances, depression or anxiety were more frequently rated as critical by pt (37.5–71.8%) than by rheum (0–26.3%, all p-values ≤0.01). Appraisal of fatigue and malaise was similar by GPs and rheum whereas sleep disturbance, depression and anxiety were similarly graded by GP and pt. Among laboratory and imaging parameters no significant differences between groups were observed mainly because several parameters were marked "don't know" by a high proportion of pt and GP. GP (57.1%) considered healthcare resource use more relevant than rheum (26.3%, p=0.038) whereas a high proportion of pt did not know about this parameter. Functional status, impact on pt's career, quality of life, mobility, self-care and usual activities were rated higher by pt (54.8–84.6%) than by rheum (23.7–44.7%, all p-values <0.01). Quality of life, impact on pt's career, self-care and usual activities were also more relevant for GP (71.4–92.9%) than for rheum (all p-values <0.05).

Conclusion: These data demonstrate a higher relevance of general symptoms, functional status and quality of life to patients with PMR compared with rheumatologists. Ratings of outcome parameters from patients and general practitioners were less discordant than those from patients and rheumatologists.

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Obese Polymyalgia Rheumatica Patients Experience More Pain and Disability and Need Higher Doses Of Glucocorticoids. Marco A. Cimmino[1], Bhaskar Dasgupta[2], Cynthia S. Crowson[3], Michael Schirmer[4], Christian Dejaco[5], Carlo Salvarani[6] and Eric L. Matteson[3]. [1]University of Genoa, Genova, Italy, [2]Southend University Hospital, Westcliff-on-Sea, United Kingdom, [3]Mayo Clinic, Rochester, MN, [4]Innsbruck Medical University, Innsbruck, Austria, [5]Medical University Graz, Graz A-8036, Austria, [6]Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy.

Background/Purpose: Obesity is not only a risk factor for osteoarthritis but also for rheumatoid arthritis (RA). In obese RA patients, disease incidence is higher and response to treatment poorer. This paper is concerned with an evaluation of the clinical characteristics at onset and of the outcome of polymyalgia rheumatica (PMR) in obese vs. non-obese patients.

Methods: 83 patients with newly diagnosed PMR from the clinical cohort studied to obtain the ACR/EULAR criteria were studied. Weight and height were obtained and the BMI calculated. Obesity was defined as a BMI≥30 kg/m^2.

Results: The mean BMI was 26.1± 3.4, with BMI ≥ 30 found in 12 patients (14.5%). The two groups were comparable in terms of age (71.6±10.5 vs 72.6±8.1 years; p=0.53), sex (59% and 58% women, respectively; p=0.96), duration of morning stiffness (190±200 vs 206±219 minutes; p=0.42), and localization of involvement. Obese patients had a higher shoulder VAS (76.6±26.1 vs 58.8±25.5; p=0.03), global pain VAS (76.4±23.7 vs 58.7±24.9; p=0.025), PMR VAS (82.3±21.9 vs 60.6±24.3; p=0.004), fatigue VAS (71.8±28.1 vs 53.7±27.2; p=0.03), and modified HAQ (1.7±0.6 vs 1.2±0.6; p=0.005). They also showed a decreased physical component of the SF36 (31.6±6.3 vs 35.7±7.1; p=0.048).

The mean dose of prednisone was not different at treatment onset between obese (16.6±7 mg) and non-obese (15.1±5.6 mg) patients (p=0.98). At the end of follow-up, the clinical and laboratory features of both obese and non-obese patients significantly improved. However, during the first 6 months of treatment obese patients needed a higher mean daily dose of prednisone in comparison with the non obese ones (8.5±3.2 mg vs 6.2±5.2 mg; p=0.021). BMI was negatively correlated with percent improvement of PMR VAS at 6 months (Spearman r= −0.24; p=0.046), indicating that higher BMI was associated with a lower percent improvement.

Conclusion: Our results support the view that the burden of PMR is higher in obese vs. non obese patients. This fact may be related to the poorer quality of life seen usually in obese individuals as well as to the increased amount of cytokines produced by the adipose tissue. However, ESR and CRP were not different in the two groups of patients, although the categorical nature of these variables (normal/abnormal) may have hampered the evaluation of possible differences.

The outcome of PMR at 6 months was not different in obese vs. non-obese patients but the former needed a significantly higher cumulative dose of prednisone. The more intuitive interpretation of this finding is that prednisone dose should be adjusted to weight because of the larger volume of distribution in obese patients. Alternatively, the increased inflammation possibly associated with obesity would need more GC.

In conclusion, obesity affects both severity of symptoms and GC utilization. BMI should be considered by clinicians when interpreting symptoms of their PMR patients and deciding their GC doses. (for the European League Against Rheumatism-American College of Rheumatology PMR classification criteria study group).

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Lower Tissue Expression Of IL 6 In Patients With Giant Cell Arteritis Presenting With a Cranial Ischaemic Compication. Lorraine O'Neill[1], Jennifer McCormick[1], Danielle Molloy[1], Douglas J. Veale[1], Conor Murphy[2], Geraldine M. McCarthy[3], Ursula Fearon[1] and Eamonn S. Molloy[1]. [1]St. Vincent's University Hospital, Dublin 4, Ireland, [2]Royal Victoria Eye and Ear Hospital, Dublin, Ireland, [3]Mater Misericordiae University Hospital, Dublin 7, Ireland.

Background/Purpose: Giant Cell Arteritis (GCA) is a granulomatous systemic vasculitis with a prediliction for the aorta and it's extracranial branches. The majority of the morbidity associated with GCA is related to its ischaemic complications of acute visual loss and stroke. It has previously been shown that patients with cranial ischaemic complications (CICs) due to GCA have lower temporal artery IL 6 expression and circulating levels of IL 6 than patients without CICs.[1]

The current study aimed to extend these previous observations by:

1. Comparing the spontaneous release of IL 6 from cultured temporal artery explants of patients with GCA and CICs to those without CICs.
2. Investigating the association between spontaneous release of IL 6 from the explant cultures and the presence of intimal hyperplasia and luminal occlusion on histopathology.

Methods: Patients with suspected GCA underwent a temporal artery biopsy and had serum biomarkers assayed at baseline.

TAB sections were sent for review to a histopathologist who was blinded to the clinical presentation.

Additional sections were cultured for 24 hours and IL 6 expression in the supernatants quantified by ELISA.

Temporal artery explants from 7 patients with GCA (3 TAB positive, 4 TAB negative & 1 patient with a documented CIC) were embedded in matrigel, stimulated with recombinant IL 6 at concentrations of 20 ng/ml and 40 ng/ml and myofibroblast outgrowths observed over a 3 week period.

Results: 30 patients had a temporal artery biopsy (TAB) that was positive for GCA. 25 had a negative or inconclusive TAB but met ACR classification criteria for GCA and were therefore included in the analysis.

11/55 (20%) patients presented with an ischaemic complication attributable to GCA.

Baseline demographics were similar between those with CICs and those without. Other than their presenting CICs, there was no difference in any of the other clinical manifestations of GCA between both groups.

Cumulative steroid dose pre biopsy was higher in those presenting with a cranial ischaemic complication than those without ($p = 0.015$) However, there was no correlation observed between cumulative steroid dose and expression of IL 6 in explant cultures.

There was a trend both towards a lower baseline CRP and IL 6 in those with CICs than those without but this was not statistically significant. (Mean CRP 33 g/L vs 49 g/L and mean IL 6 17.23 pg/ml vs 31.83 pg/ml).

Patients with CICs had significantly lower levels of of IL 6 in explant supernatants when compared to those without CICs (Mean 8.66 ng/ml/mg biopsy weight vs 18.92 ng/ml/mg biopsy weight, $p < 0.01$).

This lower tissue IL 6 production was significantly associated with both intimal hyperplasia ($p < 0.03$) and luminal occlusion ($p < 0.01$) on histopathology.

In addition, rIL 6 induced myofibroblast outgrowths at concentrations of 20 ng/ml but had a significant inhibitory effect at 40 ng/ml.

Conclusion: The study confirms the association between lower levels of IL 6 expression in patients with CICs than those without. The inhibitory effect on myofibroblast outgrowths at higher concentrations of IL 6 merits further investigation given the known involvement of myofibroblasts in the development of intimal hyperplasia and occlusion.

1. Cid et al. Circulation 2003.

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B Cells Revisited In Giant Cell Arteritis. Kornelis S.M. van der Geest, Wayel H. Abdulahad, Gerda Horst, Caroline Roozendaal, Abraham Rutgers, Annemieke M.H. Boots and Elisabeth Brouwer. University Medical Center Groningen, Groningen, Netherlands.

Background/Purpose: Giant cell arteritis (GCA) is a primary vasculitis affecting large to medium-sized arteries. Ample evidence suggests that dendritic cells, T cells and monocytes/macrophages contribute to the immunopathology of GCA. Previous reports showed that B cells are not predominant cells in temporal arteries of GCA patients (*Cid et al. AR 1989*). However, a high prevalence of various auto-antibodies in serum of GCA patients is suggestive of B cell activation in GCA (*Baerlecken et al. ARD 2012; Regent et al. ART 2011; Schmits et al. Clin Exp Immunol 2002*). Furthermore, emerging data indicate that B cells can modulate immune responses of T cells and monocytes by producing IL-10 and TNF-α (*Lund et al. Nat Rev Immunol 2010*). In the current study, we assessed the distribution of defined B cell subsets, including IL-10+ regulatory B cells and TNF-α+ effector B cells, in GCA patients before and after glucocorticoid (GC) treatment.

Methods: B cells were analyzed in peripheral blood of 15 newly-diagnosed GCA patients. In addition, we studied 40 age-matched, healthy controls (HCs) and 28 disease controls, including 17 polymyalgia rheumatica (PMR) patients and 11 rheumatoid arthritis (RA) patients. In a prospective, longitudinal study design, 39 samples were obtained from GCA and PMR patients who were in remission after 2 and 12 weeks of treatment with GCs. Serum levels of BAFF were determined. Flow cytometric staining of B cells for intracellular TNF-α and IL-10 was performed after 4 hours of stimulation with PMA and calcium ionophore in the presence of brefeldin A.

Results: Circulating B cells were decreased in newly-diagnosed GCA and PMR patients, but not in RA patients, compared to HCs. Following 2 and 12 weeks of GC treatment, B cell numbers normalized in GCA and PMR patients. This normalization was neither attributable to repopulation by immature-transitional B cells from the bone marrow, nor to compensatory hyperproliferation in the blood. Instead, already existing mature B cell subsets seemed to be mobilised towards the circulation of treated GCA and PMR patients. In particular the circulating pool of unswitched and switched memory B cells was expanded after GC treatment. B cell numbers inversely correlated with ESR, CRP and serum levels of the B cell growth factor BAFF. In newly-diagnosed GCA patients, TNF-α+ effector B cells but not IL-10+ regulatory B cells were decreased. Following treatment, numbers of TNF-α+ effector B cells and IL-10+ regulatory B cells were normal in GCA patients.

Conclusion: Our data indicate that B cells, including TNF-α+ effector B cells, are redistributed during active GCA and PMR. Following treatment, mature B cells subsets, in particular memory B cells, are mobilized to the circulation. In accordance with the high prevalence of various auto-antibodies reported in GCA and PMR, our data further suggest that activation of B cells occurs during the active stages of both diseases. Additional studies on the pro-inflammatory and regulatory role of B cells in GCA and PMR are ongoing.

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Negative Temporal Artery Biopsies: Pathologic Findings Of Patients With Biopsy-Negative Giant Cell Arteritis Compared To Those Of Patients Without Arteritis. Francesco Muratore[1], Alberto Lo Gullo[1], Alberto Cavazza[1], Giuseppe Germanò[1], Luigi Boiardi[1] and Carlo Salvarani[2]. [1]Arcispedale S Maria Nuova, IRCCS, Reggio Emilia, Italy, [2]Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy.

Background/Purpose: Temporal artery biopsy (TAB) showing transmural inflammation is considered the gold standard for the diagnosis of giant cell arteritis (GCA). A negative TAB does not rule out GCA, and a diagnosis of biopsy-negative GCA was reported in 5–25% of patients. In the absence of active mural inflammation (negative TAB), other structural changes in the wall of TA are often present and some of those have been described as "healed" or quiescent arteritis, but if these histological changes are expression of GCA is still debated. The aim of this study is to evaluate if there are histopathological features of negative TAB that allow to differentiate patients with GCA from those without.

Methods: 42 consecutive patients with negative TAB were retrospectively selected. All patients underwent TAB for suspected GCA between January 2009 and December 2012. Demographic, clinical and laboratory data at presentation and at each follow up visit were collected. A pathologist with expertise in vasculitis blinded to clinical data and final diagnosis reviewed all 42 negative TABs. Histopathologic features evaluated were: the presence of a focal medio-intimal scar with medial attenuation, intimal hyperplasia, fragmentation of inner elastic lamina (IEL), calcification, adventitial fibrosis and neoangiogenesis.

Results: After a median follow-up period of 177 days (interquartile range 38, 508), 20 of the 42 patients had a final diagnosis of GCA, while in the remaining 22 patients GCA was excluded (9 had polymyalgia rheumatica, 4 non arteritic anterior ischemic optic neuropathy, 3 fibromyalgia, 2 non-specific elevation of inflammatory markers, 1 fever of unknown origin, 1 rheumatoid arthritis, 1 ANCA associated vasculitis, 1 osteoarthitis). 1990 ACR classification criteria for GCA were satisfied in 13 of the 20 patients with GCA (65%) and in none of the 22 non-GCA patients. 12 patients (60%) with GCA and 14 patients (64%) with non-GCA were on steroid therapy when TAB was performed ($p > 0.05$). The mean prednisone dose was (mg+ SD) 23.75 +12.95 for GCA patients and 13.57 +11.67 for non-GCA patients ($p = 0.05$). Mean duration of prednisone treatment was (days+SD) 30.58+44.23 for GCA patients and 144.36+162.24 for non GCA patients ($p < 0.05$). A focal medio-intimal scar with medial attenuation was found in 15% of GCA vs 14% of non-GCA patients ($p > 0.05$). Intimal hyperplasia was present in 45% vs 59%, fragmentation of IEL in 80% vs 91%, calcification in 30% vs 18%, adventitial fibrosis in 10% vs 5% and neoangiogenesis in 10% vs 9% of GCA vs non-GCA patients respectively (all p NS). 4 patients with GCA had visual loss. A focal medio-intimal scar with medial attenuation was not observed in these 4 patients, intimal hyperplasia was observed in 2, fragmentation of IEL in all 4, calcification in 2, adventitial fibrosis in 1 and neoangiogenesis in 1. Histological findings of GCA patients with visual loss were similar to those of patients with non-GCA.

Conclusion: The histological features of negative TAB evaluated in this study do not allow to differentiate between GCA and non-GCA patients. These data suggest that in the absence of mural active inflammation, other histological changes of the TA wall are not specific for GCA.

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Serum S100A8/S100A9 and S100A12 As a Marker Of Disease Activity In Giant Cell Arteritis. Jason Springer[1], Dirk Holzinger[2], Gary S. Hoffman[3], Paul A. Monach[4], Thomas Hamilton[5], Carol A. Langford[5], Dirk Foell[6], David Cuthbertson[7], Colin O'Rourke[5], Simon Carette[8], Nader A. Khalidi[9], Carol McAlear[10], Christian Pagnoux[11], Philip Seo[12], Kenneth J. Warrington[13], Steven R. Ytterberg[13], Thomas Vogl[14], Peter A. Merkel[10], Johannes Roth[14] and Rula Hajj-Ali[3]. [1]University of Kansas Medical Center, Kansas City, KS, [2]University Muenster, Muenster, Germany, [3]Cleveland Clinic Foundation, Cleveland, OH, [4]Boston University, Boston, MA, [5]Cleveland Clinic, Cleveland, OH, [6]Department of Pediatric Rheumatology and Immunology, University of Münster, Münster, Germany, [7]University of South Florida, Tampa, FL, [8]UHN/MSH, Toronto, ON, [9]McMaster University, Hamilton, ON, [10]University of Pennsylvania, Philadelphia, PA, [11]Division of Rheumatology, Mount Sinai Hospital, Toronto, ON, [12]Johns Hopkins Vasculitis Center, Baltimore, MD, [13]Mayo Clinic, Rochester, MN, [14]University of Muenster, Muenster, Germany.

Background/Purpose: The S100 proteins (S100A8/9 complex and S100A12) are calcium binding proteins expressed during myeloid differentiation. S100 proteins are phagocyte-specific proteins that have been demonstrated to be markers of early recruited phagocytes in various inflammatory disorders. We previously demonstrated that gene expression of the S100A8/A9 and S100A12 are significantly elevated in temporal arteries in patients with giant cell arteritis (GCA), compared to controls. Furthermore, serum concentrations of S100A8/A9 and S100A12 arehigher in patients with GCA compared to healthy controls. We aimed to assess the association of S100 proteins in disease activity in GCA and their value in predicting disease activity as compared to standard inflammatory markers (CRP and ESR).

Methods: Fifty-nine patients with GCA were selected from the Vasculitis Clinical Research Consortium Longitudinal Study of GCA. Mean age was 72.3 and 44 (75%) were female. Serum concentrations of S100A8/A9 complex and S100A12 were measured by ELISA in 106 samples at times of active or inactive disease. Data on ESR and CRP values were available for 100 and 94 samples, respectively. Mixed effects model, accounting for repeat measurements, was used to compare S100A8/A9 or S100A12 levels between active and inactive disease. ROC curves were created to compare the utility of CRP and ESR, S100 proteins or a combination of all markers in predicting disease activity.

Results: Estimated mean serum S100A8/9 was significantly higher during active disease (1446 ng/mL) vs. inactive disease (1096 ng/mL), p=0.003. Mean serum S100A12 was also significantly higher during active disease (163 ng/mL) vs. inactive disease (117 ng/mL), p=0.016. The AUC for the combination of S100 proteins and standard markers of inflammation was higher than the AUC for either alone (Figure 1).

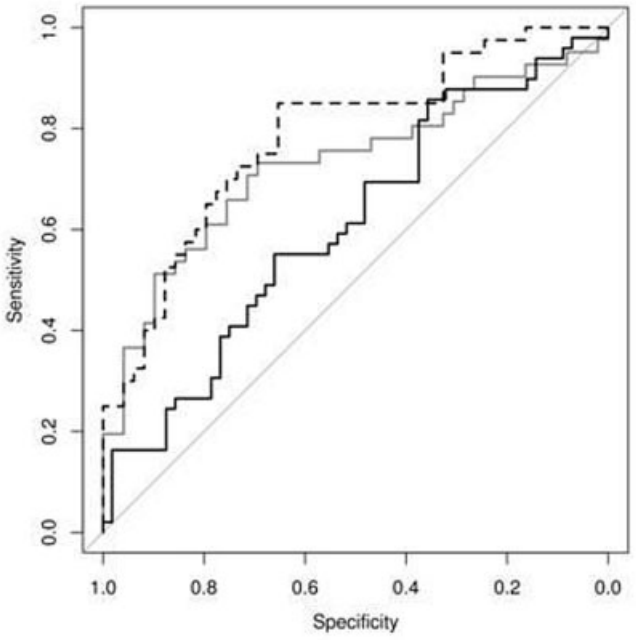

Figure 1. Estimated ROC curves for prediction of disease activity in patients with GCA. The grey line is for predictions based on CRP and ESR (AUC = 0.73). The black line is for predictions based on S100A12 and S100A8/9 (AUC = 0.61). The dashed line is the model involving all measurements (AUC = 0.79).

Conclusion: Serum S100A8/A9 and S100A12 are both significantly elevated during active disease in GCA. The combination of S100 proteins measurements with ESR and CRP enhanced the predictive value of disease activity in GCA.

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Does Fibrinogen Have a Role In The Assessment Of Patients With Giant Cell Arteritis? Lorraine O' Neill[1], Eoghan M. McCarthy[2], Anne M. Madigan[2], Geraldine M. McCarthy[2], Eamonn S. Molloy[1], Ursula Fearon[1], Douglas J. Veale[1] and Conor Murphy[3]. [1]St. Vincent's University Hospital, Dublin 4, Ireland, [2]Mater Misericordiae University Hospital, Dublin 7, Ireland, [3]Royal Victoria Eye and Ear Hospital, Dublin, Ireland.

Background/Purpose: Giant cell arteritis (GCA) in the most common systemic vasculitis in patients over 50 years of age. Considerable difficulties exist in the evaluation of patients with GCA. Accurate clinical assessment can be challenging due to the wide spectrum of clinical presentations. Temporal artery biopsy is negative in a substantial minority of patients.

The traditional biomarkers ESR and CRP are non-specific and can be negative.

Therefore development of better disease biomarkers is needed for diagnosis in GCA.

Plasma Fibrinogen has already been demonstrated in Polymyalgia Rheumatica to accurately identify those patients with quiescent disease, to be at least as useful as CRP and ESR for diagnosis of active disease and more specific for confirmation of response to treatment than either ESR or CRP.

Aim: The aim of this study was to evaluate the utility of plasma Fibrinogen in the assessment of patients with GCA.

Methods: Patients presenting with suspected new-onset GCA were prospectively enrolled. Plasma fibrinogen, ESR and CRP were assayed at baseline and 3 months following initiation of steroid therapy.

Biomarkers were also assayed in 25 age and sex matched controls attending with osteoarthritis (OA).

Demographic data and categorical variables were assessed using Fischers Exact Test. Receiver operator curves (ROC), predictive values, and likelihood ratios were calculated for all biomarkers measured. Spearman rank correlation coefficient was used to directly compare Fibrinogen, ESR and CRP.

Results: 68 patients with suspected GCA were recruited. 30 patients had positive temporal artery biopsies and of the 38 with negative biopsies, 25 met ACR criteria for GCA and were included in the ananlysis.

Plasma Fibrinogen levels were significantly elevated in patients with GCA when compared with OA controls. (Mean 4.9 g/L vs. 3.05 g/L, $p = 0.0017$). Fibrinogen levels were also significantly elevated in patients with GCA who were biopsy positive when compared to those patients fulfilling ACR criteria for GCA but who were biopsy negative (Mean 6.05 g/L vs 3.75 g/L, $p = < 0.01$) No correlation was observed between Fibrinogen and any clinical variable observed.

Fibrinogen levels also demonstrated a response to therapy. (Mean of 4.9 g /L at baseline vs. 3.5 g/L at 3 months, $p = 0.04$) Baseline Fibrinogen levels correlated with baseline ESR ($r = 0.6946$, $p < 0.0001$) and CRP ($r= 0.6951$, $p < 0.0001$. ROC analysis revealed Fibrinogen to be a less sensitive but more specific marker of GCA than CRP (Sensitivity of 67% vs. 82% and Specificity of 100% vs. 80% respectively) with comparable specificity to ESR above a cut off for ESR >30 mm/hr.

Values above the upper limit of normal for Fibrinogen (4 g/L) were associated with a positive likelihood ratio of 15.18 for GCA.

Conclusion: Plasma fibrinogen levels are elevated in patients with GCA, respond to glucocorticoid therapy and correlate with serum ESR and CRP levels. This data suggests that fibrinogen may be a more specific marker for GCA than CRP. Further research is required to define the utility of fibrinogen in assessment of disease activity in patients with GCA.

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The Birmingham Vasculitis Activity Score As a Measure Of Disease Activity In Patients With Giant Cell Arteritis. Tanaz A. Kermani[1], David Cuthbertson[2], Simon Carette[3], Gary S. Hoffman[4], Nader A. Khalidi[5], Curry L. Koening[6], Carol A. Langford[7], Kathleen McKinnon-Maksimowicz[8], Carol McAlear[9], Paul A. Monach[10], Philip Seo[11], Kenneth J. Warrington[12], Steven R. Ytterberg[12], Peter A Merkel[13] and Eric L. Matteson[12]. [1]University of California Los Angeles, Los Angeles, CA, [2]University of South Florida, Tampa, FL, [3]UHN/MSH, Toronto, ON, [4]Cleveland Clinic Foundation, Cleveland, OH, [5]McMaster University, Hamilton, ON, [6]Salt Lake City Veterans Administration, Salt Lake City, UT, [7]Cleveland Clinic, Cleveland, OH, [8]University of Pittsburgh, Pittsburgh, PA, [9]University of Pennsylvania, Philadelphia, PA, [10]Boston University, Boston, MA, [11]Johns Hopkins Vasculitis Center, Baltimore, MD, [12]Mayo Clinic, Rochester, MN, [13]University of Pennsylvania and VA Medical Center, Philadelphia, PA.

Background/Purpose: To evaluate the performance of the Birmingham Vasculitis Activity Score (BVAS), a validated tool for assessment of vasculitis disease activity, in a cohort of patients with GCA.

Methods: Patients with GCA enrolled in a prospective, multicenter, longitudinal study were included. All subjects were followed with serial standardized clinical assessments. Symptoms attributable to vasculitis, BVAS, and physician global assessments (PGA) (scale 0–10) were available at each visit. Patients with a BVAS >0 at any visit, or those with symptoms of active vasculitis, were included. Manifestations of active vasculitis captured under the "Other" category of BVAS were scored as 0. Spearman's rank correlation was used to explore the association of BVAS with other measures of disease activity including PGA, physician rated disease activity (low, moderate or high), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).

Results: During a mean (SD) follow-up of 2.3 (1.6) years, symptoms of active GCA were present in 236 visits in 136 subjects (100 female, 74%). Median (range) of BVAS1 (new or worse symptoms) was 1 (0–11), median (range) of BVAS2 (persistent symptoms) was 0 (0–5), and median (range) PGA was 4 (0–9) during the 236 episodes of active disease. In 32 encounters (14%), both BVAS1 and BVAS2 were 0. Clinical manifestations sorted by organ systems on BVAS are displayed in Table 1. Several vascular and ischemic symptoms attributed to active GCA on standardized history forms were captured in the "Other" category and did not contribute to the composite scores on BVAS, including diplopia (4 episodes, 2%), temporal artery tenderness (43 episodes, 18%), carotidynia (16 episodes, 7%), jaw/tongue claudication (65 episodes, 28%), upper extremity claudication (34 episodes, 15%), and lower extremity claudication (12 episodes, 5%).

Table 2 contains correlations of BVAS and other measures of disease activity. BVAS1 correlated with PGA and disease activity while BVAS2 was negatively correlated with both. Neither BVAS subscore correlated with ESR or CRP.

Table 1. Frequency of clinical manifestations in 236 encounters of giant cell arteritis with active disease during observation, as captured by the Birmingham Vasculitis Activity Score (BVAS). BVAS items are arranged by organ systems.

BVAS items (by organ system)	New/worse symptoms*	Persistent symptoms*
General (N=193)		
Malaise	57	17
Myalgia	51	7
Arthralgia/arthritis	49	17
Headache	94	9
Fever (<38.5 degrees Celsius)	4	2
Fever (>38.5 degrees Celsius)	2	1
Weight loss (≥2 kilograms)	24	1
*Median (range) BVAS for category	1 (0–3)	0 (0–2)
Cutaneous (N=1)		
Ulcer	1	0
*Median (range) BVAS for category	0 (0–4)	0 (0–0)
Mucous membranes/eyes (N=34)		
Mouth ulcers	0	1
Blurred vision	29	1
Sudden vision loss	12	0
*Median (range) total BVAS for category	0 (0–6)	0 (0–2)
Ear, Nose, and Throat (N=1)		
Sinus involvement	0	1
*Median (range) total BVAS for category	0 (0–0)	0 (0–1)
Chest (N=9)		
Persistent cough	8	1
*Median (range) total BVAS for category	0 (0–2)	0 (0–1)
Cardiovascular (N=2)		
Congestive heart failure	0	2
*Median (range) BVAS for category	0 (0–0)	0 (0–2)
Abdominal (N=1)		
Severe abdominal pain	1	0
*Median (range BVAS for category)	0 (0–3)	0 (0–0)
Renal (N=0)		
*Median (range) BVAS for category	0 (0–0)	0 (0–0)
Nervous system (N=4)		
Organic confusion/dementia	2	0
Stroke	1	0
Sensory peripheral neuropathy	0	1
*Median (range) BVAS for category	0 (0–9)	0 (0–3)
Other N=85	63	22

N=total number with any clinical manifestation in that organ system
*Values are number of patients with symptoms except for median BVAS scores.

Table 2. Correlations of BVAS with other parameters used to assess disease activity in GCA.

	BVAS1	p-value	BVAS2	p-value	PGA	p-value
PGA	0.45	<0.001	−0.20	0.002	–	
ESR	0.02	0.78	−0.13	0.06	0.09	0.18
CRP	0.06	0.39	−0.02	0.73	−0.003	0.98
Disease activity*	0.43	<0.001	−0.17	0.01	0.91	<0.001

BVAS= Birmingham Vasculitis Activity Score; BVAS1= score for new/worse disease activity; BVAS2= score for persistent disease activity;
GCA= Giant cell arteritis;
PGA= physician global assessment; ESR= erythrocyte sedimentation rate;
CRP= C-reactive protein.
*rated by evaluating physician as low, medium or high.

Conclusion: The BVAS has limited utility in GCA. BVAS1, but not BVAS2, correlates positively with PGA. Several patients in this study with active GCA had a BVAS of 0. Items in 7 of the 9 organ systems on BVAS are not applicable to most patients with active GCA and important symptoms attributable to GCA often fall into the "Other" BVAS section and are not captured in the composite score. Modification of the BVAS with retention of a set of general items and inclusion of large-vessel vasculitis disease-specific items may provide more accurate disease assessment in GCA.

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Large Vessel Vasculitis: Estimating Disease Activity In Patients With Inflammatory Thoracic Aortic Aneurysms. Alison Clifford, Tiffany M. Clark, Douglas Johnston, Gosta Pettersson, Eric Roselli, E. Rene Rodriguez, Edward Soltesz, Lars Svensson, Carmela Tan and Gary S. Hoffman. Cleveland Clinic Foundation, Cleveland, OH.

Background/Purpose: Thoracic aortic aneurysms due to large vessel vasculitis may be a sign of ongoing inflammation or the sequelae of previous damage to the arterial wall. Ongoing inflammation in the aorta is usually estimated indirectly using clinical features, inflammatory markers and imaging characteristics. Whether these surrogates accurately reflect inflammation within the vessel wall is not known.

Methods: We retrospectively reviewed the clinical, laboratory and imaging data for patients in whom aortitis was histologically demonstrated at the time of reconstruction for thoracic aortic aneurysms (May 2011-December 2012). ACR classification criteria were used to define vasculitis subtype. Pre- and post-operative assessments of disease activity were estimated using the NIH criteria for active disease.

Results: Among 126 consenting study patients who underwent repair of thoracic aortic aneurysms, 14 (11%) had histological features of aortitis. Thirteen specimens (93%) had persistent inflammatory infiltrates, and 1 had features of healed aortitis. Seven patients met criteria for Giant Cell Arteritis, 2 for Takayasu's arteritis, 4 for Isolated Aortitis, and 1 for Sarcoidosis. Median duration of disease prior to surgery was 35.5 months (range 0–180). At the time of surgery, only 2 of 10 patients (20%) with known systemic disease met criteria for active disease, while the remaining 8 (80%) were felt to be in clinical remission, yielding a sensitivity of 22% and specificity of 100% for the NIH criteria for determining active disease. When assessed over 1 year pre-operatively, 5 of 10 patients (50%) met criteria for active disease, increasing the sensitivity of NIH criteria to 44%. Post-operatively, only 1 of 13 (7%) patients met criteria for active disease. Two patients developed new vascular lesions during follow-up, at median of 3 months post-operatively, and 2 patients died.

Pt	Age, Sex	Presentation and Treatment (Rx)	Indication for Surgery	Diagnosis	Aneurysm size at surgery (cm)
1	67, M	2010: Dyspnea, CT: TAA (ascending)	Aneurysm & CHF	IA	7.8
2	70, F	2011: Atrial fibrillation, CT: TAA (ascending and descending)	Aneurysm & CHF	IA	Ascending: 5.0 Descending: 7.4
3	53, M	2011: Dyspnea due to pneumothorax, CT: TAA (ascending) & bullous emphysema	Aneurysm size	IA	6.1
4	62, F	2020: CHF, AI due to TAA (ascending)	Aneurysm size & CHF	IA	5.0
5	69, M	May 2008: Sarcoidosis. Bilateral optic neuritis/posterior uveitis, pneumonitis, trans-bronchial biopsy: non-necrotizing granulomas. 2012: new dyspnea, CT chest. TAA (ascending)	Aneurysm size	SARCOID	5.3
6	76, F	2004: Headache, PMR, weight loss, L arm daudi cation, absent BP L arm, ESR 59, MRA: stenoses L subclavian + axillary, ectatic thoracic aorta. Rx: prednisone. 2011: angina, CT: increased TAA (ascending) size	Aneurysm size	GCA	5.8
7	81, F	1980's: PMR. Rx: prednisone + MTX. 2005: RUQ pain, CT: TAA (ascending). Rx: prednisone.	Aneurysm size	GCA	5.0
8	66, M	2007: Headache, sweats, ESR 40–60, + TA biopsy. Rx: prednisone + MTX. 2012: visual symptoms, CT chest: TAA (ascending)	Aneurysm size	GCA	5.2
9	66, F	2007: Headache, TA tenderness, ESR 63. Not treated. 2012: new palpitations, dyspnea, CT: TAA (ascending)	Aneurysm size & CHF	GCA	5.6
10	72, F	2002: Neck/jaw pain, high ESR, L subclavian bruit. MRA: stenoses R subclavian, internal carotid, L subclavian + vertebral arteries, dilated ascending aorta. Rx: prednisone + MTX » remission. 2012: new angina, dyspnea, CT: TAA (ascending)	Aneurysm size	GCA	5.6
11	70, F	1997: PMR. Rx: prednisone × 3 yrs. 2004: TAA (ascending). 2012: dyspnea, CT: increasing aneurysm size	Aneurysm size	GCA	5.0
12	65, F	May 2012: Dyspnea & pulsatile neck mass, CTA: TAA (ascending) & innominate artery aneurysm. MRA: L vertebral stenosis, occlusion L subclavian artery	Aneurysm size	GCA	6.5
13	39, F	DEC 2012: Murmur noted. + chronic L arm weakness, lightheadedness, dyspnea. CTA: TAA (ascending), stenoses: L subclavian & axillary + aneurysm R subclavian arteries	Aneurysm size	TAK	5.1
14	30, M	2007: Sweats, weight loss, headache, ESR 80, MRA: TAA (ascending & descending) stenoses R common carotid, L subclavian, celiac & L renal arteries, L common carotid artery aneurysm. Rx: prednisone, AZA, MTX, Adalimumab	Aneurysm size	TAK	5.3

Abbreviations: Rx=treatment, CT=computerized tomography, MRA=magnetic resonance angiogram, TAA=thoracic aortic aneurysm, CHF=congestive heart failure, AI=aortic insufficiency, PMR=polymyalgia rheumatica, IA=isolated aortitis, GCA=Giant Cell Arteritis, TAK=Takayasu's arteritis, MTX=methotrexate, AZA=azathioprine, TA=temporal artery

Conclusion: At the time of surgery only 20% of patients with aortitis met criteria for active disease based on indirect clinical features, while 93% demonstrated ongoing inflammation on biopsy, indicating that indirect estimates of thoracic aortic inflammation are insensitive in patients with aneurysms. These findings emphasize the need for improved markers for assessing disease activity in patients with large vessel vasculitis.

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Cardiovascular Risk At Incidence Of Giant Cell Arteritis: A Population Based Retrospective Cohort Study. P. Deepak Udayakumar, Arun K. Chandran, Cynthia S. Crowson, Kenneth J. Warrington and Eric L. Matteson. Mayo Clinic, Rochester, MN.

Background/Purpose: Many systemic inflammatory rheumatic conditions are associated with increased cardiovascular (CV) risk. We aimed at assessing the CV risk at incidence of giant cell arteritis (GCA).

Methods: We retrospectively reviewed a population-based incidence cohort of GCA patients diagnosed between 1950 and 2009 based on American College of Rheumatology 1990 GCA classification criteria. We also included patients ' 50 years of age with elevation of erythrocyte sedimentation rate or C-reactive protein and computed tomography, magnetic resonance imaging or positron emission tomography evidence of large vessel vasculitis involving ascending aorta and its branches. We compared this cohort with age, sex and calendar year matched cohort from the same population. All subjects were longitudinally followed through all available community medical records until death, migration or April 30, 2013. Data was collected on all documented episodes of acute coronary syndrome (ACS) events prior to GCA incidence/index date and CV risk factors at GCA incidence/index date. Chi-square tests were used to compare characteristics between GCA and non-GCA cohort.

Results: We identified 245 patients in GCA cohort and 245 age, sex and calendar year matched patients in non-GCA cohort. At GCA incidence, 107 (44%) GCA subjects were on antihypertensives as opposed to 127 (52%) non-GCA subjects (p=0.08). Mean high density lipoprotein (HDL) was higher in GCA cohort [61.5 mg/dl; standard deviation (SD) 17.1] than non-GCA cohort (55.3 mg/dl; SD 17.9) (p=0.034). Mean triglycerides was lower in GCA cohort (124.2 mg/dl; SD 59.6) than non-GCA cohort (148.8 mg/dl; SD 77.5) (p=0.029). Mean low density lipoprotein (LDL) and total cholesterol were not different between the two cohorts. 23 (9.6%) subjects were on lipid lowering medication in GCA cohort as opposed to 39 (16.1%) in non-GCA cohort (p=0.032). No difference was noted in smoking status, obesity or chronic kidney disease between the two cohorts. Diabetes mellitus was present in 17 (6.9%) GCA subjects and 40 (16.3%) non-GCA subjects (p=0.001). Mean overall Framingham 10 year cardiovascular risk score was 30% (SD 19) in GCA subjects and 34% (SD 23) in non-GCA subjects (p=0.096) at incidence/index date. Positive family history of premature ACS was less frequent in GCA (2 of 26 subjects; 13%) than non-GCA cohort (10 of 32 subjects; 48%) (p=0.024). Occurrence of acute coronary syndrome (ACS) prior to GCA incidence/index date was similar between the two cohorts: 18 episodes (7.4%) in GCA cohort versus 17 episodes (6.9%) in non-GCA cohort (p=0.86).

Conclusion: Multiple cardiovascular risk factors are more favorable at incidence of GCA when compared to non-GCA subjects of similar age and gender. Anti-hypertensives and lipid lowering medications are less frequently used in GCA subjects at incidence. Framingham 10 year cardiovascular risk may be lesser at GCA incidence although this did not achieve statistical significance in our study. As GCA is a disease that almost exclusively affects the elderly, there may be a component of healthy cohort bias causing this effect.

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Serious Cardiovascular Events Risk Factors In Giant Cell Arteritis. A Population-Based Study In The French Apogee Cohort. Grégory Pugnet[1], Laurent Sailler[2], Guillaume Moulis[3], Jean-Pascal Fournier[4], Robert Bourrel[5], Jean-Louis Montastruc[6] and Maryse lapeyre-Mestre[6]. [1]Toulouse University Hospital, University of Toulouse, INSERM UMR 1027, Toulouse, France, [2]Toulouse University Hospital, Toulouse, France, [3]Toulouse University Hospital, Clinical Pharmacology Department, University of Toulouse, UMR INSERM-UPS 1027, Toulouse, France, [4]Toulouse University, INSERM UMR 1027, Toulouse, France, [5]Caisse Nationale de l'Assurance Maladie échelon régional, Midi-Pyrénées, Toulouse, France, [6]Toulouse University Hospital, INSERM U1027, University of Toulouse, France, Toulouse, France.

Background/Purpose: No population-based study has assessed serious cardiovascular events (sCVE) risk factors in Giant Cell Arteritis (GCA). The aim of our study was to identify risk factors associated with sCVE occurrence in GCA in the general population.

Methods: The APOGEE cohort includes most incident GCA patients of the Midi-Pyrénées County, south of France from January 2005 to December 2008. GCA patients are identified in the French National Health Insurance System (FNHIS) database by their international classification of diseases code, 10th version (M31.5: "GCA with polymyalgia rheumatica (PMR)" or M31.6: "GCA without PMR"). Incident cases are defined by a continuous glucocorticosteroids (GCs) course lasting for at least 6 months, and no previous exposure to GCs during the 6 preceding months. For each case two controls matched on gender and age were randomly selected in the FNIHS database. New CVE were identified by analyzing comprehensive data on drugs' reimbursement, diagnostic procedures, hospital stays and new cardiovascular diseases registered in the database. Serious CVE were defined as CVE leading to hospitalization > 24 hours or death. Serious CVE identified was: cerebrovascular disease, coronary disease, peripheral arterial disease, congestive heart failure and atrial fibrillation. Follow-up ended in April 2011. We used a multivariate Cox proportional hazards model to identify independent predictors of the first sCVE in the whole population and in GCA patients.

Results: The cohort included 103 patients (80 women, mean age 74.8 ± 9 years, mean follow-up 48.9 ± 14.8 months) and 206 controls. At study entry, there was no difference between cases and controls for cardiovascular co-morbidities except for diabetes mellitus, which was more prevalent in controls ($p<0.01$). Serious CVE occurred more frequently in GCA patients (15.5% vs. 7.8%, p= 0.014). Independent risk factors for sCVE occurrence were GCA (HR= 1,99 [1.02–3.9]; p< 0.05), age over 77 (HR= 4.31 [1.78–10.45]; p=0.001), a previous history of diabetes (HR= 2.54 [1.19–5.41]; p=0.02) or chronic heart failure (CHF) (HR= 8.24 [1.89–35.84]; p=0.005). Independent risk factors for sCVE occurrence in the GCA cohort were age over 77 (HR= 7.07 [2.04–24.47]; p= 0.002) and a previous history of CHF (HR= 8.15 [1.86–35.72]; p= 0.005). Exposure to statins for more than 18 months decreased the risk of sCVE occurrence in the whole cohort (HR= 0.26 [0.06–1.11]; p= 0.07) and in the GCA cohort (HR= 0.35 [0.11–1.09] p= 0.071).

Conclusion: GCA is an important independent cardiovascular risk factor and statins may prevent sCVE occurrence. Older GCA patients with a previous history of CHF have a very high risk of developing serious cardiovascular complication and should be monitored closely.

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Risk Of Myocardial Infarction In Patients With Giant Cell Arteritis: A Population-Based Study. Neda Amiri[1], Hyon K. Choi[2], Eric C. Sayre[2], Kamran Shojania[2] and J. Antonio Avina-Zubieta[3]. [1]University of British Columbia, Vancouver, BC, [2]Arthritis Research Centre of Canada, Richmond, BC, [3]Arthritis Research Centre of Canada, University of British Columbia, Richmond, BC.

Background/Purpose: Involvement of large arteries leading to stenosis is well-documented in giant cell arteritis (GCA), but limited data are available on the risk of coronary events. We estimated the risk of newly diagnosed MI events among incident cases with GCA compared to controls from the general population. We also explored time trends for MI since GCA diagnosis.

Methods: Our data included all visits to health professionals and hospital admissions covered by the comprehensive provincial medical services plan from January 1, 1990 until December 31, 2010 for all individuals. We conducted a matched cohort analysis among patients satisfying the following criteria: **a)** 40 years of age or older; **b)** new diagnosis of GCA on at least 2 visits within a 2-year period between Jan 1996 and Dec 2010; and **c)** use of oral glucocorticoids between 1 month before and 6 months after the diagnosis date. Ten non-GCA controls matched by birth year, sex, and calendar year of follow-up were selected from the general population for each case. Our outcome was risk of **incident MI events** based on hospitalization records or death certificate. We estimated the relative risks (RRs) of MI compared with the matched non-GCA comparison cohort, adjusting for history of angina, COPD, obesity, cardiovascular disease, diabetes, hormone replacement therapy, dyslipidemia, non-steroidal anti-inflammatory drug use, COX-2 inhibitor use, number of hospitalizations, and Charlson Comorbidity Index at baseline.

Results: Among 835 individuals with incident GCA (74% female, mean age of 75 years), 109 developed MI (incidence rate = 49.8 per 1000 person years) (**Table 1**). Compared with non-GCA individuals, the age-, sex-, and entry time-matched RRs were 3.3 (95% CI; 2.6–4.1). After adjusting for covariates, the RR remained similar (3.0; 95% CI, 2.3–4.1) (**Table 1**). The risk of developing an MI was highest in the first year following diagnosis of GCA and decreased over time, with no increased risk observed after 5 years.

Table 1. Risk of Incident MI according to GCA Status

	GCA (n = 834)	Non-GCA (n = 8,340)
Incidence Rate Ratios of MI		
MI events, N	109	401
Incidence Rate/1000 Person-Years	49.8	15.1
Age-, sex-, and entry time-matched RRs (95% CI)	3.3 (2.6–4.1)	1.0
Overall	**6.8 (4.8–9.7)**	**1.0**
< 1 year disease duration	6.8 (4.8–9.7)	1.0
1–4.9 years disease duration	2.4 (1.7–3.3)	1.0
5+ years disease duration	1.4 (0.5–3.2)	1.0
Multivariable RR (95 % CI)		
Overall	3.0 (2.3–4.1)	1.0
Females	2.9 (2.0–4.1)	1.0
Males	3.5 (2.0–6.2)	1.0

Conclusion: This large population-based study indicates a substantially increased risk of MI among GCA patients. The risk was 7 fold higher than that observed in non-GCA controls within the first year of the disease, suggesting that a high level of inflammation or associated therapy at the time of GCA diagnosis may be the culprit. These findings support the need for increased screening for MI and managing cardiovascular risk factors in GCA, particularly in the period following diagnosis.

Disclosure: N. Amiri, None; **H. K. Choi**, None; **E. C. Sayre**, None; **K. Shojania**, None; **J. A. Avina-Zubieta**, None.

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Acute Coronary Syndromes In Patients With Giant Cell Arteritis: A Population Based Retrospective Cohort Study. P. Deepak Udayakumar, Arun K. Chandran, Cynthia S. Crowson, Kenneth J. Warrington and Eric L. Matteson. Mayo Clinic, Rochester, MN.

Background/Purpose: Acute coronary syndrome (ACS) is one of the leading causes of death in the general population. We aimed at assessing the occurrence of ACS in patients with giant cell arteritis (GCA).

Methods: We retrospectively reviewed a population-based incidence cohort of patients with GCA diagnosed between 1950 and 2009 based on American College of Rheumatology 1990 GCA classification criteria. We also included patients ≥ 50 years of age with elevation of erythrocyte sedimentation rate or C-reactive protein and computed tomography, magnetic resonance imaging or positron emission tomography evidence of large vessel vasculitis involving ascending aorta and its branches. We compared this cohort with age, sex and calendar year matched cohort from the same population. All subjects were longitudinally followed through all available community medical records until death, migration or April 30, 2013. Data was collected on all documented episodes of ACS including Thrombolysis in Myocardial Infarction (TIMI) score. Cox models were used to compare the development of ACS between GCA and non-GCA cohort.

Results: We identified 245 patients in the GCA cohort and 245 age, sex and calendar year matched patients in the non-GCA cohort. No difference between the two cohorts was noted in overall ACS events [hazard ratio (HR) 0.74; confidence interval (95% CI) 0.44, 1.26]. No difference was noted in different types of ACS such as unstable angina [HR 0.41; 95% CI (0.16, 1.09)], non-ST elevation myocardial infarction (NSTEMI) [HR 0.85; 95% CI (0.39, 1.85)] and ST elevation myocardial infarction (STEMI) [HR 1.03; 95% CI (0.41, 2.62)]. Age at first ACS event after index date was similar in both cohorts. Time from index date to first ACS event was also similar in both cohorts. Overall TIMI scores for unstable angina and NSTEMI were similar in both cohorts. 10 of 26 GCA subjects (38%) underwent coronary angiography as opposed to 19 of 32 non-GCA subjects (59%) (p=0.11). Revascularization procedures including percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) were done less frequently in GCA [5 of 26 (19%)] than non-GCA subjects [16 of 32 (50%)] (p=0.015). Median length of hospital stay of first ACS event after index date was similar in both cohorts (4.5 vs 4 days). Post ACS complications including cardiogenic shock, persistent rest angina despite intervention, ventricular septal defect, mitral regurgitation and sustained ventricular arrhythmias were similar in both cohorts. 6 of 26 GCA subjects who had ACS experienced 10 recurrent events during 83 person-years of observation after the first episode as opposed to 6 of 32 non-GCA subjects who experienced 17 recurrent events during 138 person-years (rate ratio 1.00; 95% CI 0.44, 2.10).

Conclusion: There is no overall increased risk of acute coronary syndromes in patients with giant cell arteritis. Revascularization procedures are done less frequently in patients with giant cell arteritis. Overall length of hospital stay is not different in patients with giant cell arteritis who develop acute coronary syndrome.

Disclosure: P. D. Udayakumar, None; **A. K. Chandran**, None; **C. S. Crowson**, None; **K. J. Warrington**, None; **E. L. Matteson**, None.

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Infections Requiring Or Acquired During Hospitalizations In Patients With Giant Cell Arteritis - a Population Based Retrospective Cohort Study. P. Deepak Udayakumar, Arun K. Chandran, Cynthia S. Crowson, Kenneth J. Warrington and Eric L. Matteson. Mayo Clinic, Rochester, MN.

Background/Purpose: There is a general impression that the patients with giant cell arteritis (GCA) on glucocorticoid therapy are at higher risk for infections. We aimed to assess the occurrence of infections requiring or acquired during hospitalizations in patients with GCA.

Methods: We retrospectively reviewed a population-based incidence cohort of GCA patients diagnosed between 1950 and 2009 based on American College of Rheumatology 1990 GCA classification criteria. We also included patients ≥ 50 years of age with elevation of erythrocyte sedimentation rate or C-reactive protein and computed tomography, magnetic resonance imaging or positron emission tomography evidence of large vessel vasculitis involving ascending aorta and its branches. We compared this cohort with age, sex and calendar year matched cohort from the same population. All subjects were longitudinally followed through all available community medical records until death, migration or April 30, 2013. Data was collected on all documented episodes of infection requiring or acquired during hospitalization after the GCA incidence/index date. Infection rates were calculated using person-year methods.

Results: We identified 245 patients in the GCA cohort and 245 age, sex and calendar year matched patients in the non-GCA cohort. Baseline characteristics including mean age, sex and length of follow up were similar between the two groups. 74 GCA (134 episodes) and 79 non-GCA (153 episodes) subjects had infections requiring, or acquired during hospitalizations [Rate ratio (RR) 0.94; 95% confidence interval (CI) 0.74, 1.18]. 67 subjects (107 episodes) in GCA cohort and 63 subjects (110 episodes) in non-GCA cohort required hospitalization secondary to an infection [RR 1.04; 95% CI (0.80, 1.36)]. Pneumonia [RR 0.76; 95% CI (0.48, 1.17)], urinary tract infections [RR 0.81; 95% CI (0.43, 1.47)], skin and soft tissue infections [RR 0.83; 95% CI (0.36, 1.87)] accounted for the majority of infections requiring hospitalizations and had similar occurrence in both cohorts.

9 episodes of infections requiring hospitalization occurred in the first 6 months in GCA cohort as opposed to 5 in non-GCA cohort [RR 1.85; 95% CI (0.67, 6.01)]. Urinary tract infections accounted for the majority of infections requiring hospitalization in the first 6 months after GCA incidence [RR 3.93; 95% CI (0.85, 56.52)].

No difference between the two cohorts was noted in overall infections acquired during hospitalizations [RR 0.68; 95% CI (0.41, 1.08)]. Median length of hospital stay was 5 days and median duration of antibiotic use was 10 days in each cohort among infection episodes requiring hospitalizations.

Conclusion: There is no overall increased risk of infections requiring or acquired during hospitalizations in patients with giant cell arteritis on glucocorticoid therapy. There may be an increased risk of infections requiring hospitalization, especially of the urinary tract in the first six months after GCA incidence although this did not achieve statistical significance in our study. Overall length of hospital stay and duration of antibiotic use is not different in patients with GCA requiring hospitalization because of infection.

Disclosure: P. D. Udayakumar, None; **A. K. Chandran**, None; **C. S. Crowson**, None; **K. J. Warrington**, None; **E. L. Matteson**, None.

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Statins Do Not Influence Occurrence Or Prednisone Requirement Of Giant Cell Arteritis. A French Population-Based Cohort Study. Grégory Pugnet[1], Laurent Sailler[2], Robert Bourrel[3], Jean-Louis Montastruc[4] and Maryse Lapeyre-Mestre[4]. [1]Toulouse University Hospital, University of Toulouse, INSERM UMR 1027, Toulouse, France, [2]Toulouse University Hospital, Toulouse, France, [3]Caisse Nationale de l'Assurance Maladie échelon régional, Midi-Pyrénées, Toulouse, France, [4]Toulouse University Hospital, INSERM U1027, University of Toulouse, France, Toulouse, France.

Background/Purpose: Statins are widely prescribed to reduce the risk of cardiovascular ischemic events, but also present immunoregulatory effects promoting a shift from a TH-1 to a TH-2 immune response. The aim of our study was to investigate the potential relationship between exposure to statins, GCA occurrence and prednisone requirement in the general population.

Methods: The cohort includes incident GCA patients of the Midi-Pyrénées County, south of France from January 2005 to December 2008. Incident GCA cases were selected in the French National Health Insurance system database. For each patient, two age- and paired- controls were selected in the same database. Endpoints were GCA occurrence, cumulative prednisone doses and time until maintenance of low prednisone doses (LPD) (i.e < 5 mg prednisone per day for at least 6 months). Statin exposure was measured during the 6 months before the date of first prednisone prescription and as a time-dependent co-variable during the course of GCA for cases and controls. Patients were followed up to April 2011.

Results: The study included 103 patients (80 women, mean age 74.8 ± 9 years, mean follow-up 48.9 ± 14.8 months) and 206 controls. Twenty-eight (27.2%) patients versus 45 (21.8%) controls had a sustained exposure to statins before the index date (adjusted OR = 0.70 [0.4–1.2], p = 0.22). A total of 81 patients reached a maintenance of LPD during the follow-up period: respectively 48%, 70%, 85% and 89% at 2, 3, 4 and 5 years of follow-up. The mean time necessary to reached a maintenance of LPD was 24.3 ± 11.2 months. Their mean cumulative prednisone dose at this time was 11.4 ± 6.1 g. Statin exposure at diagnosis was associated with a higher rate of remission, however this effect was not present when statin exposure was treated as a time-dependent covariate (adjusted HR =1.06 [0.81–1.40], p> 0.05). Cumulative prednisone doses did not differed according to statin exposure.

Conclusion: We found no influence of statin therapy on the occurrence of GCA or on prednisone requirement in a French population-based GCA cohort.

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May Giant Cell Arteritis Be Characterized By Different Clinical Entity and Long-Term Outcome? Rosaria Talarico[1], Chiara Stagnaro[1], Claudia Ferrari[1], Anna d'Ascanio[1], Chiari Tani[1], Chiara Baldini[1], Marta Mosca[2] and Stefano Bombardieri[1]. [1]Rheumatology Unit, Pisa, Italy, [2]Rheumatology Unit, University of Pisa, Pisa, Italy.

Background/Purpose: Giant cell arteritis (GCA) represents the most common primary vasculitis of the elderly, that affect large and medium-sized arterial vessels. Growing data shown that almost one-third of the patients with GCA develop serious peripheral vascular complications during long-term follow up, and it seems that unrecognized extra-cranial involvement may be even more common.

The primary aim of this study was to explore if there are different clinical entities in a cohort of patients with GCA (i.e. symptoms compatible with cranial GCA and large-vessel GCA); a secondary aim was to evaluate long-term outcome of GCA patients with at list 5 years of follow-up.

Methods: Two hundred and ten GCA patients (34 males and 176 females, mean ± SD age 77±8 years) were retrospectively studied. Clinical symptoms at disease onset and during the follow-up, time delay until diagnosis, as well as laboratory findings at the time of diagnosis, therapeutic approach were retrospective evaluated. In order to characterized the different disease entities, overall clinical symptoms were evaluated by means of a spectrum analysis. Moreover, we evaluated long-term outcomes in patients with a minimum follow-up of 5 years. We have defined as disease flare any further clinical manifestation compatible with the clinical spectrum of GCA and/or an increase of ESR ≥ 40 mm/hour, not otherwise justifiable, that required higher doses or new introduction of GC therapy.

Results: The most frequent clinical manifestations presented at the onset included: new onset headache and/or scalp pain 77%, constitutional symptoms 46%, jaw claudicatio 36%, vision loss 34%, abnormal temporal artery on examination 32%, dizziness 29%, neuropsychiatric symptoms 29%, cough not otherwise justifiable 10%, cerebrovascular accidents 6% and hearing loss 5%. Irreversible blindness was reported in 7% of patients, mainly due to a latency period between onset and treatment of ≥ 2 months. Temporal artery biopsy was performed in 160/210 of patients, resulting positive in 58%. Globally, about 26% of subjects (55, M/F: 9/46, mean ± SD age 71±7 years) was characterized by a clinical profile compatible with extra-cranial GCA. In all case, extra-cranial involvement was confirmed by (18)F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and/or

angiography. Moreover, patients who presented symptoms compatible with large-vessel GCA were characterised by a more relapsing course compared with patients with cranial involvement GCA profile.

Conclusion: According literature data, our results confirm that GCA may be composed by more than one single entity. Extra cranial involvement due to GCA must be must be promptly recognized, because it probably may require a different prognostic and therapeutic approach.

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How Similar Are Extracranial Giant Cell Arteritis and Takayasu Arteritis? Tanaz A. Kermani[1], Cynthia S. Crowson[2], Francesco Muratore[3], Jean Schmidt[4], Eric L. Matteson[2] and Kenneth J. Warrington[2]. [1]University of California Los Angeles, Los Angeles, CA, [2]Mayo Clinic, Rochester, MN, [3]Arcispedale S Maria Nuova, IRCCS, Reggio Emilia, Italy, [4]CHU Nord, Amiens, France.

Background/Purpose: The clinical and radiographic features of giant cell arteritis (GCA) with extracranial (large-vessel) involvement can be similar to those of Takayasu arteritis (TAK) with age often being used to differentiate these two forms of large-vessel vasculitis. The aim of this study was to compare clinical and imaging characteristics of GCA and upper extremity (UE) arterial involvement with TAK.

Methods: A cohort of patients with TAK diagnosed between 1984 and 2009, and, a cohort of patients with GCA and UE arterial involvement (based on imaging) diagnosed between 1999 and 2008 have been assembled. Comparisons were performed using Kruskal-Wallis and Chi-square tests.

Results: The TAK cohort consisted of 125 patients (91% female); mean age (±SD) at diagnosis 30.9 (±10) years. The cohort of patients with GCA and UE involvement comprised of 120 patients (80% female); mean age (±SD) at diagnosis 67.8 (±7.5) years. Mean onset of symptoms prior to diagnosis was significantly longer in TAK (3.2 years) compared to GCA (0.5 years), $p<0.001$. Fever was more common in patients with TAK (29% compared to 15% with GCA, $p=0.01$). Headache frequency was similar in both groups (33% GCA versus 45% TAK, $p=0.06$). UE claudication was present in 63 patients (53%) with GCA compared to 49 patients (40%) with TAK, $p=0.04$. Lower extremity claudication was reported in 11 patients (9%) with GCA compared to 22 patients (18%) with TAK, $p=0.05$. UE blood pressure discrepancy was present in 65% with TAK versus 28% with GCA, $p<0.001$. Absent pulses were noted in 72% of the TAK cohort compared to 53% of the GCA cohort, $p=0.002$; while any bruit was present in 74% TAK and 38% GCA, $p<0.001$.

Imaging findings are in the **Table**. Involvement of the thoracic aorta, abdominal aorta, carotid arteries, innominate artery, mesenteric artery and left renal artery was more frequently observed in TAK (Table). Among patients with luminal changes of the thoracic aorta, stenotic/occlusive lesions were predominant in TAK (81% compared to 0% in GCA), whereas aneurysmal disease was more common in GCA (100% compared with 19% in TAK $p<0.001$). Similar findings were noted in the abdominal aorta. In other arterial beds, stenotic or occlusive changes were the most frequent type of lesion observed in both GCA and TAK ($p>0.05$).

Table. Distribution and type of arterial lesions in GCA compared to TAK.

Artery	GCA Total number with any lesion/total number with imaging of area (%)	TAK Total number with any lesion/total number with imaging of area (%)	p-value
Thoracic aorta	13/117 (11)	26/109 (24)	0.01
Abdominal aorta	4/69(6)	21/93 (38)	<0.001
Right carotid	10/118 (8)	46/107 (43)	<0.001
Left carotid	11/118 (9)	53/107 (50)	<0.001
Right vertebral	13/115 (11)	14/107 (13)	0.69
Left vertebral	13/115 (11)	20/107 (19)	0.11
Innominate	5/117 (4)	27/105 (26)	<0.001
Right subclavian	57/116 (49)	40/103 (39)	0.126
Left subclavian	65/117 (56)	68/103 (66)	0.11
Right axillary	42/113 (37)	16/39 (41)	0.67
Left axillary	53/115 (46)	20/39 (51)	0.57
Mesenteric	11/65 (17)	31/88 (35)	0.01
Right renal	7/65 (11)	19/89 (21)	0.08
Left renal	3/65 (5)	17/89 (19)	0.01
Right iliac	3/64 (5)	12/87 (14)	0.07
Left iliac	2/64 (3)	12/87 (14)	0.03

Conclusion: Despite some similarities, patients with UE involvement from GCA differ from TAK in clinical and imaging characteristics. Stenotic/occlusive disease was the most frequent type of arterial lesion in both groups at the primary branches of the aorta. However, the type of aortic involvement differed between the two forms of large-vessel vasculitis. Aortic aneurysms were more common in GCA while stenotic changes of the aorta were more common in TAK suggesting different pathophysiologic mechanisms or vascular response to injury.

Disclosure: T. A. Kermani, None; **C. S. Crowson**, None; **F. Muratore**, None; **J. Schmidt**, None; **E. L. Matteson**, None; **K. J. Warrington**, None.

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Clinical Implications Of Antiphospholipid Antibodies In Takayasu's Arteritis. Natasha Jordan, Holy Bezanahary and David P. D'Cruz. Louise Coote Lupus Unit, St Thomas' Hospital, London, United Kingdom.

Background/Purpose: Takayasu's arteritis (TA) is a granulomatous inflammation of unknown origin involving the aorta and its major branches. Association and implication of antiphospholipid antibodies (aPL) in the TA disease process remain controversial. The aim of this research was to ascertain if aPL positivity or the presence of Antiphospholipid Syndrome (APS) were predictive of a worse clinical outcome in TA.

Methods: Clinical data was retrospectively collected on 22 TA patients over an 11 year period (2001–2012). All patients fulfilled the ACR criteria for TA. Patients were categorised into 2 groups: a diagnosis of TA alone or a diagnosis of TA with either persistently positive anticardiolipin antibodies and/or lupus anticoagulant or a concurrent clinical diagnosis of APS. Those with APS met the Sapporo classification criteria.

Screening for lupus anticoagulant was performed using the dRVVT (dilute Russell's viper venom time) assay in accordance with standard methods. Confirmatory tests used a combination of mixing studies and correction with phospholipid. IgG and IgM anticardiolipin antibodies were measured using a standardized ELISA. Since anti-beta-2-glycoprotein-1 antibodies were not routinely measured clinically during the early stages of the study, they were not included in the analysis.

Adverse clinical outcomes included cerebrovascular accident (CVA),transient ischaemic attack (TIA), loss of vision, vascular lesions (carotid, femoral, renal coronary or other vessels) requiring stenting, angioplasty or other surgical intervention, aortic valve replacement, end-stage renal failure or death.

Results: 59% of patients had TA without aPL (n=13) and 41% had TA with a persistently positive aPL or a concurrent diagnosis of APS (n=9). Overall 7 significant vascular complications occurred in TA patients without aPL including 1 CVA, 1 TIA, 1 carotid endarterectomy and 4 angioplasty/stenting procedures. 8 such events occurred in TA patients with aPL/APS including 2 CVAs, 1 carotid endarterectomy, 1 aortic valve replacement and 4 angioplasty/stenting procedures. No patients developed end-stage renal failure or loss of vision. There were no deaths in this study cohort.

Conclusion: Persistently positive aPL and APS are present in a significant proportion of TA patients. Our concern was that these individuals may have a worse clinical outcome in terms of vascular complications. This study has shown that this is not the case and that vascular complications and need for intervention are equal in TA patients regardless of aPL positivity.

Disclosure: N. Jordan, None; **H. Bezanahary**, None; **D. P. D'Cruz**, None.

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Predictivity Of Serum Biomarkers For Disease Activity In a Prospectively Followed-Up Takayasu Arteritis Cohort: Is Serum Amyloid A Protein Better Than Conventional Acute Phase Markers? Ahmet Omma, Burak Erer, Nilufer Alpay, Nuray Gurel Polat, Ahmet Gul, Murat Inanc, Lale Ocal and Sevil Kamali. Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey.

Background/Purpose: Takayasu arteritis (TA) is a chronic vasculitis with an indolent course. Reliable diagnostic and activity markers have not yet been demonstrated. We aimed to evaluate the predictivity of conventional acute phase proteins (ESR, CRP) and other non-conventional inflammation and endothelial activity markers such as serum amilod A (SAA) protein, interleukin-6 (IL-6) and von Willebrand factor (vWF) in a TA cohort, prospectively followed-up.

Methods: Fourty-eight TA patients diagnosed according to ACR 1990 criteria and followed-up ≥ 6 months, 37 patients with granulomatosis with

poliangiitis (GPA) diagnosed according to ACR 1990 criteria and 28 healthy controls (HC) were included into the study. Demographic and clinical features of TA, GPA and HCs were recorded into a predefined protocol. ESR, CRP, SAA, IL-6 and vWF levels were analysed initially in all groups and at 3rd, 6th, 12th months visits in TA and GPA groups. Westergreen method for ESR, nephelometric assay for CRP, SAA and ELISA method for IL-6 and vWF were used. Disease activity was evaluated by Kerr criteria for TA and BVAS2003 for GPA. TA and GPA cohorts were stratified to the subgroups according to the activity. Comparisons were performed by Mann Whitney U test in subgroups. ROC curve analysis was used to identify the sensitivity and specificity of laboratory parameters for predicting activity.

Results: Mean age and disease duration were found as 40±13 yrs, 121±115 mo for TA, 47±13 yrs, 65±42 mo for GPA and mean age was 38±9 for HCs. Females were significantly high in TA cohort (%) when compared to GPA (%) (p<0,001). The percentage of active disease was 40%, 31%, 35%, 29% for TA and 32%, 19%, 11%, 13% for GPA at initial 3rd, 6th and 12th months, respectively. ESR, CRP and SAA levels were significantly high in active TA at the initial, 3rd, and 6th months visits (41±20 vs 21±12, p=<0.001 for ESR, 20±20 vs 6±10 p=<0.001 for CRP, 23±23 vs 12±29, p=0.001 for SAA at initial visit, 41±19 vs 24±17, p=0.002 for ESR, 26±28 vs 6±8, p= 0.004 for CRP, 38±59 vs 12±17, p=0.02 for SAA at the 3rd visit, 41±17 vs 24±12, p= <0.001 for ESR, 16±18 vs 4±5, p= 0.01 for CRP, 22±30 vs 10±16, p=0.002 for SAA at the 6th visit). SAA was the only marker that demonstrate the significance between subgroups at the 12th month (12±10 vs 8±11, p= 0.007). In active GPA subgroup, SAA and vWF at the 3rd visit and vWF at the 6th visit were found significantly high compared to inactive patients. Sensitivity and specificity were found as 88–70%, 79–84% for ESR levels of 35 mm/h, 83–65%, 86–84% for CRP levels of 5–8 mg/L 72–50%, 90–80% for SAA levels of 10–11 mg/L at the initial and 6th months visits in TA cohort. At the 12th month visit, SAA levels of 9 mg/L, was the only marker reaching the significant sensitivity (45%) and spesificity (83%) for predicting activity.

Conclusion: In a well established and prospective cohort of TA, SAA has found to be a comparable sensitivity and specificity with ESR and CRP for predicting activity. It's been observed that sensitivity of ESR, CRP had a trend towards to decrease in time which could be related to the decreasing activity during the follow-up. SAA was the only laboratory parameter which maintained its specificity in contrast to conventional biomarkers.

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Assessment of Patients With Takayasu's Arteritis in Routine Clinical Follow-Up With Indian Takayasu Clinical Activity Score 2010(*ITAS2010*). Fatma Alibaz-Oner and Haner Direskeneli. Marmara University, School of Medicine, Istanbul, Turkey.

Background/Purpose: ITAS2010 (Indian Takayasu Clinical Activity Score) is a new composite index developed to assess clinical activity in Takayasu's arteritis (TAK), which is weighted for vascular items. In this study, we aimed to investigate the effectiveness of ITAS2010 in the routine clinical follow-up of patients with TAK.

Methods: Patients (n=33, mean age:40.9±12,4 years, F/M:30/3) classified according to ACR criteria for TAK were enrolled. ITAS2010 forms were filled cross-sectionally at baseline for all clinical features and 2 follow-up visits prospectively, with intervals of at least 4–6 months, by including only new or worsening symptoms within the past 3 months(1).

Results: ITAS2010 was similar at baseline for both active and inactive patients [12 (5–20) vs 10 (0–19), respectively]. There was no correlation between ITAS2010 and acute phase reactants (APRs) in this visit. Similarly, change according to PGA was not reflected in ITAS in the second visit [1,15 (0–6) vs 1,4 (0–3), respectively]. Only in the third visit ITAS2010 score was observed to be significantly higher in active [1,62 (0–7)] patients compared to inactives [0,45 (0–3)](p=0,001). The total agreement between ITAS2010 and PGA was 60% (kappa: 0,096, p=0,43) and between ITAS2010 and *Kerr et al*. was 74% (kappa: 0,18, p=0,035). The total agreement between PGA and *Kerr et al*. was 71% (kappa: 0,26, p=0,005). Twelve patients were evaluated with imaging in the follow-up period (4 with PET, 8 with MR-Angiography). When we added an extra score on ITAS2010 for high APRs or positive imaging (vascular progression with radiology or increased uptake on major vascular structures with PET), the total agreement between ITAS2010 and PGA increased to 74% (kappa: 0,499, p<0,001), whereas ITAS2010 and *Kerr et al*. decreased to 51% (kappa: 0,102, p=0,06).

Conclusion: The agreement between PGA and ITAS2010 was observed to be limited in our study. However, when we combined ITAS2010 with APR or imaging, our results improved. ITAS2010 had a significant discriminatory value according to disease activity in only the third visit in our routine follow-up. These results suggest that ITAS2010 may be valuable in the long-term follow-up of patients with TAK, especially if combined with biomarkers and imaging.

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Disclosure: F. Alibaz-Oner, None; **H. Direskeneli**, None.

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Patients With TAKAYASU'S Arteritis Having Persistent ACUTE PHASE Response Usually Have An Increased MAJOR Vessel Uptake By 18F-FDG-PET/CT. Fatma Alibaz-Oner[1], Fuat Dede[1], Tunc Ones[2], H. Turgut Turoglu[1] and Haner Direskeneli[1]. [1]Marmara University, School of Medicine, Istanbul, Turkey, [2]Marmara University, School of Medicine, ISTANBUL, Turkey.

Background/Purpose: 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET/CT) is a sensitive imaging tool for large-vessel vasculitis. Although not uniformly accepted, an increased uptake by 18F-FDG PET/CT in large-vessels is accepted to be a sign of active disease in Takayasu's arteritis (TAK). In this study, we aimed to investigate the value of 18F-FDG-PET/CT for clinical assessment in a subset of TAK patients having a persistent acute phase response (APR) without any signs or symptoms of clinical disease activity.

Methods: We studied 12 patients with TAK (mean age: 39.2±14.8 years, F/M: 10/2, disease duration: 5.4 years). Patients were clinically inactive (according to the definition of activity by *Kerr et al*), while categorized as having "persistent" disease activity by physician's global assessment due only to APR. All patients were under immunosupressive treatments including corticosteroids. The severity of large-vessel 18F-FDG uptake was graded using a four-point scale from grade 0 (no uptake present) to grade III (high-grade: uptake higher than liver). Any uptake in major vessels with a grade ≥2 was accepted to be "active."

Results: Mean ESR was 55.5 (30–86) mm/h and mean CRP was 29.6 (7.7–90) mg/L. Active vasculitic lessions were observed by 18F-FDG-PET/CT in 8 of 12 (66%) of the study group, with a mean number of 2.6 (1–4) active vascular lesions. Arcus aorta was involved in 25%, ascending aorta in 20%, right brachiocephalic artery in 20%, descending aorta in 15%, abdominal aorta in 10% and left and right subclavian arteries in 5% each of the investigated vessels. A step-up treatment change was decided in 7 patients according to 18F-FDG-PET/CT results.

Conclusion: We observed increased 18F-FDG uptake in the majority of TAK patients with an increased APR, but clinically silent disease. 18F-FDG-PET/CT showed the presence and localisation of active vascular inflammation in the aorta and its branches. Although specificity of observed lesions are not clear, 18F-FDG-PET/CT imaging may influence physician's assessment of clinical activity and treatment choices in TAK.

Disclosure: F. Alibaz-Oner, None; **F. Dede**, None; **T. Ones**, None; **H. T. Turoglu**, None; **H. Direskeneli**, None.

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High Prevalence Of Metabolic Syndrome In Takayasu Arteritis: An Increased Cardiovascular Risk and Lower Adiponectin Serum Levels. Thiago Silva[1], Mauricio Levy-Neto[2], Rosa M. R. Pereira[3] and Eloisa Bonfa[4]. [1]Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [3]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [4]Universidade de Sao Paulo, São Paulo, Brazil.

Background/Purpose: The prevalence of Metabolic Syndrome (MetS) tends to be high among rheumatic patients, and cardiovascular disease is the leading cause of death in these conditions. The aim of this study is to determine the prevalence of MetS in Takayasu Arteritis patients (TA) and its association with risk factors and adipokines levels.

Methods: A cross sectional study was conducted in 45 consecutive TA women with 47 age- and body mass index (BMI)-matched healthy controls.

Results: The prevalence of MetS (IDF/AHA criteria) was higher in TA compared to controls (33.34 vs. 8.51%, $p=0.003$). TA patients had higher frequency hypertension ($p< 0.001$), dyslipidemia ($p=0.001$), insulin ($p=0.021$), HOMA-IR ($p=0.024$), apoliprotein E ($p=0.029$), resistin ($p=0.018$) and CRP ($p<0.001$) compared to healthy subjects, with similar levels of adiponectin and PAI-1 ($p>0.05$). Further analysis of TA patients with and without MetS revealed a higher frequency of overweightness/obesity (66.66 vs. 26.66%, $p=0.022$), Framingham score ≥ 1 ($p=0.032$), and lower adiponectin levels (20.37 ± 21.16 vs. 38.64 ± 22.62ug/ml, $p=0.022$) in the former group. No differences were found regarding disease duration, activity, glucocorticoid use, resistin and PAI-1 levels in these two groups of TA patients ($p>0.05$).

Conclusion: A high prevalence of MetS was observed in TA patients and this comorbidity seems to identify a subgroup of overweight/obese patients with high cardiovascular risk without a significant association with disease status. Further longitudinal studies are necessary to observe the impact of controlling this modifiable risk factor in the quality of life and survival of TA patients.

Disclosure: T. Silva, None; **M. Levy-Neto**, None; **R. M. R. Pereira**, CNPQ #300559/2009-7, 2, Federico Fondation, 2; **E. Bonfa**, None.

1684

Early Combination Immunosuppression and Serial Non-Invasive Imaging Improves Outcome In Takayasu Arteritis. Taryn Youngstein, Michael Quinn, James Peters and Justin C. Mason. Hammersmith Hospital, Imperial College London, London, United Kingdom.

Background/Purpose: Takayasu arteritis (TA) affects the aorta and its branches, pre-disposing to stenoses and aneurysmal dilatation. While morbidity remains high, evidence for efficacy of immunosuppressive therapy is relatively limited. The purpose of this study was to analyze our use of combined immunosuppression with serial non-invasive imaging, to show that early intervention and detailed monitoring improves outcome.

Methods: A longitudinal study of case notes, imaging studies and outcome data in 110 patients seen with TA from 2000–2013.

Results: All TA sub-types were found, with a mean of 3 arteries involved (range 1–9). 89% were female, with mean age at diagnosis 31.5 yrs. ^{18}FDG-CT-PET was used for detection of active disease at diagnosis and identified pre-stenotic disease. Ultrasound, magnetic resonance (MRA) and CT angiography (CTA) aided diagnosis, and also revealed pre-stenotic lesions. Combined immunosuppression was initiated at diagnosis, with 90% prescribed prednisolone, plus methotrexate (43%), azathioprine (37%), mycophenolate mofetil (9%) or cytoxan (10%). TNFa and IL-6R antagonists were used effectively in 9 patients with refractory disease. 10% had burnt out disease and were not immunosuppressed. Serial MRA was used for monitoring, revealing stable disease in 82% and sensitively detecting new stenoses/aneurysms in 9.8% of patients, many of whom had no change in ESR/CRP or clinical exam. Subsequent treatment escalation prevented progression, and MRA revealed improved arterial stenoses in 9 patients (8.2%). Echocardiography and cardiac MRI identified silent myocardial injury in 22%. MRA also aided management decisions, allowing accurate steroid titration and low maintenance doses (<10mg/d) to be safely achieved. Low dose prednisolone was continued for 38.2 ± 27.2 mths to optimize disease activity control, with no osteoporotic fractures and <2% steroid-induced diabetes detected. Cross-sectional analysis (2013) revealed a mean prednisolone dose of 3.22 ± 4.97 mgs. 50% had stopped prednisolone, 41.4% were receiving '10mg and 8.6% >10mg/d. Two deaths were recorded, both unrelated to complications of TA or its treatment.

Conclusion: Our analysis suggests that non-invasive imaging aids early diagnosis, and that prednisolone with an immunomodulator controls disease activity and can prevent and occasionally reverse stenoses. Serial MRA allows accurate monitoring of arterial anatomy and facilitates targeted titration of therapy and steroid-sparing, improving outcome and minimizing side-effects. Arterial imaging is also essential due to the relative insensitivity of ESR/CRP in assessing disease activity, and their complete suppression by novel therapies, particularly tocilizumab.

Disclosure: T. Youngstein, None; **M. Quinn**, None; **J. Peters**, None; **J. C. Mason**, None.

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Long-Term Use Of Tocilizumab For The Treatment Of Giant Cell Arteritis. Sebastian Unizony[1], John Stone[1] and Brian Keroack[2]. [1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Maine Medical Center, Tufts University Medical School, Maine, ME.

Background/Purpose: A sizeable percentage of giant cell arteritis (GCA) patients experience disease relapse upon glucocorticoid (GC) tapering, and a clearly effective GC-sparing alternative has not been identified. Interleukin (IL)-6 contributes to the pathogenesis of GCA and represents a target for therapy.

Methods: Retrospective study of 12 relapsing GCA patients treated the IL-6 receptor (IL-6R) antagonist tocilizumab (TCZ). Clinical outcomes evaluated were number of flares, ability to taper GC without disease exacerbation and safety.

Serum levels of the T-helper (T_H)1-, T_H17- and regulatory T cell-related cytokines IL-17, IFN-γ, IL-12, IL-6, IL-21, IL-22, IL-23, IL-1β, TNF-α and IL-10 were analyzed by Luminex in a group of patients who achieved remission on TCZ with or without low dose GC (n = 5), and compared with those of a group whose disease was controlled with GC monotherapy (n = 5).

Results:

Baseline characteristics: The mean follow-up of this cohort since diagnosis was 37 months (range 17–70). The mean duration of the disease at the time of TCZ initiation was 19.5 months (range 4–53). Eight subjects had failed at least one immunosuppressant (i.e., methotrexate), and four had contraindications for the use of GC.

Clinical response and GC-sparing effects: TCZ (4 mg/Kg, n = 3 and 8 mg/Kg, n = 9) was given in monthly infusions for a mean period of 16 months (range 5–26). Before and during IL-6R blockade, the patients experienced an average of 2.7 (95% CI 2–3.5) and 0.6 (95% CI 0–1.2) disease exacerbations per year, respectively (P = 0.0006). The mean daily prednisone dose of the cohort decreased from 24 mg (95% CI 15–33.5) at the time of TCZ initiation to 7 mg (95% CI 0.7–14) by the time of last evaluation (P = 0.01). On TCZ, 7 subjects maintained disease remission for a mean time of 17.5 months (range 8–26), and 5 patients flared after an average of 11 months of therapy (range 2–24). The mean prednisone dose at the time of flare in these 5 patients was 4.5 mg/day. One subject relapsed after TCZ discontinuation. Currently, 6 patients are taking ≤5 mg/day of prednisone and 3 patients are off GC. As expected, inflammatory markers normalized and IL-6 levels significantly increased in all patients receiving TCZ.

Safety: Adverse events attributable in part to TCZ included leucopenia (n = 5), transaminitis (n = 8), and pneumonia (n = 1). Autopsy on one patient who died from an unrelated cause revealed persistent vasculitis.

Cytokine analysis: There was a non-statistically significant difference in the serum cytokine concentrations measured by multiplex bead-based Luminex assays. Patients whose disease was maintained in remission on TCZ with or without low dose GC (mean prednisone dose 5 mg/day) tended to have lower levels of IL-12, IFN-γ, and IL-17, and higher levels of IL-10 than subjects in remission with GC monotherapy (mean prednisone dose 16 mg/day). IL-1β and IL-6 increased during IL-6R blockade. IL-21, IL-22, and IL-23 were not detected in the majority of cases, and the concentration of TNF-α was similar in both groups.

Conclusion: TCZ led to a significant reduction in the flare rate and GC requirement of a group of patients with highly relapsing GCA. A randomized-controlled trial of TCZ for the treatment of GCA is currently ongoing.

Disclosure: S. Unizony, None; **J. Stone**, None; **B. Keroack**, None.

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Tocilizumab In Refractory Takayasu Arteritis: a Case Series and Updated Literature Review[2]. Noemie Abisror[1], Arsene Mekinian[1], Christian Lavigne[2], Marie Anne Vandenhende[3], Michael Soussan[4] and Olivier Fain[1]. [1]Internal Medicine, Jean Verdier Hospital, Bondy, France, [2]Internal Medicine, Angers, France, [3]Internal Medicine, Bordeaux, France, [4]Nuclear Medicine, Avicennes Hospital, Bobigny, France.

Tocilizumab in refractory Takayasu arteritis: a case series and updated literature review.

Background/Purpose: The aim of this study is to analyze the efficacy and tolerance of tocilizumab in patients with Takayasu arteritis (TA).

Methods: We retrospectively studied patients with TA (ACR and/or *Ishikawa's* criteria): 5 French multicenter cases and 39 from the literature. Clinical, biological, radiological disease activity and treatment were analyzed before tocilizumab, during the follow-up and at the last available visit.

Results: Forty four patients (median age 26 years [3–65]) were included in the present study: 5 patients from the 3 French university hospitals and 39 cases from the literature review. Median follow-up after initiation of tocilizumab was 15 months [8–33]. Clinical and biological activities significantly decreased within 3 months, similarly to steroid amount (from 15 mg/day [5–75] at baseline to 10 mg/day [2–30] at 6 months; $p<0.05$) and steroid-dependence rate. Even radiological activity did not significantly decreased at 6 months, significant decrease of arterial FDG uptake was noted at 6 months. Median duration of tocilizumab treatment was 9 months [3–180]. At the last visit, tocilizumab was continued in 17/32 patients (53%), and was discontinued in the 15 remaining cases because of the remission (n=5), relapse (n=3), persistent radiological activity (n=3), cutaneous rash (n=2), severe infections (n=1) and the absence of tocilizumab financial support (n=1). No death related to tocilizumab treatment was noted.

Table 1. Characteristics of patients with TA from personal data (n=5) and literature review (n=39).

Number of evaluable patients	Baseline assessment (N=44)	3 months after beginning tocilizumab (N=30)	6 months after beginning of tocilizumab	Last visit N=44
Tocilizumab treatment	44	28 (93%)	12/15 (80%)	17/32 (53%)
Delay from baseline (months)	–	3 [2–3]	6 [4.5–6]	15 [8–33]
Clinical response				
Tocilizumab efficacy (by physician)	–	13/14 (93%)	14/18 (78%)	33/44 (75%)
Disease clinical activity	41/42 (98%)	1/14 (7%)*	3/18* (17%)*	7/34 (26%)*
Laboratory data				
Biological activity	28/29 (97%)	2/15* (13%)	2/19*(11%)	7/34 (26%)
ESR (mm/hour)	42 [8–88]	4 [0–63]	5 [0–41]*	4 [0–41]*
C-reactive protein (mg/l)	21 [8–126]*	0 [0–13]	0.5 [0–124]*	0 [0.5–17]*
Radiological data				
Radiological activity	15/22 (68%)	3/9* (33%)	5/15** (33%)	–
PET FDG vascular uptake	9/9	–	3/7* (43%)	–
SUV max	3.8 [1,3–5,3]	–	–	–
Tocilizumab associated steroids	27/30 (90%)	27/30 (90%)	8/13 (62%)	18/22 (82%)
Steroids (prednisone; mg/day)	15 [5–75]	10 [7–30]*	10 [2–30]*	5 [0–30]*

Values are medians with ranges or frequencies with percentages. ESR: erythrocyte sedimentation rate; Steroid-dependence: prednisone ≥20 mg/day; PET FDG: positron emissions tomography with fluorodesoxyglucose.
* $p<0.05$ versus baseline
** $p=0.05$

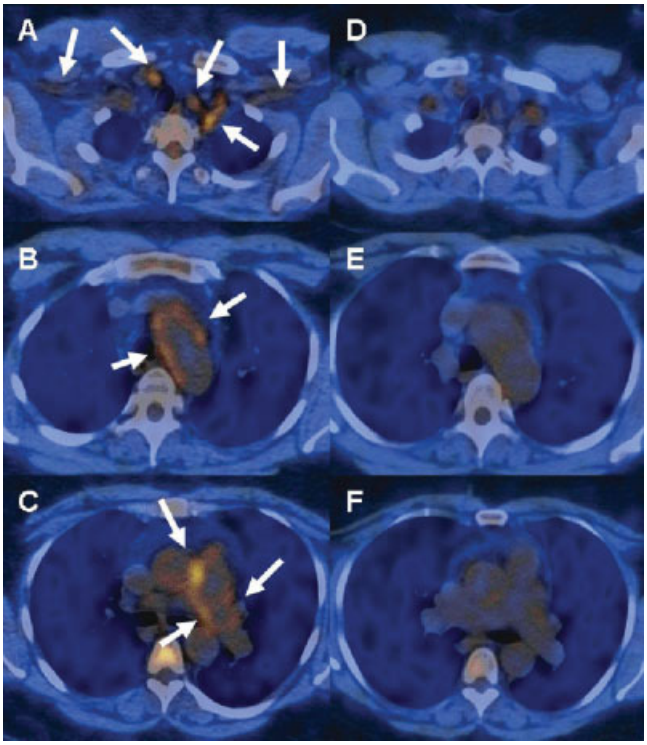

Figure 1. PET-FDG uptake before tocilizumab treatment (A, B, C) and after 6-month tocilizumab (D, E, F) in patient with Takayasu arteritis. A and D: FDG uptake in cervical and subclavians arteries; B and E: FDG uptake in aortic arch; C and F: FDG uptake in pulmonary arteries.

Conclusion: This study show the efficacy of tocilizumab in terms of clinical, biological and radiological response, as well as steroid-sparing agent. Only well-designed studies could definitely address the efficacy of tocilizumab in TA.

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Tocilizumab In Refractory Aortitis: A Multicenter Study Of 13 Patients.

Javier Loricera[1], Ricardo Blanco[1], Santos Castañeda[2], Alicia Humbría[3], Sheila Melchor[4], Jaime Calvo-Alen[5], Elena Aurrecoechea[5], Iñigo Rúa-Figueroa[6], Norberto Ortego[7], Mauricio Mínguez[8], Gabriel Herrero-Beaumont[9], Beatriz Bravo[10], Jose Rosas[11], Javier Narvaez[12], Javier Calvo[13], Rafael Ariza[14], Mercedes Freire[15], M. Enriqueta Peiró[1], Vanesa Calvo-Río[1], Francisco Ortiz-Sanjuán[1] and Miguel A. González-Gay[1]. [1]Hospital Universitario Marqués de Valdecilla. IFIMAV. Santander. Spain, Santander, Spain, [2]Hospital Universitario de La Princesa, IIS Princesa, Madrid, Spain, [3]Hospital Universitario de La Princesa. IIS Princesa. Madrid, Madrid, Spain, [4]Hospital Universitario 12 de Octubre. Madrid, MADRID, Spain, [5]Hospital Sierrallana. Torrelavega, Torrelavega, Spain, [6]Hospital Universitario Dr Negrín. Las Palmas, Las Palmas de Gran Canaria, Spain, [7]Hospital Clínico San Cecilio. Granada, Granada, Spain, [8]Hospital Universitario San Juan. Alicante, Alicante, Spain, [9]IIS-Fundación Jiménez Díaz, Madrid, Spain, [10]Hospital Virgen de las Nieves. Granada, Granada, Spain, [11]Hospital Marina Baixa. Villajoyosa, Villajoyosa, Spain, [12]Hospital Universitario de Bellvitge, Barcelona, Spain, [13]Consorcio Hospital General Universitario. Valencia, Valencia, Spain, [14]University Hospital Virgen Macarena. Sevilla, Sevilla, Spain, [15]Hospital Universitario Juan Canalejo. La Coruña, La Coruña, Spain.

Background/Purpose: Aortitis can occur alone or associated with other conditions. It is often refractory to standard immunosuppressive therapy. IL-6 has been implicated in the mechanisms leading to aortitis. Tocilizumab (TCZ) is a humanized monoclonal anti-IL6 receptor (IL-6R) antibody. Our aim was to assess the efficacy and side-effects of TCZ in patients with refractory inflammatory aortitis.

Methods: Multicenter study of 13 patients diagnosed of inflammatory aortitis due to different underlying conditions. The diagnosis of aortitis was based on imaging (CT angiography, MR angiography, PET and/or echocardiogram).

Results: Patients (12 women/1 man) had a mean age ±SD of 50.69±21.93 years (table). The underlying conditions were: Takayasu arteritis (TKY) (6 cases), giant cell arteritis (GCA) (5 cases), relapsing polychondritis (RP) (1 case) and idiopathic aortitis (1 case).

TCZ was the first biological drug in all patients with GCA, and in the case of idiopathic aortitis but in only 1 of 6 patients with TKY. In the remaining cases anti-TNF inhibitors had previously been prescribed. TCZ standard dose was 8 mg/k/iv/4 weeks.

After a median [interquartile 25–75 range (IQR)] follow-up of 13 [11–18] months most patients experienced clinical improvement and a reduction of ESR (from 46±37 mm/1st h to 6±4 mm/1st h in the last visit). Patients also had clinical improvement. At TCZ onset, 15% of patients had polymyalgia rheumatica and 31% fever. After 3 months on TCZ therapy, these manifestations had disappeared. Also, constitutional syndrome observed in 31% of patients at TCZ onset, improved following this therapy (16% at 3 months), and disappeared completely after 6 months of treatment. In addition, a reduction in the dose of corticosteroids was achieved (prednisone or equivalent dose: from 28±17 mg/day at TCZ onset to 4±3 mg/day in last visit).

TCZ was relatively safe; only in 1 patient TCZ had to be discontinued because of neutropenia.

Case	Age/ Sex	Underlying disease	Previous synthetic and/or biologic immunosuppressive drugs	Prednisone dose or equivalent (at TCZ onset) mg/ d	Prednisone dose or equivalent (at last visit) mg/d	CRP/ESR* (at TCZ onset)	CRP/ESR* (at last visit)	Follow-up with TCZ (months)	Serious side effects
1	7/F	TKY	MTX, CYM, MM, IFX, ETN	30	0	12/72	<0.1/5	24	None
2	57/F	TKY	CYM	45	5	3.33/99	0,25/2	18	None
3	26/F	TKY	MTX, AZA, IFX	50	7.5	2.8/33	0.03/2	12	None
4	16/F	TKY	MTX, ADA	50	7.5	0.5/14	0.1/7	12	None
5	45/F	TKY	MTX, AZA, MM, IFX	25	0	<0.1/28	<0.1/3	13	None
6	41/F	TKY	MTX, ADA, IFX	40	10	3.7/29	0.03/10	3	None
7	77/F	GCA	MTX	10	2.5	3.7/120	1.7/7	5	None
8	59/F	GCA	MTX	60	5	<0.1/2	<0.1/2	16	None
9	65/F	GCA	MTX	17.5	0	<0.1/3	<0.1/2	20	Suspended: neutropenia
10	67/F	GCA	MTX	10	7.5	1.9/44	1.45/13	4	None
11	74/F	GCA	MTX	0	0	0.8/46	<0.1/4	11	None
12	50/F	RP	MTX, CyA, leflunomide, CYM, IFX	30	5	0.9/13	<0.1/13	20	None
13	75/ M	Idiopathic	None	0	0	–/98	–/–	17	None

TCZ: tocilizumab; IFX: infliximab ADA: adalimumab ETN: etanercept RTX: rituximab MTX: methotrexate AZA: azathioprine CYM: cyclophosphamide CyA: cyclosporine A MM: Mycophenolate mofetil
* CRP: C-reactive protein (CRP) (mg/L)/ ESR: erythrocyte sedimentation rate in 1st hour

Conclusion: Our results indicate that TCZ is a biologic agent effective and safe in patients with inflammatory aortitis refractory to conventional drugs including corticosteroids or other biologic immunosuppressive drugs.

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Does The Treatment With Anti-Coagulants and Anti-Platelets Protect Giant Cell Arteritis Patients From Visual Manifestations? Andreas P. Diamantopoulos, Helene Hetland, Glenn Haugeberg, Dag Magnar Soldal and Geirmund Myklebust. Hospital of Southern Norway Trust, Kristiansand, Norway.

Background/Purpose: Visual manifestations such as diplopia, amaurosis fugax or blindness occur in up to half of the giant cell arteritis (GCA) patients. Some studies have shown that the use of warfarin or aspirin reduces the ischemic complications in GCA patients. Low dose aspirin is recommended by EULAR in all patients with GCA. The aim of this study was to calculate the number of GCA patients who receive low-dose aspirin after the diagnosis is made and examine whether the use of anti-coagulant or anti-platelets really protects against visual ischemic complications.

Methods: GCA patients diagnosed for the period March 2010 through May 2013 were identified retrospectively. All the patients have a positive ultrasound (halo sign) of the temporal vessels and/or large vessels (carotid, axillary) and met the American College of Rheumatology classification criteria. Initial use of aspirin or warfarin was documented. Initiation of aspirin treatment in the patients after the diagnosis was made was also registered. A chi-squared test was used for group comparison and statistical significance was defined as $p<0.05$.

Results: Fifty-one patients were diagnosed with GCA during the inclusion period. Thirteen patients suffered from visual manifestations (6 from permanent visual loss in one or both eyes). In this group, 2 patients had been on warfarin and 4 on aspirin. The corresponding numbers for the group without visual manifestations were 6 patients on warfarin and 5 on aspirin. No significant differences in visual manifestations were observed between the two groups, neither for those on warfarin ($p=0.97$) nor for those on aspirin ($p=0.15$). The number of patients who received aspirin after the diagnosis of GCA was recorded and include 11 patients (33%). Three of 7 GCA patients with visual manifestations who were not on anti-coagulation or anti-platelet treatment before diagnosis, received aspirin as a supplementary therapy.

Conclusion: In our study, which included only a small number of patients with GCA, the use of anti-coagulants or anti-platelets was not protective against visual manifestations. This is in contrast with previous published studies. Only 33% of GCA patients received anti-platelet treatment after the diagnosis of GCA was made. Further studies are warranted to clarify the role of anti-platelet treatment in GCA.

Disclosure: A. P. Diamantopoulos, None; **H. Hetland**, None; **G. Haugeberg**, None; **D. M. Soldal**, None; **G. Myklebust**, None.

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Antiplatelet Agents Decrease Ischemic Complications In Systemic Large Vessel Vasculitides: A Meta-Analysis. James Jeong[1] and Lillian J. Barra[2]. [1]Schulich School of Medicine & Dentistry, Western University, London, ON, [2]Schulich School of Medicine and Dentistry, Western University, London, ON.

Background/Purpose: Large Vessel Vasculitides (LVV) consist of Giant Cell Arteritis and Takayasu's Arteritis, which are chronic systemic autoimmune diseases characterized by inflammation of large blood vessels leading to ischemic complications. The objective of this study is to determine the effectiveness of antiplatelet agents at reducing ischemic events in patients with LVV.

Methods: We performed a random effects meta-analysis examining antiplatelet (AP) and/or anticoagulant therapy (AC) and ischemic events in large vessel vasculitis (LVV). Severe ischemic events were defined as stroke, ischemic ocular manifestations and claudication symptoms. Any ischemic event included jaw claudication in addition to the above manifestations.

Results: Seven studies met inclusion criteria. The primary study outcome was the risk of severe ischemic events in patients treated with AP/AC versus no treatment expressed as an odds ratio (OR). The risk of any ischemic event was a secondary outcome. When accounting for baseline atherosclerotic risk factors, AP/AC was protective for severe ischemic events: OR 0.20 (95% CI 0.12–0.32); as well as for any ischemic events: OR 0.33 (95% CI 0.13–0.81). Subgroup analyses established *a priori* were also performed comparing i) AP and AC therapy alone ii) ischemic events reported at baseline and follow-up. AP alone had a protective effect on ischemic events when compared to no treatment when controlling for cardiovascular risk factors (OR 0.21, 95% CI 0.09–0.50). AC did not appear to decrease ischemic events; however, there were only 2 studies that reported on AC separately from AP. On follow-up, a protective effect for AP/AC therapy was observed (OR 0.18 (95% CI 0.04–0.83)).

Conclusion: Antiplatelet therapy significantly decreases ischemic events in patients with LVV. However, in most cases, the treatment was initiated prior to the diagnosis of vasculitis. Available studies do not address whether initiating antiplatelet therapy at the time of LVV diagnosis is beneficial.

Disclosure: J. Jeong, None; **L. J. Barra**, None.

ACR Plenary Session II: Discovery 2013

Monday, October 28, 2013, 11:00 AM–12:30 PM

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Impaired Vitamin D Receptor Signaling Upregulates Transforming Growth Factor Beta (TGFβ) Signaling In Systemic Sclerosis. Pawel Zerr[1], Stefan Vollath[1], Katrin Palumbo-Zerr[1], Michal Tomcik[2], Jingang Huang[1], Alfiya Distler[1], Christian Beyer[1], Clara Dees[3], Oliver Distler[4], Georg Schett[3] and Joerg H. W. Distler[1]. [1]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Institute of Rheumatology, Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [3]University of Erlangen-Nuremberg, Erlangen, Germany, [4]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland.

Background/Purpose: Vitamin D receptor (VDR) is a member of the nuclear receptor superfamily. Its ligand, 1,25-$(OH)_2$D, is a metabolically active hormone derived from vitamin D_3. Activated VDR binds to specific VDR elements in the promoters of target genes to regulate their expression. The levels of vitamin D_3 have been shown to be significantly decreased in patients with systemic sclerosis (SSc). However, the functional consequences remain unknown. Our aim was to find a potential link between impaired VDR signaling and fibrosis.

Methods: VDR expression was analyzed by real-time PCR, Western Blot and IF. VDR agonist paricalcitol was used in in *vitro* and in *vivo* experiments. Collagen synthesis was quantified in fibroblasts overexpressing or lacking VDR. Interaction of VDR and Smad3 was shown by Co-IP. VDR was analyzed in two different mouse models of SSc: bleomycin-induced dermal fibrosis and mice overexpressing a constitutively active TGFβ receptor I (TBR).

Results: VDR mRNA levels were reduced by 78 % in skin of SSc patients compared to healthy individuals ($p = 0.02$). Similar decreases were observed on the protein level. VDR mRNA and protein levels were also decreased in the bleomycin-induced (33 %; $p = 0.01$) and the TBR-induced fibrosis (45 %; $p = 0.03$). Chronic stimulation with TGFβ strongly decreased VDR mRNA and protein levels in fibroblasts. VDR knockdown fibroblasts showed significantly increased levels of Col1a1 mRNA (+216 %; $p = 0.002$) and collagen protein (+165 %; $p = 0.01$) compared to TGFβ stimulated controls. In contrast, VDR overexpression inhibited the pro-fibrotic effects of TGFβ with decreased Col1a1 mRNA levels, collagen release and prevented differentiation into myofibroblasts. Co-IP showed that paricalcitol stimulated the formation of high affinity complexes of VDR and active, phosphorylated Smad3 in fibroblasts. Reporter assays confirmed that binding of VDR to phosphorylated Smad3 impaired the transcriptional activity of phosphorylated Smad3. Moreover, potent anti-fibrotic effects of paricalcitol were observed in different mouse models of SSc. Mice treated with paricalcitol were less sensitive to TBR induced dermal fibrosis with reduced dermal thickening (−46%, $p = 0.01$), myofibroblast counts (−69%, $p = 0.001$) and hydroxyproline content (−77%, $p = 0.02$). Paricalcitrol also significantly ameliorated bleomycin-induced fibrosis.

Conclusion: We demonstrate that VDR is a crucial regulator of TGFβ/Smad signaling. Pharmacological activation of VDR inhibits TGFβ signaling and reduces fibrosis. Impaired VDR signaling with reduced levels of its ligand vitamin D_3 may thus contribute to hyper-active TGFβ signaling and aberrant fibroblast activation in SSc. These findings may have direct clinical implications, considering the higher binding affinity and the less calcaemic effects with more prolonged administration of paricalcitol compared to the natural ligand and the potent anti-fibrotic

effects, the good tolerability and the availability of VDR agonists in clinical trials.

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The STAT1 Signaling Pathway In Giant Cell Arteritis. Bjorn Hartmann[1], Joyce Liao[2], Michael H. Weisman[3], Kenneth J. Warrington[4], Jorg J. Goronzy[1] and Cornelia M. Weyand[1]. [1]Stanford University School of Medicine, Stanford, CA, [2]Stanford University, Palo Alto, CA, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]Mayo Clinic, Rochester, MN.

Background/Purpose: In giant cell arteritis (GCA), CD4 T cells, macrophages and multinucleated giant cells form granulomatous lesions in the walls of medium and large arteries. A plethora of innate and adaptive cytokines are produced within the vasculitic infiltrates, but it is not known whether a hierarchy of cytokines exists that initiates and sustains vessel wall damage, drives intimal hyperplasia and promotes persistent immune activation. Most cytokines function by triggering JAK/STAT signaling pathways in target cells to regulate gene programs that drive cellular activation, differentiation, and survival, all critical in the maladaptive response of the inflamed artery and the acute phase response underlying systemic inflammation.

Methods: To induce experimental GCA, NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/SzJ mice (NSG) mice were engrafted with human medium-sized arteries and reconstituted with PBMC from patients with biopsy-proven GCA. Following induction of vasculitis, chimeras were treated with either dexamethasone (15 mg/kg) or tofacitinib (4 mg/kg) or both for 5 days. Explanted artery grafts or temporal artery biopsies from patients with GCA were analyzed for gene expression profiles by RT-PCR. Plasma was harvested from GCA patients and from untreated or treated reconstituted chimeras and cytokines were quantified by ELISA.

Results: To identify signaling pathways involved in vasculitis, we screened temporal artery biopsy samples and plasma from GCA patients for induction of signal transducer and activator of transcription (STAT) activity. STAT-1 transcripts were abundantly expressed in tissue lesions. The major inducer cytokine of STAT-1, IFN-γ, was 10-fold higher in GCA patients than in age-matched controls. To examine the relevance of STAT-1 signaling, we compared the effects of two classes of immunosuppressive agents (corticosteroids and the JAK/STAT-inhibitor tofacitinib, CP-690,550, a potent kinase inhibitor for JAK3 > JAK1 > JAK2) in experimentally induced vasculitis in 7 independent experiments. Dexamethasone primarily suppressed innate immunity with inhibition of dendritic cell activation (P = 0.005), IL-6 and IL-1β expression in the vascular lesions. Conversely, dexamethasone spared adaptive immunity and left IFN-γ-producing T_H1 unaffected (P = 0.98). The kinase inhibitor effectively prevented T cell accumulation in the vessel wall and suppressed IFN-γ production (P = 0.03) and signaling. JAK/STAT inhibition reduced blood levels of IFN-γ in the chimera mice by 65% (P = 0.004). The underlying mechanism involved a reprogramming of T cell trafficking, barring vasculitic T cells from arterial wall infiltration.

Conclusion: STAT-1 signaling is a key pathogenic pathway in GCA, is sustained by excessive activity of the adaptive cytokine IFN-γ and persists despite suppression of innate immunity. Retention of vasculitic T cells in the vessel wall is a major determinant of vasculitic activity and emerges as a novel therapeutic target.

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Characterization Of Changes In Gene Expression and Inflammatory Proteins In Systemic Juvenile Idiopathic Arthritis Patients On Canakinumab Therapy. Nanguneri. R Nirmala[1], Nico Wulffraat[2], Hermine Brunner[3], Pierre Quartier[4], Riva Brik[5], Liza McCann[5], Huri Ozdogan[5], Lidia Rutkowska-Sak[5], Rayfel Schneider[3], Valeria Gerloni[5], Liora Harel[6], Maria Terreri[3], Kristin Houghton[3], Rik Joos[5], Daniel Kingsbury[3], Jorge M. Lopez-Benitez[3], Arndt Brachat[7], Stephan Bek[7], Martin Schumacher[7], Marie-Anne Valentin[7], Hermann Gram[7], Ken Abrams[8], Alberto Martini[5], Nicolino Ruperto[5] and Daniel J. Lovell[3]. [1]Novartis Institutes for Biomedical Research, Cambridge, MA, [2]Pediatric Rheumatology International Trials Organization (PRINTO)-Istituto Gaslini, Genova, Italy, [3]Pediatric Rheumatology Collaborative Study Group (PRCSG), Cincinnati, OH, [4]Necker-Enfants Malades Hospital, Paris, France, [5]Paediatric Rheumatology International Trials Organization (PRINTO), Genova, Italy, [6]Schneider Children's Medical Center, Tel Aviv University, Petach Tikvah, Israel, [7]Novartis Institutes for Biomedical Research, Basel, Switzerland, [8]Novartis Pharmaceuticals Corporation, East Hanover, NJ.

Background/Purpose: Interleukin (IL)-1β plays a key role in the pathogenesis of systemic juvenile idiopathic arthritis (SJIA). Canakinumab (CAN), a selective, fully human, anti-IL-1β monoclonal antibody, has been shown to be efficacious in the treatment of SJIA. Here we present the analysis of changes in peripheral blood gene expression and inflammatory proteins in SJIA patients (pts) on CAN therapy and report the identified baseline biomarkers that predict clinical response to CAN treatment.

Methods: Levels of inflammatory biomarkers (IL-6; total IL-18) and gene expression profiles of active SJIA pts (aged 2 to <20 yrs) before and during CAN treatment enrolled in 2 phase III trials were analyzed.

Results: Gene Expression: Transcriptional changes upon CAN treatment at Day 3 were assessed. When applying cut-offs of ≥2 fold and p≤0.05, no transcript passed this filter for placebo-treated pts (n=9) or for CAN treated pts (n=11) that were ACR30 (adapted pediatric ACR) non-responders at Day 15, while 171 probesets passed the filter for pts (n=52) showing ≥ACR30 response. Pts who showed strong transcriptional changes also showed a strong ACR response (≥ACR50) at Day 15, while pts with <ACR50 at Day 15 showed a much weaker transcriptional response at Day 3. Strongly repressed genes included many known inflammation- and innate immunity-related genes (eg, TLR1, TLR4, TLR5, TLR6, TLR8), including several members of the IL-1β signaling pathway, such as IL-1β, IL1R1, IL1R2 and IL1RAP. A set of transcripts was identified for which high baseline expression levels predicted a subgroup of strong (≥ACR50) responders at Day 15. However, another subgroup of strong responders was indistinguishable from weak responders (≤ACR30) based on baseline transcript levels.

Protein markers: IL-6 protein levels were strongly reduced by Day 3 (4.7 × and 4.4 × with p=0.002 and 0.0001, n=20 and n=51 for the 2 trials), and at Day 29 (12.5 × and 8.1 × with p=0.01 and 0.00005, n=20 and n=65) while total IL-18 levels remained largely unchanged until Day 29 (n=22 and n=76) and showed a moderate reduction only at Day 57. For IL-6, stronger reduction at Day 3 and Day 29 was observed for pts who showed stronger ACR response at Day 15. Only 3 baseline samples were available from pts who developed macrophage activation syndrome during the studies.

Conclusion: CAN treatment resulted in a rapid, strong reduction of many pro-inflammatory leukocyte transcripts and serum IL-6. Compared with IL-6, IL-18 protein levels were reduced upon treatment much later and less strongly. About two thirds of pts with a strong treatment response (≥ACR50) were characterized by a set of leukocyte transcripts with high baseline levels and strong reduction upon CAN treatment. However, the remaining one third of CAN strong responders did not show these characteristic transcriptional patterns, suggesting some heterogeneity at the molecular level in SJIA pts showing strong response to CAN treatment.

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Initial Triple DMARD Therapy Is More Efficient Than Methotrexate Monotherapy In Recent Onset Rheumatoid Arthritis; 1-Year Data Of a Randomized Clinical Trial (tREACH). P.H.P. de Jong[1], J.M.W. Hazes[1], K.H. Han[2], A.M. Huisman[3], D. van Zeben[3], P.A. van der Lubbe[4], A.H. Gerards[4], B. van Schaeybroeck[5], P.B. de Sonnaville[6], M.V. Krugten[7], J.J. Luime[1] and A.E.A.M. Weel[2]. [1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]Maasstad Hospital, Rotterdam, Netherlands, [3]Sint Franciscus Gasthuis, Rotterdam, Netherlands, [4]Vlietland Hospital, Schiedam, Netherlands, [5]Albert Schweitzer Hospital, Dordrecht, Netherlands, [6]Admiraal de Ruyter hospital, Goes, Netherlands, [7]Admiraal de Ruyter Hospital, Vlissingen, Netherlands.

Background/Purpose: Recommended treatment for DMARD naïve patients is methotrexate (MTX) with or without glucocorticoids (GCs). Triple DMARD therapy however is not recommended, because well proven evidence of superior efficacy is suggested to be lacking. Furthermore possible drug toxicities might influence the physician's choice of induction therapy. Therefore, our aim is to compare one-year clinical efficacy of: (1) triple DMARD therapy vs. MTX mono-therapy and (2) oral GCs bridging therapy vs. 1 dose of intramuscular (im) GCs in patients with early RA.

Methods: The one-year data of single-blinded randomized clinical trial in patients with recent-onset arthritis (tREACH) were used. Patients were included who had a high probability (> 70%) of progressing to persistent arthritis, based on the prediction model of Visser. The Visser algorithm and 2010 criteria for RA have similar discriminative abilities to identify patients at risk of persistent arthritis at 1 year. Patients were randomized into 3 induction therapy strategies: (A) triple DMARD therapy (MTX 25 mg + sulfasalazine (SASP) 2 gr. + hydroxychloroquine (HCQ)) 400 mg with im GCs (Depomedrol 120mg), (B) triple DMARD therapy with an oral GCs tapering scheme (starting 15 mg) and (C) MTX with oral GCs similar to B. Treatment strategies were 'tightly controlled', with patients being examined every 3 months and treatment decisions based upon the original DAS thresholds for low disease activity. We investigated following response parameters over time: DAS, HAQ, using the area under the curve (AUC). We also looked at radiographic progression after 12 months of therapy, medication usage and adverse events.

Results: A total of 281 patients were included in the high probability stratum and randomly assigned to (A) (n=91), (B) (n=93) or (C) (n=97). Patients were mostly females (68%) with an average symptom duration of 166 days (95% CI: 156 – 177). At baseline 267 (95%) of patients fulfilled the 2010 criteria for RA, 216 (77%) patients were ACPA positive and 48 (16%) patients had erosions. Over time disease activity and functional ability were respectively −2·39 (−4·77 to −0·00, 95%CI) and −1·67 (−3·35 to 0·02, 95%CI) lower in patients with triple DMARD therapy compared with MTX mono-therapy. After 3 months, less treatment failure occurred in the triple DMARD therapy groups, resulting in the prescription of 50% fewer biologicals. This difference remained over time. No differences were seen between both GC bridging therapies. Respectively 15%, 30%, and 18% of patients in arm A, B, and C had radiographic progression after 1 year. No differences in serious adverse events were seen.

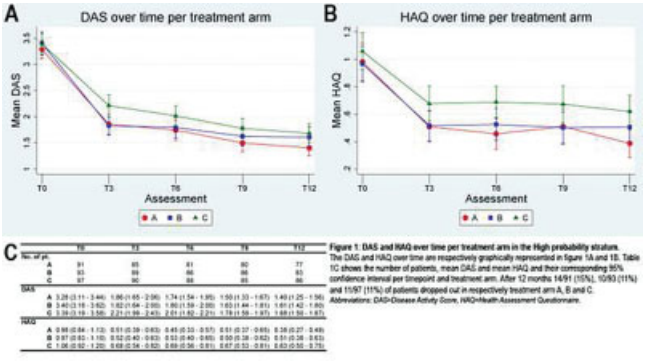

Figure 1. DAS and HAQ over time per treatment arm in the High probability stratum. The DAS and HAQ over time are respectively graphically represented in figure 1A and 1B. Table 1C shows the number of patients, mean DAS and mean HAQ and their corresponding 95% confidence interval per timepoint and treatment arm. After 12 months 14/91 (15%), 10/93 (11%) and 11/97 (11%) of patients dropped out in respectively treatment arm A, B, and C. Abbreviations: DAS=Disease Activity Score, HAQ=Health Assessment Questionnaire.

Conclusion: In patients with early RA triple DMARD therapy is superior to MTX mono-therapy even after 12 months of therapy. Furthermore both intramuscular and oral GCs can be used as bridging therapy.

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A Randomised Trial Of A Brace For Patellofemoral Osteoarthritis Targeting Knee Pain and Bone Marrow Lesions. David T. Felson[1], Matthew J. Parkes[1], Andrew D. Gait[1], Elizabeth J. Marjanovic[1], Mark Lunt[2], Charles E. Hutchinson[3], Laura Forsythe[1], Timothy F. Cootes[1] and Michael Callaghan[1]. [1]University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [3]University of Warwick, Coventry, United Kingdom.

Background/Purpose: Patellofemoral (PF) braces have been shown to increase contract area in this joint, decreasing focal stress and may also correct patellar malalignment. Bone marrow lesions (BMLs) are lesions in the subchondral bone of osteoarthritis (OA) knees on MRI that are caused in part by focal stress in the joint. Because BML size correlates with knee pain severity, because they predict structural progression and because recent evidence suggests, unlike cartilage, that their volumes fluctuate substantially in as little as 6 weeks, BML's may be a good outcome to test short term structure modification in OA trials. We performed a trial testing the efficacy of the BIOSKIN patellar tracking Q brace (Ossur, inc).

Methods: Eligible subjects had to have pain daily of >=40/100 for the last 3 months during a PF activity and on examination had tenderness over patellar facet or a positive patellar compression test. X-rays had to show KL grade 2 or 3 PFOA which was worse than tibiofemoral disease. At baseline, subjects were randomly allocated to immediate or 6 weeks provision of the brace; the trial lasted 6 weeks. Subjects with other forms of arthritis were excluded as were those ineligible for MRIs or with impaired renal function. Gadolinium MRIs were acquired on a 1.5 T MRI at baseline, and at 6 weeks. Postgadolinium fat suppressed sagittal and PD weighted axial images were used for BML's which were manually segmented (blinded to sequence and to treatment) at all time points. The primary symptom outcome was the change in pain at 6 weeks (0 – 100 VAS scale) during the PF painful activity in the more symptomatic knee and the primary structural outcome was BML volume in the PF joint of that knee (patella and trochlea). We also examined tibiofemoral (TF) BML volumes as a control untreated region. Analyses used multiple linear regression with an ITT approach.

Results: We randomised 126 subjects age 40–70 years (mean age 55.5 years (SD 7.5 years); 72 females (57.1%). Mean pain score at baseline was 64.6. Ninety of the 125 with MRI scans (72%) had PF BML's at baseline. Subjects wore the brace for a mean of 7.4 hrs/day. Six subjects withdrew during the RCT (an additional 2 did not attend one session, and therefore had only one MRI). Compared with the control group, the brace group had both a significant reduction in PF-related knee pain and a decrease in the volume of BML's in the PF but not in the TF joint (see Table).

RANDOMISED TRIAL RESULTS

Variable	NO BRACE GROUP	BRACE GROUP	Between Groups Difference	
Change @ 6 weeks In:	Mean change (95% CI)	Mean change (95% CI)	Mean difference in change (95% CI)	p
PRIMARY Symptom OUTCOME: Nominated VAS (0 – 100)	−1.29 (−6.39, 3.80)	−18.16 (−23.88, −12.44)	16.87 (9.30, 24.43)	<0.001
Primary Structural Outcome: BML Volume in PF joint (in mm^3)	102.66 (−292.80, 498.12)	−554.92 (−964.02, −145.82)	−657.58 (−1226.57, −88.59)	0.02
Secondary Structural Outcome: BML Volume in TF Joint (in mm3)	1.79 (−492.67, 496.26)	198.08 (−313.44, 709.60)	196.29 (−515.15, 907.73)	0.59

Conclusion: A patellofemoral brace is efficacious for treatment of PF OA reducing both symptoms and BML volumes in the targeted compartment. BML's may be a responsive outcome measure in OA trials.

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Ustekinumab Is Effective In Inhibiting Radiographic Progression In Patients With Active Psoriatic Arthritis: Integrated Data Analysis Of Two Phase 3, Randomized, Placebo-Controlled Studies. Iain B. McInnes[1], Christopher T. Ritchlin[2], Proton Rahman[3], Lluis Puig[4], Alice B. Gottlieb[5], Michael Song[6], Bruce Randazzo[6], Shu Li[6], Yuhua Wang[6], Alan M. Mendelsohn[6] and Arthur Kavanaugh[7]. [1]University of Glasgow, Glasgow, United Kingdom, [2]University of Rochester, Rochester, NY, [3]Memorial University, St. Johns, NF, [4]Universitat Autònoma de Barcelona, Barcelona, Spain, [5]Tufts Medical Center, Boston, MA, [6]Janssen Research & Development, LLC., Spring House, PA, [7]University of California San Diego, San Diego, CA.

Background/Purpose: We describe the effect of ustekinumab (UST), an IL-12/23 p40 inhibitor, on inhibition of progression of structural damage in patients with active psoriatic arthritis (PsA) at wk24 and wk52 in the PSUMMIT 1 and PSUMMIT 2 trials.

Methods: Adult PsA patients with active disease (≥5 SJC and ≥5 TJC; CRP≥0.3mg/dL [ULN 1.0 mg/dL]) despite DMARD and/or NSAID therapy (PSUMMIT 1, n=615; PSUMMIT 2, n=132) or previously treated with DMARD and/or NSAID, and prior anti-TNFα therapy (PSUMMIT 2, n=180) were randomized to UST45mg, 90mg, or PBO at wks 0, 4, and q12wks, thereafter. At wk16, patients with <5% improvement in TJC & SJC entered blinded early escape [EE] (PBO→UST45mg; UST45mg→90mg; 90mg→90mg). No concomitant DMARDs with the exception of MTX (approximately 50% of patients in each study) were permitted. Radiographs of hands and feet were taken at wks 0, 24, and 52 regardless of EE status, or at the time of study drug discontinuation (unless radiographs were completed within the prior 8wks). Erosions and joint space narrowing (JSN) were evaluated by independent readers blinded to treatment, patient IDs and image time sequence using PsA modified van der Heijde-Sharp (vdH-S) method (total score ranging from 0–528). The major secondary endpoint of change from baseline in total vdH-S scores at wk24 was analyzed based on a pre-specified integrated data analysis using data combined from both studies. Imputation of missing data was done using linear extrapolation or median change of 0.

Results: Baseline disease characteristics including total vdH-S, TJC, SJC and CRP were comparable between PSUMMIT 1 & 2. In the integrated analyses, both UST 45 mg and 90 mg treated patients demonstrated a significant difference in change from baseline in total vdH-S scores at wk24 vs PBO (Table). Moreover, continued inhibition was demonstrated through wk 52; patients randomized to PBO who initiated UST at wk16 or 24 demonstrated slowing of radiographic progression by wk52 (mean change in total vdH-S wk24 to wk52 of 0.08). These observations were reproduced when PSUMMIT 1 was evaluated alone. In PSUMMIT 2, a demonstrable effect of UST on inhibition of structural damage progression could not be discerned; these results may have been impacted by missing radiographic data, especially among PBO-treated patients (23% missing radiographs).

Table. Summary of Baseline and Change From Baseline in Modified van der Heijde Sharp Scores (vdH-S)

	PBO	UST 45mg	UST 90mg	UST combined
Baseline scores				
Total Modified vdHS				
Mean ± SD	28.01 ± 55.77	30.40 ± 50.69	27.97 ± 42.14	29.19 ± 46.61
Median (IQR)	9.50 (3.00, 29.50)	11.50 (3.50, 33.50)	10.50 (3.50, 34.50)	11.00 (3.50, 34.00)
N	306	303	300	603
Erosion				
Mean ± SD	14.46 ± 30.96	15.65 ± 27.48	14.64 ± 23.27	15.14 ± 25.46
Median (IQR)	4.50 (1.50, 14.50)	6.00 (2.00, 16.50)	5.00 (1.50, 18.00)	5.50 (1.50, 16.50)
N	306	303	300	603
JSN				
Mean ± SD	13.55 ± 25.72	14.75 ± 24.29	13.33 ± 20.25	14.05 ± 22.37
Median (IQR)	4.00 (0.50, 13.50)	5.00 (1.00, 18.50)	5.00 (1.00, 16.00)	5.00 (1.00, 17.00)
N	306	303	300	603
Wk 24 PSUMMIT 1 & 2 Pre-specified Integrated Analyses (Change from Baseline in vdH-S at Week 24)				
Total Modified vd*HS** (*major secondary endpoint*)				
Mean ± SD	0.97 ± 3.85	0.40 ± 2.11	0.39 ± 2.40	0.40 ± 2.26
Median (IQR)	0.00 (0.00, 1.00)	0.00 (0.00, 0.50)	0.00 (0.00, 0.50)	0.00 (0.00, 0.50)
		p = 0.017	p <0.001	p <0.001
N	310	308	309	617
Erosion				
Mean ± SD	0.57 ± 1.64	0.23 ± 1.40	0.19 ± 1.33	0.21 ± 1.37
Median (IQR)	0.00 (0.00, 0.50)	0.00 (0.00, 0.50)	0.00 (0.00, 0.50)	0.00 (0.00, 0.50)
		p = 0.002	p <0.001	p <0.001
N	310	308	309	617
JSN				
Mean ± SD	0.40 ± 2.62	0.17 ± 1.06	0.20 ± 1.75	0.19 ± 1.44
Median (IQR)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
		p = 0.466	p = 0.112	p = 0.179
N	310	308	309	617
Wk 24 PSUMMIT 1 & 2 Trial Specific Analyses: (Change from Baseline in vDH-S at Week 24)				
PSUMMIT 1				
Mean ± SD	1.20 ± 4.52	0.28 ± 1.94	0.17 ± 1.45	0.23 ± 1.71
Median (IQR)	0.00 (0.00, 1.50)	0.00 (0.00, 0.50)	0.00 (−0.25, 0.50)	0.00 (0.00, 0.50)
		p = 0.001	p <0.001	p <0.001

Conclusion: Based upon the pre-specified integrated data analysis, ustekinumab inhibits radiographic progression at wk24.

Disclosure: I. B. McInnes, Novartis, Janssen Research & Development, LLC., 8, UCB, 9; **C. T. Ritchlin**, Amgen, Janssen, UCB, Abbott (AbbVie), Regeneron, 5, Amgen, Janssen, UCB, 2; **P. Rahman**, Amgen, Abbott, BMS, Merck, Pfizer, Janssen, Hoffman-La Roche, UCB, Novartis, Sanofi-Aventis, 5, Amgen, Abbott, BMS, Merck, Pfizer, Janssen, Hoffman-La Roche, UCB, Novartis, Sanofi-Aventis, 9; **L. Puig**, Abbvie, Amgen, Janssen, Lilly, Novartis, Pfizer, VBL, 2, Celgene, Abbvie, Janssen, Novartis, MSO, Pfizer, Lex Pharma, 5; **A. B. Gottlieb**, Janssen, Amgen, Abbott (Abbvie), Novartis, Celgene, Pfizer, Lilly, Coronado, Levia, 2, Astellas, Janssen, Celgene Corp., Bristol Myers Squibb Co., Beiersdorf, Inc., Abbott Labs. (Abbvie), TEVA, Actelion, UCB, Novo Nordisk, Novartis, Dermipsor Ltd., Incyte, Pfizer, Canfite, Lilly, Coronado, Vertex, Karyopharm, CSL Behring Biotherapies for Li, 5; **M. Song**, Janssen Research & Development, LLC., 3; **B. Randazzo**, Janssen Research & Development, LLC., 3; **S. Li**, Janssen Research & Development, LLC., 3; **Y. Wang**, Janssen Research & Development, LLC., 3; **A. M. Mendelsohn**, Janssen Research & Development, LLC., 3; **A. Kavanaugh**, Janssen Research & Development, LLC., 9.

ACR Concurrent Abstract Session
Epidemiology and Health Services Research II: Epidemiology in Systemic Lupus Erythematosus and Rheumatoid Arthritis
Monday, October 28, 2013, 2:30 PM–4:00 PM

1696

Prevalence and Incidence of Systemic Lupus Erythematosus in a Population-Based Registry of American Indian and Alaska Native People in the United States, 2007–2009. Elizabeth D. Ferucci[1], Janet Johnston[2], Jasmine Gaddy[3], Lisa Sumner[4], James Posever[4], Tammy L. Choromanski[1], Caroline Gordon[5], S. Sam Lim[6] and Charles G. Helmick[7]. [1]Alaska Native Tribal Health Consortium, Anchorage, AK, [2]Univeristy of Alaska Anchorage, Anchorage, AK, [3]Oklahoma City Area Indian Health Service, Oklahoma City, OK, [4]Phoenix Indian Medical Center, Phoenix, AZ, [5]University of Birmingham, Birmingham, United Kingdom, [6]Emory University, Atlanta, GA, [7]Centers for Disease Control and Prevention, Atlanta, GA.

Background/Purpose: Estimates of the prevalence and incidence of systemic lupus erythematosus (SLE) have varied widely but have consistently been high in women and minority populations. The goal of this registry was to determine the prevalence and incidence of SLE in the US American Indian/Alaska Native (AI/AN) population.

Methods: This population-based registry was developed as a public health surveillance project within the Indian Health Service (IHS), in partnership with the Centers for Disease Control and Prevention (CDC). The denominator was individuals: 1) included in the IHS active clinical population in 2007, 2008, and/or 2009 (2 or more visits to an IHS clinic in the past 3 years, at least one of which must be to a core medical clinic); and 2) residing in a community in one of 3 specified regions (Alaska, Phoenix, and Oklahoma City IHS Areas). Potential SLE cases were identified based on International Classification of Diseases, Ninth Revision (ICD-9) codes for SLE or related connective tissue diseases in the IHS National Data Warehouse, a central repository for clinical and administrative data. Detailed medical record abstraction was performed for each potential case. Cases were defined as individuals with documentation of 4 or more of the ACR classification criteria for SLE. Prevalence and 95% confidence intervals (CI) were calculated for 2007 overall and by region, sex, and age. Age-adjusted rates were calculated using the standard projected 2000 US population. Person-time incidence rates were calculated over the years 2007–2009 overall and by region, sex, and age.

Results: Prevalence of SLE in 2007 and incidence from 2007–2009 are presented in the Table, including unadjusted and age-adjusted rates with 95% confidence intervals (CI). Age-specific prevalence rates by sex are shown in the Figure. The prevalence was highest in women, the age group 60–69, and the Phoenix Area of IHS. The groups with the highest incidence were women, those in the age group of 40–49, and the Phoenix Area of the IHS.

Table. Prevalence (2007) and Incidence (2007–2009) of SLE in the IHS lupus registry

	Prevalence (per 100,000 people)		Incidence (per 100,000 person-years)	
	Unadjusted (95% CI)	Age-adjusted (95% CI)	Unadjusted (95% CI)	Age-adjusted (95% CI)
Overall	134.5 (119.8–151.0)	177.7 (157.1–200.2)	5.9 (4.2–8.0)	7.4 (5.1–10.4)
Sex-specific				
Female	215.4 (190.3–243.7)	270.6 (237.5–307.0)	8.4 (5.8–11.8)	10.4 (6.6–14.6)
Male	35.7 (25.5–49.8)	53.8 (36.2–77.1)	2.7 (1.3–5.2)	ND
Region-specific				
Alaska	110.2 (92.8–130.8)	148.7 (123.8–177.3)	4.8 (2.9–7.5)	6.1 (3.4–10.2)
Phoenix	177.8 (149.2–211.8)	247.5 (204.5–297.3)	8.1 (5.0–12.6)	10.7 (6.2–17.5)
Oklahoma	126.9 (88.9–179.1)	138.2 (92.6–199.5)	4.3 (1.1–11.7)	ND

* ND: not determined due to small number of cases.

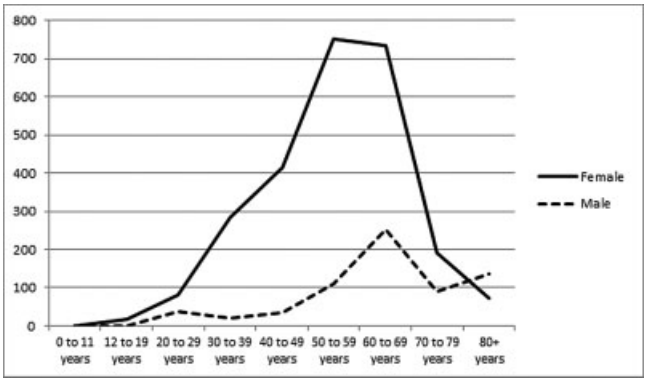

Figure. Age-specific prevalence of SLE (2007) in the IHS lupus registry

Conclusion: The first population-based lupus registry in the US AI/AN population has demonstrated high prevalence and incidence of SLE in the IHS active clinical population, especially in women. Our estimates are consistent with higher rates in minority populations, and are on the higher bound of previous estimates in the AI/AN population.

Disclosure: E. D. Ferucci, None; **J. Johnston**, None; **J. Gaddy**, None; **L. Sumner**, None; **J. Posever**, None; **T. L. Choromanski**, None; **C. Gordon**, None; **S. S. Lim**, None; **C. G. Helmick**, None.

1697

Are Patients With Rheumatoid Arthritis Still At An Increased Risk Of Tuberculosis and What Is The Role Of Biological Treatment? Elizabeth V. Arkema[1], Jerker Jonsson[2], Eva Baecklund[3], Maud Rutting[4], Judith Bruchfeld[1], Nils Feltelius[4] and Johan Askling[5]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Swedish Institute for Communicable Disease Control, Solna, Sweden, [3]Uppsala University Hospital, Uppsala, Sweden, [4]Swedish Medical Products Agency, Uppsala, Sweden, [5]Karolinska University Hospital, Stockholm, Sweden.

Background/Purpose: Anti-TNF therapy is a risk factor for clinical tuberculosis (TB), which has led to pre-treatment screening and increased vigilance. The extent to which these measures have reduced or removed the TB risk - with or without biological treatment - and how such risks differ between individual biologics remains less clear. We therefore sought to estimate the risk of TB in patients with rheumatoid arthritis (RA) 2002–2011 with and without exposure to biological therapy and to directly compare the risks between biological therapies.

Methods: Data from the Swedish National Population Registers, TB Register and the Swedish Biologics Register were used to conduct a prospective population-based national cohort study (2002–2011). We estimated the rate of TB in the general population (N=173,333), in a cohort of patients diagnosed with RA unexposed to biological therapy (N=37,770) and in a cohort of patients with RA exposed to biologicals (abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab, N=10,803). Cox models adjusting for age, sex, country of birth, education, history of diabetes, chronic obstructive pulmonary disease and cancer were used to estimate hazard ratios and 95% confidence intervals (HR; 95%CI). We estimated the risk of TB in the biological-exposed RA population compared to the unexposed, with particular attention to risks by calendar and follow-up time, and risks associated with individual biologics.

Results: Compared to the general population, RA patients *not* exposed to biologicals had a 4-fold increased risk of TB (HR 4.4 (95%CI 2.7, 7.1) 30 RA, 37 general population TB cases). We identified 19 TB cases with RA who were exposed to a biological before TB diagnosis (etanercept, infliximab, adalimumab or rituximab). The rate of TB in the biological-exposed RA population has decreased since 2002. Individuals with RA who were exposed to any biological had a multivariable-adjusted HR of 4.7 (95%CI 2.5, 9.0) compared to biological-naïve patients. The HR comparing etanercept-exposed patients to biological-naïve was 1.8 (95%CI 0.5, 6.4). The HRs for adalimumab and infliximab compared to etanercept were 3.8 (95%CI 1.0, 14.8) and 2.6 (95%CI 0.6, 11.0) respectively. One case was exposed to rituximab (HR 0.9 95%CI 0.1, 10.6).

Table. Incidence rates and hazard ratios of tuberculosis comparing biological-naïve to biological-exposed patients with RA, overall and stratified by calendar year of follow-up and total follow-up time.

Overall	Biological-Naive RA	Biological-Exposed RA	Hazard Ratio* (95% CI)
TB Cases/Person-years (py)	30/219,571	19/48,337	
Overall IR, per 100,000 py (95% CI)	13.7 (9.6, 19.6)	39.3 (25.1, 61.6)	4.7 (2.5, 9.0)
IR (95% CI) by Calendar Year			
2002–2006	16.8 (10.3, 27.5)	60.5 (32.6, 112.5)	9.5 (3.9, 22.9)
2007–2011	12.6 (7.5, 21.4)	21.0 (10.9, 40.3)	2.5 (1.0, 6.2)
IR (95% CI) by Follow-up Time			
<5 y	14.4 (9.3, 22.3)	48.3 (30.0, 77.7)	7.0 (3.4, 14.5)
≥5 y	15.0 (8.1, 27.9)	8.2 (2.0, 32.8)	1.4 (0.3, 7.1)
Drug-Specific Analysis			
Etanercept † IR (95% CI)		15.8 (5.1, 48.9)	1.0 (ref)
Infliximab † IR (95% CI)		67.2 (33.6, 134.4)	2.6 (0.6, 11.0)
Adalimumab † IR (95% CI)		61.1 (29.2, 128.3)	3.8 (1.0, 14.8)
Rituximab † IR (95% CI)		29.0 (4.1, 206.0)	0.9 (0.1, 10.6)

*Comparing biological-exposed to biological-naïve, Adjusted for age, sex, country of birth, education, cancer, diabetes, copd. In drug-specific analysis, comparing each drug to etanercept exposure.
†Exposure from date of initiation until start of next biologic.
RA Rheumatoid Arthritis; TB Tuberculosis; IR Incidence Rate; CI Confidence Interval; PY Person Years; HR Hazard Ratio.

Conclusion: The risk of TB in patients with RA is increased compared to the general population. In the past decade, the risk of TB has decreased possibly due to the introduction of pre-treatment screening but remains higher than in RA patients unexposed to biologicals. Between drug comparisons showed that the lowest risk is among those exposed etanercept, but etanercept still carries an increased risk compared to biological-unexposed. The majority of cases observed over the 10 years of follow-up occurred in biological-naïve RA patients.

Disclosure: E. V. Arkema, None; **J. Jonsson**, None; **E. Baecklund**, None; **M. Rutting**, None; **J. Bruchfeld**, None; **N. Feltelius**, None; **J. Askling**, Pfizer Inc, 2.

1698

Sex-Related Differences and Trends In Mortality Of Juvenile-Onset Systemic Lupus Erythematosus (SLE) In The United States Over The Last Forty Years, 1971–2010. Eric Y. Yen[1], Jennifer M.P. Woo[2] and Deborah K. McCurdy[1]. [1]Mattel Children's Hospital, University of California at Los Angeles, Los Angeles, CA, [2]Mattel Children's Hospital, University of California, Los Angeles, Los Angeles, CA.

Background/Purpose: To date, SLE-specific mortality studies in children and adolescents are few. Estimations of mortality in adult cohorts of SLE patients have shown that male patients often demonstrate increased mortality, suggesting worse disease severity and prognosis in males. However, these studies are limited because they estimate mortality over a finite period rather than over the lifetime of a cohort of subjects. In this study, we analyzed SLE-specific mortality data for all children and adolescents in the United States over the past 40 years and estimated the sex difference in mortality rates over their lifetime.

Methods: We studied mortality data from the National Center for Health Statistics (NCHS) from the period of 1971–2010, divided into 4 cohorts based on 10 year periods. NCHS states that over 99% of all deaths in the United States are registered. We examined death certificates for all

children and adolescents ages 0–19 years old with systemic lupus erythematosus (ICD10: M32.0, ICD9: 710.0, ICD8: 734.1) listed as the underlying cause of death. Age groups, crude mortality rates per 100,000 persons (=number of deaths/population*100,000), and adjusted crude mortality rates (thus removing the effect of sex difference in SLE prevalence) were calculated. We utilized previously published data of SLE prevalence in children according to sex as the standard population for our adjusted crude mortality calculation (=crude mortality rate/prevalence of SLE per 100,000 in females and males).

Results: Of the 3,130,638,696 mortality records examined, 716, 415, 343, and 310 SLE-specific mortalities for ages 0–19 were identified during the periods of 1971–80, 1981–90, 1991–00, 2001–10 respectively. Crude mortality rate per 100,000 children has decreased over the last forty years from 1971 to 2010 (Fig 1). The absolute numbers of deaths attributed to SLE decreased from 610 (female, 85%) and 106 (male, 15%) cases during 1971–80 to 253 (female, 82%) and 57 (male, 18%) cases during 2001–10. For all years, SLE-specific deaths were significantly greater among females than males. After adjusting for the increased SLE prevalence in females, the sex difference in mortality between females and males diminished (Fig 2).

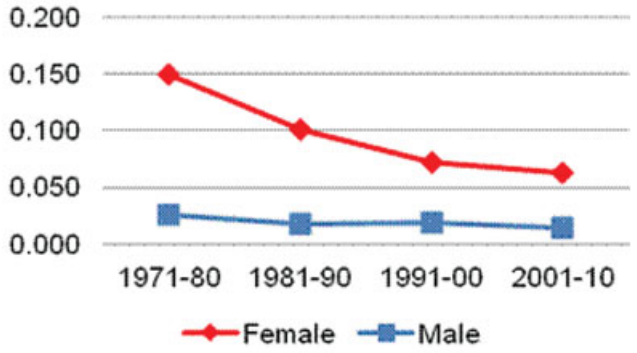

Fig. 1. SLE Crude Mortality Rate per 100,000 Children Ages 0–19 years from 1971–2010.

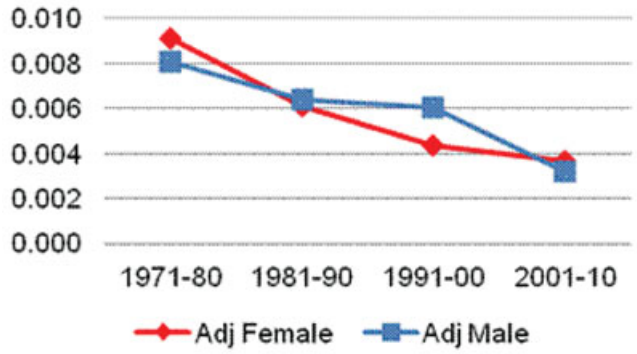

Fig. 2. Adjusted SLE Crude Mortality Rate per 100,000 Children Ages 0–19 years from 1971–2010.

Conclusion: Mortality rates from juvenile-onset SLE appear to be declining in children and adolescents over the past 40 years. Although females still account for 82% of the total deaths due to SLE in children from 2001–2010, the overall mortality rates in males are comparable to females after correcting for increased prevalence of SLE in females.

Disclosure: E. Y. Yen, None; **J. M. P. Woo**, None; **D. K. McCurdy**, None.

1699

Development Of Systemic Lupus Erythamatosus Among "Possible Systemic Lupus Erythamatosus" Patients Seen In Consultation: Long-Term Follow-Up. May Al Daabil, Bonnie L. Bermas, Tabatha Norton, Hsun Tsao, Patricia Ho, Joseph F. Merola, Peter H. Schur, Elena M. Massarotti and Karen H. Costenbader. Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Rheumatology consultation to rule out SLE is common. However, in a substantial proportion of patients, SLE can be neither confirmed nor ruled out at initial visit. We followed a cohort of patients seen in consultation and thought to have possible SLE, through their most recent visits, to examine factors associated with developing SLE.

Methods: Our Lupus Center Registry contains data on 5,032 patients who have received billing codes for SLE (ICD-9 710.0) and rheumatologist reviews for ACR Criteria for Classification. Within the registry, we identified patients: ages 18–60, seen first from January 1, 1998 to December 31, 2008; thought to have possible SLE by a board certified rheumatologist at initial visit; < 4 SLE ACR criteria at that visit; and > 2 visits > 3 months apart. Extensive review of medical records through May 15, 2013 collected: visit dates, SLE manifestations, ACR criteria, autoimmune disease serologies, prescriptions, and final diagnoses per rheumatologists. Fisher's exact and t-tests were employed to assess differences between patients with and without definitive SLE diagnoses. Multivariable logistic regression models were used to identify independent predictors of definite SLE.

Results: We identified 181 patients meeting inclusion criteria. At initial visit, mean age was 38.4 (SD 12.1) years, mean number of SLE ACR criteria was 2.6 (SD 0.9); 173 (95%) were female and 124 (68%) were white. Mean follow-up was 6.2 (SD 4.3) years. 136 (75%) of patients were prescribed hydroxychloroquine at some point. At last visit, 42 (23%) were diagnosed with SLE; 34 (19%) were thought not to have SLE, and the remaining 105 (58%) were thought still to have possible SLE. In univariable models, significantly higher proportions of patients with final definite SLE than those with possible SLE had positive ANAs, anti-dsDNA, arthritis and renal involvement, but fewer had neurologic involvement (**Table**). Definite SLE patients were also slightly younger (37 vs. 39 years) and were more likely to be non-white. A higher proportion of those with definite than with possible SLE had arthritis, anti-dsDNA and nephritis, and received hydroxychloroquine. In multivariable models, arthritis (OR 2.9, 95% CI 1.3–6.9), anti-dsDNA (OR 2.9, 95% CI 1.3–6.5) and renal involvement (OR 12.4 95% CI 1.1–135.8) were independent predictors of definite SLE. The most common diagnoses among those without ultimate SLE were fibromyalgia, Sjogren's syndrome, MCTD and cutaneous lupus. Overall, 34 (18%) were also diagnosed with autoimmune thyroid disease.

Table. Characteristics at Last Follow-up of Patients seen for Possible SLE between 1998–2008

Clinical	Definite SLE N= 42	Possible SLE N= 105	p value*	Not SLE N= 34	p value**
Mean Follow up years (±SD)	5.8 ± 3.4	5.6 ± 4.1	0.75	8.3 ± 5.0	**0.02**
Mean Age at first visit (±SD)	36.7 ± 10.5	38.9 ± 12.7	0.31	39.1 ± 11.9	0.36
Mean ACR criteria at follow up (+ SD)γ	4.1 ± 1.6	3.1 ± 1.2	**0.0002**	3.0 ± 1.4	**0.006**
Deaths in follow-up, n (%)	2 (4.8%)	3 (2.86%)	0.67	0 (0%)	0.33
Female	41 (97.6%)	100 (95.2%)	0.62	32 (94.1%)	0.58
Race/Ethnicity					
White	27 (69.23%)	72 (77.4%)	0.69	25 (78.1%)	0.46
African American	6 (15.4%)	10 (10.7%)	0.78	2 (6.2%)	0.28
Asian	3 (7.7%)	6 (5.4%)	0.71	3 (9.4%)	1.00
Hispanic	3 (7.7%)	5 (5.4%)	0.68	2 (5.4%)	1.00
Other/Multiple	3 (7.1%)	12 (11.4%)	0.55	2 (5.9 %)	1.00
Prescribed Hydroxychloroquine	37 (88.1%)	73 (69.5%)	**0.02**	26 (76.5%)	0.23
SLE Manifestations					
Malar Rash	8 (19.1%)	13 (12.4%)	0.0.31	6 (17.6%)	1.00
Discoid rash	0 (0%)	2 (1.9%)	1.00	0 (0%)	0.58
Photosensitivity	10 (23.8%)	24 (22.9%)	1.00	10 (29.4%)	0.61
Oral ulcers	7 (16.7%)	9 (8.6%)	0.24	3 (8.8%)	0.49
Arthritis	32 (76.2%)	61 (58.1%)	0.05	14 (41.2%)	**0.002**
Serositis	9 (21.4%)	13 (12.4%)	0.20	5 (14.7%)	0.56
Renal disease	3 (7.1%)	0 (0%)	**0.02**	0 (0%)	0.25
Hematologic	19 (45.2%)	36 (34.3%)	0.25	13 (38.2%)	0.64
Neurological disease	0 (0%)	4 (3.8%)	0.47	5 (14.7%)	**0.01**
Positive ANA	42 (100%)	103 (98.1%)	1.00	26 (76.5%)	**0.0009**
Positive Anti-DNA	16 (38.1%)	20 (19.1%)	**0.01**	4 (11.8%)	**0.017**
Positive Anti-Sm	4 (9.5%)	2 (1.9%)	0.05	2 (5.9%)	0.68
Positive Anti-Ro/ Anti-La	11 (26.2%)	18 (17.1%)	0.25	8 (23.5%)	1.00
Raynaud's	18 (42.9%)	46 (43.8%)	1.00	15 (44.1%)	1.00
Other Diagnoses					
Autoimmune Thyroid Disease	6 (14.3%)	20 (19.1%)	0.63	6 (17.6%)	0.76
Cutaneous Lupus	0 (0%)	1 (0.9%)	1.00	3 (8.8%)	0.08
Fibromyalgia	4 (9.5%)	6 (5.7%)	0.47	7 (20.6%)	0.20
MCTD	0 (0%)	0 (0%)	0.55	3 (8.8%)	0.09
RA	0 (0%)	0 (0%)	0.55	1 (2.9%)	0.45
Scleroderma/ Myositis	0 (0%)	3 (2.7%)	0.55	2 (5.4%)	0.19
Sjogren's Syndrome	3 (6.7%)	3 (2.9%)	0.35	6 (17.6%)	0.28

γ Two patients diagnosed with SLE fulfilled < 4 ACR criteria: one developed WHO class IV nephritis and the other developed transverse myelitis.
* p-value for Definite SLE vs. Possible SLE.
** p-Value for Definite SLE vs. Not SLE.
t-tests for continuous and Fisher's exact for categorical variables.

Conclusion: Among patients with possible SLE at initial consultation, almost 25% were diagnosed with definite SLE within 6 years and 75% received hydroxychloroquine regardless of ultimate diagnosis. Arthritis, anti-dsDNA and renal disease were independent predictors of SLE. A better means of accurately identifying those who will progress to definitive SLE among those presenting with possible SLE is necessary.

Disclosure: M. Al Daabil, None; **B. L. Bermas**, None; **T. Norton**, None; **H. Tsao**, None; **P. Ho**, None; **J. F. Merola**, None; **P. H. Schur**, None; **E. M. Massarotti**, Exagen, 2; **K. H. Costenbader**, None.

1700

Which Are The Most Common Disease Modifying Antirheumatic and Biologic Treatment Pathways For Rheumatoid Arthritis Patients? Sofia Pedro[1], Frederick Wolfe[1], James O' Dell[2] and Kaleb Michaud[3]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]University of Nebraska Medical Center, Omaha, NE, [3]National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: While guidelines and cost effectiveness analyses assume limited pathways for RA treatment, there is little known about what occurs in clinical practice. We sought to determine the most common RA treatment pathways over the past decade.

Methods: Enrolled patients provided historical and at least 1 year of prospective treatment use in an open US observational cohort from 1998 through 2012. Treatment groups included 5 DMARDs – methotrexate (MTX), hydroxychlorine (HCQ), leflunomide (LEF), sulfasalazine (SUL), and other DMARDs (OTD) – and 6 biologics – etanercept (ETA), infliximab (INF), adalimumab (ADA), abatacept (ABA), rituximab (RIT), and other biologics (OTB). We implemented sequential data mining, a technique only recently used in the field of medicine, to uncover the most frequent treatment sequences at 1% support (at least 1% of patients had the sequence). Frequent sequences can then be used to obtain association rules, a *happens-after* statement of the form A→B, given a "confidence" threshold for the probability of taking drug B after drug A. We constrained sequences to only describe consecutive and new therapeutic changes, which were presented as association rules expressed by support, confidence, lift (confidence of a rule divided by the support of the consequent) and coverage (total probability of transiting to all consequents and not switching). **Results** were further obtained within contrasted subsets defined by calendar year, age, and disease duration.

Results: With 11 RA drug groups, there were over 7448 drug pathways of the 10,119 eligible RA patients with an average of 5.6 (4.5) years of observation/patient. After implementing the 1% support and confidence thresholds, only 24 pathways remained. Most participants (54.3%) did not switch therapy and were primarily on MTX (37.1%), HCQ (14.3%), and combination MTX + HCQ (9%). Among switchers, the modal treatment pathway was MTX then switch to another DMARD (9.3% of total) or an anti-TNF biologic (9.1%) (See Table). Before 2006, patients tended to switch from MTX to an anti-TNF biologic whereas during and after 2006, non anti-TNF agents appear. This was similar for high duration patients (>5 years), whereas non anti-TNF biologics never made the use-threshold for low duration patients. The transition from MTX to anti-TNF was more frequent in patients with longer disease duration than for early RA patients. ETA was a common choice for patients <65 years whereas INF was more common for patients >65 years.

Table. Support of the Left hand side (LHS) of the rules (L(%)), Confidence (%) and Lift of the right hand side (RHS); probability of staying in the LHS (S(%)) and coverage (C(%))

LHS	L (%)	RHS (Support (%) (Confidence (%)) Lift) ADA	S ETA	C HCQ	INF	LEF	MTX	OTD	SUL	(%)	(%)
{ETA}	18	1.5 (8.3) 1.0			1.6 (8.9) 0.6	1.2 (6.9) 0.4	1.1 (6.3) 0.1			56	87
{HCQ}	20					1.3 (6.6) 0.4	3.4 (17.3) 0.4	1.0 (5.1) 0.4	1.1 (5.5) 0.7	54	89
{LEF}	18		2.8 (15.5) 0.9		2.3 (12.8) 0.9					45	74
{MTX+ HCQ}	9		1.2 (12.7) 0.7			1.5 (15.4) 0.9				49	77
{MTX}	46	1.5 (3.3) 0.4	3.8 (8.3) 0.5	2.8 (6.1) 0.3	4.2 (9.2) 0.6	4.7 (10.3) 0.6		1.6 (3.4) 0.3	1.3 (2.9) 0.4	53	97
{OTD}	13		1.0 (8.0) 0.4			1.5 (11.5) 0.6	1.2 (9.5) 0.2			50	79
{SUL}	8					1.0 (12.6) 0.7	1.1 (13.7) 0.3			43	69

Conclusion: By using sequential data mining in a large dataset, we have estimates of the idiosyncratic and myriad drug pathways taken by US RA patients. While our results provide evidence of the recent ACR RA treatment guidelines in practice, only 38.1% of switching patients were in the modal pathway. Future health models of patient treatment need to account for this heterogeneity.

Disclosure: S. Pedro, National Data Bank for Rheumatic diseases, 3; **F. Wolfe**, None; **J. O' Dell**, None; **K. Michaud**, University of Nebraska Medical Center, 3, National Data Bank for Rheumatic Diseases, 3.

ACR Concurrent Abstract Session
Genetics and Genomics of Rheumatic Disease I
Monday, October 28, 2013, 2:30 PM–4:00 PM

1701 WITHDRAWN

1702

Identification of Multiple Genetic Susceptibility Loci in Takayasu's Arteritis. Guher Saruhan-Direskeneli[1], Travis Hughes[2], Patrick S. Coit[2], Joel M. Guthridge[3], Judith A. James[3], Peter A. Merkel of behalf of the Vasculitis Clinical Research Consortium[4], Haner Direskeneli on behalf of the Turkish Takayasu Study Group[5] and Amr H. Sawalha[2]. [1]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [2]University of Michigan, Ann Arbor, MI, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]University of Pennsylvania, Philadelphia, PA, [5]Marmara University, Faculty of Medicine, Istanbul, Turkey.

Background/Purpose: Takayasu's arteritis is a rare inflammatory disease of large arteries. The etiology of Takayasu's arteritis remains poorly understood, but genetic contribution to the disease pathogenesis is supported by the confirmed genetic association with *HLAB*52*. Genomic studies in Takayasu's arteritis have not been previously performed.

Methods: We genotyped ~200,000 genetic variants in two ethnically divergent Takayasu's arteritis cohorts from Turkey (339 patients and 516 controls) and North America (112 patients and 599 controls) using a custom designed genotyping platform (Immunochip). Additional genetic variants and the classical HLA alleles were imputed and analyzed.

Results: We identified and confirmed two independent susceptibility loci within the HLA region ($r^2<0.2$): *HLA-B*/*MICA* (rs12524487, OR= 3.29, $P= 5.57\times10^{-16}$), and *HLADQB1*/ *HLA-DRB1* (rs113452171, OR= 2.34, $P= 3.74\times10^{-9}$, and rs189754752, OR=2.47, $P= 4.22\times10^{-9}$). In addition, we identified and confirmed a novel genetic association between Takayasu's arteritis and the *FCGR2A*/*FCGR3A* locus on chromosome 1 (rs10919543, OR= 1.81, $P= 5.89\times10^{-12}$). The risk allele in this locus results in increased mRNA expression of *FCGR2A*. We also established the genetic association between *IL12B* and Takayasu's arteritis (rs56167332, OR= 1.54, $P= 2.18\times10^{-8}$). An association with an additional locus on chromosome 21q22 downstream of *PSMG1* did not pass the threshold for genome-wide significance and requires replication ($P=4.39\times10^{-7}$).

Conclusion: We established multiple genetic susceptibility loci for Takayasu's arteritis with a genome-wide level of significance including two independent susceptibility loci in the HLA region, and disease susceptibility loci in *FCGR2A*/*FCGR3A* and *IL12B*.

Disclosure: G. Saruhan-Direskeneli, None; **T. Hughes**, None; **P. S. Coit**, None; **J. M. Guthridge**, None; **J. A. James**, Pfizer Inc, 2, GSK, 5; **P. A. Merkel of behalf of the Vasculitis Clinical Research Consortium**, None; **H. Direskeneli on behalf of the Turkish Takayasu Study Group**, None; **A. H. Sawalha**, None.

1703

High Density Genotyping Of Immune-Related Disease Genes Identifies 7 New Susceptibility Loci For Behçet's Disease. Masaki Takeuchi[1], Nobuhisa Mizuki[2], Akira Meguro[2], Michael J. Ombrello[3], Colleen Satorius[1], Yohei Kirino[2], Tatsukata Kawagoe[2], Duran Ustek[4], Ilknur Tugal-tutkun[5], Emire Seyahi[6], Yilmaz Ozyazgan[6], Shigeaki Ohno[7], Atsuhisa Ueda[2], Yoshiaki Ishigatsubo[2], Ahmet Gül[5], Daniel L. Kastner[1] and Elaine Remmers[1]. [1]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [2]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [3]National Institute of Arthritis Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [4]Institute of Experimental Medicine, Istanbul University, Istanbul, Turkey, [5]Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey, [6]Cerrahpasa Faculty of Medicine, Istanbul University, Istanbul, Turkey, [7]Hokkaido University Graduate School of Medicine, Hokkaido, Japan.

Background/Purpose: Genome-wide association studies have revealed susceptibility genes for many genetically complex diseases. The Immunochip is a custom array with 196,524 markers in 186 loci selected

from analysis of 12 autoimmune diseases. It enables dense genotyping of established immune disease-associated loci as well as genotyping of additional suggestive variants identified in immune diseases. Behçet's disease (BD) is a systemic vasculitis that manifests with oral ulcers, uveitis, skin inflammation, genital ulcers and inflammation in other organs. Although *HLA-B*51*, *IL10*, *IL23R*, *CCR1*, *STAT4*, *KLRC4*, and *ERAP1* have been reported to be susceptibility genes in previous studies, the pathogenesis of BD remains unclear. The purpose of this study was to perform dense genotyping of loci associated with immune diseases to identify novel susceptibility loci for BD.

Methods: In this study, 2014 Turkish BD patients and 1826 controls were densely genotyped using the Immunochip. Samples with call rate > 0.95 and markers with call rate > 0.95, minor allele frequency > 0.01, and Hardy-Weinberg equilibrium P value > 0.00001 were included. Samples from related individuals with identity by descent pi-hat > 0.18 were excluded and principal components were used to evaluate population stratification. For novel loci with association test P value $< 5\times10^{-6}$, additional SNPs in the region were imputed using 1000 Genomes data as the reference panel. Imputed SNPs with info > 0.8 were included in the comprehensive association analysis. $P < 5\times10^{-8}$ and $P < 1.67\times10^{-8}$were considered thresholds for genome-wide significance in the basic allele test analysis and the three model (additive, dominant, recessive) genotypic analysis, respectively.

Results: The basic allele association test confirmed 2 loci, *IL10* and *CCR1*, previously associated with BD and identified 4 novel loci, *IL1A-IL1B*, *SCHIP1-IL12A*, *IRF8,* and *PTPN1*, which exceeded genome-wide significance. In addition, the *FUT2* locus showed dominant model genome-wide significance in the three model genotypic analysis. Imputation data provided 2 additional novel loci with genome-wide significance, *RIPK2* and *EGR2*.

Conclusion: This immunochip dense-genotyping study identified 7 new BD susceptibility loci. These results have greatly expanded the list of genes with common variants that influence BD susceptibility. Some of these new loci implicate important pathways, such as the IL-1 pathway, which may help explain BD pathogenesis and suggest therapeutic targets.

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1704

Mapping The Shared and Distinct HLA Alleles For Seropositive and Seronegative Rheumatoid Arthritis. Buhm Han[1], Stephen Eyre[2], Dorothee Diogo[1], John Bowes[3], Yukinori Okada[1], Leonid Padyukov[4], Robert M. Plenge[1], Lars Klareskog[4], Jane Worthington[3], Peter K. Gregersen[5], Paul de Bakker[6] and Soumya Raychaudhuri[1]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [3]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [4]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [5]Feinstein Institute for Medical Research, Manhasset, NY, [6]University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: Investigators have long speculated that the two subtypes of rheumatoid arthritis (RA), anti-citrullinated protein autoantibody positive (ACPA+) and negative (ACPA-), have distinct underlying genetic factors. The MHC region is the strongest genetic risk factor to ACPA+ RA, but plays a much more modest role in ACPA− RA. To understand the similarities and differences between these two disease subtypes, we fine-mapped and compared MHC associations.

Methods: Using densely genotyped SNP data consisting of 7,222 ACPA+ RA cases, 3,339 ACPA- RA cases, and 15,870 controls from six different cohorts (Eyre et al., *Nat Gen*, 2012), we imputed and tested HLA alleles in the two RA subtypes separately.

Results: We mapped associations to ACPA+ RA using forward search conditional analysis and confirmed previously published associations at amino acid sites at positions 13 ($P < 10^{-705}$), 71, and 74 in *HLA-DRB1*, position 9 in *HLA-B*, and position 9 in *HLA-DPB1*. In addition, we identified a novel association at position 77 in *HLA-A* ($P=1.7\times10^{-8}$) located in the peptide binding groove implicating antigen presentation as the major mechanism by which MHC variation confers risk. Then in parallel we mapped associations to ACPA- RA. We recognized that ACPA- RA associations to the MHC might be confounded due to the inclusion of misclassified samples that are actually ACPA+ RA (false negative testing) or ankylosing spondylitis. We developed a novel statistical approach that estimates the proportion of misclassified samples and regresses out their effects. Using this approach we observed that each cohort consistently contained 3–9% of cases that likely had ankylosing spondylitis, and a variable number of cases that likely had ACPA+ RA. Controlling for misclassification effects, we identified the amino acid residues at position 13 in *HLA-DRB1* as strongly associated with risk (Omnibus test $P=1.2\times10^{-16}$). Serine conferred the highest risk (OR= 1.28, $P=5.7\times10^{-13}$); in stark contrast serine conferred protection to ACPA+ disease (OR=0.4). We also observed a shared association to the presence of an aspartate in position 9 in *HLA-B* ($P=1.3\times10^{-15}$, OR=1.38) with a more modest effect size than for ACPA+ disease (OR=2.1).

Conclusion: Our analysis is the first to define specific amino acid sites for ACPA- RA, and demonstrates a distinct genetic basis for ACPA+ and ACPA- RA in the MHC region. Our analysis also underscores the importance of phenotypic classification for accurate fine-mapping.

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1705

Genetic Associations In Anterior Uveitis Implicate T-Cell Co-Stimulation and Other Immune Pathways. Philip Robinson[1], Dorith Claushuis[2], Paul Leo[1], Pamela Mukhopadhyay[3], P. Wordsworth[4], Michael H. Weisman[5], Walter P. Maksymowych[6], Proton Rahman[7], Robert Inman[8], Alex Hewitt[9], Tammy M. Martin[10], James T. Rosenbaum[11], Dennis Wakefield[12], John D. Reveille[13] and Matthew A. Brown[14]. [1]University of Queensland Diamantina Insititute, Brisbane, Australia, [2]The University of Queensland Diamantina Institute, Brisbane, Australia, [3]The University of Queensland Diamantina Insititute, Brisbane, Australia, [4]University of Oxford, Oxford, United Kingdom, [5]Cedars-Sinai Medical Center, Los Angeles, CA, [6]University of Alberta, Edmonton, AB, [7]Memorial University, St. Johns, NF, [8]University of Toronto and Toronto Western Hospital, Toronto, ON, [9]University of Western Australia, Perth, Australia, [10]Oregon Health & Science Univ, Portland, OR, [11]Oregon Health and Science University, Portland, OR, [12]University of New South Wales, Sydney, Australia, [13]University of Texas Health Science Center at Houston, Houston, TX, [14]University of Queensland Diamantina Institute, Brisbane, Australia.

Background/Purpose: Anterior uveitis (AU) complicates a number of autoimmune diseases including ankylosing spondylitis (AS), Behcet's disease and sarcoidosis. It is highly heritable and HLA-B27 is the major risk factor. Functional data has suggested that AU is a T-cell mediated disease. Genes including MHC class II molecules and cytokine genes have been associated with AU. A linkage study has reported suggestive linkage at chromosome 9p21-9p24, but no non-MHC gene has been definitively associated with AU. Our aim was to use an immune focused micro-array to better characterise the genetic variants associated with AU.

Methods: Cases of AS with AU (n = 1,422), cases of AS without AU (n = 2,339), AU cases alone (n = 289) and healthy controls (HC) (n = 10,000) were recruited. The Illumina Immunochip microarray was used to genotype 190,000 autoimmune related SNPs across the genome selected for their previous identification in autoimmune phenotypes or for fine mapping of association signals already identified. Analysis was completed with the linear mixed model FaST-LMM. We report here the analysis of all AU cases compared to HC. Classical MHC alleles were imputed from genotyping data using the programme HLA*IMP.

Results: Multiple regions previously reported to be associated with AS were significantly associated. In addition, in this analysis, one rare haplotype (minor allele frequency in controls = 0.0003) spanning the genes *CCL19*, *CCL21* and *CCL27* was associated with AU at genome wide significance ($P = 2.6 \times 10^{-9}$, OR = 11.4). Taqman genotyping of the lead SNP in this haplotype was completely concordant with array genotype. Five other loci implicating *RGS21* (9.5×10^{-7}, OR 1.2), *CD28-CTLA4* (9.4×10^{-7}, OR = 1.2), *POP7* (1.6×10^{-6}, OR = 1.3), *WFDY4* (7.9×10^{-6}, OR = 1.2) and *CLECL16A* (6.4×10^{-6}, OR = 1.3)

were associated at a suggestive level of significance ($P < 1 \times 10^{-5}$). *HLA-B27* was strongly associated ($P = 1 \times 10^{-320}$, OR = 5.0). Conditioning on HLA-B*27, a protective association with HLA-B*07 was observed ($P = 1.2 \times 10^{-6}$, OR = 0.71).

Conclusion: Multiple SNPs implicating T cell function and co-stimulation, as well as complement and chemokine pathways were associated with AU. These findings indicate that whilst the genetic risk factors for AS and AU are similar, additional genetic risk variants influence the risk of developing AU that are not involved in AS itself.

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1706

Fine-Mapping Major Histocompatibility Complex Variation Associated With Ankylosing Spondylitis Susceptibility. Adrian Cortes[1], International Genetics of Ankylosing Spondylitis Consortium (IGAS)[2], Paul de Bakker[3] and Matthew A. Brown[4]. [1]The University of Queensland Diamantina Insititute, Brisbane, Australia, [2]University of Queensland Diamantina Institute, brisbane, Australia, [3]University Medical Center Utrecht, Utrecht, Netherlands, [4]University of Queensland Diamantina Institute, Brisbane, Australia.

Background/Purpose: Ankylosing spondylitis (AS) is a common, highly heritable, inflammatory arthritis. Thus far, 27 susceptibility loci have been identified in and outside the MHC in populations of European and Asian ancestry. The HLA-B*27 allele is the major genetic risk factor to AS and its role in disease aetiology remains elusive to this date. Potential mechanisms include disorders of the antigenic presentation function of HLA Class I proteins, or on abnormal intracellular effects unique to the HLA-B*27 protein variant. Prior studies have suggested that other HLA-B alleles and MHC genes are involved in AS-susceptibility. In this study we aim to better define the MHC associations of AS and to identify functional and potentially causal variants to shed light on the mechanisms by which the HLA-B*27 molecule confers risk to disease.

Methods: We successfully genotyped 7,264 MHC polymorphic SNPs in 9,069 AS affected individuals and 13,578 healthy controls of European descent using the Illumina Immunochip microarray, designed for immunogenetic studies. High-density genotype data was then followed by imputation of HLA Class I and II classical alleles and residues at polymorphic amino acid positions of HLA Class I and II proteins. Association to disease susceptibility was assessed by logistic regression correcting for population structure.

Results: As expected, strong association was observed with SNPs in the HLA-B locus (P-value $< 1 \times 10^{-320}$). Analysis of HLA-B alleles revealed other non-HLA-B*27 alleles affecting susceptibility to AS of moderate effect size (HLA-B*40:01, OR=1.13; *40:02, OR=1.59; *51:01, OR=1.36; *07:02, OR=0.77; *57:01, OR=0.73; all P-value$<5\times10^{-8}$). After controlling for the associated haplotypes in HLA-B we observed independent association signals with SNPs in the HLA-A locus (rs2975033, P-value $= 4.94 \times 10^{-10}$, OR = 1.22), which tagged the classical allele HLA-A*02:01 (P-value $= 7.95 \times 10^{-10}$, OR = 1.22), and in HLA-DRB1 (rs1126513, P-value $= 5.12 \times 10^{-8}$, OR = 1.22). Analysis of polymorphic amino acid positions demonstrated that the most significant polymorphisms in the HLA-B and HLA-DPB1 loci were amino acid residues located in the binding pocket of these molecules. We have previously shown that AS is associated with *ERAP1* polymorphisms only in HLA-B*27 carriers, which we confirm here. Additionally, we show that amongst HLA-B*27 negative cases, *ERAP1* variants are AS-associated in HLA-B*40:01-positive but not –negative subjects, indicating that *ERAP1* variants also interact with HLA-B*40:01.

Conclusion: This study has identified susceptibility alleles in MHC Class I and II loci. The identification of multiple HLA-B alleles affecting AS susceptibility and the interaction between *ERAP1* variants and the HLA-B alleles *27:02, *27:05 and *40:01 suggests that these alleles all operate by similar mechanisms to induce AS, and further supports antigen presentation as the molecular mechanism by which HLA-B*27 confers risk to disease. The presence of associated polymorphism in both HLA Class I and II loci suggests that antigen presentation to both $CD4^+$ and $CD8^+$ T lymphocytes are important in AS pathogenesis and/or tissue specificity.

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1707

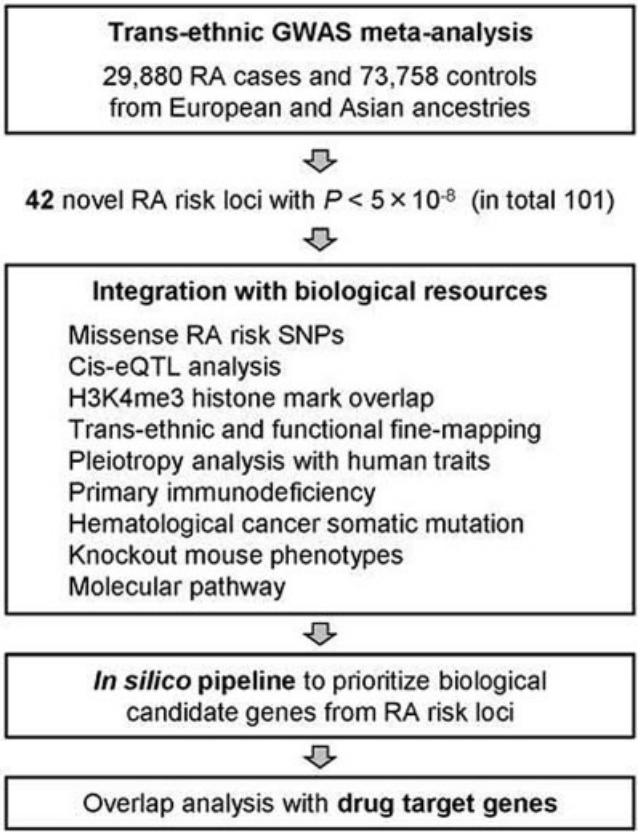
Biological Insights From Genetics Of Rheumatoid Arthritis Contribute To Drug Discovery. Yukinori Okada[1], Di Wu[2], Chikashi Terao[3], Katsunori Ikari[4], Yuta Kochi[5], Koichiro Ohmura[3], Akari Suzuki[5], Hisashi Yamanaka[4], Joshua C. Denny[6], Jeffrey D. Greenberg[7], Robert R. Graham[8], Matthew A. Brown[9], Sang-Cheol Bae[10], Jane Worthington[11], Leonid Padyukov[12], Lars Klareskog[13], Peter K. Gregersen[14], Peter M. Visscher[15], Katherine A. Siminovitch[16] and Robert M. Plenge[1]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Department of Statistics, Harvard University, Cambridge, MA, [3]Graduate School of Medicine, Kyoto University, Kyoto, Japan, [4]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [5]RIKEN, Yokohama, Japan, [6]Department of Biomedical Informatics, Vanderbilt University School of Medicine, Nashville, TN, [7]NYU Hospital for Joint Diseases, New York, NY, [8]Genentech, Inc., South San Francisco, CA, [9]The University of Queensland Diamantina Insititute, Brisbane, Australia, [10]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [11]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [12]Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden, [13]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [14]Feinstein Institute for Medical Research, Manhasset, NY, [15]Queensland Brain Institute, The University of Queensland, St Lucia, Brisbane, Australia, [16]Mount Sinai Hospital, Toronto, ON.

Background/Purpose: A major challenge in human genetics is to devise a systematic strategy to integrate disease-associated variants with diverse genomic and biological datasets to provide insight into disease pathogenesis and guide drug discovery. Here, we demonstrate one such strategy for a common autoimmune disease with no known cure, rheumatoid arthritis (RA).

Methods: We performed a trans-ethnic genome-wide association study (GWAS) and *in silico* and *de novo* replication studies in a total of >100,000 subjects of European and Asian ancestries (29,880 RA cases and 73,758 controls), by assessing ~10 million autosomal and X-chromosomal single nucleotide polymorphisms (SNPs). Using the RA risk loci obtained from the GWAS meta-analysis, we conducted an integrative analysis with a variety of biological resources: functional annotation of SNPs (missense or non-coding); cis-eQTL analysis for peripheral blood mononuclear cell (PBMC)/T cells/monocytes; H3K4me3 histone peak overlap; trans-ethnic and functional fine-mapping of candidate causal alleles; pleiotropy analysis with other human complex traits; and others. Armed with these biological insights or RA, we constructed *in silico* pipeline to prioritize biological candidate genes from the RA risk loci, and evaluated their connections to target genes for approved RA drugs.

Results: We discovered 42 novel RA risk loci at a genome-wide level of significance ($P < 5\times10^{-8}$), bringing the total to 101. The common alleles at these RA risk loci revealed: a shared genetic architecture among individuals of European and Asian ancestry; most risk alleles alter gene expression with fewer alleles altering protein structures; two-thirds of loci had pleiotropic effects on other traits, especially disorders of the immune system and inflammatory biomarkers; an overlap with genes that contribute to human primary immunodeficiency (PID) and hematological cancer somatic mutations; and specific cell types (e.g. overlap with H3K4me3 peaks in $CD4^+$ regulatory T cells) and molecular pathways (e.g., T cell, B cell, cytokine signaling) that contribute to RA pathogenesis. We also demonstrated that biological candidate RA risk genes were significantly enriched in overlap with genes that are the target of approved therapies for RA (e.g., *TNF* and *IL6R*), and further suggested that drugs approved for other indications may be repurposed for the treatment of RA (e.g., CDK4/CDK6 inhibitors used in cancers).

Conclusion: This comprehensive genetic study sheds light on fundamental pathways and genes that contribute to RA pathogenesis, and provides empirical evidence that the genetics of RA can provide important information for drug discovery efforts.



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ACR Concurrent Abstract Session
Health Services Research, Quality Measures and Quality of Care – Rheumatoid Arthritis
Monday, October 28, 2013, 2:30 AM–4:00 PM

1708

Can People With Rheumatoid Arthritis Self Monitor Their Disease Activity? Noura AL Osaimi[1], Erin Carruthers[2], Charles H Goldsmith[3], Paul M Adam[4] and Diane Lacaille[5]. [1]University of British Columbia, Vancouver, BC, [2]Arthritis Research Centre of Canada, Richmond, BC, [3]Simon Fraser University, Burnaby, BC, [4]Mary Pack Arthritis Centre, Vancouver, BC, [5]Arthritis Research Centre of Canada, University of British Columbia, Richmond, BC.

Background/Purpose: In rheumatoid arthritis (RA) the target for treatment is clinical remission or minimal disease activity. Active involvement of patients in monitoring their own disease activity could enhance treatment by providing an early warning when targets are not met, indicating the need for a visit to evaluate treatment. The objective of this study is to determine if patients can self-monitor their RA disease activity and accurately identify whether they have reached the target of low disease activity or remission.

Methods: RA disease activity states from patient self-reported data and rheumatologist evaluation were compared. All consecutive RA patients presenting for follow-up to seven participating rheumatologists were invited to participate. Consenting patients filled out a questionnaire and performed a self-report joint count. Rheumatologist joint count and lab values (CRP) were obtained from rheumatologists' charts.

RA disease activity indices (CDAI, SDAI and RAPID-4) were used to calculate disease activity, categorized into remission, low, moderate or high, according to published cut points. In patient versions of the CDAI and SDAI, physician global scores were replaced with the patient global score. Because change in treatment is recommended with moderate or high disease activity, we created two categories: remission or low vs. moderate or high. We also compared agreement across the four categories. Patient-derived and rheumatologist-derived activity states were compared using percent perfect agreement, as well as Cohen's kappa for two category comparisons, and weighted kappa, which weighs how close the agreement is to perfect agreement, for four category comparisons.

Results: We recruited forty-nine RA patients [mean (SD) RA duration: 9.9(12.3) years; mean (SD) age: 57.7(15.4) years; 76% female]. Results suggest moderate to good agreement between patient and rheumatologist assessment of disease activity state when comparing patient-derived with rheumatologist-derived CDAI and SDAI, and when comparing RAPID-4 self-report assessment with rheumatologist CDAI and SDAI.

Two Category Comparison – Remission or Low vs. Moderate or High

Comparison	% perfect agreement	Cohen's Kappa (95% CI)
Patient vs. rheumatologist CDAI	75.5%	0.51* (0.27;0.75)
Patient vs. rheumatologist SDAI	79.6%	0.59* (0.36;0.82)
RAPID4 vs. rheumatologist CDAI	79.6%	0.59* (0.36;0.82)
RAPID4 vs. rheumatologist SDAI	79.6%	0.59* (0.36;0.82)

Four Category Comparison – Remission vs. Low vs. Moderate vs. High

Comparison	% perfect agreement	Weighted Kappa (95% CI)
Patient vs. rheumatologist CDAI	51%	0.66** (0.51;0.81)
Patient vs. rheumatologist SDAI	61%	0.75** (0.64;0.87)
RAPID4 vs. rheumatologist CDAI	47%	0.69** (0.56;0.81)
RAPID4 vs. rheumatologist SDAI	49%	0.69** (0.56;0.82)

*values in 0.5–0.6 interval represent moderate agreement, all $p < 0.001$.
**values in 0.6–0.8 interval represent good agreement; all $p < 0.001$.

Conclusion: There is moderate to good agreement between patient self-assessment and rheumatologist assessment of disease activity, with little difference between instruments used. These results suggest that patients are able to assess their own disease activity, which may be helpful in guiding the need for physician visit and medication adjustments.

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1709

Rheumatoid Arthritis Patient Cardiovascular Disease Prevention Experiences: Qualitative Analysis and Implications. Christie M. Bartels[1], Sarah Tweddell[2], Barbara Bowers[3], Elizabeth Jacobs[2] and Tonya Roberts[3]. [1]University of Wisconsin School of Medicine and Public Health, Madison, WI, [2]UW School of Medicine and Public Health, Madison, WI, [3]UW School of Nursing, Madison, WI.

Background/Purpose: Although rheumatoid arthritis (RA) increases cardiovascular disease (CVD) risk, RA patients receive less CVD preventive care than peers. We previously showed gaps in lipid testing and hypertension diagnosis despite more clinic visits in RA patients compared to peers. This qualitative study aimed to examine the processes by which RA patients experience CVD preventive care in order to inform patient-centered interventions to close these gaps.

Methods: Ten adult RA patients were recruited from 3 local rheumatology clinics for interviews to evaluate CVD preventive care experiences beyond clinical documentation. Interviews were recorded, transcribed, dual coded and team reviewed using NVivo software to facilitate grounded theory analysis and interpretation (Strauss 1994).

Results: Interviewed RA patients were 70% female, ages 23–81 (mean 57). Most RA patients were unaware of increased CVD risk while all patients were aware of RA medication side effects. Those who had experienced CVD risk management described two processes by which they received CVD preventative care: 1) identifying risk and 2) action (Figure 1). The number of steps and likelihood of actions were related to the physician who identified risk. Primary care physicians were not specifically described as identifying RA-CVD risk, but ***if*** they identified traditional CVD risks were most likely to actively manage them. However, many patients described rarely seeing their PCP, which is consistent with national reports. Rheumatologists more often identified RA-specific risk, but rarely provided active CVD risk treatment or monitoring. Therefore, a particularly concerning finding was that 60% of participants perceived their rheumatologist as their main provider, since the reliance on this provider may delay or decrease treatment likelihood. A few participants alternatively described steps in which they themselves identified

RA-specific risk and self-advocated care (Fig 1. O's). Overall, most patients had no preference about who managed CVD risks, expecting that blood pressure or cholesterol would be addressed. Future work should examine actual rheumatologist and PCP CVD risk identification and actions, and provider perceptions to inform future interventions. Optimizing roles may include RA patient activation (O) and rheumatologist communication/co-management (Δ) to catalyze CVD risk identification and management.

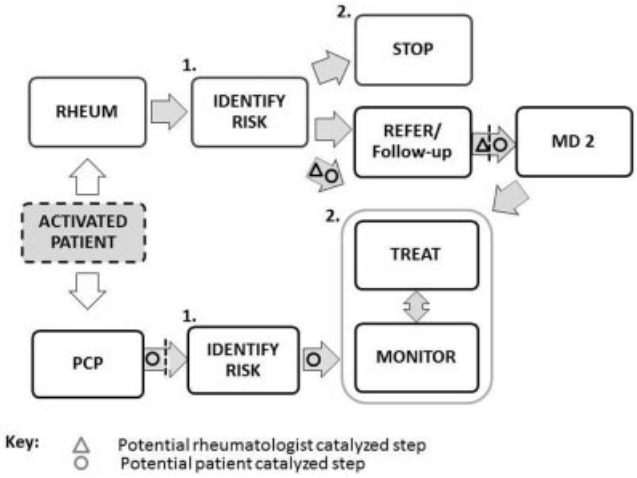

Figure 1. Process of how RA patients receive CVD preventive care.

Conclusion: Patients with RA do not report receiving consistent CVD preventive care. Most described their rheumatologist as their main doctor and noted infrequent PCP visits, though rheumatologists were less likely than PCP's to actively manage CVD risks. This suggests that RA patient activation, rheumatologist communication/co-management and advocating regular PCP care should be studied as potential interventions to close CVD-preventive care gaps in RA.

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1710 WITHDRAWN

1711

Folic Acid Prescription Among Older Adult Methotrexate Initiators Is Poor. Gabriela Schmajuk[1], Jinoos Yazdany[2], Yinghui Miao[3], David I. Daikh[2] and Michael Steinman[3]. [1]UCSF/San Francisco VA Medical Center, San Francisco, CA, [2]University of California, San Francisco, San Francisco, CA, [3]San Francisco Veterans Affairs Medical Center, San Francisco, CA.

Background/Purpose: Methotrexate (MTX) is the most commonly used disease modifying agent for rheumatoid arthritis (RA), although liver enzyme (LFT) elevations limit its use in some patients. Folic acid has been shown in a randomized controlled trial to dramatically reduce the incidence of elevated LFTs in patients taking MTX (van Ede et al, 2001). Although national guidelines recommend universal folic acid use for MTX users, the prevalence of folic acid prescription among MTX users in an older, population-based cohort of patients with rheumatic diseases is unknown.

Methods: We used national Veterans Health Administration (VHA) data to assess (1) folic acid prescription among new users of low-dose (< 40 mg/weekly), oral MTX and (2) predictors of not being prescribed folic acid. We created a national cohort of incident MTX users $\geq$ age 65 using linked medical, pharmacy, and laboratory data from the VHA during fiscal years 2007–2008. Patients were included if they had a new, $\geq$ 28-day supply of MTX dispensed and evidence of continuous use of VHA services. We excluded subjects who may have obtained care outside of the VHA by removing those with any encounter billed to Medicare. Folic acid prescription through the VHA pharmacy was assessed up to 30 days after the first MTX dispensation. We examined patients for elevated LFTs (AST or ALT $\geq 1.5 \times$ upper limit of normal) during the 6 months after the first MTX dispensation. We used multivariate regression to estimate (1) the relative risk of not being prescribed folic acid among different subgroups, and (2) the odds of LFT elevations among patients not prescribed folic acid, in both cases adjusting for demographic and clinical factors (sex, age, race, comorbid conditions, MTX dose, baseline LFT levels, # of specialty visits, and # of outpatient medications).

Results: Out of 717 new MTX users, 27% were not prescribed folic acid through the VHA pharmacy within 30 days of MTX initiation. Our cohort was mostly male (97%), white (87%), mean age 71.4 (SD 6.4), and carried a diagnosis of rheumatoid arthritis or psoriasis/psoriatic arthritis (57% and 22%, respectively). 52% of patients had a rheumatologist visit before the first MTX prescription was dispensed. Patients not followed by rheumatologists were 20% less likely (RR 0.8, 95% CI (0.7, 0.9)) to be prescribed folic acid compared with patients with a rheumatologist visit prior to their first MTX prescription, even after adjusting for the other factors listed above. Notably, patients who were not prescribed folic acid were significantly more likely to have LFT elevations after starting MTX in both univariate (9.7% vs. 5.0%, $p = 0.02$) and multivariate (OR 2.2, 95% CI (1.1, 4.2)) analysis.

Conclusion: Many new oral MTX users were not prescribed folic acid, and these patients were significantly more likely to have elevated LFTs. Rheumatologists were more likely to prescribe folic acid than other providers. Improving folic acid prescription, especially in an older adult cohort, has the potential to significantly reduce the incidence of LFT abnormalities and may allow more widespread and persistent use of MTX, an effective and inexpensive medication for RA and other rheumatic diseases.

Disclosure: G. Schmajuk, None; **J. Yazdany**, None; **Y. Miao**, None; **D. I. Daikh**, None; **M. Steinman**, None.

1712

Identification Of Factors Associated With Agreement Between Rheumatoid Arthritis Electronic Medication Lists and Prescribed Disease Modifying Treatment Plans. Ilinca D. Metes[1], Heather Eng[2], June Feng[2], G.K. Balasubramani[2], Stephen R. Wisniewski[2] and Marc C. Levesque[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA.

Background/Purpose: Federal government programs incentivize the use of Electronic Health Records (EHR) including accurate medication lists. The accuracy of a patient's EHR medication list is essential for understanding the efficacy of treatment plans and reducing adverse events. However, studies indicate that many EHR medication lists are inaccurate. Therefore, it was our aim to determine the level of agreement and to determine the factors associated with agreement between a RA patient's EHR medication list and their disease modifying treatment plan.

Methods: Subjects (n = 1,029) were drawn from the University of Pittsburgh RA Comparative Effectiveness Research (RACER) registry (2010–13). For each outpatient visit (n = 5,236) a "Gold Standard" medication list (encompassing oral disease modifying anti-rheumatic disease modifying drugs (DMARDS), biologics, and corticosteroids) was created using retrospective (n = 4,251) and prospective (n = 985) data collected through chart review of physician notes and/or patient interviews. The "Gold Standard" was compared to the EHR medication list and the measure of agreement was determined using Cohen's kappa coefficient. Patient, physician and clinic characteristics were compared between visits where medications matched vs visits where medications did not match using chi square for categorical variables and t-tests or Wilcoxon signed rank tests for continuous measures. To evaluate the characteristics associated with drug matches, a longitudinal regression model using a generalized estimating equation (GEE) method was used to account for repeated observations within a patient.

Results: Comparison of the "Gold Standard" and EHR medication lists resulted in 8,124 true positive, 95,984 true negative, 638 false positive, and 1,829 false negative medication matches. Retrospective (kappa = 0.86) and prospective (kappa = 0.85) data was combined to give an overall kappa = 0.86, with oral DMARDS having a kappa = 0.89, biologics a kappa = 0.85, and corticosteroids a kappa = 0.78. Based on the GEE, the odds ratio (OR; 95% CI) of oral DMARD, biologic and corticosteroid medication matches was decreased by having a longer prescription list (0.94; 0.93–0.96), a high % decrease in medications compared to the last visit (0.97; 0.97–0.98), having high RA disease activity by the RAPID3 (0.38; 0.29–0.51), CDAI (0.32; 0.25–0.42), or DAS28 (0.76; 0.72–0.81), and having more comorbidities as measured by the Charlson (0.90; 0.83–0.97).

Conclusion: For RA patients in a usual care setting, there was a high level of agreement between their disease modifying drug treatment plan and their EHR medication list, with the level of agreement differing

slightly between oral DMARDs, biologics and corticosteroids. A longer medication list, a high % decrease in overall medications since the last visit, being in high disease activity by the RAPID3, CDAI, or DAS28, and having more comorbidities as measured by the Charlson increased the likelihood of drug discrepancies. Using these results, our future research will focus on reducing discrepancies in the EHR medication list by implementing targeted interventions.

Disclosure: I. D. Metes, Genentech and Biogen IDEC Inc., 2; **H. Eng**, Genentech and Biogen IDEC Inc., 2; **J. Feng**, Genentech and Biogen IDEC Inc., 2; **G. K. Balasubramani**, None; **S. R. Wisniewski**, Genentech and Biogen IDEC Inc., 2; **M. C. Levesque**, Genentech and Biogen IDEC Inc., 2, Genentech and Biogen IDEC Inc., 5.

1713

Disparity In Biologic Therapy In Ethnic Minorities With Rheumatoid Arthritis: Can It All Be Due To Lack Of Access To Drug? Gail S. Kerr[1], Ted R. Mikuls[2], Christopher J. Swearingen[3], Chunqiao Luo[4] and Yusuf Yazici[5]. [1]Washington DC VAMC, Georgetown and Howard University, Washington, DC, [2]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [3]Pediatric Biostatistics, University of Arkansas for Medical Sciences, Little Rock, AR, [4]University of Arkansas for Medical Sciences, Little Rock, AR, [5]NYU Hospital for Joint Diseases and New York University School of Medicine, New York, NY.

Background/Purpose: Ethnic disparities in the administration of DMARDs exist, but the impact of differing health care systems on access in ethnic minorities treated by rheumatologists, is unknown. The Veterans Affairs RA (VARA) registry and Ethnic Minority RA Consortium (EMRAC) are prospective databases but, EMRAC patients receive RA therapies primarily through private insurance/Medicare/Medicaid coverage, while VA patients have unrestricted access. We compared these cohorts to evaluate the role of medication access in RA treatment discrepancies.

Methods: Both registries collect demographic data, RA disease severity (nodules, erosions, RF, ACPA), and activity (MDHAQ, pain, patient/MD global scores, TJC, SJC, ESR, CRP, CDAI, DAS28 and RAPID3) measures. To establish comparability between registries, equivalence tests were estimated for demographic, clinical, disease activity measures. To estimate differences in prednisone, DMARD, biologic use between health care systems, Chi-square tests of independence were used. Both equivalence tests and medication use differences between ethnic groups (Caucasians vs non-Caucasians) were examined. Finally, multivariable logistic regression was used to estimate differences in biologic use between race and health care systems adjusting for age, education, disease duration, and RAPID3.

Results: 1959 VARA and EMRAC 1083 patients were analyzed. Both cohorts had equivalent age, education and RAPID3 scores, but lacked equivalency for disease duration (VARA 13.5 + 12.2, EMRAC 10.2 +10.2 years) and MD global scores (VARA 2.0 + 2.6, EMRAC 3.1 + 2.3). VARA had more males (91%, EMRAC 15%) and Caucasians (77%, EMRAC 42%). Prednisone and DMARD use were more frequent in VARA patients (38% vs 31%, $p<0.001$; 71% vs 66%, $p=0.006$, respectively). Biologic use was reported in 422 (22%) of VARA subjects (Caucasian 21%, non-Caucasian 22%), lower than in the 391 (36%) EMRAC subjects (Caucasian 45%, non-Caucasian 33%, ($P<0.001$). While there was no difference in biologic use between non-Caucasians in each cohort (non-Caucasian 28% vs Caucasian 26%, $p=0.285$), there was interaction between ethnicity and health care systems. Caucasian EMRAC subjects had a 60% increased odds of biologic use vs non-Caucasian subjects regardless of health care system (OR=1.59, P=0.007), and a 47% increased odds compared to Caucasian VARA subjects (OR=1.5, P=0.024), adjusting for age, education, disease duration and RAPID3 score. Biologic use was not different between other ethnicity and health care system comparisons. Because of the inter-dependency between gender prevalence and health care system, gender could not be modeled in the logistic regression.

Conclusion: Comparisons of two different health care administrative systems suggest non-Caucasian RA patients with unrestricted access to treatment do not achieve similar frequency of biologic use as Caucasian patients with insurance coverage, despite comparable disease activity. However, there is no difference in biologic use amongst ethnic minorities between health care systems. Reasons for these findings require further evaluation in order to accurately assess RA treatment outcomes in diverse ethnic populations.

Disclosure: G. S. Kerr, Genentech and Biogen IDEC Inc., 2, Pfizer Inc, 2, Bristol Myers Squibb, 2; **T. R. Mikuls**, Roche/Genentech and Biogen IDEC Inc., 2; **C. J. Swearingen**, None; **C. Luo**, None; **Y. Yazici**, BMS, genentech, UCB, Abbvie, 5.

ACR Concurrent Abstract Session
Imaging in Pediatric Arthritis, Spondyloarthritis, and Osteoarthritis
Monday, October 28, 2013, 2:30 PM–4:00 PM

1714

Grey-Scale and Power Doppler Findings Of Lower Extremity Entheses In Healthy Children. Clara Lin[1] and Diana Milojevic[2]. [1]University of California-San Francisco, San Francisco, CA, [2]University of California, San Francisco, San Francisco, CA.

Background/Purpose: The aim of our study is to describe the grey-scale and Power Doppler findings in lower extremity entheses in healthy children ages 5–18 years.

Methods: Healthy patients, ages 5–18 years, were recruited for the study. Demographics, weight, and BMI were collected. Grey-scale and Power Doppler ultrasound was performed on 3 entheseal sites bilaterally, the proximal patellar ligament insertion (PPL), distal patellar ligament insertion (DPL), and Achilles tendon insertion (AT). Entheseal thickness and presence and intensity of Doppler signal (DS) were recorded. Differences in entheseal thickness and DS between contra lateral sites in the each subject were evaluated. Entheseal quality (fibrillar pattern, bony changes, and tendon/ligament contour) was also evaluated.

Results: 702 entheses were examined in 117 children ages 5–18 years with a mean age of 10.44±3.66 years. There was large variability in entheseal thickness and DS in children. Age had a weak positive correlation with thickness (R^2=0.13–0.26). Weight had the strongest correlation to thickness (R^2=0.26–0.35). Using linear regression models with generalized estimating equations techniques, multivariate analysis demonstrated that entheseal thickness at all 3 sites increases by 0.02 mm for every additional kilogram of weight (n=104, 95% CI= 0.02–0.03 mm, p= <0.0001). Using the same model, multivariate analysis demonstrated that entheseal thickness of all 3 entheseal sites is 0.25 mm larger in males than females (n=87, 95% CI= 0.02–0.47, p=0.03), and entheseal thickness in Hispanics is 0.32 mm smaller compared to non-Hispanic Whites (n=87, 95% CI=−0.60-−0.03, p=0.03). Entheseal thickness in bilateral sites correlated well with each other (Pearson's correlation coefficient=0.8–0.94), but there is some degree of variability; a difference below 27.85%, 25.88%, and 17.54% between bilateral PPL, DPL, and AT thickness, respectively, falls within the 95thpercentile of the healthy pediatric population in this study. DS was seen in 14% of all entheses in 45.3% of subjects. DS was most commonly seen in the DPL (31%). Presence and intensity of DS varied between contra lateral sites of an individual; however, DS is typically seen in the same location of each enthesis. Entheseal attachment changed with age from a completely cartilaginous to completely bony attachment. The patellar ligament contour evolved with age from a curved contour to a linear contour that is parallel to the skin surface.

Conclusion: Weight is the best predictor of entheseal thickness; however there is a large degree of variability. Contra lateral entheseal sites are comparable in thickness, and a difference below 27.85%, 25.88%, and 17.54% between bilateral PPL, DPL, and AT, respectively, falls within the 95th percentile of the healthy pediatric population in this study. DS is seen in entheses of healthy children, most commonly in the DPL, and may not be symmetric in presence or intensity in bilateral sites. Entheses in children have a homogeneous fibrillar pattern of the tendon/ligament without bony changes, and the patellar ligament contour changes with age.

Disclosure: C. Lin, None; **D. Milojevic**, None.

1715

Detection Of Enthesitis In Children With Enthesitis-Related Arthritis: Dolorimeter Examination Compared To Ultrasonography. Pamela F. Weiss[1], Nancy Chauvin[2], Andrew J. Klink[3], Russell A. Localio[4], Chris Feudtner[5], Diego Jaramillo[2], Robert A. Colbert[6], David D. Sherry[3] and Ron Keren[3]. [1]The Children's Hospital of Philadelphia, Philadelphia, PA, [2]Children's Hospital of Philadelphia, PHILADELPHIA, PA, [3]Children's Hospital of Philadelphia, Philadelphia, PA, [4]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, [5]Division of General Pediatrics, Children's Hospital of Philadelphia; University of Pennsylvania Center for Clinical Epidemiology and Biostatistics, Philadelphia, PA, [6]NIAMS NIH, Bethesda, MD.

Background/Purpose: To evaluate the distribution of enthesitis and accuracy of physical examination (PE) for the detection of enthesitis in children, using ultrasound with power Doppler (USD) as the gold standard.

Methods: We performed a prospective cross-sectional study of 30 enthesitis-related arthritis (ERA) subjects and 30 controls. The following tendon insertion sites were assessed by standardized PE with a dolorimeter and USD: common extensor on lateral humerus epicondyle, common flexor on mediaal humerus epicondyle, quadriceps at superior patella, patellar ligament at inferior patella, Achilles, and plantar fascia at calcaneus. Abnormal tendon appearance was defined as loss of fibrillar pattern, regions of hypoechogenicity, or fusiform thickening. The cortical bone insertion was assessed with power Doppler in long and transverse imaging planes, and graded as: 0, absent; 1, minimal (1 spot); 2, moderate (2 spots); 3, severe (>3 spots). Since minimal power Doppler findings have been previously identified in normal children, positive findings were defined as grade 2 or above.

Results: Median age of the ERA subjects was 13 years (IQR: 11,15). Sixty percent were male and 30% were HLA-B27+. Abnormal findings were detected most commonly by USD at the insertions of the quadriceps (30%; N= 18/60 sites), common extensor (12%; N=7/60), and Achilles (10%; N=6/60) tendons, which are different than the most common sites of enthesitis in adults with spondyloarthropathy. Fifty-seven percent (N=17/30) of ERA subjects had an abnormal USD at 1 or more entheses and 33% (N=10/30) at 2 or more entheses. Abnormal USD findings were detected in control subjects at 2% (N=1/60) of common extensor tendon insertions and at none of the remaining insertion sites. The intra-and inter-rater reliability of USD (kappa) were 0.78 (95% CI: 0.63, 0.93) and 0.81 (95% CI: 0.67, 0.95), respectively. Tenderness detected by standardized dolorimeter exam had poor positive predictive value (average, range across entheses) for USD-confirmed enthesitis. Tenderness occurred most commonly at the insertions of the patellar ligament (80%; N=48/60 sites), quadriceps (78%; N= 47/60 sites), and common extensor tendons (55%; N=33/60 sites). Eighty-seven (N=26/30) percent of subjects had tenderness at 3 or more entheses and 57% (N=17/30) at 6 or more entheses. Inter-rater reliability of dolorimeter exam for detection of enthesitis was low (kappa 0.49, 95% CI: 0.33, 0.65). In comparison to controls, ERA subjects reported more pain and had lower pain thresholds at every site, including control sites (all p-values <0.001).

Conclusion: Tenderness detected by standardized dolorimeter exam overestimated USD-confirmed enthesitis in children with ERA. Compared to USD, PE for the detection of enthesitis in children has poor accuracy and reliability. The significantly decreased pain threshold of ERA subjects at all sites likely contributed to the limited accuracy of PE. Future research is warranted regarding the utility of USD for identifying enthesitis at JIA diagnosis, accurately predicting disease progression, and guiding therapeutic decisions.

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1716

Childhood-Onset Systemic Lupus Erythematosus With Clinical Neurocognitive Dysfunction Have Lower Nodal Density and Connectivity On Diffusion Tensor Imaging. Jordan T. Jones[1], Mark DiFrancesco[1], Ahmad I. Zaal[2], Marisa S. Klein-Gitelman[3], Darren Gitelman[4], Jun Ying[5] and Hermine I. Brunner[1]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Damascus University-Children's Hospital, Damascus, Syria, [3]Children's Memorial Hospital, Chicago, IL, [4]Northwestern University, Chicago, IL, [5]University of Cincinnati, Cincinnati, OH.

Background/Purpose: Neurocognitive dysfunction (NCD) is common in childhood-onset systemic lupus erythematosus (cSLE), and often difficult to detect with current resources. Diffusion tensor imaging (DTI) is a magnetic resonance imaging technique, which allows the calculation of various measures of tissue microstructural integrity, and structural connectivity via evaluation of white matter tracts. The objectives were to use DTI to investigate specific anatomic changes in the brain in cSLE patients with and without NCD in comparison to controls, and to assess the potential of these measures for use as imaging biomarkers.

Methods: Formal neuropsychological testing using the cSLE Neurocognitive Battery (Ross et al, 2010) was done to measure cognitive ability and identify NCD in cSLE. DTI was performed in cSLE patients with NCD (cSLE-NCD; n = 6), without NCD (cSLE-noNCD; n = 9) and healthy controls (n = 14). DTI was acquired on a 3 Tesla scanner at 2mm isotropic resolution for 32 gradient directions using an echo-planar imaging protocol with TR/TE = 8800/88 ms and a b-factor of 1000 s/mm^2. DTI data were processed using FSL 4.1 (http://www.fmrib.ox.ac.uk/fs/) including eddy current correction. Diffusion tensors were calculated using the Diffusion Toolkit (http://trackvis.org/blog/tag/diffusion-toolkit/), determining the principal diffusion direction per voxel throughout the white matter. This resulted in a 3D map of fiber streamlines (FS). Structural connectivity between two brain regions was defined as the number of FS with an endpoint in each of those regions. Fiber density was defined as the number of FS passing through a region regardless of endpoints. The entire brain was divided into 116 distinct regions using a standard anatomical atlas (Tzourio-Mazoyer et al, 2002). A binary matrix summarized structural network architecture by setting a connectivity threshold at > 20 FS. Group comparisons were made for density and probability of connection to each region individually and across the entire brain.

Results: A significant decrease in density was observed for the cSLE-NCD group vs. controls (p = 0.002) or cSLE-noNCD (p= 0.001). No difference in density was found between controls and cSLE-noNCD. Connectivity over the entire brain and individual regions followed a similar pattern of significant decrease for the cSLE-NCD group.

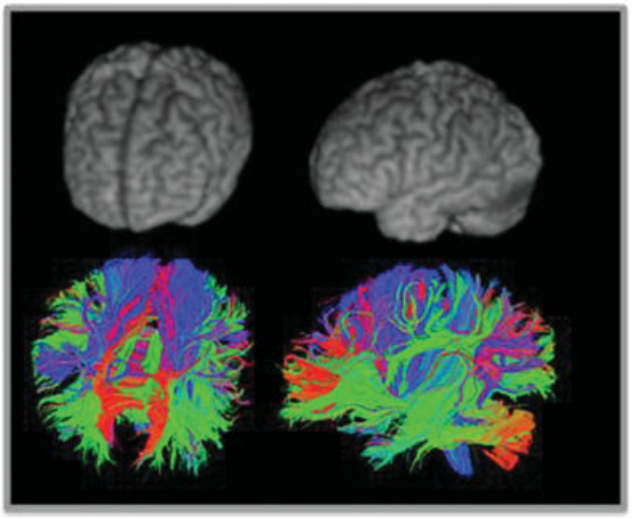

Figure 1. Tractography in single subject

Conclusion: Based on DTI, neurocognitive deficits in cSLE are associated with loss of fiber density and interregional connectivity that suggest breakdown of structural network integration. These results complement our previously reported functional and volumetric findings (DiFrancesco et al, 2013; Gitelman et al, 2013), suggesting that cSLE-NCD is associated with measurable changes in grey and white matter. If confirmed in larger cohorts, DTI abnormalities may be used as imaging biomarkers of cSLE-associated NCD.

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1717

Do Bone Marrow Edema (BME) Lesions In The Sacroiliac Joint (SIJ) Change Into Fatty Lesions Over a 3-Month Period In Patients With Axial Spondyloarthritis (axSpA)? Manouk de Hooge[1], Rosaline van den Berg[1], Victoria Navarro-Compán[1], Monique Reijnierse[1], Floris van Gaalen[1], Karen Fagerli[2], Robert Landewé[3], Maikel van Oosterhout[4], Roberta Ramonda[5], Tom Huizinga[1] and Désiréé van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Academic Medical Center, Amsterdam, Netherlands, [4]GHZ Hospital, Gouda, Netherlands, [5]University of Padova, Padova, Italy.

Background/Purpose: BME lesions may change into fatty lesions in the SIJ over time. In one study significant changes of fatty lesions in the SI joints were observed over 1 year in patients with axSpA[1]. It is unknown if similar results are found with a shorter follow-up period. Therefore we investigate whether BME lesions in the SIJ seen on MRI change into fatty lesions over a 3-month period in patients with axSpA.

Methods: Patients with back pain (≥3 months, ≤2 years, onset <45 years) from the 5 participating centres of the SPondyloArthritis Caught Early (SPACE)-cohort were included. All patients fulfilling the ASAS axSpA criteria underwent MRI-SI at baseline (MRI-SI-baseline) and after 3 months (MRI-SI-3months). MRI-SI-baseline and MRI-SI-3months were scored by 2 well-calibrated readers independently, blinded for time point, for the presence

of BME and fatty lesions on STIR and MRI T1-weighted images viewed simultaneously. BME and fatty lesions were defined present if 1 lesion was seen on ≥2 consecutive slices or if >1 lesion were seen on a single slice. The scores of baseline and 3 months were compared on quadrant level (Q) and the sum of all quadrants (8 total) was calculated to obtain patient scores. Scores of the readers are reported separately.

Results: Only axSpA patients with MRI-SI-baseline and MRI-SI-3months were included for this analysis (n=83, number of Q=664). In 62/83 patients (74.7%) reader 1 indicated the presence of BME or fatty lesions at any time point, reader 2 indicated this in 60/83 patients (72.3%). Readers agreed in 73/83 patients (88%) on the presence of lesions at any time point. Reader 1 indicated no lesions at baseline or follow-up in 410/664 Qs (61.7%) and in 131/664 Qs (19.7%) the type of lesions did not change over time. In 123/664 Qs (18.5%) lesions occurred, disappeared or changed from one type to another. In total, there were 34/664 Qs (5.1%) in which fatty lesions occurred, and 29/664 Qs (4.4%) in which fatty lesions disappeared. In only 3/664 Qs (0.5%) BME lesions on MRI-SI-baseline turned into FAT lesions on MRI-SI-3months. In the same amount of Qs the opposite thing is happening; FAT lesions change into BME lesions over time. The results of both readers show similar trends (see table).

		3 months		
	No lesions	**BME**	**FAT**	**BME & FAT**
Reader 1				
Baseline				
No lesions	410	17	22	1
BME	28	58	3	8
FAT	15	3	52	11
BME & FAT	7	4	4	21
		3months		
Reader 2				
Baseline				
No lesions	395	19	11	0
BME	32	79	4	6
FAT	4	5	56	9
BME & FAT	3	2	14	25

Conclusion: We find a lot of volatility of BME and fatty lesions over 3 months time. It is common for both lesions to occur without a previous lesion or disappear completely without leaving a mark, but it is uncommon to see BME lesions turn into fatty lesions over a period of 3 months. This observation casts serious doubts on the value of fatty lesions as a surrogate for previous inflammation.

Reference:
1 Song ARD 2011;70:1257–63

Disclosure: M. de Hooge, None; **R. van den Berg**, None; **V. Navarro-Compán**, None; **M. Reijnierse**, None; **F. van Gaalen**, None; **K. Fagerli**, None; **R. Landewé**, None; **M. van Oosterhout**, None; **R. Ramonda**, None; **T. Huizinga**, None; **D. van der Heijde**, None.

1718

Reading Of The Sacroiliac Joints On Plain Radiographs: Agreement Between Clinical Practice and Trained Central Reading Of The DESIR-Cohort. Rosaline van den Berg[1], Grégory Lenczner[2], Antoine Feydy[3], Désirée van der Heijde[1], Monique Reijnierse[1], Alain Saraux[4] and Pascal Claudepierre[2]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Henri Mondor Teaching Hospital, AP-HP, Créteil, France, [3]Paris Descartes University, Côchin Hospital, APHP, Paris, France, [4]Université Brest Occidentale, Brest, France.

Background/Purpose: In daily practice, radiologists/rheumatologist judge sacroiliac (SI) joints on X-rays (X-SI). However, reliable identification of radiographic sacroiliitis is difficult. Consequently, large inter- and intra-observer variations have been reported, even after specific training[1]. In cohorts and clinical trials the reading is usually done by ≥1 trained readers. However, in the DEvenir des Spondylarthropathies Indifferenciées Récentes (DESIR)-cohort, X-SIs at inclusion were first read by the local radiologist/rheumatologist, then by centralized read. We compared the local (by multiple readers in various centers) to centralized read (by a few trained readers) on sacroiliitis yes/no.

Methods: Patients (pts) aged 18–50 with inflammatory back pain (IBP; ≥3 months, ≤3 years) from 25 participating centers were included in the DESIR-cohort (n=708). Available baseline X-SIs were read by local radiologists/rheumatologists with access to clinical data, according to a method derived from the modified New York (mNY) criteria[2]. Grade 2 and 3 from the mNY were pooled together in 1 combined grade 'DESIR-2'. Local sacroiliitis was defined by at least unilateral grade ≥DESIR-2. Next, 2 well-calibrated centralized readers independently read all X-SIs according to the original mNY, blinded for clinical data. In case of disagreement, an experienced radiologist was adjudicator. An X-SI was marked positive if 2/3 readers agreed on bilateral ≥2 or unilateral ≥3. Agreement between the 2 centralized readers, and between the local and centralized read was calculated (Kappa; % agreement).

Results: Pts with complete X-SI data (n=689) were included in this analysis. Inter reader agreement between the 2 centralized readers is moderate (Kappa 0.54), while percentage agreement (84.3%) is good (table). The low Kappa can partially be explained by the high numbers of normal X-SIs. However, the adjudicator needed to read 108/689 X-SIs (15.7%) because of disagreement among the 2 centralized readers. Comparison between the centralized and the local read shows similar levels of agreement (table). Overall, more X-SIs are read positive by local readers (n=184) than by centralized readers (n=145). In 77 pts, X-SI was read positive by local readers but negative by centralized read; in 38 pts it was the other way around.

	Reader 2	
	modified New York +	**modified New York −**
Reader 1		
modified New York +	96	58
modified New York −	50	485
Kappa (95% CI)/ Agreement (%)	0.54 (0.46–0.62)	84.3
	Centralized score (2/3)	
	modified New York +	**modified New York −**
Local score		
DESIR mNY +	107	77
DESIR mNY −	38	468
Kappa (95% CI)/ Agreement (%)	0.54 (0.47–0.62)	83.3

Conclusion: Agreement between the centralized and local read, but also the inter reader agreement between the 2 centralized readers, is moderate, thereby showing that early detection of sacroiliitis on X-SIs is a challenge. In patients with recent onset IBP, trained readers do not perform better than local rheumatologists/radiologists in recognizing sacroiliitis on X-SI, suggesting that the role of X-SI as diagnostic criterion for axSpA should be re-evaluated.

Reference:
1 van Tubergen ARD 2003;62:519–25 [2]van der Linden A&R 1984;27:361–8

Disclosure: R. van den Berg, None; **G. Lenczner**, None; **A. Feydy**, None; **D. van der Heijde**, None; **M. Reijnierse**, None; **A. Saraux**, None; **P. Claudepierre**, None.

1719

High Reliability Was Found for Ultrasound Scoring of Osteophytes in Patients With Hand Osteoarthritis Using An Atlas As Reference; An Omeract Initiative. Hilde B. Hammer[1], Alexander Mathiessen[1], Annamaria Iagnocco[2], Emilio Filippucci[3], Frédérique Gandjbakhch[4], Marion C. Kortekaas[5], Ingrid Möller[6], Esperanza Naredo[7], Richard J. Wakefield[8], Philippe Aegerter[9] and Maria-Antonietta D'Agostino[10]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]University La Sapienza, Rome, Italy, [3]Università Politecnica delle Marche, Ancona, Italy, [4]APHP, Pitié Salpétrière Hospital, Universite Paris 6, Paris, France, [5]Leiden University Medical Center, Leiden, Netherlands, [6]Instituto Poal de Reumatologia, Barcelona, Spain, [7]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [8]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals, Leeds, United Kingdom, [9]Versailles-Saint Quentin en Yvelines University- APHP, Ambroise-Paré Hospital, Boulogne-Billancourt, France, [10]Ambroise Paré Hospital, and Versailles Saint Quentin en Yvelines University, Boulogne-Billancourt, France.

Background/Purpose: Ultrasound (US) is a sensitive method for detecting osteophytes (OP) in hand osteoarthritis (HOA). To improve the reliability of scoring OP, an US atlas has recently been published including representative OP images of finger joints scored semi-quantitatively 0 to 3 [1].

As an OMERACT exercise we wanted to explore the reliability of OP scoring of finger joints in dynamic examinations of HOA patients with use of an US atlas as reference.

Methods: One sonographer with limited experience (AM) and one experienced sonographer (HBH) had developed an US atlas of OP in HOA

[1]. Together with 8 experienced sonographers a dynamic reliability exercise was performed on scoring of OP in finger joints in patients with HOA. To gain consensus on the scoring method, a reliability test on static images was performed previous to the study, including images of each of the 15 joints to be examined (CMC1, MCP 1–5, PIP 1–5 and DIP 2–5). The images were scored individually by all the sonographers twice (several weeks apart and in a new order the second time) using the US atlas as reference, and the results collected by e-mail showed high reliability (kappa values >0.9). During the dynamic reliability exercise in patients, 5 high-end US machines (GE logic E9) were used and a paper version of the US atlas was available for the sonographers. In 10 HOA patients (5 patients examined each day for two days, all women, median (range) age 74.5 (53–77) years, all fulfilling the ACR criteria) 30 joints were examined twice with at least 3hrs interval. The intra-and inter-examiner reliability was explored by use of kappa statistics (Cohen and Light's). The prevalence of observed lesions and the percentage of exact agreement (PEA) on a 4 levels (0–3) scale and the percentage of close agreement (PCA, ' 1 score difference) were also calculated.

Results: Good to excellent intra-examiner reliability was found for all sonographers with median (range) weighed kappa values 0.80 (0.68–0.89). The prevalence of OP scores was quite evenly distributed (mean values score 0 =20%, score 1= 26%, score 2= 21% and score 3=33%). The inter-examiner reliability was also good, with mean weighted kappa 0.66 (95%CI 0.63–0.68) the first day and 0.67 (95%CI 0.65–0.70) the second day. There was high agreement between first and second OP scoring (table; PEA=Percentage exact agreement, PCA=Percentage close agreement).

	Rater 1	Rater 2	Rater 3	Rater 4	Rater 5	Rater 6	Rater 7	Rater 8	Rater 9	Rater 10
PEA	86	85	85	78	78	77	75	75	75	66
PCA	99	100	99	99	99	98	100	98	98	97

Conclusion: The present study shows that using a reference US atlas resulted in very good intra-and inter- observer reliability for dynamic scoring of OP images in patients with finger joint OA. This suggests that US could be developed as a future tool for trials on HOA patients.

Reference

1. Mathiessen A et al. Ultrasonographic assessment of osteophytes in 127 patients with hand osteoarthritis: exploring reliability and associations with MRI, radiographs and clinical joint findings. Ann Rheum Dis 2013;72:51–56.

Disclosure: H. B. Hammer, None; **A. Mathiessen**, None; **A. Iagnocco**, None; **E. Filippucci**, None; **F. Gandjbakhch**, None; **M. C. Kortekaas**, None; **I. Möller**, None; **E. Naredo**, None; **R. J. Wakefield**, None; **P. Aegerter**, None; **M. A. D'Agostino**, None.

ACR Concurrent Abstract Session
Metabolic and Crystal Arthropathies II
Monday, October 28, 2013, 2:30 PM–4:00 PM

1720

Risk Of Cardiovascular Disease and Use Of Xanthine Oxidase Inhibitors For Gout. Seoyoung C. Kim, Sebastian Schneeweiss, Niteesh Choudhry, Jun Liu, Robert J. Glynn and Daniel H. Solomon. Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Hyperuricemia and gout are associated with an increased risk of hypertension and cardiovascular disease (CVD) such as myocardial infarction (MI) and stroke. Xanthine oxidase inhibitors (XOI), allopurinol and febuxostat, are the main therapy to treat gout patients with hyperuricemia. Little is known whether treating hyperuricemia with a XOI has any effect on CVD risks. We examined the risk of CVD in gout patients initiating a XOI drug compared to untreated hyperuricemic patients.

Methods: We conducted a population-based cohort study combining two U.S. commercial insurance claims databases (2003–2012). Among adult patients with a diagnosis of gout, initiators of XOIs were identified. Serum uric acid levels at baseline were available in 15% of XOI initiators. Patients with hyperuricemia defined as the serum uric acid level ≥6.8 mg/dl were identified as a reference. For both groups, patients were required to have no use of XOIs in the 180-day baseline period. Patients with a history of malignancy were excluded. For primary 'as treated' analysis, patients were followed from the index date, the first receipt of XOI or the first high uric acid level measured after the 180-day baseline period, up to 180 days. Secondary 'as treated' analyses included the entire follow-up time from the index date. We calculated incidence rates (IR) of CVD including MI, coronary revascularization, stroke, and heart failure, based on inpatient and/or outpatient diagnosis and procedure codes. To control for baseline demographic factors, comorbidities, medications, and health care utilization, a propensity score (PS) matching with a 1:1 ratio was used. Cox proportional hazards models stratified by the PS matched pair compared the risk of CVD in XOI initiators vs. the hyperuricemic group.

Results: There were a total of 43,269 PS-matched pairs. Baseline comorbidities, medication use, and health care utilization were well-balanced between the groups. Mean age was 52.5 years and 86% male for both groups. Common comorbidities include hypertension (56%), hyperlipidemia (50%), diabetes (19%), CVD (9%), obesity (7%) and chronic kidney disease (7%). Use of systemic steroids at baseline was common (20%). The mean (SD) serum uric acid level was 8.6 (1.7) mg/dl in XOI initiators and 8.1 (3.0) mg/dl in the hyperuricemia group. The IR per 1,000 person-years was 8.03 (95% CI 6.63–9.72) for MI and 57.69 (95% CI 53.70–61.98) for composite CVD in XOI initiators, 1.13 times higher compared with the hyperuricemia group (**Table**). In secondary analyses not limited to the first 180 days of follow-up, CVD risks in XOI initiators were increased similarly to the main results (**Table**).

Table. Risk of cardiovascular diseases (CVD) associated with initiation of xanthine oxidase inhibitors: PS-matched 'as treated' analysis

	Xanthine oxidase inhibitor group (n=43,269)					Hyperuricemia group (n=43,269)				
	Follow-up limited up to 180 days				Any follow-up time	Follow-up limited up to 180 days				Any follow-up time
Outcomes	Cases	PY	IR* (95% CI)	HR (95% CI)	HR (95% CI)	Cases	PY	IR* (95% CI)	HR (95% CI)	HR (95% CI)
Myocardial infarction	105	13079.3	8.03 (6.63–9.72)	1.04 (0.76–1.43)	1.06 (0.80–1.40)	114	16712.8	6.82 (5.68–8.19)	Ref	Ref
Coronary revascularization	197	13060.2	15.08 (13.11–17.34)	0.91 (0.74–1.13)	1.04 (0.86–1.25)	235	16678.2	14.09 (12.40–16.01)	Ref	Ref
Stroke	140	13077.0	10.71 (9.08–12.64)	1.01 (0.77–1.32)	0.93 (0.73–1.17)	160	16700.0	9.58 (8.20–11.19)	Ref	Ref
Heart failure	468	13013.0	35.96 (32.85–39.37)	**1.23 (1.06–1.43)**	**1.26 (1.10–1.45)**	419	16640.9	25.18 (22.88–27.71)	Ref	Ref
Composite CVD	748	12965.7	57.69 (53.70–61.98)	**1.13 (1.00–1.27)**	**1.14 (1.03–1.27)**	733	16564.9	44.25 (41.16–47.57)	Ref	Ref

*1,000 Person-Years (PY), IR: incidence rate, HR: hazard ratio, CI, confidence interval.

Conclusion: Our study found an increased risk of CVD in gout patients initiating a XOI drug compared to patients with untreated hyperuricemia. Further research is needed on the long-term effect of XOI on CVD.

Disclosure: S. C. Kim, Pfizer Inc, 2, Pfizer and Asisa, 9; **S. Schneeweiss**, Pfizer Inc, 2, Boehringer Ingelheim, 2, Novartis Pharmaceutical Corporation, 2, WHISCON, LLC, 5, Booz and Company, 5; **N. Choudhry**, None; **J. Liu**, None; **R. J. Glynn**, AstraZeneca, 2, Novartis Pharmaceutical Corporation, 2; **D. H. Solomon**, Amgen, 2, Lilly, 2, Pfizer Inc, 9, Novartis Pharmaceutical Corporation, 9, Bristol-Myers Squibb, 9, Lilly, 9.

1721

A Prediction Tool for Incident Gout Among Those With Hyperuricemia. Liseth Siemons[1] and Eswar Krishnan[2]. [1]University of Twente, Enschede, Netherlands, [2]Stanford University, Palo Alto, CA.

Background/Purpose: The most common form of inflammatory arthritis observed in men is gout, a condition characterized by hyperuricemia and deposition of uric acid crystals in joints and surrounding tissues. It leads to unpredictable, severe attacks of acute joint inflammation, extreme pain, swelling, disability, and diminished physical and mental wellbeing. Gout affects millions of people and its prevalence is increasing. Hyperuricemia is considered a necessary, but insufficient, precursor of gout. Hence, additional risk factors have been identified, but collecting information on them all is too time-consuming. Therefore, this study aimed to develop an easy-to-use prediction tool for identifying patients with asymptomatic hyperuricemia at high risk for developing gout.

Methods: The tool was developed using data of 8,951 patients with uric acid levels >6 mg/dl from the Multiple Risk Factor Intervention Trial (MRFIT). The risk model was built using backward stepwise Cox regression analysis including 7 candidate variables and was externally validated in a nationally representative cross sectional sample from the US National Health and Nutrition Examination Survey (NHANES). Risk factors with a p-value <0.05 were retained and model accuracy was evaluated with receiver operating characteristic curve analyses by examining area under the curve (AUC) values. A simplified prediction tool was made for clinical convenience and to stratify patients into risk groups to discriminate between people at low, moderate and high risk of gout. Hazard and odds ratios were calculated for each risk stratum and logistic regression analyses were performed to determine the agreement between predicted and observed probabilities of having gout.

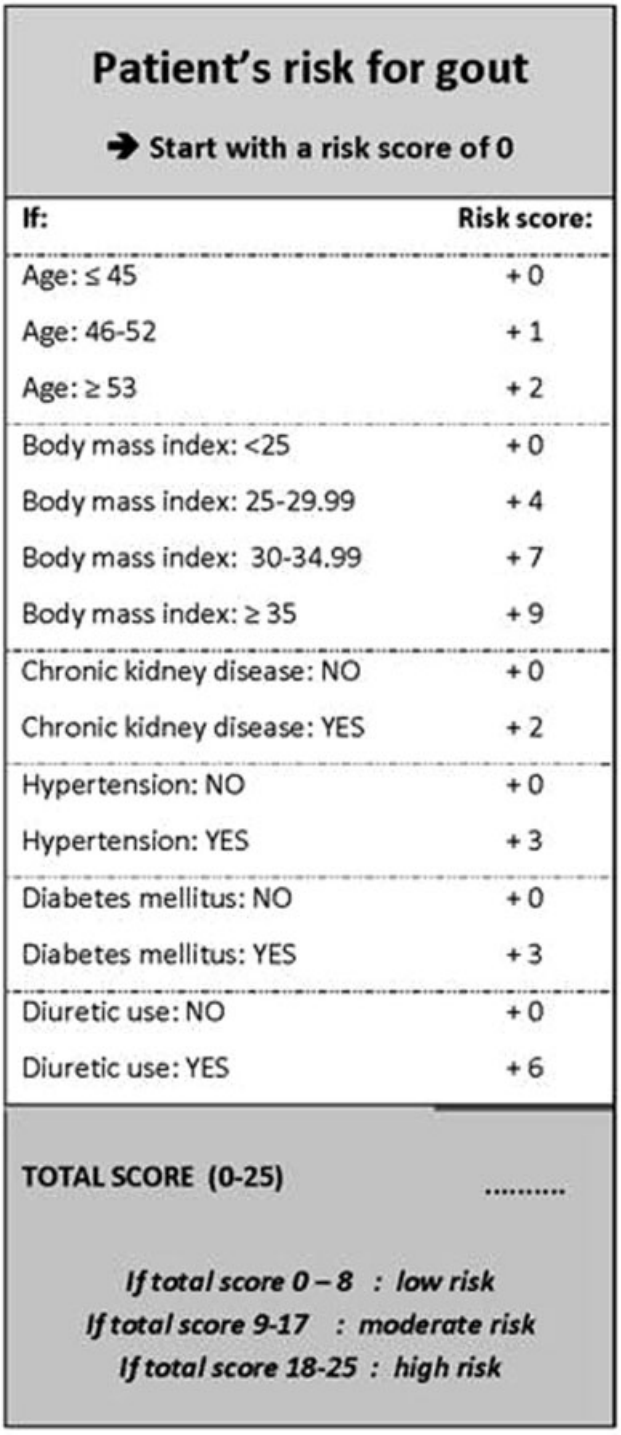

Figure 1. Scoring chart for determining a patient's risk for developing gout.

Results: 1,705 patients (19%) developed gout during the study. Gout patients reported more health complaints than non-gout patients, showing higher prevalence rates of chronic kidney disease, hypertension, and metabolic syndrome. They were also older and more likely to be obese, to smoke, and to use diuretics. Age, body mass index, chronic kidney disease, hypertension, diabetes, and diuretic use were all significant predictors for developing gout and were included in the final model (AUC value: 0.6420) which was externally validated on the NHANES data (AUC value: 0.7139). The resulting simplified prediction tool (Figure 1) discriminated well between patients from different risk strata. Hazard and odds ratios of the distinct strata showed increasing risks or odds on gout when moving from the lowest to the highest risk group and the agreement between observed and predicted probabilities of having gout was generally high.

Conclusion: The prediction tool is relevant for clinical practice since it helps physicians identifying asymptomatic hyperuricemia patients at high risk for developing gout.

Disclosure: L. Siemons, None; **E. Krishnan**, takeda, 2, takeda, 5.

1722

Does Starting Allopurinol Prolong Acute Treated Gout? Erica Hill[1], Jay B. Higgs[1], Karen Sky[2], Michelle Sit[3] and Angelique N. Collamer[4]. [1]San Antonio Military Medical Center, Fort Sam Houston, TX, [2]US Department of Veterans Affairs, Alaska VA Healthcare System, Anchorage, AK, [3]David Grant Medical Center, Travis AFB, CA, [4]Langley AFB Hospital, Langley AFB, VA.

Background/Purpose: Gout is a common cause of morbidity in the US population. Traditionally, allopurinol is not initiated during an acute episode to avoid prolonging the painful gouty attack. The 2012 ACR guidelines for management of gout suggested that urate-lowering therapy could be started during an acute gout attack, provided that effective acute management was instituted. These recommendations were based on "consensus opinion of experts, case studies, or standard of care." We conducted a 28-day, placebo-controlled, double-blind study of allopurinol initiation in patients receiving treatment for acute gout.

Methods: Pre-study power analysis suggested 32 subjects to detect a two-day difference in days to resolution (DTR) of acute gout with a power level of 0.8. Exclusion criteria included GFR $<$ 50cc/min, AST/ALT or alkaline phosphatase $>$ 1.25 times normal. The treating physician determined therapy for the acute gout attack. Standard prophylaxis, with colchicine or NSAIDs, was prescribed. Patients were assessed at five visits over 28 days. The primary endpoint was DTR of acute gout, using separate Likert scales for patient rated involved joint pain and physician exam. Secondary measures included MHAQ, physician global assessment, side effects of therapy, per protocol (completer) analysis, serum uric acid, CBC, and CMP at two and four weeks. The intent to treat analysis included any patient who took at least one pill; we assigned 28 days DTR to allopurinol dropouts and actual DTR or last study day to placebo.

Results: Thirty-six patients were randomized to 19 placebo and 17 allopurinol. One allopurinol patient dropped out before taking one pill, and was excluded from analysis. Three placebo and two allopurinol patients dropped out before day 28. The intent to treat analysis showed a statistically insignificant 4.5 days longer DTR in the allopurinol group that was reduced to two days in the per protocol analysis. Both groups had similar patient rated Likert pain scores at enrollment and at day 28. The acute gout attack resolved in all patients by the end of the study.

	Treatment Group		
	Placebo	**Allopurinol**	**P-value[1]**
ITT[2]: Days to Resolution			0.13
N	19	16	
Mean (SD)	12.53 (7.73)	17 (8.53)	
SEM	1.77	2.13	
Median [IQR]	14 [4, 20]	17.5 [13, 23]	
Min, Max	3, 24	3, 28	
PP[3]: Days to Resolution			0.5
N	16	14	
Mean (SD)	13.44 (7.78)	15.43 (7.92)	
SEM	1.95	2.12	
Median [IQR[4]]	14 [7, 21]	15 [12, 22]	
Min, Max	3, 24	3, 28	

[1] Wilcoxon test
[2] ITT [N=35]: Intent-to-treat group. Analysis of all patients as randomized at beginning of study.
[3] PP [N=30]: Per-protocol group. Analysis of patients that followed protocol.
[4] IQR: InterQuartile Range

Conclusion: There is no difference in DTR or Likert pain scales between allopurinol and placebo groups treated for acute gout. This supports the new ACR guidelines expert consensus that allopurinol may be initiated in acute gout, providing the acute attack is appropriately managed.

Disclosure: E. Hill, None; **J. B. Higgs**, None; **K. Sky**, None; **M. Sit**, None; **A. N. Collamer**, None.

1723

Lesinurad, An Inhibitor Of The Uric Acid Transporter URAT1 and a Potential Therapy For Gout, Requires URAT1 Phenylalanine 365 For High Affinity Inhibition. Philip K. Tan[1], David Hyndman[2] and Jeffrey N. Miner[2]. [1]Ardea Biosciences, San Diego, CA, [2]Ardea Biosciences, Inc., San Diego, CA.

Background/Purpose: Gout is caused by a lack of efficient excretion of uric acid, resulting in hyperuricemia and the formation of crystal deposits of uric acid. The renal uric acid transporter URAT1 is important for regulating serum uric acid levels, and URAT1 inhibitors reduce serum uric acid levels and are used as gout therapies. Here, we define a molecular interaction of a novel URAT1 inhibitor lesinurad, under clinical evaluation in patients with gout.

Methods: HEK-293T cells transiently expressing chimeric URAT1 mutants were used to measure cell-based uric acid transport activity in the presence of lesinurad and other URAT1 inhibitors. A binding assay was also developed using membrane preparations from transfected cells and radiolabeled RDEA3170, a high-affinity URAT1 inhibitor also in development for gout. Binding was measured after incubation with lesinurad and other URAT1 inhibitors.

Results: Lesinurad inhibits the uric acid transport activity of human URAT1 (hURAT1) at a 20-fold higher potency compared to rat URAT1 (rURAT1), with IC_{50}'s of 3.36 and 74.84 μM, respectively. Chimeras containing portions of the rat and human genes identified a single residue, hURAT1 phenylalanine 365, located within transmembrane segment 7, as crucial for the higher affinity interaction with lesinurad. This residue is a tyrosine in rURAT1. In particular, the single chimeric point mutant hURAT1-Tyr365 shows a significantly reduced sensitivity for inhibition by lesinurad (IC_{50} = 47.76 μM) compared to wild type hURAT1, while the converse point mutant rURAT1-Phe365 displays a significantly enhanced sensitivity (IC_{50} = 6.82 μM) compared to wild type rURAT1. Phe365 is also important for the interaction with hURAT1 to other commercially available inhibitors benzbromarone, probenecid, and sulfinpyrazone. Lesinurad, the other URAT1 inhibitors, as well as salicylate and nicotinate which are known URAT1 inhibitors at high concentrations all bind competitively at the inhibitor binding site. Among URAT1 orthologs, Phe365 occurs only in human, apes, and certain monkeys, whereas a tyrosine residue occurs in all other animals. Consistent with in vitro inhibition of URAT1, lesinurad treatment results in an increased fractional excretion of uric acid and a decrease in serum uric acid.

Conclusion: Lesinurad inhibits hURAT1 through an interaction that involves a critical residue, Phe365. The gain-of-function phenotype of rURAT1-Phe365 suggests that Phe365 directly binds to lesinurad. Phe365 is also important for the interaction with other URAT1 inhibitors, and this residue likely forms part of an inhibitor binding site within the transporter channel of URAT1.

Disclosure: P. K. Tan, Yes, Full-time Ardea Biosciences, 3; **D. Hyndman**, Ardea Biosciences, 3; **J. N. Miner**, Ardea Biosciences, 3.

1724

The Role Of Low-Grade Inflammation In The Association Between Uric Acid and Atherosclerosis: The Codam Study. José M.A. Wijnands[1], Annelies Boonen[2], Pieter C. Dagnelie[1], Marleen M.J. van Greevenbroek[1], Carla J.H. van der Kallen[1], Isabel Ferreira[1], Casper G. Schalkwijk[1], Edith J.M. Feskens[3], Sjef van der Linden[2], Coen D.A. Stehouwer[2] and Ilja C.W. Arts[1]. [1]Maastricht University, Maastricht, Netherlands, [2]Maastricht University Medical Center, Maastricht, Netherlands, [3]Wageningen University, Wageningen, Netherlands.

Background/Purpose: Uric acid may be involved in the atherosclerotic process by increasing the level of low-grade inflammation. The aims of this study were: 1) to investigate if uric acid was associated with ankle-brachial index (AAIx), carotid intima media thickness (c-IMT), and prevalent cardiovascular disease (CVD); 2) the extent to which any such association(s) could be explained by low-grade inflammation; and 3) whether these associations were different in subjects with normal (NGM) compared to disturbed (DGM) glucose metabolism. A difference between these subgroups may exist because of the influence of insulin and glucose on uric acid excretion.

Methods: We studied 530 subjects (60.6% men; mean age 58.9 $\pm$ 6.9 yrs; 52.6% NGM) with an increased risk of CVD from the Cohort on Diabetes and Atherosclerosis Maastricht (CODAM) Study. Cross-sectional associations between uric acid and CVD, AAIx and c-IMT, and the mediating role of low-grade inflammation therein, were analyzed with logistic and linear regression analyses in the total population and stratified according to glucose metabolism status. Inflammation markers (hs-CRP, TNF-α, IL-6, IL-8, SAA, sICAM-1, haptoglobin, ceruloplasmin) were standardized and combined into an average inflammation score.

Results: After adjustment for potential confounders (gender, age, BMI, waist, alcohol, smoking, physical activity, hypertension, total:HDL cholesterol, triglycerides, fasting glucose and insulin, eGFR, diuretics) plasma uric acid concentration, expressed per SD (81.3 μmol/L), was positively associated with CVD in subjects with NGM (OR=1.66, 95%CI 1.06–2.58), but not with DGM (OR=0.82, 0.56–1.22; p for interaction=0.065). Uric acid was positively associated with c-IMT in the total population (β=0.027, 95%CI 0.010–0.045) and in subjects with NGM (β=0.030, 95%CI 0.007–0.054). Although the beta coefficient was similar, uric acid was not significantly associated with c-IMT in subjects with DGM (β=0.023, 95%CI −0.004–0.050; p for interaction=0.164). There was no association between uric acid and AAIx in any of the groups. Uric acid was positively associated with low-grade inflammation in the total population (β=0.073, 95%CI 0.012–0.133) and in DGM (β=0.115, 95%CI 0.026–0.203), but not in NGM (β=0.042, 95%CI −0.044–0.128, p for interaction=0.975). The significant associations between uric acid and CVD or c-IMT were not attenuated when adding low-grade inflammation to the models.

Conclusion: We found evidence of modest associations between uric acid and CVD and c-IMT, but these were not explained by low-grade inflammation. The data suggest the effect of uric acid may be different in subjects with NGM and DGM.

Disclosure: J. M. A. Wijnands, None; **A. Boonen**, None; **P. C. Dagnelie**, None; **M. M. J. van Greevenbroek**, None; **C. J. H. van der Kallen**, None; **I. Ferreira**, None; **C. G. Schalkwijk**, None; **E. J. M. Feskens**, None; **S. van der Linden**, None; **C. D. A. Stehouwer**, None; **I. C. W. Arts**, None.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Animal Models I
Monday, October 28, 2013, 2:30 PM–4:00 PM

1725 WITHDRAWN

1726

Survivin Inhibition Disturbs Bcl-6 and Blimp-1 Control Of Lymphocyte Maturation and Alleviates Antigen-Induced Arthritis. Mattias Svensson[1], Karin Andersson[1], Malin Erlandsson[2], Ing-Marie Jonsson[2] and Maria Bokarewa[1]. [1]University of Gothenburg, Gothenburg, Sweden, [2]Göteborgs University, Göteborg, Sweden.

Background/Purpose: Survivin is a proto-oncogene known to regulate cell division and apoptosis. In patients with rheumatoid arthritis, survivin has emerged as an independent predictor of severe disease recognised by the progressive joint damage and resistance to anti-rheumatic treatment.

Objectives: In the present study we assessed if inhibition of survivin is sufficient to reduce arthritis and joint damage in experimental autoimmune models of rheumatoid arthritis.

Methods: Survivin production was inhibited by a lentiviral construct, which coded for shRNA (shSurv) suppressing survivin gene. shSurv was provided as a single injection (106-107 particles/mouse) on the day of first immunization or on the day of clinical onset of arthritis. Five independent experiments were performed. Each experiment contained the control group received non-targeting transduction particles.

Results: Intra-articular and intra-peritoneal delivery of shSurv resulted in a pronounced inhibition of survivin in spleen and in bone marrow. Inhibition of survivin, early at immunization and later at clinical signs of arthritis, significantly alleviated clinical and histological signs of arthritis and production of antigen-specific antibodies. Also, it reduced cartilage- and bone destruction in the inflamed joints in microCT. Survivin inhibition was inversely correlated to an increase of transcription repressors Bcl-6 and Blimp-1. In consistence with overexpression of Blimp-1, shSurv mice had low levels of IL-2, suppressed proliferation response and increased populations of the effector CD4+ and CD8+ cells, followed by high IL-6 and IL10 production. shSurv mice had increased populations of Tregs (CD4+Foxp3+) and Th2 cells supported by high mRNA of Foxp3 and GATA3, and high release of IL-10 and IL-4. Inhibition of survivin was associated with a sequential impairment of Bcl-6 functions and small follicular T and B cell populations, and poor affinity maturation of antigen-specific antibodies.

Conclusion: We show that survivin is the essential regulator of molecular and cellular events in the pathogenesis of arthritis. It enhances synovial proliferation and aggressive growth and participates in the mounting of antigen-dependent T and B cell responses. Importantly, survivin regulates the Bcl-6 dependent events attracting attention to the important role of this duo in the pathogenesis of rheumatoid arthritis.

Disclosure: M. Svensson, None; **K. Andersson**, None; **M. Erlandsson**, None; **I. M. Jonsson**, None; **M. Bokarewa**, None.

1727

Novel Selective Inhibitors Of Nuclear Export Attenuate Inflammation and Prevent Bone Mineral Density Loss In Multiple Preclinical Models Of Rheumatoid Arthritis. Mwanasha Hamuza[1], Yosef Landesman[1], Boris Klebanov[1], Michael Kauffman[1], Sharon Shacham[1], Judith Endres[2], David A. Fox[2] and Dilara McCauley[1]. [1]Karyopharm Therapeutics Inc., Natick, MA, [2]University of Michigan Medical Center, Ann Arbor, MI.

Background/Purpose: Exportin 1 (XPO1; also called chromosome region maintenance 1, CRM1) is a key protein that controls the export of ~220 cargo proteins and several mRNAs out of nucleus. Novel Selective Inhibitors of Nuclear Export (SINE) are oral XPO1 inhibitors that activate multiple tumor suppressor proteins and are currently in clinical development for a variety of cancers. SINE also force the nuclear retention of various cargos that play key roles in inflammation including the proteins IkB, COMMD1, FOXO, PPARγ, NRF2, RXRγ, as well as COX2 mRNA. Here, we report the *in vitro* effects of SINE on RA cells and their oral activity *in vivo* in the Collagen Induced Arthritis (CIA) and Collagen Antibody Induced Arthritis (CAIA) RA models.

Methods: The effects of SINE on fibroblast-like synoviocytes (FLS) were tested *in vitro* by 1. Time-lapse imaging to quantify the anti-proliferative effects of SINE on RA FLS cell lines. 2. Quantifying anti-proliferative effects of SINE on activation of T-cells by bacterial superantigen presented by FLS. 3. Measuring SINE inhibition of cytokine secretion by FLS stimulated by cytokine-activated T-cells. Cytokines in culture supernatants were analyzed by Luminex assay. In the CAIA model, study animals were treated with vehicle, dexamethasone or various oral doses of the SINE KPT-355 on days 4, 6, 8 and 10. In the CIA model, study animals received vehicle, dexamethasone, or KPT-355 from day 11 to day 28 on QoD or QD regimens. A standard clinical scoring system was used to quantify the clinical symptoms of arthritis in both models. In the CIA model, the levels of cytokines and pro-inflammatory markers were measured in the synovial fluid using a Luminex assay and ELISA. Bone erosion within the paws was quantified with 3D micro-tomodensitometry. Histopathology was conducted on the hind paws of rats using H&E staining.

Results: SINE inhibited RA FLS proliferation (IC_{50} ~10nM) as well as T cell responses to bacterial superantigen presented by FLS that had been pretreated with IFN-γ. SINE showed minimal cytotoxicity to these cells. SINE blocked the secretion of IL-6, IL-8 and other cytokines by FLS in a dose dependent manner (IC_{50}~100nM). In both CIA and CAIA models, KPT-355 SINE treated animals had significantly lower disease scores compared to the vehicle treated animals. In the CIA model, peak clinical scores were 1.4±0.542 with KPT-355 compared to 8.5±0.707 with the vehicle. In the CAIA model peak clinical scores were 0.56 ± 0.29 with KPT-355 compared to 7.44 ± 0.85 with vehicle. Histological analyses of SINE treated animals showed significant reduction in the degeneration of articular cartilage and inflammation in the joint spaces. KPT-355 also significantly reduced the levels of IL-1β *(p=0.0262)*, IL-6 *(p=0.0253)*, MCP-1 *(p=0.0008)* and CRP *(p=0.0003)* in the synovial fluid. Micro-CT data showed that SINE significantly prevented bone mineral density loss.

Conclusion: These studies demonstrate that SINE display potent anti-inflammatory activity, joint sparing activity, and protection from bone mineral density loss in established models of rheumatoid arthritis, justifying further development of SINE for RA.

Disclosure: M. Hamuza, Karyopharm Therapeutics Inc., 1; **Y. Landesman**, Karyopharm Therapeutics Inc., 1; **B. Klebanov**, Karyopharm Therapeutics Inc., 1; **M. Kauffman**, Karyopharm Therapeutics Inc., 1; **S. Shacham**, Karyopharm Therapeutics Inc., 1; **J. Endres**, None; **D. A. Fox**, Karyopharm, 2; **D. McCauley**, Karyopharm Therapeutics Inc., 1.

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Amelioration Of Collagen-Induced Arthritis By Modulation Of Inhibitory Apoptosis Stimulating Protein Of p53 To Activate Transcription Factor p73. Chrong-Reen Wang, Shih-Yao Chen, Ai-Li Shiau, Yuan-Tsung Li, Chia-Tse Weng, I-Ming Jou, Ming-Fei Liu and Chao-Liang Wu. College of Medicine, National Cheng Kung University, Tainan, Taiwan.

Background/Purpose: Our previous studies have demonstrated p53 mutations competent for the inactivation of wild type p53 in synovial fibroblasts (SF) from either rheumatoid arthritis patients or collagen-induced arthritis (CIA) rats; however, the pathogenic role of p73 (a transcription factor belonging to the p53 family) remains to be explored in rheumatoid joints. The 37 amino acid (37AA) peptide, a hybrid small peptide corresponding to p53 residues, inhibits the binding of p73 with inhibitory apoptosis stimulating protein of p53 (iASPP), thus activating p73 and further inducing apoptosis in p53-null cells.

Methods: Male Sprague-Dawley rats were immunized with bovine type II collagen with Freund's adjuvant on days 0 and 7 to induce arthritis, and SF were isolated from CIA rats. CIASF were transfected with adenoviral vectors encoding 37AA gene (Ad37AA), and then subjected to TUNEL, colorimetric WST-8 and real-time RT-PCR analyses to examine apoptotic status, cell viability and expression levels of p53 upregulated modulator of apoptosis (PUMA, a downstream target gene of p73), respectively. The association status of iASPP with p73 in Ad37AA-transfected CIASF was identified by immunoprecipitation with anti-iASPP, followed by immunoblot with anti-p73 antibodies. Serial expression levels of iASPP on synovium from rats were investigated by immunohistochemical (IHC) staining before and after the induction of arthritis. The therapeutic effect of Ad37AA on CIA rats were examined by intra-articular (i.a.) injection of 5×10^7 plaque-forming units into ankle joints on day 12, and evaluated by articular index and histological analyses including H&E staining and a specific surface marker of SF. Furthermore, expression levels of PUMA and IL-6 on CIA synovium were examined by immunoblot and enzyme-linked immunosorbent assay, respectively.

Results: Increased apoptosis status with reduced cell viability was found in Ad37AA-transfected CIASF as compared with control vector or mock-treated counterpart. There were significantly increased expression levels of PUMA on days 4 and 6 after the Ad37AA transfection. Decreased levels of associated p73 with iASPP were identified in Ad37AA-trasfected CIASF as compared with control vector-treated cells. Serial synovium sections revealed higher expression of iASPP in synovial lining layer after the induction of arthritis. Articular indexes of Ad37AA-injected joints were significantly smaller as compared with control vector or phosphate-buffered saline-treated ankles. There were significantly lower histological scores with milder synovial hyperplasia and bone erosion in Ad37AA-injected joints as compared with control groups. Notably, Ad37AA-treated synovium revealed up-regulation of PUMA, lower numbers of SF and decreased concentrations of IL-6.

Conclusion: These data demonstrate amelioration of CIA in rats by i.a. gene transfer of a small peptide corresponding to p53 residues via induction of apoptosis in CIASF through p73 activation. Such findings implicate a pathogenic role of p73 and the enhancement of p73-dependent pathway as a potential therapeutic strategy in rheumatoid joints.

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Cell Cycle Regulation Therapy Combined With Cytokine Blockade Enhances Anti-Arthritic Effects Without Increase Of Immune Suppression. Tadashi Hosoya, Hideyuki Iwai, Yu Yamaguchi, Nobuyuki Miyasaka and Hitoshi Kohsaka. Department of Medicine and Rheumatology, Tokyo Medical and Dental University, Tokyo, Japan.

Background/Purpose: The pathogenesis of rheumatoid arthritis (RA) is characterized by infiltration of immune cells to the synovial tissues and their hyperplasia. Aim of the current therapeutic strategies of RA is blockade of proinflammatory cytokines or inhibition of immune cell activity. Anti-tumor necrosis factor and interleukin (IL)-6 biological agents have been proven more effective than conventional oral anti-rheumatic drugs. However, they cannot induce complete remission in all patients and render treated patients susceptible to infections. Combination treatments with other molecular targeting drugs failed to enhance anti-rheumatic effects but increased adverse effects. To explore non-immunosuppressive treatment, we have focused on proliferation of synovial fibroblasts as a target pathological process. We have revealed that cell cycle regulation of synovial fibroblasts by cyclin-dependent kinase (CDK) inhibition ameliorated animal models of RA without inhibiting immune responses. A small molecule CDK4/6 inhibitor (smCDKI) has been tolerated clinically as an anti-cancer drug with the toxic effect being transient myelosuppression. The present studies were carried out to discern if smCDKI under toxic doses enhances the anti-arthritic effect of cytokine blockade and reduces their adverse effects in treating collagen induced arthritis (CIA).

Methods: DBA/1J mice were immunized with bovine type II collagen (CII) emulsified in complete Freund's adjuvant. Arthritis score and peripheral blood counts of the CIA mice treated with different doses of smCDKI were assessed. The arthritis score, radiographic score and histological score of the mice treated with smCDKI alone, with anti-IL-6 receptor antibody (IL-6R-Ab) or etanercept (ETN) alone, or with combination of smCDKI and cytokine blockade were assessed. Serum anti-CII antibodies were quantified with

enzyme-linked immunosorbent assay. CII specific proliferation of T cells derived from draining lymph nodes was assessed with thymidine incorporation assay.

Results: The smCDKI monotherapy suppressed arthritis, radiographic and histological scores of CIA dose-dependently. The therapeutic effects were observed without myelosupression. Both of IL-6R-Ab and ETN monotherapies were also effective. Their efficacy was further enhanced in the all scores when combined with smCDKI administration. Of note, the combination of smCDKI and ETN suppressed arthritis almost completely. Serum anti-CII antibody levels and CII-specific T cell proliferation were comparable among all the treated and control groups.

Conclusion: This is the first report demonstrating that combination of molecular targeting therapies exerted synergistic effects without increase in immune suppression. The smCDKI treatment combined with the anti-cytokine treatment might be more effective than anti-inflammatory monotherapy without increasing infection risks in treating RA. We hope that development of smCDKI as an anti-rheumatic drug will help to increase the remission induction rate in RA treatment without inducing infections.

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1730

Novel Role For Ly6C$^-$ Monocyte Subsets and Joint Macrophages In Mouse Model Of Rheumatoid Arthritis. Alexander Misharin[1], Carla M. Cuda[2], Rana Saber[1], Angelica K. Gierut[3], G. Kenneth Haines III[4], Steffen Jung[5] and Harris R. Perlman[1]. [1]Northwestern University, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Northwestern Med Faculty Found, Chicago, IL, [4]Yale University, New Haven, CT, [5]Weizmann Institute, Rehovot, Israel.

Background/Purpose: Monocytes and macrophages play a key role in the pathogenesis of rheumatoid arthritis. However, role of the individual subsets of monocytes and macrophages in the initiation, perpetuation and/or resolution of arthritis is unknown.

Methods: To uncover their role we utilized multiple strategies to deplete selective subsets of monocytes and macrophages in the K/BxN serum transfer arthritis mouse model: clodronate-loaded liposomes, diphtheria toxin and CD11b-DTR mice, aCCR2 antibody, adoptive transfer of monocytes.

Results: We found that contrary to the current dogma monocytes, and not neutrophils were necessary for initiation of arthritis. Moreover, we found that only non-classical Ly6C$^-$ monocytes were required for induction of arthritis, while classical Ly6C$^+$ monocytes were dispensable. Further, we identified that naïve mouse joint contains heterogeneous population of macrophages, which differ in their origin, turnover and function, namely tissue-resident macrophages and bone marrow-derived macrophages. Selective depletion of the tissue-resident macrophages accelerated development of arthritis, while depletion of bone marrow-derived macrophages had no effect on arthritis. While blood monocytes were necessary for initiation and development of arthritis, they were not necessary for its resolution. In contrast, tissue macrophages were crucial for the resolution, since their depletion delayed resolution of arthritis and was associated with increased histological joint damage.

Conclusion: These data suggest that unlike other models (myocardial infarction, infectious diseases) resolution of arthritis does not require second wave of monocyte recruitment into the joint, but rather dependent on a molecular rheostat within macrophages, which controls the switch of their phenotype from "proinflammatory/classically activated" to a "wound healing/regulatory". Phagocytosis of apoptotic neutrophils (efferocytosis) is potentially one of the mechanisms controlling this switch.

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1731

Treatment Of Innate Immune Arthritis With a Toll-Like Receptor 7 Agonist Requires Type I Interferon. Maripat Corr[1], Tomoko Hayashi[2], Dennis A. Carson[2], Howard Cottam[3] and Joshua Yang[2]. [1]Univ of California-San Diego, La Jolla, CA, [2]UCSD School of Medicine, La Jolla, CA, [3]ucsd School of Medicine, La Jolla, CA.

Background/Purpose: We previously demonstrated that repeated administration of the low molecular weight Toll-like receptor (TLR) 7 agonist (1V136) substantially reduces arthritic inflammation in mice. Here we investigated the mechanisms contributing to this potent anti-inflammatory effect using the K/BxN passive transfer model of murine arthritis.

Methods: The following mutant strains were given arthritis with 150ul K/BxN serum intraperitoneally (ip) and treated with daily subcutaneous (s.c.) injections of vehicle or 150nmol 1V136: C57BL/6, *Tlr7*$^{-/-}$, *Ifnar1*$^{-/-}$, *kit*$^{W\text{-}sh}$ (Wsh), Pretty2, and *Stat1*. Bone marrow chimeric mice were generated by irradiating C57BL/6 and *Tlr7*$^{-/-}$ mice with 10Gy and injecting these recipients with 10^7 donor bone marrow cells (BM). To assess the effects on vascular permeability mice were injected with 150ul K/BxN serum i.p. and 1mg/kg Evans blue dye intraveniously. After sacrifice the paws were removed and incubated in formamide overnight and the absorbance of the supernatant at 600nm was measured. Complete blood counts were performed by the UCSD Animal Care Program Diagnostic Laboratory.

Results: The joint swelling and arthritis scores of K/BxN serum transferred arthritis was significantly reduced by daily injections of 150nm 1V136 s.c. in C57BL/6 (WT) mice (AUC 6.6 drug treated vs. AUC 0.38 vehicle treated, $P<0.001$). Radiation bone marrow chimeric mice were tested and in WT BM>WT mice paw swelling in 1V136 treated mice was significantly less than vehicle treated controls (AUC 3.3 vs 7.4, $P<0.01$), but not in the TLR7 BM>TLR7 mice (AUC 6.7 vs 7.1, $P>0.05$). In mixed chimeras the drug was effective in the WT BM>TLR7 mice (AUC 4.9 vs 7.4, $P=0.03$), but not in the TLR7 BM>WT (AUC 6.2 vs 7.0, $P>0.05$). These data suggested that TLR7 is necessary for the activity of the compound. Mice that were defective in STAT1 and type I IFN signaling were refractory to 1V136 treatment, implicating these molecules effector molecules in the mechanism of this drug treatment. The data using BM chimeric mice suggested that radiosensitive cells were primarily involved in the beneficial effects of 1V136. A single dose of 1V136 reduced plasma extravasation in the joints of mice that received K/BxN sera. Plasma extravasation in immune complex reactions is associated with mast cell degranulation and neutrophil recruitment. Two strains of mast cell deficient mice were tested: Pretty2 and kit$^{W\text{-}sh}$ mice. The kit$^{W\text{-}sh}$ mice were refractory to treatment (AUC 7.3 vs 5.6, $P>0.05$), but the Pretty2 mice responded to 1V136 (AUC 2.2 vs 7.5, $P<0.05$). In the Pretty 2 strain the c-kit mutation is also associated with a low level of circulating neutrophils. A single dose of 1V136 significantly decreased the circulating white blood cells in WT mice ($10.6+0.22$ vs $3.9+0.44$, $P<0.01$), but not IFNAR1 null mice ($11.77+0.7$ vs $10.8+0.5$, $P<0.05$). There was no effect in the platlet counts.

Conclusion: The joint inflammation and vascular permeability observed in the passive serum transferred arthritis were significantly attenuated by 1V136 treatment. The drug requires TLR7 on bone marrow derived cells, and an intact type I interferon pathway to be fully effective.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Efficacy and Safety of Novel Entities
Monday, October 28, 2013, 2:30 PM–4:00 PM

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Efficacy and Safety Of Subcutaneous Administration Of Tabalumab, An Anti-B Cell Activating Factor Monoclonal Antibody, In Rheumatoid Arthritis: Results From a Phase 3 Multicenter, Randomized, Double-Blind Study. Mark C. Genovese[1], Gregg J. Silverman[2], Paul Emery[3], Ramesh Gupta[4], Anne Gill[5], Wendy J. Komocsar[5], Melissa Veenhuizen[5], Li Xie[5], Pierre-Yves Berclaz[5] and Chin Lee[5]. [1]Stanford University, Palo Alto, CA, [2]NYU School of Medicine, New York, NY, [3]University of Leeds, Leeds, United Kingdom, [4]Private Practice, Memphis, TN, [5]Eli Lilly and Company, Indianapolis, IN.

Background/Purpose: Tabalumab is a monoclonal antibody that neutralizes membrane-bound and soluble B cell activating factor (BAFF). These interim analyses evaluated the efficacy and safety of 2 different subcutaneous (SQ) dosing regimens of tabalumab in RA patients (pts).

Methods: 1004 pts (ITT population) were enrolled in this phase 3, multicenter, randomized, double-blind study that evaluated 2 different SQ tabalumab doses (120 mg every 4 wks [120/Q4W] or 90 mg every 2 wks

[90/Q2W]) vs. placebo over 24 wks. At wk 0, pts received an SQ loading dose that was 2 times the planned treatment dose (ie, 240 mg, 180 mg, or placebo). Eligible pts included those with or without background DMARDs having a Patient's Global Assessment of Disease Activity ≥20/100 mm. Prespecified efficacy analyses were based on a subset of pts (n=849) with ≥5/68 tender and ≥5/66 swollen joints at baseline; the primary endpoint was ACR20 at 24 wks in this subset.

Results: At baseline, the ITT population comprised mostly women (79%) who were seropositive (77%) with a mean age of 51 yrs, RA diagnosis of 6 yrs, and mean DAS28-CRP of 5.3±1.2; these baseline characteristics were similar to that of the efficacy population. For the efficacy population at wk 24, no significant differences in the percentage of pts who achieved ACR20 (NRI; range: 32%–34%) and ACR50 (NRI; range: 12%–13%), and no differences in mean DAS28-CRP (mLOCF; 4.6±1.5 to 4.7±1.5), mean HAQ-DI (mLOCF; range: 1.2±0.7 to 1.3±0.7), or percent with moderate/good EULAR28 response (mLOCF; range: 47%–50%) were observed. Efficacy results were similar between the efficacy and ITT populations. Discontinuation rates due to an AE were similar across all groups (range: 2%–4%) as were incidences of TEAEs (range: 58%–64%) and SAEs (range: 2%–4%). For the 120/Q4W, 90/Q2W, and placebo groups, incidences of events of interest were infection (23%, 26%, and 22%, respectively), injection-site reaction (6%, 10%, and 3%, respectively), and allergy/hypersensitivity reaction (2%, 5%, and 5%, respectively). Major adverse cardiovascular events were reported in two 120/Q4W pts and one 90/Q2W pt. Three deaths occurred (two 120/Q4W pts and one 90/Q2W pt). Changes in CD3-CD20+ B cells seen in the 120/Q4W and 90/Q2W groups were generally consistent with prior phase 2 results. Over the 24-wk treatment period, decreases in IgM, IgA, and IgG were also observed in both tabalumab groups vs. placebo (Table).

Table. Measures of Biologic Activity

	120 mg Q4W N=320[a]/379[b]	90 mg Q2W N=316[a]/371[b]	Placebo N=213[a]/250[b]
CRP (mg/L)[a]			
Baseline	13.3±21.1	12.1±16.2	11.7±15.2
Change at wk 24	−0.2±18.3	−0.5±14.0	−0.6±13.8
CD3-CD20+ B cells (cells/μL)[a]			
Baseline	214.2±146.1	213.2±129.9	223.4±129.0
Change at wk 24	−43.2±306.2*	−67.4±117.8*	3.5±98.5
IgM (g/L)[a]			
Baseline	1.4±0.8	1.4±0.8	1.5±1.0
Change at wk 24	−0.2±0.3*	−0.2±0.3*	0.0±0.3
IgA (g/L)[a]			
Baseline	2.8±1.3	2.9±1.3	2.8±1.2
Change at wk 24	−0.3±0.4*	−0.3±0.4*	0.1±0.6
IgG (g/L)[a]			
Baseline	12.5±3.7	12.5±3.6	12.5±3.7
Change at wk 24	−0.8±1.8*	−0.8±1.8*	0.1±1.9

Data are mean±SD.
[a]Based on efficacy population.
[b]Based on safety population (N=1000) who received ≥1 dose.
**P≤0.05 vs. placebo.*

Conclusion: Tabalumab administration had biologic activity demonstrated by changes in B cells and immunoglobulins, but no significant changes in CRP were observed. Despite showing improvements in efficacy measures with intravenous and SQ treatment in three phase 2 trials, no clear clinical benefit and no new, unexpected safety findings were observed for the tabalumab doses evaluated in this larger phase 3 study. Post-hoc analyses to help understand the disparity in responses between phase 2 and phase 3 are planned.

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Early and Sustained Improvement In Pain and Physical Function As Measured By Visual Analog Scale and Short Form-36 Physical Component Summary Score In Rheumatoid Arthritis Patients Treated With Mavrilimumab, An Investigational Anti-GM-CSFR-Alpha Monoclonal Antibody, In a Phase 2a Study.

Gerd-Rüdiger Burmester[1], Tsutomu Takeuchi[2], Olga Barbarash[3], Duncan Porter[4], Didier Saurigny[5], David Close[5], Alex Godwood[5], Yoojung Yang[6] and Ancilla W. Fernandes[6]. [1]Charite University Hospital, Berlin, Germany, [2]Keio University School of Medicine, Tokyo, Japan, [3]SIH Kemerovo Regional Clinical Hospital, Kemerovo, Russia, [4]Gartnavel General Hospital, Glasgow, United Kingdom, [5]MedImmune, Ltd, Cambridge, United Kingdom, [6]MedImmune, LLC, Gaithersburg, MD.

Background/Purpose: Rheumatoid arthritis (RA) is associated with significant pain and loss of physical function. We evaluated self-reported pain and physical function in adults patients with moderate-severe, active RA treated with mavrilimumab in combination with MTX in a 3-mo phase 2a, double-blind, placebo-controlled, ascending dose study.

Methods: Eligible patients had moderate-severe RA (DAS28-CRP ≥3.2) of ≥3 mos duration, were DMARD-IR on stable MTX (7.5–25 mg/wk), and positive for auto-antibodies ACPA and/or RF. 192 and 92 patients were randomized to subcutaneous mavrilimumab (10–100mg) and placebo, respectively, given every other wk for 12 wks. The primary endpoint was proportion of patients achieving a ≥1.2 decrease from baseline in DAS28-CRP at wk 12. Pain visual analog scale (VAS) and Short Form-36 physical component summary (SF-36 PCS) score were used to assess pain and physical function. The proportion of responders using minimal clinically important differences was assessed. In a post-hoc analysis, relationships between pain, physical function, and DAS28-CRP were examined using linear regression.

Results: At its highest dose, mavrilimumab 100mg (M100mg) met the primary endpoint vs placebo (difference, 35.5%; p<.001) at wk 12. In addition, following a single dose at wk 2, M100mg demonstrated a statistically significant improvement in the proportion of pain responders compared to placebo (difference, 16.7%; p=.034). This improvement was maintained until 4 wks after the last dose at wk 16 (difference, 24.7%; p=.007). At the first assessment of physical function (SF-36 PCS) at wk 4, M100mg demonstrated a statistically significant improvement in the response rate compared to placebo (difference, 26.7%; p=.004) (Table). This improvement was maintained to the final assessment at wk 12. The relationship between improvements in pain, physical function, and DAS28-CRP showed that, on average, a patient achieving a minimally important improvement in pain following 12 wks of M100mg also had an improvement of 5.71 (95% CI 4.04, 7.38) in the SF-36 PCS and 1.66 (95% CI −1.91, −1.41) in the DAS28-CRP score. Lower doses of mavrilimumab (10mg, 30mg, and 50mg) generally did not yield statistically significant improvements over placebo for these 3 endpoints, except for 30mg (n=49) in DAS28-CRP as early as wk 6 (difference, 25.2%; p=.004). All doses combined (n=192) achieved a response in DAS28-CRP as early as wk 4 (difference, 13.9%; p=.015).

Table. Responder Analysis[1] (%) of Patient-Reported Outcomes and DAS28-CRP at Wks 4 and 12

	Wk 4					Wk 12				
	M100mg (N=47)	PBO (N=92)	Difference	95% CI	*p*-value	M100mg (N=47)	PBO (N=92)	Difference	95% CI	*p*-value
Pain VAS	46.8	26.1	20.7	3.8, 37.4	0.022	55.3	33.7	21.6	4.2, 38.2	0.018
SF-36 PCS	70.2	43.5	26.7	9.1, 42.7	0.004	70.2	40.2	30.0	12.3, 45.3	0.001
DAS28-CRP[2]	42.6	17.4	25.2	9.2, 41.3	0.002	68.1	32.6	35.5	17.8, 50.6	<0.001

CI, confidence interval; DAS28-CRP, Disease Activity Score 28 – C-reactive Protein; M100mg, mavrilimumab 100mg; PBO, placebo
[1]Minimal clinically important difference: VAS, 20mm; SF-36 PCS, 3.1; DAS28-CRP, 1.2
[2]The mean baseline DAS28-CRP was 5.33 and 5.43 in M100mg and placebo groups, respectively.

Conclusion: Treatment with mavrilimumab 100mg resulted in an early onset and sustained improvement in pain relief and physical functioning as measured by VAS and SF-36 PCS, respectively, in moderate-severe RA patients. These findings are consistent with improvement in the disease activity (DAS28-CRP) and support further investigation of the blockade of the GM-CSF receptor with mavrilimumab in Phase 2b studies conducted in both DMARD-IR and TNF-IR patients.

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A Phase Ib Clinical Trial With Dekavil (F8-IL10), An Immunoregulatory 'Armed Antibody' For The Treatment Of Rheumatoid Arthritis, Used In Combination With Methotrexate. M. Galeazzi[1], L Bazzichi[2], E Prisco[3], G D Sebastiani[4], D. Neri[5], L Giovannoni[6], F Bacchion[7], M Bardelli[1], C Baldi[1], E Selvi[1], G Minisola[8], R Caporali[9] and S Bombardieri[10]. [1]Rheumatology Unit, University Hospital of Siena, Siena, Siena, Italy, [2]Division of Rheumatology, University of Pisa, Pisa, Pisa, Italy, [3]Deptartment of Rheumatology, University of Pavia, IRCCS Policlinico San Matteo Foundation, Pavia, Pavia, Italy, [4]Rheumatology Unit, San Camillo-Forlanini Hospital, Rome, Rome, Italy, [5]Chemistry and Applied Sciences, Swiss Federal Institute of Technology, Zurich, Zurich, Switzerland, [6]Clinical Research Unit, Philogen S.p.A., Siena, Sovicille - (SI), Italy, [7]Clinical Research Unit, Philogen S.p.A, Siena, Sovicille - (SI), Italy, [8]Rheumatology Unit, San Camillo-Forlanini Hospital, Rome, Rome, Italy, [9]Department of Rheumatology, University of Pavia, IRCSS Policlinico San Matteo Foundation, Pavia, Pavia, Italy, [10]Department of Rheumatology, University of Pisa, Pisa, Pisa, Italy.

Background/Purpose: A therapeutic strategy based on the selective delivery of an immuno-regulatory cytokine to the sites of inflammatory disease has been developed. DEKAVIL is an 'armed antibody', composed of the human F8 antibody (specific to the EDA domain of fibronectin, a marker of angiogenesis) fused to the human anti-inflammatory cytokine interleukin-10 (IL10), enabling delivery and accumulation of the cytokine specifically at sites of disease. This 'targeting' approach increases the therapeutic index of IL10. A Phase Ib clinical trial is now on-going, which features the administration of weekly doses of DEKAVIL, in combination with MTX, to patients with RA who have previously failed at least one line of anti-TNF therapy. Objectives of the study are to establish the MTD, safety and tolerability, to obtain preliminary information on efficacy and to assess the PK behavior. Here, we report the results obtained in 14 patients studied to date.

Methods: Cohorts of 3–6 patients with active RA were assigned to receive escalating doses of DEKAVIL (6, 15, 30, 60, 110, 160 and 210 μg/kg respectively) in combination with 15mg of MTX. The treatment is given as once weekly sc injection for up to 8 weeks. Standard safety evaluations performed on days 1 through 28 were used to determine the dose limiting toxicity. Response was assessed after 4 and 8 weeks of treatment according to ACR and EULAR (DAS28) criteria. The PK profile and formation of human anti-fusion protein antibodies are measured using standard methods.

Results: Responses are summarized in the attached table. All 3 patients in the first cohort (6 μg/kg) achieved ACR 50 response, accompanied by a 'good' EULAR response. In cohort 2 (15 μg/kg), patient 5 enjoyed an ACR 70 response, whereas patients 4 and 6 did not reach ACR20 despite achieving 'moderate' EULAR response. In cohort 3 (30 μg/kg) patient 8 achieved an ACR70. This was particularly striking as it was prolonged and at a late evaluation time point. Patient 7 did not achieve any ACR response, and patient 9 achieved an ACR20 response. In cohort 4 (60 μg/kg) Patient 11 achieved an ACR50 at EOT, which improved to an ACR70 response at a late evaluation time point, demonstrating an extended response period. Patient 10 achieved an ACR20 and patients 12 and 13 did not respond. In cohort 5 (110 μg/kg) patient 14 achieved an ACR20 at week 5. Trends of swollen/tender joints and DAS28 score also showed improvement. Excellent tolerability was observed, since no grade >2 adverse drug reactions were reported. A very low signal from human anti-fusion protein antibodies was occasionally detected. Several patients are still being treated and followed-up.

Conclusion: The promising safety data, together with preliminary positive signs of activity, suggest that the targeted delivery of IL10 to the site of inflammation may be beneficial to patients with RA. The extended activity periods indicate the possibility for a long lasting therapeutic potential.

Disclosure: M. Galeazzi, None; **L. Bazzichi**, None; **E. Prisco**, None; **G. D. Sebastiani**, None; **D. Neri**, Dario Neri, 1; **L. Giovannoni**, L Giovannoni, 3; **F. Bacchion**, F Bacchion, 3; **M. Bardelli**, None; **C. Baldi**, None; **E. Selvi**, None; **G. Minisola**, None; **R. Caporali**, None; **S. Bombardieri**, None.

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A Phase IIb Study Of The Efficacy and Safety Of Subcutaneous Clazakizumab (anti-IL-6 monoclonal antibody) With Or Without Methotrexate In Adults With Moderate-To-Severe Active Rheumatoid Arthritis and An Inadequate Response To Methotrexate. M Weinblatt[1], P Mease[2], E Mysler[3], T Takeuchi[4], E Drescher[5], A Berman[6], M Zilberstein[7], J Xing[7] and P Emery[8]. [1]Brigham and Women's Hospital, Boston, MA, [2]Swedish Medical Center and University of Washington, Seattle, WA, [3]Organización Médica de Investigación, Buenos Aires, Argentina, [4]Keio University, Tokyo, Japan, [5]Csolnoky Ferenc Hospital, Veszprém, Hungary, [6]Centro Médico Privado de Reumatología, Tucuman, Argentina, [7]Bristol-Myers Squibb, Princeton, NJ, [8]University of Leeds, Leeds, United Kingdom.

Background/Purpose: Clazakizumab (claza) is a humanized anti-interleukin-6 (IL-6) monoclonal antibody that potently neutralizes IL-6 signaling. This study evaluated the safety and efficacy of subcutaneous claza with or without MTX versus placebo (pbo) or adalimumab (ada).

Methods: Patients with moderate-to-severe RA and an inadequate response to MTX were randomized equally to receive pbo + MTX; 25, 100 or 200 mg claza + MTX; 100 or 200 mg claza without MTX; and ada 40 mg every other week + MTX for 24 weeks. The primary endpoint was ACR 20 response rate at Week 12. Key secondary endpoints at Week 24 were ACR 20, ACR 50 and ACR 70 response rates, Health Assessment Questionnaire-Disability Index (HAQ-DI) improvements and remission defined as Disease Activity Score (DAS)28 (C-reactive protein, CRP) <2.6, Clinical Disease Activity Index (CDAI) <2.8 and Simplified Disease Activity Index (SDAI) <3.3.

Results: 418 patients were randomized and received treatment. Baseline characteristics were balanced across the arms; 82% female, mean age 50 years, mean duration of RA 5.9 years, mean DAS28 (CRP) 5.94, and 80% rheumatoid-factor positive. The primary endpoint was met; ACR 20 response rates were statistically significantly higher in all claza arms versus pbo + MTX. All claza treatment groups were associated with improved ACR 20/50/70 response rates, HAQ-DI and remission versus pbo + MTX through Week 24. Rates of remission per DAS28 (CRP) <2.6, SDAI <3.3 and CDAI <2.8 were numerically higher in the claza + MTX arms compared with ada + MTX. Treatment with claza in combination with MTX resulted in higher response rates than monotherapy. However, no clear dose response for efficacy was noted. The rates of serious adverse events ranged from 8.3 to 13.3% in claza arms versus 3.3% for pbo + MTX and 5.1% for ada + MTX. Rates of serious infections were similar as reported for all claza arms and ada versus none in pbo. Claza was associated with mostly mild injection-site reactions, few of which led to discontinuation. As expected based on its mode of action, claza treatment was associated with increased transaminases (mainly in combination with MTX), increased lipids and hemoglobin, and decreased polymorphonuclear neutrophils and platelets.

	Pbo + MTX (n=61)	Claza 25mg + MTX (n=59)	Claza 100mg + pbo (n=60)	Claza 100mg + MTX (n=60)	Claza 200mg + pbo (n=59)	Claza 200mg + MTX (n=60)	Ada + MTX (n=59)
Week 12							
ACR 20 (primary endpoint), % (95% CI)	39.3 (27.1, 51.6)	78.0 (67.4, 88.5)	55.0 (42.4, 67.6)	71.7 (60.3, 83.1)	61.0 (48.6, 73.5)	60.0 (47.6, 72.4)	76.3 (65.4, 87.1)
p-value versus pbo		<0.001	0.042	0.001	0.015	0.015	
Week 24							
ACR 20, % (95% CI)	39.3 (27.1, 51.6)	83.1 (73.5, 92.6)	58.3 (45.9, 70.8)	63.3 (51.1, 75.5)	57.6 (45.0, 70.2)	66.7 (54.7, 78.6)	67.8 (55.9, 79.7)
ACR 50, % (95% CI)	18.0 (8.4, 27.7)	47.5 (34.7, 60.2)	36.7 (24.5, 48.9)	45.0 (32.4, 57.6)	33.9 (21.8, 46.0)	43.3 (30.8, 55.9)	49.2 (36.4, 61.9)
ACR 70, % (95% CI)	6.6 (1.8, 15.9)	27.1 (15.8, 38.5)	16.7 (7.2, 26.1)	38.3 (26.0, 50.6)	25.4 (14.3, 36.5)	30.0 (18.4, 41.6)	18.6 (8.7, 28.6)
DAS 28 (CRP) <2.6, % (95% CI)	13.1 (4.6, 21.6)	49.2 (36.4, 61.9)	28.3 (16.9, 39.7)	41.7 (29.2, 54.1)	35.6 (23.4, 47.8)	41.7 (29.2, 54.1)	23.7 (12.9, 34.6)
CDAI remission, % (95% CI)	1.6 (0.0, 8.8)	15.3 (6.1, 24.4)	6.7 (1.8, 16.2)	20.0 (9.9, 30.1)	6.8 (1.9, 16.5)	20.0 (9.9, 30.1)	8.5 (1.4, 15.6)
SDAI remission, % (95% CI)	4.9 (1.0, 13.7)	18.6 (8.7, 28.6)	6.7 (1.8, 16.2)	20.0 (9.9, 30.1)	6.8 (1.9, 16.5)	23.3 (12.6, 34.0)	8.5 (1.4, 15.6)
HAQ-DI mean change from baseline (SE)	–0.6 (0.1)	–0.7 (0.1)	–0.7(0.1)	–0.8 (0.1)	–0.6 (0.1)	–0.7 (0.1)	–0.7 (0.1)

Conclusion: Claza as monotherapy or in combination with MTX demonstrated efficacy in controlling the signs and symptoms of RA. At Week 24, remission rates with claza + MTX trended higher than with ada + MTX. Its safety profile was consistent with the known pharmacology of IL-6 blockade. Claza is a promising future treatment for RA that warrants further investigation.

Disclosure: M. Weinblatt, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, Roche/Genentech, UCB, Janssen, 5; **P. Mease**, AbbVie, Amgen, Biogen Idec, Bristol-Myers Squibb, Celgene, Crescendo, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, Vertex, 2, AbbVie, Amgen, Biogen Idec, Bristol-Myers Squibb, Celgene, Crescendo, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, Vertex, 5, AbbVie, Amgen, Biogen Idec, Bristol-Myers Squibb, Crescendo, Genentech, Janssen, Lilly, Pfizer, UCB, 8; **E. Mysler**, None; **T. Takeuchi**, Abott Japan Co., Astellas Pharma, Bristol-Myers K.K., Chugai, 8; **E. Drescher**, None; **A. Berman**, None; **M. Zilberstein**, Bristol-Myers Squibb, 3; **J. Xing**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **P. Emery**, AbbVie, BMS, Pfizer, UCB, MSD, 5, AbbVie, BMS, Pfizer, UCB, MSD, 8.

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A Randomized, Controlled, Multicenter, 2-Arm, Parallel-Group, Double-Blind Study To Demonstrate The Equivalence Of CT-P10 To Innovator Rituximab With Respect To Pharmacokinetic Profile In Patients With Rheumatoid Arthritis. Dae-Hyun Yoo[1], Won Park[2], Slawomir Jeka[3], Fidencio Cons Molina[4], Pawel Hrycaj[5], Piotr Wiland[6], Wolfgang Spieler[7], Jan Brzezicki[8], Eun Young Lee[9], Francisco G. Medina-Rodriguez[10], Pavel Shesternya[11], Sebastiao Radominski[12], Marina Stanislav[13], Volodymyr Kovalenko[14], Dong Hyuk Sheen[15], Mie Jin Lim[2], Jung-Yoon Choe[16], Sung Young Lee[17], Seung-Cheol Shim[18] and Chang-Hee Suh[19]. [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Inha University Hospital, Incheon, South Korea, [3]Clinic of Rheumatology and Connective Tissue Diseases University Hospital No 2 in Bydgoszcz Collegium Medicum UMK in Torun, Bydgoszcz, Poland, [4]Centro de Investigacion en Artritis y Osteoporosis SC, Mexicali, Mexico, [5]Poznan University of Medical Sciences, Poznan, Poland, [6]Medical University of Wroclaw, Wroclaw, Poland, [7]ZeFOR GmbH Zentrum für Forschung, Zerbst, Germany, [8]Wojewodzki Szpital Zespolony Oddzial Reumatologiczny, Elblag, Poland, [9]Division of Rheumatology, Department of Internal Medicine, Seoul National University, Seoul, South Korea, [10]Centro de Investigación Farmacológica y Biotecnológica, Mexico City, Mexico, [11]Krasnoyarsk State Medical University, Krasnoyarsk, Russia, [12]CETI Centro de Estudos em Terapias Inovadoras Ltda, Curitiba, Brazil, [13]Russian Academy of Medical Science, Moscow, Russia, [14]National Scientific Center, Kiev, Ukraine, [15]Eulji University Hospital, DaeJeon, South Korea, [16]Daegu Catholic University Medical Center, Daegu, South Korea, [17]CELLTRION, Inc., Incheon, South Korea, [18]Chungnam National University Hospital, Daejeon, South Korea, [19]Ajou University Hospital, Suwon, South Korea.

Background/Purpose: CT-P10 was developed as a biosimilar candidate to innovator rituximab (RTX), an anti-CD20 monoclonal antibody. This trial is a phase I study to demonstrate the equivalence of the pharmacokinetic (PK) profile of CT-P10 with RTX in patients with active rheumatoid arthritis (RA) who had an inadequate response or intolerant to previous antitumor necrosis factor (TNF) agents. Equivalence will be concluded if the 90% Confidence Intervals (CI) for the ratios of the geometric means of AUC_{0-last} and C_{max} between the CT-P10 and RTX groups are within 80%– 125%. The pharmacodynamics (PD), efficacy, and overall safety of both treatments were also evaluated.

Methods: One hundred and fifty-four patients with active RA were randomized 2:1 to receive 2 infusions (1000 mg, IV each) of either CT-P10 (n=103) or RTX (n=51) with a 2-week interval between infusions, both co-administered with weekly methotrexate and folic acid. The primary endpoints were area under the serum concentration-time curve from time '0' to time of last quantifiable concentration (AUC_{0-last}) and maximum serum concentration (C_{max}) (after second infusion) of the CT-P10 and RTX groups. ACR response, EULAR response, B-cell kinetics, immunogenicity and safety parameters were also evaluated up to week 24.

Results: The geometric means were 7870.84 day-μg/mL and 8010.39 day-μg/mL for AUC_{0-last} and 465.94 μg/mL and 477.52 μg/mL for C_{max} in the CT-P10 and RTX groups, respectively. The ratios (%) of the geometric means of AUC_{0-last} and C_{max} between the CT-P10 and RTX groups were 98.3% (90% CI: 89.6, 107.8) and 97.6% (90% CI: 92.0, 103.5), respectively.

The geometric mean area under the curve (AUC) of B-cell count, a comparative PD parameter, was 20.8 cells/μL for the CT-P10 group and 20.4 cells/μL for the RTX group. The ratio (%) of the geometric means of AUC for B-cell count was 102% (90% CI: 98, 106). ACR20/50/70 response rates at week 24 were 63.0%/37.0%/16.0% in the CT-P10 group and 66.7%/31.3%/14.6% in the RTX group. The proportions of patients who had a moderate or good response at week 24 were 76.8% and 79.1% for EULAR (ESR) response and 82.1% and 83.7% for EULAR (CRP) response in the CT-P10 and RTX groups, respectively.

The proportions of patients with a positive anti-drug antibody at week 24 were 17.6% (18/102) for the CT-P10 group and 17.6% (9/51) for the RTX group. A total of 166 and 88 treatment-emergent adverse events were reported for the CT-P10 and RTX groups, respectively. Serious adverse events were reported in 16.7% of CT-P10 and 17.6% of RTX patients. Infections were reported in 23.5% of CT-P10 and 25.5% of RTX patients. Infusion reactions were reported in 16.7% of CT-P10 and 19.6% of RTX patients.

Conclusion: CT-P10 and RTX were equivalent in terms of AUC_{0-last} and C_{max} in patients with active RA. Clinical efficacy for ACR20/50/70 and EULAR response rates and PD for B-cell kinetics were comparable between the two treatment groups. CT-P10 was well tolerated with a safety profile comparable to that of RTX up to week 24.

Disclosure: D. H. Yoo, CELLTRION, Inc, 5; **W. Park**, CELLTRION, Inc., 5; **S. Jeka**, CELLTRION, Inc., 2; **F. Cons Molina**, CELLTRION, Inc., 2; **P. Hrycaj**, CELLTRION, Inc., 2; **P. Wiland**, CELLTRION, Inc., 2; **W. Spieler**, CELLTRION, Inc, 2; **J. Brzezicki**, CELLTRION, Inc, 2; **E. Y. Lee**, CELLTRION, Inc, 2; **F. G. Medina-Rodriguez**, CELLTRION, Inc., 2; **P. Shesternya**, CELLTRION, Inc., 2; **S. Radominski**, CELLTRION, Inc., 2; **M. Stanislav**, CELLTRION, Inc., 2; **V. Kovalenko**, CELLTRION, Inc., 2; **D. H. Sheen**, CELLTRION, Inc., 2; **M. J. Lim**, CELLTRION, Inc., 2; **J. Y. Choe**, CELLTRION, Inc., 2; **S. Y. Lee**, CELLTRION, Inc., 3; **S. C. Shim**, CELLTRION, Inc., 2, CELLTRION, Inc., 5; **C. H. Suh**, CELLTRION, Inc., 2, CELLTRION, Inc., 5.

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Association Of *HLA-DRB1* Alleles With Clinical Responses To The Anti-Interleukin−17A Monoclonal Antibody Secukinumab In a Cohort Of Patients With Active Rheumatoid Arthritis: An Exploratory Phase 2 Biomarker Study. Gerd R Burmester[1], Patrick Durez[2], Galina Shestakova[3], Yue Li[4], Amanda Wang[5], Steve Lewitzky[5], Irina Koroleva[5], David Lee[4] and Wolfgang Hueber[4]. [1]Charité-Universitätsmedizin Berlin, Free University and Humboldt University of Berlin, Berlin, Germany, [2]Université Catholique de Louvain, Brussels, Belgium, [3]Kaluga State Pedagogical Tsiolkovsky University, Kaluga, Russia, [4]Novartis Pharma AG, Basel, Switzerland, [5]Novartis Pharma AG, Cambridge, MA.

Background/Purpose: The shared epitope (SE) may play a functional role in RA via Th17/interleukin (IL)-17 polarization (Holoshitz et al. *FEBS Lett* 2011;585:3619–26). Two phase 2 studies of secukinumab in RA suggested that *HLA-DRB1*04* allelic group and the SE could be candidate biomarkers for treatment with secukinumab. In this study, validation in an independent cohort was sought for candidate markers of response.

Methods: In a randomized, double-blind, placebo-controlled trial, patients with RA (2010 criteria), TJC ≥ 6, SJC ≥ 6, CRP > 10 mg/L, who were biologic-naive and DMARD incomplete responders or DMARD naive, were randomized 2:1 to secukinumab 6×10 mg/kg i.v. or placebo every other week (wk). Associations of treatment effect of secukinumab vs. placebo with *HLA-DRB1*04* (primary endpoint), *HLA-DRB1*SE* and protein markers RF and anti-CCP were assessed at wk 12 in 96 evaluable patients, using change from baseline in DAS28-CRP by ANCOVA, or ACR20 response by logistic regression.

Results: At baseline, 46 (72%) on secukinumab and 23 (72%) on placebo were taking concomitant DMARDs; 16% were RF/anti-CCP negative. Frequency of *HLA-DRB1*SE* and **04* was 72% and 47%, respectively. ACR20 responses at wk 12 were 87.9% for secukinumab compared to 25.0% for placebo. Change from baseline in DAS28-CRP differed significantly as early as wk 2 and continued through wk 12 (Fig 1). For change from baseline in DAS28-CRP, *HLA-DRB1*SE* status demonstrated a significant association with response to secukinumab vs. placebo (p=0.007), but the *HLA-DRB1*04* allelic group and *HLA-DRB1*0401* did not (Fig 2). Among protein markers, RF but not anti-CCP was significantly associated with both DAS28-CRP (RF p=0.022, anti-

CCP p=0.124) and ACR20 response (RF p=0.013, anti-CCP p=0.228). The small number of *HLA-DRB1*SE* non-carriers within the CCP/RF-positive subcohort precluded assessment of associations in this subgroup. Two SAEs were reported, necrotizing vasculitis and ovarian adenoma, both leading to early secukinumab discontinuation.

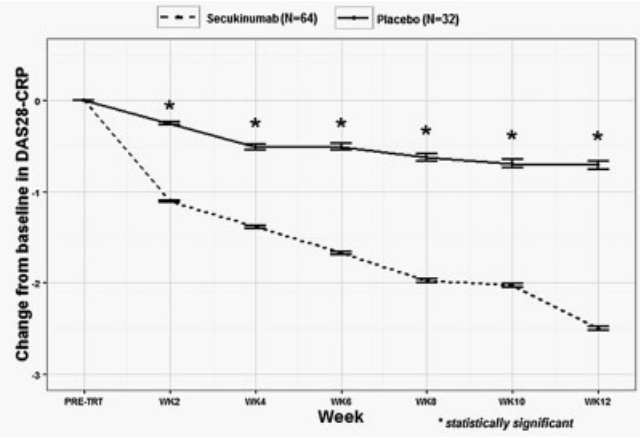

Figure 1. Secukinumab 6×10mg/kg i.v. compared to placebo for change from baseline in DAS28-CRP responses. *All p-values at post-baseline visits are <0.0005 from mixed-effects model for repeated measurements.

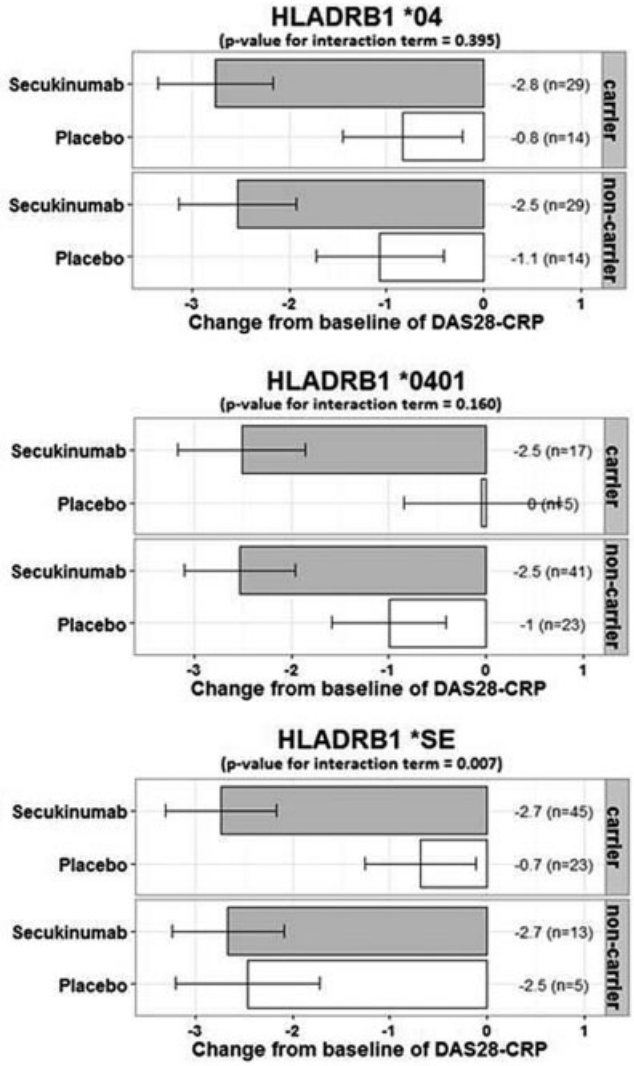

Figure 2. Biomarker associations with clinical response to secukinumab vs. placebo treatment in DAS28-CRP at week 12.

Conclusion: Secukinumab was associated with improvements in efficacy outcomes compared with placebo. *HLA-DRB1*SE* was associated with response to secukinumab vs. placebo. However, these associations are driven by lack of placebo response in carriers vs. non-carriers. Notable differences in genetic ancestry and disease activity suggest potential confounder effects. Additional studies with enhanced power are needed to confirm contributions of SE and other markers to anti-IL-17A responsiveness.

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ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Biologic Therapy
Monday, October 28, 2013, 2:30 PM–4:00 PM

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Epratuzumab Maintains Improvements In Disease Activity For Over 2 Years In Patients With Moderate-To-Severe Systemic Lupus Erythematosus: Results From An Open-Label Long-Term Extension Study.

Megan E. B. Clowse[1], Frederic Houssiau[2], Michelle A. Petri[3], Brian Kilgallen[4], Kenneth Kalunian[5], Vibeke Strand[6], Sabine Bongardt[7], Caroline Gordon[8] and Daniel J. Wallace[9]. [1]Duke University Medical Center, Durham, NC, [2]Université catholique de Louvain, Brussels, Belgium, [3]Johns Hopkins University School of Medicine, Baltimore, MD, [4]UCB Pharma, Smyrna, GA, [5]UCSD School of Medicine, La Jolla, CA, [6]Stanford University, Palo Alto, CA, [7]UCB Pharma, Brussels, Belgium, [8]University of Birmingham, Birmingham, United Kingdom, [9]Cedars-Sinai Medical Center, Los Angeles, CA.

Background/Purpose: Epratuzumab is a monoclonal antibody targeting CD22. In EMBLEM™ (dose-ranging phase IIb study), epratuzumab produced clinically relevant improvements in disease activity in patients with moderate-to-severe systemic lupus erythematosus (SLE).[1] The open-label extension (OLE) of EMBLEM™ (NCT00660881) reports long-term data on the efficacy of epratuzumab.

Methods: Patients from any EMBLEM™ arm completing 12 weeks blinded treatment and those who discontinued due to lack of efficacy but completed ≥8 weeks were eligible. In the OLE, all patients received 1200mg epratuzumab at weeks 0 and 2 of repeating 12-week cycles. Evaluation visits were at weeks 4 and 8 of each cycle. Efficacy endpoints included British Isles Lupus Assessment Group (BILAG) improvement, SLE Disease Activity Index (SLEDAI) score, Physician Global Assessment (PGA) and combined treatment response (defined as BILAG improvement without worsening, no SLEDAI worsening, no PGA worsening, relative to EMBLEM™ baseline [BL]). Observed data are reported to week 108 of OLE (last timepoint when >50% of patients reported data for BILAG). The last visit, which refers to the last available value for each subject regardless of timing, is also presented.

Results: 203 patients participated in the EMBLEM™ OLE: 95% female (n=192), 78% Caucasian (n=158), mean±SD age 39±11 yrs. 35 (17%) and 168 (83%) received placebo and epratuzumab (various doses) respectively for 12 weeks in EMBLEM™. Median (range) duration of epratuzumab exposure was 845 (75–1185) days. BILAG improvements were observed between EMBLEM™ BL and week 108 of OLE. Median BILAG total score decreased by 64%. Median (range) BILAG total score was 25.0 (12–61) at EMBLEM™ BL, 14.0 (0–57) at OLE screening, 9.0 (0–52) at week 48, 9.0 (0–52) at week 96 and 9.0 (0–52) at week 108. Last visit value was 10.0 (0–72). At week 108, 60.3% of on-going patients responded to treatment, according to combined treatment response criteria (Table). Median (range) SLEDAI total score was 12.0 (6–39) at EMBLEM™ BL, 10.0 (0–34) at OLE screening, 6.0 (0–30) at week 48, 5.0 (0–22) at week 96, 4.0 (0–24) at week 108 and last visit value was 8.0 (0–32). At week 108, 94.0% (109/116) had no worsening in SLEDAI. Median (range) PGA total score was 50.0 (9–90) at EMBLEM™ BL, 31.0 (0–96) at OLE screening, 18.0 (0–81) at week 48, 19.0 (0–73) at week 96, 17.5 (0–69) at week 108 and last visit value was 25.0 (0–94). At week 108, 97.4% (113/116) had no worsening in PGA. Corticosteroid use decreased with long-term epratuzumab use.

Table: Change in BILAG grade among subjects with BILAG grade A or B at EMBLEM™ baseline

	BILAG grade at EMBLEM™ baseline	BILAG grade (shift) at EMBLEM™ OLE screening			BILAG grade (shift) at week 108 of EMBLEM™ OLE			
Body system	A/B (Severe/ moderate disease) n	A/B (Severe/ moderate disease) n (%)	C (Stable disease) n (%)	D (Inactive disease) n (%)	N	A/B (Severe/ moderate disease) n (%)	C (Stable disease) n (%)	D (Inactive disease) n (%)
Musculoskeletal	183	101 (55.2)	48 (26.2)	34 (18.6)	106	27 (25.5)	31 (29.2)	48 (45.3)
Mucocutaneous	166	97 (58.4)	40 (24.1)	29 (17.5)	93	31 (33.3)	21 (22.6)	41 (44.1)
Cardiorespiratory	69	45 (65.2)	3 (4.3)	21 (30.4)	41	13 (31.7)	0 (0)	28 (68.3)
Neuropsychiatric	50	32 (64.0)	5 (10.0)	13 (26.0)	27	12 (44.4)	1 (3.7)	14 (51.9)
Constitutional	44	7 (15.9)	3 (6.8)	34 (77.3)	20	1 (5.0)	2 (10.0)	17 (85.0)
Renal	25	12 (48.0)	10 (40.0)	3 (12.0)	13	4 (30.8)	4 (30.8)	5 (38.5)

Conclusion: Epratuzumab was associated with sustained improvements in disease activity in patients with moderate-to-severe SLE. Responder rates were sustained beyond 2 years or increased during open-label treatment, particularly in patients previously treated with placebo.

Reference:

1. Wallace DJ, et al. Ann Rheum Dis, Online First 12 January 2013. annrheumdis-2012–202760.

Disclosure: M. E. B. Clowse, UCB Pharma, 5; **F. Houssiau**, UCB Pharma, 2, UCB Pharma, 5; **M. A. Petri**, UCB Pharma, 2, UCB Pharma, 5; **B. Kilgallen**, UCB Pharma, 1, UCB Pharma, 3; **K. Kalunian**, Genentech, Biogen IDEC Inc, Cephalon, Cypress, MedImmune, Novo Nordisk, UCB Pharma, 2, Bristol-Myers Squibb, Genentech, Biogen IDEC Inc, Anthera, MedImmune, Novo Nordisk, Zymogenetics, Serono, UCB Pharma, 5; **V. Strand**, Abbott Immunology Pharmaceuticals, Amgen Inc, AstraZeneca, Biogen Idec, Canfite Pharma, Centocor Inc, Cypress Biosciences Inc, Euro-Diagnostica Inc, Fibrogen, Forest Laboratories, Genentech, Human Genome Sciences Inc, Incyte, Novartis Pharmaceuticals Corp, 5; **S. Bongardt**, UCB Pharma, 3; **C. Gordon**, GSK, MedImmune, Merck Serono, Parexel and UCB Pharma, 5; **D. J. Wallace**, Bristol-Myers Squibb, Genentech, Biogen IDEC Inc, GlaxoSmithKline, Human Genome Sciences Inc, MedImmune, Novo Nordisk and UCB Pharma, 5.

1739

Sustained British Isles Lupus Assessment Group-Measured Improvement In Moderately-and-Severely Affected Body Systems In Patients With Systemic Lupus Erythematosus By Epratuzumab: Results From An Open-Label Extension Study. Kenneth Kalunian[1], Megan E. B. Clowse[2], Frederic Houssiau[3], Michelle A. Petri[4], Brian Kilgallen[5], Caroline Gordon[6], Vibeke Strand[7], Sabine Bongardt[8] and Daniel J. Wallace[9]. [1]UCSD School of Medicine, La Jolla, CA, [2]Duke University Medical Center, Durham, NC, [3]Université catholique de Louvain, Brussels, Belgium, [4]Johns Hopkins University School of Medicine, Baltimore, MD, [5]UCB Pharma, Raleigh, NC, [6]University of Birmingham, Birmingham, United Kingdom, [7]Stanford University, Palo Alto, CA, [8]UCB Pharma, Brussels, Belgium, [9]Cedars-Sinai Medical Center, Los Angeles, CA.

Background/Purpose: Epratuzumab is a monoclonal antibody targeting CD22. In EMBLEM™ (a dose-ranging phase IIb study), epratuzumab produced clinically relevant improvements in disease activity in patients with moderate-to-severe systemic lupus erythematosus (SLE).[1] The open-label extension (OLE) of EMBLEM™ (NCT00660881) reports long-term data on the efficacy of epratuzumab. The improvement in British Isles Lupus Assessment Group (BILAG) 2004 index according to body systems is reported.

Methods: Patients from any EMBLEM™ arm completing 12 weeks' blinded treatment and patients who discontinued due to lack of efficacy but completed ≥8 weeks were eligible. In the OLE, all patients received 1200mg epratuzumab at weeks 0 and 2 of repeating 12-week cycles. Data are reported to week 108, the last time point when more than 50% of patients reported data for BILAG improvement. Independent central readers determined BILAG grades for all 9 systems. Data for the BILAG improvement component of the combined index in body systems for which a sufficient number of patients entering the OLE (≥20) had baseline disease activity to assess response are reported. Observed case analysis are presented.

Results: Improvements from BILAG A/B scores to BILAG C or D were observed following 12 weeks of epratuzumab treatment (EMBLEM™ OLE screening) in all body systems (Table). In the musculoskeletal body system 44.8% of patients with BILAG A/B at EMBLEM™ baseline improved to BILAG C or D at EMBLEM™ OLE screening. This was 41.6%, 34.7%, 36.0%, 84.1% and 52.0% in the mucocutaneous, cardiorespiratory, neuropsychiatric, constitutional and renal body systems respectively. The percentage of patients with an improvement in baseline BILAG A/B scores to BILAG C or D was further increased up to week 108 in the EMBLEM™ OLE. At week 108 the proportion of patients with BILAG C or D exceeded 60% in the musculoskeletal, mucocutaneous, cardiorespiratory, constitutional and renal systems (observed data) (Table).

Table: Change in BILAG grade among subjects with BILAG grade A or B at EMBLEM™ baseline

	BILAG grade at EMBLEM™ baseline	BILAG grade (shift) at EMBLEM™ OLE screening			BILAG grade (shift) at week 108 of EMBLEM™ OLE			
Body system	A/B (Severe/ moderate disease) n	A/B (Severe/ moderate disease) n (%)	C (Stable disease) n (%)	D (Inactive disease) n (%)	N	A/B (Severe/ moderate disease) n (%)	C (Stable disease) n (%)	D (Inactive disease) n (%)
Musculoskeletal	183	101 (55.2)	48 (26.2)	34 (18.6)	106	27 (25.5)	31 (29.2)	48 (45.3)
Mucocutaneous	166	97 (58.4)	40 (24.1)	29 (17.5)	93	31 (33.3)	21 (22.6)	41 (44.1)
Cardiorespiratory	69	45 (65.2)	3 (4.3)	21 (30.4)	41	13 (31.7)	0 (0)	28 (68.3)
Neuropsychiatric	50	32 (64.0)	5 (10.0)	13 (26.0)	27	12 (44.4)	1 (3.7)	14 (51.9)
Constitutional	44	7 (15.9)	3 (6.8)	34 (77.3)	20	1 (5.0)	2 (10.0)	17 (85.0)
Renal	25	12 (48.0)	10 (40.0)	3 (12.0)	13	4 (30.8)	4 (30.8)	5 (38.5)

Conclusion: Treatment with epratuzumab provided BILAG improvements in disease activity in all affected body systems. Improvements were sustained and enhanced with long-term treatment. Within specific body systems, most patients had symptom reduction or absence of active disease with treatment.

References:

1. Wallace DJ. et al. Ann Rheum Dis, Online First 12 January 2013. DOI: 10.1136/annrheumdis-2012–202760.

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1740

12-Month Outcomes Associated With Belimumab In Patients With Systemic Lupus Erythematosus In Clinical Practice Settings: The Observe Study. Christopher E. Collins[1], Maria Dall'Era[2], Alan Oglesby[3], Michael B. McGuire[4], Ramesh Pappu[3], Hong Kan[3] and Charles T. Molta[5]. [1]Washington Hospital Center, Washington, DC, [2]University of California, San Francisco, San Francisco, CA, [3]GlaxoSmithKline, Research Triangle Park, NC, [4]Medical Data Analytics, Parsippany, NJ, [5]GlaxoSmithKline, King of Prussia, PA.

Background/Purpose: Large-scale clinical trials have demonstrated the clinical efficacy of belimumab in patients with systemic lupus erythematosus (SLE). We examined clinical outcomes associated with 12 months of belimumab treatment in clinical practice settings in the United States (US).

Methods: This is a multi-center retrospective chart review from community-based rheumatology practices that treated >10 SLE patients annually and had >5 yrs of practice experience (OBSErve; GSK117295). Physicians randomly identified adult SLE patients who had received ≥8 infusions of belimumab as part of their usual care. Data were collected for the 6 months prior to belimumab initiation (baseline), for the first 6 months after initiation and for Months 6–12; data included demographics, disease characteristics, disease activity assessment scores (where available), and concomitant medications. The primary outcome measure was physician impression of change in SLE disease manifestations.

Results: This interim analysis at 12 months included 384 patients (female: 89.8%; mean age: 41.8 [standard deviation: 12.3] years; Caucasian: 51.6%; African-American: 25.5%; Hispanic: 16.7%; Other: 6.3%) enrolled by 60 rheumatologists from 21 states. During the 6–12 month follow-up period, 43 patients (11.2 %) discontinued belimumab. The most common reasons for discontinuation were patient request (37.2%), medication not effective (27.9%), lack of patient compliance (20.9%), disease progression (18.6%), loss of insurance/reimbursement (7.0%) and loss to follow-up or death (7.0%).

During Months 0–6, physicians' impression of change in SLE disease showed improvements of <20%, ≥20%, ≥50% and ≥80% in 10.7%, 88.3%, 47.1% and 11.2% of patients, respectively; no change was reported for

0.5% of patients, and 0.5% were considered to have worsened. Continued improvements were observed during Months 6–12 when improvements of <20%, ≥20%, ≥50% and ≥80%, beyond those observed at Month 6, were reported in 16.1%, 70.8%, 30.2% and 10.2% of patients, respectively; no change was reported for 9.9% of patients and 3% were considered to have worsened.

Overall, 297/384 patients (77.3%) received concomitant steroids at baseline; 104/297 patients (35.0%) were able to discontinue steroids altogether at 12 months. The mean steroid dose (prednisone equivalent) among steroid users at baseline and 12 months was 19.4 mg/day and 8.4 mg/day, respectively. During the 12 month period, 6 patients initiated steroid treatment.

For the 96 (25%) patients with SELENA-SLEDAI scores at 12 months, mean score was 12.5 at baseline, 6.0 at 6 months, and 5.1 at 12 months (59.2% reduction from baseline). From baseline to 12 months, mean Physician Global Assessment scale scores improved by 58.7% (n=100) and Patient Global Assessment scale scores improved by 61.5% (n=78).

Conclusion: Overall, physicians reported continued improvement in clinical outcomes and reduction in steroid use over 12 months of treatment with belimumab 10 mg/kg plus usual care, among patients receiving ≥8 belimumab infusions.

Disclosure: C. E. Collins, GlaxoSmithKline/Human Genome Sciences, Inc., 5, GlaxoSmithKline/Human Genome Sciences, Inc., 8; **M. Dall'Era**, GlaxoSmithKline, 5; **A. Oglesby**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **M. B. McGuire**, None; **R. Pappu**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **H. Kan**, GlaxoSmithKline, 3; **C. T. Molta**, GlaxoSmithKline, 3.

1741

Correlation Of The Interferon Gene Signature With Systemic Lupus Erythematosus Disease Activity Is Dependent On The Associated Level Of The BAFF Gene Transcript. Michelle Petri[1], Laurence S. Magder[2], Hong Fang[1], Julie Czerkowicz[3], Andrea Dearth[3], Jadwiga Bienkowska[4], Norm Allaire[4], Patrick Cullen[3], Alice Thai[3] and Ann Ranger[3]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD, [3]Biogen Idec Inc, Cambridge, MA, [4]Biogen Idec Inc., Cambridge, MA.

Background/Purpose: The interferon alpha (IFN) gene signature is frequent in SLE (~50% of patients) and important in pathogenesis. However, multiple studies have found that the IFN signature does not predict flares. In SLE peripheral blood, the level of the B-cell activating factor (BAFF) transcript is highly associated with the IFN signature. We asked whether an association of the interferon gene signature with disease activity depended on the level of the BAFF transcript.

Methods: 292 patients (59% Caucasian, 34% African-American, 92% female, mean age 46 ±12 years) were enrolled in a prospective observational study. At baseline, gene expression levels were assessed in peripheral blood RNA samples using microarray (Affymetrix) and select transcripts validated with qPCR. The IFN signature "score" was calculated based on the geometric mean of the expression levels (chip signal intensity) of 16 IFN-induced genes and divided into low, medium and high groups. Patients were divided in subgroups based on BAFF and IFN signatures. Subgroups were compared with respect to frequency of clinical events in the next year. P-values were calculated using generalized estimating equations (SAS 9.2).

Results: Table 1 shows the strong correlation of the IFN signature with BAFF gene expression. Of those individuals with a high level of BAFF mRNA, 97% also had a high IFN signature.

Table 1. Number (%) of SLE Patients with Each Level of IFN Signature, by BAFF Levels

		IFN signature		
		Low	Medium	High
BAFF mRNA	Low (n=91)	77 (85%)	7 (8%)	7 (8%)
	Medium (n=88)	38 (43%)	8 (9%)	42 (48%)
	High (n=93)	1 (1%)	2 (2%)	90 (97%)

Because there were only 17 patients with medium IFN, they were pooled together with high IFN in Table 2 below.

Table 2. Proportion of Visits with Various Disease Manifestations, by IFN within BAFF Subgroups over 1 Year

	Low BAFF		Medium BAFF		High BAFF			
Disease activity	Low IFN (n=77) (304 total visits)	High IFN (n=14) (67 total visits)	Low IFN (n=38) (159 total visits)	High IFN (n=50) (210 total visits)	Low IFN (n=1) (4 total visits)	High IFN (n=92) (381 total visits)	P-value for association between IFN and item, controlling for BAFF	P-value for association between BAFF and item, controlling for IFN
Physician global assessment >1	8%	3%	24%	20%	0%	26%	0.37	0.0008
SLEDAI ≥2	34%	27%	55%	65%	0%	69%	0.55	0.0002
Urine protein/cr (≥0.5)	3%	0%	13%	14%	0%	14%	0.83	0.012
Anti-dsDNA ≥ 10	7%	7%	7%	37%	0%	36%	0.0070	0.074
C3 <79 mg/dl	3%	0%	4%	20%	20%	21%	0.018	0.028
C4 <12 mg/dl	3%	0%	7%	18%	0%	20%	0.14	0.023
ESR >20	32%	45%	50%	62%	0%	61%	0.053	0.068
SLEDAI Arthritis	1%	3%	6%	3%	0%	5%	0.84	0.29
SLEDAI Skin	19%	23%	29%	36%	0%	36%	0.28	0.19
SLEDAI Heme	3%	5%	2%	6%	0%	6%	0.27	0.88

In those patients with low or medium BAFF gene expression, there was no association between the IFN signature and global disease activity measures (such as PGA, SLEDAI). Thus, controlling for BAFF, the IFN signature was not related to global measures of disease activity (p=0.37 for PGA, p=0.55 for SLEDAI).

Conclusion: In this study, we found that the association of the IFN signature with SLE global disease parameters is dependent on the BAFF gene expression (with which it is closely correlated). The IFN gene signature, however, is associated with serologic activity (high anti-dsDNA and low complement), controlling for BAFF. These results may shed light on confusing data from anti-IFN clinical trials.

Disclosure: M. Petri, Biogen Idec Inc, 2, Biogen Idec Inc, 5; **L. S. Magder**, None; **H. Fang**, None; **J. Czerkowicz**, Biogen Idec Inc, 1, Biogen Idec Inc, 3; **A. Dearth**, Biogen Idec Inc, 1, Biogen Idec Inc, 3; **J. Bienkowska**, Biogen Idec Inc, 1, Biogen Idec Inc, 3; **N. Allaire**, Biogen Idec Inc, 1, Biogen Idec Inc, 3; **P. Cullen**, Biogen Idec Inc, 1, Biogen Idec Inc, 3; **A. Thai**, Biogen Idec Inc, 1, Biogen Idec Inc, 3; **A. Ranger**, Biogen Idec Inc, 1, Biogen Idec Inc, 3.

1742

Effects Of Blisibimod, An Inhibitor Of B Cell Activating Factor, On Serum Immunoglobulins and Infection Risk In Patients With Systemic Lupus Erythematosus: Observations From The Placebo-Controlled Pearl-SC and Open-Label Extension Studies. Richard A. Furie[1], Matthew Thomas[2], Alvina Chu[3], Renee S. Martin[3], Colin Hislop[3] and Morton A. Scheinberg[4]. [1]The Feinstein Institute for Medical Research and North Shore-Long Island Jewish Health System, Lake Success, NY, [2]Health and Research Centre, Trivandrum, Kerala, India, [3]Anthera Pharmaceuticals Inc, Hayward, CA, [4]Rheumatology Hospital Abreu Sodre Pesquisa Clínica, São Paulo, Brazil.

Background/Purpose: To evaluate the effects of subcutaneously-administered blisibimod (A-623, AMG 623), an inhibitor of B-cell activating factor (BAFF), on IgG, IgM and infection risk in patients with systemic lupus erythematosus (SLE) during the phase 2b clinical trial PEARL-SC (NCT01162681) and the ensuing open-label extension (OLE) study (NCT01305746).

Methods: 547 SLE patients with anti-double-stranded DNA or anti-nuclear antibodies and SELENA-SLEDAI score ≥6 at baseline were enrolled into the PEARL-SC study, and randomized 1:1 to receive placebo or blisibimod administered at 1 of 3 dose levels, 100 mg weekly (QW), 200 mg QW, or 200 mg every 4 weeks. In the PEARL-SC study, subjects received blinded study drug for up to 52 weeks (with a median of 37 weeks) or until the last subject completed 6 months of study drug therapy. A total of 382 subjects enrolled in the OLE study and received blisibimod. The efficacy, safety and tolerability of blisibimod in the combined studies were evaluated through March 2013 using clinical evaluations, adverse event reporting and laboratory data.

Results: Consistent with the effects of blisibimod on inflammation biomarkers reported previously (total B cell counts, C3, C4), significant decreases in immunoglobulins IgG and IgM were evident in patients in the pooled blisibimod group compared with placebo from Week 8 through Week 52 (percent changes with blisibimod vs placebo in IgG= −14.1% vs −3.9%, and IgM= −34.6% vs −9.3%, p≤0.003, N=94 at Week 52). Similarly, significant decreases in anti-dsDNA antibody titers were observed with blisibimod from Week 4 through Week 52 (−23.5% vs 7.9%, p=0.008, N=90 at Week 52). The effects of blisibimod 200mg QW were similar to

those observed in the pooled blisibimod group. In addition, after the end of the placebo-controlled study, IgG, IgM, and anti-dsDNA levels continued to be lower compared with pre-treatment levels through Week 80 (changes in IgG= −10.7%, IgM= −34.6%, N=31; change in anti dsDNA= −26.6%, N=20).

There was no difference between treatments in the numbers of subjects reporting infections: placebo 62.0% and blisibimod 58.2%. Furthermore, the mean concentrations of IgG in patients who reported infections were similar between the pooled placebo group (14.6–16.2 g/L) and the pooled blisibimod group (12.9–16.6 g/L).

Blisibimod was safe and well-tolerated at all dose levels with no meaningful imbalances in serious adverse events or infections between blisibimod and placebo. Amongst the commonly-reported AEs, imbalance was observed only with injection site reactions (200mg QW blisibimod=15%, matched placebo=7%), but these were not serious or severe and did not result in discontinuation of treatment. During the placebo-controlled study, critically low IgG levels (<4g/L) were observed in 1/280 subjects in blisibimod group compared with 0/266 subjects on placebo.

Conclusion: In patients with SLE, blisibimod induces pharmacological effects on immunoglobulins that are consistent with a BAFF-mediated inhibition of B cells and plasma cells, without adversely impacting the risk of infection. These data support further evaluation of blisibimod in patients with SLE and other B cell-mediated diseases.

Disclosure: R. A. Furie, Anthera Pharmaceuticals, 9; **M. Thomas**, None; **A. Chu**, Anthera Pharmaceuticals, 3, Anthera Pharmaceuticals, 1; **R. S. Martin**, Anthera Pharmaceuticals, 3, Anthera Pharmaceuticals, 1; **C. Hislop**, Anthera Pharmaceuticals, 1, Anthera Pharmaceuticals, 3, Anthera Pharmaceuticals, 1; **M. A. Scheinberg**, None.

1743

Administration Of AMG 557, a Human Anti-B7RP-1 (ICOSL) Antibody, Leads To The Selective Inhibition Of Anti-KLH IgG Responses In Subjects With SLE: Results Of a Phase 1 Randomized, Double-Blind, Placebo-Controlled, Sequential, Rising, Multiple-Dose Study.

Barbara Sullivan[1], Wayne H. Tsuji[2], Vishala L. Chindalore[3], Thomas D. Geppert[4], Alla Rudinskaya[5], Patricia Pardo[6], Alan Kivitz[7], C. Michael Neuwelt[8], Meggan Mackay[9], R. John Looney[10], J. Carter Thorne[11], Marilee Andrew[2], Greg Arnold[1], Michael Boedigheimer[1], Kit Chiu[1], Cherie Green[1], Arunan Kaliyaperumal[1], Christine Wang[1], Andrew Welcher[1] and James Chung[1]. [1]Amgen, Thousand Oaks, CA, [2]Amgen, Seattle, WA, [3]Anniston Medical Clinic PC, Anniston, AL, [4]Metroplex Clinical Research Center, LLC, Dallas, TX, [5]Danbury Hospital, Danbury, CT, [6]MRA Clinical Research, Miami, FL, [7]Altoona Center for Clinical Research, Duncansville, PA, [8]East Bay Rheumatology Research Institute, San Leandro, CA, [9]Feinstein Institute for Medical Research, Manhasset, NY, [10]University of Rochester, Rochester, NY, [11]Southlake Regional Health Centre, Newmarket, ON.

Background/Purpose: The interaction of inducible costimulator (ICOS) with its ligand, B7-related protein-1 (B7RP-1 or ICOSL), plays a role in T cell differentiation, cytokine production, and T cell dependent help for B cells. Blockade of the B7RP-1/ICOS pathway may be efficacious in treating SLE and other autoimmune diseases. AMG 557 is a human IgG2 monoclonal antibody that binds to B7RP-1, inhibiting its interaction with ICOS. Safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of multiple dose administration of AMG 557 were assessed in SLE subjects.

Methods: Fifty-six subjects with mild, stable SLE received multiple doses of AMG 557 or placebo in a 3:1 ratio ranging from 6 mg to 210 mg SC (every 2 weeks × 7 doses). Subjects received an intradermal injection of the neoantigen keyhole limpet hemocyanin (KLH) on days 57 and 85 (1 mg, Biosyn™). Adverse events, safety laboratory tests and disease activity were assessed. Serum AMG 557 concentrations and anti-AMG 557 binding and neutralizing antibodies were measured during the study. B7RP-1 target occupancy (TO) and an immunophenotyping panel selected for SLE and the ICOS pathway were measured in whole blood (WB) by flow cytometry. Serum protein and WB RNA biomarkers associated with SLE were measured by ELISA and microarray, respectively. Measurement of serum anti-KLH IgG and IgM antibodies was conducted by a flow cytometric bead array assay.

Results: The tolerability of multiple doses of AMG 557 up to 210 mg SC was acceptable. Most adverse events were grade 1 and 2 and no grade 3 adverse events were attributed to AMG 557. Serious adverse events were reported for 5 subjects (12%) who received AMG 557 and 2 subjects (14%) who received placebo. Serum AMG 557 exposure increased greater than dose-proportionally from 6 – 70 mg SC and approximately dose-proportionally from 70 – 210 mg SC. No subjects tested positive for neutralizing anti-AMG 557 antibodies. Mean TO was greater than 50% in the 18 mg dose group (and above) and was greater than 90% from days 71 – 141 in the 140 mg group and from days 5 – 169 in the 210 mg group. A significant reduction in anti-KLH IgG response was observed in the subjects treated with AMG 557 compared to subjects treated with placebo ($p = 0.0044$). No difference in anti-KLH IgM response was observed between the AMG 557 and placebo groups. A consistent effect of AMG 557 on SLE disease activity or SLE biomarkers was not observed.

Conclusion: Multiple doses of AMG 557 up to 210 mg SC demonstrated an acceptable safety profile. AMG 557 showed dose-proportional PK above the 70 mg dose level. Binding of AMG 557 to B7RP-1 was dose-related, reversible, and reached maximum observed levels in the 140 mg SC and greater dose groups. Significant and selective reduction in the anti-KLH IgG response was observed with AMG 557 treatment, without reduction in the anti-KLH IgM response, demonstrating a pharmacodynamic effect of multiple doses of AMG 557 in subjects with SLE and consistent with the biology of the ICOS pathway. No impact on disease activity was observed in these mild, stable SLE patients. These data support further evaluation of AMG 557 in SLE.

Disclosure: B. Sullivan, Amgen, 3, Amgen, 1; **W. H. Tsuji**, Amgen, 3, Amgen, 1; **V. L. Chindalore**, Amgen, 9; **T. D. Geppert**, Amgen, 9; **A. Rudinskaya**, Amgen, 9; **P. Pardo**, Amgen, 9; **A. Kivitz**, AbbVie, Amgen, AstraZeneca, BMS, Celgene, Genentech, Janssen, Pfizer, and UCB, 2, BMS, Genentech, UCB, AbbVie, Pfizer, 5, Pfizer, BMS, 8; **C. M. Neuwelt**, GSK and HGS, 8, Amgen, 9; **M. Mackay**, Amgen, 9; **R. J. Looney**, Amgen, 9; **J. C. Thorne**, Amgen, 5, Pfizer Inc, 5, Abbott Laboratories, 5, Bristol-Myers Squibb, 5, Centocor, Inc., 5, Merck Pharmaceuticals, 5, Roche Pharmaceuticals, 5, UCB, 5; **M. Andrew**, Amgen, 3, Amgen, 1; **G. Arnold**, Amgen, 3, Amgen, 1; **M. Boedigheimer**, Amgen, 3, Amgen, 1; **K. Chiu**, Amgen, 3, Amgen, 1; **C. Green**, Amgen, 3, Amgen, 1; **A. Kaliyaperumal**, Amgen, 3, Amgen, 1; **C. Wang**, Amgen, 3, Amgen, 1; **A. Welcher**, Amgen, 3, Amgen, 1; **J. Chung**, Amgen, 1, Amgen, 3.

ACR Concurrent Abstract Session

Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's - Clinical Aspects and Therapeutics I

Monday, October 28, 2013, 2:30 PM–4:00 PM

1744

Identifying Trajectories of Lung Function Change Over Time in Scleroderma.

Ada Man[1], Todd Davidyock[1], Laura Western[2], Michael Ieong[1], Yuqing Zhang[1] and Robert W. Simms[1]. [1]Boston University School of Medicine, Boston, MA, [2]University of Maryland, Baltimore, MD.

Background/Purpose: Interstitial lung disease (ILD) is a leading cause of scleroderma (SSc) mortality, yet little is known about how changes in lung function over time varies among patients with SSc. We sought to identify trajectories of change in % predicted forced vital capacity (% pFVC) and their associated clinical variables in SSc patients over a 12-year period.

Methods: FVC values were obtained from serial pulmonary function tests performed as part of clinical care in SSc patients at Boston University Medical Center from January 2000-August 2012. SSc diagnoses were confirmed and clinical data obtained by chart review. Patients with ≥3 FVC values were included. We described the trajectories of % pFVC change over time using a group-based mixture model (SAS Proc Traj) that identifies relatively homogenous clusters of % pFVC change within a study population. Baseline demographic and clinical variables were examined for association with the identified trajectories of change using multivariable polytomous regression.

Results: In 253 SSc patients (1613 FVC values) we identified 4 trajectory groups of % pFVC change over time: fast decline (13%), slow decline (21%), improving (45%), and normal stable (21%) (Figure). Mean

baseline % pFVC was lowest in the fast decline (56.5±16) and highest in the normal stable group (100±11.9). At baseline, the fast decline group had the highest proportion of males, African-Americans, patients with diffuse subtype, overlap features, anti-Scl70 positivity, ILD, pulmonary hypertension, myositis, and cyclophosphamide use. The normal stable group had the highest proportion of anti-centromere positive patients. In the multivariable model, younger age at baseline and at diagnosis, male sex, ILD and cyclophosphamide use were significantly associated with fast decline. Diffuse subtype was inversely associated with being in the normal stable group. Pulmonary hypertension was non-significantly associated with fast decline.

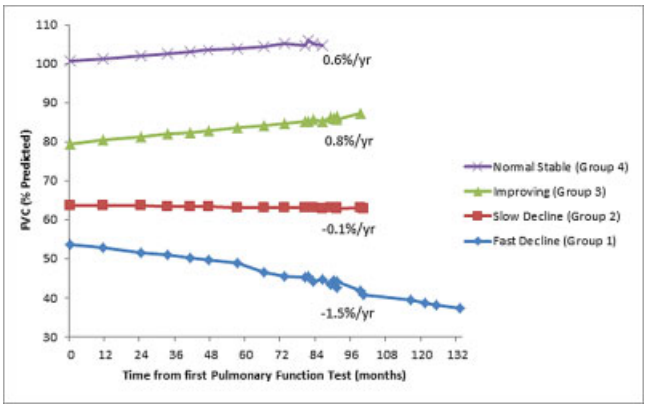

Figure. FVC Trajectories

Conclusion: SSc patients receiving standard care in a tertiary care setting presented 4 distinct trajectories of %pFVC change, with approximately 1/3 of them experiencing % pFVC decline over time. As expected, low % pFVC and ILD at baseline were associated with fast decline. Younger age, younger age at diagnosis and male sex were also associated with fast decline and are factors not consistently noted in previous studies. The identification of distinct trajectories of lung function in SSc confirms what has been anecdotally observed and allowed us to estimate the proportions of such groups. Studying risk factors according to group-based modeling may have advantages over traditional methods and may be useful in future studies of biomarkers and other patient centered outcomes.

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1745

Prediction Of Pulmonary Complications In Systemic Sclerosis - Model Development and Validation. Svetlana I. Nihtyanova[1], Benjamin E. Schreiber[2], Voon H. Ong[3], John G. Coghlan[4], Athol U. Wells[5] and Christopher P. Denton[1]. [1]Royal Free and University College Medical School, London, United Kingdom, [2]National Pulmonary Hypertension Service, London, United Kingdom, [3]The Royal Free and University College Medical School, London, United Kingdom, [4]The Royal Free Hospital NHS Foundation Trust, London, United Kingdom, [5]Department of Radiology, London, United Kingdom.

Background/Purpose: Pulmonary complications contribute substantially to systemic sclerosis (SSc) associated morbidity and are the most frequent disease-related cause of death. We explore predictors of clinically significant pulmonary fibrosis (csPF) and pulmonary hypertension (PH) in a large single-centre cohort of unselected SSc patients.

Methods: The study cohort consisted of consecutive patients with disease onset between 1995 and 1999. Multivariable Cox regression was used for model building. Continuous variables were categorised and risk points, based on the β values associated with the predictor variables were calculated. Internal validation of the model was done in an independent second cohort of consecutive SSc subjects with disease onset between 2000 and 2003.

Results: A total of 398 SSc patients, 146 with diffuse cutaneous (dc)SSc and 252 with limited cutaneous (lc)SSc, formed the predictor model derivation cohort, while 279 (130 dcSSc, 149 lcSSc) were used for model validation. Frequency of csPF was very similar in the derivation cohort (22% of lcSSc,42% of dcSSc) and the validation cohort (21% of lcSSc and 40% of dcSSc). Cumulative frequency of PH was slightly lower in the validation cohort (9% in lcSSc and 10% in dcSSc) compared to the derivation cohort (17% of lcSSc and 12%of dcSSc), potentially reflecting a shorter follow-up period.

In a multivariable analysis, significant positive predictors of csPFwere dcSSc subset (HR 1.77, p=0.027), age at onset (HR 1.02, p=0.031) and anti-topoisomerase I antibody (ATA), which was time-dependent, therefore we used its interaction term with disease duration in years (HR 1.16, p=0.001). Significant negative predictors were forced vital capacity (FVC) (HR 0.97, p=0.003), carbon monoxide diffusing capacity (DLCO) (HR 0.97, p=0.006), and anti-centromere antibodies (ACA)(HR 0.19, p=0.003). The final model using categorised variables and risk points is shown in Table1. The AUC for the model using risk points was 0.81. Risk score was calculated for all patients from the validation cohort and the AUC was 0.82.

For the PH prediction model the variables that demonstrated significant association in a multivariable analysis were age (HR 1.03, p=0.026), DLCO (HR 0.94, p<0.001), creatinine (HR 1.004, p=0.026), ATA (HR 0.41, p=0.04), anti-RNA polymerase antibody (HR 3.23, p=0.023), anti-U3RNP antibody (HR 3.92, p=0.017) and presence of renal crisis (SRC) within the first 5 years of disease (HR 0.004, p=0.009). In addition, there was one significant interaction in the model between SRC and DLCO (HR 1.08, p=0.019). Details of the model using categorical variables and risk points are presented in Table 1. The model using risk scores had AUC 0.79 which was replicated in the validation cohort.

Table 1. Multivariable analysis with categorical variables and risk score points for survival, pulmonary fibrosis and pulmonary hypertension

	Variables	β	HR	95.0% CI for HR		p-value	Points
Pulmonary fibrosis	DcSSc	0.526	1.692	1.052	2.721	0.03	1
	Age>55 years	0.306	1.358	0.866	2.127	0.182	1
	FVC 65–80%	0.542	1.719	1.005	2.939	0.048	1
	FVC<65%	1.157	3.18	1.765	5.727	<0.001	2
	DLCO≤55%	1.108	3.027	1.752	5.231	<0.001	2
	ACA	−1.728	0.178	0.061	0.519	0.002	−3
	ATAxT (5 years)	0.707	2.028	1.291	3.186	0.002	1
Pulmonary hypertension	Age>55years	0.565	1.759	0.991	3.124	0.054	1
	DLCO 55–65%	1.247	3.481	1.161	10.442	0.026	1
	DLCO<55%	2.492	12.089	4.591	31.83	<0.001	2
	Creatinine>85μmol/L	0.43	1.538	0.805	2.939	0.192	0
	ATA	−0.926	0.396	0.172	0.915	0.03	−1
	ARA	0.681	1.975	0.839	4.649	0.119	1
	AFA	1.155	3.175	1.192	8.454	0.021	1
	SRC5y	1.541	4.668	0.847	25.715	0.077	2
	SRC5y*DLCO 55–65%	−1.526	0.217	0.015	3.097	0.26	−2
	SRC5y*DLCO<55%	−2.754	0.064	0.006	0.674	0.022	−3

Conclusion: We present predictive models that could be used as clinical tools in unselected SSc cases for patient risk stratification and could facilitate cohort enrichment for event driven studies.

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Pericardial Effusions Are Not a Poor Prognostic Factor In Systemic Sclerosis Patients With Pulmonary Hypertension. Elana J. Bernstein[1], Jessica K. Gordon[1], Wei-Ti Huang[1] and Virginia D. Steen[2]. [1]Hospital for Special Surgery, New York, NY, [2]Georgetown University Medical Center, Washington, DC.

Background/Purpose: Pulmonary hypertension (PH) (defined as a mean pulmonary arterial pressure ≥ 25 mmHg on right heart catheterization) is a leading cause of death in patients with systemic sclerosis (SSc). Pericardial effusions (PEf) have been shown to be a poor prognostic indicator in patients with idiopathic pulmonary arterial hypertension (PAH). The World Health Organization (WHO) classifies PH into 5 groups based on etiology. SSc patients most commonly fall into groups 1 (PAH), 2 (PH due to left heart disease), and 3 (PH due to lung disease or hypoxemia). Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) is a multicenter, prospective registry of SSc patients with PH (SSc-PH) or at high risk for the development of PH. The aim of this study was to compare the survival of SSc-PH patients with PEf

to the survival of SSc-PH patients without PEf, and to describe the frequency and associations of PEf in SSc-PH patients.

Methods: This is a prospective cohort study of 260 SSc-PH patients who were enrolled in the PHAROS registry between 2006 and 2012. Statistical analysis was performed using the Kaplan-Meier method and chi-square test.

Results: The mean age of subjects was 60 years (± 11); 81.6% were female, 65.0% had limited cutaneous (lc) SSc, 29.5% were anti-centromere antibody (ACA) positive, and 65.8% had WHO group 1 PH. The mean duration of follow-up in PHAROS was 2.3 years (± 1.9) (see Table). The 3-year cumulative survival rate was 74.8%. Fifty-nine (22.7%) patients died during the course of follow-up. Forty-eight percent of all SSc-PH patients had a PEf at some point in their disease course – 53.0% in group 1, 37.2% in group 2, and 39.5% in group 3 (p=0.086). There was no statistically significant difference in survival between the SSc-PH patients with PEf and those without across the entire cohort, or when analyzing WHO groups 1, 2, and 3 separately. Patients with ACA were statistically significantly more likely to have had a PEf than patients with anti-Scl-70 antibody or other SSc-specific autoantibodies (58% vs. 31% vs. 47%, respectively, p<0.04). The frequency of PEf was not statistically significantly different between patients with lcSSc and diffuse cutaneous SSc; between patients of different races; or between patients who died from SSc-related causes and those who died from non-SSc-related causes.

Table. Characteristics of SSc Patients in PHAROS

Characteristics	SSc Patients (N=260)
Age – yr, mean ± SD	60.4 ± 11.3
Duration of follow-up – yr, mean ± SD	2.3 ± 1.9
Female sex – no. (%)	200/245 (81.6)
White race – no. (%)	184/244 (75.4)
Limited cutaneous SSc – no. (%)	165/254 (65.0)
WHO group 1 (PAH)	171/260 (65.8)
WHO group 2 (PH due to left heart disease)	45/260 (17.3)
WHO group 3 (PH due to lung disease or hypoxemia)	44/260 (16.9)
Pericardial effusion – no. (%)	121/252 (48.0)
Anti-centromere antibody – no. (%)	71/241 (29.5)
Anti-Scl-70 antibody – no. (%)	33/241 (13.7)
Deceased – no. (%)	59/260 (22.7)

Conclusion: Unlike in idiopathic PAH, there was no difference in survival between SSc-PH patients with PEf and those without. Thus, although PEf are common in SSc patients as a whole (19% in SSc patients at high risk for PH) – and even more common in SSc-PH patients – they are not a poor prognostic sign in SSc patients with WHO groups 1, 2, or 3 PH. SSc-PH patients with ACA were more likely to have PEf than those with anti-Scl-70 or other SSc-specific autoantibodies. The clinical significance of this association will continue to be examined via long-term follow-up of this cohort.

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Plasma MCP-1 and IL-10 Levels Predict Long-Term Progression Of Interstitial Lung Disease In Patients With Early Systemic Sclerosis. Minghua Wu, Claudia Pedroza, Gloria Salazar, Xiaodong Zhou, John D. Reveille, Maureen D. Mayes and Shervin Assassi. University of Texas Health Science Center at Houston, Houston, TX.

Background/Purpose: The currently available clinical markers are not reliable predictors of long-term progression of systemic sclerosis (SSc) related interstitial lung disease (ILD). SSc patients have a distinct cytokine profile but the predictive significance of these cytokines for long-term progression of ILD has not investigated in early SSc cohorts. Herein, we examine the predictive significance of 11 key cytokines for progression of ILD and survival in a large early SSc cohort.

Methods: The plasma levels of 9 key Th1/Th2 cytokines (IL-6, MCP-1, TNF-α, IL-8, IL-5, IL-12, IL-10, IL13, and IL1β) and two interferon inducible chemokines (IP-10 and ITAC) were determined in the baseline samples of 266 SSc patients enrolled in the GENISOS cohort. The primary outcome was decline in forced vital capacity (FVC% predicted) over time. A total of 1016 FVC measurements fulfilled the American Thoracic Society criteria and were included in the analysis. The mean follow-up time was 4.4 years. The predictive significance for long-term change in FVC was investigated by a joint analysis of longitudinal measurements (sequentially obtained FVC% predicted) and survival data. This approach allows inclusion of all FVC measurements and accounts for dependency on survival. The primary cultured skin fibroblasts from SSc patients (n=10) and matched controls (n=10) were stimulated with MCP-1 for 24 and 48hrs and measured TGF- β1 protein levels by ELISA.

Results: Diffuse skin involvement was present in 156 patients (59%) and mean disease duration at enrollment was 2.5 years. After adjustment for age, gender, and ethnicity, MCP-1 and IL-10 were significant predictors of ILD progression. MCP-1 predicted faster decline in FVC% predicted (b=−0.57, 95% CI: −1.11–−0.04, p=0.032) while IL-10 predicted a slower decline in FVC% (b=0.26, 95% CI: 0.06–0.46, p=0.01) and had a protective effect. The predictive significance of MCP-1 and IL-10 did not change substantially in a multivariable that included both cytokines in addition to age, gender, and ethnicity (b=−0.64, p=0.014 and b=0.26, p=0.008, respectively).

The other investigated cytokines did not have independent predictive significance for ILD progression. Importantly, IL-6 did not predict faster decline in FVC% predicted (p=0.35).

Plasma MCP-1 was also predictive of poorer survival (HR: 1.93, 95% CI: 1.04 – 3.58, p= 0.032) while IL-10 did not predict survival.

MCP-1 and IL-10 levels were also determined in plasma from 97 age-, gender-, and ethnicity-matched unaffected controls. Patients had higher MCP-1 and IL-10 levels than unaffected controls (p= 0.001and p=0.002, respectively).

In-vitro experiments with skin fibroblasts showed stimulation of TGF-β1 protein production with MCP-1 in patients and control fibroblasts, confirming the profibrotic effect of this cytokine.

Conclusion: MCP-1 is an important pro-fibrotic cytokine that predicts faster ILD progression and poorer survival in SSc while IL-10 predicts a slower ILD progression supporting the previously in-vitro studies indicating an anti-fibrotic effect of this cytokine. These findings can have important implications for drug and biomarker development in SSc related ILD.

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Autoantibodies To RuvBL1 and RuvBL2: A Novel Systemic Sclerosis-Related Antibody Associated With Diffuse Cutaneous and Skeletal Muscle Involvement. Kenzo Kaji[1], Noreen Fertig[2], Thomas A. Medsger Jr.[2], Takashi Sathoh[3], Kana Hoshino[3], Yasuhito Hamaguchi[1], Minoru Hasegawa[1], Mary Lucas[2], Andrew Schnure[2], Fumihide Ogawa[4], Shinichi Sato[5], Kazuhiko Takehara[1], Manabu Fujimoto[1] and Masataka Kuwana[3]. [1]Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan, [2]University of Pittsburgh, Pittsburgh, PA, [3]Keio University School of Medicine, Tokyo, Japan, [4]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [5]The University of Tokyo, Tokyo, Japan.

Background/Purpose: Detection of serum autoantibodies is useful in diagnosis, disease subgrouping, and prediction of subsequent organ involvement and prognosis in patients with systemic sclerosis (SSc). Currently, SSc-related autoantibodies consisted of at least 9 specificities, which are identified in ~80% of the entire SSc population, suggesting the possibility that other autoantibodies remain undiscovered. In this study, we have identified a novel SSc-related antibody against a complex consisting of RuvBL1 and RuvBL2 (RuvBL1/2) and evaluated its clinical correlations.

Methods: We first analyzed 316 consecutive patients with SSc, 290 disease controls including, patients with SLE, PM, DM, RA, interstitial lung disease alone, or autoimmune hepatitis, and 50 healthy subjects (Kanazawa cohort). Autoantibody specificities were analyzed using RNA and protein immunoprecipitation assays. Autoimmune targets were affinity-purified using patients' sera and subjected to liquid chromatography-mass spectrometry. SSc patients in two additional cohorts (Keio and Pittsburgh) were also included in analysis for evaluating prevalence and clinical correlations.

Results: By protein immunoprecipitation assay, 6 SSc sera (1.9%) reacted with doublets with molecular weights around 50 kDa. This antibody specificity was not detected in any sera obtained from a total of 290 disease controls or 50 healthy controls. Liquid chromatography-mass spectrometory of the partially purified autoantigen and additional immunoblots-based analysis revealed that this antibody specificity recognized RuvBL1/2, which is involved in many important cellular processes, such as transcription and DNA repair. Anti-RuvBL1/2 antibody was also found in 4 (1.5%) of 272 consecutive SSc patients in the Keio cohort, and in 5 (1.1%) of 463 consecutive SSc patients in the Pittsburgh cohort. In all three cohorts, SSc in overlap was the predominant disease subset in patients with anti-RuvBL1/2 ($P < 0.0001$). Diffuse skin thickening was more common in patients with anti-RuvBL1/2 in general and in those with SSc in overlap, compared to those without ($P < 0.04$). In terms of organ involvement, skeletal muscle involvement was frequent in patients with anti-RuvBL1/2 than those without ($P < 0.0003$). When we examined potential differences in clinical correlations between anti-RuvBL1/2 and other SSc-related antibodies associated with inflammatory myopathy, such as anti-PM-Scl and anti-Ku, age at onset was older and the proportion of males was higher in patients with anti-RuvBL1/2 than in those without ($P = 0.0001$ and 0.002, respectively). In patients with anti-RuvBL1/2, diffuse skin thickening was more prevalent ($P = 0.004$), the maximum mRSS in patients with diffuse cutaneous involvement was greater ($P = 0.001$), and dermatomyositis rashes were less common ($P = 0.01$), compared to patients with anti-PM-Scl or anti-Ku.

Conclusion: We have identified a novel SSc-related antibody reactive with a RuvBL1/2 complex, which is associated with a unique combination of clinical features, including myositis overlap and diffuse cutaneous involvement.

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Treatment Strategies and Outcomes In Patients With Systemic Sclerosis and Acute Myocardial Infarction. Priya Prakash, Dhaval Kolte, Sahil Khera, Jagadish Khanagavi, Marjan Mujib, Chandrasekar Palaniswamy, Farrah Gutwein, Sachin Sule, Wilbert S. Aronow, William H. Frishman and Julia Ash. New York Medical College, Valhalla, NY.

Background/Purpose: Systemic Sclerosis (SSc) is associated with an increased risk of cardiovascular diseases, including acute myocardial infarction (AMI). However, whether SSc influences treatment choice and in-hospital outcomes in patients with AMI remains unknown.

Methods: We used the 2002–2010 Nationwide Inpatient Sample databases to identify all patients aged ≥18 years with the principal diagnosis of AMI using International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) code 410.xx. Secondary diagnosis of SSc was confirmed with ICD-9-CM code 710.1. Patients with rheumatoid arthritis (714.0–714.2), systemic lupus erythematosus (710.0), dermatomyositis (710.3) and polymyositis (710.4) were excluded. Multivariable logistic regression was used to compare treatment choice and outcomes between AMI patients with and without SSc.

Results: From 2002–2010, among 5,966,599 patients with AMI, 3,890 (0.07%) had SSc. Patients with SSc were more likely to be younger, women, white and had a lower prevalence of smoking, dyslipidemia, obesity, hypertension, diabetes, known coronary artery diseases, carotid artery diseases, and a higher prevalence of congestive heart failure, peripheral vascular disease, chronic kidney disease, pulmonary circulation disorders, atrial fibrillation, atrioventricular block, deficiency anemia, chronic blood loss anemia, hypothyroidism and coagulopathy. SSc patients were more likely to receive medical therapy alone (OR 1.20, 95% CI 1.10–1.32, p<0.001) and thrombolysis (OR 1.47, 95% CI 1.12–1.92, p=0.005), and less likely to receive coronary artery bypass grafting (CABG) (OR 0.55, 95% CI 0.45–0.68, p<0.001), as compared to those without SSc. Utilization of percutaneous coronary intervention was similar in AMI patients with and without SSc (OR 0.97, 95% CI 0.88–1.06, p=0.486). Overall risk-adjusted in-hospital mortality was higher in patients with SSc (OR 1.60, 95% CI 1.40–1.84, p<0.001), as compared to those without SSc. Patients with SSc had less cardiogenic shock (OR 0.50, 95% CI 0.39–0.64, p<0.001), more gastrointestinal bleeding (OR 1.65 95% 1.38–1.97, p<0.001), and longer average length of stay (5.9±7.1 versus 5.1±6.1 days, p<0.001). Incidence of acute stroke was similar in AMI patients with and without SSc (OR 0.85, 95% CI 0.61–1.17, p=0.321).

Conclusion: In patients with AMI, SSc is associated with an increased use of medical therapy alone and thrombolysis, and lesser use of CABG. Compared to patients without SSc, SSc patients with AMI have higher in-hospital mortality, more gastrointestinal bleeding, less cardiogenic shock and longer length of stay.

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ACR Concurrent Abstract Session
Vasculitis II
Monday, October 28, 2013, 2:30 PM–4:00 PM

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Short and Long-Term Biological Therapy In Refractory Uveitis Of Behcet's Syndrome. Multicenter Study Of 124 Patients. Francisco Ortiz-Sanjuan[1], Vanesa Calvo-Río[1], Ricardo Blanco[2], Emma Beltrán[3], Juan Sánchez-Bursón[4], Marina Mesquida[5], Alfredo M. Adan[5], M Hernandez Grafella[3], E Valls Pascual[6], L Martínez-Costa[6], Agustí Sellas-Fernàndez[7], Miguel Cordero-Coma[8], Manuel Diaz-llopis[9], David Salom[9], Jl García Serrano[10], Norberto Ortego[10], JM Herreras[11], Alejandro Fonollosa[12], A Aparicio[13], O Maíz[14], A Blanco[14], I Torre[15], Cruz Fernández-Espartero[16], V Jovani[17], D Peitado-Lopez[18], Esperanza Pato[19], J Cruz[20], J. Carlos Fernandez-Cid[20], E. Aurrecoechea[21], M García[22], M Caracuel[23], Carlos Montilla[24], A Atanes[25], F Francisco[26], S Insua[27], S González-Suárez[28], A Sánchez-Andrade[29], F Gamero[30], Luis Linares[31], F Romero-Bueno[32], AJ García González[33], Raquel Almodovar[34], E Minguez[35], C Carrasco Cubero[36], Alejandro Olive Marques[37], J Vázquez[38], O Ruiz Moreno[39], F Jimenez-Zorzo[39], J Manero[39], Javier Loricera[1] and Miguel Angel González-Gay[1]. [1]Hospital Universitario Marqués de Valdecilla. IFIMAV. Santander. Spain, Santander, Spain, [2]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain, [3]Hospital General Universitario, Valencia, Valencia, Spain, [4]Hospital de Valme. Sevilla, Sevilla, Spain, [5]Hospital Clínic of Barcelona, Barcelona, Spain, [6]Hospital Peset Valencia, Valencia, Spain, [7]Hospital Val d'Hebron. Barcelona, Barcelona, Spain, [8]Hospital de León, León, Spain, [9]Hospital Universitario La Fe de Valencia, Valencia, Spain, [10]Hospital San Cecilio. Granada, Granada, Spain, [11]Hospital Universitario, IOBA. Valladolid, Valladolid, Spain, [12]Hospital de Cruces. Bilbao, Bilbao, Spain, [13]Hospital de Toledo., Toledo, Spain, [14]Hospital Donosti San Sebastian, San Sebastián, Spain, [15]Hospital Basurto. Bilbao, Bilbao, Spain, [16]Hospital Universitario de Móstoles, Madrid, Spain, [17]Hospital General de Alicante., Alicante, Spain, [18]Hospital Universitario La Paz Madrid, Madrid, Spain, [19]Hospital Clínico San Carlos. Madrid, Madrid, Spain, [20]Hospital de Pontevedra, Pontevedra, Spain, [21]Hospital Sierrallana. Torrelavega, Torrelavega, Spain, [22]Hospital La Princesa. Madrid, Madrid, Spain, [23]Hospital de Córdoba., Córdoba, Spain, [24]Hospital Universitario de Salamanca, Salamanca, Spain, [25]HUCA La Coruña., A Coruña, Spain, [26]Hospital Doctor Negrín Canarias., Canarias, Spain, [27]Hospital Universitario Santiago de Compostela, Santiago de Compostela, Spain, [28]Hospital Cabueñes, Gijón, Gijón, Spain, [29]Hospital Lucus Augusti Lugo, Lugo, Spain, [30]Hospital San Pedro Alcantara Caceres, Caceres, Spain, [31]Hospital Universitario Virgen de la Arrixaca. Murcia, Murcia, Spain, [32]Fundación Jimenez Díaz. Madrid, Madrid, Spain, [33]Hospital 12 de Octubre. Madrid, Madrid, Spain, [34]Hospital Universitario Fundación Alcorcón. Madrid, Alcorcon. Madrid, Spain, [35]Hospital Clínico de Zaragoza, Zaragoza, Spain, [36]Hospital de Mérida, Mérida, Spain, [37]Hospital Germans Trias i Pujol. Badalona, Barcelona, Spain, [38]Hospital de Ferrol. A Coruña, A Coruña, Spain, [39]Hospital Universitario Miguel Servet. Zaragoza, Zaragoza, Spain.

Background/Purpose: To evaluate short and long-term response to biological therapy in uveitis associated to Behçet's syndrome refractory to standard systemic treatment.

Methods: Multicenter study of 124 patients followed in uveitis units from 38 hospitals. All of them presented inadequate response to conventional therapy with corticosteroids and at least 1 systemic immunosuppressive drug.

The degree of ocular inflammation was evaluated according to "The Standardization of Uveitis Nomenclature (SUN)" (Am J Ophthalmol 2005; 140: 509–516) and macular thickness by optical coherence tomography (OCT). Comparisons were made between baseline and 1st week, 1st month, 6th month, 1st year, 2nd year, 3rd year and 4thyear. Statistical analysis was

performed using the software STATISTICA (StatSoft Inc. Tulsa, Oklahoma, USA). **Results** were expressed as mean±SD for variables with a normal distribution, or as median [25th-75th interquartile range (IQR)] when they were not normally distributed. The comparison of continuous variables was performed using the Wilcoxon test.

Results: We studied 124 patients/221 affected eyes (68 men/56 women) with a mean age of 38.6±10.4 years (range 10–67). HLA-B51 was positive in 66.1%. Besides oral steroids and before biologic therapy onset patients had received methylprednisolone i.v. boluses (34 patients), cyclosporine A (CyA) (102), methotrexate (MTX) (62) or azathioprine (AZA) (66). Anti-TNF drugs were the first choice biological agents; Infliximab (IFX) in 77 cases (62%) and adalimumab (ADA) in the remaining 47 cases (38%). They were used in 25 cases as monotherapy or in combination with: CyA (52 cases), MTX (27), AZA (17), mycophenolate (1), tacrolimus (1) or cyclophosphamide (1). The IFX regimen more frequently used were 5 mg/kg /i.v./every 4–8 weeks and ADA 40 mg/sc/EOW. In cases of refractory uveitis or intolerance to a 1stbiologic other agents were used; namely: Golimumab (4 cases), Tocilizumab (1 case), rituximab (1 case) and etanercept (1 case). The mean follow-up of anti-TNF therapy was 35.9±20.3 months. Visual acuity (VA), Tyndall, vitritis and OCT showed a rapid and statistically significant improvement at the 1^{a} week. From biological onset to 2 years mean improvement was observed in VA from 0.5±0.3 to 0.7±0.3 ($p<0.01$); tyndall from a median [IQR] of 1 [0–2] to 0 [0–0] ($p<0.01$) and vitritis, from a median [IQR] of 1 [0–2] to 0 [0–0] ($p<0.01$). At baseline, 50 patients, (80 eyes) had macular thickening (OCT>250μ) and 35 patients (49 eyes) had cystoid macular edema (CME) (OCT>300μ). The CME improved from 420±119.5 microns to 282.5±55 microns at 2 years ($p<0.01$).

The more severe side-effects observed were milliary tuberculosis and fatal lymphoma (in one case each).

	Basal active patients, N/ active eyes (%)	**1 week** active eyes (%)	**1 month** active eyes (%)	**6 months** active eyes (%)	**1 year** active eyes (%)	**2 years** active eyes (%)	**3 years** active eyes (%)	**4 years** active eyes (%)
Anterior inflammation (Tyndall)	80/57 %	51%	32.3%	19.3%	9.2%	11.7%	5.7%	6.1%
Vitritis	96/64.4%	58.4%	42.8%	24.6%	16.9%	13.9%	9.4%	5.8%
Choroiditis	28/17.6%	15.1%	12.1%	4.1%	2.5%	1.7%	0%	0%
Retinitis	45/30.7%	24.5%	14.3%	2.8%	0.5%	0.6%	1.1%	0%
Retinal vasculitis	89/61.1%	56.5%	34.8%	15.7%	7.1%	9.7%	8.2%	2.3%
Macular thickness ≥ 250 microns	55/61.4%	62.2%	56.5%	48.3%	43.5%	50%	27.3%	37.5%

Conclusion: Biological therapy, especially IFX and ADA, yields short and long-term efficacy and has a relatively safety profile in uveitis refractory to standard systemic treatment of Behcet's syndrome.

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1751

Ethnicity-Related Differences In Behçet's Disease In a French Multiethnic Country. David Saadoun[1], Mathieu Resche Rigon[1], Bertrand Wechsler[2], Du Le Thi Huong[3], Jean-Charles Piette[4] and Patrice P. Cacoub Sr.[4]. [1]Department of Internal Medicine and Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France, [2]CHU Pitié-Salpêtrière, Paris, France, [3]Groupe Hospitalier Pitié-Salpétrière, Paris, France, [4]Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Paris, France.

Background/Purpose: It has been suggested that Behçet's disease (BD) varies in its phenotypic expression in different ethnies and in different countries indicating that both environmental and genetic factors play a role in the aetiology of the condition. However, most of the evidence supporting these propositions arises from observational case series, which are subject of many sources of bias.

Objective. The present study was undertaken to investigate potential any ethnicity-related differences in the phenotype and prognosis of BD patients in a French multiethnic country.

Methods: We analyzed the phenotype and prognosis of 769 consecutive patients [median (IQR) age at diagnosis of 30.9 (24.9–37.2) years with 535 (69.6%) male] fulfilling the international criteria of classification for BD, in the 3 largest ethnic groups of our cohort [European (n=369), North African (n=350) and sub Saharan African (n=50)].

Results: Sub Saharan African BD patients had a higher frequency of arterial involvement (28% vs 13.2% vs 10.3%, p=0.004), a higher frequency of CNS involvement (48% vs 32.3% vs 29.5%, p=0.035), a higher frequency of cardiac involvement (16% vs 7.1% vs 4.3%, p=0.007), a higher rate of death (12% vs 6% vs 3.5%, p=0.029) and a lower frequency of HLA B51 allele (29.4 % vs 49.2% vs 55.8%, p=0.009) compared to those from north Africa and Europe, respectively. The 15-year mortality rate was of 19% in sub Saharan Africa's BD patients compared to 9% and 6% in those from north Africa and Europe, respectively (p=0.015). Logistic regression analysis showed that male gender (HR: 4.94, CI: 1.53–16.43), and arterial involvement (HR: 2.51, CI: 1.07–5.90) were independently associated with mortality.

Conclusion: In a French multiethnic country, sub Saharan African BD patients exhibited a worse prognosis which is likely related to their vascular phenotype.

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1752

Behçet′s Disease Activity: An Important Factor For Immunogenicity Of Unadjuvanted Influenza A/H1N1 Vaccine. Leandro L. Prado[1], Carla G.S. Saad[1], Julio C. B. Moraes[1], Ana Cristina Medeiros Ribeiro[1], Nadia E. Aikawa[1], Clovis A. Silva[1], Claudia G Schainberg[1], Percival D Sampaio-Barros[1], Alexander R. Precioso[2], Maria A. Ishida[3], Eloisa Bonfa[4] and Celio Goncalves[1]. [1]Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, [2]Instituto Butantan, São Paulo, Brazil, [3]Instituto Adolfo Lutz, São Paulo, Brazil, [4]University of Sao Paulo, Rheumatology Division, São Paulo, Brazil.

Background/Purpose: Routine annual influenza vaccination is the most effective method for preventing influenza virus infection and its complications. Influenza vaccine is recommended for all persons aged 6 months and older who do not have contraindications to vaccination. Despite those recommendations, there are no studies evaluating influenza vaccination influences on clinical manifestations in Behçet′s Disease (BD). Our objective is to evaluate short-term safety and efficacy of influenza A/California/7/2009/H1N1-like virus single vaccination and the potential deleterious effect of the vaccine in BD patients compared to healthy controls.

Methods: Eighty-five BD patients and 85 gender/age-matched healthy controls were evaluated before and 21-days after vaccination with unadjuvanted influenza A/H1N1-like virus regarding seroprotection/seroconversion, factor increase in geometric mean titre (FI-GMT), C-reactive-protein (CRP) levels and side effects. Brazilian BD Current Activity Form (BR-BDCAF) was used to assess BD activity.

Results: Seroconversion rate was significantly lower in BD patients compared to controls (69 vs. 83%, p=0.04). Similar rates of seroprotection (71 vs. 83%, p=0.06) and FI-GMT (p=0.96) were found. Interestingly, BD patients without seroconversion had significantly higher mean BR-BDCAF scores (6.0 ±4.1 vs. 3.8 ±4.3, p=0.009), with a significantly increased rate of active BD in this group (73 vs. 39%, p=0.003). Disease duration and glucocorticoid, immunosuppressors or TNF-blockers therapies did not affect seroconversion (p>0.05). Regarding side effects, patients had significantly increased rate of mild and transient reactions, such as fever (7 vs. 0%, p=0.02), headache, (27 vs. 12%, p=0.02), arthralgia (24 vs. 0.2%, p<0.001) and myalgia (25 vs. 9%, p=0.004). Moderate and severe side effects were not reported.

Conclusion: This is the first study to indicate appropriate influenza A/H1N1 vaccine safety and efficacy in BD, reinforcing its recommendation. Disease activity impaired humoral response to vaccination. Further studies are necessary to determine if a second dose would increase seroconversion rates in these patients.

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1753

An Outcome Survey Of 40 Patients With Budd-Chiari Syndrome Due To BEHÇET'S Syndrome Followed By A Single Center. Emire Seyahi, SerdaL Ugurlu, Erkan Caglar, Fatih Kantarci, Abdullah Sonsuz, Sebahattin Yurdakul and Hasan Yazici. Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey.

Background/Purpose: Budd-Chiari syndrome is a rare complication of BS with a frequency of < 1 %, and carries a high mortality rate. In a previous survey out of 14 Behcet patients with BCS, 10 (60 %) had died with a mean survival of 10 months (1). We assessed the outcome in a cohort of 40 BS patients with BCS diagnosed and followed by a single center between 1977 and 2012.

Methods: We reviewed records of about 8000 patients with BS who were registered at the multidisciplinary clinic at Cerrahpasa Medical Faculty between July 1977 and December 2012 (study closure). We identified 40 (37 M/ 3 F) patients who were diagnosed with BCS. The outcome of 40 patients was evaluated between September and December 2012. Attempts were made to contact every patient in this cohort by telephone calls or home visits. All thus contacted were called back to the outpatient clinic for a clinical evaluation, blood tests and hepatic Doppler USG. Hepatic Doppler USG specifically analyzed hepatic veins patency, intrahepatic collateral formation, caudate lobe hypertrophy, hepatomegaly, splenomegaly, and portal vein dilatation. Survival data were assessed by Kaplan-Meier analysis.

Results: A total of 40 BS patients with BCS were surveyed. The mean age of the patients at diagnosis of BS was 28.7 ± 8.6 years, and the mean age at the onset of BCS was 30.3 ± 8.5 years. A total of 35 patients received immunosuppressive treatment (cyclophophamide n= 31; azathioprine n =4) after being diagnosed with BCS. Only 2 patients had surgical interventions. One patient had percutaneous transluminal angioplasty another transjugular intrahepatic portosystemic shunting. Fifteen patients received anticoagulant treatment. Apart from this, 3 patients were treated with thrombolytic treatment which was ineffective. Additionally, 17 patients received diuretics. By the end of the study, we had the outcome information in all patients: 20 patients (19 M/1F) (50 %) had died, while the remaining 20 were alive. Of these, 17 could be re-evaluated in the clinic. Among the patients who had died, the median survival time was 8 months (IQR: 4– 54 months). The causes of mortality were mainly due to hepatic failure (n =17) (85 %). Additionally, one had died due to myocardial infarction, another due to suicide and another with unknown cause. Postmortem study was available in one patient. Mortality rate among patients diagnosed between 1977–2000 (10/15, 67 %) was somewhat higher (Log rank P= 0.75). compared to those diagnosed between 2001–2012 (10/25, 40 %), however, the difference did not reach statistical significance in the survival analysis. Final hepatic USG among 17 patients who survived showed occlusion in one ore more hepatic veins in 12, caudate lobe hypertrophy in 8, splenomegaly in 3, and portal vein dilatation in 3. It was noted that all 17 patients had multiple intrahepatic veno-venous collaterals with good drainage.

Conclusion: BCS due to BS still caries serious mortality. Mortality rate perhaps tend to decrease after 2000. Formation of intrahepatic veno-venous collaterals seem to be the only factor important in the survival.

Reference:

(1) Bayraktar Y, et al. Budd-Chiari syndrome: a common complication of Behçet's disease. Am J Gastroenterol. 1997;92:858–62.

Disclosure: E. Seyahi, None; **S. Ugurlu**, None; **E. Caglar**, None; **F. Kantarci**, None; **A. Sonsuz**, None; **S. Yurdakul**, None; **H. Yazici**, None.

1754

Safety and Efficacy Of Peg-IFNa/Ribavirin/Protease Inhibitor Combination In 34 Patients With HCV-Mixed Cryoglobulinemia Vasculitis. David Saadoun[1], Stanislas Pol[2], Vincent Thibault[3], Gilles Pialoux[4], François Blanc[5], Lucile Musset[6], Alexandre Karras[7], Olivier Decaux[8], Jean-Marc Ziza[9], Olivier Lambotte[10] and Patrice Cacoub Sr.[11]. [1]Department of Internal Medicine and Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France, [2]Hepatology, Cochin Hospital, Paris, France, [3]Virology, Pitié-Salpétrière, Paris, France, [4]hôpital Tenon, Paris, France, [5]hôpital Montpellier, Montpellier, France, [6]Laboratoire d'immunochimie, Pitié- Salpêtrière, Paris, France, [7]Hôpital Européen Georges Pompidou, APHP, Paris, France, [8]Rennes University Hospital, Rennes, France, [9]Croix Saint Simon Hospital, Paris, France, [10]Hopital Kremlin Bicêtre, Kremlin Bicêtre, France, [11]CHU Pitié-Salpêtrière, Paris, France.

Background/Purpose: The standard of care treatment of patients presenting a HCV-mixed cryoglobulinemia (MC) vasculitis includes Peg-IFNa plus Ribavirin, w/wo Rituximab. Thirty to 40% of patients are non-responders or relapsers to such combination.

Objective: To analyze the safety and efficacy of a Peg-IFNa/// Ribavirin/Protease inhibitor combination in HCV-MC vasculitis.

Methods: Open label, prospective, cohort study including 34 patients with HCV-MC vasculitis. Peg-IFNa//Ribavirin was associated to Telaprevir [375 mg three times daily for 12 weeks, 19 patients (56%) or Boceprevir (800 mg three times daily, 15 patients (44%) for 44 weeks] for 48 weeks.

Results: Mean age 58.9 years, 50% women, and 30/34 (88%) had HCV genotype 1. Twenty eight (83%) patients received previous antiviral therapy with Peg-IFNa//Ribavirin and the remaining 6 were naïve of antiviral therapy. Of the 28 patients with HCV-MC vasculitis previously treated with Peg-IFNa/Ribavirin, 16 (57.1%) were non-responders, 5 (17.8%) were partial responders and 7 (25.1%) were relapsers. Mean HCV RNA level was 5.7 Log copies/mL, mean ALT level was of 49.85 IU/mL and severe liver fibrosis (i.e. Metavir score 3 and 4) was noted in 14 (41.1%) cases. Twenty six patients had a type II MC and 7 had a type III. Main HCV-MC manifestations included purpura (n=21), polyneuropathy (n=19), arthralgia (n=14), and kidney involvement (n=9). The mean serum cryoglobulin and C4 rheumatoid factor levels were of 0.8 g/l and 0.10 g/l, respectively. Nineteen (55.9%) patients showed a complete clinical response of MC vasculitis and 15 (44.1%) were partial responders at the end of follow up. Sustained virological response (i.e. at week 60) could be assessed in 27/34 HCV MC patients and was achieved in 15 (55.5%) cases. All 34 patients experienced at least one treatment side effect including grade 3 anemia in 32%, grade 3 neutropenia in 6%, infection in 30%, pruritus in 35% and skin eruption under Telaprevir (6%). Antiviral therapy discontinuation was required in 12 (35.3%) patients for virological non-response (n=8), virological relapse (n=3) and depression (n=1).

Conclusion: Peg-IFNa///Ribavirin/protease inhibitor combination represents an effective new therapeutic option in HCV-MC vasculitis. Such therapeutic regimen should be administered cautiously considering the high rates of side effects.

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1755

Genetic Association Of Mitochondrial DNA Polymorphisms With Behçet's Disease In a Korean Population. Mi-Hye Kwon[1], Chung-Il Joung[1] and Jiwon Hwang[2]. [1]Konyang university hospital, Daejeon, South Korea, [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.

Background/Purpose: Behcet's disease (BD) is an inflammatory multisystemic disorder. Although precise etiopathogenesis should be elucidated, BD is known to be multifactorial and accumulating data suggest genetic mechanisms for the development of disorder. Variations in genomic DNAs have been investigated vigorously, while studies on mitochondrial DNAs (mtDNAs) are limited. Association between BD and mtDNA alteration is not well known yet, and there is one report about the association of m.709G>A in an Iranian population. This study was performed to investigate the potential association of mitochondrial single nucleotide polymorphisms (mtSNPs) and haplotypes with BD in a Korean population. To identify candidate mtSNPs, our group sequenced complete mtDNA genomes of patients with BD and normal controls and compared the frequency of mtSNPs.

Methods: Blood sample was collected from 20 patients and 10 healthy controls. Complete mtDNA genomes were sequenced using GeneChip® Human Mitochondrial Resequencing Array 2.0(MitoChip v2.0) (Affymetrix, Santa Clara, CA). Raw data (CEL files) were analyzed with GeneChip Sequence Analysis Software (GSEQ 4.1) and revised Cambridge reference sequence (rCRS) was used as reference sequence. Haplotypes were searched with sequences in the hypervariable region 1 and 2 with mtDNA manager (http://mtmanager.yonsei.ac.kr/). Chi square or Fisher's exact test were used to analyze the association of of mtSNPs between groups and to investigate possible association between clinical characteristics and mtSNPs. (SPSS ver. 18.0).

Results: We sequenced 16545 nucleotides from total of 16569 mitochondrial DNA nucleotides for each individual due to experimental method. With a quality score (QS) of 9, a total of 64 nucleotides were discordant with those of rCRS, and among them 6 discordant nucleotides were observed in all of the patients and healthy controls showing ethnic characteristics. m.200A>G, m.16129G>A, and m.16304T>C were more frequently observed in the patient group, while, m.150C>T was more frequent in the control group although statistically not significant. By Fisher's exact test, m.16182A>C, m.16183A>C, and m.16189T>C were associated with uveitis (p= 0.041, 0.022, and 0.014 respectively). None of the haplotypes we searched were associated with BD risk statistically, but B4a were more frequently observed in the patient group.(3 versus 0)

Conclusion: We report the first association study between BD and mitochondrial SNPs in a Korean population. In the present study, m.200A>G, m.16129G>A, m.16304T>C and m.150C>T could be novel candidate mtSNPs in BD in a Korean population.

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ACR/ARHP Combined Session
ACR/ARHP Combined Epidemiology Abstract Session
Monday, October 28, 2013, 2:30 PM–4:00 PM

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Trends In Incidence and Mortality In Rheumatoid Arthritis and Systemic Autoimmune Rheumatic Diseases In Quebec, Canada: A Population-Based Study. Sonia Jean[1], Philippe Gamache[2], Marie Hudson[3], Louis Bessette[4], Paul R. Fortin[5], Gilles Boire[6] and Sasha Bernatsky[7]. [1]National Institute of Public Health of Quebec, Quebec, QC, [2]National institute of public health of Quebec, Quebec, QC, [3]McGill University, Montreal, QC, [4]Centre Hospitalier Universitaire de Québec, pavillon CHUL, Sainte-Foy, QC, [5]Centre de Recherche du Chu de Québec et Université Laval, Quebec City, QC, [6]Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, [7]Research Institute of the McGill University Health Ctre, Montreal, QC.

Background/Purpose: Health administrative data (HAD) are a potentially efficient to conduct population-based research and are increasingly used to develop chronic disease surveillance indicators. Examining trends in incidence and mortality over time can assist in monitoring disease burden and evaluating the effectiveness of treatment. The aim of this study was to explore time trends in incidence and mortality for rheumatoid arthritis (RA) and selected systemic autoimmune rheumatic diseases (SARD).

Methods: Using case definitions for HAD available in Quebec, Canada, 2 population-based cohorts for RA and SARD (1996–2010) were defined. To identify incident cases, a period of 5 years (1996–2000) was used to exclude prevalent cases. Age and sex-specific incidence rates were calculated using the number of incident cases as the numerator and the counts of population eligible for health insurance registry as the denominator. Age-standardized incidence rates (SIR) were calculated using the 2001 age-structure of the Quebec population. Health insurance registry file was also used to identify deaths among 2 cohorts and, for each year, mortality rates in each cohort were compared with mortality rates in the general population using standardized mortality rate ratios (SRR). Joinpoint and negative binomial regression analyses were used to test for linear change in incidence rates and SRR.

Results: Prevalence of RA and SARD in 2009 were estimated at 1100.7 and 529.8 per 100,000 persons, respectively. For RA, 69.2% of cases were females, while for SARD, this percentage was 73.5%. The linear trends in SIR did not show significant change over the study period (RA p-value=0.3613, SARD p-value 0.0510) (Fig. 1 and 2). The mortality rate in RA and SARD patients was significantly higher than the expected rate in general population (2009: RA SRR=1.32, SARD SRR=1.95), and no significant improvement was observed (Fig. 3).

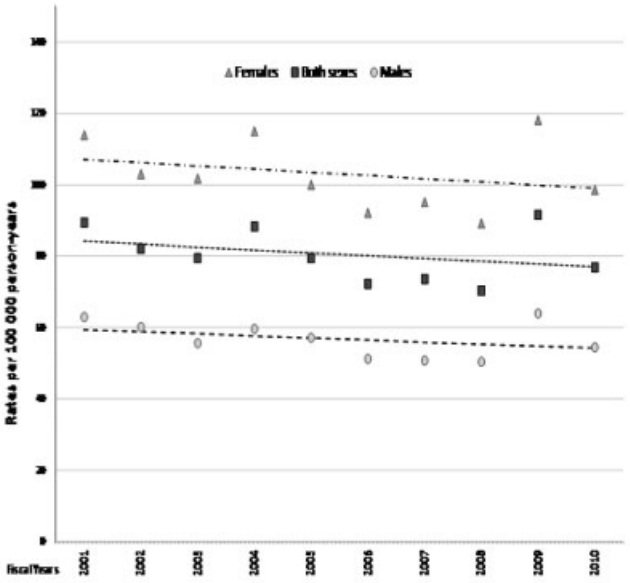

Figure 1. SIR for RA, Quebec, 2001–2010

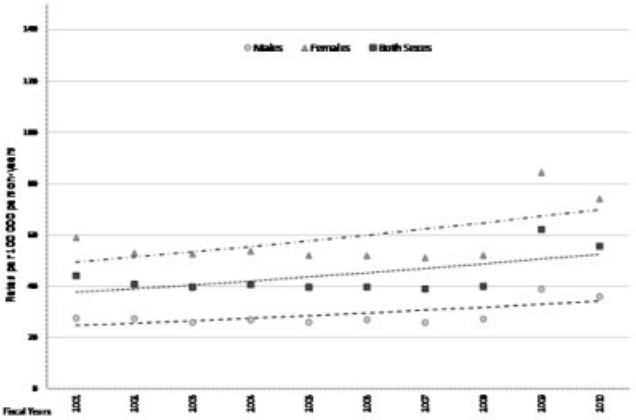

Figure 2. SIR for SARD, Quebec, 2001–2010

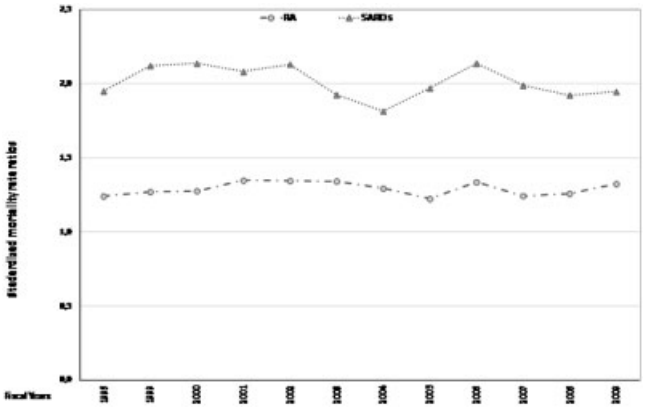

Figure. 3 SRR, Quebec, 1998–2009

Conclusion: No secular trends in SIR of RA and SARD were observed over time. The mortality was substantially higher in RA and SARD compared to general population, and remained so over the study period. This suggests further efforts are needed to optimize long-term outcomes in these diseases.

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Does Foot Pain Mediate The Effect Of Knee Osteoarthritis and Risk Of Indoor and Outdoor Falls In Older Men and Women? Uyen Sa D.T. Nguyen[1], Yuqing Zhang[1], Jingbo Niu[1], Robert H. Shmerling[2], Douglas P. Kiel[3], Suzanne G. Leveille[4], Carol A. Oatis[5] and Marian T. Hannan[3]. [1]Boston University School of Medicine, Boston, MA, [2]Beth Israel Deaconess Med Ctr, Boston, MA, [3]Hebrew SeniorLife & Harvard Medical School, Boston, MA, [4]University of Massachusetts-Boston, Boston, MA, [5]Arcadia University, Glenside, PA.

Background/Purpose: Knee osteoarthritis (OA), foot pain, and falls are common in older adults and limit mobility. We previously showed that knee OA increases the risk of indoor falls for men and outdoor falls for women. Because foot pain often accompanies knee OA and women report more foot pain than men, understanding whether the increased risk of falls in subjects with knee OA is mediated through foot pain can help us better target interventions to reduce falls. We examined the associations of knee OA with foot pain and falls, and assessed the extent that foot pain may mediate the association between knee OA and the risk of falls, and whether this varies by sex.

Methods: This study included 764 participants from the MOBILIZE Boston Study, a population-based cohort of older adults. Knee OA was assessed at baseline using the ACR clinical criteria. Falls data were prospectively collected using monthly calendars, with phone follow-up to assess location of falls. The presence of foot pain was assessed at baseline. Using negative binomial regression, we examined the sex-specific association of knee OA with the risk of indoor falls and outdoor falls adjusting for confounders. We applied a counterfactual approach of mediation analysis using logistic regression and marginal structural modeling to estimate the direct (through mechanisms excluding foot pain) and indirect (through the foot pain mechanism) effects to determine the extent that foot pain mediates the associations between knee OA and falls.

Results: Among study participants (486 women and 278 men, mean age: 78 years, mean BMI: 27.3), 25% had clinical knee OA. The proportions with foot pain were 35.8% in men with and 14.4% in men without knee OA; foot pain was reported by 33.6% and 24.5% of women with and without OA. Over an average of 2.2 years, 43% in men with and 35% in men without foot pain had ≥ 1 indoor falls while 39% and 36% of the women with and without foot pain had ≥ 1 outdoor falls. The adjusted rate ratio (RR) and 95% confidence interval (CI) for the total effect of knee OA (i.e., including both direct and indirect effects) on risk of indoor falls in men was 1.58 (95% CI: 0.99, 2.52), and on risk of outdoor falls in women was 1.70 (95% CI: 1.21, 2.40). The effect of knee OA on risk of indoor falls in men mediated by foot pain was 0.93 (95% CI: 0.73, 1.32) and on risk of outdoor falls in women was 1.00 (95%CI: 0.81, 1.25).

Table. The Association between Knee OA and Rate of Indoor and Outdoor Falls and Whether the Effect is Mediated through Foot Pain, by Men and Women

		Rate Ratio (95% CI)				
				Effect Mediated through Foot Pain Using Marginal Structural Modeling[2]		
	Falls	Unadjusted	Total Effect,[1] Adjusted for Confounders	Direct Effect	Indirect Effect	% mediated
Men	Indoor	1.39 (0.83, 2.32)	1.58 (0.99, 2.52)	1.58 (1.14, 2.18)	0.98 (0.73, 1.32)	0%
Women	Outdoor	1.64 (1.15, 2.34)	1.70 (1.21, 2.40)	1.70 (1.33, 2.16)	1.00 (0.81, 1.25)	0%

[1]Total Effect (TE) is the effect of OA that includes mechanisms with and without foot pain and is adjusted for age, BMI, use of medications (anti-depressants, anti-psychotics, anti-hypertensives, and sedatives), no. of co-morbidities (high blood pressure, stroke, heart disease, diabetes, ulcer/stomach disease, kidney disease, anemia, cancer/skin cancer, rheumatoid arthritis), and history of falls
[2]The effect of knee OA on risk of falls weighted by the probability of having foot pain conditioned on knee OA status and confounders as stated above: (a) Direct Effect (DE) is the effect of knee OA on risk of falls not through foot pain, adjusting for covariates; (b) Indirect Effect (IE) is the effect of OA mediated by foot pain on risk of falls, adjusting for covariates; (c) % mediated by foot pain, e.g., [RR(TE)-RR(DE)]/[RR(TE)-1].

Conclusion: Despite the increased risk of falls in people with OA and a strong association of knee OA and foot pain, there is no evidence that knee OA increases the risk of falls through foot pain in older men and women. The counterfactual method of mediation analysis reduces potential confounding and selection bias that occur with the conventional method of including a potential mediator in a model as a covariate. Future studies should explore other possible mechanisms through which knee OA affects the risk of indoor and outdoor falls differently for men and women.

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Low Literacy Decision Aid Enhances Knowledge and Reduces Decisional Conflict Among Diverse Population Of Adults With Rheumatoid Arthritis: Results Of a Pilot Trial. Jennifer Barton[1], Laura Trupin[2], Gina Evans-Young[3], John B. Imboden[1], Dean Schillinger[3], Victor M. Montori[4] and Edward H. Yelin[1]. [1]University of California, San Francisco, San Francisco, CA, [2]UC San Francisco, San Francisco, CA, [3]UCSF, San Francisco, CA, [4]Mayo Clinic, Rochester, MN.

Background/Purpose: Vulnerable populations with rheumatoid arthritis (RA) have poorer outcomes and report suboptimal shared decision-making communication. Patient involvement in the choice of disease modifying anti-rheumatic drugs (DMARDs) for RA may result in improved adherence and better outcomes. Our objective was to test the efficacy of an RA decision aid tool, developed for low literacy and non-English-speaking patients, to improve knowledge and enhance patient involvement in treatment decisions.

Methods: We conducted a pilot trial to test the utility of the decision aid, a set of 5 issue cards which described 12 DMARDs by frequency and mode of administration, time to onset of action, cost, side effects and contraindications. Patients at 2 university-affiliated rheumatology clinics faced with a possible medication change were enrolled consecutively into one of three arms: Arm 1 – existing medication summary guide (usual care) provided pre-clinic visit; Arm 2 – low literacy RA guide provided pre-visit; Arm 3 – low literacy guide provided pre-visit and decision aid used during visit. Immediately post-visit and during a telephone interview 3 months post-visit, subjects completed an RA knowledge questionnaire and the low-literacy version of the Decisional Conflict Scale (DCS; range 0–100; higher scores reflect more conflict). At 3 months, subjects were also asked about self-reported medication adherence. All materials were available in English, Spanish, and Chinese. DCS, knowledge, and adherence were compared by arm using linear (for DCS) or logistic regression with adjustment for gender immediately post-visit and 3 months.

Results: Of 166 patients enrolled, 88% were female, mean age 59±12; 87% were non-white; 54% spoke a language other than English; and 66% had not graduated high school. There were no statistically significant differences by study arm for education, language, or race/ethnicity; however, there were differences by gender (p=0.02). Compared with the existing guide (Arm 1, n=58), patients who received the low literacy guide plus decision aid (Arm 3, n=60), were more likely to have adequate RA knowledge (OR 3.1, 95% CI 1.4–7.0) immediately post-visit; a difference not seen at 3 months (Table). Among patients who reported a medication change during the visit, Arm 3 patients reported lower decisional conflict compared to those in Arm 1 post-visit (mean DCS 11 vs. 24, p =0.05) and at 3 months (17 vs. 32, p<0.05). Self-reported adherence did not differ by study arm at 3 months.

Conclusion: An innovative, multi-lingual, low literacy decision aid tool effectively reduced decisional conflict among vulnerable patients with RA faced with choices about DMARDs. The decision aid and medication guide also enhanced RA-specific knowledge immediately post-visit. Future studies are needed to assess the impact of the decision aid on health outcomes in vulnerable populations.

Decisional conflict, RA knowledge, and medication adherence by study arm immediately post-visit and 3-months

Instrument & time frame	Arm 1 (original guide) n = 58	Arm 2 (revised guide) n = 48	Arm 3 (revised guide & decision aid) n = 60	
Decisional conflict scale (range 0–100)				
		adjusted means (95% CI)		
Immediately post-visit	24 (16, 33)	18 (9, 26)	11 (3, 19)	*
3 months	32 (22, 40)	21 (12, 30)	17 (10, 25)	*
Adequate RA knowledge (score ≥ 7 out of 8)				
			OR (95% CI)	
Immediately post-visit	ref	1.6 (0.7, 3.4)	3.1 (1.4, 7.0)	*
3 months	ref	1.4 (0.6, 3.4)	1.8 (0.8, 4.1)	
Adherence (%)				
3 months	ref	0.4 (0.1, 0.9)	0.5 (0.2, 1.2)	

All results adjusted for gender.
*p<0.05 for difference between Arm 3 and Arm 1

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1759

The Effect Of Knee Replacement On Self-Reported Participation and Gait Speed: The Multicenter Osteoarthritis Study and The Osteoarthritis Initiative. Jessica L. Maxwell. Boston Univ Sargent College, Boston, MA.

Background/Purpose: Little research has explored participation outcomes, defined as involvement in life situations, among persons following total knee replacement (TKR). Since confounding by indication is likely in a study of TKR outcomes, we examined whether participation restriction (PR) differed among persons following TKR compared to a propensity-score matched group with symptomatic knee osteoarthritis (SxOA). Research has found differences in results between self-reported and performance measures; and, as gait speed is strongly associated with disability, we also explored whether it differs by TKR status using the same methods.

Methods: Subjects with SxOA were selected from The Multicenter Osteoarthritis (MOST) Study and the Osteoarthritis Initiative (OAI). We generated a propensity score for each subjects' odds of having a TKR based on their values of 17 TKR-associated ($p<0.2$) variables (e.g. sex, medication use, comorbidities, living situation, pre-TKR participation). Within each cohort using a greedy matching method, we matched 1 subject with SxOA, defined as radiographic evidence of knee OA and report of frequent knee pain over the last 30 days, with 1 subject with a TKR by their propensity scores. The clinic visit falling $\geq$ 1 year after the TKR date for each matched pair was used as the index visit. Participation was measured using the Late Life Disability Instrument (LLDI); and PR was defined using a previously established cut-point of $<$ 69/100 on the Instrumental Limitation subscale of the LLDI. Gait speed was calculated using the time required to ambulate 20 m on a straight walkway (m/s). Slow gait speed was defined as speed $<$ 1.0 m/s. We compared the proportion of subjects with PR and slow gait speed among the TKR and non-TKR SxOA subjects using chi square analyses. We evaluated the association between TKR status (yes/no) and PR, and TKR status and gait speed, using logistic regression.

Results: There were 258 and 247 matched pairs with post-index date PR and gait speed data, respectively. Table 1 presents the proportions of subjects with these data in each group, as well as estimates of association. The proportion with PR among the non-TKR subjects was 10% higher than that for the TKR subjects, and the proportions of subjects reporting PR was considerably higher than the subjects demonstrating slow gait speed. Having a TKR was associated with decreased odds of PR but not with slow gait speed.

Table. Proportions and odds ratios of participation restriction and slow gait speed by TKR status among propensity-score matched subjects.

	% PartRestrict	OR (95% CI)	% Slow Gait Speed	OR (95% CI)
TKR group	33	0.65 (0.5, 0.9)	17	1.1 (0.7, 1.7)
SxOA group	43	reference	16	reference
p-value	0.02		0.7	

Conclusion: In this study, TKR subjects had two-thirds the risk of participation restrictions compared with demographically and clinically similar subjects not undergoing TKR, although there was no effect of TKR on gait speed.

Disclosure: J. L. Maxwell, None;

1760

Relationships Between Driving Distance, Rheumatoid Arthritis Diagnosis, and Disease-Modifying Anti-Rheumatic Drug Receipt. Jennifer M. Polinski[1], M. Alan Brookhart[2], John Z. Ayanian[1], Jeffrey N. Katz[1], Seo Young Kim[1], Chris Tonner[3], Edward H. Yelin[3] and Daniel H. Solomon[4]. [1]Brigham and Women's Hospital, Boston, MA, [2]University of North Carolina, Chapel Hill, NC, [3]University of California, San Francisco, San Francisco, CA, [4]Harvard Medical School, Brigham and Women's Hospital, Division of Rheumatology, Division of Pharmacoepidemiology, Boston, MA.

Background/Purpose: Disease-modifying antirheumatic drugs (DMARDs) are recommended for all patients with rheumatoid arthritis (RA). Some studies estimate that almost half of patients with RA do not receive DMARDs. Distance to the nearest rheumatologist, a proxy for access to care, may explain some variability. We hypothesized that patients with RA living further from a rheumatologist would be less likely to receive an RA diagnosis and to receive DMARDs.

Methods: We obtained a list of US rheumatologists from the American College of Rheumatology. Medicare patients with Parts A, B, and linked prescription data from CVS Caremark were eligible. We calculated driving distance from patients' homes to the nearest rheumatologist. Using multivariable logistic regression, we assessed relationships between driving distance and RA diagnosis, defined using procedures for claims data, and between driving distance and DMARD receipt in 365 days of follow-up. Secondary outcomes included receipt of $\geq$1 biologic DMARD, combination DMARD use ($\geq$2 DMARDs for $\geq$60 days) and majority of time on DMARDs (days supply of $\geq$1 DMARD for $\geq$50% of days). In one set of analyses, distance was divided into quartiles: 0–2, 2.1–5.0, 5.1–15.9, $\geq$16 miles. In a second, we used pre-defined categories: 0–15, 15.1–30, 30.1–60, $\geq$60 miles.

Results: 26,590 patients had diagnosed RA. Compared to the first quartile, increased distance was associated with decreased odds of RA diagnosis: second quartile, OR=0.96 (95% CI, 0.80–1.16); third=0.88 (0.72–1.07); fourth=0.72 (0.56–0.93), p for trend=0.0099. Similar results were observed using pre-defined distance categories. Among those with RA, increased driving distance was associated with increased odds of any DMARD receipt across quartiles: second=1.15 (1.06–1.25); third=1.41 (1.29–1.54); fourth=1.32 (1.18–1.46), p for trend=0.0012. There was no relationship between pre-defined categories and any DMARD receipt: 15.1–30 miles=1.09 (0.99–1.19); 30.1–60=1.03 (0.91–1.16); $\geq$60.1=1.06 (0.91–1.23), p for trend=0.4506. Similar results were observed for combination DMARD use, but not for biologic DMARD receipt or majority of time on DMARDs (Table).

Table. Relative odds of DMARD use at 365 days, comparing the 2 approaches to define driving distance

	Quartiles of driving distance			Pre-defined categories of driving distance		
	2.1–5.0 miles	**5.1–15.9 miles**	**≥ 16 miles**	**15.1–30 miles**	**30.1–60 miles**	**≥ 60.1 miles**
Receipt of any DMARD	1.15 (1.06–1.25)	1.41 (1.29–1.54)	1.32 (1.18–1.46)	1.09 (0.99–1.19)	1.03 (0.91–1.16)	1.06 (0.91–1.23)
		p for trend: 0.0012			p for trend: 0.4506	
Receipt of a biologic DMARD	1.02 (0.87–1.19)	1.05 (0.89–1.24)	1.00 (0.81–1.22)	0.96 (0.80–1.15)	1.08 (0.86–1.35)	1.07 (0.80–1.43)
		p for trend: 0.8037			p for trend: 0.6010	
Receipt of combination DMARDs	1.09 (0.93–1.28)	1.17 (1.00–1.37)	1.23 (1.02–1.49)	1.11 (0.95–1.31)	1.16 (0.95–1.42)	1.07 (0.83–1.39)
		p for trend: 0.0837			p for trend:0.4036	
Majority of time on DMARDs	1.17 (1.07–1.28)	1.41 (1.29–1.55)	1.33 (1.19–1.49)	1.07 (0.97–1.18)	1.08 (0.95–1.22)	1.04 (0.89–1.22)
		p for trend: 0.0026			p for trend: 0.4456	

Conclusion: Increased driving distance to a rheumatologist was associated with decreased odds of RA diagnosis. Among those with diagnosed RA, the odds of DMARD use rose as distance increased from <2 to 16 miles, but not beyond, suggesting that urban residents who live closer to a rheumatologist may have other barriers to DMARD use.

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The Link Of Foot Structure and Foot Function With Falls: The Johnston County Osteoarthritis Project. Yvonne M. Golightly[1], Marian T. Hannan[2], Howard J. Hillstrom[3], Alyssa B. Dufour[2], Amanda E. Nelson[4], Adam Dore[1] and Joanne M. Jordan[4]. [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]Hebrew SeniorLife & Harvard Medical School, Boston, MA, [3]Hospital Special Surgery (HSS), New York, NY, [4]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC.

Background/Purpose: Nearly 1/3 of older adults experience at least one fall annually in the United States. Foot type (static and dynamic arch height) is related to how people walk, but the relationship to falls is unclear. Prior studies have shown differences in foot type by race with a lower arch height more common in African Americans than Caucasians. The purpose of this cross-sectional study was to evaluate the association of static foot structure and dynamic foot function with falls in a community-based study of Caucasian and African American men and women 50+ years old.

Methods: Participants in the Johnston County Osteoarthritis Project were queried: "In the last 12 months, have you had any falls of any type?" If they answered "yes", the number of falls was reported. Tekscan Matscan foot pressure scans were used to determine foot structure (modified arch index [MAI]) during standing and foot function (center of pressure excursion index [CPEI]) while walking. Foot structure (high arch $\leq$0.030, low arch $\geq$0.164, referent $>$0.030 and $<$0.164) and foot function variables (pronated $\leq$7.3, supinated $\geq$21.0, referent $>$7.3 and $<$21.0) were defined *a priori* (based on quintiles from population data), and the most extreme foot type for each participant was used in analyses. Logistic regression models were used to

estimate the association between foot types and falls (defined two ways as ≥1 fall and ≥2 falls), adjusting for the covariates of age, body mass index [BMI], gender, and race. Statistical interaction between foot types and each covariate was examined, and $p<0.10$ was considered statistically significant.

Results: Of the 1690 participants with complete falls data, 1571 participants had foot structure data and 1490 had foot function data (mean age 68 ±9 years, mean BMI 31 ± 7 kg/m^2, 67% women, 30% African American). 25% of participants reported 1+ falls in the past 12 months and 8% reported 2+ falls. Although not statistically significant ($p=0.06$), the odds of 2+ falls were 40% lower among participants with high arches compared to referent (Table). The interaction between low arches and race was $p=0.05$, and thus results were stratified by race. African Americans had a lower occurrence of falls than Caucasians. Among African Americans, those with low arches had a 75% higher odds of 1+ falls compared to referent, although these results were of borderline significance ($p=0.07$). Foot function was not associated with falls (Table).

Table. Associations between foot type and falls, adjusting for age, BMI, gender, and race

Falls definition	Foot Structure (MAI)	Total Sample N=1571		African American N=479		Caucasian N=1092		
		# of fallers/n (%)	Adjusted OR (95% CI)	# of fallers/n (%)	Adjusted OR (95% CI)	# of fallers/n (%)	Adjusted OR (95% CI)	p for interaction
1 + (Any falls vs. no falls)	Referent	134/607 (25.4)	1.00	18/128 (14.1)	1.00	136/479 (28.4)	1.00	
	Low Arch	172/614 (28.8)	1.07 (0.80, 1.43)	75/332 (22.6)	1.75 (0.96, 3.16)	77/282 (27.3)	0.88 (0.62, 1.25)	0.046
	High Arch	87/350 (24.9)	0.90 (0.66, 1.24)	2/19 (10.5)	0.74 (0.16, 3.50)	85/331 (25.7)	0.86 (0.62, 1.20)	0.900
2 + (2 or more falls vs. <2 falls)	Referent	57/607 (9.4)	1.00	8/128 (6.3)	1.00	49/479 (10.2)	1.00	
	Low Arch	55/614 (9.0)	0.86 (0.62, 1.48)	29/332 (8.7)	1.74 (0.74, 4.09)	26/282 (9.2)	0.75 (0.44, 1.27)	0.327
	High Arch	21/350 (6.0)	0.61 (0.36, 1.03)	1/19 (5.3)	0.86 (0.10, 7.33)	20/331 (6.0)	0.62 (0.36, 1.09)	0.701
Falls definition	**Foot Function (CPEI)**	**Total Sample N=1490**		**African American N=431**		**Caucasian N=1029**		
		# of fallers/n (%)	Adjusted OR (95% CI)	# of fallers/n (%)	Adjusted OR (95% CI)	# of fallers/n (%)	Adjusted OR (95% CI)	p for interaction
1 + (Any falls vs. no falls)	Referent	172/700 (24.6)	1.00	38/193 (19.7)	1.00	134/507 (26.4)	1.00	
	Pronated	83/314 (26.4)	1.06 (0.78, 1.44)	22/103 (21.4)	1.12 (0.61, 2.05)	61/211 (28.9)	1.06 (0.74, 1.52)	0.850
	Supinated	108/446 (24.2)	1.05 (0.79, 1.39)	26/135 (19.3)	0.99 (0.57, 1.73)	82/311 (26.4)	1.07 (0.77, 1.49)	0.878
2 + (2 or more falls vs. <2 falls)	Referent	58/700 (8.3)	1.00	15/193 (7.8)	1.00	43/507 (8.5)	1.00	
	Pronated	27/314 (8.6)	1.02 (0.63, 1.65)	9/103 (8.7)	0.94 (0.39, 2.30)	18/211 (8.5)	1.05 (0.58, 1.88)	0.877
	Supinated	36/446 (8.1)	1.03 (0.66, 1.59)	10/135 (7.4)	0.92 (0.40, 2.15)	26/311 (8.4)	1.04 (0.63, 1.77)	0.937

Conclusion: These cross-sectional results indicate a possible protective relationship between high arches and falls and among African Americans a positive association between low arches and falls. Future studies are needed to longitudinally examine the role of foot type in falls and to test the effectiveness of interventions for modifying foot type (e.g., orthotics) for fall prevention in populations.

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ACR Concurrent Abstract Session
Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis II: Mechanisms That Contribute to Autoimmune Inflammation
Monday, October 28, 2013, 4:30 PM–6:00 PM

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Endogenous IL-22 Regulates Th1 Responses and Plays a Pathogenic Role After the Onset of Arthritis. Shivali Justa, Xiaoqun Zhou and Sujata Sarkar. University of Arizona, Tucson, AZ.

Background/Purpose: IL-22,belongs to the IL-10 family of cytokines and is primarily produced by CD4 T, NK and LTi cells. IL-22 plays a dual role depending on the context of the disease model under study, it is protective in inflammatory bowel disease, hepatitis, myocarditis, ulcerative colitis and pathogenic in psoriasis. IL-22 knock-out mice have a reduced incidence of arthritis, while neutralization of IL-22 after onset of arthritis in IL-1 receptor antagonist knock-out mice had limited effect on joint inflammation, additionally, administration of IL-22 prior to onset of joint inflammation is associated with reduced arthritis. These findings are suggestive of a nuanced role of IL-22 in the regulation of inflammation.

Methods: CIA was induced in DBA1 mice following immunization with collagen and complete Freund's adjuvant. Arthritic mice with clinical scores of ≥ 1 and with arthritis duration of 4 days were randomized to receive anti-IL-22 or RatIgG antibody and disease progression was assessed by clinical scoring and histopathology. IL-22, IL-17 and IFN-g responses were measured by ELISA and flowcytometry. Anti-collagen antibodies were analyzed by ELISA. Expression of IL-22R1 in CD4T, CD19+ and CD11c+ cells was elucidated by flowcytometry and real time PCR.

Results: There was a significant expansion of collagen specific IL-22 responses during arthritis and IL-22 producing cells were discrete from IL-17 or IFN-g producing cells. Neutralization of IL-22 after onset of joint inflammation resulted in significantly reduced severity of arthritis and was accompanied by increase in collagen specific IFN-g responses, a modest reduction of anti-collagen IgG2a antibodies, and unaltered Th17 or IL-10 responses. To corroborate our findings, both intracellular and secreted levels of IFN-γ and IL-17 were measured and similar results were observed. CD4+T cells from arthritic mice showed increase surface expression of IL-22R1(13.3%) in comparison to naïve mice (1.50%) or mice from the initiation phase (1.97%). Flowcytometrically, IL-22R1 was detectable in CD19+ cells, however, the expression levels were similar in naïve mice, mice from initiation phase or arthritic mice. In-vitro, CD4T cells from arthritic mice when co-cultured with antigen presenting cells in the presence or absence of IL-22, suppressed or induced IFN-g respectively. In another in-vitro set up, CD19 cells from arthritic mice when cultured in the presence of recombinant IL-22, showed significant suppression of anti-collagen IgG1 and augmentation of IgG2a responses. *These* in *vitro results* are in *agreement* with our in *vivo findings* suggesting that IL-22R1 expression in T and B cells is functionally active and associated with IFN-g regulation in T cells or pathogenic anti-collagen IgG2a antibody production from B cells. Our results shows that IL-22R1 may be induced on immunocytes during inflammatory state thus enabling them to respond to IL-22.

Conclusion: Endogenous IL-22 suppresses Th1 responses and is pathogenic after onset of arthritis. IL-22R1 is upregulated in CD4 T cells during arthritis and regulates IFN-g in T cells.

Disclosure: S. Justa, None; **X. Zhou**, None; **S. Sarkar**, None.

1763

IL4–10 Synerkine: A Novel Immunoregulatory Drug To Prevent Immunopathology In Rheumatic Diseases. Sarita Hartgring[1], Cristine Steenlouws[2], C.E. Hack[2], Martin De Smet[2], Floris Lafeber[2] and J.A.G. van Roon[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]UMC Utrecht, Utrecht, Netherlands.

Background/Purpose: A considerable percentage of patients shows a limited response to biologics targeting one specific inflammatory mediator, largely because of redundancy of these mediators. An attractive alternative is inhibition of multiple proinflammatory mediators and induction of immunoregulatory activity by regulatory cytokines such as IL4 and IL10. Many studies demonstrated the strong capacity of IL4 and IL10 as stand alone drugs to inhibit inflammation and tissue-destructive responses in animal and human in vitro models. Clinical results of these cytokines, however, have been disappointing, possibly because of poor bioavailability that is mainly due to their low molecular weight and rapid renal clearance. We have executed a feasibility study to develop IL4 and IL10 as one biologic, preserving distinct characteristics of each molecule plus improving bioavailablity by increasing the molecular size. Our objective was to develop and test the anti-inflammatory properties of an IL4/IL10 fusion protein; IL4–10 synerkine.

Methods: IL4–10 synerkine was expressed in human HEK293 cells. Biochemical properties of IL4–10 synerkine were determined by western blot, size exclusion chromatography, and ELISA. Functional properties were studied by measuring the capacity of IL4–10 synerkine to regulate production of pro-inflammatory cytokines and their inhibitors, as well as proinflammatory and regulatory T cell activity, and expression Fcγ and Fcϵ receptors (FcγRI, IIa, IIb, III and FcϵR). In addition, blocking IL4 receptor and IL10 receptor strategies were performed to confirm the specific activities of IL4 and IL10.

Results: IL4–10 synerkine appeared as a glycosylated dimeric protein with a molecular size of ~70kDa. ELISA as well as immunoblotting confirmed that the IL4–10 synerkine indeed consisted of IL10 and IL4 subunits. In whole blood assays IL4–10 synerkine dose-dependently inhibited multiple pro-inflammatory cytokines, which was almost complete at 20 ng/ml (IL1β, TNFα, IL6 and IL8, all $p<0.001$). This effect was dependent on interaction with IL10R and IL4R. Oppositely, the synerkine significantly induced production of IL1RA and preserved sTNFR levels. In addition, IL4–10 synerkine strongly inhibited Th1 and Th17 cytokine secretion, while maintaining FoxP3 expression and FoxP3-expressing CD4 T cells. Finally, while IL4 up regulated FcϵR expression and IL10 up regulated expression of activating FcγRs on monocytes (all $p<0.001$), both Fcϵ and FcγR expression were largely down regulated to control levels in the presence of IL4–10 synerkine (all at least $p<0.01$).

Conclusion: The IL4–10 synerkine is a novel anti-inflammatory drug that shifts multiple proinflammatory pathways towards immunoregulation. The increased molecular mass predicts better bioavailabilty in humans than the wild-type molecules, which potentially enhances its clinical efficacy. The strong and improved inhibitory activities of IL4–10 synerkine (as compared to IL4 or IL-10 monotherapy and combination therapy) that were observed in several animal models for inflammatory pain underscores the potential for treatment of inflammatory and possibly degenerative rheumatic diseases.

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1764

Binding Of Apoptotic Fetal Cardiocytes By Anti-Ro Antibodies Stimulates uPA/uPAR-Dependent Macrophage Infiltration and M2 Type Phenotype. Paraskevi Briasouli[1], Savvas Pavlides[2], Leslie Gold[3], Mark Halushka[4] and Jill P. Buyon[5]. [1]New York University Medical Center, New York, NY, [2]New York University Medical Center, new York, NY, [3]new York University Medical Center, new York, NY, [4]John Hopkins PAthology, Baltmore, MD, [5]NYU School of Medicine, New York, NY.

Background/Purpose: Organ injury induced by antibodies characteristic of Sjogren's Syndrome and Systemic Lupus Erythematosus, while varied in the adult and fetus, may share in common a link between apoptosis and ultimate fibrosis. In congenital heart block (CHB), surface binding of maternal anti-Ro antibodies to apoptotic cardiocytes decreases their removal by healthy cardiocytes, increases uPAR-(urokinase plasminogen activator receptor) dependent uPA activation, plasmin activity and stimulation of TGFbeta signaling. Immunological staining of CHB hearts reveals extensive TGFbeta in the septal region and macrophage infiltration with intense uPA expression. Since TGFbeta mediates chemotaxis of macrophages and stimulates urokinase expression, this study evaluated the hypothesis that anti-Ro binding to apoptotic cardiocytes exploits the plasmin-mediated activation of TGFbeta to trigger macrophage infiltration and polarization to a fibrosis- associated M2 phenotype.

Methods: Chemotaxis, immunoblot and immunofluoresence assays were used.

Results: A thin membrane chemotaxis assay showed directed migration of calcein-labeled THP-1 macrophages towards supernatants from co-cultures of healthy cardiocytes and apoptotic cardiocytes incubated with IgG fractions from mothers whose sera contain anti-Ro antibodies and who had a child with CHB (opsonized apo-CHB-IgG) compared to co-cultures of healthy cardiocytes and apoptotic cardiocytes incubated with control IgG (apo-nl-IgG) (80% migration CHB-IgG vs 39% migration nl-IgG; $p=0.05$; $n=3$). The effect was similar to that induced by TGFbeta and dependent on both TGFbeta and plasmin activity since supernatants of cocultures of healthy cardiocytes with apo-CHB-IgG in the presence of either aprotinin (10 μg/mL) or TGFbeta inhibitor SD543423 1μM did not induce macrophage migration. Similar results were obtained with supernatants of healthy cardiocytes cultured with apoptotic cardiocytes incubated with affinity purified anti-Ro60 (67% migration AP60-IgG vs 30% migration nl-IgG). Immunofluoresence revealed increased surface uPA expression only on macrophages incubated with supernatants of co-cultures of healthy cardiocytes with apo-CHB-IgG. Furthermore real time PCR confirmed that the increased uPA was due to de novo mRNA expression To evaluate whether the macrophages were polarized towards a pro-fibrotic M2 phenotype, surface CD206 was assessed and increased expression of CD206 was only observed following exposure to supernatants from co-cultures of healthy cardiocytes and apo-CHB-IgG. Immunoblot analysis of THP-1 macrophages showed that IRF4 but not IRF5 knockdown, mediator of M2 and M1 macrophage associated transcriptional program respectively, led to reduced uPA expression when incubated with supernatants from cocultures of healthy cardiocytes and apo-CHB-IgG.

Conclusion: These data suggest that binding of anti-Ro antibodies to apoptotic cardiocytes by virtue of increased uPAR-dependent uPA activity triggers TGFbeta mediated macrophage infiltration and polarization towards a profibrotic M2 phenotype amplifying a cascade of events that promote myofibroblast transdifferentiation and scar.

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1765

Complement Component C5a Permits The Co-Existence Of Pathogenic Th17 Cells and Type I Interferon In Lupus. Marc C. Levesque, Sudesh Pawaria, Kelly Maers and Partha Biswas. University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Systemic lupus erythematosus (SLE) is a type I interferon (IFN-I)-driven autoimmune disorder with exaggerated B and T-helper (Th) cell responses. Th17 cells, a recently identified T-helper cell subset, have been strongly implicated in the pathogenesis of SLE. Since IFN-I suppress the generation and expansion of Th17 cells in an IL-27-dependent manner, it is unclear how pathogenic Th17 cells are generated in SLE in the presence of an environment characterized by high IFN-I levels.

Methods: To test whether C5a has any impact on IFN-I-induced IL-27 production, bone marrow derived macrophages (BMDM) from wild type (WT) mice were treated with IFN-a in the presence or absence of C5a. Supernatants of BMDM treated with IFN-a ± C5a or IFN-a ± anti-IL-27 Ab were used to differentiate naïve $CD4^+$ T cells in the presence of Th17 skewing conditions. Similarly, BMDM from $MRL.Fas^{lpr}$ mice were stimulated with a TLR7/8 agonist (IFN-I inducer) in the presence or absence of C5a. To assess the *in vivo* consequence of C5aR activation on Th17 responses, we used the pristane induced lupus model and evaluated the development of lupus nephritis, number of Th17 cells and production of IL-27 in secondary lymphoid organs and kidney in WT and $C5aR^{-/-}$ mice ($n=5$). We measured the expression of IRF-1 in $MRL.Fas^{lpr}$ macrophages in response to TLR7/8 agonist stimulation. Finally, we measured serum C5a and IL-27(p28) levels by ELISA and the frequency of Th17 cells in peripheral blood from 22 SLE patients. Results obtained from the serum ELISAs and Th17 assays were used to determine correlations between serum C5a versus IL-27, serum IL-27 and the percentage of peripheral blood Th17 cells and serum C5a and the percentage of Th17 cells. To further validate our mouse model studies in human subjects with SLE, we treated macrophages from healthy donors with serum from SLE patients in the presence or absence of neutralizing anti-C5a Ab.

Results: Activation of C5aR on macrophages blocked IFN-I-mediated IL-27 production ($p < 0.0001$) and permitted the differentiation of Th17 cells. Similar findings occurred in lupus-prone mice and C5a exhibited a negative impact on TLR7 mediated synthesis of IL-27 ($p < 0.001$). Consequently, $C5aR^{-/-}$ mice were protected from lupus nephritis and showed increased IL-27 expression ($p < 0.001$) and reduced numbers of Th17 cells in the secondary lymphoid organs and kidney ($p < 0.001$ for spleen and lymph nodes; $p < 0.05$ for kidney). Furthermore, activation of the PI3K-Akt pathway was required for inhibiting IFN regulatory factor-1(IRF-1) mediated transcription of the *IL-27(p28)* gene. In support of these mouse model studies, we found that serum from SLE patients significantly inhibited IFN-I-induced IL-27 production ($p < 0.001$), and the level of serum C5a directly correlated with the Th17 frequency in the SLE peripheral blood ($r = 0.74$; $p = 0.001$).

Conclusion: In this report, we demonstrated the negative regulation of IFN-I induced IL-27 production by C5a via the C5aR on macrophages. Our findings highlight a potential mechanism that explains how Th17 cells can develop despite strong IFN-I responses in SLE. Thus therapeutic strategies to block C5aR activation may be beneficial for controlling pathogenic Th17-mediated inflammation in SLE.

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1766

Role Of IL33 In The Inflammation Of Takayasu Arteritis. David Saadoun[1], Marlène Garrido[2], Julien Gaudric[3], Cloé Comarmond[4], Michele Rosenzwacjg[5] and Patrice Cacoub[6]. [1]Department of Internal Medicine and Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France, [2]Pitié-Salpétrière, Paris, France, [3]Department of Vascular surgery GHPS, Paris, France, [4]Hôpital Pitié Salpétrière, Paris, France, [5]Department of Immunology GHPS, Paris, France, [6]Hopital Pitié-Salpétrière, Paris, France.

Background/Purpose: Interleukin (IL)-33, a member of the IL-1 cytokine family, is a recently described novel activator of endothelial cells, which promotes adhesion molecules and proinflammatory cytokine expression in the endothelium and angiogenesis and vascular permeability. Unlike, the other IL-1 family members, IL-33 primarily induces T-helper (Th)2 immune responses and the polarisation of macrophages.

Objective: To analyse the role of IL-33 and its receptor ST2 in the pathogenesis of Takayasu arteritis (TA).

Methods: Thirty three TA patients fulfilling the ACR criteria, with active disease (aTA) or inactive disease (iTA) and 10 age-matched controls (HD) were included. We performed quantitative measurement of IL-33, analysis of cell surface markers and cytokine production by flow cytometry and Luminex. Immunohistochemical analysis of inflamed aorta from patients with TA was performed.

Results: Increased level of serum (mean ± SEM; 155 ± 69.5 vs 32.9 ± 19.6 pg/ml, respectively, p=0.040) and culture supernatants IL-33 (14.6± 3.3 vs 2.9 ±1.8 pg/ml, respectively, p=0.013) was observed in TA patients compared to HD. Level of IL-33 correlated with disease activity in TA patients (25.4± 6.5 in aTA vs 7.5 ±2.6 pg/ml in iTA, p=0.021) and with the NIH score (r^2=0.3009, p=0.0009). IL-33 level dropped in active TA patients (n=10) that become inactive (20.1± 6.7 vs 4.2 ±1.2 pg/ml, p=0.031). IL-33 was mainly produced by eosinophils, basophils, and mast cells and in a lesser extent by macrophages and CD8+ T cells. ST2 (i.e. the IL-33 receptor) was mainly expressed by eosinophils and mast cells and much weaker by macrophages and neutrophils. IL-33 and ST2 were overexpressed in the inflamed arteries of TA patients and colocalized with endothelial cells and T cells, respectively. Stimulation of purified CD4+ T cells with IL-33 increased Th2 cells.

Conclusion: These findings open new perspectives for the role of IL-33 in the pathogenesis of TA.

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1767

Gender, Race, and Soluble Mediators Distinguish Blood Relatives Who Develop Incomplete Lupus Or Classified SLE In The Lupus Autoimmunity In Relatives (LAUREL) Study. Melissa E. Munroe[1], Kendra A. Young[2], Jill M. Norris[2], Joel M. Guthridge[1], Diane L. Kamen[3], Timothy B. Niewold[4], Gary S. Gilkeson[3], Michael H. Weisman[5], Mariko L. Ishimori[5], Daniel J. Wallace[5], David R. Karp[6], John B. Harley[7] and Judith A. James[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Colorado School of Public Health, Aurora, CO, [3]Medical University of South Carolina, Charleston, SC, [4]Mayo Clinic, Rochester, MN, [5]Cedars-Sinai Medical Center, Los Angeles, CA, [6]UT Southwestern Medical Center, Dallas, TX, [7]Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Background/Purpose: Identifying populations at risk of SLE is essential to curtail inflammatory damage and identify individuals for prevention trials. Healthy blood relatives (FDRs) of lupus patients have increased risk of SLE. Some FDRs have autoantibodies and SLE clinical features, but do not meet the required <4 ACR classification criteria (incomplete lupus, ILE), while others remain unaffected. The goal of this study is to determine factors that distinguish previously healthy FDRs who subsequently develop ILE or SLE.

Methods: This study re-enrolled 436 FDRs of SLE patients who previously enrolled in a genetics study (mean time to followup = 6.3 yrs) and did not meet SLE classification criteria (144 with 0 criteria, 251 with 1–2 criteria, and 41 met 3 criteria) to determine evolution of SLE symptoms and classified disease. FDRs provided clinical and demographic information, and completed the SLE-specific portion of the CTD Screening Questionnaire (CSQ) at baseline (BL) and follow-up (FU). Medical records were reviewed for ACR classification criteria. BL and FU plasma samples were assessed for autoantibody production (ANA, anti-dsDNA, aCL, Ro, La, Sm, nRNP, and ribosomal p antibodies) and for 52 soluble inflammatory mediators (BLyS, APRIL, cytokines, chemokines, and shed TNF receptors). Samples were compared among ILE participants, FDRs who transitioned to SLE, and race/gender/age (± 5 years) matched FDRs who remained unaffected (2:1 ratio of unaffected: ILE/SLE).

Results: 56 FDRs transitioned to SLE (≥ 4 ACR criteria) and 34 were considered as ILE (cumulative ACR criteria = 3) at FU. Matched, unaffected FDRs (n=180) had significantly lower CSQ scores ($p \leq 0.0001$) at BL and FU than those with ILE or classified SLE. Initial analysis revealed a number of soluble mediators that positively correlated with the number of cumulative ACR criteria, including BL levels of MIP-1β, MCP-1, MCP-3, and Eotaxin, as well as SCF ($p \leq 0.01$). TNF superfamily member BLyS positively ($p < 0.0001$) correlated with cumulative ACR criteria, while APRIL ($p = 0.008$) and regulatory mediator TGF-β ($p = 0.002$) negatively correlated with ACR criteria. We then determined factors that differentiated FDRs with ILE or classified SLE at FU. FDRs who transitioned to SLE had significantly higher rate of arthritis and serositis ($p < 0.01$) at BL and higher levels of SCF and MCP-3 ($p < 0.02$) at BL. For FDRs who met fewer than 3 ACR criteria at BL (n = 49 with ILE or SLE at FU), FDRs with ILE at FU (n = 19) were more likely to be female ($p = 0.0002$) and had significantly higher levels of APRIL ($p < 0.04$). For FDRs with ILE at BL (n = 41), FDRs who remained at ILE (n = 15) were more likely to be European-American ($p < 0.0001$) and had significantly lower levels of MCP-3, SCF, and shed TNFRII ($p < 0.03$) than FDRs who transitioned to SLE. BL age and time between BL and FU were not significant factors in distinguishing FDRs with ILE or transition to SLE.

Conclusion: FDRs of known SLE patients demonstrate elevated inflammatory mediators that correlate with cumulative ACR criteria, distinguishing unaffected FDRs from those with ILE or who transition to SLE. Soluble mediators, as well as gender and race, distinguished FDRs with ILE or who transitioned to SLE.

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ACR Concurrent Abstract Session
Epidemiology and Health Services Research II: Healthcare Costs and Mortality in Rheumatic Disease
Monday, October 28, 2013, 4:30 PM–6:00 PM

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Value Of Arthroscopic Partial Meniscectomy In Treatment Of Symptomatic Patients With Meniscal Tears and Knee Osteoarthritis: Is More Research Warranted? Elena Losina[1], A. David Paltiel[2], Elizabeth Dervan[1], Yan Dong[1], Kurt P. Spindler[3], Lisa A. Mandl[4], Morgan Jones[5], John Wright[1] and Jeffrey N. Katz[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Yale School of Public Health, New Haven, CT, [3]Vanderbilt University, Nashville, TN, [4]Hospital for Special Surgery, New York, NY, [5]Cleveland Clinic, Cleveland, OH.

Background/Purpose: Arthroscopic partial meniscectomy (APM) is often offered to patients with symptomatic meniscal tear (MT). Recent trials in symptomatic patients with MT and knee OA (MT + OA) revealed similar pain relief in persons treated with APM and those treated with physical therapy (PT) and then referred for APM if pain persisted. We assessed expected costs and outcomes of alternative surgical and non-surgical strategies for patients with MT+OA. We examined the value of further research in this population and its likely impact on treatment decisions and their outcomes.

Methods: We used data from the Meniscal Tear in OA Research (MeTeOR) multicenter RCT (mean age 58, 76% Kellgren-Lawrence (KL) grade<3, 24% KL3) to estimate input parameters for a Markov state-transition computer simulation model. The model estimates long-term clinical and economic outcomes of management of MT+OA. We considered 3 strategies: 1) PT only, 2) APM, 3) PT with referral for APM, if PT did not relieve pain. We performed the analysis over a 10-year timeframe and considered short-term pain relief, subsequent pain onset (due to OA) and pain resolution. Transition probabilities were derived from MeTeOR and stratified by KL grade and time from treatment initiation. Pain relief 3 months after APM was 69% (95% CI: 59%-79%) among those with KL<3 and 51% (95% CI: 36%–66%) among those with KL3. Pain relief following APM among those who failed PT was worse (58% for KL<3 and 25% for KL3). Pain relief from PT alone was 49% (95% CI: 39%–58%) for KL<3 and 34% (95% CI 19%–50%) for KL3. Costs of PT ($680/3 month) and pain control ($215/quarter) were derived from MeTeOR and costs of APM ($2,800) from the Medicare Fee Schedule. We performed a probabilistic sensitivity analysis to examine the impact of parameter uncertainty on our finding. To estimate the value of further research, we assessed the expected value of partial perfect information (EVPPI), related to pain-based model parameters. We used willingness to pay (WTP) thresholds from $50k to $144K/QALY to denote programs as "cost-effective".

Results: PT alone led to quality-adjusted life expectancy of 6.96 years with costs of $4,116. Delayed APM (in those who failed PT) led to 7.009 QALYs with costs of $8,130, yielding an incremental cost-effectiveness ratio (ICER) of $80,300/QALY. Immediate APM produced both higher costs ($9,556) and lower QALYs (7.008). In persons with KL<3, the estimated ICERs were $42,200/QALY for delayed APM and $106,400/QALY for immediate APM. In persons with KL3, neither APM-based strategy had favorable cost-effectiveness. Accounting for uncertainty in parameter estimates, in persons with KL<3, the probability of immediate APM being cost-effective ranged from 35% if WTP=$50K to 50% if WTP=$144K. The EVPPI that would result from reducing uncertainty in likelihood of pain relief and subsequent development and resolution of pain was estimated at $2,700/person.

Conclusion: APM-based strategies are unlikely to be cost-effective for MT+OA, even in those with less advanced OA. However, this conclusion is sensitive to assumptions regarding short- and long-term pain relief. Given the prevalence of this condition, more research on pain parameters is warranted.

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Direct and Indirect Costs For Patients With Systemic Lupus Erythematosus In National Cohorts In Sweden. Andreas Jönsen[1], Anders A. Bengtsson[1], Christine Bengtsson[2], Iva Gunnarsson[3], Johanna Gustafsson[3], Frida Hjalte[4], Dag Leonard[5], Susanne Pettersson[3], Solbritt Rantapää Dahlqvist[6], Lars Rönnblom[7], Christopher Sjöwall[8], Katarina Steen Carlsson[4], Elisabet Svenungsson[3], Minna Willim[9] and Ola Nived[10]. [1]Lund University, Lund, Sweden, [2]Rheumatology, Umeå, Sweden, [3]Karolinska Institutet, Stockholm, Sweden, [4]Health Economy, Lund, Sweden, [5]Department of Medical Sciences, Section of Rheumatology, Uppsala University, Uppsala, Sweden, [6]Umeå University Hospital, Umeå, Sweden, [7]Section of Rheumatology, Uppsala University, Uppsala, Sweden, [8]Linköping University, Linköping, Sweden, [9]Lund University, Malmö, Sweden, [10]Rheumatology, Lund, Sweden.

Background/Purpose: To study direct and indirect costs for patients with Systemic Lupus Erythematosus (SLE) ín five defined cohorts with nationwide spread in Sweden, and to find potential predictors of cost.

Methods: All 1029 prevalent and incident cases of clinically confirmed SLE, all with at least 4 ACR classification criteria, being alive between January 1st 2003 and December 31st2010 and followed in cohorts in five out of seven university hospitals in Sweden were included. Demographics, date of diagnosis, follow up period, phenotype, disease activity (SLEDAI), organ-damage (ACR/SLICC DI), quality of life (EQ5D) and costs for SLE specific therapy was collected when available from the databases of the rheumatology units. The database at the National Board of Health and Welfare provided all costs for in-patient admissions, out-patient specialist visits and all drug prescriptions from July 2005, and from the Swedish Social Insurance Agency data was obtained about sick leave and disability pensions. The data merge was done within these National Institutions and the cost analysis at the Swedish Institute for Health Economics. All costs are expressed in 2011 price level.

Results: Eighty-eight percent were females and the mean age in 2010 was 52 years with mean disease duration of 17.7 years and approximately 75 percents of the patients were below retirement age (65 years) at the end of the study period in 2010. Annual mean inpatient days were 3.1–3.6. Annual median outpatient specialist physician visits were 6.0–7.5. Annual net sick leave days decreased from 129.8 to 95.1 during the study period. The average total annual costs in SEK 2011, was per SLE patient 208 555 SEK (=$ 33 102) of which 70 percent were indirect costs, the corresponding costs for the subgroup with nephritis was 245 523 SEK (=$ 38 970). The mean annual cost for outpatient pharmaceuticals per SLE patient was 12 888 SEK (=$ 2 046), while the annual cost for more expensive inpatient pharmaceuticals constituted only between 10 and 20 percent of the total cost for pharmaceuticals. Predictors for total costs were increasing age from the age of 40, explained by an increase in indirect costs. Total costs increased with 39 percent for every additional point in ACR/SLICC DI and with 51 percent for patients with a SLEDAI score above 3 (All p<0.01). The EQ5D decreased with increasing SLEDAI (p<0.01). By extrapolation of the study-data the total cost for SLE in Sweden in 2011 can be estimated to 1.125 billions SEK (=$ 178 millions).

Conclusion: The average annual cost for each SLE patient in Sweden is $ 33 102, with indirect costs representing approximately 70 percent and cost for pharmaceuticals only 7 percent of total costs. Significant and independent predictors of costs are increasing age, acquired organ damage and disease activity.

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1770

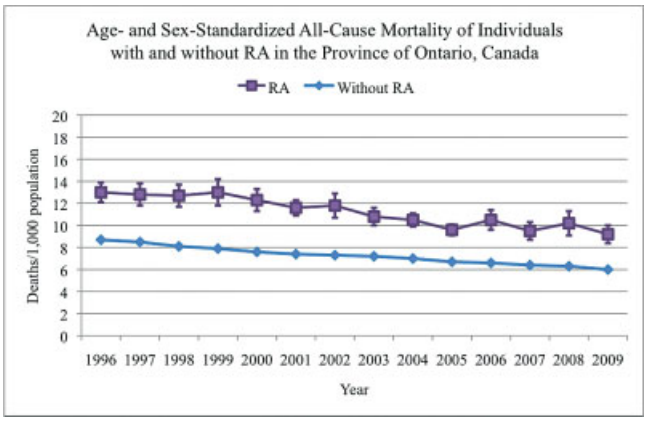
All-Cause Mortality For Patients with Rheumatoid Arthritis In a Universal Public Health Care System. Jessica Widdifield[1], J. Michael Paterson[1], Sasha Bernatsky[2], Bindee Kuriya[3], J. Carter Thorne[4], Simon Hollands[1] and Claire Bombardier[5]. [1]Institute for Clinical Evaluative Sciences, Toronto, ON, [2]McGill University, Montreal, QC, [3]Mount Sinai Hospital, University of Toronto, Toronto, ON, [4]Southlake Regional Health Centre, Newmarket, ON, [5]University of Toronto, Toronto, ON.

Background/Purpose: Studies evaluating trends in rheumatoid arthritis (RA) mortality over time have produced inconsistent results. Our aim was to estimate all-cause mortality in RA between 1996–2009, assess changes in mortality over time, and to compare mortality rates in RA with the general population.

Methods: We studied all residents in Ontario, Canada's most populous province (N~13 million). Patients with RA were identified using the Ontario RA administrative Database (ORAD), a population-based research cohort generated from administrative data using a validated RA case definition. Linking to vital statistics data, we estimated annual all-cause mortality in RA by dividing the number of deaths among RA patients by the number of RA patients in each year. To compare mortality rates over time, we standardized for age and sex using the 2001 Ontario census population estimates. Age specific and age-and-sex standardized all-cause mortality estimates are expressed as the number of deaths per 1,000 RA patients for each year of the study period. The age-and-sex-standardized all-cause mortality estimates were compared in terms of relative percentage change between 1996 and 2008. We compared changes in mortality over time in RA patients, to estimates of mortality in the general population, over the same period. Finally, standardized mortality ratios (SMRs) were calculated, which provides the ratio of the mortality rate in RA patients versus the age and sex matched general population mortality.

Results: Age-and-sex standardized all-cause mortality ranged from 13.0 deaths per 1,000 RA patients (95%CI 12.2,13.9) in 1996 to 9.2 deaths per 1,000 RA patients (95%CI 8.4,10.0) in 2010. In 2008, the age-standardized rate for RA females was 8.8 deaths per 1,000 (95%CI 8.0,9.6) compared to 12.1 deaths per 1,000 (95%CI 10.3,14.2) in males, and rates were higher among males than females in all age groups. Age-specific all-cause mortality in RA patients increased with increasing age. Comparing RA mortality trends to the general population (Figure),

since 1996, all-cause mortality decreased for RA by a relative 21.4%, with a smaller decrease (13.4%) in the general population. The SMRs for RA patients in 2000, 2004, and 2008 were 1.50 (95% CI 1.43–1.57), 1.43 (95%CI 1.37–1.50), and 1.41 (95%CI 1.35,1.47) respectively.



Conclusion: All-cause mortality for patients with RA has decreased over the past decade but remains elevated compared to the general population. Our results suggest 40–50% more deaths among RA patients compared to the general population. SMR estimates over the past decade do suggest the mortality gap may be slowly narrowing.

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Cost-Effectiveness Of Different Treatment Sequences Including Adalimumab In The Treat-To-Target Framework For Early Rheumatoid Arthritis In Germany. Malte Wolff[1], Zheng-Yi Zhou[2], James Signorovitch[2], James W. Shaw[3] and Arijit Ganguli[3]. [1]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany, [2]Analysis Group, Inc., Boston, MA, [3]AbbVie Inc., North Chicago, IL.

Background/Purpose: The 2012 German rheumatoid arthritis (RA) treatment guidelines recommend sequential use of disease-modifying antirheumatic drugs (DMARDs) in a treat-to-target (T2T) framework. Biologics are recommended for patients not responding to two conventional DMARDs or with high disease activity and indicators for poor prognosis while on initial DMARD therapy. The objective of this study was to assess the cost-effectiveness of three T2T strategies for achieving and maintaining remission among early RA patients in Germany.

Methods: A Markov model was developed to evaluate the costs and outcomes of three T2T strategies (A, B, C) among early RA patients over a 20-year time horizon from a German societal perspective. Four health states (i.e., remission and low, moderate, and severe disease activity) were defined based on the Disease Activity Score 28 joints (DAS28). At the beginning of each cycle (every 6 months), patients not achieving remission switched to the next treatment. The treatment strategies are: (A) first-line adalimumab (ADA) + methotrexate (MTX); (B) first-line MTX monotherapy, followed by a hybrid approach with ADA + MTX for patients with high disease activity and one DMARD + MTX for patients with low or moderate disease activity after MTX failure; and (C) (current recommended treatment sequence): ADA + MTX after 2 conventional DMARDs. Transition probabilities were estimated using efficacy data from randomized controlled trials. Both direct medical costs (i.e., drug and administration, monitoring, medical, and adverse event costs) and indirect costs (productivity loss) were considered; costs inputs were derived from public data or literature based on the 2012 German treatment guidelines. Utility inputs were estimated based on the OPTIMA trial. Incremental cost-effectiveness ratios (ICERs) comparing Arm A or B vs. C were computed as incremental costs per quality-adjusted life year (QALY) gained. Univariate sensitivity analyses were performed.

Results: At 20 years, Arm A led to an additional 7.8% of patients in remission and 0.280 additional QALY gained compared to Arm C; while Arm B vs. C yielded an additional 0.5% of patients in remission and 0.027 QALY gained. The incremental costs for Arms A and B vs. C over 20 years were €12,135 and €989, respectively, resulting in ICERs of €43,404 per QALY gained for Arm A vs. C and €37,206 for Arm B vs. C as well as ICERs of €9,003 per additional year in remission for Arm A vs. C and €10,609 for Arm B vs. C. Results were robust in univariate sensitivity analyses. Most scenarios (86% for A vs. C and 99% for B vs. C) yielded an ICER below an assumed willingness-to-pay threshold of €50,000 per QALY with exceptions of excluding indirect costs for both comparisons and a shorter time horizon for Arm A vs. C.

Conclusion: In a T2T framework in early RA, strategies starting with ADA + MTX and starting with MTX monotherapy followed by early switching to ADA + MTX for patients with high DAS28 were cost-effective compared with the current recommended treatment sequence with ADA + MTX use after two conventional DMARDs.

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Better Cost-Effectiveness and Worker Productivity In Triple DMARD Therapy Versus Methotrexate Monotherapy In Early Rheumatoid Arthritis; Cost-Utility Analysis Of The Treach Trial. P.H.P. de Jong[1], A.E.A.M. Weel[2], J.J. Luime[1], P.J. Barendregt[2], A.H. Gerards[3], P.A. van der Lubbe[3], M.H. de Jager[4], P.B. de Sonnaville[5], D. van Zeben[6], B.A. Grillet[7] and J.M.W. Hazes[1]. [1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]Maasstad Hospital, Rotterdam, Netherlands, [3]Vlietland Hospital, Schiedam, Netherlands, [4]Albert Schweitzer Hospital, Dordrecht, Netherlands, [5]Admiraal de Ruyter hospital, Goes, Netherlands, [6]Sint Franciscus Gasthuis, Rotterdam, Netherlands, [7]Zorgsaam Hospital, Terneuzen, Netherlands.

Background/Purpose: In the treatment in the Rotterdam Early Arthritis Cohort (tREACH) trial we showed that treatment goals were attained faster and maintained with less treatment intensifications within the initial triple DMARD therapy (iTDT) groups as opposed to the initial methotrexate (MTX) mono-therapy (iMM) group. Medication costs are just 20–50% of the total costs. Furthermore the policy for covering prescribed drugs by health insurance companies and governments is more and more influenced by cost-effectiveness. Therefore, our aim is to investigate which initial treatment regimen has the lowest costs per Quality Adjusted Life Year (QALY).

Methods: The one-year data of the tREACH trial were used. Patients were included who had a high probability (> 70%) of progressing to persistent arthritis, based on the prediction model of Visser. The Visser algorithm and 2010 criteria for RA have similar discriminative abilities to identify patients at risk of persistent arthritis at 1 year. Patients were randomized into 3 induction therapy strategies: (A) iTDT (MTX 25 mg/week + sulfasalazine 2 grams/day + hydroxychloroquine 400mg/day) with intramusculair glucocorticoids (GCs) (depomedrol 120mg), (B) iTDT with an oral GCs tapering scheme (starting 15 mg) and (C) iMM with oral GCs similar to B. We used a treat-to-target approach, with patients being examined every 3 months and treatment decisions based upon the original DAS thresholds for low disease activity. Data on QALYs, direct and indirect cost were used. Direct costs are the costs of treatment and medical consumption, whereas indirect costs are costs due to loss of productivity (i.e. sick leave and unemployment).

Results: A total of 281 patients were randomly assigned to strategy (A) (n=91), (B) (n=93) or (C) (n=97). Average QALYs (ideally 1) for treatment strategy A, B and C are given in table 1. Direct and indirect costs per QALY were higher in the iMM group compared with the iTDT groups (table 1). The difference in direct costs was due to ~40% more biological usage, from 3 months up to 1 year. Less unemployment, long-term sickness and reduction in contract hours caused the difference in indirect costs (table 2). Total costs per QALY differed significantly between treatment arm B and C (p=0.012, table 1).

Table 1: QALYs and (specified) average cost per QALY after 1 year of follow-up

	A. MTX + SASP + HCQ + im GCs (n=91)	B. MTX + SASP + HCQ + oral GCs (n=93)	C. MTX + oral GCs (n=97)
QALYs[1] (AUC)	0.75 (0.11)	0.76 (0.10)	0.73 (0.13)
Costs per QALY			
Total direct costs*	€4841 (€7225)	€5099 (€7152)	€7969 (€10307)
• Medication†	€3676 (€6758)	€3872 (€6493)	€6162 (€9618)
• Medical consumption	€1023 (€693)	€1013 (€625)	€1300 (€1264)
• Hospitalization	€143 (€874)	€215 (€1002)	€507 (€3401)
Total indirect costs‡	€7869 (€15339)	€5271 (€11624)	€9388 (€15084)
Total costs§	€12710 (€18737)	€10371 (€15602)	€17357 (€21729)

Results shown are mean(sd).
[1]QALYs are measured with the Dutch EuroQol.
*p=0.018 and p=0.028 for resp. A. vs C and B vs C. ‡p=0.037 B vs C.
†p=0.043 A vs. C §p=0.012 B vs C.
Abbreviations: AUC, area under the curve; GCs, glucocorticoids; HCQ, hydroxychloroquine; MTX, methotrexate; QALYs, Quality Adjusted Life Years; SASP,sulfasalazine

Table 2: Loss of productivity and costs during the first year of therapy, stratified for initial treatment regimen.

	A. MTX + SASP + HCQ + im GCs (n=91)	B. MTX + SASP + HCQ + oral GCs (n=93)	C. MTX + oral GCs (n=97)
Unemployment change*	-1 (-2%)	-4 (-8%)	+6 (+11%)
Loss of productivity			
Sick leave			
o Occurrence	47 (89%)	43 (81%)	46 (81%)
o Long term sickness††	10 (19%)	5 (9%)	17 (30%)
o Days absent, *median(IQR)*	3 (1 – 8)	5 (1 – 11)	4 (1 – 8)
Reduction contract hours			
o Occurrence	17 (32%)	20 (38%)	22 (39%)
o Decrease in hours, *median(IQR)*‡	18 (4 – 37)	5 (1 – 11)	29 (10 – 36)

Results shown are number (%) unless stated otherwise.
†Long term sickness is defined as absence from work longer than 160 days (Dutch friction period)
*p=0.015 and p=0.015 for respectively A vs. C and B vs. C.
†p=0.0076 B vs. C.
‡p=0.0007 B vs. C.
Abbreviations: GCs, glucocorticoids; HCQ, hydroxychloroquine; MTX, methotrexate and SASP, sulfasalazine.

Conclusion: iTDT had the lowest costs per QALY compared with iMM. Furthermore iTDT has significant better worker productivity. This underlines once again why iTDT instead of iMM is preferred as first choice in very early RA.

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1773

The Contribution Of Environmental Factors To Familial Risk Of Rheumatoid Arthritis By Serologic Phenotypes Among Women In a Longitudinal Cohort Study. Jeffrey A. Sparks[1], Chia-Yen Chen[2], Linda T. Hiraki[3], Susan Malspeis[1], Karen H. Costenbader[1] and Elizabeth W. Karlson[1]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Harvard School of Public Health, Boston, MA, [3]Brigham and Women's Hospital, Harvard School of Public Health, Boston, MA.

Background/Purpose: Familial risk of RA is composed of shared genetic and environmental factors. Previous studies exploring familial risk of RA have not incorporated environmental factors or stratified RA by serologic status. We aimed to estimate the familial risk for all, seropositive, and seronegative RA adjusting for known RA environmental risk factors.

Methods: We conducted a prospective study of family history and RA among a subset of 121,700 women followed since 1976 in the Nurses' Health Study. In 2008, 74,024 participants provided information about family history (FH) of RA or lupus by affected first-degree relative (FDR). RA cases were validated by medical record review according to the 1987 ACR criteria for RA classification. RA serologic status was defined as +RF or ACPA by chart review or laboratory measurement. Cox proportional hazards models were performed to estimate the hazard ratio (HR) and 95% confidence interval (CI) for RA phenotypes (all, seropositive, and seronegative) by affected FDR. Cox regression models were performed for any FH and environmental factors previously shown to be associated with RA (cigarette smoking pack-years, alcohol consumption, parity, breastfeeding duration, body mass index, alcohol intake, menopause, hormone use, menses regularity, and age at menarche) for each RA phenotype.

Results: In 2,082,926 person-years of follow-up in the Nurses' Health Study, we validated 532 RA cases (311 seropositive and 221 seronegative) among 74,024 women that provided information on FH. Any FH of RA or lupus in FDRs was reported in 143 (27%) cases and 6,856 (9%) non-cases. Any FH was associated with all RA (HR 3.76, 95% CI 3.10–4.57), seropositive RA (HR 4.03, 95% CI 3.14–5.17), and seronegative RA (HR 3.98, 95% CI 2.93–5.42) (**Table 1**). RA risk was greatest for those with parental FH. After adjusting for environmental factors, any FH remained significantly associated with all RA (HR 3.66, 95% CI 3.01–4.45), seropositive RA (HR 3.93, 95% CI 3.06–5.06), and seronegative RA (HR 3.84, 95% CI 2.82–5.23) (**Table 2**). After adjusting for FH, smoking >10 pack-years, overweight body mass index, and breastfeeding duration ≥12 months all remained significantly associated with RA.

Table 1. Age-adjusted hazard ratios for family history of RA or lupus by first-degree relatives (FDR: parent, sibling, or offspring) and RA phenotypes (all, seropositive, and seronegative) in the Nurses' Health Study (n=74,024).

	All RA (n=532)		Seropositive RA (n=311)		Seronegative RA (n=221)	
Family history	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
No FDR	1.0	Ref	1.0	Ref	1.0	Ref
Any FDR	3.76	3.10–4.57	4.03	3.14–5.17	3.98	2.93–5.42
1 FDR	3.46	2.81–4.25	3.72	2.85–4.85	3.56	2.56–4.96
≥2 FDRs	7.06	4.59–10.87	7.80	4.38–13.88	8.87	4.61–17.06
Parent	4.36	3.47–5.46	5.20	3.91–6.93	4.25	2.92–6.19
Sibling	3.46	2.54–4.73	3.22	2.11–4.90	4.28	2.92–6.19
Offspring	4.27	2.89–6.34	3.83	2.22–6.62	5.23	2.93–9.32

Table 2. Multivariable analyses of family history of RA or lupus in any first-degree relative (FDR) and environmental factors estimating hazard ratios for RA phenotypes (all, seropositive, and seronegative) in the Nurses' Health Study (n=74,024).

Multivariable models	All RA (n=532) HR (95% CI)	Seropositive RA (n=311) HR (95% CI)	Seronegative RA (n=221) HR (95% CI)
Family history[1]			
No FDR	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Any FDR	**3.66 (3.01–4.45)**	**3.93 (3.06–5.06)**	**3.84 (2.82–5.23)**
Cigarette smoking pack-years[2]			
Never to ≤10	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
10 to 20	**1.50 (1.15–1.94)**	**1.75 (1.27–2.41)**	1.15 (0.73–1.81)
≥20	**1.57 (1.29–1.92)**	**1.69 (1.31–2.18)**	**1.41 (1.03–1.94)**
WHO body mass index category[2]			
Normal or underweight	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Overweight	**1.26 (1.04–1.53)**	1.27 (0.99–1.62)	1.29 (0.94–1.75)
Obese	1.07 (0.83–1.37)	0.99 (0.71–1.38)	1.26 (0.86–1.85)
Alcohol intake (g/day)[2]			
Never to ≤5	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
5 to <10	0.76 (0.57–1.02)	0.72 (0.49–1.05)	0.82 (0.52–1.31)
≥10	0.99 (0.79–1.25)	0.97 (0.72–1.30)	1.02 (0.71–1.48)
Parity and breastfeeding duration[2]			
Parous, no breastfeeding	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Parous, 1–11 months	0.92 (0.75–1.13)	1.03 (0.79–1.34)	0.78 (0.56–1.09)
Parous, ≥12 months	**0.69 (0.52–0.91)**	0.77 (0.54–1.10)	**0.58 (0.37–0.90)**
Nulliparous	1.32 (0.93–1.86)	**1.54 (1.00–2.38)**	1.02 (0.57–1.84)
Menopausal status and hormone use[2]			
Post-menopausal, no hormone use	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Pre-menopausal	**0.69 (0.50–0.95)**	0.71 (0.48–1.06)	0.65 (0.39–1.09)
Post-menopausal, hormone use	1.01 (0.81–1.25)	1.02 (0.77–1.35)	1.02 (0.73–1.44)
Age at menarche[2]			
≥12 years old	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
<12 years old	0.98 (0.79–1.20)	1.07 (0.83–1.39)	0.85 (0.60–1.21)
Menses regularity[2]			
Regular	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Irregular	1.13 (0.88–1.45)	1.21 (0.88–1.66)	1.04 (0.69–1.56)

[1]Adjusted for age, cigarette smoking pack-years, WHO body mass index category, alcohol intake, parity, breastfeeding duration, menopausal status, hormone use, age at menarche, and menses regularity.
[2]Adjusted for age and any family history of RA of lupus in first-degree relatives.

Conclusion: In this large prospective cohort, women with a first-degree relative with RA or lupus had a four-fold increase in risk of RA compared to those with no family history. This association was similar for seropositive and seronegative RA and remained significant after adjusting for RA environmental risk factors, suggesting that familial RA risk is not fully explained by known environmental factors.

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ACR Concurrent Abstract Session
Muscle Biology, Myositis and Myopathies I: Insights into Mechanisms of the Idiopathic Inflammatory Myopathies
Monday, October 28, 2013, 4:30 PM–6:00 PM

1774

Sepsis Is The Leading Cause Of Hospital Mortality In Dermatomyositis/Polymyositis: Data From a Population-Based Study. Sara Murray[1], Laura Trupin[1], Chris Tonner[1], Matthew Cascino[1], Gabriela Schmajuk[1], Mary Margaretten[1], Jennifer Barton[1], Patricia P. Katz[1], Edward H. Yelin[2] and Jinoos Yazdany[1]. [1]University of California, San Francisco, San Francisco, CA, [2]UC San Francisco, San Francisco, CA.

Background/Purpose: Dermatomyositis (DM) and polymyositis (PM) are debilitating inflammatory myopathies with five-year mortality rates estimated to be 33%. However, the leading causes of inpatient mortality in these conditions have not been fully explored. In this study, we used a multi-state sample from the Healthcare Cost and Utilization Project (HCUP) to evaluate the sociodemographic and clinical predictors of inpatient mortality in patients with DM/PM.

Methods: Using the 2009 HCUP State Inpatient Databases for California, New York, Florida, Washington, and Utah, we performed a retrospective study of individuals >18 years of age who met a validated administrative definition of DM/PM. The primary outcome was death during hospitalization. Principal diagnoses were determined according to Clinical Classification Software (CCS) codes and variables for interstitial lung disease (ILD), infection, malignancy, and cardiovascular disease (CVD) were generated based on any primary or secondary ICD–9 code falling within these respective diagnostic categories. A modified Charlson Index was calculated excluding the above diagnoses. Logistic regression was used to investigate the relationship between inpatient mortality and sociodemographic characteristics (age, gender, race, income), admission characteristics (length of stay, weekend admission), and associated diagnoses (ILD, infection, malignancy, CVD).

Results: 3,300 admissions with PM/DM were identified and inpatient mortality was 3.9% (128 deaths). Subjects had an average age of 60 years (SD 17), 68% were female, 62% had DM and 38% had PM. In unadjusted analyses, age (65 years in those who died vs. 60 years in those who survived), weekend admission (27% vs. 19%), length of stay (17 vs. 7 days), more comorbidities (Charlson score of 1.4 vs. 1.3), ILD (22% vs. 12%), infection (76% vs. 36%), malignancy (21% vs. 9%), and CVD (51% vs. 29%) were all associated with mortality. Leading principal diagnoses in subjects who died were septicemia (24%), respiratory failure (17%), pneumonia (9%), aspiration pneumonitis (9%), and acute cerebrovascular disease (5%). In adjusted logistic regression, age (OR 1.09, 95% CI 1.02–1.17), weekend admission (OR 1.5, 95% CI 1.0–2.3), length of stay (OR 1.05, 95% CI 1.03–1.07), ILD (OR 2.0, 95% CI 1.2–3.1), infection (OR 4.3, 95% CI 2.8–6.5), malignancy (OR 3.2, 95% CI 1.9–5.2), and CVD (OR 2.4, 95% CI 1.6–3.5) were independently associated with mortality (see Table).

Table. Adjusted logistic regression of predictors of inpatient mortality in patients with polymyositis and dermatomyositis in a multi-state population-based sample.

	OR (95% CI)	*P*
Age (per 5 years)	**1.09 (1.02–1.17)**	**<0.05**
Female	1.3 (0.8–1.9)	0.2
Race (reference: white)		
Black	1.3 (0.8–2.1)	0.4
Hispanic	0.9 (0.5–1.6)	0.7
Asian/Pacific Islander	1.7 (0.8–3.8)	0.2
Other	2.0 (0.8–4.9)	0.2
Low Income	0.9 (0.6–1.4)	0.7
Weekend Admission	**1.5 (1.0–2.3)**	**<0.05**
Length of Stay (per 2 days)	**1.05 (1.03–1.07)**	**<0.001**
Modified Charlson Index	0.89 (0.78–1.01)	0.08
Dermatomyositis (reference polymyositis)	1.0 (0.7–1.5)	0.9
Interstitial Lung Disease	**2.0 (1.2–3.1)**	**<0.01**
Infection	**4.3 (2.8–6.5)**	**<0.001**
Malignancy	**3.2 (1.9–5.2)**	**<0.001**
Cardiovascular disease	**2.4 (1.6–3.5)**	**<0.001**

Conclusion: Among hospitalized patients with DM/PM, infection, CVD and factors associated with the disease process (ILD, malignancy) were leading causes of mortality. Sepsis was the leading cause of death in these patients, suggesting that additional attention to infection prevention in both the inpatient and outpatient settings may significantly improve outcomes.

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Use Of "Computer-Aided Lung Informatics For Pathology Evaluation and Rating" Software In High-Resolution Computed Tomography In Patients With Idiopathic Inflammatory Myopathy and Interstitial Lung Disease. Katelynn Wilton[1], Brian Bartholmai[2], Sanjay Kalra[2], Cynthia S. Crowson[2], Helen Khun[2] and Floranne C. Ernste[3]. [1]Mayo Clinic College of Medicine, Rochester, MN, [2]Mayo Clinic, Rochester, MN, [3]Mayo Clinic Rochester, Rochester, MN.

Background/Purpose: The idiopathic inflammatory myopathies (IIM) are associated with interstitial lung disease (ILD), characterized by parenchymal abnormalities on high-resolution computed tomography (HRCT). We determined the radiologic progression of IIM patients with ILD using a novel lung parenchymal scoring system, "Computer-Aided Lung Informatics for Pathology Evaluation and Rating" (CALIPER) software to record abnormalities on HRCT.

Methods: We conducted a retrospective study of dermatomyositis (DM) and polymyositis (PM) patients at a large academic institution in 2003–2011. We collected HRCT and PFT data at IIM diagnosis and 1, 3, and 5 years. HRCT images were anatomically scored using CALIPER: total volume of normal parenchyma, low attenuation areas (mild, moderate, and severe subclasses) and interstitial abnormalities (ground glass opacities, honeycombing, and reticular densities). Definition of improvement (DOI) for ILD was a $\geq$ 10% increase in total lung capacity (TLC), $\geq$ 15% increase in diffusing capacity (DLCO), and normalization of oxygen during exercise between baseline and 1 year. Spearman correlations, two group and paired t-tests were performed.

Results: We identified 172 patients with IIM and ILD (62% female; mean age 51 years; mean follow-up 4.1 years). Of those, 59 had DM, 84 had PM, 22 had anti-synthetase syndrome, and 7 were unknown. HRCT images revealed ILD in 95% of patients. Main ILD types were nonspecific interstitial pneumonia (59%), cryptogenic organizing pneumonia (23%), and usual interstitial pneumonia (9%). At year 1, improvement occurred in HRCT scans ($n = 58$) in percentage of reticular densities from $7 \pm 6\%$ to $5 \pm 6\%$ ($p < 0.001$) and interstitial abnormalities from $20 \pm 16\%$ to $17 \pm 16\%$ ($p = 0.049$), and a trend in improvement in DLCO ($n = 80$) from 56.2 ± 18.1 to 58.8 ± 16.6 percent predicted ($p = 0.053$). Baseline to year 3, improvement occurred ($n = 34$) in reticular densities ($p = 0.011$) but no difference in PFT values ($n = 64$). At year 1, 22 patients met DOI; within these, there was improvement in DLCO ($n = 22$): 46.8 ± 10.8 to 62.5 ± 12.8 ($p < 0.001$) and TLC ($n = 12$): 65.9 ± 15.4 to 73.9 ± 13.4 ($p = 0.004$). Subgroup analysis bytreatment, prednisone (group 1; $n = 43$), prednisone + other immunosuppressant (group 2; $n = 65$), other immunosuppressant (group 3; $n = 18$), and none (group 4; $n = 40$) revealed no differences in PFTs at baseline; but, in group 4 there were more interstitial abnormalities at baseline ($p = 0.050$). Baseline to year 3, group 4 worsened in interstitial abnormalities ($p = 0.036$). Progression from normal lung (green) to ground glass opacities (yellow) and reticular fibrosis (orange) also occurred despite treatment (See Figure).

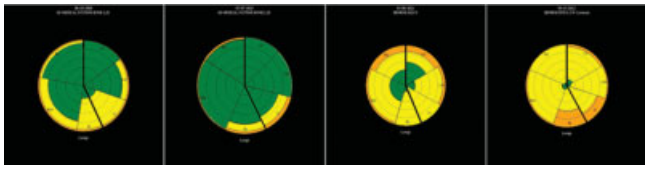

Figure. CALIPER in ILD.

Conclusion: IIM patients with ILD improve in reticular densities, low attenuation areas, and interstitial abnormalities. Progression of ILD was observed in patients without treatment. CALIPER aids in tracking ILD over time.

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1776

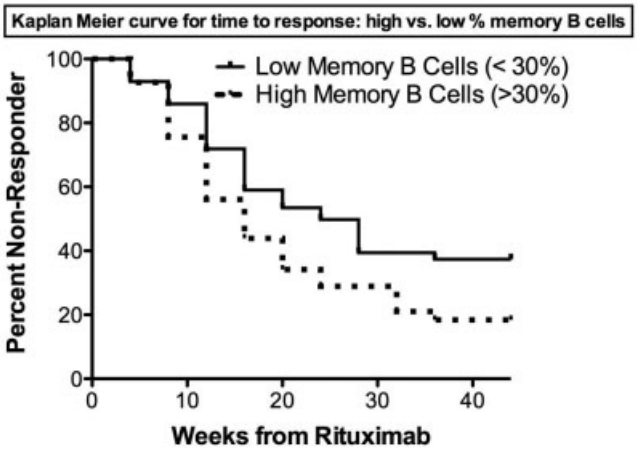
Peripheral Blood Memory B Cell Numbers Predict Clinical Response Following Rituximab Treatment Of Adult and Childhood Myositis. Rohit Aggarwal[1], Chester V. Oddis[1], Erich R Wilkerson[1], Diane Koontz[1], Ilinca D. Metes[1], Ann M. Reed[2], Dana P. Ascherman[3] and Marc C. Levesque[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Mayo Clinic, Rochester, MN, [3]University of Miami Miller School of Medicine, Miami, FL.

Background/Purpose: B cell subset numbers, especially lower memory B (Bmem) cells, predict clinical responsiveness to rituximab in several diseases including pemphigus and rheumatoid arthritis (RA). The Rituximab in Myositis (RIM) trial enrolled 200 refractory myositis subjects (76 dermatomyositis (DM), 76 polymyositis (PM), 48 juvenile dermatomyositis (JDM)). Our aim was to determine whether the numbers and relative percentage of peripheral blood B cell subsets at baseline and after rituximab predicted clinical responses in refractory myositis.

Methods: Using flow cytometry, we analyzed total B cell numbers and B cell subset (transitional/naïve/switched and unswitched Bmem/ and plasmablast) percentages at baseline, 8, 24 and 32 or 36 weeks after rituximab. We assessed 71 "responders" who met the study definition of improvement (DOI) without experiencing subsequent disease worsening and compared them to 35 "non-responders." The DOI was defined as 20% improvement in at least 3 of 6 core set disease activity measures, including MD and subject global disease activity, manual muscle testing (MMT), physical function, muscle enzymes,

and extramuscular disease activity. We used Mann-Whitney tests to determine the association of B cell subsets with response. Cox proportional hazard models were used to determine if B cell subsets predicted a better (i.e. shorter) time to response post rituximab. Spearman correlations assessed the relationship of changes in MMT and MD global post rituximab to changes in Bmem and plasmablast subsets.

Results: 97% of RIM subjects depleted their B cells to <5/ul following rituximab. There was no difference in total B cell numbers, total and % B cell subsets, or the ratios of transitional and naive:Bmem cells between responders and non responders at any time-point. There was no correlation between change in B cell subsets and the change in MD global disease activity or MMT. However, among myositis autoAb positive subjects (N=80; 58 responders, 22 non-responders), there was a significantly higher percentage of Bmem cells in responders at week 8 [median (IQR): 30.6% (17.8–45.9) vs. 21.3% (12.8–26); p = 0.009], mainly due to a higher percentage of switched Bmem cells. The total number of Bmem cells at week 8 showed a similar trend (p=0.02). The percentage of Bmem cells at week 8 was also associated with a shorter time to response (p=0.008; Figure 1), mainly due to switched memory B cells in autoAb positive subjects (p=0.004). Similar trends between clinical responsiveness and Bmem cell numbers were seen in the overall cohort as in the PM, DM, and JDM subsets but not statistically significant.



Conclusion: In contrast to RA, a higher percentage of Bmem cells at week 8 was associated with clinical responsiveness in autoAb positive myositis patients post rituximab. This suggests the presence of a subpopulation of Bmem cells in myositis associated with a favorable response following B cell depletion.

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Antibodies Against TIF1-Gamma In Cancer Associated Myositis May Precede Cancer Symptoms and Persist After Cancer Removal. Ingrid E. Lundberg[1], Lara Dani[1], Maryam Dastmalchi[2], Maria Angeles Martinez[3], Moises Labrador-Horrillo[4] and Albert Selva O'Callaghan[4]. [1]Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, [2]Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, [3]Sant Pau Hospital, Barcelona, Spain, [4]Vall d'Hebron General Hospital, Barcelona, Spain.

Background/Purpose: Antibodies against TIF1-gamma have been detected in patients with cancer associated myositis (CAM) but it is not known whether the antibodies precede the diagnosis of cancer or if the antibodies persist after successful treatment of a malignancy. We aimed to analyse levels of TIF1-gamma antibodies in longitudinally collected sera taken before cancer diagnosis and after treatment of the malignancy in patients with CAM.

Methods: From our local myositis register including 170 myositis patients we found 56 cases of CAM. Serum samples and clinical data were available from 54 patients with CAM. Serum levels of anti-TIF1gamma antibody were tested by ELISA using a commercially available purified recombinant protein (OriGene, Rockville, MD).

Results: Sera from 16 (29.6%) patients (13 females and 3 males) were positive for anti-TIF1gamma antibodies in at least one serum sample. Their mean age was 63.6 years. Of the 16 positive patients 12 had developed cancer within 3 years from myositis diagnosis, 4 after 3 years. Serum samples taken before cancer diagnosis were available from 15/54 patients and four of them were positive for anti-TIF1-gamma. Of the 16 anti-TIF1-gamma positive cases, four had sera available before cancer diagnosis and three of them were positive before cancer diagnosis. One of these patients had detectable anti-TIF1gamma antibodies up to 5 years before cancer diagnosis. Of the 16 patients positive for anti-TIF1-gamma, 12 patients had died at time of our study, 7 within 1 year from cancer diagnosis. The 7 patients who died within one year had a mean antibody level of 1976 +/− 304 au, the 5 patients who died after more than 1 year had a mean antibody level of 1036 +/− 555 au (p=0.003). Four patients were still alive at time of the investigation, between 2–13 years after cancer treatment. They were all in remission from cancer disease. Two patients became negative for anti-TIF1-gamma antibodies, these two patients were among the patients in remission at follow up.

Conclusion: Anti-TIF1-gamma antibodies can be detected before cancer diagnosis and may thus become a helpful marker to alert for cancer in patients with myositis. The levels of anti-TIF1-gamma antibodies seem to be a prognostic marker for survival in CAM.

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Physical Interactions Between Histidyl-tRNA Synthetase and Endogenous/Exogenous Alarmins Enhance Immunogenicity In a Model Of Antigen-Induced Myositis. Irina Fernandez[1], Lisa Harlow[1], William Ridgway[2] and Dana P. Ascherman[1]. [1]University of Miami Miller School of Medicine, Miami, FL, [2]University of Cincinnati, Cincinnati, OH.

Objective: To assess the biological interplay between histidyl-tRNA synthetase (HRS) and different endogenous/exogenous ligands capable of generating signals through MyD88-dependent receptor systems in idiopathic inflammatory myopathy.

Background/Purpose: Recent immunohistochemical and array-based studies of human muscle tissue implicate Toll-like receptor (TLR)- and other MyD88-dependent signaling pathways in the pathogenesis of idiopathic inflammatory myopathy. Our model of HRS-induced myositis replicates many of these observations, demonstrating that intramuscular immunization of mice with bacterially produced HRS fusion proteins preferentially triggers muscle inflammation (relative to other bacterially generated control proteins) via partially redundant MyD88-dependent signaling cascades. However, the biophysical properties endowing HRS with this unique signaling capacity remain undefined.

Methods: Binding interactions between eukaryotically expressed HRS and ligands of TLR2 (FSL-1), TLR4 (LPS), or RAGE (HMGB1) were assessed via standard solid phase ELISA following co-incubation of soluble HRS or TLR/RAGE ligands with defined concentrations of pre-bound substrate antigen. As an alternative method for detection of HRS-TLR ligand complex formation, HRS and specified ligands were pre-incubated in solution for 2 hours prior to plating in BSA-blocked ELISA wells and subsequent probing with anti-HRS serum. The ability of these complexes to signal via defined TLRs was assessed through stimulation of TLR-transfected HEK23 cells and measurement of resulting IL-8 production.

Results: ELISA-based experiments demonstrated that both human and murine HRS expressed in a eukaryotic system bound HMGB1 in dose-dependent fashion. Similarly, the TLR2 ligand FSL-1 formed complexes with baculovirus-expressed HRS that inhibited subsequent binding of HRS to BSA-blocked ELISA wells. LPS also readily formed complexes with baculovirus-expressed HRS, as evidenced by diminished ELISA-based binding of these complexes relative to HRS alone. Comparative ELISAs employing a biotinylated LPS/streptavidin-HRP probe system and various substrate antigens demonstrated that HRS bound LPS with 10–100 fold greater affinity/aviditiy than did ovalbumin or control autoantigens such as baculovirus-expressed Ro52. Corresponding to these heightened interactions with the TLR ligands LPS and FSL-1, complexes of HRS-LPS and HRS-FSL-1 synergistically activated HEK293 cells transfected with TLR4 and TLR2, respectively—producing levels of IL-8 which significantly exceeded those induced by HRS or ligand alone.

Conclusion: HRS preferentially binds various ligands of innate immune receptors with high affinity, resulting in synergistic activation of TLR2- and TLR4-mediated signaling pathways that likely contribute to human idiopathic inflammatory myopathy as well as our model of HRS-induced myositis. Of note, these findings support a more general paradigm in which autoantigens such as HRS bind endogenous/exogenous alarmins to activate innate immune signaling cascades that enhance immunogenicity and prime subsequent adaptive autoimmune responses.

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1779

A Randomized Controlled, Clinical, Histological and mRNA Profiling Pilot Study Of Endurance Exercise In Myositis. Li Alemo Munters[1], Ingela M. Loell[2], Joan Raouf[3], Maryam Dastmalchi[4], Eva Lindroos[5], Christina Ottosson[6], Yi-Wen Chen[7], Annemarie F van Delden[6], Mona Esbjörnsson[8], Marina Korotkova[9], Helene Alexanderson[10], Kanneboyina Nagaraju[7] and Ingrid E. Lundberg[2]. [1]Rheumatology Unit, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology Unit, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden, [4]Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, [5]Rheumatology Unit, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden., Stockholm, Sweden, [6]Rheumatology Unit, Karolinska University Hospital Solna, Karolinska Institutet, Stockholm, Sweden., Stockholm, Sweden, [7]Research Center for Genetic Medicine, Children's National Medical Center, Washington DC, USA., Washington DC, DC, [8]Karolinska Institutet, Huddinge, Sweden, [9]Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden, [10]Division of Physiotherapy, Karolinska Institutet, Huddinge, Stockholm, Sweden.

Background/Purpose: This pilot study is a hypothesis-driven exploratory part of a larger randomized controlled trial evaluating effects of a supervised 12-week endurance exercise program (EG) compared to a non-interventional control group (CG) in patients with established polymyositis (PM) and dermatomyositis (DM). The aim was to determine the potential mechanisms underlying the beneficial effects of endurance exercise.

Methods: A subgroup of 15 patients with paired baseline and 12 week follow-up muscle biopsies (EG n=7 and CG n=8) were included in the analysis. mRNA expression profiling and immunohistochemistry analysis of biopsies from vastus lateralis muscle were used to determine molecular changes associated with the changes in clinical assessments. Clinical assessments consisted of: Maximal oxygen uptake (VO_2 max) and cycling time to exhaustion at 65% of VO_2 max. Lactate levels in the vastus lateralis muscle were measured with microdialysis directly after the cycling. Clinical disease activity was assessed according to the International Myositis Assessment and Clinical Studies Group (IMACS) criteria.

Results: Patients in the EG clinically improved compared to the CG in cycling time ($p<0.01$) and VO_2 max ($p<0.05$), whereas lactate levels at exhaustion were decreased or unchanged. A majority of the patients in the EG were responders with reduced disease activity compared to the CG ($p<0.05$). These clinical changes were accompanied with down-regulation in genes related to inflammation and ER-stress, such as Eukaryotic translation initiation factor 2C, 4 (−2.6, $p<0.01$) and Cell adhesion molecule with homology to L1CAM (−1.6, $p<0.01$); and up-regulation in genes related to capillary growth, cytoskeletal remodeling, muscle hypertrophy, mitochondria biogenesis and protein synthesis, such as Toll-like receptor 7 (1.7 fold, $p<0.01$), Fms-related tyrosine kinase 3 ligand (4.3 fold, $p<0.01$), Insulin-like growth factor 1 receptor (1.4, $p<0.001$), Insulin receptor (1.3, $p<0.001$). The CG displayed non- synchronized regulation of genes, although up-regulation in genes related to type 1 interferon and apoptosis was determined. No significant changes were displayed in the number of T-cells and macrophages in the EG nor in the CG. The EG but not the CG showed a higher number of capillaries per mm^2 in the follow up biopsy.

Conclusion: Our data showed that endurance exercise in patients with PM and DM may induce genes involved in muscle growth and remodeling as previously reported in healthy individuals. In addition, the exercise suppressed inflammation and ER-stress accompanied with reduced clinical disease activity in the patients. The findings suggest that endurance exercise may be beneficial by activating the muscle growth program which overwrites the muscle atrophy process, and suppressing the inflammation responses in parallel in the patients' muscles.

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ACR Concurrent Abstract Session
Pediatric Rheumatology - Clinical and Therapeutic Aspects II: Autoinflammatory Disease and Systemic Juvenile Idiopathic Arthritis
Monday, October 28, 2013, 4:30 PM–6:00 PM

1780

The Randomized Placebo Phase Study of Rilonacept in the Treatment of Systemic Juvenile Idiopathic Arthritis. Norman T. Ilowite[1], Kristi Prather[2], Yuliya Lokhnygina[2], Laura E. Schanberg[3], Melissa Elder[4], Diana Milojevic[5], James W. Verbsky[6], Steven J. Spalding[7], Yukiko Kimura[8], Lisa F. Imundo[9], Marilynn G. Punaro[10], David D. Sherry[11], Stacey E. Tarvin[12], Lawrence S. Zemel[13], James D. Birmingham[14], Beth S. Gottlieb[15], Michael L. Miller[16], Kathleen M. O'Neil[17], Natasha M. Ruth[18], Carol A. Wallace[19], Nora G. Singer[20] and Christy I. Sandborg[21]. [1]The Children's Hospital at Montefiore, Bronx, NY, [2]Duke Clinical Research Institute, Durham, NC, [3]Duke University Medical Center, Durham, NC, [4]University of Florida, Gainesville, HI, [5]University of California, San Francisco, San Francisco, CA, [6]Medical College of Wisconsin, Milwaukee, WI, [7]The Cleveland Clinic, Cleveland, OH, [8]Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [9]Morgan Stanely Children's Hospital of New York-Presbyterian, Columbia University Medical Center, New York, NY, [10]Texas Scottish Rite Hospital, Dallas, TX, [11]Children's Hospital of Philadelphia, Philadelphia, PA, [12]Riley Hospital for Children, Indianapolis, IN, [13]Pediatric Rheumatology Collaborative Study Group, Cincinnati, OH, [14]Michigan State University College of Human Medicine, Grand Rapids, MI, [15]Cohen Children's Medical Center of New York, New Hyde Park, NY, [16]Childrens Memorial Hospital, Chicago, IL, [17]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [18]Medical University of South Carolina, Charleston, SC, [19]Seattle Childrens Hosp & Research Institute, Seattle, WA, [20]MetroHealth Medical Center, Cleveland, OH, [21]Stanford University, Palo Alto, CA.

Background/Purpose: The RAndomized Placebo Phase Study Of Rilonacept in the Treatment of Systemic Juvenile Idiopathic Arthritis (RAPPORT) is a multicenter controlled trial using a 4 week randomized placebo phase. The study design reasons that if a treatment is effective, subjects who begin active treatment earlier will respond sooner, on average, than subjects who begin active treatment later. Rilonacept is a fusion protein consisting of human cytokine receptor extracellular domains of both receptor components required for IL-1 signaling: the IL-1 Type I receptor and the IL-1 receptor accessory protein as well as the Fc portion of human IgG1.

Methods: RAPPORT consisted of a double-blind phase (weeks 0–4), a treatment phase (weeks 4–24) and an open label Long Term Extension phase (24 weeks −21 months). The primary endpoint was time to response, using adapted JIA ACR 30 response criteria requiring absence of fever for 2 weeks and meeting pre-specified criteria for tapering of corticosteroids during the first 12 weeks of the study. We randomized 71 children with at least 2 active joints from 20 sites 1:1 to 2 arms of the study. The rilonacept arm subjects received rilonacept (4.4mg/kg loading dose followed by weekly 2.2mg/kg subcutaneously) and placebo arm subjects received placebo for 4 weeks followed by loading dose of rilonacept at week 4 followed by weekly maintenance doses. After week 14, corticosteroids were dosed according to the treating physician.

Results: The time to response was shorter in the rilonacept arm (median 4 weeks; range 2–10 weeks) than in the placebo arm (median 6 weeks; range 2–12 weeks) (Chi-square 7.235; p=0.007). Twenty-six of 35 (79%) patients in the rilonacept arm and 13 of 33 (39%)in the placebo arm met ACR Pediatric 30 response criteria at week 4 (p=0.004); 21/35 (60%) in the rilonacept arm vs. 10/33 (30%) in the placebo arm met ACR pediatric 50 response criteria (p=0.015); 14/35 (40%) vs. 4/33 (12%) met ACR pediatric 70 criteria (p=0.013). Adverse events were similar in the two arms of the study (Table). Four subjects developed elevations in liver transaminases of ≥ 2 times the upper limit of normal (all while on rilonacept); 2 subjects developed elevations ≥5 times the upper limit of normal. In one, the

elevations resolved but recurred on re-challenge and was deemed an SAE. One subject developed EBV induced macrophage activation syndrome.

Table. Adverse Events

Variable	Double-Blind Phase		Treatment Phase		LTE Open-Label Phase
	Rilonacept (N=36)	Placebo (N=35)	Rilonacept (N=35)	Placebo (N=33)	Rilonacept (N=40)
ADVERSE EVENTS					
No. of events	16	62	81	123	110
No. of events per patient-year	5.7	23.6	6.2	11.3	3.0
Patients with an event - no. (%)	9 (25%)	19 (54%)	27 (77%)	28 (85%)	28 (70%)
Most frequently reported events - no. of patients (%)[1]					
Abdominal pain upper	1 (3%)	2 (6%)	3 (9%)	1 (3%)	0
Arthralgia	0	1 (3%)	2 (6%)	6 (18%)	1 (3%)
Cough	0	1 (3%)	2 (6%)	3 (9%)	2 (5%)
Headache	1 (3%)	6 (17%)	1 (3%)	4 (12%)	3 (8%)
Nausea	0	1 (3%)	1 (3%)	2 (6%)	3 (8%)
Pharyngitis streptococcal	0	0	2 (6%)	2 (6%)	4 (10%)
Pyrexia	0	1 (3%)	5 (14%)	1 (3%)	1 (3%)
Rash	2 (6%)	1 (3%)	1 (3%)	3 (9%)	1 (3%)
Upper respiratory tract infection	0	1 (3%)	5 (14%)	9 (27%)	2 (5%)
Vomiting	1 (3%)	2 (6%)	1 (3%)	2 (6%)	4 (10%)
SERIOUS ADVERSE EVENTS					
No. of events	0	1	3	1	8
No. of events per patient-year	0.0	0.4	0.2	0.1	0.2
Patients with an event - no. (%)	0	1 (3%)	3 (9%)	1 (3%)	6 (15%)
All reported events - no. of patients (%)					
Gastroenteritis salmonella	0	0	0	0	1 (3%)
Histiocytosis haematophagic	0	0	0	0	1 (3%)
Juvenile arthritis	0	1 (3%)	0	1 (3%)	1 (3%)
Elevated liver function tests	0	0	1 (3%)	0	0
Mental status changes	0	0	0	0	1 (3%)
Pericarditis	0	0	0	0	1 (3%)
Pharyngitis streptococcal	0	0	0	0	1 (3%)
Pyrexia	0	0	1 (3%)	0	0
Varicella	0	0	1 (3%)	0	0
Viral upper respiratory tract infection	0	0	0	0	1 (3%)
INFECTIONS					
No. of events	2	2	25	29	37
No. of events per patient-year	0.7	0.8	1.9	2.7	1.0
Patients with an event - no. (%)	2 (6%)	2 (6%)	16 (46%)	20 (61%)	14 (35%)

[1] The most frequently reported events were defined as events that occurred in at least 10% of all patients during the entire study.

Conclusion: This is the first double-blind, randomized, placebo-controlled trial of rilonacept to demonstrate efficacy in sJIA. Rilonacept treatment was relatively safe. Significant elevations in aspartate aminotransferase levels were rare but occurred more often in subjects receiving rilonacept than in those on placebo.

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Clinical Variation In Children With Mutations In *MEFV*. Karyl S Barron[1], Amanda K. Ombrello[2], Ivona Aksentijevich[3], Anne Jones[3] and Daniel L. Kastner[3]. [1]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, [2]National Human Genome Research Institute, National Institute of Health, Bethesda, MD, [3]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD.

Background/Purpose: As a referral clinic for children with periodic fevers, we see a wide variety of clinical presentations. While genetic testing is usually helpful in determining clinical course and possible treatment options, we have seen a wide variation in clinical presentation in those patients found to have a genetic mutation in one of the genes linked to periodic fever syndromes. Familial Mediterranean fever (FMF) is usually regarded as an autosomal recessive inherited disorder due to mutations in the *MEFV* gene; however we have seen a number of symptomatic children who carry only one identifiable mutation in *MEFV*. In this study, we aim to characterize the clinical presentations of children with a variety of mutations in *MEFV*.

Methods: Patients were evaluated at the National Institutes of Health. Clinical and laboratory information were collected at each visit. Genetic testing for mutations in *MEFV* was performed by GeneDx. Genomic DNA was PCR-amplified for analysis of exons 2, 3, and 10 of the *MEFV* gene. Patients were evaluated for age at onset (months), duration of episode (days), frequency (weeks), and presence or absence of fever, abdominal pain, chest pain, rash, adenopathy, oral ulcers, or sore throat associated with flares. Patients were considered as meeting the criteria for PFAPA (Periodic Fever with Aphthous Ulcers, Pharyngitis, and Adenopathy) Syndrome if they had a history of periodic fever and 2 of the following: adenopathy, oral ulcers or sore throat.

Results: 82 children with mutations in *MEFV* were evaluated: 14 had 2 exon 10 mutations, 7 had 2 exon 10 mutations + E148Q, 18 had a single exon 10 mutation, 7 had a single exon 10 mutation + E148Q, 12 had a single E148Q mutation, 9 had a single K695R mutation, and 15 had P369S/R408Q ± E148Q.

We found no significant difference in any of the factors when children with one exon 10 mutation were compared with children with two exon 10 mutations. Children heterozygous for only E148Q were similar to those with a single exon 10 mutation with the exception that a higher percentage of E148Q heterozygotes met criteria for PFAPA (42% vs. 6%, P=.015). Similarly, children heterozygous for K695R had a significantly longer duration of episode (4 days vs. 2.6, P=.01) and higher frequency of adenopathy (89% vs. 39%, P=.014), oral ulcers (67% vs. 17%, P=.009), sore throat (56% vs. 11%), and meeting criteria for PFAPA (78% vs. 6%, P<.009) when compared to children with one mutation in exon 10. Children with P369S/R408Q ± E148Q were similar to those heterozygous for an exon 10 mutation, with the exception of longer duration of episode (4 vs. 2.6 days, P=.027). While most children with one or two exon 10 mutations responded to therapy with colchicine, there was a trend for need for additional treatment options in patients with E148Q, K695R or P369S/R408Q heterozygosity.

Conclusion: A clinical presentation similar to that of PFAPA was more common in patients heterozygous for either E148Q or K695R mutations of *MEFV*. While this is not an unexpected finding in patients with E148Q, it is surprising that patients with mutations in amino acid 695 do not follow the pattern of severe disease seen historically in patients with mutations in amino acid 694.

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Chronic Atypical Neutrophilic Dermatosis With Lipodystrophy and Elevated Temperatures (CANDLE): Clinical Characterization and Initial Response To Janus Kinase Inhibition With Baricitinib. Gina A. Montealegre Sanchez[1], Adam L. Reinhardt[2], Paul Brogan[3], Yackov Berkun[4], Diane Brown[5], Peter Chira[6], Ling Gao[7], Dawn C. Chapelle[1], Nicole Plass[1], Hanna Kim[1], Michael Davis[1], Adriana Almeida de Jesus[1], Yin Liu[1], Yan Huang[1], Colleen Hadigan[8], Theo Heller[9], Zlotogorski Zlotogorski[10], John J. O'Shea[1], Chyi-chia Lee[11], Suvimol C. Hill[12], Kristina Rother[9], Massimo Gadina[1] and Raphaela T. Goldbach-Mansky[1]. [1]National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD, [2]Children's Hosp of Omaha/UNMC, Omaha, NE, [3]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy, [4]Hadassah Medical Center, Mount Scopus, Jerusalem, Israel, [5]Children's Hospital Los Angeles, Los Angeles, CA, [6]Indiana University School of Medicine, Riley Hospital for Children, Indianapolis, IN, [7]University of Arkansas for Medical Sciences, Little Rock, AR, [8]National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD, [9]National Institute of Diabetes and Digestive Kidney Diseases, NIH, Bethesda, MD, [10]Department of Dermatology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel., Jerusalem, Israel, [11]National Cancer Institute, National Institutes of Health, Bethesda, MD, [12]NIH Clinical Center, Bethesda, MD.

Background/Purpose: CANDLE, a novel autoinflammatory syndrome presents with attacks of fever, annular cutaneous plaques, persistent periorbital edema, arthritis, lymphopenia and lipodystrophy since early childhood. CANDLE is caused by mutations in *PSMB8* and other proteasome associated genes. Elevated serum IP-10 (CXCL10) levels and gene expression studies show a prominent "interferon (INF) signature", and successful *in vitro* blocking studies with small molecules that inhibit Janus kinases (JAKs)

signaling, raised the questions whether IFN could be a therapeutic target in CANDLE.

Objectives: The primary objective of this compassionate use study is to determine whether the treatment with the JAK1 and JAK2 inhibitor (baricitinib/Eli Lilly) allows a reduction in daily oral corticosteroid of at least 50%. The secondary objective is to determine whether treatment with baricitinib results in the reduction of the mean Autoinflammatory Diary Score (ADS) to below 0.5.

Methods: CANDLE patients with an ADS >0.5 who take at least 0.15mg/kg/day of oral prednisone are eligible. Paired t-test were used to compare baseline to last clinic visit data.

Results: We enrolled eight CANDLE patients, 62% males, 75% Caucasians, 37% Hispanics. Mean age at disease onset was 5 (SD±6) weeks. Most patients presented with annular lesions/periorbital erythema (88%), fever (85%) and failure to thrive (38%). At enrollment all patients had characteristic areas of lipodystrophy and joint contractures, growth delay (87%), increased intra-abdominal fat deposition (83%), and dyslipidemia (75%). Seven patients presented with anemia at baseline, mean of 11.6 g/dL, often also associated with thrombocytopenia and/or lymphopenia (the latter only patients not homozygous for *PSMB8*). MRI-confirmed myositis was present in 75% of patients. Other findings include: presence of basal ganglia calcifications (71%), peripheral calcinosis (25%), conjunctivitis/episcleritis (50%), pancreatic abnormalities (25%) and epididymitis (25%).

All patients were followed for at least 2 weeks (mean 8 months). The mean dose of baricitinib is 5 mg/day (SD±3), The mean daily autoinflammatory diary score at baseline of 1.33 dropped to 0.25 at the time of their last visit ($p<0.05$). The mean total prednisone dose of 17 mg/day (SD±7) dropped by 58% to 7 mg/day (SD±4) (~0.47 mg/kg/day), ($p<0.05$). Myositis improved in 4 out of the 5 patients and signs of bone marrow immunosuppression resolved in all patients, with improvement on Hgb, PLT and ALC counts. All other immunosuppressive medications were discontinued. Three SAEs were reported (rotavirus and CANDLE related severe neutropenia).

Conclusion: Preliminary data in eight patients with CANDLE treated with baricitinib are encouraging and suggest that targeting interferon signaling with a JAK1, JAK2 inhibitor may be a potential therapeutic regimen for CANDLE and possibly other IFN mediated autoinflammatory disorders but further data is needed.

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Canakinumab Treatment In Active Hyper-IgD With Periodic Fever Syndrome. Juan Ignacio Aróstegui[1], Inmaculada Calvo[2], Jordi Anton[3], Angel Robles[4], Jordi Yagüe[1], Ruth Viana[5], Lillian Tseng[6] and Ken Abrams[6]. [1]Hospital Clinic Barcelona, Barcelona, Spain, [2]Hospital La Fe, Valencia, Spain, [3]Hospital Sant Joan de Deu, Barcelona, Spain, [4]Hospital La Paz, Madrid, Spain, [5]Novartis Farmacéutica, S.A., Barcelona, Spain, [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ.

Background/Purpose: Hyper-IgD with periodic fever syndrome (HIDS) is a recessively inherited autoinflammatory disease due to biallelic *MVK* mutations. It is characterized by 4–6 days-long acute inflammatory episodes, which typically start during infancy and recur every 4–6 weeks. Previous studies suggested IL-1 blockade as a potential therapy. However, little information is available about the efficacy and safety of the fully human anti-IL-1b monoclonal antibody canakinumab (CAN) in active HIDS.

Methods: The present study is a multicenter, open-label, and single treatment arm study with a 6-month treatment period (TP) with CAN and a max. 6-month follow-up period (FP). Inclusion criteria were age ≥2 yr. old, biallelic *MVK* mutations, and active disease defined by ≥3 acute flares in the 6-month historical period (HP, period in which patients did not receive drugs other than symptomatic treatment with NSAIDs and/or steroids) and C-reactive protein (CRP)>10 mg/L. The CAN dose in the TP was 4 mg/kg (max. 300mg) Q6-wks, with a dose up-titration to 6mg/kg (max. 450mg) if a flare occurred during the first 6-weeks. The primary objective was to assess the efficacy of CAN to reduce the flare rate during the TP compared with the HP. Secondary objectives included evaluation of changes in key disease features, disease control during TP, time to flare after the last CAN dose and safety.

Results: Nine patients (6 F, 3 M) from 3 centers were included. Median age was 17.3 yr (5–29 yr) and median disease duration since diagnosis was 4.1 yr (1–25 yr). The median of number of flares/patient with CAN reduced from 5 (3–12) during HP to 0 (0–2). During FP 7/9 patients flared, with a median of 110 days (62–196 days) after the last CAN dose. At baseline, physicians rated 6 and 3 patients as having no or poor disease control, respectively. At day 4 of TP, all patients were rated as having good/excellent disease control. At baseline, 8/9 patients had moderate/severe fever, 8/9 had mild/moderate lymphadenopathy, 5/9 had mild/moderate abdominal pain and 4/9 had mild/moderate apthous ulcers. From day 4 of TP onwards, no patient referred fever or abdominal pain, and only one patient had mild to moderate lymphadenopathy and apthous ulcers. At baseline, the median plasma levels of CRP and serum amyloid A (SAA) were elevated (CRP: 117.7 mg/L and SAA: 688.5 mg/L; normal values ≤10 mg/L in both cases). At day 15 of TP both plasma levels normalized (CRP: 0.8 mg/L; SAA: 2.6 mg/L) and were maintained. At least one adverse event (AE) was detected in 8 patients, most of them being of mild (76%) or moderate (18%) severity. Respiratory tract infections were the most common AE detected. Two patients reported a serious AE, one patient with an acute inflammatory flare leading to hospitalization, and another one had a gastrointestinal bleed and peritonitis separately (this patient was on peritoneal dialysis from amyloidosis induced by renal failure). No AEs led to CAN discontinuation.

Conclusion: CAN in active HIDS markedly reduced the rate of acute flares, and a sustained good/excellent disease control was observed. Most AEs registered were mild/moderate and all of them were manageable. Further studies are needed to better define CAN treatment in active HIDS.

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1784

Effectiveness Of First Line Use Of Recombinant IL-1RA Treatment In Steroid naïve Systemic Juvenile Idiopathic Arthritis: Results Of a Prospective Cohort Study. S.J. Vastert[1], Wilco de Jager[1], Bo Jan Noordman[1], Dirk Holzinger[2], Wietse Kuis[1], Berent J. Prakken[1] and Nico M. Wulffraat[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]University Muenster, Muenster, Germany.

Background/Purpose: To perform a prospective cohort study with recombinant IL-1RA (Anakinra, rIL-1RA) as first-line therapy in newly onset sJIA.

Methods: Patients fulfilled the ILAR criteria for sJIA. RIL-1RA (2 mg/kg) was started as first-line therapy and patients were monitored clinically and immunologically. The protocol contained a stop strategy when in remission at 3 months.

Results: We included 20 consecutive newly onset sJIA patients and started rIL1-RA as first line treatment (in steroid naive patients). Mean follow-up was 32 months (range 12–54). After 3 months, 85% of patients showed ACRPed90 responses and 75% (15/20) were in remission on rIL-1RA alone. After 1 year, 85% of patients (17/20) displayed ACRPed90 responses / clinically inactive disease. 65% of patients (13/20) achieved this on rIL-1RA alone. However, 7/20 patients (35%) required therapy besides rIL1-RA because of persistent disease activity. Following our stop strategy, 11/15 (73%) patients with clinically inactive disease at 3 months, could stop rIL-1RA within the first year.

After two years, (n=14), 86% (12/14) of patients showed ACRPed90 responses / disease remission, either on (n=4) or off (n=8) medication. After three years (n=11), 91% of patients (10/11) showed ACRPed90 responses / disease remission, either on (n=2) or off (=8) medication.

Conclusion: This is the first prospective study describing rIL-1RA as first-line therapy in sJIA. We observed excellent clinical responses in nearly all patients within three months. The majority of responding patients could stop rIL-1RA within 1 year with preserved remission during follow-up. Approximately one-third of patients needed concomitant therapy to maintain clinical response. IL-18 and S100A proteins seem candidate biomarkers for guiding tapering.

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1785

Structural Determinants Of Low Vertebral Strength In Pediatric Systemic Lupus Erythematosus. Jon M. Burnham[1], Babette S. Zemel[1], David C. Lee[2], Tony M. Keaveny[3] and Mary Beth Leonard[1]. [1]The Children's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, [2]O.N. Diagnostics, LLC, Berkeley, CA, [3]University of California, Berkeley, CA and O.N. Diagnostics, LLC, Berkeley, CA.

Background/Purpose: Children with systemic lupus erythematosus (SLE) are at high risk for bone fragility. Studies in pediatric SLE using two-dimensional lumbar spine (LS) dual X-ray absorptiometry (DXA) demonstrate deficits in areal bone mineral density (aBMD). However, the bone structural abnormalities that lead to vertebral compression fractures are unknown. Vertebral volumetric density (vBMD), structure, and compression strength can be estimated using finite element analysis (FEA) of three-dimensional spine quantitative computed tomography (QCT) scans. We performed a cross-sectional study using QCT FEA to assess: 1) LS strength deficits in pediatric SLE and 2) structural determinants of deficits, including vertebral geometry and cortical and trabecular density.

Methods: Participants with SLE were 5–21 years of age and had SLE for at least 1 month. Controls were matched by sex, race (black vs non-black), and Tanner stage. QCT scans of the second lumbar vertebra (L2) were acquired on a Siemens Sensation 64 scanner. FEA strength and density parameters were calculated using VirtuOst 1.2 (ON Diagnostics, Berkeley, CA). DXA scans of L1–4 were obtained using a Hologic QDR 4500A bone densitometer (Apex Software v3.3). Height, body mass index (BMI), fat mass index (FMI), lean mass index (LMI) and LS aBMD Z-scores were generated using reference data from our institution. Multivariable linear regression was used to identify covariates independently associated with L2 strength.

Results: Participants with SLE (n=23, 91% female, 48% black) had a mean age of 14.1 years and significantly lower height Z-scores (−0.05 vs 0.76, p=0.02) and LMI Z-scores (−0.78 vs 0.07, p=0.006). BMI- and FMI Z-scores did not differ between SLE and controls. The median disease duration was 2.1 years (range: 0.3 to 5.8). In SLE, prednisone was prescribed in 74% (median 7.5 mg/day, range: 0–20), hydroxychloroquine in 91%, and immunosuppressants in 74%. LS aBMD Z-scores were lower in SLE (−0.89 vs 0.72, p<0.001). In controls, L2 strength was greater at higher Tanner stages (p≤0.001), adjusting for age and race (both p>0.5). The L2 strength distribution according to SLE and Tanner stage is shown (Figure). In SLE, L2 strength was 21% lower (6844 vs 8688 Newtons (N), p=0.006). The trabecular compartment strength was 26% lower (3659 vs 4913 N, p=0.003), while the cortical compartment strength was 16% lower (3186 vs 3777 N, p=0.04). Further, the inner trabecular vBMD was 18% lower (156 vs 191 mg/cm^3, p<0.001), and the cortical vBMD was 9% lower (293 vs 322 mg/cm^3, p=0.03). The strength attributable to differences in geometry alone was similar to controls (2643 vs 2840 N, p=0.18).

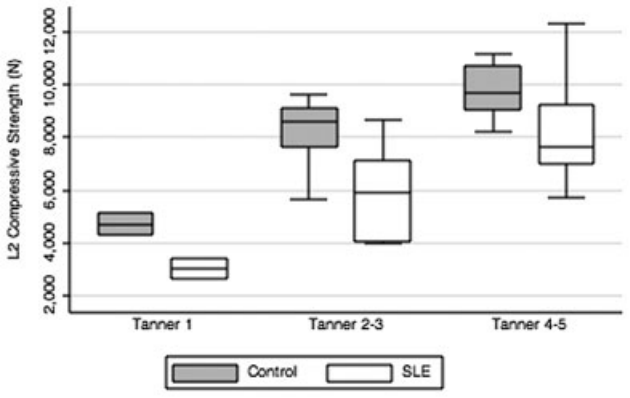

Figure. L2 strength according to Tanner stage.

Conclusion: In the first pediatric study to use vertebral FEA, we found substantial L2 vertebral strength deficits in pediatric SLE. These deficits were not driven by differences in geometry but by the lower cortical and primarily, trabecular bone density.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects III: Predictors of Disease Course in Rheumatoid Arthritis
Monday, October 28, 2013, 4:30 PM–6:00 PM

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91% Of Early RA Patients Are Positive For Serum 14–3–3η Or Its Auto-Antibodies. Walter P. Maksymowych[1], Dirkjan van Schaardenburg[2], Désirée van der Heijde[3], Robert Landewé[4], Gilles Boire[5], Maarten Boers[6], Vivian P. Bykerk[7], Edward C. Keystone[8], Katherine A. Siminovitch[9], Mairead Murphy[10] and Anthony Marotta[10]. [1]University of Alberta, Edmonton, AB, [2]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Academic Medical Center, Amsterdam, Netherlands, [5]Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, [6]VU University Medical Center, Amsterdam, Netherlands, [7]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, [8]Mount Sinai Hospital, University of Toronto, Toronto, ON, [9]Mount Sinai Hospital, Toronto, ON, [10]Augurex Life Sciences Corp, North Vancouver, BC.

Background/Purpose: Current serological markers such as RF and ACPA are useful for early diagnosis and perhaps for screening people at risk, but there remains a high unmet need for biomarkers that are present in the earliest stages of RA. The 14–3–3η serum protein is an early complementary marker to RF/ACPA and generates a specific anti-14–3–3η auto-antibody response to the native protein, that can also be measured for diagnosis. This study documents the expression of 14–3–3η auto-antibodies, their diagnostic utility and their complementarity to the 14–3–3η protein in early RA diagnosis.

Methods: 14–3–3η auto-antibody levels were measured on the Meso-Scale-Discovery electro-chemiluminescent platform in 873 patients; 254 with early RA, 324 with established RA and 295 controls. RA patients had a rheumatologist-confirmed diagnosis and early RA patients were DMARD-naïve. Controls included 10 each of psoriasis, ulcerative colitis, type 1 diabetes, and SLE, 9 with Crohn's; 5 each of Sjogren's, scleroderma, multiple sclerosis, gout and osteoporosis; 65 ankylosing spondylitis, 50 osteoarthritis and 106 healthy subjects. RA patient and control samples were provided by the co-authors, representing multiple international centers. Serum 14–3–3η protein levels were previously determined in these subjects with a positive diagnostic cut-off of > 0.19 ng/ml. Two-tailed t-tests and Mann-Whitney u-tests were used to compare differences in autoantibody levels between early RA, established RA and controls groups. Post-hoc ROC curves were generated and diagnostic utility was estimated by area under the curve (AUC) analysis.

Results: Median 14–3–3η auto-antibody levels were significantly higher in early RA subjects at 536 U/ml (154–3011) compared to established RA (223 U/ml, 64–2058), healthy (234 U/ml, 123–919), OA (258 U/ml, 125–1421) and all controls (264 U/ml, 96–1421), p values were < 0.0001 for early RA and each group. The ROC AUC for early RA versus healthy and all controls was 0.92 (95%CI 0.89 to 0.95; p <0.0001) and 0.85 (95%CI 0.82 to 0.89; p <0.0001), respectively. A best cut-off of 380 U/ml was determined based on the optimal specificity (93%) and sensitivity (77%) point on the ROC curve. The corresponding PPV and NPV were 0.97 and 0.63 and LR+ and LR- were 11.6 and 0.25. In early RA, 61% were positive for the 14–3–3η protein, 77% were positive for 14–3–3η auto-antibodies, 67% for RF and 67% for ACPA. 75% of the early RA patients were positive for either RF or ACPA and 81% for at least one of RF, ACPA or 14–3–3η. Especially notable, was that 91% of early RA patients were positive for either the 14–3–3η protein or its auto-antibodies, capturing 63% of RF/ACPA seronegative patients. A low Pearson correlation of r=−0.06 between the 14–3–3η protein and its auto-antibody titres in early RA further reinforces their high complementarity.

Conclusion: 14–3–3η biomarkers, alone and in combination with RF and ACPA identify a large proportion of Early RA patients, potentially allowing for earlier intervention and more favorable clinical outcomes.

Disclosure: W. P. Maksymowych, Augurex Life Sciences Corp, 9; **D. van Schaardenburg**, Augurex Life Sciences Corp, 2; **D. van der Heijde**, Augurex Life Sciences Corp, 5; **R. Landewé**, Augurex Life Scienes Corp, 5; **G. Boire**, Augurex Life Sciences Corp, 2; **M. Boers**, Augurex Life Sciences Corp, 5; **V. P. Bykerk**, Augurex Life Sciences Corp, 5; **E. C. Keystone**, Augurex Life Sciences Corp, 2; **K. A. Siminovitch**, Augurex Life Sciences Corp, 2; **M. Murphy**, Augurex Life Sciences Corp, 3; **A. Marotta**, Augurex Life Sciences Corp, 3.

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Does Age At Disease Onset Influence Disease Activity and Function In Rheumatoid Arthritis Patients? Results From The Ontario Best Practices Research Initiative (OBRI) Registry. Thanu Nadarajah[1], Binu Jacob[1], Pooneh Akhavan[2], Bindee Kuriya[3], Edward C. Keystone[3] and Claire Bombardier[1]. [1]University of Toronto, Toronto, ON, [2]Mount Sinai Hospital/ University of Toronto, Toronto, ON, [3]Mount Sinai Hospital, University of Toronto, Toronto, ON.

Background/Purpose: The population of elderly individuals with rheumatoid arthritis (RA) is increasing. The aim of this study was to assess whether age at disease onset affects disease activity and functional outcome in patients with RA. We hypothesized that patients with elderly-onset RA (EORA) would have more severe disease and higher disability compared to younger-onset RA (YORA) patients.

Methods: All patients enrolled in the Ontario Best Practices Research Initiative (OBRI), a clinical registry of early and established RA patients followed in routine care, were included in the study (N= 1981). Patients were categorized as EORA if their disease onset was ≥ 60 years of age (N=1516) and as YORA if disease onset occurred before 60 years (N=465). Outcomes assessed were disease activity (measured by Disease Activity Score 28 [DAS28]) and function (assessed by Health Assessment Questionnaire [HAQ]) at entry into the registry. Differences between two groups were compared using chi-square test and t-test. Separate linear regression models, adjusted for gender and disease duration were performed, with $p < 0.05$ considered statistically significant.

Results: The mean (SD) age of patients was 57.4 (12.9) years. The mean (SD) disease duration in the group was 8.5 (9.4) years. EORA patients were less likely to be rheumatoid factor and anti-citrullinated protein antibody positive ($p<0.05$). At entry into the registry, EORA patients were more likely to be on disease-modifying agents (79.4% vs. 66.1%, $p<0.001$) and steroids (27.4% vs. 22.9%, $p=0.05$), and less likely to be taking biologic therapy (12.1% vs. 25.7%, $p<0.001$) compared to YORA patients. Mean DAS28 scores were significantly higher among EORA patients compared to those with YORA (4.6 vs. 4.3, $p=0.002$). In a stratified analysis, this association was seen for those with early disease (< 2 years) but not for longer disease duration (Table 1). There was a non-significant trend towards higher HAQ scores among EORA patients compared to YORA patients. In a regression analysis with disease duration as a continuous variable, there was a significant association between EORA and higher disease activity and greater disability ($p<0.05$).

Table 1. Mean DAS28 and HAQ scores at entry into OBRI, stratified by age at disease onset and disease duration

	Mean DAS28 score			Mean HAQ score		
Disease Duration	Age at disease onset <60 years	Age at disease onset ≥ 60 years	P value (adjusted for disease duration)	Age at disease onset <60 years	Age at disease onset ≥ 60 years	P value (adjusted for disease duration)
< 2 years	4.47	4.92	0.001	1.07	1.18	0.098
2 – 5 years	4.18	4.25	0.65	1.14	1.12	0.743
>5 years	4.35	4.35	0.99	1.23	1.41	0.054

Conclusion: Research in the area of EORA has produced mixed results in terms of disease activity and functional disability. Our study demonstrates that older age at disease onset is associated with greater disease activity and functional disability at entry into OBRI. Disease duration appears to influence these outcomes. Further study is required to evaluate which components of the DAS28 may differ among EORA vs. YORA and what drives these potential differences. Furthermore, evaluating the role of factors including comorbidities is necessary to understand the reasons for higher disease activity and poor functional outcome among patients with EORA.

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The Multi-Biomarker Disease Activity Test (Vectra® DA) Estimates Risk Of Radiographic Progression For Patients With Rheumatoid Arthritis From The Leiden Early Arthritis Clinic. Wanying Li[1], DJ Haney[1], Guy Cavet[1], Thomas W. Huizinga[2], Eric H. Sasso[1] and A. H. M. van der Helm-van Mil[2]. [1]Crescendo Bioscience Inc., South San Francisco, CA, [2]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: The multi-biomarker disease activity (MBDA) blood test assesses disease activity in patients with rheumatoid arthritis (RA) using a validated algorithm to provide a score of 1 to 100. The Leiden Early Arthritis Clinic (EAC) has enrolled a population-based cohort of subjects within 2 years of RA diagnosis for long-term care. In a prior study of Leiden EAC patients receiving non-biologic-DMARDs (median RA duration 4.6 yrs.), the MBDA score was significantly better than DAS28-CRP for predicting radiographic progression. We now provide in-depth analyses of the relationship between MBDA score and radiographic progression, and the ability of MBDA score to add value to other measures for predicting radiographic progression.

Methods: This retrospective study evaluated 271 clinic visits by 163 RA patients (1987 ACR criteria) of the Leiden EAC. Clinical and blood test data were obtained at each visit, with radiographs taken then and 1 year later. At first visit, patients were receiving only DMARDs and <5% received an anti-TNF subsequently. MBDA biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL-40, leptin, resistin, SAA, CRP) were measured for each visit. Radiographic progression was assessed as change in Sharp van der Heijde score (DSHS) over one year. The association between MBDA score and radiographic progression was assessed by AUROC, by logistic quantile regression curves, and by relative risk (RR) vs. MBDA ≤25 for DSHS > 0, 3 or 5 units/yr. Frequency of DSHS >3 across MBDA categories (low: ≤29; moderate 30–44; high: >44) was assessed within categories of DAS28-CRP, CRP (≤1,1–3 and >3 mg/dL) or serologic status (sero+: RF+ and/or CCP+; sero-neg: both negative), with p-values adjusted for multiple testing.

Results: Characteristics of the 271 patient visits included median age 55 yrs., 67% female, 66%/69% RF+/anti-CCP+, median SHS 25, median MBDA score 41. The 75th and 90th quantile regression lines indicating risk of progression increased non-linearly with increasing MBDA score (AUROC = 0.72/0.77 for DSHS >3 or >5, $p < 0.001$). The increase was most prominent between groups with MBDA scores of 40–44 and 45–49. Risk increased within the high MBDA category (RR (95% CI) = 7.2 (2.4–22.6)/18.1 (6.5–29.1) for DSHS >3 or >5 for MBDA ≥60). Within categories of DAS28-CRP or CRP, and for sero-neg and sero+ patients, the low/high MBDA score subgroups had significantly lower/higher rates of progression, respectively.

Frequency of Radiographic Progression (ΔSHS >3) by Category of MBDA Score and DAS28-CRP, CRP, or Serologic Status

		MBDA Score			
	N	Low (≤29)	Moderate (>29–≤44)	High (>44)	P-value
DAS28-CRP					
Low (≤2.7)	113	8% of 37	22% of 51	44% of 25	0.008
Moderate (>2.7–≤4.1)	95	15% of 13	19% of 36	30% of 46	0.454
High (>4.1)	63	0% of 6	6% of 18	56% of 39	<0.001
CRP mg/dL					
Low (≤1)	158	9% of 53	21% of 85	50% of 20	0.003
Moderate (1–3)	80	0% of 3	5% of 20	37% of 57	0.013
High (>3)	33	NP	NP	48% of 33	NA
Serologic Status					
Positive	200	11% of 38	24% of 72	46% of 90	<0.001
Negative	70	6% of 18	3% of 32	30% of 20	0.016

NP, no patients in that category; NA, not applicable

Conclusion: In DMARD-treated patients with established RA, radiographic progression increased non-linearly with increasing MBDA score. High MBDA score was associated with increased progression even when DAS28-CRP or CRP were low, and regardless of serologic status. Low MBDA score was associated with infrequent progression. Thus, the MBDA score may help identify patients at risk for rapid radiographic progression and may add useful information to other assessments.

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1789

In Early Rheumatoid Arthritis, The 12 Individual Biomarkers That Comprise The Multiple Biomarker Disease Activity Score Relate Differentially To Clinical Response and Radiographic Progression: Results From a Randomized Trial. Karen Hambardzumyan[1], Saedis Saevarsdottir[1], Rebecca Bolce[2], Kristina Forslind[3], Sofia Ernestam[4], Ingemar F. Petersson[5], Pierre Geborek[5], David Chernoff[2], Douglas J. Haney[2], Eric H. Sasso[2] and Ronald F van Vollenhoven[1]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Crescendo Bioscience Inc., South San Francisco, CA, [3]Section of Rheumatology, Department of Medicine, Helsingborg General Hospital, Helsingborg, Sweden, [4]Karolinska University Hospital, Huddinge, Sweden, [5]Lund University, Lund, Sweden.

Background/Purpose: In early rheumatoid arthritis (eRA), clinical and radiographic predictors would be very useful for optimizing available therapies. Individual biomarkers and their combinations, such as the multibiomarker disease activity (MBDA, Vectra DA) test, can be considered for these purposes. In the SWEFOT study, patients with eRA (symptom duration < 1 year) were started on methotrexate (MTX); at 3 months, responders (DAS28 < 3.2) continued MTX monotherapy and were followed in regular care, whereas non-responders were randomized into triple DMARD therapy or the addition of infliximab group.

The objective of this study was to assess the 12 individual biomarkers that comprise the MBDA score at baseline (BL) as predictors of clinical response at 3 months and radiographic progression at 1 year in eRA.

Methods: Analyses were performed for patients from the SWEFOT trial who had BL and 3-month data of DAS28 (based on ESR), the MBDA score (which has been validated to assess disease activity in RA patients) and the 12 individual biomarkers at BL; and for a subset of patients who also had radiographs at BL and 1 year (assessed using the Van der Heijde modified Sharp score [SHS]). Patients with DAS28 > 3.2 at 3 months were considered clinical non-responders, and patients with a change in SHS > 0 as radiographic progressors ("radiological non-responders"). Group comparisons of biomarkers were performed by Mann-Whitney U test.

Results: The results are summarized in the table below. Clinical non-responders had significantly higher BL values for CRP and IL-6 compared to responders. TNF-R1 and VCAM-1 were significantly lower for non-responders, while other biomarkers and the MBDA did not differ. The patients who progressed radiographically had, at BL, significantly higher MBDA scores, inflammatory biomarkers (CRP, SSA and IL-6), MMP-1, MMP-3 and TNF-R1, as well as a trend towards higher VEGF.

Biomarkers at BL (mean±SEM)	clinical responders (n=112)	clinical non-responders (n=190)	P value	Radiographic non-progressors (n=116)	Radiographic progressors (n=120)	P value
CRP	45.8±6.22	65.5±5.42	0.048	48.2±6.39	73.35±6.84	<0.001
SAA	38.3±5.04	41.9±3.49	N.S.	33.9±4.31	48.6±4.73	0.004
IL-6	82.7±9.01	114.2±10.36	0.051	89.83±11.68	121.7±13.33	0.002
TNF-R1	2.05±0.06	1.8±0.04	0.002	1.85±0.05	2.01±0.06	0.047
MMP-1	12.1±0.94	13.9±0.71	N.S.	12.4±0.87	14.4±0.86	0.038
MMP-3	76.9±8.55	90.21±6.5	N.S.	73.4±8.26	97.64±8.21	0.010
YKL-40	103.5±9.93	106.9±6.44	N.S.	115.4±11.3	107.9±7.35	N.S.
Leptin	12.8±1.17	15.1±1.09	N.S.	16.3±1.81	13.32±1.13	N.S.
Resistin	7.23±0.26	7.31±0.21	N.S.	7.23±0.28	7.3±0.21	N.S.
EGF	196.05±12.1	187.9±8.29	N.S.	195.2±9.7	182.6±11.65	N.S.
VEGF	474±27.99	469.34±22.7	N.S.	437.4±27.24	511.2±29.12	0.069
VCAM-1	0.74±0.019	0.66±0.012	<0.001	0.67±0.016	0.72±0.018	N.S.
MBDA	57±1.3	59.6±1.14	N.S.	55.7±1.4	63.3±1.19	<0.001

Conclusion: In eRA patients treated initially with MTX, some individual biomarkers at BL may help identify those patients who are less likely to achieve DAS28 < 3.2 after 3 months of MTX therapy. Other biomarkers, as well as the MBDA score, may identify patients at higher risk for radiographic progression during the first year of therapy. These results suggest that biomarkers can differentially predict aspects of disease course in eRA.

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Serum Amyloid A Levels Model Rheumatoid Arthritis Disease Activity Better Than C-Reactive Protein Levels Especially During Treatment With Anti-Tumor Necrosis Factor α Therapy (Etanercept). Ilinca D. Metes[1], Douglas W. Chew[1], Aarat M. Patel[1], G.K. Balasubramani[2], Jeffrey R. Curtis[3], S. Louis Bridges Jr.[3], Stephen R. Wisniewski[2], Larry W. Moreland[1] and Marc C. Levesque[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, [3]University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: C reactive protein (CRP) levels have been used extensively to model disease activity in rheumatoid arthritis (RA). However, TNF antagonist therapy (and likely therapy with other biologics) reduce CRP levels, even without associated reductions in RA disease activity. Serum amyloid A (SAA) also models RA disease activity and has been suggested as a better biomarker for RA disease activity. We previously showed that TNF antagonist therapy lowered both SAA and CRP levels to a greater extent than oral disease modifying anti-rheumatic drugs (DMARDs) after adjusting for disease activity. However, TNF antagonists, compared to oral DMARDs, decreased CRP levels more than SAA levels. Our aim was to compare the effect of etanercept (ETN) and/or oral DMARD therapy on serum SAA versus CRP levels, and to determine whether SAA levels model RA disease activity better than CRP levels, especially during treatment with a TNF antagonist.

Methods: Samples were analyzed from RA subjects (n = 755) in the Treatment of Early RA (TEAR) study, a randomized, double-blind, comparative effectiveness trial. In the TEAR trial, early RA subjects with less than 2 years of disease duration were randomized to receive either combination ETN/methotrexate (MTX) therapy (n = 244), MTX/hydrochloroquine/sulfasalazine (triple oral) therapy (n = 132) or MTX monotherapy (n = 379). MTX monotherapy subjects with a DAS28-ESR > 3.2 after 6 months were stepped up to either ETN/MTX (n = 205) or triple oral therapy (n = 93). Serum samples and clinical data were collected when treatment was initiated and at 24, 48 and 102 week follow up visits. We used Spearman correlation coefficients (rho) to determine the overall relationship between SAA and CRP levels, and mixed effects models to determine the fit between 1) SAA levels and DAS28-ESR and 2) CRP levels and DAS28-ESR, for subjects treated with ETN/MTX and subjects treated with oral DMARDs, while correcting for baseline SAA and CRP levels, respectively. Akaike information criterion (AIC) and parameter estimates were used to determine model fit, with ΔAIC > 10 used as strong evidence for one model fitting better than another.

Results: At the baseline visit, SAA levels were only moderately correlated with CRP levels (rho = 0.42), and the SAA and CRP correlation was similar regardless of treatment or study visit (rho range 0.35 to 0.62). Across all subjects and time points, models of the DAS28-ESR using SAA levels were better than models using CRP; the ΔAIC between the models was 305. The model of DAS28-ESR using SAA was associated with a ~6 fold better fit vs. the CRP model for subjects treated with ETN/MTX, and a ~5 fold better fit vs. the CRP model for subjects treated with oral DMARDs (ΔAIC = 159 vs. ΔAIC = 137, respectively).

Conclusion: The lack of a strong correlation between SAA and CRP levels coupled with their different modeling of RA disease activity suggests that SAA levels may be a better biomarker for RA disease activity than CRP, especially during treatment with TNF antagonists.

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Reaching The Target Of Low Disease Activity At 6 Months Predicts Better Long-Term Functional Outcome In Patients With Early Rheumatoid Arthritis. Pooneh Akhavan[1], Bindee Kuriya[2], Edward C. Keystone[2], Juan Xiong[3], Janet E. Pope[4], Gilles Boire[5], Diane Tin[6], Boulos Haraoui[7], Carol A. Hitchon[8] and Vivian P. Bykerk[9]. [1]Early Rheumatoid Arthritis Program, Mount Sinai Hospital and University of Toronto, Toronto, ON, [2]Mount Sinai Hospital, University of Toronto, Toronto, ON, [3]Mount Sinai Hospital, Toronto, ON, [4]St Joseph Health Care, London, ON, [5]Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, [6]Southlake Regional Health Centre, Newmarket, ON, [7]Centre Hospitalier de l'Université de Montréal, Montreal, QC, [8]University of Manitoba, Winnipeg, MB, [9]Mount Sinai Hospital/University of Toronto, Toronto, ON.

Background/Purpose: Current clinical practice guidelines recommend remission, and if not possible, low disease activity (LDA) as the treatment target in

rheumatoid arthritis (RA). Patients should also be assessed frequently to facilitate achieving this target as early as possible. It has been previously shown that reaching LDA at 1 year is associated with better long-term functional and radiographic outcomes in an early RA cohort that enrolled patients prior to the introduction of T2Tconcept and the widespread use of biologics[1]. Our objective was to assess the predictive validity of reaching LDA at an earlier time point (6 mo), the desired goal in current guidelines, on future disability.

Methods: Data from Canadian early ArThritis Cohort (CATCH) including patients with early RA (symptom duration ≤ 12 mo) were used. Patients with at least two years of follow-up were included. The outcome was HAQ-DI at 2 years and the main predictor was LDA at 6 mo, measured by Clinical Disease Activity Index. Linear regression analysis was used for assessment of the impact of LDA (y/n) on HAQ at 2 years adjusting for potential confounders including baseline LDA, HAQ, age, sex, ESR, RF, use of DMARDs, steroids and biologics. We included baseline and 6-mo LDA interaction in the model and as it was not significant, removed it. As an exploratory analysis, we added the socioeconomic status (SES), pain and fibromyalgia to the model.

Results: A total of 833 patients were analyzed. Baseline characteristics included: female (75%), mean+sd age 53.3+14.2 years, symptom duration 5.9(2.9) months, HAQ 1.1(0.7), swollen joint count 8.1(6.2), tender joint count 8.7(6.7), ESR 27.9 (23.0), CDAI 27.5(14.8). More than 90% received DMARDs. Methotrexate was used in 74%, steroids in 52% and biologics in only 3% at baseline. CDAI improved to 12.0(6.2) at 6 mo and HAQ to 0.52(0.6) at 2 yrs. 389 patients (56%) were in LDA at 6 months.

In the multivariate analysis, LDA at 6 mo was a significant predictor of lower HAQ at 2 yrs ($p<.0001$) (Table). Among additional covariates added in the exploratory analysis, only the presence of fibromyalgia at baseline was associated with higher HAQ at follow-up.

Table. Multivariate analysis result. Outcome HAQ at 2 years

Predictor	Estimate	p-value
LDA at 6 mo	−0.27	<.0001
LDA at baseline	0.016	0.83
Age (year)	0.005	0.004
Sex	0.253	<.0001
Symptom duration	0.012	0.12
HAQ*	0.332	<.0001
Rheumatoid Factor	0.078	0.12
DMARD use*	0.017	0.83
Corticosteroid use*	0.071	0.13
Biologics use*	−0.001	0.99

*at BSL

Conclusion: LDA as early as 6 mo predicts less future disability. This provides further evidence to support current guidelines recommending early LDA as a desired treatment goal where remission is not possible. Considering that remission is only achieved in a minority of early RA patients, LDA appears to be a more feasible target.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Safety and Efficacy of Small Molecule Agents
Monday, October 28, 2013, 4:30 PM–6:00 PM

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Inhibition Of Chemokine Receptors CCR1 and CCR6 As Promising Therapies For Autoimmune Diseases Such As Rheumatoid Arthritis and Psoriasis. Daniel Dairaghi[1], Penglie Zhang[2], Manmohan Leleti[2], Robert Berahovich[2], Karen Ebsworth[2], Linda Ertl[2], Shichang Miao[1], Zhenhua Miao[2], Lisa Seitz[2], Joanne Tan[2], Matthew Walters[2], Yu Wang[2], Jay Powers[2], Thomas J. Schall[1] and Juan C. Jaen[1]. [1]ChemoCentryx, Inc., Mountain View, CA, [2]ChemoCentryx, Mountain View, CA.

Background/Purpose: Chemokines are key regulators of leukocyte activation and recruitment to sites of inflammation. Of particular relevance in rheumatoid arthritis (RA), the chemokine receptors CCR1 and CCR6 are thought to drive monocyte/macrophage and Th17 cell recruitment, respectively, into RA joints. We recently demonstrated the clinical benefit of our first-generation CCR1 antagonist (CCX354) in a Phase 2 trial in RA patients (Tak (2012)). Meanwhile, CCR6 is thought to be a key factor for Th17 cell activity in RA and psoriasis. To date, no therapeutic agents targeting CCR6 have progressed into clinical evaluation. Our objective is to identify orally active small molecules that selectively target either CCR1 or CCR6 and possess overall profiles suitable for clinical development.

Methods: The *in vitro* potency of CCX9588 (CCR1 antagonist) was assessed by inhibition of CCL15-mediated chemotaxis of THP-1 cells and human blood monocytes. The *in vitro*potency of CCX9664 (CCR6 antagonist) was assessed by inhibition of CCL20-mediated chemotaxis and binding using CCR6-expressing cell lines and CD4-positive human PBMC. CCX9588 and CCX9664 were assessed for their ability to block CCR1 or CCR6-mediated chemotaxis towards RA synovial fluids. The ability of a CCR6 antagonist to inhibit dermal inflammation in preclinical models of psoriasis-like disease was assessed in mice with the imiquimod and IL-23 models.

Results: CCX9588 potently blocks CCR1-mediated chemotaxis with an IC_{50} of 0.1 nM (THP-1 cells). In 100% human serum, CCX9588 blocks CCR1-mediated chemotaxis with an IC_{50} of 0.7 nM (THP-1 cells) and 0.2 nM (human monocytes). CCX9588 also completely blocks the monocyte-chemotactic activity displayed by human RA synovial fluid samples. CCX9664 potently blocks CCR6-mediated chemotaxis of CD4-positive human PBMC (IC_{50}: 24 nM). CCR6-mediated chemotactic activity of RA synovial samples was completely inhibited by CCR6 antagonists. CCX9664 significantly reduced dermal manifestations of disease in two preclinical psoriasis-like models, one induced by topical application of imiquimod and the other by dermal injections of IL-23. Both CCX9588 and CCX9664 are highly selective for CCR1 and CCR6, respectively, when tested against a wide screen of chemokine and chemoattractant receptors.

Conclusion:

CCR1: The novel second-generation CCR1 antagonist CCX9588 is about 20 times more potent on human CCR1 than the structurally distinct first-generation molecule CCX354. This new CCR1 antagonist (CCX9588) remains equally selective for CCR1 and orally bioavailable in preclinical species (Dairaghi (2011)) and was shown to block CCR1-mediated chemotaxis of human blood monocytes towards RA synovial fluid samples.

CCR6: Several chemical lead series were identified using a proprietary high-throughput screening format. Optimization of one of these series resulted in advanced molecules such as CCX9664. This molecule is highly potent on human and mouse CCR6 and displays properties conducive to its use for the treatment of diseases such as RA and psoriasis.

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Disclosure: D. Dairaghi, Chemocentryx, 1, Chemocentryx, 3; **P. Zhang**, Chemocentryx, 1, Chemocentryx, 3; **M. Leleti**, Chemocentryx, 1, Chemocentryx, 3; **R. Berahovich**, Chemocentryx, 1, Chemocentryx, 3; **K. Ebsworth**, Chemocentryx, 1, Chemocentryx, 3; **L. Ertl**, Chemocentryx, 1, Chemocentryx, 3; **S. Miao**, Chemocentryx, 1, Chemocentryx, 3; **Z. Miao**, Chemocentryx, 1, Chemocentryx, 3; **L. Seitz**, Chemocentryx, 1, Chemocentryx, 3; **J. Tan**, Chemocentryx, 1, Chemocentryx, 3; **M. Walters**, Chemocentryx, 1, Chemocentryx, 3; **Y. Wang**, Chemocentryx, 1, Chemocentryx, 3; **J. Powers**, Chemocentryx, 1, Chemocentryx, 3; **T. J. Schall**, Chemocentryx, 1, Chemocentryx, 3; **J. C. Jaen**, Chemocentryx, 1, Chemocentryx, 3.

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Oskira-1: A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Parallel-Group Study Of 2 Dosing Regimens Of Fostamatinib In Rheumatoid Arthritis Patients With An Inadequate Response To Methotrexate. Michael Weinblatt[1], Mark C. Genovese[2], Meilien Ho[3], Sally Hollis[3], Krystyna Rosiak-Jedrychowicz[4], Arthur Kavanaugh[5], David Millson[3], Gustavo Leon[6], Millie Wang[3] and Désiréé van der Heijde[7]. [1]Division of Rheumatology, Brigham & Women's Hospital, Boston, MA, [2]Stanford University, Palo Alto, CA, [3]AstraZeneca R&D Alderley Park, Macclesfield, United Kingdom, [4]Przychodnia Neuromedyka, Zyrardów, Poland, [5]University of California, San Diego, La Jolla, CA, [6]Instituto de Ginecología y Reproducción-Cirugía Mínimamente Invasiva, Surco, Peru, [7]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Fostamatinib (Fosta) is an oral SYK inhibitor. This 52-wk study (NCT01197521) compared Fosta vs placebo (PBO) + methotrexate (MTX) in patients (pts) with active RA despite MTX.

Methods: Adult pts on MTX were randomized (1:1:1) to Fosta (100 mg bid for 52 wks [Group A, n = 310] or 100 mg bid for 4 wks then 150 mg qd [Group B, n = 304]) or to PBO for 24 wks then Fosta 100 mg bid (Group C, n = 304). Non-responders at Wk 12 could leave the study and enter an active extension study. Co-primary endpoints were the proportion of pts achieving ACR20 response at Wk 24 and the change from baseline to Wk 24 in modified total Sharp score (mTSS). Secondary endpoints evaluated efficacy, safety and tolerability up to 52 wks.

Results: Demographic and baseline characteristics were well balanced across groups. Fosta Groups A and B had significantly more pts achieving ACR20 at Wk 24 vs PBO (Table, $p < 0.001$; $p = 0.006$, respectively), with 18.2% of Fosta pts achieving ACR20 as early as Wk 1 (vs 4.9% PBO). Fosta Groups A and B did not show a significant difference in mTSS at Wk 24 ($p = 0.25$; $p = 0.17$, respectively [Table]) vs PBO. The percentages of pts who did not progress (mTSS change ≤ 0.5) in Groups A, B and C were 80.7%, 77.6% and 79.5%. Key secondary efficacy endpoints were consistently favorable for Fosta Groups A and B vs PBO (Table), with better results at the higher dose, but were not tested statistically due to failure of the mTSS co-primary endpoint.

In the 24-wk PBO-controlled period, the most frequently reported AEs in pts in Groups A, B and C were hypertension (15.9%, 15.1%, 3.9%), diarrhea (13.9%, 15.1%, 3.9%) and nausea (4.2%, 6.9%, 3.6%). Serious AEs occurred in 2.9%, 4.9% and 1.6% of pts. AEs leading to discontinuation occurred in 5.2%, 9.2% and 2.6% of pts, the most frequent being diarrhea, hepatic enzyme increase, hypertension and ALT increase. Elevated BP ($\geq$ 140/90 mmHg) was observed in 44.2%, 41.6% and 19.3% of pts at $\geq$ 1 visit.

Overall exposure up to 52 wks was 111 patient-years (PY) for PBO and 569 PY for Fosta. There were 9 adjudicated CV events: 2 on PBO, and 7 on Fosta (5 in Group B, 2 in Group C). One pt on PBO died (0.9/100 PY; pulmonary embolism) and 5 died while on Fosta (0.9/100 PY; 2 in Group B [sepsis/renal failure; gastroenteritis/hypovolemic shock/cardiorespiratory failure] and 3 in Group C [septic shock/interstitial lung disease; circulatory collapse; acute renal failure/cardiorespiratory arrest]). There were 5 malignancies, all on Fosta (0.9/100 PY; 2 × non-melanoma skin cancer; 1 × gastric, renal or thyroid cancer), over 52 wks.

Table. Patient discontinuations, primary and key secondary endpoints at or up to Wk 24*

Endpoint*	Group A Fosta 100 mg bid + MTX (n = 310)	Group B Fosta 100 mg bid + MTX for the first 4 wks then 150 mg qd + MTX (n = 304)	Group C PBO + MTX (n = 304)
Patients discontinuing treatment up to Wk 24	76 (24.4%)	81 (26.5%)	(116) 37.9%
Change from baseline in mTSS score at Wk 24	0.45 (N=285)	1.29 (N=277)	0.13 (N=278)
ACR20 at Wk 24	152 (49.0%)	135 (44.4%)	104 (34.2%)
ACR50 at Wk 24	81 (26.1%)	56 (18.4%)	30 (9.9%)
ACR70 at Wk 24	32 (10.3%)	17 (5.6%)	6 (2.0%)
ACR20 at Wk 1		112 (18.2%)	15 (4.9%)
DAS28-CRP < 2.6 at Wk 12	32 (10.3%)	24 (7.9%)	6 (2.0%)
DAS28-CRP < 2.6 at Wk 24	41 (13.2%)	26 (8.6%)	15 (4.9%)
HAQ-DI reduction ≥ 0.22 at Wk 24	170 (54.8%)	153 (50.3%)	107 (35.2%)

*Pts who withdrew for any reason, including non-response at Wk 12, or had an increased MTX dose, had any DMARD initiated or received parenteral steroids in the prior 8 wks were considered non-responders at Wk 24. Non-responders at Wk 12 could be transferred to an extension study to receive Fosta 100 mg bid, however, the treatment arm to which they were initially randomized remained blinded for the duration of the study.

Conclusion: In this phase III study both Fosta regimens achieved statistical improvements in ACR20 response rate at 24 wks vs PBO in pts treated with MTX but did not show a significant difference in mTSS. The overall level of response with Fosta was not as large as observed in the phase ll (TASKi) program. Safety and tolerability findings were consistent with the profile observed in earlier studies.

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The Jak Inihibitor Tofacitinib Suppresses Synovial Jak-Stat Signalling In Rheumatoid Arthritis. D. L Boyle[1], N. Wei[2], A. K. Singhal[3], D. R. Mandel[4], P Mease[5], A. Kavanaugh[1], R. Shurmur[6], J. Hodge[7], Z. Luo[8], S. Krishnaswami[8], D. Gruben[8], S. H. Zwillich[8], K. Soma[8], J. D. Bradley[8] and G. S. Firestein[1]. [1]UCSD School of Medicine, La Jolla, CA, [2]Arthritis Treatment Center, Frederick, MD, [3]Southwest Rheumatology Research LLC, Mesquite, TX, [4]Office of David R Mandel MD, Inc., Mayfield Village, OH, [5]Seattle Rheumatology Associates, Seattle, WA, [6]Associated Internal Medicine Specialists, Battle Creek, MI, [7]Pfizer Inc, Collegeville, PA, [8]Pfizer Inc, Groton, CT.

Background/Purpose: Tofacitinib is a novel oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). The specific JAK-STAT (signal transducer and activator of transcription) pathways affected by tofacitinib in different tissues and the downstream effects on gene expression in situ are unknown. Phase 3 studies ORAL Scan[1] (A3921044 NCT00847613) and ORALStart[2] (A3921069 NCT01039688) have shown that tofacitinib reduces the progression of joint destruction; however, the underlying mechanisms are unknown. The effects of tofacitinib on synovial histopathology, gene expression, and signaling were studied and correlated with clinical response. We also evaluated the relationship of synovial, blood and urine biomarkers with inflammation and structural damage.

Methods: A randomized, double-blind, Phase 2a clinical trial (A3921073; NCT00976599) of seropositive RA patients (pts) with inadequate response to methotrexate compared tofacitinib 10 mg twice daily for 28 days (15 pts) with placebo (PBO; 14 pts). Synovial biopsies were performed on Days −7 and 28. Biopsies were analyzed by immunohistochemistry (IHC), quantitative real-time polymerase chain reaction (qPCR), and synovial tissue extracts by enzyme-linked immunosorbent assay. Clinical response was determined by disease activity score (DAS)28–4 ESR and EULAR response criteria on Day 28 in study A3921073 and at 4 months in an open label long term extension study (A3921024; NCT00413699).

Results: Tofacitinib led to EULAR moderate to good responses (11/14 pts), while PBO was ineffective (1/14 pts) on Day 28. Tofacitinib significantly reduced synovial gene expression of the matrix metalloproteases MMP1 and MMP3 ($p<0.05$) and chemokines CCL2, CXCL10, and CXCL13 ($p<0.05$). Changes in synovial phosphorylation of STAT1 and STAT3 predicted 4-month clinical responses (correlations of 0.755 and 0.874, respectively), significantly ($p=0.0018$ and $p<0.0001$). Tofacitinib significantly decreased plasma IP-10 ($p<0.005$) which is a mediator of osteoclastogenesis[3]. Urine CTX-II, an indicator of MMP-mediated type II collagen turnover and cartilage damage[4], was reduced by tofacitinib (LS mean change −122.93) compared to PBO (LS mean change −6.2) ($p=0.08$). No changes were observed in synovial inflammation scores or immune cell lineages using IHC, e.g. CD20, CD3, CD68, or qPCR.

Conclusion: The data suggest that tofacitinib modulates synovial immune and inflammatory responses. Modulation of certain JAK STAT pathways correlates with clinical response, e.g. STAT1 and STAT3-dependent IL-6, and interferon signaling. Biomarkers including MMP-3[4], IP-10[3] and urinary CTX-II[4] which are associated with an increased risk of joint damage in RA are reduced by tofacitinib. This study provides insights into the mechanism of tofacitinib's clinical efficacy and preservation of cartilage and bone.

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An Active Metabolite Contributes To The Pharmacodynamics and Efficacy Of GLPG0634, a Selective JAK1 Inhibitor. Florence Namour. Galapagos SASU, Romainville, France.

Background/Purpose: GLPG0634 is an orally-available, selective inhibitor of Janus kinase 1 (JAK1). Through inhibition of signaling pathways for cytokines involved in rheumatoid arthritis (RA), non-selective JAK inhibitors have shown long-term efficacy in treating RA but also dose-limiting side effects. Selective inhibition of JAK1 may result in an acceptable safety profile while maintaining clinical efficacy. Based on GLPG0634's moderate pharmacokinetic (PK) half-life, both once-daily (QD) and twice-daily (BID) dosing regimens have been explored in humans. QD dosing of GLPG0634 in humans has shown highly encouraging pharmacodynamic (PD) properties and early efficacy in RA in two 4-week Phase 2a studies/ Evaluate the PK, PD and efficacy of GLPG0634 and its main metabolite in healthy volunteers and patients with active RA.

Methods: GLPG0634 was dosed in healthy volunteers (N=30) at doses of 50 and 100 mg BID and 200, 300 and 450 mg QD for 10 days. In Phase 2a studies, RA patients (n=98) received doses of 100 mg BID and from 30 to 300 mg QD for 28 days, added on to a background therapy of methotrexate. The PK of GLPG0634 and its active major metabolite was evaluated. The PD was evaluated in whole blood from healthy volunteers using *ex vivo* IL-6 induced phosphorylation of STAT1 (pSTAT1) in CD4+ cells for JAK1 activity and GM-CSF induced pSTAT5 in CD33+ cells for JAK2. JAK inhibition and selectivity of the metabolite were evaluated *in vitro*.

Results: The PK for GLPG0634 following BID and QD dosing showed dose-proportionality and a mean half-life of 7 h. A major metabolite was found that showed plasma levels in humans well exceeding those of GLPG0634 and a half-life ranging from 21 to 27 h. This metabolite was found to be active with a similar selectivity for JAK1 inhibition in human whole blood as parent GLPG0634. Its overall potency as a kinase inhibitor was 10 to 20-fold lower. In healthy volunteers, IL-6 induced pSTAT1 was inhibited for the entire 24 h dosing period, including at 24 h after the last dose for QD dose regimens. No relevant inhibition of JAK2 activity was observed at any dose level. While plasma levels of parent GLPG0634 were low beyond 12 hours from the last intake, those for its active metabolite remained high. The PK profile in RA patients for GLPG0634 and its metabolite were similar to that in healthy volunteers. A QD and BID regimen for a 200 mg daily dose showed a similar high level of efficacy following 4-week treatment in RA. QD dosing was found efficacious for doses of 75 mg onwards, with mean decreases in DAS28(CRP) ranging from 1.7 to 2.8 (placebo 0.3 to 1.2), and high baseline CRP levels normalizing within 7 to 14 days.

Conclusion: The results of these studies suggest that the 24-hour maintained JAK1 inhibition and the observed clinical efficacy of QD dosing of GLPG0634 is supported by an active metabolite. The long half-life of this metabolite provides a lasting effect, though at a lower level of JAK1 inhibition than GLPG0634. The lower potency may be compensated by the high exposure. The major active metabolite supports longer lasting effects of GLPG0634 and reduces fluctuations in JAK1 inhibition. This may allow for QD dosing in a therapeutic setting, adding to dosing convenience for patients.

Disclosure: F. Namour, GALAPAGOS SASU, 3;

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12-Week Results Of a Phase 2b Dose-Ranging Study Of Baricitinib, An Oral JAK1/ JAK2 Inhibitor In Japanese Patients With Rheumatoid Arthritis On Background Methotrexate Therapy. Yoshiya Tanaka[1], Kahaku Emoto[2], Mika Tsujimoto[2], Douglas E. Schlichting[3] and William Macias[3]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Eli Lilly Japan K.K., Kobe, Japan, [3]Eli Lilly and Company, Indianapolis, IN.

Background/Purpose: Baricitinib (formerly LY3009104/INCB028050), a novel, oral inhibitor of JAK1 and JAK2 in the JAK-STAT signaling pathway, has been evaluated in a 12-week blinded phase 2b study in Japanese patients (pts) with moderate to severe rheumatoid arthritis (RA) with inadequate response to methotrexate (MTX).

Methods: Japanese RA pts, based on the 2010 ACR/EULAR criteria, with active symptoms (at least 6 swollen and 6 tender joints based on the 66/68 joint assessment) on stable MTX (6 to 16 mg/week) were randomized 2:1:1:1:1 to receive placebo (PBO) or 1of 4 once-daily baricitinib doses (1, 2, 4, or 8 mg), respectively, for 12 weeks. The primary objective was to evaluate the efficacy of baricitinib as assessed by the combined proportion of pts in the 4- and 8-mg dose groups who achieved an ACR20 response compared to PBO over 12 weeks.

Results: Of the 145 pts randomized and treated, 77% of the combined 4- and 8-mg (67% of the 4-mg and 88% of the 8-mg dose) groups achieved ACR20 responses compared with 31% of PBO-treated pts ($p \leq 0.001$) by the end of 12 weeks. Significant differences versus placebo ($p < 0.05$) were observed in the proportion of patients achieving ACR20 and ACR50 in a dose-dependent manner at Week 12 (Table1). Similarly, greater proportions of pts were judged as disease remission by DAS28CRP<2.6, SDAI≤3.3, and HAQ-DI≤0.5 in the 4- and 8-mg dose groups compared to PBO (Table 1). Over 12 weeks in the PBO and combined baricitinib groups, there were similar incidence rates of adverse events (AEs) (53% vs 55%, respectively). Most AEs were mild. There were no opportunistic infections and no deaths. Serious AEs were reported in 2 pts. Decreases in hemoglobin were small (Table 2). This was probably due to the iron supplements that were allowed during the study. Small increases in serum creatinine were seen (Table 2). Several bone metabolic markers and systemic inflammatory markers such as serum TNF-alpha and IL-6 were evaluated. Some bone markers showed dose-dependent changes from baseline. In P1NP and osteocalcin, significant decreases compared to PBO were observed only in the 4- or 8-mg group ($p < 0.05$), but not in the 1- or 2-mg group at Week 12.

Table 1. Selected Efficacy Endpoints at Week 12

Efficacy	PBO (N=49)	1 mg QD (N=24)	2 mg QD (N=24)	4 mg QD (N=24)	8 mg QD (N=24)
% ACR20*	31	67***	83***	67***	88***
% ACR50*	8	33***	46***	50***	54***
% DAS28CRP<2.6**	22	29	33	38	42
% SDAI≤3.3**	8	4	29***	17	17
% HAQ-DI≤0.5**	45	50	54	63	83***

1-sided Fisher's exact test. *non-responder imputation; **last observation; ***$p < 0.05$ vs. PBO. Abbreviations: ACR20/50 = American College of Rheumatology 20/50 responder index; DAS28CRP = Disease Activity Score 28 using C reactive protein; HAQ-DI= Health Assessment Questionnaire - Disability Index; PBO=Placebo; QD=Once-daily; SDAI=Simplified Disease Activity Index.

Table 2. Summary of Laboratory Data at Week 12: Change from Baseline

Median (Min, Max)	PBO	1 mg QD	2 mg QD	4 mg QD	8 mg QD
Hemoglobin (mmol/L)	−0.125 (−1.18, 1.06)	0.130 (−0.94, 2.54)	−0.090 (−1.42, 0.93)	0.000 (−1.30, 0.50)	−0.190 (−1.12, 1.06)
Neutrophil count (109/L)	−0.250 (−2.44, 4.76)	−0.320 (−2.94, 1.71)	−0.595 (−6.66, 1.36)	−1.120 (−6.98, 2.14)	−0.480 (−5.28, 1.22)
Creatinine (mmol/L)	0.0 (−13, 10)	4.0 (−3, 11)	3.0 (−5, 13)	5.0 (−2, 17)	5.0 (−5, 23)
HDL cholesterol (mmol/L)	−0.050 (−0.59, 0.36)	0.130 (−0.37, 0.49)	0.100 (−0.88, 0.83)	0.160 (−0.62, 0.85)	0.250 (−0.39, 0.70)
LDL cholesterol (mmol/L)	−0.050 (−0.72, 0.70)	0.130 (−0.54, 0.78)	0.255 (−1.19, 1.68)	0.310 (−0.44, 1.17)	0.465 (−2.23, 1.32)

Abbreviations: HDL=high-density lipoprotein; LDL=low-density lipoprotein; PBO=placebo; QD=once daily.

Conclusion: Clinical efficacy of baricitinib against PBO was demonstrated in this Phase 2b study of baricitinib in combination with background MTX in Japanese pts with moderate to severe RA over 12 weeks. Baricitinib was well tolerated. Safety signals observed over 12 weeks were consistent with previous studies of baricitinib in non-Japanese pts with RA.

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A Randomized, Dose-Ranging, Placebo-Controlled, 84-Day Study Of INCB039110, a Selective Janus Kinase-1 Inhibitor, In Patients With Active Rheumatoid Arthritis. Monica Luchi, Rosanne Fidelus-Gort, Diane Douglas, Haifeng Zhang, Robert Flores, Robert Newton, Peggy Scherle, Swamy Yeleswaram, Xuejun Chen and Victor Sandor. Incyte Corporation, Wilmington, DE.

Background/Purpose: To characterize the safety and efficacy of INCB039110, a novel and selective JAK1 inhibitor, in patients with active RA.

Methods: This phase 2, multicenter study (NCT01626573) was conducted in two parts in the United States. Part 1 consisted of an initial 28-day treatment period in an independent group of patients with active RA and identified a dosing range of INCB039110 that was evaluated in part 2. In part

2, presented here, patients with active RA (≥ 6 tender/≥ 4 swollen joints out of 28 examined) and CRP ≥ 6 mg/L were randomized to placebo (PBO) or INCB039110 at daily oral doses of 100 mg BID, 300 mg QD, 200 mg BID or 600 mg QD. Patients could be on stable doses of methotrexate, hydroxychloroquine, corticosteroids (< 10 mg/day) and/or sulfasalazine. Other concurrent DMARDs/biologics were excluded. The primary analysis was at the end of an 84-day PBO controlled period.

Results: Of the 60 planned patients, 40 patients have completed the Day 84 visit and were included in this analysis. Seven patients discontinued treatment. Mean age across treatment groups was 53.2 yrs and 73% were female. Mean disease duration was 9 yrs. Approximately 90% were on background DMARDs and approximately 33% had been previously treated with biologics.

Response rates at Day 84 for ACR and DAS28 CRP and mean percent change from baseline in DAS28 CRP are shown in the table.

Table. Efficacy parameters at Day 84

		INCB039110			
	PBO N=8	100 mg BID N=8	300 mg QD N=9	200 mg BID N=8	600 mg QD N=7
ACR20, n (%)	3 (38%)	4 (50%)	4 (44%)	4 (50%)	7 (100%)
ACR50, n (%)	2 (25%)	3 (38%)	4 (44%)	3 (38%)	5 (71%)
ACR70, n (%)	1 (13%)	2 (25%)	2 (22%)	1 (13%)	4 (57)
DAS28 CRP, Mean % change*	−23% (n=7)	−45% (n=5)	−49% (n=6)	−44% (n=7)	−47% (n=7)
DAS28 CRP < 2.6, n (%)	0	2 (25%)	3 (33%)	2 (25%)	3 (43%)

*Change from baseline in patients with DAS28 CRP assessment at Day 84.

Responses were observed as early as the first assessment (14 days), demonstrating a rapid onset of action. Similar ACR responses were achieved with INCB039110 regardless of background therapy or previous biologic experience.

There were no grade 3 or grade 4 AEs and no dose relationship for treatment-related AEs. One patient experienced a grade 2 ALT elevation. One patient experienced an unrelated serious AE of rib fracture. There were no serious or opportunistic infections. A dose-related increase in LDL was noted. There was no change in HDL to LDL ratio.

Conclusion: INCB039110 given once or twice daily over 84 days was generally well tolerated and demonstrated rapid and clinically meaningful responses in patients with active RA.

Disclosure: M. Luchi, Incyte Corporation, 1, Incyte Corporation, 3; **R. Fidelus-Gort**, Incyte Corporation, 1, Incyte Corporation, 3; **D. Douglas**, Incyte Corporation, 1, Incyte Corporation, 3; **H. Zhang**, Incyte Corporation, 1, Incyte Corporation, 3; **R. Flores**, Incyte Corporation, 1, Incyte Corporation, 3; **R. Newton**, Incyte Corporation, 1, Incyte Corporation, 3; **P. Scherle**, Incyte Corporation, 1, Incyte Corporation, 3; **S. Yeleswaram**, Incyte Corporation, 1, Incyte Corporation, 3; **X. Chen**, Incyte Corporation, 1, Incyte Corporation, 3; **V. Sandor**, Incyte Corporation, 1, Incyte Corporation, 3.

ACR Concurrent Abstract Session
Spondylarthropathies and Psoriatic Arthritis: Clinical Aspects and Treatment: Therapeutics and Outcomes in Spondyloarthritis
Monday, October 28, 2013, 4:30 PM–6:00 PM

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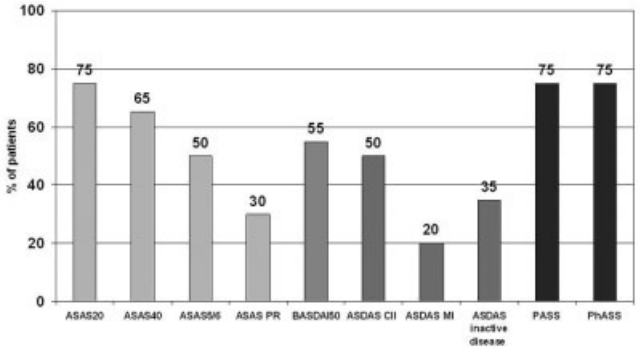
Ustekinumab For The Treatment Of Patients With Active Ankylosing Spondylitis: Results Of a 28-Week, Prospective, Open-Label, Proof-Of-Concept Study (TOPAS). Denis Poddubnyy[1], Johanna Callhoff[2], Joachim Listing[2] and Joachim Sieper[1]. [1]Charité Universitätsmedizin Berlin, Berlin, Germany, [2]German Rheumatism Research Center, Berlin, Germany.

Background/Purpose: In contrast to other inflammatory rheumatic diseases, such as rheumatoid arthritis, the therapeutic options in ankylosing spondylitis (AS) with predominant axial manifestations are limited and confined to non-steroidal anti-inflammatory drugs (NSAIDs) and, if this treatment fails, to tumour necrosis factor α blockers. Ustekinumab – a fully human monoclonal antibody against interleukin (IL)-12 and −23 – has been shown to be effective in psoriasis and is currently in phase 3 trials in psoriatic arthritis and Crohn's disease. The purpose of the current study was to investigate the short-term efficacy and safety of ustekinumab in patients with active AS.

Methods: In this prospective, open-label, proof-of-concept clinical trial (ClinicalTrials.gov identifier NCT01330901), ustekinumab in a dose of 90 mg was administered subcutaneously at baseline, week 4 and week 16 in 20 patients with active AS. Eligible patients were required to have a diagnosis of AS according to the modified New York criteria and an active disease defined as a BASDAI score of ≥ 4 despite previous NSAIDs treatment. The primary study endpoint was the proportion of patients with ASAS40 response at week 24.

Results: At week 24, ASAS40 response was reached by 65% of the patients. ASAS partial remission and a ≥50% improvement of the BASDAI were achieved in 30% and 55% of the patients, respectively. Most of the other outcome parameters also showed a clear and significant improvement (figure, table). There was no reduction of serum C-reactive protein level in the whole group, however, a clear CRP reduction occurred in the ASAS40 responder group (−1.1±7.5 mg/l) vs. the non-responder group (+3.3±3.5 mg/l), p = 0.008. Overall, ustekinumab was well tolerated: only one serious adverse event (AS worsening) was observed, there were no adverse events leading to study discontinuation, no cases of serious infections, malignancies or deaths.



ASAS PR = ASAS partial remission, ASDAS CII = ASDAS clinically important improvement (change score ≥1.1 from baseline), ASDAS MI = ASDAS major improvement (change score ≥2.0 from baseline), PASS = patient acceptable symptom state, PhASS = physician acceptable symptom state.

Figure. Response rates to ustekinumab at week 24 in patients with active AS in the TOPAS trial (n = 20).

Table. Changes in the clinical and laboratory parameter over 24 weeks in patients with active AS (n = 20) treated with ustekinumab in the TOPAS trial.

Parameter	Baseline	Week 24	p-value*
ASDAS (mean ± SD)	3.0 ± 0.6	2.0 ± 1.1	0.001
BASDAI, points NRS (mean ± SD)	5.3 ± 1.5	3.0 ± 1.8	<0.001
BASFI, points NRS (mean ± SD)	5.3 ± 1.9	3.0 ± 2.3	<0.001
BASMI (mean ± SD)	1.6 ± 1.4	1.2 ± 1.3	0.016
Patient global, points NRS (mean ± SD)	6.3 ± 1.6	3.3 ± 2.3	<0.001
General pain, points NRS (mean ± SD)	6.5 ± 1.6	3.3 ± 2.4	<0.001
Nocturnal pain, points NRS (mean ± SD)	6.5 ± 1.9	3.3 ± 2.4	<0.001
EQ-5D (mean ± SD)	0.6 ± 0.2	0.8 ± 0.1	<0.001
ASQoL (mean ± SD)	9.4 ± 3.1	5.1 ± 4.0	<0.001
ASAS NSAIDs intake score (mean ± SD)	68.7 ± 37.9	33.3 ± 33.6	0.008
CRP, mg/l (mean ± SD)	5.9 ± 5.5	6.4 ± 7.1	0.760

*Paired-samples t-test

Conclusion: In this prospective, open-label, proof-of-concept clinical trial, ustekinumab treatment seems to be effective with a significant reduction of signs and symptoms of active AS. For comparison, the ASAS40 response rates in similarly designed AS trials with methotrexate [1], abatacept [2], or anakinra [3] were 10%, 13%, or 20%, respectively.

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Disclosure: D. Poddubnyy, MSD, 5, AbbVie, MSD, Pfizer, and USB, 8; **J. Callhoff**, None; **J. Listing**, None; **J. Sieper**, AbbVie, Merck, Pfizer, UCB, 2, AbbVie, Merck, Pfizer, UCB, 5, AbbVie, Merck, Pfizer, UCB, 8.

Effect Of Certolizumab Pegol Over 48 Weeks In Patients With Axial Spondyloarthritis, Including Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis. Robert B. M. Landewé[1], Martin Rudwaleit[2], Désirée M. van der Heijde[3], Maxime Dougados[4], Philip J. Mease[5], John D. Reveille[6], Jessica Walsh[7], Alan J. Kivitz[8], Walter P. Maksymowych[9], Jürgen Braun[10], Atul A. Deodhar[11], Christian Stach[12], Bengt Hoepken[12], Pritibha Singh[12] and Joachim Sieper[13]. [1]Academic Medical Center/University of Amsterdam & Atrium Medical Center, Amsterdam, Netherlands, [2]Endokrinologikum Berlin, Berlin, Germany, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Paris-Descartes University, APHP, Cochin Hospital, Paris, France, [5]Swedish Medical Center and University of Washington, Seattle, WA, [6]University of Texas Health Science Center at Houston, Houston, TX, [7]University of Utah Hospital, Salt Lake City, UT, [8]Altoona Center for Clinical Research, Duncansville, PA, [9]University of Alberta, Edmonton, AB, [10]Rheumazentrum Ruhrgebiet, Herne, Germany, [11]Oregon Health & Science University, Portland, OR, [12]UCB Pharma, Monheim, Germany, [13]Charité Universitätesmedizin Berlin, Berlin, Germany.

Background/Purpose: Previous reports of RAPID-axSpA have demonstrated the efficacy and safety of certolizumab pegol (CZP), a PEGylated Fc-free anti-TNF, in patients (pts) with axial spondyloarthritis (axSpA) including pts with ankylosing spondylitis (AS, meeting modified New York criteria) and pts with no sacroiliitis on X-ray (non-radiographic axSpA, nr-axSpA), to Week (Wk) 24.[1] We report clinical efficacy and safety of CZP in axSpA pts to Wk48.

Methods: The ongoing RAPID-axSpA trial (NCT01087762) is double-blind and placebo (PBO) controlled to Wk24 and dose-blind to Wk48.[1] Pts fulfilled ASAS criteria[2] and had active axSpA, including both AS pts and nr-axSpA pts. Pts originally randomized to CZP (200mg Q2W or 400mg Q4W, following 400mg loading dose at Wks 0, 2, 4) continued on their assigned dose in dose-blind phase; PBO pts entering dose-blind phase were re-randomized to CZP loading dose followed by CZP 200mg Q2W or CZP 400mg Q4W after Wk24 or, for non-responders Wk16. We present efficacy data for all pts originally randomized to CZP and imaging outcomes for all pts included in the imaging sub-study (MRI set). Endpoints included ASAS20 and ASAS40 responses, ASAS PR and ASDAS outcomes. Also included were BASDAI, BASFI, BASMI-linear, total spine pain, fatigue, ASQoL, SPARCC and ASspiMRI-a. Outcomes are presented at Wk24 and Wk48. NRI was used for categorical measures and LOCF for quantitative measures. Safety sets consists of all pts treated with CZP at any stage of the 48-wk trial.

Results: 325 pts were randomized, of which 218 received CZP from Wk0. Of pts randomized to CZP at baseline (BL), 93% completed Wk24 and 88% Wk48. ASAS20, ASAS40 and ASAS PR were maintained from Wk24 to 48 (Table) and improvements from BL in BASDAI, BASFI, BASMI-linear, ASDAS and ASDAS-ID were also maintained to Wk48 (Table). Reductions in pain, fatigue and ASQoL were also observed between Wk24 and Wk48 (Table). In the MRI sub-study (CZP N=104), reduction of inflammation, as measured by SPARCC and ASspiMRI-a, was maintained to Wk48. Similar improvements were seen with both dosing regimens and in both AS and nr-axSpA subpopulations (Table). In the safety set (N=315), adverse events (AEs) occurred in 248 pts (78.7%; event rate per 100 pt-yrs=419.5), serious AEs in 25 (7.9%). Serious infections occurred in 10 (3.2%) pts, including suspected tuberculosis in 3 (1.0%) of which 1 was confirmed (from Mexico). No deaths or malignancies were reported.

Table. Maintenance of CZP efficacy at Wk24 and Wk48 in RAPID-axSpA trial

	CZP 200 mg Q2W									CZP 400mg Q4W								
Outcome	**axSpA (n = 111)**			**AS [a] (n = 65)**			**nr-axSpA (n = 46)**			**axSpA (n = 107)**			**AS [a] (n = 56)**			**nr-axSpA (n = 51)**		
Clinical [b]	Wk0	Wk24	Wk48	Wk0	Wk24	Wk48	Wk0	Wk24	Wk48	Wk0	Wk24	Wk48	Wk0	Wk24	Wk48	Wk0	Wk24	Wk48
ASAS20 (%)	—	66.7	71.2	—	67.7	72.3	—	65.2	69.6	—	68.2	72.0	—	66.1	75.0	—	70.6	68.6
ASAS40 (%)	—	51.4	53.2	—	47.7	52.3	—	56.5	54.3	—	50.5	61.7	—	55.4	64.3	—	45.1	58.8
ASAS PR (%)	—	30.6	31.5	—	30.8	29.2	—	30.4	34.8	—	29.9	28.0	—	25.0	30.4	—	35.3	25.5
ASDAS	3.9	2.0	1.9	4.0	2.1	2.0	3.7	1.9	1.8	3.8	2.1	2.0	3.8	2.1	2.0	3.8	2.1	2.1
ASDAS-CII (%)	—	73.9	76.6	—	76.9	80.0	—	69.6	71.7	—	68.2	72.0	—	71.4	76.8	—	64.7	66.7
ASDAS-MI (%)	—	45.9	49.5	—	46.2	49.2	—	45.7	50.0	—	39.3	46.7	—	39.3	50.0	—	39.2	43.1
ASDAS-ID (%)	—	29.7	35.1	—	26.2	29.2	—	34.8	43.5	—	30.8	26.2	—	28.6	28.6	—	33.3	23.5
PROs [b]	Wk0	Wk24	Wk48	Wk0	Wk24	Wk48	Wk0	Wk24	Wk48	Wk0	Wk24	Wk48	Wk0	Wk24	Wk48	Wk0	Wk24	Wk48
BASDAI	6.5	3.3	3.1	6.5	3.5	3.3	6.5	3.1	2.9	6.4	3.3	3.1	6.2	3.2	3.0	6.6	3.4	3.3
BASFI	5.3	2.9	2.6	5.6	3.3	3.0	4.8	2.3	2.1	5.4	3.1	3.0	5.7	3.3	3.2	5.1	2.9	2.8
BASMI-linear	3.7	3.1	3.0	4.2	3.5	3.5	3.1	2.5	2.3	3.8	3.2	3.2	4.3	3.7	3.7	3.3	2.7	2.7
Total spine pain [c]	7.1	3.8	3.5	7.0	4.1	3.7	7.2	3.5	3.0	6.9	3.7	3.4	6.9	3.4	3.1	6.9	4.0	3.8
Fatigue [d]	6.8	4.1	4.0	6.9	4.3	4.1	6.7	4.0	3.8	6.7	4.0	3.9	6.5	4.0	3.8	7.1	4.0	4.0
ASQoL	11.8	6.7	5.9	11.9	7.2	6.4	11.8	6.1	5.2	11.3	6.2	5.8	11.3	6.4	5.7	11.4	6.1	5.9

Presented data are mean values except where otherwise stated. [a] AS patients fulfilled modified New York criteria; [b] For the Full Analysis Set of patients originally randomized to CZP; [c] Numeric Rating Scale (NRS) scale; 0 = no pain, 10 = most severe pain. [d] NRS scale; 0 = no fatigue, 10 = severe fatigue. ASAS20: assessment of Axial SpondyloArthritis international Society 20% response criteria; ASAS40: assessment of Axial SpondyloArthritis international Society 40% response criteria; ASAS PR: assessment of Axial SpondyloArthritis international Society Partial Remission criteria; ASDAS: Ankylosing Spondylitis Disease Activity Score; ASDAS-CII: ASDAS Clinically Important Improvement; ASDAS-MI: ASDAS Major Improvement; ASDAS-ID: ASDAS Inactive Disease criteria; PROs: Patient-Reported Outcomes; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI-linear: Bath Ankylosing Spondylitis Metrology Index-linear; ASQoL: Ankylosing Spondylitis Quality of Life scale; MRI: Magnetic Resonance Imaging; SPARCC: SPondyloArthritis Research Consortium of Canada SIJ score for inflammation; ASspiMRI-a: Berlin modification of AS spine MRI score for disease activity in the spine.

Conclusion: In the RAPID-axSpA trial, improvements observed over 24 wks in clinical efficacy, patient-reported and MRI outcomes were sustained over 48 wks in both CZP dosing regimens. Similar sustained improvements in clinical, patient-reported and MRI outcomes were observed in both AS and nr-axSpA subpopulations. The safety profile was in line with that observed for CZP in RA.

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Persistent Fatty Lesions In The Vertebrae In Ankylosing Spondylitis Favor Subsequent New Syndesmophytes: Imaging Results Of a Phase III, Randomized, Placebo-Controlled Study. Kay-Geert A. Hermann[1], Xenofon Baraliakos[2], Jürgen Braun[2], Stephen Xu[3] and Benjamin Hsu[3]. [1]Charité Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, [3]Janssen Research & Development, LLC., Spring House, PA.

Background/Purpose: In ankylosing spondylitis (AS), it is hypothesized that stepwise pathologic changes in the spine begin with active inflammation, then fatty degeneration (Fat), leading to syndesmophyte formation. Using data from the golimumab (GLM) AS study (GO-RAISE), we assessed how fatty and inflammatory lesions detected by MRI related to subsequent syndesmophytes and bridging on x-ray.

Methods: In GO-RAISE, 356 patients with definite AS, BASDAI >4, and back pain score >4 were randomized to SC GLM 50mg, 100mg, or PBO q4wks. All patients were to have lateral view radiographs of the cervical and lumbar spine performed at baseline (BL), wks104 and 208. At MRI substudy sites, serial spine MRI scans in the sagittal plane were acquired using 1.5T scanners with T1 and short tau inversion recovery (STIR) sequences at BL, wk14, and wk104 for 98 patients. Two imaging readers blinded to treatment and image order independently evaluated anterior and posterior vertebral corners on x-rays for syndesmophytes/bridging. Blinded MRI reads were done using ASspiMRI-a scoring of active inflammation (Infl) in vertebral units (VU), with notation of lesional location by VU quadrant (upper, lower × anterior, posterior); and the modified ASspiMRI-c scoring method to assess structural changes including presence of Fat in each of the 23 VU. This analysis focused on percentage of vertebral corners with new syndesmophytes/bridging visible on x-ray at wk 104 and 208, and how this percentage varied by presence or absence of prior Infl or Fat lesions in the corresponding VU quadrants at BL and wk14.

Results: There were 91 patients in the substudy representing over 1200 VU (cervical, lumbar) with evaluable Fat data by MRI at BL and wk14 and corresponding vertebral corner x-ray data at wk104 and 208. Of VU with Fat at wk14, more frequently there was also Fat at BL and Fat persisting to

wk104, and Infl lesions were more frequently absent at BL than present. Overall, as assessed by both readers individually and concordantly, the percentage of corners with new syndesmophytes at wk 104 or 208 was greater in VU where Fat was persistently present at both BL and wk14, compared to those where Fat was only present at wk14. New syndesmophytes were significantly more likely to develop in VU with Fat at both BL and wk14 than those that did not have persistent fat (odds ratios for wk208 syndesmophyte/ bridging, Reader 1, 3.27; Reader 2, 2.42). The combined presence at BL of Fat and Infl lesions in a VU quadrant appeared to further increase the chance of new syndesmophytes developing at the corresponding vertebral corner ([Reader #1] 7.9% and 2.5% of corners with new syndesmophytes at wk104 for VU with BL Fat+Infl/ wk14 Fat *vs*. BL Fat-no Infl/ wk14 Fat, respectively, and [Reader #2] 4.4% and 2.7%, respectively). Conversely, for VU without Fat or Infl at BL but wk14 Fat present, only 0–1.5% of corners developed new syndesmophytes later.

Conclusion: This detailed analysis of spine MRI and radiographs at the vertebral level supports the hypothesis that in AS, fatty degeneration and active inflammation within vertebral unit favors progression toward subsequent syndesmophyte growth and ankylosis.

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1801

Relationship Between MRI and Clinical Remission In Patients With Non-Radiographic Axial Spondyloarthritis After Two Years Of Adalimumab Therapy.

Désiréé van der Heijde[1], Walter P. Maksymowych[2], Joachim Sieper[3], Robert Lambert[4], Matthew A. Brown[5], Suchitrita S. Rathmann[6], Jaclyn K. Anderson[7] and Aileen L. Pangan[6]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]University of Alberta, Edmonton, AB, [3]Charité Universitätesmedizin, Berlin, Germany, [4]University of Alberta Hospital, Edmonton, AB, [5]University of Queensland Diamantina Institute, Brisbane, Australia, [6]AbbVie Inc., North Chicago, IL, [7]AbbVie, North Chicago, IL.

Background/Purpose: Adalimumab (ADA) is currently approved in the EU for the treatment of severe non-radiographic axial spondyloarthritis (nr-axSpA), in patients (pts) with an elevated CRP and/or positive MRI who have had an inadequate response to, or are intolerant to NSAIDs. Reduction of sacroiliac joint (SIJ) and spine inflammation on MRI has been previously reported after 12 wks of ADA compared to placebo in the ABILITY-1 study. The objective of this analysis was to determine the efficacy of ADA in improving inflammation on MRI in pts with nr-axSpA and the relationship between MRI and clinical remission.

Methods: ABILITY-1 is an ongoing phase 3, randomized, controlled trial in pts with nr-axSpA who had an inadequate response, intolerance, or contraindication to NSAIDs. A 12-wk double-blind period of ADA 40 mg every other week (eow) or placebo (PBO) was followed by an open-label period in which pts could receive ADA 40 mg eow for up to an additional 144 wks. MRI of the SIJ and spine were done at baseline (BL), wks 12, 52 and 104, and were read using the SPARCC scoring system (6 discovertebral unit method for the spine) by 2 independent readers who were blinded to time sequence. Mean reader scores were used. This *post hoc* analysis evaluated the efficacy of ADA in improving MRI inflammation at wks 52 and 104 in the overall population and in the MRI+/CRP+ subpopulation (pts who had positive BL MRI [SPARCC score ≥2 for either the SIJ or spine] or elevated BL CRP). Clinical remission was defined by ASDAS inactive disease (ASDAS ID, ASDAS <1.3) and MRI remission by SPARCC score <2.

Results: 142 (69 ADA, 73 PBO) of the total efficacy population (N=185) were in the MRI+/CRP+ subpopulation. MRI obtained at wks 52 and 104 showed sustained mean improvements with long-term ADA therapy in SPARCC SIJ and spine scores for the overall population (wk 52 n=149, –3.7 and n=148, –1.2; wk 104 n=131, –3.8 and n=130, –1.4) and for the MRI+/CRP+ subpopulation (wk 52 n=116, –4.6 and n=115, –1.7; wk 104 n=102, –4.8 and n=101, –2.0). The table presents MRI and clinical remission rates among pts who had a positive MRI at BL (SPARCC score ≥2 for either the SIJ or spine). Of the 46 pts who were in ASDAS ID at wk 104, 33 (72%), 35 (76%) and 26 (57%) had MRI remission of the SIJ, spine or both SIJ and spine respectively.

Table. Patients with baseline MRI Scores ≥2 for SI joint or Spine Achieving MRI and Clinical Remission at Weeks 52 and 104

ASDAS Inactive Disease Status	SPARCC SI Joint Score		SPARCC Spine Score		SPARCC SI Joint and Spine Scores	
	<2 n	≥2 n	<2 n	≥2 n	SI Joint and Spine <2 n	SI Joint or Spine ≥2 n
Week 52				**N=101**		
In ASDAS inactive disease	37	10	32	15	26	21
Not in ASDAS inactive disease	39	15	28	26	21	33
Week 104				**N=88**		
In ASDAS inactive disease	33	13	35	11	26	20
Not in ASDAS inactive disease	33	9	19	23	18	24

N = patients who are MRI+ at baseline (MRI SPARCC score ≥2 for SI joint or spine) and with available ASDAS and MRI data. ASDAS, Ankylosing Spondylitis Disease Activity Score.

Conclusion: In ABILITY-1, ADA therapy of up to 2 yrs in nr-axSpA pts resulted in reduction of inflammation on MRI. The majority of pts in clinical remission were noted to also have MRI remission. However, resolution or absence of inflammation on MRI did not always correspond to clinical remission.

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1802

A Major Clinical Response To Anti-Tumor Necrosis Factor Agents Is Associated With a Reduced Development Of Fatty Changes In The Spine Of Patients With Ankylosing Spondylitis.

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Background/Purpose: Fatty changes (FC) on T1-weighted magnetic resonance images (MRI) have been described in the spine of patients with ankylosing spondylitis (AS). Such lesions were recently found to be related to syndesmophyte development in AS patients treated with anti-TNF agents. While TNF blockers have been shown to reduce inflammatory changes seen on STIR MRI sequences, their effect on the course of FC has not been studied in detail to date. To study the course of FC in patients with AS under anti-TNF therapy and analyse which clinical parameters are associated with the occurrence of FC.

Methods: MRI of AS patients participating in the EASIC study who had received infliximab for 2 years were blindly for the time point of examination. Presence or absence of FC was recorded for all vertebral edges (VEs) at baseline, after 24 weeks and after 2 years of treatment. Spinal radiographs at baseline and 2 years were scored by the mSASSS. Relative risk (RR) calculations were performed based on generalized estimation equations (GEE model). Poisson variation and $\chi 2$ test was used to compare MRI findings between time points.

Results: Complete sets of MRI were available of 73 patients (mean age 40.5±10.5 years, 86.3% male, HLA-B27+: 83.6%, mean BASDAI 6.5±1.4, mean disease duration 10.0±8.4 years) resulting in a total of 1,948 VEs at each time point. At baseline, FC were found in 619 VEs (31.8%). After 24 weeks of infliximab therapy, regression of FC was seen in 19 VEs (3.1%), while new FC had appeared in 133/1,329 VEs (10.0%). After 2 years, regression of FC was observed in 35/619 VEs (5.7%) and new FC were seen in 215 VEs (16.2%), while 4/1,948 VEs (0.3%) showed both regression and development to FDL at different time points. Increased inflammatory activity at baseline was significantly associated with development of FC: 34% of VEs with inflammation vs. 12.9% of VEs without (p<0.0001). Baseline mSASSS scores increased the risk of FC: RR 1.03, 95% CI: 1.01–1.04 (p=0.0003),

while a major treatment response (50% BASDAI improvement) was associated with lower risk: RR=0.85, 95% CI: 0.76–0.95 (p=0.005). Being female lowered the risk for FC by 22%: RR: 0.88, 95% CI: 0.59–1.32, p=0.544), and younger age also had some influence: RR: 0.97, 95% CI: 0.93–1.00 (p=0.0327).

Conclusion: This study confirms that FC develop in AS patients treated with TNF blockers and that inflammation may be one source of that. However, the most important finding of this analysis is that a good response to TNF blockers was associated with significantly lower risk to develop FC. Whether this leads to a decrease in new bone formation over time remains to be seen.

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1803

Is Site Of Back Pain Related To Location Of Inflammatory and Structural Lesions On MRI In Patients With Chronic Back Pain? Manouk de Hooge[1], Rosaline van den Berg[1], Floris van Gaalen[1], Victoria Navarro-Compán[1], Monique Reijnierse[1], Karen Fagerli[2], Maureen C. Turina[3], Maikel van Oosterhout[4], Roberta Ramonda[5], Tom Huizinga[1] and Désirée van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [4]GHZ Hospital, Gouda, Netherlands, [5]University of Padova, Padova, Italy.

Background/Purpose: Pain has found to be related to inflammatory lesions in thoracic, lumbar and sacroiliac joints (SIJ) sites and to structural lesions in the SIJ site in the DESIR cohort. Our aim was to evaluate if localisation of back pain, as indicated by patients, is related to location of BME lesions seen on MRI (in spine (MRI-spine) or sacroiliac joints (SIJ) (MRI-SI)) in patients with chronic back pain.

Methods: Chronic back pain patients (≥3 months, ≤2 years, onset <45 years) recruited from 5 participating centres were included in the SPondylo-Arthritis Caught Early (SPACE)-cohort. Pain was indicated by patients at different sites (thoracic, lumbar, buttock, total spine). Patients underwent MRI-spine and MRI-SI. On MRI-spine anterior/posterior BME and fatty lesions suggestive of spondylitis were scored when visible on ≥2 consecutive slices. For any other structural lesion (erosions or syndesmophytes), suggestive of spondylitis, presence on ≥ 1 slice was sufficient. On MRI-SI, BME, fatty lesions, sclerosis and erosions, suggestive of spondylitis, were scored when ≥1 lesion was present on ≥2 consecutive slices or >1 lesion on 1 slice. Presence of ankylosis on ≥1 slice was scored. MRIs were scored independently by 3 blinded, well calibrated readers. Agreement of 2/3 readers was used. Association between pain site and BME location was assessed by logistic regression analysis adjusted for gender, HLA-B27 and age at onset of back pain resulting in adjusted Odds Ratios (OR).

Results: In 296 patients, data of the location of pain, MRI-spine (n=293) and MRI-SI (n=288) was available. Mean age at pain onset was 28.9 years, 35.1% male, 38.5% HLA-B27+ and 41.9% fulfilled the ASAS axSpA classification criteria. The prevalence of pain and lesions is shown in the table. The ORs of pain and MRI lesions at same site for the different patient group are shown in the table. Pain in the thoracic site was significantly associated with BME lesions at the same site in the whole patient group. Similar ORs were found in the no-SpA and axSpA subgroups, though not significant due to the lower amount of patients. Pain was significantly associated with fatty and any structural lesions in the buttock/SIJ site in the axSpA supgroup (see table).

Prevalence of pain and lesions

	Back pain	BME lesions	Fatty lesions	Any structural lesion
Cervical	ND	5 (1.7%)	9 (3%)	16 (5.4%)
Thoracic	108 (36.5%)	52 (17.6%)	45 (15.2%)	80 (27%)
Lumbar	244 (82.4%)	65 (22%)	33 (11.1%)	59 (19.9%)
Buttock/SIJ	100 (33.8%)	67 (22.6%)	36 (12.2%)	49 (14.2%)
Total spine	10 (3.4%)	0	4 (1.4%)	8 (2.7%)
Any site in the spine	296 (100%)	95 (32.1%)	60 (25%)	101 (34.1%)

Odds ratios of pain at the same site

	OR (CI) all patients (n=296)	OR (CI) axSpA patients (n=124)	OR (CI) no-SpA patients (n=172)
BME lesions			
Thoracic site	*2.07 (1.08–3.95;p<0.03)*	2.11 (0.87–5.15)	2.54 (0.91–7.05)
Lumbar site	1.39 (0.65–3.11)	1.26 (0.47–3.40)	1.75 (0.37–8.35)
Buttock/SIJ site	0.63 (0.34–1.16)	0.55 (0.23–1.28)	0.27 (0.06–1.28)
Fatty lesions			
Thoracic site	1.10 (0.54–2.24)	1.23 (0.49–3.06)	1.13 (0.35–3.62)
Lumbar site	0.62 (0.26–1.51)	0.76 (0.23–2.44)	0.38 (0.92–1.60)
Buttock/SIJ site	1.06 (0.49–2.30)	*3.71 (1.15–11.96; p<0.03)*	0.57 (0.25–1.28)
Any structural lesion			
Thoracic site	1.23 (0.71–2.14)	1.20 (0.53–2.70)	1.49 (0.67–3.32)
Lumbar site	0.99 (0.47–2.15)	0.74 (0.27–2.01)	1.08 (0.29–4.07)
Buttock/SIJ site	1.62 (0.95–2.78)	*5.10 (1.45–17.92; p<0.01)*	0.56 (0.25–1.27)

Conclusion: The localisation of pain in the spine (thoracic, lumbar, buttock or total spine), as indicated by the patient, is significantly related to the location of BME lesions in thoracic site in patients with chronic back pain. In addition, in the subgroup with axSpA patients there is a significant relation between buttock pain and any structural lesions seen on MRI-SI.

Reference:
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ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects: Non-biologic Disease-modifying Antirheumatic Drugs
Monday, October 28, 2013, 4:30 PM–6:00 PM

1804

Effect of Mycophenolate On the White Blood Cell Count and the Frequency of Infection in Systemic Lupus Erythematosus. Ananta Subedi[1], Hong Fang[2] and Michelle Petri[2]. [1]Good Samaritan Hospital, Baltimore, MD, [2]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Leukopenia is a common manifestation of SLE. Addition of immunosuppressive therapy is of concern, in that it could worsen leukopenia; increase the risk of infection, or both. The aim of this study was to analyze the effect of mycophenolate on the white blood cell count and the rate of infection in SLE patients.

Methods: Three hundred patents within the Hopkins Lupus Cohort who were on mycophenolate mofetil were included in the study. SLE patients served as their own control (before and after mycophenolate mofetil). The white blood cell count and rate of infection were compared on the day mycophenolate was started with the white blood cell count and rate of infection at the next visit. Statistical analysis was performed using the paired t-test.

Results: At the time of the analysis, three hundred patients in the cohort were taking mycophenolate mofetil. The study population included 43% Caucasians, 47% African-Americans and 10% other ethnicities. There was a slight but not statistically significant increase in the white blood cell count (6.65±3.34 vs. 7.02±3.28, P= 0.075), after starting mycophenolate. Patients with a baseline white blood cell count less than 3,000/mm^3 did have a statistically significant increase in the white blood cell count after starting mycophenolate mofetil (2.49±0.46 vs. 4.83±2.66, P= 0.0007). In the multivariate model for factors associated with the white blood count, mycophenolate use was not statistically significant (Table 1). We also found a statistically significant increase in the rate of bacterial infection (but not viral infection) after starting mycophenolate mofetil (5% vs. 9%, P= 0.032, Table 2).

Table 1. Factors Associated with the White Blood Cell Count Adjusted for Ethnicity and Prednisone dose.

Variable	Effect on white blood cell Count	p-value
Ethnicity		
African-American vs. Caucasian	−0.91±0.33	0.0049
Other ethnicity vs. Caucasian	−0.52±0.51	0.31
Prednisone (per mg/d)	0.07±0.01	<0.0001
Mycophenolate mofetil (before vs. after)	0.20±0.18	0.28

Table 2. Frequency of Infection Before and During the Use of Mycophenolate mofetil.

Variable	Before mycophenolate mofetil (%)	After mycophenolate mofetil (%)	Adjusted p-value*
Infection (viral or bacterial)	14	18	0.087
Viral infection	10	10	0.17
Bacterial infection	5	9	0.032

* p-value adjusted for prednisone dose.

Conclusion: Leukopenia does not worsen with mycophenolate. However, mycophenolate does increase the rate of bacterial (but not viral) infection.

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1805

Hydroxychloroquine Levels Identify Four Distinct Subsets of Systemic Lupus Erythematosus Patients. Michelle Petri, Hong Fang and William Clarke. Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Hydroxychloroquine is used for both its effect on SLE disease activity (cutaneous and arthritis) and for its preventive roles (reduction in flares, renal damage, thrombosis). HCQ blood levels have been predominantly used to identify nonadherence; to date, they have not correlated well with disease activity.

Methods: 357 SLE patients (mean age 44.7, 94% female, 45% Caucasian, 45% African-American, and 10% other ethnicity) had hydroxychloroquine blood levels measured (therapeutic 500–1500 ng/mL in whole blood) and same day assessment of global disease activity by Physician Global Assessment (PGA, 0 to 3 VAS) and SELENA-SLEDAI.

Results: 53 (15%) had 0 level, meaning complete nonadherence. 110 (31%) had levels between 15–500 ng/mL indicating partial adherence. 167 (47%) had therapeutic levels. Surprisingly, 27.8% had supratherapeutic levels. This supratherapeutic group was appropriately dosed for weight, age, and renal function.

Table 1. Effect of Hydroxychloroquine level on Clinical Characteristics (as categorical variables)

Demographic Characteristics	HCQ <15 (N=53)	HCQ (15–500) (N=110)	HCQ (500–1500) (N=167)	HCQ ≥1500 (N=27)	Adjusted P-Value§	Adjusted P-value for therapeutic (≥500) vs non-therapeutic levels§
	n (%)	n (%)	n (%)	n (%)		
Gender						
Female	52 (98)	106 (96)	150 (90)	26 (96)	0.059	0.016
Male	1 (2)	4 (4)	17 (10)	1 (4)		
Ethnicity Caucasian	24 (45)	49 (45)	77 (46)	12 (44)	0.96	0.70
African-American	27 (51)	49 (45)	70 (42)	13 (48)		
Other	2 (4)	12 (11)	20 (12)	2 (7)		
Age at baseline						
≤30 years	6 (11)	16 (15)	29 (17)	6 (22)	0.63	0.29
>30 years	47 (89)	94 (85)	138 (83)	21 (78)		
Education						
≤12 years	22 (42)	41 (38)	56 (34)	12 (44)	0.74	0.55
>12 years	30 (58)	66 (62)	108 (66)	15 (56)		
Family income						
≤$50,000	32 (62)	60 (56)	82 (50)	17 (63)	0.60	0.37
>$50,000	20 (38)	47 (44)	81 (50)	10 (37)		
PGA>1	7 (15)	21 (22)	28 (18)	8 (33)	0.23	0.86
SELENA-SLEDAI>2	16 (30)	35 (32)	49 (29)	9 (33)	0.98	0.86
Prednisone >0	25 (56)	31 (33)	56 (36)	15 (63)	0.0051	0.90
Low C3	9 (17)	19 (18)	36 (22)	2 (7)	0.27	0.80
Low C4	7 (13)	16 (15)	17 (10)	1 (4)	0.25	0.11
BMI>30	15 (28)	38 (35)	51 (31)	6 (22)	0.52	0.72
Anti-dsDNA	10 (19)	19 (18)	36 (22)	5 (19)	0.88	0.64
Creatinine>1.4 mg/dl	4 (8)	10 (9)	13 (8)	4 (15)	0.56	0.83
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
PGA	0.7 (0.7)	0.7 (0.7)	0.6 (0.6)	0.9 (0.9)	0.24	0.50
SELENA-SLEDAI	2.5 (3.5)	2.4 (3.1)	2.2 (2.6)	1.9 (2.4)	0.051	0.64
Prednisone dose (mg/d)	3.1 (3.5)	3.1 (8.0)	2.6 (6.1)	7.8 (11.5)	0.0029	0.76

§Comparison between among different HCQ groups; adjusted for age, ethnicity, and gender.

Conclusion: Hydroxychloroquine blood levels remain important in assessing adherence, but they are disappointing in not being correlated with current disease activity (by PGA or SLEDAI). In fact, the identification of the "supratherapeutic" group explains this paradox, as they had greater PGA, SLEDAI, and prednisone use. Several hypotheses (patients increasing HCQ dose on their own for disease activity vs genetic differences in metabolism of HCQ) could explain a "supratherapeutic" group. Our data also indicate that nonadherence should be subdivided into two groups: complete nonadherence (15%) and partial nonadherence (31%), as the clinical implications are quite different.

Disclosure: M. Petri, None; **H. Fang**, None; **W. Clarke**, None.

1806

Association Between Hydroxychloroquine Exposure and Incidence Of Diabetes Mellitus In Systemic Lupus Erythematosus. Michelle Petri[1] and Laurence S. Magder[2]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD.

Background/Purpose: Diabetes mellitus is one of the SLICC/ACR Damage Index items and a recognized risk factor for cardiovascular disease and renal failure. In rheumatoid arthritis, hydroxychloroquine is protective against diabetes. We examined the incidence of and risk factors for diabetes in SLE.

Methods: For each month of follow-up for a patient in a large single-site clinical SLE cohort, we calculated the proportion of previous months in the cohort that hydroxychloroquine was prescribed. We then determined the rate of incident diabetes in groups defined by hydroxychloroquine exposure and other patient characteristics. Diabetes was defined based on the SLICC/ACR Damage Index.

Results: The analysis was based on 1944 SLE patients. They were 93% female. They were 55% Caucasian, 37% African American, and 8% other ethnicity. At the start of follow-up there were 632 (33%) under 30 years of age, 803 (41%) between 30 and 44, 408 (21%) age 45–59, and 101(5%) 60 or older. The mean age was 37.5 years. The mean duration of follow-up per patient was 6.6 years. 682 (35%) were followed for less than 3 years, 413 (21%) were followed for 3–6 years, 258 (13%) were followed for 6–9 years, and 591 (30%) were followed for 9 or more years.

There were 59 incident cases of diabetes out of 12,802 person-years of follow-up (rate=4.6/1000).

Table 1 shows the rates of incident diabetes in subgroups defined by demographic and medication variables. The last column shows the rate ratios found after performing a multivariable regression adjusting for all other variables in the table. In the unadjusted analysis hydroxychloroquine appears protective (RR for >75% vs. <25%=0.5, p=0.012). After adjustment, there is still some evidence of a protective effect (RR=0.6, p=0.067).

Table 1. Rates of incident diabetes, by demographic and treatment variables

Subgroup	Events/ Person-yrs	Rate per 1000 Person-yrs	Rate Ratio (95% CI)	P-value	Adjusted Rate Ratio[3]	Adjusted p-value[3]
Everyone	59/12,802	4.6				
Age						
18–39	19/5920	3.2	1.0 (REF)	0.33	1.0 (REF)	0.44
40–49	15/3414	4.4	1.4 (0.7, 2.8)	0.085	1.3 (0.6, 2.8)	0.17
50–59	13/2236	5.8	1.9 (0.9, 3.9)	0.0037	1.8 (0.8, 4.0)	0.0012
60+	12/1232	9.7	3.0 (1.4, 6.3)		3.8 (1.7, 8.4)	
Sex						
Female	57/11,858	4.8	1.0 (REF)	0.26	0.2 (0.1, 1.8)	0.16
Male	2/948	2.1	0.5 (0.1, 1.8)			
Ethnicity						
White	23/6921	3.3	1.0 (REF)	0.18	1.0 (REF)	0.50
Black	33/5197	6.3	1.9 (1.1, 3.3)	0.67	1.2 (0.7, 2.2)	0.23
Other	3/688	4.4	1.3 (0.4, 4.3)		2.2 (0.6, 7.5)	
Year						
1987–92	10/849	11.8	1.0 (REF)	0.20	1.0 (REF)	0.89
1993–98	15/1881	8.0	0.6 (0.3, 1.3)	0.0042	0.9 (0.4, 2.5)	0.12
1998–04	14/3562	3.9	0.3 (0.1, 0.7)	0.0002	0.5 (0.2, 1.2)	0.035
2005–11	20/6513	3.1	0.2 (0.1, 0.5)		0.3 (0.1, 0.9)	
BMI						
<20	4/949	4.2	1.8 (0.6, 6.2)	0.30	1.8 (0.6, 6.1)	0.32
20–25	8/3565	2.2	1.0 (REF)	1.0 (REF)	1.0 (REF)	0.058
25–30	16/3148	5.1	2.3 (1.0, 5.3)	0.058	2.3 (1.0, 5.4)	0.0052
30+	25/3557	7.0	3.1 (1.4, 6.9)	0.0055	3.2 (1.4, 7.3)	
Hydroxy-chloroquine[1]						
<25%	27/3941	6.8	1.0 (REF)	0.24	1.0 (REF)	0.42
25–75%	9/2029	4.4	0.6 (0.3, 1.4)	0.012	0.7 (0.3, 1.6)	0.066
> 75%	23/6835	3.4	0.5 (0.3, 0.9)		0.6 (0.3, 1.0)	
Prednisone[2]						
<1mg/d	15/4264	3.5	1.0 (REF)	0.66	1.0 (REF)	0.89
1–7.5 mg/d	18/4372	4.1	0.9 (0.4, 1.7)	0.17	1.1 (0.5, 2.2)	0.28
7.5+ mg/d	26/4170	6.2	1.5 (0.8, 2.8)		1.5 (0.7, 2.9)	

[1]Refers to percentage of prior months of cohort follow-up in which hydroxychloroquine was prescribed.
[2] Refers to the mean daily dose of prednisone during prior months of cohort follow-up
[3] Adjusting for all variables in the table

Conclusion: In univariate analysis, hydroxychloroquine appears protective. However, after adjustment, while the estimated RR did not change, the result was no longer statistically significant (RR=0.6, p=0.066). This is likely due to the fact that there is a strong association between hydroxychloroquine and year (it is being used much more frequently in recent years) and also a strong relationship between year and incidence of diabetes. This results in a loss of power to detect an effect of hydroxychloroquine as the regression model is trying to tease out which of the two (hydroxychloroquine vs year) are the true predictors. Although the evidence is modest (p=.066), our data are consistent with previous findings of lower rates of diabetes among those who use hydroxychloroquine.

Disclosure: M. Petri, None; **L. S. Magder**, None.

1807

Do We Know How and When To Taper and Stop In Immunosuppressants In Lupus Patients? Zahi Touma, Murray B. Urowitz, Dominique Ibanez and Dafna Gladman. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: After achieving low disease activity or remission, immunosuppressant therapies might be stopped in lupus patients, but information on whether and how this should be done is scarce.

Our aim was to determine if tapering and withdrawing immunosuppressants in patients in remission is associated with flare.

Methods: Analysis on all patients seen in The Lupus Clinic from 1987–2012 was conducted: 1) patients in clinical remission (no activity in the clinical SLEDAI-2K descriptors and absence of proteinuria, thrombocytopenia and leukopenia), 2) ≥ 25% taper of the immunosuppressant and 3) prednisone ≤7.5mg/day.

Flare was defined as: 1) any increase in the dosage or introduction of new immunosuppressant or 2) start or any increase of prednisone dosage.

4 groups were identified (Figure 1):

A: Flare after tapering and while still on immunosuppressant.

B: No flare but still on tapering immunosuppressant dose at last visit.

C: Flare after stopping immunosuppressant.

D: No flare after stopping immunosuppressant to last clinic visit or at 2 years.

Success was defined as no flare at last clinic visit if still on immunosuppressant (B) or no flare within 2 years following stopping the immunosuppressant (D).

Results: Of the 1678 lupus patients registered, 204 tapering episodes in 179 patients were identified. 162 were female with age 39.0±13.3 and lupus duration 11.2±8.5 years at tapering.

Of the 204 tapering episodes 124 (61%) were successful (B and D). Immunosuppressant was stopped in 101 episodes (C and D) (table 1).

Group A and B did not reach the point of completely stopping immunosuppressant. 55 of these 103 (53.4%) flared. In group C and D 25 of 101 (24.7%) flared. In group C the time to flare was 1.7±1.0 years. In group D, all patients stopped immunosuppressant at 1.7±1.8 years and did not flare with a mean time from tapering to censoring of the data at 3.3±1.8 years (table 2).

Table 1. 204 tapering episodes

	AZA	MTX	MMF	P values
Number of patients	109	37	39	
Number of episodes N=204	123	42	39	
Flare (% episodes)	53 (43.1%)	17 (40.5%)	10 (25.6%)	X^2=0.15
Completely stopped immunosuppressants (episodes) N (C+D)=101	58 (47.2%)	25 (59.5%)	18 (46.2%)	X^2=0.34

Figure 1. Grouping of patients

Table 2. Mean time to event results (years)

Group	Time to stop event	Time to stop immunosuppressant	Time stop immunosuppressant to event
A n=55	1.5±1.2	N/A	N/A
B n=48	2.1±2.5	N/A	N/A
C n=25	1.7±1.0	0.9±0.9	0.8±0.5
D n=76	3.3±1.8	1.7±1.8	1.6±0.6

Conclusion: Our results suggest that successful tapering and discontinuation of immunosuppressants is possible in about 1/2 of clinically stable patients. In 1/4 a subsequent flare occurred. Future research may identify which patients are most likely to successfully discontinue immunosuppressants and define an appropriate algorithm for immunosuppressant tapering.

Disclosure: Z. Touma, None; **M. B. Urowitz**, None; **D. Ibanez**, None; **D. Gladman**, None.

1808

Impact Of Baseline Disease Severity and Treatments On Outcomes In Clinical Trials Of SLE: Results From The Soccit Program. Kenneth C. Kalunian[1], Mimi Kim[2], Timothy W. Behrens[3], Sabine Bongardt[4], Paul Brunetta[5], Paola Daly[6], Nathalie Franchimont[7], Richard Furie[8], Matthew Linnik[9], Bevra H. Hahn[10], Leslie M. Hanrahan[11], Jan L. Hillson[12], Jane Salmon[13], Neil Solomons[14] and Joan T. Merrill[15]. [1]UCSD School of Medicine, La Jolla, CA, [2]Albert Einstein College of Medicine, Bronx, NY, [3]Genentech, Inc, South San Francisco, CA, [4]UCB Pharma, Brussels, Belgium, [5]Genentech, So San Francisco, CA, [6]Lupus Foundation of America, Washington DC, DC, [7]Biogen Idec Inc., Weston, MA, [8]North Shore-LIJ Health System, Lake Success, NY, [9]Lilly Research Laboratories, La Jolla, CA, [10]UCLA David Geffen School of Medicine, Los Angeles, CA, [11]Lupus Foundation of America, Washington, DC, [12]Bristol-Myers Squibb, Seattle, WA, [13]Hospital for Special Surgery, New York, NY, [14]Vifor Pharma, New York, NY, [15]Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: The Lupus Foundation of America Collective Data Analysis Initiative was established to evaluate SLE clinical trial design, using data collected from multiple studies. To evaluate the impact of baseline disease characteristics and background treatments on trial endpoints, we evaluated the effects of baseline disease severity and background medications on flare rates in non-nephritis patients.

Methods: Data from 186 SLE patients receiving standard-of-care (SOC) but no investigational agents were compiled from 3 multicenter non-nephritis Phase 2 or 3 trials. A flare (referred to as "any flare") was defined as either >/= 1 new BILAG A or >/= 2 new B scores; a severe flare was defined as the occurrence of >/= 1 new BILAG A organ score since the previous visit. Treatments compared were: azathioprine, mycophenolate mofetil (MMF), methotrexate, and other including treatments such as antimalarials or low dose prednisone alone.

Results: Those with severe disease at baseline (at least one BILAG A) were more likely to experience any flare as well as a severe flare. At baseline, mean BILAG composite scores for MMF patients was 26.2 (SD 8.2) vs 22.1 (8.5) for all other patients (p=0.01). MMF-treated patients with severe disease at baseline had the highest rate of any flare and severe flare. Flare rates in other SOC groups did not differ when compared to each other (data not shown).

Table 1. Any Flare** Stratified by Baseline Disease Severity and Background Drug

Background drug	Baseline disease severity	Total person-years	Total number of any flares	Rate of any flare	P-value†
MMF	No BILAG A	11.7	12	1.03	reference
	At least one A	19.3	46	2.39	**0.01**
Other drugs	No BILAG A	48.3	44	0.91	reference
	At least one A	51.3	72	1.40	**0.02**

** Defined as >/= 1 new BILAG A **or**>/= 2 new B scores any new A or 2+ new Bs since last visit.
† By fitting a Poisson regression model to the total number of flares and the total person-years for each background drug group.

Table 2. Severe Flare* Stratified by Baseline Disease Severity and Background Drug:

Background drug	Baseline disease severity	Total person-years	Total number of severe flares	Rate of severe flare	P-value†
MMF	No BILAG A	11.7	4	0.34	reference
	At least one A	19.3	36	1.87	**0.0013**
Other drugs	No BILAG A	48.3	21	0.43	reference
	At least one A	51.3	59	1.15	**<0.0001**

* Defined as >/= 1 new BILAG A since last visit.

Conclusion: Previously, we reported MMF to be associated with increased response rates based on a BILAG assessment, which may have been confounded by increased protocolized steroid use in studies contributing the majority of MMF-treated patients. We now report that in non-nephritis trials, patients entered on MMF had greater baseline disease, suggesting that treatment with MMF might define a sicker subset of patients. Our new data further indicate a higher propensity for all flares and severe flares in those on MMF at baseline despite increased response rates after high steroid use, consistent with the hypothesis that those more ill patients who do not respond to protocol therapy, are more likely to flare than other patients. Trial results could be confounded, then, by inconsistencies between endpoints defining response and endpoints relying more heavily on flare.

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1809

Topline Results Of The Biomarkers Of Lupus Disease (BOLD) Study: Clinical and Mechanistic Perplexities Of Lupus Treatment Trials Can Be Mitigated By Eliminating Background Immune Suppressants. Joan T. Merrill[1], Frederick W. Immermann[2], Tianhui Zhou[3], Margot O'Toole[4], Maryann Whitley[5], Andrew A. Hill[5], Ying Zhang[5], David von Schack[5], Padmalatha S. Reddy[5], Jaime L. Masferrer[4], Stan Kamp[6], Joel M. Guthridge[1], Aikaterini Thanou[1], Paul Wu[5], Theresa Paradis[5], William M. Mounts[5], Judith A. James[1] and Sudhakar T. Sridharan[2]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Pfizer Inc, Collegeville, PA, [3]Bristol Myers Squibb, Princeton, NJ, [4]independent consultant, Cambridge, MA, [5]Pfizer Inc, Cambridge, MA, [6]Oklahoma Medical Research Foundation, Oklahoma CIty, OK.

Background/Purpose: The BOLD study was designed to test the discriminatory capacity and safety of a trial design eliminating background **immune suppressants (IS)** in SLE patients (pts) with active, non-organ threatening disease.

Methods: 103 active pts (SLEDAI >/= 6 and/or >/= 2 BILAG B or 1 A) were evaluated at ***baseline (BV)*** for effects of IS on immunologic variables, then 41 pts entered a prospective phase with depomedrol injections to improve disease, withdrawal of background IS, and serial biomarker samples until flare. Designation of ***improving visits (IV)*** and ***flare visits (FV)*** were weighted by clinical opinion and confirmed by BV vs IV: universal decreases in SLEDAI, BILAG, PGA, CLASI, and joint counts (all $p<0.0001$), IV vs FV: universal increases (all $p<0.0013$).

Results: The regimen was well tolerated. Of 48 adverse events only one was serious (bleeding ulcer) and resolved. 40/41 pts flared within 24 weeks. All flares improved within 6 weeks with treatment. **Median (95% CI) Days to flare (DTF) was 56 (40–76).** This was influenced by baseline disease activity and amount of steroid given. *BILAG >/= 17* **DTF 40** (29–72) vs *BILAG < 17* **DTF 71** (43–91) (log rank p= 0.043), *depomedrol </= 240mg + BILAG >/= 17* **DTF 38** (22–76) vs *depomedrol >/= 320mg + BILAG < 17* **DTF 91** (40–107). Baseline (withdrawn) IS had no impact on DTF. 47% of pts had elevated type I interferon signature (IFN HI) defined by a novel 11 gene panel we have reported (1). 38% of Caucasians were IFN HI vs 50% Asians, 69% Native Americans and 65% African Americans (Cauc vs others: p=0.012). IFN HI pts were more likely to have antibodies to dsDNA (p=0.001) SSA/Ro (p=0.0007) RNP (p=0.0001) and Sm (p=0.01), had higher circulating BLyS (p=0.00018) and IL23 (p=0.02) but not increased CR3 membrane expression. The table below illustrates potential differences between IFN HI and LOW pts in the impact of different IS on fold expression of non-IFN RNA [e.g. Increase **(INCR)** or Decrease **(DECR),** blank cells indicate no differences.

Mechanistic Impact of Background Treatments Commonly Allowed in Lupus Trials Evaluated By Underlying IFN Signature: Fold Increase or Decrease in RNA Expression

	All Pts (n=103) vs healthy controls		Pts on AZA vs Pts on no IS		Pts on MMF vs Pts on no IS		Pts on MTX vs Pts on no IS	
Gene product	IFN HI	IFN LOW	IFN HI	IFN LOW	IFN HI	IFN LOW	IFN HI	IFN LOW
BLyS/TNFSF13B (p value)	INCR 2.43 (0.0001)				INCR 1.36 (0.018)			
IL23A (p value)	DECR 1.29 (0.04)	DECR 1.24 (0.09)	INCR 1.57 (0.029)					
CR3/ITGAM (p value)			DECR 1.27 (0.04)			DECR 1.69 (0.006)		
LGALS3BP (p value)	INCR 2.93 (0.0001)						DECR 2.77 (0.0009)	
IgE Receptr (p value)	DECR 2.13 (0.0001)			INCR 1.95 (0.053)	INCR 2.28 (0.02)		INCR 2.20 (0.051)	INCR 3.43 (0.0008)

This exploratory, biomarker analysis was not corrected for multiple comparisons.

Conclusion: The BOLD treatment regimen is safe in pts without organ threatening disease and confirms the feasibility of an efficient trial design, ensuring low placebo response rates after brief baseline steroid intervention. This allows consideration of immediate rescue treatment at time of non-response without obfuscating the endpoint, and solves the problem of conventional trials requiring year-long stability of ineffective IS. Less background IS may also decrease infection risk. All outcome measures (BILAG, SLEDAI, PGA, CLASI) performed robustly in this simplified protocol, consistent with clinician-determined improvement and flare. With improved understanding of individual treatment effects on immune targets in key patient subsets, IS might be more strategically selected for studies of sicker pts and withdrawn entirely for stable pts, improving the discriminatory capacity of lupus trials while illuminating the optimal use of medications in clinic.

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ACR Concurrent Abstract Session
Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's - Clinical Aspects and Therapeutics II
Monday, October 28, 2013, 4:30 PM–6:00 PM

1810

Evaluation Of The New American College Of Rheumatology/European League Against Rheumatism Criteria For The Classification Of Systemic Sclerosis In The Canadian Scleroderma Research Group Cohort. Hebah Alhajeri[1], Marie Hudson[1], Marvin J. Fritzler[2], Janet E. Pope[3], Canadian Scleroderma Research Group -[4] and Murray Baron[4]. [1]McGill University, Montreal, QC, [2]University of Calgary, Calgary, AB, [3]St Joseph Health Care, London, ON, [4]Jewish General Hospital, Montreal, QC.

Background/Purpose: New classification criteria for systemic sclerosis (SSc) have recently been developed. In this study, we aimed to assess the sensitivity of this classification in the patients in the Canadian Scleroderma Research Group (CSRG) cohort.

Methods: SSc patients are included in the CSRG cohort if they have a diagnosis of SSc according to a rheumatologist. The 1980 Preliminary Classification Criteria for systemic sclerosis and the new ACR/EULAR classification criteria were applied. The sensitivity of each criterion in diagnosing SSc was calculated and compared across different socio-demographic and clinical categories.

Results: A total of 1115 SSc patients were included in the study. The majority were females (86%). Overall, the sensitivity of the new criteria was higher (98.4%) than that of the 1980 criteria (87.7%). This pattern was consistent among a number of sub-groups. The new criteria detected 691 (97.5%) of the limited SSc patients whereas the 1980 criteria detected only 572 (80.7%) of limited SSc patients. Both criteria detected 100% of patients with diffuse SSc. Ninety nine percent of anti-centromere (ACA) positive patients were detected by the new criteria, whereas the sensitivity of the 1980 criteria was 78.6% in this category. The sensitivities of new and 1980 criteria were 98.1% and 92.2% respectively in negative ACA category. In patients with disease duration ^{2} 3 years, the sensitivity of the new criteria was 98.8% whereas the sensitivity of 1980 criteria was 87.2%. In patients with disease duration > 3 years, the sensitivities of new and 1980 criteria were 98.3% and 87.9% respectively. When we compared the sensitivities according to age at disease onset, we found that the new criteria had a higher sensitivity than the 1980 criteria, 98.6% and 88.8% respectively, for age of onset of ^{2} 50 years and 98% and 85.8% respectively for age of onset > 50 years. The sensitivity of the new criteria were much higher than the 1980 criteria in the ACA positive and disease duration ^{2} 3 years group, 96.9% versus 67.7%, respectively. For patients with disease duration > 3 years and positive ACA, sensitivities were 99.3% versus 81.2% for new and 1980 criteria, respectively. In patients with negative ACA and disease duration ^{2} 3 years, the sensitivity of the new criteria was 99.4% while the sensitivity of 1980 criteria were 95%. Ninety eight percent of patients with negative ACA and disease duration > 3 years were detected using the new criteria, compared with 91.3% for the 1980 criteria in the same group.

Comparison of new ACR/EULAR and 1980 classification criteria for SSc

		New criteria		1980 criteria	
	N total	N	%	N	%
Entire cohort	1115	1097	98.4%	978	87.7%
Limited	709	691	97.5%	572	80.7%
Diffuse	405	405	100.0%	405	100.0%
Anti-centromere	359	355	98.9%	282	78.6%
Not anti-centromere	668	655	98.1%	616	92.2%
Disease duration ≤3 yrs	250	247	98.8%	218	87.2%
Disease duration > 3 yrs	862	847	98.3%	758	87.9%
Male	155	155	100.0%	147	94.8%
Female	960	942	98.1%	831	86.6%
Disease onset ≤ age 50	715	705	98.6%	635	88.8%
Disease onset > age 50	395	387	98.0%	339	85.8%
Anticentromere AND Disease duration ≤ 3 yrs	65	63	96.9%	44	67.7%
Anticentromere AND Disease duration > 3 yrs	293	291	99.3%	238	81.2%
(NOT anticentromere) AND Disease duration ≤ 3 yrs	159	158	99.4%	151	95.0%
(NOT anticentromere) AND Disease duration > 3 yrs	508	496	97.6%	464	91.3%

Conclusion: Overall, the new classification criteria for SSc are substantially more sensitive than the 1980 criteria. This applies to both sexes, recent or longstanding disease and either young or older subjects. The improvement in sensitivity is most striking, however, in limited SSc or in those with ACA and especially in those with recent onset ACA positive disease.

Disclosure: H. Alhajeri, None; **M. Hudson**, None; **M. J. Fritzler**, None; **J. E. Pope**, None; **C. S. R. G. -**, None; **M. Baron**, None.

1811

Validation Of The ICD-CM-9 Code For Systemic Sclerosis Using Updated ACR/EULAR Classification Criteria. Aaliya Yaqub[1], Lorinda Chung[2], David Fiorentino[3] and Eswar Krishnan[4]. [1]Stanford Univ Medical Center, Stanford, CA, [2]Stanford University Medical Center, Palo Alto, CA, [3]Stanford University School of Medicine, Redwood City, CA, [4]Stanford University, Palo Alto, CA.

Background/Purpose: Systemic sclerosis (SSc) is a rare autoimmune disease associated with substantial morbidity. Epidemiologic studies using large administrative databases often rely on the accuracy of International Classification of Diseases-Clinical Modification-9 (ICD-CM-9) codes for case definitions of medical conditions such as SSc. A previous study of 89 hospitalized patients at a

tertiary care center found that the accuracy of ICD-CM-9 code 710.1 for determining true cases of SSc that met the 1980 ACR criteria was 45%. We sought to determine the accuracy of the ICD-CM-9 code of 710.1 for identifying cases of SSc using a large outpatient cohort of well-characterized patients.

Methods: This was a retrospective analysis of the medical records of all patients evaluated at Stanford Hospital and Clinics from 2005–2012 who have an associated ICD-CM-9 code of 710.1. True cases of SSc were defined as any of the following: a) Fulfill the 1980 American College of Rheumatology (ACR) classification criteria for SSc; b) Have at least 3 of 5 of the CREST (calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, telangiectasias) features; OR c) Fulfill preliminary ACR/European League Against Rheumatism (EULAR) revised criteria for the classification of SSc.

Results: 432 patient records were reviewed. Mean age was 57±14.5 years, 84% were female, 51% Caucasian. 21% had diffuse cutaneous disease, 66% had limited disease, and 3% were characterized as SSc sine sclerosis. 238 (55%) patients met the 1980 ACR criteria, 292 (68%) patients met CREST criteria, and 297 (69%) patients met the revised ACR/EULAR criteria. The accuracy of ICD-9-CM code 710.1 for determining true cases of SSc by any of the three classification criteria was 77%. The ICD-CM-9 code for SSc was accurate 71% of the time when the 1980 ACR criteria were applied, and 75% of the time when the CREST or ACR/EULAR revised criteria were applied.

Table 1. Clinical Characteristics of 432 Systemic Sclerosis Patients by Criteria

Classification Criteria	Percentage of patients affected
1980 ACR Criteria:	
Major criterion:	
Proximal diffuse (truncal) sclerosis (skin tightness, thickening, non-pitting induration)	42%
Minor criteria:	
• Sclerodactyly (only fingers and/or toes)	63%
• Digital pitting scars or loss of substance of the digital finger pads (pulp loss)	25%
• Bilateral basilar pulmonary fibrosis	29%
Patients who met the major criterion or 2 minor criteria:	55%
CREST Criteria	
Calcinosis	12%
Raynaud's Phenomenon	82%
Esophageal dysmotility	60%
Sclerodactyly	63%
Telangiectasias	49%
Patients who met 3 of 5 CREST criteria:	68%
Revised ACR/EULAR Criteria	
Skin thickening of the fingers	
puffy fingers	25%
whole finger distal to MCP	47%
Fingertip lesions	
digital ulcers	28%
pitting scars	21%
Abnormal nailfold capillaries	33%
Pulmonary involvement	
Pulmonary hypertension	20%
Interstitial lung disease	29%
Autoantibody profile	
Positive ANA	62%
Positive scl-70 Ab	11%
Positive anti-centromere Ab	20%
Patients who scored ≥ 9 points in the revised ACR/EULAR criteria:	69%

*Raynaud's, telangiectasia percentages already noted above.

Conclusion: We found an acceptable accuracy rate of 77% for the ICD-CM-9 code 710.1 for determining true cases of SSc according to any of 3 different classification schemes. Our study supports the validity of this ICD-CM-9 code for identifying cases of SSc for epidemiologic studies using administrative databases.

Disclosure: A. Yaqub, None; **L. Chung**, None; **D. Fiorentino**, None; **E. Krishnan**, Takeda, 2, takeda, 5.

1812

Adverse Events In Connective Tissue Disease-Associated Pulmonary Arterial Hypertension Compared To Idiopathic Pulmonary Arterial Hypertension. Rennie L. Rhee[1], Nicole B. Gabler[1], Amy Praestgaard[1], Peter A Merkel[2] and Steven M. Kawut[1]. [1]University of Pennsylvania, Philadelphia, PA, [2]University of Pennsylvania and VA Medical Center, Philadelphia, PA.

Background/Purpose: Whether the risk of treatment-related adverse events (AEs) in patients with pulmonary arterial hypertension (PAH) differs based on diagnosis, either connective tissue disease (CTD-PAH) or idiopathic (IPAH), is unknown.

Methods: This study compared the occurrence of AEs and serious AEs (SAEs) among patients with CTD-PAH vs IPAH enrolled in clinical trials of new therapies for PAH. A pooled analysis was conducted using de-identified, patient-level data from 11 randomized double-blind placebo-controlled trials of therapies for PAH submitted to the US Food and Drug Administration. These trials ranged from 3–4 months in duration. Therapies studied included endothelin receptor antagonists (ERA), phosphodiesterase-5 inhibitors (PDE-5i), and prostacyclin analogues.

Results: The study sample included 2,581 participants: 562 with CTD-PAH, including 28% with diffuse systemic sclerosis, 26% with limited systemic sclerosis, 13% with systemic lupus erythematosus, and 11% with mixed connective tissue disease, and 1,426 patients had IPAH. Patients with CTD-PAH were older, more likely to be female, and had a shorter 6-minute walk distance at baseline (Table). Patients with CTD-PAH had a higher rate of AEs (13.6 [95% CI, 9.4 – 17.9] additional events per 100 patient-years, $p < 0.001$) and had a greater risk of having at least 1 SAE (OR 1.55 [95% CI 1.18 – 2.03], $p = 0.002$) compared to patients with IPAH, after adjustment for age, race, and sex, and treatment assignment (drug or placebo). A sub-analysis of AE types showed that patients with CTD-PAH were more likely to have an infection compared to patients with IPAH (OR 1.46 [1.06 – 2.01], $p = 0.020$). In ERA trials, diagnosis modified the relationship between treatment and the occurrence of at least 1 AE (p for interaction = 0.026, OR in CTD-PAH 0.55 [95% CI 0.25–1.22], OR in IPAH 1.54 [95% CI 0.92–2.59]). In PDE-5i trials, diagnosis modified the relationship between treatment and rate of AE (p for interaction = 0.005, IRR in CTD-PAH 0.76 [95% CI 0.69–0.87], IRR of IPAH 0.96 [95% CI 0.88–1.04]).

Table. Characteristics of Study Participants

	CTD-PAH (n = 562)	IPAH (n = 1,426)	p-value
Age, years	55 ± 14	48 ± 15	< 0.001
Female sex, No. (%)	492 (88)	1,061 (74)	< 0.001
Race, No (%)			
Whit	460 (83)	1,157 (82)	0.473
Black	38 (7)	64 (4)	0.035
Other	56 (10)	196 (14)	0.026
BMI, kg/m^2	26.1 ± 5.8	27.6 ± 6.2	< 0.001
World Health Organization functional class, No (%)			
I-II	226 (41)	583 (41)	0.897
III-IV	328 (59)	835 (59)	0.897
Baseline hemodynamics			
Right atrial pressure, mmHg	8.2 ± 5.2	9.3 ± 5.7	< 0.001
Pulmonary arterial pressure, mmHg	46 ± 12	56 ± 15	< 0.001
Cardiac output, L/min	4.2 ± 1.4	4.2 ± 1.4	0.447
Cardiac index, L/min/m^2	2.4 ± 0.8	2.3 ± 0.8	0.001
Pulmonary capillary wedge pressure, mmHg	9 ± 4	9 ± 4	0.483
Pulmonary vascular resistance, Woods units	9.9 ± 6.0	12.5 ± 7.1	< 0.001
Baseline 6-minute walk distance, meters	322 ± 85	343 ± 81	< 0.001

Data are presented as mean ± standard deviation unless otherwise indicated otherwise.

Conclusion: Patients with CTD-PAH are at a higher risk of experiencing AEs and SAEs in clinical trials of therapy for PAH compared to patients with IPAH, independent of age and other potential confounders. Patients with CTD-PAH may have had less drug-associated AEs. Understanding the difference in risks of AEs for this specific population may inform the design of future trials and bring greater awareness to patients and clinicians on the safety of therapy for PAH.

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1813

Evaluation Of The Effect Of Sildenafil On The Microvascular Blood Flow and On The Endothelial Progenitor Cells In Patients With Early Systemic Sclerosis: A Randomized, Double-Blind, Placebo-Controlled Study. Fernando V. Andrigueti, Pâmela C.C. Ebbing, Maria I. Arismendi and Cristiane Kayser. Universidade Federal de São Paulo, São Paulo, Brazil.

Background/Purpose: Phosphodiesterase-5 inhibitors have been successfully used for the treatment of Raynaud's phenomenon (RP) in patients with systemic sclerosis (SSc). However, no study has evaluated the effect of these drugs in patients with early disease as well as on the number of endothelial progenitor cells (EPC) in SSc. The present study aimed to evaluate the effects of oral Sildenafil on the digital microvascular blood flow by means of Laser Doppler Imaging (LDI), in clinical features of RP, and in serum EPC levels in women with early SSc.

Methods: A randomized double-blind placebo controlled trial was conducted. Forty-one patients with RP secondary to SSc with less than 4 years of diagnosis (ACR criteria or LeRoy's criteria for Early SSc), were randomly assigned to receive oral sildenafil 100mg/day (21 patients, mean age 47.2±10.9 years) or placebo (20 patients, mean age 41.6±13.3 years) for 8 weeks. Patients were evaluated at baseline (T0), after 8 weeks of treatment (T1), and 2 weeks after the end of the treatment (T2). The primary outcome was changes in finger blood flow (FBF) measured using LDI (Moor LDI-VR) before and for 30 minutes after cold stimulus (CS). FBF values were expressed in arbitrary perfusion units (PU). Secondary endpoints included serum levels of EPCs, frequency and duration of RP attacks, RP severity, and Raynaud's Condition Score. EPCs were quantified by flow cytometry and identified by the co-expression of CD34, CD133 and vascular endothelial growth factor receptor type 2 (VEGFR2). The trial was registered on ClinicalTrials.com under the identifier NCT01347008.

Results: Basal FBF were similar between sildenafil and placebo groups (213.1±87.9 versus 256.0±119.5 PU, respectively; p=0.20) as well as in the different time-points after CS at T0. There was a significant increased in basal FBF in sildenafil group (FBF 260.0±108.0 PU; p=0.02), with no significant difference in placebo group (FBF 261.4±137.0 PU; p=1.00) after 8 weeks. There was also a significant increase in FBF values after CS in sildenafil group after 8 weeks of treatment (p<0.05), with no change in the placebo group. EPCs serum levels were similar between sildenafil and placebo groups before treatment (161.0±103.7 versus 156.6±97.5/10^6 lymphomononuclear cells, respectively; p=0.89). There were no significant changes in EPCs levels after treatment in both groups. There was a significant improvement in the duration of RP in the sildenafil group, as well as on RP severity after 8 weeks of treatment (p=0.010, p=0.031; respectively). All parameters returned to their basal values at T2. There was no significant difference in any clinical parameter evaluated in the placebo group along the study.

Conclusion: Oral Sildenafil showed to improve digital blood flow and RP symptoms in early SSc after 8 weeks of treatment, and may be a good therapeutic option for RP treatment in these patients.

Disclosure: F. V. Andrigueti, None; **P. C. C. Ebbing**, None; **M. I. Arismendi**, None; **C. Kayser**, None.

1814

The Risk Of Pulmonary Embolism and Deep Venous Thrombosis In Systemic Sclerosis: A Population-Based Cohort Study. J. Antonio Avina-Zubieta[1], Iman Hemmati[2], Eric C. Sayre[3], Kamran Shojania[2] and Hyon K. Choi[3]. [1]Arthritis Research Centre of Canada, University of British Columbia, Richmond, BC, [2]University of British Columbia, Vancouver, BC, [3]Arthritis Research Centre of Canada, Richmond, BC.

Background/Purpose: Data on the risk of pulmonary embolism (PE) and deep venous thrombosis (DVT) in patients with systemic sclerosis (SSc) is lacking. To fill this knowledge gap, we estimated the risk of newly recorded PE and DVT among incident cases of SSc compared to controls from the general population using physician billing and hospitalization databases that cover the entire population of the province of British Columbia (~ 5 million).

Patients and Methods: Our data included all visits to health professionals and hospital admissions from Jan 1990 until Dec 2010 and all dispensed medication from Sept 1995 to Dec 2010 for all individuals ≥ 18 years of age. We conducted a matched cohort analysis among patients satisfying at least one of the following criteria: **a)** diagnosis of SSc on at least two visits within a two-year period between Jan 1996 and Dec 2010 by a non-rheumatologist physician; **b)** diagnosis of SSc on at least one visit by a rheumatologist or from a hospital. To increase specificity, we excluded cases that were not confirmed by a rheumatologist if they were seen at a later point. Ten controls matched by birth year, sex, and calendar year of follow-up were selected from the general population for each case. Our outcomes were newly recorded PE and DVT events from outpatient visits, hospital, or by death certificate. For nonfatal events, we required the use of anticoagulant medications within six-months of the PE and DVT events as part of our outcome definition. We estimated relative risks (RRs) comparing SSc with age-, sex- and entry time-matched comparison cohorts, adjusting for potential cardiovascular risk factors.

Results: Among 1,284 individuals with incident SSc (83% female, mean age of 57 yrs [SD 15.0]), 21, 17, and 35 developed PE, DVT or both, respectively (incidence rates= 4.4, 3.6, and 7.5 per 1000 person years, respectively) (**Table**). Compared with non-SSc individuals (N= 12,080), the age-, sex-, and entry-time-matched RRs for PE, DVT, or both were 4.2, 4.6, and 4.7 respectively ($P<0.05$ for all). The risks were greatest within the first year after disease onset and progressively attenuated with time for all outcomes. The RRs were also significantly larger among men. After further adjustment for baseline obesity, hormone replacement therapy, dyslipidemia, Cox-2 inhibitors, Charlson's comorbidity index, alcoholism/liver disease, hypertension, sepsis, varicose veins, inflammatory bowel disease, trauma, fractures, surgery, glucocorticoids, and oral contraceptives, the RRs remained similar (**Table**).

Table. Risk of Incident PE, DVT or DVT or PE according to SSc Status

	SSc n = 1,284	Non-SSc n = 12,840
Incidence Rate Ratios of PE		
PE events, N	21	61
Incidence Rate/1000 Person-Years	4.4	1.1
Age-,sex-, and entry time-matched RRs (95% CI)	4.2 (2.4 – 6.9)	1.0
< 1 year of disease duration	10.3 (3.4 – 31.5)	1.0
1–4.9 years of disease duration	3.4 (1.4 – 7.4)	1.0
5+ years of disease duration	2.6 (0.7 – 7.7)	1.0
Multivariable RR (95% CI)	4.0 (2.3 – 7.0)	1.0
Females	2.9 (1.4 – 5.8)	1.0
Males	8.8 (2.8 – 27.3)	1.0
Incidence Rate Ratios of DVT		
PE events, N	17	45
Incidence Rate/1000 Person-Years	3.6	0.8
Age-,sex-, and entry time-matched RRs (95% CI)	4.6 (2.5 – 8.2)	1.0
< 1 year of disease duration	9.2 (3.1 – 26.8)	1.0
1–4.9 years of disease duration	3.2 (1.1 – 8.2)	1.0
5+ years of disease duration	3.1 (0.6 – 11.2)	1.0
Multivariable RR	4.7 (2.5 – 8.5)	1.0
Females	4.9 (2.5 – 9.6)	1.0
Males	3.9 (0.9 – 16.3)	1.0
Incidence Rate Ratios of PE or DVT		
PE or DVT events, N	35	91
Incidence Rate/1000 Person-Years	7.5	1.6
Age-sex-entry time matched RRs (95% CI)	4.7 (3.1 – 7.0)	
< 1 year of disease duration	8.6 (3.9 – 18.5)	1.0
1–4.9 years of disease duration	4.1 (2.1 – 7.5)	1.0
5+ years of disease duration	2.9 (1.0 – 7.2)	1.0
Multivariable RR	4.3 (2.8 – 6.7)	1.0
Females	3.7 (2.3 – 6.1)	1.0
Males	8.5 (3.4 – 21.1)	1.0

Conclusion: This large population-based study is the first to demonstrate an increased risk of PE and DVT in patients with SSc, especially among men and within the first year of disease diagnosis. These findings support the need of increased monitoring of VTE complications and risk factors in those with SSc.

Disclosure: J. A. Avina-Zubieta, None; **I. Hemmati**, None; **E. C. Sayre**, None; **K. Shojania**, None; **H. K. Choi**, None.

1815

Asymmetric Dimethylarginine Levels In The Early Detection Of Systemic Sclerosis-Related Pulmonary Arterial Hypertension. Vivek Thakkar[1], Wendy Stevens[1], David Prior[1], Joanne Sahhar[2], Janet E. Roddy[3], Jane Zochling[4], Peter Nash[5], Peter Youssef[6], Susanna Proudman[7] and Mandana Nikpour[8]. [1]St Vincent's Hospital, Melbourne, Australia, [2]Monash Medical Centre, Clayton, Australia, [3]Royal Perth Hospital, Perth, Australia, [4]Menzies Research Institute Tasmania, Hobart, Australia, [5]Nambour Hospital, Sunshine Coast, Australia, [6]Royal Prince Alfred Hospital, Sydney, Australia, [7]Royal Adelaide Hospital, Adelaide, Australia, [8]University of Melbourne, Fitzroy, Australia.

Background/Purpose: Pulmonary arterial hypertension (PAH) is a major cause of mortality in systemic sclerosis (SSc), and alterations in nitric oxide (NO) metabolism and endothelial cell function are implicated in the pathogenesis of SSc-PAH. Asymmetric dimethlyarginine (ADMA) is a novel biomarker of endothelial cell dysfunction. In this study, the clinical utility of ADMA as a screening biomarker for incident SSc-PAH was evaluated.

Methods: ADMA levels were measured in 15 consecutive treatment-naive subjects with newly-diagnosed SSc-PAH, and compared with 30 SSc-controls without PAH. ADMA levels were assayed using high performance liquid chromatography with solid phase extraction. N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were measured in the same subjects. Logistic regression models were used to evaluate the independent association of ADMA with PAH. Important correlations of ADMA were assessed using Spearman's rank correlation coefficient (rho). The optimal cut-points of ADMA and NT-proBNP that maximised desired test properties for screening were determined.

Results: The PAH group had significantly higher mean ADMA levels than the control group (0.76 ± 0.14 μM versus 0.59 ± 0.07 μM; $p < 0.0001$). ADMA levels remained significantly associated with PAH after the adjustment for specific disease characteristics, cardiovascular risk factors and other SSc-related vascular complications (all $p < 0.01$). An ADMA level ≥ 0.694 μM had a sensitivity of 86.7%, specificity of 90.0% and AUC of 0.86 for diagnosing PAH. An NT-proBNP level ≥ 209.8ng/mL had a sensitivity of 93.3%, specificity of 100% and AUC of 0.94 for diagnosing PAH. A 'purely' biomarker based screening model that combined an NT-proBNP ≥ 209.8ng/mL and/or ADMA ≥ 0.694 ng/mL resulted in a sensitivity of 100% and specificity of 90% for the detection of SSc-PAH.

Conclusion: ADMA may be an important screening biomarker for SSc-PAH. A composite 'purely' biomarker-based screening algorithm, using NT-proBNP in combination with ADMA, may achieve an excellent sensitivity (and also specificity) for the non-invasive identification of SSc-PAH.

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ARHP Concurrent Abstract Session
Rehabilitation Sciences
Monday, October 28, 2013, 4:30 PM–6:00 PM

1816

Exercise Therapy Reduces Pain Sensitivity In Patients With Knee Osteoarthritis: A Randomized Controlled Trial. Marius Henriksen[1], Louise Klokker[1], Thomas Graven-Nielsen[2], Cecilie Bartholdy[1], Tanja Schjoedt Joergensen[3], Elisabeth Bandak[1], Bente Danneskiold-Samsøe[4], Robin Christensen[4] and Henning Bliddal[1]. [1]The Parker Institute, Copenhagen University Hospital at Frederiksberg, Copenhagen F, Denmark, [2]Aalborg University, Aalborg, Denmark, [3]The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen F, Denmark, [4]The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, Frederiksberg, Denmark.

Background/Purpose: Exercise has beneficial effects on pain in patients with knee osteoarthritis (OA), yet the underlying analgesic mechanisms are ambiguous. A deeper understanding of the analgesic mechanisms of exercises in knee OA is imperative to optimize the exercise paradigm in clinical management of OA. The purpose of this study was to investigate the effects of a 12 week therapeutic exercise program on pressure pain sensitivity in patients with knee OA.

Methods: This was a randomized trial with blinded outcome assessors (NCT01545258). Participants were randomly assigned (1:1) to 12 weeks of facility-based neuromuscular exercise therapy (ET), 3 sessions per week supervised by trained physical therapists, or a no attention control group (CG). To assess pressure pain sensitivity, we used cuff pressure algometry, with an inflatable tourniquet cuff mounted on the calf of the most symptomatic leg. The co-primary outcomes were pressure pain thresholds (PPT unit: kPa) and temporal summation (TS) of pressure pain. TS was assessed by continuous recordings of pain (100 mm electronic visual analog scale (VAS)) during sustained (6 minutes) noxious pressure stimulation at PPT+25%. TS was quantified as the area under the time-VAS curve (unit: mm*s). Higher PPT and lower TS, respectively, represent less pressure pain sensitivity. Secondary outcomes included patient reported pain using the KOOS questionnaire, with higher scores representing less pain. According to the protocol, the analyses were based on the 'Per-Protocol' population (defined as participants following the protocol). Analysis of covariance adjusting for the level at baseline was used to determine differences between groups (95% confidence intervals) in the changes from baseline at week 13.

Results: 60 participants were randomized to ET (n= 31) or CG (n=29). In the ET group, six participants were lost to follow-up; in the CG five were lost and one violated the protocol (exercise outside study). Thus per protocol population included 48 participants (25 ET/23 CG). At baseline, the average PPTs were; ET: 18.1 kPa (SD 6.1), and CG: 19.1 kPa (6.8). At follow-up the PPT increased in the ET group by 1.94 kPa corresponding to a group difference in the change from baseline of 3.06 kPa (95% CI: 0.17 to 5.95; P=0.04) favoring ET. Accordingly, the ET group was stimulated at higher pressure levels in the sustained noxious pressure experiment at follow-up. The TS decreased in the ET group by 1,641 mm*s, giving a group differences in TS change of 2,608 mm*s (95%CI: 458 to 4,758; P= 0.019) favoring ET. After 12 weeks exercise, there was a statistically significant difference between groups in regard to KOOS pain of 6.8 points (95% CI 1.2 to 12.4; P= 0.0179) in favor of ET (corresponding to an effect size of 0.71).

Conclusion: A 12-week supervised neuromuscular exercise program reduces the pressure pain sensitivity, seen as a higher PPT and lower TS at follow-up in the ET group, in adjunct to a clinically relevant effect on pain estimated by KOOS. These results indicate that neuromuscular exercise therapy has beneficial effects on basic pain mechanisms, and further exploration of this effect may provide basis for optimized treatment.

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1817

The Clinical Burden Of Generalized Osteoarthritis Represented By Activity Limitations and Health Related Quality Of Life: A Cross-Sectional Study. Nienke Cuperus[1], Thea Vliet Vlieland[2], Elien Mahler[1], Clarinda Kersten[1], Thomas Hoogeboom[3] and Els van den Ende[1]. [1]Sint Maartenskliniek, Nijmegen, Netherlands, [2]University Medical Center Leiden, Leiden, Netherlands, [3]CAPHRI school for public health and primary care, CCTR centre for Care Technology Research, Maastricht University, Maastricht, Netherlands.

Background/Purpose: A growing body of evidence shows that generalized osteoarthritis (GOA) is fairly common, however research and clinical practice recommendations are mainly focused on a specific localization of osteoarthritis (OA). As a consequence the clinical burden of GOA is largely unknown. More insight into the clinical burden of GOA is needed in order to improve its management and to develop treatment tailored to the patients' needs and problems. Therefore the aim of this study was to determine the clinical burden of GOA in terms of activity limitations and health related quality of life (HRQoL).

Methods: Baseline data from a randomized controlled trial (RCT) comparing two non-pharmacological treatment programmes for patients with GOA were used. GOA was defined as having musculoskeletal complaints in >2 joint groups and having >1 objective signs of OA in >1 joint. In addition, patients had to be limited in performing daily activities (HAQ-DI score > 0.5). Patients clinically diagnosed with GOA by a rheumatologist and referred to multidisciplinary treatment completed self-reported questionnaires to assess socio-demographics, joint involvement (self-report and objective), activity limitations (HAQ-DI) and HRQoL (SF-36 physical (PCS) and mental

component summary (MCS) norm based scores). Patients were asked to report the three most important activity limitations due to GOA and to rate its severity on a visual analogue scale. Reported activity limitations were linked to the International Classification of Functioning, Disability and Health (ICF) using established linking rules.

Results: In total, 147 patients (85% female) participated in this study with a mean (SD) age of 60 (8) years. Hundred-fifteen patients (78%) reported musculoskeletal complaints in ≥ 4 joint areas. Self-reported and objective signs of OA were most common in the hands (n = 125; 85%) and knees (n = 121; 82%). Patients with GOA were moderately to severely limited in performing daily activities reflected by a mean (SD) HAQ-DI score of 1.27 (0.50). "Much difficulty" with activities such as shopping or doing chores were reported by more than half of the patients. Patients with GOA experience a markedly reduced HRQoL on the physical domain reflected by a mean (SD) PCS score of 32 (8), which is comparable with the impact of Rheumatoid Arthritis on HRQoL. Activities concerning mobility and domestic life were most frequently reported as being important activity limitations, in particular walking (Table 1).

Table 1. The ten most frequently reported, self-perceived activity problems with corresponding ICF codes and corresponding mean (SD) severity scores in 147 patients with Generalized Osteoarthritis (GOA).

ICF code	Activity	N (%)	Mean (SD) severity (0–10)
d450	Walking	71 (48)	6.7 (2.1)
d415	Maintaining a body position	46 (31)	6.4 (2.4)
d410	Changing basic body position	41 (28)	7.1 (1.8)
d640	Doing housework	35 (24)	6.9 (1.7)
d455	Moving around (climbing stairs)	35 (24)	6.5 (2.0)
d430	Lifting and carrying objects	30 (20)	6.1 (2.0)
d440	Fine hand use	25 (17)	6.5 (2.0)
d650	Caring for household objects	24 (16)	7.3 (1.7)
d920	Recreation and leisure	22 (15)	6.1 (2.2)
d475	Driving	20 (14)	6.2 (2.9)

Conclusion: The results of this study suggest a high clinical burden at least in selected patients with GOA in terms of activity limitations and HRQoL. According to the results it is conceivable that non-pharmacological treatment targets for patients with GOA may focus especially on the physical domain of HRQoL and on mobility limitations (walking in particular) as these activities are the most important for patients.

Disclosure: N. Cuperus, None; **T. Vliet Vlieland**, None; **E. Mahler**, None; **C. Kersten**, None; **T. Hoogeboom**, None; **E. van den Ende**, None.

1818

Automated Telephone-Linked Communication: A Novel Approach To Enhance Long-Term Adherence To Resistance Training Exercise Among People With Knee Osteoarthritis. Kristin Baker[1], Aileen Ledingham[1], Michael P. Lavalley[2], Julie J. Keysor[1] and David T. Felson[3]. [1]Boston University Sargent College, Boston, MA, [2]Boston University, Boston, MA, [3]University of Manchester, Manchester, United Kingdom.

Background/Purpose: Knee Osteoarthritis (OA) is one of the most common chronic musculoskeletal conditions and is a leading cause of disability. Strengthening exercise is well known to improve pain and physical function, but benefits decline as adherence to exercise ceases. Participation drops precipitously when trainer initiated instruction and social support for exercise are withdrawn. We have developed a dynamic automated telephone calling system, Boston Osteoarthritis Strengthening telephone linked-communication (BOOST TLC), to empower and motivate people with knee OA to adhere to strengthening exercise after participating in a class.

TLC is an automated, interactive conversation system that speaks with a recorded human voice. During the conversation the system asks questions, comments on the users' responses and educates and counsels them. TLC stores the users' answers in a database used to direct current and future TLC conversations. The system is run by a scheduling protocol with the ability to receive and make calls. The purpose of this abstract is to describe 1) the content of the BOOST TLC system we developed, and 2) the methods of an ongoing randomized controlled clinical trial to examine long-term exercise adherence.

Methods: We designed the BOOST TLC to 1) assess adherence to strengthening exercise in the previous 2 weeks 2) provide feedback on current adherence vs. the goals previously set in the last call 3) negotiate and set new adherence goals 4) provide education and counseling to improve adherence.

The BOOST TLC education and counseling content is derived from social cognitive theory, in which self-efficacy is a central concept, and decision-making theory, an individual's evaluation of the pros and cons of exercise. The system addresses reasons for low self-efficacy and ways to increase it, and provides education on the benefits of strengthening exercise and overcoming common barriers to exercise. In addition the BOOST TLC system utilizes the users' self-reported exercise adherence information to detect and provide special counseling to those that lapse (>3 weeks of no exercise), providing information on behavioral and cognitive strategies to help users recover from a lapse and prevent future lapses.

Subjects (N=100) with painful knee OA will be recruited from the community, participate in a 6-week strengthening class twice a week, randomized to BOOST TLC or control, and followed for 2 years. The BOOST TLC will receive biweekly calls for 6 months and monthly calls for the remaining 18 months. Data includes self-report questionnaires on pain and physical function, timed physical function tasks and isokinetic muscle strength.

Results: To date, 62 subjects are enrolled. Table 1 describes the study population.

Baseline demographics (n=62)

Gender N (%)	
Male	9 (15)
Female	53 (85)
Race and Ethnicity N (%)	
White	38 (61)
Black	16 (26)
Hispanic	1 (2)
Asian	3 (5)
Mix	1 (2)
Other	1 (2)
Refused	2 (3)
Age (years)	66.7 (7.6)
BMI	30.7 (6.4)
Worst WOMAC pain (0–20)	7.2 (3.4)
WOMAC physical function (0–68)	20.0 (9.9)
Observed physical function	
Timed up and go (seconds)	8.1 (1.8)
Stair climb (seconds)	16.0 (7.1)
Comorbidities N (%)	
Heart disease	7 (11%)
Chronic respiratory conditions	7 (11%)
Diabetes	9 (14%)

Conclusion: TLC is a low-cost approach for continued exercise instruction and counseling that has the potential to improve exercise adherence in people with knee OA.

Disclosure: K. Baker, None; **A. Ledingham**, None; **M. P. Lavalley**, Sunovion Pharmaceutical Company, 5, Associate Editor, 6; **J. J. Keysor**, None; **D. T. Felson**, None.

1819

Effectiveness Of Pilates Method For The Treatment Of Chronic Mechanical Neck PAIN. Luciana A. Cazotti[1], Anamaria Jones[1], Diego Roger Silva[1], Luiza H. C. Ribeiro[1] and Jamil Natour[2]. [1]Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [2]Universidade Federal de São Paulo, São Paulo, Brazil.

Background/Purpose: The neck pain comes from multifactorial origin and affects approximately 70% of individuals at some point in their lives being considered a frequent problem of disability. Pilates is a method of physical conditioning that has been widely used to improve posture and develop body sense. Although the symptoms of neck pain are common in the population, no study has investigated the effects of the Pilates method as a possible treatment for neck pain. The aim of this study is to assess the effectiveness of the Pilates method on pain, function and quality of life in patients with chronic mechanical neck pain.

Methods: Sixty-four patients with diagnosis of chronic mechanical neck pain for more than three months were selected to this study. Patients with symptoms of pain in the cervical spine, between the occipital and the first thoracic vertebra, both genres, age between 18 and 65 years were included. Patients with fibromyalgia, previous traumatic lesions in the spine, infections

and inflammation in the spine, cervical pain radiating to upper limbs, patients that practice of physical activity started or altered in the last 3 months, visual deficiency not corrected by glasses, diseases of the central nervous system were excluded. The patients were randomized into two groups: Pilates and control. The Pilates group (PG) realizes the drug treatment and two sessions per week of Pilates for twelve weeks. The control group (CG) realizes the drug treatment and remained on the waiting list for Pilates. Regarding drug treatment both groups were instructed to use 750mg acetaminophen every 6 hours if there is pain. Both groups were assessed for pain (VAS), function (Neck Disability Index - NDI), quality of life (SF-36), acetaminophen consumption. The evaluations were made by a blinded assessor at baseline (T0), 45 days (T45), 90 days (T90) and 180 days (T180) after baseline.

Results: Thirty-two patients were randomized to each group. The groups were homogeneous at baseline with respect to demographic and clinical characteristics, only the Body Mass Index (BMI) was not homogeneous among the groups (p = 0,023), with the GP showing higher BMI than the CG. The analysis between groups over time (ANOVA) show a statistical difference for pain (p <0,001), function (p <0,001) and quality of life [physical functioning (p = 0.019), pain (p <0,001), general health (p = 0,022), vitality (p <0.001), mental health (p = 0,012)] always with best results for the GP. Regarding medication GP consumed less analgesic than the CG (p = 0,037).

Conclusion: we conclude that the Pilates method is effective for the treatment of chronic mechanical neck pain for relive pain; improve function and quality of life and reduce analgesic consumption.

Disclosure: L. A. Cazotti, None; **A. Jones**, None; **D. R. Silva**, None; **L. H. C. Ribeiro**, None; **J. Natour**, None.

1820

Assessing 24-Hour Physical (In)Activity and Sleep In People With Early Rheumatoid Arthritis. Christopher Feehan[1], Eric C. Sayre[2], Erin Carruthers[2] and Lynne M. Feehan[3]. [1]University of British Columbia, Vancouver, BC, [2]Arthritis Research Centre of Canada, Richmond, BC, [3]Arthritis Research Centre of Canada and University of British Columbia, Vancouver, BC.

Background/Purpose: For people with inflammatory arthritis, the health benefits of physical activity (PA) and negative impact of sedentary lifestyle are clear. However, it is unclear how daily physical (in)activity and sleep may be affected in people with early rheumatoid arthritis (RA) (1). The purpose of this study was to examine measures of daily PA and sleep in people with early RA, compared to age and gender matched peers.

Methods: We recruited 30 adults diagnosed with RA in the past year and 30 age and gender matched healthy volunteers. Physical activity and sleep were measured with SenseWear Mini™ (SW) accelerometers worn over the triceps of the dominant arm for 6 days. We fit a multivariate analysis of variance model with RA status as the independent variable and a dependent variable of minutes spent in 8 categories [night - sleep; day - off body, sedentary (< 1.6), light [1.6, 3), 3, 4, 5 and ≥ 6 MET activities] across 24-hours. Overall difference (Multivariate Wilks' Lambda F-test) and post hoc differences (F-tests / Least Square Mean) in sleep and PA intensity were examined. Differences in four PA behaviours [Bouted (≥10 minutes) Moderate to Vigorous PA (MVPA, ≥ 3 METs), Intensity of Bouted MVPA, Bouted (≥ 20 minutes) Sedentary time and Overall Sleep (night + day)] were also examined with paired Student T-tests.

Results: Average age 53 y (21–73 y). Females - 24 of 30 / group**.** 3 RA / NRA pairs excluded [non-adherence (n=2), mechanical failure (n=1)]. Mean SW wear time 5.8 d (SD: 0.02) RA Participants: 73% RF or anti-CCP positive. Time since diagnosis 8 m (SD: 5). Health Assessment Questionnaire [Disability Index: Mean 0.6 (SD: 0.6), Pain VAS_{100}: Mean 21 (SD: 16)]; Tender & Swollen Joints: Mean 3 (SD: 3). Sleep and PA Intensity Comparisons (Table 1): People with early RA had a significantly different (p = 0.03) overall pattern of nighttime sleep and daytime physical (in)activity. The primary differences were significantly fewer minutes of higher PA intensity (≥ 4 METs, Mean Diff: 37m, P < 0.03), as well as a tendency for more nighttime sleep (Mean Diff: 17m, p = 0.26) and more daytime sedentary (Mean Diff: 37m, p=0.33) and light physical activity (Mean Diff: 15m, p = 0.39). PA Behavior Comparisons (Table 1): RA participants spent significantly less time in bouted MVPA (Mean Diff: −65m, p = 0.01) at a lower intensity (Mean METs: RA 3.5 vs. NRA 4.1, p = 0.01). RA participants also accumulated significantly more overall sleep (Mean Diff: 29m, p = 0.02).

Table 1. Summary of Average Daily Sleep and Physical Activity (PA) Intensity and Selected PA Behaviours in People Living With and Without Rheumatoid Arthritis (RA).

Sleep and PA Intensity Comparison: (n=54, 27 Pairs)

Post hoc Component Examined	RA [LS Mean (95% CI)]	Non-RA [LS Mean (95% CI)]	P value
Nighttime Sleep (Min)	454 (432, 476)	437 (415, 459)	0.27
Off-body Time (Min)	29 (18, 39)	28 (17, 38)	0.91
Sedentary (< 1.6) METs (Min)	642 (588, 695)	605 (551, 659)	0.33
Light PA [1.6, 3) METs (Min)	207 (183, 231)	192 (168, 216)	0.39
3 METs (Min)	78 (49, 107)	111 (82, 140)	0.11
4 METs (Min)	25 (14, 35)	47 (37, 58)	0.004
5 METs (Min)	4 (0.2, 8)	13 (9, 17)	0.002
6+ METs (Min)	2 (−2, 5)	8 (4, 11)	0.02

Selected PA Behaviour Comparison: (n=54, 27 Pairs)

PA Behaviour Examined	RA [Mean (SEM)]	Non-RA [Mean (SEM)]	*Difference (RA–Non-RA) [Mean (SEM)]	P value
Bouted (≥ 10 min) MVPA (Min)	72 (19)	137 (18)	−65 (25)	0.01
Average Intensity of MVPA (METs)	3.5 (0.2)	4.1 (0.1)	−0.6 (0.2)	0.01
Bouted (≥ 20 min) Sedentary (Min)	393 (32)	359 (29)	33 (42)	0.43
Overall (Night + Day) Sleep (Min)	482 (10)	453 (11)	29 (12)	0.02

*Negative value indicates RA less than Non-RA.

Conclusion: People living with recently diagnosed RA have markedly different patterns of sleep and physical (in)activity than age and gender matched healthy peers. These findings suggest that people living with early RA would benefit from education and support to enhance physical activity related health behaviours.

Reference:

1: Tierney et al. (2012) Physical activity in rheumatoid arthritis: a systematic review. J Phys Act Health.

Disclosure: C. Feehan, None; **E. C. Sayre**, None; **E. Carruthers**, None; **L. M. Feehan**, None.

1821

Benefits Of Progressive Muscle Strengthening Using a Swiss Ball In Patients With Ankylosing Spondylitis: A Randomized Controlled Trial. Marcelo Souza[1], Fabio Jennings[1], Hisa Morimoto[1] and Jamil Natour[2]. [1]Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [2]Universidade Federal de São Paulo, São Paulo, Brazil.

Background/Purpose: Ankylosing spondylitis (AS) is a systemic inflammatory disease that affects the physical capacity of patients globally. Exercises are recommended to the management of patients with AS, although the benefits of specific exercise programs are not yet well defined.

Objective: To evaluate the effectiveness of a progressive muscle strengthening program using a Swiss ball in improving functional capacity, muscle strength, disease activity, mobility and quality of life of patients with AS.

Methods: Sixty patients were randomized to intervention group (IG) or to control group (CG), with 30 patients in each group. Eight exercises were done by GI with free weights on a Swiss ball, 2 times per week for 16 weeks. Loads were reassessed and increased every 4 weeks. The GC continued drug therapy without any exercise, on a waiting list. The evaluations were performed by a blinded evaluator immediately before randomization and at 4, 8, 12 and 16 weeks after initiation of the study. Functional capacity were evaluated using the BASFI (Bath Ankylosing Spondylitis Functional The Index), HAQ-S (Health Assessment Questionnaire for Spondyloarthropathies), the 6-minute walk test and the Time Up and Go test. Muscle strength was assessed by the 1-repetition maximum (1 RM) test. Disease activity was measured by BASDAI (The Bath Ankylosing Spondylitis Disease Activity Index) and by dosage of ESR and C-reactive protein. The BASMI (The Bath Ankylosing Spondylitis Metrologyl Index) was used to assess spinal mobility and the SF-36 questionnaire to assess quality of life. Patients were also evaluated by Likert scale for satisfaction. In addition, the amount of analgesic and non-steroidal anti-inflammatory used was controlled.

Results: The groups were homogeneous at baseline for clinical and demographic characteristics. There was a statistically significant difference between the two groups in the improvement of strength in IG compared to the CG for the muscles used in the exercises: abdominal (p =

0.003), unilateral stroke ($p = 0.02$), squat ($p = 0.01$), triceps ($p = 0.021$) and reverse crucifix ($p = 0.02$). The IG also improved the 6-minute walk test ($p = 0.005$) at week 16 compared with the CG. We also found a statistically significant difference between groups in the Likert scale at all times ($p < 0.001$) with IG showing greater treatment satisfaction. We found no differences between groups in other variables and there was no worsening of disease activity in IG.

Conclusion: The progressive muscle strengthening using a Swiss ball is effective in improving muscle strength and walking performance in patients with AS. The exercise program has shown good tolerance assessed by patient satisfaction without deleterious effects on disease activity.

Disclosure: M. Souza, None; **F. Jennings**, None; **H. Morimoto**, None; **J. Natour**, None.

1822

Oleanolic Acid Acetate Inhibits Osteoclast Differentiation By Downregulating Phospholipase Cγ^2–calcium ion oscillation-Nuclear Factor Of Activated T Cell c1 Signaling, and Suppresses Bone Loss In Mice. Chang-Hoon Lee[1], Myeung Su Lee[1], Won Seok Lee[2], Wan-Hee Yoo[2], Ju-Young Kim[3], Jae-Min Oh[3] and Yong-Geun Jeong[4]. [1]Department of Internal Medicine, School of Medicine, Wonkwang University, Iksan, Chonbuk, South Korea, [2]Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, [3]Department of Anatomy, School of Medicine, Wonkwang University, Iksan, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, Changwon Fatima Hospital, Changwon, South Korea.

Background/Purpose: we first isolated oleanolic acid acetate (OAA), a triterpenoid compound, from *Vigna angularis*(azuki bean) to discover anti-bone resorptive agents. Many studies have identified and described the various medicinal effects of *V. angularis*extract, but the pharmacological effect is not known. Therefore, we investigated the effect and mechanism of OAA in receptor activator of nuclear factor-kB ligand (RANKL)-induced osteoclast differentiation and bone resorption.

Methods: *V. angularis* was obtained from an herbal medicine store (Jeonbuk, Korea). The plant material (10 kg) was dried, ground to a fine powder, and extracted with 95% ethanol at 70°C. The extracts were filtered through a 0.45-mm filter and concentrated under reduced pressure to yield the ethanol extracts, which were further extracted with ethyl acetate. we treated primary BMMs with various concentrations of OAA in the presence of RANKL and M-CSF. Expression of c-Fos, NFATc1, TRAP and OSCAR were determined by RT-PCR and Western blot analysis. we used a retrovirus to overexpress NFATc1 and the CA form of NFATc1 (CA-NFATc1) in BMMs and examined the effect of OAA on the MAPKs and Ca^{2+} responses in the presence of RANKL. To investigate whether OAA affects bone-resorbing activity, mature osteoclasts were cultured on hydroxyapatite-coated plates. Finally, We investigated the *in vivo* effects of OAA with an experimental animal model of bone erosion. Mice were intraperitoneally injected with LPS with or without OAA. The mice were sacrificed 8 days after the first LPS injection, and the left femurs underwent micro-CT analyses.

Results: Interestingly, OAA significantly inhibited phospholipase Cγ2 (PLCg2) phosphorylation, calcium ion (Ca^{2+}) oscillation, and nuclear factor of activated T cell c1 (NFATc1) expression in RANKL-stimulated BMMs, but did not affect RANKL-induced mitogen-activated protein kinase. OAA also inhibited the bone-resorbing activity of mature osteoclasts. Furthermore, mice treated with OAA demonstrated marked attenuation of lipopolysaccharide-induced bone erosion based on micro-computed tomography and histologic analysis of femurs.

Conclusion: Taken together, the results suggested that OAA inhibited RANKL-mediated osteoclastogenesis via PLCg2–Ca^{2+}-NFATc1 signaling *in vitro* and suppressed inflammatory bone loss *in vivo*.

Disclosure: C. H. Lee, None; **M. S. Lee**, None; **W. S. Lee**, None; **W. H. Yoo**, None; **J. Y. Kim**, None; **J. M. Oh**, None; **Y. G. Jeong**, None.

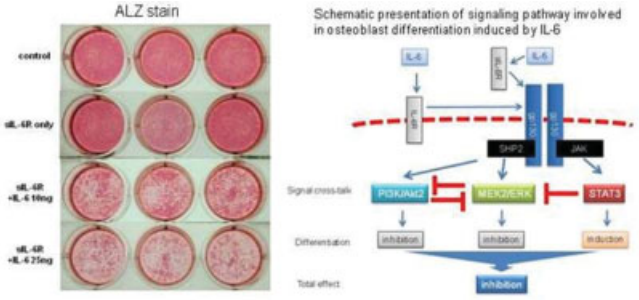
1823

IL-6 Suppresses Osteoblast Differentiation Through The SHP2/MEK2 and SHP2/Akt2 Pathways *In Vitro*. Shoichi Kaneshiro[1], Kosuke Ebina[1], Kenrin Shi[1], Chikahisa Higuchi[1], Hideki Yoshikawa[1], Jun Hashimoto[2] and Makoto Hirao[3]. [1]Osaka University Graduate School of Medicine, Suita, Japan, [2]Osaka-Minami Medical Center, Kawachinagano City, Japan, [3]Osaka Minami Medical Center, Osaka, Japan.

Background/Purpose: Interleukin-6 (IL-6), a potent inflammatory cytokine, plays a key role in the pathogenesis of rheumatoid arthritis (RA), including osteoporosis not only in inflamed joints but possibly also in whole body. Since increase of bone formation markers is recognized in RA patients treated with tocilizumab, a humanized anti- IL-6 receptor antibody, IL-6 could be thought to have negative effect on osteoblast differentiation. However, previous reports regarding the effects of IL-6 on osteoblast differentiation *in vitro* are not consistent. IL-6 activates two major intracellular signaling pathways, SHP2/MEK/ERK and JAK/STAT3, and can also lead to the activation of additional signaling cascade involving PI3K/Akt. The purpose of this study was to clarify the effect of IL-6 on osteoblast differentiation *in vitro*, with consideration of intracellular signaling pathways. Cross-talk between these pathways was also investigated.

Methods: Osteoblast differentiation was induced in murine MC3T3-E1 osteoblastic cells and primary calvarial osteoblasts with or without addition of IL-6 (soluble IL-6 receptor was used to enhance the effect of IL-6). Osteoblast differentiation was assessed by alkaline phosphatase (ALP) activity, mineralization and expression of osteoblastic gene. We examined which signaling pathways were activated by IL-6 and their effects on the differentiation were assessed by using each specific inhibitor and each knockdown.

Results: IL-6 significantly reduced ALP activity, mineralization and expression of osteoblastic gene, in a dose-dependent manner, which indicates a negative effect of IL-6 on osteoblast differentiation. Signal transduction study demonstrated that IL-6 activated not only two major signaling pathways, SHP2/MEK/ERK and JAK/STAT3, but also SHP2/PI3K/Akt2 signaling pathway. The negative effect of IL-6 on osteoblast differentiation was restored by inhibition of MEK as well as PI3K, while it was enhanced by inhibition of STAT3. Knockdown of MEK2 and Akt2 transfected with siRNA enhanced ALP activity and gene expression of Runx2. These results indicate that IL-6 negatively regulates osteoblast differentiation through SHP2/MEK2/ERK and SHP2/PI3K/Akt2 pathways, while it effects positively through JAK/STAT3. Moreover, STAT3 inhibitor enhanced IL-6-induced phosphorylation of ERK. MEK inhibitor enhanced IL-6-induced phosphorylation of Akt. PI3K/Akt inhibitor enhanced IL-6-induced phosphorylation of ERK. IL-6-induced ERK and Akt signaling pathways, both of which are downstream of SHP2, could negatively regulate each other reciprocally.



Conclusion: IL-6 could negatively regulate osteoblast differentiation through SHP2/MEK2/ERK and SHP2/PI3K/Akt2 pathways, while it effects positively through JAK/STAT3. Inhibition of MEK2 and Akt2 signaling in osteoblasts might be of potential use in the treatment of osteoporosis in RA.

Disclosure: S. Kaneshiro, None; **K. Ebina**, None; **K. Shi**, None; **C. Higuchi**, None; **H. Yoshikawa**, None; **J. Hashimoto**, None; **M. Hirao**, None.

1824

ONO-4059 - A Novel Small Molecule Dual Inhibitor Of Bruton's Tyrosine Kinase (Btk) and Tec Kinase- Suppresses Osteoclastic Bone Resorption and Inflammation. Yuko Ariza, Toshio Yoshizawa, Yoshiko Ueda, Shingo Hotta, Tomoko Yasuhiro, Masami Narita, Yutaka Shichino and Kazuhito Kawabata. Ono Pharmaceutical Co., Ltd., Osaka, Japan.

Background/Purpose: Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by leukocyte infiltration, synoviocyte hyperplasia and osteoclastogenesis, leading to erosion of the joints and cartilage, which results in stiffness, pain and swelling, making it difficult to perform daily activities. Osteoclasts are responsible for bone erosion in RA and both Bruton's tyrosine kinase (Btk) and Tec kinase have essential functions in osteoclast differentiation. ONO-4059 is a highly potent and dual oral Btk/Tec inhibitor with an IC_{50} in the sub-nmol/L range. Previous studies with ONO-4059 demonstrated that ONO-4059 significantly inhibits the macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor-κB ligand (RANKL)-driven osteoclast defferentiation. The treatment with ONO-4059 also resulted in a dose-dependent inhibition of arthritis severity and bone damage in a mouse collagen induced arthritis (CIA) model (ACR 2012). To assess the effects of ONO-4059 on bone resorption, we examined the RANKL-induced bone loss *in vivo*. In addition, the regulation of proinflammatory cytokines and MMPs in the joints of arthritic mice validating qRT-PCR was performed in another CIA model.

Methods: Female C57BL/6 mice were injected intraperitoneally with 1 mg/kg of sRANKL on days 0, 1 and 2. ONO-4059 was administered orally, twice a day in three groups of animals, at doses of 3 mg/kg, 10 mg/kg and 30 mg/kg 1 hr before the every sRANKL injection. After the last sRANKL injection, all of the mice were sacrificed and underwent peripheral quantitative computed tomograghy (pQCT) analysis. To further characterize the effect of ONO-4059 in a RANKL-induced model, the serum bone resorption markers were measured by ELISA. Gene expression profiles were determined by qPCR using samples taken from the ankle in CIA model.

Results: The injection of sRANKL resulted in a decrease in trabecular bone volume with the increase of serum TRACP5β and CTX-1. Treatment with ONO-4059 resulted in a dose-dependent suppressioin of RANKL-induced bone loss with the inhibition of TRACP5β and CTX-1. The inhibition rate of Bone Mineral Density (BMD) of ONO-4059-treated animals was 55% ($P<0.05$), 87% ($P<0.001$) and 88% ($P<0.001$) for the 3, 10 and 30 mg/kg dose groups respectively. In CIA model, MIP-1α, IL-1β, KC, IL-6, RANKL and MMP-3 production in joints of arthritic mice, as measured by determining relative arthritic/sham ratios, was significantly higher (from 5 to 20 fold), while the 3 mg/kg dose of ONO-4059 almost completely inhibited such production.

Conclusion: Btk and Tec are required for osteoclast differentiation and activation based on the genetic evidence obtained from Btk and Tec double deficient mice. Dual Btk/Tec inhibitor, ONO-4059 may be a novel therapeutic target for RA to suppress bone erosion and inflammation.

Disclosure: Y. Ariza, None; **T. Yoshizawa**, None; **Y. Ueda**, None; **S. Hotta**, None; **T. Yasuhiro**, None; **M. Narita**, None; **Y. Shichino**, None; **K. Kawabata**, None.

1825

Osteoclast Progenitors, Fibroblast-Like Cells and Draining Lymph Node Cells Induce Catecholaminergic-To-Cholinergic Transition Of Sympathetic Nerve Fibers Under Healthy Conditions But Not In Highly Inflamed Arthritic Tissue. Hubert Stangl[1], Dominique Muschter[2], Susanne Graessel[2] and Rainer H. Straub[1]. [1]Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, University Hospital of Regensburg, Regensburg, Germany, [2]Division of Experimental Orthopedic Surgery, University Hospital of Regensburg, Regensburg, Germany.

Background/Purpose: Sympathetic nerve fibers innervate bone and tissue adjacent to joints. They play an important role in bone and tissue homeostasis. Under certain conditions, sympathetic nerve fibers can change their phenotype from catecholaminergic to cholinergic (see innervation of sweat gland and periosteum). This can be important because anti-inflammatory effects of acetylcholine have been described which is mainly mediated by the α7nicotinic acetylcholine receptor. We asked whether this transition could also occur in the joint during collagen-induced arthritis (CIA) in mice or during rheumatoid arthritis (RA) and osteoarthritis (OA) in humans.

Methods: Arthritic limbs from 30 immunized C57Bl/6J mice were collected at distinct time points covering all stages of the disease. Sections of mouse limbs and synovial tissue samples obtained from 30 OA and 12 RA patients were stained for tyrosine hydroxylase (TH, noradrenergic fibers), and for vesicular acetylcholine transporter (VAChT, cholinergic fibers). For co-culture experiments, sympathetic ganglia were obtained from newborn mice and double-stained for TH and VAChT after a co-culture period of two to three days with osteoclast progenitors attained from the femoral and tibial bonemarrow as well as lymphocytes obtained from the draining lymph nodes and fibroblast-like cells isolated from the paws of adult mice.

Results: In mouse joint area, an increase in the ratio of cholinergic to catecholaminergic nerve fibers appeared at day 35 after immunization. Most of the nerve fibers were located in joint-adjacent skin or muscle tissue, and only very few were detected in synovial tissue or near erosions. In human tissue sections, we were able to show cholinergic fibers in the synovial tissue of four OA patients but in none of the RA patients. Co-cultures of sympathetic ganglia and osteoclast progenitors as well as lymphocytes and fibroblast-like cells obtained from healthy mice showed more catecholaminergic-to-cholinergic transition when compared to experiments with the respective cells from arthritic mice.

Conclusion: In men and mice, catecholaminergic-to-cholinergic transition is possible in less inflamed tissue of the joint but not in highly inflamed arthritic tissue.

Disclosure: H. Stangl, None; **D. Muschter**, None; **S. Graessel**, None; **R. H. Straub**, None.

1826

Immune Complex Formation By Adalimumab Contributes Significantly To Its Inhibitory Effect On TNF-Enhanced Human Osteoclast Development Even In The Absence Of Fc Receptor Binding. Bohdan P. Harvey and Zehra Kaymakcalan. AbbVie Bioresearch Center, Worcester, MA.

Background/Purpose: TNF-alpha (TNFa) has been shown to contribute to osteoclastogenesis independently and in conjunction with M-CSF or RANKL, two key cytokines involved in osteoclast development. Both TNFa and RANKL have been concomitantly detected in the synovial fluid of RA patients. We have previously demonstrated that TNF enhances the kinetics of RANKL-induced human osteoclastogenesis and that its effects are mitigated more effectively by the anti-TNF biologic adalimumab as compared to etanercept. Based on these findings, we sought to determine the mechanism that was responsible for this difference and to identify the TNF-receptor that is predominantly involved in TNF-enhanced osteoclastogenesis.

Methods: Primary human osteoclast precursors (OCP) were exposed to various combinations of M-CSF, RANKL and TNFa (100 ng/mL) +/− increasing equimolar concentrations of adalimumab (ADA) [whole, F(ab′)2 or Fab], etanercept (ETN) [whole or Fc-deficient (pepsin digested) molecule] or certolizumab pegol (CZP) for up to 6 days. Prior to adding to the cells, the biologics were pre-incubated with the TNFa for 30 min. To artificially generate large immune complexes (IC), polyclonal anti-human IgG Fc-specific F(ab′)2 antibody (20 μg/mL) was added to the preformed TNF:biologic complexes. To determine contribution of individual TNF receptors to TNF-mediated osteoclast development, OCP were treated with 50 μg/mL anti-human TNF-RI or -RII blocking antibodies prior to the addition of TNF. Osteoclast differentiation was determined by the presence of large multinucleated cells positive for tartrate-resistant acid phosphatase (TRAP) and by TRAP5b activity. Resorptive activity was assessed by measuring the release of cross-linked C-telopeptide of type I collagen (CTX-I) from human bone.

Results: Each of the biologics as whole molecule was able to reduce TNF-enhanced osteoclast development; however, both CZP and ADA were more effective at lower concentrations as compared to ETN (9.6, 14.4 and >130 nM, respectively). The F(ab')2 of ADA inhibited osteoclast activity to the same level as the whole IgG demonstrating that the Fc domain was not contributing to the inhibitory effects of the biologic. Following the cross-linking of the biologics with anti-human IgG to generate artificially large IC, the inhibitory effect of ADA improved two-fold, whereas etanercept suppressed osteoclast development to levels comparable to non-cross-linked ADA, suggesting that IC formation by ADA contributes to its ability to block TNF-enhanced osteoclastogenesis. As to which receptor mediates the effect of TNF on human OCP, blocking TNF-RI curtailed TNF-dependent development demonstrating that the effective anti-TNF biologics are restricting TNF access to TNF-RI.

Conclusion: The mechanistic feature that distinguishes ADA from ETN in its ability to more effectively inhibit TNF-enhanced osteoclastogenesis is its TNF binding mode. Surprisingly, the Fc domain of ADA does not contribute to its suppressive function. Overall, our results may provide a mechanistic explanation for the sustained potency of adalimumab in preventing bone erosion due to chronic TNF exposure.

Disclosure: B. P. Harvey, AbbVie Inc, 3; **Z. Kaymakcalan**, AbbVie Inc., 3.

1827

The Intraarticular Injection Of An Inhibitor Of Complex V Of Mitochondrial Respiratory Chain Induces a Pathological Response In Rat Knee Joints. Carlos Vaamonde-García[1], Jesus Loureiro[1], Eduardo López-Peláez[2], Alberto Centeno-Cortés[2], Romina R. Riveiro-Naveira[1], M. Noa Valcárcel-Ares[1], Francisco J. Blanco[3] and Maria J. López-Armada[1]. [1]Aging and Inflammation Research Lab, INIBIC-CHU A Coruña, A Coruña, Spain, [2]Experimental Surgery Unit, CHU A Coruña, A Coruña, Spain, [3]Osteoarticular and Aging Res. Lab. CIBER-BBN. INIBIC- University of A Coruña, A Coruña, Spain.

Background/Purpose: A decline of mitochondrial function has been described in OA chondrocytes and RA synoviocytes. Recent ex vivo findings support a connection between mitochondrial dysfunction and activation of inflammatory and destructive pathways in these cells. The aim of this study was to investigate in an in vivo articular model if the intraarticular injection of oligomycin, an inhibitor of mitochondrial function, induces a destructive and inflammatory response in rat knee joints.

Methods: 24 female wistar rats (180–220g) were divided into three study groups: Healthy (no intraarticular injection); Lipopolysaccharide (LPS)-

treated, positive control (left joint injected with: LPS 10mg and right joint with vehicle); and Oligomycin (OLI)-treated (left joint injected with Oligomycin 20mg and right joint with vehicle). Three intraarticular injections were carried out at 0, 2 and 5 days. Rats were sacrificed at day 6, hind paws were collected and joint tissues were obtained. Measurement of joint diameters on stimulis- and control-injected paws was performed at days 0 and 6. Histopathologic lesions were evaluated by hematoxilyn-eosin (H&E) and masson trichromic stain sections in synovial tissue and by safranin O staining in cartilage. ROS production by dihydroethidium (DHE) staining was evaluated. By RT-PCR, CINC-1, IL-1**b**, CCL-2 and TNF-**a** gene expression was analyzed in extracted cartilage. And by immunohistochemical staining, IL-8, equivalent of CINC-1, expression was localized in the joint tissue.

Results: OLI-treated hind paws significantly increased the joint diameter (0.9 ± 0.1 mm, $n=8$, $p<0.05$, vs vehicle-injected joints), similarly to LPS-treated (2 ± 0.3 mm, $n=8$, $p<0.05$, vs vehicle-injected joints). In relation, histological evaluation of synovial tissue by H&E staining revealed that joints treated with mitochondrial inhibitor present greater synovial lining hyperplasia, proliferation of subsynovial tissue and infiltration of a marked number of inflammatory cells while the right control synovial only contained a moderate synovial proliferation and inflammation (3.3 ± 0.1 vs. 2.1 ± 0.2, respectively, $n=8$, $p<0.001$, vs vehicle-injected joints). Besides, a higher increment in ROS production was detected in synovial tissue from OLI-injected knees than observed in vehicle-injected counterparts. Immunohistochemical studies on IL-8 also showed a greater expression in synovial tissue from OLI-injected joints versus those from vehicle-injected joints, coinciding with a strong neutrophils infiltration. In relation to cartilage, when the loss of matrix in this tissue by safranin O staining was evaluated no differences were observed. We also failed to detect modulations in IL-8 immunoperoxidase staining in cartilage. By contrast, when CINC-1 mRNA expression was analyzed in this tissue, a significant increment in OLI-injected joints was detected ($n=8$, $p<0.05$ vs. vehicle-injected joint), similar to those LPS-treated.

Conclusion: The data seems to support that a loss of mitochondrial function in the joint could participate in rheumatoid pathology through generating an inflammatory response in the articular tissue, contributing to the perpetuation of joint injury.

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1828

In Vivo Cartilage-Specific Deletion Of Ephrin-B2 In Mice Results In Developmental Locomotory Defects Associated With Hip Bone Abnormality. Gladys Valverde-Franco[1], Bertrand Lussier[2], David Hum[1], Jiangping Wu[3], Jean-Pierre Pelletier[1], Mohit Kapoor[1] and Johanne Martel-Pelletier[1]. [1]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [2]Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Montreal, Saint-Hyacinthe, QC, [3]Laboratory of Immunology, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC.

Background/Purpose: The ephrins and their related receptors comprise the largest subfamily of receptor protein-tyrosine kinases and have been implicated in mediating developmental events. We have previously demonstrated that a member of the ephrin family, ephrin-B2, plays a role in knee joint pathology associated with osteoarthritis (OA). Specifically, we have shown a deregulation in the production of the receptor EphB4 and its specific ligand ephrin-B2 in human subchondral bone and cartilage, and in vitro activation of this system or in vivo overexpression of EphB4 positively impacts the pathological process of OA. The aim of this study was to comprehensively delineate the in vivo role of ephrin-B2 in musculoskeletal growth and development using cartilage-specific ephrin-B2 knockout mice.

Methods: Cartilage-specific ephrin-B2 knockout (ephrin-B2KO^{CRE}) mice were generated using the LoxP-Cre system. The effect of ephrin-B2 genetic deletion was evaluated on bone development using a combination of techniques including macroscopic, histologic, morphometric, radiological, densitometer, and micro-computed tomography (micro-CT). Analyses were performed on postnatal days 0, 15, and 21 (P0, P15, P21), on 8-week-old cartilage-specific ephrin-B2KO^{CRE}mice, and in littermates with no Cre as controls.

Results: Data showed that the ephrin-B2KO^{CRE} mice exhibited developmental defects leading to abnormal locomotory patterns. Ephrin-B2KO^{CRE} mice at P15 exhibited reduced weight ($p<0.002$) and length ($p<0.01$) and, most importantly, limping and dragging of limbs apparent from the time they started to walk (about 2–3 weeks of age). Interestingly, the hip of ephrin-B2KO^{CRE} mice displayed abnormalities associated with smaller pelvic width ($p<0.03$) and hip bones ($p<0.01$), as well as reduced acetabular rim length ($p<0.05$) and angle ($p<0.05$). In addition, ephrin-B2KO^{CRE} mice had significantly smaller femur ($p<0.03$) and tibia length ($p<0.01$) and reduced bone mineral density in the total skeleton ($p<0.02$), femur ($p<0.03$) and spine ($p<0.04$). Micro-CT analyses revealed that the distal femur and proximal tibia in ephrin-B2KO^{CRE}mice had a significantly decreased bone volume/tissue volume (BV/TV; $p<0.03$, $p<0.02$), trabecular thickness (TbTh; $p<0.02$, $p<0.02$), and trabecular separation (TbS; $p<0.03$, $p<0.05$).

Conclusion: This study was the first to show that in vivo ephrin-B2 is essential for normal bone growth and development and that conditional cartilage-specific ephrin-B2 deficiency leads to significant alterations in hip bones resulting in developmental locomotory defects. The changes in the long bones are probably a secondary effect of the hip loading force abnormalities.

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1829

Carboxypeptidase B2 Down-Regulates Osteoclast Activation In Inflammation. Jason Jungsik Song[1], Sang-Won Lee[1], Yong-Beom Park[1], Soo Kon Lee[1], Lawrence Leung[2] and William H. Robinson[2]. [1]Yonsei University College of Medicine, Seoul, South Korea, [2]Stanford University School of Medicine, Stanford, CA.

Background/Purpose: Carboxypeptidase B2 (CPB2) is well established to play an anti-fibrinolytic role by removing C-terminal lysine residues from fibrin, thereby preventing its cleavage by plasmin. CPB2 also removes arginine/lysine residues from other proinflammatory substrates such as C5a, and SDF-1a. Previously we demonstrated that CPB2 plays a major role to down regulate synovial inflammation in collagen induced arthritis by down-regulating C5a (Song et al, 2011 JCI). However, its mechanism to prevent bone erosion in RA is unknown. We investigate the molecular mechanism how CPB2 prevents bone erosion.

Methods: LPS induced osteoclast (OC) activation model was performed by injection of LPS on *cpb2*$^{-/-}$ and *cpb2*$^{+/+}$ mice. On day 8, femur was collected for microCT and histology. OC precursor (OCP) population in bone marrow was evaluated by FACS. OC differentiation was evaluated by TRAP staining on OCP ex vivo culture. OCP migration was measured by transwell migration assay with C5a and SDF-1a with or without CPB2 treatment. C5a receptor expression in bone marrow was measured by FACS.

Results: As compared to wild-type (WT) mice, CPB2 deficient mice exhibited significantly more severe osteoclast activation measured by microCT after LPS injection (bone volume/total volume *cpb2*$^{-/-}$ 4.3 ± 0.3 vs *cpb2*$^{+/+}$ 7.7 ± 0.3, $p< 0.01$). There is increased OCP population in bone marrow of *cpb2*$^{-/-}$ mice (Gr1 low, CD11b high population; *cpb2*$^{-/-}$ 40% vs *cpb2*$^{+/+}$ 25.2%). There are more TRAP positive multinuclear cells from bone marrow of *cpb2*$^{-/-}$ mice as compared to *cpb2*$^{+/+}$ mice (130.6 ± 4.2 vs 107.3 ± 3.5, $p<0.01$). OCP chemotaxis was decreased by CPB treatment on C5a and SDF-1a. C5a receptor expression is increased in CPB2 deficient mice.

Conclusion: These results suggest that CPB2 plays a critical role in osteoclast migration and activation in inflammation and that this effect could be in part mediated by its down-regulation of C5a and SDF-1a. CPB2 deficient mice demonstrate more osteoclast activation in response to LPS challenge. We also demonstrated that SDF-1a, a known chemotactic factor for OCP, is a novel substrate of CPB2. Studies are underway to investigate the role of CPB2 on osteoclast activation in human rheumatoid arthritis.

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1830

Adenosine A_{2A} Receptor (A2AR) Diminishes Wear Particle (UHMWPE)-Mediated Osteolysis, Increases Bone Formation and Regulates Expression Of Axonal Guidance Proteins (AGP) By Macrophages, Osteoclasts (OC) and Osteoblasts (OB). Aranzazu Mediero[1], Tuere Wilder[1], Miguel Perez-Aso[2] and Bruce N. Cronstein[3]. [1]NYU School of Medicine, New York, NY, [2]New York University School of Medicine, New York, NY, [3]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Communication between OC and OB is critical for maintenance of bone homeostasis; both OC and OB release regulatory

messengers. Among these signaling molecules are semaphorin 3A and 4D (sema3A and sema4D). During inflammatory osteolysis bone destruction is regulated by RANKL, M-CSF, TNF, among others. A2AR ligation diminishes osteolysis and expression of RANKL, M-CSF and TNF. We therefore asked whether A2AR activation modulates OB-OC crosstalk by regulating sema3A and sema4D or their receptors PlexinA1/Neuropilin1 and PlexinB1, respectively, in a model of inflammatory osteolysis.

Methods: 1cm midline sagittal incisions were made over calvaria in 6–8 wk old C57Bl/6 mice. Calvaria were exposed to 20μl of PBS containing 3mg of UHMWPE followed by daily injections of either vehicle or CGS21680 (A2AR agonist) 1μM (n=4 each) for 14 days. XenoLight Rediject Bone Probe was injected IV and fluorescence of calvaria measured (IVIS) to assay bone formation. Sema3A/PlexinA1/Neuropilin1 and Sema4D/PlexinB1 expression were studied by RT-PCR and Western Blot in primary bone marrow-derived OC and OB in the presence/absence of CGS21680 and ZM241385 (A2AR antagonist) 1μM each.

Results: XenoLight imaging revealed a 52.5±6% reduction in bone formation after exposure to UHMWPE ($p<0.001$, n=5) and CGS21680 completely reversed this effect (11±5% increased compare to control, p=NS, n=5). In UHMWPE-exposed calvaria there was a decreased number of cells expressing Sema3A and PlexinA1 but not Neuropilin1, effects largely reversed by CGS21680. In contrast, Sema4D/PlexinB1 expressing cells, primarily macrophages and OC, were increased in UHMWPE-exposed calvaria and CGS21680 reversed these changes as well. In marrow cell cultures RANKL induced a 2.5±0.1 fold increase in Sema4D mRNA ($p<0.001$,n=4) which was blocked by CGS21680 ($p<0.001$,n=4). In contrast, PlexinA1 mRNA was enhanced by CGS21680 (9.3±0.7 fold increase vs 4.9±0.6 for RANKL, $p<0.001$,n=4) but Neuropilin1 mRNA was unchanged. Sema3A mRNA increased 3.5±0.5 fold during OB differentiation and CGS21680 enhanced this to 8.7±0.2 fold, $p<0.001$,n=3); PlexinB1 mRNA was increased 2 fold during OB differentiation and was not altered by CGS21680 exposure. Similar changes were observed in protein expression and secretion.

Conclusion: UHMWPE-induced inflammatory osteolysis involves both bone destruction and reduction of new bone formation. $A_{2A}R$ stimulation diminishes secretion of inflammatory mediators and also regulates expression of AGP that likely contribute to inflammatory osteolysis and reduction in bone production.

Disclosure: A. Mediero, Filed a patent on use of adenosine A2AR agonists to prevent prosthesis loosening (pending)., 9; **T. Wilder**, None; **M. Perez-Aso**, None; **B. N. Cronstein**, Canfite Pharma, 1, NIH, Gilead, Takeda, AstraZeneca, 2, NYU School of Medicine, 3, Merck-SeronoBristol-Myers Squibb, Novartis, CanFite Biopharmaceuticals, Cypress Laboratories, Regeneron (Westat, DSMB), Endocyte, Protalex, Allos, Inc., Savient, Gismo Therapeutics, Antares Pharmaceutical, Medivector, 5, Multiple patents on adenosine receptors and bone metabolism, pharmacology, 9.

1831

Study Of Serum Levels Of Osteocalcin (s-OC) On Patients With Diffuse Idiopathic Skeletal Hyperostosis (DISH) and Ankylosing Spondilitis (AS). Mariela Geneva-Popova[1], Stojan Andreev[2], Pavel Pavlov[1], Daniel Ilev[1] and Stanislava Popova[1]. [1]Medical University, Plovdiv, Plovdiv, Bulgaria, [2]MHAT Tokuda, Sofia, Bulgaria.

Background/Purpose: Osteocalcin (bone Gla protein), one of the basic markers for bone matabolism, has not been thoroughly studied on patients with DISH and AS. It is a specific product of the osteoblasts, in bones it connects with hydroxyapatite and in the presence of calcium it plays the role of a promoter of the accumulation of calcium in the bone matrix. That's how osteocalcin takes part in the regulation of bone ossification.

The aim of the study is to estimate the serum levels of osteocalcin on patients with DISH and AS.

Methods: s-OC is estimated on 55 patients with DISH, 25 patients with AS, 50 patients with spondylosis and 15 particularly healthy people aged 55–65, 10 particularly healthy people aged 20–25. The measuring of the s-OC is done by ELISA „sandwitch" method, with a kit of eBioscience, Austria. The statistic processing is done with SPSS 19 programme ($p<0.001$).

Results: The average measurements of s-OC of patients with DISH and AS are higher in comparison with the results of patients with spondylosis and healthy people, regardless of their age ($p<0.05$) (table 1).

Table 1. Results of average measurements of s-OC of patients with DISH, spondylosis, AS, young and old controlled in ng/ml

	Number of patients			
Disease	**Min**	**Max**	**Referent measurments**	
DISH	55	6.37 ± 0.619	0.80	23.90
Spondylitis	50	1.19 ± 0.024	0.70	1.90
AS	23	7.27 ± 1.80	0.40	41.50
Young people	10	1.22 ± 0.236	0.50	3.20
Old control group	15	1.78 ± 0.226	1.20	3.60

Conclusion: s-OC is significantly increased on patients with DISH and AS in comparison with the results of patients with spondylosis and healthy people, but it is really hard to explain the reason why at the present moment. Hypothetically, this might be a result as a sequence of events, based on which is damage of the spinal cord (stimulation of inflammatory proteins, on-going osteoporosis, compresion fractures, hyperinsulinemia which is a result from metabolic disorders, etc.), the endurance of the vertebrae is decreased and the body increases the production of osteocalcin from the osteoblasts to form compensatory more bone substance. That's how the organism adapts to the new changes.

Measuring the levels of serum osteocalcin can be used for early diagnose of DISH due to a difference between the serum levels on patients with DISH and spondylosis, with which differential diagnose is mostly done.

Disclosure: M. Geneva-Popova, None; **S. Andreev**, None; **P. Pavlov**, None; **D. Ilev**, None; **S. Popova**, None.

1832

Discovery of MicroRNAs in the Regulation of Inflammation and Bone Erosion in Rheumatoid Arthritis. Ellen M. Gravallese[1], Yukiko Maeda[1], Nicholas Farina[2], Paul Fanning[3] and Jane Lian[2]. [1]University of Massachusetts Medical School, Worcester, MA, [2]University of Vermont College of Medicine, Burlington, VT, [3]University of Massachusetts Medical School, worcester, MA.

Background/Purpose: Focal articular bone erosion in rheumatoid arthritis (RA) is mediated by osteoclasts and repair of erosion by osteoblasts is uncommon, despite the use of potent anti-inflammatory therapies. TNF treatment of primary calvarial osteoblasts from Wnt reporter (Top-gal) mice suppresses Wnt signaling activity in these cells, altering a pathway critical for osteoblast differentiation and function. Additional mechanisms inhibiting bone formation likely contribute to the persistence of articular erosion in this disease. We have shown in an animal model of RA that in the setting of resolving inflammation, repair of articular bone erosion can occur, accompanied by alterations in expression of components of the Wnt signaling pathway. MicroRNAs (miRNAs) are important regulators of skeletal remodeling and several miRNAs, including miR-23b and miR-155, have been shown to play a role in RA pathogenesis. Since miRNAs can regulate both inflammation and bone remodeling, we hypothesized that they might play a regulatory role in bone erosion in RA.

Methods: To address the potential role of miRNAs in these pathogenic events, we used a modification of the serum transfer model of RA for the study of bone erosion development and repair in which inflammation is induced, then allowed to resolve. We performed Fluidigm high-throughput expression profiling of 750 miRNAs in pooled synovial samples from non-arthritic and arthritic mice (peak inflammation, day 10), as well as mice with resolving inflammation (day 21). We also performed gene array (Affymetrix) analysis in these same RNA samples. We analyzed and compared gene and miRNA array expression, and performed gene ontology analyses to identify important pathways.

Results: We performed a principle component analysis that revealed three distinct sets of miRNAs with expression patterns that were significantly different between synovium from non-arthritic mice and mice with peak inflammation and resolving inflammation. We then compared miRNA and gene expression patterns and found 796 up-regulated genes in arthritic compared with non-arthritic synovium that are predicted targets of down-regulated miRNAs (1.5 fold or >). Relevant pathways from gene ontology analysis included extracellular matrix organization, cell cycle, inflammation, and blood vessel and bone development. We also found 639 genes to be down-regulated that are predicted targets of up-regulated miRNAs (1.5 fold or >) in arthritic compared with non-arthritic synovium. Gene ontology analysis included genes in the TGFβ signaling pathway and genes regulating skeletal development. Finally, expression of several miRNAs was significantly altered

during the resolution phase compared with peak inflammation, and some of these miRNAs may also regulate skeletal pathways.

Conclusion: In this murine model of bone erosion development and repair, we have identified miRNAs and associated genes whose relative expression is altered according to stage of inflammation/erosion. Further study of these miRNAs and regulated pathways may prove fruitful for elucidating mechanism and developing therapeutic strategies for bone remodeling.

Disclosure: E. M. Gravallese, None; **Y. Maeda**, None; **N. Farina**, None; **P. Fanning**, None; **J. Lian**, None.

1833

Combination Of TNF and IL-6 Induces Osteoclast-Like Cells With Bone-Resorption Activity Both *In Vitro* and *In Vivo*. Kazuhiro Yokota, Kojiro Sato and Toshihide Mimura. Saitama Medical University, Saitama, Japan.

Background/Purpose: Although TNF inhibitors suppress bone destruction in patients with rheumatoid arthritis (RA), TNFα stimulation alone does not directly induce osteoclasts, bone-resorbing cells. With the assumption that the combination of TNFα and IL-6 induces differentiation of osteoclast-like cells, we examined the effect of the combination on bone marrow-derived monocytes/macrophages (BMMs) and on intracellular signaling pathways.

Methods: BMMs were cultured with macrophage-colony stimulating factor (M-CSF), TNFα, IL-6, and receptor activator of nuclear factor κB ligand (RANKL). The activities of nuclear factor-κB (NF-κB), c-Fos, and nuclear factor of activated T-cells cytoplasmic 1 (NFATc1) were analyzed using an ELISA-based system, western blot analysis and immunostaining. *In vivo* administration of the cytokines into the supracalvariae of mice was performed. The effects of osteoprotegerin (OPG), the decoy receptor for RANKL, the NFAT inhibitor tacrolimus, anti-IL-1β antibody, ERK inhibitors and a novel JAK inhibitor tofacitinib were examined. The effects of RNAi for c-Fos and the genetic ablation of Stat3 were also evaluated.

Results: The combination of TNFα and IL-6 induced the differentiation of tartrate-resistant acid phosphatase (TRAP)-positive multinucleated osteoclast-like cells in a RANKL-independent manner. The osteoclast-like cells resorbed dentin slices in a manner similar to osteoclasts induced by RANKL. Activity of c-Fos and NFATc1 was significantly upregulated by TNFα and IL-6 used in combination compared to TNFα or IL-6 alone. The differentiation of osteoclast-like cells was completely inhibited by tacrolimus but not by OPG or anti-IL-1β antibody. In addition, silencing of c-Fos significantly decreased the expression level of NFATc1 mRNA and the number of osteoclast-like cells. Most interestingly, we observed no significant difference in the induction of osteoclast-like cells derived from conditional Stat3-knockout mice and control mice. In contrast, ERK inhibitors clearly exerted an inhibitory effect on the differentiation of osteoclast-like cells compared to that of osteoclasts induced by RANKL. Thus, the JAK-ERK signaling pathway is likely to regulate the differentiation of osteoclast-like cells. On the other hand, the number of TRAP-positive cells on the calvariae was significantly higher in mice administered with TNFα plus IL-6 than in mice administered with PBS, IL-6 or TNFα alone. Furthermore, tofacitinib suppressed the differentiation of osteoclast-like cells *in vitro*, and decreased the number of TRAP-positive cells and inhibited bone resorption induced by the combination of TNFα and IL-6 *in vivo*.

Conclusion: The combination of TNFα and IL-6 is a potent mediator of bone resorptive osteoclast-like cells even in the absence of RANKL. These results suggest that TNF inhibitors might suppress bone destruction by inhibiting the differentiation of osteoclast-like cells induced by the combination of TNFα and IL-6.

Disclosure: K. Yokota, None; **K. Sato**, None; **T. Mimura**, None.

1834

Abnormal Collagen Fibers Deposition In The Synovial Joints Is a Characteristic Of The Temporal Evolution Of The Diabetic rats' Model Induced By Streptozotocin. Priscila C Andrade[1], Ana Paula P. Velosa[1], Jymenez Morais[1], Edwin R. Parra[2], Cláudia Goldeinstein-Schainberg[1], Vera L. Capelozzi[2] and Walcy R. Teodoro[1]. [1]University of Sao Paulo School of Medicine, São Paulo, Brazil, [2]University of Sao Paulo School of Medicine, Sao Paulo, Brazil.

Background/Purpose: Diabetes is a causative factor in joint diseases and amplifies the damage induced by other agents as well. According to an accepted hypothesis, damaged joint tissue in diabetes is caused by an excess of advanced glycation end products, which forms covalent cross-links within collagen (COL) fibers and alters their structure and function. In this context the remodeling process of the collagen fibers in different structures in the joint probably is the trigger of the joints disorders observed in these patients. The main of this study was to analyze the synovial collagen fibers in the rat diabetic joints induced by streptozotocin and their correlation with the temporal evolution of the diabetes.

Methods: Twenty diabetic Wistar rats (2.5 months of age and 200–250g) induced by infusion of streptozotocin (35mg/kg) were divided in two groups. The first group (G1=10) was euthanized after 2 weeks of induction and the second group (G2=10) after 2 months of diabetic induction. The control (C1=10 and C2=10) groups received only saline infusion. The experimental protocol complies the rules adopted by the Brazilian College of Animal Experimentation (COBEA) and was approved by the internal Ethics Committee of the University of São Paulo Medical School, protocol # 10501/13. After the euthanasia, weight, blood glucose and plasmatic anti-carboximetilisin (ACML) analysis were performed. The synovial tissues of the knee were included in paraffin and histological sections were stained with Hematoxylin and Eosine. 4-hydroxyproline analysis, picrosirius red stained, immunofluorescence and image analysis were used to evaluated the amount of total collagen and the COL I, COL III and V in the synovial tissues.

Results: Blood glucose was statistical significant increases in the diabetic groups when compared with control groups ($p<0.005$). In contrast, the weight of the diabetic animals decreased when compared with the control groups ($p<0.001$). Increased quantities of collagen was observed by 4-hydroxyproline analysis in G2 group when compared to C2 ($p<0.005$) group. Similar situation was observed between G1 and C1 but without statistical significance. The morphology analysis showed a substitution of the sub-synovial layer fat by fibrotic tissue in the diabetic groups with important deposition of collagen fibers around small vessels. Indeed, the histomorphometry analysis showed an increased amount of coarse collagen fibers (22.70 $\pm$ 8.20) with a reduction of fine collagen fibers in G2 (16:29 $\pm$ 6:10%) when compared with C2 (14:45 $\pm$ 5:39%, 21:39 $\pm$ 6.14, respectively, $p<0.05$) group. Similar situation was observed between G1 and C1 but without statistical significance. The COL I, III and V analysis showed a statistical increased of these fibers in G2 when compared with C2. Between G1 and C1 this increase was observed but without significance.

Conclusion: The morphologic changes observed in the synovial tissues from diabetic rats and the increased amount of the collagen fibers deposition in this structure reinforce the idea that the collagen fibers deposition and remodeling are part of the pathogenic pathway progression in the joint from diabetic patients.

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1835

Dynamic Visualization Of Monocyte Migration In 3D Synovial Micromass Tissue Cultures. Clemens Scheinecker[1], Ruth Byrne[1], Karolina Dalwigk[1], Anastasiya Hladik[1], Gunter Steiner[1], Josef S. Smolen[2] and Hans Peter Kiener[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria.

Background/Purpose: Monocytes (Mo) are among the first hematopoietic cells to migrate into the inflamed synovial tissue of arthritic joints. Monocyte migration appears to be associated with the expanding synovial lining network of fibroblast-like synovial cells (FLS). Whether cognitive interaction between Mo and FLS is required for an orchestrated migratory behavior has not been analyzed so far. We analyzed Mo migratory activity under inflammatory conditions in regard to cell-cell interactions with FLS.

Methods: Human FLS were prepared from synovial tissues obtained as discarded specimens following joint arthroplasty. $CD14^+$ Mo were isolated from peripheral blood by magnetic bead sorting. FLS and Mo were labeled with fluorescent membrane dyes and cultured in spherical extracellular matrix micromasses with an average size of 1.5 mm for up to two weeks. For stimulation experiments, micromasses were cultured in medium containing 10 ng/ml of tumor necrosis factor (TNF). At different time-points cell migration was monitored in individual micromasses by real-time confocal microscopy.

Results: Cell migration could be subdivided into three successive phases of cell movement. Phase I (day 1–3 of culture) was characterized by the

formation of the synovial lining layer. Mo in close contact with FLS appeared sessile. On average 20% of Mo were in no apparent contact with FLS and displayed a mobile and seeking behavior. During phase II (day 3–7) already >95% of Mo were in contact with FLS. The majority of Mo remained sessile whereas a fraction of Mo displayed a directed cell movement with an impressive maximum speed of up to 15 mcm/min. In addition the formation of Mo cell clusters was observed. The rapid Mo migration finally ceased during phase III (day 7–14). The addition of TNF i) increased the frequency and size of Mo cell clusters during phase II two and ii) prolonged the mobility of Mo into phase III.

Conclusion: The 3D synovial tissue culture system allows to monitor and analyzed subtle migration patterns of Mo in relation to the organized synovial lining architecture. Ongoing experiments address molecular mechanism(s) of Mo – FLS interaction in order to identify potential targets for future therapeutic intervention in arthritis.

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1836

Suppression Of HDAC5 Expression By Inflammatory Cytokines Is Required To Promote CXCL Chemokine Production In RA FLS. Chiara Angiolilli[1], A.M. Grabiec[1], P.A. Kabala[1], Paul-Peter Tak[2], D. Baeten[1] and Kris A. Reedquist[1]. [1]Department of Clinical Immunology and Rheumatology Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center / currently also GlaxoSmithKline, Amsterdam, Netherlands.

Background/Purpose: Histone deacetylases (HDACs) are important regulators of gene expression and protein function in the immune system. HDAC inhibitors (HDACi) display anti-inflammatory properties in animal and in vitro models of rheumatoid arthritis (RA), as well as initial safety and efficacy in the treatment of systemic onset juvenile idiopathic arthritis1, 2.However, as most of the currently available HDACi display little selectivity or specificity for class I (HDAC 1–3, 8) and class II (HDAC 4–6, 9, 10) HDACs, the role of specific HDACs in RA is unclear.

We examined the relationship between HDAC expression and inflammation in RA synovial tissue and fibroblast-like synoviocytes (FLS).

Methods: RNA was isolated from arthroscopic synovial biopsies from 19 RA patients. MMP-1, TNFα, IL-6, and HDAC 1–10 expression was measured by quantitative PCR (qPCR). RA FLS were stimulated with IL-1β, TNFα and LPS and HDAC expression was measured by qPCR. RA FLS were transduced with adenovirus encoding control GFP or GFP-HDAC5, or transfected with control siRNA or siRNA targeting HDAC5. Effects of HDAC5 modulation on RA FLS gene and protein expression were analyzed by custom qPCR array and ELISA, respectively.

Results: Positive correlations were observed between RA synovial tissue expression of TNFα and HDAC1 (R=0.651, P=0.003) HDAC2 (R=0.523, P=0.022) and HDAC3 (R=0.570, P=0.011) and between MMP-1 and HDAC1 (R=0.501, P=0.029) and HDAC2 (R=0.512, P=0.025). A significant negative correlation was observed between synovial tissue expression HDAC5 and IL-6 (R=−.477, P=0.039), as well as HDAC5 and clinical parameters of disease activity (CRP: R=−0.664, P= 0.007; ESR: R=−0.556, P=0.013: DAS28: R=−0.567, P=0.011). HDAC5 mRNA expression was significantly and selectively reduced after RA FLS stimulation with TNFα and IL-1β, but not LPS. Of 84 genes regulated in RA FLS by IL-1β or TNFα, mRNA expression of CXCL9, CXCL10, and CXCL11, as well as CXCL10 protein, were selectively upregulated following silencing of HDAC5 expression. Conversely, mRNA expression of these chemokines was suppressed by overexpression of HDAC5 in RA FLS.

Conclusion: RA synovial expression of HDAC 1 and 2, but not class II HDACs, positively correlates with local inflammatory mediators, while HDAC5 expression negatively correlates with IL-6 mRNA expression and with disease activity parameters. HDAC5 mRNA is decreased after inflammatory stimulation, and silencing of HDAC5 leads to an increase of CXCL chemokine expression in RA FLS, an effect reversed by HDAC5 overexpression. Our results suggest an involvement of HDAC5 in the regulation of a specific subset of IL-1β induced CXCL chemokines RA FLS.

Disclosure: C. Angiolilli, None; **A. M. Grabiec**, None; **P. A. Kabala**, None; **P. P. Tak**, None; **D. Baeten**, None; **K. A. Reedquist**, None.

1837

Three-Dimension Culture Of Mesenchymal Stem Cells With Nano-Fiber Scaffold Induces Chondrogenesis and Osteogenesis. Kunihiro Yamaoka[1], Koshiro Sonomoto[1], Xiangmei Zhang[1], Masahiro Kondo[1], Shunsuke Fukuyo[1], Makoto Satake[2], Hiroaki Kaneko[2], Kazuhisa Nakano[1], Yosuke Okada[1] and Yoshiya Tanaka[1]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Integrative Technology Research Institute, Teijin Limited, Tokyo, Japan.

Background/Purpose: Development of biologics has made remission a realistic treatment goal in treatment of rheumatoid arthritis (RA). However, once bone or cartilage is destructed treatment tool aiming joint repair do not exist. On that note, treatment strategy for established RA is requisite. We have previously shown that mesenchymal stem cells (MSCs) suppress osteoclastogenesis and also differentiate into osteoblasts under the presence of inflammation. Therefore, in addition to its immunosuppressive effect, we believe that MSCs is a useful tool to develop treatment aiming joint repair. We have evaluated the applicability of poly-lactic fiber (Nano-fiber) scaffold.

Methods: MSCs from healthy donor, osteoarthritis (OA) or RA was seeded onto Nano-fiber (Nano-MSCs) and cultured in MSCs growth media (MSCGM) or osteoblast induction media (OIM) for 7~56 days. Differentiation markers for osteoblasts (RUNX2, Osteocalcin, meneralization), osteocytes (Dmp-1, MEPE) and chondrocytes (SOX9, Type II collagen, COL10A1, proteoglycan production) were evaluated.

Results: Healthy Nano-MSCs culture in OIM for 28 days induced runt-related gene 2 (RUNX2) expression and mineralization with positive Safranin O staining suggesting that Nano-hMSC induced osteoblastogenesis and chondrogenesis in parallel. When healthy Nano-MSCs was cultured in MSCGM, Safranin O positive cells and chondrocyte markers were detectable from day 14. Mineralization and osteocyte marker expression were observed on day 56 with osteocyte-like shape under the scan electron microscopy. Similar results were observed with MSCs from RA and OA patients. However, MSCs seeded onto culture flask with MSCGM did not express any of these differentiation markers. The non-canonical wingless-type MMTV integration site (Wnt) signaling pathway was suggested to play a role in these phenomena.

Conclusion: Our results suggest that MSCs simutaneously differentiate into chondrocytes, osteoblasts and osteocytes when seeded onto Nano-fiber scaffold without specific stimulation for differentiation. Since Nano-fiber is bioabsorbable, its use in combination with MSCs would be a useful tool for regeneration of destructed joints in RA and OA patients.

Disclosure: K. Yamaoka, None; **K. Sonomoto**, None; **X. Zhang**, None; **M. Kondo**, None; **S. Fukuyo**, None; **M. Satake**, teijin, 3; **H. Kaneko**, teijin, 3; **K. Nakano**, None; **Y. Okada**, None; **Y. Tanaka**, BMS, MSD, Chugai, Mitsubishi-Tanabe, Astellas, Abbvie, Daiichi-Sankyo, 2, UCB, Mitsubishi-Tanabe, Abbott, Abbvie, Eisai, Chugai, Janssen, Pfizer, Takeda, Astellas, Daiichi-Sankyo, GSK, AstraZeneca, Eli Lilly, Quintiles, MSD, Asahi Kasei, 8, UCB, Mitsubishi-Tanabe, Abbott, Abbvie, Eisai, Chugai, Janssen, Pfizer, Takeda, Astellas, Daiichi-Sankyo, GSK, AstraZeneca, Eli Lilly, Quintiles, MSD, Asahi Kasei, 5.

1838

The Use Of Three-Dimensionally Printed β-Tricalcium Phosphate/ Hydroxyapatite To Understand The Regulation Of Adenosine Receptors In Osteoclast Formation and Promotion In Bone Regeneration. Stephanie Ishack[1], Aranzazu Mediero[1], Tuere Wilder[1], John Ricci[2] and Bruce N. Cronstein[3]. [1]NYU School of Medicine, New York, NY, [2]NYU Dental School, New York, NY, [3]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Bone defects resulting from trauma or infection need timely and effective treatments to replace damaged bone. Using specialized three-dimensional (3-D) printing technology, combined with bioactive molecules, we can design custom 3-D scaffolds for bone repair. The Hydroxyapatite (HA)/Beta-Tri-Calcium Phosphate (b-TCP) scaffold components provide mechanical strength, conduct bone throughout the scaffold and remodel over time. Adenosine, acting via adenosine receptors (A_1, A_{2A}, A_{2B} and A_3), plays a critical role in regulating bone metabolism. Dipyridamole (DIPY) increases local adenosine levels by blocking cellular uptake of adenosine and stimulates bone regeneration. We tested the capacity of dipyridamole, hypothesize that with a bioactive filler, such as DIPY, these scaffolds may successfully regenerate bone over critical sized bone defects in an *in vivo* model.

Methods: 15% HA:85% b-TCP scaffolds were designed using Robocad software, fabricated using a 3-D Robot, and sintered at 1100°C for 4h. SEM

and microCT were used to examine structural aspects on pre/post-sintering, while XRD, FT-IR and ICP were used to evaluate porosity, crystalline phase quantification, and Ca:P ratio, respectively. Vehicle, BMP-2 and combination drug scaffolds (calcium sulfate + drug, calcium sulfate + drug in solution, collagen + drug in solution) were implanted in C57B6 mice with 3mm critical size defect for 2 weeks. DIPY release from scaffold was assayed *in vitro* spectrophotometrically over time. MicroCT and histological analysis were conducted to determine the degree of new bone formation and remodeling.

Results: Qualitative microstructural evaluation using SEM showed a broader pore/particle size distribution for materials sintered. The x-ray diffraction (XRD), Fourier transform infrared spectroscopy (FT-IR) and inductive coupled plasma (ICP) results showed substantial deviations in the original 15/85% HA/b-TCP formulation with the detection of ~10%calcium pyrophosphate. Also, as sintering temperature was increased, lower amounts of the HA (5% HA: ~95% b-TCP) phase was observed. DIPY release assays showed a constant 10^{-6}M release of the compound for a period of 10 days. Quantitative and qualitative results from microCT showed similar and significant bone formation and remodeling in HA/b-TCP- DIPY and HA/b-TCP-BMP-2 scaffolds (p=NS) when compared to vehicle 2 weeks after surgery. Histological analysis showed increased bone formation and osteoconduction in HA/b-TCP- DIPY scaffolds.

Conclusion: Results from the *in vitro* and *in vivo* studies demonstrate that HA/b-TCP- DIPY scaffolds are highly biocompatible and can rapidly and successfully regenerate and remodel bone in critical size defects.

Disclosure: S. Ishack, None; **A. Mediero**, Filed a patent on use of adenosine A2AR agonists to prevent prosthesis loosening (pending)., 9; **T. Wilder**, None; **J. Ricci**, None; **B. N. Cronstein**, Canfite Pharma, 1, NIH, Gilead, Takeda, AstraZeneca, 2, NYU School of Medicine, 3, Merck-SeronoBristol-Myers Squibb, Novartis, Can-Fite Biopharmaceuticals, Cypress Laboratories, Regeneron (Westat, DSMB), Endocyte, Protalex, Allos, Inc., Savient, Gismo Therapeutics, Antares Pharmaceutical, Medivector, 5, Multiple patents on adenosine receptors and bone metabolism, pharmacology, 9.

1839

Osteoclastogenesis Is Enhanced By Synovial Fluid Derived Anti-Citrullinated Proteins Antibodies In Rheumatoid Arthritis. Akilan Krishnamurthy[1], Heidi Wähämaa[2], Vijay Joshua[1], Catia Cerqueira[3], Elena Ossipova[3], Nancy Vivar Pomiano[1], Karin Lundberg[3], Vivianne Malmström[4], Per-Johan Jakobsson[1], Lars Klareskog[1], Georg Schett[5], Jimmy Ytterberg[6] and Anca I Catrina[1]. [1]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [2]Rheumatology unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden, [3]Rheumatology unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [4]Rheumatology unit, Karolinska University Hospital, Karolinska Institutet, STockholm, Sweden, Stockholm, Sweden, [5]University of Erlangen-Nuremberg, Erlangen, Germany, [6]Rheumatology Unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden.

Background/Purpose: Anti citrullinated modified vimentin antibodies isolated from peripheral blood (PB) of RA patients induce osteoclasts (OC) formation from PB derived monocytes of healthy individuals. Recently dendritic cells have been proposed as potent precursor of osteoclasts. We aimed to characterize dendritic cells derived osteoclastogenesis in ACPA+ RA and to explore the effect of anti-CCP2 antibodies containing a large array of anti-citrulline specificities on dendritic cells mediated osteoclastogenesis.

Methods: SF (n=26) samples were collected from RA patients. Total IgG were isolated first on Protein G and than on CCP2 affinity columns. CD14+ monocytes were isolated from (PB) of ACPA+ RA patients and cultured in the presence of GM-CSF and IL-4 to generate dendritic cells (DC) or M-CSF to generate macrophages (MΦ). DC's and MΦ were further differentiated to OC in the presence of RANKL and M-CSF, with or without ACPA IgG or flow through control IgG (at a final concentration of 100 ng/ml). OC were counted as multinucleated (more than 3 nuclei) TRAP+ cells. In parallel cultures were grown on osteoassay surfaces and resorbed area was quantified by computer assisted image analysis. Proteomic analysis and western blot to identify citrullinated proteins were performed on different stages of differentiation of dendritic cells derived osteoclasts.

Results: Osteoclastogenesis from DC was as efficient as osteoclastogenesis from MΦ of ACPA+ RA patients. ACPA IgG increased RANKL-driven osteoclastogenesis from both DC (from a median of 193 OC/well, interquartile variation of 86–308 in controls to a median of 418 OC/well, IQR 317–447) and MΦ (from a median of 238 OC/well, IQR 55.5–378.5 to a median of 333.5, IQR 88.8–489.3). These changes were paralleled by an increase of bone resorption areas by ACPA IgG in both the dendritic assay (from a median of 6.8%, IRQ 1.6–18.9 to a median of 10.3%, IQR 2.3–38.4) and the monocyte assay (from a median of 4.9%, IRQ 1.9–8.5 to a median of 6.9, IQR 2.7–10) No significant increase in either osteoclasts numbers or resorption areas was observed with the control flow through IgG. Interestingly when OC precursors were obtained from healthy donors, ACPA were only able to promote dendritic driven but not monocyte driven osteoclastogenesis. Similar to our previous findings in monocytes-derived osteoclasts we found a significant time dependent increase in native vimentin levels during dendritic-derived osteoclast maturation with identification of citrullinated vimentin peptides in the matured but not immature osteoclasts. Western Blotting using ACPA IgG also confirmed presence of citrullinated proteins in matured osteoclasts.

Conclusion: SF derived ACPA IgG with broad specificities enhance RANKL-driven osteoclastogenesis. While citrullinated vimentin is a potential target in mature osteoclasts, the exact contributions of each distinct ACPA specificities remains to be determined.

Disclosure: A. Krishnamurthy, None; **H. Wähämaa**, None; **V. Joshua**, None; **C. Cerqueira**, None; **E. Ossipova**, None; **N. Vivar Pomiano**, None; **K. Lundberg**, None; **V. Malmström**, None; **P. J. Jakobsson**, None; **L. Klareskog**, None; **G. Schett**, None; **J. Ytterberg**, None; **A. I. Catrina**, None.

ACR/ARHP Poster Session C
Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis II
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

1840

Increased Expression of BAFF Receptor On Monocytes Is a Contributory Factor of Hypergammaglobulinemia in Patients With Primary Sjögren's Syndrome. Keiko Yoshimoto[1], Maiko Tanaka[1], Masako Kojima[1], Hideko Ogata[1], Eriko Ishioka[1], Ayumi Nishikawa[1], Katsuya Suzuki[1], Hideto Kameda[1], Tohru Abe[2] and Tsutomu Takeuchi[1]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Saitama Medical School, Kawagoe-shi Saitama, Japan.

Background/Purpose: BAFF (B cell stimulation factor belonging to TNF family) is a cytokine which is mainly produced by monocytes, dendritic cells and T cells. We have been investigating the possible involvement of BAFF in the pathogenesis of primary Sjögren's syndrome (pSS) because BAFF plays a pivotal role in the proliferation, differentiation and survival of B cells. In our previous study, we found that BAFF robustly increased IL-6 production by pSS peripheral monocytes, and the expression level of a BAFF receptor (BAFF-R) was significantly elevated in pSS monocytes compared to that of normal monocytes. These data collectively suggest that the elevated expression of BAFF-R on monocytes is involved in activation of monocytes to promote IL-6 production. Since IL-6 promotes the differentiation of B cells, our findings may provide clues to elucidate the mechanism of the development of pSS. On the other hand, it is well known that pSS is often accompanied by hypergammaglobulinemia (HγG). However, the molecular and cellular mechanism underlying HγG is unknown. In the present study, we focused on this abnormality and investigated the possible involvement of monocytes producing IL-6 in the development of HγG.

Methods: Peripheral monocytes were cultured with or without peripheral B cells and stimulated with soluble BAFF (sBAFF) in vitro. IL-6 production by monocytes and IgG production by B cells were measured by ELISA. FACS analysis of whole blood samples was employed to analyze the expression of BAFF-R.

Results: The serum level of IgG and the proportion of BAFF-R positive monocytes ($BR^+/CD14^+$) were elevated in pSS patients as compared to those in normal individuals. Remarkably, the $BR^+/CD14^+$ ratio was positively and significantly correlated with the serum IgG level. In addition, pSS monocytes produced a significantly higher amount of IL-6 than normal monocytes upon stimulation with sBAFF in vitro, and the $BR^+/CD14^+$ ratio was positively and significantly correlated with the amount of IL-6 produced by pSS monocytes. Stimulation of co-culture of B cells and monocytes with sBAFF drastically enhanced IgG production by B cells in vitro, whereas the stimulation showed only marginal effects on IgG production when B cells were cultured in the absence of monocytes.

Conclusion: The data in the present study collectively suggest that the abnormal expression of BAFF-R on monocytes is responsible for the overproduction of IgG by B cells in pSS patients. IL-6 produced by monocytes may be involved in the differentiation of B cells to produce IgG. We presume that aberrations of monocytes may underlie the development of hypergammaglobulinemia in pSS patients.

Disclosure: K. Yoshimoto, None; **M. Tanaka**, None; **M. Kojima**, None; **H. Ogata**, None; **E. Ishioka**, None; **A. Nishikawa**, None; **K. Suzuki**, None; **H. Kameda**, None; **T. Abe**, None; **T. Takeuchi**, None.

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BAFF Induces Production of Matrix Metalloproteinase-9 By Peripheral Monocytes in Patients With Primary Sjögren's Syndrome Through a Signaling Pathway That Involves NF-Kb and PI3 Kinase. Keiko Yoshimoto[1], Maiko Tanaka[1], Masako Kojima[1], Hideko Ogata[1], Eriko Ishioka[1], Ayumi Nishikawa[1], Katsuya Suzuki[1], Hideto Kameda[1], Tohru Abe[2] and Tsutomu Takeuchi[1]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Saitama Medical School, Kawagoe-shi Saitama, Japan.

Background/Purpose: B cell activating factor of the TNF family (BAFF) regulates proliferation, differentiation and survival of B cells, and plays a pivotal role in the development of primary Sjögren's syndrome (pSS). In our previous study, we found that IL-6 production was significantly enhanced in pSS monocytes upon stimulation with BAFF. We also found that the expression level of a BAFF receptor (BAFF-R) was significantly elevated in pSS monocytes compared to that of normal monocytes. These data collectively suggest that the elevated expression of BAFF-R on monocytes is involved in activation of monocytes to promote IL-6 production. Matrix metalloproteinase-9 (MMP-9) is one of the enzymes involved in pathogenesis of autoimmune diseases. In this study, we explored possible involvement of BAFF and BAFF-R in the expression of MMP-9 in pSS monocytes.

Methods: The expression levels of BAFF-R and MMP-9 in peripheral monocytes of pSS patients (n = 19) and age matched normal individuals (n = 14) were analyzed by FACS. The cells were cultured in vitro in the presence or absence of recombinant human soluble BAFF (rhsBAFF) for 96 hrs, and the amounts of IL-6 and MMP-9 in the culture supernatants were measured by ELISA. The expression level of MMP-9 was also analyzed by quantitative PCR. Signal transduction pathways were investigated by exposing rhsBAFF-stimulated pSS monocytes to several inhibitors against NF-κB (BAY11–7082 and BAY11–7085) and PI3 kinase (LY294002).

Results: Quantitative PCR and FACS analyses revealed that stimulation of pSS moncytes with rhsBAFF drastically enhanced the expression of MMP-9 compared to that of normal monocytes. ELISA showed robust enhancement of MMP-9 production by pSS monocytes. Remarkably, the amount of MMP-9 was positively correlated with the expression level of BAFF-R on pSS monocytes, suggesting that BAFF-signaling is involved in the production of MMP-9 by pSS monocytes. Moreover, the elevated production of MMP-9 was significantly suppressed by specific inhibitors against NF-κB and PI3 kinase in a dose dependent manner.

Conclusion: The present study suggests that the BAFF signaling pathway is involved in the production of MMP-9 by pSS monocytes. The study also suggests that NF-κB and PI3 kinase are involved in the pathway.

Disclosure: K. Yoshimoto, None; **M. Tanaka**, None; **M. Kojima**, None; **H. Ogata**, None; **E. Ishioka**, None; **A. Nishikawa**, None; **K. Suzuki**, None; **H. Kameda**, None; **T. Abe**, None; **T. Takeuchi**, None.

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Pathophysiological Effects Of Free Fatty Acids On Key Cells Of Arthritis. Klaus W. Frommer[1], Andreas Schäffler[2], Stefan Rehart[3], Angela Lehr[3], Ulf Müller-Ladner[1] and Elena Neumann[1]. [1]Justus-Liebig-University of Gieβen, Kerckhoff-Klinik, Bad Nauheim, Germany, [2]Justus-Liebig-University of Giessen, Giessen, Germany, [3]Markus-Hospital, Frankfurt, Germany.

Background/Purpose: Although obesity, a known risk factor for arthritic diseases, increases mechanical stress on joints, it appears not to be the only factor being responsible for joint damage. Free fatty acid (FFA) levels, which are increased in obese compared to non-obese individuals, may therefore also play a role in different forms of arthritis. In this respect, continuously elevated FFA levels have already been linked to inflammatory cardiovascular and metabolic diseases. To test our hypothesis that FFA play role in arthritic diseases, we investigated the effect of FFA on key effector cells of arthritis.

Methods: Rheumatoid arthritis (RA) synovial fibroblasts (SF), osteoarthritis (OA) SF, psoriatic arthritis (PsA) SF, human macrovascular (HUVEC) and microvascular (HBdMEC) endothelial cells as well as human primary chondrocytes (HCH) and RA osteoblasts (OB) were stimulated *in vitro* with different saturated and unsaturated FFA within their physiological range of concentrations. FFA-induced protein secretion was determined by immunoassays. Fatty acid translocase (FAT) was inhibited by sulfosuccinimidyl oleate sodium (SSO). TLR4 signaling, which can contribute to driving arthritis, was inhibited intracellularly and extracellularly.

Results: FFA dose-dependently enhanced the secretion of the proinflammatory cytokine IL-6, the chemokines IL-8 and MCP-1, as well as the matrix-degrading enzymes MMP-1 and MMP-3 in all SF types (e.g. for RASF with lauric acid [100 μM] IL-6: 9.1-fold increase; IL-8: 14.9-fold increase; MCP-1: 2.4-fold increase; pro-MMP1: 5.1-fold increase; MMP-3: 83.6-fold increase). There was also a high dependency on the cell population. The effects on RASF were not significantly different between saturated and unsaturated FFA of variable lengths as opposed to HCH, in which saturated FFA induced a strong synthesis of IL-6 (up to 11.6-fold increase), while unsaturated FFA only had a weak effect (between 1.2- and 3.9-fold increases). OB increased IL-6 secretion to a similar degree as SF when stimulated with saturated and unsaturated FFA (100 μM). Endothelial cells, HUVEC and HBdMEC, responded only to higher concentrations of FFA (100 μM), lower concentrations of FFA (10 μM) did not induce a significant response in IL-6 secretion. Blocking fatty acid transport into the cell almost completely abrogated the effect of palmitic acid on IL-6 secretion. Both intracellular and extracellular TLR4 signaling inhibition blocked the palmitic acid-induced IL-6 secretion of RASF.

Conclusion: The data show that FFA not only play a role as high energy source in metabolism but also as contributors to articular inflammation and degradation in arthritis. Therefore, elevated FFA levels (as for example occurring in obesity) may be another element in the multifactorial pathogenesis of arthritic diseases. Additionally, in SF, TLR4 signaling is necessary for FFA-induced gene expression.

Disclosure: K. W. Frommer, None; **A. Schäffler**, None; **S. Rehart**, None; **A. Lehr**, None; **U. Müller-Ladner**, None; **E. Neumann**, None.

1843

Treatment With Staphyloccocal Protein A Which Is Immuno-Modulatory In The Murine Collagen Arthritis Model, Does Not Increase Infection Severity In Murine Listeria Or Candida Challenge Models, In Contrast To Anti-TNF Treatment. Edward Bernton[1] and Valerie Lowe[2]. [1]Protalex Inc., Summit, NJ, [2]Washington Biotechnology, Inc., Baltimore, MD.

Background/Purpose: PRTX-100 is a highly-purified GMP staphylococcal protein A (SpA) that is currently in Phase I trials in patients with active rheumatoid arthritis (RA). SpA has diverse activities in vitro and in vivo: forming immune complexes with IgG, SpA induces a "suppressor" phenotype in murine and human macrophages; IP or IV administration reduces disease severity in the murine CIA model. SpA can also inhibit activation of human monocyte-derived macrophages by LPS and gamma-IFN. SpA binds to Vh3 B-lymphocytes, and relocates with them to lymphoid tissues. Since anti-cytokine biologic DMARDS, in particular anti-TNF products, have been shown to increase patient susceptibility to pathogens such as listeria, fungi and TB, we compared the effects of SpA treatment to that of etanercept and anti-mouse TNF in murine models of Listeria and Candida infection.

Methods: For Listeria challenges, groups of 15 Balb/C mice were treated ip with either 10 mL/kg of 0.1% BSA, 15 mg/kg of etanercept, 50 or 250 μg/kg of SpA, or 0.2 mL of rabbit anti-mouse TNF antisera. After 4 hours mice were administered 5 $\times$ 10$\hat{1}$0 CFU of L. monocytogenes orally. Mice were then re-treated with drugs every 48 hours $\times$ 2. Weights and mortality were recorded daily. On Days 3, 5, and 8, five mice/group were sacrificed for spleen cultures and CFU counts. For Candida challenges, groups of 15 female CD-1 mice received the same treatments. Four hours after the first treatments they were injected IV with 2 $\times$ 10$\hat{6}$ CFU of Candida albicans. Daily weights and mortality were recorded. On days 3, 5, and 8, five mice/group were sacrificed for kidney cultures and CFU counts.

Results: Mean values for weights, bacterial load: *Listeria challenge – BSA:* 20% mortality.10% weight loss at Day 4 was regained by Day 6.

Anti-TNF: 21% weight loss on Day 5, 100% lethality by Day 6. *Etanercept:* 17% weight loss by Day 5, maintained through to end of study; no mortality. Spleen bacterial counts were higher ($p<0.05$) than with BSA treatment at Day 5. SpA, 25 or 250 μg/kg; no mortality, weight loss similar to BSA-treated mice. Lower bacterial counts at Day 5 than seen following etanercept or anti-TNF treatment. *Candida challenge – BSA:* 17% weight loss by Day 5 and 10% mortality by Day 8. *Anti-TNF:* 23% weight loss on Day 5 with 100% mortality by Day 6. Kidney yeast counts higher ($p<0.05$) than BSA group on days 3 and 5. *Etanercept:* 30% weight loss by Day 7 and 60% mortality by Day 8. Mean kidney counts higher ($p<0.05$) than BSA group at days 3, 5, and 8. *SpA groups:* weight loss similar to BSA group. Kidney counts not significantly different at days 5 and 8 from BSA group; no mortality by Day 8.

Conclusion: In contrast to etanercept or anti-TNF treatment, repeated injections of SpA at 50 or 250 μg/kg did not affect disease severity or pathogen load in these challenge models with bacterial or fungal intracellular pathogens.

Disclosure: E. Bernton, Protalex Inc, 1, Protalex Inc., 5; **V. Lowe**, Washington Biotechnology Inc., 3.

1844

Rheumatoid Arthritis, Sjogren's Syndrome and Systemic Lupus Erythematosus Patients Have a Distinct Spectrum Of Serum Anticytokine Autoantibodies. Sarthak Gupta[1], Ioanna P. Tatouli[2], Lindsey B. Rosen[1], Sarfaraz A. Hasni[3], Richard M. Siegel[3], Steven M. Holland[1], Haralampos M. Moutsopopoulos[2] and Sarah K. Browne[1]. [1]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, [2]School of Medicine, National University of Athens, Athens, Greece, [3]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD.

Background/Purpose: Anticytokine autoantibodies are pathogenic in many hematologic, pulmonary and infectious diseases. However, the prevalence and significance of anticytokine autoantibodies in rheumatic conditions is poorly characterized. We comprehensively evaluated anticytokine autoantibodies in Rheumatoid Arthritis (RA), Sjogren's Syndrome (SS) and Systemic Lupus Erythematosus (SLE).

Methods: Bio-Plex Pro Magnetic COOH beads (Bio-Rad Laboratories, Inc) were coupled with commercially available cytokines. Sera from patients with RA, SS, and SLE were compared to normals for autoantibodies against 24 cytokines. Data were acquired on a Bio-Plex 100 instrument and analyzed using Prism, version 6.0. Values above the 99th percentile for the normal controls were classified as positive.

Results: Forty-two percent of RA (Fig. 1), 21% of SS (Fig. 2), and 25% of patients with SLE (Fig. 3) tested positive for anticytokine autoantibodies. Those with RA had mostly anti-TNFa and anti-TNFb antibodies, while SS patients had autoantibodies against Interleukin (IL)-1a, IL-4, IL-6 and IL-12. SLE patients had antibodes against GM-CSF, M-CSF, interferons (IFNs) types I, II and III and IFNg-induced Protein 10 (IP-10).

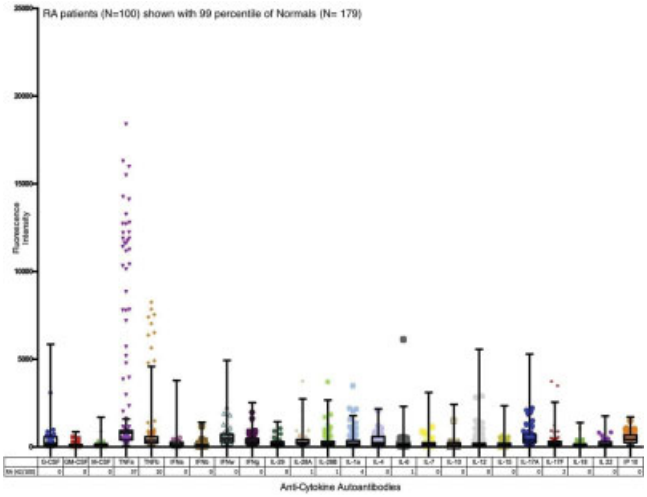

Fig. 1

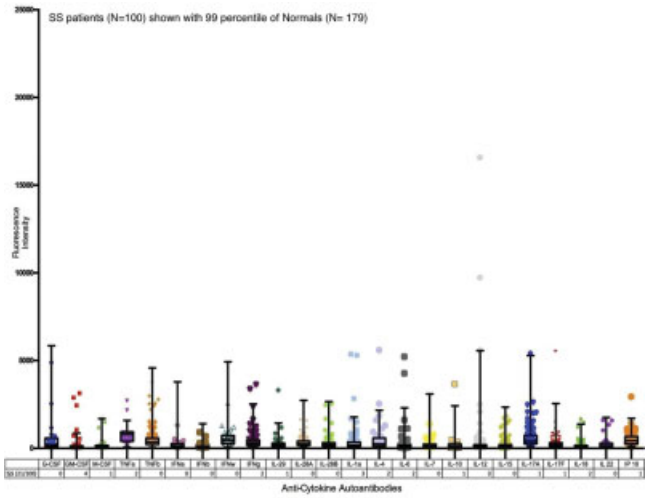

Fig. 2

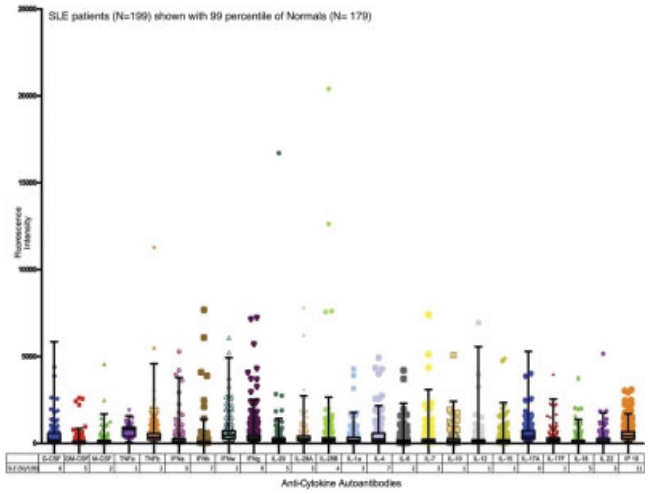

Fig. 3

Conclusion: RA, SS, and SLE had distinct spectra of anticytokine autoantibodies. Those in RA were mostly against TNFa and TNFb, probably due to monoclonal biologics; SS patients did not have many autoantibodies to TNFs or IFNs; SLE had the broadest range of autoantibodies, including those against types I and II IFNs as well as GM-CSF, M-CSF, IL-4, IL-7, IL-18 and IP-10. We confirmed autoantibodies against types I and II IFNs, GM-CSF, TNFa, TNFb, IL-1α, IL-6, IL-10, IL-12 as previously described. However, antibodies to M-CSF, IL-7, IL-17 and IL-22 have not been previously identified in rheumatologic conditions. Anti-type III IFNs (IL-29, IL-28A, IL-28B), anti-IL-4 and anti-IP-10 autoantibodies are newly recognized. These data confirm that anticytokine autoantibodies are a significant presence in autoimmune diseases and extend to more cytokines than previously appreciated. The clinical and pathophysiologic roles of these autoantibodies may teach us more about etiology and pathogenesis of rheumatic diseases.

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Soluble Type I Interferon Receptor 2 Is Elevated By Interferon Treatment and In Certain Autoimmune Diseases. Taher Fatakdawala, Michael Skawinski, Jonathan Ferriera, Tara Stauffer and Thomas Lavoie. PBL Assay Science, Piscataway, NJ.

Background/Purpose: The Type I Interferon (IFN) receptor is a heterodimer of chain 1 (IFNAR1) which is required for signaling, and chain 2 (IFNAR2) which binds tightly to IFN. Soluble forms of IFNAR2 can be produced by proteolytic cleavage or production of an alternatively spliced

transcript. Soluble IFNAR2 can be found in serum and urine however its role and regulation are poorly understood. Studies have suggested that sIFNAR2 may be elevated in multiple sclerosis (MS) patients, advanced cancer patients and hepatitis C infected patients. We have examined the sIFNAR2 in healthy donors and a small set of autoimmune patients, to determine its suitability as a member of a biomarker panel for autoimmune diseases.

Methods: Healthy donor and autoimmune Sera and plasma were commercially sourced. sIFNAR2 and IFN-Beta were determined by single analyte ELISA. IP-10 and inflammatory cytokines were determined by multiplex ELISA. IFN activity was determined by a reporter gene assay. 30 male and 30 female normal donor, 59 MS, 67 Systemic Lupus, 16 Rheumatoid Arthritis (RA), 11 Sjogren's and 10 Scleroderma samples were examined. Significance of observed differences was determined by 2-tail t-test using Welsh's correction.

Results: The average sIFNAR2 levels are 2.6±0.7 ng/ml with no difference observed between male (n=30) and female healthy donors (n=30). MS patients on IFN therapy (n=29) had significantly (p=0.0002) higher levels of sIFNAR2 than healthy donors. Those on other therapies (n=24) were not different from the healthy population but were significantly different than the MS patients on IFN therapy (p=0.0001). IFN-Beta mass was measurable in 86% of those patients treated with IFN. IP-10 levels in these patients correlated with IFN dose (r=0.747) while sIFNAR2 did not. sIFNAR2 levels showed no correlation with treatments such as vitamin-D, copaxone or natalizumab. Systemic Lupus patients (n=67) had elevated sIFNAR2 (p=<0.0001). Rheumatoid arthritis (n=16), Sjogren's (n=11) and Scleroderma patients were not significantly different from normal.

Conclusion: Only subsets of autoimmune patients show elevated sIFNAR2 levels. Although evidence of Type I IFN activation has been observed in RA, Sjogren's and Scleroderma patients the intensity is thought to be less than that observed for MS patients on IFN-therapy and Systemic Lupus. These data are consistent with a model where long term IFN signaling above a certain threshold leads to elevated sIFNAR2.

Disclosure: T. Fatakdawala, PBL Assay Science, 3; **M. Skawinski**, PBL Assay Science, 3; **J. Ferriera**, PBL Assay Science, 3; **T. Stauffer**, PBL Assay Science, 3; **T. Lavoie**, PBL Assay Science, 3.

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Mitochondrial Dysfunction Induces An Inflammatory, Tissue-Degrading, and Angiogenic Response In Normal Human Synoviocytes. M. Noa Valcárcel-Ares[1], Romina R. Riveiro-Naveira[1], Jesus Loureiro[1], Carlos Vaamonde-García[1], Laura Hermida-Carballo[1], Francisco J. Blanco[2] and Maria J. López-Armada[1]. [1]Aging and Inflammation Research Lab, INIBIC-CHU A Coruña, A Coruña, Spain, [2]Osteoarticular and Aging Res. Lab. CIBER-BBN. INIBIC- University of A Coruña, A Coruña, Spain.

Background/Purpose: Tissues affected with inflammatory arthritis (IA) are subjected to great levels of oxidative stress. Synoviocytes from IA patients present a higher rate of mitochondrial DNA mutagenesis and mitochondrial dysfunction than those from healthy donors. In this work, we studied the role of mitochondrial dysfunction in the inflammatory, tissue-degrading and angiogenic response in human synoviocytes, as those are pivotal processes occurring in IA.

Methods: Mitochondrial dysfunction was induced in normal human synoviocytes with the ATPase inhibitor oligomycin (OLI). Antimycin (AA) and paraquat (PQ) were also used. Mitochondrial polarization was evaluated by TMRM staining; and cytosolic and mitochondrial superoxide production by DHE and mitoSOX staining, respectively. Cyclooxygenase-2 (COX-2), interleukin (IL)-8, metalloproteinase (MMP)-1, MMP-3 and vascular endothelial growth factor (VEGF) mRNA expression were evaluated by RT-PCR. COX-2 protein expression was tested by flow cytometry whereas prostaglandin E_2 (PGE_2), IL-8, and MMP-1/3 levels were assayed by ELISA. In order to establish the role of ROS production, the general and mitochondria-targeted ROS scavengers N-acetylcysteine (NAC) and mitoTEMPO, respectively, were employed. The involvement of NF-kappaB was evaluated by using the inhibitor BAY. Also p65 translocation to the nucleus and NF-kappaB binding activity were assayed by immunofluorescence and EMSA, respectively. The protecting effect of the natural antioxidant resveratrol (RSV) was tested.

Results: OLI induced mitochondrial depolarization and mitochondrial and cytosolic ROS production. OLI-treated synoviocytes showed an increased inflammatory response (as determined by COX-2, PGE_2, and IL-8 expression) as well as a tissue-degrading phenotype confirmed by an increase in MMP-1/3 expression and an angiogenic potential (as evaluated by VEGF mRNA expression and tube formation assay). Besides, in the presence of IL-1β (one of the key pro-inflammatory mediators in IA affected tissues) synoviocytes with mitochondrial dysfunction exhibit a synergic effect regarding the expression of COX-2, PGE_2, and IL-8, as well as MMP-1/3 as compared with healthy synoviocytes. When the role of ROS was investigated, we found that NAC and mitoTEMPO significantly reversed the inflammatory response. Involvement of NF-kappaB was confirmed when the inflammatory response was reduced after incubation with BAY; besides, p65 translocation to the nucleus and NF-kappaB binding activity were found in synoviocytes treated with OLI and IL-1β + OLI. AA and PQ showed a similar effect on the inflammatory response. Finally, RSV clearly prevented inflammation, MMP production and the angiogenic response.

Conclusion: The present study confirms the implication of mitochondria in the proinflammatory, tissue-degrading and angiogenic response in human synoviocytes. Also mitochondrial dysfunction sensitizes these cells amplifying the effect of IL-1β. The responses of synoviocytes with dysfunctional mitochondria are mediated at least in part by mitochondrial ROS production and NF-kappaB activation. RSV has proven to be effective in controlling the deleterious effect of mitochondrial dysfunction.

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Certolizumab-Pegol Induces Reverse Signaling Through Membrane TNF Via Calcineurin Activation In Human Monocytes. Relevance In Inflammation. Jean-Frederic Boyer[1], Michel Baron[1], Delphine Nigon[2], Arnaud L. Constantin[2], Alain G. Cantagrel[1] and Jean-Luc Davignon[3]. [1]INSERM CNRS UMR 1043, Paul Sabatier University Toulouse, Toulouse, France, [2]Purpan University Hospital, Toulouse Cedex 9, France, [3]Purpan University Hospital, Toulouse, France.

Background/Purpose: Reverse signalling seems to play a role in the mode of action of anti-TNF-α agents but this pathway and its relevance are poorly understood. CD36 is a scavenger receptor implicated in the phagocytosis of senescent cells at the end of the inflammatory process. We previously demonstrated that TNF-α inhibitors increase CD36 expression in human monocytes and our results suggest a reverse signalling pathway. Casein kinase 1 phosphorylation of serine localized in the intra-cytoplasmic tail of membrane TNF-α (tmTNF) has been reported to play a role in reverse signalling. Our aim was to clarify the pathway engaged in reverse signalling induced by certolizumab-pegol and its relevance on TNF receptor (TNFR) and TLR4 signalling.

Methods: Human monocytes were isolated from peripheral blood mononuclear cells of healthy donors by plastic adherence or negative selection. The consequence of dephosphorylation of tmTNF in CD36 induction was assessed using a specific casein-kinase 1 inhibitor D4476. We searched for a putative phosphatase using cyclosporine A, a specific inhibitor of calcineurin phosphatase. An inhibitor of the endopeptidase SPPL2b, ZLL-2 ketone, was used to asses intra-membrane proteolysis of tm-TNF. CD36 and expression was analyzed by RT-qPCR and flow cytometry. IL-1 expression was induced by LPS and analysed by RT-PCR and western blot. Experiments were done at least 3 times in duplicate. Data were analyzed by Wilcoxon test matched-pairs signed-rank test and Student's paired t-test.

Results: Certolizumab-pegol and D4476 used separately respectively increased the expression of CD36. The association of both compounds potentiated this increase (p=0.02). This suggested the role of casein kinase I in the down-regulation tmTNF. The calcineurin inhibitor cyclosporine strongly inhibited the induction of CD36 observed with certolizumab-pegol (p=0.02), However, the inhibitor of intra-membrane clivage of tmTNF, ZLL-2, did not modify the induction of CD36 induced by certolizumab-pegol (p=0.2). Moreover a transfection of TNF-α linked with GFP in its intracytoplasmic tail failed to show any nuclear translocation in presence of certolizumab-pegol. These data demonstrated the absence of intramembrane proteolysis in reverse signalling induced by anti-TNF-α. IL-1 expression induced by LPS was significantly decreased by certolizumab-pegol, and this effect was inhibited by the calcineurin inhibitor cyclosporine A. Furthermore, TNFR2 did not play a role in the reverse signalling induced by tmTNF.

Conclusion: Certolizumab-pegol induced reverse signalling in human monocytes through tm-TNF. This resulted in increased CD36 expression,

down-modulation of IL-1 production induced byTLR4, but had no effect on TNFR2 signalling. Dephosphorylation of tmTNF as well as calcineurin activation were involved in certolizumab-pegol-induced reverse signalling. Taken together, these results suggest a role of reverse signalling in the regulation of inflammation by anti-TNF-α.

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Human Gingiva-Derived Mesenchymal Stromal Cells Inhibit Graft-Versus-Host Disease Through CD39 and IDO. Song Guo Zheng[1], Maogeng Chen[1], Dong Dong Chen[2], Jian Gu[1] and Yi Shen[3]. [1]University of Southern California Keck School of Medicine, Los Angeles, CA, [2]Zhoushan Hospital at Zhejiang Province, Zhoushan, China, [3]Shanghai East Hospital at Tongji University, Shanghai, China.

Background/Purpose: We recently have reported that human-derived gingival mesenchymal stem cells (GMSC) have strong capacity to suppress immune responses and T cell-mediated collagen-induced arthritis, however, it is unclear whether these cells can suppress human T cell-mediated diseases. In this project, we have developed a humanized animal model to investigate the interventional role of human GMSC in xeno-GVHD model, which is a best animal model to study human cell therapy prior to clinical trial.

Methods: Human gingival tissues were gained from discard samples from the patients who underwent dental operation. GMSC were isolated and grown from gingival tissues and cultured in α-MEM with 10%FBS for 3–6 generations. GMSC were harvested and added to human CD25 depleted CD3+ T cells for the co-culture with 0.025ng/ml anti-human CD3 antibody for in vitro suppression test. To determine the relative molecular mechanisms, various inhibitors and antagonists were added to the cultures. In vivo, sub-lethally irradiated NOD mice were given 2×10^7 peripheral blood mononuclear cell (PBMC) intravenously (IV) without (PBMC group) or with 2×10^6 GMSC (PBMC + GMSC group), while other NOD mice received 2×10^6 nTreg (PBMC + nTreg group) or 2×10^6 human fibroblast cell (PBMC + Fibroblast) for the controls. The levels of cytokines and IgG in mouse serum were measured by ELISA. Mice weight was measured twice a week and survival was monitored.

Results: We showed that GMSCs potently suppress the proliferation of human PBMC in vitro independent of cell contact. GMSC also suppress Th1, Th2 and Th17 cell differentiation. Co-transfer of human PBMC and GMSC significantly suppress IFN and IgG production, maintained weight and prolonged the mouse survival. In contrast, the adoptive transfer of human fibroblast cells did not suppress xeno-GVHD. Moreover, we demonstrated that GMSCs suppress xenogenic response of human PBMCs via CD39 and IDO signals.

Conclusion: Human GMSCs can suppress human immune responses and immune system-mediated diseases, offering a pre-clinical option to be used for modulating GVHD and other autoimmune diseases.

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Proteomic Analysis Of Connexin 43 Reveals Association With Proteins Dysfunctional Related With Osteoarthrosis. Patricia Fernández-Puente[1], Raquel Gago-Fuentes[1], Paula Carpintero-Fernández[2], Jesús Mateos[2], Maria Dolores Mayan[3] and Francisco J. Blanco[4]. [1]These authors contribute equally to this work, A Coruña, Spain, [2]Osteoarticular and Aging Research Group. Rheumatology Division, Biomedical Research Center (INIBIC). Hospital Universitario A Coruña, Xubias de Arriba 84, 15006, A Coruña, Spain, [3]Correspondence to: Ma.Dolores.Mayan.Santos@sergas.es and fblagar @sergas.es, A Coruña, Spain, [4]Osteoarticular and Aging Res. Lab. CIBER-BBN. INIBIC- University of A Coruña, A Coruña, Spain.

Background/Purpose: Human adult articular cartilage is composed of a dense extracellular matrix and specialized cells called chondrocytes. The chondrocytes are found to their own lacuna and remain in resting stage refraining form proliferation but displaying a moderate metabolic activity to maintain their surrounding matrix during the whole adult life. We have previously found that human adult chondrocytes express the gap junction (GJ) protein connexin 43 and chondrocytes in tissue have long cytoplasmic arms that physically connect two distant cells. The interaction of proteins with the C-terminal tail of Cx43 directly modulates different cellular activities such as cell growth and proliferation.

Methods: Chondrocytes were isolated by sequential digestion with trypsin-EDTA and Collagenase. Isolated cells from healthy and cartilage from osteoarthritis (OA) patients were maintained for stable short-term cell culture in DMEM supplemented with primocin and 15% FCS. Co-immunoprecipitation (IP) experiments were performed to identify the proteins that interact with the C-Terminal tail of Cx43. In-gel digestion of immunoprecipitated proteins separated by SDS-PAGE were analysed using the nano-liquid chromatography (Nano-LC, Eksigent) coupled to mass spectrometry (MALDI-TOF/TOF, Applied Biosystem). The identification of proteins was performed using ProteinPilot™ 3.0 Software. Samples were evaluated by SDS-PAGE followed by Western blotting with specific antibodies.

Results: A total of 123 were identified, of which 68 proteins were represented by at least two unique peptides. 118 proteins were specific to the Cx43 IP, not identified in the control IP performed without antibody. Identified interactors show significant enrichment for Gene Ontology (GO) processes directly linked with cytoskeleton dynamics (vimentin, a/b-tubulin or profiling-1), metabolic pathways (enolase, aldolase or GAPDH), nuclear activity (histones, nucleolin and other nucleoar proteins) and translation (several ribosomal and ribosomal-related proteins). IHC experiments showed that chondrocytes from OA patients in cartilage contain higher levels of Cx43 in the nucleus, the cytoplasm and membrane. However Cx43 was only found in the membrane of healthy chondrocytes in tissue. GO terms of proteins identified in OA samples showed an enrichment of Cx43-interactors related with cell adhesion, calmoduling binding, nucleolus or cytoskeleton related proteins in OA samples regards to healthy. However the mitochondrial proteins SOD2 or ATP5J2 were only identified in samples from healthy donors.

Conclusion: Mass-spectrometry results revealed novel functional Cx43 interactors involved in human disease and OA development emphasizing the importance of Cx43-interactions for normal development and physiology. Besides IHC experiments suggest that Cx43 interacts with nuclear and translational components especially in OA cartilage. The interaction of Cx43 with mitochondrial proteins may be involved in ischemic preconditioning as occur in other cell types.

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The Bromodomain Protein Inhibitor I-BET151 Suppresses Inflammatory and Matrix Degrading Properties Of Rheumatoid Arthritis Synovial Fibroblasts. Kerstin Klein[1], Renate E. Gay[1], Christoph Kolling[2], Lih-Ling Lin[3], Steffen Gay[1] and Caroline Ospelt[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Schultess Clinic, Zurich, Switzerland, [3]Pfizer, Cambridge, MA.

Background/Purpose: Bromodomain proteins (BRD) contain conserved acetyl-lysine binding domains that specifically recognize ϵ-N-lysine acetylation motifs, a key event in the reading process of epigenetic marks. Recently, a functional role of the BET bromodomain proteins BRD2, BRD3, and BRD4 in inflammation was described and BET inhibitors were shown to inhibit the expression of pro-inflammatory cytokines and chemokines in LPS-stimulated macrophages (Nicodeme et al., Nature. 2010). Our objectives were to evaluate the expression of the BET proteins BRD2, BRD3 and BRD4 in rheumatoid arthritis synovial fibroblasts (RASF) and to investigate the effects of the BET protein inhibitor I-BET151 on expression levels and functional properties of RASF.

Methods: The mRNA expression levels of BRD2, BRD3 and BRD4 in RASF and osteoarthritis synovial fibroblasts (OASF) were verified by quantitative Real-time PCR. RASF were treated with the inflammatory cytokines TNF-α (10 ng/ml), IL1β (1 ng/ml) and the Toll-like receptor (TLR) ligands Pam3 (100 ng/ml), pIC (10 μg/ml), and LPS (100 ng/ml) in presence or absence of I-BET151 (1 μM, R&D Systems) for 24h. The mRNA expression levels and secretion rates into cell culture supernatants of MMP1, MMP3, IL6, IL8 and CCL5 were evaluated by quantitative Real-time PCR and ELISA. Rates of proliferation and migratory properties of RASF before and after I-BET151 treatment were investigated using a BrdU-based proliferation assay and scratch assays, respectively.

Results: BRD2 (delta Ct: OASF: 5.93 $\pm$ 0.22; RASF: 5.47 $\pm$ 0.47; $p<0.01$) and BRD3 (delta Ct: OASF: 7.94 $\pm$ 0.67; RASF: 7.27 $\pm$ 0.56; $p<0.01$) mRNA levels were slightly increased in RASF (n=20) compared to OASF (n=10). On the other hand, BRD4 mRNA levels were similar in

OASF and RASF (delta Ct: OASF: 4.94 ± 0.26; RASF: 4.95 ± 0.36). Treatment of RASF (n=12) with I-BET151 significantly reduced basal IL6 mRNA levels ($p<0.001$), as well as the mRNA expression levels of IL6, IL8, MMP1, MMP3 and CCL5 after stimulation with cytokines and TLR ligands ($p<0.05$). Furthermore, basal IL6 and IL8 secretion rates were decreased after I-BET151 treatment of RASF (n=10–12) by 75.9% ($p<0.01$) and 39.4% ($p<0.01$), respectively. Both, IL6 and IL8 secretion rates remained decreased after I-BET151 treatment of RASF (n=9–12, $p<0.01$) after stimulation with cytokines and TLR ligands between 53.6 and 79%. Whereas I-BET151 significantly reduced MMP1 secretion rates only after TNF-α (71.5%, $p<0.01$), IL1β (75.6%, $p<0.01$) and pIC (32.8%, $p<0.05$) (n=12), MMP3 levels in supernatants (n=12) were reduced after stimulation with all cytokines and TLR ligands by 29.5–82.2% ($p<0.05$). CCL5 secretion was reduced in I-BET151 treated RASF (n=6) by 51.3–67.2%, depending on the stimuli. Furthermore, rates of proliferation were reduced by 61.4 ± 14.3 % ($p=0.0625$) in RASF (n=5) treated with I-BET151, whereas migratory properties of RASF (n=2) were not affected.

Conclusion: Our results demonstrate that I-BET151 is a strong suppressor of the inflammatory, matrix degrading and proliferating properties of RASF and suggest a therapeutic potential of blocking the recruitment of BET proteins to promoters of target genes in RA.

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Adenosine 2A Receptor Promotes Collagen Production By Human Fibroblasts Via Smad2/3-Independent Pathways Involving Cyclic AMP and AKT. Miguel Perez-Aso[1], Patricia Fernandez[2], Aranzazu Mediero[3], Edwin SL Chan[1] and Bruce N. Cronstein[4]. [1]New York University School of Medicine, New York, NY, [2]National Cancer Institute, NIH, Bethesda, MD, [3]NYU School of Medicine, New York, NY, [4]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Activation of Adenosine 2A Receptors ($A_{2A}R$) promotes fibrosis and collagen synthesis. However, the underlying mechanism by which $A_{2A}R$ stimulate collagen synthesis is still unclear. Previous reports indicate that cAMP, principal effector of the $A_{2A}R$, inhibits Transforming Growth Factor β1-induced collagen synthesis and has been proposed as an anti-fibrotic mediator.

Methods: Primary Human Dermal Fibroblasts (NHDF) were stimulated with increasing concentrations of the $A_{2A}R$ agonist CGS21680 or the direct adenyl cyclase (AC) activator forskolin, and results were compared to the well-known profibrotic agent TGF-β1. cAMP intracellular levels and proliferation were measured and collagen1 (Col1), collagen3 (Col3), MAPK and Smad2/3 expression were assessed by western blotting. The role of MAPK and Smads in regulating collagen synthesis was studied by use of specific inhibitors and knock-downs with siRNA.

Results: $A_{2A}R$ stimulation with CGS21680 elicited a modest cAMP increase (150.3±11% of control; $P<0.01$, n=5) which stimulated both Col1 (194.3±28% of control; $P<0.01$, n=8) and Col3 (178.4±9.8% of control; $P<0.001$, n=10) synthesis, but higher cAMP concentrations resulting from direct activation of AC by forskolin (15688±7038% of control; $P<0.01$, n=3) inhibited Col1 production (41±2% inhibition; $P<0.001$, n=3). Surprisingly, Col3 expression was increased at maximal cAMP levels (218.7±38.5% of control; $P<0.05$, n=3). Similar to Col1 expression, fibroblast proliferation increased following physiologic increases in cAMP levels induced by $A_{2A}R$ stimulation (164.7±20.8% of control; $P<0.05$, n=4) but was inhibited by greater cAMP increases resulting from forskolin incubation (26±2% inhibition; $P<0.05$, n=3). The $A_{2A}R$-mediated increase of Col1 and Col3 was mediated by an AKT-dependent pathway as shown in a dose-response of CGS21680 in the presence of two AKT inhibitors LY294002 and wortmannin (two-way ANOVA Col1: $P<0.001$, n=5 for both inhibitors; Col3: LY294002 $P<0.001$, n=5 and wortmannin $P<0.01$, n=4) while Col3, but not Col1, expression was dependent on p38MAPK activation (p38 inhibitor SB20358: two-way ANOVA $P<0.01$, n=3) and repressed by ERK (ERK1/2 siRNA: two-way ANOVA $P<0.05$, n=4). Transforming Growth Factor β1 strongly induced phosphorylation of Smad2 (426.3±136% of control; $P<0.001$, n=3) and Smad3 (1530.3±268% of control; $P<0.001$, n=3) and increased Col3 expression was prevented by Smad3 depletion (after Smad3 silencing: control *vs* CGS21680 P=non significant, n=3), whereas CGS21680 did not induce phosphorylation of either Smad2 (P=non significant, n=3) or Smad3 (P=non significant, n=3), and Smad2/3 knockdown did not prevent CGS21680-induced Col1 or Col3 increases.

Conclusion: Our results indicate that cAMP is an all-or-none intracellular switch for collagen production via the non-canonical Smad2/3-independent AKT-dependent pathway, which provides an attractive explanation for the paradox that $A_{2A}R$ induces pro-fibrotic signals via cAMP in dermal fibroblasts.

Disclosure: M. Perez-Aso, None; **P. Fernandez**, None; **A. Mediero**, Filed a patent on use of adenosine A2AR agonists to prevent prosthesis loosening (pending)., 9; **E. S. Chan**, Patent on the use of adenosine A2A antagonists for the treatment of fibrosis., 9; **B. N. Cronstein**, Canfite Pharma, 1, NIH, Gilead, Takeda, AstraZeneca, 2, NYU School of Medicine, 3, Merck-SeronoBristol-Myers Squibb, Novartis, CanFite Biopharmaceuticals, Cypress Laboratories, Regeneron (Westat, DSMB), Endocyte, Protalex, Allos, Inc., Savient, Gismo Therapeutics, Antares Pharmaceutical, Medivector, 5, Multiple patents on adenosine receptors and bone metabolism, pharmacology, 9.

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Adenosine A2A Receptors (A2AR) Promote Scarring By Repressing Mir-29a. Ross C. Radusky[1], Miguel Perez-Aso[1], Andrew G. Franks Jr.[2], Bruce N. Cronstein[3] and Edwin SL Chan[1]. [1]New York University School of Medicine, New York, NY, [2]New York University, New York, NY, [3]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: We have previously demonstrated that the nucleoside adenosine stimulates collagen production and induces dermal fibrosis *in vitro* and *in vivo*. Recent studies have demonstrated the presence and significance of microRNAs in various disease conditions and, in fibrosing conditions, diminished levels of miR-29a are found in the skin and other organs that have undergone fibrosis. We therefore determined whether adenosine A2AR stimulation regulates the expression and levels of miR29a in skin at fibrotic sites.

Methods: In this investigation, human dermal fibroblasts were treated with the A2AR specific agonist (CGS21680). Changes in miR-29a, collagen1 and collagen3 expression were analyzed by real-time PCR. An *in vivo* model of hypertrophic scarring previously described (Perez-Aso et al. 2012) was used to analyze the impact of A2AR pharmacological blockade with the specific A2AR antagonist ZM241385 on miR-29a expression in the skin: 12mm incisional wounds were splinted to promote chronic scarring in a total of 32 C57BL/6 mice. Mice were topically treated with either the A2AR antagonist or vehicle (3% carboxymethylcellulose and 7.4% DMSO) alone as a control. Scar progression was quantified using trichrome staining for collagen deposition.

Results: In *in vitro* studies A2AR stimulation with increasing concentrations of CGS21680 (0.01, 0.1 and 1μM) reduced the expression of miR-29a (table 1) and the A2AR agonist CGS21680 (1μM) stimulated an increase of both collagen1 and collagen3 (table 2). *In vivo* investigation yielded parallel results. Trichrome stains revealed that collagen deposition in the scar was reduced by topical application of the A2AR antagonist ZM241385 (2.5mg/ml). Changes in miR-29a expression in the scar were analyzed at the end of the investigation. Scarring decreased miR-29a expression by 46.3±4.8%; ($P<0.001$ *vs* unwounded skin, n=7) and A2AR blockade with the antagonist ZM241385 stimulated a dramatic increase of miR29a (191.7±4.8% of unwounded skin; ZM241385 *vs* vehicle $P<0.01$, n=7).

Table 1.

CGS21680 (μM)		0.01		0.1		1
miR-29a inhibition (%)	28.3	57.5	32.9	50.5	11.1	46

Table 2.

Collagen 1 (% of control)	143.3	252.3
Collagen 3 (% of control)	282.2	218.9

Conclusion: The findings of the present work indicate that A2AR activation represses miR-29a *in vitro* and, in a similar fashion, *in vivo*. These findings indicate that targeting A2AR may be a novel therapeutic target in scleroderma that mediates its action, at least in part, by diminishing miR29a, in promoting wound healing and preventing pathologic fibrosis such as that observed in hypertrophic scarring or scleroderma.

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Functions Of Aminopeptidase N/CD13 *In Vitro* On Rheumatoid Arthritis Synovial Cells. Rachel Morgan[1], Nilofar Behbahani-Nejad[1], Judith Endres[2] and David A. Fox[3]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan Medical Center, Ann Arbor, MI, [3]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI.

Background/Purpose: Aminopeptidase N (CD13, EC 3.4.11.2) is a metalloproteinase expressed on the surface of fibroblast like synoviocytes (FLS) that is also found in soluble form in serum and synovial fluid. We have shown that CD13 can be released from FLS in culture, and that CD13 is higher in amount and activity in Rheumatoid arthritis (RA) synovial fluids compared to osteoarthritis (OA). Recombinant human CD13 (rhCD13) can act as a chemokine for cytokine activated T cells (Tck), and it has been previously suggested but not proven that CD13 may contribute to the T cell chemotactic activity of synovial fluid. The goal of this study was to determine potential functions of CD13 in the RA joint by examining its effects on migration of T cells and FLS.

Methods: Tck were generated using IL-6, TNFα, and IL-2. Tck chemotaxis was measured using an under agarose system. Synovial fluids were immunodepleted with 591.1D7.34 (an anti-CD13 antibody developed in our laboratory) bound to agarose beads. FLS cell growth and migration were measured using an Incucyte (Essen Biosciences) imaging system. Growth was measured by confluence and migration by relative wound density. FLS were grown in 20% CMRL and switched to 10% media for assays.

Results: Pertussis toxin treatment of the Tcks prior to chemotaxis significantly reduced positive chemotaxis toward 200ng/ml rhCD13 either with a fibronectin coating ($p=0.047$) or without ($p=0.00096$), and also inhibited migration toward SDF/CXCL12 and TARC/CCL17 positive controls. Immunodepletion of synovial fluids significantly reduced chemotaxis across an uncoated surface compared to mock depleted fluids, Chemotactic Index (CI=Ln # of cells toward the chemokine – Ln # of cells toward media control) was 0.56 ± 0.21 versus -0.045 ± 0.21 $p=0.047$ pre- versus post-immunodepletion. Immunodepletion of CD13 reduced CI across a fibronectin coating, from 1.12 ± 0.43 to 0.31 ± 0.50, however it was not statistically significant. Addition of 200ng/ml rhCD13 to the depleted synovial fluids partially restored the depleted activity. Treatment of FLS with anti-CD13 mAbs 1D7 or WM15 (50ng/ml) or the chemical inhibitors, bestatin (100μM) or actinonin (10μM) significantly decreased FLS confluence at time points from 24–120hours. CD13 inhibitors were also able to significantly decrease FLS migration in a wound healing assay. Actinonin (10μM) and 1D7 (25ng/ml) both slowed migration so that wound healing was significantly lower at 48hr, while WM15 (25ng/ml) showed a significant difference by 24hr. Bestatin, however, had no significant effect on FLS migration. Addition of rhCD13 was not able to further increase cell growth or wound healing beyond FLS alone.

Conclusion: Together this data demonstrates multiple pathways by which CD13 may contribute to RA pathogenicity. CD13 significantly contributes to the chemotactic ability of synovial fluids for a population of T cells similar to those found in the RA joint. This process is mediated through a G-protein coupled receptor. Increased levels of CD13 in the RA joint may also contribute to synovial tissue hyperplasia by increasing FLS proliferation and migration.

Disclosure: R. Morgan, None; **N. Behbahani-Nejad**, None; **J. Endres**, None; **D. A. Fox**, None.

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The Involvement Of Mast Cells In The Development Of Lung Fibrosis Via Modulating Pulmonary Fibroblast Immune Function. Shinjiro Kaieda[1], Morihisa Tajiri[2], Masaki Okamoto[2], Naomi Yoshida[2], Hiroaki Ida[2], Tomoaki Hoshino[2] and Takaaki Fukuda[3]. [1]Kurume University School of Medicine, kurume, Japan, [2]Kurume University School of Medicine, Kurume, Japan, [3]Kurume University Medical Center, Kurume, Japan.

Background/Purpose: Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease of unknown etiology; the most critical event in the evolution of fibrosis is the appearance of activated myofibroblasts. Mast cells (MC) mediate a variety of inflammatory and fibrotic conditions, but their role in IPF is unclear. We examined whether MCs play a critical role in the development of pulmonary fibrosis.

Methods: Lung tissue was examined using histology and immunohistochemistry. Bioptic material was obtained from the involved lung tissue of 18 IPF patients. As control samples, we used 8 noncancerous lung sections from patients who had undergone surgery for lung cancer. We used immunohistochemistry to identify and quantify tryptase-positive MCs, prolyl-4-hydroxylase β-positive fibroblasts, and alpha-smooth muscle actin (α-SMA)-positive myofibroblasts. Co-culture of human mast cell line 1 (HMC-1) with pulmonary fibroblasts was performed in a transwell system. Fibroblasts cultured with HMC-1 cells for 7 days were cytospun and expression of α-SMA, a marker of myofibroblast differentiation, was examined by immunohistochemistry. α-SMA gene (Acta2) expression in fibroblasts, and IL-6, TGF-β, and bFGF in HMC-1 cells and fibroblasts were evaluated by RT-qPCR.

Results: MCs were significantly more numerous in IPF than control lung tissue. MCs were usually in close proximity to pulmonary fibroblasts and myofibroblasts. Up-regulation of α-SMA in fibroblasts during co-culture with MCs was confirmed by immunohistochemistry; Acta2 mRNA was also significantly elevated. In co-cultures of fibroblasts and HMC-1 cells, IL-6, TGF-b, and bFGF expression increased in the HMC-1 cells and IL-6 and TGF-b expression increased in the fibroblasts. These observations suggest an amplification loop is generated between MCs and fibroblasts, enhancing production of pro-fibrotic factors.

Conclusion: These findings suggest a novel role for MCs in the development of lung fibroblasts via induction of myofibroblast differentiation. An amplification loop between MCs and fibroblasts enhances production of pro-fibrotic factors including TGF-b and bFGF, which may contribute to myofibroblast differentiation and activation.

Disclosure: S. Kaieda, None; **M. Tajiri**, None; **M. Okamoto**, None; **N. Yoshida**, None; **H. Ida**, None; **T. Hoshino**, None; **T. Fukuda**, None.

1855

IL-6 Promotes Systemic Bone Loss Via Upregulation Of S1PR2 In Osteoclast Precursors In a Mouse Collagen-Induced Arthritis Model. Keisuke Tanaka, Misato Hashizume, Hiroto Yoshida, Miho Suzuki and Yoshihiro Matsumoto. Chugai Pharmaceutical Co., Ltd., Gotemba, Japan.

Background/Purpose: Systemic bone loss is a hallmark of rheumatoid arthritis (RA). Inflammatory cytokines such as interleukin-6 (IL-6) promote bone resorption by osteoclasts. Recent studies have shown that sphingosine-1-phosphate (S1P) controls the migration of osteoclast precursors (OCPs) between the blood and bone marrow, in part via S1P receptor 1 (S1PR1) and S1PR2 expressed on the surface of OCPs. It has been reported S1PR1 directs positive chemotaxis along an S1P gradient, and S1PR2 inhibits S1PR1 function and mediates negative chemotaxis in the direction of S1P. The purpose of this study was to investigate whether IL-6 regulates the expression of S1PR1 and S1PR2 and whether it has any influence on the localization of OCPs during the course of bone loss.

Methods: DBA/1J mice were immunized with bovine type II collagen (Day 0 and Day 21), and anti-mouse IL-6 receptor antibody (MR16-1) was administered intraperitoneally on the same days. On Day 14 or Day 35, femurs were excised and the trabecular bone volume of the distal femur was analyzed using micro-computed tomography. The percentage of OCPs ($CD11b^{+}Gr\text{-}1^{low+med}$) in the tibial bone marrow was measured by flow cytometry. S1PR1 and S1PR2 mRNA expression in OCPs from immunized mice was measured by real-time PCR. For in vitro study, OCPs were isolated from normal DBA/1J mice bone marrow by using a cell sorter, and were stimulated with IL-6. S1PR1 and S1PR2 mRNA expression in these OCPs was measured by real-time PCR. S1P-directed chemotaxis of OCPs was evaluated by using a transwell plate.

Results: Trabecular bone volume was significantly lower in immunized mice than in non-immunized control mice on Day 35. Treatment of immunized mice with MR16-1 inhibited trabecular bone loss. The percentage of OCPs in tibial bone marrow was significantly higher and the mRNA expression of S1PR2 in OCPs was significantly higher in immunized mice than in control mice on Days 14 and 35. S1PR1 mRNA expression in OCPs from immunized mice did not differ from expression in non-immunized control mice. In MR16-1 treated mice, the percentage of OCPs and S1PR2 mRNA expression were each decreased compared with that in immunized mice on Day 14 but not on Day35. IL-6 induced S1PR2 mRNA expression in OCPs in a dose-dependent manner but did not induce S1PR1 mRNA expression. IL-6 stimulation significantly decreased S1P-directed chemotaxis of OCPs.

Conclusion: These results demonstrate that IL-6 increases the percentage of OCPs in tibial bone marrow by upregulating S1PR2, and thereby plays a crucial role in systemic bone loss induced by inflammation.

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Potentiating Effects Of IL-17A, IL-17AF, IL-17F In Combination With TNF But Not With IL-1beta In Human Primary Fibroblast-Like Synoviocytes From Rheumatoid Arthritis Patients. Christine Huppertz[1], Marija Curcic Djuric[1], Robert Hennze[1], Friedrich Raulf[1], Frank Kolbinger[1], Anis Mir[1] and David Lee[2]. [1]Autoimmunity, Transplantation and Inflammatory Disease, Novartis Institutes for BioMedical Research, Novartis Pharma AG, Basel, SWITZERLAND, Basel, Switzerland, [2]Novartis Pharma AG, Basel, Switzerland.

Background/Purpose: The pro-inflammatory cytokine interleukin-17A (IL-17A) activates fibroblast-like synoviocytes (FLS) and other mesenchymal cells via the IL-17RA/RC receptor. FLS are a major source of inflammatory cytokines, chemokines and growth factors in the inflamed synovium in rheumatoid arthritis (RA) and thus contribute to disease perpetuation. Since the macrophage products TNF and IL-1β play an important role in the pathogenesis of RA, we wanted to better understand if IL-17 cytokines augment the effects of TNF or IL-1β on FLS derived from RA patients (RA-FLS) in modulating the expression of inflammatory FLS products and IL-17RA and RC expression. Furthermore, we compared the co-stimulatory effects of IL-17A, the founding member of the IL-17 cytokine family, with the less characterized but closely related cytokines IL-17AF and IL-17F.

Methods: The ability of IL-17A, IL-17-AF and IL-17F to co-stimulate mediator expression in comparison to single TNF or IL-1β stimulation was determined in criss-cross titrations of RA-FLS, and a panel of pro-inflammatory mediators including IL-6, IL-8, CXCL-1, CCL2, PGE2 and GM-CSF was determined by protein (18h) or mRNA levels (RT-PCR or Affymetrix chips analyses, upon 2, 6, 18 or 24h stimulation). Basal IL-17RA and RC expression and the effects of cytokine stimulation on receptor expression were measured by flow cytometry and quantitative RT-PCR. RA-FLS cell lines were obtained from Cell Application Inc.

Results: When tested as single stimulus *in vitro*, IL-1β was the most potent cytokine to induce the release of IL-6 and other mediators, followed by TNF. IL-17 cytokines caused only minor elevation over basal levels if used alone. Combination of IL-1β and IL-17A showed no potentiating effect on either protein or mRNA levels of IL-6, IL-8, CXCL-1, CCL2, PGE2/Cox2 and GM-CSF. In contrast, combining IL-17A with TNF, resulted in significant potentiation of IL-6, IL-8, CXCL-1, PGE2 and GM-CSF. Interestingly, this potentiation is selective as CCL2 (MCP-1) release was only dependent on TNF, indicating a different mechanism for regulation of the latter. The closely related cytokine IL-17F and the heterodimer IL-17AF showed strikingly different potencies for co-stimulation of RA-FLS with TNF, with ranking IL-17A> IL-17AF>IL-17F. To further explore the underlying mechanism of potentiation of TNF+IL-17, we examined IL-17 receptor expression on RA-FLS. Interestingly, cytokine stimulation did not upregulate the expression of IL-17RA or IL-17RC.

Conclusion: Our data show that IL-17 cytokines synergistically potentiate the effects of TNF on RA-FLS to release pro-inflammatory mediators. All three IL-17 cytokines have pro-inflammatory effects but differ in the respective potencies (IL-17A>IL-17AF>IL-17F). Combination of IL-1β and IL-17 showed no potentiation but was only additive.

Disclosure: C. Huppertz, Novartis Pharma AG, 3; **M. Curcic Djuric**, Novartis Pharma AG, 3; **R. Hennze**, Novartis Pharma AG, 3; **F. Raulf**, Novartis Pharma AG, 3; **F. Kolbinger**, Novartis Pharma AG, 3; **A. Mir**, Novartis Pharma AG, 3; **D. Lee**, Novartis Pharma AG, 3.

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Identification Of SOX5 and SOX6 As Potent Regulators Of *RANKL* Expression Contributing To Bone Erosion In Rheumatoid Arthritis and Experimental Arthritis Model. Wenfeng Tan[1], Xiaoke Feng[2], Lingxiao Xu[3], Ke Gan[1], Fang Wang[3], Miaojia Zhang[4], Hui Wu[5] and Betty P. Tsao[6]. [1]the First Affiliated Hospital of Nanjing Medical University, Nanjing, China, [2]the First Affiliated Hospital of Nanjing Medical University, China, Nanjing, China, [3]the First Affiliated Hospital of Nanjing Medical University, Nanjing, CHINA., Nanjing, China, [4]Department of Rheumatology, Jiangsu Provincial People's Hospital, Nanjing, China, [5]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [6]UCLA School of Medicine, Los Angeles, CA.

Background/Purpose: We previously reported a *RANKL*promoter SNP confers an elevated promoter activity after stimulation via binding to a SOX family transcription factor SOX5 and is associated with younger age at onset of rheumatoid arthritis (RA). Here, we examine the expression of SOX family in RA patients and to elucidate their potential role in RA pathogenesis.

Methods: SOX expression levels in PBMC, plasma, and synovium were tested using RT-PCR, ELISA and immunohistochemistry. RNA interference and immunoprecipitation were used to determine the role of SOX5 and 6 on cytokine mediated *RANKL*expression. Effect of SOX5 and 6 on bone erosion was analyzed using collagen-induced arthritis (CIA) model.

Results: Among the 9 *SOX* family genes, expression of *SOX5* and *SOX6* were robust in 42 RA PBMC and 20 RA synovium smples. Compared to 40 osteoarthritis (OA) and 40 healthy controls (HC) samples, increased expression of *SOX5* and *6* were observed consistently in PBMC ($p<0.05$, respectively), plasma ($p=0.0002$,$p=0.0378$, respectively) and synovium ($p=0.0205$,$p<0.0001$, respectively) from RA patients. Both SOX5 and 6 could be co-immunoprecipitated with Mab specific to RANKL upon TNFα and IL6 stimulation of rheumatoid fibroblast-like synoviocytes MH7A. An increase in RANKL expression was observed in MH7A after TNFα and IL6 treatment. Transfectiom with SOX5 and/or SOX6-shRNA significantly downregulated cytokine-mediated RANKL upregulation in MH7A. Intra-articular injection of lentivirus expressing shRNA for SOX5 and/or 6 gene silenced RANKL expression, suppressed arthritic development, and markedly ameliorated bone erosion inDAB/1mice of a CIA model.

Conclusion: These findings identify SOX5 and 6 as potential targets for inhibition *RANKL* expression and preventing bone erosion in RA.

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Investigating The Role Of IL-22 In The Pathogenesis Of Familial Mediterranean FEVER. Dilek Keskin[1], Goksal Keskin[1], Ali Inal[2] and Lale Ozisik[2]. [1]DYB Research and Training Hospital, Ankara, Turkey, [2]MD, Ankara, Turkey.

Background/Purpose: Familial mediterranean fever (FMF) is a familial disease characterized by recurrent episodes of febrile serositis, peritonitis, arthritis andpleuritis. Many studies have been performed as an attempt to understand the basis of the inflammatory attacts in FMF. During the acute attacts, neutrophil accumulation, elevations in acute phase reactant levels, several non specific immunological abnormalities and increased several proinflammatory cytokines, such as IL-1, IL-8, IL-6 and TNF-alpha have been described.

Th 17 cells are a new class of T-cells involved in a wide range of inflammatory disease. Th17 cells are characterized by production of IL-22 and are known to be key participants in various inflammatory disease, such as, BD, crohn'disease, sarcoidosis. IL-22 acts synergistically with TNF alpha, IL-1 beta or IL-17 and induces acute phase reactants. These findings indicate that IL-22 represents a novel type of immune mediator that is produced by immune cells which regulates tissue protection and homeostasis. So the aim of this study was to investigate the role of serum IL-22 levels in patients with FMF.

Methods: Fifty-seven patients with FMF and 18 healthy controls (8 female, 10 male; mean age 33.7 $\pm$ 2.9 years) were enrolled in this study. Thirty-nine patients were in active stage (17 female, 22 male, mean age; 31.7 $\pm$ 3.1 years, mean disease duration 6.3 $\pm$ 2.8 years) and 18 patients were in inactive stage (9 female,9 male, mean age; 34.7 $\pm$ 4.9 years, mean disease duration; 8.1 $\pm$ 4.3 years). Serum IL-22 levels were determined by ELISA.

Results: In active patients, the mean ESR was 41.9 $\pm$ 8.2 mm/h, the mean serum CRP level was 28.6 $\pm$ 6.8 mg/L and the mean serum fibrinogen level was 514.3 $\pm$ 88.3 mg/dl. In inactive patients, the mean ESR was 18.3 $\pm$ 4.7 mm/h, the mean serum CRP level was 2.4 $\pm$ 1.6 mg/L and the mean serum fibrinogen level was 197.3 $\pm$ 62.9 mg/dl. The mean serum IL-22 levels were 56.4 $\pm$ 8.5 pg/ml in patients with FMF and 21.7 $\pm$ 3.9 pg/ml in healthy controls. The mean serum IL-22 levels were 73.5 $\pm$ 7.9 pg/ml in active patients and 38.2 $\pm$ 8.3 pg/ml in inactive patients.

According to this result; serum IL-22 levels were significantly high in patients with FMF compared to healthy controls ($p<0.001$). Serum IL-22 levels were significantly high in active patients compared to inactive patients and healthy controls ($p<0.001$ and $p<0.001$ respectively).

In active FMF patients, although the mean serum IL-22 level was correlated with the mean serum fibrinogen level ($r=0.508$ $p=0.027$) and serum CRP level ($r=0.482$, $p=0.039$), the mean serum IL-22 level was not correlated with ESR ($r=0.334$, $p=0.085$).

Conclusion: The high levels of serum IL-22, in active and inactive patients with FMF suggest that IL-22 may play a significant role of in the pathogenesis of FMF.

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OX40$^+$ T Cells and OX40L$^+$ B Cells Accumulate In The Inflamed Joints and OX40 Signalling Is Skewed Towards Autoreactivity. Julie Kristine Laustsen[1], Tue Rasmussen[2], Malene Hvid[2] and Bent Deleuran[3]. [1]Aarhus University, Aarhus N, Denmark, [2]Aarhus University, Aarhus, Denmark, [3]Aarhus University Hospital, Aarhus, Denmark.

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease characterized by the presence of autoantibodies and autoreactive T cells, leading to synovitis and joint destruction. The TNF-family members OX40 and OX40L are crucial for the generation of memory T cells, which can lead to persistence of immunity, but also autoreactivity. Both molecules exist in soluble isoforms and sOX40 has been suggested to be antagonistic to the membrane bound isoform. Signals through the OX40 receptor leads to AKT phosphorylation, thereby leading to increase of anti-apoptotic signals and maintenance of the memory response, while signals through the OX40L are mediated by ERK, which upregulates survival signals in a similar manner. Objectives of the study was to investigate the bioactivity and levels of OX40 and OX40L in RA

Methods: Paired PBMCs and SFMCs from 12 RA patients were compared with PBMCs from 6 healthy volunteers (HV). Cells were stained with anti-OX40 and anti-OX40L and the cell markers CD4 and CD45RO and analysed by flow cytometry. To determine the activation pathways, cells were stimulated with sOX40 and sOX40L in a time dependent setup, followed by intracellular staining with anti-AKT and anti-ERK antibody. Phosphorylation status were analysed by phosphoflow.

Results: In the blood, increased expression of OX40 observed by memory T cells (CD4+CD45RO+) from RA patients (11.7% (5.8%-13.30%)) compared with HV (4.9% (2.8%-6.0%)), $p<0.05$. Furthermore, OX40+ memory T cells accumulated in the SF of RA patients (17.0% (11.6%-30.3%) $p<0.01$). B cells from SFMC expressed significantly more OX40L (11.8% (3.2%-25.5%)) compared with the PBMCs (2.8% (0.8%-4–8%)) from RA patients and from HV (2.4% (1.6%-3.1%)) (All $p<0.05$).The unstimulated CD4+ T cells from SFMCs and PBMCs from RA patients had significantly elevated AKT phosphorylation compared with PBMCs from HV ($p<0.01$). When stimulated with CD3 alone, the CD4+ T cells from RA patients had increased AKT phosphorylation, whereas the CD4+ T cells from HV had decreased phosphorylation. When stimulated with CD3 and sOX40L together, cells from HV more than doubled their AKT phosphorylation, while the increase in AKT phosphorylation was very modest in RA patients; however, the MFI remained elevated in RA patients through all time points. The ERK phosphorylation of RA B cells was not increased upon sOX40 stimulation, indicating that bi-directional signaling in RA B cells is absent.

Conclusion: Cells expressing OX40 and OX40L accumulate in the inflamed joints of RA patients. This supports an on-going local activity of the adaptive memory responses in RA. Further, CD4+ T cells from RA patients have significantly higher AKT phosphorylation compared with HV, and thus, have up regulated anti-apoptotic signals. The absence of B cell response after sOX40 stimulation could support the antagonistic effects of this molecule.

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Novel Proinflammatory Microvesicles That Carry LL-37 In Patients With Cutaneous Lupus. Ming-Lin Liu[1], Muhammad Bashir[2], Meena Sharma[1], Honghui Xu[2], Kevin Williams[3], Cynthia O. Anyanwu[4], Joyce Okawa[2] and Victoria P. Werth[5]. [1]University of Pennsylvania, Philadelphia, PA, [2]Philadelphia V.A. Hospital, Philadelphia, PA, [3]Temple University School of Medicine, Philadelphia, PA, [4]Philadelphia Veterans Affairs Medical Center, Philadelphia, PA, [5]University of Pennsylvania School of Medicine, Philadelphia, PA.

Background/Purpose: Cutaneous lupus erythematosus (CLE) refers to variants of lupus erythematosus (LE) with exclusively or predominantly skin manifestations. CLE is associated with accumulation of autoantibodies and infiltration of inflammatory cells in the skin. The underlying trigger for autoimmunity in CLE has not been definitively identified. Apoptosis, which generates apoptotic bodies and apoptotic blebs, the latter also known as membrane microvesicles (MVs), have been proposed to play a central role in autoimmune diseases, particularly when normal mechanisms for clearance of apoptotic cells, bodies and MVs are impaired. We and others have shown that apoptotic MVs exert pro-inflammatory properties. The role of MVs in CLE has not been studied. In addition, tobacco smoking has emerged as a risk factor for CLE, particularly severe and refractory forms, but the underlying mechanisms are unclear. Our recent publications showed that exposure of human monocyte/macrophages to tobacco smoke extract (TSE) provokes apoptosis and the release of potent, biologically active MVs. LL-37 is a cathelicidin antimicrobial peptide with proinflammatory properties that has been described as a soluble molecule or released with neutrophil *extracellular* traps (*NETs*), and is involved in autoimmune diseases. In the current study, we hypothesized a role for MVs in CLE in the transport of LL-37, a cathelicidin antimicrobial peptide with proinflammatory properties.

Methods: Blood and skin biopsy samples were collected from CLE patients and healthy control subjects. Platelet-free plasma was isolated by sequential centrifugation. Freshly harvested skin samples were rinsed with PBS, and then minced into small pieces in DMEM for later analysis of MVs. Cultured human HL-60 neutrophils, THP-1 monocytes, and peripheral blood monocytic ce lls (PBMCs) were treated without or with tobacco smoke extract (TSE), and then the cells were examined by fluorescent microscopy, and the cells and supernatants were analyzed with flow cytometry.

Results: We found that skin lesions of CLE patients contain MVs that carry LL-37. Flow cytometry analysis using cell-specific markers revealed that LL-37-positive MVs in CLE skin lesions are largely of neutrophil origin. In plasma, we found increased concentrations of circulating total- and LL-37-positive MVs in CLE patients, compared to healthy controls. Most importantly, we found that MVs isolated from the plasma of CLE patients can stimulate TNFα release from PBMCs. In addition, exposure of human HL-60 neutrophils, THP-1 monocytes, or PBMCs isolated from healthy volunteers to TSE significantly increased their production of total- and LL-37-positive MVs. Treatment of PBMCs or THP-1 monocytes with TSE induced the redistribution of LL-37 to the cell surface, a prerequisite for export of this molecule on membrane MVs.

Conclusion: Our studies indicate for the first time that extracellular LL-37 can be carried by MVs. These LL-37-positive MVs are present in skin lesions and the circulation of patients with CLE. Microvesicles in CLE can stimulate cytokine release from nearby inflammatory cells and may thereby contribute to cutaneous inflammation.

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Neurotrophins Are Involved In Vascular Remodeling Of Giant Cell Arteritis. Kim Heang Ly[1], Alexis Régent[2], Elsa Molina[3], Sofiane Saada[3], Philippe Sindou[3], Claire Le Jeunne[4], Antoine Brezin[5], Veronique witko-Sarsat[2], Philippe Bertin[6], Francois Labrousse[1], Pierre-Yves Robert[1], Anne-Laure Fauchais[7], Elisabeth Vidal[7], Luc Mouthon[8] and Marie-Odile Jauberteau[3]. [1]Limoges University Hospital, Limoges, France, [2]Institut Cochin, INSERM U1016, CNRS UMR 8104, Université Paris Descartes, Paris, France, [3]Limoges Medical School, Limoges, France, [4]Hotel-Dieu Hospital, AP-HP, Paris, Paris, France, [5]Service d'ophtalmologie, hôpital Cochin, AP-HP, Paris, France, [6]Hôpital Dupuytren, Limoges, France, [7]Department of Internal Medicine A, Dupuytren Hospital, Limoges University Hospital, Limoges, France, [8]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, Paris, France.

Background/Purpose: Giant cell arteritis (GCA) is a large-vessels vasculitis. Hhistopathological findings show cellular infiltrates, internal elastic lumina disruption and intimal hyperplasia leading to luminal stenosis. Platelet-derived growth factor (PDGF) stimulates vascular smooth muscle cells (VSMC) migration from the media to the intima initiating intimal hyperplasia. Neurotrophins (NTs) and their receptors (NTRs) belong to a family of growth factors, described in nervous system. They include the nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3). NTR include: the selective tropomyosin receptor kinase (Trk), TrkA for NGF, TrkB for BDNF and TrkC for NT-3, and a non-selective receptor p75NTR and a co-receptor, which is almost associated with p75NTR, called sortilin. NTs and NTRs are involved in cardiovascular development, blood vessel growth and VSMC functions. We hypothesized that NTs and NTRs are involved in the vascular remodeling stage of GCA.

Methods: We included consecutive patients who underwent temporal artery biopsy (TAB) for a suspicion of GCA. We develop an enzymatic digestion method to obtain VSMC from TAB (TASMC). TASMC from six GCA patients and 10 controls were used to study NT and NTR involvement in vascular remodeling of GCA.

Results: NGF, BDNF and sortilin were significantly overexpressed in GCA patients (n=22) compared to controls (n=21). NT-3 and p75NTR were only expressed in GCA patients. An overexpression of TrkB receptor was noted in GCA patients with ischemic complications. NT-3, TrkB, TrkC and sortilin trancripts were overexpressed (increase upper fivefold levels) in TASMC from GCA patients compared to controls. NTs stimulated TASMC proliferation, similarly to FCS (10%) at day 3 in both groups, this effect tended to disappear at day 4. The p75NTR blocking alone tend to decrease cell proliferation at day 3, especially in GCA patients TASMC (p=0.053). TASMC from GCA patients were significantly able to migrate in presence of exogenous BDNF in comparison to those from controls after a 24-hour exposure. Only cells from GCA were able to significantly invade matrigel chambers in presence of 10% FCS and exogenous PDGF. NGF sera concentrations were significantly higher in 30 patients with proven GCA compared to 48 controls (177 +/− 67.6 pg/mL vs 145.5 +/− 66 pg/mL, p=0.04).

Conclusion: Herein, we report for the first time, the expression and functions of NTs and their receptors, potentially involved in vascular remodelling in GCA. It is worth noting that NGF, BDNF and sortilin are significantly overexpressed in different histological layers of TA in GCA patients compared to those of controls. In addition, TrkB staining was significantly higher in TA of GCA patients with cranial ischemic events. BDNF enhances TASMC migration by binding to TrkB and p75NTR receptor. Our results provide new insight concerning NTs and their receptors in the vascular remodelling stage of GCA pathogenesis. Their overexpression could contribute to intimal hyperplasia by facilitating VSMC migration from media to intima. However further studies will be conducted to elucidate signalling pathways that allow VSMC migration in order to define new therapeutic approach in patients with GCA

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Target-Directed Development Of a Proposed Biosimilar Etanercept, GP2015: Comparability Of *In Vitro* Target Binding and Pre-Clinical Efficacy and Pharmacokinetics. Antonio da Silva[1], Ulrich Kronthaler[1], Cornelius Fritsch[2], Johann Poetzl[3], Adelheid Rohde[4], Anastassia Papandrikopoulou[1], Hans-Peter Hofmann[5] and Jan Marinus Visser[1]. [1]Sandoz Biopharmaceuticals / HEXAL AG, Holzkirchen, Germany, [2]Novartis Pharma AG, Basel, Switzerland, [3]Sandoz Biopharmaceuticals/Hexal AG, Oberhaching, Germany, [4]Sandoz Biopharmaceuticals/Hexal AG, Kundl, Austria, [5]Sandoz Biopharmaceuticals/Hexal AG, Holzkirchen, Germany.

Background/Purpose: Biosimilars are copy versions of existing biologic medicines that have lost patent exclusivity and are approved via stringent regulatory pathways. Biosimilars are designed to be similar to their reference medicinal product (originator) and can contribute to savings for health care systems that can be used to treat more patients or fund novel therapies. Development of a biosimilar involves extensive characterization of the originator product and a target-directed iterative development process to ensure a product is highly similar to the reference medicinal product. During this process, product specific post-translational properties were engineered into GP2015, a proposed biosimilar etanercept (p75TNF-R IgG1 Fc-fusion protein), to ensure similarity in functional/structural relationships with the approved reference medicinal product etanercept. At *in vitro* level, we show comparable binding affinities of both products to TNFα and FcR, as well as functional inhibition of TNFα and LTα. Data from pre-clinical models confirm *in vivo* comparability for the proposed biosimilar etanercept GP2015, in terms of PK and efficacy.

Methods: By employing surface plasmon resonance, the binding of GP2015 to TNFα and to a panel of Fc-receptors that may impact on pharmacokinetics and effector functions, was determined and compared. Bioactivity of GP2015 was measured as functional neutralization of TNFα or TNFβ in an NFκB-dependent luciferase reporter gene assay. *In vivo* efficacy was assessed in a human TNF transgenic mouse model of polyarthritis. Comparative pharmacokinetics (PK) was assessed in a single dose study in rabbits (8 mg/kg) and a multiple dose (10 s.c. administrations of 15 mg/kg over 4 weeks) study in cynomolgus monkeys.

Results: Comparative *in vitro* binding data of GP2015 and the reference medicinal product showed comparable high-affinity binding to TNFα, and similar binding affinities to the tested panel of Fc receptors within the pre-established values for the reference product. Biological neutralization of TNFα- and LTα-mediated cellular responses also displayed an overlapping pharmacological potency over a wide dose-response range. Preclinical evaluation in the polyarthritis TNFα transgenic mouse model showed similar clinical and histological response to treatment with either product when tested at a therapeutic sensitive dose. Single and multiple dose pre-clinical studies further demonstrated comparable systemic C_{max}, T_{max} and AUC of the two compounds.

Conclusion: This non-clinical similarity exercise confirms that GP2015 and the reference medicinal product are pharmacologically highly-similar with regard to target binding, anti-TNFα biological activity and PK exposure. Future clinical trial(s) are needed to provide evidence of similar efficacy and safety of GP2015 to that of the originator product.

Disclosure: A. da Silva, Sandoz / Novartis, 3; **U. Kronthaler**, Sandoz/Novartis, 3; **C. Fritsch**, Sandoz/Novartis, 3; **J. Poetzl**, Sandoz/Novartis, 3; **A. Rohde**, Sandoz/Novartis, 3; **A. Papandrikopoulou**, Sandoz/Novartis, 3; **H. P. Hofmann**, Sandoz/Novartis, 3; **J. M. Visser**, Sandoz/Novartis, 3.

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SLE Disease Activity In The Mucocutaneus, Vascular and Hematologic Systems Is Associated With An Increase In Plasma Type I Interferon Activity. Elena Gkrouzman, Mikhail Olferiev, Margaret Robotham, Mari Lliguicota, Wei-Ti Huang, Elzbieta E. Jacek, Kyriakos A. Kirou and Mary K. Crow. Hospital for Special Surgery, New York, NY.

Background/Purpose: Type I interferon (IFN-I) has been implicated in SLE pathogenesis, and cross-sectional studies have shown that IFN-I pathway activation is associated with multiple disease manifestations. To identify those clinical and laboratory features most significantly associated with high IFN-I activity, we retrospectively evaluated IFN-I in plasma samples collected longitudinally from SLE patients.

Methods: Plasma samples as well as clinical and laboratory patient data were collected longitudinally from 60 patients meeting ACR criteria for SLE. On average, 9 visits (range 2–20) per patient and 568 data points were collected. WISH cells were stimulated with either recombinant IFN-I standard, healthy donor or SLE plasma for 5 hours. Quantification of biological response was performed by qPCR using IFIT1 as the target and HPRT1 as the reference gene. A linear mixed effect model was used to build regression models and correlate IFN-I activity of plasma across all patient visits with various clinical and laboratory parameters measured longitudinally. In total, 50 laboratory and clinical variables were analyzed.

Results: The longitudinal analysis identified that visits with high IFN-I activity correlated significantly with high disease activity determined by both SLEDAI ($p<0.01$) and BILAG scores ($p<0.05$). The rise in IFN-I activity often corresponded to lupus flares ($p<0.05$). Visits of SLE patients with hematologic ($p<0.01$), mucocutaneus ($p<0.01$) or vascular ($p<0.05$) activity (according to BILAG 2000 components) were associated with an increase in IFN-I levels. Among serologic parameters, a significant increase in antibody titer against dsDNA ($p<0.01$) and erythrocyte sedimentation rate ($p<0.01$) corresponded to higher IFN-I activity. Decreases in complement component 3 ($p<0.01$), white blood cell count ($p<0.01$), and absolute neutrophil count ($p<0.01$) were also associated with high IFN-I level.

Conclusion: The measurement of IFN-I activity in SLE patient plasma represents an important experimental parameter with possible clinical implications. The WISH assay, which measures the biological activity of IFN-I, was used to establish relationships between high interferon activity and multiple clinical manifestations in a longitudinal retrospective study. Our longitudinal analysis supports a significant association of high IFN-I activity with elevated disease activity, particularly in the mucocutaneous, vascular and hematologic systems.

Disclosure: E. Gkrouzman, None; **M. Olferiev**, None; **M. Robotham**, None; **M. Lliguicota**, None; **W. T. Huang**, None; **E. E. Jacek**, None; **K. A. Kirou**, Exagen, 2; **M. K. Crow**, Pfizer Inc, 1, Johnson and Johnson, 1, Novo Nordisk, 2, Ignyta, 5, Takeda, 5, EMD Merck Serono, 5, Biogen-Idec, 5, Idera, 5, MedImmune, 5, Human Genome Sciences/GSK, 5, Roche Genentech, 5.

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Immunologic Markers and Molecular Mechanisms Associated With Increased Systemic Lupus Erythematosus Activity In Patients Not Taking Immunosuppressive Medications. Mikhail G. Dozmorov[1], Cory Giles[1], Krista M. Bean[1], Nicolas Dominguez[1], Jonathan D. Wren[1], Joan T. Merrill[1], Judith A. James[2] and Joel M. Guthridge[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation and University of Oklahoma Health Sciences Center, Oklahoma City, OK.

Background/Purpose: The course of systemic lupus erythematosus (SLE) is characterized by exacerbations (or flares) and remissions of disease activity. Predicting which patients are likely to develop high disease activity (flare more) after remission have been generally limited to assessing autoantibodies, complement products and select serum cytokine levels, such as BLyS. The goal of this study is to identify immunologic markers and molecular mechanisms associated with flare intensity in SLE patients no longer taking immunosuppressive medications.

Methods: As part of the Biomarkers of Lupus Disease (BOLD) study, 41 patients with ACR Classification Criteria for SLE, with moderately severe, but not organ-threatening disease activity, (SLEDAI $>$ 6 and/or BILAG $>$ 2 B or 1 A) were enrolled, background immunosuppressants (IS) stopped, intramuscular steroids given until disease suppression and then serially followed until clinical disease flare. In addition to autoantibody levels and extensive immunophenotyping, 52 soluble inflammatory mediators, including cytokines, chemokines, and soluble receptors, using either xMAP multiplex technology or sandwich ELISA (BLyS and APRIL), were measured. Gene expression profiling, with globin depletion, was performed on the subset of patients with available whole blood RNA samples.

Results: Hierarchical clustering of longitudinal SLEDAI profiles identified two distinct subgroups of SLE patients. After improvement, 17 patients demonstrated higher disease activity ("flare more" group), in contrast with 15 patients showing more moderate flare activity ("flare less" group) ($p=0.007$). At the baseline visit, SLE patients from the "flare more" group overexpressed 133 genes (including HLA-DQB1, CXCL5, IL15RA, CD74, and ELK1) and showed decreased expression of 104 genes, including CLEC12A, MAX, FCAR, IL4R, IL25. The patterns of differentially expressed genes were suggestive of active IFNg signaling (z-score$=2.1$) and inhibited CD28 signaling (z-score$=-2.4$). The "TNF alpha/NFkB signaling" was the most overrepresented pathway ($p=0.003$).

SLE patients who flared more had higher baseline plasma levels of Eotaxin (CCL11, $p=0.03$), and MCP-1 (CCL13, $p=0.03$) and TRAIL (TNFSF10, $p=0.04$) increased at the flare visit. They also exhibited decreased monocyte ($p=0.03$) and neutrophil ($p=0.04$) counts at the baseline visit, and decreased CD80 ($p=0.04$) at the flare visit. On the contrary, CD4+ T cells counts were increased ($p=0.05$) at baseline visit in the "flare more" group.

Conclusion: SLE patients who will flare more after withdrawal of ineffective immunosuppressants and transient amelioration of disease with steroid treatment have gene expression, cytokine protein levels and immunophenotyping biomarker signatures indicative of 1.) abnormal antigen presentation signaling manifested by decreased co-stimulatory signals, (CD80, CD28), 2.) chemoattraction of eosinophils and monocytes, and 3.) potential activation of NFkB signaling through TRAIL binding, antagonizing cell death and promoting inflammation.

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Complement Activation and Anaphylatoxin Generation In Response To Staphylococcal Protein A Exposure: Ex Vivo and In Vivo Human Studies. Edward Bernton[1], Antonio Polley[2], Susan Zondlo[2], Lynne Mitchell[3] and Dennis Hourcade[3]. [1]Protalex Inc., Summit, NJ, [2]QPS Holdings LLC, Newark, DE, [3]Washington University School of Medicine, St. Louis, MO.

Background/Purpose: PRTX-100, a highly-purified GMP staphylococcal protein A (SpA), is currently in clinical trials treating patients with active rheumatoid arthritis (RA). It has been reported that binding of SpA to rabbit Vh3 IgM antibodies could deplete complement hemolytic activity and release C3a. Furthermore, complement activation is a postulated mechanism for dosing reactions seen in several patients after overly-rapid injection of SpA. We therefore looked at ex vivo effects of: 1. Adding SpA to pooled normal serum using a highly-sensitive modified CH50 assay; and 2. Adding SpA to fresh healthy donor blood on production of stable metabolites of C3a, C4a, and C5a, which are anaphylatoxins and known vasoactive and immunomodulatory mediators. Additionally, these analytes were measured in plasma from RA patients, before and after dosing with SpA.

Methods: *CH50 studies:* Pooled normal donor serum was incubated with various concentrations of SpA or positive controls and then assayed for residual complement activity (measured as CH50). *Whole blood studies:* Heparinized blood was incubated at 37 °C with 0, 250, 500, or 2000 ng/mL of SpA or with zymosan as a positive control. At 15 and 60 minute intervals, samples were evaluated using a multiplexed cytometric bead array (CBA) assay to quantify C3a, C4a, C5a stable metabolites. *Patient studies:* EDTA/Futham plasma samples were obtained before and after the first and fifth infusion with SpA, and frozen for CBA analysis of anaphylatoxins. Sequential groups of 6 patients were infused weekly with 1.5, 3.0, 6.0, or 12 μg/kg of SpA.

Results: In the CH50 study, 3 replicate experiments were performed adding serial two-fold dilutions of SpA from 4000 to 125 ng/mL. All CH50 values averaged between 85% and 108% of serum incubated without SpA, with no SpA dose response observed. CH50 values at 4000 ng/mL SpA were 114, 106, and 98% of the serum control. Incubation with a complement-activating nanoparticle reduced hemolytic activity to undetectable levels ($<$ 5% of serum control). Using whole blood from 3 donors, and the CBA assay, C3a increased a maximum of 2.5-fold with SpA addition, compared to no addition. The mean increase with zymosan addition was 332-fold. For C4a the maximum increase was 2.3-fold compared with a mean 99-fold for zymosan addition. For C5a the maximum increase was 2.3-fold that seen for control, compared with a mean 213-fold increase with zymosan addition. Data for pre- and post-infusion samples for 47 infusions in the first 28 patients dosed, showed 7/28 had 3-fold or greater increase in C3a (range 3 to 14 fold) but only 2/28 had a 2-fold or greater increase in C4a (range 2.4 to 2.7 fold). The mean of the ratio between pre- and post-dose values was 2.1, 1.0, and 1.1 for C3a, C4a, and C5a respectively. The maximum fold increases were 14.0, 2.7, and 3.0 respectively.

Conclusion: Ex vivo experiments do not demonstrate activation of complement in serum or whole blood by SpA at concentrations of up to 4000 ng/mL (serum) or 2000 ng/mL (blood). One quarter of patients experienced a 3-fold or greater increase in C3a after SpA treatment, which was not associated with any dosing symptoms. C4a and C5a were unaffected by treatment.

Disclosure: E. Bernton, Protalex Inc, 1, Protalex Inc., 5; **A. Polley**, QPS Holdings LLC, 3; **S. Zondlo**, Employed by QPS HoldingsLLC, 3; **L. Mitchell**, None; **D. Hourcade**, None.

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Primary Human Cell BioMAP® Profiling Of Methotrexate, Tocilizumab, Adalimumab, and Tofacitinib Reveals Different Mechanisms Of Action With Distinct Phenotypic Signatures. Seng-Lai Tan[1], Alison O'Mahony[2], Ellen L. Berg[2], Kandeepan Ganeshalingam[3] and Ernest H. Choy[4]. [1]Hoffmann-La Roche, Nutley, NJ, [2]BioSeek, South San Francisco, CA, [3]F. Hoffmann-La Roche, Basel, Switzerland, [4]Cardiff University School of Medicine, Cardiff, United Kingdom.

Background/Purpose: Proinflammatory cytokines cause joint inflammation and destruction in patients with rheumatoid arthritis, as exemplified by the therapeutic success of inhibiting tumor necrosis factor alpha (TNFα) by adalimumab (ADA) and inhibiting interleukin-6 receptor (IL-6R) by tocilizumab (TCZ). Such biologic agents and small molecule inhibitors, including methotrexate (MTX) and the recently approved tofacitinib (TOF), a Janus kinase inhibitor, have diverse and potentially overlapping biological effects. The purpose of this study was to use the human primary cell–based BioMAP platform to identify similar and discriminating biological activities of TCZ, ADA, MTX, and TOF.

Methods: BioMAP systems model complex signaling networks in primary human cell types and have been used extensively to validate compounds and targets, identify mechanisms of action and potential toxicities, and determine phenotypic signatures.[1] TCZ, ADA, MTX, and TOF were profiled across a panel of 14 cell-based BioMAP systems containing early-passage primary human cells cultured alone or with different stimulus combinations. Compounds were profiled at concentrations that would cover their reported clinical plasma exposure for the respective approved dosing regimen. To examine the effects of compounds on IL-6 *trans*-signaling, parallel experiments were conducted in the presence of exogenous soluble IL-6R (sIL-6R). Compound-mediated perturbations of protein-based and clinically relevant biomarker readouts and other cellular events (eg, proliferation, cell cytotoxi-

city) were used to generate a biological activity plot (ie, BioMAP profile) that served as a multisystem signature of the activity for each compound.

Results: TCZ significantly inhibited the expression of P-selectin (4H system), IL-8 (Sag system), TNFα (BT and HDFSAg systems), IP-10 and IL-17A (HDFSAg system), and CD69 (LPS and Mphg systems), consistent with anti-inflammatory and immunomodulatory effects. In general, little overlap was reported in the BioMAP profiles for TCZ, ADA, MTX, and TOF. TOF disrupted IL-17F, but not IL-17A, production in the HDFSAg system and showed dose-dependent selectivity; the phenotypic signatures of TOF at clinically relevant doses (<1 μM) were distinct from those at higher concentrations. sIL-6R induced additional activities in the BioMAP, including inflammation-related, novel immunomodulatory and tissue/matrix remodeling effects. Importantly, TCZ, but not ADA or TOF, completely blocked all sIL-6R–related activities at concentrations corresponding to clinical plasma exposure levels.

Conclusion: TCZ, ADA, MTX, and TOF have markedly unique BioMAP signatures, indicating that these compounds exert different mechanisms of action. IL-6 signaling in BioMAP required the presence of sIL-6R for functional *trans*-signaling, which was fully reversed by TCZ but not by ADA or TOF at clinically relevant concentrations. The relevance of these findings requires confirmation in clinical studies.

Reference: 1. Berg EL et al. *J Pharmacol Toxicol Methods*. 2006;53:67–74.

Disclosure: S. L. Tan, Roche Pharmaceuticals, 5, EMD Serono, 3; **A. O'Mahony**, DiscoveRx, 1, Bioseek, a division of DiscoveRx, 3; **E. L. Berg**, DiscoveRx, 1, DiscoveRx, 3, Stanford University, 7; **K. Ganeshalingam**, F. Hoffmann-La Roche, 1, F. Hoffmann-La Roche, 3; **E. H. Choy**, Abbott Laboratories, Boehringer Ingelheim, Chelsea Therapeutics, Chugai Pharma, GSK, Jazz Pharmaceuticals, MSD, Novartis, Pierre Fabre Medicament, Roche, UCB, 2, Abbott Laboratories, Allergan, AstraZeneca, Boehringer Ingelheim, Chelsea Therapeutics, Chugai Pharma, Daiichi Sankyo, Eli Lilly, Ferring Pharmaceutical, GSK, ISIS, Jazz Pharmaceuticals, MedImmune, Merrimack Pharmaceutical, MSD, Novartis, Pfizer, Pierre F, 5, Abbott Laboratories, Boehringer Ingelheim, Chugai Pharma, Eli Lilly, Jazz Pharmaceuticals, MSD, Novartis, Pfizer, Pierre Fabre Medicament, Roche, Schering Plough, Synovate, UCB, 8.

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Profiling Cytokine Production Of B Cells From SLE Patients Upon TLR9 Stimulation. Julia Sieber[1], Capucine Daridon[2], Simon Fillatreau[3] and Thomas Dörner[4]. [1]Charité University Medicine, Berlin, Germany, [2]Charité University Medicine / German Rheumatism Research Centre Berlin (DRFZ), Berlin, Germany, [3]German Rheumatism Research Center Berlin (DRFZ), Berlin, Germany, [4]Charité university medecine/ German Rheumatism Research Centre Berlin (DRFZ), Berlin, Germany.

Background/Purpose: Beyond their antibody producing function, B cells have been shown to be potent antigen-presenting and cytokine-producing cells. In systemic lupus erythematosus (SLE), B cells have been reported to be hyper-reactive, but it is not entirely known how cytokine production changes. An important signaling mechanism in B cell hyper-reactivity is Toll-like receptor 9 (TLR-9), which is up-regulated in B cells from patients with active SLE. Therefore, the aim of this study was to profile the cytokine production by B cells upon TLR-9 activation and to compare healthy donors (HD) to SLE-patients. In addition, the capacities of B cells to produce cytokines were put in relation with disease activity (SLEDAI) and serum autoantibody titers.

Methods: Untouched B cells from 19 SLE-patients and 13 HD were purified from peripheral blood mononuclear cells and were stimulated *in vitro* using CpG for 48 hours. The culture supernatants were harvested and then tested for 28 cytokines and chemokines by Bio-Plex. The cytokine responses upon stimulation were compared between both groups and correlated with the SLEDAI and anti-dsDNA titers for SLE-patients.

Results: 24 out of 28 cytokines/chemokines measured were significantly up-regulated upon TLR-9 stimulation compared to un-stimulated B cells ($p<0.05$). Although B cells from SLE patients showed a trend to produce less cytokine than B cells from HD, no significant differences were observed. However, the amount of IL-2, IL-4, IL-7, IL-12p70, IL13, IL-15, IL-17A, Eotaxin, Basic FGF, G-CSF, GM-CSF, IFN-γ, IP-10, MIP-1α, and VEGF produced by B cells from SLE-patients inversely correlated with their SLEDAI ($p<0.05$) and even more (additionally IL-1β, IL-1ra, MIP-1β and TNF-α) with their anti-dsDNA antibody titers. Interestingly, the more $CD27^+$ memory B cells were in the cells culture from SLE-patients, the more IP-10 and TNF-α were produced.

Conclusion: This study highlighted unknown perturbations of cytokine/chemokine production by B cells in active SLE upon TLR-9 stimulation with an inverse correlation of cytokines/chemokines produced by B cells with SLEDAI and anti-dsDNA titers. Most prominent were pro-inflammatory mediators as IP-10, MIP-1α, TNF-α, and VEGF. This suggests that the known enhanced B cell proliferation and differentiation upon TLR9-stimulation possibly results in a diminished cytokine production.

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Chemokine Expression In Systemic Lupus Erythematosus. Eoghan M. McCarthy[1], Joan Ní Gabhann[2], Siobhán Smith[2], Ruth Lee[3], Gaye Cunnane[4], Michele Doran[4], Donough G. Howard[3], Paul G. O'Connell[3], Grainne M. Kearns[3] and Caroline Jefferies[2]. [1]Mater Misericordiae University Hospital, Dublin 7, Ireland, [2]Royal College of Surgeons in Ireland, Dublin, Ireland, [3]Beaumont Hospital, Dublin 9, Ireland, [4]St James's Hospital, Dublin, Ireland.

Background/Purpose: Systemic lupus erythematosus(SLE) is a systemic autoimmune disease characterised by the deregulated activation of T and B lymphocytes, production of autoantibodies and the formation of immune complexes causing tissue damage. Chemokines which are normally involved in leucocyte chemotaxis have been associated with tissue injury in SLE via leucocyte infiltration. We sought to assess the relationship between serum levels of a number of chemokines and disease activity, damage scores and clinical profiles in Caucasian SLE patients.

Methods: Serum levels of the following chemokines were determined by ELISA – CXCL10, CXCL13, CCL17 and CXCL8. Demographic data, disease activity as per SLEDAI and damage scores (SLICC) at baseline and 5 year follow-up were recorded. Active disease was defined as a SLEDAI score $>$ 6. Categorical variables were analyzed using Fisher's exact test and continuous variables by unpaired *t*-tests. The Mann-Whitney test was used in instances of non-normality.

Results: 45 patients were recruited**.** Serum levels of CXCL10, CXCL13, CCL17 and CXCL8 were higher in SLE patients than controls (Table 1).

	Patient(pg/ml) IQR range	Control(pg/ml) IQR range	P-Value
CXCL10	234.6 [85.49;499]	84.76 [46.59;107.3]	0.001
CXCL13	311.6 [131.4;545.8]	64.99 [43.49;444.4]	0.01
CCL17	117.2 [69.21;181.3]	32.93 [18.49;171.2]	0.0097
CXCL8	6.13 [4.52;10.43]	1.7 [1.27;1.985]	0.0001

Significantly higher levels of CXCL10 were observed earlier in disease course as well as in those patients with active disease (493.5pg/ml v 94.2 pg/ml, $p=0.0045$) and those who suffered damage over the 5 year follow up period (407.1pg/ml v 94.2pg/ml, $p=0.006$). CCL17 and CXCL8 were also higher in patients with active disease [CCL17 (211.7pg/ml v 108.2pg/ml, $p<0.0001$), CXCL8 (9.784pg/ml v 5.576pg/ml, $p=0.0199$)]. CXCL13 levels failed to show an association with disease activity.

Regarding clinical involvement CXCL10 levels were higher in those with CNS involvement (649.7pg/ml v 151.7pg/ml, $p = 0.02$) whilst higher levels of CCL17 were observed in those with both renal involvement (146.8pg/ml v 113.4pg/ml, $p = 0.046$) and serositis (166.8pg/ml v 108.8pg/ml, $p = 0.039$) as part of their ACR diagnostic criteria. Of note CXCL10 and CXCL8 levels were also elevated in those with immunological involvement.

When each of the chemokines was analysed with respect to antibody profile higher levels of CXCL8 were seen in patients who were La +ve versus La -ve (11.16pg/ml v 5.9pg/ml, $p = 0.04$). None of the other chemokines assayed demonstrating an association with an antibody signature.

Finally a strong correlation was seen between CXCL10 and CXCL13 levels in SLE patients (Spearman $r = 0.711$, $p < 0.001$) indicating the importance of the interferon pathway to their induction. Both CXCL8 and CCL17 levels failed to show a correlation with any of the other chemokines measured suggesting that these chemokines are driven by distinct mechanistic pathways in SLE.

Conclusion: Chemokines play an important role in the pathogenesis of SLE with CXCL10, CXCL8 and CCL17 levels all reflecting disease activity. In addition CXCL10 levels are higher in CNS involvement whilst we have demonstrated enhanced CCL17 levels in those with patients renal involvement.

Disclosure: E. M. McCarthy, None; **J. Ní Gabhann**, None; **S. Smith**, None; **R. Lee**, None; **G. Cunnane**, None; **M. Doran**, None; **D. G. Howard**, None; **P. G. O'Connell**, None; **G. M. Kearns**, None; **C. Jefferies**, None.

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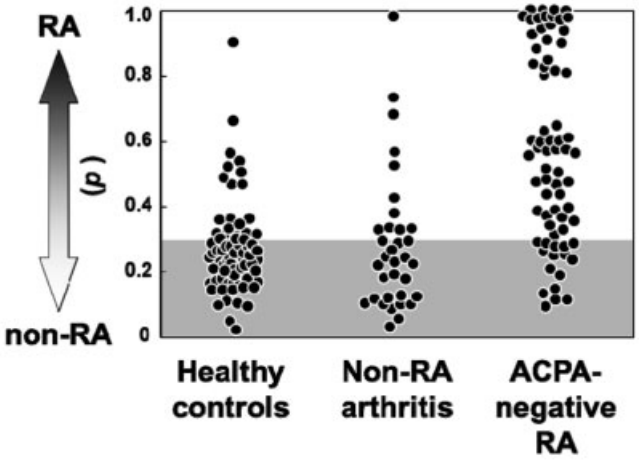
Serum Cytokine/Chemokine Profiles Are Useful For Evaluating Pathological Conditions Of Rheumatoid Arthritis and Diagnosing Anti-CCP Antibody-Negative Patients. Hitoshi Uga[1], Takahiro Okazawa[1], Yoshiaki Miyamoto[1], Takehiro Hasegawa[1], Jun Saegusa[2], Goh Tsuji[3], Sho Sendo[3], Akio Morinobu[2], Shunichi Kumagai[2] and Hirokazu Kurata[1]. [1]Sysmex Corporation, Kobe, Japan, [2]Kobe University Graduate School of Medicine, Kobe, Japan, [3]Shinko Hospital, Kobe, Japan.

Background/Purpose: The diagnosis of anti-CCP antibody (ACPA) negative rheumatoid arthritis (RA) are known to be difficult and delayed as compared with ACPA-positive RA. This study was designed to evaluate serum levels of cytokines/chemokines and to establish a new discriminating system of ACPA-negative RA patients from non-RA arthritic patients and healthy controls.

Methods: A total of 174 RA patients (mean DAS28-CRP = 2.67; 104 ACPA-positive and 70 ACPA-negative patients) diagnosed according to the ACR/EULAR 2010 classification criteria for RA, 33 non-RA arthritic (NRA) patients including seronegative spondyloarthropathy (SNSA), and 76 sex-matched healthy controls (HC) were included. By using a chemi-luminescence immunoassay, twenty-eight cytokines/chemokines, including IFN-γ, TNF-α, IL-1β, IL-4, IL-6, IL-8, IL-10, IL-17A, IL-17F, IL-23, CCL20, CXCL13, TGF-β1, were measured in the sera of the above populations. **Results** were analyzed by Mann-Whitney U-test. Discriminant analysis was performed using multiple logistic regression analysis.

Results: Our study revealed that (1) several cytokines/ chemokines, including IFN-γ, TNF-α and novel cytokines were upregulated in RA patients as compared with in healthy controls. (2) Multiple logistic regression analysis revealed that the combinations of three to five cytokines/chemokines could clearly discriminate not only ACPA-positive but also ACPA-negative RA patients from NRA patients as well as RA patients from HC (Figure 1); ACPA-negative RA: 70, NRA: 33, HC:76).



Conclusion: Our study using a chemi-luminescence immunoassay led to the identification of cytokine/chemokine profiles useful in the differential diagnosis of ACPA-negative RA from non-RA arthritis.

Disclosure: H. Uga, Sysmex Corporation, 3; **T. Okazawa**, Sysmex Corporation, 3; **Y. Miyamoto**, Sysmex Corporation, 3; **T. Hasegawa**, Sysmex Corporation, 3; **J. Saegusa**, None; **G. Tsuji**, None; **S. Sendo**, None; **A. Morinobu**, None; **S. Kumagai**, None; **H. Kurata**, Sysmex Corporation, 3.

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B-Cell Activating Factor (BAFF) and Pregnancy Outcomes. Hindi E. Stohl, Lisa Korst, Richard H. Lee and William Stohl. University of Southern California Keck School of Medicine, Los Angeles, CA.

Background/Purpose: Pregnancy often exacerbates systemic rheumatic diseases, and systemic rheumatic diseases often lead to adverse obstetric outcomes. Both rheumatic disease activity and adverse obstetrical outcomes are associated with alterations in B cells. To date, circulating levels of BAFF, a vital B cell survival factor, have not been serially evaluated in pregnancy. Accordingly, we assessed maternal and cord blood serum levels of BAFF and evaluated whether first-trimester BAFF levels are associated with adverse pregnancy outcomes.

Methods: Blood samples were collected from pregnant women with non-anomalous singleton intrauterine pregnancies receiving care at a single medical center. Participants were classified as "healthy" (n = 33), "medical disease" (n = 34), or "rheumatic disease" (n = 5) based on the presence/ absence of medical or rheumatic conditions. Age-matched non-pregnant women (n = 5) served as controls. Pregnant participants had blood samples collected at least once per trimester, at delivery, and postpartum. Additionally, cord blood was collected at delivery. Non-pregnant subjects had a single blood draw. Samples were assayed for BAFF by ELISA. Levels in women who developed spontaneous abortion (SAB; pregnancy loss prior to 20 weeks gestation), hypertensive disorders of pregnancy (HDP), or preterm delivery (PTD) were compared with levels in women without these adverse events.

Results: Median BAFF levels between "healthy" and "medical disease" participants did not differ significantly, whereas levels were elevated in women with rheumatic conditions ($p=0.04$). Median (interquartile range) first, second, and third trimester, cord blood, and postpartum BAFF levels (ng/ml)in women without rheumatic diseases were 0.63 (0.45–3.95), 0.53 (0.45–1.02), 0.59 (0.45–1.03), 1.95 (0.61–4.54), and 0.76 (0.45–1.41), respectively. In women with rheumatic conditions, levels were 0.76 (0.69–2.02), 0.78 (0.544–0.99, 0.60 (0.45–0.99), 1.14 (0.70–2.07), and 0.74 (0.45–0.97), respectively. Second and third trimester BAFF levels were significantly decreased compared to first trimester and postpartum BAFF levels ($p<0.01$ for each) in the women without rheumatic diseases, whereas levels did not significantly differ across trimesters among women with rheumatic conditions. Cord blood levels for all women were significantly elevated compared with any trimester level ($p<0.001$ for each). In contrast to the decrease in BAFF levels seen in women in the second trimester without HDP, BAFF levels increased between the first and second trimester in women who developed HDP ($p<0.01$). First trimester BAFF levels were not significantly associated with HDP ($p=0.26$) or PTD ($p=0.82$), whereas a trend towards significance was noted with SAB ($p=0.051$).

Conclusion: Elevated first-trimester BAFF levels may be associated with SAB. Moreover, the loss of the normal decline in BAFF levels between the first and second trimesters may be associated with the development of HDP. Additional subjects and samples are being collected and analyzed to confirm these initial observations. If confirmed, serum BAFF may be a useful biomarker in the management of pregnancy.

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1871

Progranulin Directly Binds To The CRD 2 and CRD3 Of TNFR Extracellular Domains. Jinlong Jian[1], Shuai Zhao[1], Qingyun Tian[1], Elena Gonzalez Gugel[1], Jyoti Mundra[1], Sardar MZ Uddin[1], Ben Liu[2], Brendon Richbourgh[1], Ryan Brunetti[1], Gerald Chan[3], Carolyn Green[4] and Chuanju Liu[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]NYU Hospital for Joint Diseases, New York Univerity, NY, [3]Atreaon, Boston, MA, [4]Atreaon, Boston, NY.

Background/Purpose: We previously reported that Progranulin (PGRN) bound to TNF receptors (TNFR) and was therapeutic in inflammatory arthritis (Tang, W., et al, *Science*, 2011). PGRN is highly cysteine-rich glycoprotein, and contains a number of internal disulfide bonds, which are critical for maintaining the proper folding and confirmation of this protein. The objective of this project is 1) to determine whether PGRN also form a complex with TNFR in immune cells, and whether PGRN affects the binding of TNFα to immune cells, 2) to compare the effects of folding of PGRN on its binding to TNFR and Sortilin, a neuronal receptor known to interact with PGRN as well, and 3) to dissect and identify the domains of TNFR required for PGRN interaction.

Methods: Co-Immunoprecipitation (CoIP) assay and TNF-α blocking assay with flow cytometry were performed to examine the association of PGRN and TNFR in immune cells and its inhibition of TNF binding to cell surface; Various protein-protein interaction assays, including Solid phase binding, Surface Plasmon Resonance, yeast-two hybrid and GST pull-down, were performed to compare the binding activity of various sources of PGRN, to determine the effects of folding of PGRN to TNFR, and to identify the domains of TNFR responsible for binding to PGRN; Differentiation of bone marrow-derived macrophages were used to measure the biological activity of PGRN with ELISA and real-time PCR.

Results: Our previous study showed that PGRN bound to TNFR in chondrocytes. Here we found that PGRN also associated with TNFR2 in splenocytes in a Co-IP assay, and PGRN blocked the binding of TNFα to splenocytes in a dose-dependent manner.

Proper folding and modification of PGRN appear to be essential for its binding to TNFR, as DTT treatment, which is known to disturb the formation of disulfide bonds in PGRN and in turn affects its folding, abolished its binding to TNFR. Interestingly, the binding of PGRN to Sortilin was actually enhanced by DTT treatment. This is probably due to the fact that the C-terminal last three amino acids (DLL) of PGRN, known to be required for Sortilin binding, are exposed in the unfolded PGRN and become more easily accessible to Sortilin. Additionally, in vitro direct protein interaction assays, including Solid phase and Surface Plasmon Resonance, and cell-based functional assays revealed 1) that some commercial PGRNs are of poor quality, and that 2) the selection of chips in Surface Plasmon Resonance is important for demonstrating the high affinity binding of PGRN to TNFR.

Yeast two hybrid assays with numerous deletion mutants of TNFR extracellular domain demonstrated that CRD2 and CRD3 of TNFR are important for the interaction with PGRN, similar to its binding to their canonical ligand TNFα. This finding was confirmed with in vitro GST pulldown and solid phase assay with recombinant proteins.

Conclusion: These findings provide the molecular basis underlying PGRN-mediated anti-inflammatory activity in various autoimmune diseases and conditions.

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ACR/ARHP Poster Session C
Genetics and Genomics of Rheumatic Disease II
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

Tuesday, October 29

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Gene-Body Mass Index Interactions Are Associated With Methotrexate Toxicity in Rheumatoid Arthritis. Stella Aslibekyan[1], Jin Sha[1], David T. Redden[1], Larry W. Moreland[2], James R. O'Dell[3], Jeffrey R. Curtis[1], Ted R. Mikuls[4], S. Louis Bridges Jr.[1] and Donna K. Arnett[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Pittsburgh, Pittsburgh, PA, [3]University of Nebraska Medical Center, Omaha, NE, [4]Omaha VA and University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: Response to methotrexate (MTX) therapy in rheumatoid arthritis (RA) is highly heterogeneous, with both genetic and environmental factors contributing to the efficacy and toxicity of the drug. However, known predictors account for a small proportion of observed variability, and interactions between genetic and environmental factors, in particularly the body mass index (BMI) have not been extensively studied.

Methods: Using data from the Treatment of Aggressive Rheumatoid Arthritis (TEAR) trial (n=755), we fit logistic regressions to test for associations between 3,127 genetic markers selected based on their biological significance and the odds of MTX toxicity, adjusting for age, sex, race, active smoking, BMI, and interactions between genetic variants and BMI. The cohort was randomly split into discovery and replication sets. Genetic variants that reached nominal statistical significance in the discovery phase were subsequently tested in the replication subset.

Results: We observed statistically significant, replicated interactions between BMI and a variant in CMYA5 (cardiomyopathy 5), a known RA susceptibility gene (P=0.005 for discovery, 0.04 for replication), as well as with a variant located near the chemokine (CCL2 and others) gene cluster (P= 0.005 for discovery, 0.05 for replication). Among carriers of at least one copy of the minor allele at either locus, the estimate of BMI effect on MTX toxicity was fourfold higher compared to wild type individuals. Both genetic variants also had significant, replicated main effects on toxicity.

Conclusion: We have identified and replicated interactions between two biologically plausible genetic variants and BMI in models of methotrexate toxicity. Our findings lay the groundwork for developing more accurate and complete algorithms of MTX response prediction in RA.

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1873

Use Of Mendelian Randomization Associates Increased Serum Urate Caused By Genetic Variation In Uric Acid Transporters With Improved Renal Function. Tony R. Merriman[1], Tanya Flynn[1], Janak de Zoysa[2], Nicola Dalbeth[3] and Kim Hughes[1]. [1]University of Otago, Dunedin, New Zealand, [2]Waitemata District Health Board, Auckland, New Zealand, [3]University of Auckland, Auckland, New Zealand.

Background/Purpose: Hyperuricemia is the central risk factor for gout. In observational studies hyperuricemia also predicts the development and progression of chronic kidney disease independent of other measured risk factors. The use of xanthine oxidase inhibitors coincides with improved renal function – whether this is due to reduced serum urate or some other physiological mechanism remains unresolved. We applied Mendelian randomization to the question – is increased serum urate, determined by genetic modulation of renal excretion, detrimental to renal function?

Methods: Data from the Atherosclerosis Risk in Communities (n=5237) and Framingham Heart (n=3033) studies were used. Mendelian randomization uses genetic variants known to be causal of a modifiable exposure (serum urate in this study) to test for association of that exposure with an outcome (renal function in this study). Mendelian randomization by the two stage least squares method was conducted with serum urate as the exposure, a genetic risk score (based on variants from 5 urate transporters; *SLC2A9, ABCG2, SLC17A1, SLC22A11, SLC22A12*) as the instrumental variable and serum creatinine (SCr) or estimated glomerular filtration rate (eGFR) as the outcome. All analysis was done using STATA 8.0 and analyses adjusted for possible confounding variables.

Results: Increased serum urate genetic risk score associated with improved renal function in men (SCr P=0.023, eGFR P=0.045) but not women (SCr P=0.73, eGFR P=0.42) (Table). Analysis of individual genetic variants revealed that the effect size associated with serum urate did not correlate with the effect size associated with renal function in the Mendelian randomization model.

Table. Mendelian randomization analysis of SU against eGFR/SCr.

	Ordinary Least Square Regression			Two Stage Least Square		
	Beta	SE	P	Beta	SE	P
SCr						
All	37.12	2.00	2.65E-75	−16.54	10.48	0.12
Males	38.51	3.01	1.11E-36	−41.65	18.38	0.023
Females	36.84	2.69	8.42E-42	4.29	12.38	0.73
eGFR						
All	−37.67	2.32	1.87E-58	8.87	11.96	0.46
Males	−35.85	3.15	1.97E-29	38.00	18.94	0.045
Females	−37.17	3.43	5.75E-27	−12.71	15.70	0.42

Ordinary least square regression: Beta is the change in SCr/eGFR attributed to a unit change in serum urate (left).
Two stage least square: Beta is the change in SCr/eGFR caused by a unit change in serum urate attributed to the genetic risk score (right).

Conclusion: Contrary to the established relationship of increased serum urate with reduced renal function, increase in serum urate caused by genetic variation in uric acid transporters results in improved renal function. The single variant analysis suggests that the renal protection could be mediated by the activity of renal transporters in increasing serum urate levels. These results justify further research into the mechanism of renal function protection mediated by xanthine oxidase inhibitors.

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1874

Genome-Wide Profiling Identifies Significant Differences Between The T-Lymphocyte and B-Lymphocyte Methylomes In Healthy Individuals. John Glossop[1], Nicola Nixon[1], Richard Emes[2], Kim Haworth[3], Jonathon Packham[1], Peter Dawes[1], Anthony Fryer[3], Derek Mattey[3] and William Farrell[3]. [1]Haywood Rheumatology Centre, Stoke-on-Trent, United Kingdom, [2]University of Nottingham, Sutton Bonnington, United Kingdom, [3]Keele University, Stoke-on-Trent, United Kingdom.

Background/Purpose: Multiple reports now describe changes to the DNA methylome in a variety of autoimmune disorders, such as rheumatoid arthritis. In many cases, these studies have analysed methylation in mixed cell populations from whole blood. However, the cellular heterogeneity inherent

in these approaches may preclude the identification of cell type-specific methylation differences, which may in turn bias identification of disease-specific changes in methylation. To address this possibility, we used genome-wide DNA methylation profiling to identify differences within matched pairs of T-lymphocytes and B-lymphocytes isolated from the blood of healthy individuals.

Methods: Peripheral blood samples were collected from 10 healthy female donors (all Caucasian non-smokers). T- and B-lymphocyte populations were isolated from each individual using magnetic beads and genomic DNA was extracted. Sodium bisulphite converted DNA was hybridised to HumanMethylation450 BeadChips to establish quantitative genome-wide DNA methylation at more than 450,000 CpG sites. Methylation status at individual CpGs was reported as a β-value on a continuous scale ranging from 0 (unmethylated) to 1 (completely methylated). Array processing and identification of differential methylation was performed using NIMBL software. Pyrosequencing was used to validate array data.

Results: Genome-wide methylation was initially determined by analysis of LINE-1 sequences and was significantly higher in B-lymphocytes than matched T-lymphocytes (69.8 vs. 65.2%, $p \leq 0.01$). Pairwise analysis identified 679 CpGs, representing 250 genes, which were differentially methylated between T-lymphocytes and B-lymphocytes. Approximately half of the sites (326; 48%) displayed β-value differences of at least 0.5, and a similar number were associated with a CpG island. The majority of the sites (76.6%) were hypermethylated in B-lymphocytes compared with T-lymphocytes. Pyrosequencing analysis of selected candidate CpGs/genes confirmed the array data in all cases. Hierarchical clustering revealed perfect segregation of the samples into two distinct clusters based on cell type. Differentially methylated genes showed enrichment for biological functions/pathways associated with leukocytes and T-lymphocytes.

Conclusion: Matched pairs of T- and B-lymphocytes from healthy individuals possess intrinsic differences in DNA methylation within a restricted set of functionally-related genes. These data provide a foundation for investigating DNA methylation in diseases in which these cell types play important and distinct roles.

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1875

A Dense Mapping Of Human Leukocyte Antigen Region For Study Of Interaction With Smoking In The Development Of Rheumatoid Arthritis. Xia Jiang[1], Henrik Källberg[1], Lisbeth Ärlestig[2], Solbritt M. Rantapää-Dahlqvist[2], Lars Klareskog[3], Leonid Padyukov[3] and Lars Alfredsson[4]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Umeå University, Umeå, Sweden, [3]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [4]Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden.

Background/Purpose: Rheumatoid arthritis (RA) is believed to have a multifactorial etiology, involving both genetic and environmental components, and can be divided into two major subsets according to the presence/absence of anti-citrullinated protein/peptide antibodies (ACPA). Smoking is the most established environmental risk factor. Despite progress from genome-wide association studies (GWAS), identified genetic variants only explain a small proportion of RA occurrence. Hypothetically, gene-environment interaction could add etiologic understanding of the disease. The aim of current study is to investigate large scale gene-environment interaction between smoking and SNPs selected of interest from an inflammatory point of view, for each of the two major RA subsets.

Methods: We analyzed data from the Swedish EIRA case-control study using logistic regression models. Smoking history was collected through questionnaires. An ever smoker was defined as a person who had ever smoked cigarettes before the index year, while a never smoker was defined as a person who had never smoked cigarettes. Genetic information was obtained from a custom made Illumina Immunochip scan. Interaction between smoking and 133648 genetic markers that passed quality control were examined for the two RA subsets (1590 ACPA positive cases, 891 ACPA negative cases; compared with 1856 matched controls). Attributable proportion (AP) due to interaction together with 95% confidence intervals (CIs) was evaluated for each smoking-SNP pair. We performed replication in a separate case-control study from northern Sweden, Umeå. In order to further validate the results we also performed interaction analysis using GWAS data on the EIRA individuals.

Results: In ACPA positive RA, 102 SNPs were significantly interacting with smoking after Bonferroni correction, all SNPs located in the HLA region (one in HLA class I region, the rest in HLA class II region) and displayed high linkage disequilibrium (LD); 51 of them were replicated in the Umeå study. No additional loci besides from chromosome 6 turned up in the GWAS validation. After adjusting for *HLA-DRB1* shared epitope (SE), 15 SNPs remained significant for ACPA positive RA, with 8 of them being replicated. For ACPA negative RA, no SNP passed threshold for significance. Through functional prediction and pathway annotation, 10 candidate genes/regions were identified for ACPA positive RA, with dominance on antigen presentation pathways (*HLA-DOB, HLA-DQA1, HLA-DQA2, HLA-DRA, HLA-DRB1, HLA-DRB5, TAP2*).

Conclusion: Our study presents the most explicit picture to date, with regard to the patterns of gene-smoking interaction in ACPA positive/negative RA, suggesting contrasting etiology of the two subsets. Except for HLA-DR, the study additionally unambiguously linked RA risk to the class I HLA, implicating the function of CD8+ T cells in RA pathogenesis.

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1876

Potential Chondrogenic Biomarkers For Cell-Based Therapy Monitoring In Osteoarthritis. Beatriz Rocha[1], Valentina Calamia[1], Vanessa Casas[2], Lucia Lourido[1], Carolina Fernandez-Costa[1], Patricia Fernandez-Puente[1], Jesus Mateos[1], Montserrat Carrascal[2], Francisco J. Blanco[1] and Cristina Ruiz-Romero[3]. [1]Osteoarticular and Aging Research Laboratory, Proteomics Unit-Associated Node to ProteoRed-ISCIII, INIBIC-CHUAC, A Coruña, Spain, [2]Laboratorio de Proteómica CSIC/UAB, Barcelona, Spain, [3]CIBER-BBN, INIBIC-CHUAC, A Coruña, Spain.

Background/Purpose: Chondrogenesis occurs as a result of mesenchymal stem cells (MSCs) condensation and chondroprogenitor cell differentiation. Following chondrogenesis, the chondrocytes remain as resting cells to form the articular cartilage. A major challenge for the osteoarthritic (OA) cartilage repair by stem cell-based approach is the understanding of this multi-step process. In this work, we have analyzed the extracellular protein expression profile of human bone marrow MSCs (hBMSCs) of osteoarthritic patients and control donors undergoing chondrogenesis, in order to compare the mechanisms involved in the cartilage extracellular matrix (ECM) remodeling that occurs during chondrogenic differentiation process.

Methods: hBMSCs isolated from 3 OA patients and controls were grown with different isotope variants of lysine and arginina (Arg6, Lys4 for the control population and Arg10, Lys8 for the OA population) during 4–6 weeks, until achievement of full labeling. The labeled populations were then subjected to differentiation in 3D cultures (micromasses) supplemented with chondrogenic inducers for 14 days. Proteins in the conditioned media from the two cell populations were combined, separated by 1D-SDS-PAGE and subjected to in-gel trypsin digestion using an automatic digestor. The resulting peptide mixtures were analyzed by nanoLC coupled on-line to an LTQ-Orbitrap XL mass spectrometer and quantified using the MaxQuant software.

Results: Real-Time PCR assays showed a relevant difference in the gene expression of collagen type II in the normal donors when compared to the OA patients. Moreover, the chondrocyte phenotype was confirmed in both cases by the proteoglycan immunostainings such as aggrecan and chondroitin-6-sulfate after 14 days in chondrogenesis. Using the proteomic approach, we compared the extracellular protein profiles of OA and normal hBMSC at the same time of differentiation. Among the 531 proteins quantified, 56 had significantly altered levels. 35 proteins displayed consistently higher levels in the OA samples compared to normal donors. Many of these proteins are cartilage specific proteoglycans such as hyaluronan and proteoglycan link protein 1, aggrecan core protein or lumican as well as some proteins with a well-known role in the pathogenesis of OA like COMP or MMP3. On the other hand, 21 proteins exhibited a significantly reduced abundance in OA patients when compared to controls. Interestingly, we detected several proteins which belong to the tenascin protein family, like tenascin-X which accelerates collagen fibril formation. We also found WISP2 decreased at day 14, suggesting a lower activity of the Wnt signaling pathway in OA cells.

Conclusion: The identification and quantification proteins secreted by OA and normal hBMSC enhance our knowledge on the extracellular

regulation of this process and allow the identification of extracellular markers of chondrogenesis. Moreover, the lower expression of some of them in OA patients (like tenascin-X or WISP2), suggest their putative role for the molecular monitorization of the chondrogenesis in cell therapy-based approaches for cartilage repair.

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1877

A Neutrophil Signature Comprised Of Low Density Granulocyte (LDG)-Enriched Genes Is Associated With Organ-Specific Disease Activity In Systemic Lupus Erythematosus. Michelle Petri[1], Hong Fang[1], Jadwiga Bienkowska[2], Andrea Dearth[3], Norm Allaire[2] and Ann Ranger[3]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Biogen Idec Inc., Cambridge, MA, [3]Biogen Idec Inc, Cambridge, MA.

Background/Purpose: The neutrophil gene signature (NGS) has recently gained interest due to new understanding of the role of neutrophils and NETosis in SLE pathogenesis. We explored the association of a neutrophil gene signature comprised of genes significantly upregulated in low-density granulocytes (LDGs) with both global and organ specific disease activity in SLE patients.

Methods: Of 292 SLE patients, 91.1% were female; 58.9% Caucasian, 33.9% African-American, and 7.2% other ethnicities. Mean age (standard deviation) at baseline was 46.0 (±11.9) years. Gene expression levels were assessed in peripheral blood RNA samples using microarray (Affymetrix). The LDG-associated gene signature was comprised of 8 genes significantly upregulated in LDGs relative to normal-density neutrophils. The LDG-associated signature "score" was calculated based on the geometric mean of the expression levels (chip signal intensity) of the 8 genes in the signature. The patients were divided into three roughly equal sized groups based on neutrophil signature "scores", and the groups compared with respect to same-day disease activity. Adjusted p-values were calculated using generalized linear models controlling for ethnicity (SAS 9.2).

Results: The NGS was high (>6) in 31.9% (N=93), medium (5–6) in 31.5% (N=92), and low (<5) in 36.6% (N=107) of patients. The LDG-associated NGS was associated with same day global activity measured both by the physician global assessment >1 (on a 0 to 3 VAS) and by SLEDAI ≥2. It was associated with renal activity by VAS, arthritis by SLEDAI, anti-dsDNA, low complement, and alopecia. It was negatively associated with the hematologic VAS.

Table 1. Association between same-day disease activity and neutrophil signature in SLE

Variable	Low Neutrophil (<5) (% patients N=107)	Med Neutrophil (5–6) (% patients N=92)	High Neutrophil (>6) (% patients N=93)	Adjusted *P*-value for Ethnicity	Adjusted *P*-value for Ethnicity, Low/Med vs High
Physician's global assessment >1	11.2	16.3	30.1	0.003	0.0011
Rash >0	27.1	33.7	33.3	0.19	0.093
Joints >0	25.2	32.6	37.6	0.15	0.12
Serositis >0	0.9	1.1	2.2	0.65	0.36
Neurologic >0	0	2.2	3.2	0.078	0.14
Renal >0	14.0	12.0	28.0	0.0085	0.0024
Hematologic >0	24.3	13.0	9.7	0.0096	0.020
SELENA SLEDAI ≥2	47.7	60.9	65.6	0.012	0.015
Hematuria	0.9	0	3.2	0.091	0.062
Proteinuria	5.6	4.4	10.8	0.18	0.072
Arthritis	0	1.1	6.5	0.0073	0.0023
Low complement	12.2	13.0	24.7	0.066	0.020
Anti-dsDNA	10.3	26.1	31.2	0.0005	0.011
Rash	2.8	7.6	7.5	0.21	0.47
Alopecia	18.7	23.9	28.0	0.011	0.0030
Mucous membrane	3.7	3.3	3.2	0.95	0.77
Pleurisy	1.0	1.1	2.2	0.65	0.36
Platelet<100	2.8	2.2	1.1	0.62	0.35
WBC<3	2.8	1.1	3.2	0.50	0.45

Conclusion: The LDG-associated gene signature was strongly associated with both global and organ-specific activity, being positively associated with arthritis and renal disease. Subsetting patients by neutrophil gene signature may be helpful in clinical trials of new biologics in SLE. In those patients with renal and musculoskeletal activity, LDGs may be a promising therapeutic target.

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Proteomics Analysis Of Cartilage Secretome: A Powerful Tool For The Discovery Of OA Biomarkers. Lucía Lourido, Valentina Calamia, Patricia Fernández-Puente, Jesus Mateos, Beatriz Rocha, Carolina Fernández-Costa, Francisco J. Blanco and Cristina Ruiz-Romero. Osteoarticular and Aging Research Laboratory, Proteomics Unit-Associated Node to ProteoRed-ISCIII, INIBIC-CHUAC, A Coruña, Spain.

Background/Purpose: Osteoarthritis (OA) is characterized by the progressive loss of cartilage structural extracellular matrix (ECM) components, mainly collagenous and non-collagenous proteins. The release of these proteins from the tissue can vary according to the stage of the disease. Characterization of molecular differences between cartilage subtypes will provide a background for better understanding OA onset and progression. The aim of this study was to perform a quantitative proteomics approach to identify and quantify those proteins released from normal (N) and OA human articular cartilages.

Methods: Tissue explants were obtained from the dissection of 4 N and 4 OA cartilages, both from femoral heads and tibial condyles. Among the OA samples, we differentiated the wounded zones (WZ) from those corresponding to the area adjacent to the lesion, or unwounded zones (UZ). The study was approved by the local ethical committee. Cartilage shavings from each donor were cut into 6 mm discs and five discs/donor were placed into 96 wells plates and incubated during 6 days (37 °C/5% CO2). The conditioned media from each condition were collected and their proteins were digested with trypsin. Each peptide mixture was labelled with different isobaric tags using the iTRAQ reagents (ABSciex). Then, labelled peptides of the different conditions were mixed, desalted and separated by liquid chromatography (LC). The resulting fractions were grouped and resolved by reversed-phase nano-LC coupled to mass spectrometry (MS). The identification and relative quantification of the proteins was carried out with Protein Pilot 3.0 software.

Results: A mean of 206 cartilage secreted proteins was identified. Measurement of the different iTRAQ tags intensities allowed the relative quantification of almost all of them. Globally, we found 35 secreted proteins with statistically significant differences in abundance ($p \leq 0.05$) between the different OA zones (WZ and UZ) when compared with N samples: 26 were increased and 9 were decreased. We classified them in 3 sets of proteins: a group of 5 proteins (CILP, CILP2, CHI3L1, SPP1, PLA2G2A) were increased specifically in UZ samples (early OA biomarkers), a group of 6 proteins (APOA1, HSPG2, CRTAC1, COL12A1, COL15A1, PRG4) were increased only in WZ samples (late OA biomarkers) and finally a group of 15 proteins were modified in both OA zones. Although some of these proteins, like CHI3L1 and PRG4, have a previously reported putative biomarker value for OA, most of them are novel candidates of the disease onset (the first group) and progression (the second and third groups). Interesting when we compared these results with those obtained from cartilage tissue extracts analysis we found that most of the proteins increased in OA cartilage secretomes (like BGN, HAPLN1, APCS, TNC, TGFBI) are decreased in cartilage proteomes and viceversa.

Conclusion: We have identified a characteristic profile of proteins released from N and OA cartilages. We describe a panel of cartilage ECM proteins with potential biomarker value. This panel will be further explored in biological fluids (synovial fluid and serum) for the development of early diagnosis and/or anti-OA therapy monitoring strategies.

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Major Histocompatibility Complex Class I Molecules Contribute To Behçet's Disease Risk Through Both Innate and Adaptive Immune Interactions. Michael J. Ombrello[1], Yohei Kirino[2], Paul de Bakker[3], Ahmet Gül[4], Elaine F. Remmers[2] and Daniel L. Kastner[2]. [1]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [2]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [3]University Medical Center Utrecht, Utrecht, Netherlands, [4]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey.

Background/Purpose: Behçet's Disease (BD) is a complex genetic disease of unknown etiology that is characterized by inflammatory lesions of the eyes, skin, and oro-genital mucosa. The class I major histocompatibility complex (MHC) molecule, *HLA-B*51* (*B*51*), is the strongest known genetic

risk factor for BD. Associations between BD and a range of other factors within the extended MHC locus (xMHC) have also been reported, however strong linkage disequilibrium across the xMHC has complicated the confident disentanglement of other BD risk factors from *B*51*.

Methods: We examined a combination of directly obtained and imputed single nucleotide polymorphism (SNP) genotypes, directly obtained *HLA-B* locus types, and imputed classical *HLA* types and polymorphic HLA amino acid residues for association with BD in 1190 BD cases and 1257 controls. Genotypes from 2832 xMHC SNPs were extracted from a genome wide SNP array, and these data were used as the basis for SNP imputation with reference data from the 1000 Genomes Project. *HLA-B* types were determined using a sequence specific oligonucleotide-based assay. We used imputation to infer classical HLA types and the identities of polymorphic amino acid residues in each classic HLA molecule. Stepwise logistic regression and conditional analyses were performed using genotype probabilities produced by imputation.

Results: SNP mapping of the xMHC identified two regions, the *HLA-B/MICA* region and the region between *HLA-F* and *HLA-A*, as independently and significantly associated with BD after respective regression analyses ($p < 1.7E-08$). Haplotype analysis of the *HLA-B/MICA* region identified a common BD-associated haplotype that included *B*51* and 48 BD-associated SNPs, yet an identical SNP haplotype that lacked *B*51* conferred no risk of BD. We found that *HLA-B*51*, *-B*15*, *-B*27*, *-B*57*, and *-A*26* each contributed to BD risk independently, while *HLA-B*49* and *-A*03* were each protective against the development of BD. Regression analyses of polymorphic amino acid residues identified independent associations between BD and nine MHC class I amino acid residues, including one that conferred risk in both HLA-A and HLA-B. The majority of the BD-associated residues clustered around the MHC class I antigen binding groove, however one residue was located in the signal peptide of HLA-B. The BD-associated risk variant, threonine, at position −21 in the signal peptide has been previously shown to produce enhanced NK cell activation and cytotoxicity by reducing inhibitory NK ligand expression, when compared to the protective variant, methionine.

Conclusion: There are multiple MHC class I antigens, including *B*51*, that independently affect BD susceptibility. Nine MHC class I amino acid residues influence BD risk, eight of which map to the antigen binding groove and imply adaptive immune involvement. One BD-associated residue is within the HLA-B signal peptide, a known point of cross-talk between the innate and adaptive immune systems, where it leads to reduced protection from NK cytotoxicity. Together, our data indicate that MHC class I molecules influence BD risk through both innate and adaptive immune mechanisms.

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1880

Global Gene Expression Profiles Reveal Genetic Signatures Of Kawasaki Disease and Disease Outcome. Long Truong Hoang[1], Chiea Chuen Khor[1], Ahmad Nazri Mohamed Naim[1], Ling Ling[1], Chisato Shimizu[2], Martin L. Hibberd[1] and Jane C. Burns[2]. [1]Genome Institute of Singapore, Singapore, Singapore, [2]UC San Diego, School of Medicine, La Jolla, CA.

Background/Purpose: Kawasaki Disease (KD) is a self-limited vasculitis of unknown etiology that predominantly affects children younger than 5 years. The inflammation associated with KD affects the arterial wall and leads to coronary artery aneurysms (CAA) in 25% of untreated KD children, making KD the most common cause of acquired heart disease in children in developed countries. Genetic predispositions are thought to influence the risk of aneurysm formation, and several gene expression profiling studies for KD were performed to describe KD-specific signatures. However, the lack of power due to limited sample size precluded definitive identification of transcriptomic signatures specific to KD. In this study, we aim to identify the gene expression signatures associated with acute KD by investigating the global gene expression profiles in large number of samples collected in paired-blood samples from acute and convalescent phases. We also investigated the transcript abundance in patients with different IVIG treatment status and different CAA outcomes.

Methods: Illumina gene expression microarray was used to characterize gene expression profiles of 171 KD patients with paired blood samples from the acute and convalescent phase of KD. Quantitative RT-PCR was used to validate the findings of the microarray. A detailed clinical and hematological data was also collected for all the patients. A generalized linear model was used to indentify differentially abundant transcripts between acute and convalescent samples, as well as between IVIG response status and CAA outcomes.

Results: Our data suggest that the complement and coagulation cascades, Toll-like receptor signaling and innate immune related responses were the most prominent pathways that were up-regulated in acute KD patients, while CD8 T cell receptor pathway such was less abundant in acute patients. Toll-like receptors (TLR2, 5 and 8), FCGR1 (A and B), FCRG2 (A and B), CD3, CD4, CD8 and CD28 were amongst the most significant transcripts. We also observed and validated 24 transcripts that were differentially expressed between IVIG responsive and IVIG-resistant KD patients which could play a pivotal role in the disease pathogenesis. These include LILRA5, IL18R1, IRAK3, SORT1 and BMX.

Conclusion: We proposed the potential genetic signatures of acute KD and signatures of IVIG treatment outcomes. The functions of these markers will be further discussed.

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1881

HLA-DRB1 Rheumatoid Arthritis Susceptibility Amino Acids Define Haplotypes Associated With Radiological Outcome. Sebastien Viatte[1], Annie Yarwood[2], Buhm Han[3], Soumya Raychaudhuri[3], Deborah P. M. Symmons[4], Jane Worthington[5] and Anne Barton[6]. [1]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, Centre for Musculoskeletal Research, Institute of Inflammation and repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [4]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [5]Arthritis Research UK Epidemiology Unit, The University of Manchester and Rheumatoid Arthritis Consortium for Immunochip (RACI), International Consortium, United Kingdom, [6]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom.

Background/Purpose: Rheumatoid arthritis (RA) is a systematic autoimmune disease caused by the interplay between environmental and genetic risk factors. The major genetic determinants of RA susceptibility comprise a group of alleles of the HLA DRB1 gene, which encode a similar amino-acid (aa) motif in the peptide binding groove of the beta chain and are collectively referred to as the shared epitope (SE). Several studies investigated different classifications of HLA-DRB1 alleles and their association with disease susceptibility. Recently, we reported a new classification system based on 3 HLA-DRB1 aa independently associated with RA susceptibility. We demonstrated that HLA-DRB1 haplotypes defined solely by aa at positions 11, 71 and 74 can be hierarchically classified regarding their effect size on RA susceptibility, ranging from risk to protective haplotypes. The impact of this classification on the prediction of radiological outcome in RA has not been studied so far.

Aims: To test whether the RA risk hierarchy within HLA-DRB1 haplotypes also associates with radiological outcome.

Methods: The Norfolk Arthritis Register (NOAR) is a primary care based inception cohort of patients with inflammatory polyarthritis (IP). Radiographs of the hands and feet were performed at baseline, year 1 and year 2 for some patients, and systematically at year 5 for all patients and scored using the Larsen technique. The HLA region of a subset of NOAR patients was densely genotyped using a custom Illumina® Infinium® array (ImmunoChip), imputed and HLA-DRB1 aa at positions 11, 71 and 74 were derived. In order to incorporate multiple records per patient over time and to fit the non-normal distribution of Larsen scores, Generalized Linear Latent and Mixed Modelling (GLLAMM) with discrete random effects and three latent classes was used to assess the association between Larsen score and HLA-DRB1 haplotypes longitudinally.

Results: 1685 NOAR patients had at least one x-ray available and 4-digit HLA-DRB1 typing with a total of 2796 x-rays. Of these, 482 were genotyped on the ImmunoChip platform. HLA-DRB1 haplotypes based on positions 11, 71 and 74 were grouped in 3 haplotype categories, based on their known effect on disease susceptibility (risk, neutral or protective). Preliminary multivariate haplotype group analysis showed a correlation between known effect sizes for susceptibility and effect sizes for severity. The protective group of HLA-DRB1 haplotypes on RA susceptibility

(Ser-Lys-Arg or Ser-Glu-Ala at 11, 71, 74, corresponding to HLA-DRB1*03:01, *11:02, *11:03, *13:01, *13:02) is protective for the development of radiological damage as well, independently of the SE.

Conclusion: Susceptibility HLA-DRB1 haplotypes define severity haplotypes as well. Protective HLA-DRB1 haplotypes on radiological severity were also identified. Since the effect size of HLA-haplotypes is likely to outweigh the effect of non-HLA single nucleotide polymorphisms in the prediction of disease outcome, our findings may be relevant in stratifying patients into different risk categories prior to the initiation of treatment.

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1882

Characterizing The C-Type Lectin Domain Family 4, Member C Gene (*CLEC4C*) Expression In Peripheral Blood From Rheumatoid Arthritis Patients. Annie Yarwood[1], Joanna Cobb[2], Kate McAllister[1], Joanne Barnes[1], Ernst R. Dow[3], Michelle A. Penny[3], Robert W. Hoffman[3] and Anne Barton[4]. [1]Arthritis Research UK Epidemiology Unit, Centre for Musculoskeletal Research, Institute of Inflammation and repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [2]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academic Health Science Centre, Central Manchester Foundation Trust, Manchester, United Kingdom, [3]Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, [4]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom.

Background/Purpose: A previous hypothesis-seeking study examining baseline phenotypic expression of mRNA in a Phase 2 clinical trial of tabalumab (also known as LA294 or LY2127399) suggested that expression of the gene *CLEC4C* might serve to help stratify patients for their clinical response to tabalumab. CLEC4C-expressing cells appear to mediate their immunoregulatory effects through direct cell-cell contact or indirectly through the production of cytokines including TGF-beta and IL-10 and appear to influence T regulatory cells via these mechanisms. We hypothesize that this immunoregulatory cell may have a role in pathogenesis of RA and may influence drug treatment response. The primary aim of our study was to characterise the phenotypic expression of the gene *CLEC4C*, as measured in peripheral blood among a well characterised cohort of rheumatoid arthritis patients receiving different therapies.

Methods: Total RNA was extracted from whole blood and converted to cDNA. A total of 322 samples were available for analysis, consisting of four groups: 1) 93 healthy controls 2) 72 RA patients with recent onset disease receiving methotrexate 3) 85 RA patients who have failed methotrexate and are receiving a TNFi 4) 72 RA patients who had failed at least one TNFi due to lack of efficacy and were receiving another biologic. Quantitative real time PCR was carried out to measure the expression of *CLEC4C* and three reference genes. *CLEC4C* expression was normalised and quantified using the delta CT method. Linear regression was used to correlate expression with treatment group.

Results: A significant difference in CLEC4C expression was observed between sample groups ($p=2.5\times10^{-5}$). CLEC4C expression was significantly higher in healthy individuals compared to all RA patients ($p=8.9\times10^{-6}$). All patient groups showed lower expression when compared to healthy controls and this difference is greatest in patients treated with biologic therapies including TNFi (Table 1).

Table 1. Linear regression results comparing CLEC4C expression in patients and healthy controls

Group	Coefficient	Standard error	P value	95% confidence interval	
Controls	Reference	—	—	—	—
MTX	−0.0018	0.0006	0.007	−0.0032	−0.0005
TNFi	−0.0027	0.0007	9.89×10^{-5}	−0.0040	−0.0013
Other Biologic	−0.0027	0.0007	0.00036	−0.0042	−0.0012

Conclusion: Differences in expression of *CLEC4C* were found between RA patients and age- and sex-matched healthy controls with statistically significant higher levels of expression of *CLEC4C* seen in healthy controls. Among RA patients the highest levels of CLEC4C were seen in the RA patients who had been treated only with methotrexate and were biological naive; lowest levels of *CLEC4C* in those treated with one or more biologic agent including TNFi. These results suggest that stratification for *CLEC4C* expression may be valuable to assure balance between patient subgroups in clinical trials in that difference in baseline *CLEC4C* expression could be a source of unanticipated bias influencing trial outcome. Finally, determining the biologic basis for these observed differences in *CLEC4C* gene expression among different subgroups of patients, based upon prior treatment, may help advance our understanding of disease pathogenesis in RA.

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Fine Mapping and Expression Of a Locus Overlapping 3 Types Of Inflammatory Arthritis. Kathryn J. A Steel[1], Anne Hinks[1], Annie Yarwood[2], Stephen Eyre[3], Edward Flynn[3], Paul Martin[1], Anne Barton[3] and Wendy Thomson[4]. [1]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Sciences Centre, Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, Centre for Musculoskeletal Research, Institute of Inflammation and repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [3]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [4]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academic Health Science Centre, Manchester, United Kingdom.

Background/Purpose: In a recent fine-mapping study using the Immunochip array, the *RUNX1* region was strongly associated with rheumatoid arthritis (RA $p=5\times10^{-10}$), juvenile idiopathic arthritis (JIA $p=1\times10^{-8}$) and psoriatic arthritis (PsA $p=6\times10^{-4}$). In each disease the SNP rs9979383 confers disease protection with odds ratios ranging from 0.8–0.9. This SNP maps approximately 290kb upstream of *RUNX1*, indicating that it may be involved in regulation of gene expression. *RUNX1* encodes a transcription factor highly expressed during chondrogenesis, which has also been shown to interact with the regulatory T cell marker *FOXP3*. Unlike many loci on the Immunochip, variation in the *RUNX1* region is not well covered, therefore further fine mapping is required.

Methods: As rs9979383 lies between two points of high recombination, SNPs between these points were selected for fine mapping. 42 common (MAF>0.05) tag SNPs ($r^2>0.9$) from the Utah residents (CEPH) with Northern and Western European ancestry (CEU) 1000 genomes July 2010 release were selected. 2255 RA cases and 1877 healthy controls from the United Kingdom Rheumatoid Arthritis Genetics Group (UKRAG) were genotyped using the Sequenom iPlex MassARRAY platform. SNPs and samples which reached >90% success rate were included in the analysis. Allelic association testing was performed using PLINK v.1.07 and functional annotation of SNPs was performed using ASSIMILATOR. To determine if rs9979383 represents an expression quantitative trait locus (eQTL), Taqman genotyping and gene expression assays were performed in 75 healthy controls from the national repository healthy volunteers study. *RUNX1* expression was normalised to 2 endogenous controls (*ACTNB* and *GAPDH*) and linear regression performed in STATA v.11.2.

Results: In the UKRAG cohort, association with rs9979383 was replicated ($p=0.02$, OR = 0.9, CI 95% 0.82–0.98) with an odds ratio of 0.9, identical to the previous RA study. No other SNPs in the region showed evidence for association. Functional annotation of this SNP indicates that it lies within a region of open chromatin with transcription factor binding potential, making it an ideal candidate for gene expression studies. In whole blood, RUNX1 expression was not correlated with genotype at rs9979383 in healthy controls ($p=0.92$) indicating that rs9979383 may alter expression of another gene or that this eQTL may only be present at a cell specific level.

Conclusion: The results indicate that the *RUNX1* association is localised to r99793983 (or SNPs in high LD) in RA but the association requires confirmation in independent JIA and PsA cohorts. Although no eQTL was observed in whole blood in healthy controls, cell specific whole transcriptome studies are currently underway to determine whether this SNP is an eQTL. Combined with the fine mapping this will inform further investigations of the role of the *RUNX1* region in the common pathogenesis of inflammatory arthritis.

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Autoantibody Specificities and Type I Interferon Pathway Activation In Idiopathic Inflammatory Myopathies. Saskia Vosslamber[1], Louise Ekholm[2], Anna Tjarnlund[2], T.D. de Jong[1], Lenka Plestilova[3], Martin Klein[4], Peter J. Charles[5], A.E. Voskuyl[1], Irene Bultink[1], Michiel Pegtel[1], J Vencovsky[6], Ingrid E. Lundberg[2] and Cornelis L. Verweij[1]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, [3]Institute of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [4]Institute of Rheumatology, Prague, Prague, Czech Republic, [5]Kennedy Institute of Rheumatology, Oxford, United Kingdom, [6]Institute of Rheumatology, Prague, Czech Republic.

Background/Purpose: Idiopathic inflammatory myopathies (IIM) are rare autoimmune diseases characterized by proximal muscle weakness and muscle inflammation. IIM are associated with several autoantibodies, which are believed to play a role in its pathogenesis. Recent studies showed involvement of an activated type I IFN pathway in a subset of patients. Here we studied the possible relationship between autoantibody specificity and type I IFN pathway activation.

Methods: Ninety-four IIM patients, diagnosed with polymyositis (PM) (n=46), dermatomyositis (DM) (n=42), or inclusion body myositis (IBM) (n=6), 47 patients with systemic lupus erythematosus (SLE) and 43 healthy controls (HC) were included. Autoantibody profiles were assessed using lineblots. A whole blood IFN score was determined in all patients and healthy controls by measuring and averaging expression levels of 29 IFN response genes using BioMark™Dynamic Arrays. Type I IFN bioactivity in serum of 47 IIM patients was determined using a bioassay. The role of IFNα as an interferogenic trigger was determined using neutralizing antibodies in sera of a subset of 25 patients.

Results: The IFN signature was present in 45% of IIM patients, irrespective of diagnosis. The IFN score was associated with disease activity for patients diagnosed with DM but not PM or IBM. In IIM patients with a mono-specific autoantibody profile, an association between the presence of an IFN signature and autoantibodies against RNA binding proteins, such as Jo-1, Ro60, SRP and U1RNP, was observed, whereas the absence of an IFN signature is associated with autoantibodies not directed against RNA-binding proteins, such as Ro-52, and PMScl. Moreover, we observed an association between the presence of an IFN signature and patients with multi-specific autoantibody profiles compared to patients with a mono-specific autoantibody profiles or patients without autoantibodies ($p = 0.038$ and $p=0.002$, respectively). The IFN score correlated with type I IFN pathway-bioactivity (n=47) (r 0.4243, p= 0.0057), which could be partly blocked by neutralizing antibodies directed against IFNα and the type I IFN receptor.

Conclusion: Overall, our findings indicate involvement of IFNα in the type I IFN activity in IIM and suggest a relationship between the presence of anti-RNA-binding protein autoantibodies and the IFN signature in IIM. This hints towards a role for RNA as trigger of type I IFN activity in IIM similarly as has been observed for SLE.

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1885

A Weighted Genetic Risk Score Using All Known Susceptibility Variants To Predict Rheumatoid Arthritis Risk. Annie Yarwood[1], Buhm Han[2], Soumya Raychaudhuri[1], John Bowes[1], Mark Lunt[3], Dimitrios A. Pappas[4], Joel M. Kremer[5], Jeffrey D. Greenberg[6], Robert M. Plenge[2], Jane Worthington[3], Anne Barton[7] and Stephen Eyre[3]. [1]Arthritis Research UK Epidemiology Unit, Centre for Musculoskeletal Research, Institute of Inflammation and repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [3]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [4]Columbia University, College of Physicians and Surgeons, New York, NY, [5]Center for Rheumatology, Albany Medical College, Albany, NY, [6]New York Hospital for Joint Diseases, New York, NY, [7]NIHR Manchester Musculoskeletal BRU, Central Manchester Foundation Trust and University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom.

Background/Purpose: Recent advances in the identification of loci associated with susceptibility to complex disease have led to methods being developed that incorporate this information into genetic screening models to identify individuals at high risk of disease. Here we present the first risk prediction model including all 46 known genetic loci associated with rheumatoid arthritis (RA) in Caucasian populations.

Methods: Weighted genetic risk scores (wGRS) were created using odds ratios from 45 RA susceptibility SNPs and a HLA-DRB1 tag SNP or imputed HLA amino acids (HLA-DRB1 amino acids 11, 71, 74 and amino acids 9 at HLA-DPB1 and HLA-B). The wGRS were tested in 11,370 RA cases and 15,536 healthy controls of known genotype from the UK, USA, Sweden, Netherlands and Spain, all cases were Caucasian, over the age of 18 and satisfied 1987 ACR criteria for RA modified for genetic studies. The risk of developing RA was assessed using logistic regression by dividing the wGRS into quintiles. The ability of the wGRS to discriminate between cases and controls was assessed by receiver operator curve (ROC) analysis and discrimination improvement tests. As several of the RA susceptibility loci included in the wGRS were identified in the cohort used in this study, the wGRS were tested in an independent European cohort of 2206 RA cases and 1863 healthy controls for validation. Validation samples were from the Consortium of Rheumatology Researchers of North America (CORRONA) registry and the Informatics for Integrating Biology and the Bedside (I2B2) centre.

Results: Individuals in the highest risk group showed significantly increased odds of developing anti-CCP positive RA compared to the lowest risk group (AUC 0.77, OR 18.00 95% CI 13.67–23.71). 4347 individuals were classed as high risk when all susceptibility factors were included in the model, interestingly this included 10.13% of our control population. The wGRS was validated in an independent cohort which showed similar results (AUC 0.78, OR 18.00 95% CI 13.67–23.71). The AUC was improved by replacing the HLA-DRB1 tag SNP with imputed HLA variation at HLA-DRB1, HLA-DPB1 and HLA-B (wGRStag AUC 0.70, wGRSfull AUC 0.77) (in CCP positive individuals). Integrated discrimination improvement tests showed an increase in sensitivity and specificity of 9% and net reclassification tests showed that including all variation in the HLA over a HLA tag SNP improves the probability of correctly identifying a high risk individual to 69.20% from 64.21% and showed an overall reclassification improvement of 58.54% between models. Comparing the full model (in CCP positive individuals) to a model containing only imputed variation at the HLA and gender showed that the addition of the susceptibility SNPs to the model only slightly improved the ROC AUC (0.74 to 0.77 respectively).

Conclusion: We have shown that in RA, even when using all known genetic susceptibility variants, prediction performance remains modest; whilst this is insufficiently accurate for general population screening, it may prove of more use in targeted studies. Our study has also highlighted the importance of including HLA variation in risk prediction models.

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Differential Methylation Related To Response To Etanercept In Patients With Rheumatoid Arthritis. Amy Webster[1], Darren Plant[2], Mark Lunt[1], Stephen Eyre[1], Edward Flynn[1], Paul Martin[3], A. G. Wilson[4], A. W. Morgan[5], John Isaacs[6], Jane Worthington[1] and Anne Barton[1]. [1]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [2]NIHR Manchester Musculoskeletal BRU, Central Manchester Foundation Trust and University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, [3]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Sciences Centre, Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom, [4]Genomic Medicine, The University of Sheffield, Sheffield, United Kingdom, [5]Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom, [6]National Institute for Health Research, Newcastle Biomedical Research Centre, Newcastle Hospitals Foundation Trust and Newcastle University, Newcastle Upon Tyne, United Kingdom.

Background/Purpose: The introduction of biologic drug therapies targeting specific components of the inflammatory response represents a huge advance in the treatment of rheumatoid arthritis (RA). Despite this, up to 40% of patients fail to respond well to these therapies. Ideally, clinicians would like to identify patients who are likely to respond to therapy as early as possible in the disease course, making identification of reliable biomarkers of response an important area of research. Recent studies suggest that epigenetic control

of gene expression may be important in RA; we have therefore hypothesized that epigenetic changes such as aberrant DNA methylation patterns may provide useful biomarkers of response to biologics.

Objectives: To identify a DNA methylation signature indicative of response to TNF-blockade therapy in patients with RA.

Methods: Patients were recruited from the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGSS) longitudinal cohort. Patients (n=72) were selected based on having an extreme response phenotype after 3 months of treatment with etanercept; 36 were good responders defined as having an endpoint DAS28<2.6, and 36 were poor responders defined as having an improvement of <0.6 or between 0.6–1.2 with an endpoint DAS28 of >5.1. Whole blood DNA from each patient, sampled before initiation of etanercept therapy, was bisulfite converted and an epigenome wide association study was conducted using the HumanMethylation450 BeadChip (Illumina). A detection threshold was applied and probes with a detection p-value of greater than 0.01 were removed. Differentially methylated positions between responders and non responders were identified by linear regression following quantile normalisation.

Results: 4 CpG sites showed differences between responders and non-responders to etanercept passing a false discovery rate of 0.05 with a ($p \leq 10^{-7}$): cg04857395, cg16426293, cg03277049, cg14862806. While none of the 4 CpG sites mapped to obvious candidate genes, the most differentially methylated probe mapped to exon 7 of *LRPAP1,* which is highly expressed in mononuclear cells. Statistical adjustment for whole blood cell composition did not qualitatively alter the results.

Conclusion: This is the first methylome wide investigation of treatment response to TNF blockade therapy in RA and, while further well powered studies are required, these preliminary data identify methylation biomarkers of response.

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1887

Interleukin-1 Receptor Antagonist (IL-1Ra) Plasma Levels Predict Radiographic Progression Of Symptomatic Knee Osteoarthritis Over 24 Months. Mukundan Attur[1], Alexander Statnikov[2], Jonathan Samuels[2], Svetlana Krasnokutsky[1], Jeffrey D. Greenberg[1], Zhiguo Li[2], Leon Rybak[2], Constantin F. Aliferis[2] and Steven B. Abramson[2]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]NYU Langone Medical Center, New York, NY.

Background/Purpose: Osteoarthritis is multi-factorial complex degenerative joint disease that leads to permanent joint damage. We and others have shown elevated levels of inflammatory and anti-inflammatory mediators in OA. Furthermore, polymorphism in IL-1RN gene has been shown to predict radiographic severity and progression in OA. There is currently great interest in the field of OA to identify biomarkers that identify patients at higher risk for disease progression and to identify biomarkers that can lead to new drug targets. This study was designed to test the hypothesis that plasma levels of IL-1Ra predict radiographic knee OA severity and progression and to examine IL-1Ra interactions with other biomarkers and confounding covariates.

Methods: 178 SKOA patients (mean age 62.5 + 10.5, mean BMI 26.7 ± 3.5) fulfilling ACR criteria for knee OA were recruited as part of an NIH-funded prospective study. Patients were followed longitudionally for 24 months with standard semi-flexed radiographs taken at 0 and 24 months, scored for overall KL grade and joint space width (JSW) by the same radiologist. SKOA patients (n=111) with medial OA and baseline JSW >0 completed the two year study. The blood samples collected at baseline were assayed for IL-1Ra by ELISA. For radiographic severity, biomarkers were evaluated between KL scores of 1, 2 with those with scores of 3, 4. Progression was defined as a change in medial JSW between baseline and 24 month radiographs of the signal knee, defined as the more symptomatic knee by the WOMAC pain scale.

Results: The mean plasma IL-1Ra level in SKOA subjects was 318.6 ± 205.8 pg/ml. Our data indicate that plasma IL-1Ra levels predicted higher risk for disease severity (KL grade), with an area under the curve (AUC) under receiver operating characteristic curve of 0.699 (p=0.0006). We found no significant association of IL-1Ra with WOMAC or VAS pain scores. In the 24-month longitudinal study we examined IL-1Ra in patients with JSN < 0 mm (*non-progressors*, 35% of cohort) and those with JSN > 0.6mm (*fast-progressors,* 38% of cohort). Baseline IL-1Ra was significantly elevated in fast-progressors (p= 0.0142) relative to non-progressors. After adjustment for BMI, age and gender, plasma IL-1Ra approached significance as a predictor of fast progression (p=0.0586). In order to determine the dependence of IL-1Ra on covariates (BMI, age, gender) we performed causal graph analysis [FCI algorithm, Spirtes et al 2000)] of continuous JSN. FCI allows discovering causality from observational data and identifying hidden confounding covariates. This method has been proven to be correct (i.e., to identify underlying causal structures that are consistent with the data) under broad distributional assumptions. Based on this analysis, plasma IL-1Ra plays a causal role and positively influences JSN independent of BMI, age and gender.

Conclusion: These findings suggest that plasma IL-1Ra is a candidate biomarker of radiographic progressive JSN. The analysis also suggests that IL-1Ra elevations are associated with causal events in OA disease progression. These observations will be further validated in a larger cohort of SKOA patients.

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1888

Transcriptional Regulation Of Peptidylarginine Deiminase Type IV: Implications For Rheumatoid Arthritis. Ali Abbas, Kevin Le, Virginia Pimmett, David A. Bell, Ewa Cairns and Rodney P. DeKoter. Schulich School of Medicine and Dentistry, Western University, London, ON.

Background/Purpose: High titers of anti-citrullinated protein/peptide antibodies (ACPA) have been detected in sera of rheumatoid arthritis (RA) patients, implicating citrullinating enzymes in the pathogenesis of RA. Peptidylarginine Deiminase Type IV (PAD4) is a member of the PAD family of citrullinating enzymes and has been linked to RA. Therefore, our aim was to determine how transcription of *PAD4* is regulated in the human myeloid lineage.

Methods: The *PAD4* transcription start site and promoter was located by 5' RACE and phylogenetic comparisons of the area identified a 200 bp conserved region. Bioinformatics analysis predicted the presence of a NFκB binding site and this was tested by luciferase assays. RT-qPCR was used to quantify *PAD4* expression in HL-60 cells treated with TNF-α to activate the canonical NFκB pathway. Finally, chromatin immunoprecipitation (ChIP) was used to determine NFκB enrichment at the *PAD4* promoter.

Results: The human *PAD4* promoter showed high biological activity. Interestingly, mutation of the predicted NFκB binding site significantly increased activity in human cell lines. *PAD4* mRNA was reduced in response to TNF-α treatment. Finally, the p50 subunit of NFκB was more highly enriched than p65 at the *PAD4* promoter.

Conclusion: We characterized the *PAD4* promoter and demonstrated that the p50 subunit of NFκB binds to the *PAD4* promoter upon NFκB activation. Our results suggest that the p50 subunit of NFκB may play a role in the repression of *PAD4* transcription during inflammation.

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1889

Genome-Wide Association Study Of Knee Radiographic Osteoarthritis In African-American Populations. Youfang Liu[1], Michelle S. Yau[2], Laura Yerges-Armstrong[2], M C. Hochberg[3], Braxton D. Mitchell[2], Rebecca D. Jackson[4], Jordan B. Renner[5], David Duggan[6] and Joanne M. Jordan[7]. [1]Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]University of Maryland School of Medicine, Baltimore, MD, [3]University of Maryland, Baltimore, MD, [4]Ohio State University, Columbus, OH, [5]University of North Carolina at Chapel Hill, Chapel Hill, NC, [6]TGen, Pheonix, AZ, [7]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC.

Background/Purpose: Few SNPs and susceptibility genes have been identified in previous genome-wide and candidate gene association studies for knee radiographic osteoarthritis (OA). Nearly all studies have been conducted in European Caucasian and Asian populations with few data published on genetics of knee OA in African-Americans. For this reason we have performed a genome-wide association study (GWAS) of knee OA in African Americans.

Methods: In total, 1217 African-American participants from two cohorts, the Johnston County Osteoarthritis Project (JoCo, 590 subjects) and the Osteoarthritis Initiative (OAI, 627 subjects), were included in the analysis. This sample size provides 80% power to detect odds ratios of 1.55–1.70 for minor allele frequencies ranging from 0.10–0.50. Knee OA cases were defined as having a Kellgren-Lawrence (KL) grade of 2 or higher in at least one knee, whereas controls were defined as having KL grade of 0 or 1 in both knees. Genome wide genotyping was completed using the Illumina 2.5M platform for OAI and Illumina Infinium 1M-Duo array for JoCo. Imputation was conducted with Minimach using the combined 1000 Genome CEU and YRI reference panels. Single marker analysis was conducted using logistic regression with adjustment for age, sex, body mass index (BMI) and principal components. We combined GWAS results from the two data sets using the meta-analyses as implemented in the METAL software program.

Results: No SNP reached the significant level at 10e-8. However, we identified 24 SNPs with P-value less than 5×10−6. Among the 24 SNPs, three are located in the coding regions of genes (*FLJ2052*, *RRAGD* and *ATP8A2*). *FLJ 2052* codes a hypothetical protein, whose biological function is unknown. *RRAGD* (Ras-Related GTP Binding D) codes a monomeric guanine nucleotide-binding protein. By binding GTP or GDP, small G proteins act as molecular switches in numerous cell processes and signaling pathways. *ATP8A2*(ATPase Class I Type 8A Member 2) codes a member of ATPase. It is well known that ATPases import and export many of the metabolites necessary for cell metabolism. However, the molecules carried by ATP8A2 are unknown. None of these genes has been implicated in OA development in Caucasian populations.

	N_samples	Age Mean (sd)	BMI Mean (sd)	Sex %women
JoCo_AA				
Case	293	63.98 (10.78)	34.70 (8.76)	68.94
Control	297	58.55 (9.63)	30.14 (6.27)	61.95
All	590	61.24 (10.57)	32.40 (7.93)	65.42
OAI_AA				
Case	449	59.63 (8.37)	31.92 (4.58)	69.71
Control	178	57.38 (8.25)	29.04 (4.59)	61.24
All	627	58.99 (8.39)	31.10 (4.76)	67.30

CHR	POS	SNP	Gene	Allele1	Allele2	Direction	Study	Beta	SE_Beta	P-value
5	16608874	rs890824	FLJ2052	t	c	—	META	—	—	3.93E-06
							JoCo	−0.7948	0.2234	0.000374
							OAI	−0.5875	0.1972	0.002898
6	90120883	rs1407192	RRAGD	c	g	—	META	—	—	3.77E-06
							JoCo	−0.6490	0.2142	0.002448
							OAI	−0.7592	0.2167	0.00046
13	26095937	rs34622730	ATP8A2	a	g	++	META	—	—	4.34E-06
							JoCo	0.4618	0.1509	0.002212
							OAI	0.5141	0.1498	0.000599

Conclusion: We identified three genes associated with knee OA with P-value < 5×10−6 in African Americans. *RRAGD* and *ATP8A2* are both involved in various cell processes and signaling pathways. Further analysis, including pathway analysis, will be performed to determine if these biological pathways or protein networks have a role to play in knee osteoarthritis.

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1890

Chemokine Receptor Polymorphisms On Chromosome 3 Are Associated With Anticitrullinated Protein Antibody Specificities In African Americans With Rheumatoid Arthritis. Richard J. Reynolds[1], Maria I. Danila[2], Jeremy Sokolove[3], William H. Robinson[4], Doyt L. Conn[5], Beth L. Jonas[6], Leigh F. Callahan[7], Larry W. Moreland[8], Richard D. Brasington[9], Edwin A. Smith[10], Peter K. Gregersen[11] and S. Louis Bridges Jr.[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Univ of Alabama-Birmingham, Birmingham, AL, [3]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [4]Stanford University School of Medicine, Stanford, CA, [5]Emory Univ School of Medicine, Atlanta, GA, [6]University of North Carolina at Chapel Hill, Chapel Hill, NC, [7]University of North Carolina, Chapel Hill, NC, [8]University of Pittsburgh, Pittsburgh, PA, [9]Washington Univ School of Med, St. Louis, MO, [10]Med Univ of South Carolina, Charleston, SC, [11]Feinstein Institute for Medical Research, Manhasset, NY.

Background/Purpose: ACPA antibody specificities to citrullinated autoantigens (e.g., histones, vimentin, fibrinogen) are associated with the preclinical phase of RA and may predict the onset of synovitis. However, it is not known whether individual antibody response to different citrullinated peptides has a genetic basis. Here we report that non-HLA polymorphisms known to be associated with autoimmune disease are associated with ACPA specificities in African-Americans with RA.

Methods: 449 (RF+ or anti-CCP+) African-American RA patients genotyped on the Immunochip array (~200K SNPs from a variety of autoimmune diseases) were analyzed. 90% individual and 98.5% SNP call rates were used as quality control thresholds. Using a custom Bio-Plex™ bead-based autoantibody assay platform, we measured autoantibodies targeting different RA associated citrullinated autoantigens: vimentin, fibrinogen, histone 2A (H2A), histone 2B (H2B), and apolipoprotein A1 (Apo A1). Linear regression was used to fit models of ln (ACPA Ab) conditional on sex, disease duration, proportion European admixture and minor allele copies for ~167K markers that met quality control.

Results: In addition to an association with the MHC region (known to be associated with ACPA+ RA), we found additive allelic effects on anti-citrullinated H2A (anti-cit H2A) indicating a strong association in a non-MHC region on chromosome 3 (Figure 1). For anti-cit H2A and anti-cit H2B there were 43 and 48 associations, respectively, with p value < 0.001 between 45.9 and 46.4 Mb. The association signal with strong LD support was verified for both anti-cit H2A (Figure 2) and anti-cit H2B. The strongest SNP association was rs4683166 (MAF = 0.45) for both anti-cit H2A (p-value= 1.5e-05) and anti-cit H2B (p-value = 1.0e-05), and indicated an increasing relationship of minor alleles (G) and Ab concentration. In addition, rs4683166 was associated with anti-cit vimentin (p=0.0045), and anti-cit ApoA1 (p=0.024), but not anti-cit fibrinogen (p=0.15). rs4683166 was not associated with RA suceptibility (p-value = 0.18 for difference in MAF between 662 RA cases and 876 African-American controls).

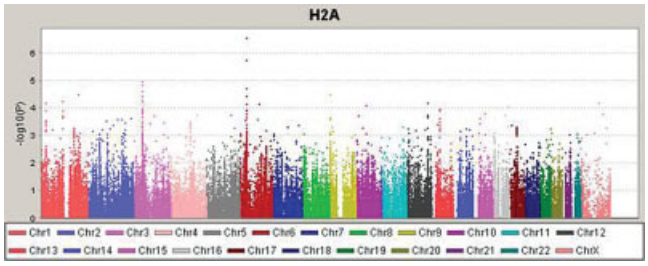

Figure 1. Manhattan plot of loci associated with serum anti-cit H2A levels.

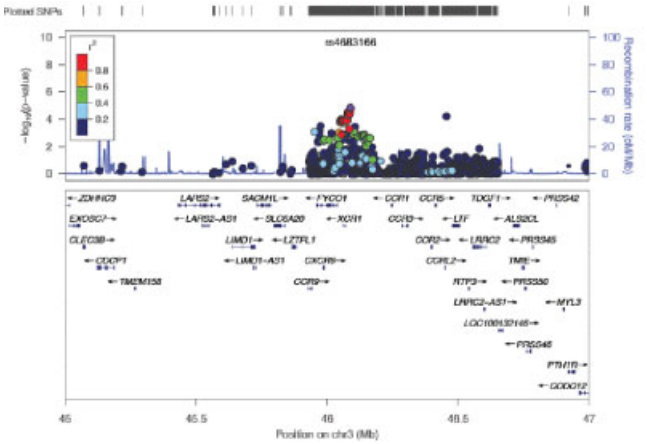

Figure 2. Zoomplot indicating the strongest chr 3 association signal.

Conclusion: The presence of antibodies to citrullinated autoantigens appears to have a strong non-MHC association near the XCR1 chemokine receptor on human chromosome 3. These results suggest there may be a significant genetic basis for disease specific antibodies in RA.

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1891

Proteomic Profile Of Tears: Can It Help To Diagnose Juvenile Arthritis - Associated Uveitis Prior To The Clinical Signs Of Joints Inflammation.
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Background/Purpose: Approximately 6% of all cases of uveitis arise in children (Nguyen, Foster, 1998). One of the common causes of uveitis is Juvenile Idiopathic Arthritis (JIA). Up to 20% of JIA children have uveitis (Kesen et al., 2008) and often uveitis is the initial clinical manifestation of JIA, the delay of arthritis can be estimated at years which complicates treatment for uveitis and lead to blindness. During the last years the number of proteins identified in tears increased from 200 (Herber et al., 2001) of only 17 (Zhou et al., 2003) different molecular weights (MW) to 491 (de Souza et al., 2006) and 80 chemokines, cytokines, and growth factors (Sack et al., 2005). Objective: to reveal protein markers of JIA-associated uveitis in tears using high-resolution mass-spectrometry.

Methods: Patients with uveitis were examined by ophthalmologists and rheumatologists and the standard clinical protocol was used to diagnose the disease. Tear samples drawn from 13 JIA-patients and 3 healthy subjects were analyzed. Tears were collected on a filter paper, digested with trypsin and the peptides were purified on Zip tips. The samples were loaded to nano C18 column attached to Shimadzu nano LC coupled in-line to LTQ Orbitrap XL tandem mass spectrometer (Thermo Fischer Scientific, GA, USA). The mass spectra of the peptides were detected with a data-dependent 4-event scan method (a survey FT-MS parent scan followed by sequential data-dependent FT-MS/MS scans on the three most abundant peptide ions from the parent scan). Proteins were identified from the mass spectra results with Proteome Discoverer software for protein database search using the International Protein Index (IPI) Human Protein Database (version 1.79). Quantification was conducted using SIEVE.

Results: About 3000 proteins were detected in tears. Among those, 236 proteins (MW 7.4 – 466 kDa) were chosen as candidates for early diagnosis of the JIA-associated uveitis. Besides the rheumatoid factors RF-ET12, RF-IP14, RF-IP24, cytokines and T-cell receptor alpha-chain, we identified anti-CD40 single-chain antibody fragment A49, inhibiting protein CD40 which is a member of the TNF-receptor superfamily, lipocalin-1 precursor, associated with immune response and prostaglandin synthesis, clusterin inhibiting the cytolytic reaction of complement components, anti-TNF-alfa antibody light chain Fab fragment, protein phosphatase, regulatory subunit 15B, which plays a role in cell progression, apoptosis and regulation of membrane receptors and channels, DMBT/8kb.2 protein, which takes part in the interaction of tumor cells and the immune system.

Conclusion: Our pilot study demonstrates the benefits of high resolution mass- spectrometry for analysis and development of molecular signatures which can be used in future diagnostics. Earlier it was shown that induced anterior uveitis in the eyes of rats can be described in terms of proteins drawn from the anterior chamber (Sobn et al., 2000), which result is close to our terms of description. Our results support the suggestion that it is possible to identify protein markers of JIA-associated uveitis in tears prior to the clinical signs of arthritis.

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1892

High-Throughput Immunoglobulin G Fab Glycosylation Profiling Reveals Differential Glycosylation On Fab and Fc.
Albert Bondt[1], Yoann Rombouts[2], Maurice H.J. Selman[2], Radboud JEM Dolhain[1] and Manfred Wuhrer[2]. [1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Rheumatoid arthritis is known to improve during pregnancy, and a flare of disease activity is observed after delivery (1). N-glycosylation of the constant region (Fc) of immunoglobulin (Ig) G has been associated with these observations (2). However, glycosylation of the antigen binding fragment (Fab) of IgG might also play a role. Fab glycosylation has been suggested to influence affinity to antigen, and antibody half-life (3, 4). Analysis of Fab glycosylation is challenging because of the hypervariable properties of IgG Fab. Here we describe a newly developed highly specific method for the analysis of Fab N-glycosylation.

Methods: Sera were collected three times during pregnancy and three times after delivery from healthy individuals participating in a prospective cohort study on Pregnancy induced Amelioration of Rheumatoid Arthritis (PARA-study). IgG was affinity purified from the sera using IgG-Fc (Hu) beads. Using FabRICATOR® enzyme IgG was cleaved in two ½ Fc portions and a $F(ab')_2$ portion. Fc and $F(ab')_2$ were separated, and glycans were released followed by automated MALDI-TOF measurement to establish the levels as well as patterns of glycosylation.

Results: In healthy pregnant individuals Fc and Fab show distinct glycosylation patterns (Figure 1). Levels of galactosylation and sialylation are higher on Fab compared to Fc (±94% vs. ±60% and ±60% vs. ±15%, respectively). However, while major changes occur in these features on IgG Fc during pregnancy, the levels appear to be stable at the Fab portion. On the other hand, fucosylation and bisecting N-acetylglucosamine do not change drastically on the Fc portion with pregnancy, while pronounced lowered levels of both glycosylation features are observed during pregnancy in these individuals.

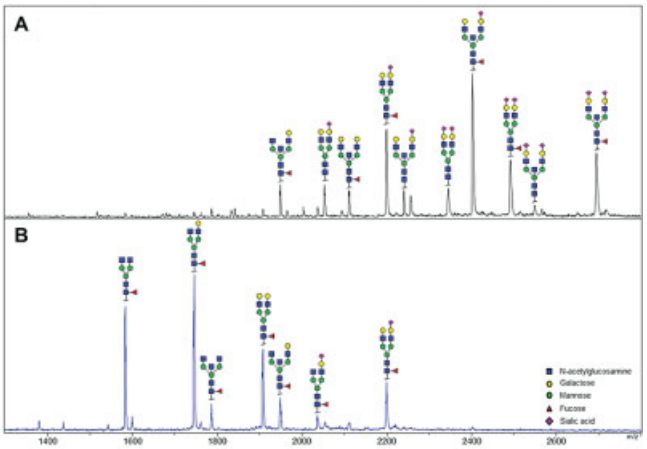

Figure 1. Typical IgG Fab (**A**) and Fc (**B**) spectra showing distinguishable AA-labeled glycans

Conclusion: Data obtained from serum of healthy pregnant individuals reveals differential glycosylation on Fab compared to Fc. Fab and Fc were found to show distinct glycosylation changes with pregnancy. In the near future we will apply this method to RA patient sera to identify whether Fc or Fab glycosylation could be a bigger effector in the improvement of RA during pregnancy.

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1893

Altered DNA Methylation Profiles In Individuals With Osteoarthritis.
Kathryn A Bailey[1], Daniel Rojas[2], Nikhil Umesh[1], Lisa Smeester[1], Tristan De Buysscher[3], Jordan B. Renner[4], Joanne M. Jordan[5] and Rebecca C. Fry[1]. [1]Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]Curriculum in Toxicology, Univeristy of North Carolina at Chapel Hill, Chapel Hill, NC, [3]Center for Bioinformatics, University of North Carolina at Chapel Hill, Chapel Hill, NC, [4]University of North Carolina at Chapel Hill, Chapel Hill, NC, [5]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC.

Background/Purpose: Major risk factors associated with osteoarthritis (OA) development include age, joint stress/injury, obesity, and genetic

predisposition. In recent years, the role epigenetic processes that may be associated with OA have been of increasing interest both as factors implicated in disease development and as powerful diagnostic tools. Here, we set out to identify 5-methyl cytosine DNA methylation patterns associated with OA in participants of the Johnston County Osteoarthritis Project (JoCo OA), an ongoing study of North Carolinians of over 20 years.

Methods: Genomic DNA was isolated from peripheral blood mononuclear cells (PMNCs) collected from 20 Caucasian, non-smoking, non-drinking women from the JoCo OA cohort. Methylated regions of PMNC 5-methyl cytosine DNA were isolated and amplified using the Methylated CpG Island Recovery Assay (MIRA) and subsequently hybridized to Affymetrix® Human Promoter 1.0R arrays. Controlling for known confounders (e.g. age and body mass index (BMI)), we compared the promoter DNA methylation profiles of >14,000 promoter regions of genes from women with knee OA (n=8) to women without knee OA (n=12) using regression analysis. Differentially methylated genes were analyzed for associated biological functions, diseases, canonical pathways and molecular networks.

Results: A total of 68 genes were identified that had statistically significant differences in promoter DNA methylation levels in women with knee OA compared to women without knee OA. Most of these genes (n=61) showed hypomethylation in their promoter regions in individuals with knee OA. Analyses of associated biological functions, pathways and molecular networks revealed an enrichment of genes involved in varied cellular functions including tissue development, metabolism, and inflammation (Table). Several of these genes have prior associations with OA, namely connective tissue growth factor (*CTGF*), eyes absent homolog 4 (*Drosophila*)(*EYA4*), growth hormone receptor (*GHR*), and homeobox A2 (*HOXA2*).

Table. Most significant biological functions, canonical pathways and molecular networks associated with differentially methylated genes in individuals with OA.

Biological functions	***p*-value**
Embryonic development	5.77×10^{-6}–3.58×10^{-2}
Organismal development	5.77×10^{-6}–3.58×10^{-2}
Tissue development	5.77×10^{-6}–3.58×10^{-2}
Auditory and vestibular system development and function	1.63×10^{-5}–3.31×10^{-2}
Organ morphology	1.63×10^{-6}–3.58×10^{-2}
Canonical pathways	***p*-value**
PRPP biosynthesis I	8.37×10^{-3}
Tetrapyrrole biosynthesis II	8.37×10^{-3}
Glycogen biosynthesis II	1.67×10^{-2}
NF-kB activation by viruses	1.67×10^{-2}
Heme biosynthesis II	1.82×10^{-2}
Molecular network functions	***p*-value**
Hematological disease, nutritional disease, tissue morphology	$<10^{-40}$
Cellular assembly and organization, cellular function and maintenance, cell cycle	$<10^{-32}$
Cellular growth and proliferation, auditory and vestibular system development and function, embryonic development	$>10^{-27}$
Connective tissue disorders, developmental disorder, hereditary disorder	$<10^{-12}$
Molecular transport, RNA trafficking, RNA post-translational modification	$<10^{-10}$

Conclusion: We identified genes in PBMCs with altered promoter DNA methylation levels associated with knee OA in this pilot study. Expanding these analyses to include more individuals from the JoCo OA cohort will determine if these DNA methylation profiles may serve as biomarkers of OA and/or provide insight into the role epigenetic alterations may play in OA development.

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Association Of Alleles and Amino Acids Of The Major Histocompatibility Complex Class I Chain-Related Gene A With Psoriatic Disease. Remy Pollock, Fawnda Pellett, Renise Ayearst, Fatima Abji, Dafna Gladman and Vinod Chandran. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: We previously reported associations between alleles of the major histocompatibility complex class I chain-related gene A (*MICA*) and psoriatic disease that were independent of *HLA-B* despite their tight linkage disequilibrium. In a larger cohort of patients, we sought to investigate the association with *MICA* alleles and determine if associations are evident at the amino acid level.

Methods: Caucasian psoriatic disease patients [786 PsA patients satisfying CASPAR criteria and 358 psoriasis patients without arthritis (PsC)], and 717 unaffected controls were recruited from a large cohort. *MICA* and *HLA-B* allelic typing was performed by PCR-SSO. Univariate logistic regressions were performed using *MICA* and *HLA-B* alleles as predictor variables for psoriatic disease compared to controls, and PsA compared to PsC. Multivariate logistic regressions used significant *MICA* alleles with significant *HLA-B* alleles as covariates. *MICA-HLA-B* haplotypes were estimated using the EM algorithm and differences between subject groups were analyzed using SNP & Variation Suite 7 software. *MICA* alleles were converted into amino acids at each polymorphic site of the mature MICA protein and analyzed for differences between groups.

Results: PsA patients were 58% male, mean age (s.d.) at diagnosis of psoriasis 28 (14.4) years, age at PsA diagnosis 36 (13.0) years, and PASI 5.3 (8.1). Psoriasis patients were 55% male, mean age at diagnosis of psoriasis 30 (16.6) years, and PASI 5.3 (4.9). Controls were 43% male. *MICA**002:01, *004, *007:01, *008:01, *009:01, *010:01, *016, *017, and *027 were associated with psoriatic disease compared to controls, and *MICA** 007:01 and *017 were associated with PsA compared to PsC in univariate analyses ($p<0.05$). After adjusting for *HLA-B* alleles, only *MICA**016 was independently associated with psoriatic disease (OR=2.1, $p<0.01$), and *MICA** 007:01 with PsA (OR=3.2, $p=0.04$). Haplotypes *MICA** 016-*B**3501 (OR=3.2, $p<0.01$), *MICA**017-*B**5701 (OR=2.5, $p<0.01$) and *MICA**002:01-*B**3801 (OR=6.5, $p<0.01$) were among those increased in psoriatic disease compared to controls. Haplotype *MICA**007:01-*B**2705 (OR=4.1, $p<0.01$) was increased in PsA compared to PsC, while haplotypes *MICA**017-*B**5701 (OR=0.54, $p<0.01$) and *MICA**008:01-*B** 1302 (OR=0.42, $p<0.01$) were decreased. Methionine at amino acid position 129 (M129), which is present in *MICA**002:01, *007:01 and *017, was associated with psoriatic disease compared to controls (OR=1.9, $p<0.01$), and was strongly associated with amino acids G206, W210, S215, C36, and K173. Arginine at position 91 (R91), which is unique to *MICA** 017, was decreased in PsA compared with psoriasis patients (OR=0.57, $p<0.01$).

Conclusion: We confirmed the HLA-B-independent association of *MICA**016 with psoriatic disease, and found a new association between *MICA**007:01 and PsA. *MICA* alleles containing the M129 amino acid are associated with psoriatic disease, while the *MICA**017 allele containing the R91 amino acid are protective against PsA in psoriasis patients. Further genetic and structural studies are needed to understand the significance of these findings.

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1895

Identification Of Aberrant Pathways In Osteoarthritis Using RNA-Seq. Kathleen M. Fisch[1], Masahiko Saito[2], Ryuichiro Akagi[1], Stuart Duffy[1], Andrew I. Su[1] and Martin K. Lotz[1]. [1]The Scripps Research Institute, La Jolla, CA, [2]Toho University Sakura Medical Center, Sakura, China.

Background/Purpose: Osteoarthritis (OA) is a prevalent joint disease that is characterized by the destruction of articular cartilage, although the disease process affects all joint tissues. Understanding the biology of joint homeostasis and the mechanisms of disease will increase our understanding of OA, particularly as it relates to aging. This long-term study aims to integrate genomic, epigenetic, transcriptomic and proteomic data on both normal and OA joint tissues to build a multidimensional molecular profile for OA and aging. The first phase of this project explores the gene expression profiles of articular cartilage from normal and OA human knee joints. In this study, we identified differentially expressed genes between normal and OA articular cartilage using RNA-sequencing (RNA-seq) to discover key biological pathways that are dysregulated in OA.

Methods: We extracted total RNA from full-thickness articular cartilage from 10 human donors (5 normal and 5 severe OA) using the Ambion RNAqueous Kit and prepared RNA libraries for sequencing using the NuGen Encore Complete RNA-Seq DR Multiplex System. Sequencing was performed on an Illumina HiSeq 2000 (single-end, 100bp reads). Raw data were checked for quality using FASTQC, and the raw FASTQ files were aligned to the human genome (hg19) using TOPHAT2. Aligned transcripts were assembled with CUFFLINKS2 and differentially expressed (DE) transcripts were determined using CUFFDIFF2 with a false discovery rate q-value of 0.05, fragment bias correction and upper quartile normalization. We con-

ducted a signaling pathway impact analysis using the Bioconductor packages SPIA and Graphite with the KEGG, Reactome, BioCarta and National Cancer Institute/Nature Pathway Interaction Databases (NCI/NPID) to identify potential functional pathways dysregulated in OA.

Results: A total of 2,180 DE genes were discovered between OA and normal human cartilage. Of these DE genes, 1,428 were significantly up-regulated in OA and 752 were significantly down-regulated in OA (Table 1). The five DE genes with the largest fold-change that were up-regulated in OA include COL1A1, THY1, TGFBI, CLDN7, and SLPI. The five DE genes with the largest fold-change that were down-regulated in OA include ADM, CHPF2, HILPDA, SERPINA10 and NRF1. Signaling pathway impact analysis revealed 11 significantly perturbed pathways in OA (Table 2).

Table 1. Gene/Isoform Expression Summary

Genes	Normal	OA
Total Genes expressed	28,554	28,711
Normal Only	1,388	
OA Only		1,545
Up-regulated		1,428
Down-regulated		752
Known Isoforms	**Normal**	**OA**
Total Known Isoforms expressed	55,997	54,268
Normal Only	5,099	
OA Only		3,370
Up-regulated		961
Down-regulated		267
Potentially Novel Isoforms	**Normal**	**OA**
Novel Isoforms Expressed	13,100	12,683
Normal Only	851	
OA Only		434
Up-regulated		3,252
Down-regulated		3,755

Genes, known isoforms and novel isoforms expressed in normal and OA articular cartilage. Expression determined by CuffDiff, after Benjamini-Hochberg correction. Up−/− Down regulated genes are those where there is a 2-fold or greater difference that is significantly differentially expressed. The fold change is the ratio of OA FPKM to normal FPKM.

Table 2. Pathways identified as significantly dysregulated in Osteoarthritis by signaling pathway impact analysis.

Pathway	Database	pSize	NDE	pNDE	tA	pPERT	pG	pGFdr	pGFWER	Status
ECM-receptor Interaction	KEGG	85	11	2.1E-06	2.8E+01	5.0E-06	2.8E-10	3.4E-08	3.4E-08	Activated
Hypoxic and oxygen homeostasis regulation of HIF-1-alpha	NCI/NPID	74	13	5.8E-09	0.0E+00	1.0E+00	1.2E-07	6.8E-06	1.1E-05	Inhibited
HIF-1-alpha transcription factor network	NCI/NPID	62	12	7.1E-09	0.0E+00	1.0E+00	1.4E-07	6.8E-06	1.4E-05	Inhibited
Smooth muscle contraction	Reactome	24	7	5.2E-07	4.7E+00	5.5E-01	4.6E-06	1.2E-03	1.2E-03	Activated
Focal adhesion	KEGG	200	15	3.1E-05	4.8E+01	2.6E-02	1.2E-05	7.4E-04	1.5E-03	Activated
Systemic Lupus Erythematosus	KEGG	131	4	3.2E-01	2.1E+01	5.0E-06	2.2E-05	9.3E-04	2.8E-03	Activated
HIF-2-alpha transcription factor network	NCI/NPID	29	7	2.1E-06	0.0E+00	1.0E+00	3.0E-05	9.7E-04	2.9E-03	Inhibited
Circadian Rhythym	KEGG	22	6	5.4E-06	−2.6E-01	9.7E-01	6.9E-05	2.1E-03	8.5E-03	Inhibited
C-MYB transcription factor network	NCI/NPID	75	9	3.3E-05	−1.7E+00	4.7E-01	1.9E-04	4.4E-03	1.8E-02	Inhibited
E-cadherin signaling events	NCI/NPID	247	17	2.8E-05	−5.2E+00	6.8E-01	2.3E-04	4.4E-03	2.2E-02	Inhibited
Syndecan-4 mediated signaling events	NCI/NPID	184	11	2.2E-03	2.0E+01	1.4E-02	3.5E-04	5.7E-03	3.4E-02	Activated

pSize: number of genes in the pathway; *NDE:* number of DE genes in pathway; *pNDE:* Probability to observe at least NDE genes in the pathway; *tA:* observed total perturbation accumulation in the pathway; *pPERT:* probability to observe a total accumulation more extreme than tA by chance; *pG:* p-value obtained by combinging pNDE and pPERT; *pGFdr:* False discovery rate; *pGFWER:* Bonferroni adjusted global p-values; Status: Direction in which the pathway is perturbed.

Conclusion: This transcriptome analysis of OA articular cartilage reveals complex gene expression patterns and pathways that are involved in the disease. These results provide preliminary insights into an integrated, molecular understanding of OA.

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1896

Arthritis Associated Sequence Alterations Within a Genetic Susceptibility Region Of Mouse Chromosome 3; A Genomic Region Which Is Syntenic With a Prominent Non-MHC Locus In Rheumatoid Arthritis.

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Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease that results in inflammatory destruction of synovial joints in affected patients. The involvement of genetic and epigenetic factors in RA is recognized, but not well understood. Using proteoglycan (PG)-induced arthritis (PGIA), an autoimmune mouse model of RA, previously we identified a genomic region in mouse chromosome 3 (mChr3) which was associated with PGIA susceptibility independently of MHC. The goals of the present study were (i) to generate MHC-matched PGIA-susceptible and -resistant interval-specific congenic (IVSC) strains in order to narrow this genomic region to a size that can be sequenced by next generation sequencing (NGS) methods, and (ii) to identify disease-associated genomic alterations/mutations (e.g., nucleotide insertions or deletions: "indels") within this region in PGIA-susceptible and resistant IVSC mice.

Methods: IVSC strains were created by intercrossing MHC-matched PGIA-resistant DBA/2 and PGIA-susceptible BALB/c strains, which resulted in IVSC offspring carrying partially overlapping DBA/2 genomic segments within mChr3 on a full BALB/c background. Heterozygous mice with the same narrow genomic intervals were mated and homozygous offspring were tested for susceptibility to PGIA. On the basis of arthritis incidence and severity in IVSC mice, a 21 Mbp region of Chr3 (99.4–120.4 Mbp) was selected, and sequenced by NGS in parent and IVSC mice (n=16). All sequence alterations were compiled into a database and analyzed using GeneSpring NGS software (Agilent) and Microsoft Visual Studio program scripts.

Results: The sequenced 21 Mbp genomic region of mChr3 contained a total of 164,380 nucleotide changes (mutations) in DBA/2 and BALB/c as compared to the corresponding core (reference) C57BL/6 genomic sequences. Of these mutations, 42% were unique to BALB/c and 21% were unique to DBA/2. However, less than 1% of the mutations were located within protein coding (exonic) regions. All missense exonic mutations were predicted to have negligible or no effect on RNA or protein sequences, and no nonsense mutation was found. A total of 4,429 mutations were located within the region containing the *Ptpn22* and *Cd2* genes and their flanking sequences, which have been reported to harbor RA-associated SNPs on human Chr1. However, a number of indels found in the intergenic regions *Ptpn22* and *Cd2* loci of mChr3 were predicted to create or eliminate binding sites for potentially important transcription factors.

Conclusion: We have identified arthritis-associated sequence alterations within a genomic region of mChr3 containing the *Ptpn22* and *Cd2* genes in mice, which region is syntenic with a prominent RA susceptibility locus on human Chr1. Although the majority of the mutations are located within non-coding sequences, they may alter the binding of transcription factors or epigenetic modulators to promoter regions, thus affecting the transcription of the neighboring genes. Our finding warrant further genetic, epigenetic, and functional studies on this arthritis-associated locus in mice and humans.

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Algorithms Using Genome-Wide SNP Analysis For Prediction Of Progression Of Joint Space Narrowing Or Erosion In Rheumatoid Arthritis Patients Using Data From Multiple Medical Cohorts.

Tsukasa Matsubara[1], Satoru Koyano[2], Yoshitada Sakai[3], Keiko Funahashi[2], Takako Miura[1], Kosuke Okuda[1], Takeshi Nakamura[1], Akira Sagawa[4], Takeo Sakurai[5], Hiroaki Matsuno[6], Tomomaro Izumihara[7] and Eisuke Shono[8]. [1]Matsubara Mayflower Hospital, Kato, Japan, [2]Research Institute of Joint Diseases, Kobe, Japan, [3]Kobe University, Kobe, Japan, [4]Sagawa Akira Rheumatology Clinic, Sapporo, Japan, [5]Inoue Hospital, Takasaki, Japan, [6]Matsuno Clinic for Rheumatic Diseases, Toyama, Japan, [7]Izumihara Rheumatic and Medical Clinic, Kagoshima, Japan, [8]Shono Rheumatology Clinic, Fukuoka, Japan.

Background/Purpose: Although not yet fully possible, ideally, since patients with rapidly progressing joint space narrowing/erosion exist, predicting progression of joint space narrowing/erosion would be pivotal in establishing treatment strategy for individual RA patients. Also, it is important to distinguish the effectiveness between TNF biologics and non-TNF biologics in joint space narrowing progression-type/erosion progression-type patients for determining the best treatment strategy. We developed SNP algorithms with an aim of enabling prediction of progression of joint space narrowing/erosion by means of genome-wide SNP analysis using multiple medical cohorts.

Methods: One-hundred twenty-four RA patients with disease duration of 5 years or less from 6 different hospitals were enrolled. All patients were treated with biologics after the using DMARDs. We defined patients with

rapid progression of joint space narrowing and with rapid progression of erosion by the ratio between joint space narrowing/erosion score in each patient. Twenty-five patients had joint space narrowing/erosion score of ≧ 5 (rapid progression of joint space narrowing), 99 had joint space narrowing/erosion score of < 5 (slow progression of joint space narrowing), 21 had an erosion/joint space narrowing score of ≧1 (rapid progression of erosion), and 103 had erosion/joint space narrowing score of < 1 (slow progression of erosion). Case-controlled analyses between 278,347 SNPs and progression of joint space narrowing/erosion (rapid vs. slow) were examined by Fisher's exact tests. We selected 10 SNPs closely associated with progression of joint space narrowing/erosion ($p < 0.0001$). We then scored a relationship between each SNP and progression of joint space narrowing/erosion, the estimated total score of the 10 SNPs (estimated scoring in each SNP was as follows: homo allele in the majority in rapid progression group: +1 point, hetero allele: 0 point, and homo allele in the majority of slow progression group: −1 point), and examined relationships between the rapid and slow group, and the total score.

Results: Accuracy ((true positive+true negative)/total), specificity (true negative/(false positive+true negative)) and sensitivity (true positive/(true positive+false negative)) of the algorithm for distinguishing the rapid progressing joint space narrowing group from the slow progressing group ranged from 80–88%. Accuracy, specificity and sensitivity of the algorithm for distinguishing the rapid progressing erosion group from the slow progressing group ranged from 86–95%. It is therefore suggested that this SNP algorithm may enable the prediction of rapidly progressing joint space narrowing/erosion. Though neither effectiveness of TNF-biologics nor non-TNF biologics correlated to the score of erosion progression-type and/or joint space narrowing progression-type patients ($p > 0.05$), with progressive type of erosion, tocilizumab treatment tended to be effective.

Conclusion: This highly accurate algorithm using SNP analysis may be useful in initially diagnosing rapid progression of joint space narrowing and/or erosion, and, in this way, may contribute to establishing a treatment strategy for individual RA patients.

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Repression Of Wolf-Hischhorn Syndrome Candidate-1 (WHSC1) Contributes To The Osteoarthritis-Inducing Cartilage Loss Of Functions. Francisco Espinoza[1], Yves-Marie Pers[2], Paul Chuchana[3], Jean Marc Brondello[4] and Christian Jorgensen[2]. [1]INSERM U844, MONTPELLIER, France, [2]Inserm U844, CHU saint-Eloi, Université Montpellier 1, CHU Lapeyronie, Montpellier, France, [3]INSERM U844, Montpellier, France, [4]UM1, Montpellier, France.

Background/Purpose: Accumulation of senescent $p16^{INK4A}$-positive cells within numerous tissues through out life span contributes to the onset of several age-related disease such as intervertebral disc degenerescence or osteoarthritis (OA). These cells are believed to induce tissue degenerescence and age-dependent loss of functions through the establishment of one senescence-associated secretory phenotype (SASP) including pro-inflammatory cytokines (e.g IL-6, IL-8) and hypertrophic-associated matrix degrading enzymes (e.g MMP1/13 and ADAMTS5). Understanding the molecular mechanism in particular epigenetic regulators leading to the establishment of such deleterious secretome, is a next challenge. Here, we investigate the role and the regulation of the histone H3K36Me2 methyltranferase, WHSC1 (NSD2/MMSET) in cartilage loss of functions in OA.

Methods: We used primary human OA chondrocytes, specific siRNA interference, western-blot, transient transfection, IL-1b treatment, RT-qPCR, Elisa and statistical analysis.

Results: We found that WHSC1 mRNA expression is reduced in OA senescent-like cartilage compared to healthy donors. WHSC1 mRNA and protein levels are as well reduced in human primary chondrocytes following IL-1b chronic treatment. By a loss of function experiment based on specific siRNA against WHSC1, we found an up-regulation of MMP1, MMP13 and ADAMTS5 mRNA accumulation but not pro-inflammatory cytokines (IL-8, IL-6) in primary chondrocytes. As result, WHSC1-depleted chondrocytes show a reduced expression in Aggrecan and a slight increase production in GAG.

Conclusion: Our preliminary data demonstrate that WHSC1 impacts articular homeostasis maintenance by repressing part of the senescence-associated secretome induced in OA. Further experiments are required in particular for understanding how WHSC1-dependent epigenetic regulation of these hypertrophic-associated matrix-remodeling factors, occurs.

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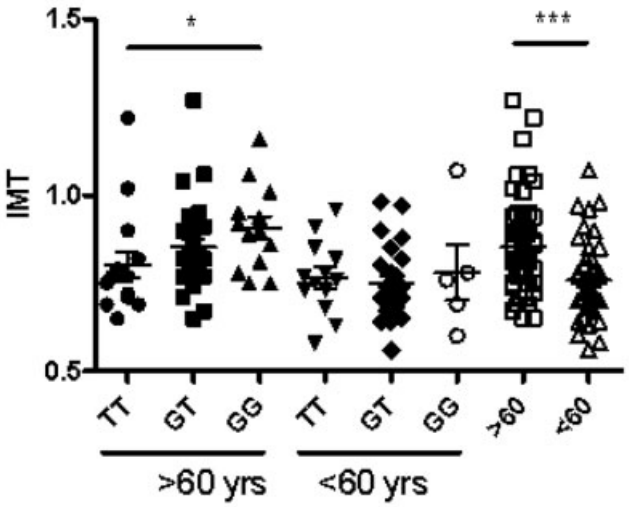
1899

Interferon Regulatory Factor 5 Gene Variant rs2004640 Is Associated With Carotid Intimal Medial Thickness In Rheumatoid Arthritis Patients. Saskia Vosslamber, Alper M. van Sijl, Carina Bos, A.E. Voskuyl, Michael T. Nurmohamed and Cornelis L. Verweij, VU. University Medical Center, Amsterdam, Netherlands.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory joint disease which is associated with an increased cardiovascular (CV) risk.. An important process in atherogenesis is cell growth and hyperplasia. Interferons (IFNs), especially IFNβ, are known inhibitors of vascular smooth muscle cell proliferation and intimal hyperplasia. Interferon regulatory factor 5 (*IRF5*) is a major regulator of IFN production and genetic variants in *IRF5* are known to stimulate the consecutive production of type I IFNs. In the current study, we investigate the effect of *IRF5* gene variants on preclinical atherosclerosis, measured with carotid intima media thickness (cIMT) in RA patients.

Methods: Peripheral blood DNA was obtained in a subgroup of 101 RA patients from the CARRÉ study. *IRF5* SNPs rs2004640 was determined using Taqman Genotyping assay. cIMT was determined by B-mode ultrasonography. Linear regression analyses were used to investigate the association between cIMT and *IRF5* genotypes, adjusted for demographic and cardiovascular factors (age, sex, cholesterol blood pressure and smoking).

Results: RA patients carrying the rs2004640 T-allele have significant lower cIMT compared to homozygote G-allele carriers ($P<0.005$). This effect is stronger when patients are homozygous for the T allele compared to the wildtype allele ($P<0.005$). Age was shown to be an effect-modifier for the association and the strongest association between cIMT and rs2004640 was seen in patients older than 60. Linear regression analysis in patients older than 60 showed that the rs2004640 TT-genotype was associated with lower cIMT (regression coefficient −0.107 (C.I. −0.205; −0.008), $p=0.035$) which remained significant after adjustment for demographic and cardiovascular risk factors (regression coefficient −0.111 (C.I.−0.202; −0.02), $p=0.020$).



Conclusion: We demonstrate for the first time that the *IRF5* gene variant rs2004640, which is associated with enhanced type I IFN activity, is associated with preclinical atherosclerosis in RA patients, independent of cardiovascular risk factors. The genetic variant of *IRF5* rs2004640 T-allele, which leads to enhanced type I IFN levels, is related to lower cIMT in RA. As reduced activity of IFN-beta is highly associated with both atherosclerosis and inflammation, these results might implicate IFN as an important cytokine responsible for the increased rate of CV disease in RA.

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Mass Spectrometry-Based Salivary Proteomics For The Discovery Of Novel Diagnostic Biomarkers For Primary Sjögren's Syndrome and Its Clinical Subsets. Camillo Giacomelli[1], Chiara Baldini[1], Francesca Sernissi[1], Daniela Martini[1], Pasquale Pepe[2], Nicoletta Luciano[1], Francesco Ferro[1], Chiara Tani[1], Marta Mosca[3] and Stefano Bombardieri[1]. [1]Rheumatology Unit, Pisa, Italy, [2]Institute of Clinical Physiology, National Research Council, Pisa, Italy, [3]Rheumatology Unit, University of Pisa, Pisa, Italy.

Background/Purpose: Nowadays, the advances of novel proteomic technologies are encouraging research projects for generating reliable diagnostic biomarkers for primary Sjögren's syndrome (pSS) to be used in both clinical settings and in clinical trials. Aim of this study was to identify the most significant salivary biomarkers in pSS using proteomic methods and to correlate pSS patients' salivary proteomic profile to the different histological and immunological aspects of the disease.

Methods: Salivary samples from patients affected by pSS, and sex- and age-matched healthy volunteers (HC) were consecutively collected from May 2012 to February 2013. The ProteinChip System, Series 4000 Personal Edition (Ciphergen Biosystems, Inc) was used to perform SELDI-TOF-MS. The cation exchange array CM10 (Bio-Rad) was selected. Chips were read on a Ciphergen Express Data Manager – Personal Edition (version 3.5). SELDI-TOF-MS data were analyzed by using Mann-Whitney non-parametric test for univariate analysis coupled with a classification and regression tree (CART) algorithm in the multivariate setting. Only significant variables ($p<0.05$) at the univariate analysis were included in the CART algorithm.

Results: Unstimulated whole saliva samples were collected from 72 consecutive unselected female patients with pSS and from 29 sex- and age-matched HC**.** A total of 75 peaks were detected at the SELDI-TOF-MS. We found that 25 peaks were significantly different in the pSS patient group with respect to HC ($P<0.05$). Among these 25 peaks, the selected CART tree indentified 7149 m/z, 7192 m/z, 13507 m/z, 13714 m/z, 16547 m/z, 24059 m/z as best independent biomarkers able to discriminate between pSS and HC with a sensitivity of 96%, a specificity of 70% and a global cross validated error of 29%. Peaks of 7192 m/z, 24059 m/z and two further peaks of 28674 m/z and 33285 m/z were also significantly different in the group of pSS patients with parenchymal inhomogenicity at the salivary gland ultrasonography. Furthermore, in pSS patients with high focus score at the minor salivary gland biopsy and in pSS patients positive for anti-Ro/SSA antibodies, peaks of 4205 m/z and 22232 m/z and peaks of 3502 m/z and 4808 m/z were differently expressed, respectively.

Conclusion: This study supports the use of high throughput technologies to approach the challenge of the discovery of new, accurate diagnostic biomarkers for pSS and its clinical subsets.

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1901

Genetic Variants In *OPG* and *ANKH* Are Associated With Severity Ofankylosis In Ankylosing Spondylitis In a Korean Cohort. Il-Hoon Sung[1], Tae-Hwan Kim[1], Young Bin Joo[1], So-Young Bang[2], Seunghun Lee[3], Kyung-Bin Joo[4], Proton Rahman[5], Darren D. O'Rielly[5] and Robert Inman[6]. [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Hanyang University Guri Hospital, Guri, South Korea, [3]Hanyang University College of Medicine, Seoul, South Korea, [4]Hanynag University, Seoul, South Korea, [5]Memorial University, St. Johns, NF, [6]University of Toronto and Toronto Western Hospital, Toronto, ON.

Background/Purpose: Spinal ankylosis, which represents the most severe radiologic change in ankylosing spondylitis (AS), is associated with permanent work disability as well as decreased quality of life. Clinically, male sex, younger age at symptom onset, smoking, and elevated C-reactive protein level have been identified as factors associated with radiologic severity. However, genetic factors associated with radiologic severity remains elusiveal though AS is thought to be largely genetically determined. Thus, weset out to investigate which polymorphisms among genes involved in bone formation was associated with radiologic severity. Particular emphasis was placed on genes involved in WNT/β-catenin pathway and their respective antagonists or agonists. We also set out to investigate possible genetic-environmental interactions which could also impact AS radiologic severity.

Methods: A total of 417 Korean AS patients were enrolled and were classified into two groups based on the radiologic severity as defined by mSASSS: (1) Severe ankylosis (2) Control AS. Severe ankylosis was defined in the cases which had two intervertebral adjacent bridges (mSASSS score 2 at each site) and/or fusion (mSASSS score 3 at each site) in the lumbar spine or cervical spine. Control AS was defined in the cases which had no or only 1 syndesmophytes or bridging. There were 148 patients in the first group and 259 patients in the second. A total of 366 single nucleotide polymorphisms within 52 genes were genotyped using the Sequenom MassARRAY® system (iPLEX GOLD). Odds ratios (OR) and 95% confidence interval (95% CI) were analysed by logistic regression controlling for age and disease duration as covariates to identify the genetic predictors of radiologic severity.

Results: SNP *rs1032128* (in *OPG* or *TNFRSF11B*) and *rs2453327* (in *ANKH*) showed the most significant associations with severe ankylosis($P=6.49\times10^{-4}$, OR = 0.56, 95%, and $P=1.08\times10^{-3}$, OR = 1.72, respectively) after adjusting age and disease duration. In multivariate analyses, smoking(OR = 1.87, 95% CI 1.19–2.95) was significantly associated with severity ofankylosis. The combination of smoking and SNP *rs1032128 A* increased the risk of ankylosis 4.56-fold (95% CI 2.104–9.889) comparing to that of nonsmoker and SNP *rs1032128G*,and the combination of smoking and SNP *rs2453327* Tincreased the risk of ankylosis 2.89-fold(95% CI 1.586–5.277) comparing to that of nonsmoker and SNP *rs2453327* C.

Conclusion: Genetic polymorphisms in the bone-related genes *OPG* and *ANKH*demonstrate a significant association with severity of ankylosis in Korean AS, and theseassociationsareenhancedin smoker.

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1902

Characterization Of HLA-DRB1 Distribution By 3rd Hypervariable Region Sequence In Systemic Sclerosis and Control Populations. Coline, A. Gentil[1], Hilary S. Gammill[1], Christine, T. Luu[1] and J. Lee Nelson[2]. [1]Fred Hutchinson Cancer Research Center, SEATTLE, WA, [2]Fred Hutchinson Cancer Rsch, Seattle, WA.

Background/Purpose: HLA class II genes are associated with a wide spectrum of autoimmune diseases. Specific alleles at the DRB1, DQA1 and DQB1 loci are associated with systemic sclerosis (SSc) risk and/or clinical characteristics such as autoantibody profile. HLA nomenclature, particularly for the HLA-DRB1 locus, evolved utilizing serological typing reagents resulting in "a language of HLA" with initial grouping based primarily on antibody recognition of the HLA molecule. However, the third hypervariable region (3rd HVR) is the important site for T cell recognition, and the T cell perspective may be more important for autoimmune diseases including SSc. We therefore conducted an analysis based on the different amino acid sequences of the 3rd HVR (aa 67–74) irrespective of the HLA allele group. We sought to test the hypotheses that 1) overall charge of the amino acids in the 3rd HVR (positive, neutral or negative) differs for SSc patients compared to controls and 2) 3rd HVR charge differs for maternally-inherited vs. paternally-inherited HLA-DRB1 alleles.

Methods: We studied 254 control women and 133 women with SSc. HLA genotyping for DRB1 was performed by a PCR sequence-specific oligonucleotide probe method. Family studies were conducted to determine which HLA haplotype was maternally- or paternally-inherited. The data were then categorized according to which of 24 different 3rd HVR sequences was encoded by each allele. Next the 3rd HVR sequences were grouped according to whether they resulted overall in a positive, neutral or negative charge. Analyses were done by chi square.

Results: The overall distribution of the 3rd HVR sequences was significantly different in the SSc compared to the control population ($p=0.0005$), a difference primarily driven by enrichment of the FLED sequence present in the DRB1*1104 allele among the SSc population ($p=0.001$). No difference was observed for the overall 3rd HVR charge comparing the two populations. However, interestingly, among SSc patients, 3rd HVR charge differed by maternal vs. paternal haplotype ($p=0.0001$), a difference not seen among controls.

Conclusion: We observed a significant difference in the distribution of HLA-DRB1 alleles when classified according to the 3rd HVR, and especially an enrichment of the FLED sequence among SSc patients compared to

controls. This result indicates a possible role for 3rd HVR amino acid sequences in SSc. Polymorphism of amino acid sequences in the 3rd HVR can result in overall differences in charge. Our surprising observation of a significantly skewed distribution of 3rd HVR charge in maternal vs. paternal HLA haplotype in SSc patients but not in controls suggests a potential epigenetic effect that could contribute to SSc pathogenesis.

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1903

***PIK3CD* Overexpression In The Synovial Membrane Of Rheumatoid Arthritis Patients Is Associated With Response To Anti-TNF Therapy.** Antonio Julià[1], Gabriela Ávila[1], Raquel Celis[2], Raimon Sanmarti[3], Julio Ramirez[4], Sara Marsal[1] and Juan D. Cañete[5]. [1]Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [2]Hospital Clínic, Barcelona, Spain, [3]Hospital Clínic of Barcelona, Barcelona, Spain, [4]Hospital Clinic, Barcelona, Spain, [5]Hospital Clínic de Barcelona, Barcelona, Spain.

Background/Purpose: The mechanisms by which Rheumatoid Arthritis (RA) patients do not respond to TNF blockade are still poorly characterized. The goal of this study is to identify in synovial tissue (ST) of RA patients the genes that best characterize the profile of response to anti-TNF, therapy by using whole genome gene expression analysis.

Methods: Whole genome expression analysis of >21,000 genes was performed using Illumina WG-6 BeadChip microarrays in ST obtained by arthroscopy of RA patients before starting anti-TNF therapy. The clinical response was determined after 20 weeks of therapy using the EULAR criteria. The genes most significantly associated with the anti-TNF response were validated by quantitative RT-PCR. Changes in ST protein expression induced by anti-TNF therapy were quantified by immunochemistry and Digital Image Analysis.

Results: Eleven RA patients were included and a total of 135 genes were found to be differentially expressed between responders and non-responders after multiple test correction. The functional analysis of the overexpressed genes in the non-responder group (n=76 genes) identified a highly significant enrichment of genes expressed in peripheral blood CD14+ monocytes (similarity score Kappa=1.00, P=3.56e-5). We validated by RT-PCR the genes showing the most significant differential expression: *PIK3CD* (P= 7.11E-18) and *CX3CL1* (P=7.39E-12). Synovial tissue expression of PIK3CD protein before and after 5 months of anti-TNF therapy showed a significant reduction (P=0.035) only in those patients with a positive clinical response.

Conclusion: Our findings suggest that *PIK3CD* could be a useful biomarker of response to TNF blockade.

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1904

Gene Expression In Whole Blood Predicts The Abatacept–Methotrexate Combination Responsiveness In Rheumatoid Arthritis: Preliminary Results From The Power Doppler Ultrasonography IM101–179 Study. T Lequerré[1], C Derambure[1], MA D'Agostino[2], M Hiron[3], P Gaudin[4], C Gaillez[5], M Le Bars[5] and O Vittecoq[1]. [1]Rouen University Hospital & Inserm U905, Rouen, France, [2]AP-HP Ambroise Paré Hospital, Boulogne-Billancourt, France, [3]Rouen University Hospital & Inserm, Rouen, France, [4]CHU Hôpital Sud, Grenoble, France, [5]Bristol-Myers Squibb, Rueil Malmaison, France.

Background/Purpose: The overall response rate (defined as low disease activity [LDA] related to DAS28[CRP]) to abatacept associated with MTX was 57.1% at 6 months in the 6-month open-label abatacept Power Doppler Ultrasonography (PDUS; IM101–179) study in patients with RA and inadequate response to MTX.[1–3] The objective of this exploratory analysis was to identify potential predictors of response to the abatacept–MTX combination by whole blood gene expression profiling in order to optimize treatment choice.

Methods: 104 patients with active RA and inadequate response to MTX were treated with abatacept + MTX at the approved doses. Whole blood in Paxgene tubes was collected for each RA patient at baseline. At 6 months, RA patients were categorized as responders if DAS28 was ≤3.2 (LDA) and non-responders if DAS28 was >3.2. Baseline RNAs from a first set of RA patients (n=44) were hybridized to a whole human genome 4 × 44K microarray Agilent slide to identify a gene combination able to separate responders and non-responders with the GeneSpring GX software. A *t*-test with false discovery rate correction for multiple testing ($p<0.05$) was used to determine mRNAs differentially regulated between responders and non-responders. This gene combination was validated with a second set of RA patients (n=32) by qRT-PCR.

Results: Among these 104 RA patients, 28 were excluded from the following analysis because of missing clinical data (n=13), poor integrity of whole blood mRNA (RIN< 7) (n=6), low concentration rate for reverse transcription (n=7), qRT-PCR failures (n=2). Responders (n=45) and non-responders (n=31) had similar baseline characteristics.[1] In a first set of 44 enrolled RA patients (25 responders and 19 non-responders), 87 mRNAs identified by microarray analysis were expressed as a function of the response to treatment and an unsupervised hierarchical clustering almost perfectly separated these responders from non-responders. The informativeness of 12 of these 87 transcripts (selected with the lowest p-value), as measured by qRT-PCR, was re-assessed in a second set of 32 RA patients (20 responders and 12 non-responders). The combined levels of these 12 transcripts properly classified 23 out of 32 patients with a sensitivity of 80%, a specificity of 66.7%, a positive predictive value of 80%, and a negative predictive value of 66.8%. This combination enriched with more genes is in progress in order to better classify the second set of RA patients.

Conclusion: Our gene profiling results obtained by a non-invasive procedure have generated a list of 12 candidate genes that were associated with a response to abatacept combined with MTX in this study. This combination of genes needs to be further validated in other RA studies to support their utility as a potential diagnostic assay for predicting abatacept response in an effort to personalize treatment for RA.

1. D'Agostino MA et al. *Ann Rheum Dis* 2012;**71**(Suppl 3):86. 2. D'Agostino MA, et al. *Arthritis Rheum* 2012;**64**(Suppl):S352. 3. D'Agostino MA, et al. *Arthritis Rheum* 2012;**64**(Suppl):S353.

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1905

Protein Profiles Of Peripheral Blood Mononuclear Cells As a Biomarker For Behcet's Disease. Manae Kurokawa[1], Takuya Yoshioka[2], Toshiyuki Sato[1], Kouhei Nagai[1], Nobuko Iizuka[1], Mitsumi Arito[1], Yukiko Takakuwa[2], Hiromasa Nakano[2], Seido Ooka[2], Naoya Suematsu[1], Kazuki Okamoto[1], HIroshi Nakamura[3], Noboru Suzuki[2], Shoichi Ozaki[2] and Tomohiro Kato[1]. [1]St. Marianna University Graduate School of Medicine, Kawasaki, Japan, [2]St. Marianna University School of Medicine, Kawasaki, Japan, [3]Nippon Medical School, Bunkyo-ku, Japan.

Background/Purpose: To investigate the pathophysiology of Behcet's disease (BD) and find biomarker candidates for the disease, we analyzed protein profiles of peripheral blood mononuclear cells (PBMCs).

Methods: Proteins, extracted from PBMCs, were comprehensively analyzed in 16 patients with BD, 16 patients with rheumatoid arthritis (RA), and 16 healthy control subjects (HC) by 2-dimensional differential gel electrophoresis (2D-DIGE). Differently expressed proteins were identified by mass spectrometry.

Results: In total, 563 protein spots were detected. Intensity of 25 and 115 spots showed at least 1.2-fold intensity difference between the BD and HC groups and between the BD and RA groups, respectively ($p<0.05$). We completely discriminated between the BD and HC groups and between the BD and RA groups by multivariate analysis of intensity of 23 and 35 spots, respectively. The protein spots with significantly different intensity and also selected by the multivariate analysis included proteins functionally related to cytoskeleton, transcription/translation, T cell activation, bone turnover, regulating apoptosis, and microbial infection. Interestingly, intensity of only 3 protein spots provided area under the receiver operating characteristic curves (AUROC) of 0.922 for discrimination between the BD and HC groups. Similarly, intensity of 2 protein spots provided AUROC of 0.883 for discrimination between the BD and RA groups.

Conclusion: PBMC protein profiles, especially those of the 3 and 2 proteins, would be candidate biomarkers for BD. The identified PBMC proteins may play important roles in the pathophysiology of BD.

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ACR/ARHP Poster Session C
Health Services Research, Quality Measures and Quality of Care – Innovations in Health Care Delivery
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

1906

Comparison Of Decision Rules For Identifying Patients With Systemic Lupus Erythematosus (SLE) In Administrative Healthcare Databases. John G. Hanly, Kara Thompson and Chris Skedgel. Dalhousie University and Capital Health, Halifax, NS.

Background/Purpose: Identification of SLE cases in administrative healthcare databases is used to estimate disease frequency, healthcare utilization and cost. The optimal methodology for achieving this is unclear. Our aim was to validate and compare a range of decision rules that can be applied to administrative databases to identify patients with SLE.

Methods: The study was conducted at a single academic medical center. Administrative health care data from a geographic area with approximately 1 million people who had access to universal healthcare was utilized. A retrospective cohort study was performed through the Population Health Research Unit at our institution and utilized data from existing administrative databases. These included information on hospital discharges and physician billings over a 10 year period. Each SLE study subject was matched by age and gender to 4 randomly selected control subjects in the same datasets but without a diagnosis of SLE or other connective tissue diseases. A total of 7 decision rules, some derived from previous studies, were applied to the administrative data to identify SLE cases. The sensitivity, specificity, overall accuracy, positive (PPV) and negative (NPV) predictive values of these rules was compared to the diagnosis of a rheumatologist in the academic medical center determined by chart review.

Results:

Decision Rule	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)
#1 MacLean	81.5 (77.2, 85.3)	96.6 (95.5, 97.4)	93.6 (94.3, 96.5)
#2 MacLean/Lacaille	51.5 (46.3, 56.7)	98.1 (97.2, 98.7)	88.7 (87.4, 90.5)
#3 Shipton	79.6 (75.2, 83.6)	96.5 (95.5, 97.4)	93.1 (93.8, 96.0)
#4 Hospitalization	41.0 (36.0, 46.2)	99.9 (99.6, 100.0)	88.2 (85.2, 88.7)
#5 Rheumatologist	83.4 (79.2, 87.0)	98.7 (97.9, 99.2)	95.6 (94.9, 96.9)
#6 Combination	85.3 (81.2, 88.7)	98.0 (97.1, 98.6)	95.4 (95.3, 97.3)
#7 Single admin	86.6 (82.7, 89.9)	92.4 (90.7, 93.7)	91.3 (95.4, 97.4)

Decision Rule	PPV (95% CI)	NPV (95% CI)
#1 MacLean	85.6 (81.5, 89.1)	95.4 (94.3, 96.4)
#2 MacLean/Lacaille	86.9 (81.7, 91.0)	89.0 (87.4, 90.5)
#3 Shipton	85.1 (80.9, 88.7)	95.0 (93.8, 96.0)
#4 Hospitalization	99.4 (96.4, 100.0)	87.1 (85.5, 88.7)
#5 Rheumatologist	95.0 (90.8, 96.3)	96.0 (94.8, 96.9)
#6 Combination	91.4 (87.9, 94.1)	96.4 (95.3, 97.3)
#7 Single admin	74.1 (69.7, 78.1)	96.5 (95.4, 97.4)

Conclusion: The performance of decision rules for the identification of SLE cases in administrative healthcare databases is variable and should be considered when comparing data across studies. This variability may be used to advantage in study design when, for example, either sensitivity or specificity is the most critical issue for different population health research questions.

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1907

Acceptability Of Various Technology-Based Communication Modalities In a Rheumatology Clinic. Lisa A. Davis[1], Phat Luong[2], Sushmitha Bobba[2], Hannah Dischinger[2], Itziar Quinzanos[3] and Liron Caplan[2]. [1]Denver Health and Hospital Authority, Denver, CO, [2]Denver Veterans Affairs Medical Center, Denver, CO, [3]University of Colorado School of Medicine, Aurora, CO.

Background/Purpose: Technological advances have diversified the communication modalities of patients and healthcare providers. These include conveying information through telephone, internet portals, short-message service (SMS, "texting"), and electronic mail (email). The acceptability and preference for the use of these methods, however, likely varies by patient population. In order to assess the technology use and preferences of the U.S. veterans in our clinic, we administered an anonymous survey.

Methods: A convenience sample of patients in our rheumatology clinic at the Denver Veterans Affairs Medical Center completed a brief survey printed on paper. This survey assessed their access to technology, speed of responding to messages, barriers to technology use, and acceptability of various technologies as a means of communicating with their healthcare providers (0 to 10 Likert scale). Linear regression was used to explore the relationship of age and gender to the acceptability of each communication modality.

Results: The mean age of subjects (n=50) was 56 years, 84% were male, and 96% spoke English as their primary language. A majority had access to a computer (84%) and possessed an email address (78%). Similarly, 84% possessed a mobile phone; of those who possessed a mobile phone, 57.4% and 66.7%, respectively, had internet and texting ability. Of those who had texting, 28.2% found the cost of texting prohibitive for communicating with healthcare providers. The acceptability of various modalities (a score of at least 5 on the 10 point scale) as a means of contact with their healthcare providers was as follows: telephone call (80%), email (56%), internet-based portal (54%) and texting (42%). In a linear regression predicting the level of acceptability of each technology for communicating with the healthcare provider, only age was associated with texting. For every 10 years increase in age, the acceptability of texting declined by 1.4 points (95% CI −2.2 to −0.5, p-value 0.002).

Table 2. Use and preference of technology in US veterans in a rheumatology clinic

Variable	Cohort n	Cohort mean, %	Cohort with specified equipment* n	Cohort with specified equipment* mean, %
Age (mean)		56.2		
Gender, male (M)	42	84.0		
Primary language (%)				
English	48	96.0		
Spanish	2	4.0		
Access to a computer (%)	42	84.0		
Currently possesses an email address (%)	39	78.0	39	92.9
Frequency of email use (%)				
No email	9	18.0		
Once a month or less	7	14.0	5	12.8
Once a week	6	12.0	6	15.4
Most days	6	12.0	6	15.4
Everyday	11	22.0	11	28.2
Several times a day	11	22.0	11	28.2
How quickly patient responds to email (%)				
No email	9	18.0		
Weekly	4	8.0	4	10.3
Every few days	13	26.0	12	30.8
Daily	11	22.0	11	28.2
Every few hours	11	22.0	10	25.6
Every few minutes	2	4.0	2	5.1
Currently possesses a mobile phone (%)	42	84.0		
Internet access on mobile phone (%)	27	54.0	26	61.9
Current texting capability, (%)	32	64.0	32	76.2
Cost of texting prohibitive, (%)	11	22.0	6	18.8
How quickly patient responds to texts (%)				
Do not text	20	40.0	3	9.4
Weekly	1	2.0	1	3.1
Every few days	2	4.0	1	3.1
Daily	3	6.0	3	9.4
Within a few hours	9	18.0	9	28.1
Within a few minutes	15	30.0	15	46.9
Average rating on Likert scale (mean)				
Email	50	4.9	39	6.1
Text	50	3.8	32	5.7
Web portal	50	4.4	42	5.2
Phone call	50	7.1		
Wish to be contacted by doctor's office (Likert scale >=5) (%)				
Email	28	56.0	28	71.8
Text	21	42.0	21	65.6
Web portal	27	54.0	27	64.3
Phone call	40	80.0		

* The mean or % among those subjects with the specified equipment. For example, the "frequency of email"item only includes responses from those subjects with email, rather than the cohort as a whole.

Conclusion: Many of our patients have access to various communication modalities. Individual veterans display preferences for each of the modalities, but the majority wishes to communicate with their healthcare providers via telephone. Age only predicts the acceptability of texting, where increasing age was associated with less enthusiasm for this form of communication.

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1908

Quality Of Life and Adherence To Treatment In Patients Managed In Nursing Clinics In Rheumatology. Santiago Muñoz-Fernández[1], Pablo Lazaro[2], Antonio Javier Blasco[2], Sandra Fortea Gracia[3], Laura Cano-García[4], Jose A. Roman Ivorra[5], Raquel Almodóvar González[6], José Santos Rey Rey[7], Teresa Navío-Marco[8] and Mercedes Cabañas[2]. [1]Hospital Universitario Infanta Sofía, San Sebastián de los Reyes (Madrid), Spain, [2]Advanced Techniques in Health Services Research (TAISS), Madrid, Spain, [3]Hospital de Sagunto, Sagunto, Spain, [4]Hospital Regional Universitario Carlos Haya, Málaga, Spain, [5]Hospital Universitario y Politécnico La Fe, Valencia, Spain, [6]Hospital Universitario Fundación Alcorcón, Madrid, Spain, [7]Complejo Hospitalario de Toledo, Toledo, Spain, [8]Hospital Universitario Infanta Leonor, Madrid, Spain.

Background/Purpose: Nursing clinics in rheumatology (NCR) are organizational models in the field of nursing care. However, little is known about the NCR outcomes. The purpose of this research is to evaluate differences between centers with and without NCR in patients' quality of life and treatment adherence.

Methods: Cross-sectional study carried out in rheumatology departments of 39 Spanish public hospitals from July to December 2012. The minimum requisites that the department must have to be defined as NCR were: 1) A nursing office, but not necessarily every day of the week; 2) at least one specialist nurse, at full or part time; 3) nurse appointment book; and 4) a dedicated telephone. Patients inclusion criteria were: 1) older than 18 years; 2) diagnosed of rheumatoid arthritis (RA) or ankylosing spondylitis (AS); 3) treated with at least one DMARD or a biologic; and 4) signing the informed consent. Data were collected through a survey with case report forms (CRF) completed by rheumatologists and patients. Sociodemographic, disease characteristics, treatment, quality of life and adherence variables were collected. The EuroQol-5D (EQ-5D) and Morisky-Green test were used to assess the quality of life and adherence to treatment, respectively. Regional and hospitals research and ethics committees approved the project protocol and CRFs.

Results: Twenty one centers were NCR and 18 were no-NCR. The NCR centers included 181 patients (142 RA and 39 AS) and the no-NCR centers included 212 patients (160 RA and 52 AS). There were no statistically significant differences between NCR and no-NCR patients in: age [mean±SD, years] (53.2±11.8 vs. 56.3±13.5), gender [male, %] (29.8 vs. 38.7), rheumatic disease [RA, %] (78.5 vs. 75.5), years diagnosed (10.6±8.8 vs. 9.5±8.9), treatment [only biologics, only DMARDs, both %] (23.8, 39.2, 37.0 vs. 23.6, 46.7, 29.7, respectively), DAS-28 (2.87±1.28 vs. 2.97±1.19) and HAQ (0.81±0.68 vs. 0.88±0.68) in patients with RA, and BASDAI (3.44±2.41 vs. 3.68±2.31) and BASFI (3.15±2.78 vs. 3.85±2.60) in patients with AS. No statistical differences were observed between NCR and no-NCR in EQ-5D index (0.68±0.21 vs. 0.66±0.21) and EQ-5D Visual Analogue Scale (64.6±21.0 vs. 64.5±20.5). Patients from NCR have a better adherence to treatment than the no-NCR patients [adherent patients, %] (79.0 vs. 69.3; p=0.03).

Conclusion: Patients managed in rheumatology departments with NCR have clinical characteristics, treatment patterns and quality of life similar to patients managed in centers without NCR, however, they have better adherence to treatment.

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1909

Interpretation Of Patient Reported Outcomes Measurement Information System (PROMIS) By Rheumatologists. Vivek Nagaraja, David A. Fox, Sheeja Francis, Ora Singer, Puja Khanna, Timothy Laing, Rory Marks, Seetha U. Monrad, Vladimir M. Ognenovski, Kristine Phillips and Dinesh Khanna. University of Michigan Medical Center, Ann Arbor, MI.

Background/Purpose: The National Institutes of Health Patient Reported Outcomes Measurement Information System (PROMIS¨) roadmap initiative is a cooperative research program designed to develop, evaluate, and standardize item banks to measure patient-reported outcomes (PROs) across different medical conditions as well as the US population (www.nihpromis.org). It has comprehensive items banks that assess physical, mental, and social well-being. The aim of this study was to assess the interpretation of PROMIS report by rheumatologists at the University of Michigan (UM) Hospital.

Methods: Four focus group discussions consisting of eleven rheumatologists were held at UM Health System. The panelists were first presented with an overview of PROMIS process followed by a series of patient reports With a focus on the evaluating which report was feasible to use in day-to-day practice and clinically meaningful, the following questions were asked by: (i) What do you think of this report? (ii) Do you understand what this report is communicating? (iii) Is there anything you would change about this report to make this better?

Results: All the rheumatologists agreed on the following suggestions: (i) Representation of the item scores as thermal graphs or "heat map" was easier to interpret (ii) Provide average scores for the U.S. population and rheumatology patients, (iii) Provide both average and percentile scores, and (iv) Provide pictorial depiction of most bothersome symptom and urgency for referral. Based on these discussions, we modified the PROMIS heat map (Figure 1) to include: (i) average scores for rheumatologic disorders (bold square), (ii), an open diamond to indicate the individual scores of the patients, and (iii) thickness of the diamond indicates the severity of these symptoms in the patient with an urgency for intervention (thicker equates to greater urgency).

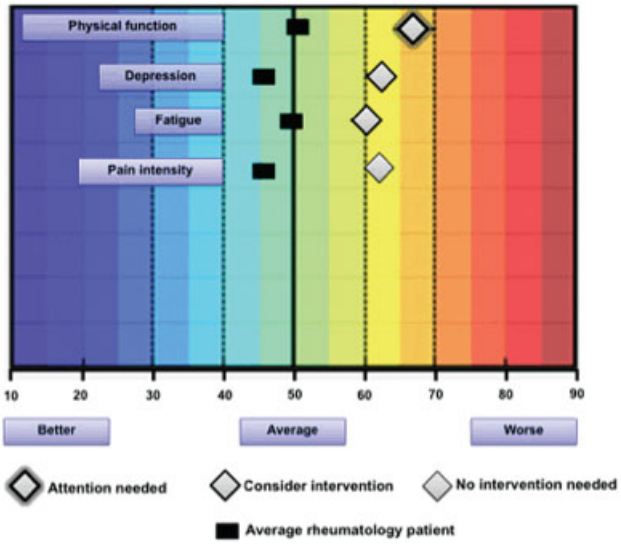

Figure 1. Format of PROMIS report after incorporating the suggestions

Conclusion: This presents the first step to assess feasibility of incorporating PRO in rheumatology practice at UM. The PROMIS report card when integrated with the electronic medical record can contribute towards meaningful use. It may improve patient satisfaction and physician-patient relationship. Our long-term goal is to integrate PROMIS into a busy academic practice and assess its effectiveness.

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1910

Validation Of The Mayo Hip Questionnaire: Validity and Sensitivity To Change. Jasvinder A. Singh[1], Cathy Schleck[2], W. Scott Harmsen[3] and David Lewallen[4]. [1]University of Alabama, Tuscaloosa, AL, [2]Mayo Clinic College of Medicine, Rochester, MN, [3]Mayo Clinic, Rochester, MN, [4]Mayo Clinic college of medicine, Rochester, MN.

Background/Purpose: Mayo Hip questionnaire has previously been shown to have face, content and test-retest reliability. Our objective was to assess the validity and responsiveness of the Mayo Hip Questionnaire.

Methods: We used data from the Mayo Clinic Total Joint Registry to assess the validity of Mayo Hip questionnaire, by including patients who underwent primary total hip arthroplasty (THA) between 1993–2005 and responded to the baseline and 2-year post-primary THA Mayo Hip questionnaire. Mayo hip questionnaire assesses the domains of pain, function and mobility; reliability and construct validity has been previously established. It generates a total score clinical score ranging 0–80 (Excellent result is 72–80 points, good is 64–71 points, fair is 56–63 points, and poor is less than 55 points). Convergent/divergent validity was examined with the association of select demographics (age, gender, number of joints involved) at baseline with Mayo hip scores using linear regression analyses. Minimally Clinically Important Difference (MCID) and Really Important Difference (RID) were calculated corresponding to "somewhat better now" and "much better now", respectively in response to patient-reported anchor at 2-years- Compared to your condition before the surgery, how would you rate your hip now? For discriminant ability, we calculated a) effect size by taking the change in respective score from baseline to 2-years and dividing the result by the standard deviation at baseline and b) the standardized response mean, defined as the mean change in the patient score with improvement at 2-years divided by the SD of the changed scores.

Results: For primary THA, there are 2,311 hips with both a baseline and a 2-year data. The sample consisted of 1,097 males (47.5%)and 1,214 females (52.5%). The mean age at surgery (SD) is 64 (13), median was 66 (range, 15–92). Age and gender were significantly associated Mayo Hip score at 2-years post-THA ($p<0.001$); and the number of joints involved was not associated ($p=0.98$). MCID was 24.8 and RID threshold was 37.1. Effect size at 2-years was large, 2.26 and the Standardized Response Mean was 2.25.

Conclusion: The Mayo Hip questionnaire is a valid and sensitive outcome measure for patients undergoing primary THA. This study provides further validation of this previously validated scale. Further validation in revision THA and in more diverse populations will provide more support to its validation as an outcome instrument.

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How Are Actual Patterns Of Care For a Health System In Rheumatology In Comparison With Validated Quality Measures? Susan Mathew, Tarun S. Sharma, Oscar Quintero, Olga Bailey, Debra Webb, Eric D. Newman and Androniki Bili. Geisinger Medical Center, Danville, PA.

Background/Purpose: The American College of Rheumatology (ACR) in 2008 and 2012 published guidelines for the use of disease modifying anti-rheumatic drugs (DMARD) and biologics in rheumatoid arthritis (RA) in an attempt to improve quality and decrease variability in RA care. In addition, in 2012, a unique population management program for RA was initiated in our institution, an academic tertiary center, designed to improve quality and safety while reducing cost of care in RA. The aim of the present project was to characterize the variability in RA care provided in the rheumatology practice in our institution, according the ACR and local measures.

Methods: Data on 80 consecutive patients with newly diagnosed RA between 1/1/2010 and 8/1/2011 with at least 18 month follow-up period were extracted through the electronic health records (EHR). RA diagnosis was made based on ICD-9 code 714.0 by a rheumatologist. Additional data were extracted by manual review of the EHR by four of the authors. The primary objective was to measure practice patterns in RA care and DMARD use according to selected quality measures. Secondary objective was to compare the actual vs. perceived RA care rendered by rheumatologists. For that purpose, we used a survey with questions regarding DMARD use in RA that had been administered earlier to all staff rheumatologists and fellows as part of our population management program. The results of this survey were termed "perceived" care. This was compared to the actual RA care delivered by these providers, based on data extracted from the EHR, termed "actual" care.

Results: Results are shown in Table 1. We achieved >60% in disease activity and functional measures, DMARD use and PPD before starting a biologic, but <50% in obtaining a disease activity measure in at least 50% of the visits, and administering pneumococcal and influenza vaccinations in patients on DMARDs. MTX median starting dose was 12.5 (min 7.5, max 20) mg/weekly; switch from oral to injectable MTX was only 9%, although physician perception was 20%; and, the median time patients were treated with MTX prior to starting a biologic was 6 (min 1, max 6) months with physician perception being 4 months.

Table 1. Actual and Perceived Patterns of RA care

Category	Process	National Guideline or Quality Measure	Actual (N = 80) median or %	Actual (N = 80) variability	Perceived median	Perceived variability
RA Care	Disease Activity (CDAI ≥1) measured atleast once	Y	70%		n/a	
	Disease Activity (CDAI >50% visits)	Y	43%		n/a	
	Function (MDHAQ) measured atleast once	Y	66%		n/a	
	Hand Xrays measured in 1st 6 months	N	59%		90%*	(0,100)
	Feet Xrays measured in 1st 6 months	N	31%		50%*	(0,100)
	Sed Rate measured at baseline	N	76%		n/a	
	Time between visits	N	3 months	(1,6)	1.5*	(1,3)
DMARD Use	Any DMARD use	Y	88%		n/a	
	MTX start dose	N	12.5	(7.5, 20)	15	(7.5, 15)
	Switch from oral to subq MTX	N	9%		20%*	(5, 60)
	MTX dose before biologic	N	15	(0, 20)	20*	(17.5, 20)
	Time on MTX before biologic	N	6 months	(0, 23)	4	(3, 9)
DMARD Safety	MTX Baseline Lab tests	Y	93%		n/a	
	MTX Interval between lab tests	Y	3 months	(1,6)	2	(1,3)
	PPD before Biologic	Y	78%		n/a	
	Influenza vaccine	Y	48%		n/a	
	Pneumococcals Vaccine	Y	48%		n/a	
	CXR before MTX	N	65%		n/a	

CDAI: clinical disease activity index; DMARD: disease modifying anti rheumatic drug; RA: Rheumatoid arthritis; MDHAQ: modified Health Assessment Questionnaire; MTX, Methotrexate; PPD: purified protein derivative for TB, *$p<0.009$.

Conclusion: Our results showed there is need for improvement in several selected measures in RA care. Improvement in quality should aim to increase the routine collection of disease activity measures, greater use of injectable MTX and vaccinations. Cost reduction should aim to reduce variability in MTX use prior to starting biologics in terms of both time and dosages and in laboratory monitoring. There were also differences in the perception of rheumatologists about the care they deliver and the actual care that is delivered. Results of this study will be used as a benchmark for ACR measures and our population management program, in order to examine ways to reduce variability and improve quality in the care provided to RA patients.

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Do Persons With SLE In Poverty Rate Interactions With Providers and Health Plans Differently? Edward H. Yelin[1], Chris Tonner[2], Laura Trupin[2] and Jinoos Yazdany[2]. [1]UC San Francisco, San Francisco, CA, [2]University of California, San Francisco, San Francisco, CA.

Background/Purpose: We previously showed that poverty is associated with the quantity, type, and technical quality of care in SLE.[1] Here we assess whether poverty is associated with ratings of interpersonal aspects of care about providers and health plans.

Methods: We analyzed data from the UCSF Lupus Outcomes Study (LOS), a national sample of persons with SLE interviewed annually using a structured telephone survey. The survey includes batteries from the Consumer Assessment of Health Plans (CAHPS) developed by the Agency for Healthcare Research and Quality and the Interpersonal Processes of Care Scales (IPC) developed by Stewart, et al. (Health Serv Res 2007; 42: 1235–1256) for respondents to rate care along six dimensions of interpersonal processes of care about providers (patient-provider communication, shared decision-making, and trust in provider) and health plans (promptness/timeliness of care, care coordination, and

assessment of health plan). Scores in the CAHPS and IPC items were transformed to a uniform 0 (lowest) −100 (highest) rating scale. Ratings on the six dimensions were regressed on whether respondents had household income ≤ 125% of the Federal poverty level for their household size with and without the following covariates: demographics (age by category, race/ethnicity, language spoken at home), presence and source of health insurance (public, employer, other), HMO vs. fee-for-service coverage, specialty of main SLE provider, and health status (BILD index of damage, SLAQ index of activity, and CESD index of depressive symptoms).

Results: In 2012, the LOS included 793 respondents living in 40 states. Mean (SD, range) age was 52 years(13, 20–86), duration of SLE was 19 years(9, 1–55), SLAQ was 11(8, 0–47) and BILD was 2.1(2.1, 0–13); 93% were female, 42% non-white, 19% ≤ high school, and 16% met the study definition of poverty. For the six dimensions evaluated, highest ratings were for patient/provider communication (90, 95%CI: 89,91), trust in provider (89, 95%CI:88,90), while lowest ratings were for shared decision-making between patient and provider (43, 95%CI:41,46). In bivariate analysis, poverty was associated with significantly lower ratings of patient-provider communication, trust in provider, timeliness of care, and evaluation of health plan. In multivariate analysis, poverty was not associated with any dimension of care.

Ratings of Six Dimensions of Care by Poverty Status

	Provider			Health Plan		
	Pt/Provider Commun.	Shared Decisions	Trust	Promptness/ Timeliness	Care Coord.	Evaluation Heath Plan
	ratings 0–100 (95% CI)					
All	90 (89, 91)	43 (41, 46)	89 (88, 90)	74 (72, 76)	77 (74, 79)	81 (80, 82)
Bivariate model	*		*	*		*
POVERTY	86 (84, 89)	40 (34, 46)	86 (82, 89)	68 (63, 73)	71 (65, 77)	75 (71, 79)
Not POVERTY	91 (90, 92)	44 (41, 46)	90 (88, 91)	75 (73, 77)	78 (75, 81)	82 (81, 84)
Multivariate model						
POVERTY	88 (84, 92)	37 (27, 47)	87 (82, 93)	67 (59, 74)	75 (65, 85)	75 (70, 80)
Not POVERTY	89 (86, 92)	43 (35, 52)	88 (83, 92)	69 (62, 75)	75 (67, 83)	79 (75, 83)

* $p<0.05$ for difference by poverty status

[1] Arthritis Care Res 2010; 62: 888–895; J Gen Int Med 2012; 27: 1326–1333.

Conclusion: Unlike objective measures of quantity, type, and technical quality of care, after adjustment, poverty is not associated with subjective assessments of interpersonal processes of care about providers and health plans.

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Expectations RA Patients Have For Their Treatment - A Comparison Of Clinical Results For Biologic and Disease-Modifying Anti-Rheumatic Drug Treated Patients Using Multiple Medical Cohorts. Tsukasa Matsubara[1], Hiroaki Matsuno[1], Tomomaro Izumihara[1], Yuichi Takahashi[1], Akira Sagawa[1], Motohiro Oribe[1], Eisuke Shono[1], Kensuke Kume[1], Masanori Adachi[1], Yuichi Nishioka[1], Nobumasa Miyake[1], Keisuke Hashimoto[1], Toshikaki Miyamoto[1], Shigeto Kiyokawa[1], Tomohiko Yoshida[1], Syoichi Kondo[1], Yoshiki Shiohira[1], Takanori Azuma[1], Yukio Sato[1], Masaaki Yoshida[1], Kenji Mannami[1], Akihiko Nakamura[1], Yasuhiko Hirabarashi[1], Keiko Funahashi[2] and James E. Middleton[3]. [1]Japanese Clinician's Biologic Research Group, Kobe, Japan, [2]Matsubara Mayflower Hospital, Kato, Japan, [3]Research Institute of Joint Diseases, Kobe, Japan.

Background/Purpose: Treat to Target (T2T) primary principal - "The treatment of rheumatoid arthritis must be based on a shared decision between patient and rheumatologist". Japan uses T2T, but its impact on patients is not yet clear. To better understand T2T implementation, a large scale survey was conducted using a multi-cohort study.

Methods: A survey was given to 4489 RA outpatients in multiple facilities in Japan; contents included; age, gender, medical history, and comments on; 1) things to know before administration, 2) expectations of medication, 3) disappointment with medication, 4) anxiety switching medication 5) biologics experience, 6) goals for treatment, 7) satisfaction level, 8) questions and expectation of doctors, 9) treatment fees, 10) impression of biologics, 11) injections, 12) desires for the future. For further analysis the total results from respondents were divided into 2 groups; Biologics (BG), 1728 patients, and DMARDs Group (DG), 2264 patients.

Results: Eighty-two point five percent of the respondents were female and 27% had disease duration of 10–20 years. Usage; DG 80% BG, 35%. For 'expectations of medication', 35% responded with 'assured improvement of the condition' while 22% responded 'reduced destruction or deformation of joints'; no difference between groups. In BG more patients (22%) hoped for long-lasting efficacy than in DG (14%). 'Experience of disappointment' was 22% in total, but the rate of BG was twice that of DG; reason for disappointment for BG was lack of efficacy, however, for DG it was adverse events. The reason for 'anxiety when switching' was mainly 'adverse events' and 'efficacy' in both groups, but 'diminishing efficacy' showed a higher rate in BG, related with the reason for disappointment. In both groups the 'goals for treatment' was mostly 'the improvement of QOL' and 'reduced destruction/deformation of joints', but 'reduced destruction/deformation of joints' for BG were 1.5 times that of DG. BG wanted more information about future treatment. In DG, 70% were willing to spend up to ¥10,000 a month, as opposed to 30% in BG, suggesting BG understood the cost of biologics. For injections, many in both groups, responded 'troublesome' or 'frightening', but the image was higher for self-injection, especially in DG, but, half the respondents in BG chose 'convenient'.

Conclusion: Expectations for medication in terms of assured improvement of conditions and prevention for joint destruction, were confirmed with results of a single-institution study 2 years ago. But, rate of 'long-lasting efficacy of drugs' was higher in BG this time. Data indicated BG showed these tendencies after secondary failure, which was also suggested in both studies. The patients in BG, due to knowledge of prevention of joint destruction, have higher treatment goals than DG. The comparison between 2 groups indicated once patients experience high efficacy, they can tolerate self-injection and higher fees. We should be aware that what Japanese RA patients are expecting is assured improvement of condition including prevention from joint destruction and long-lasting efficacy. Our study indicates steady implementation of T2T while patients are receiving good education, clearly understanding 3 standards for remission of RA.

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Patient and Physician Perspectives On Family Planning and Pregnancy Issues In Systemic Inflammatory Diseases: Mind The Gap! Megan E. B. Clowse[1], Eliza Chakravarty[2], Daphnee S. Pushparajah[3], Sarah Mertens[3] and Caroline Gordon[4]. [1]Duke University Medical Center, Durham, NC, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]UCB Pharma, Brussels, Belgium, [4]University of Birmingham, Birmingham, United Kingdom.

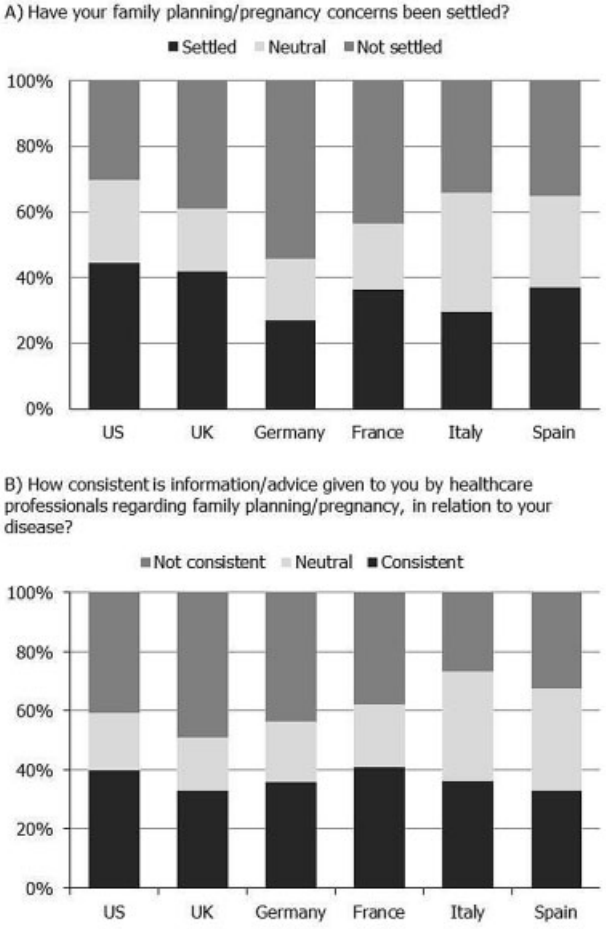
Background/Purpose: Autoimmune and inflammatory diseases often affect women of reproductive age and can impact pregnancy outcomes. This patient (pt) group has important concerns about family planning and pregnancy (FPP), however little research has been undertaken into whether such concerns are adequately addressed in current clinical practice. The aim was to identify FPP issues for female pts of child-bearing age and to assess whether current clinical practice routinely provides adequate support to alleviate these concerns.

Methods: Two online surveys were undertaken to identify FPP issues for both pts and physicians. The surveys were designed to gauge whether there is a gap in the communication by examining the frequency of dialogue on these topics between physicians and pts, alongside assessment of pt satisfaction regarding these discussions. Physician survey was designed to elicit both spontaneous (open-ended questions) and prompted (closed questions) responses: rheumatologists were surveyed in Germany (N=50), France (N=50), Italy (N=50) and the USA (N=100) while

gastroenterologists were surveyed in the USA (N=100). Pt survey was targeted at premenopausal women (aged 20–45 years of age; N=969) and delivered in USA, UK, Germany, France, Italy and Spain.

Results: 32–56% of physicians spontaneously reported having discussed FPP with their female pts of child-bearing age across all countries surveyed. When prompted, the majority of rheumatologists (74–92%) and gastroenterologists (74%) reported having discussed conception/pregnancy with female pts; however, less than half reported discussing FPP with their pt's treating GP/gynaecologist. Even though physicians report discussing FPP with their female pts, the majority of pts report their concerns relating to FPP are not adequately addressed/settled during their medical appointments (Figure 1A); although responses did vary across countries. Furthermore, only 30–40% of pts considered advice/information to be consistent across multiple healthcare professionals (Figure 1B). Female pts receiving medication for their condition were more concerned about FPP than those not receiving medication (63% vs 32%, respectively), and <5% reported discussing FPP when their condition was stable enough to become pregnant.

Figure 1: Settlement of patient concerns and consistency of advice received by patients from healthcare professionals



Conclusion: Female pts who suffer chronic inflammatory disease have important FPP concerns. The majority of pts, however, do not feel that their FPP concerns are adequately addressed in current clinical practice and report that they receive inconsistent advice from the various healthcare professionals who manage different aspects of their care. There is a clear need for provision of up-to-date and consistent information/support to female pts suffering inflammatory diseases, including the key importance of disease control when/before planning pregnancy.

Disclosure: M. E. B. Clowse, UCB Pharma, 5; **E. Chakravarty**, UCB Pharma, 5; **D. S. Pushparajah**, UCB Pharma, 3; **S. Mertens**, UCB Pharma, 3; **C. Gordon**, None.

1915 WITHDRAWN

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Approaches and Challenges To Reducing Wait Times For Total Hip and Knee Replacement. Aileen M. Davis[1], Cheryl Cott[2], Rose Wong[3], Michel Landry[4], Linda C. Li[5], Allyson Jones[6], Cy Frank[7], Sydney C. Lineker[8], Louise Bergeron[9], Rhona McGlasson[10], Gillian A. Hawker[11], Dianne P. Mosher[12], Susan B. Jaglal[13], Richard Birtwhistle[14], Sherry Bar[15] and Elizabeth M. Badley[16]. [1]Division of Health Care and Outcomes Research, Toronto Western Research Institute, University Health Network, Ontario, ON, [2]Divison of Health Care and Outcomes Research, Toronto Western Research Institute, University Health Network, Toronto, ON, [3]Division of Health Care & Outcomes Research, Toronto Western Research Institute, University Health Network, Toronto, ON, [4]Department of Community and Family Medicine, Physical Therapy Division, Duke University Medical Center, Durham, NC, [5]Arthritis Centre of Canada, Richmond, BC, [6]University of Alberta, Edmonton, AB, [7]Alberta Bone and Joint Institute and Department of Surgery, University of Calgary, Calgary, AB, [8]The Arthritis Society, Toronto, ON, [9]Canadian Arthritis Patient Alliance, Ottawa, ON, [10]Bone and Joint Canada, Toronto, ON, [11]Women's College Research Institute, University of Toronto, Toronto, ON, [12]University of Calgary, Calgary, AB, [13]Department of Physical Therapy, University of Toronto, Toronto, ON, [14]Centre for Studies in Primary Care and Family Medicine and Community Health and Epidemiology, Queen's University, Kingston, ON, [15]British Columbia Ministry of Health Services, Victoria, BC, [16]Toronto Western Research Institute, University Health Network, Toronto, ON.

Background/Purpose: Due to obesity, the growing prevalence of hip and knee osteoarthritis and boarder indications for hip and knee replacement, there is increasing pressure on developed countries to provide total joint replacement (TJR) in a timely manner. In Canada, reduction of wait times for TJR was a priority in the 2004 Health Accord (at that time it was not uncommon for waits to exceed 100 weeks) and, as a result, provinces instituted various strategies to reduce the wait. This work describes the approach taken by three provinces to achieve a target 26 week wait from patient/surgeon decision for surgery to surgery for 90% of people.

Methods: This research used a policy case study approach with review of government documents, non-governmental organization reports and published literature for Federal and Provincial policy and descriptions of programs/models of care related to TJR implemented by British Columbia (BC), Alberta (AB) and Ontario (ON). Additionally, one-on-one interviews (n=28) were conducted with policy makers, individuals in key leadership roles, program directors and managers to further understand provincial approaches. Transcribed interviews were analyzed thematically for activities targeted at reducing TJR wait times conducted within each province.

Results: Arthritis prevalence (15–16% over age 15) and health human resources (4 orthopaedic surgeons per 100,000 population) were similar across provinces with each challenged to provide service in low density regions. Although all provinces implemented efficiencies through standardized care pathways and processes to improve operating room access, there were different approaches relating to access to surgical consultation (e.g. referral central intake, triage and who conducted it based on availability, scope of practice, and how programs/providers were funded). AB focused on a case manager who also aided the patient in system navigation; ON focused on rehabilitation professionals working in advanced practice roles for triage; and, BC implemented a variety of approaches, driven by local champions and context. A provincial platform to drive change was critical for success, as were evidence-informed experts who had the authority to make decisions and champion change, and financial resources to support change, program implementation and sustainability. All provinces decreased wait times but, as shown in table 1 (fourth quarter data from fiscal 2012/13), at a provincial level and in the majority of institutions, challenges continue in meeting target wait times.

	Province	Number of primary joint replacements	Wait time (number of weeks for 90%)	Hospitals meeting target	Trend 2010 to 2013
Knee	BC	1255	32.8	12/29	–
	AB	1599	39.1	5/13	+
	ON	8903*	33.1	24/56	+
Hip	BC	1833	37.5	14/29	–
	AB	971	38.9	6/13	+
	ON	–	27.1	33/56	NA

*combined hip and knee

Conclusion: Although sharing common elements in approach, provincial TJR wait time strategies were variable. Despite reductions results have varied across the provinces. This raises questions of whether benchmarks are attainable and how such strategies will be sustained in times of fiscal constraint and rising demand for TJR.

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Falls Among Hospitalized Orthopedic Patients: A Prospective Case-Control Study. Lisa A. Mandl, Wei-Ti Huang, Jaimie Lee, Tina Bailey, Danielle Edwards, Patricia Quinlan, Mayu Sasaki and Steven K. Magid. Hospital for Special Surgery, New York, NY.

Background/Purpose: This study evaluated rates and predictors of falls among adult orthopedic in-patients at a musculoskeletal specialty hospital.

Methods: Researchers prospectively studied falls from 5/2/10–5/1/12. Two controls were matched to every fall on age, post-operative day (POD), type of orthopedic procedure, and each assigned the index time that their case fell. Data were collected via chart review and patient questionnaire. Medical record data for controls was abstracted from last note prior to the index time or first note after. Differences between cases and controls were compared using t-test or chi-square test, as appropriate. A multivariate logistic regression was performed to identify predictors of falls.

Results: There were 169 falls during the study timeframe. The fall rate was 0.65 of in-patient orthopedic admissions; 1.67 falls/1000 in-patient days. The average age of cases was 68.4 yrs, (SD 12.7), 55% were women, mean BMI was 29.4, (SD 6.5), and average POD was 2.9 (SD 2.5). One patient fell twice. 39.5% of falls occurred in total knee replacements (TKR), 23.3% in total hip replacements (THR), 25.8% in spine procedures, 9.6% in lower extremity procedures and 1.8% in upper extremity procedures. 92% of falls occurred in the patients' room. Neither a known history of falls nor wearing a "falls risk" bracelet was associated with falling. Fallers were less likely to use a crutch or cane, more likely to use a walker, and more likely to be in a single occupancy room. Cases walked significantly fewer feet and required significantly more physical therapy (PT) ambulation assistance than controls. 31% of falls involved using the bathroom. Of 168 first falls, 28 (17%) resulted in injuries, most of which were minor. 8 falls (4.8%) resulted in 10 serious adverse events (AEs), including 4 dehiscence/return OR, 3 transfer to a higher level of care, 2 dislocations and 1 fracture. There we no deaths or intracranial/epidural bleeds.

In a logistic regression controlling for significant univariate predictors (single room occupancy, confusion, being assigned canes/crutches, using a walker or needing physical therapy assistance to ambulate) the only predictors of falls were confusion (OR 2.6; 95% CI 1.4–4.8) and using a walker (OR 28.6; 95% CI 6.5–125.0). Being in a double occupancy room was borderline protective against falling (OR 0.55; 95% CI 0.3–1.003). Among TKR, having a femoral block trended towards being associated with falls (p-value=0.057). There were no significant predictors of AEs.

Table 1. Comparisons of Patients Who Fell vs. Controls*

Characteristic	Fall Cases (n = 168)	Controls (n = 317**)	P-value
Sex			
Female	92 (55%)	179 (56%)	0.72
Distance (feet) able to ambulate with assistive device	48.9 (SD = 66.5)	64.4 (SD = 86.8)	0.049
Room Size†			
Double room	124 (80%)	262 (89%)	0.011
Single, or Double-Single	31 (20%)	33 (11%)	
Chart documented confusion	34 (20%)	29 (9%)	<0.001
Assigned a cane or crutches at fall/index time	162 (96%)	278 (88%)	0.0016
Walker used during fall/index time	142 (85%)	325 (99%)	<0.001
Ambulation Assistance by Physical Therapist			0.005
Max or Moderate	24 (15%)	33 (11%)	
Minimal	39 (25%)	97 (31%)	
Contact Guard	56 (35%)	84 (27%)	
Supervision or independent	13 (8%)	57 (19%)	
Not Tested	27 (17%)	37 (12%)	
Recorded prior history of falling	58 (36%)	82 (26%)	0.09
Patient wearing a yellow risk bracelet	45 (28%)	60 (19%)	0.13
Pre-operative urinary issues (incontinence, nocruria, urgency/frequency)	49 (30%)	84 (27%)	0.62

* Controls were assigned index time and date based on the time and date their matched case itself
** 2:1 controls could not be identified for 14 cases
† double room = two beds and two patients; a single room = one bed and one patient; double-single rooms size of a double room with one bed and one patient.

Conclusion: The rate of falls and AEs in this patient population was low. This large series identifies confusion and using a walker as being predictive of falling among orthopedic in-patients. Larger studies are needed to confirm these results, and to inform fall prevention strategies in this rapidly growing group of patients.

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Adoption Of New Electronic Medical Records May Inhibit Documentation Of Physician Quality Reporting System. Minzi Chen, William E. Davis, Austin Fraser, Jerald M. Zakem, Eve Scopelitis, Kismet Collins, MD, Tamika A. Webb-Detiege and Robert Quinet. Ochsner Medical Center, New Orleans, LA.

Background/Purpose: Lower back pain (LBP) is a common complaint in the general population and accounts for 2.5% of all outpatient office visits. Critical assessment and documentation of the clinical features of LBP are essential for accurate diagnosis and proper care. Medicare has established physician quality reporting system (PQRS) guidelines for back pain. An incentive is given to clinicians who successfully report 3 or more PQRS measurements for a minimum of 50–80% applicable Medicare Part B FFS patients from January 1 to December 31. Clinicians not compliant with reporting system will receive a service penalty that will be applied in 2015. Electronic medical records (EMR) are promoted as tools for performance improvement. We investigated the impact of education and conversion to a comprehensive EMR (EPIC) on physicians' documentation and compliance with the quality reporting system guidelines.

Methods: We initiated a performance improvement project by retrospectively reviewing 100 charts (20 from each of 5 clinicians) for Medicare PQRS guidelines for low back pain. Content of the PQRS documentation assessed includes initial comprehensive assessment using standardized assessment tools for pain, functioning status, warning signs, prior treatment response and employment status, physical examination including straight leg raise and neurological exam, advice for normal activities, and advice against bed rest. Results were reviewed with the clinicians, in conjunction with a didactic review of the PQRS guidelines. A comprehensive EMR system (EPIC) was launched shortly after the first chart review. Subsequently, 100 (20 from each of 5 physicians) charts were reviewed to measure change in documentation. An additional plan-do-study-act cycle was performed after working with the software development team to embed PQRS measurement guidelines within the EMR system.

Results: The overall percentage for prior lecture documentation was 36.75%, post lecture and EMR/EPIC system implementation was 19.59%. The compliance rate for pre-lecture comprehensive initial assessment was 34%, physical exam 46%, advice for normal activity 55%, and advice against bed rest 12%. The post-lecture/EMR comprehensive initial assessment was 23.3%, physical exam 27.5%, advice for normal activity 23.95%, and advice against bed rest 3.61%. Documentation declined significantly after education and EPIC implementation. A standard template for documentation ("smartphrase") was developed to facilitate physician documentation. The impact of this EMR enhancement on documentation is being measured and will be reported.

Conclusion: Initial implementation of the EMR had a significant *negative* impact on physician documentation of back pain for PQRS reporting in spite of physician education. An electronic template with built in PQRS guidelines may improve physician documentation and quality of care.

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Rheumatology-Ophthalmology Collaborative Uveitis Units May Improve The Diagnostic Approach Of This Pathology: Experience From a Uveitis Unit In a Secondary Spanish Hospital. Elena Aurrecoechea[1], Ana Diez del Corral[2], Angel de la Mora[2], Jaime Calvo-Alén[3] and Ernesto Romera[4]. [1]Hospital Sierrallana. Torrelavega, Torrelavega, Spain, [2]Ophthalmology Unit Hospital Sierrallana, Torrelavega, Spain, [3]Hospital Universitario Sierrallana, Torrelavega, Spain, [4]Hospital Sierrallana Torrelavega, Torrelavega, Spain.

Background/Purpose: Uveitis is defined as an intraocular inflammation, and may be associated to a systemic disease, it has a worldwide distribution, and it is a significant cause of blindness. As such the creation of Uveitis Units with the association of Rheumatologists and Ophthalmologists is highly recommended. The aim of this study is analyze the Etiology of the Uveitis diagnosed in the first three years of this unit and share our experience.

Methods: This study includes 125 patients, new and long standing, with Uveitis examined in the last three years. All patients were evaluated by the Ophthalmologist and the Rheumatologist including a detailed history and examination. A questionnaire about family and medical history were given (a Spanish translation from uveitis.org questionnaire), and guided by the evaluation a blood test, chest ray, OCT, retinal angiography or other test were ordered as needed.

Results: The most common form of uveitis was anterior uveitis (67.2%) and the most common diagnoses were Idiopathic (44%), Ankylosing spondylitis (17.8%), Herpes (14.3%), HLA-B27 (9.5%), Fuchs Heterochromic Iridocyclitis(3.5%).

The second most common uveitis type was posterior uveitis (16.8%) and the most common diagnoses were toxoplasmosis (42.9%), Serpiginous choroidopathy (23.8%), idiopathic (23.8%), Tuberculosis (4.8%) and Vogt Koyanagi Harada disease (4.8%).

Panuveitis was diagnosed in 8.8% of the cases and the most frequent causes were idiopathic (54%), Behçet's disease (18.8%), Endophthalmitis (9%), and Toxoplasmosis (9%).

The less frequent type of uveitis was intermediate uveitis with 7.2% of the diagnoses, most of the cases were idiopathic (66.6%), but sarcoidosis (11%), syphilis (11%), and multiple sclerosis (11%) were other etiologies found.

There were no eyes with final visual acuity worse than 20/200 in these 3 years with non-infectious uveitis.

Anterior Uveitis	67.2%	Intermediate Uveitis	7.2%	Posterior Uveitis	16.8%	Panuveitis	8.8%
Idiopathic	44%	*Idiopathic*	66.6%	Toxoplasmosis	42.9%	*Idiopathic*	54.4%
Ankylosing Spondylitis	17.8%	Multiple Sclerosis	11%	Serpiginous choroidopathy	23.8%	Behçet's disease	18.8%
Herpes	14.3%	Syphilis	11%	Idiopathic	23.8%	Endophthalmitis	9%
HLA-B27+	9.5%	Sarcoidosis	11%	Tuberculosis	4.8%	Toxoplasmosis	9%
Fuchs heterochromic Iridocyclitis	3.5%			VKH	4.8%		
Psoriasis	2.4%						
Sarcoidosis	2.4%						
AIJ	2.4%						
TINU	1.2%						
IBD	1.2%						
Rheumatoid arthritis	1.2%						

Conclusion: This secondary center based study shows the type and etiology of uveitis in our population, and how a multidisciplinary approach can improve the rate of diagnosis and prognosis for patients permitting a ready access to new and better treatments in an effective way, leading to a satisfying experience for the Rheumatologist and Ophthalmologist alike.

Disclosure: E. Aurrecoechea, None; **A. Diez del Corral**, None; **A. de la Mora**, None; **J. Calvo-Alén**, None; **E. Romera**, None.

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Determining The Vaccination Rates Of American College Of Rheumatology Recommended Vaccines Among Veterans With Rheumatoid Arthritis – A Quality Indicator. Puneet Bajaj, Melinda Collins and Ranjan Roy. VA Medical Center, Northport, NY.

Background/Purpose: American College of Rheumatology (ACR) guidelines recommends the administration of killed vaccines [pneumococcal, influenza and hepatitis B (HepB)], recombinant human papillomavirus (HPV) vaccine and live attenuated herpes zoster (HZV) vaccinations prior to therapy with DMARDs or biologic agents. HepB vaccination is indicated if hepatitis risk factors are present. Rheumatoid arthritis (RA) patients already on a DMARD or a biologic agent, vaccination with pneumococcal, influenza, HepB and HPV vaccine should be administered as indicated. RA patients already on a DMARD (non biologics) may be vaccinated with HZV vaccine.

Objective: The question addressed in this quality improvement project was to ascertain whether veterans with RA at our VA Medical Center (VAMC), are being vaccinated as per ACR guidelines.

Methods: A retrospective chart review was performed. Patients were identified using clinic encounters with an associated ICD9 code for RA (714.0, 714.2) in the Computerized Patient Record System (CPRS) at our VAMC, from January 1, 2011 through April 23, 2013. Charts were searched using several keywords, for documentation of these vaccinations, either offered or received.

Results: A total of 330 RA patients were identified, of which 251 were included. Out of the 79 patients excluded, 59 did not have a definitive diagnosis of RA and 20 had insufficient records. The mean age was 74 years, 92% males and 88% Caucasian. Among the included patients 54.5% had been treated with methotrexate, 35.8% hydroxychloroquine, 65% corticosteroids, 15% sulfazalazine, 6.7% leflunamide, 1.6% azathioprine and 38.6% with a biologic agent. Out of the patients who had been on a DMARD or biologic agent, 95.6% were either offered or received influenza vaccine, 93% pneumococcal vaccine, and 20.5% HZV vaccine. In addition, 1.5% had received Hep B vaccine. HPV vaccine was not indicated as per the vaccination guidelines due to age limitations. In a subset analysis, 53.4% of the patients either received or were offered influenza vaccine in each of the last three years (2010, 2011, 2012), 24% patients in two of the last three years, 17.5% patients only once and the remaining 5.1% were not offered the vaccine.

Conclusion: At our center, documented pneumococcal vaccination rates were high but annual influenza and HZV vaccination rates were suboptimal.

The low HZV vaccination rate could be due to some patients already on biologic agents prior to the vaccine approval in 2006 and initial difficulties in obtaining the vaccine. Annual influenza vaccination rates were less than desired. This could be due to missed annual follow ups, unavailable documentation of vaccination administered outside the VAMC & patients who had expired. HepB vaccination rate was also low; however, analysis regarding the presence of hepatitis risk factors was not performed.

Limitations of our analysis were unavailability of vaccination data prior to 1999 before CPRS was implemented and difficulty in obtaining data from outside the VA.

Better adherence to vaccination guidelines and documentation is required. This may be achieved through interventions such as physician and nursing staff education, and use of clinical reminders in CPRS.

Disclosure: P. Bajaj, None; **M. Collins**, None; **R. Roy**, None.

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Ask The Rheumatologist: Evaluating The Use Of a Patient Centered Web Based Service. Steven J. Katz. University of Alberta, Edmonton, AB.

Background/Purpose: Previous studies have demonstrated growing and significant patient use of the internet as a health resource. Yet, many web based resources have been shown to have poor quality, or lack the information being sought. An Ask the Rheumatologist service was established as an enhancement of a local rheumatology website. This study aims to examine the characteristics of the users of this service over its first year in operation and whether it can be a means to creating a dynamic website.

Methods: An Ask-the-Rheumatologist webpage was established on the www.EdmontonRheumatology.com website in January 2012., a site representing rheumatologists in Edmonton, Alberta, Canada. Each submitter provided a first name, city/country, and his/her question. The webpage explicitly states responses will not be provided for those questions that address specific patient care issues. A descriptive evaluation of the questions submitted between January and December 2012 was undertaken, examining the number of webpage visits, number of questions submitted, number of answers posted, gender and location of submitters when provided, general category of question, and whether or not the answer to the question could be found at least partially elsewhere on the website.

Results: The Ask the Rheumatologist webpage was visited 1484 times in 2012. 61 questions were submitted by 48 females, 10 males, and 3 who could not be identified. 29 questions were submitted from Edmonton, 21 from other Canadian centers, and 11 from other centers around the world. 33 submitters identified having a rheumatic disease themselves, with the

most common being rheumatoid arthritis (N=12), followed by fibromyalgia (N=4) and systemic lupus (N=4). 29 submitters included their personal experience. were most common (N=16), followed by disease treatment (N=14), investigations and natural treatment options (N=5), genetics and pregnancy (N=2). 11 questions were deemed inappropriate, most commonly because of a request to see a rheumatologist. Answers to 22 questions (36%) asked could be at least partially found elsewhere on the website. 31 questions (51%) were selected with answers posted throughout the year on the webpage.

Conclusion: An Ask the Rheumatologist webpage was a well used service upon its introduction. It provided answers to specific patient concerns, and in half the cases, provided information that was otherwise not available on the website, thereby allowing the site to adapt to user needs. By doing so, it provides another means to optimize care and education for those with rheumatic diseases.

Disclosure: S. J. Katz, None;

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Determinants Of Patient Satisfaction In An Academic Rheumatology Practice. Abhijeet Danve, Jennifer H. Ku, Helena Pang, Thien Hoang, Alana Ralston, Dongseok Choi and James T. Rosenbaum. Oregon Health and Science University, Portland, OR.

Background/Purpose: Patient satisfaction has emerged as an important measure of physician performance and criterion for compensation in the US. Factors contributing to patient satisfaction are incompletely understood especially in chronic rheumatic diseases. The aim of this study was to identify various factors associated with patient satisfaction.

Methods: This was a cross-sectional study conducted at Oregon Health & Science University's rheumatology clinic. Consented patients' satisfaction of their clinic visit was measured on a 0 to 10 numerical rating visual analogue scale, anchored by 10 verbal descriptions ranging from extremely dissatisfied to extremely satisfied. We collected demographic and clinical data including diagnosis; size of problem list; depression (identified by documentation or antidepressant use in absence of other indications); use of narcotics, biologic agents, or steroid injections; investigations like blood tests, x-rays, or MRI; or hospitalization in past 1 year. The impact of characteristics like attending physician versus physician in training, provider's gender, new versus follow up visit, wait time, number of telephone and email encounters was studied. Statistical analysis was performed using descriptive statistics and quantile regression.

Results: We enrolled 300 patients between January and June of 2013. Mean age was 50 years (s.d. 15.2); 74.3% were female; 92% were white. Common diagnoses included lupus/MCTD (n=49, 16.3%), fibromyalgia (42, 14.0%), seronegative arthritides (39, 13.0%), rheumatoid arthritis (35, 11.7%), vasculitides (26, 8.7%), osteoarthritis (20, 6.7%) and others (89, 29.7%). In the univariate analysis, female gender (regression coefficient [rc] 4.62; 95% CI 0.52, 8.71; $p=0.03$) and follow-up visits (rc 8.01; 95% CI 6.74, 9.44; $p<0.01$) were associated with higher satisfaction. Afternoon appointments (rc −5.20; 95% CI −8.73, −1.67; $p<0.01$), female providers (rc −7.50; 95% CI −9.54, −5.48; $p<0.01$), use of narcotics (rc −4.62; 95% CI −8.8, −0.44; $p=0.03$) or an MRI in the past year (rc −5.78; 95% CI −10.83, −0.72; $p=0.03$) were associated with lower patient satisfaction. At multivariate analysis, an MRI in the past year (rc −4.42; 95% CI −5.86, −0.44; $p=0.02$) and afternoon appointments (rc −3.15; 95% CI −5.86, −0.44; $p=0.02$) remained significantly associated with lower satisfaction. Other factors like age, race, diagnosis, presence of fibromyalgia, depression, obesity, biologic use, steroid injections and quality of life did not affect satisfaction.

Conclusion: Patient satisfaction is playing an increasing role in patient centered outcomes and physician reimbursement. Accordingly, it is critical to understand what drives satisfaction.

We found that female gender, follow-up visits, male providers and morning appointments were associated with higher satisfaction. Contrary to our expectations, use of narcotics and an MRI in the past year had a negative influence on satisfaction when controlling for covariates. Interestingly, diagnosis of fibromyalgia, obesity, depression, steroid injections and use of biologic agents did not affect satisfaction. The validation of these results should be tested in other practices.

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A Study To Determine Patient Satisfaction With a Nurse-Led Injection Clinic In Rheumatology. Margaret Saldanha[1], Kathleen Brown[1], Dawn Heap[1], Cynthia Mech[1], Melissa Deamude[1], Kathy Kislinsky[1], Debbie McClory[2], Alpesh Shah[3] and William G. Bensen[4]. [1]Rheumatology Health Team, St. Joseph's Hospital Hamilton, Hamilton, ON, [2]Rheumatology Health Team Hamilton, Hamilton, ON, [3]Rheumatology Health Team, Dr. Bensen's Rheumatology Clinic, Hamilton, ON, [4]St. Joseph's Hospital and McMaster University, Hamilton, ON.

Background/Purpose: There is a widening care gap in Canada between patients who need Rheumatology care and the capacity of the system to deliver that care in a timely manner. At St. Joseph's Hospital and McMaster University in Hamilton we have developed several models of team-based care with trained rheumatology nurses.

One successful team -based model has been a nurse managed injection clinic treating patients with inflammatory arthritis or soft tissue pain. All patients fill out a health check questionnaire and authorize their consent before receiving injections, ensuring patient safety. Nurses use a set of directives written by the rheumatologist as guidelines for the clinic with a Rheumatologist always present on site.

This clinic, run twice weekly, allows immediate access and assessment of patients with flares or potentially needing steroid injections. Currently this clinic administers nearly 100 injections per week. The purpose of this study was to assess patient perspectives on how they view this team -based model as compared to a traditional MD model which historically would cause a delay of treatment by 8–10 weeks before an assessment of their disease was possible.

Methods: A cross-sectional study sampling 217 consecutive patients who attended the nurse-led injection clinic was conducted at Dr. Bensen's Rheumatology Practice in Hamilton, Canada from May 2013 to June 2013. Patients were given a structured self-administered questionnaire to determine their satisfaction with the steroid injection clinic run by the nurses. Those that have English as a second language were excluded as well as anyone who wasn't able to understand and follow directions on the questionnaire. Efficacy and relevance was assessed by patients answering eight qualitative questions.

Results: The results of this study indicated that patients were offered timely access to care at critical times when they were experiencing a flare of disease symptoms. 83% of patients responded that their pain was better managed in this clinic. 96% of patients affirmed that they were able to be seen within 2 weeks of their onset of symptoms. All patients surveyed felt comfortable discussing their health issues with the nurse and felt confident in the nurse's assessment and injection techniques. Overall the patients reported that because of this nurse led injection clinic model their quality of life living with a rheumatologic condition improved.

Conclusion: Our results show that a nurse run steroid injection clinic is both valued by patients for pain and inflammation management and is readily available. This demonstrates a high degree of satisfaction with the nurse run program and they feel very strongly that without this clinic their pain management would not be optimal. Without this clinic, patients indicated that they would seek treatment elsewhere, mostly with their family doctors, emergency rooms, or walk-in clinics, resulting in further congestion in an already overwhelmed healthcare system. This study determined that nurse run steroid injection clinics are both needed and valued by our patients in Hamilton, Canada.

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Cleveland Clinic Dual Energy X-Ray Absorptiometry Registry, A Web-Based Tool Designed For Efficient Collection Of Bone Density and Osteoporosis Related Clinical Risk Factor Data. Chad L. Deal, Gregory J. Strnad, Robert A. Overman and Boris Bershadsky. Cleveland Clinic, Cleveland, OH.

Background/Purpose: A patient registry is an organized system that collects uniform data to allow evaluation of specific outcomes for a population with a particular disease. They can enable observation of the natural history of disease, clinical/cost effectiveness, treatment, quality of care, and factors that influence prognosis and outcomes. Osteoporosis research using administrative claims lacks clinical characteristics including bone mineral density (BMD) and fracture risk. To fill this gap a dual energy x-ray

absorptiometry (DXA) registry was established at the Cleveland Clinic (CCF) in 2009.

Methods: The CCF DXA Data Entry System is a web-based intranet tool designed to capture data important to patient care and osteoporosis research. The system receives real-time scheduling messages from the electronic medical record, generates an online data collection form for each DXA bone density scan appointment, and pre-loads them with patients' demographic information.. DXA technologists log in from any workstation connected to the intranet and are guided through a data entry page for each appointment that helps to ensure complete and accurate data collection. Data on bone density (T and Z-scores, g/cm2), self-reported osteoporosis treatment, and FRAX® clinical risk factors are recorded. From 2009 through 2012, data on a total of 35,373 patients were entered into the registry, which represents 83.6% of the eligible population (4.3% missing data, 12.1% refused) and are stored in a secure SQL Server database and have been successfully linked with 99.1% of patients' medical record data using Explorys Inc. proprietary software. In 2013, FRAX®10-year risk of major osteoporotic fracture and hip fracture was computed for all registry subjects.

Results: The registry includes 28,095 postmenopausal women, 5,079 men ≥50, 1,549 premenopausal women, and 650 men <50. Of these, 11.9% of postmenopausal women, 9.6% of men ≥50, 4.8% of premenopausal women, and 6.5% of men <50 have now had a 2nd DXA. To date we have investigated the relationship between registry data (FRAX®clinical risk factors and bone mineral density) and initiation of drug therapies per NOF guidelines, evaluated the frequency of DXA in organ transplant patients, and the rate of osteoporosis therapy in glucocorticoid treated subjects, among other projects. We found that 62.4% of rheumatologists and 52.2% of non-rheumatologists had started osteoporosis therapy within 365 days after their patient had a T-score ≤ 2.5, that 78% of patients on glucocorticoids had osteoporosis therapy initiated within 6-months, and that 42.5% of patients with a T-score <−2.5 had a follow-up DXA within 3-years. Ongoing projects includes evaluation of premenopausal women (n= 176) and men <50 (n= 161) with Z-score ≤ 2.0 (low bone mass for age), glucocorticoid users, effect of BMI and vitamin D on BMD, changes in BMD over time, and possible interventions for patients with a T-score ≤−2.5 who do not report osteoporosis therapy.

Conclusion: The CCF DXA Registry has enrolled 35, 373 patients with approximately 10–15,000 new patients each year. This large and longitudinal registry offers opportunities to monitor quality indicators, assess patient care, and conduct observational and interventional research.

Disclosure: C. L. Deal, None; **G. J. Strnad**, None; **R. A. Overman**, None; **B. Bershadsky**, None.

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Patient Satisfaction with an Associate Teaching Hospital Clinical Trial Unit In North-East London. Genevieve Casey[1], Carey Tierney[2], Hasan Tahir[2], Simon Donnelly[2] and Judith Bubbear[2]. [1]Barts and the London Medical School, London, United Kingdom, [2]Barts Health NHS Trust, London, United Kingdom.

Background/Purpose: Compared to patient satisfaction with general medical care little is known about patient satisfaction within clinical trials. Clinical trials are a time and resource demand for patients without necessarily a guarantee of receiving the active compound. Given the importance in developing new therapies and medicines, and outcomes overall we were keen to examine patient satisfaction within the unit we run and thoughts and experiences with regard to clinical trials.

Whipps Cross University Hospital is an Associate Teaching Hospital in North-East London serving a population of around 400,000 with a commercially run research unit. Our unit currently runs 14 trials and sees 20–30 patients each week. The clinical trials mainly test biological therapies in autoimmune rheumatic diseases.

Methods: We could not find a validated satisfaction survey for patients in clinical trials. We modified a survey by Madsen et al. using clinical trials with inflammatory bowel disease. The survey had 21 questions. Every patient attending the unit at least 3 times was surveyed from April - June 2013.

Results: 38 surveys were completed. Patient satisfaction with clinical trials and the research unit is positive. 71% reported a very positive attitude towards these trials, 79% indicated they would participate again and 79% would recommend a friend or family member to participate.

81% of respondents felt it was 'always' necessary to examine new drugs using a clinical trial design, 31% were 'hesitant' about randomization and 48% about blinding. 53% said it was 'very important' to them to recognise staff at each visit and 74% indicate this aspect influences their attitudes towards clinical trials 'a lot'.

One respondent reported the trial was 'too time consuming', two that they 'could have used more time' and the remainder felt time allocation was 'OK'.

Getting the 'new' drug, being closely monitored, having a 'good relationship' with doctors/nurses, and helping future patients, were all 'very important' motives for participating in the trial with the majority of the respondents.

Conclusion: Our results are similar to those reported by Madsen et al. The attitudes towards blinding and randomization could perhaps be addressed by providing more education about the necessity of blinding and randomization prior to trial participation.

Madsen et al identified having a single physician design their trials results in high patient satisfaction. Our survey also shows participants value recognising the same staff at each visit and may be undervalued by trial designers in a busy setting.

Overall, patient satisfaction with clinical trials was high and clinicians should feel confident when referring patients for inclusion in clinical trials.

Disclosure: G. Casey, None; **C. Tierney**, None; **H. Tahir**, None; **S. Donnelly**, None; **J. Bubbear**, None.

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Validation Of The Hospital For Special Surgery Knee Questionnaire: Convergent Validity, Responsiveness and Sensitivity To Change. Jasvinder A. Singh[1], Cathy Schleck[2], W. Scott Harmsen[3] and David Lewallen[4]. [1]University of Alabama, Tuscaloosa, AL, [2]Mayo Clinic College of Medicine, Rochester, MN, [3]Mayo Clinic, Rochester, MN, [4]Mayo Clinic college of medicine, Rochester, MN.

Background/Purpose: Hospital for Special Surgery (HSS) Knee questionnaire has previously been shown to have construct validity. Our objective was to further assess the validity and responsiveness of HSS Knee Questionnaire.

Methods: We used data from the Mayo Clinic Total Joint Registry to assess the validity of HSS Knee questionnaire, by including patients who underwent primary total knee arthroplasty (TKA) between 1993–2005 and responded to the baseline and 2-year post-primary TKA HSS Knee questionnaire. HSS Knee questionnaire combines pain, function, range of motion and muscle strength to derive a total score. Convergent/divergent validity was examined with the association of select demographics (age, gender, number of joints involved) at baseline with HSS Knee scores using linear regression and correlation analyses. Minimally Clinically Important Difference (MCID) and Really Important Difference (RID) were calculated corresponding to "somewhat better now" and "much better now" patient responses, respectively to the question at 2-years- Compared to your condition before the surgery, how would you rate your knee now? For discriminant ability, we calculated effect size by taking the change in respective score from baseline to 2-years and dividing the result by the standard deviation at baseline.

Results: For primary TKA, there were 5,280 knees with both a baseline and a 2-year data. The sample consisted of *2,375* males (45%) and 2,905 females (55%). The mean age at surgery (SD) is 68 (10), median age was 69 (range, 17–93). Male sex, body mass index, Deyo-Charlson index and the number of lower extremity joints involved were significantly associated with HSS scores ($p<0.001$). HSS correlated highly with knee society score (KSS; correlation coefficient 0.52, $p<0.001$) and KSS function (0.65, $p<0.001$). Age was not significantly associated ($p<0.34$). MCID and RID thresholds were 8.29 and 25.97 respectively. Effect size was 2.95 at 2-years and the standardized response mean was 1.85. HSS score at 2-years in the lowest category had odds ratio of 5.15 (95% confidence interval: 2.73,9.71; $p<0.001$) for revision of index TKA 2-years or later after primary TKA. Preoperatively only 0.03% and 0.1% were at the floor and ceiling, respectively. At 2-years, 0% and 17% scores were the floor and ceiling, respectively.

Conclusion: The HSS Knee questionnaire is a valid and sensitive outcome measure for patients undergoing primary TKA. Further validation in independent patient samples will improve its usability in more patient populations.

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Assessing Adherence To Choosing Wisely® Recommendations Regarding Antinuclear Antibody and Antinuclear Antibody Subserology Testing In An Urban Community Health System. Adam Carlson[1], Jinoos Yazdany[1], Kara Lynch[2] and Laura Trupin[1]. [1]UC San Francisco, San Francisco, CA, [2]San Francisco General Hospital, San Francisco, CA.

Background/Purpose: As part of the American Board of Internal Medicine's Choosing Wisely Campaign®, the ACR published recommendations in 2013 advising clinicians against ordering anti-nuclear antibody (ANA) subserologies in the absence of a positive ANA and a clinical suspicion for an underlying immune mediated disease. Subserology testing for SSA and Jo-1 was considered a reasonable exception this rule. Previously published guidelines also recommend against obtaining serial ANAs. In this study, we sought to assess the current practice patterns for ordering ANAs and ANA subserologies at an urban community hospital and its affiliated outpatient clinics.

Methods: Laboratory data was compiled for all patients who underwent testing for an ANA or any of several ANA subserologies (dsDNA, Smith, RNP, SSA, SSB, Scl-70, Centromere, and Jo-1) at the San Francisco General Hospital clinical laboratory between January 2012 and January 2013. All ANAs were measured by immunofluorescence, and all subserologies were measured by enzyme linked immunosorbant assay. Data were analyzed to generate descriptive information regarding the frequency and origin of ANA and ANA subserology ordering

Results: A total of 2514 patients underwent testing for either an ANA or an ANA subserology during the study period. A total of 2350 patients underwent initial ANA testing of whom 123 (5.2%) underwent serial ANA evaluations. Repeated ANA tests were ordered either from primary care clinics or on inpatient services and not from subspecialty clinics (Table 1). A positive initial ANA (defined as a titer >1:40) was found in 524 (23%) patients, and a negative initial ANA was found in 1810 (77%) patients. Of those patients whose initial ANA was negative, 117 (6%) went on to have a subserology checked. From this group, 58 (50%) patients were tested for SSA and 12 (10%) were tested for Jo-1. ANA subserologies were therefore ordered inappropriately in 47 (2%) patients whose initial ANA was negative. Over a one year period, 170 (7%) patients with an initial ANA test underwent subsequent ANA or ANA subserology testing that was counter to current recommendations.

Table 1. Initial and serial ANA testing between 2012 and 2013 in an urban community hospital health system.

Clinical Setting	Initial ANA N=2350	Serial ANA N=123
Primary Care	1832 (78%)	77 (63%)
Specialty Outpatient	402 (17%)	0
Emergency Department/Urgent Care	44 (2%)	0
Inpatient hospitalization	255 (11%)	46 (37%)

Conclusion: Inappropriate ANA and ANA subserology testing were relatively infrequent in our safety net health system, which provides care to poor and medically indigent patients. Serial ANA testing was three times more common than inappropriate subserology testing. Measures aimed at reducing repeated ANAs ordered from primary care clinics and on inpatient services would likely be most efficacious in reducing unnecessary testing.

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Outcomes Of The Fast-Track Pathway In Giant Cell Arteritis: A Sight Saver. Pravin Patil[1], Win Win Maw[1], Katerina Achilleos[1], Christian Dejaco[2], Mark Williams[3], Tochukwu Adizie[4], Dimitrios Christidis[5], Frances Borg[1] and Bhaskar Dasgupta[4]. [1]Southend University Hospital, Westcliff-on-sea, United Kingdom, [2]Medical University Graz, Graz A-8036, Austria, [3]Southend University Hospital, Westcliff on sea, United Kingdom, [4]Southend University Hospital, Westcliff-on-Sea, United Kingdom, [5]Southend University Hospital, Westcliffe on sea, United Kingdom.

Background/Purpose: Giant cell arteritis (GCA) is a medical emergency, with permanent visual loss occurring in about 20–30% of patients. We have identified that delayed recognition, multiplicity of referral routes and absence of a standard pathway of care increases the complications rate in GCA. We report our experience of developing and implementation of a fast-track referral pathway (FTP) to reduce the incidence of sight loss in GCA.

Methods: All patients with suspected GCA seen between Jan 2012 to Dec 2012 were enrolled into a FTP. Patients were started immediately on high dose glucocorticosteroids (GC) by the referring doctor and seen by a rheumatologist within one working day. We compared data from the FTP with that of a longitudinal cohort of suspected GCA patients seen through standard referral routes between January 2009 and December 2012. A logistic regression method was used to investigate the effect of several variables on sight loss.

Results: GCA was diagnosed in 46 (56.8%) patients in the standard pathway and in 33 (58.9%) in the FTP. As shown in table 1, complete sight loss was more commonly observed in standard compared to FTP [n=17 (37.0%) versus 3 (9.1%), p=0.005 in univariate and p=0.007 in multivariate analysis adjusting for clinical risk factors of sight loss]. There was no difference in the staring dose of GC or the number of patients receiving intravenous GC in both groups.

In the standard pathway, a higher proportion of GCA patients were referred to other specialties before rheumatology [n=11 (23.9%) vs. n=5 (15.2%), p=0.34]. The majority of patients in FTP were seen within a day of presenting to general practitioner compared to a median time of 3.0 (1.0–71.0 days) in the standard pathway (p=0.068). Interestingly, a significantly lower number of patients who subsequently lost sight presented with headache [n=13 (65.0%)] compared to those who did not lose sight [57 (98.3), p<0.001].

Table 1. Types of sight loss in conventional and fast track pathways

Type of sight loss	GCA–conventional (n=17)	GCA–fast track (n=3)
Partial, monocular¥	6 (35.3)	1 (33.3)
Complete, monocular¥	8 (47.1)	2 (66.7)
Partial, binocular¥	0	0
Complete, binocular¥	3 (17.6)	0

¥ n (percentage)

Conclusion: Implementation of a GCA fast track pathway led to a reduction of permanent sight loss in newly referred GCA patients. The effect is explained by a reduction of the delay in treatment of GCA as well as by other, difficult to measure factors including increased awareness of GCA by public and general practitioners and reduction in the multiplicity of referral routes to rheumatology clinic. We recommend adoption of the FTP as a standard of care for GCA.

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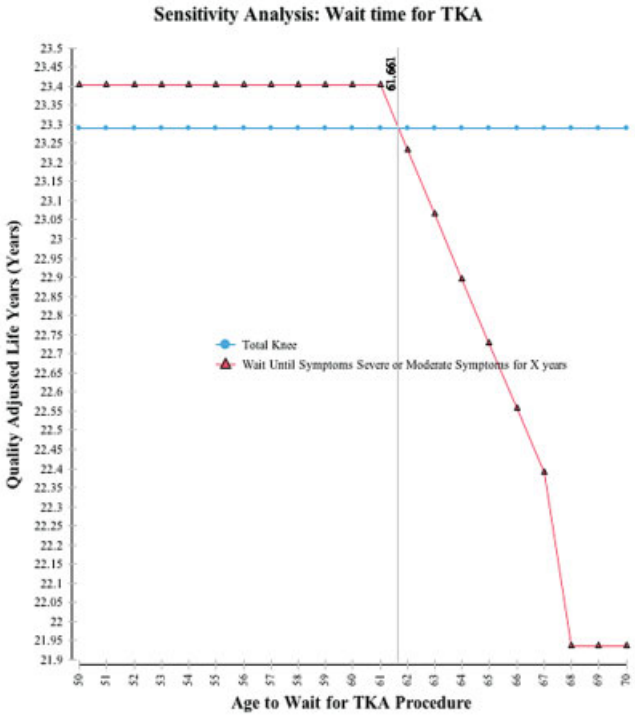
Timing Of Total Knee Arthroplasty: A Decision Analysis. Darena Tulanont[1], Haily Vora[1], Roopa Akkineni[2] and Daniel A. Albert[1]. [1]The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH, [2]Dartmouth-Hitchcock Medical Center, Lebanon, NH.

Background/Purpose: Total Knee Arthroplasty (TKA) reduces pain and restores mobility. However, replacement joints have limited durability and patients have to weight the benefits of having a knee replacement versus its lifespan, especially since revision arthroplasty has a higher complication rate and poorer outcomes. The objective of this study is to determine the trade-off between undergoing TKA versus delaying TKA and thereby reducing the chance of revision.

Methods: A Markov state-transition model was constructed to assess wait-times in patients undergoing TKA. The model estimated the quality-adjusted-life-years (QALYs) for patients undergoing TKA at age 50 versus waiting until moderate or severe symptoms occur. The model simulated a hypothetical cohort of patients 50-years and older. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) was used to classify mild, moderate and severe symptom levels. Probabilities and quality adjustment measures were extracted from published literature. Sensitivity analyses were performed on utilities for pain and wait time to undergo TKA. The model was simulated over the lifetime of an individual.

Results: Compared to waiting until age 65, performing TKA at age 50 regardless of symptoms is the preferred strategy [22.73 QALYs versus 23.29 QALYs]. However, sensitivity analysis demonstrates that waiting is preferred for mild pain when utility is greater than 0.85; and moderate pain when utility is greater than 0.72. In patients with severe pain TKA is always favored over waiting. For a 50-year old patient with mild pain the natural history of

osteoarthritis suggests progression to moderate or severe pain. Thus, our model indicates that patients presenting with mild pain will wait an average of 11.7 years (age 61.7 years; 23.40 QALYs) for TKA in order to maximize expected utility.



Conclusion: TKA is the preferred strategy in individuals with severe knee pain. For patients having mild pain, it is preferable to wait until moderate or severe pain develops.

Disclosure: D. Tulanont, None; **H. Vora**, None; **R. Akkineni**, None; **D. A. Albert**, None.

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Patients' Response To a Sleep Question and Disease Activity In Multiple Rheumatic Conditions. Sapna Sangani[1] and Martin J. Bergman[2]. [1]Mercy Catholic Medical Center, Lansdowne, PA, [2]Drexel University College of Medicine, Philadelphia, PA.

Background/Purpose: Sleep disturbances can have an impact on the quality of life of any individual. Research studies have shown a significant association between sleep disturbances and a number of chronic inflammatory conditions, including Asthma and Crohn's disease. This study aims to determine the significance of sleep disturbances in patients diagnosed with various rheumatic conditions, and its association with disease activity levels.

Methods: All patients with any rheumatologic diagnosis attending a single rheumatology practice were asked to complete a MDHAQ. The MDHAQ includes sections regarding function, pain, patient global estimate, a patient self-reported joint count, fatigue, exercise, AM stiffness and a brief psychological profile. The MDHAQ includes 3 psychological profile queries, including "Over the past week, were you able to get a good night's sleep?" The responses are 0–3 which stand for, 0=without difficulty, 1= with some difficulty, 2= with much difficulty, 3=unable to do. RAPID3 is an index of the 3 patient-reported outcome measures: physical function, pain and patient global estimate. RAPID3 can be calculated from a MDHAQ in less than 10 seconds. Patients are then characterized into disease activity categories ("remission", "low disease activity", "moderate disease activity", "high disease activity"), according to established criteria. Using a random visit for each patient, linear regression models were determined using the composite score value as the dependent variable, and "sleep" as the independent variable, to determine possible interactions between "sleep"score and disease activity scores. All statistical analyses were performed using Stata v12.

Results: We analyzed data on total of 786 patients diagnosed with a non-overlapping rheumatic disease and who had completed the MDHAQ survey. The number of patients diagnosed with a particular rheumatic disease is shown in the table below. The rheumatic conditions studied are Rheumatoid Arthritis (RA), Osteoarthritis (OA), Fibromyalgia, SLE, Psoriatic Arthritis (PsA), Spondyloarthropathies, and Gout. A "linear" worsening of RAPID3 was seen with each increment of sleep variable.

Table.

Rheumatic conditions	Observation	Sleepinc=0 (p-value)	Sleepinc=1 (p-value)	Sleepinc=2 (p-value)	Sleepinc=3 (p-value)	R-squared
Rheumatoid Arthritis (RA)	195	5.38 (<0.01)	10.69 (<0.01)	15.45 (<0.01)	17.40 (<0.01)	0.33
Osteoarthritis (OA)	232	9.31 (<0.01)	11.38 (<0.01)	15.73 (<0.01)	17.98 (<0.01)	0.17
Fibromyalgia	52	9.96 (<0.01)	13.51 (<0.01)	18.39 (<0.01)	19.79 (<0.01)	0.25
SLE	53	4.54 (0.003)	8.4 (<0.01)	13.91 (<0.01)	12.16 (0.008)	0.23
Psoriatic Arthritis (PsA)	60	5.34 (<0.01)	10.35 (<0.01)	16.24 (<0.01)	19.77 (<0.01)	0.42
Spondyloarthropathies	113	4.82 (<0.01)	10.04 (<0.01)	16.96 (<0.01)	20.16 (<0.01)	0.52
Gout	81	5.20 (<0.01)	9.82 (<0.01)	17.10 (<0.01)	21.05 (<0.01)	0.37

Conclusion: Interestingly, patients affected by a myriad of chronic inflammatory rheumatic diseases perceive significant sleep disturbances, at any given point of time during the course of their disease process. Patients with worse sleep scores are less likely to be in low disease activity as measured by RAPID3. Interventions in chronic rheumatic diseases are often targeted to impact symptoms of joint pain / function. Further interventions may be needed to improve strategies designed for the improvement of psychological profile, especially sleep disorders.

Disclosure: S. Sangani, None; **M. J. Bergman**, None.

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Models Of Care For Arthritis: Drivers, Facilitators and Barriers To Their Development and Implementation. Aileen M. Davis[1], Cheryl Cott[2], Rose Wong[3], Michel Landry[4], Linda Li[5], Allyson Jones[6], Cy Frank[7], Sydney C. Lineker[8], Louise Bergeron[9], Gillian A. Hawker[10], Dianne P. Mosher[11], Vandana Ahluwalia[12], Michel Zummer[13], Susan B. Jaglal[14], Rhona McGlasson[15], Richard Birtwhistle[16], Sherry Bar[17] and Elizabeth M. Badley[18]. [1]Division of Health Care and Outcomes Research, Toronto Western Research Institute, University Health Network, Ontario, ON, [2]Divison of Health Care and Outcomes Research, Toronto Western Research Institute, University Health Network, Toronto, ON, [3]Division of Health Care & Outcomes Research, Toronto Western Research Institute, University Health Network, Toronto, ON, [4]Department of Community and Family Medicine, Physical Therapy Division, Duke University Medical Center, Durham, NC, [5]Arthritis Centre of Canada and Department of Physical Therapy, University of British Columbia, Vancouver, BC, [6]University of Alberta, Edmonton, AB, [7]Alberta Bone and Joint Institute and Department of Surgery, University of Calgary, Calgary, AB, [8]The Arthritis Society, Toronto, ON, [9]Canadian Arthritis Patient Alliance, Ottawa, ON, [10]Women's College Research Institute, University of Toronto, Toronto, ON, [11]University of Calgary, Calgary, AB, [12]Past President, Ontario Rheumatology Association, Brampton, ON, [13]Ch Maisonneuve-Rosemont, Montreal, QC, [14]Department of Physical Therapy, University of Toronto, Toronto, ON, [15]Bone and Joint Canada, Toronto, ON, [16]Centre for Studies in Primary Care and Family Medicine and Community Health and Epidemiology, Queen's University, Kingston, ON, [17]British Columbia Ministry of Health Services, Victoria, BC, [18]Toronto Western Research Institute, University Health Network, Toronto, ON.

Background/Purpose: Management of arthritis is a growing concern given disease prevalence and limited health care resources. In the context of a larger project investigating innovative models of care (MOC) delivery for people with arthritis, this study sought to identify the drivers, facilitators and barriers to the MOC development and implementation in British Columbia (BC), Alberta (AB) and Ontario (ON), Canada.

Methods: This study used embedded case methodology, with triangulation of documents from peer-reviewed literature, reports, working papers of MOC, health human resources (HHR), etc.; population/administrative data regarding utilization of care; and, semi-structured, one-on-one stakeholder interviews with health planners, decision-makers, program managers, and care providers. Thematic analysis using a constant comparative approach was used to identify drivers, facilitators and barriers to models/innovative processes of providing care.

Results: 79 key informants interviews (BC=24, AB=22, ON=33) of which 28 (BC=9, AB=10, ON=9) were in-depth interviews related to drivers, facilitators, and barriers were conducted between 2009 and 2012. In addition to traditional primary care to specialist referral, MOC identified included community-based direct access to services, multi-disciplinary and inter-disciplinary care. Various processes were implemented to enhance access and care provision: therapists with skills in arthritis assessment and management were embedded in primary care; specialty multi-disciplinary musculoskeletal clinics were established to interface with primary care; therapists with advanced arthritis skills practiced in triage roles to expedite priority referrals for the rheumatologist; and, health professionals traveled to smaller communities to provide service and/or utilized telehealth. For both inflammatory (IA) and non-IA, MOC developed were driven and facilitated by local factors including a local champion and the willingness of local providers to work together. In BC, this was further influenced by centralized control of resources. In AB, provincial chronic disease management policy and resources facilitated care for people with non-IA, although the resources were not viewed as sufficient to meet need. For IA services, barriers included challenges with primary care identification of need for and access to a rheumatologist; limited HHR and skill sets, particularly in rural/remote communities (this also posed challenges in providing multi-disciplinary care); and, geographically dispersed and small populations. For non-IA services, lack of recognition as a priority in local, regional, and provincial jurisdictions and limited community resources and chronic disease management resources also were barriers.

Conclusion: MOC varied greatly and local factors drove care provision for people with arthritis. Policies that facilitate arthritis management as a priority at local, regional and provincial levels, greater collaboration and linkages with community resources and increased health providers with the necessary skill sets are required to address current barriers to care for people with arthritis.

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Shared Decision Making In Early Knee Osteoarthritis: Perspectives Of Older Adults With Overweight and Obesity and Health Care Providers. Alicia Zbehlik[1], Mary Meinke[2] and Stephen Bartels[1]. [1]The Center for Aging Research, The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH, [2]The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH.

Background/Purpose: Knee osteoarthritis (KOA) is the most common form of mobility disability in the United States yet those at highest risk—older adults with overweight and obesity—continue to have unmet needs regarding their KOA care. People with early KOA receive arthroscopic surgery proven to have no benefit and receive little information regarding exercise and weight loss that may modify the course of their disease. Although shared decision making (SDM) and decision aids (DAs) are effective strategies to reduce unnecessary procedures by guiding patients to make informed decisions incorporating their personal values, SDM and DAs are not widely used. To our knowledge, studies have not simultaneously compared patient and provider preferences of multiple decision making tools in early KOA. Our study examines three DAs for early KOA: (1) Osteoarthritis Option Grids, (2) the "Managing Early-Stage Knee Osteoarthritis" booklet, and (3) "What are my options for managing hip or knee osteoarthritis?: A stepped decision aid." Evaluating DA preferences of both patients and providers will serve as a first step to build and implement a system of effective early KOA care that supports lifestyle modification for older adults who are overweight or obese.

Methods: This on-going study employs a cross-sectional, qualitative design using focus groups of patients and providers. We recruit English-speaking participants by flier, word of mouth, and referral. The patient group (n=35) inclusion criteria are: a) Body Mass Index =>/25 kg/m^2; b) age =>/ 60 years, and; c) the diagnosis of KOA or a positive screen for knee OA on The Knee and Hip OA Screening Questionnaire. The provider group (n=35) is recruited through word of mouth and by email invitation. Providers that care for adults with OA in an academic or community setting are included. Plan is for five focus groups per target population, or until thematic saturation is reached. Each group uses a semi-structured format and lasts 60 to 90 minutes. The taped sessions are de-identified by a transcriptionist. Transcripts are coded and for the generation of themes by two researchers using a qualitative data analysis software program.

Results: Preliminary results from patient focus groups conducted during May 2013 show emerging themes include costs of care, lack of information about treatment options, and challenges in communicating with providers. Patients demonstrated an interest in SDM and DAs, but had little prior exposure to the tools. They also commented on the granularity and visual presentation of evidence, the lack of details regarding exercise options available, and the logistics of distributing DAs. Participants were enthusiastic about shared medical appointments. Patients gravitated towards the booklet format, but appreciated the unique characteristics of all the decision aids. They felt the DA's would be useful before, during, and after a clinic appointment and would assist with provider communication.

Conclusion: Preliminary results indicate that patients respond to a variety of early KOA decision aids and are eager to engage providers in shared decision making. Patients are concerned about costs of care, a theme not incorporated into any of the decision aids.

Disclosure: A. Zbehlik, None; **M. Meinke**, None; **S. Bartels**, None.

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Crowdsourcing Using The Audience Response System To Solve Medical Problems: A Pilot Study. Antoine G. Sreih[1] and Fadi Aldaghlawi[2]. [1]The University of Pennsylvania, Philadelphia, PA, [2]Weiss Memorial Hospital, chicago, IL.

Background/Purpose: When faced with unclear diagnostic or therapeutic uncertainties, patients often seek further clinical opinions. Similarly, when in doubt, physicians seek expert opinions to assist with clinical care and minimize errors. The audience response system (ARS) has been traditionally used to test knowledge and improve the educational experience. However, ARS can be used to solicit crowd opinion (crowdsourcing) for specific medical questions. In this proof-of-concept pilot study, we sought to examine the ability of professional crowds to correctly answer difficult medical questions using the ARS.

Methods: This study analyzed data on answers to questions based on clinical vignettes administered during the 2009, 2010, and 2011 ACR/ARHP scientific meetings for which the ARS was used. Questions were considered evidence-based or expert-based. All questions were multiple-choice format. The crowd chose the answers independently and anonymously using remote control panels. Questions were considered answered correctly if the majority of the crowd chose the correct answer. To minimize the influence of the speaker on the crowd, only questions administered prior to any medical discussion were used for this study. As a validation group and to determine if physicians other than rheumatologists were able to answer correctly, 10 randomly chosen ACR/ARHP questions were administered using the ARS during medical Grand Rounds at 2 academic institutions. The percentage of correct answers was calculated. Chi- square test was used to analyze the data.

Results: 93 ARS questions were administered during three consecutive ACR/ARHP scientific meetings. 21 questions were excluded because they either had unknown answers (12 questions) or were administered following medical discussions (9 questions). A total of 72 questions were included in the study, of which 59 had evidence-based and 13 had expert-based answers. The number of multiple-choice answers for each question ranged from 2 to 8 choices, with 97% having at least 4 choices. Vasculitis was the most common topic covered (19%) followed by rheumatoid arthritis (16%). 41 of 59 evidence-based questions (70%) were answered correctly ($p<0.0001$), and 8 of 13 expert-based questions (62%) were answered similarly to what an expert would answer ($p<0.0001$). The mean percentage of people answering correctly was 59 $\pm$ 18 %. The mean difference in percentage between the correct answer and the next best answer was 37 $\pm$ 26 %. 23 of 72 (32%) questions were answered incorrectly. Of those, the correct answer was the second best answer in the majority of questions (66%). For the validation groups, 7/10 (70%) and 9/10 (90%) questions from each institution were answered correctly, mirroring the results seen at the ACR/ARHP meetings.

Conclusion: Regardless of their specialty, professional crowds as a whole are able to answer difficult clinical questions and solve clinical vignettes using the ARS. Their answers frequently match evidence and expert answers. In the age of crowdsourcing and wide Internet use, professional crowds may serve as a source for solving difficult clinical questions.

Disclosure: A. G. Sreih, None; **F. Aldaghlawi**, None.

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Scores On The Multidimensional Health Assessment Questionnaire (MDHAQ) For "Walk 2 Miles Or 3 Kilometers," "Poor Sleep," and "Participate In Recreation," Are Higher, Indicating Poorer Status, Than Scores For 8 Activities Derived From The Health Assessment Questionnaire (HAQ). Kathryn Gibson[1], Sung-Hoon Park[2] and Theodore Pincus[3]. [1]Liverpool Hospital and University of New South Wales, Sydney, Australia, [2]Catholic University of Daegu School of Medicine, Daegu, South Korea, [3]NYU Hospital for Joint Diseases and New York University School of Medicine, New York, NY.

Background/Purpose: The HAQ *[Arthritis Rheum 1980;23:137]* has been used in almost all rheumatoid arthritis (RA) clinical trials conducted over the last two decades, and provides scores for the 3 patient self-report components of the RA Core Data Set: physical function, pain, and patient global estimate. However, RA patients now have significantly better clinical status than in previous decades *[Arthritis Rheum 2005;52:1009],* and some patients who experience functional disability score "0" on the HAQ, suggesting "normal" function. Furthermore, psychosocial issues remain important barriers to optimal outcomes. The MDHAQ includes 13 queries in the user-friendly HAQ format, 8 activities of daily living (ADL) from (and identical to) the HAQ, and 5 items not found on the HAQ: 2 complex activities, "walk 2 miles or 3 kilometers" and "participate in recreation and sports as you would like;" as well as 3 queries concerning poor sleep, anxiety and depression. Some of the unique MDHAQ items have been documented to recognize problems in patients with normal HAQ scores, but the traditional HAQ continues to be widely used in most clinical research. We analyzed mean scores for each of the 13 MDHAQ items in an Australian rheumatology setting.

Methods: All patients are asked to complete an MDHAQ in the reception area while waiting to see the physician. The MDHAQ queries 13 items: ability to perform 8 ADL from the HAQ (see Table, A-H), 2 complex activities ("walk 2 miles or 3 kilometers" and "participate in recreation and sports as you would like"), and 3 psychological items: "get a good night's sleep," "deal with anxiety," and "deal with depression." The patient-friendly HAQ format provides 4 response options: without any difficulty=0, with some difficulty=1, with much difficulty=2, and unable to do=3. The first 112 completed MDHAQs from 118 patients (3 patients had language barriers and 3 refused) were analyzed for the mean scores of 13 MDHAQ items, all scored 0–3, in 3 groups: all patients (n=112), RA patients (n=44) and patients with other diagnoses (n=68). Median levels of the 13 items were compared in the 3 groups; statistical significance of differences was analyzed using 2×2 Wilcoxon signed rank tests.

Results: Highest scores, >1 on a 0–3 scale, were seen for 3 of the 13 items: "walk 3 kilometers," "participate in recreation and sports as you would like," and "poor sleep." Similar patterns were seen in all patients, and subgroups of RA and other patients. Scores for 3 of the 5 MDHAQ items not found on the HAQ were significantly higher than scores for the other 10 items in all patients and "other" patients, and than 9 of 10 other items in RA patients ($p < 0.001$).

Table. Mean scores for 13 items on MDHAQ (0–3 score range)

Questionnaire item	All Patients (n=12)	RA (n=44)	Other Diagnoses (n=68)
A. Dress yourself	0.64	0.60	0.66
B. Get in and out of bed	0.51	0.42	0.58
C. Lift full cup/glass to your mouth	0.13	0.21	0.07
D. Walk outdoors on flat ground	0.44	0.40	0.47
E. Wash/dry your entire body	0.50	0.51	0.49
F. Bend down to pick up clothing off floor	0.81	0.60	0.94
G. Turn on taps/faucets	0.55	0.63	0.51
H. Get in and out of car/bus	0.89	0.89	0.90
I. Walk 2 miles or 3 kilometers	1.54	1.66	1.45
J. Participate in recreation/sports	1.31	1.26	1.34
K. Sleep	1.30	1.05	1.47
L. Anixety	0.69	0.51	0.74
M. Depression	0.70	<0.001*	<0.001

* $p<0.001$ except for K vs H ($P=0.125$), using Wilcoxon signed rank tests.

Conclusion: The MDHAQ recognizes patient problems that are not captured by the HAQ, which may be of value in clinical management and to document improvement over time. The MDHAQ might be considered for usual clinical care as well as for clinical trials.

Disclosure: K. Gibson, None; **S. H. Park**, None; **T. Pincus**, None.

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Validation Of The Cutaneous Dermatomyositis Disease Area and Severity Index: Characterizing Severity and Assessing Responsiveness To Clinical Change. Cynthia O. Anyanwu[1], David Fiorentino[2], Lorinda Chung[3], Yanli Wang[4], Kathleen J. Propert[4] and Victoria P. Werth[5]. [1]Philadelphia Veterans Affairs Medical Center, Philadelphia, PA, [2]Stanford University School of Medicine, Redwood City, CA, [3]Stanford University Medical Center, Palo Alto, CA, [4]University of Pennsylvania, Philadelphia, PA, [5]University of Pennsylvania School of Medicine, Philadelphia, PA.

Background/Purpose: Translational research and clinical trials necessitate validated outcome measures to reliably assess disease progression and treatment efficacy. The Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), a disease-specific and skin-based outcome measure, was developed for use in clinical trials and longitudinal patient assessment. The reliability and validity of this instrument have been established.[1] The goal of this study is to assess responsiveness of this tool and characterize severity and clinical response of cutaneous dermatomyositis (DM) using the CDASI.

Methods: In this two-center prospective database study the skin of patients with clinical or histologic evidence of DM was evaluated. Patients were evaluated using clinical instruments including the CDASI, a physician global assessment (PGA) 5-point Likert scale measuring disease severity (none, mild, moderate, severe, extremely severe), a PGA 0 – 10 cm visual analog scale (VAS) of disease severity and a PGA 3-point Likert scale that captured change in disease severity since the last visit (improved, worse, no change). The severity analysis compared CDASI scores for patients with mild disease to those with moderate and severe disease according to the PGA 5-point Likert. The PGA 3-point Likert and PGA VAS were used to evaluate responsiveness. Clinical response was defined as a rating of "improved" on the PGA 3-point Likert or a change in VAS scores of at least 2 cm. Statistical analysis included logistic regression models using generalized estimating equations to account for correlation among patients. A receiver operating characteristic curve was used with each model to determine cutoffs.

Results: A total of 199 patients from two sites completed up to 12 study visits each. Study participants were 79% female and 78% Caucasian. Disease subtype was classified as classic in 65% of patients and skin predominant in 35%. Separate site-specific analyses were performed due to interactions between study site and score in both the severity and responsiveness analyses. Baseline CDASI scores at the two sites range from 0 to 47 (median 17) and 0 to 48 (median 21). Data collected at one site resulted in a cutoff of 19 to differentiate mild from moderate and severe disease while at the second site CDASI scores of 14 or less characterized mild disease. Compared to the PGA VAS, the PGA 3-point Likert may be a less reliable measure of clinical response. Using a PGA VAS to assess responsiveness we found that improvement in CDASI scores of 4 or 5 indicates a clinically significant change.

Conclusion: Inter-rater variations in the use of the external PGA Likert and VAS gold measures may account for the differences between sites. The above results suggest that the CDASI is a valid and responsive tool for the evaluation of cutaneous dermatomyositis but randomized controlled trials are needed to confirm these results.

Reference: 1. Goreshi R, Okawa J, Rose M et al. Evaluation of reliability, validity, and responsiveness of the CDASI and the CAT-BM. *J Invest Dermatol* 2012; 132:1117–24.

Disclosure: C. O. Anyanwu, None; **D. Fiorentino**, None; **L. Chung**, None; **Y. Wang**, None; **K. J. Propert**, None; **V. P. Werth**, University of Pennsylvania holds the copyright for the CDASI, 7.

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Quality Of Care In Patients At Risk For Pulmonary Involvement: Assessment Of Pulmonary Screening In Systemic Sclerosis and Myositis Patients In a General Rheumatology Clinic. Michael G. Indelicato[1], Janet E. Lewis[2], Vincent J. Giuliano[1] and Donald L. Kimpel[2]. [1]University of Virginia, Charlottesville, VA, [2]University of Virginia School of Medicine, Charlottesville, VA.

Background/Purpose: As a quality assessment tool to evaluate patient care in a general Rheumatology Clinic, we determined the frequency of screening for pulmonary hypertension and interstitial lung involvement in a subset of patients at high risk. Involvement of the respiratory system is common in Systemic Sclerosis (SS) and Polymyositis/Dermatomyositis (PM/DM). Interstitial Lung Disease (ILD) and Pulmonary Arterial Hypertension (PAH) can lead to significant morbidity. These complications are now

the leading cause of death in systemic sclerosis. The prevalence of pulmonary involvement in PM/DM is variable, but has been reported to be close to 50%. ILD is a negative prognostic factor in these patients. General medical opinion is that Pulmonary Function Tests (PFTs) are suitable as a screening tool, but that a High Resolution Computed Tomography (HRCT) scan is crucial for the initial diagnosis of ILD. In addition, an echocardiogram is recommended to evaluate for PAH. However, there are no uniform guidelines for screening and the frequency with which these studies should be repeated. Published data suggests that screening assessments are not done routinely, so to establish a baseline for quality of care,we determined the frequency of pulmonary evaluation in our clinic population.

Methods: All patients were seen in our outpatient Rheumatology clinic from January 1, 2010 to December 31, 2011. Patients were identified based on diagnosis codes, and diagnoses confirmed by chart review. Charts were reviewed to determine if screening for ILD and PAH had been performed within 24 months of the index visit. ILD was classified by FVC < 70% or suggestive findings on CT imaging. If PAH was suggested by either decreased DLCO on PFTs or increased RVSP on echocardiogram, a right heart catheterization (RHC) was needed to confirm the presence of PAH.

Results: Of the 91 patients categorized, 44 had a diagnosis of SS, while 47 carried a diagnosis of PM/DM. Of the 44 patients with SS, nearly all patients were screened for ILD with PFTs (38/44, 86%) and PAH with echocardiogram (40/44, 91%). 16 had ILD and 10 had PAH. A total of 4 patients had both ILD and PAH. All 10 patients with PAH were confirmed with RHC. All patients with ILD had a HRCT at baseline. Of the 47 patients with PM/DM, about 61% (29/47) of the patients were screened for ILD with PFTs and just 28% (13/47) were screened for PAH with echocardiogram. 18 had ILD, while only 1 had PAH, confirmed on RHC. The 1 patient with PAH, also had ILD. All patients with ILD did have a HRCT obtained at baseline.

Conclusion: In our SS patients, 86% and 91% or our patients were screened for ILD and PAH respectively. For patients with PM/DM, although our screening percentage for ILD was lower compared to the SS group, the high frequency of ILD noted in PM/DM patients in prior studies suggests that routine screening is warranted. Only 28% of our PM/DM patients were screened for PAH. The association of PAH with PM/DM is not as well documented, however it remains good practice that patients with progressive dyspnea despite optimal treatment for ILD, should undergo evaluation for PAH. Future studies will assess the ongoing screening patterns, and address the rate of disease progression and the incidence of new onset ILD or PAH in this patient population.

Disclosure: M. G. Indelicato, None; **J. E. Lewis**, None; **V. J. Giuliano**, None; **D. L. Kimpel**, None.

ACR/ARHP Poster Session C
ARHP Health Services Research
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

1937

The Role Of Rural Residence In Low Back Pain. Elizabeth G. Salt[1], Yevgeniya Gokun[1], Heather Bush[1] and Leslie J. Crofford[2]. [1]University of Kentucky, Lexington, KY, [2]Vanderbilt University, Nashville, TN.

Background/Purpose: Low back pain (LBP) affects 67% to 84% of persons residing in industrialized countries.[1] With an estimated 2% of the workforce being compensated for work days lost to back injuries, LBP is responsible for the more lost workdays and disability claims than any other health condition.[2,3] The combined direct and indirect costs have been estimated to be $90 billion annually.[3]

Of Kentucky's 29,886 occupational injuries (2010–2011), 28% were low back injuries.[4] Ninety-two of Kentucky's 120 counties are designated as medically underserved populations; 71 of these 92 counties are designated as rural areas (2013 USDA Rural/Urban Continuum Codes).[5] We aim to report the percentage of women who report LBP per Kentucky county, compare rates of LBP in rural versus urban counties, and report predictors of LBP.

Methods: We extracted data (county of residence, self-reported LBP, and demographics) from the Kentucky Women's Health Registry, a database with over 16,000 women participants, and used descriptive statistics, two-sample t-tests with unequal variances, and multiple linear regression modeling during data analysis. Data was weight-adjusted based on the percentage of the county population represented in the database.

Results: Approximately 27.3% (standard deviation (SD)=6%; range=9–46%) (median=27%; mode=27%) of those women residing in an urban county reported LBP; 33.5% of women residing in a rural area reported LBP (SD=9.3%; range=17–64%) (median=33%; mode=35%). Of all Kentucky women, 31.7% (SD=8.9%; range=10–64%) (median=31%; mode=27%) reported having low back pain (Table 1). Using two-sample t-tests, those women who lived in a rural area were significantly more likely to report LBP when compared to those women residing in an urban area ($p<.0001$). Predictors of LBP using multiple linear regression modeling (residence, disability status, body mass index (BMI), physical activity, and age), were rural residence and BMI. Women residing in a rural county were 5.1% more likely to report LBP compared to urban counties ($p=0.0016$) and for every 5 unit increase in BMI, there was a 9.1% increase in the likelihood of reported LBP ($p=0.0005$).

Table 1. LBP per rural/urban continuum code.

	N	% reporting LBP	Std. Deviation
1.00	14	29.7%	.06
2.00	11	26.8%	.03
3.00	10	24.4%	.07
4.00*	2	29.5%	.01
5.00*	4	27.8%	.04
6.00*	19	35.0%	.08
7.00*	24	29.9%	.07
8.00*	11	31.0%	.07
9.00*	25	38.2%	.12
Total	120	31.7%	.09

*Rural area- 2013 USDA Rural/Urban Continuum Codes.

Conclusion: Study findings suggest that women with increased BMI who reside in a rural area are significantly more likely to report LBP; thus a significant health disparity has identified.

Disclosure: E. G. Salt, None; **Y. Gokun**, None; **H. Bush**, None; **L. J. Crofford**, None.

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A Description Of Therapies Used For Low Back Pain. Elizabeth G. Salt, Yevgeniya Gokun and Jeffery Talbert. University of Kentucky, Lexington, KY.

Background/Purpose: An estimated 67% to 84% of persons residing in industrialized countries suffer from low back pain (LBP), and 2% of all workers are compensated for work days lost to back injuries.[1–3] Of the 29,886 occupational injuries reported in Kentucky in 2010–2011, 28% were low back injuries.[4] The combined direct and indirect costs of LBP have been estimated to be 90 billion U.S. dollars annually.[3] An estimated 13% of direct costs are spent on primary care and pharmacy services.[1] Many pharmaceuticals such as opioids have only "fair" evidence to support their use. Yet the number of opioid analgesic prescriptions for LBP have increased dramatically – In 1998, 16% of all opioid prescriptions were written for LBP, while 40% of opioid prescriptions were written for LBP in 2004.[2,3] In the Clinical Guidelines for the Diagnosis and Treatment of LBP, Chou and colleagues[2] recommend treating patients who fail self-care with proven non-pharmacologic therapies (ex. cognitive behavioral therapy) stating the level of evidence to support this therapy as "good."[2] We will report the treatments provided to patients with the diagnosis of LBP using a private insurance dataset which represents a sample of 15 million patients annually across the US.

Methods: We extracted de-identified patient health claims data from persons residing in Kentucky with the diagnosis of LBP or related terms using ICD-9 codes (ex. 724.2 (lumbago)) along with treatments received using CPT codes (ex. 97001 (physical therapy evaluation)) and medication records from January 1, 2007 to December 31, 2009. Descriptive statistics were used to report the percentage of patients receiving the various treatments for LBP.

Results: Approximately 25% of patients with LBP received a service administered by a physical therapist (ex. evaluation, iontophoresis). Approximately 16% received exercise therapy and only 6% received psychological services. Similarly, despite the frequency in which occupation affects LBP, less than 1% of patients received occupational therapy (Table 1).[2] Yet,

approximately 55% of patients filled a prescription for an opioid analgesic (Table 2).

Table 1. Therapies among patients with the diagnosis of LBP in Kentucky (N=15,335).

Therapy	n (unweighted %)
Surgical Procedure	
Yes	25 (0.2%)
No	15,310 (99.8%)
Physical Therapy Evaluation	
Yes	1,347 (8.8%)
No	13,988 (91.2%)
Physical Therapy Re-Evaluation	
Yes	113 (0.7%)
No	15,222 (99.3%)
Manual Therapy	
Yes	1,777 (11.6%)
No	13,558 (88.4%)
Therapeutic Activities	
Yes	748 (4.9%)
No	14,587 (95.1%)
Neuromuscular Re-Education	
Yes	626 (4.1%)
No	14,709 (95.9%)
Aquatic Therapy	
Yes	19 (0.1%)
No	15,316 (99.9%)
Gait Training	
Yes	50 (0.3%)
No	15,285 (99.7%)
Electrical Stimulation	
Yes	316 (2.1%)
No	15,019 (97.9%)
Hot/Cold Packs	
Yes	222 (1.5%)
No	15,113 (98.5%)
Iontophoresis	
Yes	938 (6.1%)
No	14,397 (93.9%)
Occupational Therapy Evaluation	
Yes	50 (0.3%)
No	15,285 (99.7%)
Occupational Therapy Re-Evaluation	
Yes	6 (0.04%)
No	15,329 (99.96%)
Massage	
Yes	15 (0.1%)
No	15,320 (99.9%)
Self-Care Training	
Yes	370 (2.4%)
No	14,965 (97.6%)
Exercise Therapy	
Yes	2,441 (15.9%)
No	12,894 (84.1%)
Traction	
Yes	1,681 (11.0%)
No	13,654 (89.0%)
Biofeedback	
Yes	2 (0.01%)
No	15,333 (99.99%)
Psychological Therapy	
Yes	942 (6.1%)
No	14,393 (93.9%)

Table 2. Medication usage among patients with the diagnosis of LBP in Kentucky (N=15,335).

Medication	*n* (unweighted %)
Opiate-analgesic (ex. hydrocodone, oxycodone, codeine)	
Yes	8,508 (55.5%)
No	7,268 (47.4%)
Steroid	
Yes	4,959 (32.3%)
No	10,376 (67.7%)
Benzodiazepine	
Yes	2,065 (13.5%)
No	13,270 (86.5%)
Hypnotic	
Yes	869 (5.7%)
No	14,466 (94.3%)
Muscle Relaxer	
Yes	3,897 (25.4%)
No	11,438 (74.6%)
Non-Steroidal Anti-Inflammatory Drug (NSAID)	
Yes	6,220 (40.6%)
No	9,115 (59.4%)
Analgesic (ex. tramadol, lidocaine patches)	
Yes	2,113 (13.8%)
No	13,222 (86.2%)
Sedative	
Yes	387 (2.5%)
No	14,948 (97.5%)
Anticonvulsant	
Yes	525 (3.4%)
No	14,810 (96.6%)

Conclusion: The various treatment options that are available for LBP are not received by patients in Kentucky, a predominantly rural, medically underserved state.[5]

Disclosure: E. G. Salt, None; **Y. Gokun**, None; **J. Talbert**, None.

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Assessing The Increasing Costs To Manage Patients With Gout By State. Aaron Davis[1] and Jason Wreath[2]. [1]Goutchoices.com, San Clemente, CA, [2]Symphony Health, Phoenix, AZ.

Background/Purpose: Gout is a chronic progressive disease and worldwide prevalence is increasing. After over 40 years with limited and inexpensive treatments several new and more expensive treatment options are available. Although gout treatment guidelines are well established, variances in treatment patterns exist. The objective was to identify the rate of gout by state and estimate the budget impact of treating patients with chronic urate lowering and acute gout treatments.

Methods: Estimates from NHANES were used to project the rate of gout by state and compared to Symphony Health Solutions' ProMetis longitudinal patient data. Symphony Health Solutions' PHAST database provides destailed estimates of chronic and acute pharmaceutical treatments for gout. Looking at prevelance rates across states and treatment estimates between 2007 and 2012 costs by state by yearare estimated and presented in constant dollars using published wholesale acquisition costs for drugs.

Results: In 2011 gout is estimated to impact 9.2 million individuals based on NHANES estimates. Total gout pharmaceutical spend in the 2012 data was $1.038 billion, a 918% increase since 2007. Total number of prescriptions for gout rose 27% over the same time period. The costs of gout treatments vary: allopurinol at less than a dollar a day, febuxostat $2,250 per year; and pegloticase has the potential to cost as much as $100,000 per year. Acute and prophylaxic treatment colchicine now costs between $4.94 and $9.88 per day. Four states were identified accounting for approximately 30% of all pharmaceutical spending on gout; California, Florida, Texas and New York. Although colchicine does not treat the underlying urate burden found in patients with gout it accounted for over 55% of the total drug spend for patients with gout in in 2012; up from less than 20% in 2007. Among urate lowering therapies, febuxostat accounted for 60% of pharmaceutical costs, yet, allopurinol accounted for 93% of all fills across the U.S. State-by-state differences were seen in the utilization of urate lowering therapies, with higher colchicine prescribing leading to increased drug expenditure within certain states. Hawaii (1377%), South Carolina (1324%) and Georgia (1274%) have been most affected by increasing gout treatment costs, driven primarily by colchicine prescribing.

Conclusion: With an aging population and increasing rates of obesity, the rate of gout will continue to rise in the US. Recently launched drugs have increased the drug spend on gout. Forthcoming and likely expensive treatments will further add to the pharmaceutical budget impact of gout in the coming years. Reviewing treatment patterns within geographies will identify opportunities for gout education; including early identification, lifestyle management, treating the underlying cause of the disease vs. symptoms and utilization of effective generic medications. Early identification and treatment with effective generic medications will offer savings to the health care system.

Disclosure: A. Davis, None; **J. Wreath**, None.

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The Development Of A National Systemic Sclerosis Service In Ireland Incorporating A National Registry. Mairead Murray[1], Emese Balogh[2] and Douglas J. Veale[3]. [1]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [2]Translation Research Group, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [3]St. Vincent's University Hospital, Dublin 4, Ireland.

Background/Purpose: Systemic Sclerosis (SSc) is a rare autoimmune connective tissue disease with an increasing burden for health care systems. National SSc registries have proven to be useful internationally to capture and track patient information in chronic diseases, such an example is the irish SSc registry running from 2011. The objective of our study was to characterize disease trends in the Irish SSc cohort.

Methods: A standard proforma was devised to capture relevant data fields for both the Irish Registry and European Scleroderma Trials and Research Group Registry (EUSTAR). Physical and functional assessments were carried out and captured. SSc cases in the Irish and EUSTAR database entered from March 2011-June 2012 were analysed in the following subsets (n= 67): limited (lcSSc), diffuse (dcSSc), and overlap/undifferentiated (Other) disease in comparison with each other.

Results: Mean±SD patient age was 57.41±13.22 years with disease onset of 13.95±10.19 years. LcSSc patients were older than dcSSc and Other counterparts (p=0.021). Beside the expected female predominance in each group, there were more male patients in the dcSSc vs any other groups (p=0.018). The onset of Raynaud's Phenomenon was the shortest in dcSsc with 9.6+7.4 yrs (lcSSc: 15+10.8, Other: 15+10.4) and other SSc related symptoms also presented earlier in this subset with 6.13+5.9 yrs (lcSSc: 9.5+9.1, Other: 9.28+7.5 yrs). Gastrointestinal involvement was similar in each group (66.7%, 62%, 55%). DcSSc group was more frequently affected by cardiovascular (40% vs 25.8% vs 15%), lung (42.9% vs 16.7% vs 36.4 %) and musculoskeletal involvement (60% vs 20% vs 50%, p=0.0015) than lcSSc and Other subsets. The dcSSc group also manifested higher modified Rodnan skin scores (mRSS) than their counterparts (p<0.001). Comparing dcSSc with lcSSc based on a background of lung fibrosis, pulmonary arterial hypertension (PAH) was greater in the diffuse group (13.3% vs 9.7%, p=0.0015) as well as digital ulcer occurrence (13.3% vs 6.5%). LcSSc showed less frequent capillaroscopic scleroderma pattern (70% vs 100%) and aScl70 positivity (10.3% vs 58.3%, p<0.0001), however ACA positivity was higher compared to dcSSc (57.1 vs 25.0 %, p=0.002).

Conclusion: This is the first snapshot of disease characteristics of systemic sclerosis patients participating in the Irish SSc registry and EUSTAR. The continued enrolment of all SSc patients onto a national registry will facilitate the improvement in disease classification of the different subsets in the Irish population. A specialist nurse dedicated to SSc patients has been vital for information gathering to facilitate future research into this complex, challenging disease.

Disclosure: M. Murray, AbbVie, Pfizer, MSD, Roche, 2; **E. Balogh**, AbbVie, Pfizer, MSD, Roche, 2; **D. J. Veale**, AbbVie, Pfizer, MSD, Roche, 2, Pfizer, Roche, 5, Abbott, Pfizer, MSD, Roche, 8.

ACR/ARHP Poster Session C
Imaging in Rheumatoid Arthritis
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

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Imaging Atherosclerotic Plaque Inflammation In RA: Methodology and Initial Findings In a Single Centre Cohort. Sarah Skeoch[1], Penny Hubbard[2], Heather Williams[2], Dongxiang Xu[3], Sun Jie[3], Niranjan Balu[3], Wei Zhang[3], Jacqueline James[4], Thomas Hatsukami[3], Chun Yuan[3], M. Yvonne Alexander[5], Paul Hockings[6], John Waterton[7] and Ian N. Bruce[4]. [1]Arthritis Research UK Epidemiology Unit and NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [2]University of Manchester, Manchester, United Kingdom, [3]University of Washington, Seattle, WA, [4]Central Manchester University Hospitals Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom, [5]Healthcare Science Research Institute, Manchester Metropolitan University, Manchester, United Kingdom, [6]Astra Zeneca, Mölndal, Sweden, [7]Astra Zeneca, MACCLESFIELD, United Kingdom.

Background/Purpose: Chronic inflammation in RA may contribute to an unstable atherosclerotic plaque phenotype. Dynamic contrast enhanced MRI (DCE MRI) can be used to image carotid plaque neovascularisation and vascular permeability. Contrast agent distribution into the plaque, measured via the transfer constant (K^{trans}), correlates with macrophage content and microvessel density on non-RA carotid endarterectomy specimens. Positron emission tomography with fludeoxyglucose (^{18}F) (FDG-PET) can be used to quantify inflammation in carotid plaque and also correlates well with macrophage content. We aimed to employ these imaging techniques to assess plaque inflammation, for the first time, in RA.

Methods: RA patients, aged 40–65 years old were recruited and underwent a clinical and serological evaluation of RA disease and cardiovascular risk. All patients were screened for carotid plaque using B-mode Doppler ultrasound (US). Patients with plaque >2mm thickness had a carotid DCE MRI on a 3 Tesla scanner. Images were analysed by 2 blinded readers at the Vascular Imaging Laboratory, University of Washington, using a semi-automated analysis software package (Cascade; University of Washington, Seattle, WA). Patients with no history of cancer or recent infection underwent a carotid FDG-PET-CT scan. Plaque was localised using MR and CT then FDG uptake in the region of interest (ROI) was measured by calculating the standardised uptake value (SUV^{max}).

Results: 57 patients were screened, of whom 29 (51%) had ultrasound evidence of carotid plaque and 12 (21%) had a plaque >2mm. 2 MR scans were incomplete (1 due to pain, 1 due to claustrophobia) so MRI data were avail-
able on 10 patients; 5 patients also had FDG-PET-CT. The median (IQR) age and disease duration of the 10 patients undergoing imaging was 57 (55,59) and 9 (2, 20) years respectively. The median (IQR) DAS28 score was 5.15 (4.69, 6.55) and all patients were seropositive. No patients had a history of cerebrovascular disease.

On MRI, plaque >2mm thick was confirmed in 6 (60%) cases. The median (IQR) vessel stenosis was 54.5 (42,70)% and contrast enhancement was seen in all 6 cases (see figure 1), with a median K^{trans} value of 0.046 (0.023, 0.105)min^{-1}. Preliminary analysis of PET images demonstrated uptake in all cases with a median (IQR) SUV^{max}= 2.22 (1.67, 2.95). There was no significant correlation between imaging and clinical parameters.

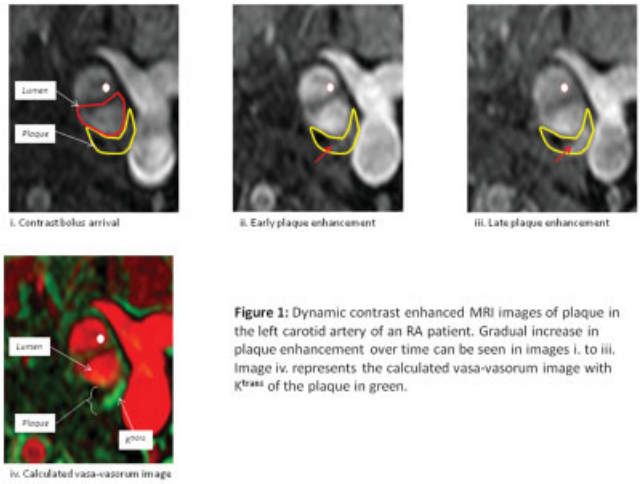

Figure 1: Dynamic contrast enhanced MRI images of plaque in the left carotid artery of an RA patient. Gradual increase in plaque enhancement over time can be seen in images i. to iii. Image iv. represents the calculated vasa-vasorum image with K^{trans} of the plaque in green.

Conclusion: Our preliminary study shows that atherosclerotic plaque inflammation can be detected using both 3T MRI and PET in RA patients. The discrepancy between MRI and US findings may be due to measurement error on US or flow artefact on MRI. A larger sample size and a comparator cohort will enable us to further determine the characteristics of atherosclerotic plaque inflammation in RA patients.

Disclosure: S. Skeoch, None; **P. Hubbard**, None; **H. Williams**, None; **D. Xu**, VP. Diagnostics Inc., 5; **S. Jie**, None; **N. Balu**, None; **W. Zhang**, None; **J. James**, None; **T. Hatsukami**, National Institute of Health and Philips Healthcare, 2; **C. Yuan**, NIH, Philips Healthcare, and VPDiagnostics Inc.., 2, ImagePace and Boehringer-Ingelheim, 5; **M. Y. Alexander**, None; **P. Hockings**, None; **J. Waterton**, None; **I. N. Bruce**, None.

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Ultrasound Shows Tenosynovitis to be Frequently Present as Well As Sensitive to Change in RA Patients On Biologic Medication. Hilde B. Hammer. Diakonhjemmet Hospital, Oslo, Norway.

Background/Purpose: Ultrasound (US) (grey scale (GS) and power Doppler (PD)) is a sensitive tool for examination of tenosynovitis in patients with rheumatoid arthritis (RA). The extensor carpi ulnaris (ECU) and tibialis posterior (TP) tendons have been shown to be frequently inflamed in RA patients and improve during treatment. Even so, only few of the US joint scores include these tendons in disease assessments. The present objective was to examine by US the frequency of involvement of the ECU and TP tendons as well as explore their sensitivity to change during biologic medication.

Methods: A total of 108 RA patients (aged mean (SD) 52.6 (12.9) years, 87% women, disease duration 7 (6) years, 84% anti-CCP positive)

were consecutively included when starting biologic treatment (infliximab (n=17); etanercept (n=36); adalimumab (n=9); certolizumab (n=2); golimumab (n=5); rituximab (n=26); tocilizumab (n=8); abatacept (n=5)) and examined bilaterally by US of the ECU and TP tendons at baseline and after 1, 2, 3, 6 and 12 months (performed by HBH on Siemens Acuson Antares Excellence version, with standard setting throughout the study). Tenosynovitis was scored semi-quantitatively 0–3 for presence of GS and PD pathology. The frequencies of tendon involvement at baseline (percentage of patients) as well as the sum scores of GS and PD at all examinations were calculated, and the changes in US sum scores from baseline were explored by paired samples T-test.

Results: The distribution of GS and PD scores of the ECU and TP tendons are shown in table 1. The sum GS and PD scores decreased significantly from baseline to all of the follow-up examinations ($p \leq 0.001$) as illustrated in figure 1.

Percentages of patients with tenosynovitis at baseline.

	Extensor carpi ulnaris				Tibialis posterior			
	Grey scale		Power Doppler		Grey scale		Power Doppler	
	Right	Left	Right	Left	Right	Left	Right	Left
Score 0	67	56	81	80	62	67	76	77
Score 1	18	21	7	9	19	15	11	10
Score 2	14	16	11	8	15	9	11	7
Score 3	1	7	1	3	4	9	2	6

Conclusion: More than one third of the patients had GS synovitis and more than one fifth of the patients had PD activity in the ECU and/or TP tendons at baseline, and both GS and PD sum scores decreased significantly during biologic medication. The frequent involvement of the ECU and TP tendons as well as their sensitivity to change during treatment, support the inclusion of these tendons in models of joint scoring of RA patients on biologic medication.

Disclosure: H. B. Hammer, None;

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Results of a Reliability Exercise for the Grading of Tendon Rupture in Patients With Rheumatoid Arthritis, using a Consensus-Based Ultrasound Score. George A. W. Bruyn[1], Petra Hanova[2], Annamaria Iagnocco[3], Maria-Antonietta d'Agostino[4], Lene Terslev[5], I. Moller[6], Peter V. Balint[7], E. Filippucci[8], Carlos Pineda[9], Marina Backhaus[10], Richard van Vugt[11], Richard J. Wakefield[12], Paul Baudoin[1], Kei Ikeda[13], Artur Bachta[14], Helen I. Keen[15], Levent Oczakar[16], Sibel Z. Aydin[17], Marwin Gutierrez[18], Peter Mandl[19] and Esperanza Naredo[20]. [1]MC Groep hospitals, Lelystad, Netherlands, [2]Institute of Rheumatology, Prague, Prague, Czech Republic, [3]University La Sapienza, Rome, Italy, [4]Versailles-Saint Quentin en Yvelines University-APHP, Ambroise-Paré Hospital, Boulogne-Billancourt, France, [5]The Parker Institute, Copenhagen, Denmark, [6]Instituto Poal, Barcelona, Spain, [7]National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, [8]University Politecnica delle Marche, Ancona, Italy, [9]Instituto Nacional de Rehabilitacion, Mexico City, Mexico, [10]Charite University Hospital, Berlin, Germany, [11]VU Medisch Centrum, Amsterdam, Netherlands, [12]University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [13]Chiba University Hospital, Chiba, Japan, [14]Military Medical Institute, Warsaw, Poland, [15]UWA, Perth, Australia, [16]Hacettepe University Medical School, Ankara, Turkey, [17]Medeniyet University, Goztepe Training and Research Hospital, Istanbul, Turkey, [18]Università Politecnica delle Marche, Ancona, Italy, [19]Medical University of Vienna, Vienna, Austria, [20]Hospital General Universitario Gregorio Marañón, Madrid, Spain.

Background/Purpose: To develop the first ultrasound (US) scoring system of tendon rupture in rheumatoid arthritis (RA) and assess its intra- and inter-observer reliability.

Methods: We undertook a Delphi consensus process on US defined tendon damage and US scoring system of tendon damage in RA among 35 rheumatologists expert in musculoskeletal US from 16 countries. Then, we assessed the intra- and interobserver reliability of US in scoring tendon damage on B-mode. Twelve patients with RA with symptoms of hands or feet were recruited. Twelve rheumatologists expert in musculoskeletal US consecutively performed a blind and independent US examination for tendon damage in B mode of five wrist extensor compartments and one ankle tendon of each patient bilaterally in two rounds. Intra- and inter-observer reliability were assessed by kappa coefficients. Reliability of tendon compartments was assessed by ICC.

Results: Five men and seven women were included. Median age was 66.5 years, range 36–74. Rheumatoid factor positivity was present in 8 patients (67%), anti-CCP+ in five (42%). Median DAS28 was 3.79, range 2.41–5.6. A three-grade semiquantitative scoring system was agreed for scoring tendon damage in B-mode, where grade 0 stands for normal tendon, grade 1 for partial rupture, and grade 2 for complete tendon rupture, respectively. Overall, 3456 investigations of tendon compartments were carried out. US scoring showed the following prevalences: grade 0 (N=2652, 76.7%); grade 1 (N=727, 21%), and grade 2 (N=77, 2.3%). The mean intra-observer reliability for tendon damage scoring was excellent (kappa value 0.91). The mean interobserver reliability assessment showed good kappa values (kappa value 0.75). The most reliable tendons were the extensor digiti minimi, the extensor carpi ulnaris, and the tibialis posterior.

Conclusion: US is a reproducible tool for evaluating tendon damage in RA. In addition, this study supports a novel reliable US scoring system for tendon rupture. The scoring system should at least include the extensor digiti minimi, the extensor carpi ulnaris, and the tibialis posterior tendons.

Disclosure: G. A. W. Bruyn, Vertex, 7; **P. Hanova**, None; **A. Iagnocco**, None; **M. A. d'Agostino**, BMS, Abbvie, Pfizer, Roche, 8, BMS, 5, Elsevier, 7; **L. Terslev**, None; **I. Moller**, None; **P. V. Balint**, None; **E. Filippucci**, None; **C. Pineda**, None; **M. Backhaus**, None; **R. van Vugt**, None; **R. J. Wakefield**, None; **P. Baudoin**, None; **K. Ikeda**, None; **A. Bachta**, None; **H. I. Keen**, None; **L. Oczakar**, None; **S. Z. Aydin**, None; **M. Gutierrez**, None; **P. Mandl**, None; **E. Naredo**, None.

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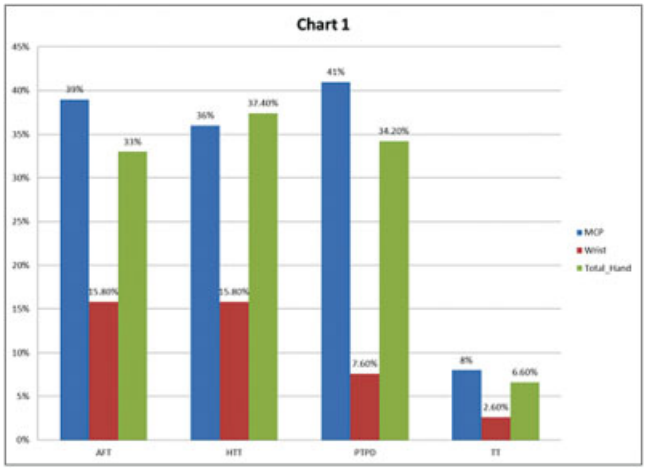
Ultrasound Characteristics Of Extensor Tendon Abnormalities and Peritendinous Fluid In Rheumatoid Arthritis. Laurie Ann Ramrattan and Gurjit S. Kaeley. University of Florida, Jacksonville, FL.

Background/Purpose: Rheumatoid arthritis (RA) is synonymous for involving synovial lined structures such as joints and tendon sheaths. Alterations in the extensor tendons overlying the metacarpophalangeal (MCP) joints which do not have synovial sheaths and which do not normally communicate with the joint recess have been observed with sonography but have not been clearly characterized. We report findings from a sonographic pilot study regarding changes in the MCP extensor tendons in patients with RA. These findings will lead to further study of the etiology and importance of these findings.

Methods: A retrospective cross-sectional study was done on 26 RA patients who had ultrasounds (US) of their hands between June 2010 and April 2012. Scans of the dorsal wrist and dorsal and volar 2nd- 5th MCP joints had been recorded in these patients. Esaote MyLab 70 ultrasound machine was used with a 12–18MHz LA 435 probe. The studies were re-read by GSK and B-mode and Power Doppler (PD) joint activity were scored. Changes in the extensor tendons were examined for the presence of B-Mode ultrastructural changes and PD. B- mode changes included anechoic fluid around the tendons (AFT), hypoechoic tissue around the tendon (HTT), tendon thickening (TT), tendon rupture (TR) and tendon calcifications (TC). The presence of vascularity around the tendon-Peritendon power doppler (PTPD) was recorded dichotomously. Joint erosions and tenosynovitis was also recorded.

Results: 26 patients, 77% were women, mean age of 56 years, mean body mass index of 31 and mean duration of disease 159 months were studied. PTPD and AFT were the highest findings, 41% and 39% respectively, observed around the extensor tendons at the level of the MCP. At the wrist, distal to the retinaculum, AFT and HHT were the dominant findings in 15.8 % of hands. TT was the least common finding, being found in 8% of hands at the MCP and 2.6% at the wrist. Joint erosions were noted in 50% of hands at the wrist. One patient had PD signal around the annular hood of the extensor tendon complex. B-Mode and Power Doppler were scored semiquantitatively from 0–3. Levels of activity were stratified in the following tertiles, 0–0.9, 1–1.9 and 2–3.The overall level of disease activity was high. Forty- four percent of patients had B-Mode score (BMS) in the upper tertile at the MCPs and 88% had a BMS in the upper tertile at the wrist. Twenty- eight percent of the patients had a Power Doppler score (PDS) in the upper tertile at the MCPs, and 67% at the wrist. Although the greatest joint activity was noted at the wrist, the extensor tendons at the MCPs displayed the greatest frequency of pathological changes.



Conclusion: Significant changes at the dorsal extensor tendon of the MCP joints were AFT, HTT, PTPD and TT. Although these findings have been reported in the past, they have not been fully characterized. Further studies are needed to define the etiology and significance of these findings.

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Comparison Of Selected Joint Evaluation With Comprehensive Assessment In Musculoskeletal Ultrasonography For Detection Of Synovitis In Rheumatoid Arthritis. Ryusuke Yoshimi, Atsushi Ihata, Yosuke Kunishita, Daiga Kishimoto, Reikou Kamiyama, Kaoru Minegishi, Maasa Hama, Yohei Kirino, Yukiko Asami, Atsuhisa Ueda, Mitsuhiro Takeno, Ichiro Aoki and Yoshiaki Ishigatsubo. Yokohama City University Graduate School of Medicine, Yokohama, Japan.

Background/Purpose: Musculoskeletal ultrasonography (US) is recognized as a useful tool for the diagnosis and monitoring of rheumatoid arthritis (RA), though a standard procedure has not been established. Scanning all joints is ideal but not practical for routine examinations. Therefore, it is important to determine which joints should be examined. Here we investigated the optimal number and combination of joints to be assessed by power Doppler (PD) US in daily practice for RA.

Methods: PDUS were performed in 24 joints, including all PIP, MCP, bilateral wrist and knee joints in 234 patients with RA. PD signals were scored semiquantitatively from 0 to 3 in each joint, and total PD score-24 was calculated by summing them up as comprehensive assessment. We examined correlations of total PD score-24 with individual joint PD scores and the sum PD scores of 8 sets of arbitrarily selected joint combinations. The sensitivity and negative predictive value (NPV) of the individual sets of selected joint examination for the detection of active synovitis were also evaluated.

Results: Positive PD signals were more frequently found in bilateral wrist, knee, MCP 2 and 3 joints than the other joints. The individual PD scores of these 8 joints also showed higher correlation coefficients with total PD score-24 ($r_s \geq 0.4$). There was no significant laterality in PD scores except for PIP 4 joints ($P = 0.037$). In wrist, the PD score was significantly lower in each region (radial, medial or ulnar region) as compared to that from the assessment of whole joint ($P = 7.6 \times 10^{-7}$, 9.8×10^{-3} and 1.2×10^{-4}, respectively). Among the sum PD scores of the 8 sets of selected joint combinations, that of the combination of 8 joints (total PD score-8), including bilateral MCP 2, 3, wrist, and knee joints, showed the highest sensitivity and NPV (Table 1; 98.1% and 96.2%, respectively). Discrepancy between the comprehensive 24 joint assessment and the selected 8 joint assessment was found in only 3 of 234 patients including 76 patients in US remission. Moreover, total PD score-8 showed very high correlation with the total PD score-24 (Table 1 and Figure 1; $r_s = 0.97$, $P < 0.01$). Comparison with other sets of joint combinations revealed that the wrist and knee joints had the stronger impacts on the correlation and the other parameters.

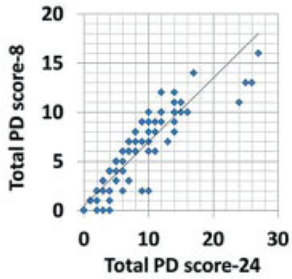

Figure 1 Total PD score-8 correlates well with total PD score-24.

Table 1. Sensitivities, NPVs and correlation coefficients of the different joint combinations for the detection of active synovitis

Joint combination	Sensitivity (%)	NPV (%)	Correlation coefficient (r_s)[a]
Bilateral MCP 2, 3, wrists & knees[b]	98.1	96.2	0.97
Bilateral MCP 2, wrists & knees	97.5	95.0	0.96
Bilateral wrists & knees	96.8	93.8	0.93
Bilateral MCP 2, 3 & wrists	88.0	80.0	0.89
Bilateral wrists	86.1	77.6	0.84
Bilateral knees	38.0	43.7	0.55
All MCPs	34.8	42.5	0.69
All PIPs	22.8	38.4	0.52

[a]Spearman's rank correlation coefficients between total PD score-24 and sum PD scores of the different joint combination ($P < 0.01$ for all the correlations). [b]Total PD score-8.

Conclusion: This study suggests that US examination in the selected 8 joints, including the bilateral wrist, knee, MCP 2 and 3 joints, is simple and efficient enough for making the diagnosis, monitoring disease activity, and judging imaging remission of RA in daily practice.

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Can Satisfactory Reliability Of The 7-Joint Ultrasound Score Be Attained By Inexperienced Readers In a Single Calibration Exercise? Results From The Biodam Program. Marina Backhaus[1], Stephanie G. Werner[1], Sarah Ohrndorf[4], Shafeeq Alraqi[2], Sean Crowther[3], Sukhvinder Dhillon[3], Navjot Dhindsa[4], Arthur J. Fernandes[5], Oliver M. FitzGerald[2], Hilde B. Hammer[6], Christophe Hudry[7], Sandrine Jousse-Joulin[8], Robert GW Lambert[3], Maggie Larche[9], Anouck Remy-Moulard[10], Lene Terslev[11], Ramin Yazdani[12], Rana Dadashova[13], Joel Paschke[13] and Walter P. Maksymowych[3]. [1]Charite University Hospital, Berlin, Germany, [2]St. Vincent's University Hospital, Dublin, Ireland, [3]University of Alberta, Edmonton, AB, [4]University of Manitoba, Winnipeg, MB, [5]Universite de Sherbrooke, Sherbrooke, QC, [6]Diakonhjemmet Hospital, Oslo, Norway, [7]Hopital Cochin, Paris, France, [8]CHU de la Cavale Blanche, Brest, France, [9]McMaster University, Hamilton, ON, [10]Hopital Peyronie, Montpellier, France, [11]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [12]St. Clare's Mercy Hospital, St. John's, NF, [13]CaRE Arthritis, Edmonton, AB.

Background/Purpose: While ultrasound assessment of patients with RA using the 7-joint score (US7) demonstrates reliability in the hands of experienced readers it is unclear to what degree this has external validity, and whether satisfactory calibration can be attained over the course of a single calibration exercise conducted over one day at a single location. We aimed to assess the feasibility and impact on inter-reader reliability of a one-day structured program of training based on an eCRF designed to provide real-time feedback on reader reliability during the process of scanning.

Methods: Six patients with rheumatoid arthritis were examined by 12 sonologists from 6 countries and 12 centers in 6 rater pairs who performed the US7 score (1). The US7 score includes the clinically dominant wrist, the second and third metacarpophalangeal (MCP) and proximal interphalangeal joints, and the second and fifth metatarsophalangeal (MTP) joints, which were evaluated for synovitis (SYN), tenosynovitis/paratenonitis (TS), and erosions (ER) from the dorsal side and palmar/plantar aspects by gray-scale (GS) and power Doppler (PD) ultrasound. Additional lateral scans were performed at the MCP2 and MTP5 joints. Scores were entered into an eCRF custom designed to provide immediate calculation of reliability data (eCaRe-US reliability). Training of readers focused on the most discrepant features observed in exercise 1. All reader pairs repeated

the examination in different patient order. Mean (SD) weighted kappa values, mean (SD) per cent agreement rates, inter-observer intra-class correlation (ICC) for summed scores (SYN, TS, ER) were calculated.

Results: Improvement in reliability was mainly observed in assessment of SYN-GS and PD. Primary regions of improvement in SYN-GS were dorso-median and ulnar wrist (k 0.31 to 0.54 and 0.17 to 0.34), PIP2 and 3 dorsal (k 0.03 to 1 and 0.13 to 1), MCP2 and 3 palmar (k 0.04 to 0.37 and 0.06 to 1.0), and MTP5 dorsal (k 0.06 to 1.0). Improvement in detection of SYN-PD was mainly observed in the wrist. Regions where reliability was not improved were MCP2 dorsal, PIP2 and 3 palmar, and MTP2 dorsal. Erosion assessment was lengthy and considered challenging for routine practice.

	Ex	SYN-GS	SYN-PD	TS-GS	TS-PD	ER
% agree	1	39.8 (25.9)	75.6 (25.9)	60.0 (19.0)	80.0 (13.9)	67.8 (24.0)
	1	48.7 (41.6)	73.1 (26.0)	53.3 (32.1)	80.0 (18.3)	nd
kappa	1	0.12 (0.10)	0.53 (0.47)	0.40 (0.22)	0.40 (0.42)	0.29 (0.35)
	2	0.47 (0.40)	0.45 (0.43)	0.31 (0.31)	0.30 (0.41)	nd
ICC	1	0.63	0.53	0.60	0.45	0.55
	2	0.84	0.77	0.56	0.37	nd

Conclusion: Substantial enhancement of reliability for detection of synovitis by ultrasound may be observed with limited calibration of inexperienced readers. We have identified specific regions that require more intensive calibration, specifically, MCP2 dorsal, PIP2 and 3 palmar, and MTP2 dorsal.

1. Backhaus M, et al. Arthritis Rheum 2009;61:1194

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The 7-Joint Ultrasound Score Is a Feasible Tool For Evaluating Joint Inflammation In Rheumatoid Arthritis Patients. Experience Among Rheumatologists With Basic Or Intermediate Level Of Ultrasound Training. Jana Hurnakova[1], Jakub Zavada[2], Herman F. Mann[2], Ladislav Senolt[1], Martin Klein[1], Petra Hanova[1], Sarka Forejtova[1], Marta Olejarova[1], Olga Ruzickova[1], Olga Sleglova[1] and Karel Pavelka[1]. [1]Institute of Rheumatology, Prague, Prague, Czech Republic, [2]1st Faculty of Medicine, Charles University, Prague, Prague, Czech Republic.

Background/Purpose: Musculoskeletal ultrasound plays an increasingly important role in monitoring disease activity and therapy response. German US-7 score is a recently introduced ultrasound scoring index to assess soft tissue changes and bone erosions in patients with RA[1]. US7 score has been shown to be a viable method to monitor disease activity when performed by skilled ultrasonographers.

Our aim was to investigate the value of the German US7 score among non-experts users in daily rheumatologic practice.

Methods: One hundred patients with rheumatoid arthritis (81 females, 19 males; 25 with early and 75 with long-standing arthritis) treated with conventional DMARDs (N=84 patients) and/or biologics (N=12 patients) were enrolled. At each visit (baseline, after 3 and 6 months), clinical (TJC, SJC, DAS28), laboratory (CRP, FW) and ultrasound assessments were performed in blinded manner. Distinct pathologic features detected by ultrasound examination were assessed by eight physicians in seven joint areas (wrist, second and third metacarpophalangeal and proximal interphalangeal, and second and fifth metacarpophalangeal joints) of the clinically dominant hand and foot according to the German US7 score. Synovitis and tenosynovial vascularity due to inflammation were scored according to a 4-point semiquantitative scale (0–3) in Grey Scale (GS) and Power Doppler (PD). Tenosynovitis (GS) and erosions were scored binary (on a yes or no basis). All values are shown as mean±SD. Followed parameters and correlations were statistically analysed as a change from baseline to second follow-up using Spearman′s correlation coefficients. P values less than 0.05 were considered as statistically significant.

Results: In this study, serum levels of C-reactive protein decreased from 7.13±8.69 at baseline to 5.71±6.6 mg/l after 6 months and DAS28 changed from 3.78±1.65 at baseline to 3.14±1.43 after 6 months. Similarly, total synovitis score in GS decreased from 7.42±6.66 at baseline to 5.05±5.29 after 6 months, synovitis score in PD decreased from 4.16±5.14 at baseline to 2.74±3.10 after 6 months. Significant correlations between change in DAS28 and synovitis improvement in GS ($R=0.371$, $p<0.001$), PD ($R=0.448$, $p<0.001$) and tenosynovitis in PD ($R=0.348$, $p<0.0016$) over 6 months were observed. Furthermore, synovitis in GS correlated significantly with synovitis in PD ($R=0.445$, $p<0.001$).

Conclusion: Our results show, that the German US-7 scoring system correlates well with clinical disease activity assessment even in the hands of non-expert users and thus, is a feasible tool for use in daily practice. It may be suggested that the decrease in all investigated parameters during the study period might be due to the implementation of ultrasound as a part of disease activity control influencing the treatment strategy.

References: 1. Backhaus M, Ohrndorf S, Kellner H, et al. Evaluation of a novel 7-joint ultrasound score in daily rheumatologic practice: a pilot project. Arthritis Rheum. 2009;61:1194–201.

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Power Doppler Ultrasound 7-Joint Score Vs. Simplified Disease Activity Index In Rheumatoid Arthritis Associated With Fibromyalgia. Rafael Chakr[1], Marina Behar[1], José A. Mendonça[2], Daniela Cervantes[1], Nizele Calegaro[1], Nicole Andrade[1], Iuri Siqueira[1], Daniel Zanchet[1], Andrese Gasparin[1], Penélope Esther Palominos[1], Charles Kohem[3], Odirlei Andre Monticielo[1], Claiton Brenol[4], Ricardo M. Xavier[1] and João Carlos T. Brenol[1]. [1]Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [2]Pontifical Catholic University of Campinas / Institute of Clinical Research – IPECC, Campinas, Brazil, [3]Brazilian Registry of Spondyloarthritis, São Paulo, Brazil, [4]Universidade Federal do Rio Grande do Sul, Porto Alegre RS, Brazil.

Background/Purpose: Fibromyalgia (FM) falsely increases rheumatoid arthritis (RA) disease activity clinical composite scores, such as the simplified disease activity index (SDAI), recently incorporated into ACR/EULAR definitions of remission in RA clinical trials (1–3). Allegedly, an objective assessment tool such as ultrasound is less prone to overestimation. The power Doppler (PDUS) US7 (0 to 39) semiquantitatively measures synovial neoangiogenesis as an objective estimation of RA disease activity. Our goal is to investigate whether PDUS US7 performs better than SDAI in disease activity evaluation among RA patients with FM.

Methods: A matched case-control study of RA women with FM (cases) and without FM (control) selected participants from a University-based arthritis clinic. Controls were matched for RA duration and rheumatoid factor positivity. Subjects with concomitant diseases potentially causing arthritis were not included. SDAI and PDUS US7 were calculated by a blinded assessor. Student′s *t* test of paired means and Pearson′s correlation coefficient were done for between groups comparisons. All participants signed informed consent.

Results: Thirty six cases (age = 55 ± 12.9 years, FIQ = 54.5 ± 21.1) and 36 controls (age = 55 ± 12.1 years) presented statistically different SDAI (30.6 ± 14.2 vs. 16.3 ± 10.3, $P<0.001$) but similar PDUS US7 (5.9 ± 4.2 vs. 5.8 ± 3.1, $P>0.05$). SDAI and PDUS US7 showed weak correlation among cases ($r = 0.18$, $P>0.05$) and moderate correlation among controls ($r = 0.62$, $P<0.05$). Arbitrarily considering PDUS US7 as the "gold standard" for RA disease activity assessment, SDAI had six times more false moderate/high individuals among cases as compared to controls (specificity of 54% in cases and 89% in controls).

Conclusion: PDUS US7 does not seem to be falsely increased by FM among RA patients, as opposed to SDAI. Longitudinal studies are necessary to clarify if ultrasound-based treatment decision decreases adverse events and costs in patients with RA and FM.

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Assessment Of Wrist Joint Inflammation In Patients With Rheumatoid Arthritis By Quantitative Two- and Three-Dimensional Power Doppler Ultrasonography. Hsin-Hua Chen. National Yang-Ming University, Taipei, Taiwan.

Background/Purpose: To assess the intra-operator and inter-operator reliability of two-dimensional (2D) and three-dimensional (3D)-power Doppler ultrasonography (PDUS) computer-aided quantification data for wrist joint vascularity.

Methods: This is a single-center, cross-sectional outpatient study using convenience sampling. Patients fitting the1987 ACR classification criteria for rheumatoid arthritis having at least one painful swollen wrist at the rheumatology clinic of Taichung Veterans General Hospital regardless of their DAS28 scores were enrolled. 2D- and 3D-PDUS examinations of swollen wrist joints were performed using a high-resolution, real-time ultrasound equipment (Phillips iU22 intelligent 3D ultrasound system, USA) with two transducers sequentially. One is a 5–13 MHz broadband linear array transducer (volumetric transducer) that is able to do a 2D scan and an automatic volume scan. The other is a "hockey stick", 7–15 MHz broadband linear transducer. The participants underwent three consecutive 2D PDUS assessment using the "hockey stick" linear transducer and the volumetric transducer, and three consecutive 3D PDUS assessment using the volumetric transducer in a dark room at room temperature (25βC) within 30 minutes of clinical evaluation by two sonographers (HH Chen and KL Lai). The vascular software, QLAB, provided by the Philips performed quantification analyses, including the area/volume, vascularization index (VI), flow index (FI) and vascularization flow index (VFI) for 2D- and 3D-PDUS respectively. Inter-operator and intra-operator reliability of computer-aided quantification are assessed by calculating intra-class correlation coefficients (ICCs).

Results: A total of 60 wrists in 48 RA patients were evaluated. The intra-operator ICCs of area, VI, FI, and VFI for 2D PDUS were 0.966, 0.952, 0.933 and 0.947 assessed by the "hockey stick" linear transducer, and were 0.972, 0.979, 0.814 and 0.979 assessed by the volumetric probe. The intra-operator ICCs of volume, VI, FI, and VFI for 3D-PDUS were 0.939, 0.965, 0.871, and 0.964. The inter-operator ICCs of area, VI, FI, and VFI for 2D-PDUS were 0.971, 0.968, 0.884, and 0.962 assessed by the "hockey stick" linear transducer, and were 0.977, 0.974, 0.837, and 0.973 assessed by the volumetric transducer. The inter-operator ICCs of volume, VI, FI, and VFI for 3D-PDUS were 0.388, 0.983, 0.874, and 0.983. The mean $\pm$ SD 2D VFI obtained by the "hockey stick" linear transducer was significantly higher than that obtained by the volumetric transducer (12.58 ± 8.57 vs. 10.66 ± 8.11, $p = 0.008$).

Conclusion: The present study demonstrates good intra-operator and inter-operator reliabilities of both 2D- and 3D-PDUS computer-aided quantification data for wrist joint vascularity in patients with RA. The 7–15 MHz "hockey stick" linear transducer detects greater Doppler signals than the 5–13 MHz volumetric transducer.

Disclosure: H. H. Chen, None;

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Relationship Between Radiographic Joint Space Narrowing, Sonographic Cartilage Thickness and Anatomy In Rheumatoid Arthritis and Control Joints. Peter Mandl[1], Gabriela Supp[1], Gabor Baksa[2], Daniel Aletaha[3], Reka Kurucz[4], Dora Niedermayer[2], Helga Radner[3], Paul Studenic[3], Peter V. Balint[4] and Josef S. Smolen[5]. [1]Medical University of Vienna, Vienna, Austria, [2]Semmelweis University, Budapest, Hungary, [3]Medical University Vienna, Vienna, Austria, [4]National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, [5]Medical University of Vienna and Hietzing Hospital, Vienna, Austria.

Background/Purpose: To validate ultrasound (US) for measuring cartilage thickness, by evaluating cartilage thickness on cadaver specimens of metacarpophalangeal (MCP) joints by US and conventional measurement. To correlate cartilage thickness measured by US with joint space narrowing (JSN) and joint space width (JSW) as assessed on conventional radiographs in MCP joints of patients with rheumatoid arthritis (RA).

Methods: Forty-three consecutive patients with RA were evaluated by US at our outpatient clinic. Bilateral MCP joints of 35 consecutive patients, who had hand x-rays taken within the last 12 months and additionally cadaver specimens of MCP 2–5 joints (n=12) were assessed by ultrasonography and histology. The cartilage layer of the metacarpal heads and proximal phalangeal bases of digits 2–5 were assessed bilaterally using a 15 Mhz linear transducer (GE Logic E9) from dorsal longitudinal and transverse views in midline, with the joints in 90° flexion. Cartilage thickness was measured in mm with an integrated caliper on static images. Both JSW and JSN were evaluated on conventional posterior-anterior radiographs. JSW was quantified as the shortest distance between the subchondral bone plates along the force-bearing axis of the joint using a standard measurement tool of the applied picture archiving and communication system; while JSN was evaluated using the van der Heijde modified Sharp scoring method (vdHS). Ankylosed or luxated joints were not included. Metacarpal cartilage thickness (MCT) of cadaver MCP joints was evaluated using a stereoscopic magnifying loupe and digitised image software. Cartilage thickness was correlated with x-ray findings using Spearman's or Pearson's correlation. Intra- and interobserver reliability of US and agreement between US and anatomic measurement were assessed by estimating the intraclass correlation coefficient (ICC).

Results: Agreement (ICC) between US and anatomic measurement of MCT on cadaver specimens of MCP joints (n=12) was 0.62 while the smallest detectable difference was 0.028 mm. Intra- and interobserver reliability of the US measurement of MCT in patients was 0.77 and 0.62 respectively. In the clinical group mean age was 63.1 ± 11.3 years, mean disease duration was 10.6 ± 7.8 years, mean CDAI was 7.76 ± 7.1; 82.9% were female and 54.1% were rheumatoid factor positive. US measurement of MCT of MCP 2–5 in patients was 0.38+/−0,17 mm. MCT of individual joints of the left and right hand correlated with individual MCP JSN ($r = -0.799$ and -0.702, respectively; $p<0.01$) and individual MCP JSW ($r=0.588$ and 0.401, respectively; $p<0.01$). The sum score of MCS for MCP joint 2–5 correlated with total MCP JSW ($r=0.771$, $p<0.01$), total JSN ($r=-0.412$, $p<0.05$), sum erosion score of the vdHS ($r=-0.500$, $p<0.01$) and the total vdHS ($r=-0.576$, $p<0.01$). No significant correlation was found between phalangeal cartilage thickness and JSN.

Conclusion: Both JSW and JSN by radiography indeed represent cartilage thickness at least in MCP joints. US is a validated tool for measuring MCT. When radiographic scoring is not available, US measurement of MCT might be a feasible alternative to depict cartilage damage in patients with RA. Phalangeal cartilage thickness has no added value beyond the measurement of MCT.

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The Spring Ligament Window: A Unique Sonoanatomic View Into a Complex Rheumatoid Joint. Joanne Kitchen[1], I. Moller[2], Maribel Miguel-Perez[3] and David A. Bong[4]. [1]Instituto Poal de Reumatolgia, Barcelona, Spain, [2]Instituto Poal, Barcelona, Spain, [3]University of Barcelona, Barcelona, Spain, [4]Instituto Poal de Reumatologia, Barcelona, Spain.

Background/Purpose: The calcaneonavicular or spring ligament (SL) is a group of 3 stout non-elastic fibrocartilaginous bands in the medial mid-foot that is important in maintaining the long arch of the foot & is an integral component of the articular socket for the head of the talus. In its entirety this socket is referred to as the "acetabulum pedis" of the talocalcaneonavicular(TCN) joint & is analogous to the acetabulum of the hip allowing a wide range of motion: gliding, rotation, inversion & eversion. There is also a synovial gliding layer externally where it effaces the overlying posterior tibialis tendon (PTT) sheath. The SL provides a "window" (SLW) to assess synovial disease with direct visualization of articulating surfaces & a prominent tendon sheath. High frequency musculoskeletal ultrasound (MSUS) visualization of the SL has been described in both normal subjects & patients with non-rheumatic mid-foot disorders. This study aims to evaluate the joint-ligament complex in cadaveric specimens & to utilize MSUS to view the TCN joint & measure the ligament in controls & rheumatoid arthritis (RA) patients.

Methods: MSUS (GE P6 machine, 5–16MHz transducer) was performed on 4 fresh cadaveric feet. The SLW was obtained in long-axis over the articulating cartilaginous surface of the medial aspect of the head of

the talus by fixing the distal end of the vertically oriented probe over the sustentaculum tali & rotating the proximal end of the probe counterclockwise from vertical until the medial aspect of the talar head was visualized. The transverse diameter of the SL at the midpoint of the interface of the talar cartilage & the articulating portion of the ligament was measured. This axis of the probe was marked on the cadaver foot surface & the refrozen specimen was cut with a band saw along this axis. Specimens were examined & measured with calipers, by two physicians blinded to each other's findings.

Healthy controls & RA patients underwent MSUS while supine with the ankle in a neutral position. The SLW was visualized as described above. Thus, the view obtained included the sustentaculum tali, the PTT, the sharp bony acoustic medial border of the talus with its distinct anechoic cartilage surface & the overlying hyperechoic fibrillar ligament. The spring ligament diameter was measured.

Results: The medial aspect of the TCN joint was easily identified with MSUS in cadaver, healthy & rheumatoid feet through the SLW using the technique described above & offered a unique view into the interior joint. The mean transverse diameter of the cadaveric ligament was 0.55cm (Range = 0.475 – 0.625cm) by MSUS & 0.58cm (Range = 0.47 – 0.7cm) by caliper anatomic measurement (n = 4). There was no significant difference between MSUS & anatomic measurement (p = 0.767). In RA patients (n = 28) mean transverse diameter by MSUS was 0.384cm (Range = 0.21 – 0.6cm) & in healthy controls (n = 10) it was 0.39cm (Range = 0.35 – 0.47cm), with no significant difference between groups (p = 0.392).

Conclusion: The SLW should be considered as part of the routine MSUS examination in rheumatic diseases affecting the foot & offers a unique intra-articular perspective.

Disclosure: J. Kitchen, None; **I. Moller**, None; **M. Miguel-Perez**, None; **D. A. Bong**, None.

1952

The Value Of An Automated Ultrasound System In The Detection Of Synovitis. Ruediger Mueller[1], Mathias Gruenke[2], Joerg Wendler[3], Florian Schuch[3], Karina Hofmann-Preiss[4], Ina Boettger[4], Ruediger Jakobs[5], Hendrik Schulze-Koops[6] and Johannes von Kempis[1]. [1]Kantonsspital St. Gallen, St. Gallen, Switzerland, [2]Medizinische Klinik IV, University of Munich, Munich, Germany, [3]Schwerpunktpraxis Rheumatologie, Erlangen, Germany, [4]Institut für bildgebende Diagnostik und Therapie, Erlangen, Germany, [5]Siemens AG, Erlangen, Germany, [6]University of Munich, Munich, Germany.

Background/Purpose: The detection of joint swelling caused by synovitis is important for the diagnosis and assessment of inflammatory arthritis. Ultrasound (US) and MRI have proven to be more sensitive and reliable than physical examination, but a comprehensive examination of affected joints with these techniques is time consuming and expensive. The automated breast volume scanner (ABVS) was developed to acquire serial B-mode pictures of the female breast and these data can be analysed in all three dimensions.

Objectives: To analyse the value of automated grey scale B mode US employing the ABVS system in detecting synovitis of the finger joints compared to manual ultrasound and physical examination, using MRI as gold standard.

Methods: 19 consecutive patients suffering from rheumatoid (n=15) or psoriatic (n=4) arthritis with at least one swollen finger joint were included. Automated and manual US were conducted using the ACUSON S2000™. The ABVS transducer was equipped with a linear array used with a frequency of 11 MHz. Each automatic sweep of the scanner generated 15.4 × 16.8 × 2.5 cm volume data sets. The system was set to perform an automatic scanning time of 65 s per scan with a slice thickness of 0.5 mm. The dorsal and palmar side of each hand were scanned separately. Multiplanar reconstruction enabled examination of the images at multiple levels for the presence of synovitis.

Results: Automated US detected 12.0, manual ultrasound 14.2, MRI 13.4, and clinical examination 4.1 swollen joints on average, respectively, per patient. The inter-observer reliability of both assessors for automated and manual US, MRI, and physical examination, was 66.9%, 72.7%, 95.1%, and 88.9%, respectively. A double assessor detection of joint swelling with MRI was used as gold standard. For the other methods, single observer detection was chosen. 84.3% of the joints classified as positive on MRI were confirmed by automated ultrasound, 85.5% on manual US, and 36.0 on physical examination. This translated into a sensitivity of 83.5%, 85.5%, and 36.0% for the three methods, respectively.

Conclusion: Automated US is a simple and time sparing option for the effective detection of synovitis in patients with inflammatory arthritis.

Disclosure: R. Mueller, None; **M. Gruenke**, None; **J. Wendler**, None; **F. Schuch**, None; **K. Hofmann-Preiss**, None; **I. Boettger**, None; **R. Jakobs**, Employe of Siemens, 3; **H. Schulze-Koops**, None; **J. von Kempis**, None.

1953

The Progression of Cartilage Damage in Rheumatoid Arthritis: A Three Year Prospective 3T- Magnetic Resonance Imaging Study Examining Predictive Factors. Fiona M. McQueen[1], Alexandra McHaffie[2], Andrew Clarke[2], Arier Lee[1], Quentin Reeves[2], Barbara Curteis[1] and Nicola Dalbeth[2]. [1]University of Auckland, Auckland, New Zealand, [2]Auckland District Health Board, Auckland, New Zealand.

Background/Purpose: Cartilage damage impacts on patient disability in RA. The aims of this MRI study were to investigate cartilage damage over 3 years and determine predictive factors.

Methods: 38 RA patients and 22 controls were enrolled at t=0 (2009). After 3 years, clinical and MRI data were available in 28 patients and 15 controls. 3T MRI scans were scored for cartilage damage, bone erosion, synovitis and osteitis. A model was developed to predict cartilage damage from baseline parameters.

Results: Inter-reader reliability for the Auckland MRI cartilage score (AMRICS) (1) was high for status scores (ICC 0.90 [0.81–0.95]) and moderate for change scores (ICC 0.58 [0.24–0.77]). AMRICS scores were highly correlated with the OMERACT MRI joint space narrowing (jsn) and XR jsn scores (r =0.96, p<0.0001 and 0.80, p<0.0001 respectively). AMRICS change scores were greater for RA patients than controls (p = 0.06 and p = 0.04 for the 2 readers) (Figure 1). Using linear regression, the baseline MRI cartilage score was the strongest predictor of the 3 year MRI cartilage score but synovitis and osteitis scores were also predictive (R2 = 0.67, 0.37 and 0.39 respectively). Baseline radial osteitis predicted increased cartilage scores at the radiolunate and radioscaphoid joints, (p = 0.0001 and 0.0012 respectively) and synovitis at radioulnar, radiocarpal and intercarpal-carpometacarpal joints also influenced 3 year cartilage scores (p values of 0.001, 0.04 and 0.01 respectively). Using multiple linear regression with outcome of cartilage damage at 3 years the optimal model predicted 76% of the variance of the 3-year AMRICS (R2 = 0.76), the strongest component being the baseline cartilage score (R2 = 0.67). The baseline MRI erosion score was also predictive but to a lesser degree (R2 = 0.47). When the outcome of bone erosion score was used, the strongest predictor was baseline erosion score (R2 = 0.87, p < 0.0001), while baseline cartilage score was less predictive (R2 = 0.49, p = 0.01). These data would support the hypothesis that some patients favour one damage pathway over the other so that those who develop erosions tend to erode further (E-progressors) while those who damage cartilage continue preferentially in that manner (C-progressors) (Figure 2).

1) McQueen FM et al. *Ann Rheum Dis* 2010;**69:** 1971–75.

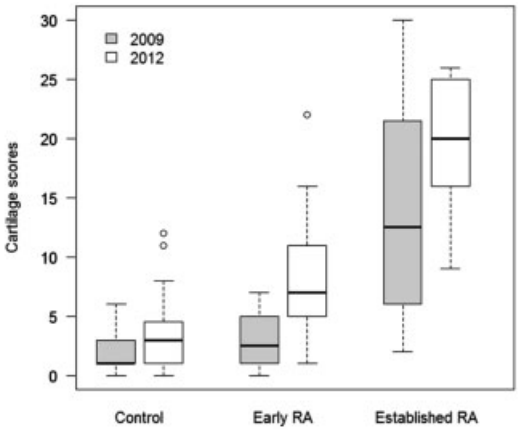


Figure 1. Progression of cartilage scores over 3 years in controls and RA

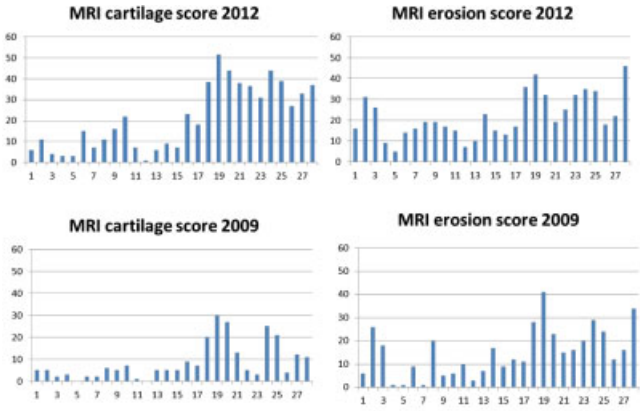


Figure 2. MRI cartilage and erosion scores at baseline and 3 years showing each patient as a bar.

Conclusion: MRI cartilage damage progression is preceded by osteitis and synovitis but is most influenced by pre-existing cartilage damage suggesting primacy of the cartilage damage pathway in certain patients.

Disclosure: F. M. McQueen, None; **A. McHaffie**, None; **A. Clarke**, None; **A. Lee**, None; **Q. Reeves**, Specialist Radiology and MRI, 3; **B. Curteis**, None; **N. Dalbeth**, None.

1954

Advantages Of a Combined Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) For Hand and Feet: Does The Ramris Of The Hand Alone Underestimate Disease Activity and Progression? Dr. Philipp Sewerin[1], Dr. Christian Buchbender[1], Dr. Stefan Vordenbäumen[1], Dr. Axel Scherer[1], Dr. Falk Miese[1], Dr. Ralph Brinks[2], Dr. Hans-Jörg Wittsack[1], Prof. Dr. Gerald Antoch[1], Prof. Dr. Matthias Schneider[2] and Prof. Dr. Benedikt Ostendorf[1]. [1]Univ. Duesseldorf, Düsseldorf, Germany, [2]Univ. Duesseldorf, Duesseldorf, Germany.

Background/Purpose: To evaluate a combined rheumatoid arthritis magnetic resonance imaging score (RAMRIS) for hand and foot (HaF-score) in rheumatoid arthritis (RA).

Methods: Magnetic resonance imaging (MRI) of the dominant hand and foot of 26 consecutive, ACPA positive RA patients before and 6 months after initiation of methotrexate was obtained. RAMRIS of the hand was complemented by corresponding scoring of the foot (MTP I-V; HaF-score). DAS28 and a tender and swollen joint count of the joints scored in MRI were recorded. Changes in these scores (Δ) were assessed.

Results: ΔHaF-score correlated significantly with ΔDAS28 (r = 0.835, 95%-CI 0.661–0.923). Correlations to ΔDAS28 were best for changes in the synovitis subscore (0.695) and bone marrow edema (0.754). Correlations to ΔDAS28 were significantly better for of the ΔHaF-score than ΔRAMRIS (0.662, 0.369–0.835, p=0.0361). All patients with at least moderate response (EULAR criteria, n=11) had continuing disease activity on MRI without improvement in the HaF-score, including five cases with new erosions, three of them at the feet. Similarly, 12 patients had an improved joint count without improvement of the HaF-score. 6 of these discrepant findings were attributable to the foot. No patient fulfilled SDAI remission criteria.

Conclusion: The HaF-score identifies patients with continuing disease activity despite clinical response that would have been missed by consideration of the traditional RAMRIS or the DAS28 alone. Response as opposed to remission may be an insufficient goal in RA as all patients showed continuing disease activity, especially at the feet.

Disclosure: D. P. Sewerin, None; **D. C. Buchbender**, None; **D. S. Vordenbäumen**, None; **D. A. Scherer**, None; **D. F. Miese**, None; **D. R. Brinks**, None; **D. H. J. Wittsack**, None; **P. D. G. Antoch**, None; **P. D. M. Schneider**, None; **P. D. B. Ostendorf**, None.

1955

Biochemical MRI With Gagcest (Glycosaminoglycan Chemical Exchange Saturation Transfer Imaging) Of Finger Joint Cartilage In Rheumatoid Arthritis. Dr. Philipp Sewerin[1], Dr. Christoph Schleich[2], Prof. Dr. Benedikt Ostendorf[1], Dr. Stefan Vordenbäumen[1], Prof. Dr. Gerald Antoch[1], Prof. Dr. Matthias Schneider[2] and Dr. Falk Miese[1]. [1]Univ. Duesseldorf, Düsseldorf, Germany, [2]Univ. Duesseldorf, Duesseldorf, Germany.

Background/Purpose: Rheumathoid arthritis (RA) predominantly involves finger joints. Cartilage damage promotes synovitis and has previously been shown to be predictive for bone erosions. gagCEST has recently been demonstrated to visualize biochemical alterations of cartilage in knee joints of patients following cartilage repair surgery as well as in intervertebral discs without using contrast agents. The purpose of our study was to test the feasibility of gagCEST imaging in finger joint cartilage in healthy volunteers and patients with RA to assess cartilage damage as a first step of bone destruction in RA patients.

Methods: Six healthy volunteers (mean age 33; range: 21–45 years) and four patients with ACPA and rheumatoid factor positive rheumatoid arthritis (age 58; range: 52–64 years, 2 men, 2 women, mean DAS28 4,8) were examined at a 3T MR scanner (Siemens Magnetom Trio) using two loop coils (4 cm diameter), one fixed on the palmar, the other on the dorsal side of the second metacarpophalangeal joint (MCP). For gagCEST imaging, CEST effects were prepared by a train of Gaussian RF pulses followed by signal readout with a 3D RF spoiled GRE sequence. The CEST curves were calculated for each pixel and were shifted for the water resonance to appear at 0 ppm of the Z-Spectrum. The CEST effect of the cartilage was measured with the glycosaminoglycan saturation transfer [ST = CEST (+1.3 ppm) – CEST (−1.3 ppm)/CEST (+1.3 ppm)]. Joint space width (JSW) as a morphologic feature of cartilage integrity was measured.

Results: Cartilage ST values were significantly lower in patients with seropositive rheumatoid arthritis compared to healthy volunteers (13.58 ± 6.11 vs. 27.38 ± 4.52; p=0.011). Cartilage CEST curves showed a decrease of CEST effect between 1.2 and 2.2 ppm, which corresponds to the resonance frequency of hydroxyl protons of glycosaminoglycans. There was no significant difference in JSW between healthy volunteers and RA patients.

Conclusion: gagCEST imaging revealed alterations in finger cartilage of seropositive RA patients compared to healthy controls in the absence of cartilage thinning. gagCEST is a potentially useful biomarker for imaging cartilage loss as a first step of inflammation and bone destruction in RA patients.

Disclosure: D. P. Sewerin, None; **D. C. Schleich**, None; **P. D. B. Ostendorf**, None; **D. S. Vordenbäumen**, None; **P. D. G. Antoch**, None; **P. D. M. Schneider**, None; **D. F. Miese**, None.

1956

The Effect Of Initial Methotrexate Therapy On Cartilage Composition In Early Rheumatoid Arthritis: Follow-Up With Biochemical MRI Of Finger Cartilage. Dr. Philipp Sewerin[1], Dr. Falk Miese[1], Dr. Hans-Jörg Wittsack[1], Dr. Stefan Vordenbäumen[1], Dr. Christoph Schleich[2], Prof. Dr. Gerald Antoch[1], Prof. Dr. Matthias Schneider[2] and Prof. Dr. Benedikt Ostendorf[1]. [1]Univ. Duesseldorf, Düsseldorf, Germany, [2]Univ. Duesseldorf, Duesseldorf, Germany.

Background/Purpose: To test for initial status and subsequent recovery of cartilage glycosaminoglycane content in metacarpophalangeal joints (MCP) in patients with early rheumatoid arthritis (eRA) undergoing Methotrexate (MTX) therapy with delayed Gd(DTPA)2-enhanced MRI of the cartilage (dGEMRIC).

Methods: MCP II and III in 19 patients with eRA (disease duration less than 3 month) and 13 healthy volunteers were examined (eRA patients: 13 females, six males, mean age 51 years, range 25–69; eRA 6 months follow-up patients: 7 females, one male, mean age 48 years, range 33–68; healthy volunteers: ten females, three males, mean age 51 years, range 25–66). All eRA patients received methotrexate (MTX, monotherapy, 15mg subcutaneously). Laboratory parameters collected at baseline and follow-up were: ESR, CRP (mg/dl), DAS28. Remission was defined as DAS28<2,6. dGEMRIC was acquired using the variable flip angle techique (VFA). dGEMRIC index was measured in phalangeal and metacarpal cartilage of MCP II and III with manually drawn region-of-interest evaluation. Cartilage thickness was determined as a conventional measure of cartilage integrity. Statistical analysis used non-parametric Mann-Whitney-U-Test to test for significant differences between the groups.

Results: dGEMRIC index was significantly decreased in MCP-joints of eRA patients compared to healthy subjects at T0 (healthy volunteers: MCP II 488 ms ± 90 ms, MCP III 523 ms ± 100 ms; eRA patients: MCP II 414 ms ± 119 ms (p<0.05), MCP III 415 ms ± 132 ms (p<0.05)). Cartilage thickness was not significantly different between the groups. Following initial MTX therapy, remission (DAS28<2,6) was achieved in six out of eight patients. Mean increase of dGEMRIC index was 12 ms ± 180 ms (n.s.).

Conclusion: In therapy naive early RA, there was a decrease in cartilage glycosaminoglycane content in metacarpophalangeal joints in comparison to healthy controls in the MCP joints II und III. Glycosaminoglycane content as assessed with dGEMRIC of normal appearing finger cartilage did not significantly change after a six month MTX monotherapy despite clinical remission

(based on DAS28) and could be a hint for silent progression. dGEMRIC may be a possible tool for studies on cartilage protection in RA therapy.

Disclosure: D. P. Sewerin, None; **D. F. Miese**, None; **D. H. J. Wittsack**, None; **D. S. Vordenbäumen**, None; **D. C. Schleich**, None; **P. D. G. Antoch**, None; **P. D. M. Schneider**, None; **P. D. B. Ostendorf**, None.

1957

Correlation Of Structural Abnormalities Of The Wrist and Metacarpophalangeal Joints Evaluated By High-Resolution Peripheral Quantitative Computed Tomography, 3 Tesla MRI and Conventional Radiographs In Rheumatoid Arthritis. Chan Hee Lee[1], Waraporn Srikhum[2], Andrew J. Burghardt[1], Warapat Virayavanich[3], Thomas M. Link[1], John B. Imboden[1] and Xiaojuan Li[1]. [1]University of California, San Francisco, San Francisco, CA, [2]Thammasat University, Pathumthani, Thailand, [3]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Background/Purpose: Early detection of joint inflammation and tissue damage are critical for patient management in rheumatoid arthritis (RA). High-resolution peripheral quantitative computed tomography (HR-pQCT) is an emerging modality for the assessment of bone damage in RA, including erosions and deterioration of bone microarchitecture. The goal of this study was to examine the correlation of structural changes evaluated by HR-pQCT, 3 Tesla (T) MRI and conventional radiographs (CR) in RA.

Methods: In sixteen RA patients, HR-pQCT of the second and third metacarpophalangeal joints (MCP) as well as the wrist joints, 3 T MRI of the wrists joint and CR of both hands and feet were performed. Ten patients had 1 year follow-up CR. CRs were graded according to the Modified Sharp/ van der Heijde Score (MSS). Bone erosions were evaluated in HR-pQCT and MRI for number, grade and maximum dimension. Bone marrow edema pattern (BMEP) was quantified from MRI for volume, signal intensity and lesion burden using in-house developed software. Spearman's rank correlation coefficients between MSS by CR, bone erosion by HR-pQCT, bone erosion and BME by MRI were calculated.

Results: Fifteen patients (93.8%) had evidence of erosions in HR-pQCT. MRI erosions and BME were found in 13 patients (81.3%). Baseline total MSS was significantly correlated with HR-pQCT erosion measures, MRI erosion measures and MRI BMEP volume ($r = 0.59 – 0.90$, $p < 0.05$). The erosion detection sensitivity of MRI was 85.7% (42/49) and CR was 60.9% (53/87) when HR-pQCT was considered as a reference method. In the 10 patients who had both baseline and one year follow up CRs, the mean difference between baseline and follow up MSS (delta MSS) was 1.2. There was no significant correlation between delta MSS and HR-pQCT/MRI erosion measures at baseline, but a trend was observed toward a correlation between delta MSS and MRI BMEP volume and burden.

As a result of inflammation, initially BMEP will develop without erosion (stage 1). After this stage, early erosion will develop, which can be very small and can be identified only on HR-pQCT, which is the most sensitive modality for the detection of erosion but no on other modalities such as MRI and CR (stage 2). As the disease progresses, the size of erosion becomes larger and can be detected by both HR-pQCT and MRI (stage 3). Finally, the erosion is becoming large enough to be shown by all 3 modalities, CR, HR-pQCT and MRI (stage 4).

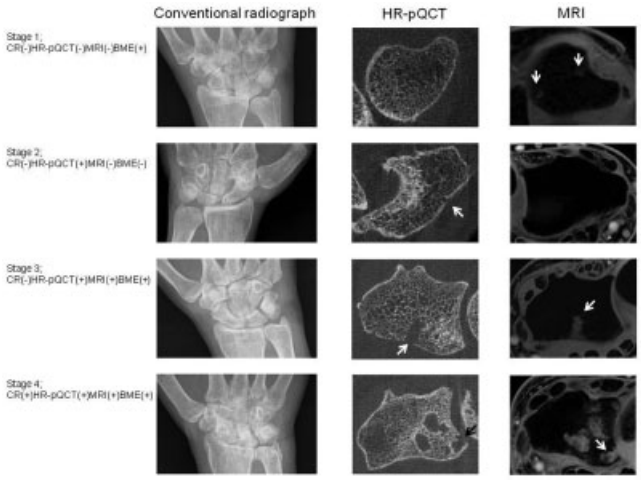


Figure 1. The stages of erosion by HR-pQCT, MRI and CR in RA hands.

Conclusion: HR-pQCT detects more and smaller bone erosions compared to MRI and CR. In addition, 3 T MRI can also provide quantitative measurement of BMEP. From the erosion findings by HR-pQCT, MRI and CR, and the BME observation by MRI, we may suggest the stages of erosion in RA, shown in Figure 1. The combination of HR-pQCT and MRI is a powerful mean to evaluate joint inflammation and bone damage, and MRI BMEP potentially could predict disease progression in patients with RA.

Disclosure: C. H. Lee, None; **W. Srikhum**, None; **A. J. Burghardt**, None; **W. Virayavanich**, None; **T. M. Link**, None; **J. B. Imboden**, None; **X. Li**, None.

1958

Does Evaluation Of Hand Bone Loss By Digital x-Ray Radiogrammetry Within The First 3 Months After Diagnosis Of Rheumatoid Arthrits Identify Patients At Risk For Radiological Progression? Ewa H. Berglin[1] and Solbritt M. Rantapaa-Dahlqvist[2]. [1]Institution of Public health and clinical medicine/ Rheumatology, University of Umeå, Umeå, Sweden, [2]Institution of Public health and clinical medicine/ Rheumatology, University of Umeå, Umeå, Sweden, Umea, Sweden.

Background/Purpose: To evaluate the usefulness of assement of hand bone loss in prediction of radiological progression in patients with early rheumatoid arthritis (RA).

Methods: Patients with early RA (< 12 months of symptoms) were consequtively included in the study and treated according to the Swedish guidelines. Hand bone mineral density (BMD) was measured with digital x-ray radiogrammetry (DXR) at inclusion and after 3 months and the difference between the two assessments was related to clinical measurements and to the radiological outcome (Larsen score) at one year follow-up.

Results: Sixty-eight patients (71% females) with disease duration of (mean (SD)) 5.28 (2.79) months were included. The BMD decreased significantly for the whole cohort from (mean, (SD)) 0.571(0.0918) to 0.567 (0.0933) g/cm^2 ($P = 0.0001$). Seventeen percent of the patients had a decrease of > 2.50 mg/cm^2/month which was regarded as considerable bone loss (CBL). The level of C-reactive protein (CRP) at inclusion was significantly higher among patients with CBL compared with patients with less bone loss ($P=0.007$). Female patients with DAS28 above 2.6 at 3 months had significantly higher rate of bone loss (mean (SD) 1.745 (1.715) vs 0.667 (1.530) mg/cm^2, $P = 0.038$) and a significantly higher increase in Larsen score between inclusion and 1 year mean (SD) 0.94 (1.211) vs 2.08 (2.060), $P = 0.029$ than female patients with DAS28< 2.6. Mean value (SD) of Larsen score at inclusion was 5.5 (5.53) and 7.1 (6.00) at 1 year ($P < 0.0001$). There was a tendency, although not statistically significant, of greater difference in Larsen score between inclusion and 1 year in patients with CBL compared with patients with less bone loss (data not shown).

Conclusion: Hand bone loss was significant already at 3 months after diagnosis of RA. It was related to measures of inflammation and with a trend suggesting a relationship with radiological progression

Disclosure: E. H. Berglin, None; **S. M. Rantapaa-Dahlqvist**, None.

1959

Extremity MRI Scans of the Hand and the Diagnosis of Inflammatory Arthritis: Findings in Patients With a Clinical Diagnosis of RA, Non-Inflammatory Arthritis and Fibromyalgia. Robert S. Katz[1], Hannah Bond[2] and Anthony Farkasch[2]. [1]Rush Medical College, Chicago, IL, [2]Rheumatology Associates, Chicago, IL.

Background/Purpose: Low field extremity MRI has been utilized to evaluate patients for inflammatory arthritis and to follow their progress on immunosuppressive and biologic therapy. The interpretation is performed by radiologists experienced in evaluating extremity MRI scans, but how often do the findings agree with the clinical evaluation? The purpose was to evaluate hand and wrist pain to determine whether patients have changes of inflammatory arthritis and are good candidates for immunosuppressive or biologic therapy.

Methods: We analyzed our rheumatology office practice patients who had extremity MRI of the hand and wrist performed in 2010 through 2012. All patients received low field MRI evaluations of the wrist and hand, using an Esoate.2 Tesla C Scanner. We compared the patient's clinical diagnosis to the MRI findings. The MRI radiologists assessed whether synovitis was present and its intensity and location, the presence of osteitis; bone erosions and joint space narrowing.

Results: Mild synovitis was frequently reported in patients with fibromyalgia. Erosions were occasionally seen in fibromyalgia patients, but they were almost always solitary or a few small erosions whereas, as expected, in rheumatoid arthritis the synovitis was more intense and the erosions were more frequent and more extensive. Osteitis was reported in RA and OA patients and helped distinguish their MRI scans from those with fibromyalgia.

Clinical Diagnosis	Number of Patients	Interpreted as Rheumatoid Arthritis	Interpreted as Inflamatory Arthritis	Interpreted as Neither Rheumatoid or Inflamatory Arthritis	Outcome
Rheumatoid arthritis	47	11 (23.4%)	2 (4.3%)	34 (72.3%)	72.3% were under read
Osteoarthritis	17	2 (11.7%)	1 (5.9%)	14 (82.4%)	82.4% matched the clinical diagnosis of non-inflamatory
Fibromyalgia	84	12 (14.0%)	4 (5.0%)	68 (81.%)	19% were over read
Systemic Lupus Erythemosus	11	2 (18.2%)	0	9 (81.8%)	
Other (PMR, Derm)	2	0	0	2 (100.0%)	

Conclusion: We conclude that MRI scans of the extremities are helpful in evaluating patients with hand pain, but caution is necessary to avoid over-interpretation of mild findings, especially mild synovitis and small and rare erosions. Patients with inflammatory arthritis had moderate to severe synovitis that was present in more locations (the MCP joints, PIP joints, and the carpal joints) than patients with the clinical diagnosis of non-inflammatory arthritis, or fibromyalgia. However, a few patients thought originally to have fibromyalgia were considered for treatment of inflammatory arthritis based on the MRI findings. Mild synovitis without gadolinium is difficult to evaluate accurately. 72.3% of patients with RA were not interpreted as consistent with this diagnosis indicating either effective treatment or under interpretation of MRI findings.

The MRI scans of patients with fibromyalgia and non-inflammatory arthritis are frequently reported as abnormal. Mild changes on extremity MRI can be seen in patients with fibromyalgia and should not lead to a change of diagnosis. The same applies to those with non-inflammatory arthritis. Generally, a distinction can be made compared to those with inflammatory arthritis based on the intensity and widespread distribution of the synovitis, the number and size of erosions, and the presence of osteitis.

Over-interpretation and under interpretation of extremity MRI by experienced radiologists is common.

Disclosure: R. S. Katz, None; **H. Bond**, None; **A. Farkasch**, None.

1960

Combination Of Magnetic Resonance Imaging-Proven Osteitis With 2010 RA Classification Criteria Improves The Diagnostic Probability Of Early Rheumatoid Arthritis Whose Disease Duration Less Than 6 Months. Mami Tamai[1], Junko Kita[2], Yoshikazu Nakashima[2], Ayako Nishino[2], Takahisa Suzuki[2], Yoshiro Horai[2], Akitomo Okada[3], Tomohiro Koga[2], Shin-ya Kawashiri[2], Naoki Iwamoto[2], Kunihiro Ichinose[2], Kazuhiko Arima[2], Satoshi Yamasaki[4], Hideki Nakamura[2], Tomoki Origuchi[2], Masataka Uetani[2], Aya Fukushima[2], Kiyoshi Aoyagi[2], Katsumi Eguchi[5] and Atsushi Kawakami[2]. [1]Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan, [4]Hiroshima University Hospital, Hiroshima, Japan, [5]Sasebo City General Hospital, Sasebo, Nagasaki, Japan.

Background/Purpose: In the articles describing the 2010 rheumatoid arthritis (RA) classification criteria, it is stated that additional evidence of joint injury from imaging techniques such as magnetic resonance imaging (MRI) may be used for confirmation of the clinical findings. MRI is able to detect synovitis, tenosynovitis, osteitis and bone erosion. Among these, osteitis, is supposed to be the best surrogate MRI feature for differentiating RA from other rheumatic diseases. This study is undertaken to investigate whether MRI-proven osteitis improves the diagnostic performance of the 2010 RA classification criteria among early arthritis patients.

Methods: All of early arthritis patients, whose disease duration at entry less than 6 months, were recruited in the present study from Nagasaki University Early Arthritis Cohort. Patients whose diagnoses were compatible with rheumatic diseases other than RA or obvious to plain radiographic erosion at entry, were excluded. All of the subjects underwent physical examination, blood tests, and gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA)-enhanced MRI on the same day. Gold-standard RA was defined as the patients receiving disease-modifying antirheumatic drugs during the first year. The diagnostic performance of the 2010 RA criteria with or without the finding of MRI-proven joint injury was investigated.

Results: One hundred sixty-four patients, whose median disease duration at entry was 2 months, were recruited. The median values for age, CRP (mg/l), prevalence of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA) at examination were 54 years, 2.0, 40.2% and 34.1%, respectively. The 2010 RA classification criteria classified RA with a sensitivity of 62.4%, a specificity of 83.1%, a positive predictive value (PPV) of 82.9%, a negative predictive value (NPV) of 62.8%, accuracy of 71.3%. Osteitis was the most specific MRI finding in gold-standard RA. We have proposed a decision-tree algorithm that involves initially applying the 2010 RA classification criteria, and if the patients do not fulfill 2010 RA classification criteria, the MRI-proven osteitis rule is introduced. The tree algorithm has been shown to differentiate patients more efficiently than the 2010 RA classification criteria alone, exhibiting a sensitivity of 79.6%, a specificity of 76.1%, a PPV of 81.3%, a NPV of 74.0%, accuracy of 78.0%.

Conclusion: The present data indicate that the combination of MRI-proven osteitis with the 2010 RA classification criteria improves the diagnostic probability of RA at an early stage.

Disclosure: M. Tamai, None; **J. Kita**, None; **Y. Nakashima**, None; **A. Nishino**, None; **T. Suzuki**, None; **Y. Horai**, None; **A. Okada**, None; **T. Koga**, None; **S. Y. Kawashiri**, None; **N. Iwamoto**, None; **K. Ichinose**, None; **K. Arima**, None; **S. Yamasaki**, None; **H. Nakamura**, None; **T. Origuchi**, None; **M. Uetani**, None; **A. Fukushima**, None; **K. Aoyagi**, None; **K. Eguchi**, UCB Pharma, 5; **A. Kawakami**, None.

1961

The Diagnostic Utility Of Musculoskeletal Ultrasound In Early Arthritis – a Probabilistic (Bayesian) Approach. Hamed Rezaei[1], Erik af Klint[1], Yogan Kisten[1] and Ronald F. van Vollenhoven[2]. [1]The Karolinska Institute, Stockholm, Sweden, [2]Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), the Karolinska Institute, Stockholm, Sweden.

Background/Purpose: While musculoskeletal ultrasound examination (MSUS) is used increasingly in the work-up of patients with inflammatory joint disease, the exact diagnostic utility has not been established. We sought to apply a prospective, probabilistic (Bayesian) approach to quantify the diagnostic utility of MSUS.

Methods: All patients referred to our clinic for evaluation of arthritis were eligible, unless a prior diagnosis was indicated or a certain diagnosis could be made based on the information in the referral letter. Patients were assessed by history and physical examination including joint examination, laboratory testing including acute-phase reactants, RF, and ACPA, and plain x-ray of hands, wrists and feet if clinically indicated. A diagnostic assessment was then performed by the responsible physician where the probability of a) any inflammatory joint disease and b) rheumatoid arthritis was given on a 5-point scale ranging from unlikely (0–20% probability) to very likely (80–100% probability). Subsequently, an ultrasound examination of the wrist, MCP, PIP 2–5 in both hands, MTP 2–5 in both feet and also symptomatic joints was performed by HR and the results of the examination presented to the responsible physician. The latter then assessed the diagnostic probabilities again, using the same scale. The proportions of patients with maximal and minimal diagnostic certainty pre-test and post-test were compared by Fisher exact test.

Results: 67 patients were included, 52 were female, average (SD) age 47.9 (16.5) years. Symptom duration 8.9 (4.0) months, 15 patients were positive for RF and 12 for ACPA. The pre-test and post-test probability distributions for (any) inflammatory joint disease and for RA are given in the table. The final diagnoses in these patients were RA (15), other inflammatory joint diseases (21), non-inflammatory joint disease (31).

With regard to a diagnosis of (any) inflammatory joint disease, the proportion of patient for whom diagnostic certainty was maximal (<20% OR >80% likelihood) was 20/67 (29.9%) before MSUS and 42/67 (62.7%) after MSUS (p=0.0002). With regard to a diagnosis of RA, the proportions were 21/67 (31.3%) pre-test and 39/67 (58.2%) post-test (p=0.003). Parallel reductions were seen in the proportions of patients with greatest diagnostic uncertainty (40–60% likelihood), from 24/67 (35.8%) to 10/67 (14.9%) (p=0.0093) and from 17/67 (25.3%) to 4/67 (6.0%) (p=0.0035), respectively.

	any inflammatory disease (n patients in group)		rheumatoid arthritis (n patients in group)	
Diagnostic probability	Pre-test	Post-test	Pre-test	Post-test
<20%	4	14	12	27
20–40%	14	10	26	17
40–60%	24	10	17	4
60–80%	9	5	3	7
>80%	16	28	9	12

Conclusion: In this probabilistic (Bayesian) analysis, musculoskeletal ultrasound when added to routine physical and laboratory examination greatly increased the diagnostic certainty in patients referred for the evaluation of arthritis.

Disclosure: H. Rezaei, None; **E. af Klint**, None; **Y. Kisten**, None; **R. F. van Vollenhoven**, AbbVie, BMS, GSK, Merck, Pfizer, Roche, UCB, 2, AbbVie, AstraZeneca, Biotest, BMS, GSK, Lilly, Merck, Pfizer, Roche, UCB, Vertex, 5.

1962

The Value Of the 2010 ACR/EULAR Rheumatoid Arthritis Classification Criteria For The Prognosis Of Early Arthritis: Evaluation Of Erosion Development With Ultrasonography. Nevsun Inanc, Fatma Alibaz-Oner, Meryem Can, Pamir Atagündüz and Haner Direskeneli. Marmara University, School of Medicine, Istanbul, Turkey.

Background/Purpose: The 2010 ACR/EULAR Rheumatoid Arthritis(RA) classification criteria was developed to diagnose the early arthritis patients who will progress destructive disease and to start early treatment. We aimed to investigate the value of these classification criteria for the prognosis of early arthritis patients with the evaluation of the longitudinal ultrasonographic(US) examination for the development of erosions.

Methods: The study included patients presenting with at least one swollen joints to "Early arthritis Clinic" between 2009 and 2012. The patients having symptom duration less than 24 months were recruited to the study. Clinical evaluation(tender/swollen joint counts, DAS28 and HAQ scores) and US examination of erosion at 2nd MCP, 5th MCP, 2nd PIP ulnar styloid and 5th MTP joints were performed prospectively at the lateral approach longitudinally and transversally for the determination of the erosion at baseline and 12months.

Results: A total of 71 patients (F/M:53/18) were recruited to the study. The mean age was 38.2± 14.2, mean symptom duration was 6.4 (0–24) months. At baseline assessment, 46.5% (n:33) of patients were classified as RA according to 2010 ACR/EULAR criteria and others were diagnosed as undiffererentiated arthritis(UA) after excluding other possible diagnosis.

At baseline, higher percentage of patients whom was diagnosed as RA according to 2010 ACR/EULAR criteria (44 % vs 23%, p= 0.072) were found to have erosive changes with the US examination. Furthermore, a tendency was observed for the progression of erosive disease, in terms of increased number of erosive joints, in patients diagnosed according to 2010 criteria vs patients diagnosed as UA (32% vs 10 %, p=0.072) at follow-up. Positive RF was also determined as a predictor of erosions by US (35% vs 11%, p=0.053).

Conclusion: Among patients with early arthritis fulfilling the 2010 ACR/EULAR RA criteria had erosive disease at diagnosis and increased frequency of erosions during the follow-up. Early evaluation of the joints by US can be used for the early detection of erosive patients which may predict the prognosis of RA.

Disclosure: N. Inanc, None; **F. Alibaz-Oner**, None; **M. Can**, None; **P. Atagündüz**, None; **H. Direskeneli**, None.

1963

Ultrasonography Is Helpful For Optimizing The Diagnosis Of Early Rheumatoid Arthritis. Maasa Hama, Darisuren Tsolmon, Kaoru Minegishi, Ryusuke Yoshimi, Yohei Kirino, Atsuhisa Ueda, Mitsuhiro Takeno, Ichiro Aoki and Yoshiaki Ishigatsubo. Yokohama City University Graduate School of Medicine, Yokohama, Japan.

Background/Purpose: 2010 ACR–EULAR criteria enable us to make diagnosis of early rheumatoid arhtiritis (RA) with no erosion revealed by X-ray. However, the criteria potentially possess two critical issues. One is that some seronegative patients with polyarthritis may be excluded from RA even if they met 1987 ACR criteria. The other is that seropositive patients with arthralgia may be included in RA even in absence of synovitis, if "no synovitis" is not appropriately proven. In this study we assessed the roles of ultrasonography (US) in the diagnosis of early rheumatoid arthritis when the new criteria were applied clinically.

Methods: We retrospectively examined 122 undiagnosed patients who first visited our hospital from 2009 to 2011 due to joint symptoms without any previous therapies except for NSAIDs. The patients who started to receive anti-rheumatic therapy during the one-year observation period were categorized into the RA group. At the study entry, 10 joints (second proximal interphalangeal, second and third metacarpophalangeal joints, wrists and knees) were assessed by US using gray-scale (GS) and power Doppler (PD) scoring.

Results: Fifty and 72 patients were divided into RA group and non-RA group, respectively. Fulfillment of the 2010 ACR-EULAR criteria in the RA group was 70% at the first visit and 96% at the end of study. When applying US synovitis to □esynovitis' in the scoring system of the 2010 criteria in addition to routine works, sensitivity of the criteria in RA diagnosis increased from 70% to 82% at the first visit. According to ROC analysis, diagnostic findings of US in early RA are the presence of more than 1 joint with GS score.

Table. ROC analysis of each US parameter in differentiation of RA from non-RA.

	AUC	Cut off value	Youden Index	sensitivity (%)	specificity (%)
No. of GS≥1 joints	0.735	4	0.373	72	65.3
No. of GS≥2 joints	0.76	1	0.481	80	68.1
No. of PD≥1 joints	0.753	1	0.458	68	77.8
Sum of GS score of 10 joints	0.766	5	0.427	76	66.7
Sum of PD score of 10 joints	0.754	1	0.444	68	76.4
tenosynovitis	0.608	1 (+)	0.444	34	87.5
synovitis in wrist	0.706	1 (+)	0.412	62	79.2

Conclusion: US contributes to making early diagnosis of RA, especially in patients having no clinically apparent arthritis and seronegative patients. It is also useful to determine the optimal initiation of anti-rheumatic therapy.

Disclosure: M. Hama, None; **D. Tsolmon**, None; **K. Minegishi**, None; **R. Yoshimi**, None; **Y. Kirino**, None; **A. Ueda**, None; **M. Takeno**, None; **I. Aoki**, None; **Y. Ishigatsubo**, None.

1964

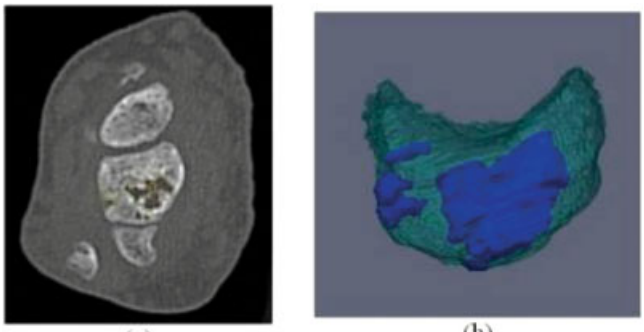
Quantitative Erosion Volume Measurement From Computed Tomography. Jeffrey W. Duryea[1], Daniel H. Solomon[2], Bing LU[3], Ruby Russell[1], Roger Han[1], Ellen M. Gravallese[4] and Jonathan Kay[5]. [1]Brigham and Women's Hospital, Boston, MA, [2]Harvard Medical School, Brigham and Women's Hospital, Division of Rheumatology, Division of Pharmacoepidemiology, Boston, MA, [3]Brigham & Women's Hospital and Harvard Medical School, Boston, MA, [4]UMass Memorial Medical Center, Worcester, MA, [5]UMass Memorial Medical Center and University of Massachusetts Medical School, Worcester, MA.

Background/Purpose: Rheumatoid arthritis (RA) causes two key structural changes that are visible on plain radiographs: narrowing of the joint space width (JSN) and erosion of the juxta-articular bone. Hand radiography is a low-cost and widely available tool to assess RA and is used extensively in clinical studies. However, plain radiography provides only a two-dimensional (2D) projection of structures that have a complex three-dimensional (3D) shape. Highly accurate quantification of erosion size will become increasingly important to use in longitudinal

studies of RA treatment and may also be useful to monitor drug therapy in routine patient care. Computed tomography (CT) provides superb imaging of bone margins and, as a 3D modality, it is ideal to measure erosion volume.

Methods: We have developed a semi-automated software method to segment (outline) the margins of erosions in 3D, from high-resolution CT scans of the hand and wrist, and to calculate erosion volume. A reader operates the software and guides the computer to segment the erosions on each CT slice. Figure 1 illustrates a CT slice with erosion (a) and its 3D rendering (b). The method was validated using CT scans of both hands and wrists from 5 subjects (10 hands) with moderate to severe RA. Each hand was scanned twice during a single session, after repositioning subjects between scans. The repositioning reproducibility for the 10 hands was quantified using intra-cluster correlation (ICC), the root-mean square standard deviation (RMSSD), and the coefficient of variation (CoV) (Table). For each scan, we measured the erosion volume of the total hand and wrist, as well as for two sub-regions: sub-region 1 included the radius, ulna, carpal bones and carpometacarpal (CMC) joints and sub-region 2 included the PIP, MCP, and DIP joints.

Results: See table. The total erosion volume for the 10 hands ranged from 34.5 mm^3 to 1,492.4 mm^3. The ICC values demonstrate excellent correlation. The RMSSD and CoV suggest that this technique should be capable of detecting erosion volume change on the order of 20 to 30 mm^3 or 4–7 percent.



(a) (b)

	Total	Subregion 1	Subregion 2
Intra-cluster correlation	1.00	0.99	0.97
Root Mean Square, Standard Deviation (mm^3)	22.9	17.3	30.1
Coefficient of variation	5.3%	4.0 %	7.0%

Conclusion: Our semi-automated high-resolution CT method reproducibly detects and quantifies the volume of juxta-articular erosions in RA and can be applied to studies of RA treatment to detect longitudinal changes in erosion volume.

Disclosure: J. W. Duryea, Eli Lily Inc., 2; **D. H. Solomon**, Lilly, Amgen, CORRONA, 2, Lilly, Novartis, BMS, Pfizer, 6, Lilly, BMS, Novartis, 9; **B. LU**, Lilly Inc., 2; **R. Russell**, Eli Lilly Inc., 2; **R. Han**, Eli Lilly Inc, 5; **E. M. Gravallese**, Eli Lilly Inc., 2; **J. Kay**, Ardea Biosciences, Eli Lilly, Fidia Farmacutici, SpA, Pfizer, Roche, Sanofi-Aventis, 2, Amgen, Baxter Healthcare Corporation, BMS, Celgene, fourteen22 Inc., Genentech, Hospira, Inc., Horizon Pharma, Inc., Janssen, Medac Pharma Inc., PanGenetics, B.V., Pfizer, Roche, Savient Pharmaceuticals, Inc., Sun Pharmaceutical Industries Ltd., UCB,, 5.

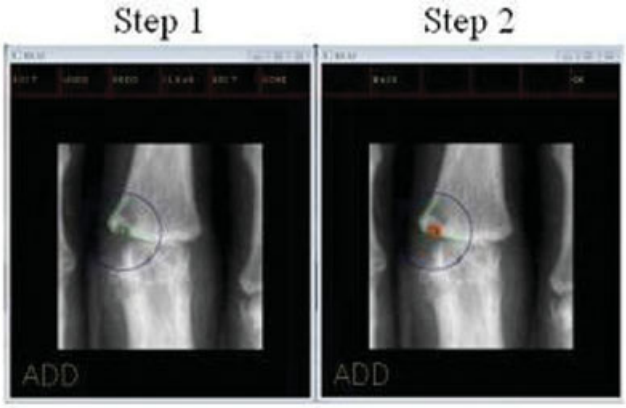
1965

Performance Of a Computer-Based Method To Measure Erosions In Rheumatoid Arthritis: A Longitudinal Study. Jeremy Wortman[1], Stacy Smith[1], Frederick Wolfe[2] and Jeffrey W. Duryea[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]National Data Bank for Rheumatic Diseases, Wichita, KS.

Background/Purpose: To describe the methodology of a novel computer-based technique for outlining erosions on plain radiographs in rheumatoid arthritis (RA) patients, and assess the responsiveness and correlation with the Sharp erosion score.

Methods: A sample of 112 patients with mild to severe rheumatoid arthritis, for whom serial (baseline and one follow-up) bilateral hand radiographs were available, was obtained from the National Databank for Rheumatic Diseases. A radiologist, blinded to time point, used the software to outline the erosions at each MCP and PIP joint. Severely diseased joints were excluded. The computer-based method partially automates the process of outlining erosions on hand radiographs, and calculates erosion area (see figure). For 99 subjects, the total Sharp erosion score for the MCP and PIP joints of digits 2 to 5 was available. Because all radiographs were acquired prior to the advent of DMARDS, we expected radiographic damage to increase with time. Therefore, the chronological order of serial radiographs was used as the standard to assess performance. The percent change and standardized response mean (SRM) were used to quantify responsiveness, and linear regression established the correlation with the Sharp score.

Results: 78% of subjects showed an increase in erosion area over time, and 5% showed no change. Changes in the computer-based and Sharp methods were highly correlated ($r = 0.75$, $p < 0.01$). The SRM was 0.46. The reader time was approximately 0.6 minutes per hand radiograph.



Conclusion: The computer-based method is fast and can accurately assess progression of disease in patients with RA. The high correlation of the software measure with the Sharp score suggests it can be used as a surrogate for this measure.

Disclosure: J. Wortman, None; **S. Smith**, None; **F. Wolfe**, None; **J. W. Duryea**, None.

1966

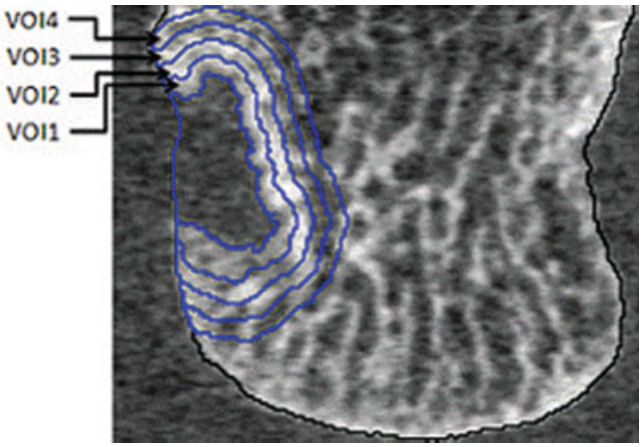
Longitudinal Quantification Of Bone Erosions In Patients With Rheumatoid Arthritis Using High-Resolution Computed Tomography. Dominique Toepfer, Stephanie Finzel, Oleg Museyko, Georg Schett and Klaus Engelke. University of Erlangen-Nuremberg, Erlangen, Germany.

Background/Purpose: Diagnosis and monitoring of patients with rheumatoid arthritis (RA) is based on radiographs or MRI, therefore the sensitivity to detect small changes of bone erosions is limited. We developed a fully 3D automated method for precise quantification of longitudinal changes of erosion size and shape in high resolution peripheral quantitative computed tomography (HR-pQCT) images of the metacarpophalangeal (MCP) joints.

Methods: HR-pQCT images of the second to fourth MCP joint from 17 RA patients were acquired on an XtremeCT scanner (Scanco, Switzerland) with an isotropic voxel size of 82μm. Patients were scanned at baseline and after 1.1±0.6 years. In order to reduce precision errors baseline (BL) and follow-up (FU) datasets were 3D rigidly registered using the periosteal surfaces to ensure identical segmentation of the cortical breaks. Erosions were then segmented independently in both BL and FU data. We evaluated change in volume, surface area, and sphericity (a measure between 0 and 1 for how closely the erosion resembles a sphere). We also dilated each erosion surface to obtain 4 concentric volumes of interest (VOIs 1–4, see figure), in which BMD was measured. The patients were treated using either Methotrexate (MTX, N=10, mean age±SD 55.8±19 years, 2 males) or tumor necrosis factor inhibitors (TNFi, N=7, 45.5±12.8 years, 1 male) and group differences were also analyzed.

Results: 37 Erosions were analyzed in both BL and FU. % change in erosion volume correlated significantly ($p<0.01$) in all 4 VOIs with % change in BMD. Spearman's rho were −0.58 (VOI1), −0.64 (VOI2), −0.62 (VOI3) and −0.45 (VOI4). % differences (Mean±SD) between the

two treatment groups were 14.3±51.3, 13.8±44.7 and −2.7±10 in the MTX group (21 erosions) for volume, surface area and sphericity, respectively, and −11±31.5, −8.9±27.6 and 3.9±17.9 in the TNFi group (16 erosions). % BMD changes in VOIs 1 to 4 were −0.6±11.2, 0.6±12.2, −0.1±9.8 and −0.6±7.8 in the MTX group and 7.7±18.5, 10.7±23.5, 8.6±16.8 and 5.8±12.4 in the TNFi group. These differences were not significant, probably due to the small sample size.



Conclusion: We developed an automated, precise and fully 3D framework for longitudinal evaluation of changes in bone erosions in HR-pQCT images. Under treatment changes in erosion volume negatively correlated with BMD changes in the vicinity of the erosion. The loss of periarticular bone mass as a sign of inflammatory activity in RA has already been suggested in radiographic studies; interestingly, BMD did not further decrease (MTX) or increased (TNFi) after one year. However, it is still unclear, whether this is of predictive value for monitoring of disease activity. A limitation of the HR-pQCT technique are motion artifacts due to long scan times (~8min), impairing image quality.

Disclosure: D. Toepfer, None; **S. Finzel**, None; **O. Museyko**, None; **G. Schett**, None; **K. Engelke**, None.

1967

Computer-Aided and Manual Quantifications Of MRI Synovitis, Bone Edema, Erosion and Semi-Quantitative Cartilage Loss In Rheumatoid Arthritis. Haitao Yang[1], Julien Rivoire[2], Michael Hoppe[2], John B. Imboden[2], Thomas M Link[2] and Xiaojuan Li[2]. [1]The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [2]University of California, San Francisco, San Francisco, CA.

Background/Purpose: Early diagnosis and early detection of therapeutic response within the so called "window of opportunity" in rheumatoid arthritis (RA) are essential for superior clinical and functional outcome. Magnetic Resonance Imaging (MRI) is the only modality for allowing simultaneous assessment of all the structural changes involved in RA such as synovitis, cartilage damage, bone marrow edema pattern, bone erosion and tendonsynovitis. Fast and reliable MRI quantitative methods are significant to evaluate disease activity and assist management for RA patients.

The objectives of this study were to investigate the reliability of multiple computer-aided and manual quantifications for MRI synovitis, bone marrow edema pattern, erosion and semi-quantitative cartilage loss of wrists with RA.

Methods: Wrist imaging was performed with 3T MRI in 16 patients with RA and 3 healthy controls. Computer-aided semiautomatic quantifications for synovitis volume and perfusion (maximum enhancement (E) and steepest slope (S)), bone marrow edema pattern (BMEP) volume, signal intensity and perfusion (E and S), and erosion dimension were measured using in-house developed software, and compared with the OMERACT-RAMRIS classification. In addition a semi-quantitative MRI wrist cartilage loss score system was developed. Intra-Class Correlation (ICC) coefficients were calculated to examine intra- and inter-operator reproducibility; Spearman correlation coefficients were calculated between MRI quantifications, RAMRIS, and radiographic Sharp van der Heijde score.

Results: The intra- and inter-observer ICC were 0.97 and 0.89 for synovitis volume quantification, respectively. The intra- and inter-reader ICC for erosion dimension measurement were 0.91 and 0.93, respectively. The synovitis volume, BMEP volume and signal intensity, and erosion dimension were significantly correlated with the corresponding RAMRIS sub-scores (r from 0.727 to 0.900). Regarding perfusion, no significant correlation was found between synovitis perfusion, BMEP perfusion and RAMRIS scores except for between synovitis E, synovitis volume and synovitis RAMRIS ($r = 0.928$, $p = 0.002$; $r = 0.798$, $p = 0.017$), and between synovitis and BMEP perfusion E ($r = 0.900$, $p = 0.037$). The intra- and inter-reader ICC of the MRI cartilage loss score were 0.98 and 0.99 respectively. The MRI cartilage loss score was significantly correlated with the hand Sharp van der Heijde joint space narrowing score ($r = 0.635$, $p = 0.008$).

Conclusion: Multiple computer-aided and manual quantitative methods can be used to quantify MRI pathologies in RA and showed excellent reliability compared with RAMRIS. The quantitative methods have the potential to be more sensitive for detecting early and subtle changes than conventional scoring systems, and thus may be helpful with early diagnosis and providing critical monitoring after treatment.

Disclosure: H. Yang, None; **J. Rivoire**, None; **M. Hoppe**, None; **J. B. Imboden**, None; **T. M. Link**, None; **X. Li**, None.

1968

A Novel, Feasible and Reliable Method Of Radiographic Scoring Of Rheumatoid Arthritis. Priyanka Vashisht[1], Harlan Sayles[2], Ted R. Mikuls[3] and Alan R. Erickson[4]. [1]Creighton University Medical Center, Omaha, NE, [2]University of Nebraska Medical Center, Omaha, NE, [3]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [4]Omaha VA and University of Nebraska Medical Center, LaVista, NE.

Background/Purpose: Radiographs of the hands and feet are used to evaluate the disease course of rheumatoid arthritis (RA) with several scoring systems previously described. However, most of them are time-intensive, require specialized expertise and are thus not practical for use in routine clinical care. We assessed a novel method of radiographic scoring using the VARA (Veterans Affairs RA) registry. The goal of our study was to compare radiographic scores using the 'VARA method' with a well-established scoring method (Sharp score) and to assess the correlations and agreement between these two approaches.

Methods: The study was done on a multi-center database of veterans with RA. A total of 198 patients were studied. Bilateral hand radiographs were read by an experienced rheumatologist trained in the Sharp scoring method and radiographic scores were calculated independently by the Sharp and VARA methods. The simplified VARA method involves assessments for the presence of erosions and joint space narrowing in 3 joint regions of the hand- including wrist, metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints. The same individual joints are also evaluated for the Sharp score. For VARA scoring, the presence of erosion or narrowing each gives a score of 1 and absence gives a score of 0. The maximum erosion and narrowing score for each hand is 3 each and minimum score is 0. Thus, the range for the total cumulative VARA score is 0 to 6 while the range in Sharp score is 0 to 314.

Correlations of the two systems were examined by calculating non-parametric Pearson correlations while formal agreement for the two approaches in capturing the presence of erosions and narrowing were assessed through calculation of a kappa coefficient. A sub-analysis was done to estimate time needed to complete the scoring for each individual set of radiographs.

Results: Of the RA patients examined (n=198), there were moderate and highly statistically significant correlations between the VARA and Sharp scores ($r = 0.66$, $p < 0.001$ for erosion score and $r = 0.68$, $p < 0.001$ for narrowing score). The average time needed for VARA scoring is 3.3 minutes, whereas time for the Sharp score is 7–9 minutes. Additionally, there is near perfect agreement between the 2 methods with highly significant p-values in the detection of any erosion or any joint space narrowing (kappa = 0.984 for erosion and kappa = 1.00 for narrowing; p-value < 0.001).

Conclusion: The VARA method demonstrates significant correlations with the standard radiographic Sharp scoring method. The average calculation time decreases by 2/3rd when VARA method is adopted and it appears to provide a meaningful quantitative measure of global joint involvement in RA at a single point of time. Potential disadvantages of this novel scoring method include limitations in sensitivity that may preclude its use in identifying small changes in disease progression over a period of time.

Nevertheless, the VARA method is a very practical method of radiographic scoring and may be particularly useful for observational studies and in clinical practice where quantitative assessments of joint damage at a single time point are needed.

Disclosure: P. Vashisht, None; **H. Sayles**, None; **T. R. Mikuls**, None; **A. R. Erickson**, None.

1969

Ankle Joint Involvement In Rheumatoid Arthritis. An Ultrasound Study Using High Resolution- and Colour Doppler Ultrasound. Mohammed Alsuwaidi[1], Boris P. Ehrenstein[1], Martin Fleck[2] and Wolfgang Hartung[1]. [1]Asklepios Clinic Bad Abbach, Bad Abbach, Germany, [2]University Medical Center of Regensburg, Regensburg, Germany.

Background/Purpose: Despite a pivotal role for RA patients mobility, the ankle joints are frequently neglected, and omitted in activity scoring systems including DAS 28. In addition, only few studies have assessed pathologies detected by ultrasonography of the ankle in symptomatic RA patients (1). Therefore, the type and degree of involvement of the ankle joints were evaluated in established RA patients regardless of symptomatology or duration of illness utilizing standardized high resolution musculoskeletal ultrasound (MSUS) including colour Doppler ultrasonography (CDUS).

Methods: A total number of 89 ankle joints of 45 consecutive RA patients fulfilling the ACR/EULAR classification criteria 2010 were examined using MSUS (*Logic E9, GE Healthcare, Buckinghamshire, GB with* a *ML6–15 linear probe with 6–15 MHz*) and CDUS according to the EULAR MSUS guidelines (2). In addition, the talonavicular, the intertarsal- and the tarso-metatarsal joints were investigated. Furthermore, ankle pain (VAS score 0–10) and loss of function were recorded for each patient individually.

Results: 45 RA patients (32 female, 13 male) with a median age of 61 years (range 28–81) and a disease duration of 5 years (0–43 range) were enrolled in our study. The median DAS28 was 5,0 (range 0,8 −7,8). Ankle pain was recorded for 27 patients, whereas 18 patients were completely asymptomatic regarding the ankles. Overall, the predominant pathology was arthritis of the tibiotalar and/or talonaviclar joint in 64% of the patients (29 out of 45), followed by tenosynovitis of the flexor tendons in 44% of the patients (20 out of 45). Pathologic B-mode findings were observed in 85% of the symptomatic patients (23/27), however, also 61% of the asymptomatic patients (11/18) exhibited pathologic B-mode findings (p=0.06). CDUS activity was higher in the subgroup of symptomatic patients with 33% (9/27) compared to 17% of asymptomatic patients (3/18) (p=0.13), for detailed information table 1.

Pathologies Joints	Arthritis only tibiotalar	Arthritis tibiotalar and talonavicular	Arthritis only talonavicular	Tenosynovitis (M. tibialis posterior +/− or M. flexor digitorum)	CDUS positive Arthritis or Tenosynovitits
All ankles (n = 89)	29	16	1	20	12
Symptomatic patients (n = 27)	17	12	1	15	9
Asymptomatic patients (n = 18)	12	4	0	5	3

Conclusion: Most frequent pathologies detected by MSUS were arthritis of the tibiotalar and talonavicular joint, followed by tenosynovitis of the flexor tendons. Pathologic findings are also common in asymptomatic patients with RA, whereas CDUS activity is predominately observed in symptomatic patients.

References:

[1] Suzuki T, Okamoto A, Clin Exp Rheumatol 2013, 31 (2): 281–284. [2] Backhaus M, Burmester G-R, Gerber T et al., Ann Rheum Dis 2001, 60: 641–649

Disclosure: M. Alsuwaidi, None; **B. P. Ehrenstein**, None; **M. Fleck**, None; **W. Hartung**, None.

1970

The Utility Of Fluorescence Optical Imaging For Detecting Clinically Silent Synovitis Of The Hands and Wrists. Yogan Kisten[1], Noémi Györi[2], Hamed Rezaei[1], Anna Karlsson[2], Carolina Romanus[2], Ronald van Vollenhoven[3] and Erik af Klint[1]. [1]The Karolinska Institute, Stockholm, Sweden, [2]Unit for Clinical Therapy Research Inflammaroty Diseases (ClinTRID) Department of Medicine, the Karolinska Insitute, Stockholm, Sweden, [3]Unit for Clinical Research Therapy. Inflammatory Diseases (ClinTrid), Karolinska Institute, Stockholm, Sweden.

Background/Purpose: The detection of subclinical synovial inflammation ("silent synovitis") would be of critical importance for the detection of rheumatoid arthritis (RA) in its earliest pathophysiological stage ("pre-RA"), and it has been suggested that ultrasound (US) with power Doppler (PD) can be a useful technology to achieve this. Fluorescence optical imaging (FOI,"Rheumascan") is a novel imaging modality for the hands based on the use of an intravenous fluorescence dye that allows imaging of the hands with increased optical signal in areas of high perfusion and/or capillary leakage. Here, we investigated whether FOI could be used in lieu of US/PD for ascertaining subclinical syovitis in the hands and wrists.

Methods: A total of 748 joints of the bilateral hands and wrists, including 3 wrist joints, 5 MCPs, 5 PIPs, and 4 DIPs in 22 patients (15 female, 7 male) aged between 19 and 84 years old, with inflammatory arthritis (RA:9, JIA, gout psoriatic arthritis, SLE, and other diagnoses, 1–2 each) were examined clinically, by US and FOI. Joints were considered clinically inflamed when both swollen and tender, and non-inflamed otherwise. Ultrasound was considered positive for synovitis if both thickening on grey scale and Doppler signal were present. FOI was considered positive by visual inspection of the images.

Results: Out of 748 joints, 71 (9%) were considered inflamed by clinical examination and 677 were not. Of the clinically non-inflamed joints, exactly 100 were inflamed by US. Of these joints, 80 were inflamed by FOI and 20 were not. Thus, the sensitivity of FOI for detecting sub-clinical synovitis when defined as a positive US in the absence of clinical inflammation was 80%. Out of the 577 joints that were non-inflamed clinically and non-inflamed by ultrasound, 26 had inflammation by FOI, yielding a specificity of 95%.

Conclusion: Under the assumption that US can correctly identify sub-clinical synovitis in clinically non-inflamed joints (using the combination of clinical examination and US as the "gold standard"), the sensitivity of FOI for detecting subclinical synovitis in the hands and wrists is 80% and the specificity 95%. These metrics suggest that it may be a useful tool in the setting of identifying patients with very early synovial inflammation of the hands and/or wrists.

Disclosure: Y. Kisten, None; **N. Györi**, None; **H. Rezaei**, None; **A. Karlsson**, None; **C. Romanus**, None; **R. van Vollenhoven**, None; **E. af Klint**, None.

1971

The Four Finger Examination Technique Is Superior To The Standard Two Finger Technique To Detect Metacarpal Phalangeal Joint Swelling In Rheumatoid Arthritis - A Validation By Power Doppler Ultrasound. Mohammed Omair[1], Pooneh Akhavan[1], Ali Naraghi[1], Deborah Weber[2], Shikha Mittoo[1], Melissa Weber[2], Juan Xiong[3] and Edward C. Keystone[1]. [1]Mount Sinai Hospital/University of Toronto, Toronto, ON, [2]Mount Sinai Hospital, Toronto, ON, [3]Mount Sinai Hospital, University of Toronto, Toronto, ON.

Background/Purpose: Swollen joints (SJs) are a strong clinical predictor of radiographic progression in rheumatoid arthritis (RA). The metacarpal phalangeal joints (MCP) SJs are particularly relevant since they are the earliest joints demonstrating radiographic progression. Thus, more sensitive detection of less obvious SJs is important for improved assessment of disease activity.

A novel four finger (FF) examination technique was developed to be more sensitive than the two finger (TF) technique in the detection of less clinically apparent joint swelling.

Methods: To compare the sensitivity of the FF vs. TF technique to detect synovitis by ultrasound (US). We compared the FF vs. TF examination technique in 180 MCPs in 18 RA patients. The population was comprised of 94.4% females, mean age of 55.8 years and mean disease duration of 19.9 yrs. Patients were examined twice on the same day by 4 rheumatologists; 2 performed FF and 2 used the TF technique. SJs

were determined by palpation defined by being either (1) ballotable or (2) spongy (non-ballotable swelling). TJs were also assessed. We evaluated the agreement between the SJ/TJ examination techniques with US using grey scale, power Doppler (PD) positivity, or the presence of an effusion.

Results: Consistent with previous literature, the inter-observer agreement (IA) using Kappa statistics was poor to moderate for both SJ techniques. We therefore evaluated only joints in which there was agreement between the 2 examiners for each SJ technique. With the TF and FF techniques respectively, there were 115 & 134 SJs in which there was agreement for the joints being ballotable and 99 & 122 SJs for being spongy. The Kappa agreement between FF and TF techniques respectively, for ballottement by PD was 0.55 vs 0.27; by grey scale 0.35 vs. 0.12, and by effusion: 0.18 vs. 0.08. For SJ detected by being spongy, the relationship between FF and TF was the same, but the Kappas were lower. The agreement between TJs and US was extremely poor with mean Kappas for the 4 examiners for PD of 0.07; for grey scale: 0.06 and for effusion: −0.08.

Conclusion: The results of this study demonstrate that for MCPs, the FF technique is more sensitive than the TF technique for detection of synovitis as determined by US and therefore a better examination technique for clinical decision making. Of significance, the data provide strong support for the importance of detecting SJs (rather than TJs) as a prognostic guide for structural damage in RA.

Disclosure: M. Omair, None; **P. Akhavan**, None; **A. Naraghi**, None; **D. Weber**, None; **S. Mittoo**, None; **M. Weber**, None; **J. Xiong**, None; **E. C. Keystone**, None.

1972

Erosion Case Definition and Scoring Reliability Exercise Using a New Outcome Measurement Tool, High-Resolution Peripheral Quantitative Computed Tomography, In Rheumatoid Arthritis. Cheryl Barnabe[1], Dominique Toepfer[2], Hubert Marotte[3], Ellen-Margrethe Hauge[4], Andrea Scharmga[5], Roland Kocijan[6], Sebastian Kraus[2], Kresten K. Keller[4], Joost de Jong[5], Jeroen Williams[5] and Stephanie Finzel[2]. [1]University of Calgary, Calgary, AB, [2]University of Erlangen-Nuremberg, Erlangen, Germany, [3]Inserm U1059, Saint-Etienne, France, [4]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [5]Maastricht University, Maastricht, Netherlands, [6]Academic Teaching Hospital of Medical University Vienna, Vienna, Austria.

Background/Purpose: High-resolution peripheral quantitative computed tomography (HR-pQCT) is a novel imaging instrument for bony damage in rheumatoid arthritis (RA). Agreement on a case definition for pathologic erosions is required given the sensitivity of HR-pQCT for detecting cortical bone disruptions. The reliability of erosion detection and measurement between readers is crucial to evaluate with this new technology, as HR-pQCT is undergoing validation as an outcome measurement tool.

Methods: HR-pQCT images of the 2nd and 3rd metacarpophalangeal joints of RA patients and control subjects were used in an iterative process to achieve consensus on a case definition for erosions. This case definition was applied by 10 independent readers to score 82 joints. Each surface (radial, ulnar, palmar, dorsal) of the proximal phalanx and metacarpal head were characterized for image quality, the presence of a cortical break, the appearance of the cortical defect (physiological or pathological) and a total count of the number of pathologic erosions. Pathologic erosions were further characterized in 2 perpendicular planes for their maximum width and depth.

Results: The case definition of erosion was based on the size and shape of the defect so as to eliminate physiological (eg vessel channel) defects. Of the 656 surfaces analyzed in the reliability exercise, 6 (0.9%) were felt to be of inadequate quality for analysis by the 10 readers and were removed. Inter-reader reliability for erosion detection was excellent with a kappa score of 0.9024 ($p<0.0001$), with higher kappa scores between experienced readers. Images with discrepant scoring by more than 2 readers were reviewed as a group a second time, with resolution of all cases except for 2 which were lower quality images with multiple bony pathologies overlapping each other(eg vessel channels with superimposed osteophytes masquerading as erosions). Erosion size ranged from 0.16 to 0.89 mm in maximal width and 0.028 to 0.801 mm in maximal depth, with up to 6.3% variability in measurement between readers.

Conclusion: We have devised a new case definition for erosions visualized with a novel sensitive imaging tool. Inter-reader reliability for erosion detection and measurement is high, yielding promise to use HR-pQCT as an outcome measurement tool for bony damage.

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1973

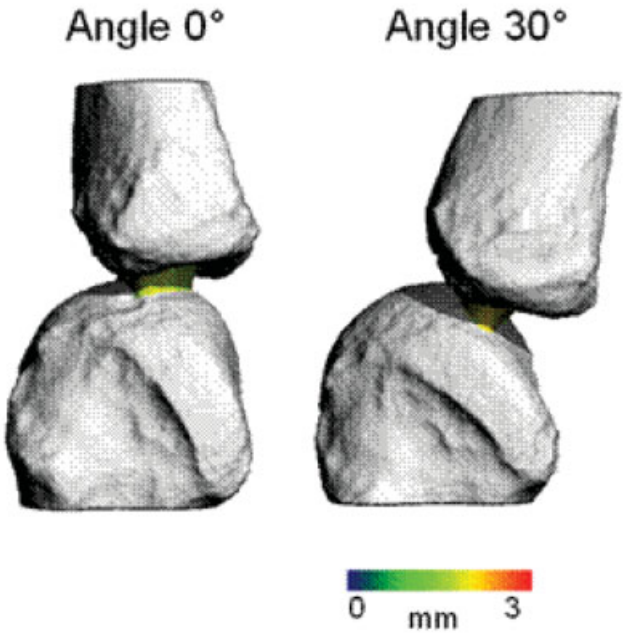
Importance Of Hand Positioning In 3D Joint Space Morphology Assessment. Stephanie Boutroy[1], Elodie Hirschenhahn[1], Emile Youssof[2], Hervé Locrelle[2], Thierry Thomas[2], Roland Chapurlat[3] and Hubert Marotte[2]. [1]INSERM U1033 and University of Lyon, Hôpital Edouard Herriot, Lyon, France, [2]INSERM U1059 and University Hospital, Hôpital Nord, Saint-Etienne, France, [3]INSERM UMR 1033 and University of Lyon, Hôpital Edouard Herriot, Lyon, France.

Background/Purpose: Precise quantification of joint space morphology (JSM) is an important factor for early diagnosis and monitoring of disease activity and therapeutic responses in rheumatoid arthritis (RA). Patients with active RA usually present painful, stiff and swollen joints and have difficulties in stretching their joints. Positioning of these patients is a major concern for accurate assessment as it is responsible for an important variability in cross-sectional and longitudinal studies.

We have developed a method to characterize 3D JSM of the metacarpophalangeal (MCP) joint by high resolution peripheral quantitative computed tomography (HR-pQCT). We assessed the impact on JSM of measurements performed with a 0° and a 30° flexion of the MCP joints, which we assume would be convenient for most active RA patients.

Methods: We performed HR-pQCT on the second metacarpophalangeal (MCP) joints of twelve *ex vivo* hands (3 men, 3 women, mean age = 77±9 yrs) and developed an automated algorithm to compute joint space volume (JSV), mean, minimal and maximal joint space width (JSW, JSW.MIN, JSW.MAX), as well as its distribution (JSW.SD) and asymmetry (JSW.AS, ratio of JSW.MAX over JSW.MIN). MCPs were scanned with a 0° and a 30° degree angle, with an inclined custom cast. The effects of different hand positioning were assessed by paired t-test.

Results: Angles between metacarpal and phalangeal bones were retrospectively verified on the reconstructed 3D images, with mean values of 5.2±4.5° (ranging from 0° to 12°) and 29.5±3.7° (ranging from 25° to 35°).



Positioning markedly impacted the mean and maximum values of joint space width. JSW was 16.4% thicker (2.00±0.38 vs. 1.72±0.30 mm; p=0.001) and JSW.MAX was increased by 12.5% (2.32±0.34 vs. 2.07±0.34 mm; p=0.001) when measured at 30° compared to 0° respectively. Its impact was less marked on joint space volume (64±22 vs. 59±17 mm^3; 8.9%; p=0.29), minimum joint space width (1.28±

0.22 vs. 1.18±0.31 mm; 8.7%; p=0.23) and asymmetry of joint space width (1.85±0.30 vs. 1.68±0.42; 10.2%; p=0.09), at 30° compared to 0° respectively. The heterogeneity of the joint space width (JSW.SD) was not affected by hand positions (0.22±0.09 vs. 0.21±0.08 mm; p=0.88).

Conclusion: This study suggests that positioning remains a major concern even with a 3D quantification of JSM. On the basis of active RA patient comfort, the use of a fixed-inclined cast would probably be the most appropriate method to accurately follow-up disease activity.

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1974

Assessing Validity Of Low Field Magnetic Resonance Imaging (MRI) for Joint Inflammation and Damage In Wrist/Hand Rheumatoid Arthritis (RA) - A Systematic Literature Review (SLR). OM Troum[1], OL Pimienta[1], TG Woodworth[2], O Morgacheva[2], V Ranganath[3] and D E Furst[2]. [1]Keck School of Medicine, University of Southern California, Los Angeles, CA, [2]David Geffen School of Medicine, University of California, Los Angeles, CA, [3]David Geffen School of Medicine, UCLA, Los Angeles, CA.

Background/Purpose: Radiographic scoring of erosions and joint space narrowing (JSN) of the hand/wrist is standard to evaluate RA joint damage for regulatory approval of DMARDs; however, MRI has demonstrated its superiority in assessing joint inflammation and damage in clinical trials. MRI field strength impacts feasibility, image quality and cost. Measurement methods using high field (hf) ≥1.0 tesla (T) MRI requires large machines and specialized space. Low field (lf) <1.0T MRI has also demonstrated utility in clinical trials and is easily performed in a clinical office setting. We report the results of an SLR examining Outcome Measures in Rheumatology Clinical Trials (OMERACT) RA MRI scoring (RAMRIS) validation for lf images of RA wrist/hand.

Methods: We searched PubMed with Cochrane hedge for articles from 1970 to Aug 2012 using search terms enabling relevant data extraction. Data included: demographics/RA features in adults, MRI field strength (<1.0 T), wrist/hand images assessing ≥1 joint feature: synovitis, bone marrow edema (BME)/osteitis, erosions, JSN, tenosynovitis, in addition to measurement method and validity evidence. We applied OMERACT validity definitions: face, criterion, content, construct, also assessing reliability, responsiveness, discrimination, and feasibility. Quality was determined by Cochrane Handbook criteria, adapted for imaging research.

Results: 35 lf MRI articles met criteria for extraction. RAMRIS was most often used, as with our previous SLR evaluating ≥1.0T MRI. Altogether, 16 articles using <1.0T/RAMRIS were analyzed, seeking validated MRI measures: 0.2T (13 articles, including 3 RCTs), 0.6T (2 articles), and 0.3T (1 article). 5 articles compared lf to high field (hf) MRI. Table 1 shows lf MRI validation data. There is indirect criterion validity for synovitis and erosions: 2 articles compared lf to hf MRI for synovitis and 2 others for erosions. One study provided good erosion score correlation between lf MRI and computed tomography, and another one with x-ray. Validating data with 0.2T included prediction of x-ray progression, sensitivity to change by 4 weeks, and intra/inter reliability for synovitis, BME, and erosions. Data currently lacking include discrimination for synovitis, BME, erosions, construct discriminant for erosions, and validation for JSN or tenosynovitis.

Table 1. Number of articles providing validity data for RAMRIS measurement with lf MRI

Validity Feature	Content	Construct Discriminant	Construct Convergent	Responsiveness to change	Intra-rater reliability	Inter-rater reliability	Discrimination
Definition	Measures across age range, disease duration, treatments	Correlation with clinical assessment of joint status	Correlation between scores - same health component- 2 different instruments	Sensitivity to change	Within reader ICCs	≥2 readers ICCs	Differentiates between treatment groups
Synovitis	+7	+3	+2	+4	+3	+4	0
Osteitis/BME	+4	+1	+4	+3	+3	+2	0
Erosions	+7	0	+3	+5	+4	+3	0
JSN	0	0	0	0	0	0	0
Tenosynovitis	+1	0	0	0	0	+1	0

Conclusion: Using a rigorous PRISMA-compliant SLR to examine low field MRI/RAMRIS of the RA wrist/hand, we found 0.2T MRI is partially validated to measure synovitis, BME/osteitis, and erosions. To finalize validation, evidence for discrimination between treatment groups for synovitis, BME, erosions, and discriminant construct validity for erosions are needed.

Disclosure: O. Troum, Bristol Myers Squibb, 2; **O. Pimienta**, Bristol Myers Squibb, 2; **T. Woodworth**, Bristol Myers Squibb, 2; **O. Morgacheva**, None; **V. Ranganath**, None; **D. E. Furst**, None.

1975

Cardiovascular Risk Stratification In Rheumatic Diseases: Carotid Ultrasound Is More Sensitive Than Coronary Artery Calcification Score To Detect Subclinical atherosclerosis In Patients With Rheumatoid Arthritis. Francisco Ortiz-Sanjuán[1], Alfonso Corrales[2], José Antonio Parra[3], Carlos González-Juanatey[4], Montserrat Santos[1], Javier Rueda[1], Ricardo Blanco[2], Vanesa Calvo-Río[1], Javier Loricera[1], Javier Llorca[5] and Miguel A González-Gay[1]. [1]Hospital Universitario Marqués de Valdecilla. IFIMAV. Santander. Spain, Santander, Spain, [2]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain, [3]Radiology Division, Hospital Universitario Marqués de Valdecilla, Santander, Spain, [4]Cardiology Division, Hospital Lucus Augusti, Lugo, Spain, [5]School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), Santander, Spain.

Background/Purpose: Rheumatoid arthritis (RA) is a disease associated to accelerated atherogenesis leading to increased incidenceof cardiovascular (CV) mortality. Adequate stratification of the CV risk in patients with RA is still far from being completely established. Several validated noninvasive imaging techniques may be useful to determine subclinical atherosclerosis, such as the assessment of carotid intima-media thickness (cIMT) and the presence of plaques by carotid ultrasonography (US) and the assessment of coronary artery calcification (CAC) by the Multi-Detector Computed Tomography (MDCT). Objective: To determine the ability of CAC Score (CACS) and carotid US to detect subclinical atherosclerosis in patients with RA.

Methods: A set of 104 consecutive RA patients without history of CV events was studied to determine CACS, cIMT and carotid plaques. The Systematic Coronary Risk Evaluation (SCORE) modified according to the EULAR recommendations (mSCORE) was also assessed.

Results: The mean disease duration was 10.8 years, 72.1% had rheumatoid factor and/or anti-CCP positivity and 16.4% extra-articular manifestations. Nine were excluded because they had type 2 diabetes mellitus or chronic kidney disease. CV risk was categorized in the remaining 95 RA patients according to the mSCORE as follows (Table 1): low (n=21), moderate (n=60) and high/very high risk (n=14). Most patients with low mSCORE (16/21; 76.2%) had normal CACS (zero), and none of them CACS>100. However, a high number of patients with carotid plaques was disclosed in the groups with CACS 0 (23/40; 57.5%) or CACS 1–100 (29/38; 76.3%). Seventy-two (75.8%) of the 95 patients fulfilled definitions for high/very high CV as they had mSCORE ≥5% or mSCORE <5% plus one of the following findings: severe carotid US findings (cIMT>0.9 mm and/or plaques) or CACS>100 (Table 2). A CACS>100 showed sensitivity similar to mSCORE (23.6% versus 19.4%). In contrast, the presence of severe carotid US findings allowed identifying most patients that met definitions for high/very high CV risk (70/72; sensitivity 97.2% [95% CI: 90.3–99.7]).

Table 1. SCORE risk, mSCORE risk im 95 RA patients without CV events. EULAR mSCORE according to the CACS>100, cIMT > 0.90 mm and carotid plaques

	SCORE	mSCORE	mSCORE CACS	mSCORE Carotid US cIMT	mSCORE Carotid US	mSCORE Carotid US cIMT >0.90 mm and/or carotid plaques n=70 (%)
Cardiovascular Risk	n	n	CACS >100 n = 17 (%)	>0.90 mm n=14 (%)	Carotid plaques n=69 (%)	
Low (<1%)	21	21	0/21 (0.0)	0/21 (0.0)	7/21 (33.3)	7/21 (33.3)
Moderate (≥1% and <5%)	63	60	12/60 (20.0)	8/60 (13.3)	51/60 (85.0)	51/60 (85.0)
High (≥ 5% and <10%)	9	10	4/10 (40.0)	5/10 (50.0)	8/10 (80.0)	9/10 (90.0)
Very High (≥10%)	2	4	1/4 (25.0)	1/4 (25.0)	3/4 (75.0)	3/4 (75.0)
High plus Very High	11	14	5/14 (35.7)	6/14 (42.8)	11/14 (78.6)	12/14 (85.7)

Table 2. Sensitivity of high/very high CV risk in RA patients without CV events, using EULAR mSCORE, carotid US findings (cIMT>0.90 mm or plaques) or CACS >100

Gold standard	n=72/95
mSCORE >5%	n=14 of 72 19.4% (95% CI:11.1–30.5)
CACS >100	n=17 of 72 23.6% (95% CI:14.4–35.1)
cIMT >0.90 mm and/or carotid plaques	n=70 of 72 97.2% (95% CI: 90.3–99.7)
mSCORE >5% or mSCORE <5% plus CACS >100	n=26 of 72 36.1% (95% CI:25.2–48.3)
mSCORE >5% or nSCORE <5% plus one of the following: cIMT >0.90 mm or carotid plaques	n=72 of 72 100% (95% CI:95.0–100)

Note: Gold Standard for high/very high cardiovascular risk: a) mSCORE ≥5% or b) mSCORE <5% plus one of the following: severe carotid US findings (cIMT>0.90 mm or carotid plaques) or CACS>100

Conclusion: Carotid US is more sensitive than CACS for the detection of subclinical atherosclerosis in RA.

Disclosure: F. Ortiz-Sanjuán, None; **A. Corrales**, None; **J. A. Parra**, None; **C. González-Juanatey**, None; **M. Santos**, None; **J. Rueda**, None; **R. Blanco**, None; **V. Calvo-Río**, None; **J. Loricera**, None; **J. Llorca**, None; **M. A. González-Gay**, None.

1976

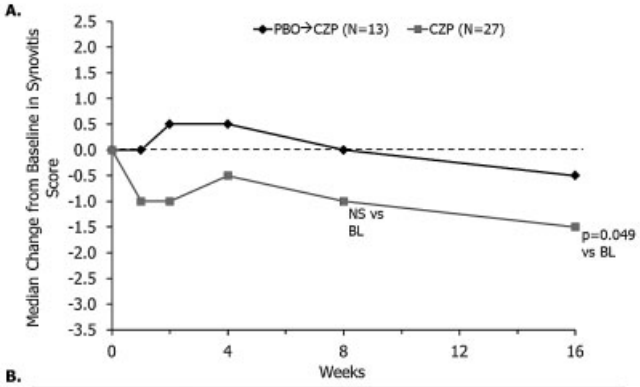
Magnetic Resonance Imaging-Assessment Of Early Response To Certolizumab Pegol In Rheumatoid Arthritis: A Randomized, Double-Blind, Placebo-Controlled Phase IIIb Study Applying Magnetic Resonance Imaging At Week 0, 1, 2, 4, 8 and 16. Mikkel Ostergaard[1], Lennart Jacobsson[2], Christopher Schaufelberger[3], Michael Sejer-Hansen[4], Johannes Bijlsma[5], Anna Dudek[6], Maria Rell-Bakalarska[7], Fabienne Staelens[8], Robert Haake[9], Britt Sundman-Engberg[10] and Henning Bliddal[11]. [1]Copenhagen Center for Arthritis Research, Glostrup, Denmark, [2]Section of Rheumatology, Malmö, Sweden, [3]Sahlgrens' Hospital, Göteborg, Sweden, [4]Rheumatology Clinic, Copenhagen, Denmark, [5]University Medical Center, Utrecht, Netherlands, [6]Medica Pro Familia, Warsaw, Poland, [7]Rheuma Medicus, Warsaw, Poland, [8]UCB Pharma, Brussels, Belgium, [9]UCB Pharma, Raleigh, NC, [10]UCB Pharma, Stockholm, Sweden, [11]Department of Rheumatology, Frederiksberg, Denmark.

Background/Purpose: The OMERACT rheumatoid arthritis (RA) magnetic resonance imaging (MRI) scoring system (RAMRIS) is a validated scoring system for assessment of synovitis, bone edema and bone erosion. Previous studies have reported that TNF inhibitors improve RAMRIS scores, but it is not known how early this occurs. The rapid clinical efficacy of certolizumab pegol (CZP), a PEGylated Fc-free anti-TNF, in RA has been reported.[1] This study aimed to identify the first time point of a MRI-verified response to CZP in RA patients.

Methods: MARVELOUS (NCT01235598) is a Phase IIIb multicenter, randomized, double-blind (DB), placebo (PBO)-controlled (during initial 2 weeks) study. Eligible patients were randomized (2:1) to receive either CZP Q2W (400mg at Wks 0–4, then 200mg every 2 weeks to Wk16) or PBO at Day 0, then CZP Q2W (400mg Wks 2–6, then 200mg every 2 weeks to Wk16). Contrast enhanced MRI of one hand and wrist was acquired at Baseline (Wk0) and Wks 1, 2, 4, 8 and 16. Primary endpoint was change from Wk0 in OMERACT RAMRIS synovitis score in the CZP group. The first significance test was conducted at Wk16 and continued to earlier time points if prior test proved significant. All MRIs were analyzed by an experienced reader, blinded to subject identity, study treatment and time point; all six time points were read simultaneously. Change in bone edema, bone erosion and clinical parameters were secondary outcomes. LOCF imputation was used for synovitis and observed data for other outcomes. Safety variables were also assessed, including AEs, and laboratory parameters.

Results: 40 pts were randomized and treated: CZP group n=27 and PBO–CZP n=13. During the DB phase, 4 patients discontinued treatment (1 PBO, 3 CZP). In the CZP group a significant reduction from baseline in synovitis score was reported at Wk16 (median change= −1.5, p=0.049) (Figure A); reductions in synovitis score were not significant at Wk8, precluding further testing of earlier time points. In the CZP group, bone edema score was also significantly reduced at Wk16 (−2.5, p=0.031) (Figure B), whereas there was no significant change from Wk0 in bone erosion score. For all RAMRIS parameters (synovitis, bone edema, bone erosion), very good intra-reader reliability (intra-class correlations >0.90) was observed. Most AEs were mild or moderate, with low incidence of withdrawals due to AEs. There were no serious infections or deaths.

Figure: A. Median change from baseline in synovitis score; B. Synovitis and bone edema scores.



B.

Outcome	CZP (N=27) Week 1	Week 2	Week 4	Week 8	Week 16
CFB Synovitis Score (estimated using Hodges-Lehmann median) (95% CI)	-1.0 (-2.5,0.0)	-1.0 (-2.0,0.5)	-0.5 (-1.5,0.5)	-1.0 (-3.0,0.0; NS)	-1.5 (-3.0,0.0; p=0.049)
CFB Bone Edema Score (estimated using Hodges-Lehmann median) (95% CI)	-1.0 (-2.5,1.0)	0.0 (-1.5,1.0)	-1.0 (-2.5,0.0)	-1.0 (-3.0,1.0; NS)	-2.5 (-5.0,0.0; p=0.031)

For CZP change from BL, the first significance test was conducted at Wk16, and continued to earlier time points if prior test proved significant. Once a non-significant result was obtained no further testing was allowed. BL: Baseline; CFB: Change from Baseline; CI: Confidence Interval; CZP: Certolizumab Pegol; NS: Non-Significant; PBO: Placebo

Conclusion: In this first study with multiple MRIs following initiation of biological therapy, CZP successfully reduced the OMERACT RAMRIS synovitis and bone edema score as measured by MRI as early as Wk16, despite small sample size and the technical challenges of reading 6 time points simultaneously. This study documents the effect of CZP and provides essential information on the optimal timing of MRI and sample sizes for subsequent larger clinical trials.

Reference:

1. Keystone, E. Arthritis Rheum 2008;58(11):3319–3329

Disclosure: M. Ostergaard, Abbott, Pfizer and Centocor, 2, Abbott, Pfizer, Merck, Roche, UCB Pharma, 5, Abbott, Pfizer, Merck, BMS, UCB and Mundipharma, 8; **L. Jacobsson**, Pfizer, 2, Abbvie, BMS, MSD, Pfizer, UCB, 9; **C. Schaufelberger**, None; **M. Sejer-Hansen**, UCB Pharma, 5; **J. Bijlsma**, UCB-NL, 2, Nordic Countries symposium of UCB, 8; **A. Dudek**, None; **M. Rell-Bakalarska**, None; **F. Staelens**, UCB Pharma, 3; **R. Haake**, UCB Pharma, 3; **B. Sundman-Engberg**, UCB Pharma, 3; **H. Bliddal**, Abbott, Amgen, AstraZeneca, Aventis, Axellus, Bristol Myers Squibb, Cambridge Nutritional Foods, Dansk Droge, Eurovita, Ferrosan, GlaxoSmithKline, Hoechst, LEO, Lundbeck, MSD, Mundipharma, Norpharma, NOVO, NutriCare, Nycomed, Pfizer, Pharmacia, Pierre-Fab, 5, Abbott, Amgen, AstraZeneca, Aventis, Axellus, Bristol Myers Squibb, Cambridge Nutritional Foods, Dansk Droge, Eurovita, Ferrosan, GlaxoSmithKline, Hoechst, LEO, Lundbeck, MSD, Mundipharma, Norpharma, NOVO, NutriCare, Nycomed, Pfizer, Pharmacia, Pierre-Fab, 2.

1977

Remission At 3 Or 6 Months and Radiographic Non-Progression At 12 Months In Methotrexate-Naïve Rheumatoid Arthritis Patients Treated With Tofacitinib Or Methotrexate: A Post-Hoc Analysis Of The ORAL Start Trial. V. Strand[1], D. van der Heijde[2], R. Landewe[3], E. B. Lee[4], B. Wilkinson[5], S. H. Zwillich[5], J. Bradley[5], C. Mebus[5], B. Benda[6] and D. Gruben[5]. [1]Stanford University, Palo Alto, CA, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Academic Medical Center / University of Amsterdam, Amsterdam, Netherlands, [4]Seoul National University, Seoul, South Korea, [5]Pfizer Inc, Groton, CT, [6]Pfizer Inc, Collegeville, PA.

Background/Purpose: Tofacitinib is a novel, oral Janus kinase (JAK) inhibitor for the treatment of RA. The importance of "treat to target" in RA to attain remission and subsequently prevent structural damage is established.

Objectives: To examine the relationship between attainment of clinical remission at Months (Mo) 3 or 6 with inhibition of radiographic progression at Mo 12 in methotrexate (MTX)-naïve patients (pts) in the Phase 3, 24-mo ORAL Start trial (NCT01039688). Pre-planned interim 1-year analyses, including primary efficacy endpoints, were reported previously.[1]

Methods: 952 pts were randomized 2:2:1 to tofacitinib 5 mg BID, 10 mg BID or MTX. Endpoints included remission defined by DAS28-4(ESR) <2.6, SDAI ≤3.3, CDAI ≤2.8 and ACR-EULAR Boolean-based criteria by

observed data and van der Heijde modified Total Sharp Score (mTSS) linear extrapolation; the definition of non-progression was change from baseline in mTSS ≤0.5. Rates were calculated for radiographic non-progression at Mo 12 by remission at Mo 3 or 6.

Results: Across all definitions of remission, rates at Mo 3 and 6 were lower with MTX (3–8% and 11–14%; N=186) than tofacitinib 5 (29–46% and 37–49%; N=371) and 10 mg BID (39–64% and 73–84%; N=395). The positive predictive values of remission by various criteria at Mo 3 or 6 for radiographic non-progression at Mo 12 are presented in the table. Across all definitions of remission, a high proportion of pts receiving tofacitinib 10 mg BID in remission at Mo 3 and 6, respectively, had no radiographic progression at Mo 12 (94–95% and 89–92%). For pts receiving tofacitinib 5 mg BID, 69–80% were in remission at Mo 3 and had no radiographic progression at Mo 12, according to the stringency of the definition utilized, which increased to 78–85% for Mo 6 remission. 83–100% of the few patients on MTX in remission at Mo 3 or 6 had no radiographic progression at Mo 12. The proportion of pts who failed to achieve radiographic non-progression at Mo 12 following remission at Mo 3 and 6 (not shown in table) were: tofacitinib 5 mg BID, 18–31% and 15–22%; tofacitinib 10 mg BID, 5–15% and 7–14%; MTX, 0–36% and 7–38%, respectively. Among the patients who did not achieve remission at Mo 3 and 6 (not shown in table), more pts receiving tofacitinib still achieved radiologic non-progression than with MTX (tofacitinib 5 mg BID, 80–83% and 82–84%; tofacitinib 10 mg BID, 85–94% and 85–92%; MTX, 63–100% and 60–93%).

	Tofacitinib 5 mg BID (N=371) (n/N) % [95% CI]	Tofacitinib 10 mg BID (N=395) (n/N) % [95% CI]	Methotrexate (N=186) (n/N) % [95% CI]
Remission Criteria^ at Month 3 to Positively Predict Nonprogression@ in mTSS at Month 12			
DAS28-4(ESR)	**(36/46)**78.3% [63.6,89.1]	**(60/64)**93.8% [84.8,98.3]	**(8/8)**100.0% [63.1,100.0]
SDAI	**(28/35)**80.0% [63.1,91.6]	**(51/54)**94.4% [84.6,98.8]	**(4/4)**100.0% [39.7,100.0]
CDAI	**(26/33)**78.8% [61.1,91.0]	**(42/44)**95.5% [84.5,99.4]	**(5/6)**83.3% [35.9, 99.6]
ACR-EULAR Boolean	**(20/29)**69.0% [49.2,84.7]	**(37/39)**94.9% [82.7,99.4]	**(3/3)**100.0% [29.2,100.0]
Remission Criteria^ at Month 6 to Positively Predict Nonprogression@ in mTSS at Month 12			
DAS28-4(ESR)	**(41/49)**83.7% [70.3,92.7]	**(70/78)**89.7% [80.8,95.5]	**(12/13)**92.3% [64.0, 99.8]
SDAI	**(37/44)**84.1% [69.9,93.4]	**(77/84)**91.7% [83.6,96.6]	**(13/14)**92.9% [66.1, 99.8]
CDAI	**(35/41)**85.4% [70.8,94.4]	**(72/78)**92.3% [84.0,97.1]	**(12/13)**92.3% [64.0, 99.8]
ACR-EULAR Boolean	**(29/37)**78.4% [61.8,90.2]	**(68/73)**93.2% [84.7,97.7]	**(10/11)**90.9% [58.7, 99.8]

^Remission definitions: DAS28-4(ESR), Disease Activity Score for 28-joint counts and erythrocyte sedimentation rate <2.6; SDAI, simplified disease activity index ≤3.3; CDAI, clinical disease activity index ≤2.8; ACR-EULAR Boolean requires ≤1 swollen and ≤1 tender joint, Patient Global (0–10) ≤1, C-Reactive Protein (mg/dL) ≤1.
@Nonprogression in modified Total Sharp Score (mTSS) (change ≤0.5) at Month 12, imputed using linear extrapolation.

Conclusion: These results indicate that clinical remission within 3 or 6 months of treatment initiation has limited value in predicting radiological non-progression at Mo 12 in MTX-naïve RA pts treated with tofacitinib. This may be due to the high proportion of pts achieving radiological non-progression with tofacitinib treatment overall, in that pts who do not achieve remission criteria at Mo 3 or 6 may still benefit from structure preservation through Mo 12.

Reference:
1. Lee EB et al. Arthritis Rheum 2012; 64(10 [supplement]):S1049

Disclosure: V. Strand, Pfizer Inc, 5; **D. van der Heijde**, Pfizer Inc, 5, Pfizer Inc, 4; **R. Landewe**, Pfizer, Janssen, Merck, Abbott, 2, Pfizer, Janssen, Merck, Abbott, Amgen, Astra, BMS, Centocor, GSK, UCS, Vertex, 5; **E. B. Lee**, Pfizer Inc, 5; **B. Wilkinson**, Pfizer Inc, 1, Pfizer Inc, 3; **S. H. Zwillich**, Pfizer Inc, 1, Pfizer Inc, 3; **J. Bradley**, Pfizer Inc, 1, Pfizer Inc, 3; **C. Mebus**, Pfizer Inc., 1, Pfizer Inc., 3; **B. Benda**, Pfizer Inc, 1, Pfizer Inc, 3; **D. Gruben**, Pfizer Inc, 1, Pfizer Inc, 3.

1978

The Effect Of Certolizumab On Lymphatic Volume and Flow In Rheumatoid Arthritis Patients With Acute Flare. Homaira Rahimi, Vaseem Chengazi, Gregory Dieudonne, Edward M. Schwarz and Christopher T. Ritchlin. University of Rochester, Rochester, NY.

Background/Purpose: Episodic flare occurs in rheumatoid arthritis (RA) but the mechanisms of this process are not well understood. Our prior reports on MRI analysis of joints in murine arthritis models showed expanded volume and increased contrast enhancement in the popliteal node draining inflamed knees prior to arthritic flare. In the expanded node, B cells translocate to paracortical sinuses, the node suddenly collapses and there is loss of efferent lymphatic drainage and rapid onset of synovitis. Two models of flare dependent on disease duration were identified. In acute flare, joint inflammation overwhelms the lymphatics and can be effectively treated with anti-inflammatories (i.e. anti-TNF). However, mice with chronic arthritis that flare lack an efferent lymphatic pulse and are unable to normalize lymphatic function or mediate arthritic flare. To examine if similar lymph node (LN) volume and lymphatic function is altered in adult RA patients, we performed MRIs of affected joints and LN and measured lymphatic flow in RA patients with acute flare, before and after certolizumab therapy.

Methods: Eight RA patients with active flare of a single wrist or knee underwent 3T pre and post contrast MRIs at baseline and 18 weeks after certolizumab. LN volumes of the popliteal or epitrochlear nodes were quantified. A subset of 3 patients underwent radiocolloid Technetium sulfur tracing (RTS) to assess lymphatic flow in the affected and unaffected extremity. RTS studies were read by a radiologist blinded to the extremity with joint flare.

Results: Of eight patients, all had improvement in disease activity score (DAS) and all six of eight with LN noted on MRI had alterations of total LN volume (Table 1.) Of those six patients, all but one had a decrease in total LN volume. Three patients underwent RTS and MRI. Patient 1 had foot- inguinal transit time (tt) of 15min to the affected extremity that increased after treatment to 65min (normal tt is 60min), showing normalization of lymphatic flow after treatment. Patient 2 had foot -inguinal tt of 15min to the affected extremity that increased after treatment to 24min, showing deceleration in lymphatic flow. Patient 7 had long standing disease and markedly decreased lymphatic flow (hand-axillary tt >75 min, normal tt is 30min) prior to treatment that did not change with therapy; no nodes were visible on MRI pre or post treatment.

Table 1.

Patient	Disease Length (yr)	LN Volume (mm^3) Pretreat	LN Volume (mm^3) Posttreat	DAS 0 mo	DAS 6 mo	ΔLN volume	ΔDAS
1	0.5	1309	891	6.14	5.13	−0.32	−0.17
2	8	4613	3037	4.93	3.45	−0.34	−0.30
3	7	3701	2124	6.41	4.07	−0.43	−0.37
4	1	5126	6601	3.94	2.45	+0.32	−0.38
5	6	622	464	5.26	2.1	−0.36	−0.60
6	0.5	134.9	742	5.23	4.35	−0.45	−0.17
7	17	0	0	3.7	1.81	0	−0.51
8	10	0	0	5.34	4.87	0	−0.09

Conclusion: LN volume and lymphatic flow are altered in response to anti-TNF therapy. Specifically, total LN volume decreased with certolizumab and patients with shorter disease duration appear to improve lymphatic flow, whereas patients with long-standing disease may not normalize lymphatic flow. Thus, similar to murine inflammatory arthritis, there may be an early versus chronic model of arthritic flare in which lymphatic function is a key factor and treatment response may depend on how severely lymphatic function is compromised.

Disclosure: H. Rahimi, None; **V. Chengazi**, None; **G. Dieudonne**, None; **E. M. Schwarz**, None; **C. T. Ritchlin**, Amgen, Janssen, UCB, Abbott (AbbVie), Regeneron, 5, Amgen, Janssen, UCB, 2.

ACR/ARHP Poster Session C
ARHP Imaging of Rheumatic Disease: Research Methodology
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

1979

Occupational Balance Questionnaire: From People's Perspectives To A Patient Reported Outcome. Mona Dür[1], Gunter Steiner[1], Michaela Stoffer[1], Alexandra Kautzky-Willer[1], Veronika Fialka-Moser[1], Clemens Dejaco[1], Birgit Prodinger[2], Alexa Binder[3], Josef S. Smolen[4] and Tanja A. Stamm[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Swiss Paraplegic Group, Nottwil, Switzerland, Notwill, Switzerland, [3]Hospital Goettlicher Heiland, Vienna, Austria, [4]Medical University of Vienna and Hietzing Hospital, Vienna, Austria.

Background/Purpose: Occupational balance is one of the foundations on which occupational therapy is based. Occupational balance is defined diversely and mainly derived from the perspective of occupational therapists.

Empirical evidence for occupational balance, as well as instruments to assess occupational balance based on qualitative analysis is scarce. The aim of the present project was to develop a questionnaire on occupational balance and explore measurement properties in the data of people with and without chronically autoimmune diseases.

Methods: The study consisted of three parts: a development of the occupational balance questionnaire based on a qualitative study, an exploration of its internal consistency and content validity conducted with Rasch analysis, and a suggestion for a revised version. Findings of the Rasch analysis and patient feedback were used to develop a revised version of the questionnaire. A German version was designed first which was translated back and forward into an English version according to the standard procedure by three native speakers. Patients were involved into item generation. This study was a part of a larger study, named the GOBI study – Gender, Occupational balance and Immunology.

Results: We developed seven questionnaire items based on the analysis of the life stories of 90 people with and without chronic autoimmune diseases (table 1). The inclusion of people's perspectives into item generation, contributes to the content validity of the questionnaire. The Rasch analysis of the data from 251 people, 132 patients with rheumatoid arthritis, 43 patients with systemic lupus erythematous and 76 healthy people showed a person separation index of 0.51. These findings indicate questionable internal consistency and that occupational balance might not be a unidimensional construct. Consequently, a revised version was developed with the involvement of 10 further patients and 10 healthy people.

Table 1. Items of the revised occupational balance questionnaire

Nr.	Item
1	How often do you find your activities of daily living too simple?
2	How often do you find your activities of daily living too difficult?
3	Do you generally receive enough appreciation for activities of daily living?
4	How much is your health affected by your activities of daily living?
5	Do you get enough rest and sleep?
6	Do your daily activities provide sufficient alternations between active and non-active actions, such as an alteration to posture or physical position, perhaps between sitting and standing?
7	How well can you adapt your activities of daily living to changed living conditions, such as a changed state of health, a change of profession, or a change in the family circle?
8	Could you take sufficient care of yourself while caring for another (such as a family member, loved one, etc.)?

Conclusion: To our knowledge, this is one of the first studies, developing a patient reported outcome measure for occupational balance using qualitative research, the involvement of patients into item generation, and an exploration of internal consistency and construct validity in quantitative data. In this study we found seven underlying dimensions of occupational balance on which we based the questionnaire items. The findings of the Rasch analysis resulted in a need of a revised version which needs to be validated in further research.

Disclosure: M. Dür, FWF Austrian Science Fund, 2; **G. Steiner**, None; **M. Stoffer**, None; **A. Kautzky-Willer**, None; **V. Fialka-Moser**, None; **C. Dejaco**, None; **B. Prodinger**, None; **A. Binder**, None; **J. S. Smolen**, None; **T. A. Stamm**, None.

1980

Validation Of The Fox-Walk Test In People With Rheumatoid Arthritis. Birgitta Nordgren[1], Cecilia Fridén[1], Eva Jansson[2], Ted Österlund[3], Wilhelmus Johannes Andreas Grooten[1], Christina H. Opava[2] and Anette Rickenlund[2]. [1]Karolinska Institutet, SE 14183 Huddinge, Sweden, [2]Karolinska Institutet, Huddinge, Sweden, [3]Karolinska University Hospital, Huddinge, Sweden.

Background/Purpose: Aerobic capacity tests are important to evaluate exercise programs and to encourage individuals to a physically active lifestyle. Maximum aerobic tests in a laboratory setting are expensive and not always feasible for people with RA. Therefore several self monitoring submaximal tests have been developed. The Fox-walk test was designed to make it possible for healthy individuals to monitor their aerobic capacity themselves. The test is performed on tracks of different lengths and are located at several public places throughout Sweden and some other European countries. The test has earlier been shown to be reliable in people with RA. The aim of our study was to validate the Fox-walk test against measured maximum oxygen uptake (measured VO_{2max}) in people with RA.

Methods: Twenty seven subjects (81% female), mean (SD) age 62 (8.1) diagnosed with RA since 17.2 (11.7) years, activity limitation with the Stanford Health Assessment Questionnaire, (HAQ) 0.412 (0.421) and DAS 28, 2.44 (0.82) participated in the study. The subjects performed the measured VO_{2max} (Alpha version 4.5, Jaeger, KFA-2028-01) and a 774 m Fox-walk test track within one week. To estimate VO_{2max}, the walking time was recorded and age, gender, BMI, the height of the person and the topography of the track was taken into account.

Results: Mean (SD) for the measured VO_{2max} and the Fox-walk test was 33.2 (7.8) ml/kg/min and 44.2 (7.1) respectively. There was a significant difference between the two tests ($p<0.0001$). The correlation between the two tests was moderate, $r = 0.52$, ($p = 0.006$) and showed an overestimation of aerobic capacity in the Fox-walk test compared to the measured VO_{2max} test.

Conclusion: Since our earlier study showed high reliability of the Fox-walk test and the present study showed a moderate correlation compared to the measured VO_{2max} test, it could be recommended as an easy way to monitor aerobic capacity without supervision from health professionals. However, most people were overestimated in the Fox-walk test and the formula could possibly be adjusted to people with RA.

Disclosure: B. Nordgren, None; **C. Fridén**, None; **E. Jansson**, None; **T. Österlund**, None; **W. J. A. Grooten**, None; **C. H. Opava**, None; **A. Rickenlund**, None.

1981

Developing International Consensus Definitions Of Improvement For Adult and Juvenile Dermatomyositis and Polymyositis. Saad Feroz[1], Nicolino. Ruperto[2], Jiri Vencovsky[3], Peter A. Lachenbruch[1], Brian Erman[4], Adam Huber[5], Brian M. Feldman[6], Ingrid E. Lundberg[7], Angela Pistorio[8], Howard Rockette[9], Frederick W. Miller[1], Rohit Aggarwal[9], Lisa G. Rider[1], for The ACR-EULAR Myositis Response Criteria Project Group[1], Angelo Ravelli[10], Clarissa Pilkington[11] and Sheila K. Oliveira[12]. [1]NIEHS, NIH, Bethesda, MD, [2]PRINTO, IRCCS G. Gaslini, Genoa, Italy, [3]Institute of Rheumatology, Department of Clinical and Experimental Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [4]SRA International, Research Triangle Park, NC, [5]IWK Health Centre, Halifax, NS, [6]Hospital for Sick Children, Toronto, ON, [7]Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, [8]PRINTO, Genoa, Italy, [9]University of Pittsburgh, Pittsburgh, PA, [10]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy, [11]Great Ormond Street Hospital, London, United Kingdom, [12]Instituto de Pediatria e Puericultura Martagão Gesteira (IPPMG) da Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil.

Background/Purpose: IMACS and PRINTO have developed preliminary core set activity measures and definitions of improvement (DOIs). However, these were developed from small and partially retrospective data sets. The current project will develop and further validate DOIs for adult and juvenile dermatomyositis (DM) and polymyositis (PM), and the first definition of major clinical improvement for use in therapeutic trials.

Methods: A repository of 8 natural history studies and 8 clinical trials in DM/PM was used to create 270 adult and 299 pediatric patient profiles consisting of core set activity measures on two visits. Clinical experts completed a questionnaire on their experience with the core set measures and care of myositis patients. Experts, randomized into survey groups based on experience, rated the degree of improvement in patient profiles.

Results: Sixty-six adult specialists (39 rheumatologist, 11 neurologists, 7 dermatologists, 7 other), saw an average of 82 adult DM/PM patients and practiced an average of 18.6 years. Fifty-two percent of adult experts had experience with 5 of 6 core set measures. Sixty-nine pediatric specialists, primarily rheumatologists, saw an average of 28 juvenile DM patients and practiced an average of 19.7 years. Forty-nine percent had experience with all core set measures and 34% had experience with 7 or 8 of 9 measures. Adult and pediatric experts had participated in an average of 1.5 trials utilizing IMACs measures; pediatric experts participated in 1 trial using PRINTO measures. Patient profiles indicated a moderate degree of activity (median MD global activity of 2 and 5, Patient/parent global activity of 5 and 4.9, MMT-8 score of 70 and 54, Extra-Muscular global activity of 1.7 in adult and 5.0 in pediatric profiles). Profiles varied in their degree of improvement based on the IMACS preliminary DOI (52% adult and 77% of pediatric profiles met DOI20%, 18% adult and 54% of pediatric profiles met DOI60%, and 48% adult and 23% of pediatric profiles were not improved by the DOI). Four-hundred-seven DOIs have been drafted to be tested for sensitivity and specificity, based on the number of measures and the degree of change corresponding to consensus clinical improvement, and inclusion of FDA's recommendation to incorporate patient-reported outcomes. Additional DOIs will be created by logistic regression analysis of the ratings of patient profiles.

The top performing DOIs will be externally validated with data from 4 randomized controlled trials.

Conclusion: A DOI for minimal and major clinical response will be developed and fully validated for adult and juvenile DM/PM using large natural history and clinical trial datasets. These internationally accepted consensus DOIs should facilitate new trials and enhance development of future therapies for myositis patients.

Disclosure: S. Feroz, None; **N. Ruperto**, ACR-EULAR, The UK Myositis Support Group, Cure JM Foundation, and The Myositis Association, 2; **J. Vencovsky**, ACR-EULAR, the UK Myositis Support Group, Cure JM Foundation, The Myositis Association, 2; **P. A. Lachenbruch**, ACR-EULAR, NIEHS, 5; **B. Erman**, NIEHS, 9; **A. Huber**, None; **B. M. Feldman**, None; **I. E. Lundberg**, Brisol Myers Squibb, 2, Novartis Pharmaceutical Corporation, 5; **A. Pistorio**, ACR-EULAR, 2; **H. Rockette**, ACR-EULAR, NIEHS, 2; **F. W. Miller**, ACR-EULAR, NIEHS, NIH Office of Rare Diseases, NIAMS, the UK Myositis Support Group, Cure JM Foundation, The Myositis Association, 2; **R. Aggarwal**, ACR-EULAR, the UK Myositis Support Group, Cure JM Foundation, The Myositis Association, 2; **L. G. Rider**, ACR-EULAR, NIEHS, NIH Office of Rare Diseases, NIAMS, the UK Myositis Support Group, Cure JM Foundation, The Myositis Association, 2; **F. T. ACR-EULAR Myositis Response Criteria Project Group**, None; **A. Ravelli**, None; **C. Pilkington**, Great Ormond Street Hospital Charity, 2, Great Ormond Street Hospital Trust, 3, UCB SLE trial, 5, President of British Society for Paediatric and Adolescent Rheumatology, 6; **S. K. Oliveira**, None.

1982

Development and Validation Of Medication Assessment Tools Specific For Rheumatoid Arthritis. Louise Grech[1], Bernard Coleiro[1], Anthony Serracino Inglott[2], Lilian M. Azzopardi[2], Victor Ferrito[2] and Andrew A. Borg[1]. [1]Mater Dei Hospital, Msida, Malta, [2]University of Malta, Msida, Malta.

Background/Purpose: Medication assessment tools can be defined as evidence-based instruments intended for the evaluation of prescribing trends and monitoring of adherence to established guidelines. Medication assessment tools have been specifically designed and implemented in the management of heart failure, coronary artery disease, asthma, diabetes mellitus and pain management in cancer. The objective of the study was to develop and validate medication assessment tools specific for rheumatoid arthritis (RA) in order to provide a systematic and standardised instrument ensuring evidence based practice in RA management.

Methods: Guidelines, recommendations and standards on RA and its management as set out by the American College of Rheumatology (ACR), the European League against Rheumatism (EULAR), the British Society for Rheumatology (BSR) and the National Institute for Clinical Excellence (NICE) were used to develop the Rheumatoid Arthritis Medication Assessment Tool (RhMAT). The summary of product characteristics for each drug included in the RhMAT were used as reference criteria. The medication assessment tool was designed in the form of a table bearing in mind that the tool will be used in a busy clinic where time can be limited. The RhMAT was validated by an expert panel who assessed the practicality, presentation, robustness and validity of the tool according to the data provided.

Results: The developed RhMAT was designed in the form of a table consisting of 11 separate sections dealing with general criteria for RA, use of analgesics, methotrexate, sulphasalazine, hydroxychloroquine, leflunomide, gold injections, general prebiologic screening, biologic therapy, use of glucocorticoids, remission cases. Table1 is an extract from the RhMAT and outlines part of the methotrexate section.

Table 1. Extract from "RhMAT"

Methotrexate	N/A	Yes	No justified	No unjustified	Insufficient Data	Comments	Reference
1 Used as first line DMARD in the absence of contraindications							
2 Pre-treatment screening including Chest X ray, CBC, ESR, CRP, LFTs, U&Es, Creatinine have been completed							
3 Regular monitoring according to monitoring protocol schedule including mouth ulcers, nausea and vomiting and dyspnoea							
4 Contraindications namely pregnancy, breastfeeding, active local or systemic infection, bone marrow suppression excluded							
5 The patient has been prescribed methotrexate at a dose that is unambiguously expressed as a *ONCE A WEEK* administration							

The expert panel validating the developed RhMAT consisted of 3 consultant rheumatologists, 2 academic pharmacists, an academic science professor and a rheumatology nurse specialist. Following the expert panel review one of the statements was split into 2 separate statements to increase specificity. This was repeated for another statement.

Conclusion: Medication assessment tools have been shown to be effective instruments providing a one-atop measure which can be used both as a clinical audit tool as well as a tool which supports best practice for a number of chronic diseases. The developed RhMAT is a comprehensive, user-friendly checlist tool designed to be used in a busy adult rheumatology out-patient clinic ensuring safer prescribing of rheumatological drugs.

Disclosure: L. Grech, None; **B. Coleiro**, None; **A. Serracino Inglott**, None; **L. M. Azzopardi**, None; **V. Ferrito**, None; **A. A. Borg**, None.

ACR/ARHP Poster Session C
Metabolic and Crystal Arthropathies II
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

1983

Prevalence Of Birefringent Crystals In Three Inflammation-Prone Tissues. Jane Park, Divya Soman, Martine P. Roudier and Peter A. Simkin. University of Washington, Seattle, WA.

Background/Purpose: When serum is hyperuricemic, so too are all interstitial fluids other than CSF and sweat. Anecdotally, urate crystals deposit as grossly visible tophi in many non-articular organs, including cardiac valves, but no microscopic studies of crystal prevalence have been done at those sites. Are the tophi unique, or are they the tip of a crystalline iceberg? Evidence from new imaging modalities including dual energy CT and ultrasound suggest that they may be surprisingly common.

Just as urate crystals drive gouty arthritis, such deposits may be a factor in extraarticular inflammation. Higher urate levels within prostatic secretions have correlated with symptoms of chronic prostatitis, and a single placebo-controlled study found that allopurinol decreased prostatic urate secretion and improved subjective pain. In addition, gout and hyperuricemia are now accepted as independent risk factors for coronary artery disease and all-cause mortality, and allopurinol use may lead to decreased mortality. The cardiac risk has been attributed to hyperuricemia, but the possibility of arterial urate crystals has not been considered. If present, such crystals could cause intimal inflammation leading to coronary thrombosis. To investigate this possibility, we used polarizing microscopy to examine tissues from 3 sites of enigmatic inflammation: coronary arteries, cardiac valves, and prostates.

Methods: Tissues were: 1. Alcohol-fixed and H&E stained coronary arteries (left anterior descending, right coronary, and circumflex) from 50 explanted hearts collected from 2000–2003. 2. Twenty-three alcohol-fixed, unstained aortic valves from replacement surgery done in 2011–2013. 3. Frozen, unstained, non-malignant regions of 40 consecutive prostatectomies for cancer in 2012–2013. Clinical data regarding gout and hyperuricemia were unavailable or incomplete for all subjects.

Results:

Tissue	Source	Gender	Age	N	Number of positive specimens	% positive
Coronary	Explant	M + F	Any	50	6	12%
Prostate	Cancer surgery	M	61.2 ± 7.2	40	19	47.5%
Aortic valve	Explant	M + F	62.3 ± 17.0	23	1	4.3%

Conclusion: We have observed birefringent crystals, primarily negatively so, in 12% of coronary arteries, 48% of prostates, and 4% aortic valves examined thus far. Alcohol fixation, rather than formalin which is known to dissolve urate crystals, and polarizing microscopy are necessary in order to recognize urate crystals in pathologic tissues.

"Gouty arteritis" should be considered as a possible factor in ischemic heart disease. We hope these tools will be applied by pathologists conducting autopsies on patients who have suffered fatal myocardial infarctions. In addition, if our preliminary findings are confirmed within the prostate, further studies will be indicated with urate lowering agents and anti-inflammatory drugs known to be effective in gouty arthritis.

Disclosure: J. Park, Takeda Pharmaceuticals, 2; **D. Soman**, None; **M. P. Roudier**, None; **P. A. Simkin**, Takeda Pharmaceuticals, 2.

1984

Impact Of Educational Attainment On Health-Related Quality Of Life and Healthcare Utilization Among Veterans With Gout. Cleopatra Aquino-Beaton[1], Jay E. Persselin[1], Ari Weinreb[1], Meika A Fang[1], Jasvinder A. Singh[2], Erin Duffy[3], David Elashoff[4], Puja Khanna[5] and Dinesh Khanna[6]. [1]VA Greater Los Angeles Healthcare System, Los Angeles, CA, [2]University of Alabama, Tuscaloosa, AL, [3]University of California Los Angeles, Los Angeles, CA, [4]UCLA Department of Medicine Statistics Core, Los Angeles, CA, [5]Ann Arbor VA, Ann Arbor, MI, [6]University of Michigan Medical Center, Ann Arbor, MI.

Background/Purpose: Gout is a debilitating, chronic disease that requires ongoing treatment and effective self-management. Successful gout treatment depends on multiple factors, including educational attainment. Adequate health literacy enables patients with chronic illnesses, including gout, to better manage their disease and overall health. Evidence suggests that higher health literacy and education may be associated with better self-care and personal health management. Gout is associated with poor health-related quality of life (HRQoL) and greater healthcare utilization (HCU) among US Veterans. However, there is little research on the impact of educational attainment on HRQoL and HCU.

Methods: 186 gout patients with varying levels of educational attainment were recruited in rheumatology and primary care clinics at the West Los Angeles, CA and Birmingham, AL VA facilities. Patients' clinical status, HRQoL, and HCU were assessed every 3 months for a 12-month period. Educational attainment was self-reported at baseline and patients were categorized into two education levels: 1) No post-high school education and, 2) post-high school (some college, college degree, or graduate school education). HRQoL were measured using the SF-36, HAQ-DI and Gout Impact Scales (GIS) of the Gout Assessment Questionnaire (GAQ). Patients and physicians independently scored the severity of gout on a 0–10 scale. HCU was assessed with the UCSD Health Care Utilization Questionnaire. Demographics, clinical characteristics, HRQoL and HCU of patients with and without post-high school education were compared using Wilcoxon rank sum and Fisher exact tests. P-values less than 0.05 were considered significant.

Results: There were 46 patients with no post-high school education and 138 patients with education beyond high school; 2 patients did not provide their education. Patients with post-high school education were significantly younger than their counterparts, but there was no difference between groups with respect to race, ethnicity or gender (Table). The clinical characteristics, patient severity scores, SF-36, HAQ-DI and GIS scores did not differ between educational attainment groups. However, physician scores for severity of gout were higher for patients with no post-high school education compared to those with higher education. Patients with post-high school education reported a significantly higher frequency of medical office visits (MD, DO, or NP), phone calls to physician or medical staff, and urgent care visits (triage center or emergency department) during the 3-month period prior to baseline.

Patient Characteristics by Educational Attainment

		No Post-High School Education N=46	Post-High School Education N=138	p-value
Age (Years)	Mean(SD)	69.9 (9.6)	62.8 (10.8)	0.0001
Gender (Male)	N (%)	45 (97.8%)	135 (97.8%)	0.99
Race:				
Caucasian	N (%)	32 (69.6%)	73 (52.9%)	0.08
African American	N (%)	9 (19.6%)	51 (37.0%)	
Other	N (%)	5 (10.9%)	14 (10.1%)	
Hispanic or Latino Ethnicity	N (%)	7 (18.9%)	13 (10.7%)	0.18
Tophi Diagnosed	N (%)	11 (25.6%)	24 (18.7%)	0.34
Serum Urate Level	Mean (SD)	8.3 (3.6)	8.3 (3.4)	0.72
Number of Charlson Comorbidities	Mean (SD)	3.0 (2.4)	3.5 (2.2)	0.58
ACR Functional Class:				
I & II	N (%)	19 (76.0%)	69 (85.2%)	0.29
III & IV	N (%)	6 (24.0%)	12 (14.8%)	
Recent Gout Attack (<4 weeks)	N (%)	24 (52.2%)	79 (58.5%)	0.20
Patient Severity Assessment (0–10)*	Mean (SD)	6.0 (3.0)	5.6 (3.2)	0.50
Physician Severity Assessment (0–10)*	Mean (SD)	3.9 (2.9)	2.8 (2.6)	0.05
SF-36 Physical Component Summary	Mean (SD)	37.4 (12.5)	38.8 (9.4)	0.45
SF-36 Mental Component Summary	Mean (SD)	47.2 (13.8)	42.9 (13.9)	0.07
HAQ-DI Composite Score (0–3)*	Mean (SD)	0.8 (0.6)	0.8 (0.6)	0.63
Average GIS Score (0–100)*	Mean (SD)	53.0 (19.6)	55.5 (19.8)	0.49
Healthcare Utilization over 3 Months Number of:				
Visits to MD, DO, or NP	Mean (SD)	2.4 (2.6)	4.4 (4.7)	0.0006
Phone calls to MD or medical staff	Mean (SD)	0.7 (1.7)	2.0 (3.3)	0.0002
Triage, urgent care, or ER visits	Mean (SD)	0.3 (0.6)	0.7 (1.0)	0.02
Home-healthcare visits	Mean (SD)	0.2 (0.9)	0.7 (2.8)	0.22
Days as inpatient	Mean (SD)	0.6 (2.1)	2.3 (11.1)	0.10
Outpatient surgeries or procedures	Mean (SD)	0.3 (1.0)	0.3 (0.8)	0.96

*Higher score= worse HRQoL

Conclusion: VA patients with lower educational attainment had significantly higher physician severity scores, utilized fewer outpatient and urgent care services despite similarities in clinical characteristics and HRQoL as their more educated peers.

Disclosure: C. Aquino-Beaton, None; **J. E. Persselin**, None; **A. Weinreb**, None; **M. A. Fang**, None; **J. A. Singh**, Takeda, Savient, 2, Savient, Takeda, Ardea, Regeneron, Allergan, 5, URL pharmaceuicals Novartis, 5; **E. Duffy**, None; **D. Elashoff**, None; **P. Khanna**, Takeda, 9; **D. Khanna**, NIH, 2, Scleroderma Foundation, 2, Actelion Pharmaceuticals US, 5, Actelion Pharmaceuticals US, 8, Gilead, 5, United Therapeutics, 5, United Therapeutics, 8, Roche Pharmaceuticals, 5, BMS, 5, DIGNA, 5, Merck Pharmaceuticals, 5.

1985

Prescription Patterns Of Colchicine Before and After Food and Drug Administration Approval. Eswar Krishnan[1], Jasvinder A. Singh[2] and Linjun Chen[1]. [1]Stanford University, Palo Alto, CA, [2]University of Alabama, Tuscaloosa, AL.

Background/Purpose: Colchicine, a commonly used drug, had never been subjected to rigorous safety and efficacy studies prior to 2009, when under Hatch-Waxman ACT (1984) and the Unapproved Drug Initiative, the Food and Drug Administration approved a proprietary version of colchicine (Colcrys®) for treatment of acute gout flare. The approved dose was much lower than that used traditionally. One assumption for the FDA approval of colchicine was that proprietary versions of the previously unapproved products would enhance patient safety by encouraging more rational prescribing practices. The goal of this study was to test this assumption using clinical data.

Methods: The data used for the present study was retrieved from the STRIDE (Stanford Translational Research Integrated Database Environment) database that includes electronic medical record data from 15 million clinical encounters with 1.6 million unique patients. After validating diagnosis of gout by chart review we identified 970 records of gout utilizing colchicine from 2006 to 2012. High-dose colchicine (HDC) and very-high-dose colchicine (VHDC) prescriptions were defined as more than 1.8 mg/day and 3.0 mg/day respectively. Factors associated with HDC and VHDC were analyzed using logistic regression models. Although Colcrys ® was approved in June 2009 we assumed that the earliest time for discernible impact to be January 1, 2010.

Results: Before and after 2010, the mean age and mean serum creatinine were similar, while the proportion of women and mean serum uric acid were statistically different (Table). The proportion of patients using HDC/VHDC decreased from 11.7%/8.6% before 2010 to 4.0%/3.7% after 2010, representing an unadjusted odds ratio of 0.3 (0.2, 0.6)/0.4 (0.2, 0.8) and age-sex-adjusted odds ratio of 0.3 (0.2, 0.6)/0.4 (0.2, 0.8). The utilization of high-dose colchicine has been declining steadily even before the introduction of Colcrys®, while the utilization of very-high-dose colchicine declined after 2007 and was steady through 2007 to 2009 and then declined after 2010(Figure). In multivariable logistic regressions that adjusted for age, sex and renal function, the odds ratio for HDC/VHDC 2010–2012 compared to the preceding years (2006–2009) was 0.4 (0.2, 0.6)/0.5 (0.2, 0.9).

	2006–2009	2010–2012
Mean Age in years (SD)	65.7 (17.8)	67.3 (14.8)
Proportion of women*	17.9%	23.4%
Mean serum creatinine in mg/dL (SD)	1.3 (1.0)	1.4 (1.4)
Mean serum uric acid in mg/dL (SD)*	7.3 (2.8)	6.4 (2.5)

SD: standard deviation; * Statistically different ($p<0.05$)

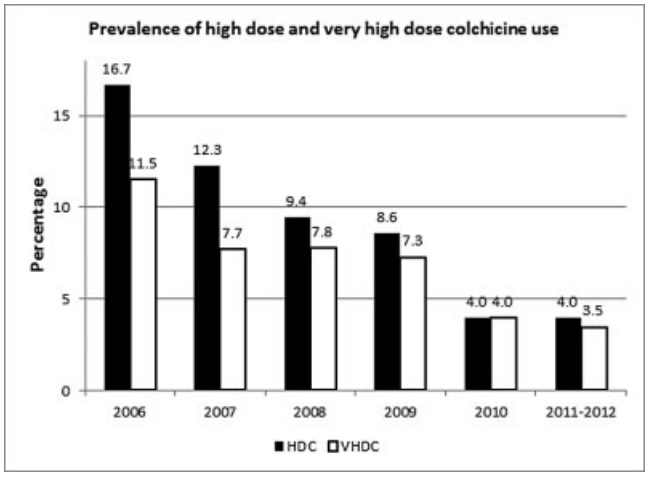


Figure.

Conclusion: Colchicine dosing has been declining over time. Statistically this is unrelated to the approval of Colcrys® under the FDA Unapproved Drug Initiative.

Disclosure: E. Krishnan, takeda, mboles, Ardea, 2, Takeda, Metabolex, 5; **J. A. Singh**, None; **L. Chen**, None.

1986

Colchicine Use and The Risk Of Myocardial Infarction Among Gout Patients: Results From a Community-Based, Informatics-Driven Retrospective Cohort Study. Daria B. Crittenden[1], Binita Shah[2], Steven P. Sedlis[2], Christopher J. Swearingen[3], Eric S. Wagner[4], Yvette M. Henry[4], Peter B. Berger[4], Bruce N. Cronstein[1] and Michael H. Pillinger[1]. [1]NYU School of Medicine, Division of Rheumatology, New York, NY, [2]NYU School of Medicine, Division of Cardiology, New York, NY, [3]Pediatric Biostatistics, University of Arkansas for Medical Sciences, Little Rock, AR, [4]Geisinger Health System, Cardiovascular Center for Clinical Research, Danville, PA.

Background/Purpose: Gout patients have an increased risk of myocardial infarction (MI). Since atherosclerosis and plaque rupture are inflammatory processes, anti-inflammatory gout medications might also reduce MI. Colchicine inhibits inflammatory cells implicated in gout and MI; our prior study suggests that colchicine might reduce MI in gout patients (Crittenden, J Rheum 2012). To further assess the effect of colchicine on risk of MI, we performed a retrospective cohort study of patients in the Geisinger Health System, a large community-based health care system.

Methods: We analyzed Geisinger's electronic records and identified all patients in the Geisinger Health Plan with ICD-9 codes for gout on at least two different encounters between 2001–12. Patients were separated into 2 groups: chronic ($>$ 30 days; n=628) and no colchicine (controls; n=2436) use. Patients with $>$ 0 but $\leq$ 30 days of use were excluded from analysis. For patients in each cohort, we set the index date as 1st colchicine use or 1st gout diagnosis date (colchicine and controls, respectively). For colchicine users, we defined a colchicine lapse as any period of non-use $\geq$ 2 weeks after medication cessation, to account for the kinetics of colchicine elimination. The primary outcome was MI during the study period. Demographic and baseline clinical features were compared between the 2 groups using equivalence tests (20% margin). Difference in frequency of MI between groups was estimated using Chi-square test and logistic regression adjusting for age, diabetes, heart failure, prior MI, and length of follow-up.

Results: Of the 3064 patients who met the inclusion criteria, 2316 (76%) were male and 3010 (98%) were white. The 2 groups were equivalent with regard to age, sex, hypertension, hyperlipidemia, allopurinol use (45 vs 43%), and mean serum urate (7.8 vs 8.0 mg/dL). Forty-eight MIs were reported during the study period; 35 (1.4%) in the control group vs 5 (0.8%) among active colchicine users (OR=1.78, P=0.22), and 8 (1.3%) during colchicine lapse or after its final discontinuation. The odds of MI were larger in the control vs colchicine group using logistic regression, though the effect lessened over time (OR at 6 months = 2.29 [P=0.263] at 2 years = 1.35 [P=0.609]). In contrast, the MI incident rate/1000 person-years of exposure was higher in the colchicine group (6.3 vs 2.3, P=0.064), probably relating to a much longer follow-up (i.e. denominator) for the control group (14,996 vs 796 person-years). Among colchicine users overall, the incidence rate of MI during periods of active use was lower than during lapse periods (6.3 vs 11.2/1000 person-years [P=0.324]).

Conclusion: Active colchicine users demonstrated trends toward a reduced incidence of MI and reduced odds of MI in the first 2 years of observation vs controls. Colchicine users also had a reduced risk of MI during periods of active use vs lapse. In contrast, MI person-year incidence rate was higher among the colchicine users vs controls, possibly a consequence of the much longer observation period in the control group. Overall, the number of MI events was unexpectedly low, limiting our ability to draw conclusions; additional studies are needed to clarify the potential cardioprotective effect of colchicine.

Disclosure: D. B. Crittenden, None; **B. Shah**, Takeda Pharmaceuticals, 2, Guerbet, 2; **S. P. Sedlis**, None; **C. J. Swearingen**, None; **E. S. Wagner**, None; **Y. M. Henry**, None; **P. B. Berger**, None; **B. N. Cronstein**, Canfite Pharma, 1, NIH, Gilead, Takeda, AstraZeneca, 2, NYU School of Medicine, 3, Merck-SeronoBristol-Myers Squibb, Novartis, CanFite Biopharmaceuticals, Cypress Laboratories, Regeneron (Westat, DSMB), Endocyte, Protalex, Allos, Inc., Savient, Gismo Therapeutics, Antares Pharmaceutical, Medivector, 5, Multiple patents on adenosine receptors and bone metabolism, pharmacology, 9; **M. H. Pillinger**, Takeda Pharmaceuticals, 2, Savient Pharmaceuticals, 2.

1987

LIVER Outcomes In Gout Patients Treated With Febuxostat and Altered LIVER Function TESTS. Fernando Perez-Ruiz and Ana M. Herrero-Beites. BioCruces Health Institute, Baracaldo, Spain.

Background/Purpose: patients with significantly altered liver function test (LFTs) at screening do not qualify for clinical trials. Therefore, scarce data are available on the impact on altered LFTs with febuxostat. To assess whether febuxostat has an impact in LFTs in patients with altered LFTs at baseline, compared with patients with normal LFTs.

Methods: prospective follow-up of a cohort of patients initiating febuxostat for hyperuricemia of gout. ASAT, ALAT, and GGT were measured at baseline and at 3–6–12 months during follow-up. Child-Plough stage $>$ 1 were not included. General characteristics of patients were obtained at entrance in the cohort, including parameters of gout severity, previous urate-lowering therapy, ethanol intake, hyperlipidemia, renal function impairment, and diabetes. Altered LFTs were defined as ASAT/ALAT $>$ 1.5 or GGT $>$ 2.5 upper normal limit (UNL). Liver ultrasonography was obtained prior to febuxostat in patients with altered LFTs at baseline and in those who developed altered LFTs during follow-up.

Results: 86 patients included, 83, 69, and 59 patients with data at 3, 6, and 12 months of follow-up, respectively, 96% with previous failure or intolerance/adverse events to at least one urate-lowering drug. General comorbidities: 47% renal function impairment (11% CKD 4–5), 29% ethanol intake $>$ 20 g/day, 70% hypertension, 50% hyperlipidemia, 22% diabetes, 40% on diuretics, and 26% heart failure; 35% on the upper stratum of the Kaiser Permanent Pyramid of complexity. Of 23 (27%) patients with altered LFTs at baseline (ASAT, ALAT, and GGT were altered in 4, 9, and 18 % respectively), diseases were: 1 von Gierke Disease, 1 liver transplantation, 1 hemochromatosis, 2 alcoholic cirrhosis, 3 stasis liver due to heart failure, and 9 fatty liver. Six patients had altered LFTs but normal ultrasonography. Altered LFTs at baseline were more prevalent in patients with previous high ethanol intake (14/25 vs. 12/61, 56% vs. 19%, respectively; p$<$0.05).

No patient withdrew due to altered liver function test. Three patients developed sustained altered LFTs, ultrasonography showing lithiasis, fatty liver, and iron overload and four patients showed normalization of LFTs during follow-up. There was no significant change in paired means in any LFTs but a descent of ASAT/ALAT at 6 months and of GGT at 6 and 12 months (Table).

	ASAT 0/3	ASAT 0/6	ASAT 0/12	ALAT 0/3	ASAT 0/6	ASAT 0/12	GGT 0/3	GGT 0/6	GGT 0/12	P
All	29 ± 15	29 ± 15	29 ± 15	35 ± 26	36 ± 28	34 ± 25	68 ± 71	63 ± 59	64 ± 61	All NS
	30 ± 19	29 ± 17	27 ± 15	36 ± 31	37 ± 31	32 ± 29	66 ± 75	56 ± 45	61±57	
Normal LFTs	23 ± 7	23 ± 7	23 ± 6	27 ± 13	27 ± 13	27 ± 13	35 ± 20	37 ± 20	38 ± 21	All NS
	25 ± 11	25 ± 14	24 ± 13	31 ± 27	31 ± 27	29 ± 31	35 ± 23	39 ± 28	41 ± 37	
Altered LFTs	45 ± 20	48 ± 18	45 ± 19	55 ± 38	60 ± 40	55 ± 39	146 ± 88	132 ± 70	141 ± 75	*<0.05
	40 ± 27	40 ± 20	35 ± 17*	51 ± 39	51 ± 37	38 ± 22*	140 ± 101	101 ± 52**	119±64***	<0.01

Conclusion: in this prospective cohort of patients with severe gout but not liver insufficiency, patients with altered LFTs, including patients including chronic liver disease, showed no signal of worsening of LFTs compared to patients with normal LFTs at baseline. There was even an improvement in LFTs in the long-term in patients with previously altered LFTs.

Disclosure: F. Perez-Ruiz, Menarini International, 5, SOBI, 5, AstraZeneca, 5, Menarini, 8; **A. M. Herrero-Beites**, None.

1988

Self-Reported Gout, Comorbidities and Healthcare Resource Utilization Data From The 2012 United States National Health and Wellness Survey. Jasvinder A. Singh[1], Kathy Annunziata[2] and Puja Khanna[3]. [1]University of Alabama, Tuscaloosa, AL, [2]Kantar Health, Princeton, NJ, [3]University of Michigan Medical Center, Ann Arbor, MI.

Background/Purpose: Hyperuricemia and gout are associated with major cardiovascular and metabolic comorbidities. Recently published data on comorbidities and gout epidemiology in the US have been drawn from the 2007–2008 National Health and Nutrition Examination Survey (NHANES),[1,2] thus underscoring the need for current information. Here we present data from the subscription-based 2010–2012 National Health and Wellness Survey (NHWS; Kantar Health).

Methods: The NHWS is an Internet-based survey of adults aged ≥18 years providing self-reported information on treatment, healthcare attitudes and behaviors, disease and demographic characteristics (N=71,157). Mean values were weighted/projected to match gender, age, and race in accordance with current US Census Bureau data. NHWS members were recruited from

the Lightspeed Research panel, whose members were recruited through e-mail and Web site advertisements, and other panels. All participants provided informed consent and were nominally compensated.

Results: The majority of respondents were men (77%) and mean time since gout diagnosis was 12.3 years. Close to half of these patients (42%) were age 65 years or older. A large proportion of gout patients were unaware of their serum uric acid (sUA) levels (71%); 17% reported sUA below 6 mg/dL and 13% reported sUA >6 mg/dL. Gout was classified as mild in 52%, moderate in 33% and severe in 15%. Table 1 shows key comorbidities and healthcare utilization for the NHWS cohorts with and without gout; Table 2 displays trends over time. Respondents with gout had significantly higher utilization of inpatient, outpatient, and emergency room services and were hospitalized more often than respondents without gout. The overall prevalence of gout in the 2012 NHWS was 2.4%, slightly higher than that reported by the NHWS in 2011 (2%) and 2010 (1.7%) but lower than that reported using NHANES 2007–2008 (3.9%).

Table 1. Characteristics of Gout vs No Gout Populations

	Total Sample 2012	US Adults No Gout	US Adults w/ Gout	US Adults w/ Gout and Rx	US Adults w/ Gout, No Rx
NHWS sample	N=71,157	n=69,161	n=1996	n=1347	n=649
Total projected to US population	230.3M	224.7M	5.6M	3.7M	1.9M
% Men	48	48	77	79	72
Mean age (years)	46.4	46.1	60.4	61.6	58
Pain	34	34	53*	51	56
Self-Reported Comorbidities (% of sample)					
Hypertension	26	25	66	69	60
Hypercholesterolemia	25	24	56*	59	51**
Diabetes	10	10	30*	33	24**
Arthritis other than gout	20	20	52*	54	47**
Healthcare Resource Utilization (% of sample with 1 or more visits)					
Visited GP in past 6 months	47	47	69*	72	63**
Visited HCP in past 6 months	72	72	90*	93	84**
Visited ER in past 6 months	12	12	17*	18	15
Hospitalized in past 6 months	7	6	11*	13	8**
Mean Healthcare Resource Utilization					
Mean # visits in past 6 months	3.4	3.3	5.6*	6.0	4.7**

* Denotes statistical significance vs the sample with no gout.
** Denotes statistical significance vs gout with Rx.

Table 2. Medication Usage and Treatment Patterns Over Time

	2010	2011	2012
% With Gout on Rx	68%	66%	66%
Allopurinol	NA	NA	75%
Febuxostat	NA	NA	7%
Patient Attitudes			
% with gout who consult HCP when ill	38%	36%	35%
% with gout who prefer self-treatment with OTC products	23%	20%	19%
Resource Utilization			
% visited GP in past 6 months	NA	67%	69%
% visited any HCP in past 6 months	93%	90%	90%
Mean # visits in past 6 months	6.3	6	5.6
% visited ER in past 6 months	22%	19%	17%
% hospitalized in past 6 months	16%	13%	11%

Conclusion: Current data from the NHWS demonstrated a higher incidence of comorbidities and gout when compared to NHANES III. This difference could be attributed to mode of survey administration (Internet vs home-based) along with the growing epidemic of obesity. Trends from 3 years showed modest reductions in healthcare utilization over time that are promising and have implications for gout-related healthcare cost.

References:

1. Zhu et al. Am J Med. 2012.
2. Singh J. Curr Rheumatol Rep. 2013.

Disclosure: J. A. Singh, Takeda, Savient, 2, Savient, Takeda, Ardea, Regeneron, Allergan, URL Pharmaceuticals and Novartis., 5; **K. Annunziata**, Kantar Health, 3; **P. Khanna**, Takeda, 9.

1989

Determinants Of Functional Disability In Patients With Gout: Longitudinal Analysis From a Multicentre Observational Study Of The Italian Society For Rheumatology.

Carlo Alberto Scirè[1], Maria Manara[1], Greta Carrara[1], Marco A. Cimmino[2], Marcello Govoni[3], Fausto Salaffi[4], Leonardo Punzi[5], Carlomaurizio Montecucco[6], Marco Matucci-Cerinic[7] and Giovanni Minisola[8]. [1]Epidemiology Unit -Italian Society for Rheumatology, Milano, Italy, [2]University of Genoa, Genova, Italy, [3]Section of Rheumatology - Department of Clinical and Experimental Medicine - University of Ferrara, Ferrara, Italy, [4]Rheumatology Unit - Polytechnic University of the Marche, Jesi, Italy, [5]University of Padova, Padova, Italy, [6]University and IRCCS Policlinico S. Matteo Foundation, Pavia, Italy, [7]University of Florence, Azienda Ospedaliera Careggi, Florence, Italy, [8]Rheumatology Unit, San Camillo-Forlanini Hospital, Rome, Italy.

Background/Purpose: Gout is the most prevalent arthritis and significantly impacts on function. Beside the influence of concurrent comorbidities, identifying disease-related prognostic factors may help to improve management and prevent disability. This study primarily aims to evaluate the independent association of disease-related factors with functional disability over time in patients with gout.

Methods: This is prospective analysis of a multicentre cohort study including a random sample of patients with prevalent clinically diagnosed gout from 30 rheumatology centres across Italy (KING Study, promoted by SIR, NCT01549210) recruited between June 2011 and January 2012. All patients underwent full clinical evaluation, including general health variables (socio-demographics, life-styles, comorbidities and treatments), and gout-related variables (diagnosis, duration, pattern of disease, previous and current treatment, VAS pain and patient global, joint examination, tophi burden and serum uric acid (sUA) levels). Primary outcome was defined as persistency of or worsening of functional disability (according to the following HAQ classes: absent= 0–0.5; mild= 0.5–1; moderate= 1–2; severe= 2–3). The relationship between predictors and outcomes was modelled using logistic models, and results presented as crude and adjusted odds ratios (OR) and 95%CI. Generalised linear models explored longitudinal association between gout-related variables and functional outcome. Missing data were imputed using switching regression on 10 datasets.

Results: A total of 446 patients were included in the analyses. M:F ratio was 9:1 M:F, mean (SD) age 63.9 (11.6) years and median (IQR) disease duration 3.8 (1.5–10.1) years; 92% fulfilled ACR preliminary classification criteria for gout, 19.9% had tophaceous gout; mean (SD) sUA level was 6.3(1.7), and 81% were on treatment with xantine-oxidase inhibitors (68% allopurinol and 13% febuxostat).

Factors associated with worse functional outcome after 12 months are reported in Table.

	12-month functional outcome		
Gout-related variables	Crude OR [95% CI]	Adj OR [95% CI]$^{\mu}$	Adj OR [95% CI]$^{\#}$
Disease duration (>5yrs)	2.13 (1.32–3.44)	2.17 (1.31–3.57)	1.94 (1.16–3.27)
Number of attacks last year	1.07 (1.01–1.14)	1.08 (1.01–1.16)	1.06 (0.99–1.14)
Attacks last month	2.44 (1.48–4.01)	2.87 (1.70–4.87)	2.75 (1.59–4.76)
Presence of tophi	2.06 (1.20–3.54)	1.87 (1.06–3.29)	1.62 (0.90–2.92)
Number of swollen joints (66)	1.31 (1.19–1.46)	1.30 (1.17–1.44)	1.26(1.14–1.40)
Number of tender joints (68)	1.23 (1.15–1.32)	1.22 (1.14–1.31)	1.19 (1.11–1.27)
Serum Uric Acid (>6mg/dl)	1.67 (1.01–2.77)	2.11 (1.22–3.63)	1.95 (1.10–3.45)
Urate lowering treatment	1.06 (0.57–1.97)	1.01 (0.52–1.94)	0.84 (0.43–1.65)
Current NSAID or colchicine	3.02 (1.78–5.12)	2.99 (1.72–5.18)	2.88 (1.63–5.10)
Previous steroid	2.38 (1.43–3.96)	2.20 (1.28–3.77)	1.90 (1.08–3.37)

$^{\mu}$ *adjusted for age and gender.*
$^{\#}$ *adjusted for age, gender, comorbidities*

Variations over time of the following gout-related variables associated with statistically significant variation on HAQ score: swollen and tender joint count, VAS pain and patient global, number of attacks. Tophi and sUA showed only a marginal association.

Conclusion: disease-specific variables independently impact on function over time, suggesting that stricter control of the disease may improve the excess of disability observed in gout.

Disclosure: C. A. Scirè, None; **M. Manara**, None; **G. Carrara**, None; **M. A. Cimmino**, None; **M. Govoni**, None; **F. Salaffi**, None; **L. Punzi**, None; **C. Montecucco**, None; **M. Matucci-Cerinic**, None; **G. Minisola**, None.

1990

Treatment Of ACUTE Gout In The Emergency Department Evaluated According To The 2012 American College Of Rheumatology Guidelines. Naomi Schlesinger[1], Tina Chang Young[2], Diane C. Radvanski[3], Dirk Moore[4] and Robert Eisenstein[5]. [1]UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, [2]UMDNJ/School of Public Health, Piscataway, NJ, [3]Robert Wood Johnson Medical School, New Brunswick, NJ, [4]UMDNJ - School of Public Health, Piscataway, NJ, [5]UMDNJ- Robert Wood Johnson Medical School, New Brunswick, NJ.

Background/Purpose: Acute gout attacks account for a substantial number of emergency department (ED) visits. Our aim was to record acute gout treatment in the ED and evaluate the treatment according to the 2012 American College of Rheumatology (ACR) guidelines (Khanna D et al. *Arthritis Care Res.* 2012; 64:1447–61).

Methods: Retrospective chart review of consecutive patients with acute gout seen in the ED 1/01/2004 - 12/31/2010. Patients included if their diagnosis field included the word gout. Variables included: age, years of gout, number of attacks/year, comorbidities, medications and involved joints.

Descriptive and summary statistics were performed on all variables. Subgroup analysis, sensitivity analysis and exploratory data performed where applicable.

Results: 541 acute gout patient visits recorded in the ED over 7 years. Mean patient age: 54 (range 20–96); 79% were men. 118 (22%): first attack. 75%: attack duration ≤ 3 days. Most commonly affected: lower extremity joints.

Of the 541 visits, 355 (66%) given drug treatment in the ED; 186 (34%) not given a medication during their visit. Medications given: NSAIDs: 56 % (n=198): (toradol 19% (n=69); indomethacin 19% (n=66); Ibuprofen 14% (n=49); naproxen 3% (n=11)); opiates 54% (n=190); colchicine 9% (n=32); prednisone 9% (n=32). 154 (28%) not given drugs during visit received prescriptions. 6% (n=32) given no drugs during visit nor did they receive a prescription.

An anti-inflammatory drug given during 44% (n=239) of visits. 75% (n=408) given an anti-inflammatory drug prescription. 40% (n=216) given an anti-inflammatory drug during visit and a prescription. 110 (20%) not given an anti-inflammatory drug during visit nor a prescription.

35% (n=190) given an opiate (oxycodone/acetaminophen) during the ED visit and 52% (n=282) a prescription.

Monotherapy given during 74% (n=262) of visits.

During 13.4% (n=72) of visits patient reported being on colchicine prophylaxis. Patients on colchicine prophylaxis significantly more likely to receive colchicine for their acute attack than those not on prophylaxis (p=0.005).

Conclusion: According to the ACR guidelines, first-line anti-inflammatory drugs for the treatment of acute gout include oral colchicine, NSAIDs and corticosteroids, yet during 56% of acute gout ED visits, anti-inflammatory drugs not given. The ACR guidelines propose treatment be continued for 7–10 days yet only 40% given anti-inflammatory drugs in the ED and prescriptions. We suggest that 60% did not receive optimal treatment for acute gout. The ACR guidelines suggest that colchicine is not recommended when attack occurred in a patient on colchicine prophylaxis yet patients on chronic prophylaxis significantly more likely to receive colchicine for their acute attack. Opiates commonly given in the ED for acute gout; however, analgesia alone does not treat gouty inflammation (not addressed in guidelines). Combination of colchicine and NSAIDs suggested for severe and unresponsive attacks by ACR guidelines, yet in 76% of patient visits receiving combination therapy, an opiate was combined with an NSAID or prednisone.

Further studies are needed for development of evidence-based guidelines tailored to the ED to help improve treatment of acute gout in the ED.

Disclosure: N. Schlesinger, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, Sobi, 5, Novartis Pharmaceutical Corporation; Takeda, Savient, 8, Novartis Pharmaceutical Corporation, Takeda, Savient, Sobi, 9; **T. Chang Young**, None; **D. C. Radvanski**, None; **D. Moore**, None; **R. Eisenstein**, None.

1991

Gout In Ambulatory Care Settings In The US: 1993–2009. Eswar Krishnan and Linjun Chen. Stanford University, Palo Alto, CA.

Background/Purpose: Gouty arthritis (gout) is primarily cared for in ambulatory care settings. Yet, there are few nationally representative data on ambulatory health care utilization of this condition. The goal of this study is to analyze the quantity of visits for gout and its trends in the US between 1993 and 2009.

Methods: We combined the data from National Ambulatory Medical Care Surveys (NAMCS) and National Hospital Ambulatory Medical Care Surveys (NHAMCS) from 1993 to 2009 where the unit of analysis was the outpatient visit. Gout visit was defined as a visit with physician-prescribed gout diagnosis, or a visit associated with a prescription of allopurinol or colchicine. Patients younger than 20 or older than 90 were excluded. Data were analyzed using SVY suite of commands in STATA. Time trends were tested using Poisson regressions.

Results: For men, the annual number of visits for gout increased from 2.9 million at 1993 to 8.9 million at 2009; for women, it increased from 1.2 million to 3.2 million. The total number of visits for gout increased from 4.1 million at 1993 to 12.1 million at 2009. The increase of gout visits was highly significant (p<0.001) (Figure 1). When examined as a proportion of all ambulatory care visits, the proportion of gout visits increased from 13.0 per 1000 (10.0‰, 17.2‰) to 25.5 per 1000 (21.0‰, 31.1‰) among men and 3.2 per 1000 (2.0‰, 5.1‰) to 5.8 per 1000 (4.4‰, 7.7‰) among women (Figure 2). The increase was evident in all age groups but was large only among the 60+ age group. Overall, in age-gender adjusted Poisson regressions the 2006–2009 time period was associated with a relative risk for 1.6 (1.4, 1.9) compared to the 1993–2005 time period.

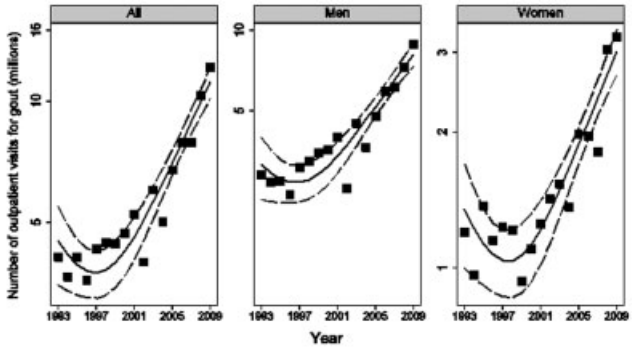


Figure 1.

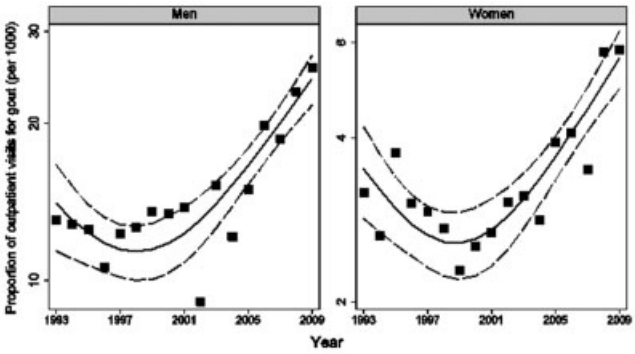


Figure 2.

Conclusion: The frequency of gout increased over three fold between 1993 and 2009, and most of the increase occurred after 2005. The gout awareness campaign funded by the industry could be the explanatory factor.

Disclosure: E. Krishnan, Takeda, 2, Takeda, 5; **L. Chen**, None.

1992

Trends In Outpatient Treatment Of Gout In The US: From 1993 To 2009. Eswar Krishnan and Linjun Chen. Stanford University, Palo Alto, CA.

Background/Purpose: Gouty arthritis (gout) is primarily managed in the community by primary care providers. Relatively little is known about the treatment patterns as well as time trends in general population settings.

Methods: We combined the data from National Ambulatory Medical Care Surveys (NAMCS) and National Hospital Ambulatory Medical Care Surveys (NHAMCS) from 1993 to 2009. Presence of a physician determined diagnosis of gout or prescription of allopurinol/colchicine was

considered to signify a gout visit. We assessed the prescription of gout medications classified as allopurinol, colchicine, oral corticosteroids, any Non-Steroidal Anti-inflammatory drugs (NSAIDs) and Non-Coxib NSAIDs. We also studied the prescription pattern of aspirin as a 'control' group. Time trends were analyzed using weighted logistic regression models.

Results: Time trends in the use of medications are shown in the Figure. The trends for colchicine and steroids were not statistically significant. In logistic regressions that adjusted for age and sex, each advancing year was associated with a significant increase in the use of allopurinol with an odds ratio of 1.02 ((1.00,1.05), p=0.048) and the use of aspirin with an odds ratio of 1.09 (1.05,1.12). The use of Non-Coxib NSAIDs decreased with a yearly odds ratio of 0.96 (0.94, 0.99). There were no significant trends in other medications. The estimate of visits with concurrent prescriptions of allopurinol and probenecid was negligible. Overall, the combination of colchicine and any one of the NSAIDs were prescribed in 3.5 million (2.4 to 4.6 million) gout patients, representing 3.6% (2.6%, 4.8%) of all gout visits. The proportion of such combinations increased from 2.0% (1.2%, 3.3%) in the 1993–2000 period to 4.3% (3.1%, 6.1%) in the 2001–2009 period. In unadjusted logistic regression this change represented an odds ratio of 2.4 (1.3, 4.5) and in age-sex adjusted logistic regression the odds ratio was unchanged. Combination of NSAIDs and steroids was rare, and was prescribed in 1.7% gout visits (1.1%, 2.8%). These proportions were similar in the 1993–2000 and 2001–2009 periods: 1.3% (0.6%, 2.8%) and 1.9% (1.1%, 3.5%) respectively.

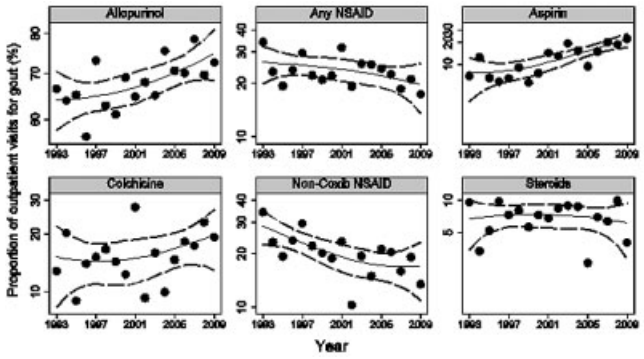


Figure.

Conclusion: Distinct trends of gout medication use were observed signifying decrease in NSAIDs and increase in allopurinol. The utilization of colchicine and steroids has remained steady over time. Combination of different classes of anti-inflammatory therapies was infrequent.

Disclosure: E. Krishnan, Takeda, 2, Takeda, 5; **L. Chen**, None.

1993

Geographic Variations Of Gout Epidemiology In The United Kingdom: A Nationwide Population Study. Chang-Fu Kuo[1], Michael Doherty[2], Matthew J. Grainge[2] and Weiya Zhang[2]. [1]Chang Gung Memorial Hospital, Taipei, Taiwan, [2]University of Nottingham, Nottingham, United Kingdom.

Background/Purpose: To examine geographic variations of gout prevalence, incidence and management in the United Kingdom.

Methods: We used the Clinical Practice Research Data-link (CPRD) to estimate the prevalence, incidence of gout, consultation rate for gout, percentage under urate-lowering treatment (ULT) and time to first prescription of ULT in each of 13 areas in the United Kingdom: North East, North West, Yorkshire & The Humber, East Midlands, West Midlands, East of England, South West, South Central, London, South East Coast, Northern Ireland, Scotland and Wales.

Results: Overall prevalence of gout was 2.51% (95% CI, 2.50%μ2.52%) and incidence was 1.87 (95% CI, 1.83–1.91) per 1000 person-years in the UK in 2012. The prevalence and incidence vary throughout the country (Figure 1). The highest prevalence was in North East (3.11% [3.00%–3.23%]) and Wales (2.98% [2.93–3.03]); the highest incidence as also in these 2 regions (2.30 [95% CI, 2.26–2.35] and 2.20 [95% CI, 2.15–2.24] per 1,000 patient-years respectively). Among prevalent gout patients in 2012, only 50,453 patients (43.6%) were under medical attention (with at least one consultation with a gout diagnosis or a prescription containing ULT). Management of gout in terms of percentage given ULT also varies between regions, partially in line with the variation of prevalence (Table 1). In general only one-third of prevalent cases were given ULT, and only one quarter of incident cases received ULT within one year from diagnosis.

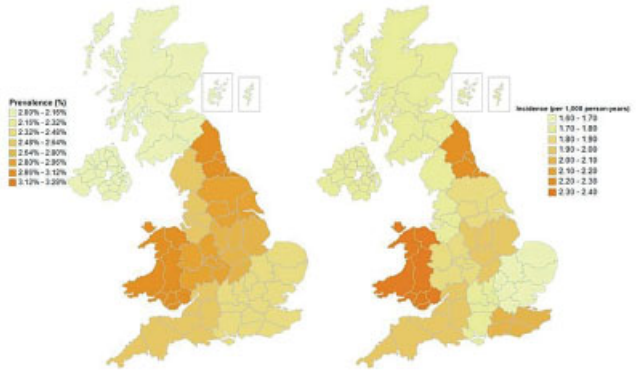


Figure 1. Geographic variations in the prevalence and incidence of gout

Table 1. Regional variation in gout management of gout in the United Kingdom in 2012

Area	Prevalent cases		Incident cases	
	Consulted	Treated by ULT	ULT by 6 months	ULT by 12 months
Overall	43.8%	31.1%	16.1%	23.3%
North East	36.4%	37.7%	16.6%	20.2%
North West	43.2%	31.8%	19.2%	26.7%
Yorkshire & The Humber	39.0%	24.9%	8.6%	16.0%
East Midlands	44.5%	25.7%	6.6%	10.3%
West Midlands	38.2%	27.5%	14.4%	20.6%
East of England	44.1%	32.3%	14.7%	21.8%
South West	37.1%	29.6%	11.4%	18.3%
South Central	44.2%	26.0%	12.6%	17.9%
London	43.9%	35.1%	18.0%	28.0%
South East Coast	37.7%	30.6%	17.0%	23.9%
Northern Ireland	46.7%	29.3%	18.0%	24.7%
Scotland	65.9%	37.8%	22.1%	30.1%
Wales	44.7%	30.7%	15.1%	21.1%

Conclusion: A regional variation of gout prevalence and incidence in the UK was observed. Only a minority of people with gout receive ULT and this aspect of gout management also varied between regions, suggesting a need for further education of general practitioners with respect to understanding of gout and its mangement.

Disclosure: C. F. Kuo, None; **M. Doherty**, None; **M. J. Grainge**, None; **W. Zhang**, None.

1994

Performance Of Gout Impact Scale Of The Gout Assessment Questionnaire In a Longitudinal Observational Study Of Patients With Gout. Puja Khanna[1], Cleopatra Aquino-Beaton[2], Jasvinder A. Singh[3], Erin Duffy[4], David Elashoff[5] and Dinesh Khanna[6]. [1]University of Michigan Medical Center, Ann Arbor, MI, [2]VA Greater Los Angeles Healthcare System, Los Angeles, CA, [3]University of Alabama, Tuscaloosa, AL, [4]University of California Los Angeles, Los Angeles, CA, [5]UCLA Department of Medicine Statistics Core, Los Angeles, CA, [6]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI.

Background/Purpose: Gout Assessment Questionnaire (GAQ2.0) is a validated disease-specific measure used to evaluate patient reported outcomes in gout studies. The objective was to evaluate the correlates of Gout Impact Scale (GIS) of GAQ2.0 and change over time in a prospective cohort of patients.

Methods: 186 gout patients were recruited in a 9-month longitudinal study at 2 VA centers where data on HRQOL using SF36 v2 (higher score

denotes better health), Health Assessment Questionnaire, HAQ-DI (0–3, higher score indicates worse function) and GIS (higher score denotes greater impact of disease) was administered. The GIS has 5 domains: gout concern overall, gout medication side effects, well-being during attack, unmet gout treatment needs, and gout concern during attack; GIS scores range from 0 to 100, where a higher score indicates worse health. Demographics, education level, acute flare frequency, Charlson comorbidities (CCI), serum urate (sUA), serum creatinine, functional class, and patient and physician rating of the severity of gout on a 0–10 scale, were assessed. Spearman Correlations were calculated between baseline GIS domains scores and SF-36 PCS & MCS, HAQ-DI Score, CCI, sUA, and age. Multivariate linear regression was used to assess demographic and clinical predictors of total GIS score at baseline. Paired Wilcoxon sign rank tests were used to assess change in GIS between baseline and last visit. P-values <0.05 were considered significant.

Results: Mean age (SD) of patients was 64.6 (10.9) years, they were predominantly male (98%); 57% Caucasian, 32% African American, 13% Hispanic, and 94% who graduated high school. Mean sUA was 8.3 mg/dL (3.4), physician assessment of gout severity was 3.1 (2.7) and patient gout-severity assessment was 5.7 (3.1). Moderate negative correlations were noted between SF-36 PCS and GIS scores ($r=-0.29$) and well-being during attack ($r=-0.39$); whereas SF 36 MCS showed higher correlation with GIS domains ranging from 0.35–0.43, all $p<0.001$. HAQ-DI was significantly correlated with GIS, ($r=0.32$, $p<0.001$). Average GIS scores correlated with age ($r=0.4$, $p<0.001$). GIS score was significant higher than those with self-reported recent attack of gout within $^{2}3$ months from baseline compared to those without a recent attack. Younger age and experiencing an attack within last 3 months were predictive of higher total GIS score in multivariate linear regression analyses. A significant decrease in GIS scores was observed from baseline to 9-month period in the domains (Table).

Domains of GIS	Change from Month 9 to baseline, N=148, Mean (SD)
Gout Concern Overall	−8.7 (21.7)***
Gout Medications Side Effects	−2.0 (22.5)
Unmet Gout treatment Need	−4.0 (18.8)**
Well Being During Attack	−6.6 (19.5)***
Gout Concern During Attack	−4.1 (19.6)*
Total GIS	−3.3(13.3)***

*P<0.05; **p<0.01; *** p<0.001

Conclusion: GIS is a disease-specific measure that adequately captures the impact of gout over time. This study provides comprehensive validity of GIS in gout that meets the OMERACT filters.

Disclosure: P. Khanna, NIH, 2; **C. Aquino-Beaton**, None; **J. A. Singh**, Takeda, Savient, 2, Savient, Takeda, Ardea, Regeneron, Allergan, 5, URL pharmaceuicals Novartis, 5; **E. Duffy**, None; **D. Elashoff**, None; **D. Khanna**, NIH, 2, Scleroderma Foundation, 2.

1995

Serum Homocysteine Related To Decreased Renal Function In Chronic Gouty Patients. Jung-Soo Song, Jin Su Kim and Sang Tae Choi. Chung-Ang University College of Medicine, Seoul, South Korea.

Background/Purpose: Homocysteine is a non-essential amino acid formed by the conversion of methionine to cysteine. Hyperhomocysteinemia is a risk factor for cardiovascular events by inducing reactive oxygen species and impairing endothelial function. Gout is also associated with several comorbidities including cardiovascular disease (CVD). Hyperhomocysteinemia and gout are both related to CVD, however, there are few reports about serum homocysteine levels in gout patients and the results reveal discrepancies. In this study, we investigated whether or not homocysteine levels are elevated in patients with chronic gout and which factors are associated with elevated homocysteine levels.

Methods: 91 male patients with chronic gout and 97 age-matched healthy male controls were included in this study, and the averages of age were 51.19 ± 15.08 and 51.57 ± 17.01 years old, respectively. Serum homocysteine, uric acid (UA), blood urea nitrogen (BUN), creatinine (Cr) and other laboratory findings were tested for all participants. Serum homocysteine levels were measured by a competitive immunoassay using direct chemiluminescent (Siemens Centaur Immunoassay Systems, USA). The estimated glomurular filtration rate (eGFR) was calculated using modification of diet in renal disease (MDRD) formula, then the stages of chronic kidney disease (CKD) were classified according to eGFR levels.

Results: The chronic gout group were not significantly different from the control group in serum uric acid levels (6.15 ± 2.23 mg/dL vs 5.82 ± 1.22 mg/dL, $p = 0.214$). However, the patients with chronic gout showed much higher serum homocysteine levels than healthy controls (13.96 ± 4.05 μmol/L vs 12.67 ± 3.51 μmol/L, $p = 0.022$). Serum homocysteine levels were not different between the groups that are treated with allopurinol and with benzbromarone. The patients at stages 1 or 2 of CKD had significantly lower serum homocysteine levels than the patients at stage 3 of CKD (12.99 ± 4.81 μmol/L, 13.17 ± 2.97 μmol/L, and 17.45 ± 4.68 μmol/L, $p < 0.001$). In patients with chronic gout, serum homocysteine levels showed the positive correlations with serum BUN and Cr levels, and the negative correlation with eGFR and systolic blood pressure ($r = 0.429$, $p < 0.001$; $r = 0.435$, $p < 0.001$; $r = -0.413$, $p < 0.001$; $r = -0.251$, $p < 0.025$, respectively). However, serum homocysteine levels are uncorrelated with serum uric acid levels or cholesterol profiles. In multiple linear analyses, serum homocysteine level was affected by eGFR ($\beta = -0.385$, $p < 0.001$), however, was not affected by the serum uric acid level.

Conclusion: Serum homocysteine levels were higher in the male patients with chronic gout than in the healthy male controls. Hyperhomocysteinemia in gouty patients could be related not with serum uric acid levels, but with decreased renal function.

Disclosure: J. S. Song, None; **J. S. Kim**, None; **S. T. Choi**, None.

1996

Racial/Ethnicity Differences In Health-Related Quality Of Life (HRQOL), Functional Ability and Health Care Utilization In Gout Patients. Aseem Bharat[1], Jasvinder A. Singh[2], Puja Khanna[3], Cleopatra Aquino-Beaton[4], Jay E. Persselin[4], Erin Duffy[5], David Elashoff[6] and Dinesh Khanna[7]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Alabama, Tuscaloosa, AL, [3]University of Michigan Medical Center, Ann Arbor, MI, [4]VA Greater Los Angeles Healthcare System, Los Angeles, CA, [5]University of California Los Angeles, Los Angeles, CA, [6]UCLA Department of Medicine Statistics Core, Los Angeles, CA, [7]University of Michigan, Ann Arbor, MI.

Background/Purpose: Due to limited/no data for race/ethnicity, our objective was to assess whether HRQOL functional ability and health care utilization in gout patients differs by race/ethnicity.

Methods: This prospective cohort study included 186 veterans with gout (predominantly male) recruited at Veterans Affairs (VA) rheumatology and primary care clinics at the West Los Angeles, CA and Birmingham, AL facilities. We assessed HRQOL (with short-form 36 and the Gout Impact Scales (GIS) of the Gout Assessment Questionnaire (GAQ)); functional ability with Health assessment questionnaire-disability index (HAQ-DI); and health care utilization (patient self-reported University of California at San Diego (UCSD) Health Care Utilization Questionnaire) every 3 months for a 9-month period. Comparisons were made using the student's t test or the chi-square, Wilcoxon rank sum test or Fisher exact test, as appropriate.

Results: Race/ethnicity data were available for 167 patients, 107 Caucasian and 60 African-American. The cohort mean age was 64.6 years, 98% were men, 13% Hispanic or Latino, 6% did not graduate high school, 21% had gouty tophi, the mean serum urate was 8.3.

Compared to Caucasians, African-American gout patients were younger (61.1 vs. 67.3 years, $p=0.0003$), had higher serum urate (9.6 vs. 7.9 mg/dl, $p=0.005$), but similar patient (6.0 vs. 5.4, $p=0.27$) and physician assessment (3.3 vs. 2.9, $p=0.53$) of gout severity.

HRQOL Differences: African American patients with gout had lower scores on SF-36 mental health, role emotional, social functioning domains and MCS (but not PCS) relative to White patients ($P \leq 0.04$ for all; table 1).

On the GIS, African American scored higher in the areas of gout concern overall, unmet treatment need, well-being during attacks, concern during attacks, and overall average GIS (Table 2), but not medication side effects.

Functional limitation: Compared to Caucasians, African American had higher/worse HAQ scores overall and lower scores in 5 of the 8 activity domains of Dressing & Grooming, Arising, Eating, Walking, and Grip, indicating more difficulty with these tasks (Table 1).

Table 1. SF-36 (Higher score indicates better health) and HAQ scores (Higher score indicates worse health)

SF-36 T-Score Values	White N=107 Mean (SD)	African American N=60 Mean (SD)	T-test p-value
Physical Functioning (PF)	37.3 (12.1)	34.1 (12.4)	0.12
Role Limitation Physical (RP)	37.5 (12.4)	33.8 (12.1)	0.06
Pain (BP)	42.6 (12.2)	39.6 (12.6)	0.13
General Health (GH)	43.3 (5.1)	43.5 (4.9)	0.82
Emotional Well-being (MH)	46.3 (12.6)	40.8 (12.9)	0.008
Role Limitation Emotional (RE)	40.6 (16.0)	31.3 (17.0)	0.0005
Social Functioning (SF)	41.5 (12.3)	37.3 (12.8)	0.04
Energy Fatigue (VT)	45.8 (11.3)	45.2 (8.4)	0.71
Physical Health Component (PCS)	38.7 (10.4)	38.1 (10.0)	0.72
Mental Health Component (MCS)	46.2 (14.2)	39.5 (12.9)	0.003

HAQ	White N=105 Mean (SD) [Median (IQR)]	African American N=60 Mean (SD) [Median (IQR)]	Wilcoxon rank sum p-value
Dressing & Grooming	0.58 (0.74) [0.00 (1.00)]	0.87 (0.70) [1.00 (1.00)]	0.005
Arising	0.68 (0.69) [1.00 (1.00)]	0.98 (0.89) [1.00 (2.00)]	0.04
Eating	0.31 (0.67) [0.00 (0.00)]	0.52 (0.65) [1.00 (1.00)]	0.01
Walking	0.73 (0.81) [1.00 (1.00)]	1.10 (1.02) [1.00 (2.00)]	0.03
Hygiene	0.70 (0.89) [0.00 (1.00)]	0.80 (0.92) [1.00 (1.00)]	0.41
Reach	0.81 (0.82) [1.00 (1.00)]	0.82 (0.70) [1.00 (1.00)]	0.70
Grip	0.44 (0.72) [0.00 (1.00)]	0.95 (0.90) [1.00 (1.50)]	0.0001
Activities	1.10 (0.99) [1.00 (2.00)]	1.33 (1.13) [1.00 (2.00)]	0.23
HAQ Composite Score	0.67 (0.55) [0.63 (1.00)]	0.93 (0.68) [0.88 (1.13)]	0.02

Table 2. GIS by Race (Higher score indicates worse health)

GIS	White N=107 Mean (SD) [Median (IQR)]	African American N=60 Mean (SD) [Median (IQR)]	Wilcoxon rank sum p-value
Concern Overall	64.3 (27.9) [75.0 (50.0)]	73.6 (24.6) [75.0 (37.5)]	0.04
Medication Side Effects	48.8 (27.6) [50.0 (37.5)]	54.6 (28.9) [50.0 (50.0)]	0.16
Unmet Treatment Need	33.9 (18.6) [25.0 (16.7)]	41.4 (20.3) [33.3 (33.3)]	0.01
Well Being During Attack	51.1 (26.2) [52.3 (47.7)]	61.5 (25.5) [64.8 (36.4)]	0.01
Concern During Attack	50.0 (25.2) [50.0 (50.0)]	60.4 (26.5) [62.5 (43.8)]	0.01
Average GIS Score	50.8 (18.9) [51.6 (28.1)]	60.3 (19.6) [62.5 (32.3)]	0.004

Conclusion: This is the first prospective cohort study to show that African-American patients with gout have significantly worse emotional, social, and mental wellbeing/HRQOL and functional ability than Caucasians. Further research is needed into the determinants of this poorer HRQOL and function to target interventions to modifiable mediators of this relationship.

Disclosure: A. Bharat, None; **J. A. Singh**, Takeda, Savient, 2, Savient, Takeda, Ardea, Regeneron, Allergan, 5, URL pharmaceuicals Novartis, 5; **P. Khanna**, None; **C. Aquino-Beaton**, None; **J. E. Persselin**, None; **E. Duffy**, None; **D. Elashoff**, None; **D. Khanna**, savient, 2, Savient, Takeda, and AZ, 5.

1997

Health Care Utilization In Gout Patients: A Prospective Multicenter Cohort Study. Jasvinder A. Singh[1], Aseem Bharat[2], Puja Khanna[3], Cleopatra Aquino-Beaton[4], Jay E. Persselin[4], Erin Duffy[5], David Elashoff[6] and Dinesh Khanna[7]. [1]University of Alabama, Tuscaloosa, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]University of Michigan Medical Center, Ann Arbor, MI, [4]VA Greater Los Angeles Healthcare System, Los Angeles, CA, [5]University of California Los Angeles, Los Angeles, CA, [6]UCLA Department of Medicine Statistics Core, Los Angeles, CA, [7]University of Michigan, Ann Arbor, MI.

Background/Purpose: Because of the chronic nature of the disease, gout is associated with more co-morbidities, poor health-related quality of life (HRQoL) and more healthcare utilization (HCU). Therefore, the cost of care associated with gout management is rising. There is lack of evidence that describes the predictions of health care utilization in patients with gout. The objective of this study is to assess health care utilization and its predictors in patients with gout.

Methods: We conducted a prospective cohort study of 186 veterans with gout (predominantly male) recruited at Veterans Affairs (VA) rheumatology and primary care clinics at the West Los Angeles, CA and Birmingham, AL facilities. We assessed overall health care utilization with the patient self-reported University of California at San Diego (UCSD) Health Care Utilization Questionnaire and gout-specific health care utilization on the Gout Assessment Questionnaire (GAQ) every 3 months for a 9-month period. We collected data including patient demographics, education level, comorbidity, serum urate (in mg/dl) and patient and physician rating of the severity of gout on a 0–10 scale, HRQOL assessment with SF-36, and the Gout Impact Scales (GIS) of the GAQ and functional ability assessed with Health Assessment Questionnaire-Disability Index (HAQ-DI), were assessed. Comparisons were made using the student's t test or the chi-square, Wilcoxon rank sum test or Fisher exact test, as appropriate. Zero-inflated Poisson regression was used to assess potential predictors of gout-related HCU.

Results: The cohort mean age was 64.6 years, 98% were men, 13% Hispanic or Latino, 6% did not graduate high school, the mean serum urate was 8.3, mean physician gout severity assessment was 3.1 and mean patient gout severity assessment was 5.7. Mean Deyo-Charlson score was 3.1.

Overall health care Utilization: There were a mean of 3.9 visits to the health care provider in the past 3 months and 1.7 telephone calls to the provider or medical staff (Table). 17% had 1 or more inpatient visits in the past 3 months, 41% had 1 or more ER/urgent care/triage center visits and 16% with any outpatient procedure or surgery (Table).

Gout-specific health care utilization: During the past year, patients had a mean of 1.5 visits to rheumatologist, 2 visits to primary care doctor (Table). 7% had 1 or more inpatient visits in the past year related to gout, 26% had 1 or more ER visits related to gout and 33% with any urgent care/walk-in visit related to gout (Table).

	Patients with at least one visit/call N			Patients with at least one visit/call %			Number of visits/calls Mean (SD)		
Healthcare Utilization	Total N=186	BHAM N=74	LA N=112	Total N=186	BHAM N=74	LA N=112	Total N=186	BHAM N=74	LA N=112
Overall HCU, prior 3 months:									
Number of visits to MD, DO, or NP	163	63	100	92%	88%	95%	3.9 (4.3)	2.8 (2.5)	4.6 (5.1)
Number of phone calls to MD or medical staff	85	32	53	48%	44%	50%	1.7 (3.1)	1.4 (2.3)	1.9 (3.5)
Number of times to a triage, urgent care center, or emergency room	74	31	43	41%	43%	40%	0.6 (0.9)	0.6 (0.9)	0.6 (1.0)
Number of home visits by healthcare provider	16	6	10	9%	8%	9%	0.6 (2.4)	0.5 (1.9)	0.6 (2.8)
Number of days as inpatient	31	11	20	17%	15%	19%	1.8 (9.6)	0.6 (1.6)	2.7 (12.3)
Number of outpatient surgeries or procedures	27	15	12	16%	23%	12%	0.3 (0.9)	0.4 (1.1)	0.2 (0.7)
Gout related HCU, prior year:									
Rheumatologist	97	20	77	53%	28%	70%	1.5 (2.0)	1.2 (2.4)	1.7 (2.4)
Primary Care Doctor	128	57	71	71%	79%	66%	2.0 (1.9)	2.0 (1.5)	2.0 (1.5)
Nurse Practitioner or Physician's Assistant	53	8	45	31%	12%	43%	0.8 (1.6)	0.2 (0.7)	1.2 (0.7)
Walk-in or Urgent Care Clinic	57	21	36	33%	31%	34%	0.7 (1.5)	0.6 (0.9)	0.8 (0.9)
Emergency Room at a hospital	45	22	23	26%	31%	22%	0.4 (0.8)	0.4 (0.8)	0.4 (0.8)
Hospital Over-night Stay	17	5	12	10%	7%	11%	0.7 (7.5)	0.1 (0.4)	1.1 (0.4)

Conclusion: This cohort study is the first prospective cohort study to examine health care utilization in patients with gout. We have described patterns of health care utilization by patients with gout in the U.S. Future studies need to examine whether modifiable predictors of utilization can be targeted to reduce the overall and gout-related utilization in patients.

Disclosure: J. A. Singh, Takeda, Savient, 2, Savient, Takeda, Ardea, Regeneron, Allergan, 5, URL pharmaceuicals Novartis, 5; **A. Bharat**, None; **P. Khanna**, None; **C. Aquino-Beaton**, None; **J. E. Persselin**, None; **E. Duffy**, None; **D. Elashoff**, None; **D. Khanna**, savient, 2, Savient, Takeda, and AZ, 5.

1998

The Risk Of Subsequent Attacks In Patients With Incident Gout: A Population-Based Study. Nour Zleik, Clement J. Michet, Helen Khun, Cynthia S. Crowson, Eric L. Matteson and Tim Bongartz. Mayo Clinic, Rochester, MN.

Background/Purpose: While there appears to be consensus that non-pharmacological uric acid lowering therapies (diet and lifestyle modifications) should be initiated in every patient presenting with gout, there is much less agreement as to when urate lowering drugs should be considered. Expert opinion ranges from starting uric acid lowering therapy after the first attack of gouty arthritis through a more cautious approach where therapy is only started in patients with more than 3 attacks per year. We aimed to assemble a population based cohort of patients with newly diagnosed gout to determine the risk of additional flares after an initial gout attack and explore the role of various demographic, clinical and laboratory predictors that may aid the clinician in quantifying this risk.

Methods: We examined a population-based incidence cohort of patients with gout, diagnosed according to the New York, Rome or ACR preliminary criteria in Rochester, Minnesota, between Jan 1st 1989 and Dec 31st 1992. All subjects were followed longitudinally through their complete community medical records, until death, migration or July 1st 2012. We used descriptive statistics to delineate the frequency and number of subsequent flares of gouty arthritis in our cohort. In addition, we utilized a conditional frailty model (accounting for multiple flares per subject) to explore risk factors of subsequent flares after an initial diagnosis of gout.

Results: 158 patients with incident gout were identified among Rochester residents within the 4 year time period. Subjects were followed for a mean (SD) of 13.4 (8.5) years. The majority of patients were male (73.4%) and the mean age (SD) at gout onset was 59.2.0 (17.8). Isolated podagra was the most common form of joint involvement at disease onset (74.7%) and the mean (SD) serum uric acid level was 8.1 (1.6) mg/dl. 111 patients (70.3%) developed at least 1 subsequent flare, with a total of 381 subsequent flares during the entire follow-up period. Patients with the highest risk of subsequent flares had an initial joint involvement other than first MTP joint (odds ratio 1.5, 95% CI 1.1, 2.2) and a high serum uric acid level at baseline (OR 1.35, 95% CI 1.2, 1.5). Age, gender, BMI, alcohol consumption, lipid levels and starting uric acid lowering therapy were not significant predictors of subsequent flare risk.

Conclusion: The majority of patients in our population-based cohort did develop at least one subsequent flare after a initial diagnosis of gout, with a 20-year cumulative incidence of more than 80 percent. Joint involvement other than the first MTP1 joint and the serum uric acid level were significant predictors of subsequent flare risk and should be taken into account when deciding on the timing of starting uric acid lowering therapy.

Disclosure: N. Zleik, None; **C. J. Michet**, None; **H. Khun**, None; **C. S. Crowson**, None; **E. L. Matteson**, None; **T. Bongartz**, None.

1999

Hospitalization and Flare Risk In Patients With Established Gout: A Population-Based Study. Nour Zleik, Clement J. Michet, Helen Khun, Cynthia S. Crowson, Eric L. Matteson and Tim Bongartz. Mayo Clinic, Rochester, MN.

Background/Purpose: Hospitalization of patients with gout may be associated with an increased risk of arthritic flares, due to administration of IV fluids, discontinuation of established uric acid lowering therapies and other medication changes. While previous studies have suggested an association of gouty arthritis and hospitalization, the absolute flare risk has not been identified. We aimed to assemble a population based cohort of patients with newly diagnosed gout to determine the risk of flares with future hospitalizations and explore the role of various predictors that may be associated with an increased risk of in-hospital gout flares.

Methods: We examined a population-based incidence cohort of patients with gout, diagnosed according to the New York, Rome or ACR preliminary criteria between Jan 1st 1989 and Dec 31st 1992. All subjects were followed longitudinally through their complete community medical records, until death, migration or July 1st 2012. Hospitalizations of each subject were recorded and hospital records were evaluated for a possible flare of gouty arthritis. Person-year methods were used to calculate the rate of flares of gouty arthritis during hospitalizations and out-of-hospital. In addition, we utilized a conditional frailty model (accounting for multiple flares per subject) to explore risk factors of in-hospital gout flares.

Results: 159 patients with incident gout were identified within the 4 year time period. Subjects were followed for a mean (SD) of 13.4 (8.5) years. The majority of patients were male (73.4%) and the mean age (SD) at gout onset was 59.2.0 (17.8). 107 patients (67%) did have at least 1 hospitalization, with a total of 382 hospitalizations during the entire follow-up period. 12 of these 382 hospitalizations were complicated by a flare of gouty arthritis during a total of 1548 hospital days (4.2 total person-years) compared to 370 out-of hospital flares during 2117 person-years of follow-up. The rate of flares during hospitalization was 7.7 per 1000 person-years compared to 0.5 per 1000 person-years out-of-hospital. Hospitalization was associated with a significantly increased risk of gout flares (Rate Ratio: 16.8; 95% CI: 8.8, 27.7).Various possible predictors of gout flares during hospitalization were evaluated, including discontinuation of established uric acid lowering therapy, administration of IV fluids, ICU admission, use of diuretics and reason for admission. None of these factors could be identified as a statistically significant predictor of in-hospital flares.

Conclusion: Hospitalization does represent a significant risk factor for flares of gouty arthritis in patients with a prior diagnosis of gout. Future studies will have to clarify if there are patient subgroups that are at particular risk and if inpatient care related measures can help to prevent arthritic flares during hospitalization.

Disclosure: N. Zleik, None; **C. J. Michet**, None; **H. Khun**, None; **C. S. Crowson**, None; **E. L. Matteson**, Hoffmann-La Roche, Inc., 2, Pfizer Inc, 2, Novartis Pharmaceutical Corporation, 2, Mesoblast, 2, UCB Pharma, 2, Genentech and Biogen IDEC Inc., 2, Celegene, 2, Ardea Biosciences, 2; **T. Bongartz**, None.

2000

Changes In The Prevalence Of Gout In The United States General Population Between 1960 and 2010: The National Health and Nutrition Examination Surveys. Eswar Krishnan and Linjun Chen. Stanford University, Palo Alto, CA.

Background/Purpose: Despite the widely shared impression that the prevalence of gouty arthritis (gout) has increased over time in the US few population data are available.

Methods: We compared the age-gender specific prevalence proportions of self-reported gout from the 1959–1962 and 2009–2010 cycles of National Health and Nutrition Examination Surveys (NHANES). Using mid-period Census data we estimated and compared population-prevalence rates. Age, sex and risk factor adjusted changes were assessed using Poisson regressions.

Results: The estimated number of cases of gout in the US increased from about 1.1 million in 1960 to 8.1 million in 2010. The proportion of respondents with gout in NHANES increased from 1.1% to 3.7% whereas the unadjusted population-based prevalence of gout increased from 6 per 1000 to 26 per 1000. The increased prevalence was evident among all adults, men and women but was statistically significant and of larger magnitude among those 65 years and older (Figure 1, 2). The proportion of women in the population with gout remained unchanged at 31%. The mean age of the prevalent gout among adults (age>=18) increased from 54 years to 61 years among men and 57 years to 65 years among women. The age-sex adjusted prevalence rate ratio was 2.9 (2.1, 4.1). In Poisson regressions adjusted for age and waist circumference, the prevalence rate ratio decreased to 1.57 (1.18, 2.11). When men and women were studied separately in these regressions, the increase in prevalence was evident among men with rate ratio 1.77 (1.20, 2.60) but not among women with rate ratio 1.16 (0.74, 1.80). When hypertension and diabetes were added to the above model, the prevalence rate ratio was 1.86 (1.28, 2.71) for men and 1.21 (0.81, 2.11) for women.

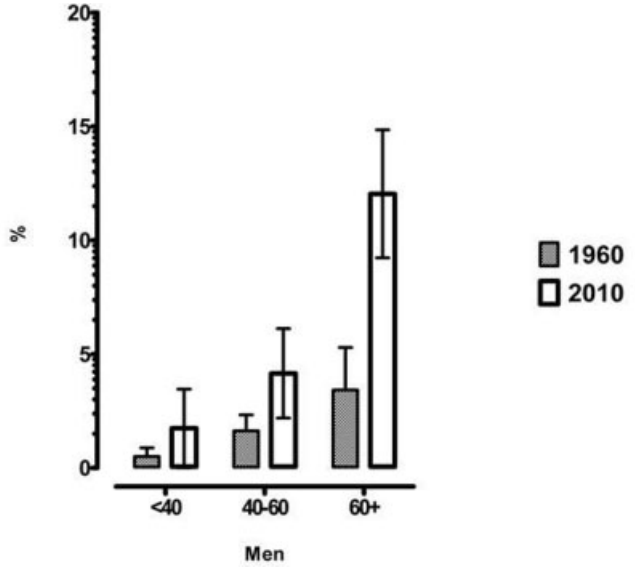


Figure 1.

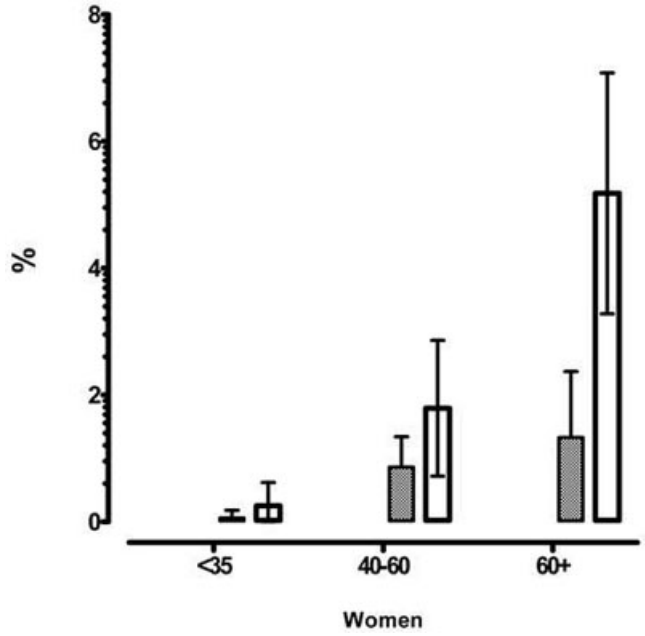


Figure 2.

Conclusion: The population burden of illness from gout has increased substantially in absolute and relative terms in the past 50 years. Both genders and all age groups witnessed increasing rate, the highest rise being evident in men older than 65 years. This increase was explained entirely by increase in abdominal adiposity among women. Among men, however, increased prevalence of abdominal adiposity, hypertension, diabetes, increasing population age only partly explained the increase. At least some of the observed increase could be due to greater disease awareness as the case definition was based on self-report.

Disclosure: E. Krishnan, Takeda, 2, Takeda, 2; **L. Chen**, None.

2001

Kaiser Permanent Pyramid In Patients With Gout: The Most Severe Gout Is Associated To The Most Complex Patients. Fernando Perez-Ruiz, Ana M. Herrero-Beites and Amaya Martinez-Galarza. BioCruces Health Institute, Baracaldo, Spain.

Background/Purpose: gout is well known to be associated with comorbid conditions; the *Kaiser Permanente Pyramid* (KPP) identify high risk people (two higher strata) in the population, in order to support them in an individualized and multidisciplinary management, respectively, to avoid admissions. This study intends to evaluate whether severity of gout is also associated with higher KPP.

Methods: prospective cohort of follow-up of gout patients in whom KPP distribution was endorsed by the health system in the patients electronic file from Sept 2012. Comorbid conditions known to be cardiovascular risk factors (hypertension, glomerular filtration, diabetes, hyperlipidemia, vascular events), were recorded in the patientsx record file at baseline. In addition, evaluation of the severity of gout according to the number of flares (previous year), joint distribution, presence of subcutaneous tophi, and X-ray abnormalities related to gout, along with acute kidney injury related to the previous use of NSAIDs were also recorded at baseline evaluation.

Results: 256 patients, 92.2% men, 77% crystal and 11% hs-ultrasound based diagnosis, have been evaluated using the KPP. KPP higher strata included 132 (51.5%) of all the patients: 72 (28.1%) considered as high risk /disease care patients and 60 (23.4%) as very complex/case management patients. Comorbidities associated with gout were much more prevalent in the two higher strata of KPP (Table), but also showed that polyarticular distribution, presence of tophi, and X-ray abnormalities were more prevalent in these patients. Interestingly, previous acute kidney injury attributed to NSAIDs was ten-fold in these high-risk patients compared to low-risk patients.

KPP	Age (yr)	Women (%)	Onset (yr)	FGR (ml/min)	HT (%)	DM (%)	HLP (%)	VE (%)	Flares (yr)	Poly (%)	Tophi (%)	X-ray (%)	AKI (%)
0–1 N=124	55 ± 11	4.0	8.4 ± 8.4	53 ± 26	36	7	55	11	4 ± 4	37	35	46	1.6
2–3 N=132	67 ± 11**	11.4**	7.3 ± 7.1	89 ± 24**	73	30**	55	56**	4 ± 6	58**	46*	70**	15.9**

Conclusion: Patients with the highest clinical complexity according to Kaiser Permanente Pyramid also showed the most severe gout, indicating that these complex-severe patients could well deserve specific rheumatologic or even multidisciplinary management.

Disclosure: F. Perez-Ruiz, Menarini International, 5, SOBI, 5, AstraZeneca, 5, Menarini, 8; **A. M. Herrero-Beites**, None; **A. Martinez-Galarza**, None.

2002

Prophylactic Duration and Serum Uric Acid Level Are Associated With Gout Flare During Urate Lowering Treatment. Hyo-Jin Choi[1], Chan Hee Lee[2], Sang Tae Choi[3], Jung-Soo Song[3], Hyoun-Ah Kim[4], Chang-Hee Suh[5], Hoyeon Joo[6], Ki Chul Shin[7] and Hanjoo Baek[1]. [1]Gachon University Gil Hospital, Incheon, South Korea, [2]NHIC Ilsan Hospital, Goyang-si, South Korea, [3]Chung-Ang University College of Medicine, Seoul, South Korea, [4]Ajou University School of Medicine, Suwon, South Korea, [5]Ajou University Hospital, Suwon, South Korea, [6]Inha University Hospital, Incheon, South Korea, [7]Seoul National University College of Medicine, Seoul, South Korea.

Background/Purpose: To evaluate the clinical factors on gout flare during urate lowering treatment

Methods: We retrospectively examined data derived from 228 patients who had been treated with urate lowering agent more than six months after stopping prophylactic medication at multicenter rheumatology clinics. Demographic data (age, sex, disease duration, tophi and comorbidity), clinical and laboratory features including presence of gout flare during only urate lowering treatment, kinds and dose of urate lowering agents, serum uric acid, fasting glucose, lipid profile and creatinine clearance were collected at the initiation of urate lowering treatment and at the six months after stopping prophylaxis.

Results: Mean age of patients was 51.3 years, mean disease duration was 28.9 months, and mean body mass index was 27.5. Male to female ratio was 225:3. Starting urate lowering agents were allopurinol 84.6%, febuxostat 0.9%, and uricosuric agents 14.5%. Seventy-seven patients among 228 cases (33.8%) had experienced at least 1 gouty attack during only urate lowering therapy. Mean duration of prophylactic medication was shorter in flare group (9.1 months) than in non- flare group (11.3 months, $p=0.042$). At the time of stopping prophylaxis, mean serum uric acid level was 6.2 mg/dL (6.5 mg/dL vs. 6.0 mg/dL, $p=0.071$). According to the duration of prophylactic treatment ($<$ 6months, $\geq$6months), there were more frequent flares in the $<$ 6 months group than $\geq$ 6 months group (41.7% vs. 25.7%, $p=0.012$). At the time of stopping prophylaxis, mean serum uric acid level was 6.8 mg/dL vs. 5.6 mg/dL, $p=0.000$ respectively.

Conclusion: Prophylactic duration more than six months and target serum uric acid level (<6mg/dL) at the time of stopping prophylaxis are favorable factors for recurrent gout flare during urate lowering treatment

Disclosure: H. J. Choi, None; **C. H. Lee**, None; **S. T. Choi**, None; **J. S. Song**, None; **H. A. Kim**, None; **C. H. Suh**, None; **H. Joo**, None; **K. C. Shin**, None; **H. Baek**, None.

2003

Outcome Of Gout Patients Placed On Febuxostat After Failing To Reach Serum Urate Target With Allopurinol. Hind Hatoum[1], Dinesh Khanna[2], Aki Shiozawa[3], Swu-Jane Lin[4], Kasem Akhras[5] and Puja Khanna[6]. [1]University of Illinois at Chicago, chicago, IL, [2]University of Michigan, Ann Arbor, MI, [3]Takeda Pharmaceuticals International, Inc, Deerfield, IL, [4]University of Illinois at Chicago, Chicago, IL, [5]Formerly of Takeda Pharmaceuticals International, Inc, Deerfield, IL, [6]University of Michigan Medical Center, Ann Arbor, MI.

Background/Purpose: The 2012 American College of Rheumatology (ACR) gout guidelines recommends allopurinol or febuxostat as first-line urate-lowering therapy (ULT). Purpose of this study was to compare outcomes in ULT-treated patients who were initiated and maintained on either allopurinol or febuxostat. In addition to outcomes of those switched to febuxostat after failing to reach target serum urate (sUA) ≤ 6mg/dL on allopurinol.

Methods: Centricity Electronic Medical Record database of ambulatory care by GE was used. Patients ≥18 years of age, with newly diagnosed with gout (ICD-9, 274.xx) on or after 2005, and initiated on allopurinol or febuxostat were included. Study index date was defined as date of first initiated ULT in patients with at least 6 months of data pre- and post study index. Patients were followed to date of last record. Primary study endpoint was reaching target sUA <6mg/dL within 6 months from index date. Descriptive statistics and bivariate analyses were performed on proportions of patients who reached target sUA among groups of allopurinol-throughout, febuxostat-throughout, or allopurinol-switched-to-febuxostat.

Results: Study cohort consisted of 16,366 patients who used allopurinol throughout, 884 patients used febuxostat throughout, 505 patients switched to febuxostat after failing targeted sUA with allopurinol. Within 6 months after switching to febuxostat, 36.8% of 505 patients who failed to reach target sUA on allopurinol achieved the goal sUA <6mg/dL. The proportion of allopurinol-switched-to-febuxostat who reached target sUA level was significantly higher than that among the allopurinol-throughout patients (36.8 vs. 28.9%, p=0.001), however, significantly lower than that among the febuxostat-throughout patients (36.8% vs. 46.0%, p=0.003, Figure). The 6-month average sUA after switching was 5.4 mg/dL, representing 39% reduction from the mean value of 8.6 mg/dL at time of switch. At the end of available records, 244/505 (48.3%) reached target. For these patients who reached target sUA, the mean (SD) days to switch from allopurinol was 197 (165 days), and the mean days of febuxostat treatment after the switch was 111 (137 days). The only significant difference between those who reached or did not reach sUA target was that the former group was significantly older (Table).

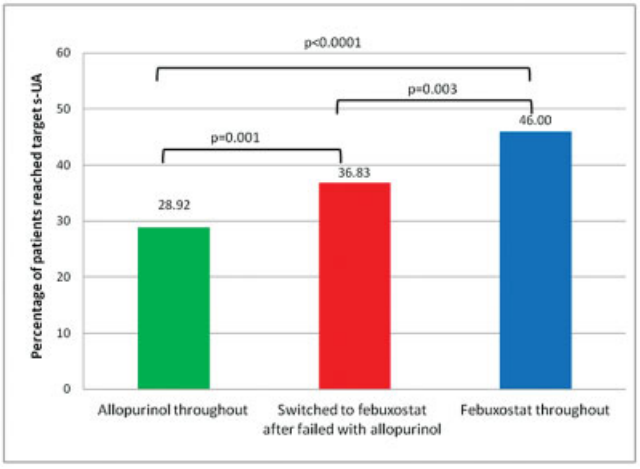


Figure 1. Proportion of patients reached sUA goal in 6 months of initiating ULT or switching.

Table 1. Bivariate analyses comparing between allopurinol patients who reached or did not reach sUA goal after switched to febuxostat

Variable	Did not reach goal after switch (N = 261)	Reached goal after switch (N = 244)	P value
Age, mean (SD)	61.84 (14.21)	65.02 (12.57)	0.0083
CCI, mean (SD)	0.45 (0.96)	0.38 (0.87)	0.3840
Gender, n (%)			
Female	79 (30.27)	91 (37.30)	0.0949
Race, n (%)			0.2098
Asian	4 (1.53)	4 (1.64)	
Black	29 (11.11)	19 (7.79)	
Hispanic	3 (1.15)	3 (1.23)	
Unknown	119 (45.59)	94 (38.52)	
White	106 (40.61)	124 (50.82)	
Gout diagnosis year, n (%)			0.8442
2005	6 (2.30)	4 (1.64)	
2006	5 (1.92)	6 (2.46)	
2007	19 (7.28)	16 (6.56)	
2008	35 (13.41)	30 (12.30)	
2009	92 (35.25)	77 (31.56)	
2010 & 2011	104 (39.85)	111 (45.49)	
BMI group, n (%)			0.3827
Underweight	0 (0)	1 (0.49)	
Normal	14 (6.39)	19 (9.22)	
Pre-obese	42 (19.18)	45 (21.84)	
Obese	163 (74.43)	141 (68.45)	
Baseline eGRF, ml/min, n (%)			0.3621
<15	0 (0.00)	3 (1.55)	
15≈<30	23 (12.11)	30 (15.46)	
30≈<60	105 (55.26)	102 (52.58)	
60≈<90	49 (25.79)	44 (22.68)	
>90	13 (6.84)	15 (7.73)	
Baseline serum UA level group, n (%)			0.3398
<6 mg/dL	2 (1.16)	4 (2.38)	
>=6–<7 mg/dL	8 (4.62)	12 (7.14)	
>=7–<8 mg/dL	19 (10.98)	22 (13.10)	
>=8–<9 mg/dL	39 (22.54)	46 (27.38)	
>=9 mg/dl	105 (60.69)	84 (50.00)	
Baseline Tophi diagnosis, n (%)	5 (1.92)	3 (1.23)	0.7256

Conclusion: Proportion of patients reaching target sUA levels varied significantly in patients utilizing ULT. Those who switched from allopurinol to febuxostat did significantly better than those who stayed on allopurinol in reaching target sUA but worse than those who started on febuxostat from the beginning.

Disclosure: H. Hatoum, Hind Hatoum, 5; **D. Khanna**, Dinesh Khanna, 5, Dinesh Khanna, 2; **A. Shiozawa**, Takeda Pharmaceuticals International, 3; **S. J. Lin**, Swu-Jane Lin, 5; **K. Akhras**, Kasem Akhras, 3; **P. Khanna**, Puja Khanna, 5, Puja Khanna, 8.

2004

Kidney Disease Is An Independent Risk Factor For Incident Gout. Weiqi Wang[1], Vidula Bhole[2] and Eswar Krishnan[3]. [1]Stanford University, Palo Alto, CA, [2]EpiSolutions Consultancy Services, Thane, India, [3]Stanford University, Palo Alto, CA.

Background/Purpose: Even though the prevalence of chronic kidney disease (CKD) has been shown to be dispoportionarely high among those with gout, there have been scant data on temporal relationship between the two.

Methods: We analyzed data from the Framingham heart study (FHS) spanning 52 years from 1948 to 2000, over 26 study visits. Gout was defined as X-ray identified gout or physician diagnosed gout or usage of any gout medication or self-reported gout or presence of individual gout history. CKD was defined as physician diagnosed CKD or presence of CKD history. Hypertension was defined as systolic blood pressure >= 140 mm Hg or diastolic blood pressure >= 90 mm Hg or usage of anti-hypertensive medications. The alcohol and tobacco usage were self-reported. Diabetes and BMI was defined according to FHS official review. Statistical analyses were performed using Cox proportional hazard regression models, where the dependent variable was the time to incident gout. All covariates that entered the multivariable models (CKD, sex, age, BMI, hypertension, diabetes, usage

of alcohol and tobacco) were treated as time varying in the regression models. Missing values were addressed by multiple imputations.

Results: There were 5079 participants that were included, among whom 815 had CKD. At the baseline the proportion of men was 45.17%. Overall there were 414 incident cases of gout during the follow up. The incidence rate per thousand person-years of gout in the CKD group was 4.37 and in the non-CKD group was 2.53. The unadjusted and age adjusted hazard ratio of CKD were 1.48 (95% confidence interval 1.15–1.90) and 1.48 (1.15–1.90) respectively. In multivariable Cox models, CKD was associated with a hazard ratio of 1.68 (1.23–2.29).

Conclusion: CKD is a risk factor for gout, independent of gender, increasing age, obesity, hypertension, diabetes, usage of tobacco and alcohol.

Disclosure: W. Wang, None; **V. Bhole**, None; **E. Krishnan**, Takeda, 2, takeda, 5.

2005

Predictors Of Outcomes In Tophaceous Gout- Results From a Prospective Cohort At The Veterans Affairs. Puja Khanna[1], Cleopatra Aquino-Beaton[2], Jasvinder A. Singh[3], Erin Duffy[4], David Elashoff[5] and Dinesh Khanna[6]. [1]Ann Arbor VA, Ann Arbor, MI, [2]VA Greater Los Angeles Healthcare System, Los Angeles, CA, [3]University of Alabama, Tuscaloosa, AL, [4]University of California Los Angeles, Los Angeles, CA, [5]UCLA Department of Medicine Statistics Core, Los Angeles, CA, [6]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI.

Background/Purpose: Tophaceous gout is a chronic inflammatory arthritis that causes debilitating acute attacks and associated with exponential resource utilization. Our objective was to define predictors of tophaceous gout in a prospective cohort.

Methods: 112 veterans with gout were recruited from rheumatology and primary care clinics at a single VA facility and followed for a total of 4 visits 3 months apart. Joint counts and presence of tophus was assessed by providers. HRQOL was evaluated with SF-36 v2, Health assessment questionnaire-disability index (HAQ-DI), and Gout Impact Scale (GIS) of $GAQ_{2.0}$. Patient demographics, duration of gout, Charlson comorbidities (CCI), serum urate (sUA), and patient and physician rating of the severity of gout on a 0–10 scale were assessed. Comparisons were made using the student's t test or the chi-square, Wilcoxon rank sum test or Fisher exact test, as appropriate, p-value < 0.5 was considered statistically significant. Age, race, physician severity score, functional class, disease duration, alcohol use, and number of comorbidities were considered as predictors of having tophaceous gout in univariate and multivariate logistic regression models.

Results: Patients diagnosed with tophaceous gout (N=35) were similar to patients without tophaceous gout (N=74) with respect to age, gender, race, alcohol use, duration of gout, polyarticular involvement, sUA and number of Charlson comorbidities, serum creatinine, and sUA (Table). Physician gout severity scores were significantly greater among patients with tophaceous gout; however, there was no difference in patient severity scores between groups. SF-36 scores indicated that the tophaceous group had worse physical functioning (p =0.04), bodily pain (p=0.07), total PCS scores (p=0.07), and gout concern overall domain of GIS (p=0.07). Physician severity score was the only significant predictor of outcomes identified after controlling for age, race, physician severity score, functional class, disease duration, alcohol use, and number of comorbidities.

Table 1. Patient Characteristics, Non-Tophaceous and Tophaceous

		Total Cohort N=112	Non-Tophaceous N=74	Tophaceous N=35	p-value
Age (Years)	Mean (SD)	65.7 (11.2)	65.5 (12.1)	66.5 (9.8)	0.68$^{\alpha}$
Gender (Male)	N (%)	106 (97.3)	72 (97.3)	34 (97.1)	0.99$^{\beta}$
Race					
Caucasian	N (%)	76 (67.86)	47(63.51)	26 (74.29)	0.29$^{\beta}$
African American	N (%)	17 (15.18)	15 (20.27)	2 (5.71)	
Other	N (%)	19 (16.96)	12 (16.22)	7 (20.00)	
Alcohol Use	N (%)	39 (35.1)	27 (36.5)	11 (32.4)	0.75$^{\epsilon}$
Duration of Gout	Mean (SD)	13.9 (12.9)	12.7 (12.3)	15.7 (14.0)	0.31$^{\gamma}$
Polyarticular Involvement (>3 joints)	N (%)	37 (36.3)	22 (32.4)	14(45.2)	0.22$^{\epsilon}$
# of Comorbidities (CCI)	Mean (SD)	3.9 (2.5)	3.6 (2.3)	4.5(2.6)	0.12$^{\gamma}$
Physician Severity Score	Mean (SD)	3.0 (2.5)	2.3 (2.1)	4.4(2.9)	<0.0001$^{\alpha}$
Patient Severity Score	Mean (SD)		6.0 (2.9)	6.5 (3.4)	0.44$^{\alpha}$
Radiographic evidence of erosion or tophi	N (%)	35 (70.0)	16 (53.3)	19 (95.0)	0.002$^{\beta}$
Serum Urate	Mean (SD)	7.5 (1.9)	7.8 (2.0)	7.1 (1.6)	0.09$^{\gamma}$
Serum Creatinine	Mean (SD)	1.4 (0.9)	1.5 (0.9)	1.3 (0.5)	0.60$^{\gamma}$

α=T-test; β=Fisher Exact test; γ=Wilcoxon test;ϵ=Chi-square test

Conclusion: Physicians rated tophaceous gout patients as having more severe disease. Surprisingly, conventional predictors of tophaceous gout such as disease duration, kidney disease, and sUA were similar in tophaceous and non-tophaceous groups. This may be reflective of the VA population that has a higher burden of urate even in the non-tophaceous patients.

Disclosure: P. Khanna, NIH, 2; **C. Aquino-Beaton**, None; **J. A. Singh**, Takeda, Savient, 2, Savient, Takeda, Ardea, Regeneron, Allergan, 5, URL pharmaceuicals Novartis, 5; **E. Duffy**, None; **D. Elashoff**, None; **D. Khanna**, NIH, 2, Scleroderma Foundation, 2.

2006

Uric Acid Level Is Not An Independent Predictor Of Cardiovascular Diseases In Gout Patients With Treatment; Long-Term Follow-Up Data In Single Tertiary Center In South Korea. Seulkee Lee[1], Eun-Jung Park[2], Jinseok Kim[2], Chan Hong Jeon[3], Hyungjin Kim[1], Jaejoon Lee[4], Eun-Mi Koh[1] and Hoon-Suk Cha[4]. [1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Jeju National University Hospital, Jeju, South Korea, [3]Soonchunhyang University College of Medicine, Bucheon, South Korea, [4]Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea.

Background/Purpose: Hyperuricemia and gout are closely related conditions that are prevalent worldwide. A possible link between hyperuricemia and cardiovascular diseases (CVD) has been a debated clinical topic for many decades. In particular, no study showed long-term cumulative effect of serum uric acid on CVD in gout patients with treatment.

The aim of this study is to evaluate the cardiovascular outcomes and determined cumulative impact of long-term uric acid level on CVD in gout patients with uric acid lowering treatment.

Methods: All patients who had first visit for gout at Samsung Medical Center between 1995 and 2002 and follow-up until December 2012 or expired during follow-up period were included and retrospective analyzed. Demographics, laboratory data and cardiovascular outcomes were evaluated. Mixed effect model and multi-variable analysis were used to determine the cumulative effect of long-term, repeated uric acid level on CVD.

Results: Two-hundred seventy-three patients with gout were observed. Of these, 49 (17.9 %) patients developed at least one of the CVD during follow-up period. Seven of the 49 patients showed two different kinds of CVD. Twenty-nine cases of coronary heart disease (CHD) or congestive heart failure (CHF), 24 cases of cerebral infarction or transient ischemic attack (TIA) and 4 cases of peripheral arterial occlusive diseases (PAOD). Mean age of diagnosis of gout was 45.4 and mean follow-up duration was 11.5 years. Baseline characteristics between patients with or without CVD showed no significant difference except incidence of hypertension. The cumulative effect of long-term uric acid level on CVD did not showed statistical significance according to mixed effect model ($P = 0.13$) and also multivariable analysis after adjusting confounding factors ($P = 0.07$). Chronic kidney disease (CKD), duration of gout and hypertension were risk factors for CVD in gout patient with uric acid lowering treatment by multi-variable analysis ($P = 0.01$, $P = 0.01$ and $P= 0.01$, respectively)

Conclusion: Our data demonstrated a long-term cumulative effect of uric acid may a cause for factors that are in the causal pathway for CVD rather than an independent predictor for CVD in gout patients with uric acid lowering treatment. CKD, duration of gout and hypertension were found to be the sole predictors for CVD in gout patients with treatment.

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2007

Using Natural Language Processing and Machine Learning To Identify Gout Flares From Electronic Clinical Notes. Chengyi Zheng[1], Nazia Rashid[2], T. Craig Cheetham[3], Yi-Lin Wu[3] and Gerald D. Levy[4]. [1]Kaiser Permanente Southern California, Pasadena, CA, [2]Kaiser Permanente Southern California, Downey, CA, [3]Kaiser Permanente, Downey, CA, [4]Southern California Permanente Medical Group, Downey, CA.

Background/Purpose: Gout flares are the most common manifestation of gout. Gout flares are not well documented by diagnosis codes and are not adequately captured when conducting retrospective database analyses. Recently, in 2009, a code for acute gouty flare (ICD9 – 274.01) became available, but has yet to be widely adopted. We implemented a computer based method to automatically identify gout flares using Natural Language

Processing (NLP) and Machine Learning (ML). NLP aims to understand human languages and facilitates the utilization of the information in the free text. Machine Learning is aimed to train a computer system from data and then used to make decisions on new data.

Methods: A retrospective review was conducted between 1/1/2007 to 12/31/2010 from Kaiser Permanente Southern California Region. Patients > 18 years, with a diagnosis of gout (ICD9 274.xx) and on urate-lowering therapy were identified. 599,317 notes for 16,519 patients were retrieved. A training dataset of 1,264 notes was created by selecting 100 random patients. A Rheumatologist reviewed these notes to classify each note as gout flare or not. 1,192 notes from another 100 random selected patients were created and independently reviewed by two Rheumatologists to create the gold standard. A list of key words and phrases were used in the NLP algorithm which was used to capture different aspects of gout flares. The NLP results were used as features of the ML system which helped to achieve better specificity without significant loss in sensitivity. Both NLP+ML algorithms were developed using the training dataset then applied to all of the notes. Gout flares were also identified using claims data as proposed in published literature, which was then compared to the gold standard as well.

Results: Out of the 599,317 notes, the NLP system identified 49,415 notes as gout flare. ML system further classified them into 18,869 positive and 30,546 negative cases. Flares occurred within 30 days are merged. For the 16,519 patients, the NLP+ML system identified 1,402 patients with >= 3 flares, 5,954 with 1–2 flares, and 9,163 with no flare. Our method significantly identified more flare cases (18,869 vs. 7,861) and patients (7,356 vs. 5,458) compared to the method using the claims data.

On task of identifying flare for each note, our method achieved sensitivity of 84.8% and specificity of 92.2%. On task of identifying patients who had flares, our method had sensitivity of 98.5% and specificity of 96.4%. On task of identifying patients who had 3 or more flares, our method had sensitivity of 93.5% and specificity of 84.6%. The NLP+ML method is consistently better than the claims data approach and it even out-performed the two rheumatologist reviewers on task of identifying patients with gout flares.

Conclusion: A combination of NLP and ML is able to accurately and efficiently identify patients with gout flares. This is the first successful use of a computer controlled algorithm to identify gout flares from the clinical notes. It demonstrates that NLP could be a valuable tool to identify populations of patients who experience gout flares for more intensive therapy, ultimately getting them to serum urate goal, and help reducing overall costs associated to gout flares.

Disclosure: C. Zheng, None; **N. Rashid**, None; **T. C. Cheetham**, None; **Y. L. Wu**, None; **G. D. Levy**, None.

2008

Assessing Treat To Target In Gout Patients With and Without Tophi. Leslie R. Harrold[1], Carol Etzel[2], Bruce Schechter[3], Raymond L. Malamet[3], Vanessa Cox[4] and Jeffrey D. Greenberg[5]. [1]University of Massachusetts Medical School, Worcester, MA, [2]UT MD Anderson, Houston, TX, [3]Savient Pharmaceuticals, Inc., Bridgewater, NJ, [4]CORRONA, Inc, Southborough, MA, [5]NYU Hospital for Joint Diseases, New York, NY.

Background/Purpose: Little is known regarding the differences in characteristics between patients with tophaceous gout compared to those without tophi. We examined these differences in a national cohort of gout patients.

Methods: Patients enrolled by their rheumatologist within the Consortium of Rheumatology Researchers of North America (CORRONA) gout registry between 11/1/12 and 5/12/13 were included. All gout patients were eligible for enrollment regardless of disease severity, disease activity or medication use. Data was gathered at the time of routine clinical visits from patients and their treating rheumatologists including demographics, gout characteristics, comorbid conditions, current treatments, laboratory results and physical exam findings, including presence of tophi. Specifically we examined medication use and successful compliance with respect to target treatment goals (e.g., gouty flares and serum urate levels).

Results: There were 54 rheumatologists across the US who enrolled 524 gout patients who were predominately men (79%), with a mean age of 64 years (±13.6), disease duration of 10 years (± 9.6), and maximum uric acid level of 9 (±2.1) at the time of diagnosis. Associated cardiovascular disease was common in both those with tophi (n=116) and those without (n=407) (73% vs. 65%, p=0.12). Patients with tophi were more likely to have chronic kidney disease (29% vs. 14%, p=0.001). There was a trend towards a greater prevalence of diabetes mellitus in patients with tophi (25% vs. 19%, p=0.192) In addition, those with tophi, more often had to avoid the use of nonsteroidal anti-inflammatory drugs for acute gouty flares (33% vs. 20%, p<0.01). While use of urate-lowering therapy was common in those with tophi (60% allopurinol, 28% febuxostat, 5% pegloticase and 3% probenecid), only 58% of patients had achieved a SUA ≤6mg/dl (39% <5mg/dl). Both those with and without tophi had active disease with a mean of 4 and 3 gout flares respectively in the prior 12 months.

Conclusion: Most of the gout patients had active disease and not reached target SUA levels. Those with tophi are more likely to have chronic kidney disease and were less likely to be able to tolerate commonly prescribed medications to treat gouty flares.

Disclosure: L. R. Harrold, CORRONA, Inc., 5; **C. Etzel**, CORRONA, Inc., 3; **B. Schechter**, Savient Pharmaceuticals, Inc., 3, Savient Pharmaceuticals, Inc., 1; **R. L. Malamet**, Savient Pharmaceuticals, Inc., 3, Savient Pharmaceuticals, Inc., 1; **V. Cox**, CORRONA, Inc., 3; **J. D. Greenberg**, CORRONA, Inc., 1, CORRONA, Inc, 5, AstraZeneca, 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5.

2009

Outcome Of Allopurinol Or Febuxostat Treatment In Gout Patients Naïve To Urate-Lowering Therapy. Puja Khanna[1], Hind Hatoum[2], Swu-Jane Lin[3], Aki Shiozawa[4], Kasem Akhras[5] and Dinesh Khanna[1]. [1]University of Michigan Medical Center, Ann Arbor, MI, [2]University of Illinois at Chicago, chicago, IL, [3]University of Illinois at Chicago, Chicago, IL, [4]Takeda Pharmaceuticals International, Inc, Deerfield, IL, [5]Formerly of Takeda Pharmaceuticals International, Inc, Deerfield, IL.

Background/Purpose: In the US, 3.9% (8.3 million) of the population have self-reported gout, and 21.4% (43.3 million) have hyperuricemia. The 2012 ACR guidelines recommend febuxostat or allopurinol as first line urate-lowering therapy (ULT). In this study, outcomes in ULT-naïve patients in community clinics were investigated based on prescriptions patterns for allopurinol or febuxostat.

Methods: Centricity Electronic Medical Record database of ambulatory care by General Electric was used. Patients (≥18 years of age), newly diagnosed with gout (ICD-9, 274.xx) on or after 2005 and initiated on allopurinol or febuxostat were included. Study index date was defined as date of first initiated ULT in patients with at least 6 months of data pre- and post study index. Study groups consisted of patients first prescribed either ULT. Patients were followed to date of last record. Primary study endpoint was reaching target serum urate (sUA) of <6mg/dL in 6 months from index. Descriptive statistics and bivariate analyses were performed. Logistic regressions compared the likelihood to reach target sUA after either ULT accounting for several relevant covariates such as age, gender, baseline sUA and Charlson co-morbidity index (CCI).

Results: 17,199 (93.5%) patients started on allopurinol and 1190 (6.5%) patients started on febuxostat were enrolled. Overall study cohort had a mean age of 63.7±13.3 (standard deviation, SD), with 69.4% male, and 79.7% white. Mean follow-up duration from index to last record was 541.5±237.9 days. No significant differences between 2 ULT-treated groups were found for age, CCI, gender, race, or in having hypertension. Febuxostat group was more likely to have lower estimated glomerular filtration rate (eGFR; 46.4% vs 34.7% with <60 ml/min), higher overall mean baseline sUA (68.8% vs 68.0% with >=8 mg/dL), and twice as many with tophi (1.68% vs 0.88%), all p<0.05. Among the overall study cohort, 10,871 patients (59.1%) had sUA level after initiating ULT. 59.12% of the patients had documented sUA levels after initiation of ULT. Patients who had sUA measurement post study index date included 10,119 (93.1%) in the allopurinol and 752 (6.9%) in the febuxostat groups. Proportions reaching target were 29.2% in the allopurinol group and 42.2% in the febuxostat group (p<0.05) at 6-month follow-up. At 2 years post initiating ULT, 58.2 % of the patients in the febuxostat and 48.4% in the allopurinol treated groups reached target sUA levels (p<0.05).

Conclusion: Among ULT naïve patients, those starting with febuxostat had higher baseline sUA, higher tophi and worse eGFR than those starting with allopurinol. In spite of their more advanced or severe gout, febuxostat treated patients were significantly more likely to achieve target sUA at 6 months. Since more than 40% of the patients did not have documented sUA levels after initiation of ULT and doses were not factored into the analysis, the generalizability of the study results is hindered. Also study duration may have impacted the reported findings.

Disclosure: P. Khanna, Puja Khanna, 5, Puja Khanna, 8; **H. Hatoum**, Hind Hatoum, 5; **S. J. Lin**, Swu-Jane Lin, 5; **A. Shiozawa**, Takeda Pharmaceuticals International, 3; **K. Akhras**, Kasem Akhras, 3; **D. Khanna**, AstraZeneca Takeda Pharmaceuticals International, Savient, 5, National Institutes of Health, Savient, 2.

2010

Erdheim-Chester Disease: A Monocentric Series Of 96 Patients. Julien Haroche[1], Laurent Arnaud[1], Fleur Cohen-Aubart[1], Baptiste Hervier[1], David Saadoun[1], Nathalie Costedoat-Chalumeau[2], Sophie Besnard[3], Kim Heang Ly[4], Michel Pavic[5], Jean-Gabriel Fuzibet[6], Loic Raffray[7], Laurent Aaron[8], Pascal Bindi[9], António Marinho[10], Bjorn Blomberg[11], Juan Salvatierra[12], Claudia Dechant[13], Aude Rigolet[14], François Lifermann[15], Jo Caers[16], Catherine Veyssier-Belot[17], Bertrand Wechsler[1], Lucienne Michaux[18], Giorgio Graziani[19] and Zahir Amoura[1]. [1]Hôpital Pitié-Salpêtrière, AP-HP, UPMC Univ Paris 06 & French National Reference Center For Systemic Lupus and Antiphospholipid Syndrome, Paris, France, [2]Hopital Cochin, Paris, France, [3]Pontchaillou University Hospital, Rennes, Rennes, France, [4]Limoges University Hospital, Limoges, France, [5]HIA Desgenettes, Lyon, France, Lyon, France, [6]Internal Medicine, Hôpital de l'Archet 1, CHU de Nice, Nice, France, [7]CHU de Bordeaux, Bordeaux, France, [8]Hôpital Jacques Coeur, Bourges, Bourges, France, [9]Department of medicine A, Centre Hospitalier de Verdun, Verdun, France, [10]Unidade de Imunologia Clínica, Porto, Portugal, [11]University of Bergen, Norway, Bergen, France, [12]University Hospital San Cecilio, Granada, Spain, [13]University of Munich, Munich, Germany, [14]Pitie-Salpetriere Hospital, Paris, France, [15]CH de Dax, Dax, France, [16]Centre Hospitalier Universitaire de Liège Domaine Universitaire du Sart Tilman, Liège, Belgium, [17]CHI Poissy Saint-Germain-en-Laye, Saint-Germain-en-Laye, France, [18]Cliniques Universitaires Saint-Luc UCL Bruxelles, Bruxelles, Belgium, [19]Istituto Clinico Humanitas IRCCS, Rozzano-Milano, Italy, Milan, Italy.

Background/Purpose: Erdheim-Chester disease (ECD) is a rare non-Langerhans form of histiocytosis characterized by an infiltration of foamy CD68+ CD1a- histiocytes. More than 500 cases of this disease have been reported since its first description in 1930.

Methods: The aim of this study was to describe a single-centre series of 96 consecutive ECD patients hospitalized at least once between 1992 and 2013 in the departement of internal medicine of Pitié-Salpêtrière hospital, Paris, France.

The geographic origin of patients referred to our tertiary care centre is international: 75 are french residents, while 21 patients come from Germany, UK, Eire, Belgium, Spain, Portugal, Israel, Norway and South Africa.

Results: Patients were 75 men and 21 women. Median age at diagnosis was 54.6 years (5–81 yr). In the present series the mean diagnostic delay is 2 yr (0–35yr). Mean follow-up between diagnostic and last news is 37.3 months (1.63–376 months). Fifty-five patients (56%) had peri-renal. Forty patients (42%) had a peri-aortic sheathing of the whole aorta ("coated aorta"), 33 (34%) a pericardial involvement, 29 (30%) a coronary involvement, 20 (21%) a reno-vascular hypertension, 34 (35%) a pseudotumoral infiltration of the right atrium. Twenty-two patients (23%) had an exophthalmos, 24 (25%) a xanthelasma often in peri-orbital spaces, 29 (30%) a diabetes insipidus, and 38 (40%) an involvement of the central nervous system (CNS), among which 17 (18%) with a cerebellar involvement. Twenty-one patients (22%) had hydronephrosis, 35 (36%) a pulmonary involvement, often asymptomatic. Seventy-four patients (80%) had high C-reactive protein values.

Eighty-seven patients (91%) have been treated with interferon alpha (IFNα) or Pegylated IFNα, with high doses when facing CNS and/or cardiac involvements. Twenty-two patients died (23%). We were able to identify a $BRAF^{V600E}$ mutation among 27 of the 53 patients (51%) among which tissue samples were exploitable. Seven of these patients with multisystemic ECD, refractory and/or intolerant to IFNα, have been treated with BRAF inhibitors (vemurefenib) with spectacular and sustained responses.

Conclusion: We report the world largest's monocentric series of ECD patients. The prognosis, which largely depends on the presence of CNS involvement, is variable. First line of treatment remains IFNα, which use is associated with improved survival in ECD is an independent prognostic factor of survival of ECD. Nevertheless, long-term therapy with IFNα may be poorly tolerated, and the place of BRAF inhibition, particularly for $BRAF^{V600E}$ mutated patients with life-threatening forms of the disease, should be studied in larger scale.

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2011

Osseous Sarcoidosis: Clinical Presentation, Treatment, and Outcomes. Experience From a Large Tertiary Care Academic Hospital. Jeffrey A. Sparks[1], Jakob I. McSparron[2], Christopher H. Fanta[2] and Jonathan S. Coblyn[2]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Sarcoidosis is a systemic inflammatory disease characterized by the formation of non-caseating granulomas. Osseous involvement in sarcoidosis is a rare manifestation and has infrequently been reported. The distribution of lesions, clinical presentation, treatment strategies, and outcomes of patients with osseous sarcoidosis are unclear. We have reviewed our experience with osseous sarcoidosis to better characterize these clinical features.

Methods: Potential cases of osseous sarcoidosis seen at a large tertiary care academic hospital by the Division of Rheumatology, Immunology and Allergy and the Division of Pulmonary and Critical Care Medicine were identified through directed inquiry and electronic health record queries. Cases were defined as having pathologic evidence of non-caseating granulomas on bone biopsy or evidence of osseous lesions on imaging attributable to sarcoidosis by the radiologist, treating clinician, and reviewer. Characteristics of the clinical presentation, treatment, and outcomes were obtained from thorough medical record review.

Results: We identified 19 cases of osseous sarcoidosis (9 with biopsy-proven disease and 10 with diagnosis based on imaging and clinical presentation). Osseous lesions were detected by imaging during the initial presentation for sarcoidosis in 11 of 19 cases (58%). In those who had a prior established diagnosis of sarcoidosis, the mean duration of sarcoidosis before osseous detection by imaging was 4.8 years. The mean duration between detection of lesions on imaging and definitive clinical diagnosis in those who had a bone biopsy was 344 days. Other systemic features of sarcoidosis were present in 18 out of 19 cases (95%). Hilar lymphadenopathy was present in most cases (16 out of 19, 84%). Symptoms were present in 10 out of 19 cases (53%) and consisted mostly of low back pain, arthralgias/arthritis, and soft tissue swelling. Lesions were detected by magnetic resonance imaging (13 cases) and positron emission tomography (8 cases). All patients had more than one bone involved. Most patients (89%) had axial involvement, primarily in the pelvis and lumbar spine, and required no specific treatment if lesions were discovered incidentally. A minority of cases (9/19, 47%) were treated specifically for osseous sarcoidosis, mostly with prednisone and hydroxychloroquine. Two cases required multiple medications, including anti-tumor necrosis factor therapy, for refractory symptomatic osseous sarcoidosis. At last follow-up, 16 out of 19 (84%) patients were asymptomatic from osseous lesions.

Conclusion: We have identified the largest series of osseous sarcoidosis and characterized its clinical presentation, treatment, and outcomes. Patients with osseous sarcoidosis had multiple bones affected and generally had other systemic manifestations of sarcoidosis. A minority of patients required treatment of their osseous sarcoidosis for relief of symptoms and most patients were symptom-free at last follow-up.

Disclosure: J. A. Sparks, None; **J. I. McSparron**, None; **C. H. Fanta**, UpToDate and McGraw-Hill, 7; **J. S. Coblyn**, CVS, 5.

2012

Gender Influences On Organ Manifestations In a New Orleans Sarcoidosis Population. Adam Janot[1], McCall Walker[2], Mary Yu[1], Harmanjot K. Grewal[3], Matthew R. Lammi[4] and Lesley Ann Saketkoo[5]. [1]Louisiana State University Health Sciences Center, New Orleans, LA, [2]LSUHSC School of Medicine, New Orleans, LA, [3]Lousiana State University Health Sciences Center, New Orleans, LA, [4]Louisiana State University Health Sciences Center, Pulmonary and Critical Medicine, New Orleans, LA, [5]LSU HSC - New Orleans, Sections of Rheumatology and Pulmonary Medicine, New Orleans, LA.

Background/Purpose: Sarcoidosis is a multi-organ disease in which pulmonary manifestations predominate. The skin, eyes, heart, gastrointestinal tract (GI), reticuloendothelial, renal and nervous systems are also commonly involved. Prior studies have shown a gender association with organ-specific manifestations. Male gender is associated with more severe radiographic abnormalities and female gender with more frequent extra-pulmonary manifestations (EPM). We conducted a survey of gender-based differences in organ-specific manifestations of sarcoidosis.

Methods: A retrospective chart review on patients seen in clinics from a single institution from 2006–2012 with biopsy-proven sarcoidosis and a diagnosis >1 year were included. Data were collected on sex, smoking status, EPM (cutaneous, ocular, cardiac, neurologic, GI, and renal), chest radiographs and pulmonary function testing (PFT).

Gender differences between EPMs and pulmonary sarcoidosis (defined as chest radiographic findings consistent with hilar adenopathy and pulmonary fibrosis) were calculated. Differences in forced vital capacity (FVC), total lung capacity (TLC), and diffusion capacity of lung for carbon monoxide (DLCO) were calculated using a t-test for the mean. PFTs were stratified by time of diagnosis in five year intervals. PFT results were averaged if more than one test was done in a five year period.

Results: Of 511 charts reviewed, 156 patients (50 Male, 106 Female) met inclusion criteria. Ocular sarcoidosis (OS) was more frequent in males (M=28.0%, F=10.4%, p=0.005) with an odds ratio of 3.35(95% CI 1.40 to 8.08). Gender was not a significant risk factor for other EPMs, nor for all EPMs combined.

The presence of pulmonary sarcoidosis was not associated with gender. PFTs showed significant gender difference (Table 1). Males demonstrated worse FVC (M=69.0 ± 0.71% predicted, F=82.2 ± 20.35% predicted, p=0.03) and TLC (M=63.0 ± 0.71% predicted, F=78.86 ± 16.37% predicted, p=0.003) at 5–10 years post diagnosis. DLCO was significantly lower in females compared to males at 10–15 years post diagnosis (M= 72.0 ± 4.24% predicted, F=55.33 ± 15.17% predicted, p= 0.02). There was no significant difference in smoking status between male and female groups with pulmonary sarcoid (p=0.11).

Table 1. Percent Predicted FVC, TLC, and DLCO at 5 year intervals from time of diagnosis

Time of PFT relative to diagnosis	0–5 years			5–10 years			10–15 years		
PFT	FVC	TLC	DLCO	FVC	TLC	DLCO	FVC	TLC	DLCO
Males	77.2 ± 16.9 n=22	69.8 ± 15.8 n=22	64.3 ± 18.0 n=22	69.0 ± 0.7 n=2	63.0 ± 0.7 n=2	59.0 ± 12.7 n=2	92.7 ± 11.0 n=3	77.5 ± 9.2 n=2	72.0 ± 4.2 n=2
Females	79.0 ± 18.0 n=39	77.9 ± 15.6 n=36	62.2 ± 25.9 n=36	82.2 ± 20.4 n=14	78.9 ± 16.4 n=14	66.6 ± 21.1 n=14	86.2 ± 19.9 n=9	76.2 ± 10.7 n=9	55.3 ± 15.2 n=9
p-value	0.71	0.06	0.72	0.03	0.003	0.55	0.51	0.88	0.02

Conclusion: Male gender is an independent risk factor for OS. Though gender was not associated with radiographic sarcoidosis, when controlled for smoking, a difference in increased severity of restrictive lung disease was suggested in a very small group of males at 5–10 year post diagnosis. Interestingly, females demonstrated a lower diffusion capacity at 10–15 years after diagnosis; the implications for underlying pulmonary vascular disease with disease duration are unclear.

Disclosure: A. Janot, None; **M. Walker**, None; **M. Yu**, None; **H. K. Grewal**, None; **M. R. Lammi**, None; **L. A. Saketkoo**, None.

2013

Biologic Therapy In Refractory Uveitis Of Sarcoidosis. Multicenter Study Of 16 Patients. Javier Loricera[1], Vanesa Calvo-Río[1], Ricardo Blanco[2], Marina Mesquida[3], Alfredo M. Adan[3], JM Herreras[4], A Aparicio[5], MJ Moreno Ramos[6], MJ Moreno Martínez[6], LF Linares Ferrando[6], M Hernández Martínez[6], D Peitado-Lopez[7], Miguel Cordero-Coma[8], Jl García Serrano[9], Norberto Ortego[9], O Maíz[10], A Blanco[10], Juan Sánchez-Bursón[11], S González-Suárez[12], Alejandro Fonollosa[13], Montserrat Santos-Gómez[1], F. Ortiz-Sanjuán[1] and Miguel Angel González-Gay[1]. [1]Hospital Universitario Marqués de Valdecilla. IFIMAV. Santander. Spain, Santander, Spain, [2]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain, [3]Hospital Clínic of Barcelona, Barcelona, Spain, [4]Hospital Universitario, IOBA. Valladolid, Valladolid, Spain, [5]Hospital de Toledo., Toledo, Spain, [6]Hospital Clínico Universitario Virgen de la Arrixaca. Murcia, Murcia, Spain, [7]Hospital Universitario La Paz Madrid, Madrid, Spain, [8]Hospital de León, León, Spain, [9]Hospital San Cecilio. Granada, Granada, Spain, [10]Hospital Donosti San Sebastian, San Sebastián, Spain, [11]Hospital de Valme. Sevilla, Sevilla, Spain, [12]Hospital Cabueñes, Gijón, Gijón, Spain, [13]Hospital de Cruces. Bilbao, Bilbao, Spain.

Background/Purpose: Uveitis related to sarcoidosis is a potentially severe complication. Corticosteroids are the first line of treatment. In refractory cases or in those with unacceptable side effects, traditional synthetic immunosuppressive drugs are used. TNF-α has been implicated in the pathogenesis of sarcoidosis. Our aim was to evaluate both short and long-term response to anti-TNF therapy in uveitis associated to sarcoidosis refractory to standard systemic treatment.

Methods: Multicenter study of 16 patients followed in the uveitis units from 12 hospitals. All of them presented inadequate response or intolerance to conventional therapy with corticosteroids and at least 1 systemic synthetic immunosuppressive drug.

The degree of ocular inflammation was evaluated according to "The Standardization of Uveitis Nomenclature (SUN) Working Group" (Am J Ophthalmol 2005; 140: 509–516), and macular thickness by optical coherence tomography (OCT). Results were expressed as mean± SD for variables with a normal distribution, or as median [25th-75th interquartile range (IQR)] when they were not normally distributed. Comparison of continuous variables was performed using the Wilcoxon test.

Results: We studied 16 patients/ 27 affected eyes (7 men, 9 women) with a mean age of 38.4±17.2 years (range 13–76). Angiotensin-Converting Enzyme (ACE) was elevated at 56.2% of patients. We observed bilateral hilar lymphadenopathy (56.2%), lung parenchymal involvement (43.7%), peripheral lymph nodes (37.5%) and involvement of other organs (56.2%). In 31.2% of patients the diagnosis was confirmed by a biopsy. The most frequent pattern of ocular involvement was bilateral chronic relapsing panuveitis and the most characteristic findings were Mutton-fat keratic precipitates and snowballs in vitreous. Besides oral corticosteroids and before the onset of biologic therapy patients had received i.v. boluses of methylprednisolone (1 patient), methotrexate (MTX) (12), cyclosporine A (CyA) (5), or azathioprine (AZA) (3). The first biologic agent used was: infliximab (IFX) in 7 cases (43.7 %) and adalimumab (ADA) in 9 cases (56.3 %). They were used in 3 cases as monotherapy and in the remaining cases in combination with: MTX (10), AZA (2) and Mycophenolate mofetil (1). IFX 5 mg/kg /i.v./every 4–8 weeks and ADA 40 mg/sc/2 weeks were the most patterns of administration. During the follow-up, due to intolerance, IFX was successfully switched to golimumab in 2 cases. The mean duration of follow-up after the onset of anti-TNF therapy was 27.7±16.8 months. Overall, improvement was observed after 2 years of therapy: Baseline results versus results after 2 years of biologic therapy were the following: Visual acuity (VA): baseline 0.6± 0.3; after 2 years: 0.8±0.2; p=0.03; Tyndall from a median [IQR] of 1 [0–3] to 0 [0–2] (p=0.017) and vitritis, from a median [IQR] of 0 [0–3] to 0 [0–1] (p=0.03). At baseline, 6 patients, (9 eyes) had macular thickening (OCT>250μ) and 6 patients (7 eyes) had cystoid macular edema (CME) (OCT>300μ). CME improved from 372±58.3 microns to 241±1.4 microns at 2 years (p=0.17).

Conclusion: Anti-TNF therapy seems effective in patients with uveitis secondary to sarcoidosis refractory to conventional immunosuppressive therapy.

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2014

Cigarette Smoking and Male Sex Are Independent Risk Factors For Ocular Sarcoidosis. Adam Janot[1], Dörte Huscher[2], McCall Walker[3], Harmanjot K. Grewal[4], Mary Yu[1], Matthew R. Lammi[5] and Lesley Ann Saketkoo[6]. [1]Louisiana State University Health Sciences Center, New Orleans, LA, [2]Charité University Hospital and German Rheumatism Research Centre, a Leibniz Institute, Berlin, Germany, [3]LSUHSC School of Medicine, New Orleans, LA, [4]Lousiana State University Health Sciences Center, New Orleans, LA, [5]Louisiana State University Health Sciences Center, Pulmonary and Critical Medicine, New Orleans, LA, [6]LSU HSC - New Orleans, Sections of Rheumatology and Pulmonary Medicine, New Orleans, LA.

Background/Purpose: Sarcoidosis is a multi-organ system granulomatous disease of unknown origin with an incidence of 1–40/100,000. Though pulmonary manifestations are predominant, ocular morbidity is characteristic. Ocular Sarcoidosis (OS) affects 25–50% of patients with sarcoidosis and can lead to blindness. To date, no studies have sought to determine risk factors for OS.

Methods: A retrospective chart review was conducted at a single institution with inclusion criteria of biopsy-proven sarcoidosis with a duration of >1 year and a documented smoking status. Variables collected were ages at time of diagnosis (of any organ) and at time of chart review, race, sex, smoking status, quantity of tobacco exposure, and presence (or history) of OS. Disease duration is defined as the difference of age at diagnosis and age time of chart review. Group comparisons were done by t-test and by

Mann-Whitney tests where applicable. Univariate and multivariate regression analysis were done to identify independent risk factors.

Results: Of 269 charts reviewed, 109 patients met inclusion criteria. Characteristics of patients with and without OS are shown in table 1. In the OS group, the portion of smokers (71.4%) was significantly higher than in the group without OS (42.0%, p=0.027). There was no significant difference (p=0.605) in the median number of pack years between smokers with OS (13 [7, 28]) and those without OS (16.5 [7, 25]). Furthermore, the OS group consisted of more male patients (57.1% versus 26.1%, p=0.009). Median disease duration of sarcoidosis was also higher in patients with OS (10 years versus 4 years, p=0.031).

Through multivariate regression analysis, tobacco exposure (OR=5.24, p=0.007, 95% CI 1.58–17.41) and male sex (OR=7.48, p=0.002, 95% CI 2.152–26.006) were found to be independent risk factors for the development of OS.

Table 1. Characteristics of patients with and without OS

	No OS (n=88)	With OS (n=21)	p-value
Sex			
Female	65 (73.9%)	9 (42.9%)	0.009
Male	23 (26.1%)	12 (57.1%)	
Age at onset of sarcoidosis (median, IQR)	41 (35, 49)	43 (33, 49)	0.863
Disease duration (median, IQR)	4 (2, 12)	10 (4, 15)	0.031
Race			
Black	78 (88.6%)	19 (90.5%)	1.000
White	5 (5.7%)	0	
Hispanic	0	1 (4.8%)	(black vs. all other)
Middle Eastern	1 (1.1%)	0 (0.0%)	
Unknown	4 (4.5%)	1 (4.8%)	
Smoking Status			
Never smoker	51 (58.0%)	6 (28.6%)	0.027
Ever smoker	37 (42.0%)	15 (71.4%)	
Pack years of ever smokers (median; IQR)	13 (7, 28)	16.5 (7, 25)	0.605

Conclusion: Male sex and tobacco exposure (regardless of pack years) are independent risk factors for development of OS. Disease duration did not withstand multivariate analysis in this moderately sized group. However, screening for OS should not remit in patients with known sarcoidosis until defined in larger prospective populations.

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2015

Sarcoid Arthritis In World Trade Center Exposed New York City Firefighters Presenting As a Unique Clinical Subset. Konstantinos Loupasakis[1], Jessica Berman[2], Michelle S Glaser[3], Nadia Jaber[4], Rachel Zeig-Owens[4], Mayris P Webber[4], Michael D Weiden[4], Anna Nolan[4], Kerry J Kelly[4] and David J Prezant[5]. [1]Hospital for Special Surgery Weill Cornell Medical College, New York, NY, [2]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, [3]Montefiore Medical Center, Bronx, NY, [4]Bureau of Health Services Fire Department of New York, Brooklyn, NY, [5]Montefiore Medical Center Albert Einstein College of Medicine, Bronx, NY.

Background/Purpose: Sarcoidosis is a multisystem disease characterized by the formation of non-caseating granulomas with lungs being predominantly affected and the joints in up to 40%. Acute joint manifestations occur in 25–40% of patients and are often self-limited with only 1–4% of patients developing a more chronic arthritis, requiring more aggressive therapy, due to persistence or progression. We previously reported an increased incidence of sarcoidosis among Fire Department of the City of New York (FDNY) firefighters prior to 9/11/01 and an even higher incidence after World Trade Center (WTC) exposure. We now describe a series of FDNY firefighters who developed sarcoidosis following WTC rescue/recovery work with severe chronic polyarthritis as a significant component of their disease.

Methods: All FDNY WTC-exposed firefighters with polyarticular sarcoidosis are followed jointly by the WTC Health Program at FDNY and the Rheumatology Division at the Hospital for Special Surgery (HSS). Patient demographics, WTC-exposure information, smoking status, date of diagnosis, and pulmonary findings were obtained from FDNY's WTC database. Joint findings (symptoms, duration, distribution of joints involved, treatments, and response) were obtained from HSS chart review.

Results: 11 male firefighters developed polyarticular arthritis after WTC-exposure; 2 had been diagnosed with sarcoidosis pre-9/11/01. All were never smokers and arrived at the WTC-site within 2 weeks after 9/11/01. Their median age was 37.7 years (IQR = 31.6–40.8), with a median of 6.9 years (IQR=4.4–13.2) of FDNY firefighting service pre-9/11/01. All had biopsy-proven pulmonary sarcoidosis, 9 by transbronchial or mediastinal lymph node biopsy, 1 by liver and bone biopsy and 1 by Kveim testing. All had normal pulmonary function tests at presentation. Duration from WTC-exposure to diagnosis of pulmonary sarcoidosis was 7.7 years (IQR=5.8–9.5). Polyarticular arthritis was part of the initial presentation in 9 patients who developed sarcoidosis post-9/11/01. In 2 patients with pre-9/11/01 sarcoidosis, polyarticular arthritis occurred after WTC exposure, 5 and 10 years after their initial diagnosis. Polyarthritis was symmetrical, involving large joints (n=1), small and large joints (n=10) and ankles (n=10). All had normal ESR and CRP; negative anti-CCP and Quantiferon or PPD. Only one had a positive RF and all but two had normal ACE levels. All required additional disease modifying agents for steroid sparing (stepwise progression from hydroxychloroquine->methotrexate->TNF-blocking agent). Adequate disease control was obtained with hydroxychloroquine (n=1); methotrexate (n=3); and anti-TNF agents (n=6).

Conclusion: Chronic polyarthritis appears to be an important manifestation of sarcoidosis in FDNY firefighters with sarcoidosis and WTC-exposure. Their arthritis appears to be chronic and most have not responded adequately to oral DMARDs, generally necessitating the addition of anti-TNF agents. Further studies are needed in order to determine the generalizability of these findings to other groups with varying levels of WTC-exposure or with non-WTC environmental/occupational exposures.

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2016

Inflamamatory Myositis-Increased Incidence In Fire Department Of New York Firefighters After World Trade Center Exposure. Basit Qayyum[1], Michelle S Glaser[2], Nadia Jaber[3], Rachel Zeig-Owens[2], Mayris P Webber[3], Anna Nolan[3], Kerry J Kelly[3] and David J Prezant[4]. [1]New York University School of Medicine, New York, NY, [2]Montefiore Medical Center, Bronx, NY, [3]Bureau of Health Services Fire Department of New York, Brooklyn, NY, [4]Montefiore Medical Center Albert Einstein College of Medicine, Bronx, NY.

Background/Purpose: Inflammatory myositis (IM) is extremely rare in white middle-aged males. Incidence rates in males ranging from 0.25 to 5 per million. We describe a series of Fire Department of the City of New York (FDNY) firefighters who developed IM following World Trade Center (WTC) exposures.

Methods: FDNY WTC-exposed firefighters with IM are followed jointly by the WTC Health Program at FDNY and the Rheumatology Division at the New York University, School of Medicine. Patient demographics, WTC-exposure information, smoking status, diagnoses (including date of diagnosis), and pulmonary findings were obtained from FDNY's WTC database. Findings (symptoms, duration, muscles involved, treatments, and response) were obtained from chart review.

Results: Seven firefighters developed IM after WTC-exposure. Duration from WTC-exposure to IM diagnosis was 4.6 years (IQR=1.5–6.2). The average annual incidence rate was 9.2 per million. No cases had been reported at FDNY pre-9/11/01 (15 year prior database search). All were white males who arrived at the WTC-site within two weeks after 9/11/01. Three cases are never smokers, while four cases are ever-smokers. None had a family history of IM or autoimmune disease. Their median age on 9/11/01 was 45.5 years (IQR = 43.2–55.6), with a median of 20 years (IQR=15.8–31.0) of FDNY firefighting service pre-9/11/01. All presented with bilateral proximal muscle weakness and pain most noticeable in the pelvic girdle and quadriceps, and elevated creatine kinase. None had skin involvement; one patient developed interstitial lung disease (anti-Jo antibodies) and died two years after lung transplantation; and one patient had inclusion body myositis (IBM) on muscle biopsy. All but two patients responded to corticosteroids and methotrexate with dramatic improvement and one patient had complete resolution without need for maintenance medication. Two patients (one with anti-Jo antibodies and one with IBM) required monthly intravenous immunoglobulin.

Conclusion: The incidence of IM appears to be increased in male FDNY firefighters after WTC-exposure, however further studies are needed to confirm this. Additionally, studies are needed in order to determine the generalizability of these findings to other groups with varying levels of WTC-exposure or with non-WTC environmental/occupational exposures.

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2017

Hyper Ferritinemia Suggests a High Frequency Of Macrophage Activation Syndrome In a Large Adult Severe Sepsis Cohort: A Role For Anakinra?
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Background/Purpose: Inreased ferritin levels are protective during infection whereas but very very high level are associated with MAS in rheumatologic disease cTo determine frequency of macrophage activation syndrome (MAS) in a sepsis cohort defined by using ferritin level (> 2,000), and to compare outcome, organ involvement and response to anakinra in sepsis across levels of Ferritinemia.

Methods: Remaining sera and data from "interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial" (Opal, et. al. Crit Care Med. 1997 Jul;25(7): 1115–24.) was analysed. Ferritin was measured in the remaining sera of de-identified subjects from this study (levels beyond 6,000 were not further diluted). Subgroups were defined based on serum ferritin ranges (0–499, 500–999, 1000–1999, above 2000 μg/L). Post hoc statistical analysis included: descriptive statistics, rank test, ANOVA, Cox regression.

Results: Sera and data were available for ferritin measurement in 120/756 original study cohort (ages 22–85; 41.6% women). Demographics and 28-day outcome with or without anakinra in the ferritin subgroups are shown in Table. The Ferritin subgroup 500–999 had higher 28 day survival than other subgroups (18/21, 85.7%)(p <.05?), which was decreased with anakinra (100% alive in placebo vs. 82.4% with anakinra). The Ferritin subgroup >2000 (24/29, 24.2%) showed lower 28-day survival, which was increased with anakinra (40% with placebo vs. 57.9% with anakinra).

Ferritin Range	Group N (%) (Total 120)	Age Range	Woman (%)	28 Day Alive	28 Day Alive	
					Anakinra	Placebo
0–499	42 (35.0)	25–85	18/42 (42.9)	27 (64.3)	17/27 (62.9)	10/15 (67.7)
500–999	21 (17.5)	22–83	7/21 (33.3)	**18 (85.7)**	**14/17(82.4)**	**4/4 (100)**
1000–1999	28 (23.3)	22–81	15/28 (53.6)	18 (64.3)	16/25 (64.0)	2/3 (67.7)
2000	29 (24.2)	28–76	10/29 (34.5)	**15 (51.8)**	**11/19(57.9)**	**4/10 (40)**

Conclusion: As hypothesized, an increased Ferritin 500–1000 showed a protective inflammatory response in adult severe sepsis patients, whereasvery high Ferritin levels > 2,000 μg/L may signify immune dysregulation and concurrent MAS (25% of adult severe sepsis patients). Given the high mortality of unrecognized MAS in adults with rheumatic diseases (up to 64% reported) further stuies are warranted both evaluating ferritin in the diagnosis of, and anakinra in the treatment of severe sepsis associated MAS (Ferritin > 2,000).

Disclosure: B. Shakoory, None; **J. A. Carcillo**, None; **S. Opal**, None.

2018

Hemophagocytic Lymphohistiocytosis As a Clinical Syndrome Of Autoimmune Diseases, Haematology, Oncology and Infectious Diseases.
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Background/Purpose: Hemophagocytic Lymphohistiocytosis (HLH) is a severe and acute inflammatory syndrome usually fatal without treatment. HLH includes a spectrum of diseases produced by the proliferation and activation of T-cells and macrophages. The macrophage activation syndrome (MAS) is a variant of secondary HLH that occurs in autoimmune diseases.

Methods: A retrospective search was performed by reviewing medical reports with HLH diagnosed between December 2008 and June 2013 at the Donostia University Hospital, Spain. Inclusion criteria were to meet the diagnostic criteria for HLH and had a bone marrow biopsy with hemophagocytic cells. The qualitative variables were: etiologies, triggers, treatments, causes of death and causes of admission in Intensive Care Unit (ICU); and the dichotomous were: sex, fever, organomegaly, mortality and ICU admission. The quantitative variables were: age, laboratory findings, diagnosis delay (days from the admission to the bone marrow biopsy), hospital and ICU stay. The quantitative variables were showed with median and interquartile range (IR).

Results: Thirteen patients (7 men) with median age of 54 years (IR 34–61) were studied. Table 1 shows demographic characteristics, aetiologies, triggers, hospital stay, diagnosis delay, treatments and mortality of patients with diagnosis of secondary HLH. The diagnostic delay median was 14 days (IR 9–18) and the median hospital stay was 38 days (RI 30–61). Patient 9 continued at the end of this paper. Six patients were admitted to the I.C.U. (patients 3, 4, 6, 7, 8 and 9), the main cause of diagnosis admission was multi-organ dysfunction syndrome (MODS). The overall mortality rate was 30.1%, died 3 due MODS (patients 6, 7 and 8) and 1 due massive haemoptysis (patient 11). The only clinical criterion common to all patients was fever. Patient 12 was the only one without organomegaly. The diagnostic criteria and other laboratory data of each patient are given in table 2. All patients had at least one bone marrow biopsy with hemophagocytics cells; patient 3 also had hemophagocytics cells in the ascitic fluid.

Table 1. Demographics caracteristics, aetiologies, triggers, evolution, treatments and final resolution of patients with secondary HLH in at Donostia University Hospital.

	Id	Aetiologies	Probable triggers	A	S	H.S.	D.D.	Treatments	Final
Rheumatogical Diseases.	**1**	Onset of S.L.E.	The disease itself.	57	M	38 days	3 days	1) Immunoglobulins. 2) Steroids. 3) Cyclosporine.	Cure
	2	A.S.D.	*Pneumococcus, CMV, Herpes simplex* and *Parvovirus B19.*	30	F	10 days	7 days	1) Steroids. 2) Cyclosporine.	Cure
	3	Onset of A.S.D.	The disease itself.	35	F	37 days	14 days	1) Steroids. 2) Cyclosporine. 3) Anakinra.	Cure
	4	Onset of S.L.E.	The disease itself.	16	M	120 days	18 days	1) Steroids. 2) Immunoglobulins. 3) Cyclosporine. 4) Anakinra.	Cure
Hematooncological Diseases.	**5**	Onset of non-Hodgkin B and T cells lymphoma.	The disease itself.	34	M	22 days	6 days	1) Campath-CHOP. 2) RTX-CHOP.	Cure
	6	Acute myeloid leukemia.	HLA allogeneic bone marrow transplant.	65	M	100 days	9 days	1) Steroids. 2) Cyclosporine.	Death
	7	Onset of splenic large B-cell lymphoma.	The disease itself.	77	F	61 days	31 days	1) Steroids. 2) Immunoglobulins. 3) Cyclosporine. 4) Anakinra. 5) Tocilizumab.	Death
	8	Onset of extranodal NK cell lymphoma.	*Epstein Barr virus.*	55	M	38 days	27 days	1) Steroids. 2) Immunoglobulins. 3) CHOP.	Death
	9	Onset of splenic large B-cell lymphoma.	The disease itself.	54	F	140 days	14 days	1) Steroids. 2) Ciclosporina. 3) Anakinra. 4) Tocilizumab. 5) R-CHOP.	Still admitted
Infectious Diseases.	**10**	Sepsis due to *Campylobacter jejuni.*	The disease itself.	61	M	31 days	18 days	1) Immunoglobulins. 2) Steroids	Cure
	11	Stage C3 H.I.V.	*Pneumocistis jiroveci* or/and the disease itself.	30	F	17 days	12 days	1) Steroids. 2) Immunoglobulins.	Death
Oncologic Disease.	**12**	Grade IV glioblastoma multiforme	Chemotherapy with temozolomide.	78	M	30 days	15 days	1) Immunoglobulins. 2) Steroids.	Cure
Unknown disease.	13	Unknown disease	Unknown trigger	40	F	56 days	18 days	1) Steroids. 2) Immunoglobulins. 3) Cyclosporine	Cure

Id: identification, A: Age in years, S: Sex, H.S: Hospital stay, D.D: Diagnosis delay, S.L.E: Systemic Lupus Erythematosus, A.S.D: Adult's Still Disease, CMV: Cytomegalovirus, RTX: Rituximab, NK: Natural Killers, H.I.V: Human Immunodeficiency Virus, CHOP: cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone. M: Male, F: Female.

Table 2. Analytical characteristics of patients with secondary HLH at the Donostia University Hospital.

ID	Hb	Plt	Leu	Neu	Tg	Fbr	Fer	GOT	GPT	LDH	TB	INR	PT	FA	GGT
Rheumatogical Diseases.															
1	8.9	117000	1200	580	417	NA	15300	1080	608	824	0.5	1.1	5.6	275	922
2	9.8	8000	2340	1130	254	212	2389	395	566	959	1.1	NA	NA	341	243
3	7.3	5600	3340	1006	604	103	175266	1318	596	7748	12.7	1.6	4.4	431	584
4	6.1	72000	1660	650	412	77	15359	512	199	993	5.2	2	4	297	681
Hemato-oncological Diseases.															
5	7.4	22000	820	360	382	NA	NA	86	104	259	0.8	1.3	4.3	231	114
6	5.9	2000	0	0	340	NA	16796	277	385	352	11.5	1.4	3.9	262	1132
7	7	16000	50	0	227	287	2868	175	270	1120	2.5	4.7	4	142	266
8	7.4	17000	1300	2000	427	103	53695	199	108	1145	3.4	1.05	4.7	435	1162
9	6.6	4000	10	0	1134	670	16705	419	147	2490	12.4	1.57	4.3	811	1062
Infectious Diseases.															
10	7.8	9000	1010	0	471	214	10938	134	234	441	1.7	1.1	5.6	73	96
11	7.3	10000	3090	2320	274	NA	9755	23	32	752	1.6	1.4	5.4	172	227
Oncologic Disease.															
12	8.6	5000	480	230	149	NA	NA	54	88	426	3.7	1.9	3.1	68	173
Unknown Disease															
13	7.5	15000	5790	3030	561	513	2422	50	46	564	1.1	1.48	4.6	407	491
Median	7.4	10000	1200	580	412	212	15300	199	199	824	2.5	1.46	4.35	275	491
P25	7	5600	480	0	274	103	6311.5	86	104	441	1.1	1.26	4	172	227
P75	7.8	17000	2340	1130	471	287	16750.5	419	385	1120	5.2	1.64	4.88	407	922

Hb: hemoglobin (mg/dl). Plt: platelets (ul). Neu: neutrophils (/ul). Tg: triglycerides (mg/dl). Fbr: fibrinogen (mg/dl). Fer: Ferritin (ng/ml). GOT Glutamic oxalacetic transaminase (mg/dl). GPT: Glutamic-pyruvic transaminase (mg/dl) LDH: Lactate dehydrogenase (IU/l). TB: Total bilirubin (mg/dl). INR: International normalized ratio TP: Total proteins (g/dl). ALP: Alkaline phosphatase (mg/dl). GGT: Gamma glutyl transferase (IU/L). NA: No test performed.

Conclusion: 1) Hemophagocytics cells not only can be found in bone marrow, lymph nodes and spleen, but also in other pathological body fluids such as ascitic fluid, being a simpler method that could be performed before the biopsy or in doubt of it.

2) The mortality may be influenced by the aetiology and trigger of the HLH, the delay in diagnosis and the delay of immunosuppressive treatment. Patients with hematologic diseases had worse prognosis.

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2019

Kikuchi-Fujimoto disease: Features and Outcome Of 91 Patients In France. Guillaume Dumas[1], Virginie Prendki[2], Julien Haroche[3], Patrice Cacoub[4], Zahir Amoura[3], Lionel Galicier[5], Olivier Meyer[6], Christophe Rapp[1], Christophe Deligny[7], Bertrand Godeau[8], Elisabeth Aslangul[9], Olivier Lambotte[10], Thomas Papo[11], Jacques Pouchot[12], Mohamed Hamidou[13], Gilles Grateau[14], Eric Hachulla[15], Thierry Carmoi[16], Robin Dhote[17], Magdalena Gerin[18], Arsene Mekinian[18], Fréderique Charlotte[4], Dominique Farge[5], Thierry Molina[9] and Olivier Fain[18]. [1]Hôpital d'Instruction des Armées Bégin, Saint Mandé, France, [2]Hôpitaux Universitaires de Genève, Genève, Switzerland, [3]Hôpital Pitié-Salpêtrière, AP-HP, UPMC Univ Paris 06 & French National Reference Center For Systemic Lupus and Antiphospholipid Syndrome, Paris, France, [4]Hopital Pitié-Salpétrière, Paris, France, [5]Hopital St Louis, AP-HP, Paris, France, [6]Bichat University Hospital, Paris, France, [7]Centre hospitalier Universitaire de Fort de France, Fort de France, Martinique, [8]University of Paris, AP-HP, Hôpital Mondor Créteil, Creteil, France, [9]hôpital Hotel Dieu, AP-HP, Paris, France, [10]Hopital Kremlin Bicêtre, Kremlin Bicêtre, France, [11]University Paris-7, INSERM U699, APHP, Bichat Hospital, Paris, France, [12]Hôpital Européen Georges Pompidou, AP-HP, Paris, France, [13]Nantes University Hospital, Nantes, France, [14]Hopital Tenon, Paris, France, [15]University Hospital Lilles, Lille CEDEX, France, [16]Hôpital d'Instrcution des Armées du Val de Grace, Paris, France, [17]Avicenne University Hospital, Bobigny, France, [18]Hôpital Jean Verdier, AP-HP, Bondy, France.

Background/Purpose: Kikuchi Fujimoto disease (KFD) constitutes a rare cause of cervical lymphadenitis, usually reported in Asia. Data about this disease are scarce in Europe. The primary endpoint of this study was to describe KFD epidemiology in France. Secondary endpoints were to analyze more specifically the most severe expression of this disease, and forms associated with systemic lupus erythematosus (SLE).

Methods: Retrospective observational study of KFD cases diagnosed in thirteen hospitals in France, between January 1989 and January 2011.

Results: 91 patients were included. 70 (77%) were female with a mean (+/− SD) age of 30+/−10.4 years. 33% of patients came from Europe, 32% from Africa or the Caribbean, 15.4% from Maghreb and 13% from Asia. Eighteen patients presented a history of systemic disease, eleven of them having systemic lupus erythematosus. Cervical lymphadenitis was present in 90% of the cases, and generalized lymphadenomegaly in 52%. Hepatomegaly and splenomegaly were found in 14.8% of the patients, and deep-seated lymphadenitis in 18% of them. Adenitis was associated with fever in 67%, asthenia in 74.4%, weight-loss in 51.2% of the total number of patients. Regarding extra-nodal manifestations we can list cutaneous involvement (32.9%), arthralgia and myalgia (34.1%), and more rarely aseptic meningitis (n=2) or hemophagocytic lymphohistiocytosis (n=3). Laboratory findings brought up lymphopenia for 63.8% of the patients and inflammatory syndrome for 56.4% of them. Anti-nuclear (ANA) and anti ds-DNA antibodies were detected in respectively 45.2% and 18% of tested patients. A viral infection was diagnosed for 8.8% of the studied cases. Corticosteroid treatment was used in the treatment of 32% of the patients, hydroxychloroquine in 17.6% and intravenous immunoglobulins in a total of 3 patients. Even though good prognosis was observed, relapse occured for 21% of the patients. Considering the 33 patients presenting with ANA, systemic lupus erythematosus was diagnosed concomitantly in 10 cases, and within the next year in 2 cases. 6 patients did not develop SLE and 6 patients were lost to follow up (median (Q1-Q3) follow up of 19 [3–39] month).

Weight loss, arthralgia, cutaneous involvement and ANA were associated with SLE ($p<0.05$). Male sex and lymphopenia were factors associated with severity of the disease ($p<0.05$).

Conclusion: KFD not exclusively occurs in Asian population. Associated SLE must be investigated. A prospective study is warranted to determine risk factors for SLE in patients with KFD.

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2020

Clinical Characteristics In Japanese Patients With IgG4-Related Disease. Kazu Hamada, Yoshinori Taniguchi, Yoshiko Shimamura, Koji Ogata, Kosuke Inoue, Taro Horino, Yoshitaka Kumon, Kahori Hirose, Masamitsu Hyodo and Yoshio Terada, MD. Nankoku, Japan.

Background/Purpose: IgG4-related disease (IgG4-RD) is the new entity, which is a multisystem and fibroinflammatory condition. It is characterized by progressive scarring and dysfunction of affected organs and tissues including the pancreas, hepatobiliary tree, kidneys, salivary glands, retroperitoneum and lungs, etc. New diagnostic imaging methods for IgG4-RD have been sought. Recent several reports showed that FDG-PET/CT scans accurately, and safely identifies the multiple organs' involvements in IgG4-RD patients. To evaluate clinical characteristics, including laboratory and FDG-PET/CT findings, of Japanese patients with IgG4-RD.

Methods: The clinical symptoms, laboratory, pathological and FDG-PET/CT findings of Japanese patients with IgG4-RD (n=13) were assessed. Several laboratory data of IgG4-RD with multiple organs' involvements (n=6), IgG4-RD with limited organ's involvement (n=7) and ANCA-associated vasculitis, one of hyper-IL-6 syndromes, (n=10) were comparatively examined. All data are presented as mean ± SD.

Results: IgG4-RD patients (mean age 68±11; male/female 10/3) had xerostomia and bilateral submandibular glands enlargement. As complication, 3 had bronchial asthma, 2 had chronic thyroiditis and 1 had ulcerative colitis. FDG-PET/CT imaging revealed enlargement and increase of FDG accumulation of the bilateral submandibular glands, mediastinal lymph node, lung, spleen, kidney, periaorta and prostate. Interestingly, a part of these organs was asymptomatic. Follow-up FDG-PET/CT after steroid treatment, with no symptoms, showed a significant decrease in FDG accumulation in IgG4-RD lesions. The serum IgG4 level was 847±711 mg/dl (normal 8–135 mg/dl). Four cases with hypocomplementemia and elevated immunocomplex of 13 IgG4-RD cases revealed renal involvements (tubulointerstitial nephritis), and moreover, these 4 cases also had interstitial lung involvements. Notably, cholinesterase (ChE) and total cholesterol (T-cho) levels in IgG4-RD cases with multiple organs' involvements (n=6) significantly decreased from these levels in IgG4-RD with limited organ's involvement (n=7) and ANCA-associated vasculitis (n=10) ($p<0.05$).

Conclusion: When we diagnose IgG4-RD, it is important to differentiate hyper-IL-6 syndrome. FDG-PET/CT imaging and measuring serum ChE and T-cho levels might help us not only to evaluate widespread lesions and monitor disease activity in IgG4-RD, but also to differentiate other disorders. We must investigate further cases of IgG4-RD in order to elucidate its pathophysiology and mechanisms of development.

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2021

The Proportion Of IgG4-Related Aortitis In Patients Diagnosed As Chronic Inflammation Of Aorta In Pathology. Bon San Koo[1], Bin Yoo[1], Chang-Keun Lee[1], You Jae Kim[1], Seokchan Hong[1], Yong-Gil Kim[1], Wook Jang Seo[2] and Kyung joo Ahn[3]. [1]University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [2]Seoul Veterans Hospital, Seoul, South Korea, [3]KEPCO medical center, Seoul, South Korea.

Background/Purpose: The purpose of our study was to identify the proportion of IgG4-related aortitis in patients diagnosed with chronic inflammation of aorta in pathology and evaluate histological and clinical characteristics of IgG4-related aortitis.

Methods: We searched electronic medical records of pathologic reports including description of chronic inflammation in aorta specimen. Forty-seven patients had chronic inflammation of aorta and immunostaining of IgG4 were performed on all biopsy specimen of aorta. If IgG4 positive plasma cell counts were more than 50 per high power field (HPF) and IgG4/IgG ratio were more than 40% with dense lymphoplasmacytic infiltration, fibrosis, or obliterative phlebitis, the patient classified as IgG4-related aortitis.

Results: Total 47 patients who had chronic inflammation in pathologic specimen of aorta were identified which consisted of 29 idiopathic aortitis, 6 takayasu's arteritis, 6 behcet's disease, 3 infection, 3 graft failure patients. Among 29 idiopathic aortitis patients, three patients (10.3%) were classified as IgG4-related aortitis patients. The mean IgG4 positive plasma cell counts of IgG4-related aortitis and idiopathic aortitis were 120.0 ± 52.0 and 7.1 ± 11.7, respectively. One patients had thoracic aortic aneurysm and two patients had abdominal aortic aneurysm. The mean age of IgG4-related aortitis and idiopathic

aortitis was 67.0 ± 2.0 and 54.7 ± 15.5 years, respectively (p=0.086). The sex ratio was all male (100%) in IgG4-related aortitis and 19 male in idiopathic aortitis (65%). In one IgG4-related aortitis patient, chronic pancreatitis with atrophy was observed. All IgG4-related aortitis patients underwent surgical treatement with no immunosuppressant. There was no recurrence of IgG4-related aortitis during follow-up period (45.3 ± 28.7 months).

Conclusion: The ratio of IgG4-related aortitis patients was 10% in patients which were diagnosed as idiopathic aortitis in the past. Although the small number of IgG4-related aortitis was found, the old and male patient who had chronic inflammation of aorta with no secondary cause might be related to IgG4-related disease.

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2022

The Comparison Between IgG4-Related Retroperitoneal Fibrosis and Idiopathic Retroperitoneal Fibrosis. Bon San Koo[1], Bin Yoo[1], Chang-Keun Lee[1], Yong-Gil Kim[1], You Jae Kim[1], Seokchan Hong[1], Wook Jang Seo[2] and Kyung joo Ahn[3]. [1]University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [2]Seoul Veterans Hospital, Seoul, South Korea, [3]KEPCO Medical Center, Seoul, South Korea.

Background/Purpose: The purpose of our study was to identify the ratio of IgG4-related retroperitoneal fibrosis (RPF) which were diagnosed as idiopathic RPF and investigate histological and clinical characteristics of IgG4-related RPF.

Methods: We retrospectively reviewed the medical records of 41 RPF patients in a tertiary care medical center between January 2000 and January 2013. We identified 20 pathologies which were obtained from biopsy or surgery. Immunostaining of IgG4 and histopathologic examination was performed in all surgical pathologies according to 2012 consensus statement on the pathology of IgG4-related disease. Clinical characteristics were also compared between IgG4-related RPF and idiopathic RPF.

Results: In a total 20 RPF cases, more than 30 IgG4 positive plasma cells were identified in 10 cases with dense lymphoplasmacytic infiltrate, storiform fibrosis, or obliterative phlebitis (IgG4 related RPF), but a few (°Å5) IgG4 positive or IgG4 negative cases were also identified in 10 cases (idiopathic RPF). Among 10 IgG4-related RPF, highly suggestive and probable features of IgG4 related RPF in histology were shown in 8 cases and 2 cases, respectively. In comparison between IgG4 related and idiopathic RPF, recurrence rate of IgG4-related RPF (60%) was higher than that of idiopathic RPF (10%) (p=0.032) (figure 1). Initial and 3 month cumulative steroid dosages were not different between two groups.

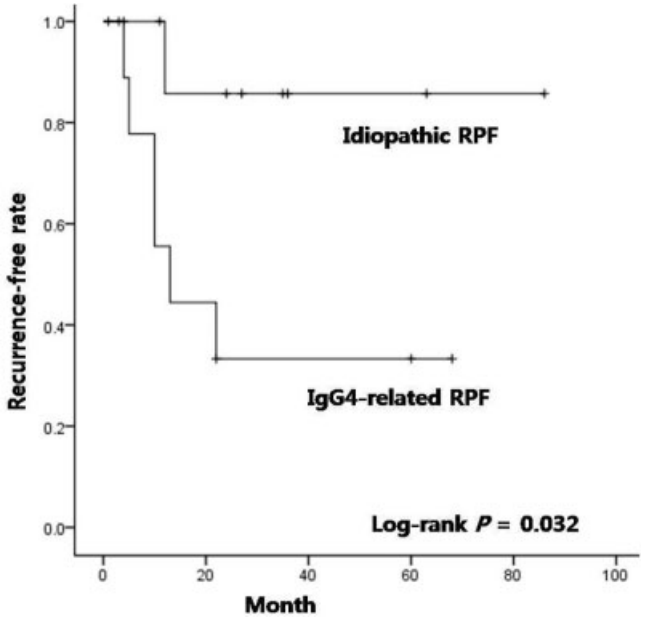

Figure 1. The recurrence-free rate of IgG4-related and idiopathic retroperitoneal fibrosis

Conclusion: We found that IgG4 related RPF according to 2012 consensus statement on the pathology of IgG4-related disease was 50% of the patients who had been diagnosed as idiopathic RPF in the past. We suggested that more aggressive therapy might be considered in IgG4-related RPF to reduce recurrence rate initially.

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2023

IgG4-Related Midline Destructive Lesion: Expanding The Spectrum Of Organ Involvement In IgG4-Related Disease. Emanuel Della Torre[1], Donald Krause[2], Vikram Deshpande[1], Vinay Mahajan[3], Hamid Mattoo[3], Shiv Pillai[1] and John Stone[3]. [1]Massachusetts General Hospital, Boston, MA, [2]St. Joseph's Hospital, Bangor, ME, [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Midline destructive lesion (MDL) is a fibroinflammatory condition involving the nose, paranasal sinuses, and palate with relentless erosion through contiguous facial structures. A variety of historical terms, including "lethal midline granuloma", have been used to describe MDL. The characteristic lesion is an ulcerative process that occurs in the nose and palate associated with epithelium and cartilage loss, leadingultimately to functional deformity. MDL may occur in a variety of inflammatory, neoplastic, and infectious disorders, but the diagnosis remains elusive in a significant proportion of idiopathic cases. We report three patients with MDLwhose cases were marked by clinical, serological, and histopathological features diagnostic of IgG4-related disease (IgG4-RD).

Methods: We evaluated three patients with MDL involving the soft palate and uvula. Two patients also had nasal septal perforations. We investigated the clinical and radiological features of each case, performed flow cytometry on peripheral blood to determine the concentration of IgG4+ plasmablasts, and reviewed the histopathology, performing immunostaining for IgG and IgG4.

Results: The three patients, one man and two women, were aged 54, 38, and 27, respectively. All three patients were heavy, current tobacco smokers. One patient had a remote history of intranasal cocaine use but had not used cocaine for six years before the onset of her palatal and nasal symptoms. Onset of symptoms was subacutein all patients and, in view of the extent of the tissue destruction, the lesions appeared (in retrospect) to have occurred with remarkably little symptomatology. The processes began as small ulcers in the soft palate that evolved slowly into palatal perforations. The onset and progression of nasal septal perforation was equally subacute and subclinical.

Two patients had obtained prostheses to plug their soft palate defects, facilitate speech, and prevent nasal regurgitation of liquids and food. The third patient had remnants of food within her nasal cavity. Physical examination demonstrated a hypernasalspeechquality and florid palatal and nasal septal lesions. The uvulae were absent in all three cases. There were no obvious sites of disease beyond the soft palate and nasal cavity, but diagnostic imaging is awaited presently in one patient. Infections, malignancies, and autoimmune disorders were excluded by extensive serological, microbiological, and histopathological examinations.

The serum IgG4 concentrations were normal in all three patients (96, 119, and 11 mg/dL, respectively; normal < 121 mg/dL)(the third patient had been treated with rituximab). However, all three patients had substantial elevations of IgG4+ plasmablastin blood, with concentrations of 85,200/ml, 3835/ml, and 7351/ml, respectively (normal < 300/ml). Pathologyin all three cases showedtypical histopathological features of IgG4-RD: a diffuse lymphoplasmacytic infiltratewith an abundance of IgG4-positive plasma cells, a mild to moderate tissue eosinophilia, storiform fibrosis, and obliterative phlebitis.

Conclusion: IgG4-RD is a cause of midline destructive lesions involving the soft palate, uvula, and nasal septum.

Disclosure: E. Della Torre, None; **D. Krause**, None; **V. Deshpande**, None; **V. Mahajan**, None; **H. Mattoo**, None; **S. Pillai**, None; **J. Stone**, None.

2024

Elevated IgG4+ Plasmablasts In Patients With Active, Untreated IgG4-Related Disease. Zachary S. Wallace[1], Vinay Mahajan[2], Mollie Carruthers[1], Hamid Mattoo[2], Shiv Pillai[1] and John H. Stone[1]. [1]Massachusetts General Hospital, Boston, MA, [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: IgG4-delated disease (IgG4-RD) is an immune-mediate condition responsible for inflammatory lesions that can affect nearly every organ. Diagnosis is challenging as it relies upon classic histopathology and immunohistochemical findings as well as careful pathology interpretation

and clinicopathologic correlation. No single finding, including the IgG4+ plasma cell infiltrate or the serum IgG4 concentration, is diagnostic. Paramount is the ability to distinguish IgG4-RD from clinically similar conditions such as malignancies. A biomarker to identify patients with active disease would improve diagnosis and may help distinguish subtypes. Here we describe the clinical characteristics of patients with active, untreated IgG4-RD and an elevated IgG4+ plasmablast level.

Methods: This study was approved by the institutional review board and all subjects provided informed, written consent. All patients had histopathologic proof and clinical features consistent with their IgG4-RD diagnoses. Nineteen IgG4-RD patients with active, untreated disease were evaluated and their blood sample findings were compared with those of ten healthy controls. Patients' disease activity was scored by the IgG4-RD Responder Index (RI) where an RI>/= 3 is regarded as active disease. Flow cytometry was used to measure absolute plasmablast count per ml by gating peripheral blood for $IgG4^+$, $CD19^{low}CD20^-CD38^+CD27^+$. Serum IgG4 levels were measured by nephelometry. Student's t-tests were used to compare the groups.

Results: The mean age of the IgG4-RD group was 58 years (range: 41–77 years) and 14 (74%) were male. Nine of the IgG4-RD patients had at least 3 organs involved; the remainder had active IgG4-RD in only 1 or 2 organs. The mean IgG4-RD RI was 11.2 (range: 3–36). The mean ages of the healthy controls was 42.5 years, six of whom were males. All of the IgG4-RD patients had an elevated IgG4+ plasmablast concentrations (normal <500 /ml; mean: 14,316 /ml; range: 732–85,208 /ml). In contrast, the mean plasmablast concentration among healthy controls was 63/ml (range: 1–156/ml; p=0.02). Among IgG4-RD patients, eight (42%) had normal serum IgG4 concentrations (nl< 135mg/dL; mean: 58.3 mg/dL; range: 5.3–123 mg/dL). The mean IgG4+ plasmablast concentration did not differ significantly according to the presence or absence of an elevated serum IgG4 concentration (means =14,249/ml & 13,169/ml, respectively; p=0.94). Patients with a normal serum IgG4 concentration were more likely to have single organ disease as well as lower inflammatory markers; in contrast, patients with an elevated serum IgG4 concentration were more likely to have 3 or more organs involved (64% vs. 25%, p=0.10) and abnormal inflammatory markers (p<0.05 for C3 & CRP; p=0.15 for ESR & C4). The serum plasmablast concentration correlated with the number of organs affected by IgG4-RD (R^2= 0.80).

Conclusion: IgG4-RD appears to be associated with an elevated blood concentration of IgG4+ plasmablasts. This finding may be highly specific for IgG4-RD and may be superior in sensitivity to the serum IgG4. Further investigations of serum IgG4+ plasmablast concentrations in IgG4-RD and other immune mediated conditions are appropriate.

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2025

Distinctive Expression Profiles Of Long Intergenic Non-Coding RNA Between Polymyalgia Rheumatica and Rheumatoid Arthritis Might Contains Helpful Suggestions For Understanding and Discriminating These Diseases. Yoshinobu Koyama[1], Motohiko Tanino[2], Hirokazu Shiraishi[3], Shuji Nagano[3], Toshiyuki Ota[3] and Toshie Higuchi[1]. [1]Okayama Red Cross General Hospital, Okayama, Japan, [2]DNA Chip Research Inc., Yokohama, Japan, [3]Iizuka Hospital, Iizuka, Japan.

Background/Purpose: There are many clinical similarities between polymyalgia rheumatica (PMR) and rheumatoid arthritis (RA). It has been reported that the specificity for discriminating PMR from RA was up to 70% with using 2012 EULAR/ACR provisional classification criteria. The recent technology of microarrays had made it possible to reveal the expression profiles of non-coding RNAs together with protein-coding RNAs (pcRNAs). So far, the differences of these expression profiles between PMR and RA have not been elucidated. In this study, we tried to identify the gene expression signature that may distinguish PMR from RA.

Methods: The study included 71 RA, 17 PMR and 11 osteoarthritis (OA) patients. Peripheral blood was drawn from the patients who were newly diagnosed. The samples were prepared and subjected to RNA extraction. Messenger RNA levels were then measured with using Agilent whole human genome 60K, and the log-transformed raw intensity data were normalized with a quantile algorithm. Based on the differences in gene expression among RA, PMR and OA by ANOVA, differentially expressed genes (DEGs) were selected, and then subjected to a hierarchical clustering with assessment of the statistical robustness. In order to discriminate RA from PMR, we also performed discriminant analysis with using DEGs selected by t-test.

Results: The hierarchical clustering showed major 3 clusters with using expression profiles of 556 pcRNAs selected from top1000 DEGs. OA samples were aggregated in the edge of 1st cluster, while PMR samples were distributed among RA samples. In the top 100 DEGs between RA vs. OA, OA vs. PMR and PMR vs. RA, the long intergenic non-coding RNAs (lincRNAs) accounted for 7%, 9% and 26% respectively. In the comparison of PMR with RA, 86% of the 26 lincRNAs were upregulated in PMR. With using top 49 DEGs containing both pcRNAs and lincRNAs, PMR is differentiated from RA with retrospective accuracy of 98.9% by discriminant analysis. The accuracy was also calculated as 94.3% with leave-one-out (LOO) cross-validation. Meanwhile, with using only 14 lincRNAs, it was calculated as 92.0% for retrospective accuracy and as 86.4% for LOO cross-validation. In comparison with pcRNAs, performance of the discriminant analysis with using lincRNAs was better, if the number of applied genes was same. When the 26 lincRNAs were selected, expression profile-based hierarchical clustering of all samples showed major 3 clusters. Although PMR and OA samples were distributed in RA samples, most of PMR and OA samples were segregated into 1st and 2nd clusters respectively; while 3rd cluster was consist only of RA samples. Analysis of clinical characteristics suggests that the averages of RF/CCP titers of patients in the 3rd cluster were significantly lower as compare with RA patients in other clusters.

Conclusion: The similarity of gene expression profile between PMR and RA would give us the explanation of the difficulty in the differential diagnosis. However, if genes are selected properly, evaluation of expression profiles might be a promising tool for the diagnosis. Although we are only beginning to understand the nature and extent of the involvement of lincRNAs in diseases, our results inspire us to investigate about lincRNAs in rheumatic diseases.

Disclosure: Y. Koyama, None; **M. Tanino**, None; **H. Shiraishi**, None; **S. Nagano**, None; **T. Ota**, None; **T. Higuchi**, None.

2026

Initial Dose Of Prednisolone For Japanese Patients With Polymyalgia Rheumatica. Akiko Aoki, Hiroshi Oka and Mitsuyuki Nakamura. Tokyo Medical University Hachioji Medical Center, Tokyo, Japan.

Background/Purpose: Polymyalgia rheumatica (PMR) is a common inflammatory condition of elderly persons. Clinical symptoms respond to low-dose glucocorticoids, but treatment is often required for several years. The recent UK guideline and a systematic review reported the adequate initial dose of prednisolone (PSL) was 15 or 20 mg daily. PSL doses as mg/kg body weight (PSL/BW) might be too large in lighter-build patients. Majority of PMR patients in Japan are smaller and lighter than the patients in Western countries.

We evaluated the initial doses of PSL and clinical course of the Japanese patients.

Methods: This was a retrospective study in a single hospital. We studied 15 patients with a diagnosis of PMR according to modified Bird's criteria (CRP positive instead of ESR>40). They presented to our hospital from April 2011 to April 2013. Patients who had the following symptoms were excluded; recent temporal or occipital pain, tender, swollen temporal artery, jaw claudication, and impairment of vision.

The patients were divided into 2 subgroups based on the initial PSL/BW: less than 0.3 mg/kg PSL (group L) and more than 0.3 mg/kg (group H). Remission was defined as the absence of symptoms more than one month after the withdrawal of PSL. Relapse was defined by the recurrence of clinical symptoms accompanied by serum CRP elevation, requiring PSL increase. We collected the demographic and clinical data from the medical records.

Statistical significance of differences between two groups of patients was determined by Mann-Whitney U test and chi-squared test. Analyses were performed using JMP ver9.

Results: The median follow-up was 14 months (range 2 to 18 months). Among the 15 patients, ten were women. Nine of 10 women and 1 of 5 men were weighing less than 50 kg. PSL Initial doses were 15 mg in 7 patients, 5mg in 5 patients, 20mg in 2 patients, and 5mg in 1 patient. The mean PSL/BW was 0.29 mg/kg/day. Eight patients belonged to group L, the other to group H. There was no significant difference in follow-up months, sex, age, BW, and serum CRP at diagnosis between two groups. In addition, the clinical course, including the relapse and PSL withdrawal rate, were similar in two groups.

Table. Characteristics of 15 patients and comparisons of outcome between 2 groups

			group L (<0.3mg/kg)	group H (>or=0.3mg/kg)	
		n=15	n=8	n=7	p
Follow-up period (months)	median (IQR)	14 (10,17)	13 (5,16)	14 (10,18)	0.6
Women	n (%)	10 (67%)	5 (63%)	5 (71%)	0.7
Age at diagnosis (years)	median (IQR)	75 (71,81)	80 (72,83)	72 (69,78)	0.1
Body weight at diagnosis (kg)	median (IQR)	44 (40,52)	50 (40,55)	44 (40,45)	0.2
PSL initial (mg/day)	median (IQR)	15 (10,15)	15 (10,15)	15 (15,20)	0.004*
Initial PSL dose per body weight (PSL/BW)	mean (SD)	0.29 (0.09)	0.22 (0.05)	0.37 (0.04)	<0.01*
Serum CRP (mg/dl) at diagnosis	median (IQR)	7.9 (4,12.7)	7.5 (3,13)	7.9 (4,13)	1
Days until first dose reduction of PSL	median (IQR)	38 (28,59)	51 (37,61)	35 (28,38)	0.08
Days until tapering to PSL 7.5 or 8 mg	median (IQR)	62 (40,103)	50 (35,61)	70 (63,150)	0.1
More than one relapse	n (%)	10 (67%)	5 (62%)	5 (71%)	0.7
PSL withdrawal	n (%)	4 (27%)	3 (38%)	1 (14%)	0.3

Conclusion: Initial dose of PSL/BW < 0.3mg/kg was equally effective to that of PSL/BW >0.3mg/kg. Calculating the initial PSL dose by BW might be more appropriate for especially elderly low-body weight women in Japan without deteriorating their prognosis.

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2027

Treatment Of Refractory Adult-Onset Still's Disease With Abatacept: Report Of Five Cases. Hye Jin Oh[1], Myung Jae Yun[2], Kyong Rok Kim[2], Sang Hyun Joo[2], Jae Myung Lee[2], Jin Kyun Park[2], Eun Bong Lee[2], Yeong Wook Song[1] and Eun Young Lee[2]. [1]Seoul National University Hospital, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea.

Background/Purpose: Adult onset Still's disease (AOSD) is a rare disorder of unknown etiology and systemic inflammatory disorder characterized by spiking fever, arthritis, evanescent rash and leukocytosis. Up to 80% of patients with AOSD were controlled with non-steroidal anti-inflammatory drugs, corticosteroid, disease-modifying antirheumatic drugs (DMARDs), particularly methotrexate. Some AOSD patients do not response to conventional DMARDs or biologic therapy including tumor necrosis factor-α inhibitor. Abatacept, cytotoxic lymphocyte antigen 4 (CTLA4) immunoglobulin, is a biologic agent which blocks the co-stimulation of T-lymphocytes and currently is approved for use in rheumatoid arthritis. Therefore we report the use of abatacept in the treatment of five patients with AOSD manifested by severe polyarthritis unresponsive to treatment with corticosteroid, methotrexate, TNF-α inhibitors or tocilizumab.

Subjects & Methods: Four female and one male patients with the diagnosis of AOSD according to the Yamagushi criteria of 1992 were treated with abatacept. Median disease duration of those patients was 5.7 years. They do not response to glucocorticoid, disease-modifying antirheumatic drugs including methotrexate, and TNF-α inhibitor treatment before abatacept. Two patients of them were treated with tocillizumab but, we discontinued the agents due to the uneffectiveness or infusion reaction. After administering two 500mg infusions of abatacept 2 weeks apart initially, abatacept was administered every 4 week. Clinical efficacy and adverse events, changes in the values of routine laboratory parameters were evaluated at each visit.

Results: The major symptom is the polyarthritis in four patients and fever and myalgia in one. One patient improved remarkably in tender joint counts and swollen joints (17à6, 9à 0) after 6 months treatment with abatacept. Another two patients showed no change in joint counts but, there is the improvement of systemic symptoms. Also in one patient with systemic symptom, fever and myalgia resolved after abatacept treatment. ESR and CRP were declined in three patients, but did not changed in the other two patients. AOSD patients have received abatacept treatment for between seven and thirteen months. Throughout this period all patients have no serious adverse event including infection and some benefits from this treatment, with improvement in their clinical symptoms, joint counts, and serological disease activity.

Conclusion: Abatacept was administered in five patients with AOSD failing traditional DMARDs, anti-TNF-α and anti-IL-6 therapies, with some beneficial outcome. These our data suggest the potential therapeutic benefit of abatacept treatment in AOSD.

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2028

Efficacy and Safety Of Biologic Agents In Adult-Onset Still's Disease: A Long-Term Follow-Up Of 19 Patients At a Single Referral Center. Giulio Cavalli[1], Stefano Franchini[2], Alvise Berti[2], Corrado Campochiaro[2], Barbara Guglielmi[2], Maria Grazia Sabbadini[2], Elena Baldissera[3] and Lorenzo Dagna[1]. [1]San Raffaele Scientific Institute, Milan, Italy, [2]Vita-Salute San Raffaele University, Milan, Italy, [3]Vita-Salute San Raffaele University, Milano, Italy.

Background/Purpose: No data comparing the long-term outcome of Adult-Onset Still's Disease (AOSD) patients treated with different biological drugs is currently available. We evaluated the efficacy and safety of different biological agents in a cohort of 19 AOSD patients followed-up at a single referral center, and compared the results with the current knowledge.

Methods: Nineteen Italian AOSD patients were treated with biological agents and followed-up at our institution for at least 24 months between 1998 and 2013. For each case we retrospectively evaluated disease course, efficacy of treatment, and potential adverse effects. Efficacy was evaluated as 'Complete response' (CR: absence of articular and systemic manifestations, normalization of inflammatory indexes, >50% reduction in the corticosteroid dosage), 'Partial response' (PR: clinical improvement without normalization of inflammatory markers, nor >50% reduction in the dose of steroids), or 'Treatment failure' (TF: persistence/worsening of disease manifestations, persistent elevation of inflammatory markers, or need for an increased dose of corticosteroids despite 2 months of treatment). We compared our data with the current literature on the topic.

Results: Nineteen patients with AOSD refractory to conventional therapies were administered biological agents. The average duration of follow-up after initiation of biologic agents was 5 years. Overall, the different biologic drug regimens induced an improvement of systemic and articular manifestations in 17 (89%) patients. Anakinra was used in all 19 patients; etanercept, tocilizumab and adalimumab were used in 6, 4, and 1 patient, respectively. Fifteen patients responded to anakinra (79%; CR 68%; PR 11%). A minority of patients (4 out of 19, 21%) did not respond to anakinra; three of them (16%) responded to tocilizumab, and one (5%) responded to adalimumab. Etanercept was used unsuccessfully in six patients. A decrease in the dose of corticosteroids and immunosuppressants was possible in all patients (discontinuation: 56%; >25% reduction: 44%). A reduction in the dose of the immunosuppressive drugs was possible in 14 patients (74% of the cohort; discontinuation, 21%; reduction 53%). Three patients experienced herpes zoster reactivation while on treatment.

Conclusion: Biological agents represent a pivotal therapeutic resource for AOSD patients refractory to conventional treatment and display a good safety profile. IL-1 blockade with anakinra represented the mainstay of treatment. Both anakinra and tocilizumab treatments were more effective than TNF-α blockers. IL-6 blockade may be more effective than IL-1 blockade in a group of patients with chronic articular involvement. Most of the patients in whom treatment with biologics proved poorly effective had already developed irreversible structural damages before the biologic treatment was started. It is thus conceivable that a more prompt initiation of biological agents could be beneficial in patients with severe AOSD.

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2029

Exposure-Response Modeling Of Canakinumab In The Avoidance Of Flares In Children With Systemic Juvenile Idiopathic Arthritis. Yuan Xiong[1], Wenping Wang[1], William Ebling[1], Haiying Sun[1], Olivier Luttringer[2], Ken Abrams[1], Nicola Ruperto[3] and Hermine Brunner[4]. [1]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [2]Novartis Pharma AG, Basel, Switzerland, [3]Istituto Gaslini, Genova, Italy, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Background/Purpose: Canakinumab (CAN), a fully human selective anti-IL-1β monoclonal antibody, has been shown to be efficacious in systemic juvenile idiopathic arthritis (SJIA), resulting in significantly longer times to flare vs. placebo (PBO).[1] The objectives of the study were to 1) To explore the relationship between SJIA flare reduction and CAN exposure (4mg/kg/ every 4 weeks) with consideration of patient baseline characteristics using a discrete hazard (flare) simulation model. 2) To predict the effects of body weight-tiered CAN dosing regimens at 1 to 6 mg/kg every 4 weeks on SJIA flare rates compared with PBO.

Methods: Plasma concentrations were modeled for patients treated with CAN (n=50) or PBO after CAN treatment (n=50) and used to predict flare risk by a validated and qualified simulation of the CAN exposure-flare hazard relationship. The model considered both PBO and CAN treatments and multiple covariates, including baseline steroid dose, heterogeneity of the population with respect to disease severity (which had a varying influence on risk of an early flare), and declining CAN concentrations over time due to washout in patients on PBO (after receiving CAN). The final simulation model was also used to explore the dose-response relationship between SJIA flare hazard and CAN dose in a simulated trial (1000 simulations), that modeled 700 patients randomized to 1 of 7 treatment arms: PBO, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, and 6 mg/kg (all every 4 weeks) of CAN.

Results: The final simulation model successfully re-produced the Kaplan-Meier curves observed in the phase III program, with significant differences in flare hazard ($p<0.001$) between treatment arms. Higher CAN plasma concentrations were associated with lower flare hazard. Differences in the corticosteroid dose at baseline, age, gender, body weight, daily steroid usage, and level of adapted ACR response to CAN were not significant predictors of flare risk. Based on simulation, the probability of flare (90% CI) over 12 months was 63% (55%, 71%) for the PBO arm. CAN at 4mg/kg/every 4 weeks reduced the flare rate over PBO by 39% (28%, 49%), consistent with the clinical data observed. Based on simulation, CAN at 1, 2, 3, 4, 5, and 6 mg/kg every 4 weeks was associated with annual flare rates of 37% (28%, 47%), 30% (24%, 38%), 26% (21%, 33%), 24% (19%, 30%), 22% (17%, 27%), and 21% (16%, 26%), respectively. Relative to the approved CAN dose, the model predicted a change in flare probability of +13%, +6%, +2%, −2%, and −3% for the 1, 2, 3, 5, and 6 mg/kg every 4 weeks doses, respectively.

Conclusion: The simulations support 4 mg/kg every 4 weeks as the appropriate dose for preventing SJIA flare events. Doses greater than 4 mg/kg provide only marginal gain in flare reduction over 12 months, while doses less than 4 mg/kg relatively increase the risk of experiencing a flare.

Reference:

1. Ruperto et al N Engl J Med 2012; 367(25):2396–2406

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2030

Comparative Immunogenicity Of Tumor Necrosis Factor Inhibitors: Impact On Clinical Efficacy and Tolerability In The Management Of Autoimmune Diseases: A Systematic Review and Meta-Analysis.

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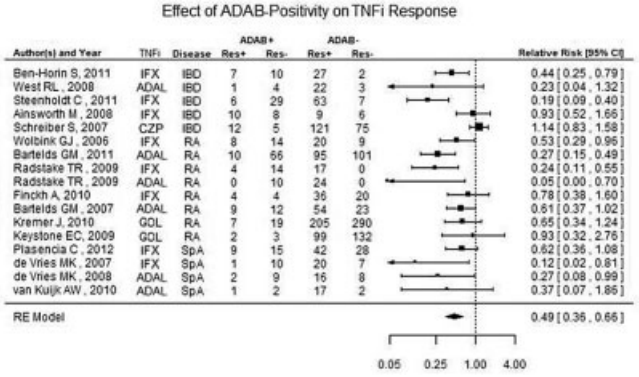
Background/Purpose: Tumor necrosis factor inhibitors (TNFi) are a mainstay in the treatment of rheumatoid arthritis (RA), as well as the management of spondyloarthritis (SpA) and inflammatory bowel disease (IBD). Unfortunately, a significant portion of patients taking these drugs require escalating doses to achieve response, while others lose response altogether. This may be due to the development of antibodies against TNFi.

Objectives: To examine the immunogenicity of TNFi (adalimumab (ADAL), infliximab (IFX), etanercept (ETA), golimumab (GOL), and certolizumab pegol (CZP)) in RA, SpA, IBD, and to examine the potential effect of anti-drug antibodies (ADAB) on the loss of clinical response through a systematic literature review (SLR) and meta-analysis.

Methods: A comprehensive literature search using 3 databases (Pubmed, Web of Science (WOS), and the Cochrane library) was conducted to identify studies examining the immunogenicity of TNFi in autoimmune diseases from 1966 and December 1, 2012. Studies eligible for inclusions required that they be in English, be randomized controlled trials, observational studies or case reports of more than 5 patients, and that patients were 18 years of age or older. Studies were excluded if they were strictly genetic with no clinical correlate, if the patients had concomitant cancer within 5 years of the study, or if the patients had a renal disease requiring dialysis. Double extraction was followed by a third extraction for disagreements. Random effect models were generated for the meta-analysis of the 48 studies to estimate the effects of ADAB on TNFi response.

Results: A total of 8861 patients from 48 studies matching the inclusion/exclusion criteria were examined. Trial durations were from 8 to 522 weeks. Overall, ADAB were detected in 18% [95% CI (0.14–0.23)] of the patients. 30% of those taking IFX developed ADAB [95% CI (0.23–0.37)], compared to 23% [95% CI (0.18–0.29)] for ADAL, 4% [95% CI (0.00–0.08)] for GOL, 4% [95% CI (0.08–0.16)] for ETA, and 6% [95% CI (0.02–0.11)] for CZP. The use of concomitant immunosuppressives (IS) (methotrexate (MTX), 6-mercaptopurine, azathioprine, and others) reduced ADAB formation in all patients by 31% [relative risk (RR) 0.69, 95% CI (0.59–0.81)]. Figure 1 shows that ADAB reduced clinical response by 51% overall, although most of the data derived from IFX (8 articles) and ADAL (6 articles). Under the random effect model, the summary effect for infliximab was RR 0.46 [95% CI (0.3–0.69)]; for ADAL the RR was 0.35 [95% CI (0.2–0.58)]; both estimates are statistically significant.



Conclusion: All five TNFi are associated with anti-drug antibodies. Concomitant immunosuppresives reduced ADAB. ADAB are associated with a reduced clinical response.

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2031

GRAID – Interim Analysis Of The Retrospective German Register In Autoimmune Diseases.

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Background/Purpose: Autoimmune diseases are characterized by high morbidity and lead frequently to physical disability and loss of income. They are the third most important disease group following cardiovascular and tumour diseases. Beyond clinical studies the GRAID registry evaluates primarily safety aspects of the use of all biological therapies in clinical routine off-label settings.

Methods: Following GRAID1, GRAID2 is a retrospective, non-interventional multicentre registry using online data collection starting 2010. Whereas GRAID1 included only rituximab therapies, in GRAID2 all patients with an initial off-label-treatment with biologics since August 2006 can be enrolled. The retrospective documentation comprises case history, diagnosis, course of disease including safety and global efficacy.

Results: While GRAID1 included 370 patients, the interim analysis of GRAID2 is based on additional 125 patients (mean age 47.4 years; 62.4% female) refractory to conventional therapies covering 119.2 patient years (py) of biologics therapy up to now. As in GRAID1 the most frequent diagnosis was systemic lupus erythematosus (SLE; GRAID1 23.0%, GRAID2 20.0%). Further diagnoses in GRAID2 were ANCA associated vasculitides (AAV; 16.0%), overlap syndromes (8.0%), arthritis (non-RA/ankylosing spondylitis/psoriasis arthritis; 7.2%), fever syndromes (6.4%), progressive systemic sclerosis (3.2%), Sjögren's syndrome (3.2%), macrophage activation syndrome (3.2%), polymyalgia rheumatica/cranial arteritis (2.4%), poly-/dermatomyositis (1.6%) and cryoglobulinaemic vasculitis (0.8%). Other main diagnoses were found in 28.0%. Main pre-treatments comprised steroids (69.6%) and azathioprine (50.4%). Most frequent biologics used were rituximab (71.2%), tocilizumab (12.0%), infliximab (8.0%), anakinra (3.2%), adalimumab (1.6%) and certolizumab (0.8%). In SLE and AAV rituximab was the only therapy used and in overlap syndromes it was most frequently used (90.0%). In arthritis and fever syndromes tocilizumab was applied most frequently (55.6% and 50.0%, resp.). After 6–7 months, data were available for 21/89 rituximab patients incl. 13 patients (61.9%) with general symptoms as clinical manifestation: Complete remission found in 3/13 patients (23.1%), partial remission in 4/13 patients (30.8%) and no substantial change in 6/13 patients (46.2%). After first application the tolerability of biologics was assessed as "very good"/"good" by physicians in 92.8% of patients. Altogether, 110 adverse events (AEs) occurred in 44 patients incl. 20 infections in 17 patients representing a rate of 16.8/100 py. 4 serious infections were reported, representing a rate of 3.4/100 py. In total, 12 serious AEs were reported in 8 patients. 2 patients (1.6%) died (pneumonia fungal and leukaemia).

Conclusion: GRAID1 has shown that off-label therapy with rituximab can be effective and well-tolerated in several autoimmune diseases. As data on off-label use are valuable to get data on therapeutic options for patients in urgent need, GRAID2 continues to collect data of a broader range of biologics and autoimmune diseases. Up to now, the data indicate benefits for the patients as well and safety results corresponding to GRAID1.

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2032

How Does Age At Onset Influence Autoimmune Rheumatic Diseases?
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Background/Purpose: Age at onset of disease (AOD) refers to the time period at which a patient experiences the first sign (s) and symptom(s). AOD varies among autoimmune diseases (ADs) and has been related to prognosis in some of them. Genetic, epigenetic, and environmental factors may influence the AOD. The objective was to evaluate the influence of AOD on the clinical course and outcome in adult patients (> 17 years) with autoimmune rheumatic diseases, namely rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Sjögren's syndrome (SS).

Methods: This was a cross sectional analytical study in which 1,082 consecutive adult patients fulfilling international criteria for RA (n=517), SLE (n=271), and SS (n=294) were included. Information on patients socio-demographic and cumulative clinical and laboratory data were obtained by interview, standardized report form, physical examination and chart review. Early AOD was categorized according to the *lower quartile*of AOD in every AD (i.e., 17–34 years in RA, 17–23 years in SLE, and 17–35 years in SS). Data were analysed by Fisher's exact test, Chi square and Kruskal–Wallis test.

Results: There were significant differences between important demographic and clinical variables according to AOD (Table). Early AOD was associated with a more severe clinical course in RA and SLE. No relevant differences between early-SS and late-SS were observed. Late-AOD was associated with environmental exposure in RA and SLE.

Disease	*Early-AOD*	*Late-AOD*
RA	Female Higher educational level Higher joint involvement Extraarticular manifest	Environmental exposure Cardiovascular disease Higher body mass index Higher waist to hip ratio
SLE	Cutaneous involvement Antiphospholipid antibodies Renal compromise	Environmental exposure
SS	Cutaneous vasculitis	

Conclusion: Our findings support the hypothesis of an influence of AOD on illness course in patients with ADs. Early-onset traits are more sensitive to genetic influence while late-onset to environmental variation. These results may serve to design better strategies aimed to discover the etiological factors of ADs.

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2033

Mortality Prognostic Factors Of Patients With Systemic Autoimmune Diseases Admitted To An Intensive Care Unit.
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Background/Purpose: To identify mortality prognostic factors of patients with systemic autoimmune diseases (SAD) admitted in a medical intensive care unit (ICU).

Methods: Retrospective observational study including all patients with SAD admitted to a medical ICU of a tertiary referral centre between January 1999 and December 2012. Only patients with the diagnosis of SAD according to accepted criteria made prior to ICU admission or during hospitalization were selected. Patients with short term irreversible disease and those with an ICU stay less than 48 hours were excluded. The reason for ICU admission, clinical follow-up, immunosuppressive treatment received before ICU admission, and outcome were collected. Mortality prognostic factors were identified through logistic regression analysis.

Results: Seventy patients accounting for 75 ICU admissions (48 [68.6%] women) with mean (SD) age of 54 (19.3) years were included. Five patients were admitted twice. Twenty-three (30.7%) patients had systemic lupus erythematosus (SLE) (mean SLE Disease Activity Index [SLEDAI] at ICU admission 8.2 (5.6) [range 0–20]); 23 (30.7%) had systemic vasculitis (mean Birmingham Vasculitis Activity Score [BVAS] 14.5 (9.3) [range 0–33]); 7 (9.3%) systemic sclerosis; 7 (9.3%) dermatomyositis, and 5 (6.7%) had Sjögren′s syndrome. The reasons for ICU admission were infection in 26 (34.7%), followed by autoimmune disease flare-up in 17 (22.7%). Other complications related or not with the SAD were present in 26 (34.7%) patients. The mean Acute Physiology and Chronic Health Evaluation (APACHE II) at admission was 16.5 (6.5) (range 5–31). At the end of follow-up, 29 (41.4%) patients had died, 10 (14.2%) during the stay at ICU, 7 (10%) during hospitalization, and 12 (17.1%) after hospital discharge. A logistic regression model showed that multiorgan failure (respiratory failure [p=0.032], renal failure [p=0.017]), and the need of renal replacement therapy [p=0.007] were risk factors associated with increased mortality. In addition, corticosteroid therapy [p<0.005] and the need of intravenous immunoglobulin treatment [p<0.005] during the stay at ICU, and the use of cyclophosphamide in the previous six months [p=0.016] of ICU admission, were also risk factors associated with increased mortality.

Conclusion: The most prevalent SAD admitted to a medical ICU were SLE and systemic vasculitis being infections the main reason for admission. The presence of respiratory and renal failure, the need of renal replacement therapy, the need of corticosteroid or intravenous immunoglobulin during the stay in ICU and the use of cyclophosphamide before the admission were factors associated with increased risk of mortality.

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2034

Does Mixed Connective Tissue Disease Or Sharp's Syndrome Really Exist? Anne Barbarini[1], Christelle Sordet[1], Emmanuel Chatelus[1], Rose-Marie Javier[1], Joelle Goetz[1], Francois Lefebvre[2], Jacques-Eric Gottenberg[1], Thierry Martin[3] and Jean Sibilia[1]. [1]Strasbourg University Hospital, Strasbourg, France, [2]Strasbourg University Hospital, strasbourg, France, [3]IBMC, Strasbourg, France.

Background/Purpose: The existence of Mixed Connective Tissue Disease (MCTD) has often been discussed in literature and its diagnostic criteria are very heterogeneous. Anti-U1-RNP antibodies are not specific, but their presence is obligatory for the diagnosis of MCTD. To determine whether MCTD exist as a distinct entity, we analyse their frequency in a group of anti-U1-RNP positive patients and their diagnostic evolution rate at the end of follow-up. We studied the predictive value of some clinical and biological factors for diagnostic transformation.

Methods: We have selected retrospectively 103 patients from January 2006 to May 2011. The only inclusion criterion was the presence of anti-U1-RNP antibodies. We have studied medical information at the time of first presentation, at each visit and at the last follow-up visit. The selected patients were classified into one group of connective tissue disease if they fulfilled the following classification criteria: ARA for Rheumatoid Arthritis (RA), ACR for Systemic Lupus Erythematous (SLE), Leroy and Medsger for Systemic Scleroderma (SS), American and European criteria for Sjögren's Disease (SD), Bohan and Peter for myopathies, Alarcón-Segovia for MCTD. Patients fulfilling more than one or respectively none of the connective tissue disease criteria were classified as Overlap Syndrome (OS) or Undifferentiated Connective Tissue Disease (UCTD) respectively. The initial diagnosis was reviewed after each visit. Anti-U1-RNP antibodies were detected by immune-dot or radial immune-diffusion. We used Student's test or Fisher's test for statistical analyze ($p \leq 0.05$).

Results: 103 patients were anti-U1-RNP positive. 98 patients had a diagnosis of a connective tissue disease at the initial presentation and were followed up between January 2006 and May 2011: 20 UCTD, 10 MCTD, 5 OS, and 63 defined connective tissue diseases (48 SLE; 7 SD, 5 SS; 3 RA). The diagnosis of MTCD was rare (10.2% at first presentation and only 5.1% at the end of follow-up). 60% of the initial MCTD's have evolved into 2 SLE and 4 OS in a medium delay of 7.3 years [2–16] by the end of follow-up. No predictive factors for diagnostic evolution were identified ($p > 0.05$). Anti-U1-RNP antibodies were associated with a high proportion of SLE (49%) and OS (26%) at the end of follow-up. Visceral complications were frequently observed in our patient group (54%).

Conclusion: MCTD is probably an intermediate stage towards an evolution into a well-defined connective tissue disease. We underline the importance of a systematic and long follow-up for all anti-U1-RNP positive patients which are at high risk to develop more than one connective tissue disease and visceral complications over time.

Disclosure: A. Barbarini, None; **C. Sordet**, None; **E. Chatelus**, None; **R. M. Javier**, None; **J. Goetz**, None; **F. Lefebvre**, None; **J. E. Gottenberg**, None; **T. Martin**, None; **J. Sibilia**, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5.

2035

Description Of 142 Cases Of Relapsing Polychondritis Followed In a Single Center Since 2000. Jeremie Dion[1], Nathalie Costedoat-Chalumeau[1], Damien Sene[2], Judith Cohen-Bittan[3], Gaëlle Leroux[3], Camille Francès[4] and Jean-Charles Piette[3]. [1]Hopital Cochin, Paris, France, [2]Hopital Lariboisière, Paris, France, [3]CHU Pitié-Salpêtrière, Paris, France, [4]Hopital Tenon, Paris, France.

Background/Purpose: Relapsing polychondritis (RP) is a rare condition characterized by recurrent inflammation of cartilaginous tissues and systemic manifestations. Data on prognosis available from the latest large series published in 1986 indicate a 5- and 10-year survival after diagnosis of 74% and 55%, respectively [1]. The purpose of this study is to describe a recent series of patients with RP.

Methods: 142 patients with a diagnostic of RP according to Michet's criteria were included in this monocentric retrospective study. All the patients were seen at least once since 2000. The median year of diagnosis was 2002 (1974 to 2011).

Results: 56 men (39%) and 86 female (61%) were included. The mean age at first symptoms was 43.5±15 years, and was higher for men (47±15 vs 41±15 p=0.02). The median delay of diagnosis was 1 year (1 to 25). The mean number of initial symptoms was 1.85±1, and main first symptoms consisted of nasal or auricular chondritis (59%), joint (32%), ophthalmologic (18%), general (15%) or cutaneous (15 %) manifestations. During a median evolution of 11 years (1 to 41), all the patients presented chondritis: auricular in 89%, nasal in 63%, laryngeal in 43%, chondrocostal in 40%, and tracheobronchial in 22%. Nasal and ear deformations occurred in 15 and 10% respectively. Other manifestations were articular in 69%, ophthalmological in 56% (episcleritis or scleritis in 41%, uveitis in 13%, keratitis in 4%), cochleovestibular in 34%, (deafness in 27% and vestibular syndrome in 20%), cardiac in 27% (including aortic valve insufficiency in 17% and cardiac surgery in 5%), cutaneous in 30% and neurological in 11%.

A concomitant hematological disease was present in 14%: myelodysplasic syndrome in 8% and others in 6%. Myelodysplasic syndrome affected only men in our series ($p=8\times10^{-6}$), and was associated with older age (63 vs 41years; $p=4\times10^{-6}$) and cutaneous involvement (p=0.0001). Deep vein thrombosis occurred in 11% of the patient.

58% of the patients had an inflammatory syndrome during disease's flares with a median CRP level of 80 mg/l (10 to 379 mg/l). Antinuclear antibodies were found in 20%, anti-neutrophil cytoplasmic antibodies in 10%, rheumatoid factor in 13% (17/129).

An autoimmune disease was associated in 22% (including Sjogren syndrome in 9%, autoimmune thyroiditis in 6%, systemic lupus erythematosus in 4%).

Corticosteroids were used in 94%, methotrexate in 49%, dapsone in 38%, colchicine in 32%, azathioprine in 25%, mycophenolate mofetil in 19%, cyclophosphamide in 17%, TNF-alfa inhibitors in 11%, rituximab in 7%, anakinra in 3% and autologous stem cell transplantation in 2%.During the evolution, 18% were hospitalized for an infection and 13% were transferred in Intensive Care Unit.

To avoid selection bias, we studied the survival in the 87 patients who had a diagnosis of RP after 2000. After a median follow up of 7 years, the 5- and 10-years survival after diagnosis were of 95% and 91%, respectively.

Conclusion: Compared with previous studies, the prognosis of RP has greatly improved.

[1]: Michet et al. Ann Intern Med. 1986;104:74–8.

Disclosure: J. Dion, None; **N. Costedoat-Chalumeau**, None; **D. Sene**, None; **J. Cohen-Bittan**, None; **G. Leroux**, None; **C. Francès**, None; **J. C. Piette**, None.

2036

Biologic Therapy For Relapsing Polychondritis: Old and New Efficacy Indices. Mattia Baldini, Patrizia Aiello, Mirta Tiraboschi, Maria Grazia Sabbadini and Elena Baldissera. Ospedale San Raffaele and Università Vita-Salute San Raffaele, Milano, Italy.

Background/Purpose: The inflammatory milieu in affected tissues from Relapsing Polychondritis (RP) is rich in TNF-α, IL-1-β and IL-6. Cytokine-targeted biologic therapies has therefore been proposed in patients with active disease despite conventional treatment (steroids + DMARDs). Given the rarity of the disease, no randomized controlled trial has been published yet; moreover, different outcomes are considered in each study. Recently, an international study group published Relapsing Polychondritis Disease Activity Index (RPDAI). We report our experience on the efficacy of biologic therapy in RP evaluating both conventional indexes and the RPDAI.

Methods: The efficacy of each drug has been assessed considering the reduction of ESR, CRP, steroid dose and RPDAI at two time points (6 months, 12 months).

Results: From 2004 on 8 RP patients have been treated with biologic therapies. Anti-TNF (i.e. etanercept, n=4; infliximab, n=1; golimumab, n=1) or anakinra were used as 1st line biologics in 6 and 2 patients, respectively. In the anti-TNF group: 2 patients (both on etanercept) achieved long-term remission (mean follow-up 54 months and one could discontinue the drug without disease flare), while 4 were switched to anakinra (n=2) or to another anti-TNF (n=2) after a mean of 25 months because of efficacy loss (n=3) or intolerable injection-site reaction (n=1). Both patients on 1st line anakinra therapy were switched to etanercept after a mean of 17 months because of efficacy loss. Among the patients on 2nd line biologic therapy, 2 (out of 4) from the anti-TNF group (on etanercept and adalimumab, respectively) and 1 (out of 2) from the anakinra group achieved long-term remission (mean follow-up 43 months). Tocilizumab was successfully used as a 3rd line agent after anti-TNF (n=2) or anakinra (n=1) failure (mean follow-up 7.5 months). In total, 17 biologic therapies have been used in 8 patients. Anti-TNF agents (n=9), and in particular etanercept (n=6) were the most used biologics, followed by anakinra (n=4), and tocilizumab (n=3). At 6 months, tocilizumab was effective in 100% of cases (n=3), anakinra in 50%, ant-TNF in

12% (etanercept in 40%). At 12 months, anti-TNF were effective in 67% (etanercept in 60%) and anakinra in 50% (no follow-up at 12 months is yet available for tocilizumab), RPDAI and ESR variation from baseline were the best indicators of efficacy at 12 months. Interestingly, RPDAI and steroid dose variation at 6 months were the best predictors of the outcome at 12 months.

Conclusion: Cytokine-targeted drugs are promising therapies for RP resistant to conventional therapy. Variations at 6 months in ESR levels and RPDAI score may be predictors of the long term efficacy of anti-TNF and anakinra.

Disclosure: M. Baldini, None; **P. Aiello**, None; **M. Tiraboschi**, None; **M. G. Sabbadini**, None; **E. Baldissera**, None.

2037

Isolated Anti-Ro52 Antibody – Significance and Clinical Association. Yogesh Singh[1], Pravin Patil[2], Hilary Longhurst[3], Garry Clarke[3] and Bhaskar Dasgupta[4]. [1]Southend university hospital, Westcliff-on-sea, United Kingdom, [2]Southend University Hospital, Westcliff-on-sea, United Kingdom, [3]Southend University Hospital, Westcliff on sea, United Kingdom, [4]Southend University Hospital, Westcliff-on-Sea, United Kingdom.

Background/Purpose: Antibodies against Ro-52 (TRIM21) have been described in patients with a broad spectrum of autoimmune diseases. Anti-Ro52 antibodies are the most common immunological markers detected in the idiopathic inflammatory myopathies. The significance and clinical association of isolated anti-Ro52 anti-body is not well known.

Methods: This is a retrospective study of patients who had isolated Ro52 positivity on ENA screen. Patients were identified from the immunology laboratory records. Search was limited to year 2009 to 2012. Medical records of patients with isolated Ro-52 were reviewed for clinical details.

Results: Thirty eight patients had isolated anti-Ro52 antibody positivity on ENA screen. The median age was 68 years and 26 were female. ANA was positive in 28 (73%). The prevalence of pulmonary manifestations in presence of anti-Ro52 antibodies was high (9/38, 23%). One patient had an undifferentiated connective tissue disease with interstitial lung disease, 4 had idiopathic pulmonary fibrosis, 2 with malignancy (bronchogenic −1, lung metastases – 1) and remaining 2 patients had suspected malignancy (bronchogenic).

Clinical manifestations of autoimmune diseases were observed only in 21 (55%) patients with Ro 52 positivity (Table 1). A severe form of ITP requiring splenectomy was seen in 2 patients. It was associated with present or past malignancy in 8 (18%) patients and out of these 3 had an underlying auto-immune disease. In another 3 patients malignancy was strongly suspected based on clinical features, imaging findings but histological confirmation could not be obtained due to untimely demise of these patients.

Table 1. Disease association with anti-Ro52 antibody

Systemic autoimmune disease (N=11)	Organ specific autoimmune disease (N=6)	Malignancy (N=9 malignancies in 8 patients)	Suspected malignancy (N=3)	Others (N=13)
Rheumatoid arthritis-2	AIH-2	**Current malignancy**	Brochogenic-2	Stroke-2
Scleroderma myositis overlap-1	Coeliac disease-1	Prostate-1	Lymphoma-1	Chronic diarrhea-1
LcSSc with ITP-1	Pernicious anemia-1	Malignant melanoma-1		General weakness-1
Primary Sjogren's-1	PBC-1	Gastric-1		Secondary pulmonary hypertension-1
Antiphosphilipid syndrome-1	ITP-1	Colon-1		Sepsis-1
Polymyalgia rheumatica-1	Idiopathic pulmonary fibrosis-4	Bronchogenic-1		Alcoholic cirrhosis of liver-1
Dermatomyositis-1		Breast-1#		Elevated ALP-1
UCTD-1		**Previous malignancy**		Generalized tingling-1
GPA-1		Endometrial-1$		
PsA-1		Ovarian-1*		
		Hodgkin's disease-1*		

Patient with GPA had previous breast cancer which was treated, now presented with lung metastases.$ Previous history of endometrial cancer, now presented with stroke.* In the patient with PsA, previous history of treated ovarian cancer and Hodgkin's disease. UCTD – undifferentiated connective tissue disease, GPA – granulomatous polyangiitis, PsA – Psoriatic arthritis, AIH – Autoimmune hepatitis, PBC – Primary biliary cirrhosis, ITP – Idiopathic thrombocytopenia, ALP – Alkaline phosphatase

Conclusion: Ro 52 antibody is commonly seen in non-autoimmune disorders. Presence of isolated anti-Ro52 antibody is associated with pulmonary involvement. It may represent the primary site for loss of tolerance and generation auto-antibodies. It can be seen in conditions other than autoimmune diseases. In our cohort anti-Ro52 was seen in association with malignancy. The role of Ro52 antibody as anti-cancer immune response should be studied further.

Disclosure: Y. Singh, None; **P. Patil**, None; **H. Longhurst**, None; **G. Clarke**, None; **B. Dasgupta**, None.

2038

Congenital Heart Block Related With Maternal Autoimmune Diseases: Descriptive Analysis Of a Series Of 17 Cases. Pamela Inés Doti[1], Ona Escoda[1], Sergi Cesar-Diaz[2], Narcís Masoller[3], Irene Teixidó[3], Josep Maria Martinez[3], Georgia Sarquella-Brugada[2] and Gerard Espinosa[1]. [1]Department of Autoimmune Diseases, Hospital Clínic, Barcelona, Barcelona, Spain, [2]Arrhythmia Unit, Cardiology Section, Hospital Sant Joan de Déu, Barcelona, Barcelona, Spain, [3]Maternal Fetal Medicine Department, Hospital Clínic, Bacelona, Barcelona, Spain.

Background/Purpose: To describe the clinical characteristics of maternal autoimmune-mediated fetal congenital heart block (CHB) in a cohort of pregnant women from an Autoimmune Diseases Pregnancy Clinic.

Methods: Retrospective observational study of all women presenting with CHB in our Autoimmune Diseases Pregnancy Clinic from January 1997 to December 2012. In addition, outcome of live newborn with CHB is also described.

Results: Thirteen patients accounting for 17 episodes of CHB were identified. One patient had three episodes and two patients had two episodes each one. The mean (SD) age was 31.3 (5.3) years. Six (46.2%) patients had Sjögren's syndrome and the remaining 7 (53.8%) were asymptomatic carriers of auto-antibodies. All patients had anti-Ro antibodies and 10/12 (83.3%) had anti-La antibodies. Anti-Ro52 antibody was positive in the 4 women in which it was performed. The mean gestational age at the time of CHB was 21.8 (2.9) weeks (range 18–28). Complete cardiac block (CCB) was detected in 12 (70.6%) fetuses and second-degree CHB in 5 (29.4%). During pregnancy, 4 of them progressed to CCB whereas the remaining changed to first-degree CHB. Severe complications were detected in 5 fetuses (3 hydrops fetalis, 2 fetal growth restriction). Regarding the maternal treatment at diagnosis, only 2 were receiving low-dose corticosteroids, associated with hidroycloroquine and azathioprine in each one, respectively.

Six cases of CHB were treated with dexamethasone, two with ritodrine and one with the association of dexamethasone, ritodrine and terbutaline. Despite the pharmacological intervention, pregnancy was interrupted in 9 (52.9%) cases. Finally, there were 8 newborns (7 males [87.5%]) with mean age at delivery of 37.2 (1.5) weeks (range 34.5–39).

Elective cesarean was the preferred technique of delivery in all cases. Seven out of 8 (87.5%) newborns were diagnosed of symmetric intrauterine growth restriction. In two cases, Apgar test at first minute was less than 7, because of severe oligohydramnios and meconium aspiration syndrome. Apgar test at 5 and 10 minutes was 9 in all cases.

All newborns were diagnosed of CCB, except one who had first-degree CHB. Half of newborns needed temporal endovascular pacemaker within the 24 hours of life. Two cases showed heart failure signs. A definitive epicardial pacemaker was placed in all cases within 2 weeks of life. Of the remaining patients without a neonatal pacemaker requirement, two needed a pacemaker due to chronotropic and electric insufficiency, at 4 and 14 years old, respectively. Two patients didn't need a pacemaker due to a good ventricular rate without symptoms and first-degree CHB. One case of CCB with a pacemaker died due to congestive cardiac insufficiency related to a dilated cardiomyopathy (4 months old). Currently, mean age of the 7 living patients is 7 years (range 2–16).

Four women with previous CHB received intravenous immunoglobulins in a subsequent pregnancy being ineffective in two of them.

Conclusion: CHB is a severe complication related to anti-Ro/La antibodies. Therapy is ineffective and most of the surviving patients will require neonatal pacemaker.

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Micro and Nanoparticles As Possible Causative-Prognostic Co-Factors Of Mixed Cryoglobulinemia Syndrome. Erica Artoni[1], Gian Luca Sighinolfi[1], Daniele Campioli[2], Marco Sebastiani[1], Dilia Giuggioli[1] and Clodoveo Ferri[1]. [1]University of Modena and Reggio Emilia, Modena, Italy, [2]Azienda Ospedaliera - Policlino di Modena, Modena, Italy.

Background/Purpose: We previously demonstrated that patients affected by membranoproliferative glomerulonephritis and mixed cryoglobulinemia syndrome (MCs) show the presence of circulating micro and nanoparticles (MPs and NPs) as possible causative/prognostic co-factors. This pilot study aimed to evaluate the possible role of occupational/environmental agents in

the etiopathogenesis of MCs by investigating the patients' exposure to both MPs and NPs.

Methods: We investigated 20 consecutive HCV-positive MCs patients without renal involvement compared to 10 healthy, sex-/age-matched volunteers. All subjects completed a questionnaire concerning demographic data, dietary and smoking habits, prosthesis implants, air pollution, occupational and medical history. Environmental Scanning Electron Microscopy (ESEM) has been employed to detect inorganic MPs and NPs and to evaluate their presence in subjects with and without MCs. Energy Dispersive X-ray Spectroscopy (EDS) microanalysis was used to chemically characterize the elemental composition of the particles. Blood serum samples were spotted on metal free cover slips in a sterile environment. The complex of particles (MPs and NPs) was quantified using the number of spots (NS) containing inorganic particles in a fixed mapping area for each sample. Levels of NS were assessed statistically with Mann-Whitney U test.

Results: Patients displayed higher serum levels of MPs/NPs particles (NS 36.67 ± 18.18, $p < 0.0003$), compared to controls (NS 5.62 ± 6.25), independently of smoking habits. A direct correlation between the presence of particles and patients occupational exposure, environmental pollution and prosthesis implants was found. EDS microanalysis revealed that the particles have complex compositions, which includes several elements like Si, Fe, Al, Ti, Zn, Cu, Mn, and Ni.

Conclusion: The ESEM analyses were a valuable tool to detect particulate matter in the serum samples. The complex of MPs/NPs particles was greater in MCs patients than in healthy subjects. These preliminary data suggest that, in addition to HCV infection, particulate complex might represent an environmental co-factor in the etiopathogenesis of MCs.

Disclosure: E. Artoni, None; **G. L. Sighinolfi**, None; **D. Campioli**, None; **M. Sebastiani**, None; **D. Giuggioli**, None; **C. Ferri**, None.

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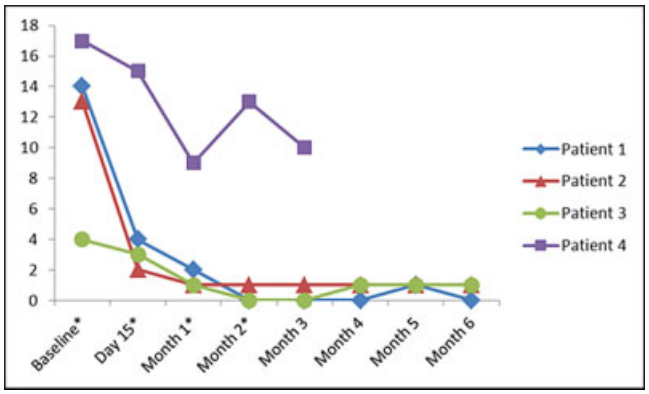
Pilot Study Of Abatacept In Patients With Refractory Autoimmune Chronic Urticaria. Clifton O. Bingham III[1], Marilyn Towns[1] and Susan J. Bartlett[2]. [1]Johns Hopkins University, Baltimore, MD, [2]McGill University, Montreal, QC.

Background/Purpose: Associations between chronic urticaria (CU) with autoantibodies and other autoimmune conditions have implicated T cells in CU initiation and/or propagation. Many patients (pts) have symptoms that require chronic corticosteroids (CCS) and/or immunomodulatory therapies. We conducted an investigator-initiated pilot study to assess the safety and potential efficacy of abatacept (ABA) in pts with CU.

Methods: Pts with refractory CU were enrolled in an open-label study of intravenous (IV) ABA (750–1000 mg per body weight) administered at baseline, 2 wk, 4 wk, and 8 wk (clinicaltrials.gov NCT00886795). Pts had required previous CCS and failed other immunomodulators. If symptoms improved, sequential tapering of CCS and/or antihistamines was permitted. Outcomes included Dermatology Life Quality Index (DLQI), urticaria severity score, number of hives, interference with sleep and daily activities, MD and Pt assessments of response, and SF-36. Safety was carefully monitored during infusions; adverse events were recorded using the OMERACT Rheumatology CTCAE v2.0. Funding and study drug were provided by BMS, who had no role in study conduct, data analysis, or decision to submit abstract.

Results: Four pts (2M/2F) were enrolled (32–51 yo; urticaria duration: 3–29 yr). Prior immunomodulatory therapies included sulfasalazine (SSZ), hydroxychloroquine (HCQ), methotrexate, azathioprine, adalimumab, mycophenolate, and cyclosporine. At baseline 2 pts were on CCS, 1 was on SSZ, and 1 was on HCQ, continued per protocol. All pts improved from their baseline clinical state by 3 months (mo), in terms of most pt-reported outcomes and in MD-reported variables. Three pts had complete urticaria resolution. One pt improved from baseline but remained symptomatic and exited at 3 mo. For all pts there was considerable improvement in DLQI (Figure). In 3 pts, background medications were tapered (CCS elimination in 1; antihistamine tapering in 3). Two pts continue to do well off ABA, requiring only periodic non-sedating antihistamines for intermittent pruritus (Time since last ABA infusion 7 mo and 24 mo). One pt had recurrent urticaria approximately 3 mo after last ABA infusion, with response rapidly recaptured with SQ ABA administered outside the study. ABA infusions were well-tolerated with no worsening urticaria, angioedema, or anaphylaxis. Upper respiratory infections (mild) were consistent with ABA studies for other indications.



DLQI over time (MID in CU 2.24–3.1). Timing of Abatacept infusions indicated with *.

Conclusion: A 2 mo intervention with IV ABA led to improvement in 4 pts with immunomodulatory therapy-resistant CU. For 3 pts there was a rapid and complete response; in the 4th there was a clinically detectable improvement. Limitations are the small number of pts and open-label design. These results suggest a fundamental role for T cells in CU pathogenesis.

Disclosure: C. O. Bingham III, BMS, 5, BMS, 2; **M. Towns**, None; **S. J. Bartlett**, None.

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Pregnancy Outcomes In Women Exposed To Golimumab. Amy G. Lau[1], Michael Clark[1], Diane D. Harrison[1], Anja Geldhof[2], Riikka Nissinen[2] and Marilyn Sanders[1]. [1]Janssen Research & Development, LLC., Horsham, PA, [2]Janssen Biologics Europe, Leiden, Netherlands.

Background/Purpose: Rheumatologic conditions and inflammatory bowel disease can affect women of childbearing potential. Golimumab (GLM) is approved for rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and ulcerative colitis (UC). GLM should be used during pregnancy only if clearly needed. For RA and some PsA patients, GLM is administered with methotrexate (MTX), an agent with teratogenic and abortifacient properties. To characterize pregnancy outcomes in patients treated with GLM, data obtained from maternal exposure to GLM are presented.

Methods: This dataset includes individual patient cases reported to the manufacturer through 06 April 2013. Cases retrieved included prospectively reported (ie, pregnancy outcome not known when first reported) and retrospectively reported (ie, pregnancy outcome known when first reported) maternal exposures to GLM for all approved indications during pregnancy or within 2 months prior to conception, and a reported pregnancy outcome. Cases originated from various sources, including spontaneous reporting, clinical studies, and registries.

Results: Forty pregnancy reports with reported outcomes (24 RA; 1 PsA; 5 AS; 10 UC) were identified (32 prospective, 8 retrospective). Of these 40 pregnancies, 30 were reported from clinical trials. Average maternal age was 33.2 years. Of the 40 pregnancy reports, 19 (47.5%) resulted in live births, 13 (32.5%) resulted in spontaneous abortion, 7 (17.5%) resulted in induced abortion, and 1 (2.5%) resulted in ectopic pregnancy (Table). One spontaneous prospectively reported patient case (2.5%) reported a congenital anomaly with an unspecified birth defect resulting in intrauterine death and an induced abortion. Of the 13 reports with a pregnancy outcome of spontaneous abortion, 4 (30.8%) patients received MTX concomitantly with GLM, as compared to 3 out of 19 (15.8%) reports in the GLM exposed pregnancies resulting in live births. In the 1 pregnancy with a congenital anomaly, the patient had used MTX, but the timing of MTX use was not available.

Table. Summary of pregnancy outcomes in patients treated with GLM for RA, PsA, AS, and UC

Pregnancy Outcome	RA, PsA, AS, and UC Patient Cases		
	Count (%)	Congenital Anomaly	MTX[a]
Live birth	19 (47.5)	0	3
Spontaneous abortion	13 (32.5)	0	4
Elective/Induced abortion	6 (15.0)	1	2
Abortion planned	1 (2.5)	0	0
Ectopic pregnancy	1 (2.5)	0	1
Total	**40**	**1**	**10**

a: Patient received MTX at the time of conception/during pregnancy.
KEY: AS=Ankylosing spondylitis; MTX=Methotrexate; PsA=Psoriatric arthritis; RA=Rheumatoid arthritis; UC=Ulcerative colitis.

Conclusion: This review of pregnancy outcomes after GLM exposure in utero reported 1 congenital anomaly in a small number (40) of pregnancies; the rate of congenital anomalies was consistent with the background rate. Out of the 40 pregnancies, 32.5% reported spontaneous abortions. Of those pregnancies, 30.8% of the patients received MTX, an agent which is contraindicated in pregnant women due to its teratogenic and aborifacient properties. Limitations of this analysis included the lack of a direct comparison group, the variable amount of data available in the reports, and the possible bias towards reporting more negative outcomes in retrospective cases.

Disclosure: A. G. Lau, Janssen Research & Development, LLC., 3; **M. Clark**, Janssen Research & Development, LLC., 3; **D. D. Harrison**, Janssen Research & Development, LLC., 3; **A. Geldhof**, Janssen Biologics Europe, 3; **R. Nissinen**, Janssen Biologics Europe, 3; **M. Sanders**, Janssen Research & Development, LLC., 3.

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Pregnancy Outcomes In Women With Rheumatologic Conditions Exposed To Infliximab. Sirisha Kalari[1], Fredrik Granath[2], Chun-Yuan Guo[1], Diane D. Harrison[1], Gabriella Bröms[2], Anja Geldhof[3], Riikka Nissinen[3], Marilyn Sanders[1], Mika Gissler[4], Lars Pedersen[5], Henrik Toft Sorensen[5] and Helle Kieler[2]. [1]Janssen Research & Development, LLC., Horsham, PA, [2]Karolinska Institutet, Stockholm, Sweden, [3]Janssen Biologics Europe, Leiden, Netherlands, [4]National Institute for Health and Welfare, Helsinki, Finland, [5]Aarhus University Hospital, Aarhus, Denmark.

Background/Purpose: RA, AS, and PsA are approved indications for infliximab (IFX). In the US, IFX is a pregnancy Category B drug. For RA and some PsA patients, IFX is administered with MTX, an agent with teratogenic and abortifacient properties. To characterize pregnancy outcomes in rheumatology patients treated with IFX, data available to the manufacturer through spontaneous reporting and through a pregnancy registry are presented.

Methods: Data from the Company safety database on individual, spontaneously reported pregnancies worldwide through Feb 23, 2013 were analyzed. The analysis focused on prospectively reported (ie, pregnancy outcome not known when first reported) cases of maternal IFX use for RA, AS, or PsA during pregnancy or within 2 months prior to conception and a known pregnancy outcome. In addition, data through Dec 31, 2010 from a Company-sponsored pregnancy registry study, undertaken to address health authority post-marketing commitments for IFX-exposed pregnancies, were analyzed; data were obtained from national medical registries in Sweden, Denmark and Finland. Maternal characteristics and pregnancy outcomes (births beyond 22 weeks of gestation) were analyzed among RA, AS, and PsA patients exposed to IFX or non-biologic systemic therapy during pregnancy or within 3 months prior to conception.

Results: 56 prospective reports (37 RA; 12 AS; 6 PsA; 1 RA&AS) of IFX exposure during pregnancy were identified. Mean maternal age was 31 years. 76.8% resulted in a live birth. Birth defects were reported for 3 live births: intestinal malrotation (1), hypospadias (1), and cardiac/coronary artery perforation (1). Of the 56 reports, MTX use was reported in 10 (8 RA), including the hypospadias case; it is possible that additional RA patients may have been exposed to MTX during their pregnancy. 23.2% of the pregnancies resulted in an induced (7) or spontaneous abortion [SAB] (6); 4 of the latter had MTX exposure. In the registry study, 27 IFX-exposed pregnancies were identified (18 RA; 5 AS; 4 PsA). Mean maternal age was 31.2 years. Birth defect was reported in 1 of the 27 IFX-exposed infants (atrial septal defect/metatarsus varus) and in 133 of the 1,974 infants exposed to non-biologic systemic therapy.

Conclusion: Review of pregnancy outcomes after IFX exposure in utero showed that 76.8% of spontaneous, prospectively reported pregnancies with known outcomes resulted in live births. The most frequently identified congenital anomalies were cardiovascular defects, the most common birth defect in the general population. While there did not appear to be an increased rate of birth defects compared to the general population, the rates in both datasets were based on small study populations. Additionally, the use of MTX, an agent contraindicated in pregnant women, was reported in more than half of the SABs. Spontaneous reporting is limited by the lack of a direct comparison group, the variable amount of data provided, and a possible reporting bias towards more serious cases. The registry study was limited to the Nordic population and data only included births from 22 weeks of gestation onwards.

Disclosure: S. Kalari, Janssen Research & Development, LLC., 3; **F. Granath**, Karolinska Insitutet, 3; **C. Y. Guo**, Janssen Research & Development, LLC., 3; **D. D. Harrison**, Janssen Research & Development, LLC., 3; **G. Bröms**, None; **A. Geldhof**, Janssen Biologics Europe, 3; **R. Nissinen**, Janssen Biologics Europe, 3; **M. Sanders**, Janssen Research & Development, LLC., 3; **M. Gissler**, None; **L. Pedersen**, None; **H. T. Sorensen**, Janssen Research & Development, LLC., 9; **H. Kieler**, None.

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Perinatal Exposure To Traditional and Biologic Disease Modifying Antirheumatic Drugs In Rheumatic Diseases: A Systematic Review Of Congenital Outcomes. Corisande Baldwin[1], Sharan Rai[2], J. Antonio Avina-Zubieta[3] and Mary De Vera[2]. [1]University of British Columbia, Vancouver, BC, [2]Arthritis Research Centre of Canada, Richmond, BC, [3]Arthritis Research Centre of Canada, University of British Columbia, Richmond, BC.

Background/Purpose: Despite the high incidence of rheumatic diseases during reproductive years, little is known about the perinatal impact of traditional and biologic disease modifying antirheumatic drugs (DMARDs). Systematic reviews of the evidence, which are widely based on case reports and cross-sectional studies, are scarce; only one exists on the use of methotrexate in pregnancy. Our objective was to systematically review the evidence on the perinatal use of traditional and biologic DMARDs on congenital malformation outcomes in babies born to women with rheumatic diseases.

Methods: We conducted a systematic search of MEDLINE (1946-), EMBASE (1974-), and INTERNATIONAL PHARMACEUTICAL ABSTRACTS (1970-) databases for peer-reviewed articles. Inclusion criteria were: 1) study sample that included women with rheumatic disease; 2) use of traditional and/or biologic DMARDs during pregnancy; and 3) congenital malformation outcome(s) reported. To ensure wide capture, we did not set limits on study design. We extracted information on study design, data source, number of exposed pregnancies, type of DMARD, type of exposure (single DMARD or combination), number of live births, and number of congenital malformations reported. While not the focus of our review, we extracted data on other perinatal outcomes in live births including prematurity and birthweight.

Results: We identified 1,141 articles and report on 53 that met eligibility criteria. We divided studies according to those with no unexposed comparison groups (case report [21], case series [17], cross-sectional [5], and surveys [3]) and observational studies and trials with unexposed comparators (cohort study [6] and controlled trial [1]). With respect to the former group, most studies reported primarily on single DMARD exposures with cyclophosphamide and methotrexate most widely studied among traditional DMARDs and etanercept and adalimumab among biologics. For traditional DMARDs, eligible studies reported 176 pregnancies among women with rheumatic diseases, 134 live births, and 12 malformations. For biologics, eligible studies included 11 pregnancies with rheumatic disease, 11 live births, and 1 malformation. Studies that included a comparator group were limited to traditional DMARDs, namely hydroxychloroquine, and report no differences between groups. Overall, data on DMARDs and congenital malformations are largely limited, particularly with biologics. We also identified the need for better reporting in terms of identifying patients with rheumatic disease, directly attributing medication exposures to patients, and delineating timing of medication use to pregnancy course.

Conclusion: This is the first systematic review on the use of both traditional and biologic DMARDs during pregnancy among women with rheumatic diseases, with focus on congenital malformations. Findings confirm the limited number of studies in this area. As controlled trials in this patient population are unlikely, systematic reporting and reviewing of medication exposures and perinatal outcomes provides a valuable resource for synthesizing evidence on the use of DMARDs among women with rheumatic diseases during pregnancy.

Disclosure: C. Baldwin, None; **S. Rai**, None; **J. A. Avina-Zubieta**, None; **M. De Vera**, None.

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Birth Outcomes In Childbearing Women Treated With Thiopurines: A Meta-Analysis. Zeinab F. Saleh, Raveendhara R. Bannuru, William F. Harvey and Timothy E. McAlindon. Tufts Medical Center, Boston, MA.

Background/Purpose: The thiopurines azathioprine (AZA) and 6-mercaptopurine (6-MP) are effective treatments for many rheumatic and autoimmune conditions. These medications have a category D classification from the US FDA. In humans, few studies have evaluated their safety in pregnancy, and most of them have focused on women with Inflammatory Bowel Disease (IBD). We performed an updated meta-analysis to study their effect on birth outcomes for any indication, not only IBD.

Methods: We searched Medline and the Cochrane database from inception to May 2013 for articles reporting birth outcomes in all women who took thiopurines within 3 months prior to conception and/or during pregnancy.

Outcomes of interest were incidence of congenital abnormalities (CAs), low birth weight (LBW; <2,500 g) and/or preterm birth (PTB; <37 weeks gestation). We calculated the Relative Risk (RR) for each outcome. Data were combined using a random effects model, and heterogeneity was assessed using an I^2 score.

Results: Fifteen case-control studies met inclusion criteria. We could not identify any study exclusively including patients with rheumatic conditions. A total of 1184 pregnancies were exposed to thiopurines, and 5955 disease-matched pregnancies were not exposed. There were 13 studies reporting on CAs, 10 on LBW, and 15 on PTB. Analysis of the studies that reported thiopurine exposure indicated an association with increase in CAs, but did not reach statistical significance (RR 1.35; 95% CI 0.99–1.85; I^2 = 0%). No statistically significant difference was found for LBW (RR 1.17; 95% CI 0.63–2.18; I^2 = 79%). Similarly, there was no significant increase of PTB (RR 1.28; 95% CI 0.88–1.86; I^2 = 69%).

Table 1. Characteristics of included studies

Study	Study design	Thiopurine	Indication	Thiopurine exposed pregnancies (N)	Disease-matched pregnancies unexposed to thiopurine (N)**
Casanova, 2013	RC	AZA or 6-MP	IBD	187	318
Perales-Puchalt 2012	RC	AZA	KT	8	16
Mahadevan 2012	PC	AZA or 6-MP	IBD	279	326
Coelho 2011	PC	AZA or 6-MP	IBD	86	129
Shim 2011	RC	AZA or 6-MP	IBD	19	74
Cleary 2009	RC	AZA	IBD	324	1739
Langagergaard 2007	RC	AZA or 6-MP	Any indication*	65	174
Norgard 2007	RC	AZA or 6-MP	IBD	26	880
Schramm 2006	RC	AZA	AIH	14	28
Dejaco 2005	PC	AZA or 6-MP	IBD	33	35
Francella 2003	RC	6-MP	IBD	39	92
Heneghan 2001	RC	AZA	AIH	15	20
Kallen 1998	RC	AZA	Any indication*	33	2104
Haugen 1994	RC	AZA	KT	35	11
Pahl 1993	RC	AZA	KT	21	9

*: includes IBD, rheumatic diseases, Myasthenia Gravis, Interstitial lung disease, glomeruloneprhitis and others.
** disease-matched pregnancies were either on other immunosuppressant or on no medication.
RC: Retrospective Cohort; PC: Prospective Cohort; AZA: Azathioprine; 6-MP: 6-Mercaptopurine. IBD: Inflammatory Bowel Disease; KT: kidney Transplant; AIH: Autoimmune Hepatitis

Conclusion: We found that thiopurine use at the time of conception and/or during pregnancy in women with autoimmune conditions is not associated with CAs, LBW or PTB. There was a positive association with increased risk of congenital malformations, but this might be due to potential confounders, such as disease activity or use of other immunosuppressants. Overall, the results are reassuring, but welcome larger prospective studies reporting more data on disease activity during pregnancy. Interestingly, although only 2 trials included patients with rheumatic diseases, it is reassuring that all 15 studies used the same doses of thiopurines that rheumatologists use in practice. These results could be helpful in discussing therapy with patients considering pregnancy.

Disclosure: Z. F. Saleh, None; **R. R. Bannuru**, None; **W. F. Harvey**, None; **T. E. McAlindon**, None.

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Long QT and Hydroxychloroquine; A Poorly Recognised Problem In Rheumatology Patients. Andra Negoescu[1], Andrew Thornback[2], Eugene Wong[2] and Andrew J. Ostor[2]. [1]Rheumatology Research Unit, Addenbrooke's Hospital, Cambridge, United Kingdom, [2]Addenbrooke's Hospital, Cambridge, United Kingdom.

Background/Purpose: Hydoxychloroquine (HCQ) is widely used for the treatment of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) with a side-effect profile including myopathy and cardiotoxicity. Acute HCQ poisoning has been reported to cause a prolonged QT interval, hypokalaemia and a prolonged QRS complex. RA itself is an independent risk factor for cardiovascular (CV) disease and a recent study has shown that patients are 40% more likely to develop atrial fibrillation. Our objective was to determine if alterations in cardiac conductivity with HCQ is appreciated and whether patients should undergo monitoring ECGs.

Methods: A retrospective analysis of our electronic medical records was undertaken to determine whether patients had had an ECG prior to, and at least 6 months after, starting HCQ and whether there had been a resultant change in the QT interval. Only resting standard 12-lead ECGs with both QT and QTc interval values measured were used. A past history of cardiac disease, arrhythmias or other medications know to prolong the QT interval were documented. The threshold for diagnosis of long QT syndrome was a QTc interval of 450 ms.

Results: 1537 patients currently taking HCQ were identified. 102 patients were found to have had ECGs before, and at least 6 months after, starting HCQ therapy. Of these only 19 patients had suitable ECGs for analysis. This comprised 16 females and 3 males, with a mean age of 62.5 years (range 19–87). CV risk factors included hypertension (n=7), obesity (n=5), ischaemic heart disease (n=4), deep vein thromboses (n=3) and cerebral vascular accidents (n=3). Known diagnoses of arrhythmias included atrial fibrillation (n=2), supraventricular tachycardia (n=1) and an unspecified arrhythmia (n=1). The patients had been on HCQ therapy for a mean of 3.6 years (range 1.3–9.2) and were receiving either 200 mg (n=4) or 400 mg (n=15) per day. The initial ECGs had a mean QTc interval of 424 ms (range 377–584). The post HCQ ECGs had a mean QTc interval of 449 ms (range 387–620). The mean change in QTc was 25 ms (range 66–143). Overall 4 patients had a long QTc prior and 8 patients after initiation of HCQ therapy (table 1). 8 patients were also taking ≥1 medication known to prolong the QT interval.

Table 1.

Patient	QTc Change	Years on HCQ	Cumulative Dose
1	−66	5.0	733
2	143	1.8	277
3	7	7.2	1058
4	62	1.2	199
5	9	2.8	297
6	28	2.4	219
7	−49	1.6	246
8	47	5.8	637
9	31	4.5	669
10	40	3.4	503
11	90	2.4	370
12	42	2.1	317
13	8	5.6	825
14	20	2.1	323
15	−6	9.2	1313
16	57	4.5	336
17	47	2.3	353
18	−38	1.8	281
19	0	3.6	269
Average	**25**	3.6	485

Conclusion: The appreciation of potential drug-induced arrhythmias in Rheumatology patients to date has not been well described. Our analysis showed a trend in prolongation of the QTc following treatment with HCQ. As we examined only a surrogate outcome, namely a change in QTc interval, we were unable to determine whether this was clinically relevant. It is difficult to distinguish whether the ECG changes observed were due to HCQ or due to other factors. Nevertheless as only a small number of patients had ECGs we have highlighted the under-recognition of this particular problem. In order to truly determine HCQ as a culprit, a prospective study is required in this area.

Disclosure: A. Negoescu, None; **A. Thornback**, None; **E. Wong**, None; **A. J. Ostor**, None.

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Lower-Dose Indomethacin Submicron Particle Capsules' Efficacy In Acute Pain: Results From Two Phase 3 Studies. Roy D. Altman[1], Allan Gibofsky[2], Mark Jaros[3] and Clarence Young[4]. [1]UCLA, Los Angeles, CA, [2]Hospital for Special Surgery, New York, NY, [3]Summit Analytical, Denver, CO, [4]Iroko Pharmaceuticals, Philadelphia, PA.

Background/Purpose: Indomethacin is used to treat acute gouty arthritis and other acute pain conditions but, like other NSAIDs, is associated with dose-related gastrointestinal, cardiovascular, and renal complications. A US Food and Drug Administration Public Health Advisory recommended that physicians use NSAIDs at "the lowest effective dose for the shortest duration consistent with individual patient treatment goals." A challenge with using existing NSAIDs at lower doses is achieving efficacy. New, submicron particle NSAIDs with enhanced absorption are under investigation to evaluate efficacy at lower doses than commercially available NSAIDs. We report the results of two phase 3 studies that evaluated investigational, lower-dose indomethacin submicron particle capsules compared with placebo in patients with acute pain following elective surgery.

Methods: Two phase 3, multi-center, randomized, double-blind studies enrolled patients 18 to 65 years of age undergoing bunionectomy with

osteotomy and internal fixation under regional anesthesia. Patients with a pain intensity rating of ≥40 mm/100-mm by Visual Analog Scale following surgery received indomethacin submicron particle capsules (40 mg three times daily [TID] or twice daily [BID], or 20 mg TID), or placebo. One study included celecoxib (400 mg loading dose followed by 200 mg BID). The primary endpoint was the overall (summed) pain intensity difference measured by Visual Analog Scale over 48 h.

Results: Overall, 835 patients were enrolled in both studies with >350 patients in each study. In study 1, all doses of indomethacin submicron particle capsules provided significantly better analgesia than placebo ($P \leq 0.046$). While celecoxib led to some pain control, it did not achieve statistical significance compared with placebo ($P = 0.103$; **Table**). In study 2, indomethacin submicron particle capsules 40 mg TID ($P = 0.034$) and BID ($P = 0.023$) provided significantly better analgesia than placebo (**Table**). In both studies, adverse events were generally similar across treatment groups and included nausea, localized post-procedural edema, dizziness, and headache.

Table.

	Indomethacin Submicron 40 mg TID	Indomethacin Submicron 40 mg BID	Indomethacin Submicron 20 mg TID	Celecoxib 200 mg BID, 400 mg loading dose	Placebo
			Study 1		
n	93	91	91	93	94
SPID-48					
Least squares mean ± SE	509.6 ± 91.9	328.0 ± 92.9	380.5 ± 92.9	279.4 ± 91.9	67.8 ± 91.4
P-value vs placebo	<0.001	0.046	0.017	0.103	
			Study 2		
n	94	93	92	N/A	94
SPID-48					
Least squares mean ± SE	598.5 ± 105.7	623.0 ± 106.2	342.8 ± 106.8	N/A	280.9 ± 105.8
P-value vs placebo	0.034	0.023	0.680	N/A	

TID, three times daily; BID, twice daily; SPID-48, overall (summed) pain intensity difference measured by Visual Analog Scale over 48 h; SE, standard error; N/A, not available.

Conclusion: Investigational, lower-dose indomethacin submicron particle capsules provided effective analgesia in two phase 3 studies in patients with acute pain following elective surgery. Indomethacin submicron particle capsules are a potentially promising lower-dose option for patients with acute pain.

Disclosure: R. D. Altman, Ferring Pharmaceuticals, 9, McNeil Consumer & Specialty Pharmaceuticals, 5, DePuy Synthes, 5, Imprimis Pharmaceuticals, Inc, 5, Oletec, 5; **A. Gibofsky**, GlaxoSmithKline plc, 1, Bristol-Myers Squibb, 1, Johnson & Johnson, 1, Horizon Phartmaceuticals, 5, Iroko Pharmaceuticals, 5, Abbott Laboratories, 9, Amgen, Inc, 9, Genentech, Inc, 9; **M. Jaros**, Summit Analytical, 3; **C. Young**, Iroko Pharmaceuticals LLC, 3.

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Lower-Dose Indomethacin Submicron Particle Capsules' Combined Safety From Two Phase 3 Studies In Patients With Acute Pain Following Elective Surgery. Allan Gibofsky[1], Roy D. Altman[2], Clarence Young[3], Daniel Solorio[4] and Jennifer Nezzer[5]. [1]Hospital for Special Surgery, New York, NY, [2]UCLA, Los Angeles, CA, [3]Iroko Pharmaceuticals, Philadelphia, PA, [4]Iroko Pharmaceuticals, LLC, Philadelphia, PA, [5]Premier Research, Philadelphia, PA.

Background/Purpose: Indomethacin is prescribed to treat acute pain and inflammation but, like other NSAIDs, is associated with dose-dependent gastrointestinal, cardiovascular, and renal adverse events (AEs). A US Food and Drug Administration Public Health Advisory recommended that physicians use NSAIDs at "the lowest effective dose for the shortest duration consistent with individual patient treatment goals." The efficacy of new, submicron particle NSAIDs with enhanced absorption is being evaluated at lower doses than commercially available NSAIDs. We present safety and tolerability data from two phase 3 studies evaluating the analgesic efficacy and safety of investigational, lower-dose indomethacin submicron particle capsules in patients with acute pain following elective surgery.

Methods: Two phase 3, randomized, multi-center, double-blind studies enrolled patients 18 to 65 years of age undergoing bunionectomy with osteotomy and internal fixation under regional anesthesia. Patients with a pain intensity rating of ≥40 mm/100-mm Visual Analog Scale following surgery received indomethacin submicron particle capsules (40 mg three times daily [TID] or twice daily [BID], or 20 mg TID), or placebo. One study included celecoxib (400 mg loading dose followed by 200 mg BID). Safety assessments included an overall summary of AEs by severity and seriousness.

Results: The pooled safety population included 835 patients. AEs were similar across treatment groups (**Table**). The most common AEs were nausea, post-procedural edema, headache, dizziness, vomiting, post-procedural hemorrhage, and constipation. There were no severe cardiovascular, gastrointestinal, or renal AEs. One serious AE, deep vein thrombosis, occurred in the indomethacin submicron particle capsules 40 mg BID treatment group and was determined by the investigator to be unrelated to the study drug. Seven patients withdrew from the trials due to an AE. AEs leading to withdrawal included one case each of uvulitis, angioedema, pyrexia, anxiety, and nausea, and 2 cases of urticaria.

Adverse Event	Indomethacin Submicron 40 mg TID (n = 187) n (%)	Indomethacin Submicron 40 mg BID (n = 184) n (%)	Indomethacin Submicron 20 mg TID (n = 183) n (%)	Combined Indomethacin Submicron (n = 554) n (%)	Celecoxib 200 mg BID, 400 mg loading dose (n = 93)[a] n (%)	Placebo (n = 188) n (%)
Any AE	131 (70.1)	148 (80.4)	137 (74.9)	416 (75.1)	68 (73.1)	142 (75.5)
Nausea	62 (33.2)	60 (32.6)	63 (34.4)	185 (33.4)	30 (32.3)	67 (35.6)
Post-procedural edema	44 (23.5)	40 (21.7)	48 (26.2)	132 (23.8)	25 (26.9)	60 (31.9)
Headache	29 (15.5)	25 (13.6)	20 (10.9)	74 (13.4)	5 (5.4)	21 (11.2)
Dizziness	28 (15.0)	26 (14.1)	18 (9.8)	72 (13.0)	7 (7.5)	32 (17.0)
Vomiting	14 (7.5)	19 (10.3)	21 (11.5)	54 (9.7)	3 (3.2)	21 (11.2)
Post-procedural hemorrhage	9 (4.8)	20 (10.9)	9 (4.9)	38 (6.9)	8 (8.6)	11 (5.9)
Constipation	7 (3.7)	9 (4.9)	11 (6.0)	27 (4.9)	3 (3.2)	9 (4.8)

AE, adverse event; BID, twice daily; TID, three times daily. [a]Only study 1 had a celecoxib treatment arm.

Conclusion: Indomethacin submicron particle capsules were generally well-tolerated in two phase 3 studies in patients with acute pain following elective surgery. Based on emerging efficacy data, investigational, lower-dose indomethacin submicron particle capsules represent a potentially promising lower-dose option for treating acute pain.

Disclosure: A. Gibofsky, GlaxoSmithKline plc, 1, Bristol-Myers Squibb, 1, Johnson & Johnson, 1, Horizon Phartmaceuticals, 5, Iroko Pharmaceuticals, 5, Abbott Laboratories, 9, Amgen, Inc, 9, Genentech, Inc, 9; **R. D. Altman**, Ferring Pharmaceuticals, 9, McNeil Consumer & Specialty Pharmaceuticals, 5, DePuy Synthes, 5, Imprimis Pharmaceuticals, Inc, 5, Oletec, 5; **C. Young**, Iroko Pharmaceuticals LLC, 3; **D. Solorio**, Iroko Pharmaceuticals, LLC, 3; **J. Nezzer**, Premier Research, 3.

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Risk Factors For Glucocorticoids-Induced Diabetes In Patients With Rheumatic Diseases. Takayuki Katsuyama[1], Sayaka Aoki[2], Ken-ei Sada[1], Yuriko Yamamura[1], Haruki Watanabe[1], Eri Katsuyama[1], Mariko Narazaki[1], Noriko Tatebe[1], Koichi Sugiyama[1], Katsue S. Watanabe[1], Hiroshi Wakabayashi[1], Tomoko Kawabata[1], Jun Wada[2] and Hirofumi Makino[1]. [1]Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan, [2]Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.

Background/Purpose: Since the efficacy of glucocorticoids for various rheumatic diseases was reported, glucocorticoids are still one of the important therapeutic agents in the current treatment of autoimmune disease. However, various adverse effects of glucocorticoids have been recognized and glucocorticoids-induced diabetes mellitus (GC-DM) is one of the critical systemic adverse effects of glucocorticoids. We conducted a single center retrospective cohort study to reveal risk factors for GC-DM.

Methods: We enrolled inpatients with newly diagnosed rheumatic disease from April 2006 to February 2013 in our department. Patients with previously diagnosed DM, defined as hemoglobin A1c (HbA1c) more than or equal to 6.5% or fasting plasma glucose (FPG) more than or equal to 126 mg/dl on admission, were excluded from the study. Each patient's baseline data included age, sex, underlying disease, smoking history, body mass index (BMI), family history of DM, FPG, HbA1c, eGFR, cholesterol, and triglyceride. We also collected the information of initial treatment including the maximum and the cumulative dosage of glucocorticoids and the concomitant use of methylprednisolone pulse therapy in four weeks. Primary end point of this study is the development of DM defined as fasting glucose not less than 126 mg/dl and/or postprandial glucose not less than 200 mg/dl at least twice after the initiation of glucocorticoids. We compared the characteristics and treatment status between GC-DM group and non DM group using paired *t* test and a Chi-square test. In order to identify independent risk factors for GC-DM, the extracted variables in the univariate analysis were entered into multivariate analysis using the logistic regression model.

Results: 26 male and 49 female patients (60.2± 17.1 years of age) consisting of 30 with systemic vasculitis, 15 with myositis and 11 with systemic lupus erythematosus were enrolled in the present study. The mean maximum dosage of glucocorticoids was 0.76 mg/kg/day and 20 patients (26.7 %) received methylprednisolone pulse therapy. 46 of 75 patients (61.6 %) developed GC-DM within 4 weeks. All patients with GC-DM showed the rise in postprandial blood glucose levels, while FPG levels of most patients were within normal range. The mean age and HbA1c levels at onset were significantly higher in GC-DM group than that in non-DM group (66.6 vs. 50.1 years p=0.002, 5.85 vs. 5.54 % p=0.034, respectively). No difference was found between two groups with the mode and dose of glucocorticoids. The patients with vasculitis developed GC-DM more frequently than those with SLE (73.3 % vs. 27.3 % p=0.006) while the mean age at disease onset is older in patients with vasculitis than those in patients with SLE (68.7 vs. 36.6 years p=0.008). In multivariate analysis, older age (more than or equal to 65 years) and higher levels of HbA1c (> 5.9%) were detected as independent risk factors for GC-DM (Odds ratio; 4.28 and 5.24, respectively).

Conclusion: Under the treatment with moderate or high dose of glucocorticoids, monitoring the postprandial glucose level is recommended particularly in patients with older age or higher levels of HbA1c for monitoring the development of GC-DM.

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Comparison Of Corticosteroid Plus Lidocaine Or Lidocaine Alone In Patients Receiving Celecoxib For The Treatment Of Acute Shoulder Or Trochanteric Bursitis: A Randomized, Double-Blind, Placebo Controlled Trial. Muhammad Imran[1], Haritha Narla[2], Jo A. Wick[3] and Herbert B. Lindsley[3]. [1]Kansas University Medical center, Kansas city, MO, [2]Kansas university Medical Center, kansas city, MO, [3]Kansas University Med Ctr, Kansas City, KS.

Background/Purpose: Bursitis is a self-limiting disorder in the majority of patients and typically responds to conservative measures. However, corticosteroid injections may be necessary in recurrent cases. The purpose of this study is to determine the efficacy of corticosteroid injection of methylprednisolone acetate with lidocaine versus lidocaine alone, in addition to celecoxib for subdeltoid and greater trochanteric bursitis in a randomized, double blind, placebo controlled trial.

Methods: 30 patients in our rheumatology clinic with acute or recurrent subdeltoid or trochanteric bursitis were randomized into an experimental group [n=15, 4 subdeltoid and 11 trochanteric bursitis] and a control group [n=15, 4 subdeltoid and 11 trochanteric bursitis]. Subjects with subdeltoid bursitis in the experimental group received methylprednisolone acetate (long acting) 80 mg (1.0 ml) plus lidocaine 20 mg (2.0 ml) into the subdeltoid bursa. The control group received lidocaine 20mg (2.0 ml) plus normal saline (1.0 ml). Subjects with trochanteric bursitis in the experimental group received methylprednisolone acetate (long acting) 120 mg (1.5 ml) plus lidocaine 30 mg (3.0 ml); the control group received 30 mg lidocaine plus normal saline (1.5 ml). Each group also received celecoxib 600 mg for the first day (a 400 mg initial dose followed by 200 mg later in the day) then 200 mg BID for 13 days. All subjects were treated for 14 days.

The primary end point was improvement of VAS (visual analog score) for bursal pain; secondary end points included improvement of VAS for fatigue, sleep, and global function; and bursal tenderness by palpation.

VAS for bursal pain, fatigue, sleep, and global function was scaled from 0 to 10 and bursal tenderness was scaled from 0 to 4.

Results: 30 subjects completed the study with 15 subjects in each group. The primary end point was met, periarticular corticosteroid significantly reduced VAS for bursal pain in experimental group compared to controls). The secondary end points also were met, improvement trends were noted for fatigue, sleep and global function; and bursal tenderness by palpation.

	Treatment Group			*Control Group*		
Variables	Day 0 [Mean SD]	Day 14 [mean (SD)]	% improvement	Day 0 [Mean SD]	Day 14 [mean (SD)]	% improvement
Bursal Pain	6.3 (2.2)	2.3 (2.2)	63	6.6 (2.3)	5.4 (3.0)	18
Fatigue	7.0 (3.2)	4.3 (3.4)	38	6.0 (2.9)	5.5 (3.2)	25
Sleep	6.9 (2.5)	3.0 (2.8)	56	6.3 (2.7)	4.3 (3.3)	31
Global Function	5.8 (2.5)	2.1 (2.0)	63	5.8 (2.2)	4.3 (2.1)	25
Bursal Tenderness (left shoulder)	1.9 (1.2)	1.4 (0.78)	26	2.0 (1.10)	1.75 (1.20)	12
CRP (mg/dl)	0.6 (0.4)	0.6 (0.5)	0	0.6 (0.4)	1.2 (2.3)	−100

Conclusion: Three of four VAS outcomes exceeded 50% improvement in the experimental group, whereas with the control group no VAS outcomes exceeded (31%). Periarticular corticosteroid plus lidocaine in addition to full dose of celecoxib enhances short term benefits of treatment for bursitis.

Disclosure: M. Imran, None; **H. Narla**, None; **J. A. Wick**, None; **H. B. Lindsley**, None.

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Arthralgia Occurring Under Aromatase Inhibitor Treatment For Breast Cancer. A Prospective Study. Daniel Wendling[1], Helene Letho-Gyselinck[1], Xavier Guillot[2], Clément Prati[3] and Xavier Pivot[2]. [1]Minjoz University Hospital, Besancon, France, [2]CHRU Besançon, Besançon, France, [3]CHU J Minjoz, Besancon, France.

Background/Purpose: Treatment with third generation aromatase inhibitors (AI) is associated with occurrence of arthralgia, with an incidence ranging from 25 to 45 %. In these patients, arthralgia may also be related to other conditions such as osteoarthritis, common tendinitis or auto immune diseases.

The aim of this study was to study patients treated with AI and reporting arthralgia, and comparing patients with new onset to patients with pre existing arthralgia and exacerbation under AI, to look for associated etiologic factors.

Methods: Patients followed in a tertiary oncology center for breast cancer treated with AI and reporting arthralgia were prospectively screened for rheumatologic clinical evaluation, as well as biologic (ESR, CRP, RF, ANA, ACPA) or imaging (X-Rays of symptomatic regions) investigation. Type of cancer, duration, treatment, type of AI, duration of AI treatment. Patients were divided in two groups: patients with new onset of arthralgia under AI, and patients with pre existing and exacerbation of arthralgia under AI. The two groups are compared using t test for quantitative variables (significance: p less than 0.05).

Results: Seventy five women were included, mean age (SD): 64.8 (9.2) years, time from cancer diagnosis: 34 (25) months. Adjuvant chemotherapy and/or radiotherapy were noted in respectively 52 and 64 cases. AI was Anastrozole (n = 6), Letrozole (55), Exemestane (14). Mean duration AI treatment since onset or exacerbation of arthralgia: 179 (224) days. Mean number of painful joints: 7.6 (9.7); locations (number of patients):shoulder 36, elbow 22, wrist 25, MCP 27, PIP 26, knee 26, MTP28. Mean ESR: 29 (25)mm/h; CRP: 3 (7.6) mg/l). New onset arthralgia: n = 38; pre existing and exacerbation of arthralgia: n = 37. No statistical differences were found between these two groups for type of cancer, presence of chemotherapy or radiotherapy, presence of metastases, duration and type of AI treatment, VAS pain, number and distribution of tender joints, ESR, CRP, ANA, RF, ACPA positivity, and radiographic findings. Positive lymph nodes and radiographic signs of rotator cuff dysfunction were statistically more frequent in the pre existing and exacerbation group. Some specific diagnoses were done after evaluation: 2 CREST syndrome (one in each group), 1 RA and 1 Sjögren syndrome in the new onset symptom group.

Conclusion: Arthralgia under AI treatment is frequent. Our study argues for an absence of specificity of these arthralgia, without particular difference between new onset or exacerbation of pre existing arthralgia, auto immune disease seem more frequent in the new onset symptom group, and thus possibly related to anti aromatase therapy.

Disclosure: D. Wendling, None; **H. Letho-Gyselinck**, None; **X. Guillot**, None; **C. Prati**, None; **X. Pivot**, None.

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Characteristics and Comparison Of Patients With Cystic Fibrosis With and Without Arthritis. Heather O. Tory[1], Karen Herlyn[2], David Zurakowski[3], Angela S. Pizzo[4], Robert P. Sundel[5] and Peter A. Merkel[6]. [1]Boston Children's Hospital, Boston, MA, [2]University Hospital Schleswig-Holstein, Lübeck, Germany, [3]Boston Children's Hospital, Boston, MA, [4]Mercy Hospital, Portland, ME, [5]Boston Children's Hospital and Harvard Medical School, Boston, MA, [6]University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Cystic Fibrosis (CF) is a common genetic mutation in Caucasian populations. Many patients have musculoskeletal complaints and 12% develop arthritis, including CF arthropathy (CFA), a poorly

understood entity of episodic mono or polyarthritis, and other inflammatory arthropathies. Prior studies have been limited to small patient cohorts showing no clear association with disease severity or complications, or specific laboratory results. Thus, diagnostic criteria are not well defined and the pathogenesis remains unclear. The goal of this study was to compare disease characteristics and laboratory findings between patients with CF with and without arthritis from a large cohort.

Methods: Patients with CF seen at 2 tertiary care hospitals over a 6 year period were screened for musculoskeletal symptoms via questionnaire or referral. Patients with symptoms underwent a comprehensive evaluation including chart review, medical history and physical examination by a rheumatologist, laboratory testing and pulmonary function testing. Patients were diagnosed with arthritis if they had physician documented evidence of joint effusion, warmth, or limited range of motion. Age- and gender-matched control patients with CF without arthritis were also evaluated. Comparisons between cases and controls were made by univariate and multivariate logistic regression analyses to identify independent markers of arthritis.

Results: The study cohort consists of 25 patients with CF and arthritis and 72 without arthritis. Demographic features were similar with no differences in the presence of disease complications (**Table 1**). Univariate analysis did find a higher percentage of rheumatoid factor (RF) positivity in patients with arthritis compared to patients without arthritis (18% vs. 3%, p = 0.04), with no other between group differences (**Table 2**). Regression analysis suggested this association held (p=0.05) after controlling for other markers of disease severity (age, IgG level, and FEV1).

Table 1. Comparison of demographic features and disease complications between groups

Patient Characteristics	Cystic Fibrosis Patients with Arthritis (n=25)	Cystic Fibrosis Patients without Arthritis (n=72)	p value
Demographic features			
Female, no. (%)	14 (56)	38 (53)	0.82
Age at visit, median (range) in years	25.1 (4.6–55.9)	26.6 (5–43.8)	0. 93
Body mass index, mean (SD) kg/m^2	19.6 (3.9)	20.6 (3.6)	0.33
Family history of autoimmunity, no. (%)	0 (0)	4 (6)	0.57
Complications of cystic fibrosis, no. (%)			
Allergic bronchopulmonary aspergilosis	2 (10)	8 (12)	1
Bowel obstruction	8 (35)	14 (20)	0.17
Diabetes mellitus/pancreatic	8 (35)	20 (29)	0.61
Hepatitis/cirrhosis	6 (26)	7 (10)	0.08
Hepatobiliary/gallbladder	4 (17)	9 (13)	0.73
Malabsorption/intestinal	19 (83)	57 (83)	1
Nasal polyps	16 (70)	34 (49)	0.15
Pulmonary	23 (100)	62 (90)	0.19

Table 2. Comparison of laboratory features among groups

Laboratory Features	Cystic Fibrosis Patients with Arthritis (n=25)	Cystic Fibrosis Patients without Arthritis (n=72)	p value
Albumin, g/dL	3.9 (0.5)	3.9 (0.53)	0.83
ALT, units/L	28.8 (18.8)	37.3 (31.4)	0.21
Amylase, units/L	39.8 (23.6)	51.1 (32.9)	0.13
ANA present, no. (%)	3 (14)	13 (22)	0.54
AST, units/L	27.2 (17.5)	32.5 (24.3)	0.33
CH50, units/mL	232 (63)	206 (58)	0.15
Cholesterol, mg/dL	151 (50)	141.2 (43)	0.40
Immune complexes, median (IQR)	11.5 (5.8, 15)	9 (3, 12)	0.21
Creatinine, mg/dL	0.82 (0.38)	0.83 (0.26)	0.93
CRP, median (IQR) mg/dL	5.7 (3, 14.4)	3.1 (3, 18)	0.71
Cryoglobulin present, no. (%)	1 (5)	3 (5)	1
ESR, mm/hr	26.9 (21.6)	24 (23.1)	0.60
FEV1, % predicted	62.5 (26.2)	63.5 (29.8)	0.89
FVC, % predicted	75.5 (22.6)	78.8 (25.6)	0.61
Glucose, mg/dL	114 (59)	120 (81)	0.76
Hematocrit, %	38 (4)	39 (4)	0.23
IgG, mg/dL	1258 (441)	1383 (554)	0.33
Platelet, cells/uL	284 (110)	304 (92)	0.37
Rheumatoid factor present, no. (%)	4 (18)	2 (3)	0.04
Total bilirubin, mg/dL	0.45 (0.21)	0.47 (0.58)	0.84
Triglyceride, mg/dL	131 (94)	110 (63)	0.27
White blood cell, 103-cells/uL	9.4 (2.3)	9.7 (3.3)	0.75

Data are mean (SD) unless otherwise indicated. IQR = interquartile range.

Conclusion: In this largest cohort to date, patients with CF and arthritis were more likely to have a positive RF compared to patients without arthritis, suggesting that the pathophysiology may be related to accumulation of antigenic immune markers. There were no other differences, indicating that the etiology and spectrum of disease may vary and requires additional exploration, including genotype evaluation and longitudinal follow-up.

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The Prevalence and Pattern Of Self Reported Joint Symptoms In Cystic Fibrosis. Carl Orr[1], Cormac McCarthy[1], Johan Meurling[1], Paul G. O'Connell[2], Cedric Gunaratnam[1] and Noel G McElvaney[1]. [1]Royal College of Surgeons in Ireland, Dublin, Ireland, [2]Beaumont Hospital, Dublin 9, Ireland.

Background/Purpose: Arthritis in cystic fibrosis (CF) can be very incapacitating, and it is mainly of three types: CF arthritis, hypertrophic osteoarthropathy, and arthritis due to co-existent conditions and drug reactions [1]. Episodic arthritis occurring in patients with cystic fibrosis has been recognised [2]. However, although joint manifestations are common in children with cystic fibrosis (CF), they have received little attention in adults [3]. The prevalence of joint pain in the CF patients has been reported variously as: 12.9% [4], 2–8.5% of patients [3] and 4.5% in patients aged over 10 [5]. Our experience suggested that the prevalence may be higher than that previously reported.

Methods: Rheumatic symptoms and signs of 55 adult patients with CF (age 18 to 63 years) were determined by questionnaire and phone interview. The questionnaire was designed to elicit the pattern of joint problems, as well as to determine features of definite inflammatory problems which included joint swelling, difficulty with function (e.g. making a fist) and morning stiffness lasting greater than 1 hour.

Results: 63.6% (35/55) reported ever having experienced joint pain, but only 37.1% of those who reported experiencing pain at any point said that it had affected important activities in their lives. 16.4% (9/55) reported more than one hour of morning stiffness in their joints. 30.9% (17/55) reported joint swelling or difficulty making a fist.

In those that reported pain, 60% (21/35) reported wrist pain, with 42.9% (9/21) of these patients reporting wrist swelling. 16.4% (9/55) of the total cohort had experienced both wrist pain and swelling.

In those that reported pain, 57.1% (20/35) reported hand pain, with 60% (12/20) reporting swelling and 65% (13/20) having difficulty making a fist. Inflammatory symptoms (difficulty making a fist or hand swelling) were reported in 80% (16/20) of those with hand pain.

Knee 80% (28/35), ankle 60% (21/35) and foot 31.4% (11/35) pain were cited by those reporting pain.

Symmetrical disease in time was reported in 48.6% (17/35) patients.

Conclusion: The prevalence of joint symptoms by self-report in our CF cohort far exceed that reported in previous studies. The age of the cohort would suggest that joint pain is being reported more commonly in patients with CF than in subjects of similar age who do not have CF.

The reported symptoms of swelling and morning stiffness suggest that the problems may be inflammatory in up to 30% of patients with CF.

No definite pattern of involvement could be identified in this study.

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Efficacy Of Intermittent Intra-Venous Cyclophosphamide and Cyclosporin A Combination Therapy For Rapidly Progressive Interstitial Lung Disease With Dermatomyositis Associated With Anti-Melanoma Differentiation-Associated Gene 5 Autoantibody Titer. Noriko Sasaki, Shinji Sato, Shinichi Nogi, Naofumi Chinen, Kiri Honda, Eiko Saito, Chiho Yamada and Yasuo Suzuki. Tokai University School of Medicine, Isehara, Japan.

Background/Purpose: Anti-Melanoma Differentiation-Associated Gene 5 (MDA5) autoantibody is present specifically in patients with dermatomyositis (DM), especially those with few or no muscle manifestations (clinically amyopathic dermatomyositis: CADM). It is strongly associated with rapidly progressive interstitial lung disease (RP-ILD). Recently, an association between anti-MDA5 antibody titer measured by enzyme-linked immunosorbent assay (ELISA) and disease activity has been reported in addition to its diagnostic utility for CADM with RP-ILD. However, the relationship between antibody titer and efficacy of intermittent intra-venous cyclophosphamide and cyclosporin A combination therapy had not been reported.

Methods: 7 patients with CADM and RP-ILD positive for anti-MDA5 antibody by RNA and protein immunoprecipitation assay who were seen at our University between 2011 and 2012 were retrospectively evaluated for anti-MDA5 antibody and lung involvement. Anti-MDA5 antibody titers were determined by a previously established ELISA. Patients received combination therapy consisting of intermittent intra-venous cyclophosphamide (0.5 g/m^2/month), cyclosporin A (2–4 mg/kg/day) and high dose corticosteroid (1 mg/kg/day orally, then tapering gradually) including pulse therapy (1,000 mg/day for 3 days) over 24–48 weeks. Associations between anti-MDA5 titer and the change in high resolution computed tomography (HRCT) findings after improvement of lung involvement or outcome were analyzed. HRCT findings were evaluated by alveolar and interstitial score proposed by Kazerooni et al.

Results: The combination therapy was effective for all 7 CADM and RP-ILD patients and none of them died during follow-up. There was no correlation between the mean alveolar score and the mean titer of anti-MDA5 antibody before treatment ($r=-0.36$; $P=0.44$). The mean titer of anti-MDA5 antibody significantly decreased after treatment (130.8 units vs. 15.3 units, $P=0.016$, cut-off level = ~15 unit). In parallel with the reduced antibody titer, respiratory symptoms improved in all patients and the mean alveolar score significantly decreased after treatment (10.9 vs. 7.6, $P=0.012$), whearas no changes were seen in the mean interstitial score. After improvement of RP-ILD, anti-MDA5 titer remained under the cut-off level over time in 5 of 7 (71%) patients.

Conclusion: These results emphasize the clinical importance of using anti-MDA5 antibodies to monitor disease activity of lung involvement and to evaluate the response to treatment in patients with DM and RP-ILD.

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Efficacy and Safety Of Low-Intensity Resistance Training Combined With Vascular Occlusion In Polymyositis and Dermatomyositis. Melina Mattar[1], Luiz A. Perandini[1], Thalita Dassouki[2], Samuel K. Shinjo[1], Bruno Gualano[3], Hamilton Roschel[3], Fernanda R. Lima[4] and Ana Lucia S. Pinto[1]. [1]University of Sao Paulo, Rheumatology Division, LACRE, Sao Paulo, Brazil, [2]Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, [3]University of Sao Paulo, School of Physical Education and Sport, Sao Paulo, Brazil, [4]University of Sao Paulo, Rheumatology Division, Sao Paulo, Brazil.

Background/Purpose: Previous studies have demonstrated that low-intensity resistance training combined with vascular occlusion (VO) improves muscle strength to the magnitude of traditional high-intensity resistance training in healthy subjects. We, therefore, aimed to determine whether low-intensity resistance training combined with VO is safe and effective to improve muscle strength, functional capacity and quality of life in patients with polymyositis (PM) and dermatomyositis (DM).

Methods: Thirteen patients (4 PM and 9 DM according to Bohan and Peter's criteria, 1975) from the Outpatient Myopathy Unit of our tertiary Center, with complete clinical response to the treatment (age: 45.6±8.8 years; disease duration: 5.4±2.9 years; body mass index (BMI): 31.0±6.6kg/m^2; VO_2max: 23.3±6.9mL/kg/min) were submitted to a 12-week supervised exercise program that consisted of resistance exercises at low-intensity [30% of one repetition maximum (1RM)] combined with VO (70% of the total occlusion pressure of the tibial posterior artery). Clinical questionnaires [36-item short form health survey (SF-36), the health assessment quality (HAQ) and the visual analogue scale (VAS)], muscle strength (1RM of leg press and leg extension), functional capacity [time stands (TS) and timed up and go (TUG) tests] and serum muscle enzymes were assessed before (PRE) and after (POST) the exercise program. The pharmacological treatment remained unchanged at least three months prior to study entry and throughout the protocol.

Results: Comparison of pre- and post-exercise intervention revealed that all patients had significant improvements in muscle strength (leg-press: 128±62 *vs*. 155±78kg, $P=0.001$; leg-extension: 37±10 *vs*. 46±13kg, $P=0.001$) and muscle function (TS: 13±2 *vs*. 15±2, $P=0.001$; TUG: 6.9±1.1 *vs*. 6.6±1.0s, $P=0.002$). Additionally, improvement in quality of life, as measured by the SF-36 (Physical component: 41.6±7.2 *vs*. 50.0±7.4, $P=0.001$; Mental component: 42.7±13.0 *vs*. 56.0±10.1, $P = 0.008$), HAQ (1.58±1.98 *vs*. 0.60±0.62, $P=0.007$) and VAS (VAS patient: 4.6±2.9 *vs*. 1.6±1.2cm, $P=0.024$; VAS physician: 2.7±1.2 *vs*. 1.2±0.6cm, $P=0.001$). Of note, no change in serum levels of creatine kinase (195±76 *vs*. 224±171IU/L, $P=0.944$) and aldolase (3.9±1.5 *vs*. 3.1±1.6IU/L, $P=0.265$).

Conclusion: The present work provides novel evidence that a low-intensity resistance training program combined with VO is safe and effective in improving muscle strength, functional capacity, and quality of life in PM and DM patients.

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Killer T Cell Inhibition By CD226 Blockade For Treatment Of Inflammatory Myopathy. Hitoshi Kohsaka[1], Nao Tateishi[1], Shinya Hirata[2], Kazuko Shibuya[3], Akira Shibuya[3] and Nobuyuki Miyasaka[4]. [1]Department of Medicine and Rheumatology, Tokyo Medical and Dental University, Tokyo, Japan, [2]Kumamoto University School of Medicine, Kumamoto, Japan, [3]Department of Immunology, University of Tsukuba, Ibaraki, Japan, [4]Tokyo Medical and Dental University, Tokyo, Japan.

Background/Purpose: Current treatment strategy of polymyositis/dermatomyositis calls for administration of high dose glucocorticoids and additional immunosupressants when necessary. These options are based largely on successful experiences in treatment of other systemic autoimmune disorders. This is partly because no appropriate animal models were available for basic and preclinical studies. We have developed a new polymyositis model, C-protein induced myositis (CIM) of mice, and disclosed that muscle-reactive killer CD8 T cells and activation of muscular innate immunity are both critical therapeutic targets specific for myositis. To develop a new treatment that addresses specific pathology, CD226 (DNAM-1), which expressed on T cells to promote killer cell function upon interaction with its ligands, was investigated as a candidate therapeutic target.

Methods: Expression of CD112 and CD155, both of which are ligands of CD226, was studied with RT-PCR and immunostaining. In vitro effects of CD226 ligation on CD8 T cells were studied by stimulating mouse splenic CD8 T cells with monoclonal anti-CD226 antibodies (Tx42) and anti-CD3 antibodies immobilized onto microtiter wells. IFNγ in the culture supernatants was quantified with specific ELISA. Mice were immunized with recombinant skeletal muscle C-protein fragments/complete Freund's adjuvant for CIM induction and treated with intact Tx42, F(ab')2 of Tx42, or controls. Treatment was initiated before or after the myositis onset.

Results: C2C12 myoblasts and C2C12-derived myotubes expressed CD155 but not CD112 at the mRNA and protein levels. Mouse muscle tissues expressed CD155 mRNA. In vitro treatment of splenic CD8 T cells with immobilized Tx42 augmented IFNγ secretion when the T cells were stimulated with anti-CD3 antibodies. The augmentation was more obvious when the CD3 antibody concentration was low. CIM was ameliorated when immunized mice were treated with F(ab′)2 of Tx42 both in preventive and therapeutic protocols. Intact Tx42 was not effective in either protocol.

Conclusion: Muscles express CD155, which is a ligand of CD226. Blockade of CD226 with Tx42 F(ab')2, but not with intact Tx42, suppressed CIM. In vitro agonistic effects of immobilized Tx42 in CD8 T cell activation suggested that abrogation of Fc mediated cross-linking by F(ab')2 preparation is essential for the therapeutic effects of the anti-CD226 antibodies. Killer cell inhibition by CD226 blockade should be a new therapeutic approach that addresses specific pathology of polymyositis and possibly dermatomyositis.

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Use Of Biologics In Polymyositis and Dermatomyositis – A National Register Study. John Svensson[1], Anna Tjärnlund[2], Balsam Hanna[3], Sara Magnusson Bucher[4], Johan Askling[1], Ingrid E. Lundberg[5] and Maryam Dastmalchi[6]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Stockholm, Sweden, [3]Sahlgrenska University Hospital, Gothenburg, Sweden, [4]Örebro University Hospital, Örebro, Sweden, [5]Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, [6]Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Biologics have been used off-label in treatment of refractory polymyositis (PM) and dermatomyositis (DM). In this study we aimed to describe the use of biologics in patients with PM and DM based on national registries in Sweden.

Methods: Patients were identified by linking the national patient care registers, listing all in-patients and out-patient visits seen by specialists to the prescribed drug register, the Swedish Rheumatology Quality register (SRQ) and the Swedish Myositis Network (SWEMYONET). To retrieve information on demographics, effectiveness and safety we used information in SRQ, SWEMYONET and patient records. Effectiveness was based on an overall assessment of clinical outcome in the patient records, serum levels of creatine phosphokinase (CPK) and prednisolone dose. Clinical data were collected at start of treatment, at last follow up within 12 months or at discontinuation of biological treatment. Therapies stopped within 3 months were excluded from effectiveness evaluation. Safety was evaluated by the number of patients stopping treatment due to adverse events within 12 months.

Results: 63 patients treated with at least one biologic (36 PM, 27 DM, mean age 60 (12), 45 women, 18 men) were identified at 11 different centers between 2001 and 2011. All identified cases were refractory to previous medication with mean 2.5 (1.3) DMARDS beings used prior to start of biologic therapy. Multiple biological treatments were common with 7 patients treated with 2 different biologics and 7 patients treated with 3 different biologics.

Rituximab (RTX) was the most often used biological agent (Table 1). No new treatment with anakinra (ANA) had been started after 2009 and no new treatment with TNF-inhibitors (TNFi) had been started after 2003. One treatment with tocilizumab was identified in 2011 but was stopped after 2 months due to a lung infection.

Table 1. Demographics and outcome measures of biologics in PM and DM

	rituximab	abatacept	anakinra	TNF-inhibitors*
n	42	13	15	13
PM:DM	1.0:1	1.2:1	2.0:1	3.3:1
F:M	1.8:1	5.5:1	4.0:1	2.3:1
Disease duration, years median (range)	4.0 (0.2–35)	7.7 (0.6–35.9)	8.2 (3.5–28.8)	7.4 (1–12.3)
Follow up, months median (range)	6.6 (3.6–12.7)	9.6 (5–12.9)	5.9 (3.1–10.9)	6.1 (3.2–12.4)
Treatment duration, months median (range)	12.0 (0–103.4)	18.5 (1.8–53.1)	6.0 (0.8–30.8)	4.3 (0–75.5)
Stopped due to side effects n(%)	5 (11.9%)	1 (7.7%)	7 (46.7%)	4 (30.1%)
Overall responder** n(%)	27 (69.2%)	8 (66.7%)	4 (36.4%)	2 (22.2%)
CKP-25%*** n(%)	10 (62.5%)	3 (50.0%)	1 (20.0%)	0 (0.0%)
CPK, μkat/L median (range)				
Before	8.4 (0.6–111.6)	7.4 (0.33–39.3)	3.7 (1.2–30.9)	1.9 (1.2–12.6)
After	1.8 (0.4–147.6)	6.6 (1.2–31.4)	4.0 (1.2–28.3)	2.0 (1.2–16.8)
Daily prednisone dose, mg median (range)				
Before	10.0 (0–80)	10.0 (2.5–100)	7.5 (0–50)	11.3 (0–15)
After	10.0 (0–30)	8.1 (0–15)	8.8 (0–20)	10.0 (0–20)

PM = polymyositis, DM = dermatomyositis, F = female, M = male, CPK = creatinine phospokinase
* 1 etanercept, 12 infliximab, **According to patient records, ***Number of patients having a ≥25% decrease of CPK if serum levels at start of treatment > Upper limit of normal.

No statistical difference could be found for any of the biologics when comparing CPK level and prednisolone dose before and after treatment. 3 patients stopped their treatment due to disease remission. They were all treated with RTX. The most common adverse events leading to discontinuation were infections, and for ANA local injection reaction.

Conclusion: We found an increasing use of RTX and ABA in patients with PM and DM. In this population we found an overall favorable response to RTX and ABA in 65% of patients but less often to ANA and TNFi. A reduction of elevated CPK levels was observed more often after RTX and ABA treatment compared to ANA and TNFi treatment. RTX and ABA seemed to be well tolerated by patients.

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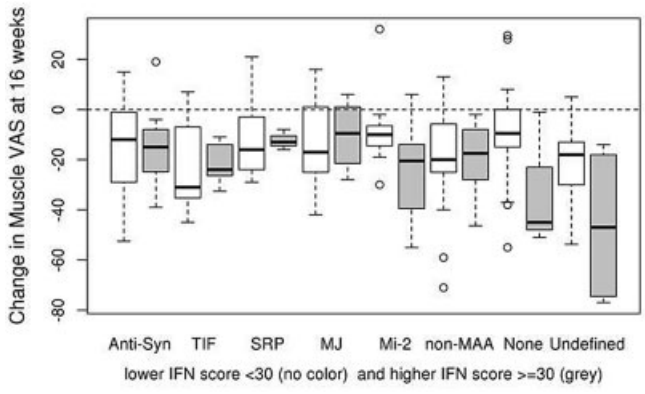
Biomarker and Serologic Predictors Of Clinical Improvement After B Cell Depletion In Refractory Adult and Juvenile Dermatomyositis (DM) and Adult Polymyositis (PM) - The RIM (Rituximab in Myositis) Trial. Ann M. Reed[1], Cynthia S. Crowson[1], Molly S. Hein[1], Consuelo Lopez de Padilla[1], Helen Khun[1], Rohit Aggarwal[2], Dana P. Ascherman[3], Marc C. Levesque[2] and Chester V. Oddis[2]. [1]Mayo Clinic, Rochester, MN, [2]University of Pittsburgh, Pittsburgh, PA, [3]University of Miami Miller School of Medicine, Miami, FL.

Background/Purpose: The aim of this study was to examine the longitudinal utility of a biomarker signature in conjunction with myositis autoantibodies (autoAbs) as biomarkers of disease outcome in refractory myositis patients treated with B cell depletion (BCD).

Methods: In the RIM Trial, all subjects received 1 gram of rituximab on 2 consecutive weeks. Using start of treatment as baseline, serum samples (n=177) were analyzed at 0, 8, 16, and 24 weeks after BCD with multiplexed sandwich immunoassays (Meso Scale Discovery) to quantify type-1 IFN-regulated and other pro-inflammatory chemokines and cytokines. Biomarker scores were generated based on a priori assignment from literature review for serum levels from the following pathways: type-1 IFN-inducible (IP-10, I-TAC, MCP1), Th1 (IFNγ, TNFα, IL2), Th2 (IL4, IL5, IL10, IL12, IL13), Th17 (IL6, IL17, IL1b) and regulatory cytokines (IL10 and TNFa). Biomarker scores are defined as the normalized sum of cytokine/chemokine levels adjusted to a 100-point scale. Myositis autoAbs (anti-synthetase (anti-syn) n=28, TIF1-g n=19, Mi-2 n=25, SRP n=21, MJ n=18, non-myositis associated (non-MAA) n=24, unidentified autoantibody n=9, and no autoantibodies n=33) determined by immunoprecipitation at baseline, were correlated with outcome measures. Kruskal-Wallis rank sum test was used for comparisons.

Results: The mean (SD) values for muscle disease and physician global disease activity VAS scores (0–100 mm) were 46 (22) and 49 (19). IFN scores (median values) were higher at baseline in patients with anti-syn; (43), TIF1-g (31) and Mi-2 (30) compared with other autoAb groups ($p<0.001$). No significant improvement in biomarker scores was detected at 8 weeks. However, at 16 weeks after BCD anti-syn and Mi-2 autoAb (+) patients and non-MAA had a greater improvement in IFN scores (−6.7, −6.1 and −7.2 $p<.001$) while TIF1-g (+) patients worsened by 7.0. The change in IFN score at 16 weeks correlated with percent change in muscle ($r=0.27$, $p<0.001$) and physician VAS ($r=0.16$, $p=0.06$). High IFN scores at baseline (>30) demonstrated the greatest clinical improvement based on global and muscle VAS among patients in certain autoAb groups (e.g., Mi-2, none and "undefined") (IFN score-autoAb interaction $p=0.075$; Figure).



Regulatory scores were higher at baseline in patients with anti-syn (31) and non-MAA (32) vs. other groups (p=0.01). Regulatory score improved at 16 weeks in anti-syn (−5.8) and Mi-2 (−3.4) and non-MAA (−7.2, p=0.028). Th1 scores decreased in the anti-syn, Mi-2, non-MAA and to a lesser extent in the TIF-g group at 16 weeks (p=0.039) with the greatest improvement at 24 weeks (p=0.014) suggesting a longer time to improvement if the Th1 score is elevated. Th17 remained unchanged.

Conclusion: Biomarker signatures in conjunction with autoAbs prior to treatment help guide response to BCD in refractory myositis. In addition, biomarker and clinical response is greatest at 16 weeks after BCD.

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Evidence For Immunotherapy In Polymyositis and Dermatomyositis: A Systematic Review. Erin Vermaak[1] and Neil J McHugh[2]. [1]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [2]Department of Pharmacy and Pharmacology, University of Bath, Bath, United Kingdom.

Background/Purpose: Dermatomyositis (DM) and polymyositis (PM) are rare chronic inflammatory disorders of muscle. The morbidity and mortality associated with these conditions remains significant despite treatment, which typically begins with high-dose corticosteroids. Second-line agents are commonly used in clinical practice, however there are no clear evidence-based guidelines directing their use. We systematically assessed the evidence for immunotherapy in DM and PM.

Methods: Relevant studies were identified through Ovid Medline and PubMed database searches. Bibliographies of relevant studies were scrutinized for other potentially relevant citations, and research registers of ongoing trials and international conference proceedings were examined to identify research in progress or data as yet unpublished. Randomized controlled trials and experimental studies without true randomization (quasi-randomized) including adult patients with definite or probable DM or PM were evaluated. Trials involving patients with possible, early or mild disease were excluded, as were those where diagnostic certainty was unknown or diagnostic criteria had not been specified. Any type of immunotherapy was considered. Improvement in muscle strength was the primary outcome. Secondary outcomes included improvements in patient and physician global scores, physical function and muscle enzymes. Studies not assessing these outcomes were excluded. Using predetermined criteria, the two authors independently selected trials for inclusion and then assessed these for quality.

Results: 1697 citations were retrieved. 13 trials were identified as potentially relevant, 3 were excluded after full text review. 2 further trials were identified after hand-searching reference lists. 12 studies were selected for full analysis, including a total of 522 participants. Differences in trial design and quality, and variable reporting of baseline characteristics and outcomes made direct comparison impossible. Although no one treatment can be recommended on the basis of this review, improved outcomes were demonstrated with a number of agents including methotrexate, azathioprine, ciclosporin and intravenous immunoglobulin. Plasmapheresis and leukapheresis were of no benefit. Biologics were well tolerated but were not demonstrated to be of benefit.

Study	Intervention	Conclusion
Bunch *et al* 1980	Pred + AZA vs. Pred + Placebo	No additional benefit with AZA at 3 months
Hollingworth *et al* 1982	ALG + AZA vs. Pred	NS trend toward benefit with ALG + AZA
Miller *et al* 1992	PEX vs. Leukapheresis vs. Sham apheresis	PEX/Leukapheresis of no benefit
Dalakas *et al* 1993	IVIg vs. Placebo	IVIg beneficial in refractory DM
Villalba *et al* 1998	MTX + AZA + Pred vs. IV MTX + Pred	NS trend toward benefit with MTX + AZA
Vencovsky *et al* 2000	CsA + Pred vs. MTX + Pred	MTX and CsA equivalent, but MTX better tolerated
Coyle *et al* 2008	IFX vs. Placebo	IFX is well tolerated, but has limited efficacy
Van de Vlekkert *et al* 2010	Pred vs. Dex	Dex not superior to Pred, but fewer side effects
The Muscle Study Group 2011	Pred +ETAN vs. Pred + Placebo	No additional benefit with ETAN, but has steroid-sparing effect
Miyasaka *et al* 2011	IVIg vs. Placebo	IVIg of no benefit in cortico-steroid-refractory PM/DM
Choy *et al* 2011	Pred vs. Pred + MTX vs. Pred + CsA vs. Pred + MTX + CsA	Adding immunosuppressants to corticosteroid therapy offers no additional benefit
Oddis *et al* 2013	Ritux early vs. Ritux late	No significant difference between groups, but 83% met DOI

ALG, anti-lymphocyte globulin; AZA, azathioprine; CsA, ciclosporin; Dex, dexamethasone; ETAN, etanercept; IFX, infliximab; IV, intravenous; IVIg, intravenous immunoglobulin; MTX, methotrexate; NS, non-significant; PEX, plasma exchange; Pred, prednisolone; Ritux, rituximab.

Conclusion: More high quality randomized controlled trials are needed to establish the role of second-line agents, in particular biologics, in the treatment of DM and PM.

Disclosure: E. Vermaak, None; **N. J. McHugh**, None.

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Mortality In Polymyositis and Dermatomyositis: A Single Centre Study. Erin Vermaak[1], Gavin Shaddick[2] and Neil J McHugh[3]. [1]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [2]University of Bath, Bath, United Kingdom, [3]Department of Pharmacy and Pharmacology, University of Bath, Bath, United Kingdom.

Background/Purpose: PM and DM are rare chronic inflammatory disorders of muscle, and data on long-term prognosis and outcomes are lacking. Previous studies have reported 5-year survival rates of 60–75% and standardized mortality ratios (SMRs) ranging from 1.75 to 2.92. Through a better understanding of mortality and its causes, those at increased risk of premature death can be identified and treated accordingly, thereby improving management of these conditions, and therefore also outcomes. The aim of this study was to determine whether the mortality of a cohort of patients with polymyositis (PM) and dermatomyositis (DM) is significantly different from that of the general UK population, and whether the presence or absence of myositis-specific and myositis-associated autoantibodies influences mortality.

Methods: Patients entered onto the myositis database at our tertiary referral centre were included. Information on patient deaths was collected retrospectively. The National Health Service (NHS) Strategic Tracing Service was used to establish which patients had died and which were still alive. Date and cause of death was confirmed by death certificate from the Registry of Births, Marriages and Deaths. Standardized mortality ratios (SMR) were calculated by matching the patient data to single-year, 5-year age-banded England and Wales data from the Office of National Statistics.

Results: Out of 86 patients with PM and DM (57 PM, 65 female), there were 21 deaths – 15 female and 6 male. The SMR for the total cohort was 2.20 (95% CI 1.36–3.36), for PM was 2.12 (95% CI 1.16–3.56) and for DM was 2.38 (95% CI 0.96–4.90). SMRs were higher in females compared with males overall and in the PM subgroup, however the SMR was higher in males with DM compared with females. There was a trend towards higher death rates in those without myositis-specific or myositis-associated autoantibodies (OR 2.11, 95% CI 0.68–7.43). The leading causes of death were infection (33%), malignancy (28.6%) and cardiovascular disease (23.8%).

Conclusion: Patients with PM and DM are at 120% increased risk of mortality; and infections, cardiovascular disease and malignancy account for the majority of deaths. Females, in particular those with PM, and autoantibody-negative patients are at higher risk of death. Early identification and aggressive management of infections, thorough cardiovascular evaluation, and targeted malignancy screening may improve outcomes in these conditions.

Disclosure: E. Vermaak, None; **G. Shaddick**, None; **N. J. McHugh**, None.

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Influence Of Anti-Ro/SSA Autoantibodies On Cinical Characteristic Of a Cohort Of Myositis Patients. Simone Barsotti[1], Rossella Neri[1], Valentina Iacopetti[2], Chiara Baldini[1], Nicoletta Luciano[1], Antonio Tavoni[3], Anna d'Ascanio[1] and Stefano Bombardieri[1]. [1]Rheumatology Unit, Pisa, Italy, [2]Internal medicine, Barga, Italy, [3]Immunoallergology unit, Pisa, Italy.

Background/Purpose: Idiopathic inflammatory myopathies (IIM) are a group of acquired diseases, characterized by immunoflogistic processes primarily involving the skeletal muscle. Myositis-associated antibodies are frequently detected in IIM patients' sera, particularly in those with overlap syndromes; more specifically, the clinical relevance of anti-Ro/SSA has not been fully elucidated. Aim of this study is to establish the prevalence of Ro/SSA in a single centre cohort of patient with IIM followed in our Rheumatology Unit and to investigate their influence on the IIM clinical expression.

Methods: Clinical charts of patients diagnosed as IIM according with Bohan e Peter criteria and followed between 1974 and 2012 were retrospectively examined. Antibodies antiRo/SSA were determined by counter-immunoelectrophoresis. Epidemiological, clinical, laboratory, instrumental and histological features of the patients were collected.

Results: a total of two hundred and forty six patients affected by IIM were identified; 21 (8.6%) were positive for anti-Ro/SSA antibodies. The anti-Ro/

SSA positivity was associated with xerostomia 12/21 ($p<0.001$) and xerophthalmia 14/21 ($p<0.001$). A biopsy of accessory salivary glands was performed in 10 patients resulting positive in 9/10; moreover a strict association with an overlapping Sjögren's Syndrome (IIM/SS) diagnosed according to AECG criteria was found in 11/21 cases ($p=0.000$). The anti-Ro/SSA positivity was also associated with patients' reported "dysphagia" in IIM patients ($p=0.035$) and with the use of intravenous immunoglobulins ($p<0.001$). By contrast, no differences were found in the prevalence of abnormalities at the oesophagus x-ray examination between anti-Ro/SSA positive and negative patients. No differences were also found between the two groups regarding: sex, age, subset of disease (polymyositis, dermatomyositis, inclusion body myositis), muscular or cutaneous involvement, pulmonary fibrosis, incidence of neoplasm, creatinine phosphokinase or other muscular necrosis enzyme, association with anti-Jo-1 autoantibodies.

Conclusion: In IIM patients the positivity for the anti-Ro/SSA antibodies is associated, as attended, with secondary SS. The increased prevalence of subjective dysphagia reported by patients positive for anti-Ro/SSA might be partially related to the oral dryness which may worsen the IIM oesophageal involvement.

Further prospective studies are required to elucidate the pathogenic mechanisms of dysphagia in IIM patients and the therapeutic implication of our findings.

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Good Inter-Rater Reliability Of Myositis Experts In Assessing Clinical Improvement. Rohit Aggarwal[1], Nicolino. Ruperto[2], Brian Erman[3], Saad Feroz[4], Jiri Vencovsky[5], Adam Huber[6], Sheila K. Oliveira[7], Angela Pistorio[8], Clarissa Pilkington[9], Angelo Ravelli[10], Brian M. Feldman[11], Howard Rockette[1], Frederick W. Miller[4], Peter A. Lachenbruch[4] and Lisa G. Rider[4]. [1]University of Pittsburgh, Pittsburgh, PA, [2]PRINTO, IRCCS G. Gaslini, Genoa, Italy, [3]National Institute of Health, Bethesda, DC, [4]NIEHS, NIH, Bethesda, MD, [5]Institute of Rheumatology, Prague, Czech Republic, [6]IWK Health Centre, Halifax, NS, [7]Instituto de Pediatria e Puericultura Martagão Gesteira (IPPMG) da Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil, [8]PRINTO, Genoa, Italy, [9]Great Ormond Street Hospital, London, United Kingdom, [10]Istituto Giannina Gaslini, Genova, Italy, [11]Hospital for Sick Children, Toronto, ON.

Background/Purpose: IMACS and PRINTO have developed preliminary core set activity measures and definitions of improvement (DOIs) for adult or juvenile dermatomyositis (DM) and polymyositis (PM). Our aim was to evaluate the inter-rater reliability and consensus among myositis experts rating patient profiles on clinical improvement, given core set measures and their change.

Methods: Fifteen adult and 15 juvenile myositis profiles using IMACS core-set measures (baseline and follow up) were evaluated by 30 adult and 29 pediatric myositis experts. PRINTO profiles on the same 15 juvenile DM patients were also evaluated. by 29 pediatric experts. Experts rated improvement on each profile as a) Likert scale: no improvement or worsening, minimal, moderate and major improvement, b) on the degree of improvement (0–10 scale). Percent agreement, kappa, Cronbach's α, analysis of variance, and intra-class correlation (ICC) were used to determine overall inter-rater reliability, as well as that of different groups of myositis experts (adult (N=30) vs. pediatric specialists (N=29), more vs. less experienced, rheumatologist (N=50) vs. non-rheumatologist (N=9), North American (N=30) vs. other location (N=29)).

Results: Consensus (≥70%) on minimal clinically significant improvement was reached on all profiles. Eleven of 15 adult DM/PM profiles, 12/15 IMACS and 12/15 PRINTO juvenile DM profiles were rated as at least minimally improved. For all profiles, different group of raters reached the same consensus on at least minimal improvement. There was substantial agreement among all individual raters (kappa 0.64) and very high agreement between different group of raters for minimal and major clinical improvement (Table 1). The agreement between PRINTO and IMACS profiles on the same patients was poor (Table1), primarily because there was a difference in the consensus as to whether the patient improved or not in 4 juvenile profiles. Results were not explained by geographical differences between North American and European evaluators or by a better familiarity of PRINTO members with PRINTO measures. ICC was high for all raters (0.82) as well as different group of raters (Table1). Cronbach's α for all profiles was very high (≥0.98) for improvement on the Likert scale and in the degree of improvement (0–10 scale). There was no difference in degrees of improvement rated by different group of myositis experts. However, IMACS profiles had a different degree of improvement as compared to the PRINTO profiles from the same pediatric patients.

Table 1. Inter-rater reliability among various groups myositis experts on clinical improvement

Groups	Minimal Improvement		Major Improvement		Improvement on Likert scale	Degree of improvement
	% agreement	Kappa	% agreement	Kappa	ICC	ICC
Adult (n=30) vs. Pediatric (n=29)	93.3%	0.83	93.3%	0.83	0.82	0.81
North American(n=30) vs. Other location (n=29)	100%	1.0	93.3%	0.84	0.82	0.81
More vs. less experienced	93.3%	0.83	93.3%	0.84	0.82	0.82
Rheumatologist (n=50) vs. Non-rheumatologist (n=9)	90%	0.74	96.6%	0.93	0.82	0.81
IMACS (n=15) vs. PRINTO (n=15) pediatric profiles	73.3%	0.16	60%	0.25	0.80	0.79

Conclusion: Inter-rater reliability among myositis experts was excellent in assessing minimal and major improvement in patient profiles. The agreement between ratings in IMACS and PRINTO profiles was poor. These results will aide in the development of new DOIs for minimal and major clinical response for myositis.

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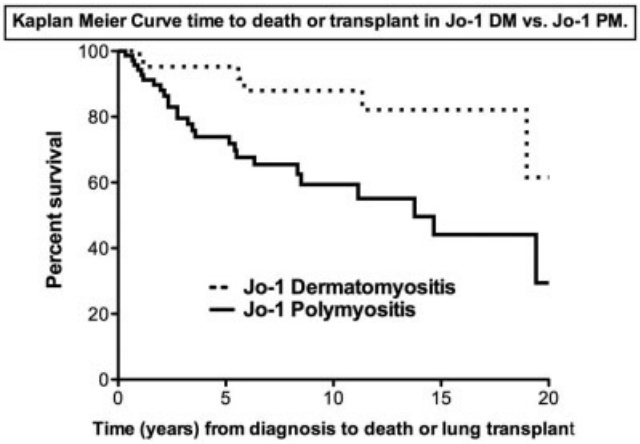
Clinical Features and Outcome In Polymyositis Vs. Dermatomyositis Patients With The Anti-Jo-1 Autoantibody. Rohit Aggarwal, Diane Koontz, Zengbiao Qi and Chester V. Oddis. University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: The clinical characteristics of dermatomyositis (DM) patients possessing the anti-Jo-1 autoantibody (autoAb) are not well known. We analyzed the clinical features and prognosis of Jo-1+ DM patients (Jo-1 DM) compared to Jo-1+ polymyositis (Jo-1 PM) patients.

Methods: Jo-1+ patients were identified from a prospectively collected computer and serum database of adult myositis (n=856) patients seen from 1985 to 2012. Anti-Jo-1 was detected by immunoprecipitation and immunodiffusion in our research laboratory and probable or definite PM and DM were defined using Bohan and Peter criteria. Amyopathic and hypomyopathic DM was included in the DM cohort as per Sontheimer criteria. Designation of overlap syndrome and undifferentiated connective tissue disease (UCTD) was based on clinical diagnosis. Demographics, clinical and laboratory features were compared between Jo-1 DM and Jo-1 PM. Chi-square and t-tests were used for comparison. Survival (time to death) and pulmonary survival (death or transplant) was compared between the two groups from diagnosis using log rank test.

Results: 140 Jo-1+ patients in our cohort had available clinical data. 31% (44/140) were diagnosed as DM including 4 amyopathic DM and 11 hypomyopathic DM, 53% (74/140) had PM and 16% (22/140) had overlap or UCTD. There was no difference in gender (female 78% vs. 65%), age at diagnosis [mean (SD) years: 43.7 (12.8) vs. 47.1 (12.7)] or ethnicity (Caucasians: 87% vs. 88%) in Jo-1 DM vs. Jo-1 PM. All Jo-1 DM patients (except 3) had classic DM rashes including a heliotrope rash or Gottron papules or sign. Among DM rashes, Gottron papules, Gottron sign, heliotrope, other DM rashes (V-rash or shawl sign), periungual erythema, mechanics hands and periorbital edema were seen in 26%, 55%, 24%, 26%, 31%, 67% and 14%, respectively. There was no difference in Jo-1 DM vs. Jo-1 PM in the following CTD features: arthritis (46 %) vs. 44%), fever (31% vs. 52%), Raynaud (38% vs. 36%), dysphagia (21% vs. 19%), cardiac (4% vs. 3%) or primary pulmonary hypertension (5% vs. 3%). Mechanics hands were more common in Jo-1 DM as compared to Jo-1 PM (67% vs. 17%, $p=0.001$). Pulmonary involvement was very common and similar in both groups (89% vs. 95%) mostly due to pulmonary fibrosis (84% vs. 92%). Dyspnea (76% vs. 72%) or O_2 supplementation (19% vs. 37%) was common in both groups as was muscle involvement (similar peak CK, proximal weakness and peak muscle disease activity (VAS) on the MDAAT). Significantly ($p<0.01$)

fewer Jo-1 DM patients died [13.6% (6/44) vs. 33.3% (24/72)] as compared to Jo-1 PM. Cumulative survival and pulmonary survival (death or transplant) from diagnosis was significant better in patients with Jo-1 DM vs. Jo-1 PM ($p < 0.004$).



Conclusion: One-third of Jo-1+ patients have DM. Jo-1 DM and Jo-1 PM have similar clinical characteristics except for the rashes of DM and mechanic hands. DM Jo-1 patients had a better prognosis than Jo-1 PM.

Disclosure: R. Aggarwal, None; **D. Koontz**, None; **Z. Qi**, None; **C. V. Oddis**, None.

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Identification Of Autoantibodies To Tyrosyl–Transfer RNA Synthetase Associated With Anti-Synthetase Syndrome. Yuko Okamoto[1], Yasuhiro Katsumata[1], Yasushi Kawaguchi[1], Koji Tahara[2], Kaori Ito[2], Hiroaki Hattori[2], Takahisa Gono[1], Kae Takagi[1], Masanori Hanaoka[1], Yuko Ota[1], Hidenaga Kawasumi[1] and Hisashi Yamanaka[1]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]BML, Saitama, Japan.

Background/Purpose: Autoantibodies directed against the aminoacyl transfer RNA (tRNA) synthetases are associated with myositis, arthritis, Raynaud's phenomenon, mechanic's hands, fever, and interstitial lung disease, clinically referred to as the anti–synthetase syndrome. A preliminary report has described the detection of an autoantibody to tyrosyl–tRNA synthetase (TyrRS) in only one patient with features of anti–synthetase syndrome. In addition, it has also been reported that TyrRS can be split into two fragments with distinct cytokine activities. We aimed to identify further patients with anti–TyrRS autoantibodies using other assays than previously reported methods and elucidate their clinical significance.

Methods: Multiple assays were performed to detect anti–TyrRS antibodies in the sera of patients with active polymyositis/dermatomyositis patients. First, recombinant human TyrRS protein coupled with a His-tag was expressed in *Escherichia coli*. Autoantibodies against the recombinant human TyrRS in sera of patients with polymyositis/dermatomyositis were quantified by employing solid phase direct enzyme–linked immunosorbent assay (ELISA). Second, the recombinant human TyrRS was electrophoresed and transferred to PVDF membranes. Western blot was performed with the serum samples and anti–human IgG secondary antibodies. Third, TyrRS–transfected HeLaS3 cells were immunoprecipitated with sample serum. Then, the antibody–protein complex captured with μMACS™ Protein G MicroBeads was loaded onto a μColumn. The eluted immunoprecipitates were subjected to the SDS–polyaclylamidegel electrophoresis, and western blotted with rabbit anti–TyrRS polyclonal antibodies. In addition, the titer of anti–TyrRS antibodies was evaluated by ELISA before and after treatment among the patients with positive anti–TyrRS antibodies at the initial evaluation. Control sera were obtained from normal healthy control subjects. The clinical features of the patients with positive anti–TyrRS antibodies were analyzed. This study was approved by the ethics committee of our institution, and the principles of the Helsinki Declaration were followed throughout the study.

Results: Sera from three patients with polymyositis/dermatomyositis showed significantly high O.D. values in ELISA, significant bands of 59 kDa protein of TyrRS at the same place as anti–His tag antibody in Western blot, and significant bands at the same place as the recombinant human TyrRS in immunoprecipitation assay. These data strongly suggest that these sera had autoantibodies to TyrRS. These patients had myositis, interstitial lung disease, arthritis, Raynaud's phenomenon, and fever. In two of the three patients, anti–TyrRS antibody titers decreased as clinical diseases were ameliorated following treatment.

Conclusion: This study reconfirmed the presence of anti–TyrRS antibody in the setting of the anti–synthetase syndrome and strengthens the association of anti–synthetases with these conditions.

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An Autoimmune Myositis-Overlap Syndrome Associated With Autoantibodies To Nuclear Pore Complexes - Description and Long-Term Follow-Up Of The Anti-Nup Syndrome. Catherine Isabelle[1], Marie-Christine Dabauvalle[2], Marvin J. Fritzler[3], Ira N. Targoff[4], Rose Goldstein[5], Yves Troyanov[1], Michel Gagné[1], Jean-Pierre Raynauld[1] and Jean-Luc Senécal[1]. [1]Division of Rheumatology, Centre Hospitalier de l'Université de Montréal, Montreal, QC, [2]University of Würzburg, Würzburg, Germany, [3]University of Calgary, Calgary, AB, [4]Oklahoma Medical Research Foun, Oklahoma City, OK, [5]McGill University, Montreal, QC.

Background/Purpose: Autoimmune myositis encompasses various myositis-overlap syndromes, each one being identified by the presence of serum marker autoantibodies. We describe a novel myositis-overlap syndrome in four patients characterized by the presence of a unique immunological marker, autoantibodies to nuclear pore complexes.

Methods: Clinical features and sera were collected from French Canadian patients followed prospectively since 1984 at the Connective Tissue Disease Clinic, Centre Hospitalier de l'Université de Montréal. Reactivity with nuclear pore complexes was identified by indirect immunofluorescence on HEp-2 cells displaying a positive ANA with a distinct punctate peripheral (rim) fluorescent pattern of the nuclear envelope, and confirmed by immunoelectron microscopy.

Results: In a cohort of 100 French Canadian patients with autoimmune myositis, sera from 4 (4%) patients displayed a high titer ANA with a fluorescent pattern characteristic of nuclear pore complexes. Clinically, these four patients shared a clinical phenotype characterized by prominent myositis in association with erosive, anti-CCP positive and rheumatoid factor positive arthritis, trigeminal neuropathy, mild interstitial lung disease, Raynaud phenomenon and weight loss. The myositis was typically chronic, relapsing and refractory to corticosteroids alone, but remitted with the addition of a second immunomodulating drug. There was no clinical or laboratory evidence of liver disease. The prognosis was good with 100% long-term survival. The nuclear pore complex fluorescent ANA pattern was not observed in sera from 393 adult patients with systemic sclerosis (n=112), mixed connective tissue disease (n=35), systemic lupus (n=94), rheumatoid arthritis (n=45), or other rheumatic diseases (n=107) nor was it observed in 62 normal adults.

Autoantibodies to nuclear pore complexes were predominantly of IgG isotype. No other IgG autoantibody markers for defined connective tissue diseases or overlap syndromes were present, indicating a selective and highly focused immune response. In three patients, anti-nuclear pore complex autoantibody titers varied in parallel with myositis activity, suggesting a pathogenic link to pathophysiology. The nuclear pore complex proteins, i.e. nucleoporins (nup), recognized by these sera were heterogeneous and included Nup358/RanBP2 (n=2 patients), Nup90 (n=1), and Nup62 (n=1). Taken altogether the data suggested that nup autoantigens themselves drive the anti-nup autoimmune response. Immunogenetically, the four patients shared the DQA1*0501 allele associated with increased susceptibility for autoimmune myositis.

Conclusion: We report a novel subset of autoimmune myositis in our population of French Canadian patients with connective tissue diseases. This syndrome is recognized by the presence of a unique immunologic marker, autoantibodies to nuclear pore complexes that react with nups, consistent with an "anti-nup syndrome".

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The Prevalence and Clinical Usefulness Of Anti-NXP-2 Autoantibodies In Chinese Patients With Idiopathic Inflammatory Myopathies. Xin Lu[1], Guochun Wang[2], Qinglin Peng[2], Kai Yuan[2] and Hanbo Yang[2]. [1]China-Japan Friendship Hospital, Beijing, China, Beijing, China, [2]China-Japan Friendship Hospital, Beijing, China.

Background/Purpose: To determine the sera levels of anti-NXP-2 antibodies and their clinical association in Chinese patients with idiopathic inflammatory myopathies(IIM).

Methods: Sera from 198 Chinese patients with IIM including 15 Juvenile dermatomyositis (JDM), 133 dermatomyositis(DM) and 50 polymyositis (PM), other connective tissue diseases(CTD) including 70 systemic lupus erythematosus (SLE), 60 rheumatoid arthritis (RA), 25 systemic sclerosis(SSc), 46 primary Sjogren's syndrome(PSS), 10 mixed connective tissue disease(MCTD) and 60 healthy controls were measured by enzyme linked immunosorbent assay. The positive sera were further examined by immunoprecipitation assay. We analyzed the distribution of these autoantibodies in each groups and evaluated the association between autoantibodies and clinical features of IIM.

Results: The positive rate of anti-NXP-2 autoantibodies in IIM patients was 5%, patients with JDM 20%, DM 3.7% and PM 4%, respectively. The positive rate of anti-NXP-2 autoantibodies were statistical differences within JDM, DM and PM groups($P=0.043$). There was no positive for the antibodies from patients with other CTD as well as healthy controls. Anti-NXP-2-positive patients had significantly younger age compared with anti-NXP-2-negative patients($t=-2.09, P<0.05$). The incidence of calcinosis in the anti-NXP2-positive patients was significantly higher than that in the negative patients($P<0.01$).There were no statistical differences between positive and negative groups for gender, duration, arthritis, rash, dysphagia, myalgia, myasthenia, Raynaud's phenomenon, interstitial lung disease and concomitant with cancer($P>0.05$). In laboratory examination, the sera levels of aspartate aminotransferase, IgA, complement C3 were significantly increased in anti-NXP-2-positive patients than those in anti-NXP-2-negative patients($P<0.05$). However, there was no significantly statistical differences between two groups for sera levels of creatine kinase, lactate dehydrogenase, hydroxybutyrate dehydrogenase, alanine aminotransferase, γ-glutamyltranspeptidase, erythrocyte sedimentation rate, C-reactive Protein and the positive rate of tumor markers ($P>0.05$). Among the three anti-NXP-2-positive JDM patients, two patients showed calcinosis and myasthenia, one of them who died 10 months later had increasing level of anti-NXP-2 autoantidodies, severe myasthenia and rapid progress.

Conclusion: This study first reported the sera levels of anti-NXP-2 autoantibodies in Chinese patients with IIM and other CTD. We found that anti-NXP-2 autoantibodies only exist in patients with IIM. Anti-NXP-2 autoantibodies were associated with young-onset IIM and calcinosis.

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Distinct Arthropaties In Patients With Anti-Aminoacyl tRNA Synthetase Antibodies: Utility Of Autoantibody Profiles In Discrimination. Yuko Kaneko, Hironari Hanaoka, Michito Hirakata, Tsutomu Takeuchi and Masataka Kuwana. Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: Arthritis is observed frequently in patients with anti-aminoacyl transfer RNA synthetase (ARS) autoantibodies and is usually not destructive like rheumatoid arthritis (RA). Despite several case reports with anti-ARS antibodies and with deforming arthritis, there is a controversy as to whether this is associated with anti-ARS antibody itself or concomitant RA. Moreover, previous reports focusing on articular involvement have been limited to anti-Jo-1 antibody, and it is still unclear whether arthropathies are common among anti-ARS antibodies. The aim of this study is to clarify the characteristics of arthropathies associated with anti-ARS antibody, focusing on structural damage and autoantibody profiles.

Methods: Fifty-six patients with anti-ARS antibodies were enrolled in this study from consecutive patients who visited Keio University Hospital between1983 and 2011, based on joint symptoms and availability of hand X-rays. Their clinical characteristics, anti-cyclic citrullinated peptide (anti-CCP) antibody, rheumatoid factor (RF), and hand X-ray findings were retrospectively examined.

Results: The anti-ARS specificities in 56 patients enrolled included Jo-1 in 28, EJ in 9, OJ in 1, PL-7 in 7, PL-12 in 5, and KS in 6. At the time of X-ray evaluation, the mean age was 57.6 years and the mean disease duration from onset of joint symptoms was 9.4 years. RF and anti-CCP antibody were positive in 25 (45 %) and 16 (29 %), respectively. Significant X-ray changes were found in 20 patients (36%). According to the patterns of X-ray findings garnered with cluster analysis, the patients were divided into two groups; Group A of 12 patients (21%) mainly with erosions and ankylosis, and Group B of 8 (14%) with the subluxations and periarticular calcinosis. When we compared the characteristics of these two groups, Group A showed the significantly higher rates of positive RF and anti-CCP with any anti-ARS specificities than Group B (83% versus 38%, and 75% versus 13%, respectively), consistent with the serologic features of RA. In contrast, all patients in group B were positive for anti-Jo-1 antibody independent of RF or anti-CCP.

Conclusion: Autoantibody profiles, including RF, anti-CCP, and individual anti-ARS specificity, are useful in classifying anti-ARS-associated arthropathies into a comorbid RA and a peculiar anti-Jo-1-related arthropathy.

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Autoantibodies Associated With Inflammatory Myopathy and Other Systemic Autoimmune Rheumatic Diseases In Sera From Breast Cancer Patients. Monica Vázquez-Del Mercado[1], Adrian Daneri-Navarro[2], Beatriz Teresita Martín-Márquez[3], Raul Vargas Ramirez[4], Diego Velasco-Sanchez[5], Jason Y.F. Chan[6], S. John Calise[6], Edward K.L. Chan[6] and Minoru Satoh[6]. [1]Universidad de Guadalajara, Guadalajara, Jalisco, México, Mexico, [2]Laboratorio de Inmunología, CUCS, Universidad de Guadalajara, Guadalajara, Mexico, [3]Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético, Guadalajara, Mexico, [4]Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético,, Guadalajara, Mexico, [5]1. Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético, CUCS, Universidad de Guadalajara, Guadalajara, Mexico, [6]University of Florida, Gainesville, FL.

Background/Purpose: Various autoantibodies have been reported in cancer patients, however, results are inconsistent. In dermatomyositis (DM), striking association between autoantibodies to p155/140 (transcription intermediary factor (TIF) 1gamma/alpha) and malignancy has been documented in several recent studies, however, whether this autoantibody specificity can also be found in malignancy without DM is not known. In the present study, anti-TIF1gamma/alpha and other specificities found in systemic autoimmune rheumatic diseases (SARD) were examined in breast cancer patients.

Methods: 152 unselected breast cancer patients were enrolled to the study. Clinical information was collected from medical record and serum autoantibodies were tested by immunoprecipitation (IP) of ^{35}S-methionine-labeled K562 cell extract and anti-Ro52 and -TIF1gamma ELISA. Immunofluorescence antinuclear antibodies (ANA) using HEp-2 slide were also tested.

Results: By IP, anti-TIF1gamma/alpha was found in 2 cases and anti-PM-Scl was found in one case among myositis-specific autoantibodies. Interestingly, no other myositis-specific autoantibodies, scleroderma specific anti-topoisomerase I and –RNA polymerase III, or SLE-specific anti-Sm or ribosomal P antibodies were found. Among autoantibodies associated with SARD but not specific for particular diagnoses, anti-Su/Argonaute 2 (Ago 2) was found in 3% (4/152), anti-Ro60 in 4% (6/152) by IP and anti-Ro52 was positive in 6% (9/152) by ELISA. Anti-U1RNP or anti-Sm was not found, however, interestingly, rare autoantibodies specific for U5RNP were found in 2 cases. A case with anti-TIF1gamma/alpha also had anti-Ro60 and Su/Ago2 but all other cases had only one specific autoantibodies listed above. As a whole, 14.5% (22/152) of breast cancer patients had autoantibodies associated with SARD. Although autoantibody specificities that are generally common in SARD and occasionally found in healthy individuals, such as anti-Ro60, Ro52 and Su were the most common, 2 cases of anti-TIF1gamma/alpha and anti-U5RNP seems significant because other disease-specific autoantibodies were not detected. Among 152 breast cancer patients, 6 had rheumatoid arthritis (RA) and one had ankylosing spondylitis but none had polymyositis/dermatomyositis, scleroderma or SLE. All specific autoantibodies detected were not associated with the presence of rheumatic diseases except one case of RA with anti-Ro52.

Conclusion: Although the specificities that are generally common in SARD (anti-Ro60, Ro52 and Su) were most common, unique specificities such as anti-TIF1gamma/alpha and anti-U5RNP was found in sera from breast cancer patients.

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Comparison Of Radioimmunoprecipitation Versus Antigen Specific Assays For Identification Of Myositis Specific Autoantibodies In Dermatomyositis Patients. Eun Ha Kang[1], Eun Young Lee[2], Yun Jong Lee[3], Eun Bong Lee[4] and Yeong Wook Song[2]. [1]Seoul National University Bundang Hospital, Seongnam-si, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul National University, Seoul, South Korea, [3]Rheumatology, Seoul National University, Seoul, South Korea, [4]Seoul National University College of Medicine, Seoul, South Korea.

Background/Purpose: To confirm the antigen specificities of autoantibodies that precipitate 140 kDa (anti-p140) or 155/140 kDa polypeptides (anti-p155/140) on radioimmunoprecipitation (RIP) in Korean patients with dermatomyositis (DM).

Methods: Forty nine sera from patients who had been diagnosed as having inflammatory myopathy according to Bohan and Peter criteria were examined using RIP. Subsequently, 17 serum samples of DM patients who were found to have either anti-p140 ($n = 9$) or anti-p155/140 antibodies ($n = 8$) were examined using enzyme-linked immunosorbent assay (for anti-MDA5 antibodies) and immunoblotting (for anti-MJ/NXP-2 and anti-TIF-1γ antibodies).

Results: Seven out of nine anti-p140 antibody positive patients were found to have anti-MDA5 antibodies. The rest two had anti-MJ/NXP-2 antibodies with no interstitial lung disease (ILD). The association of anti-MDA5 antibody with rapidly progressive ILD was found to be significant (4/8 vs. 0/41, $p = 0.0003$). All eight anti-p155/140 antibody positive patients were found to have anti-TIF-1γ antibodies, showing a significant association between anti-TIF-1γ antibody and cancer-associated DM (5/8 vs. 6/41, $p = 0.009$). Anti-TIF-1γ and anti-MDA5 antibodies were simultaneously detected in one patient with anti-p155/140 antibody, who suffered HIV infection and non-Hodgkin's lymphoma.

Conclusion: Although radioimmunoprecipitation still looks to be a good screening tool, confirmation with antigen-specific assays seems mandatory. The associations between anti-MDA5 antibody and rapidly progressive ILD and between anti-TIF-1γ antibody and cancer-associated DM were confirmed in Korean patients with DM.

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Serum Interferon-α Is a Biomarker To Reflect The Disease Activity In Patients With Anti-Melanoma Differentiation-Associated Gene 5 (MDA5) Antibody-Positive Dermatomyositis. Yoshiro Horai[1], Tomohiro Koga[1], Keita Fujikawa[2], Ayuko Takatani[1], Ayako Nishino[1], Yoshikazu Nakashima[3], Takahisa Suzuki[3], Shin-ya Kawashiri[1], Naoki Iwamoto[3], Kunihiro Ichinose[3], Mami Tamai[3], Hideki Nakamura[3], Hiroaki Ida[4], Yuji Ishimatsu[5], Hiroshi Mukae[6], Yasuhito Hamaguchi[7], Manabu Fujimoto[7], Masataka Kuwana[8], Tomoki Origuchi[1], Shigeru Kohno[5] and Atsushi Kawakami[3]. [1]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]Isahaya Health Insurance General Hospital, Isahaya, Japan, [3]Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [4]Kurume University School of Medicine, Kurume, Japan, [5]Department of Molecular Microbiology and Immunology, Nagasaki University School of Medicine, Nagasaki, Japan, Nagasaki, Japan, [6]Department of Respiratory Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, Kitakyushu, Japan, [7]Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan, [8]Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: The pathogenesis of anti-melanoma differentiation-associated gene 5 (MDA5) antibody (Ab)-positive dermatomyositis (DM), which often complicates rapidly progressive interstitial lung disease (RPILD), is thought to be associated with double-stranded RNA virus infection. Some serum factors, including interferon-a (IFN-a), are found to be elevated in these patients. Recent investigations have reported that high serum ferritin and the titer of anti-MDA5 Ab are poor prognosis factors in patients with anti-MDA5 Ab-positive DM. The aim of this study is to clarify the clinical importance of measurement of serum type I IFNs in patients with anti-MDA5 Ab-positive DM.

Methods: The study population consisted of 30 patients (22 females and 8 males) with DM: Ten patients were anti-MDA5 Ab-positive whereas the remaining 20 were anti-MDA5 Ab-negative, respectively. All of the 10 anti-MDA5 Ab-positive sera were also positive with anti-clinically amyopathic dermatomyositis (CADM) 140kDa polypeptide Abs detected by immunoprecipitation assay. Clinical diagnosis of DM was made by either Sontheimer's criteria for CADM or Bohan and Peter's criteria for classical DM. Serum IFN-a, IFN-b, interleukin 18 (IL-18), ferritin and the titer of anti-MDA5 Ab at initial visit were measured by each enzyme-linked immunosorbent assay (ELISA). Clinical characteristics, such as the diagnosis of CADM or classical DM and the presence of RPILD, were confirmed by medical records and the associations of IFNs with the other variables were examined. All of the patients gave their informed consent to be subjected to the protocol that was approved by the Institutional Review Board of Nagasaki University.

Results: Eleven patients were diagnosed as CADM whereas the remaining 19 patients as classical DM, respectively. RPILD was confirmed in 10 patients. The presence of CADM and RPILD as well as serum concentrations of IFN-a and ferritin were significantly higher in anti-MDA5 Ab-positive DM patients as compared with anti-MDA5 Ab-negative DM patients. However, there was no difference in serum concentrations of IFN-b and IL-18 between the two patients groups. Furthermore, clear positive correlations were found between IFN-a and the titer of anti-MDA5 Ab ($r = 0.54$, $p = 0.0037$) and between IFN-a and ferritin ($r = 0.49$, $p = 0.0086$), respectively.

Conclusion: Serum IFN-α level is high in anti-MDA5 Ab-positive DM patients presenting clinical characteristics with CADM and RPILD. Considering good correlations of IFN-a with the titer of MDA5 Ab and ferritin, serum IFN-α is considered as a biomarker to reflect the disease activity in patients with anti-MDA5 Ab-positive DM.

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Cytokine Profiles In Polymyositis and Dermatomyositis Complicated With Anti-Melanoma Differentiation-Associated Gene 5 Antibody-Associated Interstitial Lung Disease Or Anti-Aminoacyl tRNA Synthetase Antibody-Associated Interstitial Lung Disease. Takahisa Gono, Yasushi Kawaguchi, Hirotaka Kaneko, Yasuhiro Katsumata, Masanori Hanaoka, Sayuri Kataoka, Hidenaga Kawasumi, Kae Takagi, Hisae Ichida, Sayumi Baba, Yuko Okamoto, Yuko Ota and Hisashi Yamanaka. Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Polymyositis (PM)/dermatomyositis (DM) are often complicated with interstitial lung disease (ILD). In PM/DM, complication with ILD is associated with anti-aminoacyl-tRNA synthetase (ARS), including Jo-1 Ab or anti-melanoma differentiation-associated gene 5 (MDA-5) Ab. Clinically amyopathic DM (CADM) patients with anti-MDA-5 Ab have frequent complications with rapidly progressive (RP) ILD, especially in East Asia, where it is classified as acute interstitial pneumonia and reflects diffuse alveolar damage upon pathological examination. In contrast, chronic ILD is frequently observed in anti-ARS Ab-associated PM/DM, which responds well to treatment with corticosteroids. The response to treatment and the mortality rate are different between anti-MDA-5 Ab-associated ILD (anti-MDA-5-ILD) and anti-ARS Ab-associated ILD (anti-ARS-ILD). The differences in pathophysiology between these two Ab-associated ILD subsets remain unknown. Therefore, we investigate various serum cytokines in patients with PM/DM with ILD, and then clarify the differences in pathophysiology between anti-MDA-5-ILD and anti-ARS-ILD.

Methods: We evaluated the serum cytokine profiles of 38 patients with PM/DM and compared the cytokine profiles of 17 patients without ILD (non-ILD subset) and 21 patients with ILD (ILD subset), as well as the anti-MDA5-ILD and anti-ARS-ILD subsets. The levels of serum cytokines, including IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17, TNF-α, IFN-α, IFN-γ, and interferon γ-inducible 10-kd (IP-10), were measured by multiplex assay. In addition, serum was obtained from 15 healthy controls (HCs).

Results: Serum IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, IFN-α, IFN-γ and IP-10 were significantly higher in PM/DM patients than HCs. Moreover, the levels of IL-4, IL-6, IL-8, IL-10, TNF-α and IP-10 were significantly higher in the ILD subset than the non-ILD subset. By multivariate analysis, TNF-α was the most significant cytokine (P = 0.0006, odds ratio 1.4, CI 1.1–2.2) associated with PM/DM with ILD. Regarding to the comparison between 10 patients with anti-MDA-5-ILD and 11 patients with anti-ARS-ILD, IL-8 level was significantly higher in the anti-MDA-5-ILD subset than the anti-ARS-ILD subset. Lower levels of IL-4 and higher levels of IL-10 and IFN-α were found in the anti-MDA-5-ILD subset than those in the anti-ARS-ILD subset. By multivariate analysis, IL-8 was the most cytokine that was most significantly associated with anti-MDA-5-ILD (P = 0.0006, odds ratio 1.5, confidence interval [CI] 1.1–3.0). In addition, the IL-4 level was inversely associated with anti-MDA-5-ILD (P = 0.01, odds ratio 0.8, CI 0.6–0.98). Moreover, the ratio of serum IL-4 to IFN-γ, which may reflect a balance between T helper 1 (T_H1) and 2 (T_H2) cells, was lower in anti-MDA-5-ILD (median value 0.16) than in anti-ARS-ILD (median value 2.0).

Conclusion: TNF-α is an especially important in contributing to ILD in PM/DM. Serum IL-8 levels and the balance between IL-4 and IFN-γ may contribute to the differences in pathophysiology between chronic ILD (anti-ARS-ILD) and RP-ILD (anti-MDA-5-ILD).

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Adipokines Contribute To The Inflammatory Response In Adult and Juvenile Myositis. Molly S. Hein[1], Cynthia S. Crowson[1], Helen Khun[1], Consuelo Lopez de Padilla[1], Erik J. Peterson[2], Emily Baechler[3] and Ann M. Reed[1]. [1]Mayo Clinic, Rochester, MN, [2]University of Minnesota Medical School, Minneapolis, MN, [3]University of Minnesota, Minneapolis, MN.

Background/Purpose: Recently adipokines have been implicated for their role in regulating immune and inflammatory responses in autoimmune disease. To test the hypothesis that adipokines are predictive of dermatomyositis (DM) disease activity and inflammatory response, we analyzed blood cell gene expression of four adipokines, adiponectin (ADIPOQ), visfatin (NAMPT), leptin (LEP), and resistin (RETN) in juvenile (JDM) and adult (DM) patients.

Methods: For this study PAXgene vacutainers were collected for 14 DM, 23 JDM, and for adult (n = 5), and pediatric (n = 6) non-inflammatory controls. The IMACS core set myositis disease activity measure for physician global visual analog scale (Global VAS) scores (0–10 cm) was collected for myositis cases at time of blood draw. Total RNA was isolated with on-column DNase treatment according to manufacturer's protocol (PreAnalytiX). The expression levels of ADIPOQ, NAMPT, LEP, RETN, IL6, and housekeeping genes GAPDH, B2M, and ACTB were generated using a custom RT^2 Profiler PCR Array. Genes were first normalized to the mean of three housekeeping genes. Relative quantification of gene expression was then normalized to the mean of adult and pediatric controls respectively Wilcoxon tests and Spearman Correlation methods were used for analysis.

Results: The mean(range) age(years) and gender are as follows: JDM 9.7(3.7–17.1) (65% female), DM 50.1(23.0–72.8)(79% female), pediatric controls 12.4(8.2–16.5)(50% female), adult controls 39.8(25.2–61.4)(60% female). DM and control groups were Caucasian. The JDM group can be described as follows; 68.2% Non-Hispanic, 9.1% African American, 4.5%, American Indian, 4.5% Indian, 4.5% Middle Eastern, 4.5% Pacific Islander, and 4.5% unknown. In this population 79% of DM and 35% of JDM cases were receiving prednisone or an equivalent. Median BMI in the DM group was 25.9(19.7 – 51.2) and 17.2(13.8 –30.0) in JDM (median percentile 65.5(range 2–99)).

LEP, RETN, and NAMPT, all adipokines thought to promote inflammation were consistently up-regulated in all myositis cases compared to all controls, p=0.036, p=0.046 and p=0.013 (Table 1). ADIPOQ, known to have both anti- and pro- inflammatory effects in RA and SLE, did not appear to be dysregulated in the cases. p=0.400(Table 1). Increased RETN correlated with elevated disease activity represented by Global VAS in our myositis population (r=0.39, p=0.017). The magnitude of change in gene expression still held when groups were separated into juvenile and adult categories however statistical significance was not reached.

Table 1. Relative Quantification of Adipokines in DM and JDM

Gene	Control N=11	DM/JDM N=37	P value
LEP	−0.2 (1.0)	0.4 (0.6)	0.036*
RETN	−0.2 (0.8)	0.7 (1.3)	0.046*
ADIPOQ	−3.6 (3.6)	−5.0 (2.7)	0.400
NAMPT	−0.4 (1.3)	0.9 (1.3)	0.013*

Conclusion: Elevated adipokines levels in JDM and DM may serve as beneficial biomarkers that allow a practitioner to better monitor disease activity and potentially predict disease flares.

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Decreased Number Of Circulating NK Cells and Dramatic Lack Of IFN-Gamma Production In Patients With Antisynthetase Syndrome. Baptiste Hervier[1], Yves Allenbach[1], Fleur Cohen-Aubart[1], Micheline Pha[2], Lenaig Mescam-Mancini[3], David Saadoun[1], Alexis Mathian[1], Olivier Benveniste[1] and Vincent Vieillard[2]. [1]Pitié-Salpêtrière Hospital, APHP, Paris, France, [2]INSERM UMR-S 945, UPMC, Paris, France, [3]University hospital, Grenoble, France.

Background/Purpose: Antisynthetase syndrome (ASS) is a rare autoimmune myositis associated with interstitial lung disease (ILD) and characterized by specific anti-tRNA-synthetase autoantibodies (ARS). To date, the pathogenesis of ASS remains largely unknown and the involvement of innate immune cells, such as Natural Killer (NK) cells is poorly described. The aim of this study was to conduct the first extensive analysis of the phenotype and functional properties of NK cells in ASS.

Methods: This monocentric study included 14 ASS patients (woman/man=13, median age 51, range 29–77) and 7 healthy controls (w/m=6, median age 30, range 22–42). Patients were divided into 2 groups, based on their ASS activity: active myositis (myalgia/muscle weakness with elevated creatine-kinase) or deteriorating ILD (> 10% decrease in lung vital capacity) leading to disease-modifying antirheumatic drug use, distinguished patients with active (n=6) *vs* inactive (n=8) ASS. NK cell phenotype was performed by flow cytometry after staining with an appropriate antibody cocktail: CD16, CD57, CD69; Natural Cytotoxicity Receptors (NKp30 and NKp44); pan-KIR, NKG2A-C-D and ILT2. Assessment of NK cell functions was performed spontaneously or after an interleukin-12 and −18 overnight stimulation, in the presence of K562 target cells, at a 1/1 ratio. Degranulation was evaluated by CD107a detection, and production of TNFα and IFNγ was measured by specific intracellular-staining. Comparisons between patient groups were performed using the Mann-Whitney test; a p-value < 0.05 was considered significant.

Results: Myositis and ILD occurred each in 12/14 patients (median time from onset: 4 years, range 1–22) and the distribution of ARS was anti-Jo1 (n=9), anti-PL12 (n=4) and anti-PL7 (n=1). Patients (n=12) were receiving stable doses of steroids (n=10, median 10 mg/d, range 5–20) and/or immunosuppressive drugs, including Methotrexate (n=5), Mycophenolate Mophetil (n=3) or Hydroxychloroquine (n=3). Patients with ASS had a normal percentage of NK cells among circulating lymphocytes (9.6 ± 6.4%) but a dramatically low absolute count: 89 ± 73/mm^3 (*vs* controls: 221 ± 100/mm^3, p=0.02). NK cells from ASS patients were indistinguishable from those of controls in term of the cell-surface expression of NK receptors. However, NKp30, a receptor involved in NK cell-Dendritic cell crosstalk, was decreased in active ASS patients as compared to both inactive patients and controls (50.3 ± 25.7% vs 80.6 ±11.2% and 85.4 ± 7.4, p=0.03 and 0.01, respectively).

Functional activities revealed no differences between ASS patients and controls, regarding both spontaneous degranulation capacities (29.7 ± 13.4% *vs* 21.8 ± 9.4%, p=0.14) and intracellular-TNFa production after stimulation (4 ± 4.4% *vs* 6,2 ± 6.4%, p=0.25). Conversely, IFNg production was dramatically decreased after stimulation in ASS patients *vs* controls (12.7 ± 14.0% *vs*31.3 ± 12.9%, p=0.01) and seemed not related to treatments.

Conclusion: Although quantitatively decreased, NK cells mainly displayed a normal phenotype in ASS. However, NK cells from patients with ASS had a significantly decreased capacity to produce IFNg, suggesting that they may play an immune regulatory role in favor of a TH2/TH1 imbalance.

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Clinical and Prognostic Factors Associated With Survival In Mexican Patients With Idiopathic Inflammatory Myopathies. Angeles Shunashy Galindo-Feria[1], Jorge Rojas-Serrano[2] and Andrea Hinojosa-Azaola[1]. [1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico.

Background/Purpose: Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of autoimmune diseases, with low prevalence and 5-year survival of 70–95%. Previous studies in Mexican IIM patients suggest differences compared to other ethnic groups in clinical presentation, response to treatment, prognosis and autoantibodies. The aim of this study was to estimate the survivor function of IIM Mexican patients and identify factors associated to mortality.

Methods: This is a retrospective cohort study including patients with Dermatomyositis (DM) and Polymyositis (PM) according to Bohan and Peter's criteria, seen at a tertiary care center from January 1985 to January 2012. Baseline demographic, clinical variables, comorbidities, systemic manifestations and muscular strength were registered. The time to death, last medical evaluation or loss of follow up was obtained. Censoring time was established as the last medical visit. Univariate and multivariate Cox regression analysis were done to analyze factors associated with mortality. All analysis were two tailed, alpha was set at 5%.

Results: 304 DM and 71 PM patients were included, 70% female. At baseline evaluation, patients with DM were younger ($p<0.005$) and PM patients had higher CPK levels ($p<0.004$). DM patients had lower survivor function than those with PM during the first 4 years of follow up (log Rank test, $p<0.041$, Fig. 1). Respiratory failure secondary to pneumonia was the principal cause of death in DM patients (26/56, (46%)). Miscellaneous causes were responsible of death in PM patients. In univariate analysis, the variables associated with mortality during the first 4 years of disease in DM patients were: Age at onset (HR 1.03, 95% CI 1.01–1.05, $p<0.001$), cancer (HR 2.58, 95% CI 1.33–5.04, $p<0.02$), muscular strength (HR 0.60, 95% CI 0.45–0.80, $p< 0.002$), hemoglobin (HR 0.78, 95% CI 0.68–0.89, $p<0.0001$), serum albumin (HR 0.33, 95% CI 0.23–0.42, $p<0.001$), creatinine (HR 1.88, 95% CI 1.08–3.27, $p<0.03$), platelet count (HR 0.99, 95% CI 0.990–0.999, $p<0.04$), ever use of methotrexate and azathioprine (RM 0.19, 95% CI 0.09–0.40, $p<0.0001$). In the multivariate analysis, age at onset (HR 1.03, 95% CI 1.01–1.06, $p<0.002$), cancer (HR 2.55, 95% CI 1.1–6.4, $p<0.05$) and muscular strength (HR 0.54, 95% CI 0.34–0.84, $p<0.006$) were independent factors associated with mortality. In patients with PM, the only variable associated with mortality was cancer (HR 8.22, 95% CI 1.5–44.98, $p<0.02$).

Conclusion: Patients with DM had lower survival rate during the first 4 years of disease than patients with PM. Respiratory failure secondary to pneumonia was the main cause of death in DM patients. Factors associated to mortality differed in DM and PM. In DM patients, age of disease onset, cancer, and level of muscle strength were associated with mortality; in PM patients only cancer was associated.

Disclosure: A. S. Galindo-Feria, None; **J. Rojas-Serrano**, None; **A. Hinojosa-Azaola**, None.

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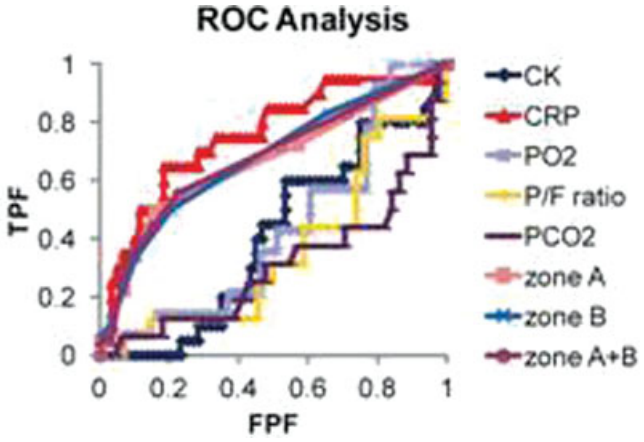
The Analysis Of Prognostic Factors In Patients With Inflammatory Myopathies and Amyopathic Dermatomiositis Complicated With Interstitial Lung Disease. Maasa Hama, Yumiko Sugiyama, Yohei Kirino, Yosuke Kunishita, Daiga Kishimoto, Reikou Kamiyama, Kaoru Minegishi, Ryusuke Yoshimi, Yukiko Asami, Atsuhisa Ueda, Mitsuhiro Takeno, Ichiro Aoki and Yoshiaki Ishigatsubo. Yokohama City University Graduate School of Medicine, Yokohama, Japan.

Background/Purpose: Because interstitial lung disease (ILD) is one of the most critical manifestations and can be lethal in inflammatory myopathies (IM), especially amyopathic dermatomiositis (ADM), it is important to determine prognostic factors for survival. We investigated clinical features which are associated with fatal events in IM patients having ILD.

Methods: We retrospectively analyzed clinical features, laboratory and HRCT findings, pulmonary function, and therapeutic regimens with clinical outcomes in 144 patients who were diagnosed with IM at the two hospitals of Yokohama City University from 1993 to 2012. Diagnoses of IM and clinical ADM were made according to Bohan and Peter criteria and modified Sontheimer's criteria, respectively. DM patients who did not met the ADM criteria were categorized as myopathic DM (MDM). The distribution and extent of ILD lesions were evaluated based on the percentage of the lung parenchyma involved in each of the four-divided lung zones (A to D) from upper to lower.

Results: HRCT showed ILD lesions in 83 of 144 IM patients (58%); polymyositis (PM) 18, MDM 40, ADM 25. Routine malignant screening detected cancers in 13 (16%). Twenty patients (24%) including 2 PM, 13 MDM and 5 ADM died during follow-up period (median 49 mo. (0.5–235 mo.)) due to respiratory failure (11 patients), infection (6), and malignancy (5). Of them 12 died within 7 months after the diagnosis. The levels of serum CK, P (PaO2)/F (FiO2) ratio, and PCO2 before therapy were significantly lower in non-survivors than survivors (CK; 817±1235 vs. 1809±2773, $p=0.03$, P/F ratio; 344±92.6 vs. 398±87, $p=0.04$, PCO2; 36.2±5.2 vs. 38.8±3.9, $p=0.04$). Moreover, high CRP (non-survivors 4.65±6.94, survivors 1.15±2.56 ($p=0.04$)) and high ILD scores in the upper lung field (Zone A; 1.5±1.2, 0.8±0.9 ($p=0.01$), Zone B; 1.8±1.4, 1.0±1.0 ($p=0.01$), Zone A+B; 3.3±2.5, 1.8±1.9 ($p=0.01$), respectively) were closely associated with lethal events (Figure). All of 9 patients who required mechanical ventilatory support died. Intensive combination immunosuppressive therapies with PSL, IVCY, and calcineurin inhibitors were conducted in 20 patients including 10 MDM, and 10 ADM patients with lower CK and hypocapnia, because they were likely to progress fatal respiratory failure rapidly as clinically ADM associated ILD. Of them, 8 non-survivors, who showed lower CO2 level at the diagnosis than survivors (32.9±3.0 vs. 36.4±4.1, $p=0.076$), died within short term from diagnosis (median 2 mo. (1–51 mo.)) because of respiratory failure (5 patients) and/or infection (4 patients).



Conclusion: The present study revealed that some MDM patients as well as ADM patients developed lethal ILD especially when low CK, high CRP, hypocapnia, and expanded upper lung field lesions were found. More rapid and intensive therapies including prophylactic procedures against infections are necessary to manage IM associated ILD before type I respiratory failure progresses.

Disclosure: M. Hama, None; **Y. Sugiyama**, None; **Y. Kirino**, None; **Y. Kunishita**, None; **D. Kishimoto**, None; **R. Kamiyama**, None; **K. Minegishi**, None; **R. Yoshimi**, None; **Y. Asami**, None; **A. Ueda**, None; **M. Takeno**, None; **I. Aoki**, None; **Y. Ishigatsubo**, None.

2075

Analysis Of The Associations Between Serum Ferritin and Cytokines In Pulmonary Disease Activity With Polymyositis/Dermatomyositis. Hidenaga Kawasumi, Takahisa Gono, Yasushi Kawaguchi, Yasuhiro Katsumata, Masanori Hanaoka, Sayuri Kataoka, Kae Takagi, Hisae Ichida, Sayumi Baba, Yuko Okamoto, Yuko Ota and Hisashi Yamanaka. Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Polymyositis (PM) / dermatomyositis (DM) is occasionally complicated by interstitial lung disease (ILD), and ILD is a prognostic factor in PM/DM. We previously reported that high levels of serum ferritin are associated with the severity and prognosis of ILD in patients with PM/DM. Hyperferritinemia could be associated with a cytokine storm in rapidly progressive ILD associated with PM/DM. The reason for the serum ferritin increase in ILD with PM/DM is unknown. We investigated the associations between the serum ferritin levels and various cytokines in patients with PM/DM.

Methods: This retrospective study included 38 patients admitted to our hospital with PM/DM. Among 38 patients, PM/DM was a complication of ILD in 21 patients. Serum cytokines (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17, TNF-α, INF-α, INF-γ and IP-10) were measured by a multiplex assay. Global disease activity and the disease activity of ILD were evaluated by the Myositis Intention to Treat Activity Index (MITAX) and the pulmonary visual analogue scale (Pulmonary VAS), which the International Myositis Assessment and Clinical Studies Group has proposed and recommended, respectively. We analyzed the associations between the disease activity, serum ferritin and cytokines.

Results: The MITAX was significantly correlated with the following: ferritin (r_s=0.53), IL-6 (r_s=0.61), IL-8 (r_s=0.37), IL-10 (r_s=0.44), TNF-α (r_s=0.58) and IP-10 (r_s=0.47). The Pulmonary VAS was significantly correlated with the following: ferritin (r_s=0.62), IL-8 (r_s=0.45), IL-10 (r_s=0.46), TNF-α (r_s=0.45) and IP-10 (r_s=0.33). The serum ferritin levels were significantly correlated with IL-6 (r_s=0.40), IL-8 (r_s=0.57), IL-10 (r_s=0.50) and TNF-α (r_s=0.34). To clarify the degree to which these cytokines contribute to the ferritin levels, we performed a multiple linear regression analysis. IL-6 (t=3.6, p=0.0010), IL-8 (t=4.8, $p<0.0001$) and IL-10 (t=5.7, $p<0.0001$) were significantly associated with the ferritin levels.

Conclusion: Serum ferritin was correlated with the pulmonary disease activity and with global disease activity in PM/DM. IL-6, IL-8 and IL-10 were significant factors that contributed to the serum ferritin levels. The regulation of these cytokines might be a possible treatment strategy for ILD with PM/DM.

Disclosure: H. Kawasumi, None; **T. Gono**, None; **Y. Kawaguchi**, None; **Y. Katsumata**, None; **M. Hanaoka**, None; **S. Kataoka**, None; **K. Takagi**, None; **H. Ichida**, None; **S. Baba**, None; **Y. Okamoto**, None; **Y. Ota**, None; **H. Yamanaka**, None.

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Oxidation Products Of Arachidonic Acid and Linoleic Acid Are Increased In High Density Lipoprotein From Patients With Dermatomyositis and Polymyositis. Christina Charles-Schoeman, Yuen Yin Lee, Ani Shahbazian, David Meriwether, Geraldine Navarro, John D. FitzGerald and Srinivasa T. Reddy. UCLA David Geffen School of Medicine, Los Angeles, CA.

Background/Purpose: Oxidation products of arachidonic acid and linoleic acid including hydroxyeicosatetraenoic acids (HETEs) and hydroxyoctadecadienoic acids (HODEs), respectively, play an important role in the pathogenesis of atherosclerosis and have been associated with endothelial cell activation. HETEs and HODEs contribute to the oxidation of low density lipoprotein (LDL) and their accumulation in high density lipoprotein (HDL) impairs HDL function, which increases risk of vascular damage. The current work evaluated the levels of HETEs and HODEs in HDL isolated from patients with dermatomyositis (DM) and polymyositis (PM) since vascular damage is implicated in the pathogenesis of both muscle and lung disease in DM/PM patients.

Methods: HDL was isolated by ultracentrifugation from plasma of 12 DM patients, 12 PM patients and 12 healthy controls. 5-HETE, 12-HETE, 15-HETE, 9-HODE, and 13-HODE levels in HDL were measured by mass spectrometry as described previously (Imaizumi et al. *Drug Metab Lett.* 2010; 4(3): 139–48). HDL's anti-inflammatory function was measured by a cell free assay as described previously (Charles-Schoeman et al. *Arthritis Rheum.* 2009; 60(10): 2870–9). Lipoprotein cholesterol levels were determined by standard methods.

Results: 5-HETE, 15-HETE, 9-HODE and 13-HODE levels were significantly increased in HDL from patients with PM compared to healthy controls (see Table). 5-HETE was also significantly increased in HDL from DM patients compared to controls and was significantly correlated with the HDL inflammatory index (r = 0.41, p=0.01); higher HDL-associated 5-HETE was associated with worse anti-oxidant capacity of HDL. Myositis patients with interstitial lung disease (ILD) (n=14) had higher 13-HODE, 12-HETE, and 5-HETE levels in HDL compared to myositis patients without ILD (n=10) (p values= 0.05, 0.06, and 0.13 respectively). Patients with moderate to severe ILD suggested by the diffusing *capacity* of the *lungs* for carbon monoxide (*DLCO*) <50% of predicted also showed trends for higher HDL-associated 5-HETE, 12-HETE, and 13-HODE levels compared to ILD patients with less severe disease (DLCO >50%) (see Table). 5-HETE and 12-HETE levels were inversely correlated with DLCO, r = −0.58 (p=0.02) and r = −0.49 (p=0.05), respectively.

	Healthy Control (n=12)	Polymyositis (n=12)	Dermatomyositis (n=12)
Age (years)	48 ± 13	52 ± 8	49 ± 9
Sex (% female)	67%	58%	83%
Ethnicity (% hispanic)	42%	45%	17%
Total Cholesterol (mg/dL)	184 ± 28	204 ± 50	191 ± 39
LDL Cholesterol (mg/dL)	112 ± 25	113 ± 51	122 ± 39
HDL Cholesterol (mg/dL)	55 ± 13	67 ± 39	52 ± 13
Triglycerides (mg/dL)	90 ± 39	156 ± 54*	124 ± 54
ESR (mm/hr)	6 ± 7	38 ± 23*	50 ± 27*
HS-CRP (mg/L)	0.6 ± 0.5	7.9 ± 8.9*	12.2 ± 13.2*
HDL Inflammatory Index (HII)	0.80±0.15*	1.20 ± 0.42*	1.49 ± 0.67*
5-HETE (pg/75μg HDL-C)	12721 ± 4493	65125 ± 18732*	32460 ± 28569*
12-HETE (pg/75μg HDL-C)	321 ± 234	585 ± 406	810 ± 831
15-HETE (pg/75μg HDL-C)	12 ± 9	36 ± 22*	18 ± 15
9-HODE (pg/75μg HDL-C)	57 ± 97	213 ± 167*	110 ± 110
13-HODE (pg/75μg HDL-C)	158 ± 111	472 ± 149*	308 ± 355

	ILD (n=14)	No ILD (n=10)
5-HETE (pg/75μg HDL-C)	54968 ± 25630	40147 ± 32351
12-HETE (pg/75μg HDL-C)	938 ± 766	362 ± 136
13-HODE (pg/75μg HDL-C)	481 ± 279	263 ± 236

	ILD (DLCO >50) (n=6)	ILD (DLCO ≥ 50) (n=7)
5-HETE (pg/75μg HDL-C)	64867 ± 24687	53143 ± 21244
12-HETE (pg/75μg HDL-C)	1117 ± 658	542 ± 466
13-HODE (pg/75μg HDL-C)	567 ± 319	357 ± 192

All values mean ± standard deviation. *p value ≤ 0.05 compared to controls.
Note: Recent DLCO value not available for one patient with known ILD.

Conclusion: Oxidation products of arachidonic acid and linoleic acid are increased in HDL from patients with PM and DM compared to healthy controls. Increased 5-HETE in HDL was associated with impaired HDL anti-oxidant function and was inversely associated with DLCO in patients with myositis. Our results suggest that therapeutic agents such as apoA-I mimetic peptides, which bind oxidized fatty acids and reduce vascular damage and lung injury in animal models, may warrant further investigation in DM/PM patients.

Disclosure: C. Charles-Schoeman, None; **Y. Y. Lee**, None; **A. Shahbazian**, None; **D. Meriwether**, None; **G. Navarro**, None; **J. D. FitzGerald**, None; **S. T. Reddy**, None.

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Inflammatory Lung Disease a Potential Risk Factor For Onset Of Inflammatory Myopathies. Ingrid E. Lundberg[1], Sevim Barbasso Helmers[2] and Lars Alfredsson[3]. [1]Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, [2]Institute of Environmental Medicine, Unit of Cardiovascular Epidemiology, Karolinska Institutet, Stockholm, Sweden, [3]Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Although the etiology of inflammatory myopathies is unclear, there are data indicating that myositis occurs as a result of complex interactions between genes and environmental/life style factors.

The aim of this study was to assess the association between lung disease and the risk of developing inflammatory myopathies, myositis.

Methods: In this population-based case-control study, 179 incident adult myositis cases diagnosed between 1995 and 1997 were identified from the Swedish inpatient registry. Verification of diagnosis was performed through patient records. The analysis was based on responses from a questionnaire on exposures to environmental factors from 100 cases that were alive and fulfilled the inclusion criteria and from 402 randomly selected population controls matched to cases on birth of date, gender and residency. Exposure was based upon self-reports of preceding inflammatory lung disease (pneumonia, tuberculosis or sarcoidosis). The association between inflammatory lung disease and risk of developing myositis was evaluated by calculating odds ratio (OR) together with 95% confidence interval (CI) by means of logistic regression.

Results: There was a suggestive association between preceding inflammatory lung disease and diagnosis of myositis: adjusted OR = 1,5 (CI (95%) = 0.9–2.6). The number of cases and controls that reported inflammatory lung disease *(i.*e. pneumonia, tuberculosis or sarcoidosis) was 42 (42%) and 112 (28%), respectively. Overall recorded signs of ILD were found in 16% of the cases, mainly based on results from chest radiography. Out of 12 cases with ILD, nine (75%) had reported inflammatory lung disease in the questionnaire, while the corresponding frequency for cases without ILD was 36%. The median duration between the lung disease and first symptom of myositis was 30 years.

Conclusion: Subjects with a history of a preceding inflammatory lung disease had an increased risk to develop myositis compared to those without such disease. Inflammatory lung disease could thus be a potential risk factor for onset of inflammatory myopathies, in particular for the subset of patients with ILD, or it may be a parallel phenomenon.

Disclosure: I. E. Lundberg, BMS, 2, Novartis Pharmaceutical Corporation, 5; **S. Barbasso Helmers**, None; **L. Alfredsson**, None.

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Pulmonary Hypertension In Anti-Jo1 Syndrome. Nilofar Syed, Ruchi Yadav, Colin O'Rourke and Soumya Chatterjee. Cleveland Clinic, Cleveland, OH.

Background/Purpose: Antisynthetase syndrome is characterized by fever, myositis, interstitial lung disease (ILD), inflammatory arthritis, mechanic's hands, and Raynaud phenomenon. The most commonly reported form of antisynthetase syndrome has been associated with anti-Jo1 antibody and ILD is a major determinant of prognosis. However, the presence of pulmonary hypertension (PH) in anti-Jo1 syndrome had not been systematically evaluated in the past.

Methods: We conducted a retrospective chart review of patients with anti-Jo1 syndrome. Patients were evaluated both for ILD and/or PH. ILD was diagnosed on the basis of high resolution CT (HRCT) scan of lungs and PH had to be confirmed on right heart catheterization (RHC). The pattern and severity of ILD on HRCT scan was graded by a radiologist and each lung lobe was individually quantified with a score from 1 to 4 according to percentage of lobar involvement. A score of 1 represented <25% lobar involvement, 2: ≥ 25% but < 50%, 3: ≥ 50 % but < 75%, and 4: ≥ 75% involvement. Summation of individual lobar scores provided the overall ILD severity score. Fibrosis (reticular and honeycomb scores) and inflammation indices (ground glass opacity and mixed score) were also calculated *(Ooi et al. Acta Radiologica. 2003)*.

Results: We identified 116 patients with positive anti-Jo1 antibody, of which 13 were found to have RHC-confirmed PH and were included in this study. All 13 patients also had ILD. Mean age at diagnosis of antisynthetase syndrome was 51 years and mean age at diagnosis of pulmonary hypertension was 58 years. Of the 13 patients, 8 had mild PH (mean pulmonary artery pressure (mPAP): 25–40 mmHg), 4 had moderate PH (mPAP: 41–55 mmHg), and 1 had severe PH (mPAP: >55 mmHg). The predominant type of lung injury observed in these patients was inflammation, not fibrosis. For the same degree of ILD severity (Figure 1), there was significant variability in the severity of PH, indicating that PH in anti-Jo1 syndrome is not solely secondary to ILD, but is also a result of an independent inflammatory and/or fibro-proliferative process affecting the pulmonary microvasculature. The correlations between mPAP and overall ILD severity, inflammation index, or fibrosis index were not statistically significant.

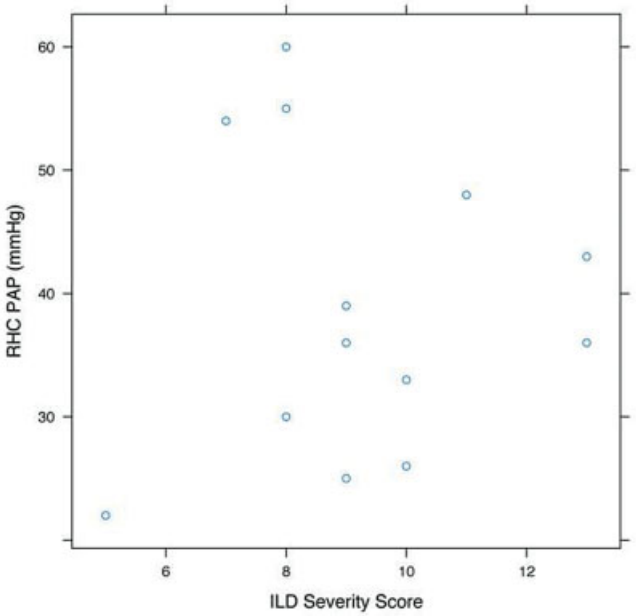

Figure 1.

Conclusion: Our findings suggest that chronic hypoxic pulmonary vasoconstriction or vascular obstruction/destruction associated with progressive ILD are not the sole mechanisms in the pathogenesis of PH in anti-Jo1 syndrome. It is likely that an obliterative pulmonary vasculopathy (possibly resulting from proliferation of endothelial and vascular smooth muscle cells) co-exists and plays an important role in the pathogenesis. Therefore, it may be appropriate to consider routine screening of anti-Jo1 syndrome patients at the onset of disease and periodically thereafter, in order to have maximum impact of vasoactive therapy on the outcome.

Disclosure: N. Syed, None; **R. Yadav**, None; **C. O'Rourke**, None; **S. Chatterjee**, None.

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Serum Interferon α, β and Interleukin-18 Are Associated With Disease Activity Of Rapidly Progressive Interstitial Lung Disease In Patients With Clinical Amyopathic Dermatomyositis. Shinji Sato, Noriko Sasaki, Shinichi Nogi, Naofumi Chinen, Kiri Honda, Eiko Saito, Chiho Yamada and Yasuo Suzuki. Tokai University School of Medicine, Isehara, Japan.

Background/Purpose: It is well known that rapidly progressive interstitial lung disease (RP-ILD) in patients with dermatomyositis (DM) is associated with poor outcome. Previous findings suggested that interferon alfa (IFNα), interferon beta (IFNβ) and interleukin-18 (IL-18) might play an important role in the pathogenesis of DM (including the DM subtype clinically amyopathic dermatomyositis, CADM) and RP-ILD. The aim of this study was to determine whether levels of IFNα, IFNβ, IL-18 and other cytokines were associated with disease activity in CADM and RP-ILD.

Methods: Serum samples and clinical data were collected from 28 patients diagnosed as having DM with or without RP-ILD (14 with RP-ILD, 9 with chronic ILD and 5 without ILD), 4 other connective tissue diseases (CTD) and 4 normal healthy controls (NHC). Serum IFNα, IFNβ, IL-18 and other proinflammatory cytokines were quantified by commercially-available enzyme-linked immunosorbent assay (ELISA) kits over the disease course and related to disease activity.

Results: IFNα was detected in 7 of 28 (25%) DM serum samples before treatment. All 7 patients who had high IFNα concentration were diagnosed as CADM and RP-ILD. IFNα decreased significantly and was no longer detectable after treatment which reduced symptoms (33.8 pg/ml vs. 0.0 pg/ml, P=0.019). In contrast, no IFNα was detected in any sera from DM without RP-ILD, other CTD or NHC. Sera from 14 of 28 (50%) patients with DM had high IFNβ in contrast to only 1 of 8 (13%) with other CTD and NHC. Nine of 14 (64%) sera with IFNβ before treatment were from CADM with RP-ILD patients. As with IFNα, IFNβ levels of 7 CADM and RP-ILD patients who responded to therapy and survived decreased significantly after improvement of pulmonary symptoms (108.9 pg/ml vs. 38.3 pg/ml, P=0.027). IL-18 was detected in all sera from DM with or without RP-ILD as well as other CTD and NHC before treatment. Serum IL-18 levels in CADM with RP-ILD, as well as in DM without RP-ILD, decreased significantly, parelleling symptom improvement (70.2 pg/ml vs. 25.0 pg/ml, P=0.017). Serum IL-17A, IL-23 and BAFF were not detected in any DM patient or NHC.

Conclusion: These results suggest that serum IFNα, IFNβ and IL-18 levels might be involved in the pathogenesis of RP-ILD and CADM, and might represent a useful biomarker of disease activity.

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Pregnancy Outcomes In Adult Patients With Dermatomyositis and Polymyositis. Lorinda Chung[1], David Fiorentino[2], Shufeng Li[3] and Eliza Chakravarty[4]. [1]Stanford Univ Medical Center, Palo Alto, CA, [2]Stanford University School of Medicine, Redwood City, CA, [3]Stanford University School of Medicine, Stanford, CA, [4]Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: Dermatomyositis (DM) and polymyositis (PM) are autoimmune inflammatory myopathies that frequently affect females of child-bearing potential. Small studies have indicated that active disease during pregnancy may result in intra-uterine growth restriction (IUGR) and fetal loss. We sought to assess pregnancy outcomes of adult DM and PM patients compared with the general obstetric population using a U.S. hospitalization dataset.

Methods: We used the Nationwide Inpatient Sample (NIS) (1993–2007) to estimate the number of obstetric hospitalizations and deliveries among women > 18 years of age with DM and PM. Controls were from the general obstetric population hospitalized in 2007. Pregnancy outcomes included length of hospital stay (LOS), hypertensive disorders including preeclampsia and eclampsia (HTN), premature rupture of membranes (PROM), IUGR, and cesarean delivery (C-section). Multivariate regression analyses were performed using maternal age, race/ethnicity, antiphospholipid antibody syndrome (APLA), diabetes mellitus, renal failure, and interstitial lung disease (ILD) as covariates.

Results: We compared 4.1 million deliveries in the general obstetric population to 459 that occurred in women with DM and 404 in women with PM. Patients with DM and PM were slightly older than controls (28±6 years vs 27±6 years, p<.0001), and more were African American than controls (DM 30% vs 15%, p=.002; PM 46% vs 15%, p <.0001). Renal failure and ILD were more common in both the DM and PM groups, while diabetes and APLA were more common in DM compared with controls. In univariate analysis, LOS was significantly longer in the DM and PM groups compared with controls (3.8±3.5 in DM and 4.9±6.3 in PM vs. 2.7±2.7 days in controls, p<.0001 for both) (Table). In multivariate analyses, DM (OR 1.6, 95%CI 0.9–2.9) and PM (OR 2.4, 95%CI 1.5–3.9) were associated with an increased odds of HTN compared with controls, though this did not reach statistical significance in the DM group. Interestingly, DM was associated with a decreased odds of IUGR (OR 0.7, 95%CI 0.6–0.9). There were no differences in rates of PROM or C-section in the DM or PM patients compared with controls.

Table 1. Obstetric Outcomes by Diagnosis

Group	LOS (d, mean±SD)	p-value vs. control	HTN (%)	p-value vs. control	PROM (%)	p-value vs. control	IUGR (%)	p-value vs. control	C-section (%)	p-value vs. control
DM	3.8 ± 3.5	<.0001	17.3	0.0004	5.3	0.37	1.7	0.92	25	0.33
PM	4.9 ± 6.3	<.0001	24.2	<.0001	4.6	0.55	4.6	0.02	27.3	0.7
CONTROL	2.7 ± 2.7		8.8		3.6		1.8		28.9	

Conclusion: Our data suggest that patients with DM and PM may be at increased risk of preeclampsia and eclampsia. We did not find an increased risk for IUGR in these patients. Vigilant monitoring of blood pressure may be advisable in pregnant patients with DM and PM.

Disclosure: L. Chung, None; **D. Fiorentino**, None; **S. Li**, None; **E. Chakravarty**, None.

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Role Of Muscle Persistent CD28null T Cells In Glucocorticoid Therapy Resistance In Myositis Patients. Jayesh Pandya, Ingela M. Loell, Mohammad Shahadat Hossain, Mei Zong, Sukanya Raghavan, Ingrid E. Lundberg and Vivianne Malmström. Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Polymyositis (PM) and dermatomyositis (DM) are characterized by infiltration of T cells and macrophages in skeletal muscle tissue. Conventional immunosuppressive treatment has limited effects on infiltrating cells. In this context, CD28null T cells are interesting, which display properties of proinflammatory killer cells and are suggested to be resistant to apoptosis *in vivo*. Recently, it was found in our lab that after conventional glucocorticoid treatment, the relative number of regulatory T cells (Treg) was unchanged or decreased, while the CD28null T cell proportion was mainly increased in muscle tissue of myositis patients. (Loell et al; ACR 2011, *Arthritis Rheum 2011;63 Suppl 10:233)*. This leads to our working hypothesis that CD28null T cells are resistant to immunosuppression mediated by glucocorticoids in the setting of myositis. An additional explanation could be a lack of sensitivity in the CD28null population towards Treg mediated suppression.

The aim of this study was to investigate the clinical relevance of persistent CD28null T cells in myositis patients treated with glucocorticoids and to further evaluate immunosuppressive effects of both glucocorticoids and Treg on CD28null T cells *in vitro*.

Methods: Immunohistochemistry for CD3, FOXP3 and CD28null surrogate marker CD244 was performed on muscle tissue obtained from 14 patients with PM/DM, treated with glucocorticoids and additional immunosuppressive drugs for 8 (4–16) months. For clinical evaluation, muscle performance was measured by Functional Index at biopsy time points. Post treatment 5 years follow up for disease activity was done by Myositis Intention To Treat Activity Index (MITAX). *In vitro* immunosuppression assays were performed on anti-CD3 activated PBMCs from 6 myositis patients and 6 healthy donors. To quantify % suppression, reduction in CD69 (early T cell activation marker) on activated T cells upon glucocorticoid and Treg addition was measured by flow cytometry.

Results: At group level, patients improved in Functional Index measurement. However, patients with Functional Index <75% post treatment were found to display higher level of CD244+(CD28null) T cells (median 14,cells/mm^2, *p=0.01*) in post treatment muscle biopsies compared to those with high Functional Index (>75%) (median 1 cell/mm^2). Patient disease activity MITAX correlated with the number of CD244+ cells/mm^2 post treatment (Rho=0.74, p=0.04). In *in vitro* immunosuppression assays, CD4+CD28null T cells displayed lower sensitivity towards glucocorticoid-mediated suppression (median suppression: patients 46.8%, healthy 51.6%) compared to CD28+ counterparts (68.5%, 80.7%) in both myositis patients and healthy donors. CD4+CD28null T cells were also less sensitive than CD28+ counterparts towards Treg mediated suppression (median: 18% versus 57.2%). No clear trend could be observed in CD8+ compartment.

Conclusion: Above *in vivo* and *in vitro* findings suggest that poor outcome from the glucocorticoid therapy in myositis patients is linked to persistence of CD28null T cells in muscle tissue, which are relatively resistant to both glucocorticoid and Treg mediated immunosuppression.

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2082

Interferon-Regulated Chemokine and Innate Cytokine Scores Identify Refractory Myositis Patients That Respond Better To Rtuximab Therapy. Consuelo Lopez de Padilla[1], Cynthia S. Crowson[1], Molly S. Hein[1], Helen Khun[1], Rohit Aggarwal[2], Marc C. Levesque[2], Dana P. Ascherman[3], Chester V. Oddis[2] and Ann M. Reed[1]. [1]Mayo Clinic, Rochester, MN, [2]University of Pittsburgh, Pittsburgh, PA, [3]University of Miami, Miami, FL.

Background/Purpose: Serum cytokines play an important role in the pathogenesis of myositis by initiating and perpetuating various cellular and humoral autoimmune processes. The aim of this study was to measure interferon (IFN)-inducible chemokines, Th1, Th2, Th17, innate, and regulatory cytokines in patients with refractory idiopathic inflammatory myositis (IIM) to identify a biomarker signature to predict responsiveness to rituximab.

Methods: In a randomized, placebo-phase trial (Rituximab in Myositis (RIM)), 200 refractory IIM subjects received 1 gm of rituximab on 2 consecutive weeks – weeks 0/1 (Early) or weeks 8/9 (Late). Serum samples were collected at baseline, 8, and 16 weeks following treatment. Multiplexed sandwich immunoassays (Meso Scale Discovery) were used to measure IFN-regulated chemokines and other pro- and anti-inflammatory cytokines specific to differentiation of specific T cell and innate pathways. Cytokine scores were computed for **Th1** (IFNy, TNFα, and IL2), **Th2** (IL4, IL5, IL10, IL12, and 1L 13), **Th17** (IL6, IL17, IL1β), **innate** (IFNα, MCP-1, MCP-2, MIG, MIP-1β, IP-10, I-TAC, IL18), **IFN-regulated chemokine** (I-TAC, IP-10, MCP-1), and **regulatory** (IL10, TNFα) factors. IMACS core set myositis disease activity measures (physician global, patient global, MMT, HAQ, muscle enzyme, and extramuscular visual analog scale (VAS) scores (0–100 mm) and Myositis Disease Activity global VAS were collected at each visit. Changes in IFN chemokine and cytokines and VAS scores between time points were calculated, and were correlated using Spearman methods.

Results: We analyzed data available for 177 myositis subjects (mean age (SD)/disease duration (SD) 37(19)/5(7) years, 73% female, 70% Caucasian. The mean (SD) values for muscle disease activity and physician global disease activity VAS scores were 46(22) and 49(19) cm, respectively. Increased levels of Th2, Th17 and innate cytokines were observed 16 weeks after the start of treatment (p = 0.05, p = 0.02, p < 0.001, respectively), while the levels of regulatory cytokines were reduced (p < 0.001). IFNCK, Th1, Th2, Th17, innate, and regulatory cytokine scores at baseline were positively correlated with physician global VAS at the start of treatment (r=0.20 [P=.01], r=0.29 [P<.001], r=0.16 [P=.03], r=0.18 [P=.02], (r=0.19 [P=.01], and (r=0.19 [P=.01], respectively); while Th1, Th2, and Th17 cytokine scores correlated positively with muscle disease activity VAS at the start of

treatment (r=0.22 [P=.003], r=0.17 [P=0.02], (r=0.22 [P=.003], respectively). Higher baseline IFNCK and innate cytokine scores were predictive of better response in physician global VAS at 16 weeks after treatment (r= −0.167 [P=.03], (r= −0.15 [P=.05], respectively). In addition, baseline IFNCK, innate and regulatory cytokine scores correlated with muscle improvement on the MDAAT at 8 weeks ([r= −0.19, P=.01], [r= −0.20, P=.01], [r= −0.21, P=.005] respectively) while baseline IFNCK and innate cytokine scores correlated with muscle improvement at 16 weeks ([r= −0.17, P=.03], [r= −0.16, P=.04], respectively).

Conclusion: IFNCK and innate cytokine scores before treatment may help to identify rituximab responsiveness in refractory myositis patients.

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2083

Environmental Factors Associated With Disease Flare In Juvenile and Adult Dermatomyositis. Gulnara Mamyrova[1], Lisa G. Rider[2], Olcay Jones[3], Alison Ehrlich[4], Lauren M. Pachman[5], Robert Nickeson[6], Lisa G. Criscione-Schreiber[7], Frederick W. Miller[2], Lawrence K. Jung[8] and James D. Katz[1]. [1]George Washington University, Washington, DC, [2]NIEHS, NIH, Bethesda, MD, [3]Walter Reed National Military Medical Center, Bethesda, MD, [4]The George Washington University, Washington, DC, [5]Division of Pediatric Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, [6]All Children's Hospital, St Petersburg, FL, [7]Duke University School of Medicine, Durham, NC, [8]Children's National Medical Center, Washington, DC.

Background/Purpose: To assess environmental factors in relationship to increased disease activity (flare) in juvenile and adult dermatomyositis (DM).

Methods: An online survey was conducted for juvenile and adult DM patients from the US and Canada who were ≥1 year from diagnosis. Patients were recruited through myositis clinics and by a patient support group. The survey examined: exposures during the 6 months prior to disease flare, if the patient experienced a flare within the past 2 years, or in the past 6 months, if the patient did not have a flare. Exposures assessed included smoking, sun exposure, infections, medications, vaccines, stressful life events, and sport activities. Differences were evaluated by Chi-square and Fisher's exact tests.

Results: Of 210 participants meeting probable or definite Bohan and Peter criteria (164 juvenile and 46 adult DM patients), 134 (63.8%) (103 juvenile and 31 adult DM) experienced a flare and 76 (36.2%) (61 juvenile and 15 adult DM) participants did not experience a disease flare within the past 2 years. For those reporting a disease flare, the mean duration to flare was 13 months for JDM and 10 months for DM. Eighty percent of patients with a flare were female vs. 70% of those without flare; 85% were Caucasian. Patients with flare were less often 0–5 years of age compared to those who did not flare (2.2% vs. 15.8%, p=0.0004). Patients with a disease flare more often reported that their myositis worsened after sun exposure (44.4% vs. 28.6%, p=0.03, OR=1.99, 95% CI: 1.1–3.7), but the use of photoprotective measures was similar between both groups. Infections were more frequently recorded in the preceding 6 months in those who flared vs. those who did not, including UTI (10.2% vs. 0.0%, p= 0.005, OR=16.4, CI: 0.96–280.2) and gastroenteritis (16.5% vs. 5.8%, p=0.04, OR=3.2, CI: 1.1–9.8). Patients who flared more frequently used NSAIDs (63.4% vs. 36.8%; p=0.0003, OR=3.0, CI: 1.7–5.3) or blood pressure medicines (12.7% vs. 3.9%, p=0.049, OR=3.5, CI: 1.0–12.5). HPV vaccine was more frequent in those who flared vs. those who did not (8.2% vs. 0.0%, p=0.032, OR=10.0, CI: 0.6–175.5). Patients who flared tended to experience more frequent serious financial difficulties compared to those who did not (17.2% vs. 7.9%, p= 0.06, OR=2.4, CI: 0.9–6.2), but other stressful life events did not differ. Patients with a flare more often exercised 1–5 times a week (74.7% vs. 57.7%, p=0.06, OR=2.2, CI: 1.02–4.6). There was no difference in smoking exposure between the two groups.

Conclusion: Sun exposure, certain infections, medications, and vaccines, which have been associated with illness onset, may also play a role in disease flares in patients with adult and juvenile DM.

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2084

Increasing Incidence Of Immune Mediated Necrotizing Myopathy In A Single Center. Martin Klein[1], Herman F. Mann[1], Josef Zámecník[2] and Jiri Vencovsky[3]. [1]Institute of Rheumatology, Prague, Prague, Czech Republic, [2]2nd Medical School and University Hospital Motol, Charles University, Prague, Czech Republic, Prague, Czech Republic, [3]Institute of Rheumatology, Prague, Czech Republic.

Background/Purpose: Immune mediated necrotizing myopathy (IMNM), characterized histologically by predominant myofiber necrosis with minimal or no inflammatory infiltrate and clinically by response to immunosuppressive therapy, is a relatively newly recognized category of idiopathic inflammatory myopathy (IIM). IMNM itself is a heterogeneous group with some cases associated with presence of anti-SRP, anti-HMGCR or, less frequently, antisynthetase antibodies. The relative frequency of IMNM compared to other IIM subtypes and the temporal pattern of its incidence is not known.

Methods: We have performed a retrospective evaluation of muscle biopsy results, clinical and laboratory data including antibody associations of all patients newly diagnosed with IIM in the Institute of Rheumatology between the year 2004 and February 2013. All biopsies were interpreted by a single experienced pathologist, results were subcategorized as necrotizing myopathy (NM), polymyositis (PM), dermatomyositis (DM), non-specific myositis (N-SM) or non-classifiable (NC).

Results: A total of 315 biopsies were performed, with 206 obtained from patients who fulfilled Bohan and Peter criteria for IIM (definite or probable category). 20 cases were histologically classified as NM, all of them were IMNM based on history, biopsy and clinical features. In the remaining 186 biopsies 24 were subcategorized as PM, 39 as DM, 77 as N-SM and 46 as NC. There were no IMNMs diagnosed between 2004 and 2007, subsequently 2–3 cases of IMNM per year were seen during the period of 2008 to 2011 with a sudden increase to 9 cases (36% of all biopsies) in the year 2012. This trend was confirmed in the first two months of 2013 (Figure 1). Three IMNM patients were positive for anti-SRP antibodies, two were anti-Jo1 positive, one had anti PM-Scl antibodies, one had isolated anti-Ro52 positivity and two were ANA positive with no identifiable antibody. Interestingly anti-CCP antibodies, considered highly specific for rheumatoid arthritis (RA), were detected in two IMNM patients. Anti-HMGCR antibodies were not tested. Nine patients with IMNM (45%) had no detectable autoantibodies (all of them diagnosed in or after 2011), six of them were exposed to statins before developing IMNM. Only two other patients had a history of statin use (one anti-Jo1 positive diagnosed in 2008 and one with anti-CCP diagnosed in 2012).

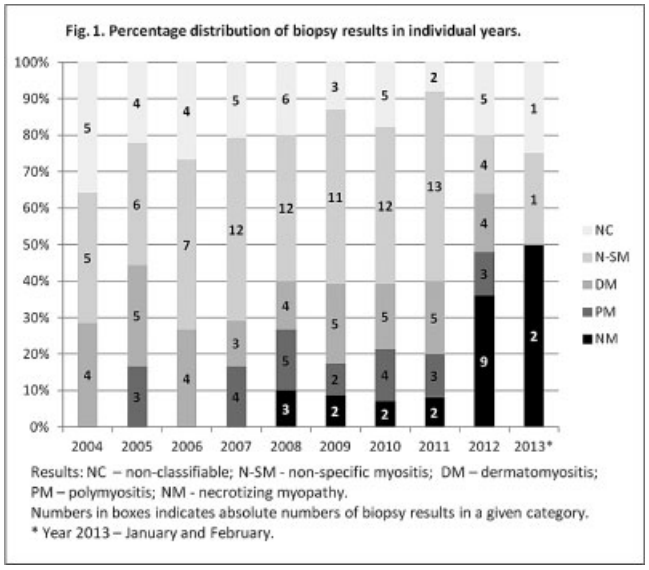

Figure 1.

Conclusion: We have observed an increasing incidence of immune mediated necrotizing myopathy, which cannot be explained by changes of referral pattern or biopsy reporting. There has been an increasing number of statin exposed IMNM patients since 2011.

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2085

Identification Of Clinical Features and Risk Factors Associated With Calcinosis In Adult Patients With Dermatomyositis. Antonia Valenzuela[1], Lorinda Chung[2], Livia Casciola-Rosen[3], Antony Rosen[3] and David Fiorentino[4]. [1]Stanford University School of Medicine, Palo Alto, CA, [2]Stanford University Medical Center, Palo Alto, CA, [3]Johns Hopkins University, Baltimore, MD, [4]Stanford University School of Medicine, Redwood City, CA.

Background/Purpose: Prior studies have estimated that 20% of adult dermatomyositis (DM) patients suffer from calcinosis. Although calcinosis is related to persistent disease activity, poor treatment adherence, and therapy refractoriness in juvenile DM (JDM) patients, risk factors for calcinosis in the adult DM population have not been extensively studied. Antibodies to nuclear matrix protein 2 (NXP-2) have been associated with calcinosis in JDM patients but only one study has shown a trend for this association in adult DM. We aimed to determine the prevalence of calcinosis and to identify associated clinical features in a large cohort of adult DM patients.

Methods: This is a cross-sectional study of 126 patients diagnosed with DM at Stanford University Medical Center between 01/2006 and 01/2013. Calcinosis was defined as the presence of calcium deposition in the skin and/or subcutaneous tissues as determined by physical examination and/or radiography. Logistic regression was used to obtain odds ratios (OR) relating calcinosis to various clinical features using both univariate and multivariate analyses.

Results: 94% of patients had DM-specific or myositis-specific autoantibodies (against NXP-2, transcription intermediary factor-gamma (TIF-g), melanoma differentiation antigen 5 (MDA-5), sumoyl activating enzyme (SAE1/2), Mi-2, or Jo-1). A total of 14 (11%) patients had calcinosis. In univariate analysis, longer disease duration (OR=1.1, 95%CI 1.01–1.3, p=0.03), digital ulcers (OR=9.8, 95%CI 2.9–33.6, p=0.0003), interstitial lung disease (OR=6.5, 95%CI 1.9–22.2, p=0.003), autoantibodies to MDA-5 (OR=5.1, 95%CI 1.4–17.8, p=0.01) and antibodies to Ro52 (OR=3.5, 95%CI 1.1–11.0, p=0.04) were positively associated with calcinosis while autoantibodies to TIF-g were negatively associated with calcinosis (OR=0.19, 95%CI 0.04–0.91, p=0.04). The association between anti-NXP-2 and calcinosis reached statistical significance only in multivariate analysis (OR=7.6, 95%CI 1.5–39.2, p=0.01), while MDA-5 and TIF-g were no longer significantly associated in these models. Because of the known association between MDA-5 and digital ulcers, we evaluated a multivariate model excluding digital ulcers, and found that MDA-5 positivity was highly predictive of calcinosis (OR=6.9, 95%CI 1.8–27, p=0.005). Digital ulcers were strongly associated with calcinosis in all multivariate models, independent of the underlying autoantibody present (Table 1).

Table 1. Predictors of calcinosis in multivariate analyses.

	OR	95%CI	p-value
Multivariate model 1			
Disease duration	1.2	1.04–1.38	0.01
Digital ulcers	23.1	4.74–112	<0.001
NXP-2	7.6	1.48–39.2	0.01
Multivariate model 2			
Disease duration	1.17	1.04–1.33	0.01
Digital ulcers	12.8	2.12–77.2	0.005
MDA-5	1.19	0.17–8.04	0.85
Multivariate model 3			
Disease duration	1.16	1.03–1.3	0.01
MDA-5	6.9	1.76–27	0.005
Multivariate model 4			
Disease duration	1.16	1.03–1.33	0.01
Digital ulcers	13.9	3.31–58.6	0.0003
TIF-g	0.24	0.04–1.25	0.09

Conclusion: Calcinosis was a relatively uncommon clinical feature in our cohort of DM patients. We found an association between calcinosis and anti-NXP-2 autoantibodies as well as a novel association with digital ulcers. A common vascular mechanism may underlie the development of both calcinosis and digital ulcers in patients with DM.

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Defining The Prevalence and Associated Risk Factors For Calcinosis In Adult Dermatomyositis Patients. Jessie Werner[1], Jason Liebowitz[2], Andrew L. Mammen[3] and Lisa Christopher-Stine[4]. [1]University of Maryland School of Medicine, Baltimore, MD, [2]Johns Hopkins University School of Medicine, Baltimore, MD, [3]Johns Hopkins, Baltimore, MD, [4]Johns Hopkins University, Baltimore, MD.

Background/Purpose: Calcinosis is known to be associated with junvenile dermatomyositis, but the prevalence and risk factors associated with the development of calcinosis in adult dermatomyositis (DM) patients is unknown. We sought to quantify this burden by estimating the prevalence of calcinosis by patient self- report, and identifying associated risk factors for calcinosis in adult DM patients.

Methods: After obtaining IRB approval, a standardized telephone interview and retrospective chart review of 50 consecutive adult DM patients evaluated between 5/1/97 and 1/1/13 at a single tertiary care center was conducted. Variables collected included: self-reported anatomic location of calcinosis if present; laboratory data including myositis specific antibodies (MSAs); signs and symptoms of dermatomyositis; calcinosis treatment history; and immunosuppressant agents used. Patients were separated into 2 groups – those who developed calcinosis over the course of their disease and those who did not.

Results: Of the 50 patients, 76% were female, 19 (38%) developed calcinosis over their disease course (89% of whom were female), and 84% had at least one positive MSA. MDA5 was the only MSA which was significantly associated with calcinosis. The mean time between symptom onset and diagnosis of dermatomyositis was 16 months. The mean time between the diagnosis of dermatomyositis and development of calcinosis was 21 months. Patients with calcinosis scored lower on the SF-36v2 compared to patients without calcinosis (39.52 vs. 44.17; p=0.055). Furthermore, patients with calcinosis scored higher (indicating a higher degree of difficulty performing activities of daily living) compared to patients without calcinosis (0.93 vs. 0.69; p=0.096) on the Stanford Health Assessment Questionnaire Disability Scale (HAQ). Calcinosis patients also reported worse joint pain (4.0 vs. 3.06 on a 10 point scale).

Conclusion: Calcinosis is a common complication of adult dermatomyositis patients. Calcinosis risk factors included the specific MSA, MDA5. Patients with calcinosis have more difficulty performing activities of daily living, experience more joint pain, and rate their physical health worse than patients who do not have calcinosis.

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2087

Utility and Reliability Of Digital Nailfold Capillaroscopy In Children With Juvenile Dermatomyositis: Three Methods. Gabrielle A. Morgan[1], Adam Ostrower[1], Chiang-Ching Huang[2] and Lauren M. Pachman[1]. [1]Ann & Robert H. Lurie Children's Hospital of Chicago Research Center, Chicago, IL, [2]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Nailfold Capillaroscopy (NFC) is a non-invasive assessment of the nailfold area of the fingers which aids in the diagnosis of Juvenile Dermatomyositis (JDM) by providing images where the number of capillary end row loops/ mm (ERL) can be both visualized and counted. Previous studies documented that ERL numbers are usually decreased at diagnosis and often change over time. Although many NFC studies employ non-digital methods of photo capture and analysis, new digital tools are well adapted for NFC photography, but their reliability is unknown. The objective of this study was to explore the utility and reliability of digital methods of NFC in children with JDM.

Methods: First, the relationship between the Disease Activity Score (DAS) and end row capillary loops (ERL) was explored. 109 untreated children with JDM (78% females, 92% White or Hispanic, mean age 6.7 ± 3.4 years, mean duration of untreated disease 11.2 ± 16.9 months) had DAS and NFC obtained at diagnosis (IRB# 2012–14858), using the non-digital method. To assess the standardization of the digital method, 12 randomly selected treated patients with JDM (42% Female, mean age 14.8± 6.4 years, White or Hispanic) were enrolled (IRB# 2011–14651). NFC was performed on 8 fingers on each of the 12 patients, using three methods, by the same experienced investigator; there were 2 readers. The first method, freeze frame video microscopy (FFVM), produced photos that were printed and not digitally stored. For each method, the NFC were analyzed by counting the ERL per mm, which were then averaged. DermLite II ProHR (DL) (portable) and Leica Z6APO stereomicroscope (LS) (stationary) served as the two digital methods for image acquisition. These photos were analyzed with Adobe Photoshop CS5 using the same ERL formula. All 288 images were evaluated by each of the two investigators, one very experienced in NFC analysis (R1), and one a novice (R2).

Results: Untreated children with JDM had a significant negative correlation between skin DAS and ERL (p=.0027), which was not found for muscle DAS and ERL (p= 0.43). Both digital methods, DL and LS, were quite reliable in

terms of quantification of the number of ERL, compared with the FFVM, when read by R1 (r_c= 0.833, r_c=.846, Concordance Correlation Coefficient). R2's reliability was low using both digital methods (DL r= 0.436, LS r= 0.543). This lack of concordance between the readers was further documented when DL was compared to LS (R1 r_c= 0.832, R2 r_c= 0.41). The data from both the experienced and the novice investigators were concordant using the FFVM images (r_c= 0.834); however, the inter-rater reliability was poor when R1 and R2 were compared for the digital methods (DL r_c= 0.676, LS= 0.577).

Conclusion: NFC can be used in the clinical setting to assess skin associated vascular changes in JDM, providing the ERL number at diagnosis and over time to assess the vasculopathy. FFVM is more easily interpreted by a novice, but digital methods pose a challenge to the novice. However, when read by an experienced investigator, the results from both methods are highly concordant. We speculate that this new, easily accessible technology may allow NFC to become a standard of care for children with JDM.

Disclosure: G. A. Morgan, None; **A. Ostrower**, None; **C. C. Huang**, None; **L. M. Pachman**, None.

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The Percentage Of Th17 Cells Correlates with the Expression Of Microrna-206 In Patients With Dermatomyositis. Xinyi Tang and Shengjun Wang. Department of Immunology, Jiangsu University, Zhenjiang, China.

Background/Purpose: DM (dermatomyositis) is a subtype of inflammatory myopathies, which is a rare autoimmune disease of skeletal muscle. Although the pathogenic mechanism of DM is still unclear, it was considered as a CD4+T cells driven disease. It was reported that IL-17, a key cytokine of Th17 cells, has been detected in the inflammatory infiltrates of patients with DM. But there is no study focusing on the alteration of Th17 cells in the peripheral blood of patients with DM. In addition to RORC, Kruppel-like factor 4 (KLF4), a transcription factor of cell differentiation, stem cell properties, and malignant transformation, is another positive regulator of Th17 differentiation.

Methods: Thirteen patients with DM were included in this study. The diagnosis was based on commonly accepted clinical and laboratory criteria. Peripheral blood samples were obtained from all patients. The serum concentrations of CK and LDH is by biochemistry test. Healthy subjects were included, ranging from 32 to 50 year old. All of the control subjects were free of a history of DM diseases. All samples were taken in accordance with the regulations and approval of the Affiliated People's Hospital of Jiangsu University.

Results: We analyzed the proportion of Th17 cells in PBMCs of DM patients by flow cytometry. The percentage of Th17 cells was significant increased in PBMCs from patients with DM compared with healthy controls. qRT-PCR analysis displays an enhanced expression of IL-17mRNA in the PBMCs from DM patients, with lower expression in healthy controls. To further document the state of Th17 cells in DM patients, we analyzed the expression of RORC mRNA, which plays a considerable role in differentiation of human Th17 cells. As expected, the expression of RORC mRNA in PBMCs from DM patients is significant higher than that from healthy controls. We found that there was a positive correlation between the percentages of Th17 cells and serum level of CK, but not with level of LDH. This result demonstrated that the percentage of Th17 cells could reflect the severity of DM in some extent. In addition, we found that DM patients have significant increased serum concentration of IL-6 and TGF-βin comparison with healthy controls. In addition, serum concentrations of IL-1$\beta$is higher in DM patients compared with healthy controls, but this difference did not reach statistical significant. To further analyze the influential factor of Th17 cells enhancement in DM patients, we considered searching the miRNA which may influence the enhancement of Th17 cells. KLF4 is one of the targets of miR-206, and an inverse relationship between miR-206 and KLF4 in human has been confirmed. After acquired the increased expression of KLF4 mRNA in PBMCs of DM patients, we verified the decreased expression of miR-206 in PBMCs and serum of DM patients.

Conclusion: Our data collectively suggest that there is an enhanced frequency of Th17 lymphocytes in DM patients, the augmented expression of KLF4 mRNA may cause by the attenuated expression of miR-206, and the high level of KLF4 mRNA evokes the proportion of Th17 cells in DM patients. And besides the potential role of proinflammatory cytokines, the attenuated expression of miR-206 may regulate the percentage of Th17 cells in DM patients in some extend.

Disclosure: X. Tang, None; **S. Wang**, None.

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Downregulation Of Mir-10a Is Associated With Increased Von Willebrand Factor Antigen, Disease Activity Score and Earlier Diagnosis In Children With Untreated Juvenile Dermatomyositis. Dong Xu[1], Akadia Kachaochana[1], Gabrielle A. Morgan[1], Chiang-Ching Huang[2] and Lauren M. Pachman[1]. [1]Ann & Robert H. Lurie Children's Hospital of Chicago Research Center, Chicago, IL, [2]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: We previously reported (Arthritis Rheum 2012;64 Suppl 10:1670) that miRNA array studies of diagnostic muscle biopsies obtained from untreated children with Juvenile Dermatomyositis (JDM) identified 19 differentially expressed miRNAs in JDM muscle compared to healthy orthopedic controls. Downregulation of miR-10a and miR-10b headed the list with fold changes of −1.96, adjusted p=0.0028, and fold change of −1.62, adjusted p value= 0.0027, respectively. miR-10a and miR-10b are located on separate chromosomes (2 and 17) and regulate the NFκB pathway which controls the synthesis of inflammatory mediators. We confirmed that plasma levels of IL-6, IL-8, TNF-α, MCP-1, VCAM-1, but not IL-1β, were elevated in untreated JDM compared to controls. The purpose of the present study was to determine association of the miR-10a and miR-10b downregulation in the muscle with customary clinical and laboratory findings in untreated children with JDM.

Methods: After obtaining informed consent, 24 children: 11 with a short duration of untreated disease (DUD) of less than 3 months and 13 with a long DUD of greater than 3 months were enrolled; 17 were girls. Of the 24, 19 were White and 5 were Hispanic. The children were enrolled at the time of diagnosis and their clinical and diagnostic laboratory data examined in relation to the expression levels (qPCR) of miR-10a and miR-10b in the diagnostic muscle biopsy. The clinical variables considered were disease activity scores (DAS, skin, muscle, total score), nailfold capillary end row loop number (ERL) and the blood level of von Willebrand factor antigen (vWF:Ag), DUD, and the presence of the TNF-α−308 A allele. Healthy orthopedic patients donated muscle from the trunk or proximal limbs as controls.

Results: Of note, decreased miR-10a, but not miR-10b, was associated with: a short DUD of less than 3 months, p=0.014; the presence of the A allele at the promoter region of TNF-α−308, p=0.006; an elevated DAS Total, p=0.03; and increased vWF:Ag level, p=0.004. There was no association of either decreased miR-10a or miR-10b with loss of ERL.

Conclusion: Downregulation of miR-10a, but not miR-10b, was associated with increased vWF:Ag, indicating damaged endothelial cells, and a more severe disease onset with a higher DAS, contributing to earlier diagnosis and a shorter DUD. We conclude that miR-10a downregulation is a critical factor in JDM pathophysiology and speculate that it may be a potential therapeutic target early in the disease course.

Disclosure: D. Xu, None; **A. Kachaochana**, None; **G. A. Morgan**, None; **C. C. Huang**, None; **L. M. Pachman**, None.

ACR/ARHP Poster Session C
ARHP Orthopedics, Low Back Pain and Rehabilitation: Rehabilitation Sciences
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

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The Effects of Commercially Available Footwear On Foot Pain and Disability in People With Gout: A Feasibility Study. Keith Rome[1], Sarah Stewart[1], Alain Vandal[2], Peter J. Gow[3], Peter J. McNair[1] and Nicola Dalbeth[4]. [1]AUT University, Auckland, New Zealand, [2]Counties Manukau District Health Board, Auckland, New Zealand, [3]Middlemore Hospital, Auckland, New Zealand, [4]University of Auckland, Auckland, New Zealand.

Background/Purpose: The non-pharmacological management goals for people with foot-related rheumatic diseases are pain management, preservation of foot function and patient mobility. One of the therapeutic components that may achieve these goals is footwear. To date, no clinical trials have examined the impact of footwear as an intervention for people with gout. The aim of this study was, first, to determine the factors that are important to people with gout in their choice of walking shoes, and thereafter to determine whether those chosen shoes could reduce foot pain and musculoskeletal disability in people with gout over 8 weeks.

Methods: Thirty-six people with gout participated in a randomised, single-blind, crossover trial, followed by an 8-week prospective observational study. Four walking shoes were included into the trial based upon cost and footwear characteristics (Helix Viper, Dunlop Apollo, Dunlop Asteroid, ASICS Cardio Zip). Perceived comfort and footwear acceptability were determined for each shoe; participants selected a shoe for the observational study. The primary outcome of the crossover trial was perceived comfort of the footwear. The primary endpoint of the observational study was foot pain visual analogue scale.

Results: The Cardio Zip shoe was selected by 21/36 (58%) participants. The Cardio Zip was reported as comfortable by 81% and well-fitting by 62% participants ($p=0.004$ and 0.03 compared with other shoes respectively). Compared with baseline, scores at 8-weeks decreased in foot pain ($p=0.03$), general pain ($p=0.012$), Health Assessment Questionnaire (HAQ)-II ($p=-0.016$) and Leeds Foot Impact Scale (LFIS) impairment subscale ($p=0.03$). No significant differences were observed in other patient reported outcomes including patient global assessment, LFIS activity subscale, and Lower Limb Task Questionnaire subscales (all $p>0.10$). We observed significant differences between participants' own shoes and the Cardio Zip for foot pain ($p=0.002$), general pain ($p=0.001$), HAQ-II ($p=0.002$) and LFIS impairment subscale ($p=0.004$) after 8 weeks. The other three shoes did not improve pain or disability.

Conclusion: Footwear with good cushioning, motion control and adequate width may reduce foot pain and disability in people with gout.

Disclosure: K. Rome, None; **S. Stewart**, None; **A. Vandal**, None; **P. J. Gow**, None; **P. J. McNair**, None; **N. Dalbeth**, None.

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Adaptation and Preliminary Testing of An Arthritis Walking Program to Reduce Joint Pain for Elderly Breast Cancer Survivors On Aromatase Inhibitor Therapy. Kirsten A. Nyrop[1], Betsy Hackney[1], Rebecca J. Cleveland[1], Mary Altpeter[1], Hyman Muss[2] and Leigh F. Callahan[3]. [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, [3]University of North Carolina, Chapel Hill, NC.

Background/Purpose: Joint pain/stiffness/achiness (arthralgia) is a common side-effect among postmenopausal women with breast cancer (BC) who are hormone receptor positive (HR+) for whom standard adjuvant endocrine treatment includes an aromatase inhibitor (AI). AI discontinuation due to side-effect severity is an estimated 20–32%. There is a need for effective alternative or adjunctive approaches to arthralgia management that enable BC survivors to remain on AI therapy while optimizing as pain-free a life as possible. This study investigates the feasibility of adapting and testing an evidence-based self-directed 6-week physical activity program (PA) for adults with arthritis – Arthritis Foundation's *Walk With Ease (WWE)* – among female BC survivors age 65+ on AIs who report joint pain.

Methods: ***Design:*** *Mixed methods design:* (a) semi-structured interviews (qualitative) to adapt the *WWE* program and (b) one-arm pre-post pilot test (quantitative) to gather preliminary data on program impact. Initial sample of 10 BC survivors completed questionnaires and interviews about barriers and facilitators to moderate intensity PA; findings were used to develop an insert (*WWE-Breast Cancer*) for the *WWE* workbook. New sample of 20 was recruited to participate in the *WWE* program, complete pre- and post-intervention questionnaires, and complete a post-intervention interview to refine the *WWE-Breast Cancer* insert. ***Recruitment:*** BC survivors age 65+ were recruited through the oncology clinic of a university-affiliated hospital. ***Eligibility:*** age 65+; Stage I-III breast cancer; currently on AI therapy; self-reported joint pain/stiffness; physician permission to engage in PA; English speaking. ***Measures:*** (1) walking – number of days per week and number of minutes per walk, and (2) visual analog scales (VAS) for joint pain, fatigue and stiffness. ***Statistics:*** t-test evaluation of changes in mean values.

Results: Total sample (N=30) – mean age 70 (range 65–87), 90% Caucasian, 30% < high school degree. Within the walking sample (N=20): 100% would recommend *WWE* to other breast cancer survivors experiencing joint pain or stiffness; 100% thought they had learned how joint pain or stiffness could be lessened by physical activity, and how to safely engage in moderate-intensity physical activity; 90% thought *WWE* had motivated them to become more physically active, and how to overcome physical and mental barriers to walking; and 90% were fairly to extremely confident they would continue walking. At 6 weeks, all three walking measures showed significant improvements: number of times increased by 1.9 (effect size = 0.68, $p<0.001$), number of minutes increased by 8.8 (effect size = 0.48, $p<0.05$), and total minutes per week increased by 62.6 (effect size = 0.53, $p<0.001$). Mean joint pain decreased 10% ($p=0.63$), fatigue decreased 19% ($p=0.31$), joint stiffness decreased 32% ($p=0.07$).

Conclusion: A moderate-intensity self-directed walking program is feasible for elderly breast cancer patients on AI therapy who have joint pain. The program significantly increased total walking time per week over a 6 week period and was perceived as informative and motivational.

Disclosure: K. A. Nyrop, None; **B. Hackney**, None; **R. J. Cleveland**, None; **M. Altpeter**, None; **H. Muss**, None; **L. F. Callahan**, None.

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Strengthening Exercises Using A Swiss Ball Improve Symptoms and Muscle Performance Of Patients With Fibromyalgia: A Randomized Controlled Study. Josiander Arakaki Sr., UNIFESP, sao paulo, Brazil.

Background/Purpose: Fibromyalgia (FM) is a disorder characterized by chronic widespread pain, fatigue and reduced muscle strength. Exercise is fundamental to the treatment of FM and muscle strengthening programs have shown evidence of effectiveness in improving the symptoms of the syndrome.

Methods: Sixty patients classified with FM were selected and randomized into two groups: intervention group (IG) that conducted strengthening exercises using a Swiss ball, and control group (CG) that performed stretching exercises. The trainings were conducted three times per week, lasting 40 minutes, for 12 weeks. The IG (n = 30) performed 8 strengthening exercises using a Swiss ball with the aim of recruiting the major muscle groups: lateral raise (deltoid), simultaneous threads (biceps), squat (quadriceps), *French* triceps (triceps), abdominal (rectus abdominis), unilateral stroke (latissimus dorsi), crucifix (pectoralis major) and reverse crucifix (rhomboid and trapezius). The CG (n = 30) performed stretching exercises of the same muscle groups exercised by IG. The outcome measures were: VAS (visual analogue scale) for pain; one repetition maximum (1RM) test to assess muscle strength; FIQ (Fibromyalgia Impact Questionnaire) to assess the impact of the disease; and SF-36 (Short Form Health Survey) to assess quality of life. All participants underwent an evaluation at the beginning and after 6 and 12 weeks of training.

Results: The two groups were homogeneous regarding demographic and clinical characteristics at baseline. The IG showed statistically significant improvement ($p<0.05$) in VAS and FIQ compared to GC in T6 and T12. In addition, the IG showed improvement of muscle strength in almost all prescribed exercises compared to the control group. Both groups improved general quality of life, but without significant differences between groups. No adverse events were reported in both groups.

Conclusion: The treatment of fibromyalgia with strengthening exercises using a Swiss ball determined improvement in pain, quality of life related to disease and muscle strength compared with the stretching exercises without deleterious effects.

Disclosure: J. Arakaki Sr., None;

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A Comparison Of Performance On The Keital Functional Test By Persons With Rheumatoid Arthritis and Systemic Sclerosis. Janet L. Poole, Amy New and Christina Garcia. University of New Mexico, Albuquerque, NM.

Background/Purpose: Mobility is necessary for participation in all areas of daily life including self-care, work and leisure. In rheumatic conditions such as rheumatoid arthritis (RA) and systemic sclerosis (SSc), mobility can be compromised due to decreased joint motion, muscle weakness and pain in the lower extremities. While the lower extremity impairments in RA have been studied, less attention has been paid to lower extremity involvement in persons with SSc. Therefore the purpose of the study is to compare lower extremity impairments in persons with RA, SSc and healthy controls.

Methods: Fifty eight persons with RA, 64 persons with SSc and 30 healthy controls were evaluated with the Keital Functional Test (KFT), a performance based test of functional joint motion and strength that has been shown to be an important predictor of disability and mortality in people with RA. Only the 15 items from the KFT that related to lower extremity function in an upright position were used. There are specific ordinal scoring criteria for each item. Scores for 11 items range from 0 (no limitation) to 2 (impossible).

Two items (rise from a chair and walk 30 minutes) range from 0 (no problem) to 6 (impossible) while two other items (going up and down stairs) are scored from 0 (7 seconds, no rail) to 5 (impossible). Demographic information on age, disease duration, gender, employment status and health status was also collected. Analysis of variance compared the three groups on item scores and total scores on the KFT.

Results: There were no significant differences between the 3 groups for any of the demographic variables except for perceived health status (p =.001) and employment status (p =.001). Perceive health was significantly better in the HC group and significantly more HC were working full time compared to the RA and SSc groups. On the KFT, there were significant differences between the HC group and RA and SSc groups for 5 items and the total score: rising from a chair (p =.007), squatting (p =.001), walking 30 meters (p = 001), walking downstairs (p = 001), walking upstairs (p = 001), and the total score (p = 001). There were no significant differences for 7 items: standing on heels, standing on the right leg, standing on the left leg, placing right foot on chair for hip and knee flexion, placing left foot on chair, placing right heel on chair for hip flexion and knee extension, and placing left heel on chair. All 3 groups scored significantly different from each other for external rotation of the right hip (p = 001) in that the HC group has the highest external rotation and the SSc group had the least. For external rotation of the left hip, there was only a significant difference between the RA and HC group.

Conclusion: The results show that persons with RA and SSc have greater lower extremity involvement than HC and suggest areas that could be targeted for intervention. The results also show that persons with SSc do have lower extremity impairments which have not been examined, other than walking speed and time, in other studies.

Disclosure: J. L. Poole, None; **A. New**, None; **C. Garcia**, None.

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Do Exercise Interventions For Total Hip Arthroplasty Have Therapeutic Validity? A Sensitivity Analysis Of Trials Included In a Cochrane Systematic Review. Marie D. Westby[1], Shirin Kazemi[2] and Dina L. Jones[3]. [1]University of Alberta, Edmonton, AB, [2]Mary Pack Arthritis Program, Vancouver, BC, [3]West Virginia University, Morgantown, WV.

Background/Purpose: Therapeutic exercise is the most common element of rehabilitation after total hip arthroplasty (THA). To elicit a training effect, interventions must be performed at sufficient doses (frequency, intensity, time, type) as recommended by the American College of Sports Medicine (ACSM). Evaluating the quality of primary studies' interventions is not part of Cochrane review methodology. Yet, judging an intervention's likelihood of providing a training effect would inform the assessment of clinical heterogeneity and interpretation of results. Hoogeboom *et al.* developed a 9-item CONsensus on Therapeutic Exercise aNd Training (CONTENT) scale to assess the therapeutic validity (i.e., quality) of exercise interventions. Thus, the purpose of this study was to 1) assess the therapeutic validity of exercise interventions included in a systematic review of post-acute physical therapy after THA; and 2) determine if they meet ACSM guidelines.

Methods: The methodological quality and results of the Cochrane review were previously presented. This study included trials from the review that focused on exercise interventions. Two researchers (MW & SK) independently extracted data on ACSM exercise dose and overall duration, and applied the CONTENT scale to assess therapeutic validity. Each of the 9 items were rated 'yes' or 'no' and 'meeting' or 'not meeting' ACSM guidelines. Studies scoring ≥6 were considered to have high therapeutic validity. Disagreements between raters were resolved through discussion and a tie-breaker (DJ) when necessary. Frequency counts and proportions were calculated to determine the number of CONTENT and ACSM items met. We calculated Cohen's kappa (*k*) coefficient with 95% confidence intervals for individual and overall CONTENT items to determine strength of agreement between raters. Kappa coefficients ≥ 0.60 represented good agreement.

Results: Of the 14 trials in the Cochrane review, 11 were exercise interventions of strength training alone (n=3), neuromotor training alone (n=2), and both (n=6). Overall, there was substantial agreement between the 2 raters (*k* 0.71 [CI 0.56, 0.86]) with absolute agreement on 86 of 99 (87%) CONTENT items. Perfect agreement was obtained on items addressing patient selection and exercise intensity and lowest agreement (*k* 0.23 [CI 0.40, 0.86]) for exercise monitoring/progression. Two interventions were therapeutically valid (Table 1). No interventions met the ACSM criteria. The details most often missing were exercise type and intensity.

Table 1. Therapeutic validity scores and ACSM criteria met by each study

Study	Exercise mode(s)	Therapeutic Validity (0–9)	ACSM Exercise Parameters Met
Galea et al 2008	Strength	3	F I T T **D**
	Neuromotor		F * **T T D**
Heiberg et al 2012	Strength	7	F I T T **D**
	Neuromotor		F * **T T D**
Hesse et al 2003	Neuromotor	5	**F** * **T** T D
Liebs et al 2010	Neuromotor	2	**F** * T T D
Liebs et al 2012	Strength	2	**F** I T T D
	Neuromotor		**F** * T T D
Mikkelsen et al 2012	Strength	2	F I T T **D**
Nyberg et al 2002	Strength	0	F I T T **D**
	Neuromotor		F * T T **D**
Scherak et al 1998	Strength	0	F I T T D
	Neuromotor		**F** * T T D
Stršm et al 2006	Strength	0	F I T T **D**
Suetta et al 2004	Strength	7	**F I T** T **D**
Trudelle-Jackson et al 2004	Strength	4	**F** I T T **D**
	Neuromotor		F * T T **D**

ACSM Criteria - Bolded letter means criteria met: **F**=frequency, **I**=intensity, **T**=timing, **T**=type, **D**=duration of intervention. *=intensity not applicable for neuromotor exercise.

Conclusion: This is one of the few analyses conducted to address therapeutic validity of exercise interventions. Post-THA exercise interventions have low therapeutic validity and fail to meet ACSM exercise prescription criteria for health benefits. The conclusions of individual trials, and our and other systematic reviews of THA exercise interventions should be interpreted with caution.

Disclosure: M. D. Westby, None; **S. Kazemi**, None; **D. L. Jones**, None.

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Hand Exercises Significantly Improved Activity Performance, Grip Strength and Pain In Women With Hand Osteoarthritis - Results From a Randomised Controlled Trial. Toril Hennig[1], Liv Haehre[1], Vivian Tryving Hornburg[1], Petter Mowinckel[2], Ellen Sauar Norli[1] and Ingvild Kjeken[2]. [1]Martina Hansens Hospital, Gjettum, Norway, [2]Diakonhjemmet Hospital, Oslo, Norway.

Background/Purpose: Even if hand exercises is regarded as a core treatment for individuals with hand osteoarthritis (HOA), the evidence for the effect is limited. The main aim of this study, therefore, was to evaluate the effect of a hand exercise program in women with HOA.

Methods: In this observer blinded, randomised controlled trial ((ISRTCN79019063), 40 women with HOA received information and instruction in hand exercises (E-group), and 40 women received information only (control (C)-group). The exercise program followed the American College of Sports Medicine recommendations for developing muscular strength and flexibility in older frail adults, and included a warm-up period, two exercises to maintain/increase flexibility of the MCP, PIP and DIP joints, one exercise to strengthen the thumb extensors and abductors to maintain thumb web space and increase thumb stability, one exercise to increase grip strength, and a stretching exercise to prevent thumb adduction deformities. E-group participants recorded date, duration of the exercise session and pain following exercising in a diary, and received eight follow-up telephone calls during the three month study period.

Primary outcome was activity performance measured by the Patient Specific Functional Scale (PSFS) on a 0–10 scale (10=good performance). Secondary outcomes included measures of grip strength, joint mobility, thumb web space, pain, disease activity, stiffness and fatigue. Analysis of covariance was used to estimate between group differences at three months follow-up, with scores at three months as dependent variable, taking baseline values as covariates.

Results: Seventyone participants (mean age 60.8, SD 7.0) completed all assessments. Median number (min, max) of exercise sessions in the E-group in the study period was 37 (26, 43), and median time used pr session was 23.6 minutes (10.4, 42.0).Hand exercises was associated with significant improvement in the PSFS score (adjusted mean difference in change between groups 1.4, p<0.001).Concerning secondary outcomes, hand exercises significantly predicted improvement in fatigue, (mean adjusted differences in change between groups −1.1, p=0.05), in joint pain (−1.1, p=0.02), in grip strength in right (53.5 N, p<0.001) and left (44.6 N, p<0.001) hand, in thumb web

space of the right (0.6, p=0.018) and left (0.7, p=0.007) hand, and in the FIHOA activity performance score (−3.2, p<0.001).

While measures of joint mobility in general were stable in the E-group, there was a trend towards deterioration in the C-group, with a significant increase in flexion deficit of 5.4 mm in the right hand (p=0.009).

Conclusion: Hand exercises is well tolerated and significantly improves activity performance, grip strength and pain in women with HOA.

Disclosure: T. Hennig, None; **L. Haehre**, None; **V. T. Hornburg**, None; **P. Mowinckel**, None; **E. S. Norli**, None; **I. Kjeken**, None.

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Impaired Shoulder-Arm Mobility and Muscle Function In Patients With Systemic Sclerosis. Helene Alexanderson[1], Fia Bringby[2], Annica Nordin[3], Lena Björnådal[3], Elisabet Svenungsson[4] and Carina Boström[5]. [1]Division of Physiotherapy, Karolinska Institutet, Huddinge, Stockholm, Sweden, [2]Capio Arthro Clinic, Stockholm, Sweden, [3]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [4]Karolinska Institutet, Stockholm, Sweden, [5]Division of Physiotherapy, Karolinska Institutet Huddinge, Stockholm, Sweden.

Background/Purpose: Patients with systemic sclerosis (SSc) have reduced hand function and self-reported limitations in daily activities. Few studies have explored limitations in shoulder-arm mobility and muscle function, or if there are differences in physical function between diffuse cutaneous (dcSSc) and limited cutaneous (lcSSc) SSc. The purpose of this study was to describe objectively assessed shoulder-arm mobility, lower extremity muscle function and muscle endurance in SSc and evaluate possible differences between lcSSc and dcSSc.

Methods: 121 consecutive patients with Systemic sclerosis were included in this cross sectional study. Shoulder-arm mobility were examined using the Shoulder Function Assessment Scale (SFA) including 5 tasks (each task scored between 1–6 with maximum score 30, where 6 and 30 = no limitation), lower extremity muscle function was measured by Timed stands test (TST) and muscle endurance in shoulder- and hip flexors were assessed by the Functional Index 2 (FI-2) (maximal number of repetitions, 60 = 100%).

Results: Mean age was 61 (SD + 16) years, 83% were female, and median disease duration was 9 Q1-Q3 (4–15) years. 96 patients had lcSSc and 25 had dcSSc. The SFA score in the whole patient group were 27 (25–29) and 28 (26–29) on the right and left side respectively. Patients with dcSSc had median SFA "hand to back" score 5 (4–6) and median "hand to seat" score of 5 (4–6) compared to patients with lcSSc with corresponding median values of 6 (4–6) and 6 (5–6) respectively (p<0.01-p<0.05). 50% of both patients with lcSSc and patients with dcSSc had lower muscle function assessed by the TST compared to age- and gender matched reference values but there were no differences in TST between the two patient groups. There was also no difference in FI-2 scores between dcSSc and lcSSc. The whole group had 40 (28–83) % and 38 (32–72) % of maximal FI-2 shoulder flexion score on the right and left sides, and 40 (23–63) % and 37 (23–62) % of maximal FI-2 hip flexion score on the right and left sides. Preliminary reference values for the FI-2 indicate that healthy individuals aged 40–65 years perform in mean 100 % of maximal score with a range of 50–100%.

Conclusion: Patients with SSc have mild limitations in shoulder-arm mobility, although patients with dcSSc were more limited in specific tasks than patients with lcSSc. Patients with SSc have reduced muscle function compared to reference values. These results highlights the importance of assessing shoulder-arm mobility and muscle function as well as a need for further research to identify exercise interventions to target these limitations.

Disclosure: H. Alexanderson, None; **F. Bringby**, None; **A. Nordin**, None; **L. Björnådal**, None; **E. Svenungsson**, None; **C. Boström**, None.

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Evaluation Of An Advanced Practice Physiotherapist Role in Rheumatology. Chandra Farrer. University of Toronto, Toronto, ON.

Background/Purpose: Arthritis affects 4.6 million Canadians and is the leading cause of disability in Canada. Many Canadians do not have access to a family physician. There are currently 353 rheumatologists practicing in Canada. Of these, 44% are 55 and older. The need for arthritis care in Canada, in the context of limited health human resources, has led to evolving models of care. Extended practice roles for physiotherapists, occupational therapists and nurses have been implemented to address access to care and wait times and thereby decrease the burden of illness. Within our setting, the Advanced Practice Physiotherapist role has expanded to ordering x-rays, laboratory tests and more recently to intra-articular joint injections of the knee and shoulder. The purpose of this study is to evaluate the impact of the Advanced Practice Physiotherapist role in Rheumatology clinics.

Methods: Patient Volumes, wait times, and diagnosis information was collected from April 2009 using patient service information. Volumes of patients, seen by the Advanced Practice Physiotherapist, requiring x-ray, laboratory tests and intra-articular joint injection were also collected. Patient satisfaction was collected from April 2009-Sept 2009 on consecutive patients.

Results: The Advanced Practice Physiotherapist had 1711 total patient visits. Wait times in the clinic have trended downward, while overall clinic volumes have remained stable. Diagnosis classification are: Osteoarthritis (40.33%), Inflammatory Arthritis (37.58%), non-articular rheumatism (14.32%), other (4.32%) and chronic pain (3.51%).Patient's reported being "extremely satisfied" or "very satisfied" with the Advanced Practice Physiotherapist skills/knowledge, recommendations for care, explanation of assessment results and answers given to questions. Intra-articular joint injections have been required for 7.89% of visits, laboratory tests 23.38% of visits and x-rays 16.19% of visits.

Conclusion: The Advanced Practice Physiotherapist role has evolved since April 2009 by gradually expanding the scope of practice to ordering x-rays, laboratory tests and more recently intra-articular joint injections. There has been a positive trend towards decreasing wait times while maintaining overall Rheumatology clinic volumes. Patient satisfaction with the role has been high. Further research is needed to demonstrate efficacy of intra-articular joint injections performed by the advanced practice physiotherapist as this is a new endeavour for our clinic. Cost effectiveness and efficiency of the model need to be addressed in future.

Disclosure: C. Farrer, None;

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What Elements Of Physical Therapy Interventions Contribute To Improved Outcomes Following Total Knee Arthroplasty. Joshua K Johnson[1], Traci E DeWan[1], Kelly L Donahue[1], Wenjun Li[2], Patricia D. Franklin[2] and Carol A. Oatis[1]. [1]Arcadia University, Glenside, PA, [2]University of Massachusetts Medical School, Worcester, MA.

Background/Purpose: Functional outcomes are variable among patients following total knee arthroplasty (TKA). Evidence is lacking to support best practices in rehabilitation to optimize functional outcomes. The purpose of this research was to determine associations of post-operative function defined by standardized patient report and objective PT evaluation with timing, amount, and content of physical therapy (PT) services in TKA patients.

Methods: We requested 142 and received 91 outpatient (OP) and 27 home care (HC) PT records for patients participating in a randomized behavioral trial for patients who had received a unilateral primary TKA, had completed the 6-month study assessment and their post-TKA PT rehabilitation. PT researchers performed a retrospective review of PT intervention data from 37 facilities, recording intervention type, frequency and dosage data for each subject during their terminal course of PT services. Performance outcomes measured at 6 month post TKA included flexion range of motion (ROM), timed stair climb (TSC) and WOMAC physical function (PF). Linear regression models assessed associations between PT intervention frequency and content (i.e., open and closed chain (CC) exercises and progressions) and 6 month outcomes, with and without adjusting for gender, age, baseline physical component score of SF-36, WOMAC PF, and number of comorbid conditions.

Results: 91 records, including 74 (81%) OP and 17 (19%) HC from 37 facilities, contained complete exercise information. Number of PT interventions, number of CC interventions and progressions and number of CC exercises per visit were associated with improved TSC (p <.05) with coefficients ranging from -.45 to -.99. Number of CC progressions was also associated with improved ROM (1.41; p<.01). Earlier initiation of OC exercises was associated with improved WOMAC PF scores. Adjusted coefficients revealed similar associations between the number of progressions of CC exercises and improved TSC (p <.05) and knee flexion ROM (p <.01), between number of CC exercises per PT visit and ROM and between OC exercises and WOMAC PF. Number of PT visits did not predict outcomes. An increased number of passive interventions predicted poorer ROM outcomes (p <.01).

Conclusion: Preliminary data suggest that the number and progressions of CC exercises used per visit and over the episode of care contribute to improved objective performance outcomes following TKA. Timing of exercise initiation contributes to improved patient-reported outcomes. Content, dosage and timing of PT exercises rather than number of visits appear to be predictive of performance outcomes. Further research is needed to clarify the role of PT content, dosage and intensity in optimizing functional outcomes following TKA.

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Global Postural Reeducation To TREAT Chronic LOW Back PAIN: Randomized, Controlled Trial. Priscila Almeida Lawand[1], Imperio Lombardi Jr[2], Carla Caires Sardim[1], Luiza H. C. Ribeiro[1], Anamaria Jones[1] and Jamil Natour[3]. [1]Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [2]Universidade Federal de Sao Paulo, Santos, Brazil, [3]Universidade Federal de São Paulo, São Paulo, Brazil.

Background/Purpose: Low back pain (LBP) is a major cause of physical limitations and absenteeism at work throughout the world. A number of studies have demonstrated the effectiveness of therapeutic exercises on reducing pain symptoms and improving function in patients with chronic LBP. Global Postural Reeducation (GPR) technique theoretically consists of a reestablishment of the balance in the myofascial tension of different chains of muscles. GPR is based on the notion that a shortened muscle creates compensations in other proximal or distal muscles. One systematic review assessed the use of GPR for different conditions of the musculoskeletal system and found only one RCT that demonstrated a significant improvement in functional capacity in patients with ankylosing spondylitis. However, there are no previous randomized, controlled, clinical trials assessing the effectiveness of GPR on chronic LBP. The purpose of this study were to assess the effectiveness of global postural reeducation (GPR) on pain, function, quality of life and depressive symptoms in patients with chronic LBP.

Methods: Sixty-one patients with chronic LBP were randomly allocated to either the GPR group or a control group. Patients in the GPR group underwent one weekly 60-minute session of GPR for a period of 12 weeks. The control group remained on the waiting list under clinical treatment, with no physical intervention. Pain, function capacity, quality of life and depressive symptoms were assessed using a visual analog scale (VAS), the Roland-Morris questionnaire (RMQ), the Medical Outcomes Study Short-Form 36-Item Health Survey (SF-36) and the Beck Inventory, respectively. The evaluations were performed by a blinded examiner at baseline, three months and six months after the initial evaluation and the data were analysis using an intention to treat approach.

Results: The GPR group demonstrated significant improvements in pain ($p<0.001$) and function ($p<0.001$) as well as the domains: pain ($p=0.047$), emotional aspects ($p=0.008$), limitation in physical functioning ($p=0.040$), vitality ($p=0.003$) and mental health ($p=0.034$) of the SF-36.

Conclusion: Based on the findings, GPR proved to be effective regarding pain, function and some domains of quality of life in chronic LBP patients.

Disclosure: P. A. Lawand, None; **I. Lombardi Jr**, None; **C. C. Sardim**, None; **L. H. C. Ribeiro**, None; **A. Jones**, None; **J. Natour**, None.

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A Scoping Review On Leisure Activity Expectations After Total Hip Or Knee Arthroplasty Due To Arthritis. Dina L. Jones and Nirupama Semmalidinne. West Virginia University, Morgantown, WV.

Background/Purpose: It is important that patient expectations are met after total hip (THA) or knee (TKA) arthroplasty in order to maximize outcomes and satisfaction. Although patients state that return to leisure activities is a priority, few studies have focused on their expectations for return to these activities. We conducted a scoping review to determine: 1) the types of studies that have been conducted on leisure activity expectations after THA/TKA, 2) how expectations have been measured, 3) if expectations are met, and 4) if expectations can be modified.

Methods: Scoping reviews are used to determine the extent, range, and nature of the scientific literature when experimental studies are lacking. This review was conducted using the 6-stage framework of Arksey and O'Malley (identify research question, identify relevant studies, select studies, chart data, report results, and consultation). The review included cohort and experimental studies of patients, aged 18 years or more, who received primary THA/TKA due to arthritis, and included a pre-operative assessment of leisure activity expectations and data on if they were met or modified. Electronic database searches (e.g., MEDLINE, CINAHL) were conducted by a medical librarian. The studies were independently screened for eligibility by 2 researchers during 3 rounds of review (title, abstract, and full-text). A descriptive analytical method was used to summarize the data according to published methods. Cohen's kappa coefficient with 95% CI was used to determine inter-rater agreement.

Results: Of the 242 articles identified, 169 titles, 60 abstracts, and 15 full-text articles were screened for eligibility. The rater agreement for each round was 0.47 (CI 0.32, 0.63), 0.61 (CI 0.35, 0.86), and 1.0 (CI 1, 1), respectively. The review included 5 studies. Four studies used a cohort design to determine if expectations were met after surgery (follow-up between 1 and 5 years). Only 1 randomized controlled trial attempted to modify expectations prior to surgery using an educational class with hip- or knee-specific information. Expectations were measured by questionnaire (self- or phone-administered) and presented as an overall score (summation of Likert scale responses) or in MET-hours per week. Only 1 study measured the expected dose (frequency, intensity, time, type) of activity. Expectations exceeded post-operative ability at 5 years in 1 study, and were not met in another. Two studies estimated that expectations were met in 10% to 43% of patients. The randomized controlled trial reported that expectations could be modified.

Conclusion: This scoping review demonstrated that few studies focused on patient expectations for leisure activity after THA/TKA, and even fewer attempted to modify expectations. Expectations were not consistently met, but they are capable of being modified. Future studies should assess the expected dose of activity that patients expect to achieve to ensure that they will be active enough to maintain health. More studies are needed to test educational interventions in patients undergoing joint replacement. Educating patients about appropriate activity expectations could improve the health and activity levels of this population.

Disclosure: D. L. Jones, None; **N. Semmalidinne**, None.

2101

Barriers To Improving Physical Activity In Patients With Systemic Lupus Erythematosus: The Activity and Nutrition Trial In Lupus To Energize and Renew (ANTLER) Pilot Study. Linda S. Ehrlich-Jones[1], Grace E. Ahn[2], Christine Pellegrini[3] and Rosalind Ramsey-Goldman[3]. [1]Rehabilitation Institute Chicago, Chicago, IL, [2]Northwestern University, Chicago, IL, [3]Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Current literature indicates that exercise is safe and effective in improving fatigue, depression, aerobic capacity, and health-related quality of life in systemic lupus erythematosus (SLE). Only 28% of SLE patients self-report that they meet the US government public health goal of at least 150 minutes/week of moderate to vigorous intensity physical activity (PA). Some barriers to PA for patients with SLE include fatigue, exposure to sunlight, pain, depression, sleep disturbance and hematologic and bony abnormalities predisposing to bleeding and fracture. We assessed barriers to PA as well as goals to improving PA before and after a behavioral intervention in a group of patients with SLE.

Methods: In a mixed-methods pilot study of 8 SLE adults, we identified barriers to increasing their PA using the Arthritis Comprehensive Treatment Assessment. In addition, we identified goals they would like to achieve over the next 6 weeks to increase their PA. All participants completed the Motives for Physical Activity Measure-Revised (MPAM-R), a questionnaire to assess the strength of five motives for participating in PA, at baseline and completion of the study. Individual coaching sessions were held at baseline and 6 weeks with a healthy lifestyle coach (exercise physiologist or occupational therapist) to review their barriers to PA and the achievement of their goals at the end of the study. Participants were also offered 3 group educational sessions highlighting PA, healthy nutrition and motivation to behavior change.

Results: The sample consisted of 6 women and 2 men, mean age 47 years (SD=7.75) and included 50% African-American, Asian and Caucasian (25% each). Sixty-two percent were married. At baseline, 8 participants participated in an individual coaching session; 7 completed the 3 group educational sessions and the individual session at the end of the study. At the baseline visit, 6 participants identified feeling tired or

washed out, 5 identified motivation and 4 identified pain as barriers to doing PA. PA goals included: going to the gym (treadmill, elliptical, swimming and strength training), doing yoga or Zumba classes. Post-intervention, 4 participants stated an increase in their level of satisfaction with their PA. Fatigue, pain and motivation continued to be barriers to increasing PA. Mean MPAM-R subscale change scores for enjoyment (4.01), social (2.18), and appearance (1.56), all increased post-intervention, while change scores for competence (−0.48) and fitness (−0.57) remained relatively the same.

Conclusion: Fatigue, pain and motivation appear to be the most common barriers to increasing PA in this pilot study. Enjoyment, appearance and social motives for PA appeared to increase post intervention. A larger clinical trial is needed to confirm these findings.

Disclosure: L. S. Ehrlich-Jones, None; **G. E. Ahn**, None; **C. Pellegrini**, None; **R. Ramsey-Goldman**, None.

2102

The Effect Of a Novel System Of Insoles Using Styrene Foam Beads On Foot Deformities In RA Patients. Yoshitada Sakai[1], Akira Hashiramoto[2], Yoshiko Kawasaki[2], Takaichi Okano[2], Takahiro Takeda[3], Naomi Yagi[3] and Yutaka Hata[3]. [1]Kobe University Graduate School of Medicine, Kobe, Japan, [2]Kobe University Hospital, Kobe, Japan, [3]Graduate School of Engineering, University of Hyogo, Himeji, Japan.

Background/Purpose: Foot deformities in RA patients decrease their ADL and QOL because of pain and corns.

Custom-made insoles are often prescribed for the patients with these deformities, however, the effect of these is not enough, because of their difficulties of casting and adaptation. Previous study showed that casting by footprint has the difficulty of the reflection of the plantar pressure change by foot motion at walk.

Therefore, we developed a novel system of insoles using styrene foam beads for deformities of foot, and analyzed the gait of the RA patients with foot deformities wearing our novel insoles.

Methods: Eight RA patients (all females, average age: 65.1±8.4 years old) with foot deformities were enrolled in this study. All patients met the classification criteria of the American College of Rheumatology 1987 or the 2010 rheumatoid arthritis classification criteria.

The novel insoles were made by styrene foam beads, deaerated by pressure, and memorize the plantar shapes (Tatsuno Cork Kogyo Co., Ltd, Tatsuno, Japan).

The novel insoles were inserted into slippers (Grizzly Michel, HAFLINGER, Goslar, Germany).

We compared their gaits with bare feet, our novel insoles or low rebound slippers (DAISO Industries Co., Ltd., Saijo, Japan) using a mat type load distribution sensor (Allow industry, Japan).

The parameters of our analysis were visual analog scale (VAS) of the general gait impression (including pain and ease to walk, best: 0mm, worst: 100mm), gait speed, step length, width of center of gravity during gait, and max load of sole pressure. Gate parameter data were converted %Bare-feet, and statistical analysis were performed using Kruskal-Wallis test.

Results: The data of VAS during their gaits and max load of sole pressure were significantly decreased by using the our novel insoles compared with bare feet (Bare-feet 64.6±28.6, Low rebound slippers(LRS) 48.3±25.7, Our insole 18.1±12.5). The data of gait speed, step length and max load of sole pressure were significantly increased compared with bare feet (Step length: Bare 100%, LRS 109.0±0.1%, Ours 109.8±0.1%. Gait Speed: Bare 100% LRS 106.0±0.1%, Ours: 107.1±0.1% Max load: Bare 100%, LRS 55.8±0.1, Ours 51.1±0.1%). The width of center of gravity during gait was significantly decreased by using the novel insole compared with low rebound slippers (Bare100%, LRS 109.0±0.1%, Ours 95.5±0.1%).

Conclusion: In this study, we investigated the gait analysis of RA patients with foot deformity and pain using our novel insoles. The gait parameters were improved using our insoles, and pain is decreased. In addition, from the comparison of low rebound slippers, our insole could contribute the compatibility of gait stability and reducing pain.

The limitation of this study is no investigation of the long time follow up and the durability of insoles.

Our novel insoles may be useful for the treatment of foot deformities in RA patients.

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2103

Relationships Between Self-Efficacy, Outcome Expectancy, and Outcomes In Older Adults With Osteoarthritis Of The Knee and Hypertension: Baseline Results. Elizabeth A. Schlenk, Deborah Crowley-Lisowski, Sarah Twerski, Alice Fallon, Alyssa Sartore, Susan Sereika, Joan Rogers, G. Kelley Fitzgerald and C. Kent Kwoh. University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Staying Active with Arthritis (STAR), an intervention guided by Bandura's Self-Efficacy Theory, is being investigated in an ongoing clinical trial of an individually delivered, home-based, 6-month lower extremity exercise and fitness walking program with older adults with osteoarthritis of the knee and hypertension treated with anti-hypertensive medication. We hypothesized that at baseline, self-efficacy and outcome expectancy (perceived therapeutic efficacy) would be related to relevant outcomes being measured in the STAR Study.

Methods: A descriptive correlational design was used for this study (N=107). Belief measures included McAuley's Self-Efficacy Scales for Exercise and Barriers to Exercise; Lorig's Arthritis Self-Efficacy Scales for Pain, Function, and Other Symptoms; and Perceived Therapeutic Efficacy Scale for arthritis (PTES-A) and hypertension (PTES-H). Outcome measures included systolic (SBP) and diastolic (DBP) blood pressure; 6-minute walk; Short Physical Performance Battery (SPPB); WOMAC Scales for Knee Function and Pain; SF36 Bodily Pain (BP) Scale, Physical Component Score (PCS), and Mental Component Score (MCS); Brief Fatigue Inventory (BFI); and quadriceps strength (QS) by MicroFET2 dynamometer. Multiple regression analyses were performed to identify significant independent predictors of the outcomes. Significance level was set at.05.

Results: Participants were on average 65 (SD=8) years of age, 73% (n=78) female, 76% (n=81) white, 42% (n=45) married, and 47% (n=50) employed, with 77% (n=81) having more than a high school education and 54% (n=48) having a family income <$50,000. There were no significant group differences in demographics or outcomes so the intervention and attention control groups were combined. Multiple regression analyses found that Exercise Self-Efficacy predicted 6-minute walk (p=.038) and SPPB (p=.022). Arthritis Self-Efficacy Pain was related to SBP (p=.002) and DBP (p=.001). Arthritis Self-Efficacy Function was predictive of DBP (p=.015), 6-minute walk (p<.0001), SPPB (p<.0001), PCS (p=.003), MCS (p=.021), and right (p=.030) and left (p=.020) knee QS. Arthritis Self-Efficacy Other Symptoms was associated with SBP (p=.032), DBP (p=.001), WOMAC Function (p=.008), WOMAC Pain (p=.023), SF-36 BP (p=.021), MCS (p<.0001), and BFI (p=.008). PTES-A predicted SBP (p=.031), WOMAC Function (p=.028), and WOMAC Pain (p=.035). PTES-H was related to WOMAC Pain (p=.019).

Conclusion: At baseline, Exercise Self-Efficacy predicted performance-based functional status as anticipated. Arthritis Self-Efficacy Pain was positively related to SBP and DBP, contrary to expectation. Arthritis Self-Efficacy Function and Other Symptoms predicted most outcomes in expected directions. Outcome expectancy predicted fewer outcomes. Future plans include examining the effect of the STAR intervention on self-efficacy and outcome expectancy and the extent to which self-efficacy and outcome expectancy act as mediators between the STAR intervention and outcomes.

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2104

Exercise For Ankylosing Spondylitis: It's Still Important. Janet Millner[1], John Barron[2], Kirsty Beinke[3], Rachael Butterworth[4], Briony Chasle[5], Lindsay Dutton[6], Margaret Lewington[7], Errol Lim[4], Tony Morley[8], Jennie O'Reilly[9], Kathryn Pickering[10] and Jane Zochling[1]. [1]Menzies Research Institute Tasmania, Hobart, Australia, [2]Eastwood Physiotherapy, Adelaide, Australia, [3]Adelaide West Pilates Physiotherapy, Adelaide, Australia, [4]BJC Health, Sydney, Australia, [5]South East Sydney Area Health Service, Sydney, Australia, [6]Royal Perth Hospital, Perth, Australia, [7]Hydrohealth, Brisbane, Australia, [8]Physio Plus, Lismore, Australia, [9]Physiotherapy, Melbourne, Australia, [10]Curtin University, Perth, Australia.

Background/Purpose: Previous systematic reviews [1] and international consensus [2] have agreed that exercise is beneficial in ankylosing spondylitis (AS), and this concept is widely supported by patient groups.

However, there is a paucity of information to guide exercise prescription. There is a need for more information about different types of exercise, how long, to what intensity and how often it should be performed for maximal improvement. Results from studies on spa therapy and hospital in-patients may not be directly transferrable to other countries where most exercise therapy is prescribed on an outpatient basis. Finally, improvements in disease management with biological medication have raised questions about the relevance of exercise as a core component of management. This collaborative project, combining evidence with expertise, was therefore established to develop practical recommendations to guide Australian exercise prescription for individuals with AS.

Methods: Ten Physiotherapists participated in discussion rounds, to determine a set of eight key topic areas, using modified Delphi methodology. A systematic literature review was conducted for each topic, and a range of evidence analysed for level, quality and relevance to the clinical question and local setting. Ten recommendations were developed, based on the integration of available evidence and expert opinion. The importance of the recommendations was validated by surveying both patient and health professional groups.

Results: A total of 202 papers were allocated to the key topic areas, the majority being surveys, cohort and case-controlled studies. Effect sizes were calculated for 20 randomised controlled trials, the range being 0.12–4.96. Exercise recommendations were developed for the following areas: assessment/evaluation; monitoring of exercise prescription; safety; biological therapy; ankylosing spondylitis-specific exercise; physical activity levels; setting; dosage and compliance. The average Strength of Recommendation was 9.0/10 (range 8.79–9.3) for patients and 9.5/10 (range 9.2–9.8) for health professionals. Valuable patient feedback was obtained regarding the relationship between health professional assessment / monitoring and compliance/ dosage.

Conclusion: Although insufficient evidence was found to recommend one type of exercise over another, the group concluded that other factors, such as targeted exercise, safety, dosage and compliance were of equal priority, and that exercise prescription remains important (and is additive) for those patients also receiving biological therapy. Widespread dissemination of the recommendations will support appropriate exercise prescription as a key component for optimal patient outcomes.

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2105

Differences In Spinal Mobility Measures In Relation To Disease Duration and Between Subgroups With Axial Spondyloarthritis.

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Background/Purpose: Spinal mobility is a core domain for research and clinical practice in Ankylosing Spondylitis (AS) but less studied in undifferentiated SpA (USpA). Our objective was to study the change of commonly used spinal mobility measures stratified on disease duration in patients with AS and differences in these measures in AS vs. USpA.

Methods: Patients with AS or USpA were identified from a cohort attending a specialist clinic. A cross sectional studie were the first measures of spinal mobility for each patient recorded during 1999 to 2012 were analyzed. Disease duration was split into tertiles, (<17 years (G1), 18–30 years (G2) and >31 years (G3)). Differences between AS G1/G2/G3 were calculated with Kruskal-Wallis. Differences between AS and USpA were controlled for sex and disease duration (ANCOVA).

Results: 126 patients with AS vs. 57 with USpA were included in the study, mean (SD) age 48.4 (13.7) vs. 41.6 (11.4) years and 23% vs. 46% were women. In AS, lumbar, and thoracic measures, vital capacity and the BASMI composite score were the first measures to deteriorate in relation to disease duration (G1 vs. G2, $p<0.035$). Late in the disease all measures had deteriorated (G1 vs. G3, $p<0.036$). Patients with USpA presented better scores in lumbar, hip and thoracic spinal measures ($p<0.05$), data controlled for sex and disease duration. In early disease (<17 years) also cervical measures ($p<0.05$) were less affected compared to patients with AS.

Conclusion: The first measures to significantly change during the disease course in AS were the lumbar and thoracic mobility measures and the BASMI score. As expected, patients with USpA were less affected in mobility than patients with AS.

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2106

Aquatic Exercise Training For Fibromyalgia: A Systematic Review.

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Background/Purpose: Fibromyalgia (FM) is a chronic pain condition leading to reduced physical function. Exercise training is recommended for people with FM. We examined randomized controlled trials (RCTs) to evaluate benefits and harms of aquatic exercise training (AQ) in adults with FM.

Methods: We searched 9 electronic databases. Selection criteria included full text publication of an RCT of AQ for adults diagnosed with FM, and provision of between-group outcome data. Studies were excluded if exercise in water was <50% of the full intervention. Pairs of reviewers independently screened and selected articles, assessed risk of bias, and extracted data on 24 outcomes in 4 domains: wellness, symptoms, physical fitness and adverse effects. Discordance was resolved through discussion. Benefits and harms of the interventions were evaluated using standardized mean differences (SMD) and 95% CI, with meta-analysis carried out when applicable.

Results: We screened 1856 citations, 766 abstracts, and 156 full-text articles. Fourteen RCTs examined AQ with a total of 820 participants. AQ was compared to control (9 studies) and to land exercise (5 studies). Risk of bias was rated low for randomization, incomplete outcome data, selective reporting, other bias, and blinding of outcome assessors. Allocation concealment, and blinding of participants and care providers were rated as unclear or high risk. Differences (SMD [95% CI]) between the AQ vs control were: multidimensional function −0.55 [−0.83, −0.27], self-reported physical function −0.44 [−0.76, −0.11], pain −0.53 [−0.76, −0.31], stiffness −1.08 [−2.05, −0.11], strength 0.63 [0.20, 1.05], and cardiovascular submaximal function 0.56 [0.27, 0.85] all favouring AQ ($p < 0.05$). Attrition was similar in AQ and control groups. Adverse effects were poorly reported, with no serious adverse effects reported. Differences (SMD [95%CI] for AQ compared to land exercise were: strength −0.74 [−1.44, −0.04] favoring land, and sleep −0.75 [−1.32, −0.17] favoring AQ. Older participants with longer disease duration and less pain/impact of disease at baseline responded better to AQ than their counterparts. Greater exercise frequency, accumulated pool time, and length of program were also associated with better results

Conclusion: Low to moderate quality evidence suggests that AQ is beneficial for improving wellness, symptoms and fitness and that no serious adverse effects result from the intervention. Very low to moderate quality evidence suggests that there are no differences in benefits between AQ and land exercise except in muscle strength (evidence favoring land) and sleep (one study favoring aquatic).

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2107

Benefitial Effects Of a Simple Stretching Exercise Program For Patients With Ankylosing Spondylitis: A Randomized Controlled Trial.

Andréa L. Gallinaro[1], Carla G.S. Saad[1], Claudia Goldenstein-Schainberg[1], Percival D sampaio-Barros[1], Julio C. B. Moraes[1], Hamilton Roschel[2], Ana Lucia S. Pinto[1] and Celio R. Gonçalves[1]. [1]Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, [2]Universidade de São Paulo, Faculdade de Educação Física e Esporte, São Paulo, Brazil.

Background/Purpose: Static and dynamic stretching exercises are applied in Ankylosing Spondylitis (AS) patients to preserve and restore

the axial mobility. However, there are no data regarding a specific rehabilitation program including solely stretching in patients with low/moderate disease activity. We, therefore, assessed the efficacy of a stretching program on mobility, functional capacity and disease activity of AS patients.

Methods: Forty sedentary AS patients with low/moderate disease activity according to Ankylosing Spondylitis Disease Activity Scores (ASDAS <2.1) and with stable medication during at least 3 months prior to study entry were included. AS patients were randomly assigned to receive a simple stretching supervised exercise program or no exercise (control group). Exercise group sessions were performed twice a week, for sixteen weeks. This supervised program comprised of 30 minutes of outdoor dynamic and static stretching exercises for the spine and limbs, using only a chair. Mobility, disease activity and functional capacity parameters were evaluated blinded for treatment, at baseline and after 16 weeks.

Results: At study entry patients had mean ± SD age of 47.1 ± 11.5 years, mean disease duration of 17.6 ± 10 years and mean BASMI of 4.7 ± 2.1. All patients were receiving anti-inflammatory drugs and 30% were using anti-TNF therapy. Thirty nine AS patients completed this trial. Patient's attendance of 14.8 ± 8.3 sessions was registered. Comparing baseline to 16 weeks, the exercise group presented significant improvement in mobility dimensions such as Pavelka's trunk rotation [1.4 (0.9) vs. 2.2 (1.8) cm, $p=0.03$], cervical rotation [43.9 (23.5) vs. 53.9 (22.3) degrees, $p=0.012$], tragus-coronoid distance [12.2 (3.7) vs. 9.3 (2.0) cm, $p=0.0001$], mento-coronoid distance [13.7 (5.4) vs. 9.6 (2.3) cm, $p=0.03$], minor intermaleolar distance [0.9 (1.3) vs. 0.2 (0.5) cm, $p=0.01$] and trunk lateral flexion [7.5 (5.1) vs. 9.5 (5.7) cm, $p=0.03$]. Exercise group also had improvement in total BASMI ($p=0.004$). In contrast, comparing control group at baseline vs. 16 weeks, no difference was observed in all mobility parameters assessed and a significant worsening was observed in BASFI ($p=0.02$), BAS-G ($p=0.006$) and ASDAS ($p=0.03$).

Conclusion: Our findings provide novel evidence that a simple stretching program has a significant beneficial mobility effects on AS patients with long disease duration and low/moderate disease activity (ClinicalTrials.gov, number NCT01690273).

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2108

Pre- and Postoperative Physical Therapy In Total Hip and Knee Replacement Surgery: A Multi Center Study. Wilfred FH Peter[1], Claire Tilbury[2], Rutger Tordoir[3], Suzan Verdegaal[3], Ron Onstenk[4], Menno Benard[5], Stephan Vehmeijer[5], Enrike van der Linden-van der Zwaag[2], Eric Vermeulen[2], Rob Nelissen[2] and Thea Vliet Vlieland[6]. [1]Reade, center for rehabilitation and rheumatology, Amsterdam, Nicaragua, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Rijnland Hospital, Leiderdorp, Netherlands, [4]Het Groene Hart Hospital, Gouda, Netherlands, [5]Reinier de Graaf Hospital, Delft, Netherlands, [6]Leids University Medical Center, Leiden, Netherlands.

Background/Purpose: Physical therapy shown to be effective after Total Hip and Knee Arthroplasty. Less evidence is available for preoperative physical therapy in Total Hip and Knee. Little is known on what the actual characteristics, frequency and duration of physical therapy after Total Hip and Knee in daily practice are. The aim of the study was to describe the extent and content of pre- and postoperative physical therapy before and after Total Hip and Total Knee surgery.

Methods: To 1005 patients in 4 hospitals who received Total Hip and Knee in 2011 were sent a survey in 2012 regarding physical therapy (referral, setting, frequency, duration, content and satisfaction) before and after surgery, sociodemographic characteristics and health status.

Results: 522 patients (282 Total Hip en 240 Total Knee) responded (52%). 210 (40%) received preoperative physical therapy and 514 (98%) postoperative physical therapy (no differences between Total Hip en Total Knee). Total knee patients had significant higher average Body Mass Index, significant more co morbidity, and significant lower level of physical functioning compared with Total Hip patients.

More patients were referred by the orthopedic surgeon after surgery (77%) than before surgery (36%) and for Total Knee than for Total Hip. The most consistently reported exercise modalities ($>$ 60% of patients) were preoperatively aerobic exercise and walking stairs, and postoperatively aerobic exercises, muscle strengthening exercises, range of motion exercises, walking stairs, rising/sitting and gait training.

Both before and after surgery significant more Total Knee patients reported receiving strengthening exercises (55% before, 65% after) and passive Range of Motion exercises (51% before, 60% after) compared to Total Hip patients (32% before, 57% after and 36% before, 37% after, respectively).

Total Hip and Knee patients who received physical therapy in secondary care before physical therapy in primary care were older and had a lower level of physical functioning compared to patients who only received physical therapy in primary care.

Total Hip and Knee patients were more satisfied with physical therapy after than before surgery.

Conclusion: A considerable number of patients received physical therapy before Total Hip and Knee surgery. There is a great variation of provided treatment modalities after, but particularly before surgery. Differences between hip and knee patients were reported by patients. These results indicates that more research into the potential benefits of physical therapy for specific groups of patients undergoing Total Hip or Knee surgery and into effective treatment modalities is needed. Distinction should be made between hip and knee patients.

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Quality Indicators For Physical Therapy Management In Hip and Knee Osteoarthritis and Rheumatoid Arthritis. Wilfred FH Peter[1], Emalie Hurkmans[2], Philip van der Wees[3], Erik Hendriks[4], Rob de Bie[4], Leti van Bodegom-Vos[1] and Theodora P.M. Vliet Vlieland[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]University of Applied Sciences, Vienna, Austria, [3]Radboud University, Nijmegen, Netherlands, [4]University of Maastricht, Maastricht, Netherlands.

Background/Purpose: Physical therapy is recommended in several guidelines on the management of osteoarthritis and rheumatoid arthritis. Currently, no specific quality indicators for physical therapy in patients with Osteoarthritis and Rheumatoid Arthritis are available. The aim of this study was to develop quality indicators for the physical therapy management of patients with Osteoarthritis and Rheumatoid Arthritis.

Methods: The first concept quality indicators were derived from the recommendations included in two recent Dutch physical therapy evidence based practice guidelines for Osteoarthritis and Rheumatoid Arthritis, according to guidelines for the development of quality indicators.

Two multidisciplinary expert group (Osteoarthritis and Rheumatoid Arthritis) of 19 persons were composed containing patients; 1 patient representative from the Dutch Arthritis association; physical therapists; general practitioners; rheumatologists; orthopaedic surgeon; rehabilitation physician; occupational therapist; and researchers. Using Delphi rounds, the expert group could suggest other topics for the set of indicators, and then scored all topics with respect to relevance (score range 0=not at all relevant to 9=extremely relevant) and feasibility of measuring. Potential topics were selected if a score of >6 was obtained by $>75\%$ of the experts regarding aspect representing good quality of physical therapy care. Indicators with scores 5 or 6 were again entered into a Delphi round and selected for the final set based on comments of the expert arguments. Selected quality indicators were then combined and reformulated by the project group.

Results: In Osteoarthritis an initial set of 23 indicators were selected. Based on relevance score >6 eleven indicators were first selected. Based on experts' comments 3 indicators were rejected, and the remaining 9 indicators were partly combined and reformulated into 6 items, resulting in a final set of 17 indicators for physical therapy in Osteoarthritis.

For physical therapy in Rheumatoid Arthritis an initial set of 27 indicators were selected. Based on relevance sore > 6 ten indicators were first selected. After comments of the experts 3 items were rejected, and 14 items were partly combined and reformulated into 7 indicators for the final set, resulting in a final set of 17 quality indicators for physical therapy in Rheumatoid Arthritis.

Both quality indicator sets containing 16 process indicators (regarding initial assessment, treatment and evaluation) and one outcome indicator.

The majority of multidisciplinary experts in Osteoarthritis and Rheumatoid Arthritis stated the final indicators were measurable, and data should preferably conducted by consulting (electronic) patient files.

Conclusion: Two sets of 17 quality indicators for physical therapy management in Osteoarthritis and Rheumatoid Arthritis were developed and made suitable to measure quality of physical therapy care in daily clinical practice. The clinimetric properties reliability and discriminative power need to be investigated in future research.

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Who Will Achieve Individually Set Goals After Arthritis Team Rehabilitation? Sofia Hagel[1], Elisabet Lindqvist[1] and Ann B. I. Bremander[2]. [1]Lund University and Skåne University Hospital, Lund, Sweden, [2]Lund University, Lund, Sweden.

Background/Purpose: To study goal achievement among patients with chronic inflammatory arthritis after arthritis rehabilitation performed in multidisciplinary team rehabilitation programs.

Methods: 146 consecutive patients with rheumatoid arthritis (RA) and spondylarthritis (SpA), age 18 years or older, completing arthritis rehabilitation for 5 days or more at 2 rheumatology specialist units were included in this study. At admission and discharge the patients were evaluated with measures on functioning (HAQ), self efficacy (ASES), psychological health (Hopkins Symptom Checklist – HSCL-25), pain and fatigue (NRS) and on health related quality of life (HRQoL) as captured by the EQ-5D and the SF-36. Comorbidity and social demographics was also reported. The patients, in cooperation with the health professionals, set individual goals for their rehabilitation period. At discharge the patients reported if the goal was achieved completely, partially or not at all.

Non parametric statistical analyses were performed and Chi2 and Kruskal-Wallis analyses were used to study the relationship between goal achievement and baseline and change variables.

Results: 108/146 patients reported whether goals were achieved or not, and were included in further analyses. 76% were females and 55% had RA. At baseline median age was 54 years (IQR 17), median HAQ 0.88 (IQR 0.88), median HRQoL as captured by the EQ-5D 0.62 (IQR 0.57) and median psychological wellbeing according to HSCL-25 1.62 (IQR 0.68). The patients reported median fatigue 6.0 (IQR 4.0) and median pain 5.0 (IQR 3.0) when entering the rehabilitation program that lasted for median 18 days (IQR 2).

58/108 patients (54%) rated their goal to be completely achieved, 40 patients (37%) reported partial goal achievement while 10 (9%) patients had not achieved their goal. Positive reporting of having followed the recommendations (compliance) during the rehabilitation period was obtained from 100 (93%) of the patients.

Change after intervention and compliance did not affect reports of goal achievement after rehabilitation. Females reported goal achievement more often than men did ($p=0.019$). Those not achieving their goals reported less psychological wellbeing (HSCL-25, $p=0.011$) at admission together with reports of worse pain (SF-36bp, $p=0.011$).

Conclusion: 54% of the included patients reported complete goal achievement after arthritis team rehabilitation. Neither change after intervention nor compliance affected patients' reports of goal achievement. Female patients were more prone to achieve their goals while patients experiencing less psychological wellbeing or more pain at baseline were less prone to report goal achievement.

Disclosure: S. Hagel, None; **E. Lindqvist**, None; **A. B. I. Bremander**, None.

2111

The Impact Of Centralized Pain On Long-Term Analgesic Response To Lower Extremity Joint Arthroplasty: A Prospective, Observational Cohort Study. Chad M. Brummett[1], Andrew Urquhart[2], Brian Hallstrom[2], Alex Tsodikov[3], David A. Williams[4] and Daniel J. Clauw[5]. [1]University of Michigan Medical School, Ann Arbor, MI, [2]University of Michigan Health System, Ann Arbor, MI, [3]School of Public Health, University of Michigan, Ann Arbor, MI, [4]Univ of MI Hlth System-Lobby M, Ann Arbor, MI, [5]University of Michigan, Ann Arbor, MI.

Background/Purpose: In cross-sectional studies, depression and pain in other locations have been reported as predicting poorer outcomes following total knee and hip arthroplasty. These factors may be better explained by a common pathophysiology of aberrant central pain processing as is seen in conditions like fibromyalgia. We hypothesized that patients with altered central pain processing would be less likely to report pain improvement after lower extremity joint arthroplasty.

Methods: Patients were preoperatively phenotyped using validated self-reported, including the Brief Pain Inventory, PainDETECT, WOMAC, Hospital Anxiety and Depression Scale, Catastrophizing, health information (opioid use, ASA Status, BMI, primary anesthetic), and demographics. Participants also completed the American College of Rheumatology (ACR) survey criteria for fibromyalgia as a surrogate of centralized pain, which is a measure of widespread pain and an assessment of symptoms such as fatigue or trouble thinking. Patients were re-assessed using the same preoperative phenotype at 6-months postoperatively. Data were analyzed using R 2.15.2. A linear model was used to regress the change in pain responses at surgical site and overall on a set of covariates including the baseline pain value.

Results: 598 of the 851 patients approached agreed to participate (70.3%). A total of 454 patients completed the 6-month outcome follow-up (75.9%) and were included in the outcome analyses. Preoperatively, patients with higher fibromyalgia survey scores were significantly younger, more likely to be female, less educated, more likely to be on disability or unemployed, and more likely to be taking preoperative opioids ($p < 0.05$ for each comparison). Patients with higher scores on the fibromyalgia survey also reported higher pain severity overall and at the surgical site, higher WOMAC scores, and had a more negative psychological profile ($p < 0.0001$ for each comparison). When adjusting for other covariates, patients with higher preoperative pain and educational status showed more improvement in overall pain (Table 1). Higher fibromyalgia survey scores, higher BMI, use of opioids preoperatively, and African American race were independently predictive of less improvement in pain overall. Similar results were obtained when regressing for the change in surgical site pain.

Table 1. Regression model for 6-month change in overall body pain.

	Estimate (regression coefficient)	SE	p-value
(Intercept)	−0.078	0.54	0.88
Pain in Surgical Site	0.93	0.044	<0.00001
Advanced education	−0.59	0.26	0.021
Fibromyalgia Survey Score	0.14	0.02	<0.00001
African American race	1.48	0.55	0.0087
Body Mass Index	0.029	0.015	0.045
Preoperative use of opioids	0.49	0.19	0.012

The composite score of the pain severity questions for the BPI were used to assess the change in overall body pain from baseline to 6-mo after surgery. Independent predictors of outcome are noted in the table. Covariates with a negative estimated indicate a reduction or improvement in pain overtime, while covariates associated with poor outcomes have a positive estimate. In addition to previously described predictors of arthorplasty outcome, the fibromyalgia survey score (measure of cantralised pain) independently predicted poorer outcomes in pain with a 0.14 decrease in change in pain (0–10 scale) for every 1 point increase on the fibromyalgia survey measure (0–31 scale). SE = standard error.

Conclusion: In this large, prospective, observational cohort study, the ACR survey criteria for fibromyalgia differentiated patients preoperatively and was independently predictive of poorer long-term outcomes when

assessing both the change in the surgical site and overall body pain. Altered central pain processing may explain some of the variance in outcomes previously described in lower extremity joint arthroplasty. This simple, validated, self-report measure may add value in selecting appropriate candidates for arthroplasty.

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Hip and Knee Arthroplasty In Patients With Rheumatoid Arthritis: Results From The Australian Orthopaedic Association National Joint Replacement Registry: 2003 To 2011. Andrew Lim[1], Stephen Graves[2], Yen Liu[2], Lionel Schachna[1] and Russell R. Buchanan[1]. [1]Austin Health, Melbourne, Australia, [2]Australian Orthopaedic Association National Joint Replacement Registry, Adelaide, Australia.

Background/Purpose: Total Joint Replacement in rheumatoid arthritis (RA) patients is a marker of disease severity. Whilst the rate of total hip (THA) and total knee arthroplasties (TKA) are increasing in Australia, this may not be the case for those patients with rheumatoid arthritis. Currently, there are no published data examining the rates of hip and knee joint replacement surgery, revision rates and mortality following total joint arthroplasty in rheumatoid arthritis over time in Australia. The aim of the study was to determine if the rate of THA and TKA undertaken for RA in Australia has changed since 2003. A secondary aim was to assess the outcome of both THA and TKA undertaken for RA versus Osteoarthritis (OA) during the study period.

Methods: The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) collects validated data on all THA and TKA procedures throughout Australia. Registry data include patient demographics, diagnosis, prosthesis type and features, method of fixation and surgical technique. Patient specific outcomes are determined by linking the primary procedure to any subsequent revision or death. Data collection commenced in 1999 and full national data collection was achieved in mid-2002. All hospitals in Australia that perform joint replacement surgery contribute to this registry. A Chi-Square test was used to compare the distribution of RA and OA in THA and TKA. Kaplan-Meier estimates of survivorship and Cox Proportional hazards models were used to compare revision rates and mortality.

Results: The proportion of both THA and TKA undertaken for RA decreased significantly between 2003 and 2011, THA; 1.74% vs 0.84% (chi^2=71.9, p<0.0001) and TKA; 2.38% vs 1.15% (chi^2=135.7, p< 0.0001).

There was no significant difference in the overall rate of revision for primary THA undertaken for RA and OA (HR=1.20, 95CI, 0.98–1.48, p=0.074) but revision rates were higher for dislocation in RA (HR=2.36, 95CI, 1.68–3.31, p<0.001). There is a significantly higher rate of mortality in RA following THA (HR=2.03, 95CI, 1.76–2.33, p<0.001).

There was a significantly lower rate of revision for primary TKA undertaken for RA compared to OA after 9 months (9mths-2yrs: HR=0.38, 95CI, 0.25–0.58, p<0.001, 2–2.5yrs: HR=0.27, 95CI, 0.10–0.72, p=0.009 and 2.5+yrs: HR=0.67, 95CI, 0.48–0.93, p=0.016). TKA for RA has a significantly higher rate of mortality than patients with OA in TKA (HR=2.07, 95CI, 1.84–2.32, p<0.001).

Conclusion: A reduction in the total numbers of THA and TKA in RA patients across Australia has occurred over the last 9 years. The lesser numbers may be the result of improvements in disease control but further studies are needed to clarify. Outcomes of both THA and TKA undertaken for RA appear different when compared to OA.

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Glucosamine–Chondroitin Sulfate Reduces Pain, Disability and Non-Steroidal Anti-Inflammatory Drug consumption In Patients With Chronic Low Back Pain: A Large, Community-Based, Pilot, Open Prospective Study. Gurkirpal Singh[1], Liudmila Alekseeva[2], Valeriy Alekseev[3] and Evgeny Nasonov[4]. [1]ICORE, Woodside, CA, [2]State Institute of Rheumatology of Russian Academy of Medical Sciences, Moscow, Russia, [3]First Moscow State Medical University, Moscow, Russia, [4]State NII of Rheumatology of Russian Academy of Sciences, Moscow, Russia.

Background/Purpose: The Global Burden of Diseases, Injuries, and Risk Factors Study 2010 identified low back pain as the leading cause of Years Lived with Disability (YLD) worldwide. In 2010, low back pain (LBP) accounted for over 83 million YLDs, and was the number one cause of YLD in all developed countries in the world (1). LBP continues to create diagnostic and therapeutic challenges due to its unclear etiology and multiple interventions of uncertain efficacy. Significant proportion of LBP may be attributed to osteoarthritis (OA) and degenerative changes in the spine (2). Glucosamine-chondroitin sulfate (GCS) combination is widely used in the treatment of OA, despite conflicting evidence of its efficacy; however there are few prospective scientific investigations of its therapeutic merits in the management of LBP.

Objective: To study the efficacy and safety of GCS in the community management of LBP in a large-scale open pilot prospective observational study.

Methods: We enrolled patients between 40 and 65 years of age who had LBP for at least 12 weeks with a pain intensity >3 on a 0–10 point visual analogue scale (VAS). Major exclusion criteria were the presence of fibromyalgia, degenerative spondylolisthesis, and alcohol and/or drug abuse. All patients were treated with ARTRA (combination of glucosamine hydrochloride 500 mg and chondroitin sulfate 500 mg in tablet form; Unipharm Inc.) at a dose of 1 tab bid for the first month and then 1 tab daily for the next two months. The primary endpoint was pain intensity (at rest and movement) as measured on a 0–10 point VAS. Secondary endpoints included the Oswestry Disability Index, patient global assessment of efficacy (0–5 scale) and NSAID consumption.

Results: We present results from a planned interim analysis of the study in the first 2,344 patients (mean age 52.1 years, 67% women). Patients reported an improvement in pain at rest from mean (+ SD) of 5.2 + 2.6 at study entry to 1.4+1.6 at 3 months (p<0.01). Pain at movement decreased from 6.7+1.7 to 2.3 +1.8 (p<0.01). The Oswestry disability index improved by almost 75%, from 20.8+9.4 to 5.7+6.3 (p<0.01) at 3 months. NSAIDs were used by 63.5% of patients at study entry; at 3 months of treatment, only 6.7% of patients required NSAIDs for pain control. An adverse event (AE) was reported by 156 (6.7%) patients (mostly gastrointestinal in origin, such as nausea, abdominal pain and dry mouth) but only 2 patients deemed the AE to be severe enough to discontinue therapy.

Conclusion: Although open and uncontrolled, this pilot, community-based efficacy and safety study shows dramatic reductions in pain and disability, and in particular, a 90% reduction in NSAID consumption in patients with LBP treated with GCS. With its benign safety profile, GCS therapy deserves serious evaluation in the management of LBP in a prospective randomized double-blinded clinical trial.

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2114

Hip Fracture Risk Factors To One Year and In-Hospital Mortality, a Prospective Cohort In South Brazil. Tiango Aguiar Ribeiro[1], Melissa Orlandin Premaor[1], João Alberto Larangeira[1], Michel Luft[1], Luiz Giulian Brito[1], Leonardo Waihrich Guterres[1] and Odirlei Andre Monticielo[2]. [1]Federal University of Santa Maria (UFSM), Santa Maria, Brazil, [2]Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

Background/Purpose: Hip fractures is considered one of the most common and serious injury in the elderly life and have been associated with increased morbidity and mortality. Several risk factors are associated with these elevated rates of mortality, such as the surgical delay, ASA score, type of fracture, gender and comorbidities. The aim of this study was to define risk factors for death one year after hip fracture and in-hospital stay in a public university hospital.

Methods: The study design was a prospective cohort study from April 2005 to April 2011 and it was realized in a tertiary public university hospital. Subjects were followed since the admission until hospital discharge and an appointment was scheduled in one year time. ASA score, gender, fracture type, comorbidities, date of birth, date of admission to

hospital and discharge were collected. The statistic analyze was performed using SPSS 18.0. To attribute one year mortality risk factors a Cox's Regression analyze was performed and to define in-hospital mortality risk factors a Logistic Regression was used. Significant findings was considered those with a p-value=0.05. The survival time was analyzed by Kaplan Meier curves and Long-Rank test was made to identify differences between gender groups, ASA groups and fracture type groups.

Results: 450 patients were initially included on this study. 7.1% lost their follow up. 418 subjects were included in final analysis. Of whom, 4.3% have died in-hospital and 15.3% died at one year time. Female gender represents 76.1% (318) and male corresponds to 23.9% (100). The mean age of patients was 79.82±7.26 years. The mean of time to surgery was 7.1±5.4 days with an IQR (Interquartile Range) from 3–9 days. In-hospital stay mean time was 12.2±11.5 days with and IQR from 6–14 days. The variables that were significant in the univariate Cox's analyze were time to surgery, ASA score, Ischemic Heart Disease and in-hospital stay. The risk factors to one year mortality were ASA scores and time to surgery. In the Logistic Regression the in hospital death risk factors were ASA score and age. The overall survival time was 330.3±4.6 SE days (Standard Error). Differences in the survival time was observed in ASA groups (between ASA group 1 – ASA I to II – and ASA group 2 – ASA III to V).

Conclusion: ASA score is a useful tool to evaluate the clinical status of patient and to reduce in-hospital and one year mortality. Moreover, surgical delay is a risk factor that has potential to be modified.

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Social Networks and Hip Replacement Outcomes In Rheumatoid Arthritis and Osteoarthritis. Danielle Ramsden-Stein, Wei-Ti Huang, Rebecca Zhu, Susan M. Goodman, Mark P. Figgie, Michael Alexiades and Lisa A. Mandl. Hospital for Special Surgery, New York, NY.

Background/Purpose: Social isolation is an independent risk factor for poor health outcomes. It is unknown if the degree of social isolation differs between RA and OA patients after total hip replacement (THR), or if social isolation is associated with poorer outcomes. This study evaluates the association between social isolation, measured by the Berkman-Syme Social Network Index, and post-operative pain and function in RA and OA patients who have undergone THR.

Methods: Primary and revision RA and OA THR patients enrolled in a large volume, single center arthroplasty registry from May 2007-February 2011 and were alive at follow-up were eligible to participate. RA cases were validated via chart review and were matched 3:1 to OA cases on age (+/− 5 years), sex, procedure type (primary or revision) and year of surgery, to control for both expected differences between patient populations and time since surgery. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) and demographic information were collected pre-operatively and between 2 and 5 years post-operatively. In addition, the Berkman-Syme Social Network Index (BSSNI) was administered between 2 and 5 years post-operatively. The BSSNI was divided into four categories, with the most isolated category being the referent group.

Results: 132/223 (59.2%) RA and 392/561 OA (69.8%) responded. Demographics were similar in both groups (Table 1). RA and OA had similar proportions of very socially isolated patients. Overall, the most socially isolated patients had worse postoperative WOMAC pain (p-value=0.013) and WOMAC function (p-value= 0.0025). This relationship was statistically significant for OA patients, (WOMAC pain p-value=0.0029 and WOMAC function p-value= 0.048), and showed similar trends but was not statistically significant in RA patients. In a multivariate regression controlling for disease (OA vs. RA), education, race, and SF-36 Physical Component Score (PCS), being socially isolated was independently associated with poor (WOMAC < 60) post-op pain, (OR 2.9; 95% CI 1.07–7.25, p-value=0.04) but not poor post-op function, (OR 2.1; 95% CI 0.77–5.52; p-value=0.15). This model also showed that RA was statistically significantly associated with poor post-op function (OR 3.2, 95% CI 1.57–6.52, p-value=0.001), but not with poor post-op pain (OR 1.92; 95% CI 0.86–4.28, p-value=0.11).

Table 1.

	RA N = 132			OA N = 392		
	Very Socially isolated n = 11	Socially integrated N = 121	p-value	Very Socially isolated n = 34	Socially integrated N = 358	p-value
Age-years (SD)	66.1 (16.2)	62.8 (14.2)	0.47	59.3 (14.6)	62.8 (12.4)	0.12
Female (%)	9 (82%)	94 (78%)	0.79	25 (74%)	275 (77%)	0.67
White (%)	7 (64%)	96 (79%)	0.23	31 (91%)	329 (92%)	0.88
Education (%) (Some college or above)	6 (86%)	72 (81%)	0.75	30 (88%)	320 (90%)	0.76
BMI (SD)	24.2 (3.3)	26.5 (5.7)	0.34	29.6 (7.8)	26.7 (5.6)	0.11
PCS (SD)	25.6 (4.9)	29.1 (8.5)	0.28	30.7 (9.3)	33.5 (9.4)	0.12
Revision (%)	3 (27%)	22 (18%)	0.46	8 (24%)	77 (22%)	0.78
Pre-Operative WOMAC Pain (SD) Lower=worse pain	36.7 (17.5)	48.2 (21.3)	0.20	49.6 (22.8)	56.1 (20.3)	0.09
Post-Operative WOMAC Pain (SD) Lower=worse pain	80.0	86.32	0.34	86.9	92.8	**0.013**
Poor Post-Operative Pain (WOMAC <60) (%)	2 (20%)	17 (16%)	0.72	5 (15%)	17 (5%)	**0.016**
Pre-Operative WOMAC Function (SD) Lower=worse function	37.7 (8.5)	41.0 (20.4)	0.72	49.5 (19.8)	52.4 (20.3)	0.51
Post-Operative WOMAC Function (SD) Lower=worse function	69.7	78.49	0.24	81.64	90.16	**0.0021**
Poor Post-Operative Function (WOMAC <60) (%)	3 (30%)	26 (24%)	0.69	5 (15%)	18 (5%)	**0.02**

Conclusion: Being socially isolated is associated with an almost 3x increased odds of poor pain after THR, controlling for multiple potential confounders. Furthermore, social isolation appears to be more significant in OA, which comprises the vast majority of THR cases. Further prospective studies should be done to evaluate whether interventions to improve social networks can improve pain after THR.

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Diabetes: A Risk Factor For Poor Function Outcome After Total Knee Arthroplasty. Jasvinder A. Singh[1] and David Lewallen[2]. [1]University of Alabama, Tuscaloosa, AL, [2]Mayo Clinic College of Medicine, Rochester, MN.

Background/Purpose: Previous studies have not provided any conclusive evidence whether patients with diabetes have worse patient-reported outcomes after joint replacement than patients without diabetes. Our objective was to assess the association of diabetes with postoperative limitation of activities of daily living (ADLs) after primary total knee arthroplasty (TKA).

Methods: We used the prospectively collected data from the Mayo Clinic Total Joint Registry to assess the association of diabetes and diabetes with complications with moderate-severe ADL limitation 2- and 5-years after primary TKA. Multivariable logistic regression with general estimating equations adjusted for preoperative ADL limitation, comorbidity and demographic and clinical covariates. Odds ratio (OR) and 95% confidence interval (CI) are presented.

Results: 7,139 primary TKAs at 2-years and 4,234 at 5-years constituted the cohorts. In multivariable-adjusted analyses, diabetes was associated with higher odds of moderate-severe limitation at 2- and 5-years, 1.71 (95% CI: 1.26, 2.32; P=0.001) and 1.66 (95% CI: 1.13, 2.46; P=0.01). Respective ORs for patients with diabetes with complications were 2.73 (95% CI: 1.47, 5.07; P=0.001) and 2.73 (95% CI: 1.21, 6.15; P=0.016). Sensitivity analyses that adjusted for anxiety and depression or anxiety, depression and ipsilateral hip involvement showed minimal attenuation of magnitude of the association.

Conclusion: In this large study of patients who underwent primary TKA, diabetes as well as its severity were independently associated with poorer functional outcome. Given the increasing rates of both diabetes as well as arthroplasty, more insight is needed into disease-related and treatment-related factors that underlie this higher risk of ADL limitation in diabetics. Poor functional outcomes may be preventable by modifying the control of diabetes and associated comorbidity in pre- and post-arthroplasty periods.

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The Effect Of Statin Therapy On Venous Thromboembolism After Hip Or Knee Arthroplasty. Anne R. Bass[1], Yuo-Yu Lee[2], Stephen Lyman[2], Geoffrey H. Westrich[2] and Brian F. Gage[3]. [1]Hospital for Special Surgery Weill Cornell Medical College, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]Washington University School of Medicine in St. Louis, St. Louis, MO.

Background/Purpose: Patients undergoing hip and knee arthroplasty are at high risk of venous thromboembolism (VTE). HMG Co-A reductases ("statins") can reduce the risk of post-operative cardiovascular complications in some populations undergoing cardiac or non-cardiac surgery, and may reduce the risk of venous thromboembolism (VTE) in healthy adults. We used the Hospital for Special Surgery Legacy Registry (HSS Registry) to determine whether statins protect against VTE after arthroplasty.

Methods: Of the 20,764 patients in the HSS Registry who underwent hip or knee arthroplasty between July 1, 2007 and December 31, 2011, 16183 returned 6-month questionnaires. VTE was identified using hospital discharge ICD-9 codes and self report on 6-month questionnaires. Self-reports of VTE were validated through a structured telephone interview. Among the patients who returned 6-month questionnaires, 230 patients (1.4%) experienced VTE postoperatively (76 pulmonary embolism (PE), 173 deep vein thrombosis (DVT), 19 both). We performed logistic regression to determine the risk of postoperative VTE in patients taking statins.

Results: Forty percent of patients in the HSS Registry were on statins. Compared to patients not on statins, patients on statins were older (68.9 vs 63 years), heavier (BMI 29.6 vs 28.3) and more commonly male (49.2% vs 38.5%). More patients on statins underwent knee (as opposed to hip) arthroplasty (52.4% vs 42.9%) and fewer underwent bilateral arthroplasty (6.5% vs 9.4%). Patients on statins had a longer length of stay (5.0 vs 4.9 days) and were more commonly discharged to a rehabilitation center (46.9% vs 37.9%). More patients on statins had coronary artery disease (22.5% vs 4.2%), congestive heart failure (1.5% vs 0.7%), and diabetes (15% vs 5.7%) while fewer had rheumatoid arthritis (2.75% vs 4.1%). More patients on statins received warfarin rather than aspirin as VTE prophylaxis (61.8% vs 50.6%). These differences were all significant, $p<0.001$. In logistic regression analysis statins were associated with a lower rate of PE (OR 0.6, 95% CI 0.4–0.98) but not DVT (OR 1.3, 95% CI 0.9–1.7) or total VTE (OR 0.97, 95% CI 0.7–1.3).

Conclusion: In this observational cohort, statins protected against PE but not total VTE following hip or knee arthroplasty. Given significant differences in the characteristics of patients on statins and those not on statins, a prospective randomized controlled trial is needed to determine whether statins protect these patients from VTE.

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Pregnancy Does Not Adversely Affect Post-Operative Pain and Function In Women With Total Hip Arthroplasty. Lindsay Lally, Lisa A. Mandl, Rebecca Zhu, Wei-Ti Huang, Mark P. Figgie, Michael Alexiades and Susan M. Goodman. Hospital for Special Surgery, New York, NY.

Background/Purpose: Women of childbearing age undergo total hip arthroplasty (THA), yet little is known about effect of pregnancy on THA. We compared patients with a post-THA pregnancy to those with a pregnancy pre-THA or nulliparous.

Methods: Women ages 18–45 enrolled in an arthroplasty registry between 5/1/07 and 12/31/11 were identified. Information about the first pregnancy post-THA and the last pregnancy pre- THA was queried for demographics, WOMAC, and the HSS Expectations Score. 3 groups: nulliparous, pregnancy pre-THA, pregnancy post-THA.

Results: 325 eligible women identified; 171 (52.6%) responded, no significant differences between responders and non-responders. 79 women (46.2%) were never pregnant, 82 (47.4%) had pregnancy pre-THA and 10 (6.4%) had a completed pregnancy post-THA. Women with pregnancy pre-THA were older (40.7 years SD 4.3) than post-THA, (37.2 years SD 4.2) or nulliparous, (35.0 years SD 7.9) p -value<0.001. THA were performed for hip dysplasia (28.1%), osteoarthritis (26.3%), inflammatory arthritis (24.0%), osteonecrosis (15.2%), fracture (5.8%) and other (1.1%). There was no difference in race, education, BMI, or reason for THA. Time between delivery and THA: 85.3 months (SD 66.1) for pre-pregnancy THA; 25.6 months (SD 7.9) for post-THA pregnancy. There were no differences in birth weight, parity, weight gain, or pregnancy complications. There was no difference in delivery; vaginal (64% vs. 88% p-value=0.58), Cesarean (25% vs. 3% p-value=0.58). There were no significant differences in pre-operative or post-THA WOMAC, Expectations or satisfaction (p-value=0.61). There were no differences for groin, back or knee pain during pregnancy. 90% reported "great" or "more improvement than I ever dreamed" in quality of life after THA.

	No pregnancy (N=79)	Pregnancy pre THA (N=82)	Pregnancy post THA (N=10)	P value
Age, yr (SD)	35.0 (7.9)	40.7 (4.3)	37.2 (4.2)	<0.001
Race, n (%)				0.35
Caucasian	63 (81)	69 (85)	9 (90)	
Hispanic, n (%)	12 (16)	6 (8)	1 (10)	0.29
Education level, n (%)				0.83
High school graduate	4 (6)	4 (6)	2 (25)	
College graduate	28 (42)	28 (41)	3 (38)	
Masters/professional degree	22 (33)	25 (36)	2 (25)	
Reason for THA surgery, n (%)				0.17
Inflammatory arthritis	24 (30)	12 (15)	4 (40)	
Osteoarthritis	18 (23)	24 (30)	3 (30)	
Fracture	4 (5)	4 (5)	1 (10)	
Congenital hip dysplasia	21 (27)	25 (31)	2 (20)	
Osteonecrosis	10 (13)	16 (20)	0	
Other	2 (2)	0	0	
Deyo comorbidity				0.69
0	61 (78)	66 (84)	5 (83)	
1–2	17 (22)	13 (16)	1 (17)	
WOMAC pre-THA				
Pain, mean (SD)	50.5 (20.2)	50.4 (18.0)	60.0 (15.8)	0.61
Function, mean (SD)	48.9 (20.3)	51.7 (18.3)	54.7 (15.8)	0.63
Expectation score, mean (SD)	81.1 (14.7)	86.5 (12.9)	86.8 (12.8)	0.13
WOMAC post-THA				
Pain, mean (SD)	85.2 (18.8)	84.9 (15.8)	92.5 (5.9)	0.4
Function, mean (SD)	87.6 (22.1)	91.1 (15.3)	93.5 (6.4)	0.39
Overall THA satisfaction				0.62
Very satisfied, n (%)	40 (87)	70 (86)	9 (90)	
Very dissatisfied, n (%)	0	1 (1)	0	
Pregnancy				
Age at pregnancy, yr (SD)		40.7 (4.3)	37.2 (4.2)	0.06
Weight gain, lbs (SD)		35.1 (19.2)	30.1 (13.6)	0.48
Uncomplicated delivery, n (%)		62 (78)	8 (89)	0.46
Vaginal delivery, n (%)		52 (64)	7 (88)	0.58
Elective Cesarean, n (%)		20 (25)	1 (13)	0.58
Unanticipated Cesarean, n (%)		7 (9)	0	0.58
Singletons		77 (95)	9 (90)	0.51
Twins		4 (5%)	1 (10)	0.51
Weight of baby, lbs (SD)		7.5 (1.5)	7.3 (0.6)	0.8
Back pain, n (%)		36 (45)	5 (56)	0.55
Groin pain, n (%)		17 (22)	1 (11)	0.46
Knee pain, n (%)		11 (14)	2 (22)	0.52
Parity at time of survey response				0.34
1, n (%)		29 (35)	4 (44)	
2, n (%)		31 (38)	4 (44)	
3, n (%)		19 (23)	0	
>3, n (%)		3 (4)	1 (11)	

WOMAC scale: 1–100; higher is better

Conclusion: There were no differences in post-operative pain, function or quality of life between women with post-THA pregnancy, pre-THA pregnancy, or nulliparous women, and no differences in pregnancy outcomes or complications. Pregnancy following THA had no adverse effects on pain or function.

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Higher Mortality In Males Compared To Females Undergoing Total Knee Or Total Hip Arthroplasty: A Study Of National Time Trends, 2003–2010. Jasvinder A. Singh[1] and Rekha Ramachandaran[2]. [1]University of Alabama, Tuscaloosa, AL, [2]University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: To assess the time-trends in gender differences in mortality after primary total knee and total hip arthroplasty (TKA and THA) by rural or urban residence.

Methods: We used the Nationwide Inpatient Sample (NIS) data from 1998 to 2010 to examine time-trends by gender in TKA and THA. Rates were calculated for the U.S. population.

Results: Mortality rates were higher in males compared to females through the study period. In 2003, mortality rates in rural females, rural males, urban females and urban males after primary TKA were: 115, 279, 140 and 230 per 100,000, respectively. Respective numbers for primary THA were: 326, 346, 360 and 168. In 2010, similar differences were seen by gender in both rural and urban dwelling females and males: (1) urban: 70, 92, 29 and 131; and (2) rural 145, 154, 94, 211, respectively. In all cohorts, a significant reduction in mortality was noted. The rate of reduction of mortality over time was most noticeable in rural-dwelling women among all groups.

Table 1. Mortality per 100,000 by gender in rural/urban residents

	Urban Residence			
	THA		TKA	
	Female	Male	Female	Male
2003	115.3	278.7	326.2	345.8
2004	104.7	199.0	251.6	238.3
2005	81.8	144.5	212.4	209.2
2006	76.1	153.6	171.6	213.5
2007	66.2	114.8	157.1	237.6
2008	82.3	123.2	173.1	173.0
2009	60.0	85.8	152.3	171.0
2010	69.5	92.1	144.8	154.2
	Rural residence			
	THA		TKA	
	Female	Male	Female	Male
2003	139.7	230.1	360.1	167.6
2004	119.8	144.3	462.2	307.7
2005	151.5	138.7	189.9	357.5
2006	79.3	161.1	199.7	239.1
2007	63.9	107.1	268.8	244.4
2008	51.4	115.1	273.4	259.7
2009	51.7	136.6	183.3	169.2
2010	28.8	131.4	94.4	211.3

Conclusion: The mortality rates following primary TKA and THA has decreased significantly over the last 7 years from 2003 to 2010. Mortality is higher in males compared to females, a difference that has not changed over time. More insights are need into understanding what factors contribute to lower mortality in females.

Disclosure: J. A. Singh, Takeda, Savient, 2, Savient, Takeda, Ardea, Regeneron, Allergan, 5, URL pharmaceuicals Novartis, 5; **R. Ramachandaran**, None.

2120

Total Knee Replacement Outcomes In Patients With Psoriatic Arthritis, Osteoarthritis With Cutaneous Psoriasis, and Osteoarthritis. Lisa A. Mandl, Rebecca Zhu, Wei-Ti Huang, Michael Alexiades, Mark P. Figgie and Susan M. Goodman. Hospital for Special Surgery, New York, NY.

Background/Purpose: Outcomes of total knee replacements (TKR) in psoriatic arthritis (PsA) are poorly studied. Previous studies are conflicting, often not separating inflammatory PsA from osteoarthritis (OA) with cutaneous psoriasis (PsC). This study evaluates TKR outcomes in PsA compared to both PsC+OA and OA alone.

Methods: This study utilized cases from a high volume single institution TKR registry enrolled between 5/2007 and 12/2011. Potential PsA cases were identified by ICD-9 code (696.0-.1) and matched 4:1 (on age (+/− 2.5 years), primary vs. revision and date of surgery) with OA TKR. TKR with other rheumatic diseases or fractures were excluded. Patient reported outcomes were collected at baseline and 2 years; non-responders received an additional questionnaire at 3–5 years. Differences between groups were compared using ANOVA, and multivariate logistic regressions were performed to identify independent predictors of poor post-operative pain and function, (WOMAC < 60).

Results: 253 potential PsA were identified; 76 PsA and 155 PsC+OA were validated by chart review. Post-op. self-report data were available in 76% PsA, 74% PsC+OA and 65% OA. 2% of self-reported outcomes were elicited 3–5 years post-op. PsA were younger than PsC+OA or OA, (p-value=0.009). PsA and PsC+OA had more co-morbidities and worse ASA class. More PsA and PsC+OA were previous smokers, more PsC+OA were current smokers. 71% of PsA were on biologics or non-biologic DMARDs compared to 5% of PsC+OA. There was no statistically significant difference in pre-or post-op WOMAC pain, WOMAC function or SF-12 physical component scores (PCS) scores between groups. Post-op. SF-12 mental component scores (MCS) scores were worse in PsA and PsC+OA (p-values=0.04). EQ-5D scores were worse both pre- and post-op. in PsA. Overall satisfaction with TKA was equally high for all groups, with > 70% being very satisfied (p-value=0.66). In a multivariate regression controlling for multiple potential cofounders, a diagnosis of PsA or PsC+OA did not statistically significantly increase the odds of either poor post-op. pain or function. Primary TKR had much lower odds of poor post-op pain or function, and worse pre-op. function was statistically significantly associated with poor post-op. function. No other variables were significant.

Table 1. Demographic Data

	PsA (N=76)	PsC+OA (N=155)	OA (N=547)*	P-Value
Age, years (SD)	63.5 (10.5)	67.5 (9.7)	67.0 (9.7)	**0.009**
BMI (SD)	29.5 (5.2)	30.5 (6.1)	29.8 (7.5)	0.48
Male, n (%)	35 (46%)	68 (44%)	199 (36%)	0.09
Caucasian, n (%)	72 (95%)	150 (97%)	488 (89%)	**0.007**
≥College Education, n (%)	30 (71%)	60 (67%)	308 (64%)	0.59
Pre-operative WOMAC Pain (SD)	54.3 (18.6)	54.7 (16.0)	55.4 (17.2)	0.89
Post-operative WOMAC Pain (SD)	86.8 (16.1)	88.0 (16.2)	87.6 (15.8)	0.91
Pre-operative WOMAC Function (SD)	50.9 (14.4)	55.4 (15.0)	55.7 (17.5)	0.31
Post-operative WOMAC Function (SD)	84.0 (17.2)	85.7 (19.3)	86.2 (15.8)	0.68
Pre-operative SF-12 PCS (SD)	43.7 (10.3)	45.4 (9.4)	45.7 (9.8)	0.69
Post-operative SF-12 PCS (SD)	43.0 (10.6)	46.3 (9.9)	46.4 (9.9)	0.07
Pre-operative SF-12 MCS (SD)	52.0 (9.2)	48.2 (11.1)	53.1 (9.1)	0.09
Post-operative SF-12 MCS (SD)	51.8 (9.5)	51.9 (9.5)	54.1 (8.7)	**0.04**
Pre-operative EQ-5D Score (SD)	0.6 (0.2)	0.6 (0.2)	0.7 (0.2)	**0.008**
Post-operative EQ-5D Score (SD)	0.7 (0.2)	0.8 (0.2)	0.8 (0.2)	**<0.001**
ASA Class, n (%)				**0.02**
Class 1	0 (0%)	1 (1%)	16 (3%)	
Class 2	52 (68%)	126 (81%)	426 (78%)	
Class 3/4	24 (32%)	28 (18%)	105 (19%)	
Deyo comorbidities, n (%)				**<0.001**
0 comorbidities	38 (50%)	109 (71%)	401 (74%)	
1–2 comorbidities	36 (47%)	40 (26%)	134 (25%)	
3+ comorbidities	2 (3%)	5 (3%)	10 (2%)	
Do you currently smoke?, n (%)			**<0.001**	
Yes	0 (0%)	6 (8%)	9 (2%)	
No, but I smoked previously	25 (57%)	50 (66%)	268 (50%)	
Never	19 (43%)	20 (26%)	257 (48%)	
5 (best)	18 (45%)	32 (48%)		

* 547/843 cases were available for analysis.

Table 2. Predictors of Having Poor Post-Operative Pain or Function (WOMAC <60) After THR*

	Poor Post-Operative Pain WOMAC (<60) Odds Ratio (95% CI)	Poor Post-Operative Function WOMAC (<60) Odds Ratio (95% CI)
PsC+OA vs. OA	0.64 (0.08, 5.24)	1.11 (0.23, 5.54)
PsA vs. OA	0.88 (0.18, 4.26)	0.37 (0.05, 3.07)
Primary vs. Revision	**0.32 (0.11, 0.99)**	**0.20 (0.07, 0.56)**
Pre-operative WOMAC Pain	0.997 (0.96, 1.03)	1.01 (0.98, 1.05)
Pre-operative WOMAC Function	0.98 (0.94, 1.01)	**0.96 (0.93, 0.998)**

*Multivariate regression controlling for gender, diagnosis, BMI, number of comorbidities, primary vs. revision surgery, smoker status, pre-operative WOMAC pain and function, pre-operative MCS.

Conclusion: Despite having worse pre-op. health status, patients with PsA and PsC+OA have equally good post-op. pain and function compared

with OA, and are equally satisfied. PsA have clinically significantly worse post-op. MCS. This information should be communicated to PsA and PsC+OA patients contemplating TKR.

Disclosure: L. A. Mandl, None; **R. Zhu**, None; **W. T. Huang**, None; **M. Alexiades**, None; **M. P. Figgie**, Mekanika, 1, Ethicon, 2; **S. M. Goodman**, None.

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Total Hip Arthroplasty Outcomes In Patients With Psoriatic Arthritis, Osteoarthritis With Cutaneous Psoriasis, and Osteoarthritis. Lisa A. Mandl, Rebecca Zhu, Wei-Ti Huang, Michael Alexiades, Mark P. Figgie and Susan M. Goodman. Hospital for Special Surgery, New York, NY.

Background/Purpose: Outcomes of total hip replacements (THR) in psoriatic arthritis (PsA) are poorly studied. Previous studies are conflicting, often not separating inflammatory PsA from osteoarthritis (OA) with cutaneous psoriasis (PsC). This study evaluates THR outcomes in PsA compared to both PsC+OA and OA alone.

Methods: This study utilized cases from a high volume single institution THR registry enrolled between 5/2007 and 12/2011. Potential PsA cases were identified by ICD-9 code (696.0-.1) and matched 4:1 (on age, primary vs. revision and date of surgery) with OA THR. THR with other rheumatic disease or fractures were excluded. Patient reported outcomes were collected at baseline and 2 years; non-responders received an additional questionnaire at 3–5 years. Differences between groups were compared using ANOVA, and multivariate logistic regressions were performed to identify independent predictors of poor post-op pain and function, (WOMAC < 60). This study was IRB approved.

Results: 289 potential PsA were identified; 69 PsA and 167 PsC+OA were validated by chart review. Post-op self-report data were available in 64% PsA, 63% PsC+OA and 83% OA. 4% of self-reported outcomes were elicited 3–5 years post-op. There was no difference in race, age or education between groups. PsA and PsC+OA had more co-morbidities (0 Deyo co-morbidities: PsA 61% vs. PsC+OA 68% vs. OA 80%; p-value=0.004) and worse ASA class. More PsA and PsC+OA were current or previous smokers. 87% of PsA were on biologics or non-biologic DMARDs compared to 7% of PsC+OA. There was no statistically significant difference in pre-or post-op WOMAC pain or function or SF-12 PCS scores between groups. SF-12 MCS scores were higher in OA both pre-and post-operatively (p-values=0.003 and <0.001 respectively). EQ-5D scores were worse both pre-and post-operatively in PsA and PsC+OA (p-value=0.006 and p-value<0.001). Overall satisfaction with THA was equally high for all groups, with > 80% being very satisfied (p-value=0.82). In multivariate logistic regressions, (Table 2), a diagnosis of PsA or PsC+OA did not statistically significantly increase the odds of either poor post-op pain or function. Revision THR had much higher odds of poor post-op pain, and worse pre-op pain and function were statistically associated with poor post-op pain and function, respectively. Current smoking has >3x increased odds of poor post-op pain and function.

Table 1. Demographic Data

	PsA (N=69)	PsC+OA (N=167)	OA (N=771*)	P-Value
Male, n (%)	36 (52%)	92 (55%)	343 (45%)	**0.035**
Age, years (SD)	60.6 (11.2)	63.6 (11.9)	63.2 (11.0)	0.14
BMI (SD)	29.6 (5.1)	29.3 (6.5)	27.6 (5.2)	**<0.001**
Caucasian, n (%)	43 (93%)	93 (98%)	715 (94%)	0.26
Pre-operative SF-12 MCS (SD)	47.9 (13.8)	46.9 (12.9)	51.2 (12.3)	**0.003**
Post-op SF-12 MCS (SD)	50.8 (10.9)	49.4 (11.6)	53.5 (9.5)	**<0.001**
Pre-operative EQ-5D (SD)	0.6 (0.2)	0.6 (0.2)	0.7 (0.2)	**0.006**
Post-op EQ-5D (SD)	0.6 (0.3)	0.7 (0.2)	0.8 (0.2)	**<0.001**
ASA Class, n (%)				**<0.001**
Class 1	0 (0%)	12 (7%)	70 (9%)	
Class 2	47 (68%)	116 (69%)	590 (77%)	
Class 3	22 (32%)	36 (22%)	110 (14%)	
Class 4	0 (0%)	3 (2%)	1 (0%)	
≥College Education, n (%)	27 (75%)	48 (72%)	559 (74%)	0.91
Pre-op WOMAC Pain (SD)	52.9 (17.0)	55.6 (17.4)	54.6 (18.6)	0.74
Post-op WOMAC Pain (SD)	84.5 (20.2)	84.6 (20.3)	83.7 (22.6)	0.92
Pre-op WOMAC Function (SD)	49.3 (17.2)	50.7 (18.8)	51.1 (19.1)	0.85
Post-op WOMAC Function (SD)	83.0 (19.9)	81.0 (21.8)	80.5 (23.7)	0.82
Do you currently smoke?				**0.005**
Yes	4 (9%)	2 (2%)	29 (4%)	
No, but I smoked previously	26 (60%)	58 (61%)	345 (46%)	
Never	13 (30%)	35 (37%)	371 (50%)	

*771/931 OA control data were available for analysis.

Table 2. Predictors of Having Poor Post-Operative Pain or Function (WOMAC <60) After THR*

	Poor Post-Operative Pain WOMAC (<60) Odds Ratio (95% CI)	Poor Post-Operative Function WOMAC (<60) Odds Ratio (95% CI)
PsC+OA vs. OA	1.00 (0.46, 2.19)	1.01 (0.49, 2.08)
PsA vs OA	0.83 (0.28, 2.43)	0.83 (0.29, 2.38)
Primary vs. Revision	**0.40 (0.19, 0.84)**	0.73 (0.35, 1.56)
Current Smoker vs Never Smoked	**3.44 (1.40, 8.49)**	**3.60 (1.47, 8.82)**
Past Smoker vs Never Smoked	1.02 (0.67, 1.55)	1.32 (0.89, 1.98)
Pre-operative WOMAC Pain	**0.95 (0.93, 0.97)**	1.01 (0.99, 1.03)
Pre-operative WOMAC Function	1.00 (0.98, 1.02)	**0.95 (0.93, 0.97)**

*Multivariate regression controlling for gender, diagnosis, BMI, ASA class, number of comorbidities, primary vs revision surgery, smoker status, pre-operative WOMAC pain and function, pre-operative MCS, Pre-operative EQ Score.

Conclusion: Despite worse pre-operative health status, PsA or PsC+OA were not independent risk factors for poor THR outcomes. These results should be communicated to PsA and PsC+OA patients contemplating THR.

Disclosure: L. A. Mandl, None; **R. Zhu**, None; **W. T. Huang**, None; **M. Alexiades**, None; **M. P. Figgie**, Mekanika, 1, Ethicon, 2; **S. M. Goodman**, None.

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Mechanical Back Pain Demonstrates Better Response To Celecoxib Than Acetaminophen Despite Lack Of MRI-Defined Inflammatory Changes In The Spine. Dinny Wallis[1], Finbar (Barry) D. O'Shea[2], David Salonen[3], Nigil Haroon[1], Ammepa Anton[4], Laura A. Passalent[1], Rebecca Morton[5], Christopher Hawke[1], Joan Blair[1] and Robert D. Inman[1]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]St James's Hospital, Dublin, Ireland, [3]University Health Network, Toronto, ON, [4]Toronto Western Research Institute, Toronto, ON, [5]University Health Network- Toronto Western Hospital, Toronto, ON.

Background/Purpose: Chronic back pain affects a significant proportion of the population. MRI-defined inflammatory lesions have been used to differentiate between axial spondyloarthritis and mechanical back pain, but the frequency of inflammatory lesions in mechanical back pain has not been ascertained. The efficacy of celecoxib in chronic, mechanical back pain and its effects on MRI inflammatory lesions have not been established.

Methods: A randomized, double-blind trial of celecoxib versus acetaminophen was conducted. Fifty two patients (52% male, mean age 40y)with back pain for at least 3 months, a total back pain score ≥4/10 and without clinical or radiographic evidence of axial spondyloarthritis were randomized to celecoxib (200mg twice daily, n=25) or acetaminophen (500mg twice daily, n=27) for four weeks. Total back pain, Oswestry Disability Index (ODI), nocturnal back pain, patient global assessment, morning stiffness, SF-36 mental component scale (MCS) and physical component scale (PCS), CRP, ESR and Spondyloarthritis Research Consortium of Canada (SPARCC) MRI index for inflammation of the sacroiliac joints (SIJ) and spine were measured at baseline and four weeks.

Results: A greater improvement was observed for celecoxib than for acetaminophen in total back pain (p=0.01), Oswestry Disability Index (p=0.003) and nocturnal back pain (p=0.01). A trend was observed for greater improvement in patient global assessment with celecoxib (p=0.07). The SPARCC MRI index was low at baseline and no change was seen over four weeks in either treatment group.

Table 1. Mean (SD) outcome measures from baseline to week 4

	Acetaminophen (n=27)				Celecoxib (n=25)				P value for change in acetaminophen group versus change in celecoxib group
	Baseline	Week 4	Mean of differences	P value	Baseline	Week 4	Mean of differences	P value	
Total back pain (0–10)	5.8 (2.1)	5.1 (2.4)	−0.7 (1.8)	0.04	6.5 (1.7)	4.2 (2.6)	−2.3 (2.6)	0.0001	0.01
ODI (0–100)	19.2 (9.1)	17.6 (10.0)	−1.6 (4.3)	0.08	20.3 (8.2)	13.1 (8.9)	−7.1 (7.8)	0.0002	0.003
Nocturnal back pain (0–10)	4.5 (2.5)	4.8 (2.8)	0.3 (2.8)	0.59	4.7 (2.3)	3.0 (2.7)	−1.7 (2.6)	0.003	0.01
Patient global (0–10)	4.6 (2.1)	4.1 (2.4)	−0.5 (1.7)	0.16	4.7 (2.8)	3.0 (2.6)	−1.7 (2.8)	0.0066	0.07
Morning stiffness (0–10)	5.0 (2.7)	4.4 (2.5)	−0.6 (1.8)	0.12	3.0 (2.8)	2.5 (2.6)	0-.6 (2.9)	0.34	-
SF-36 MCS	47.4 (9.6)	47.7 (10.2)	0.3 (6.3)	0.82	44.7 (11.6)	47.7 (12.1)	3.0 (12.2)	0.24	-
SF-36 PCS	39.0 (11.4)	41.9 (11.1)	2.8 (5.7)	0.02	39.5 (9.2)	44.1 (9.2)	4.6 (6.6)	0.0025	0.38
CRP (mg/L)	2.7 (4.4)	2.2 (4.1)	−0.5 (3.8)	0.51	2.1 (2.2)	2.1 (2.4)	0.0	>0.99	-
ESR (mm/h)	8.4 (9.5)	6.7 (7.4)	−1.7 (3.6)	0.02	5.0 (4.0)	5.3 (4.0)	0.3 (3.9)	0.71	-
MRI index SIJ (0–72)	1.6 (2.3)	1.6 (2.3)	0.1 (0.4)	0.48	0.9 (1.6)	0.9 (1.4)	−0.02 (1.06)	0.93	-
MRI index spine (0–108)	4.3 (4.8)	4.8 (5.3)	0.49 (1.44)	0.09	6.03 (4.60)	5.63	−0.41 (1.04)	0.06	-

Conclusion: To our knowledge, this is the first study to demonstrate the efficacy of celecoxib compared with acetaminophen in chronic mechanical back pain. MRI-defined inflammatory lesions were infrequent. This finding has implications for the specificity of MRI-defined inflammatory lesions in axial spondyloarthritis.

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Assessment Of Gesture Behavior and Knowledge On Low Back Pain Among Nurses. Hisa Morimoto[1], Anamaria Jones[1] and Jamil Natour[2]. [1]Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [2]Universidade Federal de São Paulo, São Paulo, Brazil.

Background/Purpose: Low back pain is a public health problem throughout the world. Particularly in the nursing profession, this condition is related to absenteeism and lawsuits. Emotional, physical and psychosocial forms of stress in the workplace are determinant factors of the onset and perpetuation of low back pain. The aim of the present study was to evaluate gesture behavior and knowledge on low back pain among nurses with and without low back pain and correlate these factors with pain, physical functioning and quality of life.

Methods: An observational, controlled, cross-sectional study was carried out involving 120 female nurses at the São Paulo Hospital (Brazil): 60 with low back pain and 60 without low back pain (control group). The two groups were matched for age. The following were the inclusion criteria for the group with back pain: actively exercising the nursing profession; age between 18 and 65 years; work performed in infirmary, emergency ward and/or intensive care unit; minimum daily workload of six hours; and self-report of low back pain on the majority of days in the previous three months with an intensity greater than 3 cm on a visual analogue scale (VAS ranging from 0 to 10 cm). The same inclusion criteria were employed for the control group, without low back pain. Individuals involved in litigation, those with a history of back surgery and pregnant women were excluded from the study. The measures used for the evaluation were the Gesture Behavior Test, Low Back Pain Knowledge Questionnaire, VAS for low back pain, Roland Morris Disability Questionnaire and the Medical Outcomes Study 36-item Short–Form Health Survey (SF-36) to assess quality of life.

Results: Mean age in both groups was 31 years. In the group with low back pain, the mean VAS score was 5.6 cm and the mean score on the Roland Morris questionnaire was 2.7. No statistically differences between groups were found regarding the scores of the Low Back Pain Knowledge Questionnaire or Gesture Behavior Test ($p=0.531$ and $p=0.292$, respectively). Statistically lower scores were found in the group with low back pain for the following SF-36 domains: physical functioning ($p<0.001$), physical role ($p=0.015$), pain ($p=0.001$), general health perceptions ($p=0.015$), vitality ($p<0.001$) and mental health ($p=0.001$).

Conclusion: No differences were found when comparing nurses with or without low back pain regarding gesture behavior or knowledge on low back pain. Nurses with low back pain showed a decrease in some domains of quality of life.

Disclosure: H. Morimoto, None; **A. Jones**, None; **J. Natour**, None.

2124

Piriformis Muscle Syndrome: Diagnostic Criteria and Treatment Of a Monocentric Series Of 250 Cases. Fabrice Michel[1], Pierre Decavel[1], Laurent Tatu[1], Etienne Aleton[1], Guy Monnier[1], Bernard Parratte[1] and Eric Toussirot[2]. [1]University Hospital, Besançon, France, [2]CIC Biotherapy 506 and Rheumatology and EA 4266 Pathogens and Inflammation, Besançon, France.

Background/Purpose: Piriformis Muscle Syndrome (PMS) is caused by sciatic nerve compression in the infrapiriformis canal. However, its pathophysiology is poorly understood and this syndrome is difficult to diagnose. This study aimed to propose a clinical assessment score for facilitating PMS diagnosis and to develop a treatment strategy.

Methods: 250 patients versus 30 control patients with disco-radicular conflict, plus 30 healthy control subjects were enrolled in this study. A range of tests (Freiberg, FAIR [Flexion-Adduction-Internal Rotation], heel-contralateral knee manoeuvre and Beatty test) were used to produce a diagnostic score for PMS and an optimum treatment strategy was proposed (muscle relaxant medication, intense self-rehabilitation program, Onabotulinumtoxin A injection in the cases of non-response to rehabilitation and then surgery for the refractory cases).

Results: A 12-point clinical scoring system (Table) was devised and a diagnosis of PMS was considered 'probable' when it was ≥ 8. Sensitivity and specificity of the score were 96.4% and 100%, respectively, while the positive predictive value was 100% and negative predictive value was 86.9%. Combined medication and rehabilitation treatments had a cure rate of 51.2%. 122 patients (48.8%) were unresponsive to treatment and received Onabotulinumtoxin A. Visual Analogue Scale results were 'Very good/Good' in 77%, 'Average' in 7.4% and 'Poor' in 15.6%. 15 of 19 patients unresponsive to treatment underwent surgery with 'Very good/Good' results in 12 cases

Table. Proposal for a clinical scoring system for the diagnosis of Piriformis Muscle Syndrome. FAIR: Flexion-Adduction-Internal Rotation; HCLK: heel contralateral knee. Piriformis muscle syndrome: Probable if score greater than or equal to 8; Unlikely if score less than 8 and greater or equal to 6; Not considered if score less than 6.

criteria	point
Unilateral or bilateral buttock pain with fluctuating periods without pain throughout the course of the day	1
No lower back pain	1
Axial spinal palpation painless (L2 to S1)	1
Negative Lasegue's manoeuvre	1
Seated position (often for a prolonged period) triggering buttock pain and/or sciatic pain	1
Sciatic pain with fluctuating periods without pain throughout the course of the day	1
Buttock pain next to the projection of the piriformis muscle reproduced by Stretching manoeuvres (FAIR, Freiberg, HCLK)	1
Contraction resisted manoeuvres (Beatty)	1
Palpation	1
Sciatic pain (L5, S1 or truncal sciatic area) reproduced by the extension of clinical manoeuvres (several tens of seconds)	1
Stretching Resisted contraction	1
Absence of perineal irradiation	1
Total	12

Conclusion: the proposed evaluation score may facilitate PMS diagnosis and treatment standardisation. Rehabilitation has a major role associated in half of the cases with botulinum toxin injections.

Disclosure: F. Michel, None; **P. Decavel**, None; **L. Tatu**, None; **E. Aleton**, None; **G. Monnier**, None; **B. Parratte**, None; **E. Toussirot**, None.

2125

Comparison Of The Effectiveness Of Local Anesthetic and Corticosteroid Injections For The Treatment Of Piriformis Syndrome. Tugce Ozekli Misirlioglu, Kenan Akgun, Meryem Gul Erden and Tuba Erbilir. Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey.

Background/Purpose: Piriformis syndrome (PS), which is characterized by pain radiating to gluteal region and posterior leg, is accepted as one of the causes of sciatica. Although the importance of local piriformis muscle injections whenever PS is clinically suspected has been shown in many studies, there is not enough study considering the clinical efficacy of these injections. The objective of this study was to compare the effectiveness of ultrasound (US)-guided local anesthetic (LA) and corticosteroid (CS) injections for the treatment of PS.

Methods: Fifty-seven patients with a pre-diagnosis of PS after clinical evaluation were included in this prospective randomized double-blind study. After baseline assessments that were done by the first physiatrist, subjects who were blinded to group allocation, were randomized by the second physiatrist. US-guided injections of 4 cc of lidocaine 2% (LA group) and 4 cc of lidocaine 2%+1 cc of betametazone dipropionate (LA+CS group) with a 22-gauge 88 mm Spinocan were done by the third physiatrist with a Diasus dynamic imaging US equipped with a 5- to 10- MHz multifrequency transducer. The patients whose pain resolved 50% and more were included in the study. Seven patients whose injection tests were negative were excluded from the study. Each group contained 25 patients with a diagnosis of PS. The subjects were re-assessed by the first physiatrist with physical examination and Likert Analogue Scale (LAS) and Numeric Rating Scale (NRS) at the 1st week, the 1st and 3rd months after the injection.

Results: The difference between two groups was analyzed with Pillai's Trace, which is a multivariate analysis from general linear models. No statistically significant difference (p>0,05) was detected between the groups in NRS score values at resting (p=0.814), night (p=0.830) and in motion (p=0.145) and LAS values with long duration of sitting (p=0.547), standing (p=0.898) and lying (p=0.326) with evaluations at the baseline, 1st week, 1st and 3rd months after the injection. Each group was compared within itself by Friedman test, which is used for non-parametric repeated measures. A statistically highly significant (p<0,005) reduction of pain was evaluated through NRS scores at resting (p=0.001), in motion (p=0.001) and at night (p=0.001) and and LAS values with long duration of sitting (p=0.001), standing (p=0.001) and lying (p=0.001) in both of the groups.

Conclusion: LA injections for the PS were found to be clinically effective. However, addition of CS to LA did not give an additional benefit. This gives us the idea that PS has similar features with the other myofascial pain syndromes and responds well to trigger point injections.

Disclosure: T. Ozekli Misirlioglu, None; **K. Akgun**, None; **M. G. Erden**, None; **T. Erbilir**, None.

2126

Time Trends In Total Ankle Arthroplasty: A Study Of The U.S. National Inpatient Sample. Jasvinder A. Singh[1] and Rekha Ramachandaran[2]. [1]University of Alabama, Tuscaloosa, AL, [2]University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: To assess the time-trends in utilization, clinical characteristics and outcomes of patients undergoing total ankle arthroplasty (TAA) in the U.S.

Methods: We used the Nationwide Inpatient Sample (NIS) data from 1998 to 2010 to examine time-trends in TAA. Rates were calculated for the U.S. population. We used the Cochran Armitage test for trend to test for trend across the years. We compared the first and the last period for trends using, ANOVA and chi-squared test as appropriately.

Results: TAA utilization rate increased from 0.12 per 100,000 in 1998 to 0.84 per 100,000 in 2010. The Cochran Armitage test for trend across years yielded a significant p-value of <0.0001. In females and males, the rate increased from 0.14 to 0.88 per 100,000 (p<0.0001 for time-trend) and from 0.11 to 0.81 per 100,000 (p<0.0001 for time-trend), respectively. Compared to the 1998–99, significantly fewer patients <50 years (37% fewer) and more patients ≥80 years (85% higher) in 2009–10 underwent TAA (p <0.0001). Compared to 1998–99, RA was less frequently the underlying diagnosis (55% reduction) and a greater proportion of patients had Deyo-Charlson index of 2 or more (33% more) in 2009–10. Comparing 1998–99 to 2009–10, we noted a slight decrease in the length of stay from 2.7 to 2.5 days (17% reduction), slight increase in the proportion of patients being discharged to inpatient facility from 12.9% to 14.1% (12% increase) and no change in mortality, 0.13% to 0.12% (9% decrease).

Conclusion: The utilization rate of TAA is rapidly increasing in the U.S. Underlying diagnosis and medical comorbidity has changed over time that can impact the type and frequency of complications after TAA. Further studies are needed to assess how the outcomes and complications of TAA have evolved over time.

Disclosure: J. A. Singh, Takeda, Savient, 2, Savient, Takeda, Ardea, Regeneron, Allergan, 5, URL pharmaceuicals Novartis, 5; **R. Ramachandaran**, None.

2127

Recurrences Of Hallux Valgus Deformity After Implant Surgery For Greater Toe In Rheumatoid Arthritis. Yuichi Mochida[1], Katsushi Ishii[1], Yuji Yamada[1], Naoto Mitsugi[1] and Tomoyuki Saito[2]. [1]Yokohama City University Medical Center, Yokohama, Japan, [2]Yokohama City University School of Medicine, Yokohama, Japan.

Background/Purpose: In advanced cases of rheumatoid arthritis (RA), Swanson implant have been widely usedfor hallux valgus deformity. Although the results for this surgery were acceptable, relatively high incidence of recurrence of hallux valgus deformity were reported. In this study, we analyzed the incidence of the recurrence of hallux valgus deformity after Swanson implant, then analyzed for the factors which affect the recurrence of the hallux valgus.

Methods: Post-operative radiological results of implant surgery for hallux in RA with the minimum follow-up of 12 months after surgery were analyzed in 54 cases, 87 joints (male 3cases, female 51cases). The mean age at the time of surgery was 67.7 ± 6.9 years (53~84). The mean duration after surgery was 40.8 ± 21.6 months (12~93). Post-operative hallux valgus angle (HVA) were analyzed at pre-, immediate after surgery, 6 months after surgery, and final follow-up. The changes of HVA between immediate after surgery and the final follow-up were calculated. The radiological results were evaluated using modified Granberry's grading. The toe lengths of hallux including soft tissue shadow after surgery were divided into three groups using the radiographical of each toe as follows; Type 1 (hallux length is 3 mm longer than 2nd toe length), Type 3 (hallux length is 3 mm shorter than 2nd toe length), and Type 2 (hallux length is within 3 mm of 2ndtoe length).

Results: The averaged HVA was significantly decreased after surgery, and maintained during follow-up period. There were no statistical correlation between the changes of HVA and follow-up period, pre-operative HVA, and HVA at immediate after surgery. For the toe lengths of hallux, 24 cases were Type 1, 20 cases were Type 2, and 11 cases were Type 3. Type 3 showed significantly less changes of HVA when compared to Type 1. Also, with the shortening of the length of hallux by toe lengths type, the HVA at the final follow-up was significantly decreased. There were no relationship between HVA and Granberry's grading.

Conclusion: Improvement of disease activity of RA, essentially due to introduction of methotrexate and biological agents, total number of RA surgery, especially for large joints has been decreasing. In contrast, the number of surgeries for small joints such as finger and toe arthroplasty are increasing. Based on this recent trend of changes of surgery, better clinical and radiological results for small joints will be needed to improve patients' quality of life. Our result clearly showed that the shorter the lengths of hallux, significantly less changes of HVA and HVA at the final follow-up, that may reflect better surgical results of hallux valgus deformity.

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ACR/ARHP Poster Session C
Osteoarthritis - Clinical Aspects II: Symptoms and Therapeutics in Osteoarthritis
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

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Longitudinal Relation Of Sensitization To Incident Knee Pain, Incident Symptomatic Knee Osteoarthritis and Increase In Pain Severity: The Multicenter Osteoarthritis Study. Tuhina Neogi[1], Michael C. Nevitt[2], Joachim Scholz[3], Lars Arendt-Nielsen[4], Clifford Woolf[5], Laurence A. Bradley[6], Emily Sisson[1] and Laura Frey-Law[7]. [1]Boston University School of Medicine, Boston, MA, [2]University of California, San Francisco, San Francisco, CA, [3]Columbia University, New York, NY, [4]Center for Sensory-Motor Interaction, Aalborg, Denmark, [5]Children's Hospital Boston, Boston, MA, [6]Univ of Alabama-Birmingham, Birmingham, AL, [7]University of Iowa, Iowa City, IA.

Background/Purpose: Peripheral and central sensitization is associated with knee pain severity in knee osteoarthritis (OA). Whether sensitization occurs prior to or only concurrently with development of OA pain is not known as no prior study has had longitudinal assessments. We examined the relation of 2 measurements of sensitization to the incidence of knee pain and of symptomatic knee OA, and change in pain severity over 2 years.

Methods: The Multicenter Osteoarthritis (MOST) Study is a NIH-funded longitudinal cohort of persons with or at risk of knee OA. Subjects had x-rays and pain questionnaires obtained at each study visit, and a standardized somatosensory evaluation of mechanical temporal summation and pressure pain thresholds (PPT) at the wrist and patella at 60 mo. Temporal summation was defined by increased pain during repeated mechanical stimulation (1 Hz × 30-sec) with a 60g monofilament. PPT was assessed with an algometer (1cm^2 tip, 0.5 Kg/sec) as the point at which the subject felt the pressure change to slight pain. The average of 3 PPT trials was categorized into sex-specific tertiles. Lower PPT indicates more sensitivity. Incident consistent frequent knee pain (CFKP, pain on most days of the past 30 days on both a telephone screen and clinic visit) at the 84-mo visit was determined from among knees that did not have CFKP at the 60-mo visit. Incident symptomatic knee OA (SxOA) at the 84-mo visit was defined as radiographic knee OA (ROA, KL grade ≥2) plus CFKP, assessed among knees free of pain at the 60-mo visit with or without ROA. We examined the relation of the somatosensory tests to incident CFKP and incident SxOA using logistic regression with GEE. We also assessed the relation of change in these

somatosensory measures among all knees with change in WOMAC pain between the 60- and 84-mo visits using linear regression. All analyses were adjusted for potential confounders (see Table for list).

Results: A total of 2308 subjects analyzed met eligibility criteria for these analyses (mean age 67.6, mean BMI 30.9, 61% female). Neither temporal summation nor PPT were associated with incident CFKP or incident SxOA. However, a decrease in PPT (sensitivity) over 2 years was associated with increased pain severity (Table).

Table. Temporal summation and PPT on Incident CFKP, Incident SxOA and Increase in WOMAC pain

		Temporal Summation			
		Wrist*		Patella*	
		Yes	No	Yes	No
Incident CFKP (N=1250)	N (% incidence)	480 (17.5%)	770 (16.6%)	995 (13.6%)	1570 (11.6%)
	Adj OR (95% CI)	1.11 (0.79–1.56)	1.0 (ref)	1.16 (0.89–1.52)	1.0 (ref)
Incident SxOA (N=1171)	N (% incidence)	445 (11.0%)	726 (12.0%)	965 (8.5%)	1539 (8.2%)
	Adj OR (95% CI)	0.89 (0.59–1.35)	1.0 (ref)	1.03 (0.74–1.43)	1.0 (ref)
Increase in pain# (WOMAC) (N=1163)	N	293#	870	443#	1515
	Adj beta (95% CI)	Increase in WOMAC pain with incident temporal summation:			
		0.302 (−0.032, 0.636), p=0.06		0.261 (−0.084, 0.606), p=0.1	

		PPT Tertiles					
		Wrist			Patella		
		Low	Mid	High	Low	Mid	High
Incident CFKP (N=1234)	N (% incidence)	376 (19.4%)	434 (15.2%)	424 (16.5%)	729 (14.3%)	890 (11.0%)	924 (11.9%)
	Adj OR (95% CI)	1.17 (0.8–1.7)	0.90 (0.6–1.3)	1.0 (ref)	1.06 (0.8–1.5)	0.91 (0.7–1.2)	1.0 (ref)
	p for trend			0.4			0.6
Incident SxOA (N=1154)	N (% incidence)	357 (10.6%)	403 (11.2%)	396 (12.6%)	706 (8.5%)	875 (7.1)	901 (9.2%)
	Adj OR (95% CI)	0.79 (0.5–1.3)	0.91 (0.6–1.4)	1.0 (ref)	0.78 (0.5–1.1)	0.71 (0.5–1.0)	1.0 (ref)
	p for trend		0.6			0.2	
Increase in pain (WOMAC) (N=1895)	Adj beta (95% CI)	Increase in WOMAC pain for every unit increase in PPT:					
			0.104 (0.025, 0.184), p=0.01			0.173 (0.117, 0.230), p<0.0001	

*Wrist: person-based analyses; Patella: knee-based analyses
# These analyses examined the relation of incident temporal summation to change in WOMAC pain.
Adj=adjusted for potential confounders: age, sex, BMI, race, knee injury, KL, depressive symptoms, catastrophizing, widespread pain CFKP = consistent frequent knee pain; SxOA=symptomatic knee OA

Conclusion: While measures of sensitization are associated with knee OA pain presence and severity cross-sectionally, they were not related longitudinally to development of new pain symptoms over 2 years. However, decreases in PPT over 2 years were associated with increased pain severity. Enhanced pain sensitivity coinciding with new/increased knee pain may be mediated by sensitization or an imbalance between descending facilitation and inhibition. These results suggest that such changes may not necessarily precede development of knee pain, but may influence the experience of pain and its severity only once pain has been established.

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2129

The Diagnostic Utility Of Anterior Knee Pain and Pain With Activities In Identifying Knees With MRI-Detected Structural Damage In The Patellofemoral Joint: The Multicenter Osteoarthritis Study.

Joshua J. Stefanik[1], Tuhina Neogi[2], Jingbo Niu[2], Neil A. Segal[3], Cora E. Lewis[4], Michael C. Nevitt[5], Frank Roemer[6], Ali Guermazi[1] and David T. Felson[2]. [1]Boston University, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]University of Iowa, Iowa City, IA, [4]University of Alabama, Birmingham, Birmingham, AL, [5]University of California, San Francisco, San Francisco, CA, [6]Klinikum Augsburg, Augsburg, Germany.

Background/Purpose: It is widely thought that patellofemoral joint (PFJ) pathology, a source of symptoms in knee osteoarthritis (OA), can be identified using patient history and pain location but this has not been evaluated in an OA population where tibiofemoral joint (TFJ) OA is also frequent. Treatment for PFJ and TFJ disease may differ making the identification of PFJ disease clinically important. Using MRI to identify knees with isolated PFJ disease, we sought to determine the diagnostic utility of anterior knee pain (AKP) and pain with specific activities to identify knees with isolated PFJ structural damage.

Methods: The Multicenter Osteoarthritis Study (MOST) is a NIH-funded prospective cohort study of older adults with or at risk of knee OA. We used data from the 60-month visit, the first visit at which a knee pain map was obtained, limiting our sample to knees with pain, aching, or stiffness in the past year. Subjects identified painful areas around their knee on the knee pain map, which was used to define AKP. Maximal WOMAC pain score was used to classify pain with stairs and walking on level ground (its absence might rule in PFJ pathology) to test their utility in identifying isolated PFJ damage. On MRIs from the same study visit, cartilage damage and bone marrow lesions (BMLs) were semi-quantitatively scored using the Whole Organ Magnetic Resonance Imaging Score. Knees with isolated PFJ damage (full-thickness cartilage loss or a BML in the PFJ and without either full-thickness cartilage loss or BML in the TFJ), isolated TFJ damage, and no structural damage were included (i.e., those with damage in both compartments were excluded). We determined the sensitivity (Sn), specificity (Sp), positive and negative predictive values (PPV and NPV) for AKP, pain with stairs, absence of pain with walking, and the combination of AKP and pain with stairs in identifying isolated PFJ damage. In sensitivity analyses we assessed pain with stair climbing vs. descending separately.

Results: 407 knees met our inclusion criteria (of 1185 knees with MRI read at 60 months). Of these, 193 (47%) had isolated PFJ damage, while 214 (53%) had either no damage (102; 25%) or isolated TFJ damage (112; 28%). AKP or activity pain showed only moderate or low Sn or Sp and correspondingly low PPV and NPV for identifying isolated PFJ (see table). Absence of moderate pain with walking had the greatest Sn (93%) but poor Sp. The combination of AKP and pain with stairs had the greatest Sp (82%) and but had low Sn (29%). We found similar results with other definitions of structural damage, WOMAC pain, and pain with stair climbing vs. descending.

Diagnostic utility of clinical symptoms commonly thought to indicate PFJ involvement with isolated PFJ structural damage (comparing knees with isolated PFJ damage to knees with either isolated TJF damage or no damage)

	Sensitivity	Specificity	PPV	NPV
Anterior knee pain	**60%**	**53%**	**53%**	**59%**
Pain with stairs (≥ minimal)	**74%**	**33%**	**50%**	**58%**
Pain with stairs (≥ moderate)	**40%**	**70%**	**54%**	**56%**
Absence of pain with walking (≤ minimal)	**58%**	**50%**	**48%**	**54%**
Absence of pain with walking (≤ moderate)	**93%**	**13%**	**49%**	**68%**
Anterior knee pain + pain with stairs (≥ minimal)	**49%**	**64%**	**56%**	**58%**
Anterior knee pain + pain with stairs (≥ moderate)	**29%**	**82%**	**60%**	**56%**

Conclusion: Location of and specific activity-related pain do not appear to highly discriminate underlying isolated PFJ pathology from isolated TFJ or lack of damage. Clinical exam parameters (e.g., localized tenderness on exam) may perform better in identifying isolated PFJ structural damage than patient-reported measures.

Disclosure: J. J. Stefanik, None; **T. Neogi**, None; **J. Niu**, None; **N. A. Segal**, None; **C. E. Lewis**, None; **M. C. Nevitt**, None; **F. Roemer**, None; **A. Guermazi**, Boston Imaging Core Lab, 1, Merck Serono, 5, Sanofi-Aventis Pharmaceutical, 5, TissueGene, 5; **D. T. Felson**, None.

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Factors Associated With Two-Year Pain Experience Outcome In Knee Osteoarthritis.

Jamie E. Rayahin[1], Joan S. Chmiel[2], Orit Almagor[3], Laura Belisle[2], Alison H. Chang[2], Kirsten Moisio[2], Karen W. Hayes[2], Yunhui Zhang[2] and Leena Sharma[2]. [1]University of Illinois, Chicago, Chicago, IL, [2]Northwestern University, Chicago, IL, [3]Northwestern University Medical School, Chicago, IL.

Background/Purpose: Few strategies to improve pain outcome in knee OA exist, in part because methods to evaluate this outcome are not established. ICOAP development included formulation of pain experience stages (Hawker 2008): 1) predictable pain, known trigger, only limiting

high impact activity; 2) mixed predictable/unpredictable pain, more constant, affecting some daily activities; 3) pain constant, superimposed unpredictable, major activity avoidance. We hypothesized that the probability of a good pain experience outcome is associated inversely with baseline depression and pain catastrophizing and directly with self-efficacy and social support.

Methods: Study participants (all with knee OA) reported pain stage (no pain, or stages 1, 2, or 3) at baseline and 2 years. 1-month test-retest reliability was excellent (weighted $\kappa = 0.85$; n = 28). Baseline assessments utilized the Geriatric Depression Scale, Pain Catastrophizing Scale, function Arthritis Self-Efficacy Scale, and MOS Social Support Survey. Good outcome was defined: baseline → 2-year reports of (no pain or stage 1) → (no pain or stage 1) or (stage 2 or 3) → (no pain or stage 1). Poor outcome was: (stage 2 or 3) → (stage 2 or 3) or (no pain or stage 1) → (stage 2 or 3). In multivariable logistic regression, pain outcome was the dependent variable, and all baseline variables with univariate $p \leq 0.20$ potential predictors.

Results: 212 persons [163 (77%) women, mean age 65 (10, SD), BMI 28.5 (5.7)] comprised the sample. 136 (64%) had a good pain outcome and 76 (36%) a poor outcome. Several baseline factors were associated with good pain outcome in univariate analyses (Table 1). In multivariable analysis, higher self-efficacy was associated with a significantly higher likelihood of good outcome; higher pain catastrophizing and BMI were associated with a lower likelihood of good outcome (Table 2).

Table 1. Baseline Characteristics of Good and Poor 2-Year Pain Experience Outcome Groups

Baseline Characteristics	Good Pain Experience Outcome* (n = 136 persons)	Poor Pain Experience Outcome* (n = 76 persons)	p value
Pain catastrophizing (higher score worse)	4.3 (4.7)	10.6 (8.5)	<0.0001
Self-efficacy (higher better)	27.1 (3.5)	22.8 (6.4)	<0.0001
Social support (higher better)	58.0 (16.4)	55.9 (15.2)	0.66
Age, years	65.7 (10.1)	62.7 (10.0)	0.91
Women, number (%)	107 (78.7%)	56 (73.7%)	0.50
BMI, kg/m^2	27.1 (4.6)	31.1 (6.6)	0.0004
Extensor strength, N-M (worse of R and L)	108.6(28.0)	97.6 (30.4)	0.40
K/L grade (worse of R and L)			0.0045
0–1	16 (11.8%)	7 (9.2%)	
2	77 (56.6%)	26 (34.2%)	
3	18 (13.2%)	16 (21.1%)	
4	25 (18.4%)	27 (35.5%)	
Depression (presence)**	2 (1.5%)	3 (3.9%)	0.35
Comorbidity***	0.8 (1.4)	1.5 (2.2)	<0.0001
Back pain, number (%)	93 (68.4%)	62 (81.6%)	0.052
Hip pain, number (%)	56 (41.2%)	33 (43.4%)	0.77
Physical activity (PASE)	152.8 (73.5)	157.8 (99.4)	0.0023
Medication use, number (%)	52 (38.2%)	43 (56.6%)	0.014

*Value shown is mean (SD) unless otherwise indicated
**p value for depressive symptoms as a continuous variable also exceeded 0.20
***Comorbidity questionnaire modification of Charlson Index (continuous)

Table 2. Multivariable Logistic Regression Model: Associations between Baseline Covariables and Baseline-to-2-Year Good Pain Experience Outcome (Dependent Variable)

Independent Variable	Adjusted Odds Ratio (95% CI)
Pain catastrophizing per 1 unit	***0.87 (0.82–0.93)***
Self-efficacy per 1 unit	***1.12 (1.03–1.22)***
BMI per 1 kg/m^2	***0.93 (0.86–0.995)***
K/L grade 2 (vs. 0–1, reference)	2.08 (0.59–7.33)
K/L grade 3 (vs. 0–1, reference)	0.33 (0.08–1.32)
K/L grade 4 (vs. 0–1, reference)	0.52 (0.14–1.97)
Comorbidity per 1 unit	0.86 (0.67–1.09)
Back pain (vs. no back pain, reference)	0.55 (0.23–1.36)
Physical activity (PASE) per 1 unit	0.997 (0.993–1.001)
Medication use (vs. no use, reference)	0.67 (0.32–1.38)

Findings are adjusted for all other variables in the table.

Conclusion: The odds of a good 2-year pain experience outcome in knee OA were lower in persons with greater pain catastrophizing and/or higher BMI, and higher in persons with greater self-efficacy. Specifically targeting these factors may help improve pain outcome in knee OA.

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2131

Osteoarthritis Pain: Variability and Clinical Correlations. Thomas J. Schnitzer, Renita Yeasted, Leijan Huang, Jennifer Duffecy, Mark Begale and A. Vania Apkarian. Northwestern University, Chicago, IL.

Background/Purpose: Although osteoarthritis (OA) is an intensely studied model of chronic pain, little is known about the temporal dynamics of OA pain intensity and how this correlates with physical function and other clinically meaningful outcomes. In this study, we collected pain ratings from individuals with knee OA at a granular level (several times per day) over 3 months to explore the temporal properties of OA pain and examine its association with other patient-reported outcomes.

Methods: Two OA populations were evaluated: one from a placebo arm of a large OA clinical trial and the other from a convenience sample of OA individuals. Participants had to be ≥40 years of age, meet the ACR definition for knee OA, have a minimum pain intensity of ≥4 on Numeric Rating Scale pain (0: no pain, 10: worst possible). All participants were asked to either report their pain on an electronic tablet twice daily (clinical trial) or on their cellphones (3 times per day) over 12–16 weeks and reported sleep performance and activity at 4 weekly clinic visits. To characterize the statistical properties of the time series of pain ratings, the means of the pain ratings in three blocks were calculated and compared by one way analysis of covariance. As well, fractal dimension, D, was calculated using rescaled range analysis to characterize the OA participants' pain fluctuations.

Results: 78 individuals were studied in the clinical trial and 35 individuals in the cell-phone collection study. Demographics of the two groups were both similar and typical of an OA population (data not shown). The distribution and mean fractal dimension, D, for the two populations were similar (Fig. 1), mean $D = 1.69 \pm 0.03$ for the clinical trial population (A) and mean $D = 1.65 \pm 0.04$ for the convenience sample (B). Data collected by cell phone demonstrated a close correlation between pain intensity and physical activity for the same day (Fig. 2) and a strong correlation between clinic sleep score rating and cell phone reported pain the preceding day ($r = 0.39$, $p < 0.001$).

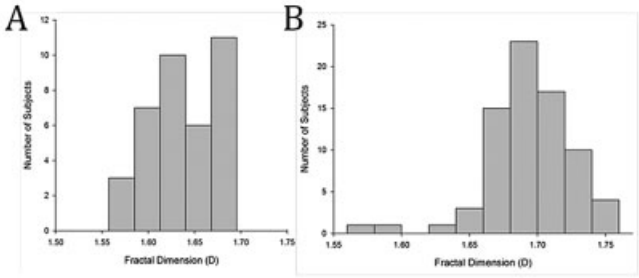

Figure 1.

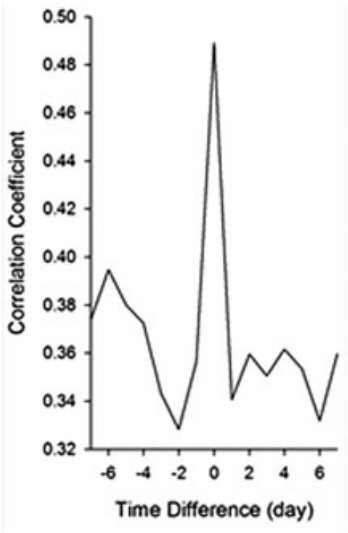

Figure 2.

Conclusion: This is the first study to characterize the temporal dynamics of OA pain. The finding of an anti-persistent time series in 2 separate populations provides strong confirmatory evidence of this pain pattern. These results are similar to those reported for chronic low back pain and in contrast

to purely neuropathic pain and acute pain. The anti-persistent pattern of pain is consistent with the concept of central pain processes activated to modulate peripheral pain input in OA. A strong temporal association between self-reported OA pain and physical function and sleep was also seen.

Disclosure: T. J. Schnitzer, None; **R. Yeasted**, None; **L. Huang**, None; **J. Duffecy**, None; **M. Begale**, None; **A. V. Apkarian**, None.

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Short-Run Transitions In Pain States: Reflections Of Multiple Outcome Clinical Measures of Inadequate Pain Relief among Patients With Knee Osteoarthiritis. Stephanie Taylor[1], Christopher Black[2], Paul M. Peloso[3], Philip G. Conaghan[4], Leah Stokes[2], Mart A.F.J. van de Laar[5], François Rannou[6], Nigel K. Arden[7] and Panagiotis Mavros[2]. [1]Merck & Co., Inc., Whitehouse Station, NJ, [2]Merck, Whitehouse Station, NJ, [3]Merck Sharp & Dohme Corp., Rahway, NJ, [4]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [5]University of Twente & Medisch Spectrum Twente, Enschede, Netherlands, [6]Physical Medicine and Rehabilitation Service, Paris-Descartes University, Cochin Hospital, Paris, France, [7]Oxford NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, United Kingdom.

Background/Purpose: Despite the importance of pain management in osteoarthritis (OA), there has been limited evidence confirming the adequacy of measuring pain relief in clinical practice setting. The objective of the Survey of Real World Therapies in Osteoarthritis (SORT) is to evaluate short run (30 days) changes in pain relief and its association with overall pain, physical functioning, stiffness and quality of life in patients with knee OA.

Methods: SORT, a 12-month prospective multinational study enrolled participants with knee OA receiving analgesics. Inadequate Pain Relief (IPR) was defined as a score of >4, indicating "moderate or greater pain", on BPI Question "What is your pain on average?". The Short-Form (SF)-12 and WOMAC were administered to measure quality of life, pain, stiffness, and physical function. Baseline and month one data were used to assess short run dynamics of knee OA management.

Results: 1254 participants were included: 67.3% women; mean age 68 years (SD=9.4); mean OA duration 5.9 years (SD=6.2). IPR was reported by 54% of the cohort. Overall, NSAIDs (64.1%) were used most often; followed by paracetamol (39.8%) and medications containing opioids (20.2%). IPR participants (vs. non-IPR) used more opioid containing medications (24.7% vs. 14.8%, p< 0.001). IPR participants (vs. non-IPR) differed QOL on: WOMAC Stiffness (115 vs. 67, p< 0.001), Pain (266 vs. 136, p< 0.001), Physical Function (892 vs. 459, p<0.001); SF-12 General Health (fair/poor 47% vs. 27%, p<0.001); Additionally, there were differences in IPR participants' report of response to treatment (fair, poor and no response 67% vs. 43%, p<0.001) as compared to non-IPR.

After 30 days, 28% of participants reported changes in pain relief, which was equally distributed (14% each) between the two baseline pain relief states. Participants whose pain relief state worsened experienced an average increase in pain measured by the BPI (27%) and WOMAC (9%). These participants also displayed worsened physical functioning (8%), greater knee stiffness (4%), as well as a decrease in health-related quality of life as measured by the physical component summary score (PCS) (2.1%) and mental component score (MCS) (2.7%).

In contrast, for those participants whose pain relief state improved, the BPI and WOMAC pain measurements improved 28% and 12%, respectively. Similarly, improvements were seen in physical functioning (8%), stiffness (11%) and both SF-12 components (1.8% each).

Conclusion: Short run changes in pain relief status were positively associated with significant changes in both the physical (PCS) and mental (MCS) components of SF-12, and the 3 domains of the WOMAC.

Disclosure: S. Taylor, Merck, 3; **C. Black**, Merck Pharmaceuticals, 3; **P. M. Peloso**, Merck Pharmaceuticals, 3; **P. G. Conaghan**, None; **L. Stokes**, Merck Pharmaceuticals, 3; **M. A. F. J. van de Laar**, None; **F. Rannou**, None; **N. K. Arden**, None; **P. Mavros**, Merck Pharmaceuticals, 3.

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Neuropathic Pain After Primary Total Hip and Knee Arthroplasty. Anne Lubbeke[1], Gabor J. Puskas[1], Domizio Suva[1], Sylvette Bas[1], Cem Gabay[1], Axel Finckh[2] and Pierre Hoffmeyer[1]. [1]Geneva University Hospitals, Geneva, Switzerland, [2]Geneva University Hospital, Geneva, Switzerland.

Background/Purpose: A sizeable number of patients continue to suffer from pain after total joint arthroplasty (TJA). The reason for this is not well established in many cases, and the presence of persistent postsurgical pain (PPSP) of neuropathic origin has been suggested. Possible mechanisms include intraoperative nerve injury, local inflammation, and central sensitization. Little is known about neuropathic pain after joint replacement, but its prevalence has been estimated at 5%.

Leptin could play a role in peripheral pain sensitization via its pro-inflammatory cytokine-like function. Moreover, animal models have suggested a possible influence of leptin in the development of neuropathic pain. In previous studies we found that high leptin concentrations were associated with greater pain preoperatively as well as 1 year postoperative.

Our objectives were to (1) assess the prevalence of neuropathic pain 2 years after TJA, (2) describe its influence on pain, function, general health and satisfaction after surgery, and (3) identify preoperatively assessed predictors (including leptin) of PPSP of neuropathic origin.

Methods: Prospective cohort study including patients with total hip and knee arthroplasty operated upon for primary OA in a large orthopaedic center between 1 and 12/2010. Prior to surgery baseline characteristics were recorded and leptin concentrations were sampled from blood (n= 175 TJAs) and assessed using an ELISA kit. At 2 years postoperative, the following outcomes of interest were assessed via questionnaire: (1) Presence of neuropathic pain measured with Neuropathic Pain Diagnostic Questionnaire (DN4); (2) Pain, function and general health measured with WOMAC, VAS pain, SF-12; and (3) Satisfaction.

Results: 275 TJAs were included, 161 THAs and 114 TKAs. Mean age was 72 (±9) years, mean BMI 28 kg/m^2, 62% were women.

Neuropathic pain at 2 years postoperative was reported by 5 THA (3.1%) and 11 TKA patients (9.6%). Presence of neuropathic pain was associated with significantly higher PPSP level, lower function, worse general health and low satisfaction (see Table). Eight of the 16 patients with neuropathic pain indicated they would not undergo the operation again.

Prior to surgery patients with neuropathic pain (vs. those without) had a significantly higher BMI (32 vs. 27 kg/m^2), higher ASA scores, more often OA of contra-lateral joints, greater pain (WOMAC pain 29 vs. 41), as well as significantly higher serum leptin concentrations (37 vs. 24 ng/ml, p=0.020). The latter association was seen in obese (55 vs. 44 ng/ml) and in non-obese patients (23 vs. 16 ng/ml).

Table. Patient-reported outcomes 2 years after TJA according to presence or absence of neuropathic pain

	Neuropathic pain yes (n=16)	Neuropathic pain no (n=259)	Risk difference (95% CI)
Very satisfied/satisfied (%)	8 (50.0)	223 (86.1)	36.1 (11.2; 61.0)
Would not undergo surgery again (%)	8 (50.0)	15 (5.8)	44.2 (19.5; 68.9)
Scores, mean, SD	27.0 (±4.7)		**Mean difference (95% CI)**
Pain (VAS)	5.5 (±1.6)	1.6 (±2.0)	3.9 (2.8; 4.9)
WOMAC pain	50.3 (±18.0)	83.6 (±18.7)	−33.3 (−42.7; −23.8)
WOMAC function	48.7 (±21.0)	74.6 (±20.9)	−25.9 (−36.5; −15.2)
SF-12 mcs	38.0 (±5.6)	48.0 (±10.3)	−10.0 (−15.2; −4.6)
SF-12 pcs	33.8 (±6.1)	42.5 (±9.4)	−8.7 (−13.6; −3.9)

Conclusion: Neuropathic pain is more frequent after knee than after hip arthroplasty. Its presence is associated with poor outcomes. Whether leptin is involved in the pathogenesis and /or a useful preoperative marker of neuropathic pain, merits further investigation.

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Responsiveness and Predictive Ability Of The Knee Society Scale (KSS) Score. Jasvinder A. Singh[1], Cathy Schleck[2], W. Scott Harmsen[3] and David Lewallen[4]. [1]University of Alabama, Tuscaloosa, AL, [2]Mayo Clinic College of Medicine, Rochester, MN, [3]Mayo Clinic, Rochester, MN, [4]Mayo Clinic college of medicine, Rochester, MN.

Background/Purpose: The KSS questionnaire has previously been shown to have face, content and construct validity and test-retest reliability. Our objective was to assess the Responsiveness and Predictive Ability of the KSS.

Methods: We used data from the Mayo Clinic Total Joint Registry to assess the validity of KSS questionnaire, by including patients who underwent primary total knee arthroplasty (TKA) between 1993–2005 and responded to the baseline and 2-year post-primary TKA KSS questionnaire. KSS questionnaire generates three domain scores: KSS function score

(walking, stairs and use of knee supports), range of motion and KSS score (pain, range of motion and stability) scores. Convergent/divergent validity was examined with the association of select demographics (age, gender, number of joints involved) at baseline with KSS scores using linear regression and correlation analyses. Responsiveness was assessed with Minimally Clinically Important Difference (MCID) and Really Important Difference (RID) were calculated corresponding to "somewhat better now" and "much better now" patient responses, respectively to the question at 2-years-Compared to your condition before the surgery, how would you rate your knee now? For discriminant ability, we calculated effect size by taking the change in respective score from baseline to 2-years and dividing the result by the standard deviation at baseline. Predictive ability was assessed by association of improvement in KSS function (categorized as <=10, 11–40 and >40) and KSS scores at 2-years (minus preoperative scores; categorized as <= 35, 36–63, and 64–95) with revision surgery at time after 2-years.

Results: For primary TKA, there were 5,280 knees with both a baseline and a 2-year data. The sample consisted of 2,375 males (45%) and 2,905 females (55%). The mean age at surgery (SD) is 68 (10), median age was 70 (range, 17–93).

MCID and RID thresholds were as follows: KSS function score, 7.0 and 29.3; KSS score, 27.7 and 51.0; range of motion, 11.7 and 20.4. Respective effect sizes at 2-years were large, 1.37 for function score, 2.60 for knee score and 1.56 for range of motion; and consistent with effect sizes for other validated scales for arthroplasty.

Improvement in KSS-function score was associated significantly with the risk of revision after 2-years (Table 1); total KSS score showed a trend towards significant association (p=0.07)

Table 1. Predictive ability of KSS score for revision TKA

	Hazard ratio (95% CI)	p-value
Improvement in KSS-function (n=4270 with 179 events)		
<= 10 vs. 41–100	1.87 (1.23, 2.83)	0.003
11–40 vs.41–100	1.18 (0.78, 1.78)	0.43
Improvement in KSS (n=785 with 13 events*)		
<= 35 vs. 64–95	16.63 (2.07, 2150)	0.07
36–63 vs. 64–95	4.95 (0.56, 658)	0.31

*186 TKAs did not have data to calculate KSS scores

Conclusion: KSS and KSS-function scores are responsive in patients undergoing primary TKA. KSS scores can predict the risk of early revision after primary TKA. These findings imply that a regular monitoring of patient-reported outcomes of pain and function may allow signal detection for early TKA revision.

Disclosure: J. A. Singh, Takeda, Savient, 2, Savient, Takeda, Ardea, Regeneron, Allergan, 5, URL pharmaceuicals Novartis, 5; **C. Schleck**, None; **W. S. Harmsen**, None; **D. Lewallen**, DePuy, Stryker, Biomet and Zimmer., 2, Zimmer, Orthosonic and Osteotech, 7, Pipeline, 5, Pipeline, 1.

2135

Musculoskeletal Pain Explains Differences In Function At Time Of Surgery In Black TKR and THR Patients. Anthony Porter[1], Wenjun Li[1], Leslie R. Harrold[1], Milagros Rosal[1], Philip Noble[2], David Ayers[1], Patricia D. Franklin[1] and Jeroan Allison[1]. [1]University of Massachusetts Medical School, Worcester, MA, [2]Baylor College of Medicine, Houston, TX.

Background/Purpose: The existence of racial disparities in total knee (TKR) and total hip (THR) replacement outcomes is well established but not well understood. The burden of musculoskeletal co-morbidities was investigated among black and white TKR and THR patients at the time of surgery to assess whether that explains disparities in a prospective cohort.

Methods: Descriptive analyses were performed on a cohort of 3,306 TKR and 2,439 THR patients. Data collected include sociodemographics (age, gender, race), body mass index (BMI), modified Charlson co-morbidity scores, operative joint pain severity using the Knee Injury/Hip Disability and Osteoarthritis Outcome Scores (KOOS/HOOS,), function based on the Short Form 36 (SF-36) Physical Component Score (PCS), emotional health using the SF-36 Mental Component Score (MCS), and musculoskeletal co-morbidity using the KOOS/HOOS (number of nonoperative hip and knee joints with moderate to severe pain; range 0–3) and Oswestry Disability Index (ODI). Factors associated with pre-operative pain and function were examined using multivariable stepwise linear regression models.

Results: At time of surgery, black TKR patients were significantly younger (62.0 vs. 66.9 years old), female (69.7% vs. 60.8%), heavier (34.6 vs. 31.3 BMI), exhibited higher prevalence of 2–5 medical co-morbidities (17.0% vs. 9.2%), poorer emotional health (47.4 vs. 52.1), poorer surgical knee pain (43.4 vs. 53.2), poorer function (31.3 vs. 33.1), and more pain in other weight-bearing joints than whites (p<0.02). In regression models, after adjusting for these independent variables, race did not explain the differences in surgical knee pain and function at time of surgery (−4.3–0.8 p>0.05), while moderate to severe pain in up to three lower extremity joints had a significant effect (−23.4–[−15.9], p<0.0001).

At time of surgery, black THR patients were significantly younger (59.9 vs. 64.7 years old), heavier (31.7 vs. 29.1 BMI), exhibited higher prevalence of 2–5 medical co-morbidities (14.1% vs. 6.9%), poorer emotional health (47.0 vs. 50.9), greater surgical hip pain (39.3 vs. 49.2), poorer function (30.0 vs. 31.6), and more pain in other weight-bearing joints than whites (p<0.04). In regression models, after adjusting for these independent variables, race did not explain the differences in surgical hip pain and function at time of surgery (−3.1–3.3, p>0.05), while moderate to severe pain in up to three lower extremity joints had a significant effect (−19.9−(−11.9), p<0.0001).

Conclusion: Black patients exhibit poorer function at the time of surgery compared to whites. This difference was influenced by a greater burden of musculoskeletal pain in the large weight-bering joints in the legs. Racial disparities have been well established in previous studies. In this sample, musculoskeletal co-morbid pain was found to explain much of the poorer pre-operative function seen in black patients.

Disclosure: A. Porter, None; **W. Li**, AHRQ, 2; **L. R. Harrold**, CORRONA, Inc., 5; **M. Rosal**, NIH/NIAMS, 2; **P. Noble**, Zimmer, Omni Sciences Inc., DePuy, J+J, 5; **D. Ayers**, AHRQ, Zimmer, 2; **P. D. Franklin**, NIAMS-NIH, NLM-NIH, AHRQ, Zimmer,, 2; **J. Allison**, AHRQ, 2.

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Does Functional Gain and Pain Relief After TKR and THR Differ By Patient Obese Status? Wenjun Li[1], Leslie R. Harrold[1], Jeroan Allison[1], Courtland Lewis[2], Thomas Bowen[3], Patricia D. Franklin[1] and David Ayers[1]. [1]University of Massachusetts Medical School, Worcester, MA, [2]Hartford Hospital, Hartford, CT, [3]Geisinger, Danville, PA.

Background/Purpose: Obesity is an important predictor of functional status and pain after total knee (TKR) and total hip (THR) replacement. However, variations in pre-post TKR and THR changes in function and pain by obesity status remain to be examined.

Methods: Pre- and 6 month post TKR data on physical function and pain were collected on 1,533 primary TKR and 1,118 primary THR patients between 5/2011 and 10/2012. Data included demographics, comorbidities, operative joint pain severity based on the Knee Injury/Hip Disability and Osteoarthritis Outcome Score (KOOS/HOOS), physical function (SF-36 PCS), mental health (SF-36 MCS), and musculoskeletal burden of illness. Pre-post changes in PCS and pain were analyzed using descriptive statistics and linear mixed models that accounted for the clustering of patients within clinic.

Results: Approximately 14% of TKR patients were under or normal weight (BMI<25), 33% overweight (BMI: 25.1–30), 29% obese (BMI: 30.1–35), 15% severely obese (BMI: 35.1–40) and 9% morbidly obese (BMI>40). Patients had average age of 67 years, included 61% women and 93% whites. Patients with greater level of obesity had lower PCS at baseline (p<0.001) and 6 month (p<0.001). However, pre-TKR to 6 month post-TKR change in PCS did not differ by level of obesity (p=0.554), and had an overall mean (SE) of 9.7 (0.23). Patients with greater levels of obesity had worse pain scores at baseline (p<0.001) but greater change in pain between pre-TKR and 6 months post-TKR (p=0.001). As a result, average pain scores at 6 months were similar across levels of obesity (p=0.150), and had an overall mean (SE) of 84.9 (0.40).

Approximately 27% THR patients were under/normal weight (BMI<25), 38% overweight (BMI: 25.1–30), 23% obese (BMI: 30.1–35), 9% severely obese (BMI: 35.1–40) and 4% morbidly obese (BMI>40). Patients had average age of 66 years, included 62% women and 95% whites. Greater level of obesity was associated with lower PCS at baseline (p<0.001) and 6 month (p<0.001). Mean change in pre-to-six month PCS was greater in patients with BMI <35 when compared to BMI>35 (14 vs. 11.5) Greater level of obesity was associated with a poorer baseline pain score (p<0.001) but larger change in post-op pain at (p=0.001). At 6 months, pain scores did not differ by level of obesity (p=0.068) with a mean score greater than 90.

Conclusion: At 6 months after TKR, severely obese patients (BMI>35) reported improvements in pain and function equal to or greater than patients with BMI<35. At 6 months after THR, all patients reported significant functional gains although patients with BMI>35 had lower mean functional gain than those with BMI<35. All patients reported excellent pain relief.

Disclosure: W. Li, AHRQ, 2; **L. R. Harrold**, CORRONA, Inc., 5; **J. Allison**, AHRQ, 2; **C. Lewis**, None; **T. Bowen**, None; **P. D. Franklin**, NIAMS-NIH, NLM-NIH, AHRQ, Zimmer,, 2; **D. Ayers**, AHRQ, Zimmer, 2.

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Important Predictors Of Patient-Reported Outcomes After TKR and THR Are Not Included In Risk Models Based On Administrative Data. Patricia D. Franklin[1], Leslie R. Harrold[1], Wenjun Li[1], Jeroan Allison[1], David Ayers[1] and Courtland Lewis[2]. [1]University of Massachusetts Medical School, Worcester, MA, [2]Hartford Hospital, Hartford, CT.

Background/Purpose: Because total knee (TKR) and total hip (THR) replacement surgery is performed to relieve pain and improve physical function in patients with advanced arthritis, there is growing demand to use patient-reported outcomes (PROs) to assess TKR effectiveness. The UK and others now require PRO assessment after TKR. Thus, a clear understanding of pre-existing clinical factors that influence PROs after surgery is needed before comparing PROs across providers. We evaluated the roles of medical and musculoskeletal comorbidities in explaining variation in 6 month post-TKR and THR pain relief and functional gain.

Methods: A US cohort of 1,578 TKR and 1,166 THR patients reported sociodemographic (age, sex, race), BMI, modified Charlson comorbidity, arthritic disease severity (Hip Disability/Knee Injury and Osteoarthritis Outcome Scores (HOOS/KOOS)) in both knees and hips, lumbar disease using the Oswestry Disabiity Index (ODI), emotional health based on the Short Form 36 (SF-36) Mental Component Score (MCS), and physical function (SF-36 PCS). Predictors of change in pre-to-6 month post-TKR and post-THR pain and function were examined using linear mixed models adjusting for clustering within site.

Results: TKR patients had a mean age of 66 years, mean BMI of 31.5, and were 62% female and 6.8% black. Nine percent (9%) reported Charlson of 2–5, 15% with Charlson of 6, 7% moderate/severe pain in 2–3 knee/hip joints, and 26% moderate/severe lumbar pain. After adjusting for sociodemographic factors, significant predictors of poorer 6 month post-THR *pain* included poorer emotional health, higher Charlson comorbidities and any lumbar pain at time of THR. These factors also predicted poorer 6 month *function*.

THR patients had a mean age of 64 years, mean BMI of 29.2, and were 61% female and 4% black. Six percent (6%) reported Charlson of 2–5, 15% with Charlson of 6, 9% moderate/severe pain in 2–3 knee/hip joints, and 34% moderate/severe lumbar pain. After adjusting for sociodemographic factors, significant predictors of poorer 6 month post-THR *pain* included poorer emotional health, Charlson of 1, and severe lumbar pain at time of THR. These factors also predicted poorer 6 month *function*, as well as greater BMI and moderate/severe pain in non-operative knees/hips.

Conclusion: Before adopting PROs as a standard measure of TKR or THR effectiveness, a complete understanding of pre-existing clinical factors associated with poorer pain relief and functional gain is needed. These analyses suggest that greater musculoskeletal, as well as medical, comorbid conditions are associated post-operative patient-reported outcomes and should be included in risk-adjustment models.

Disclosure: P. D. Franklin, NIAMS-NIH, NLM-NIH, AHRQ, Zimmer,, 2; **L. R. Harrold**, CORRONA, Inc., 5; **W. Li**, AHRQ, 2; **J. Allison**, AHRQ, 2; **D. Ayers**, AHRQ, Zimmer, 2; **C. Lewis**, None.

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The Impact Of Arthritis Type On Post-TJR Functional Gain: Outcomes In RA Vs. OA Patients. Leslie R. Harrold[1], David Ayers[1], Brian Curtin[2], George Reed[1] and Patricia D. Franklin[1]. [1]University of Massachusetts Medical School, Worcester, MA, [2]Virginia Commonwealth University Medical Center, Richmond, VA.

Background/Purpose: Total joint arthroplasty (TJA) is commonly used in rheumatoid arthritis (RA) patients and yet there is little available information quantifying pain relief and functional gain following surgery and how that differs from the osteoarthritis (OA) population. Therefore we examined 6-month functional outcomes of TJR in a population-based observational cohort of RA and OA patients who underwent total hip (THR) or knee (TKR) replacement.

Methods: Patients undergoing primary TJR from 7/1/11 through 12/3/12 were identified from the FORCE-TJR national research consortium which enrolls patients from 111 surgeons across 27 states in the US. The registry gathers data on patient demographics, underlying type of arthritis, body mass index, non-arthritis comorbid conditions, arthritis in lower extremity large joints, back pain, operative joint pain severity based on the Knee Injury/Hip Disability and Osteoarthritis Outcome Score (KOOS/HOOS), function based on the Short Form 36 Physical Component Score (PCS), and mental health using the SF-36 Mental Component Score (MCS). Descriptive statistics were performed as well as linear regressions examining the influence of arthritis type on pain relief and functional gain.

Results: There were 136 RA and 1493 OA patients who underwent primary TKR, and 83 RA and 1139 OA patients who underwent primary THR. Among TKR patients, RA patients were more likely to be nonwhite (14% vs. 7%, $p=0.001$), unmarried (43% vs. 29%, $p<0.001$), have lower emotional health (47 vs. 53, $p<0.001$) with an annual income of ≤$45,000 (57% vs. 36%, $p<0.001$)) as well as greater operative joint pain (50 vs. 54, $p<0.01$) and impairment in functioning (32 vs 34, $p=0.02$). Similarly, RA THR patients were more likely to be nonwhite (14% vs. 6%, $p=0.005$), have lower emotional health (46 vs. 52, $p<0.001$) with an annual income of ≤$45,000 (54% vs. 34%, $p<0.001$) with worse operative joint pain (42 vs. 49, $p<0.001$) and functioning (28 vs 32, $p<0.001$). In unadjusted analyses, RA patients undergoing TKR as compared to OA patients had less functional gain 6 months post-surgery (7.0 vs. 9.8, $p<0.001$) but similar pain relief (31.9 vs. 31.1, $p=0.66$). With adjustment for sociodemographic and clinical factors as well as clustering by physician, RA patients had both less improvement in function (−2.5; 95% CI −4.2 to −0.7) and reduction in pain (−4.0; 95% CI −7.9 to 0.1). In contrast, RA patients who undergo THR have similar functional gain (12.6 vs. 14.0, $p=0.23$) and pain relief (45.9 vs. 41.9, $p=0.09$) as compared to OA patients in both unadjusted and adjusted analyses.

Conclusion: RA patients have less functional improvement and pain relief as compared to those with OA when undergoing TKR but similar when undergoing THR. More investigation is needed to assess whether there are modifiable factors that may be targeted for intervention to improve outcomes for RA patients undergoing TKR.

Disclosure: L. R. Harrold, CORRONA, Inc., 5; **D. Ayers**, AHRQ, Zimmer, 2; **B. Curtin**, None; **G. Reed**, Corrona, Inc, 3; **P. D. Franklin**, NIAMS-NIH, NLM-NIH, AHRQ, Zimmer,, 2.

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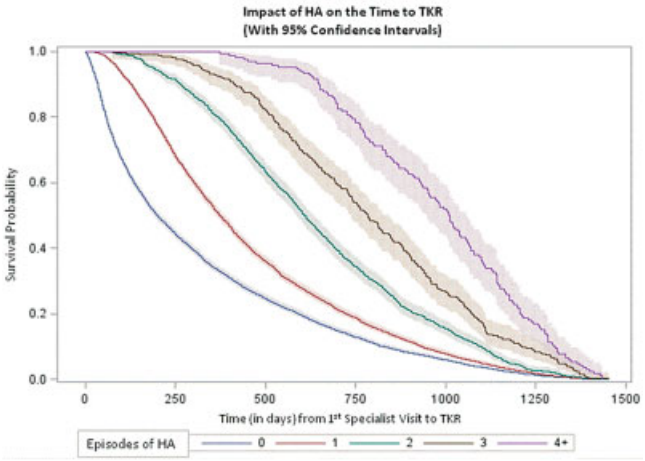
Do Hyaluronic Acid Injections Delay Total Knee Replacement Surgery? Thomas Abbott[1], Roy D. Altman[2], Robert Dimeff[3], Michael Fredericson[4], Vijay Vad[5], Peter Vitanzo Jr.[6], Sashi Yadalam[1], Ronald Levine[1], Brad Bisson[7] and Samir Bhattacharyya[7]. [1]Johnson & Johnson, New Brunswick, NJ, [2]UCLA, Los Angeles, CA, [3]UT Southwestern Medical Center, Dallas, TX, [4]Stanford University School of Medicine, Menlo Park, CA, [5]Weill Cornell Medical College, NY, NY, [6]Rothman Institute, Philadelphia, PA, [7]DePuy Synthes Mitek Sports Medicine, Raynham, MA.

Background/Purpose: More than 27 million adults in the US have knee osteoarthritis (OA), a painful and life-altering disease. Various non-pharmacologic and pharmacologic agents are recommended to alleviate pain, inflammation, and to improve function. When patients have inadequate response to these therapies, viscosupplementation with hyaluronic acid (HA) injections helps restore synovial fluid properties in the knee, leading to less pain and improved clinical outcomes. Total knee replacement (TKR) usually is reserved as the final treatment option. The present study examined the impact of the use of HA injections in delaying TKR in patients with knee OA.

Methods: A retrospective analysis of the Truven Marketscan databases was performed. All OA patients continuously enrolled during calendar year January, 2007 through December, 2011, that went on to TKR. Two cohorts were identified with this population: A cohort of patients receiving HA injections and the second cohort with no HA injections. Time-to-event analyses were performed in both cohorts, where the starting time was defined as the patients' 1st visit to an OA specialist (primarily orthopedic surgeons), and the ending point was TKR. The initial visit had to have occurred after January, 2008, providing a 12-month clean period. HA usage was grouped into episodes of treatment, where successive HA injections within 15 days were grouped into the same episode. An episode encompassed one course of a series of weekly injections or a single injection of HA, based on the standard

use of HA. A propensity scoring methodology was implemented to adjust for baseline characteristics of patients in HA and non-HA cohorts.

Results: The number of patients in the HA and non-HA cohorts were 7,000 and 19,627, respectively. Of the 7,000 HA patients, we successfully propensity score matched 6,891 with the non-HA cohort (98%) with caliper of 0.001. The majority of the patients were female (66%). The median times from the initial specialist visit to TKR were 199 and 443 days for non-HA cohort and HA cohort with one episode of HA treatment, respectively. There was a well defined "dose response curve", with each treatment episode increasing the median gap by on average 202 days. As an example, for HA cohort with 3 and 4 or more episodes of treatments, the median times to TKR were 784 (585 days delay) and 1,009 (810 days delay) days, respectively.



Conclusion: This observational, descriptive analysis of an administrative database provides evidence that HA injections delay patients' progression to TKR (up to approximately 2.2 years documented in the present study population). Although the analysis attempted to control for disease severity by propensity score matching, there could be remaining differences between the HA and non-HA populations not recorded in the database which could affect the interpretation of the results.

Disclosure: T. Abbott, Johnson & Johnson, 3; **R. D. Altman**, DePuy Synthes Mitek Sports Medicine, 5; **R. Dimeff**, DePuy Synthes Mitek Sports Medicine, 5; **M. Fredericson**, DePuy Synthes Mitek Sports Medicine, 5; **V. Vad**, DePuy Synthes Mitek Sports Medicine, 5; **P. Vitanzo Jr.**, DePuy Synthes Mitek Sports Medicine, 5; **S. Yadalam**, Johnson & Johnson, 3; **R. Levine**, Johnson & Johnson, 3; **B. Bisson**, DePuy Synthes Mitek Sports Medicine, 3; **S. Bhattacharyya**, DePuy Synthes Mitek Sports Medicine, 3.

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Effects Of Intra-Articular Hyaluronic Acid Injections On Gait Pattern In Patients With Knee Osteoarthritis. Bilal Uysal, Aysegul Ketenci, Sina Esmaeilzadeh and Dilsad Sindel. Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey.

Background/Purpose: The aim of this study was to determine the effects of intra-articular hyaluronic acid (HA) injections on gait pattern of both injected and un-injected knees with motion analysis in patients with knee osteoarthritis (OA).

Methods: In a prospective study 49 eligible patients who had knee OA according to the American College of Rheumatology criteria and had grade II-III knee OA in the X-ray examination according to Kellgren and Lawrence Grading Scale, were included in the study. The HA was injected into the affected joints in 62 knees, once a week for three weeks. Gait analysis was performed at baseline, end of treatment protocol and 6-month after treatment by the ELITE Motion Analysis System (BTS S.p.a., Milan, Italy) and two force plates. The motion analysis was assessed by the Davis protocol.

Results: The mean age of patients was 56.7 ± 6.3 (45–65) years; 45 (91.8%) were women. The ground reaction force was significantly decreased in the injected knees ($p<0.05$); however, there was no significant decrease ($p>0.05$) in the ground reaction force over six months. The extensor and flexor moments of the injected knees were significantly decreased ($p<0.05$) at the end of therapy and 6-month assessments compared with the un-injected knees ($p>0.05$). There were no significant changes in the walking velocity, stride time and stride length in both injected and un-injected knees over six months ($p>0.05$).

Conclusion: Our data suggest that intra-articular HA injections can reduce the ground reaction forces and flexion-extension moments, and consequently, lead to decrease in knee loading and improvement in the symptoms.

Disclosure: B. Uysal, None; **A. Ketenci**, None; **S. Esmaeilzadeh**, None; **D. Sindel**, None.

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Interphalangeal Intra-Articular Injection With Triamcinolone Hexacetonide: Assessment Of effectiveness In Hand Osteoarthritis. Natalia de Oliva Spolidoro[1], Jamil Natour[2], Rita N.V. Furtado[3], Flavia S. Machado[3] and Hilda A. Oliveira[2]. [1]Universidade Federal de São Paulo - Unifesp, São Paulo, Brazil, [2]Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [3]Universidade Federal de São Paulo, São Paulo, Brazil.

Background/Purpose: Despite being a very prevalent joint condition, there is a lack of studies on the effectiveness of the intra-articular injection (IAI) of corticosteroids in interphalangeal joints (IPs) with osteoarthritis (OA).

Methods: A randomized, controlled, double-blind trial was carried out involving 60 OA hands patients (proximal or distal IPs), allocated in two groups. The TH/LD group (n=30) received IAI in the most symptomatic IP with 0.1ml of 2% lidocaine and triamcinolone hexacetonide(TH) at a dose of 4mg(0.2ml) and 6mg(0.3ml) in the distal and proximal IPs, respectively. The LD group (n=30) received IAI with only 0.1ml of 2% lidocaine. The patients were evaluated by blinded raters at baseline (T0) and one, four, eight and twelve weeks (T1, T4, T8 and T12) after the procedure. Outcome measures: Visual Analogic Scale(VAS: 0 to 10cm) for pain in the IP at rest (VASr) and during movement (VASm), VAS for swelling (VASs), goniometry(°), grip strength(kgf), pinch strength(kgf) and hand function (COCHIN questionnaire and AUSCAN index). Ultrasound evaluation: Quantitative measure (in mm) of synovial hypertrophy in palmar and dorsal joint recesses of IP injected. The level of significance in the statistical analysis was set to 5% ($p<0.05$).

Results: Females accounted for 96.67%of the sample (58 patients). Mean age was 60.7 ± 8.2 years. Mean disease duration was 5.0 ± 3.6 years. Twenty-nine proximal (48.3%) and 31 distal (51.7%) IPs received IAI, with no significant differences between groups. Significant intra-group improvements ($p<0.05$) were found in both groups, with the exception of grip and pinch strength. Reductions in the VAS for pain at rest and during movement were found in both groups one week after IAI ($p=0.000$). A reduction in the VASs occurred from T4 to T12 in the TH/LD group ($p=0.000$), whereas a reduction in VASs only occurred at T8 in the LD group($p=0.008$).Both groups exhibited goniometric improvements only at T8($p=0.02$). Pulp-to-pulp and tripod pinch strength exhibited improvements beginning at T4($p=0.001$) and T8($p=0.000$), respectively. Hand function (COCHIN and AUSCAN) exhibited significant improvement beginning at T4($p=0.047$ and $p=0.000$, respectively), which was maintained through to the end of the study only with regard to the AUSCAN index ($p=0.001$).In the ultrasound evaluation, reductions in the quantitative measure of dorsal and palmar synovial hypertrophy occurred in both groups at T4($p=0.024$)and T8($p=0.005$), respectively. In the intergroup evaluation VASm ($p=0,014$) and VASs ($p=0,022$) showed better response in group TH/LD. There were no statistically significant differences intergroup for other variables. No substantial adverse effects were observed.

Conclusion: Proximal and distal IPs IAI with TH was effective in reducing swelling and joint movement pain in OA hands patients.

Disclosure: N. D. O. Spolidoro, None; **J. Natour**, None; **R. N. V. Furtado**, None; **F. S. Machado**, None; **H. A. Oliveira**, None.

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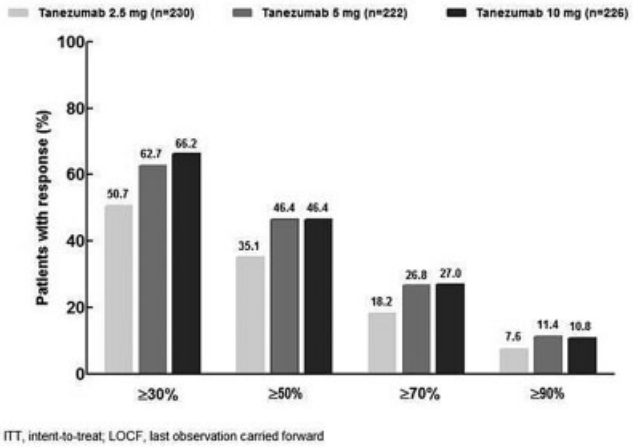
Long-Term Safety and Efficacy Of Subcutaneous Tanezumab In Patients With Knee Or Hip Osteoarthritis (NCT00994890). Leslie Tive[1], Eugene J. Dabezies[2], Robert J. Fountaine[3], Mark T. Brown[3], Michael D. Smith[3], Kenneth M. Verburg[3] and Christine R. West[4]. [1]Pfizer Inc, New York, NY, [2]Pensacola Research Consultants, Pensacola, FL, [3]Pfizer, Inc., Groton, CT, [4]Pfizer, Williamston, MI.

Background/Purpose: Tanezumab (TNZ), a monoclonal antibody that inhibits nerve growth factor, reduces hip or knee osteoarthritis (OA) pain. A non-controlled, randomized, double-blind study of TNZ 2.5, 5, and 10 mg administered by subcutaneous (SC) injection at 8-week intervals was conducted in patients with hip or knee OA.

Methods: Patients (N=678) with moderate to severe knee or hip OA were randomized in a 1:1:1 ratio and treated with TNZ 2.5 mg (n=230), 5 mg (n=222), or 10 mg (n=226) every 8 weeks. Efficacy analyses included change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain and Physical Function subscales, Patient's Global Assessment of OA (PGAO), and percentage of patients with ≥30%, ≥50%, ≥70%, and ≥90% improvement in WOMAC Pain. Safety assessments included adverse event (AE) documentation, physical and neurological examinations, and laboratory tests.

Results: The study discontinued prematurely due to a FDA partial clinical hold on TNZ non-cancer pain studies. Patients received 1 to 4 TNZ doses. Mean study treatment duration was 180, 191, and 187 days for TNZ 2.5, 5, and 10 mg treatment, respectively. TNZ 10 mg and TNZ 5 mg provided similar improvements from Baseline at Weeks 8 and 16 in WOMAC Pain, Physical Function, and PGAO; improvements were greater than with TNZ 2.5 mg. More patients had ≥30%, ≥50%, ≥70%, and ≥90% improvement in WOMAC Pain at Weeks 8 (Figure) and 16 with TNZ 10 and 5 mg than with TNZ 2.5 mg. Overall AE incidence was greatest with TNZ 10 mg (80.1%), followed by TNZ 5 mg (76.1%), and 2.5 mg (68.7%). The most frequently reported AEs were arthralgia, injection site reaction, and paresthesia. Osteonecrosis (ON) was reported as an AE in 4 patients (1.8%) treated with TNZ 10 mg, 4 patients (1.8%) in the TNZ 5 mg group, and 1 patient (0.4%) in the TNZ 2.5 mg group. Thirty-four patients had an all-cause total joint replacement. Of these, 22 (64.7%) events inclusive of the 9 cases of ON were subsequently adjudicated by a blinded external adjudication committee and none were adjudicated to primary ON. The percentage of patients with no new or worsened neurological examination abnormality at last assessment ranged from 82% to 88% across groups.

Figure. Reduction in WOMAC Pain Subscale for Week 8 (ITT, LOCF)



ITT, intent-to-treat; LOCF, last observation carried forward

Conclusion: Overall, SC TNZ provided improvements in Pain, Physical Function, and PGAO at all doses. TNZ 5 and 2.5 mg were better tolerated than TNZ 10 mg.

Disclosure: L. Tive, Pfizer Inc, 1, Pfizer Inc, 3; **E. J. Dabezies**, Pfizer Inc, 9; **R. J. Fountaine**, Pfizer Inc, 1, Pfizer Inc, 3; **M. T. Brown**, Pfizer Inc, 1, Pfizer Inc, 3; **M. D. Smith**, Pfizer Inc, 1, Pfizer Inc, 3; **K. M. Verburg**, Pfizer Inc, 1, Pfizer Inc, 3; **C. R. West**, Pfizer Inc, 1, Pfizer Inc, 3.

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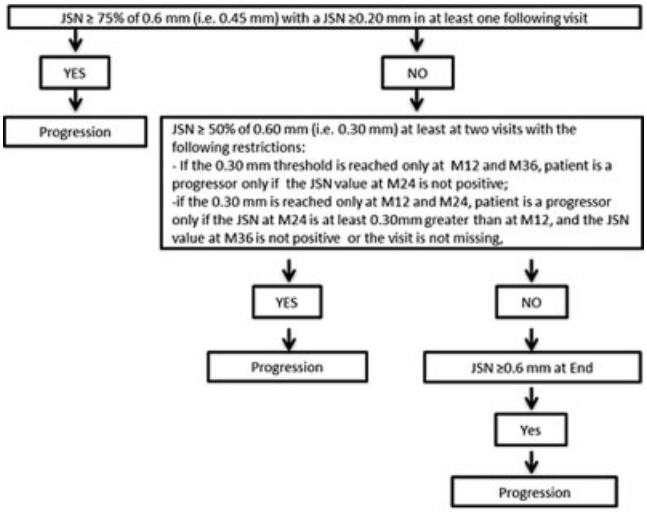
Strontium Ranelate Significantly Decreases Radiological Progression Using a New Definition For Radiological Progression In Patients With Primary Knee Osteoarthritis Treated With Strontium Ranelate. Olivier Bruyere[1], Roland Chapurlat[2], Cyrus Cooper[3] and Jean-Yves Reginster[1]. [1]University of Liège, Liège, Belgium, [2]INSERM UMR 1033 and University of Lyon, Hôpital Edouard Herriot, Lyon, France, [3]MRC Lifecourse Epidemiology Unit, Southampton, United Kingdom.

Background/Purpose: Strontium ranelate (SrRan) 2g/day has demonstrated a structure-modifying activity associated with symptoms improvement in patients with knee OA in a large, randomised, placebo-controlled, double-blind phase-III 3-year study. The objective of a planned analysis was to describe the efficacy of SrRan on radiological progression with a new definition of radiological progressing patients. This definition is based on an algorithm which aimed to ensure the robustness of the changes in JSW taking into account JSW change consistency over time. These radiological progressing patients have been demonstrated to be at higher risk of knee surgery[1].

Methods: 1683 patients with symptomatic primary knee OA (ACR criteria) were included and randomly assigned to SrRan 1g, 2g or placebo for 3 years. Percentage of radiological progressors between baseline and last observation were compared across groups in the intention to treat and per protocol populations using a chi-square test. A logistic model with adjustment on risk factors (age, BMI and Kellgren-Lawrence grade) was also carried out. Radiological progressors were defined as described below (exploratory method):



Results: The ITT set included 1371 (82% of the randomised set) patients. Age was 63±7 years, BMI was 30±5 kg/m^2, JSW was 3.5±0.8 mm. 61% were KL II. 69% were female. There were significantly fewer radiological progressors between baseline and last observation in the SrRan groups than in the placebo group: 23.8% ($p<0.001$), 25.3% ($p<0.001$) in the SrRan 1g and 2g groups respectively compared to the placebo group (41.7%%). The RRR (and NNT) compared to placebo were 42.9% (NNT=6) and 39.3% (NNT=7) in the 1g and 2g group, respectively. Results are confirmed on the per protocol population (N=865): 26.4% ($p<0.001$); 27.6% ($p<0.001$) in the SrRan 1g and 2g compared to 49.0% in the placebo group. After adjustment on confounding factors results are similar.

Conclusion: Strontium ranelate 1 and 2g/day significantly reduce the number of knee OA patients with a significant radiological progression suggesting a long-term beneficial effect on knee OA-related surgery.

Reference:

1 Bruyere et al, 2012. Prediction of knee surgery in patients with osteoarthritis by the use of a new definition of X-ray progression. 2012.Ost Int.23 (suppl2). S363.

Disclosure: O. Bruyere, IBSA, Merck Sharp Dohme, Nutraveris, Novartis, Pfizer, Rottapharm, Servier, Theramex, 2; **R. Chapurlat**, Servier, 2; **C. Cooper**, Amgen, ABBH, Novartis, Pfizer, Merck Sharp and Dohme, Eli Lilly, Servier, 5; **J. Y. Reginster**, Servier, Novartis, Negma, Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed, NPS, Theramex, UCB, 5, Merck Sharp and Dohme, Lilly, Rottapharm, IBSA, Genevrier, Novartis, Servier, Roche, GlaxoSmithKline, Teijin, Teva, Ebewee Pharma, Zodiac, Analis, Theramex, Nycomed, Novo-Nordisk, 9, Bristol Myers Squibb, Merck Sharp and Dohme, Rottapham, Teva, Lilly Novartis, Roche, GlaxiSmithKline, Amgen, Servier, 2.

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Prevention Of Radiological Progression In Patients With Primary Knee Osteoarthritis With Strontium Ranelate. Jean-Yves Reginster[1], Roland Chapurlat[2], Francis Berenbaum[3], P. Nash[4], O. Zamani[5], Martine Cohen-Solal[6], Gerolamo Bianchi[7], Jaime Branco[8], F. Navarro[9] and Cyrus Cooper[10]. [1]University of Liège, Liège, Belgium, [2]INSERM UMR 1033 and University of Lyon, Hôpital Edouard Herriot, Lyon, France, [3]AP-HP, St Antoine Hospital, Paris, France, [4]University of Queensland, Brisbane, Australia, [5]Rheumazentrum Favoriten, Wien, Austria, [6]INSERM U606 Hôpital Lariboisière, Centre Viggo Petersen, Paris, France, [7]ASL3 Genovese, Genoa, Italy, [8]Centro Hospitalar de Lisboa Ocidental, Hospital Egas Moniz, Lisboa, Portugal, [9]University Hospital Virgen Macarena, Sevilla, Spain, [10]MRC Lifecourse Epidemiology Unit, Southampton, United Kingdom.

Background/Purpose: Strontium ranelate (SrRan) has demonstrated a structure-modifying activity with symptomatic improvement in patients with

knee osteoarthritis (OA). This analysis aimed to compare the proportion of patients in whom radiological OA progression was prevented between groups, considering different cut-offs of JSN.

Methods: SEKOIA study included patients with symptomatic primary knee OA (Kellgren and Lawrence [KL] grade 2 or 3, JSW:2.5–5 mm) randomly allocated to SrRan 1 or 2 g/day or placebo. Primary endpoint was JSW radiographic change over 3 years in the medial compartment. JSW was measured yearly with validated computer-assisted centralized reading method. Patients with no relevant radiological OA progression were defined as those with a JSW loss from baseline to End, lower than 0.1mm, 0.2 mm or 0.3 mm. Patients who withdrew from the study were counted as non-responder. Treatment groups were compared to placebo using a chi^2 test.

Results: ITT set included 1371 (82% of the randomized set) patients. Age was 63±7 years, BMI was 30±5 kg/m2, JSW was 3.5±0.8 mm. 61% were KL II. 69% were female. A significantly greater proportion of patients in SrRan1g and 2g groups had no radiological progression compared to placebo: 40.5% and 44.1% vs. 32.8% ($p=0.017$ and $p<0.01$) with the 0.3 mm threshold. It corresponds to a proportion of responders increased by 24% and 34% in the SrRan 1g and 2g groups compared to placebo, with a number of patients needed to be treated (NNT) of 13 and 9. Similar results were observed at additional JSN cut-offs:

	Strontium ranelate 1 g (N = 445)	Strontium ranelate 2 g (N = 454)	Placebo (N = 472)
Responders: JSN ≥ −0.1 mm			
Patients who responded, n (%)	130 (29.21)	136 (29.96)	101 (21.40)
p-value	**0.006**	**0.003**	
RRR	**36.0**	**40.0**	
NNT	13	12	
Responders: JSN ≥ −0.2 mm			
Patients who responded, n (%)	161 (36.18)	173 (38.11)	133 (28.18)
p-value	**0.009**	**0.001**	
RRR	**28.4**	**35.2**	
NNT	**13**	**10**	
Responders: JSN ≥ −0.3 mm			
Patients who responded, n (%)	180 (40.5)	200 (44.05)	155 (32.80)
p-value	**0.017**	**<0.001**	
RRR	**23.5**	**34.3**	
NNT	**13**	**9**	

Conclusion: Treatment with SrRan is associated with a significantly greater number of patients without OA radiological progression over 3 years.

Disclosure: J. Y. Reginster, Servier, Novartis, Negma, Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed, NPS, Theramex, UCB, 5, Merck Sharp and Dohme, Lilly, Rottapharm, IBSA, Genevrier, Novartis, Servier, Roche, GlaxoSmithKline, Teijin, Teva, Ebewee Pharma, Zodiac, Analis, Theramex, Nycomed, Novo-Nordisk, 9, Bristol Myers Squibb, Merck Sharp and Dohme, Rottapham, Teva, Lilly Novartis, Roche, GlaxiSmithKline, Amgen, Servier, 2; **R. Chapurlat**, Servier, 2; **F. Berenbaum**, Servier, 2; **P. Nash**, Servier, 5; **O. Zamani**, None; **M. Cohen-Solal**, Servier, 5; **G. Bianchi**, Servier, 5; **J. Branco**, Servier, 5; **F. Navarro**, None; **C. Cooper**, Amgen, ABBH, Novartis, Pfizer, Merck Sharp and Dohme, Eli Lilly, Servier, 5.

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Impact On Cartilage Volume Changes Over Time Of Conventional Treatment and Of Glucosamine and Chondroitin Sulfate In Knee Osteoarthritis Patients: Data From The Osteoarthritis Initiative Cohort. Johanne Martel-Pelletier[1], Camille Roubille[1], Jean-Pierre Raynauld[1], François Abram[2], Pierre Dodin[2], Marc Dorais[3], Philippe Delorme[1] and Jean-Pierre Pelletier[1]. [1]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [2]Imaging Research & Development, ArthroLab Inc., Montreal, QC, [3]StatSciences Inc., Notre-Dame de l'Île Perrot, QC.

Background/Purpose: To explore, using data from participants enrolled in the progression cohort of the Osteoarthritis Initiative (OAI), the effects of conventional knee osteoarthritis (OA) pharmacological treatment and those of the SySADOA glucosamine and chondroitin sulfate (Glu/CS) on disease structural changes.

Methods: Six hundred knee OA subjects were included in a 24-consecutive-month follow-up study with annual knee X-rays and magnetic resonance imaging (MRI) of the most symptomatic (greatest WOMAC pain) knee. Participants were further stratified based on whether or not they received OA conventional pharmacological treatment and/or Glu/CS. The main outcomes were the loss of joint space width (JSW) and the loss of cartilage volume measured by MRI using a newly developed fully-automated system.

Results: Three hundred participants reported taking (+) (n=300) or not (−) (n=300) OA treatment (analgesic/NSAIDs) for 24 months, with or without Glu/CS. The +analgesic/NSAIDs subjects showed higher WOMAC scores ($p<0.0001$) and smaller JSW ($p=0.013$), reflecting a more severe disease at baseline vs. the -analgesic/NSAIDs participants. In the -analgesic/NSAIDs group, a reduction in the cartilage volume loss at 24 months in the medial central plateau ($p=0.007$ univariate and $p=0.03$ multivariate analysis) was found in those taking Glu/CS. In the +analgesic/NSAIDs group, the subjects receiving Glu/CS demonstrated less cartilage volume loss in the plateau at 12 months ($p=0.05$) and in the central plateau at 24 months ($p=0.05$). In addition, in the +analgesic/NSAIDs group, participants taking Glu/CS and having a JSW at baseline greater than the median (less severe disease) had less cartilage volume loss at both 12 and 24 months in the lateral plateau ($p=0.02$ and 0.03, respectively). By contrast, in all groups, no significant reduction in JSW over time was found.

Conclusion: In both the +analgesic/NSAIDs and -analgesic/NSAIDs groups, participants who received Glu/CS had reduced cartilage volume loss over 24 months mainly on the plateau when assessed with qMRI, arguing for a targeted DMOAD effect of Glu/CS, which could not be identified by X-ray alone.

Disclosure: J. Martel-Pelletier, ArthroLab, 4, Bioiberica, 5; **C. Roubille**, None; **J. P. Raynauld**, ArthroLab, 5; **F. Abram**, ArthroLab, 3; **P. Dodin**, ArthroLab, 3; **M. Dorais**, ArthroLab, 5; **P. Delorme**, None; **J. P. Pelletier**, ArthroLab, 4, Bioiberica, 5.

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Effects Of Chondroitin Sulfate On Brain Response To Painful Stimulation In Knee Osteoarthritis Patients: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Jordi Monfort[1], Jesús Pujol[1], O Contreras-Rodriguez[1], Jone Llorente-Onaindia[1], M López-Solà[1], Laura Blanco-Hinojo[1], J Deus[1], H Ortiz[1], Francisco Montañés[1], M Campillo[1], Pere Benito[1], Laura Sánchez[2], Marta Herrero[2] and Josep Vergés[3]. [1]Hospital del Mar, Barcelona, Spain, [2]Bioiberica, Barcelona, Spain, [3]Pre-Clinical and Clinical R&D Area, Pharmascience Division, BIOIBERICA S.A., Barcelona, Spain.

Background/Purpose: Knee osteoarthritis (OA) is a degenerative joint disease causing symptoms in 12% of people over the age of 65. A variety of treatments have been tested to alleviate knee OA symptoms, most being focused on reducing pain through analgesic or anti-inflammatory actions. Clinical studies have reported a beneficial effect of pharmaceutical-grade chondroitin sulfate (CS) on knee pain, and a parallel reduction in the rate of decline in joint space width. Nevertheless, not all clinical trials have been successful and reports exist suggesting that CS is not equally effective in all clinical situations (Clegg 2006). Inherent problems with efficacy assessment of pain medication are the lack of objective pain measurements and the large variability of subjective pain ratings. The aim of the present fMRI study was to objectively identify the effects of CS treatment on the brain response to pressure painful stimulation in patients with symptomatic knee osteoarthritis.

Methods: Phase IV, randomized, double-blind clinical trial in which patients received CS (pharmaceutical-grade manufactured by Bioibérica) 800 mg/day or placebo for a 4-month treatment course. Patients were assessed at baseline and after four-month of treatment. Two fMRI tests were conducted in each session by applying painful pressure on the knee medial interline (pain sensitive maneuver) and on the patella surface (cartilage selective targeting). The main outcome measurement was attenuation of the response evoked by knee painful stimulation in the pain-processing brain system.

Results: Twenty-two evaluable patients received CS and 27 placebo. No effects of CS were detected using the knee interline pressure test. Patients receiving CS showed a tendency to report reduced subjective pain after treatment during patella pressure test ($p=0.077$), but no significant group by session interaction was demonstrated. fMRI of patella pain, showed a larger activation reduction in the CS group than in placebo in a

posterior mesencephalon region including the periaqueductal gray (PAG). The entire PAG cluster (238 voxels) with significant interaction showed a pre>post-treatment difference at $p<0.05$ (peak difference at $x=-10$, $y=-34$, $z=-16$; $t=2.4$, $p=0.007$). In this paired analysis, the CS group showed significant activation reduction in the primary somatosensory cortex (including the cortical representation of the leg) and extending to the primary motor cortex and posterior supplementary motor area. Group by session interaction consistently revealed a tendency for this cortical change to be larger in the CS than in placebo (peak interaction $x=2$, $y=-6$, $z=72$; $t=2.96$, $p=0.002$ and 43 voxels -subthreshold- with $p<0.01$).

Conclusion: fMRI was sensitive to objectify CS effects on brain response to knee painful stimulation. The current work yields further support to the utility of fMRI to objectify treatment effects on OA pain. The positive treatment effect of CS on brain was identified on pain elicited by pressure on patellofemoral cartilage, where the cartilage component of pain is a relevant factor. This result is consistent with the known CS mechanisms of action and the results obtained in previous clinical trials.

Disclosure: J. Monfort, None; **J. Pujol**, None; **O. Contreras-Rodriguez**, None; **J. Llorente-Onaindia**, None; **M. López-Solà**, None; **L. Blanco-Hinojo**, None; **J. Deus**, None; **H. Ortiz**, None; **F. Montañés**, None; **M. Campillo**, None; **P. Benito**, None; **L. Sánchez**, Bioiberica, 3; **M. Herrero**, Bioiberica, 3; **J. Vergés**, Bioiberica, 3.

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Effect Of Fish Oil On Structural Progression In Knee Osteoarthritis: A Two Year Randomized, Double-Blind Clinical Trial Comparing High Dose With Low Dose. Catherine L. Hill[1], Graeme Jones[2], Susan Lester[3], Ruth Battersby[1], Tanya Fedorova[4], Kristen Hynes[5], Susanna Proudman[6], Leslie G. Cleland[6] and Lyn March[7]. [1]The Queen Elizabeth Hospital, Woodville, Australia, [2]Menzies Research Institute Tasmania, University of Tasmania, Hobart, 7000, Australia, [3]Queen Elizabeth Hospital, Woodville South, Australia, [4]University of Sydney, St Leonards, Australia, [5]University of Tasmania, Hobart, Australia, [6]Royal Adelaide Hospital, Adelaide, Australia, [7]University of Sydney Institute of Bone and Joint Research, Royal North Shore Hospital, St Leonards, Australia.

Background/Purpose: Fish oil is widely used for the symptomatic treatment of osteoarthritis. However, its effect on cartilage volume has not previously been investigated in an RCT. The objective of this study was to determine whether high dose fish oil is superior to low dose fish oil in retarding structural progression of symptomatic knee osteoarthritis.

Methods: Investigator initiated, government funded, randomized, double-blind, multicenter 24 month trial. Patients older than 40 years, with knee OA as defined by the ACR clinical criteria, suffering from regular knee pain were randomized 1:1 to (1) high dose fish oil liquid (EPA 18% and DHA 12%) 15mL/day or (2) low dose fish oil (blend of fish oil and sunola oil in a ratio of 1:9) 15mL/day. Each oil was also flavored with citrus to provide a comparable taste and ensure masking. Prior to randomization, a 4- week run in period with a similar oil was performed to exclude patients who were intolerant to liquid fish oil. Baseline knee radiographs were scored according to OARSI atlas. The co-primary end point was change in cartilage volume (medial tibial, lateral tibial, patellotibial) from baseline to 24 months. The co-primary endpoint of WOMAC pain score has previously been reported. Analysis of paired MRI data was performed, according to intention-to-treat and per-protocol analysis.

Results: Participants ($N=202$) were 49% female, mean age 60.9 yrs (SE 0.7), mean BMI 29.0 (SE 4.7). There was significantly greater and earlier dropout in the high dose group (34.6%, median 3 months), compared to the low dose group (19.8%, median 7.5 months). Participants from one site were excluded ($n=51$) due to technical MRI issue with baseline MRI data and a further 35 participants were excluded due to lack of paired MRI data. There was similar baseline characteristics in each group, except for gender (low dose group 38% female, high dose 58% female, $p=0.025$). The OARSI joint space narrowing and osteophyte scores were not different between groups. In intention to treat analysis ($n=116$), both groups demonstrated preservation or a slight increase in cartilage volume in each compartment over time with no significant difference seen between the two groups (Table 1). Similarly, per protocol analysis ($n=99$) demonstrated no decrease over time or difference between groups. There was no difference in results when males and females were analyzed separately.

Table 1.

		CHANGE FROM BASELINE (ITT)			Delta-Delta[1]		
MRI	Group	mean	sd	$p\text{-val}_{change}$	mean	sd	$p\text{-value}_{H\ vs\ L\ change}$
Lateral tibial	LowDose	0.015	0.027	0.58	0.000	0.038	1.00
	High Dose	0.015	0.026	0.57			
Medial tibial	LowDose	0.015	0.029	0.60	0.020	0.040	0.63
	High Dose	0.035	0.028	0.63			
Patellotibial	LowDose	0.027	0.040	0.50	0.030	0.055	0.59
	High Dose	0.003	0.039	0.94			

Conclusion: High dose fish oil supplementation for 2 years was not significantly different in its effect on cartilage volume in patients with symptomatic knee OA, when compared to low dose fish oil. The lack of a decrease in both groups is unexpected and may imply that both therapies have chondroprotective properties.

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2148

Use Of Low Dose Aspirin Is Associated With Reduced Medial Tibial Cartilage Loss In Symptomatic Osteoarthritis: DATA From A Cohort Study. Anita Wluka[1], Changhai Ding[2], Yuanyuan Wang[1], Graeme Jones[3], Andrew Teichtahl[1] and Flavia Cicuttini[4]. [1]Monash University, Melbourne, Australia, [2]Menzies Research Institute Tasmania, University of Tasmania, Hobart, 7000, Australia, [3]Menzies Research Institute, Tasmania, Australia, [4]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, 3004, Australia.

Background/Purpose: Inflammation and vascular disease have recently been shown to play a role in the pathogenesis of osteoarthritis (OA). Low dose aspirin is commonly used in the prevention of cardiovascular disease. Its effects have been attributed to a variety of actions, including anti-inflammatory effects and effects on platelet function (both anti-thrombotic and anti-inflammatory) and lipids. However whether it affects human joints has not been studied. The aim of this study was to examine whether the use of low dose aspirin affects change in knee cartilage volume over 2 years.

Methods: 117 people with symptomatic knee OA underwent magnetic resonance imasging of the knee at baseline and 2 years later. Medial and lateral tibial cartilage volumes were measured using validated methods. Annual absolute change and annual percentage change in cartilage volume were calculated. Information about regular low dose aspirin use was collected at baseline, 6, 12 and 24 months. Participants who reported taking regular low dose aspirin (< 150 mg per day) at more than 1 time point were defined as being aspirin users.

Results: Twenty six participants reported taking aspirin at more than one visit, with 91 not taking aspirin. At baseline, the only significant difference between the 2 groups was that those taking aspirin were older than those who did not ($p = 0.03$). In those taking aspirin, annual change in medial tibial cartilage volume and annual percentage change in cartilage volume was approximately half that seen in those not taking aspirin (−50 vs. −102 mm 3 and −2.5% vs. −5.5%, respectively, $P=0.04$ for both). These differences became more significant after adjusting for age, gender, body mass index, initial cartilage volume and severity of radiographic change in the medial compartment. The annual change in medial tibial cartilage volume was −40 mm 3 (95% confidence interval (CI) −83, 1.3) in aspirin users vs. −105 mm3 (95% CI −127, −82) in nonaspirin users ($P = 0.009$ for difference). The annual percentage change in medial tibial cartilage volume was −2.0% (95% CI −4.6, 0.53) in aspirin users vs. −5.6% (95% CI −6.9, −4.0) in non-aspirin users ($P=0.02$ for difference). There were no significant differences observed in change in lateral tibial cartilage volume.

Conclusion: This study showed that in people with knee OA, the use of low dose aspirin was associated with reduced medial tibial cartilage loss over 2 years. This requires confirmation in a randomised controlled trial. If this hypothesis were proven, aspirin may provide a cost effective disease modifying therapy for OA as it is a cheap medication that is already in common use and known to be well tolerated.

Disclosure: A. Wluka, None; **C. Ding**, None; **Y. Wang**, None; **G. Jones**, None; **A. Teichtahl**, None; **F. Cicuttini**, None.

2149

Safety Of Lower-Dose Diclofenac Submicron Particle Capsules Dosed Up To 12 Weeks In Patients With Osteoarthritis. Clarence Young[1] and Marc C. Hochberg[2]. [1]Iroko Pharmaceuticals, Philadelphia, PA, [2]University of Maryland, Baltimore, MD.

Background/Purpose: Osteoarthritis (OA) is the most common cause of disability in the US and is frequently managed with non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs, including diclofenac, are associated with dose-related gastrointestinal, cardiovascular, and renal adverse events (AEs). As a result, the US Food and Drug Administration issued a Public Health Advisory encouraging physicians to prescribe NSAIDs at "the lowest effective dose for the shortest duration consistent with individual patient treatment goals." The efficacy of new, submicron particle NSAIDs is under investigation. These drugs have enhanced absorption and may be efficacious at lower doses than commercially available NSAIDs. We report phase 3 safety data in patients with OA pain dosed up to 12 weeks with diclofenac submicron particle capsules.

Methods: This randomized, multicenter, double-blind, parallel-group study enrolled 305 patients 41 to 90 years of age with OA of the hip or knee, which was documented radiologically (Kellgren-Lawrence grade II–III). Enrolled patients were chronic NSAID and/or acetaminophen users with a WOMAC pain subscore ≥40 mm/100-mm at baseline and a documented OA pain "flare" (increase in WOMAC pain subscale ≥15 mm) following NSAID discontinuation. Patients received either diclofenac submicron particle capsules 35 mg TID or BID, or placebo. The primary endpoint was mean change from baseline in WOMAC pain subscore at week 12. Safety and tolerability were also assessed.

Results: Most patients were female (203/305, 66.6%) with an age (mean ± SD) of 61.6 ± 8.9 years. Diclofenac submicron particle capsules 35 mg TID provided significantly better pain relief than placebo (P = 0.0024) with numerical evidence of pain relief in the diclofenac submicron particle capsules 35 mg BID treatment group, although this did not achieve statistical significance (P = 0.0795). The most frequent AEs (>3% in any treatment group) were generally similar across treatment groups (**Table**). Serious AEs occurred in 3.0% (9/305) of patients and were generally comparable across treatment groups. No serious gastrointestinal bleeds or cardiovascular or renal AEs occurred in any treatment group. The most frequent AEs in patients who withdrew from the study (≥1% in any treatment group) included diarrhea (3/305, 1.0%), upper abdominal pain (3/305, 1.0%), and alanine aminotransferase elevation (3/305, 1.0%). There was no difference across treatment groups for withdrawals due to AEs.

Adverse Event	Diclofenac Submicron 35 mg TID (n = 98) n (%)	Diclofenac Submicron 35 mg BID (n = 104) n (%)	Placebo (n = 103) n (%)
Nausea	9 (9.2)	5 (4.8)	2 (1.9)
Diarrhea	7 (7.1)	5 (4.8)	3 (2.9)
Headache	6 (6.1)	2 (1.9)	3 (2.9)
Constipation	4 (4.1)	3 (2.9)	4 (3.9)
URI	3 (3.1)	3 (2.9)	6 (5.8)
Upper abdominal pain	3 (3.1)	3 (2.9)	1 (1.0)
Nasopharyngitis	1 (1.0)	5 (4.8)	5 (4.9)
Sinusitis	3 (3.1)	2 (1.9)	1 (1.0)
Serum creatinine elevation	3 (3.1)	1 (1.0)	0 (0.0)
Dyspepsia	3 (3.1)	1 (1.0)	1 (1.0)
ALT elevation	3 (3.1)	1 (1.0)	0 (0.0)
UTI	2 (2.0)	0 (0.0)	4 (3.9)

TID = three times daily; BID = twice daily; URI = upper respiratory tract infection ALT = alanine aminotransferase; UTI = urinary tract infection.

Conclusion: Investigational, lower-dose diclofenac submicron particle capsules were generally well-tolerated in a phase 3 study of patients with OA. No serious gastrointestinal bleeds or cardiovascular or renal AEs occurred over 12 weeks of treatment.

Disclosure: C. Young, Iroko Pharmaceuticals LLC, 3; **M. C. Hochberg**, Abbvie, Inc, 5, Bioiberica SA, 5, Eli Lilly and Company, 5, Genentech, Inc, 5, Iroko Pharmaceuticals, LLC, 5, Merck, Inc, 5, Novartis Pharma AG, 5, Pfizer, Inc, 5, Savient Pharmaceuticals, 5.

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Comparative Effectiveness Of Pharmacological Interventions For Knee Osteoarthritis: A Network Meta-Analysis. Raveendhara R. Bannuru[1], Timothy E. McAlindon[1], John B. Wong[1], David Kent[1] and Christopher Schmid[2]. [1]Tufts Medical Center, Boston, MA, [2]Brown University, Providence, RI.

Background/Purpose: With the rapidly aging US population and obesity epidemic, the prevalence of knee osteoarthritis (OA) is increasing exponentially. Although a wide variety of symptomatic interventions are available, head to head comparisons are limited, and no study compares all of the treatment options against each other.

To date, we have relied on traditional meta-analysis, which only provides the relative merits of options compared directly in randomized controlled trials (RCTs) for a given condition. Network meta-analysis—an innovative approach for comparing multiple interventions in a single analysis- combines direct (head to head) and indirect (through a common comparator) evidence to increase power and precision for the effect estimates and also assigns probabilities of superiority. This approach can determine the relative comparative effectiveness of interventions that have never been compared directly in a single trial.

Methods: We searched Medline, EMBASE, Web of Science and Cochrane Database from inception to April 2013 with no language restrictions and actively sought unpublished data. We included RCTs conducted in adults with knee OA comparing two or more of the following most widely prescribed treatments: acetaminophen, non-selective NSAIDs (diclofenac, ibuprofen, naproxen), Cox-2 selective NSAIDs (celecoxib), intra-articular (IA) corticosteroids, IA hyaluronic acid, oral placebo and IA placebo. We calculated effect sizes for pain and function for each study at 12 weeks from baseline. We performed network meta-analysis using a Bayesian random effects model with non-informative priors.

Results: Of the 127 eligible RCTs, 124 reported pain and 72 reported function outcomes. These trials included 29,842 participants with an age range of 45–75 years (Figure 1). The proportion of women ranged from 28%–100%. For pain, all treatments were better than oral placebo and all were better significantly except for IA placebo (Figure 2). For function, oral treatments had effect sizes similar to pain, but IA treatments had a smaller effect size though comparable to oral treatments.

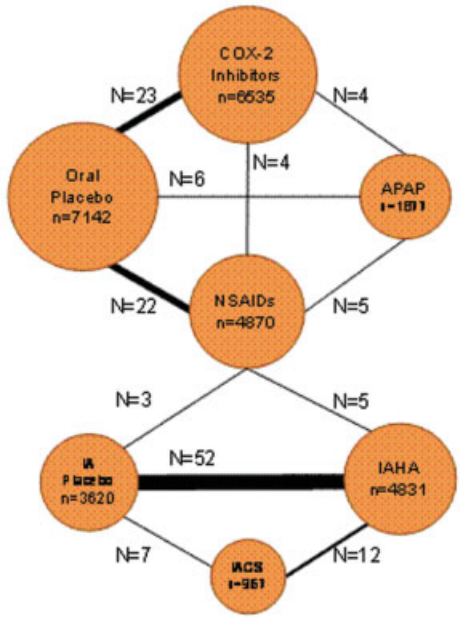

Figure 1. Network of Treatment Comparisons for Pain

Circle size reflects n of participants and the line width reflects N of direct comparisons. No connecting line between two circles indicates that there was no direct comparison between the two treatments. *APAP*=Acetaminophen; *IA*=Intra-articular; *IAHA*=Intra-articular hyaluronic acid; *IAGS*=Intra-articular Corticosteroids

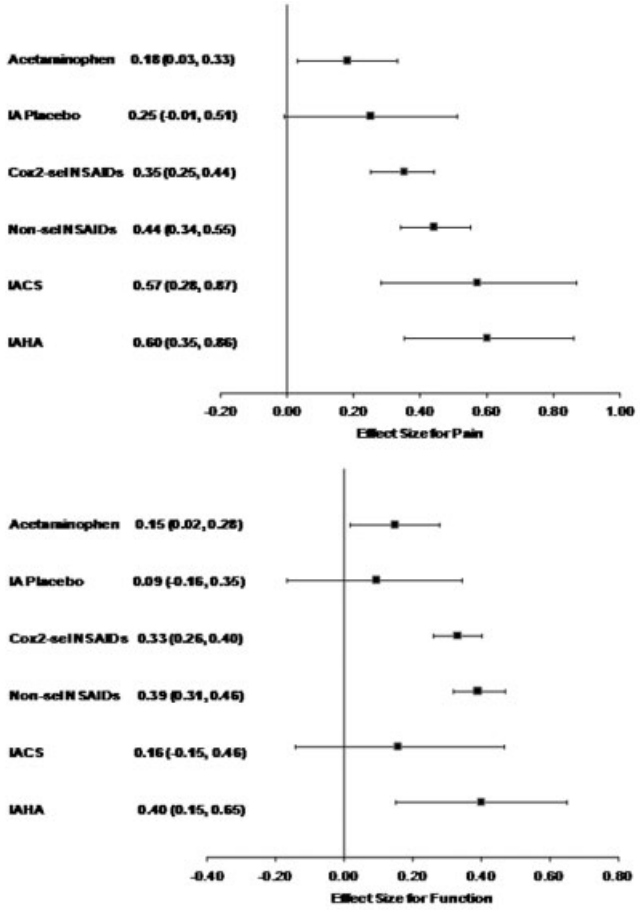

Figure 2. Treatment Effects Relative to Oral Placebo for Pain and Function

Positive effect size favors treatment over oral placebo; IA=Intra-articular; IAC=Intra-articular corticosteroids; IAHA=Intra-articular hyaluronic acid

Conclusion: For knee OA pain, IA treatments were more efficacious than oral treatments may be because of the integrated IA placebo effect. Both cox-2 selective and non-selective NSAIDs were substantially better than acetaminophen. This information along with the safety profile and relative cost would be helpful for clinicians in choosing care tailored to individual patient. This novel method may be of additional value for the treatment guideline groups, who would like to weigh multiple interventions against a common comparison.

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Synergistic Effect of Combining BioniCare® in an Unloading Brace for Osteoarthritis of the Knee. Thomas Zizic[1], David S. Hungerford[2], Edmund J. MacLaughlin[3], Craig Mines[4], Shaili Deveshwar[5], Theresa Lawrence Ford[6], Cynthia Elliott[6], John R. Principe[7], Jack S. Tuber[8] and Joy Schechtman[9]. [1]The Johns Hopkins University School of Medicine, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, [3]The Johns Hopkins University School of Medicine, Cambridge, MD, [4]East Side OrthoCare, Snellville, GA, [5]Sports Medicine and Orthopedic Center, Greensboro, NC, [6]North Georgia Rheumatology, Lawrenceville, GA, [7]WellBeingMD, Palos Heights, IL, [8]The Johns Hopkins University, Baltimore, Maryland, Baltimore, MD, [9]SunValley Arthritis Center, Peoria, AZ.

Background/Purpose: The purpose of this study was to see if incorporating the BioniCare device into an unloading brace would produce more rapid improvement, greater compliance and therefore greater effectiveness

Methods: 289 patients who were treated with BioniCare alone served as historical controls and were compared with 225 patients treated with BioniCare combined with VQ's OActive unloading brace. A generalized linear model repeated measures analysis of change from baseline was performed, with sex, age, treatment (BioniCare in knee OActive unloading brace versus BioniCare alone), cumulative device use at each month of follow-up (1, 3, 6 and 12 months), and baseline score as predictors of the model.

Results: It was demonstrated that BioniCare combined with the OActive unloading brace was superior to BioniCare alone. Except for Sleep Pain, and Physicians Global Assessment which trended toward statistical significance, there was statistically significant superiority of BioniCare treatment combined with an unloading brace as compared to BioniCare alone. (Table I) With the exception of the one month evaluation of pain while sleeping at night, all seven outcome measures were superior with BioniCare combined in the OActive unloading brace as compared to BioniCare alone at 1,3,6 and 12 months of treatment. After three months of treatment both groups had a moderate effect size in all outcome parameters. As can be seen in the illustrative figures, the patient global assessment, patient pain on walking up and down stairs, and the physician global assessment had a large effect size (>1.0) at one year in the BioniCare combined with the unloading brace group. (Figures 1, 2) In the combined group, the effect size approached 1.0 with pain on walking on a flat surface (figure 2).

Efficacy End-point	Estimate Treatment Difference	Std Err	Chi-Square Test	p-value
48 hr. OA Pain	0.2060	0.0527	15.28	<.0001
MD Global Assessment	0.0927	0.0532	3.04	0.0814
OA Pain	0.1864	0.0516	13.07	0.0003
PT Global Assessment	0.2066	0.0543	14.48	0.0001
Sleep Pain	0.0295	0.0553	0.29	0.5933
Up/Down Stairs	0.2684	0.0582	21.29	<.0001
Walking Pain	0.2119	0.0536	15.65	<.0001

NOTE: Treatment effect as estimated from a generalized linear model of repeated measures

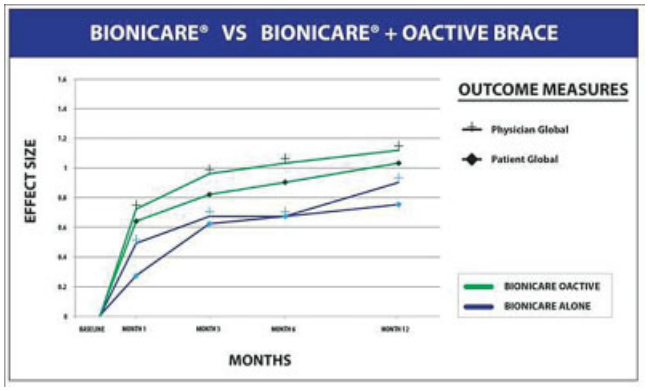

Fig. 1. Change From Baseline Time Physician and Patient Global

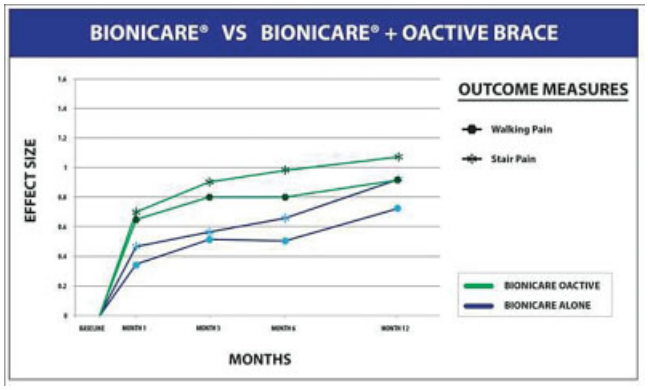

Fig. 2. Change From Baseline Time Walking Pain and Stair Pain

Conclusion: There is an additive benefit of combining an unloading brace with BioniCare device treatment and the advantage of this combination continued throughout the study and was apparent even after one year of treatment.

Disclosure: T. Zizic, VQ OrthoCare, 5; **D. S. Hungerford**, None; **E. J. MacLaughlin**, None; **C. Mines**, None; **S. Deveshwar**, None; **T. L. Ford**, None; **C. Elliott**, None; **J. R. Principe**, None; **J. S. Tuber**, None; **J. Schechtman**, None.

2152

Predicting Benefit From Lateral Wedge Orthotics Using Radiographic Parameters In Medial Knee Osteoarthritis. Berna Goker[1], Roy H. Lidtke[2], Laura E. Thorp[2], Markus A. Wimmer[2] and Joel A. Block[2]. [1]Gazi University, Ankara, Turkey, [2]Rush University Medical Center, Chicago, IL.

Background/Purpose: Lateral wedge foot orthosis have been used therapeutically in patients with medial knee osteoarthritis (OA) with inconsistent results. The current theory suggests they reduce medial knee loading by shifting the ground reaction force vector, and thereby potentially modify progression of OA. Predicting a beneficial result from usage of lateral wedge orthotics is crucial since results to-date suggest that responses in large groups of subjects are heterogeneous. We aimed to investigate radiographic parameters in patients with medial knee OA that might prospectively distinguish those who benefit from lateral wedge from those who do not.

Methods: Participants (n=109) with radiographic (KL grades 2–3) and symptomatic (at least 30mm pain of 100 mm scale while walking) medial compartment knee OA were enrolled in a previously reported 36 month double blind study to clinically assess a 7 degree lateral wedge custom foot orthosis versus a neutral 0 degree posted control. In the current study, 35 patients in the lateral wedge arm who had complete data were included. Subjects underwent gait analyses. Post hoc analysis identified a group as 'unloaders' if knee adduction moments gradually decreased over time with the use of wedge. Image J software (US NIH, Bethesta, MD, http://rsbweb.nih.gov/ij/) was used to measure radiographic parameters that included: knee alignment angle, tibial shaft angle measured at three levels: from tibial plateau to the tibial plafond (long axis), from mid tibial level to plafon and from lower third of tibia to plafond (lower axis), as well as the narrowest joint space widths of the hip, knee and ankle joints. The difference between the varus angle of tibial long axis and tibial lower axis was calculated for each patient to estimate the varus angulation of the distal 1/3 of the tibial shaft. Correlations of radiographic parameters were analyzed in the entire group. Non-parametric tests were used for statistical analysis to compare groups. A p value of ≤ 0.05 was considered significant.

Results: Twenty patients were classified as 'unloaders' while 15 were noted to be unresponsive to the therapy. These responsive unloaders had larger distal tibial varus angle compared to those who did not have significant reduction in knee adduction moments with lateral wedge (median(IQR) 1.3(0.8) vs. 0.6(1.5) degrees, respectively, p=0.042). None of the other radiographic parameters studied differed between those who benefitted from lateral wedge and those who did not. Importantly, assessment of the difference between the tibial long axis and the lower one third tibial axis (lower angle minus long axis) revealed a significant correlation with the knee alignment angle (r=0.26, p=0.01).

Conclusion: The correlation between the knee alignment angle and the difference between tibial long axis and lower one third tibial axis suggests that as the knee presents with more varus, there is a varus bend in the lower tibia. Specifically, curvature of the lower tibia appears to be the primary varus deformity seen in the lower extremity with medial knee OA. These results suggest that distal tibial varus could be a radiographic parameter predicting a beneficial result from a lateral wedge orthotic in patients with medial knee OA.

Disclosure: B. Goker, None; **R. H. Lidtke**, None; **L. E. Thorp**, None; **M. A. Wimmer**, None; **J. A. Block**, Ferring, Inc., 5, PL Pharma, Inc., 9.

2153

Arrest Of Progressive Loss Of Vibratory Perception In Knee Osteoarthritis: Effects Of a 48 Week Biomechanical Intervention. Najia Shakoor, Roy H. Lidtke, Louis F. Fogg, Laura E. Thorp, Markus A. Wimmer, Rachel A. Mikolaitis and Joel A. Block. Rush University Medical Center, Chicago, IL.

Background/Purpose: Somatosensory function has been shown to be altered in knee osteoarthritis (OA); for example, we previously observed that in knee OA there are generalized deficits of vibratory perception in the upper and the lower extremity compared to age-matched controls, though it remains unclear whether these deficits worsen during the course of OA. Biomechanical interventions that reduce dynamic loading during gait are promising strategies that may improve pain and retard disease progression, though their relationship to somatosensory function is unknown. Here, we present data from a double-blind randomized controlled study of a flexible shoe ("mobility" shoe), which has previously been shown to reduce medial compartment knee loading, on the progression of vibratory deficits in participants with knee OA.

Methods: Participants were enrolled in a randomized controlled study of a flexible-soled shoe ("mobility" shoe) vs an identical appearing "control" shoe with stiffer sole. This was a 6-month primary study and participants had the opportunity to continue for an additional 18 months. Here we evaluate the interim 48 week data. All participants had radiographic (KL grades ≥ 2) and symptomatic (at least 30/100 mm on VAS) medial compartment knee OA. In those with bilateral OA, the most symptomatic side was considered the "affected" side. Investigators and participants were blinded to shoe assignment. Vibratory perception threshold (VPT) was measured using a biothesiometer that provided vibratory stimulation at multiple predetermined anatomic sites, including an upper extremity site. VPT was recorded as the first sensation of vibration (volts).

Results: 50 participants were randomized, 22 to the active "mobility" shoe and 28 to the control group. 24 participants continued with the study extension, 11 in the "mobility" group (7 female, mean age 59±4 years) and 13 in the control group (10 female, mean age 52±9 years). Changes in VPT at the various sites are summarized in Table 1. VPT worsened significantly over 48 weeks at each site in the control group except the medial ankle, but there were no significant changes in the mobility group. Changes in VPT were not correlated with baseline age or with pain improvement.

	Mobility group				Control group			
	Baseline VPT (volts)	48 week VPT (volts)	Effect size	p value for difference	Baseline VPT (volts)	48 week VPT (volts)	Effect size	p value for difference
1st MTP	15.1±10.0	15.4±7.9	−0.03	0.91	11.2±5.7	13.4±6.1	−0.73	0.02
Medial ankle	18.6±8.2	18.1±5.0	0.07	0.81	15.7±6.9	17.0±6.9	−0.21	0.45
Lateral ankle	19.6±11.0	16.6±4.0	0.29	0.36	14.3±6.3	17±6.2	−0.59	0.05
Medial knee	18.1±8.8	17.5±5.7	0.07	0.81	15.4±7.3	19.0±10.1	−0.73	0.02
Lateral knee	17.2±6.0	18.5±6.5	−0.21	0.50	15.6±7.1	19.8±8.8	−0.60	0.05
Tibial tuberosity	15.8±5.3	17.3±6.6	−0.26	0.40	13.3±4.8	16.2±4.7	−0.65	0.03
Radial styloid	9.0±1.4	9.3±2.0	−0.14	0.64	7.1±2.3	8.2±1.8	−0.69	0.03

Conclusion: Lower extremity OA is known to be associated with altered somatosensory function, including vibratory perception deficits. Here we demonstrate that in knee OA, vibratory perception worsens significantly over time. In addition, alteration in footwear with sustained mechanical unloading during gait appears to arrest that progression of vibratory loss both in the affected lower extremity as well as in the upper extremity in such patients. The clinical significance and relationship of these findings to OA disease progression need better elucidation in future studies.

Disclosure: N. Shakoor, Dr. Comfort shoe, 7; **R. H. Lidtke**, Dr. Comfort, 7, Dr. Comfort, 5; **L. F. Fogg**, None; **L. E. Thorp**, None; **M. A. Wimmer**, None; **R. A. Mikolaitis**, None; **J. A. Block**, Ferring, Inc., 5, PL Pharma, Inc., 9.

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Improvement In Clinical Symptoms After 48 Weeks Of Wearing Flexible Footwear In Osteoarthritis Of Knee: A Randomized Placebo-Controlled Study. Najia Shakoor, Roy H. Lidtke, Louis F. Fogg, Laura E. Thorp, Markus A. Wimmer, Rachel A. Mikolaitis and Joel A. Block. Rush University Medical Center, Chicago, IL.

Background/Purpose: Osteoarthritis (OA), the most common form of arthritis, is a major cause of pain and disability. Biomechanical interventions that reduce dynamic loading are a promising strategy to improve pain and retard disease progression, though prior studies in OA have not shown dramatic efficacy. In addition, the large placebo effect inherent in studies of OA pain make it difficult to prove clinical efficacy in short studies. Here, we present data from a double-blind randomized controlled study of a flexible shoe ("mobility" shoe), which has previously been shown to reduce medial compartment knee loading, on self-reported clinical outcomes over 48 weeks.

Methods: Participants were enrolled in a 6-month randomized controlled study of a flexible soled shoe (mobility shoe) vs identical appearing control shoe with stiffer sole. Participants had the opportunity to continue the study for an additional 18 months. Here, we evaluate the interim 48 week data. All participants had radiographic (KL grades ≥ 2) and symptomatic (at least 30/100 mm pain on VAS) medial compartment knee OA. Investigators and participants were blinded to shoe assignment. Baseline and follow up clinical symptoms were evaluated using WOMAC visual analog scales and modified KOOS questionnaires. Data were evaluated to determine "responders" according to modified OMERACT-OARSI responder criteria, with Chi-squared analysis to evaluate the difference in number of responders. Independent samples t-test was used to evaluate differences in percent improvement in WOMAC and KOOS subscales between the groups.

Results: 50 participants were enrolled in the randomized controlled trial, 22 to the active "mobility" shoe and 28 to the control group. 24 participants continued with the study extension, 11 in the "mobility" group (7 female, mean age 59±4 years) and 13 in the control group (10 female, mean age 52±9 years). Changes in pain and symptoms over 48 weeks are detailed in the Table. Overall, there were greater improvements in pain, function and quality of life measures in the active mobility group vs control group. Changes in pain were not correlated with age. In addition, using OMERACT-OARSI response criteria, the mobility group had significantly more responders (10 out of 11) than the control group (6 out of 13), (Chi squared= 5.37, df=1, p=0.023). Thus, participants who wore the flexible shoe were 1.98 times more likely to show clinical improvement than those in the control.

Table.

	Improvement in mobility group (%±SD)	Improvement in control group (%±SD)	p value for difference between groups
WOMAC pain	73±26	37±57	0.06
WOMAC function	70±40	40±70	0.22
WOMAC stiffness	73±30	41±44	0.05
KOOS symptoms	13±21	4±19	0.05
KOOS pain	39±56	6±35	0.10
KOOS quality of life	42±66	11±37	0.02
KOOS sports and recreation	67±200	29±33	0.55

Conclusion: These data demonstrate significant clinical improvements in the active group, assigned to flexible footwear, compared to a non-flexible footwear control group, including a higher percentage of OMERACT-OARSI responders and greater percent improvements in self-reported clinical outcomes measures in the active group. Notwithstanding the small numbers, these results suggest optimism for the long term efficacy of biomechanical interventions for knee OA.

Disclosure: N. Shakoor, Dr. Comfort, 7; **R. H. Lidtke**, Dr. Comfort, 7, Dr. Comfort, 5; **L. F. Fogg**, None; **L. E. Thorp**, None; **M. A. Wimmer**, None; **R. A. Mikolaitis**, None; **J. A. Block**, Ferring, Inc., 5, PL Pharma, Inc., 9.

2155

Beneficial Effect Of Long-Term Use Of a Low-Cost Minimalist Footwear On Joint Load, Clinical, and Functional Aspects Of Elderly Women With Knee Osteoarthritis. Francis Trombini-Souza[1], Alessandra Matias[1], Mariane Yokota[1], Marco Butugan[1], Ivye Pereira[1], Claudia Goldenstein-Schainberg[2], Ricardo Fuller[3] and Isabel C.N. Sacco[1]. [1]School of Medicine, University of São Paulo, São Paulo, Brazil, [2]Reumatologia, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, [3]University of Sao Paulo, São Paulo, Brazil.

Background/Purpose: Positive outcomes of minimalist shoes on reduction of overload in patients with knee osteoarthritis (OA) have been highlighted. We have recently shown beneficial effects of acute use of a low-cost minimalist flat, flexible and non-heeled footwear in aged women with knee OA. Based on the chronic aspect of the disease, we now aim to investigate the long-term effects of this same footwear on gait biomechanics, clinical, and functional features of elderly women affected by knee OA.

Methods: Twenty-eight elderly women with grade 2 or 3 Kellgren and Lawrence knee OA were randomized and allocated to either intervention group (IG, n=16) which wore this minimalist shoe (Moleca) for 6 months for at least 6 hours daily, or to control group (CG, n=12) which did not wear these nor similar shoes. Physical therapy treatment was not allowed throughout the study. A diary was used to record the amount of daily use of the footwear intervention and paracetamol intake; every 2 weeks, adherence to treatment was verified through phone calls. All patients were assessed at baseline, 3th and 6th month by a physician and a physiotherapist, both blinded to group allocation. Primary outcome was pain WOMAC score and secondary ones were global WOMAC; joint stiffness and disability WOMAC scores; amount of paracetamol rescue medication intake over 6 months; knee adduction moment (KAM) during gait; knee edema and joint effusion. Multiple imputation methods and intention-to-treat analysis were performed. Treatment-time interactions were detected by general linear models of analysis of variance for repeated measure. Statistical significance is based at $\alpha = 5\%$.

Results: Interaction effect was observed for WOMAC pain (p=.007), function (p=.035) and WOMAC total score (p=.012). The percentage changes are in table 1. IG experienced a reduction by 18% (p=.043) in first peak KAM, 39% (p=.025) in KAM during midstance phase, and 29% (p=.041) in KAM impulse compared with CG at the end of intervention. Paracetamol intake was lower IG vs. CG at 4th (p=.004), 5th (p=.006) and 6thmonths (p=.012). Clinical aspects as knee edema and effusion did not present any difference in both IG and GC at the end of intervention.

Table 1. Percentage of change in the 3rd and in the 6th month by both groups in the WOMAC scores.

Variable	Group	6thmonth	
WOMAC Pain (% reduction)	*Intervention*	47%	60%
	Control	32%	16% *(n. s.)*
WOMAC Function (% improvement)	*Intervention*	45%	51%
	Control	25%	14% *(n. s.)*
WOMAC Total (% improvement)	*Intervention*	46%	52%
	Control	24%	15% *(n. s.)*

Conclusion: Long-term use of this flat, flexible and non-heeled shoe proved to be beneficial in elderly women with knee OA and thus can be prescribed as a low-cost non-invasive treatment capable to decrease pain and knee overload, and to improve overall function.

Disclosure: F. Trombini-Souza, State of Sao Paulo Research Foundation (FAPESP), 2; **A. Matias**, State of Sao Paulo Research Foundation (FAPESP), 2; **M. Yokota**, State of Sao Paulo Research Foundation (FAPESP), 2; **M. Butugan**, None; **I. Pereira**, None; **C. Goldenstein-Schainberg**, None; **R. Fuller**, None; **I. C. N. Sacco**, National Council for Scientific and Technological Development (CNPq), 2.

2156

Weight Change Has A Disease Modifying Effect On Knee Structure and Symptoms In Obese Individuals Without Diagnosed Knee Osteoarthritis. Andrew Teichtahl[1], Anita Wluka[1], Stephanie Tanamas[1], Yuanyuan Wang[1], Boyd Strauss[1], Joseph Proietto[2], John Dixon[3], Graeme Jones[4], Andrew Forbes[1] and Flavia Cicuttini[5]. [1]Monash University, Melbourne, Australia, [2]University of Melbourne, Melbourne, Australia, [3]Baker Institute, Melbourne, Australia, [4]Menzies Research Institute, Tasmania, Australia, [5]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, 3004, Australia.

Background/Purpose: Although the strongest modifiable risk factor for the development of knee osteoarthritis (OA) is obesity, there are a paucity of data examining the effects of weight change on knee joint structures and symptoms. This study examined the effect of weight change on change in knee cartilage volume and symptoms in an obese cohort.

Methods: 112 obese subjects (BMI ≥ 30 kg m^{-2}), unselected for any musculoskeletal disease, were recruited from various community sources to examine the effect of obesity on musculoskeletal health. Tibial cartilage volume, determined by magnetic resonance imaging, and knee symptoms, determined by the Western Ontario and McMaster Osteoarthritis Index (WOMAC), were collected at baseline and an average of 2.3 years later.

Results: Percentage weight change was associated with change in medial tibial cartilage volume (β −1.3mm^3, 95% CI −2.4 to −0.1 mm^3, p = 0.03) that was consistent throughout the spectrum of weight loss through to mild weight gain. Percentage weight change was not associated with change in the lateral tibial (p = 0.93) or patella (p = 0.32) cartilage volumes. Percentage weight change was associated with change in all WOMAC sub-scales (all p ≤ 0.01): pain (β −1.8mm, 95% CI −3.2 to −0.4mm), stiffness (β −1.6mm, 95% CI −2.5 to −0.7mm) and function (β −6.9mm, 95% CI −11.6 to −2.1mm).

Conclusion: The linearity of effect implies that weight loss reduces medial cartilage volume loss and improved knee symptoms, and weight gain increases medial cartilage volume loss and worsens knee symptoms. These results suggest that in obese people, even small amounts of weight change have a disease modifying effect on both knee joint structure and symptoms. While weight loss is an important primary management strategy in obese individuals, avoidance of further weight gain should also be a clinical goal.

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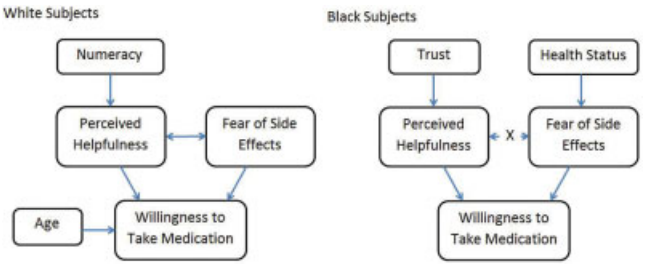
2157

Understanding Differences Between Black and White Patients' Reactions to New Treatment. Liana Fraenkel[1], Richard L. Street Jr.[2] and Ellen Peters[3]. [1]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare System, New Haven, CT, [2]Texas A&M University, College Station, TX, [3]Ohio State University, Columbus, OH.

Background/Purpose: Numerous studies have found that Black patients are more risk averse than their White counterparts. In clinical practice, patients make judgments based on oral information provided to them by their physicians; yet most studies have examined patients' perceptions using written information. The objective of this study was to examine the factors underlying Black and White patients' treatment preference after hearing about a new medication described to them orally by a physician.

Methods: Subjects with a connective tissue disease, recruited from University-affiliated rheumatology practices, listened to a professionally-recorded standardized description of a medication. Prior to hearing the description, demographic and clinical characteristics (by self-report), trust in physicians and subjective numeracy (using validated scales) were ascertained. Helpfulness of the proposed treatment, fear about the side effects, and willingness to take the medication were measured using 7-point numeric rating scales. Kendall Tau b correlation coefficients between subjects' characteristics and their perceptions related to the medication are reported.

Results: We interviewed 284 subjects: 71 Black [mean (SD) age = 50.4 (13.5); 83% female] and 213 White [mean (SD) age 57.4 (14.7); 73% female]. Increased helpfulness and less fear of side effects were associated with increased willingness to take the medication among Black ($r = 0.60$, $p<0.0001$ and $r = -0.22$, $p=0.02$, respectively) and White subjects ($r = 0.49$, $p<.0001$ and $r = -0.36$, $p<.0001$, respectively). Older age was associated with decreased willingness to take the medication among White subjects only. Health status, trust and subjective numeracy did not have a direct effect on willingness to take the medication in either Black or White subjects. However, higher subjective numeracy was associated with increased perceived helpfulness in White subjects ($r = 0.125$, $p=0.005$), while greater trust was associated with increased perceived helpfulness ($r = 0.20$, $p=0.02$) in Black subjects. Poor health status was associated with greater fear ($r=0.247$, $p=0.01$) in Black subjects only. Helpfulness and fear were inversely correlated in White ($r = -0.126$, $p<.0001$), but not Black subjects ($r = 0.007$, $p=0.9$).



Conclusion: After hearing about a medication, Black subjects' treatment preferences were indirectly influenced by self-reported health status and trust and directly influenced by perceived helpfulness of the proposed treatment and fear of the side effects. In contrast, White subjects' treatment preferences were indirectly influenced by numeracy and directly influenced by age, perceived helpfulness and fear of the side effects. An inverse relationship between perceived helpfulness and fear (indicative of a confounding effect) was observed among White, but not Black subjects. The factors that influence how Black and White patients respond to information about medications differ.

Disclosure: L. Fraenkel, None; **R. L. Street Jr.**, None; **E. Peters**, None.

2158

Do Numbers Make a Difference? Liana Fraenkel[1], Evan Wilhelms[2] and Valerie Reyna[2]. [1]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare System, New Haven, CT, [2]Cornell University, Ithica, NY.

Background/Purpose: Patients frequently overweigh the risks associated with rare adverse events (AEs). This is particularly true for biologics associated with extremely rare AEs. As a result, significant efforts have been made to determine how best to present numerical information when describing the probabilities of rare AEs. What is unclear, however, is whether precise numeric estimates influence decision making or behavioral intentions.

Methods: We administered a survey to college students to examine the influence of probabilities and risk perceptions (worry, riskiness and gist evaluations) on subjects' stated likelihood of starting a medication. In this context, gist evaluations refer to the subjective meaning attached to the risk of the specified AE. We first described the impact of rheumatoid arthritis and subsequently asked subjects to imagine themselves as a patient with this disease in a clinical encounter during which a physician described a new treatment option to them. Route of administration, benefit, and cost were held constant. We varied current health state (able versus unable to maintain current level of activity and responsibilities), type of AE (pneumonia versus cancer) and probability of the AE (1 in 100, 1 in 1,000, 1 in 10,000 and 1 in 100,000). Each subject responded to a single, randomly-assigned scenario. Linear regression models were constructed to examine the association between current health state, type of AE, the probability of the AE and risk perceptions (worry, riskiness, and gist evaluations) with the likelihood of starting the medication (measured on a 5-point scale) after adjusting for age, gender, ethnicity, and numeracy (measured using the modified Lipkus-Peters numeracy scale). Levels of gist evaluations and ethnicity were treated as dummy variables.

Results: 415 subjects completed the survey. Their mean (SD) age was 19.8 (1.8). 72.5% were woman, and 55.7% were Caucasian, 5.5% were Black and 25.7% Asian. The mean (SD) numeracy score was 0.74 (0.20). Health state, type of AE, probability, worry, riskiness, and gist evaluations were associated with likelihood of taking the medication when evaluated separately. In the full model (containing all predictors and covariates), current health state and all three risk perceptions remained significantly associated with likelihood of taking the medication, while numeric probability was not (See Table).

Table. Predictors of willingness to take the medication

Parameter Estimates				
			Hypothesis Test	
Parameter	**B**	**Std. Error**	**Wald Chi-Square**	**Sig.**
(Intercept)	4.704	.7948	35.030	.000
Current Health State	.258	.0868	8.862	.003
Adverse Event	−.126	.0927	1.839	.175
Probability of Adverse Event	−.108	.1480	.531	.466
Gist = doesn't matter how small risk is	−.458	.1309	12.241	.000
Gist = even though risk is small, unacceptable	−.727	.1471	24.387	.000
Gist = risk is so small, nothing to worry about	.532	.1146	21.577	.000
Gist = risk is small, but reasonable	Reference			
Riskiness	−.178	.0608	8.591	.003
Worry	−.228	.0559	16.698	.000
Numeracy	−.494	.6697	.544	.461
Probability * Numeracy[1]	.209	.1919	1.183	.277
Gender	−.105	.0968	1.186	.276
Age	.009	.0239	.129	.720
Ethnicity = White Hispanic	−.150	.2059	.534	.465
Ethnicity = Other	−.315	.1702	3.431	.064
Ethnicity = Asian	−.215	.1019	4.456	.035
Ethnicity = Black	−.223	.1946	1.314	.252
Ethnicity = White non-Hispanic	Reference			

1: Interaction term between probability and numeracy.

Conclusion: Risk perceptions predict subjects' willingness to take medication, while probabilistic information does not. The results suggest that decision support must extend beyond presentation of probabilistic information in order to ensure informed choice.

Disclosure: L. Fraenkel, None; **E. Wilhelms**, None; **V. Reyna**, None.

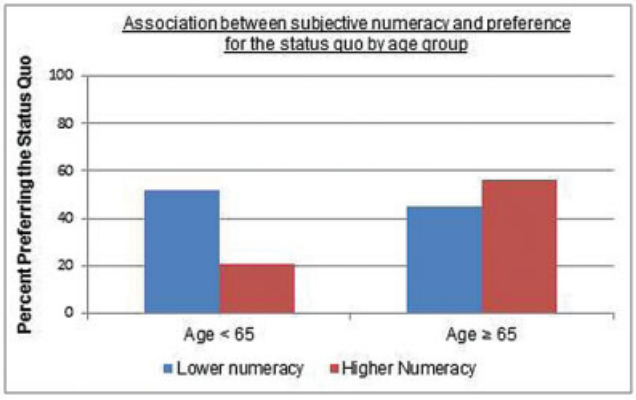
2159

Understanding the Preference to Stay With the Status Quo. Liana Fraenkel[1], Meaghan Cunningham[2] and Ellen Peters[3]. [1]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare System, New Haven, CT, [2]Yale University School of Medicine, New Haven, CT, [3]Ohio State University, Columbus, OH.

Background/Purpose: Preference for the status quo is prevalent in patients with rheumatic disease and may be harmful in decisions for which there is strong evidence that a change in treatment is likely to improve outcomes, such as in active rheumatoid arthritis. The objective of this study was to 1) examine the influence of numeracy and emotion on patients' preference for the status quo, i.e., to remain with their current treatment, and 2) to determine whether age modifies these relationships.

Methods: Subjects with active rheumatoid arthritis, under the care of a rheumatologist and currently taking at least one DMARD, participated in an interview between 4/2/2009 and 10/26/2010. Numeracy was measured using the Subjective Numeracy Scale. Emotion was measured using the item: "If you were considering whether or not to start a new medication, how would you feel?" on a scale ranging from 1= "extremely worried" to 7= "extremely hopeful about what could happen." Treatment preference was measured using an Adaptive Conjoint Analysis survey. Associations between numeracy and emotion with preference for the status quo were measured using logistic regression. We also examined interactions between mean centered numeracy and emotion with mean centered age on preference for the status quo.

Results: Of 205 eligible subjects, 156 agreed to participate. The mean (SD) age was 59 (13), and the majority were female (85%), White (82%), and had some college education (70%). Overall, 39% preferred the status quo alternative. Preference for the status quo (vs preference to make a treatment change) was associated with lower subjective numeracy [median (IQR) = 32 (17) vs 38 (11), p= 0.001] and less hopefulness [median (IQR) = 5 (4) vs 7 (2), p= 0.003]. The association between both numeracy and emotion with preference for the status quo remained significant after controlling for variables found to be associated ($p \leq 0.05$) with preference for the status quo in bivariate analyses (age, race, employment, and current biologic use). However, the impact of emotion [Adjusted odds ratio (95% CI) = 0.75 (0.6–0.90), p=0.002], was much larger than that of numeracy [Adjusted odds ratio (95% CI) = 0.96 (0.92–0.99), p=0.028]. Higher numeracy was protective against status quo preferences in subjects less than 65 years of age but not in older subjects (see Figure). We found no interaction between age and emotion on preference.



Conclusion: The results highlight the strong influence of emotion (i.e. hopefulness) on patients' willingness to consider a change in treatment, and suggest that targeting numeracy alone may not improve the quality of decision making unless patient motivation is also considered.

Disclosure: L. Fraenkel, None; **M. Cunningham**, None; **E. Peters**, None.

2160

The Journey to Diagnosis in As/Axial Spondyloarthritis - the Psychological Impact of Delay. Jane Martindale and Lynne Goodacre. Lancaster University, Lancaster, United Kingdom.

Background/Purpose: It is not uncommon for 8 to 11 years to pass between symptoms onset and definitive diagnosis of AS/axial SpA (Gran 1997, Feldtkeller, 2003). We are not yet fully conversant with all of the factors influencing this delay. The aim of this study was to conduct an in-depth exploration of the 'journey' to diagnosis of people with AS/SpA to gain insights into the experience, potential barriers and facilitators in this process.

Methods: Ethical approval was obtained for a qualitative phenomenological study embedded within a longitudinal cohort study of people newly diagnosed with AS/AxialSpA in the UK. 10 participants from 2 sites meeting the inclusion criteria, gave consent to be interviewed at diagnosis utilising an in-depth semi-structured approach. Interviews were recorded and transcribed verbatim. Thematic analysis comprised an iterative, interpretative process in which a systematic and rigorous approach was used to ensure that codes, code frameworks and themes were grounded within the data, to ensure credibility and trustworthiness.

Results: 7 males and 3 females consented to participate; age mean (SD) 40.2 (7.7) years (range: 26 – 49), with reported years of symptoms before diagnosis being 10.1 (7.3) years. Analysis identified 4 key themes: 'Trying to work out what was wrong' describes the worry that was associated with knowing that something was wrong and how this was complicated by the variability and the severity of the back pain participants were experiencing. 'Fighting for a diagnosis' encompasses an overall sense that participants felt that their back pain was being dismissed. Participants described having to be persistent and 'fighting' to be referred to a specialist, and a sense that they were not being believed. 'The impact of being given a diagnosis' describes the contradictory emotions of relief and empowerment associated with being believed, and the worries and uncertainty about the future. 'The impact of delayed diagnosis' describes the negative psychological price that people paid including desperation, distress, depression and feeling disheartened. For those in employment continuing to work had been challenging with the stigmatisation of a 'bad back'. Insights were provided also into the emotional price paid by family members during this journey to diagnosis.

Conclusion: These insights have identified that people endure a multiplicity of problems and psychological distress to achieve a diagnosis. Delay in diagnosis may be associated with lack of familiarity and knowledge of AS/axial SpA by the population and healthcare professionals, highlighting the importance of campaigns to bring this condition to the public domain. Clinicians need to consider the potential impact of the 'journey to diagnosis' on clinical management once a diagnosis has been made.

Disclosure: J. Martindale, None; **L. Goodacre**, None.

2161

Biopsychosocial Typologies of Pain in a Cohort of Patients With Systemic Sclerosis. Erin L. Merz[1], Vanessa L. Malcarne[1], Shervin Assassi[2], Deepthi Nair[2], Tiffany Graham[2], Brayden Yellman[2], Rosa M. Estrada-Y-Martin[2] and Maureen D. Mayes[2]. [1]SDSU/UCSD Joint Doctoral Program in Clinical Psychology, San Diego, CA, [2]University of Texas Health Science Center at Houston, Houston, TX.

Background/Purpose: Despite being a common problem in Systemic Sclerosis, the extant literature on pain has primarily focused on biomedical correlates, or bivariate relationships with a few psychological characteristics. There is a need to investigate the more heuristic biopsychosocial model, which incorporates the simultaneous contributions of medical, psychological, and social variables in understanding pain.

Methods: Patients with Systemic Sclerosis ($N = 333$) received clinical exams and completed self-report surveys at enrollment to the *Genetics versus ENvironment In Scleroderma Outcome Study*. Latent profile analysis was used to derive biopsychosocial profiles of patients using clinical indicators of disease severity (modified Rodnan skin score, percent predicted forced vital lung capacity), perceived physical health, health worry, mental health, and social support. The resultant profiles were examined in relation to pain and pain medication usage.

Results: A 3-profile solution provided the best fit to the data. Based on the biopsychosocial indicators, the profiles were characterized as *Managing* ($n = 217$), *Resilient* ($n = 86$), and *Distressed* ($n = 30$). Both the *Managing* and *Distressed* groups had relatively less severe skin thickening and percent predicted forced vital lung capacity, but the *Distressed* group reported much poorer perceived physical health, mental health, and social support. The *Resilient* group had a much more severe disease manifestation; however, *Resilient* patients mirrored the *Managing* group with relatively better psychosocial functioning. Between-group differences for pain emerged, with the *Distressed* group, whose disease was less severe than the *Resilient* group, reporting the highest pain and the greatest utilization of acetaminophen/nonsteroidal anti-inflammatory drugs, tramadol, and narcotic pain medication.

Conclusion: Clinicians should consider biopsychosocial characteristics as contributing factors to the experience of pain in patients with Systemic Sclerosis. Although disease severity is a risk factor for pain, psychological and social characteristics are also important in understanding disease-related pain. Patients with characteristics similar to those in the *Distressed* profile may be at an increased risk for pain and would likely benefit from a referral to a behavioral health or other ancillary service providers for an adjunct treatment for pain management, rather than relying solely on pharmacological therapies.

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2162

Physical, Psychological, and Social Impacts Of Restricting Back Pain: The Older Person's Perspective. Una E. Makris[1], Trisha V. Melhado[2], Simon C. Lee[2], Heidi A. Hamann[2], Lisa M. Walke[3], Thomas M. Gill[3] and Liana Fraenkel[4]. [1]UT Southwestern Medical Center, VA Medical Center, Dallas, TX, [2]UT Southwestern Medical Center, Dallas, TX, [3]Yale University, New Haven, CT, [4]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare System, New Haven, CT.

Background/Purpose: Although back pain is the most common type of pain reported by older adults, we have a limited understanding of its impact on the daily life of older persons. Qualitative research can capture the lived experience of back pain severe enough to result in restricted activity (hereafter referred to as restricting back pain), in older persons and help to identify patient-reported dimensions of this experience. In this qualitative study, we explored older persons' perspectives, experiences, and attitudes regarding how restricting back pain impacts various dimensions of daily life.

Methods: We recruited participants who reported restricting back pain during the previous 3 months from the Yale PEP Study, a longitudinal study of community-living persons. In-depth, semi-structured interviews were conducted in the participants' home by a single investigator (UM). The interviewer's guide explored the character and clinical course of restricting back pain as well as its impact on activities of daily life, including symptom management and quality of life, social relationships, coping strategies and other adaptive behaviors, including questions about other illnesses or conditions. Interviews were transcribed and independently coded by 4 reviewers using iterative thematic analysis (NVivo 9). Thematic codes were created to categorize the nuances of participants' restricting back pain experiences. To ensure inter-coder reliability, coding discrepancies were resolved through group discussion until consensus was reached. Recruitment stopped once no new codes emerged from the data, indicating theoretical saturation.

Results: We interviewed 23 participants (age range: 83–98, 57% women, 91% non-Hispanic white, 4% non-Hispanic black, and 4% Hispanic). All participants described the perceived consequences of restricting back pain on daily activities and quality of life. Specifically, analysis revealed that restricting back pain impacted participants' quality of life physically (including sleep), psychologically and socially. The participants described how restricting back pain resulted in social isolation that subsequently influenced psychological well-being. Salient quotes illustrating several of the prominent themes are listed below.

Quotes of restricting back pain impact by theme

Theme	Sample Quote
Physical impact	–It's very debilitating, both mentally and physically, because I'm not able to do what I want to do. My head says yes and my body says no.
Sleep impact	–Well, I really don't get a good rest at night. When I'm turning this way and that way because of the back pain.
Psychological/social impact	–I'm not as open as I used to be. I'm not, I don't get out there and talk with everybody. I'm usually, I stay in my house. I don't go out that much.
	–I guess it makes me depressed because I can't get outÉI don't see people and I'm a people person.
	–It's a writing group upstairs that I used to go and we wrote poetry and little stories. I used to love to participate in that and I won't even [go] up there by myselfÉI can't stand the pain of sitting in a groupÉif I take the pills or something to help, then I can't concentrate.

Conclusion: Thematic analysis revealed that restricting back pain in older persons has variable physical, psychological and social consequences. A better understanding of how older persons experience restricting back pain will enable clinicians and researchers to focus on the dimensions of the pain experience most relevant to this population and may help to identify novel measurable factors that can improve quality of care in older persons with back pain.

Disclosure: U. E. Makris, None; **T. V. Melhado**, None; **S. C. Lee**, None; **H. A. Hamann**, None; **L. M. Walke**, None; **T. M. Gill**, None; **L. Fraenkel**, None.

2163

Predictors Of No Improvement In Subjective Health Perception In Newly Diagnosed Rheumatoid Athritis Patients With a Good DAS28 Response At 12 Months In The Dutch Rheumatoid Arthritis Monitoring Tight Control Cohort. Martijn Oude Voshaar[1], Erik Taal[1], Peter M. ten Klooster[1], Harald E. Vonkeman[2] and Mart A.F.J. van De Laar[3]. [1]University of Twente, Enschede, Netherlands, [2]Medisch Spectrum Twente, Enschede, Netherlands, [3]Medisch Spectrum Twente & University of Twente, Enschede, Netherlands.

Background/Purpose: Modern treatment strategies are highly successful in reducing disease activity in rheumatoid arthritis (RA). However, changes in clinical measures of disease activity may not always correspond with a patient's own opinions of improvement. Purpose of this study is to identify subjective predictors of self-reported health changes in patients with a good clinical response after one year of treatment in a tight control study.

Methods: Data from newly diagnosed patients of the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort who completed baseline and 12 months assessments was used for this study. Patients who achieved a good DAS28 response at 12 months were selected for analysis. Subjective change in health was assessed with the SF-36 health transition question (Compared to one year ago, how would you rate your health in general now?). Scores were dichotomized (improved vs not improved) for analysis. Binary logistic regression analysis was performed to identify predictors of patient reported health changes. Twelve month changes in DAS28 scores was added as predictor in the first step; changes in scores on SF-36 subscales were added in a second step. The general health scale of the SF-36 was excluded. Cohen's standardized effect size (e.s.) statistic (d) was calculated for 12 month change scores of significant predictors and compared between improvers and non-improvers.

Results: A good DAS28 response after 12 months of treatment was achieved by 162 (57%) out of 282 patients. Of these, 40 (24.7%) did not consider their health to have improved since starting treatment (non-improvers). Baseline SF-36 subscale scores did not significantly differ between improvers and non-improvers. Twelve month change scores in bodily pain (OR = 1.03, p = 0.04) and vitality (OR = 1.03, p = 0.04) were significant multivariate predictors of self-reported health improvement. About 19% of the variance in self-reported health changes was explained by the final model (Nagelkerke's R^2 = 0.19), whereas the model containing only DAS28 change scores explained about 6% of variance (Nagelkerke's R^2 = 0.06). Mean (SD) bodily pain scores improved from 38.9 (± 18.6) to 74.7 (±19.8) over 12 months for improvers (e.s.= 1.87) and from 41.8 (±19.8) to 62.9 (±19.6) for non-improvers (e.s.= 1.06). Mean (SD) vitality scores improved from 52.8 (±19.8) to 66.7 (±16.8) in improvers (e.s. = 0.71) and from 53.12 (±18.9) to 56.56 (±18.9) for non-improvers (e.s. = 0.17).

Conclusion: The majority of patients with a good DAS28 response after one year of tight control treatment also considered their health to have improved. However, a substantial minority did not consider their health to have improved, despite significant clinical improvements in disease activity. These results suggest that clinical improvements do not necessarily equate to improved subjective health. One possible explanation is that pain and fatigue are patient reported outcomes that may not be adequately represented in current clinical outcome measures in RA research.

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2164

Rituximab In The Treatment Of Children With Systemic LUPUS Erythematosus: ONE Year Analysis Of 12 Patients. Ekaterina Alexeeva[1], Rina Denisova[1], Saniya Valieva[1], Tatyana Bzarova[1], Kseniya Isayeva[1], Tatyana Sleptsova[1], Elena Mitenko[1], Evgeniya Chistyakova[2], Anna Fetisova[1] and Elena Semikina[3]. [1]Scientific Center of Children's Health of RAMS, Moscow, Russia, [2]I.M.Sechenov First Moscow State Medical University, Moscow, Russia, [3]Scientific Center of Children's Health of RAMS, Moscw, Russia.

Background/Purpose: Treatment of childhood systemic lupus erythematosus (SLE) is an ongoing problem because of the severity of the disease in some patients and the side-effects of the currently available immunosuppressive agents. B-cell depletion might be useful and effective treatment for this disease according to researches in adults.

Purpose: To assess the clinical and basic serological consequences of rituximab treatment in patients with systemic lupus erythematosus who have failed conventional immunosuppression.

Methods: An open study of 12 patients with severe SLE followed for a minimum of 12 months is reported: 12 patients – 6 months, 11 patients – 12 months. Disease activity in these patients was assessed every 6 months using the SELENA SLEDAI, System Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index and estimates of anti-double-stranded DNA antibodies and serum C3, C4 levels, number of CD20 B lymphocytes. During the follow-up period, significant side-effects were sought and the reduction in oral prednisolone was recorded too. Background therapy included cyclophosphamide, plasmapheresis, intravenous immunoglobulin, methylprednisolone pulse therapy, mycophenolate mofetil. Rituximab was given 375mg/m^2 weekly, [1]4. All patients were treated with prednisolone and immunosupressive agents.

Results: 11 patients were female and 1 male. At the initiation of rituximab treatment the mean age was 14.6 yr (range 10–17.5) and the mean disease duration was 3.6 yr (range 0.3–13.2). 5 had lupus nephritis. All parameters improved from in 6 and 12 months after rituximab treatment: the SELENA SLEDAI score from 16 (range 4–25) to 3 (range 0–14) (p=0.002) and 1 (range 0–4) (p<0.001), SLICC/ACR Damage Index from 3,5 (range 0–6) to 2 (range 0–4) (p=0.02) and 1 (range 0–4) (p<0.05), serum C4 from 0,13 (range 0,01–0,9) to 0,24 (range 0.06–1.25) (p=0.04) and 0,43 (range 0.09–0.66) (p<0.01) (normal range 0.14 – 0.47 g/l) and double-stranded DNA binding from 73,5 (range 0–250) to 8,9 (range 0–130) (p=0.04) and 1,9 (range 0–80) (p<0.01) (normal range 0 – 20 ME/ml). B-lymphocyte depletion was observed in all patients in the peripheral blood after 6 and 12months (p<0.01). The mean daily prednisolone dose fell from 0.8 mg/kg (range 0.4–1.5) to 0.5 mg/kg (range 0.2–0.8) and 0.2 (range 0.15–0.7) (p<0.01). Proteinuria was improved in 5 patients from 5.6 gr/day (range 0.3–15) to 1.7 gr/day (range 0.3–5.0) (p=0.06) and 0,2 gr/day (range 0.3–1.0). There were no flares follow up period. Serious Adverse events were registered: pneumonia (n=2), neutropenia (n=5), herpes Zoster infection (n=3), hypogammaglobulinemia (n=8).

Conclusion: In this open study of patients who had failed conventional immunosuppressive therapy, considerable utility in the use of B-cell depletion has been demonstrated. Our data provide strong support for the performance of a full doubleblind control trial.

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2165

Efficacy and Safety Of Biologic Agents In Patients With Poly-Articular Juvenile Idiopathic Arthritis: Network Meta-Analysis Of Randomized Controlled Withdrawal Trials. Gil Amarilyo[1], Simon Tarp[2], Ivan Foeldvari[3], Neta Cohen[1], Tracy D. Pope[4], Jennifer M.P. Woo[5], Robin Christensen[2] and Daniel E. Furst[4]. [1]Dana-Dwek Children's hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [2]Musculoskeletal Statistics Unit, The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, [3]Hamburger Zentrum für Kinder- und Jugendrheumatologie, Klinikum Eilbek, Hamburg, Germany, [4]David Geffen School of Medicine, University of California, Los Angeles, CA, [5]Mattel Children's Hospital, University of California, Los Angeles, Los Angeles, CA.

Background/Purpose: Although various biologic agents (BAs) are in use for polyarticular juvenile idiopathic arthritis (pJIA), a combined meta-analytic summary comparing the efficacy and safety among them in pJIA is lacking. An often applied trial design in pJIA, called withdrawal trials, consists of an open-label run-in phase where all patients receive active drug. After this phase, only those who respond to treatment enter the double-blind phase and are randomized to continue on drug or on placebo. Our objective was to compare the efficacy and safety of BAs in pJIA using all currently available randomized withdrawal trials (wRCTs) [1].

Methods: A systematic search of MEDLINE, EMBASE, CENTRAL and clinicaltrials.gov was performed. Eligible wRCTs included patients with pJIA where BAs, at any dose, were compared with another BA or placebo. Efficacy was evaluated with disease flare (as defined by the authors) and ACRPedi30, 50, and 70. Safety was evaluated by examining patients with adverse events (AEs) and serious AEs (SAEs). Two reviewers extracted data, and a third confirmed. A network meta-analysis was used to compare BAs, based on a mixed-effects logistic regression model (modeled in SAS) [2]. This approach combined statistical inference from both direct and indirect comparisons of the treatment effects between BAs. Results are reported as odds ratios with 95% confidence intervals (OR [95%CI]).

Results: Of 490 references identified, 23 were reviewed in detail and 5 wRCTs were included: abatacept, adalimumab, anakinra, etanercept and tocilizumab, one trial each, all vs. placebo. Nearly all placebo comparisons showed statistically significant efficacy ($P < 0.05$) for flare (Table 1) and for ACRPedi 30, 50 and 70; the anakinra trial did not report ACRpedi measures and etanercept was not different for ACRpedi70 (2.30 [0.73;7.29]; $P = 0.16$). There were no differences ($P > 0.05$) among BAs for efficacy. SAEs occurred very infrequently (0–8%) and an analysis was not possibly (Table 2). As noted in Table 2 there were no differences for AEs when compared to placebo or among BAs.

Table 1. Disease Flare, Biologic agents vs. other biologic agents or placebo

Biologic agent	Biologic agent/Placebo	OR Flare	Lower 95% CI	Upper 95% CI	*P*
Abatacept	Adalimumab	0.581	0.167	2.024	0.394
Abatacept	Anakinra	1.005	0.200	5.052	0.995
Abatacept	Etanercept	1.282	0.285	5.775	0.746
Abatacept	Placebo	0.207	0.081	0.531	0.001
Abatacept	Tocilizumab	0.622	0.181	2.140	0.451
Adalimumab	Anakinra	1.728	0.361	8.268	0.493
Adalimumab	Etanercept	2.204	0.516	9.417	0.286
Adalimumab	Placebo	0.356	0.152	0.836	0.018
Adalimumab	Tocilizumab	1.069	0.331	3.447	0.911
Anakinra	Etanercept	1.276	0.217	7.513	0.788
Anakinra	Placebo	0.206	0.054	0.790	0.021
Anakinra	Tocilizumab	0.618	0.130	2.935	0.545
Etanercept	Placebo	0.162	0.048	0.543	0.003
Etanercept	Tocilizumab	0.485	0.114	2.054	0.326
Tocilizumab	Placebo	0.334	0.145	0.767	0.010

Table 2. SAEs events and Biologic agents vs. other biologic agents or placebo

Biologic agent	Biologic agent/Placebo	SAEs/ patients	SAEs/ patients	OR AEs	Lower 95% CI	Upper 95% CI	*P*
Abatacept	Adalimumab	0/60	1/30	0.653	0.257	1.659	0.371
Abatacept	Anakinra	0/60	0/25	1.084	0.336	3.491	0.893
Abatacept	Placebo*	0/60	2/62	1.093	0.559	2.136	0.796
Abatacept	Tocilizumab	0/60	3/82	1.099	0.453	2.663	0.835
Adalimumab	Anakinra	1/30	0/25	1.659	0.508	5.412	0.402
Adalimumab	Placebo*	1/30	0/28	1.672	0.836	3.343	0.146
Adalimumab	Tocilizumab	1/30	3/82	1.681	0.682	4.146	0.259
Anakinra	Placebo*	0/25	0/25	1.008	0.368	2.760	0.987
Anakinra	Tocilizumab	0/25	3/82	1.014	0.322	3.193	0.982
Tocilizumab	Placebo*	3/82	3/81	0.995	0.532	1.859	0.986

Odds ratios (OR [95% CI]) and *P*-values for AEs. Note: etanercept SAE and AE data were not available. For SAE events in the placebo group is for the individual trial, for AE placebo refer to the combined placebo group in the analysis.

Conclusion: Overall BAs were effective and safe when compared placebo. There were no differences among BAs for either efficacy or safety. Based on these data, other considerations such as price and availability should be used to decide among BAs when treating pJIA patients as no personalized biomarkers etc. are available at present. Long term safety will be better examined in the biologic registries currently accruing data in JIA.

References:
[1] Amarilyo G, et al. PROSPERO. 2013;CRD42013004736
[2] Singh JA, et al. CMAJ. 2009;181(11):787–96

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Infection Risk With Tumor Necrosis Factor Inhibitor Use In Polyarticular Juvenile Idiopathic Arthritis. Caroline Y Chang, Rika Meyer and Katherine AB Marzan. Children's Hospital Los Angeles, Los Angeles, CA.

Background/Purpose: Tumor Necrosis Factor inhibitors (TNFi) are extremely effective in treating Juvenile Idiopathic Arthritis (JIA). However, TNF-α is critical in immune function, raising concerns of increased infection(INF) rates in patients(pts) on TNFi. With current pediatric data primarily from drug registries and hospitalized patient data, it is unclear whether pediatric pts on TNFi have increased risk of INF, and if so, what types.

Methods: This is a retrospective cohort study of pts seen in our institution's pediatric rheumatology clinic with polyarticular JIA (pJIA) between 1/1/00 and 11/30/11. Demographic information (Table 1), diagnosis, medication history, and documented INFs (Table 2), classified as mild, moderate, and severe, were obtained from the medical record. Rates of INF were calculated and compared for pts on no immunosuppressants (IS), methotrexate(MTX), TNFi, and MTX plus TNFi (MTX+TNFi) (Table 3). Time periods on other IS or systemic corticosteroids were excluded. The data was evaluated in two ways: 1) each pt was analyzed under the therapy category that they were treated with for the longest length of time for that period of time, and 2) pts who had been on multiple categories of medications were analyzed with a paired t-test.

Results: 239 pts with pJIA were included in the study with a mean follow-up of 4.46 ± 2.91 years and a total of 531 INFs in 1067 patient years. Both analyses demonstrated that pts on MTX and MTX+TNFi had significantly higher INF rates than those on no IS ($p<.001$, $p<.0005$ and $p<.0005$, $p<.0005$), with INF rate ratios (IRR) of 3.2 (95%CI 2.1–4.8), and 5.5 (95% CI 3.7–8.2). Pts on MTX+TNFi also had significantly more INFs than those on TNFi ($p=.02$, $p=.001$, IRR 2.8 (95% CI 2.1–3.8)). Paired t-tests showed significantly higher INF rates in those on TNFi compared to no IS ($p<.001$, IRR 2.0 (95% CI 1.2–3.1)), and MTX+TNFi compared to MTX ($p=.004$, IRR 1.7(95% CI 1.4–2.1)). There was no significant difference between pts on MTX or TNFi.

Table 1. Demographic Information

	N = 239 (%)
Female Sex	195 (81)
Ethnicity	
Hispanic	146 (61)
Non-Hispanic	93 (39)
Age at disease onset, mean years (range)	9.6 (0.8–18)
Mean follow-up, years (SD)	4.46 (2.91)
Total patient years	1067
Number of Patients Exposed to:	
Systemic Corticosteroids	63
Other immunosuppressants	32

Table 2. Documented Infections

Mild	Moderate	Severe
Upper Respiratory Illnesses	Soft tissue Infections	Pneumonia
Pharyngitis	-Abscess/Cellulitis	EBV with hepatitis
Otitis Media	Pneumonia	Pyelonephritis
Urinary Tract Infection	Varicella Zoster	Systemic Coccidiomycosis
Gastroenteritis		
Nonspecific viral infections		
Mild skin infections		
-Impetigo, Paronychiae		
Superficial fungal infections		

Table 3. Infection Rates

Medication Category	Number of Patients N =234*	Mean infections/100 patient year(SD)
No Immunosuppression	34	12 (29)**
Methotrexate	58	54 (66)
Methotrexate + TNFi	85	61 (70)***
TNFi	37	30 (37)

* 5 excluded given same amount of time in multiple groups
** Significantly different compared to MTX and MTX + TNF $p = .001$, $p <.0005$
*** Significantly different compared to TNF alone $p = .022$

Conclusion: Pts with pJIA treated with MTX, MTX+TNFi, and TNFi have higher rates of INF than those on no IS, with increased rates of INF with each additional medication. However, TNFi do not put pts at a significantly higher risk of INF than MTX. Notably, there were predominantly mild INFs, with only 29 moderate and 5 severe INFs during the course of the study.

Disclosure: C. Y. Chang, None; **R. Meyer**, None; **K. A. Marzan**, None.

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23-Valent Polysaccharide Pneumococcal Vaccine in Juvenile Idiopathic Arthritis Patients: Anti-Tumor Necrosis Factor Therapy Role in Short and Long-Term Immunogenicity. Nadia E. Aikawa[1], Ivan L.A. França[2], Ana C. M. Ribeiro[2], Adriana M. Sallum[2], Eloisa Bonfa[3] and Clovis A. Silva[2]. [1]Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, [2]University of São Paulo, São Paulo, Brazil, [3]University of São Paulo, Sao Paulo, Brazil.

Background/Purpose: There is no study regarding short and long-term assessments of 23-valent polysaccharide pneumococcal vaccine (PPV23) in juvenile idiopathic arthritis (JIA) under biologic therapy. The objectives of this study were to assess the humoral response of the PPV23 in JIA patients pre- and post-anti-TNF therapy and controls without this treatment. The possible influence of demographic data, disease activity and treatment on immunogenicity and the potential deleterious effect of vaccine on disease itself were also evaluated.

Methods: 17 JIA patients immediately pre-anti-TNF (etanercept 0.8 mg/kg/week, Group 1) and 10 JIA patients on stable dose of methotrexate (median dose 0.8 mg/kg/week, Group 2) received one dose of pneumococcal vaccine. All patients were evaluated pre-vaccination, 2 months and 12 months post-vaccination for 7 pneumoccocal serotypes (4, 6b, 9v, 14, 18c, 19f, 23f). Serology for each serotype was performed by enzyme immunoassay. The immunogenicity endpoints included the seroprotection rate (SP) (percentage of subjects achieving antibodies titers ≥1.3 micrograms/mL), seroconversion rate (SP) (percentage of subjects with a minimum of 2-fold rise in post-vaccination antibodies titers) and the geometric mean concentration of antibodies (GMC). Adequate vaccine response was considered when SC occurred for at least 50% of vaccine serotypes. Patient and physician visual analogue scales (VAS), Childhood Health Assessment Questionnaire (CHAQ), number of active joints, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were evaluated before and after vaccination.

Results: Group 1 and Group 2 were comparable regarding current age (11.6 vs. 9.2 years, $p=0.15$), female gender (47 vs. 40%, $p=1.0$), age at diagnosis (7.6 vs. 7.1 years, $p=0.9$) and disease duration (3.7 vs. 2 years, $p=0.1$). The frequency of glucocorticoids and non-biologic drugs (methotrexate, leflunomide and cyclosporine) was similar in both groups ($p>0.05$). Patients in Group 1 had significantly higher number of active joints (4 vs. 0, $p=0.02$), limited joints (6 vs. 2, $p=0.01$) and ESR (31 vs. 15 mm/1sthour, $p=0.03$) compared to Group 2. Both groups were alike regarding pre-immunization SP and GMC ($p>0.05$). Two months and 12 months after vaccination, SP, SC and GMC for all pneumoccocal serotypes were similar in JIA patients with and without anti-TNF therapy ($p>0.05$). Moreover, the frequency of patients achieving adequate vaccine response at 2 months (53 vs. 30%, $p=0.424$) and 12 months (36 vs. 40%, $p=1.0$) were similar in both groups. There was a significant decrease in disease parameters, including morning stiffness duration ($p=0.001$), number of active joints ($p<0.001$), CRP ($p=0.045$), patient's, parent's and physician's VAS ($p<0.05$) and CHAQ ($p=0.01$) in Group 1. In Group 2, all parameters remained unchanged after immunization ($p>0.05$). Further comparison of patients with and without adequate response at two months revealed no influence of demographic, clinical and laboratorial JIA parameters ($p>0.05$). Serious adverse events were not observed.

Conclusion: Anti-TNF therapy has no deleterious effect on PPV23 short and long-term immunogenicity in JIA patients and this response does not seem to influence disease parameters.

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Temporomandibular Joint Involvement and Quality Of Life In Juvenile Idiopathic Arthritis. Paula Frid[1], Ellen Nordal[2], Francesca Bovis[3], Denise Marafon[3], Donato De Angelis[3], Sheila Oliveira[3], Fabrizia Corona[3], Gabrieli Simonini[3], Joyce Davidson[3], Helen Foster[3], Rik Joos[3], Ivan Foeldvari[3], Michel Steenks[3], Pekka Lahdenne[3], Pavla Dolezalova[3], Elena Palmisani[3], Alberto Martini[3], Angela Pistorio[3] and Nicolino Ruperto[3]. [1]Public Dental Service Competence Centre of Northen Norway, Tromso, Norway, [2]University of Tromsø, Tromsø, Norway, [3]Istituto Giannina Gaslini, Pediatria II, Reumatologia, Paediatric Rheumatology International Trials Organisation (PRINTO) Coordinating Center, Genoa, Italy, Genoa, Italy.

Background/Purpose: Temporomandibular joint (TMJ) arthritis in childhood is seen in a substantial percentage of children with Juvenile idiopathic arthritis (JIA) and may lead to reduced mouth opening, pain and craniomandibular growth disturbances. The purpose of this study was to assess the prevalence of TMJ involvement in a JIA cohort and the association between TMJ involvement and other disease variables such as cervical spine and upper limb involvement, and the impact of TMJ involvement on daily life.

Methods: This descriptive study is based on data from a cross-sectional sample from 32 countries worldwide between 1998–2000, diagnosed with JIA, enrolled for validation of the Child Health Assessment Questionnaire (C-HAQ) and Child Health Questionnaire (CHQ), and also children enrolled in the PRINTO Methotrexate (MTX) trial. Disease activity and quality of life were assessed. Diagnosis of TMJ involvement was based on clinical assessment of the presence of swelling or limitation of motion (LOM) with pain and/or tenderness in at least one TMJ.

Results: Of the 3344 children included, 68.3% were female and 45.8% were diagnosed with persistent or extended oligoarthritis. The prevalence of TMJ involvement was 11.6%. TMJ involvement was strongly associated with polyarthritis (odds ratio (OR) 9.8 (confidence interval (CI) 6.1–15.8)), systemic (OR 7.4 (CI 4.5–12.3)) and extended oligoarthritis (OR 6.7 (CI 4.0 – 11.1)) > 2 joints with LOM in upper limb > 2 (OR 9.8 (CI 7.5 – 12.7)) and cervical involvement (OR 7.8 (CI 6.2–9.8)) in univariate analysis. Finally, a multivariate logistic regression model with the disease activity measures, polyarticular JIA course, active joints >5, MTX use, female gender, age at visit, higher CHAQ scores, erythrocyte sedimentation rate (ESR), positive rheumatoid factor (RF) and other variables was performed; we underline the role of the following predictors in the association with the TMJ involvement: cervical spine involvement (3.0 (CI 2.2–4.0)), eating difficulties (1.2 (CI 1.0–1.4)) and superior limb involvement (1.1 (CI 1.0–1.1)).

Conclusion: The prevalence of TMJ involvement was low in this large cohort compared with other studies probably due to a diagnosis based on clinical diagnostic criteria only. However, we found significant associations between TMJ involvement and cervical spine involvement, upper limb involvement, and eating difficulties. Further studies with both clinical and imaging diagnostic assessment of TMJ involvement in a longitudinal cohort study are warranted.

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Short Term Efficacy Of Biologic Agents In Patients With Systemic Juvenile Idiopathic Arthritis: Network Meta-Analysis Of Randomized Trials. Simon Tarp[1], Gil Amarilyo[2], Ivan Foeldvari[3], Neta Cohen[2], Tracy D. Pope[4], Jennifer M.P. Woo[5], Robin Christensen[1] and Daniel E. Furst[4]. [1]Musculoskeletal Statistics Unit, The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, [2]Dana-Dwek Children's hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [3]Hamburger Zentrum für Kinder- und Jugendrheumatologie, Klinikum Eilbek, Hamburg, Germany, [4]David Geffen School of Medicine, University of California, Los Angeles, CA, [5]Mattel Children's Hospital, University of California, Los Angeles, Los Angeles, CA.

Background/Purpose: Systemic juvenile idiopathic arthritis (SJIA) is a severe subtype of JIA, which includes systemic features such as fever, rash, elevated inflammatory markers along with poly-arthritis. It is frequently resistant to treatment. Until recently, patients were treated mainly with large doses of glucocorticoids. Breakthroughs in understanding the pathogenesis of SJIA have led to the evaluation of biologics, which block the pro-inflammatory cytokines interleukin (IL)-1 or IL-6 and their receptors.

Our objective was to compare the short-term efficacy of biologics in SJIA [1].

Methods: A systematic search in MEDLINE, EMBASE, CENTRAL and clinicaltrials.gov was performed. Eligible Randomized controlled trials (RCTs) included patients with SJIA where biologics, at any dose, were compared with another biologic or placebo. In SJIA a modified ACR pediatric (ACRPedi) response is often used with the required addition that systemic features need to be abrogated. Efficacy was evaluated with modified ACRPedi30, 50, and 70. Two reviewers extracted data and a third confirmed data. The network meta-analysis was based on a mixed-effects logistic regression model (modeled in SAS) [2] combining statistical inference from both direct and indirect comparisons of the treatment effects between biologics. Results were reported as odds ratios with 95% confidence intervals (OR [95%CI]).

Results: Of 490 references identified, 23 were reviewed in detail, and 4 RCTs were eligible for inclusion: anakinra, canakinumab, rilonacept and tocilizumab, one trial each all vs. placebo. Rilonacept was statistically significantly ($P < 0.05$) different from placebo for ACRPedi50, but not for ACRPedi30 or 70 ($P > 0.05$); anakinra, canakinumab and tocilizumab were statistically superior to placebo for ACRpedi 30,50 and 70, Figure 1. Comparing biologics, rilonacept treated patients were statistically less likely to respond than those treated with canakinumab or tocilizumab, Figure 2. All other biologics were comparable revealing no statistical signal ($P > 0.05$).

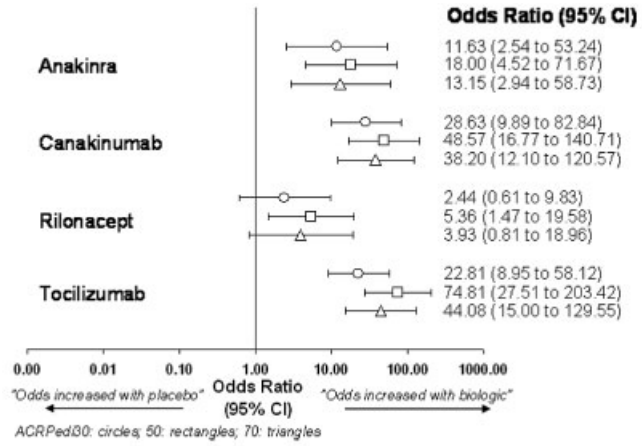

Figure 1. Biologic compared to placebo

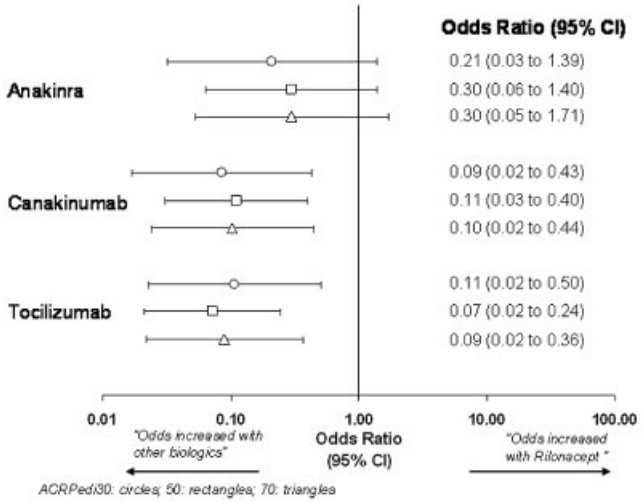

Figure 2. Rilonacept compared to other Biologic

Conclusion: This network meta-analysis of short term RCTs presents empirical evidence that canakinumab and tocilizumab were more effective than rilonacept. These results might be influenced by factors such as various study durations (tocilizumab 12 weeks; all other only 4 weeks), and variation in definitions of modified ACRPedi across trials.

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[2] Singh JA, et al. CMAJ. 2009;181(11):787–96

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2170

Efficacy and Safety Of Long-Term Rituximab Use In Patients With Systemic Juvenile Idiopathic Arthritis: The Results Of 5-Year Follow-Up In Real Clinical Practice. Ekaterina Alexeeva[1], Alexander Baranov[2], Saniya Valieva[2], Tatyana Bzarova[2], Rina Denisova[2], Kseniya Isayeva[2], Tatyana Sleptsova[2], Elena Mitenko[2], Evgeniya Chistyakova[1], Anna Fetisova[2], Elena Semikina[3] and Svetlana Akulova[2]. [1]I.M.Sechenov First Moscow State Medical University, Moscow, Russia, [2]Scientific Center of Children's Health of RAMS, Moscow, Russia, [3]Scientific Center of Children's Health of RAMS, Moscw, Russia.

Background/Purpose: To assess the efficacy and safety of rituximab (RT) treatment in long-term follow-up of children with systemic juvenile idiopathic arthritis (sJIA).

Methods: The results of the treatment of 60 children with sJIA (33 girls and 27 boys) aged from 1 year to 18 years (mean −8.7 y) were analyzed. Duration of disease at the time of RT prescription was 5.3 y on average. At the start of RT treatment, all children had arthritis and severe systemic manifestations. Previously 32 patients were treated with MT, 28 with MT+CsA, 56 with GK i/v, 32 with GK i/a, 36 with oral prednisolon, 19 with TNF blockers 5 with tocilizumab. ACR_{pedi} criteria and criteria of inactive disease and remission (Wallace) were used. The dose of RT was 375 mg/m^2 per infusion, weekly, 4 sequential weeks. One course of RT treatment was performed to 60 patients; two courses - to 36 patients, three courses – to 19 patients; 4 courses – to 5 patients, 5 courses – to 3 patients. The effect of therapy was assessed in 60 patients after 6 months, in 45 after 1 y, in 39 after 2 y, in 32 after 3 y; in 27 after 4 y; in 9 patients after 5 y.

Results: after 6 months of follow up remission of systemic manifestations was documented in 45 (75%) patients. Improvement by $ACR_{pedi30/50/70}$ was achieved by 65, 40 and 35% of patients, respectively; inactive disease by 15 (25%) patients. By month 12 (n=45) improvement by $ACR_{pedi30/50/70}$ was achieved by 80, 55, 45% of patients, respectively; inactive disease by 18 (30%) patients. After 2 (n=39), 3 (n=32), 4 (n=27) years of follow up improvement by $ACR_{pedi30/50/70/90}$ was observed in 90, 80, 75, 70%; 90, 85, 80 and 75% and 98, 95, 95 and 93% of patients, respectively; inactive disease and remission in 43, 33, 33% of patients. In all patients (n=9) who was followed up 5 years remission of disease was documented. Within all period of observation disease remission was documented in 26 (43%) patients, remission of systemic manifestations in 45 (75%) patients. Mean duration - 18 (6;32) and 25 (6; 41) months, respectively.

The second course of RT was made within 18 (6; 32) months in 36 patients after documentation of inactive disease, the third course - within 26 (6; 32) months, the forth course – within 38 (8; 42) months.

RT was discontinued in 39 (65%) patients within 18 (6;32) months due to primary inefficacy in 15 (25%) patients, partial efficacy 8 (13%) (active arthritis), flare of arthritis in 4 (7%) patients, flare of systemic manifestations in 7 (12%). Other patients turned 18 years old and were lost for follow-up.

Within all period of observation the following were reported: infusion reactions 0,8 AE/100 patient years; 0,7 infectious AE/100 patient year; 0,34 Infectious SAE/100 patient year (pneumonia pneumocystic carini); neutropenia 0,35 AE/100 patient year, decrease in serum concentrations Ig 0,25 AE/100 patient years.

Conclusion: RT may be effective in very severe course of sJIA resistant to immunosuppressive drugs, GK and other biologics. RT induced disease remission in 43% of patients and remission of systemic manifestations in 75% of patients. Infectious AEs and SAEs are controlled by antibiotics, non- infectious AEs by IVIG, and GM-CSF.

Disclosure: E. Alexeeva, Roche, Abbott, Pfizer, BMS, Centocor, Novartis, 2, Roche, Merck, Abbott, BMS, Medac, Novartis, Pfizer, 8; **A. Baranov**, None; **S. Valieva**, None; **T. Bzarova**, None; **R. Denisova**, None; **K. Isayeva**, None; **T. Sleptsova**, None; **E. Mitenko**, None; **E. Chistyakova**, None; **A. Fetisova**, None; **E. Semikina**, None; **S. Akulova**, None.

2171

Identification Of Best Cutoff Points and Clinical Signs Specific For Early Recognition Of Macrophage Activation Syndrome In Active Systemic Juvenile Idiopathic Arthritis. Mikhail Kostik, Margarita Dubko, Ludmila Snegireva, Vera Masalova, Tatyana Kornishina, Natalya Abramova, Irina Chikova, Natalya Glebova, Ekaterina Kuchinskaya, Eugenia Balbotkina, Olga Kalshnikova and Vyacheslav Chasnyk. Saint-Petersburg State Pediatric Medical University, Saint-Petersburg, Russia.

Background/Purpose: Macrophage activation syndrome (MAS) – is a severe life-threatening hematological condition, mostly complicated systemic juvenile idiopathic arthritis (SJIA). Early detection of MAS can lead to appropriate therapeutic interventions and change the outcomes. There are no strict criteria for early MAS detection in SJIA. Currently applied HLH criteria can determinate only advanced stage of MAS, which lead to delay diagnosis, late start of specific treatment and associated with poor outcomes. There are several sets of preliminary criteria of MAS in SJIA.

The aim of our study was to detect early clinical and laboratorial signs able to discriminate MAS from active SJIA without MAS.

Methods: our retrospective study was based on reviewing of medical charts of children who were admitted to our rheumatology department in 2005–2013 with SJIA and definite MAS (n=18) and active SJIA without MAS (n=40). We utilized the A.Ravelli criteria (2002, 2005, 2011) for detecting MAS. We evaluated demographic data, data related to SJIA and MAS. We used the main characteristic clinical and laboratorial markers of MAS only at the moment of MAS confirmation. We calculated cutoff points for MAS parameters (ROC-analysis), performed analysis of sensitivity and specificity and identified predictors.

Results: Several clinical signs were relevant to MAS in SJIA: oligoarthicular disease course (OR=5.6 [95%CI:1.6–19.4], p=0.005), splenomegaly (OR=67.6 [3.8–1205.9], p=0.000004), coagulopathy (OR=7.0 [1.9–26.1], p=0.006), lung (OR=11.3 [2.8–45.2], p=0.0001) and kidney involvement, realized in proteinuria<1.0g/24 h (OR=42.1 [2.2–801.2], p=0.0001). The involvement of wrist (OR=0.2 [0.1–0.8], p=0.03), MCP (OR=0.1 [0.0–0.9], p=0.02) and PIP joints (OR=0.1 [0.0–0.6], p=0.005) were protective against MAS development. The best cutoffs for laboratorial parameters, related to MAS are in table.

Parameter	Sensitivity	Specifisity	OR (95%CI)	AUC (95%CI)	p
Hb≤90 g/l	72.2	80.0	10.4 (2.9–37.8)	0.77 (0.64–0.87)	0.0001
WBC≤9.9*10^9/l	83.3	90.0	35.0 (7.4–165.6)	0.92 (0.81–0.97)	0.0000001
PLT≤211*10^9/l	88.9	100.0	534.6 (24.3–1747.8)	0.98 (0.9–0.997)	0.0000001
ALT>72.9 U/l	64.7	85.0	10.4 (2.8–38.9)	0.81 (0.68–0.9)	0.0002
AST>59.7 U/l	82.4	92.1	54.4 (9.8–302.9)	0.88 (0.76–0.95)	0.0000001
LDH>882 U/l	75.0	100.0	158.3 (7.9–3169.1)	0.91 (0.79–0.976)	0.0000001
GGTP>35 U/l	83.3	60.0	7.5 (1.2–47.1)	0.68 (0.47–0.85)	0.047
ALP>736.2	27.3	100.0	30.1 (1.4–638.4)	0.58 (0.43–0.72)	0.01
Total protein≤63g/l	64.7	97.5	71.5 (7.8–658.5)	0.84 (0.71–0.92)	0.0000001
Albumin≤29.3 g/l	100.0	92.5	375.0 (18.4–7661.8)	0.98 (0.9–0.997)	0.0000001
Prothrombin≤77%	71.4	92.3	30.0 (2.9–313.5)	0.81 (0.61–0.93)	0.0008
Fibrinogen≤1.8 g/l	64.3	100.0	46.6 (2.3–947.8)	0.88 (0.7–0.97)	0.001
Ferritin>400 μg/l	100.0	76.0	87.0 (4.5–1671.7)	0.92 (0.78–0.98)	0.000005
CRP>113 mg/l	52.9	89.5	9.6 (2.3–39.1)	0.59 (0.45–0.72)	0.001
ESR≤10 mm/h	61.1	92.5	19.4 (4.3–87.8)	0.78 (0.65–0.88)	0.0001
Na^+ ≤137 mmol/l	66.7	81.1	8.0 (2.1–31.0)	0.79 (0.65–0.0.89)	0.003
Active joints≤6	83.3	59.0	7.2 (1.8–29.0)	0.74 (0.61–0.85)	0.003

Conclusion: We detected clinical and laboratorial markers which can help to early recognition of MAS in children with active SJIA.

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2172

Single MVK Mutation and Recurrent Fevers. Karyl S. Barron[1], Amanda K. Ombrello[2], Donald P. Goldsmith[3], Ivona Aksentijevich[2], Anne Jones[2] and Daniel L. Kastner[2]. [1]National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD, [2]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [3]St Christopher's Hospital for Children/ Drexel College of Medicine, Philadelphia, PA.

Background/Purpose: HyperIgD syndrome is an autoinflammatory disorder caused by mutations in the *MVK* gene. While mutations in most patients follow autosomal recessive inheritance, we have identified a cohort of patients with recurrent fevers and only 1 mutation in the *MVK* gene. The purpose of this study was to compare clinical features in those with 1 vs. 2 *MVK* mutations and to report therapeutic responses in all.

Methods: Patients were evaluated at the National Institutes of Health. Clinical and laboratory information were collected at each visit.

Results: 31 pts with mutations in *MVK* were evaluated: 22 had 2 mutations (21 with V377I and 1 other mutation; 1 with V203A/H380R), 9 had only 1 mutation after testing the whole gene (8 with V377I, 1 with I268V). The carrier frequency of V377I in our control Caucasian population is 0.3% (2/739).

Clinical or laboratory presentation at the time of a flare was compared between the 2 groups. There was no significant difference with regard to age of onset, duration of flares, frequency of flares, flares after immunization, GI symptoms, oral ulcers, sore throat, arthralgia, or adenopathy associated with flares. Rash was more common in pts with 2 mutations, 20/22 compared to 4/9 in those with one mutation ($p=.01$). Level of IgA was increased in those with 2 mutations (452 ± 230 mg/dl) compared to those with 1 mutation (230 ± 175) ($p=.01$), as well as level of IgD (95 ± 95, 2 mutations, vs. 8.3 ± 7.4, 1 mutation, $p=.01$).

Since there was no significant difference in clinical presentation, other than presence of rash and levels of IgA and IgD, pts were considered together to evaluate their therapeutic responses. Prednisone given at the time of a flare was helpful in 18/25, however one patient developed steroid psychosis. Colchicine was given to 8 pts and 7 showed no improvement or worsening. 15 pts tried montelukast: 4 reported some improvement, however 11 reported no improvement or worsening. Intermittent anakinra at the time of a flare was helpful in 14/19 pts, not helpful in 3 and too early to assess in 2 patients. One patient developed acute renal failure shortly after initiating intermittent anakinra therapy. Of the 9 pts receiving weekly etanercept, 4 showed some improvement and 5 showed no improvement of worsening (with one patient developing massive lymphadenopathy). 3 pts have required daily anakinra and shown a favorable response.

Conclusion: Aside from the presence of rash and higher IgA and IgD levels in those children with 2 *MVK* mutations, there are no significant clinical differences between those patients with 1 or 2 mutations. The relatively small number of children with 1 mutation may influence the analyses, but thus far there are no clear trends that allow identification or predictability of the disease course in children with either 1 or 2 mutations. Given the higher frequency of V377I heterozygotes in our patient cohort compared to the general population, our data suggest that under some circumstances this may be associated with recurrent fevers. Therapeutic options for children with MVK mutations include intermittent prednisone or anakinra, either given intermittently or daily; however, not all patients respond to therapy and there are associated adverse events in some patients.

Disclosure: K. S. Barron, None; **A. K. Ombrello**, None; **D. P. Goldsmith**, None; **I. Aksentijevich**, None; **A. Jones**, None; **D. L. Kastner**, None.

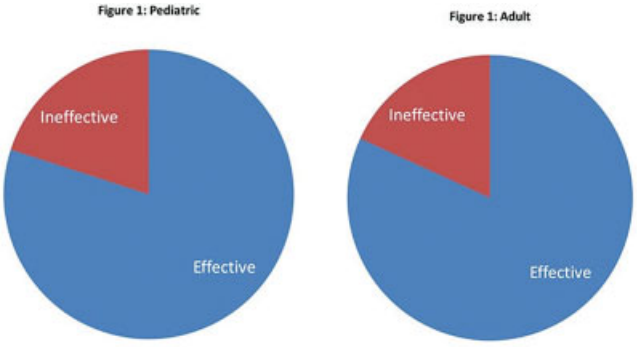
2173

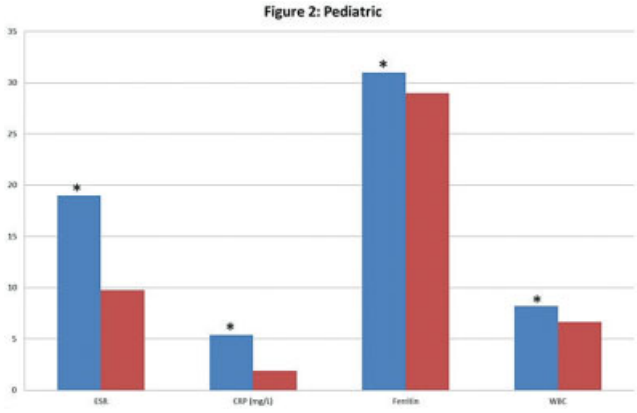
The Interleukin-1 Receptor Antagonist Anakinra Is Effective In The Treatment Of Undifferentiated Periodic Fever Syndromes. Daniella M. Schwartz[1], Runsheng Wang[2], Karyl S Barron[3], Daniel L. Kastner[4] and Amanda K. Ombrello[5]. [1]National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD, [2]NIH/NIAMS, Rheumatology fellowship and training branch, Bethesda, MD, [3]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, [4]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [5]National Human Genome Research Institute, National Institute of Health, Bethesda, MD.

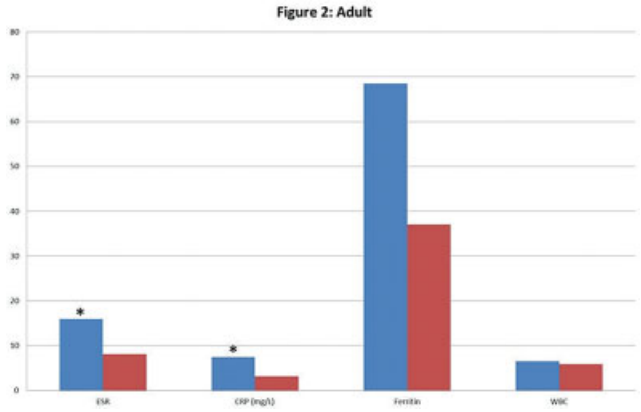
Background/Purpose: The autoinflammatory diseases are a group of disorders associated with dysregulation of the innate immune system. They are characterized by recurrent episodes of fever and systemic inflammation, typically presenting in early childhood. Since 1999, genetic causes have been discovered for several autoinflammatory diseases. Many patients with periodic fevers, however, are negative when tested for these mutations. Although the efficacy of interleukin-1 (IL-1) blockade in the known autoinflammatory diseases is established, this has not been systematically explored in the treatment of mutation-negative periodic fever syndromes. We describe our experience treating this heterogeneous group of children with the IL-1 receptor antagonist anakinra.

Methods: Records from patients enrolled in protocol 94-HG-0105 "Genetics and Pathophysiology of Familial Mediterranean Fever and Related Disorders" who were prescribed anakinra from 2009–2013 were reviewed. Patients were identified who had tested negative by commercially available methods for mutations known to cause autoinflammatory disease (MEFV, TNFRSF1A, NLRP3, and MVK). Results were confirmed by targeted sequencing. Medical records were reviewed for response to treatment based on patient-reported improvement in number or severity of flares. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell (WBC) count, and ferritin values before and after treatment were obtained.

Results: Of 69 pediatric patients prescribed anakinra, 56 tested negative for mutations known to cause periodic fevers; longitudinal data were available in 35 children. 28 of 35 (80%) patients described a clinical response to anakinra (Figure 1). Decreases in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell (WBC) count, and ferritin were statistically significant. Adverse reactions were minimal and consisted solely of injection site reactions. Of note, similar results were seen in the adult population, with 18 of 22 (82%) of patients describing a clinical response to anakinra, and statistically significant reduction in ESR and CRP.







Conclusion: Anakinra is safe and effective in the treatment of undifferentiated periodic fever syndromes.

Disclosure: D. M. Schwartz, None; **R. Wang**, None; **K. S. Barron**, None; **D. L. Kastner**, None; **A. K. Ombrello**, None.

2174

Urinalysis Monitoring In Children With Henoch-Schönlein Purpura: Is It Time To Revise? Hao Wang[1], Manasita Tanya[2], Justin Hung Tiong Tan[2], Sook Fun Hoh[2], Lena Das[2] and Thaschawee Arkachaisri[3]. [1]Duke-NUS Graduate Medical School, Singapore, Singapore, [2]KK Women's and Children's Hospital, Singapore, Singapore, [3]KK Women's and Children's Hospital and Duke-NUS Graduate Medical School, Singapore, Singapore.

Background/Purpose: Major complication of Henoch-Schönlein Purpura (HSP) is renal impairment. Recommended urinalysis (UA) monitoring over a period of 2 years has been a common practice in many pediatric rheumatology centers. Cost-effectiveness following this guideline is questionable. We explore the natural history of UA outcomes in our inception HSP cohort.

Methods: Patients with HSP with at least 6 mo follow-up and seen between 3/2009 and 6/2013, at our institute were recruited. A 2-year UA monitoring protocol was adopted (monthly for 6 mo, if normal then every 3 months for 18 mo). Minimal renal involvement was defined as isolated hematuria (urine RBC > 5/hpf) and/or proteinuria (urine protein > 1+), and renal impairment as presentation of nephritic, nephrotic symptoms, or renal failure. Recurrent HSP were excluded. Kaplan-Meier estimate and log-rank test were used to analyze the differences between groups for time to event. Logistic regression was used to assess relationships of cofactors.

Results: 56 patients (43% F) were analyzed. The ethnicity of our cohort reflected Singapore racial distribution. Majority of referrals (80%) were admitted. The median duration of follow up was 17.2 (10.6–24.2) mo. Over 1/2 of patients had subcutaneous edema and elevated serum IgA. 29 patients presented with abnormal UA at diagnosis (n=16, 55.2%, 5/16 developed renal impairment within 2 mo) or during follow up (n=13, 44.8%). Only one patient (7.7%) developed abnormal UA after 6 mo. UA was normalized in 24 patients during follow up, within a median time of 9.1 (95% CI: 3.5–14.6) mo. No association between demographic or clinical features and different renal outcomes was unveiled. Among patients with no renal impairment, an earlier subsidence of renal involvement ($p = 0.009$) was noted in patients with normal UA at diagnosis (n=13, median time: 2.9 mo, 95% CI: 1.5–4.4; 11 cases (84.6%) resolved by 12 mo), compared to children with abnormal UA at diagnosis (n=7, median time: 15.7 mo, 95% CI: 6.7–24.7). Non-renal indication of prednisolone use did not affect time to UA subsidence ($p = 0.32$).

Table 1. Patient characteristics, treatments and outcomes

DEMOGRAPHIC			
Age of Onset (years) (Median, IQR)	4.8 (3.8–6.5)		
Race	Chinese 43 (76.8%), Malay 8 (14.3%), Indian 1 (1.8%), Others 4 (7.1%)		
CLINICAL MANIFESTATIONS			
Previous infection	32 (57.1%)		
Rash	56 (100%)		
Subcutaneous edema	35 (62.5%)		
Abdominal pain	24 (42.9%)		
Arthritis	5 (8.9%)		
High IgA[a]	27 (64.1%)		
ESR (Median, IQR)[b] (Reference: 0–10 mm/50 min)	20.0 (10.0–32.0)		
CRP (Median, IQR)[c] (Reference: 0–9.9 mg/L)	8.6 (5.3–30.4)		
WBC (Median, IQR)[d] (Reference: 5.5–15.5×10^9/L)	11.9 (9.6–13.9)		
Platelets (Median, IQR) [d] (Reference: 150–450×10^9/L)	363.0 (303.8–459.8)		
TREATMENT			
Prednisolone	Renal impairment	N	5
		Duration (weeks) (median, IQR)	33.6 (23.5–51.8)
	Other indications	N	29
		Duration (weeks) (median, IQR)	8.0 (4.0–9.9)
Immunosuppressant		3 (5.4%)	
RENAL OUTCOME			
Normal UA at diagnosis	40 (71.4%)	Normal UA during follow up	27 (67.5%)
		Minimal renal involvement during follow up	13 (32.5%) **Abnormal UA** 29 (51.8%)
Minimal renal involvement at diagnosis	16 (28.6%)	Renal involvement resolved during follow up	7 (43.8%)
		Renal involvement persisted	4 (25.0%)
		Renal impairment during follow up	5 (31.3%)

a: Out of 41 patients with IgA tested, as per normal range for age.
b: Erythrocyte sedimentation rate, out of 39 patients with ESR tested.
c: C-reative protein, out of 35 patients with CRP tested.
d: White blood cells and platelets, out of 50 patients with CBC tested.

Conclusion: Several observations were demonstrated in our cohort: 1. One-third of normal UA at diagnosis developed abnormal UA and majority (92.3%) did so within the first 6 months. 2. Resolution of abnormal UA at diagnosis was slower than that of abnormal UA later. 3. As expected, the use of corticosteroids had no effect on time to UA resolution. With these findings, we propose a shorter duration of UA monitoring to 6 months in HSP patients with normal UA at diagnosis and follow up. A shorter duration of 12 months from onset of abnormal UA may be adequate for HSP patients with normal UA at diagnosis. Patients with abnormal UA at diagnosis may be followed up for a minimum of 24 months. This proposal is being evaluated and validated in our longitudinal cohort study with collaboration with other centers in the region.

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2175

Systematic Analysis and Pathologic Findings In Young Adults With Sudden Death Attributed To Kawasaki Disease In Childhood. Chisato Shimizu[1], Alka Sood[1], Hubert Lau[1], Steven Campman[2] and Jane C. Burns[1]. [1]UC San Diego, School of Medicine, La Jolla, CA, [2]San Diego County Medical Examiner Office, La Jolla, CA.

Background/Purpose: Coronary artery aneurysms (CAA) may remain silent after Kawasaki disease (KD) until adulthood when myocardial ischemia can lead to sudden death. CAA attributed to antecedent KD were present in 5% of young adults (<40 years (yrs)) evaluated for symptoms of myocardial ischemia by coronary angiography (Daniels et al. 2012). We postulated that there would be young adults with sudden, unexpected death due to CAA from KD who would have a state-mandated autopsy performed by the Medical Examiner (ME).

Methods: We systematically reviewed all autopsy cases < 35 yrs of age from 1997–2012 at the San Diego County ME Office with a cardiovascular cause of death. Cases were excluded if another medical condition was listed as a contributing factor to death including trauma, substance abuse, suicide, cancer, congenital heart disease, morbid obesity, diabetes, hypertension, or hyperlipidemia. We reviewed the ME records for demographic data, clinical history, and gross and histologic autopsy findings. For the two cases adjudicated as KD, the parents of the decedents were interviewed following written informed consent.

Results: There were 154 cases that met inclusion criteria and122 cases (80%) met exclusion criteria. Of the 32 cases reviewed, two (6.25%) had CAA described in the autopsy report. Case 1 was a 30-yr old Hispanic male with no significant medical history or cardiovascular risk factors who collapsed after a boxing work out. Cause of death was myocardial infarction due to thrombosis of the left anterior descending (LAD) aneurysm. Histologic findings included myocardial fibrosis a re-canalized aneurysm in right coronary artery (RCA) with multiple

lumens, and calcification of the LAD aneurysm wall with thinned media and organized and acute thrombus. Interview of the parents revealed a possible KD-compatible illness in childhood diagnosed as scarlet fever. Case 2 was a 22-yr old Korean male who collapsed during vigorous exercise. Sudden cardiac death was associated with chronic ischemic changes due to a partially occluded 15mm aneurysm at the bifurcation of the LMCA and LAD with diffuse calcification. There were two 6mm aneurysms of the RCA. There was patchy fibrosis throughout the myocardium. Interview of the mother revealed that this patient had been diagnosed with KD complicated by giant aneurysms at age 2.75 yrs. He had been maintained on aspirin therapy under the care of a cardiologist until he left home at age 20 yrs. Detailed immunohistochemical studies of these two cases are pending.

Conclusion: In an ME office serving a population of approximately 3 million people, 2/154 (1.3%) of cardiovascular deaths in persons <35 yrs could be attributed to CV complications of KD in childhood. Pathologic findings that support a diagnosis of antecedent KD include aneurysms with or without thrombosis, recanalization, or stenosis, luminal myofibroblastic proliferation, and CA wall calcification. Antecedent KD leading to myocardial ischemia or thrombosed aneurysms should be considered in the evaluation of all cases of sudden, unexpected death in young adults.

Disclosure: C. Shimizu, None; **A. Sood**, None; **H. Lau**, None; **S. Campman**, None; **J. C. Burns**, None.

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Relationships Between Physician and Patient Scored Clinical Outcome Measures In Pediatric Localized Scleroderma. Kaveh Ardalan, Christina Kelsey and Kathryn S. Torok. Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA.

Background/Purpose: Pediatric localized scleroderma (LS) is an autoimmune disease of the skin and underlying tissue leading to sclerosis and complications such as joint contractures. The impact of this disease on children and their parents has not been well described. Most published studies on LS outcomes have centered on physician based cutaneous assessment. Patient based outcomes are a critical component of research in disease management and clinical trials. The Childhood Dermatology Life Quality Index (CDLQI) is a quality of life (QOL) measure designed for pediatric skin conditions. The aim of this study is to explore the relationships between physician and patient scored measures of disease outcomes in pediatric localized scleroderma as compared to the CDLQI.

Methods: Patients included in this cohort were those with completed CDLQIs enrolled in the National Registry for Childhood Onset Scleroderma from 2007–2013. The following measures were extracted from the database for each patient; the modified Localized Scleroderma Skin Severity Index (mLoSSI), the Localized Scleroderma Damage Index (LoSDI), Physician Global Assessment of Activity, Damage and Severity (PGA-A, PGA-D, and PGA-S), CDLQI and patient and parent Global Assessment of Disease Impact (GA-Pt, GA-Par). Relationships between the physician and patient reported clinical measures were examined using Spearman's correlations ($p<0.05$).

Results: Sixty-eight subjects were identified. The majority were female (72%) and Caucasian (94%), and were representative of the major LS subtypes in pediatric onset disease. The median age of onset was 7.8 years old (IQR 4.4–10.3) and age at first clinic visit was 11.2 years old (IQR 8.1–14.7). Fifty-six patients had follow-up visits to include in the analyses. The relationships between the clinical outcomes and QOL measures at the initial and follow-up visits were similar. The median CDLQI decreased from 3 (IQR 1–7) at initial visit to 2 (IQR 1–4) at follow-up visits. The impact of disease on patient and parent decreased accordingly, with median GA-Pt 37.5 (IQR 8.8–64.3) at baseline and 9 (IQR 2–23.5) at follow-up, and median GA-Par 43 (IQR 9–67) at initial visit and 12 (5.0–33.8) at follow-up visit. CDLQI moderately and significantly correlated with the GA-par and GA-patient (rho = 0.584, 0.591, respectively). The GA-pt and GA-par were moderately and significantly related to each other (rho = 0.615). The clinician-scored outcome measures did not show a strong correlation to the CDLQI. At the initial visit, the LoSDI was weakly though significantly correlated (rho=0.256), and at the follow-up visits the PGA-A was weakly though significantly correlated (rho=0.284) to the CDLQI.

Conclusion: At this time, clinical outcomes in LS are based primarily on physician scored measures. However, the CDLQI did not correlate to the physician scored measures in this sample, but it did correlate to the patient's and parents' overall perception of disease impact. This study suggests that patient and parent global assessments are measuring the same underlying construct as the CDLQI but further study will be required to better clarify the nature of this construct and the reasons for the disconnect between the CDLQI and physician scored disease measures.

Disclosure: K. Ardalan, None; **C. Kelsey**, None; **K. S. Torok**, None.

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A Pilot Study Of Juvenile Localized Scleroderma (jLS) Consensus Treatment Plans. Suzanne C. Li[1], Kathryn S. Torok[2], Mara L. Becker[3], Fatma Dedeoglu[4], Robert C. Fuhlbrigge[5], Gloria C. Higgins[6], Sandy D. Hong[7], Maria F. Ibarra[3], Ronald M. Laxer[8], Thomas G. Mason II[9], Elena Pope[8], Marilynn G. Punaro[10], C. Egla Rabinovich[11], Katie G. Stewart[12], Christina Kelsey[13], Brian Feldman[14], Themba Nyrienda[15] and Knut M. Wittkowski[16]. [1]Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [2]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [3]Children's Mercy Hospital, Kansas City, MO, [4]Boston Childrens Hosp, Boston, MA, [5]Childrens Hospital, Boston, MA, [6]Nationwide Childrens Hosp, Columbus, OH, [7]U of Iowa Children's Hosp, Iowa City, IA, [8]The Hospital for Sick Children, Toronto, ON, [9]Mayo Clinic Rochester, Rochester, MN, [10]University of Texas Southwestern Medical Center, Dallas, TX, [11]Duke Univ Med Ctr, Durham, NC, [12]Texas Scottish Rite Hospital, Dallas, TX, [13]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [14]Hospital for Sick Kids, Toronto, ON, [15]Hackensack University Medical Center, Hackensack, NJ, [16]Rockefeller University, New York, NY.

Background/Purpose: Purpose: To evaluate clinical assessment tools and standardized treatment regimens (consensus treatment plans, CTPs) developed for juvenile localized scleroderma (jLS)

jLS is a chronic, inflammatory and fibrosing disease often associated with severe morbidity in the growing child. Over 20% of the jLS subjects enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry have joint contractures and >10% have a limb length difference. A major issue with evaluating the relative efficacy of the many reported treatments has been the lack of agreed upon assessments and criteria for evaluating treatment response. Our CARRA subgroup recently developed jLS disease assessments, response criteria, and CTPs that reflect current treatment practices of CARRA members, and the performance characteristics of these tools and feasibility of conducting comparative effectiveness treatment studies will be evaluated in a pilot study.

Methods: We are conducting a prospective, multi-center (10 CARRA sites), 1 year observational study of a cohort of 50 jLS patients beginning treatment with one of three methotrexate (MTX)-based CTPs (MTX alone, MTX with oral corticosteroids [CS], or MTX with intravenous CS), with study data entered into the existing web-based CARRA Registry. The treating physician determines which CTP to use. Collected data includes scoring of clinical activity and damage parameters, scoring of joint/limb morbidity; medication log; adverse events; physician global assessments (PGA) for activity, damage, and response to treatment; and patient and parent quality of life measures. There is an optional patient sample collection substudy. A reliability workshop meeting was held at study onset to review and evaluate the reliability of scoring the clinical assessments with 14 study physicians scoring 13 jLS patient volunteers two times.

Results: There was moderate inter-rater reliability for clinical activity and damage scoring (Kendall's coefficient 0.628 and 0.508, respectively), and high intra-rater reliability (average Spearman's rho 0.783 for activity, 0.743 for damage). Some parameters appeared more problematic, with lower reliability scores found for the activity parameters of lesion warmth, violaceous color, and skin thickness of lesion edge, and for the damage parameters hypopigmentation, and dermal atrophy. Since study enrollment began in 12/2012, 18 subjects from 9 sites have been enrolled. Nearly all subjects have agreed to participate in the optional biosample collection

Conclusion: We have currently achieved 36% of our target enrollment of 50 jLS subjects into our pilot study. This study enables evaluation and refinement of clinical tools for assessing disease state and treatment response based upon patient data. This study will allow us to evaluate feasibility issues related to the developed CTPs and with conducting comparative effectiveness treatment studies. Because the biorepository being developed is linked to extensive clinical data in a prospective registry, these samples potentially will allow the identification of biomarkers associated with good versus poor outcome, as well as better understanding of disease pathogenesis.

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Juvenile Onset Systemic Sclerosis: Clinical and Serological Features, and Mortality In Comparison With Adult Onset Disease. Juan G. Ovalles-Bonilla, Francisco Javier López-Longo, Indalecio Monteagudo, Esperanza Naredo, Carlos Gonzalez Fernandez, María Montoro Alvarez, Lina Martínez-Estupiñán, Juan C. Nieto, Julia Martínez-Barrio, Michelle Hinojosa, Natalia Bello, Belen Serrano, Carmen Mata and Luis Carreño. Hospital General Universitario Gregorio Marañón, Madrid, Spain.

Background/Purpose: Currently data regarding long-term outcome of juvenile systemic sclerosis (jSSc) is scarce. To describe the differences between patients with jSSc versus adult onset evaluated at a single medical center.

Methods: Patients with disease onset before the age of 17 years were included in the jSSc group, while subjects with SSc onset after age 18 formed the adult-onset cohort. The 2 groups were compared with respect to disease classification, clinical, serological data, and mortality.

Results: Seventeen jSSc cases seen between 1986 and 2011 were compared with 120 adult onset SSc cases. Mean age at onset in the jSSc group was 11.7±3.9 years, and the mean disease duration at the last follow-up was 19.3±7.8 years. The sex distribution was 7.5:1 (female:male). Among juvenile cases, 58.8% had diffuse SSc, while 41.2% had limited SSc. The clinical features seen in juvenile patients were: articular manifestations (arthralgia, arthritis, contractures and weakness) in the 100% of cases, Raynaud's phenomenon in 94%, digital ulcers and telangiectasia in 53%, interstitial lung disease in 11.8%. Antinuclear antibody was positive in 100%, and anti-U1RNP in 64.7%. A global mortality of 17.6% was seen. Articular manifestations, anti-DNA and anti-U1RNP were seen more frequently in the jSSc group. Adult onset SSc develop a higher frequency of sclerodactyly and interstitial lung disease.

Table 1. Clinical and serologic features, and mortality in comparison with adult onset disease

FEATURES (%)	Juvenile SSc n=17	Adult SSc n=120	p
Age at disease onset ± DE	11.7±3.9	46.5±14.4	<0.001
Disease duration ± DE	19.3±7.8	14.6±10.5	0.07
Diffuse SSc	10 (58.8)	52 (43.3)	0.23
Limited SSc	7 (41.2)	68 (56.7)	
sclerodactyly	5 (29.4)	68 (56.7)	0.03
Telangiectasia	9 (52.9)	74 (61.7)	0.49
Digital ulcers	9 (52.9)	80 (66.7)	0.27
Raynaud's phenomenon	16 (94.1)	111 (92.5)	0.81
Pulmonary Hypertension	2 (11.8)	9 (7.5)	0.54
Interstitial lung disease	2 (11.8)	49 (40.8)	0.02
Articular manifestations	17 (100)	71 (67.5)	0.005
Renal manifestations	3 (17.6)	17 (14.2)	0.70
Anti-centromere	3 (17.6)	36 (30)	0.29
Anti-Scl-70	2 (11.8)	30 (26.1)	0.19
ANA	17 (100)	109 (90.8)	0.19
Anti-DNA	5 (31.2)	11 (9.9)	0.016
Anti-U1RNP	11 (64.7)	13 (12.9)	<0.001
Mortality	3 (17.6)	31 (25.8)	0.46

jSSc: Juvenile Systemic Sclerosis, **SSc:** Systemic Sclerosis, **ANA:** antinuclear antibodies

Conclusion: Diffuse SSc, limited SSc, calcinosis, digital ulcers, pulmonary hypertension, anti-centromere, anti-Scl-70 and mortality shows a similar distribution between the 2 groups. Patients with jSSc presented a lower frequency of interstitial lung disease and sclerodactyly, but a higher expression of anti-DNA and anti-U1RNP.

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Consensus: What Agent To Use When First-Line Vasodilatadors Fail In Raynaud's Phenomenon Or Digital Ulcers Secondary To Juvenile Systemic Sclerosis? Marìa M. Katsicas[1], Mariana Gonzalez[2] and Ricardo A. G. Russo[3]. [1]Hospital de Pediatrìa Garrahan, Buenos Aires, Argentina, [2]Hospital de Pediatría Garrahan, Buenos Aires, Argentina, [3]Hospital de Pediatria Garrahan, Buenos Aires, Argentina.

Background/Purpose: Juvenile Systemic Sclerosis (JSS) is characterized by Raynaud's phenomenon (RP) and digital ulcers (DU).Conventional therapy includes calcium channel blockers (CCB). A growing number of vasodilators is available for treatment of refractory patients but there is no clear evidence of the best option. To aid clinical decision-making, an expert consensus was undertaken. Our objective was to identify the best therapeutic options and define the sequence of 2nd line vasodilators for RP and DU.

Methods: Steps in the process of consensus were: a) Identification of expert panel (EP) members, b) Identification of 2nd line vasodilators c) selection of outcome measures to define RP and DU improvement, d) systematic literature review; e) summary report of the latest scientific evidence f) expert consensus meeting; g) rating of the strength of evidence. RAND/UCLA appropriateness method was used for rating the medical decision: items were rated on a 9-point scale for each drug option. There were 2 scoring rounds: 1) anonymous and independent rating of the appropriateness of vasodilators based on scientific evidence and best clinical judgment. 2) Differences in scoring were discussed at a face-to-face meeting in a second rating round. Consensus was reached on appropriate / inappropriateness.

Results: The EP included 10 physicians from a tertiary center who are involved in the care of patients with JSS: 3 pediatric rheumatologists, 2 dermatologists, 1 pediatrician, 1 gastroenterologist, 1 nephrologist, 1 nutricionist, 1 pharmacologist, and a moderator. The EP identified 4 drugs for analysis: bosentan, iloprost, sildenafil, and trepostinil. Outcome measures were selected according to the literature references and EP judgment. RP improvement definition: ≥ 30% improvement according to the physician (in a visual analogue scale, VAS) and ≥ 30 % improvement in at least 2 patient-related domains (pain or function). Patient domains were: a) number of episodes, b) pain in a VAS, c) function (impaired activity of daily living, VAS), d) RP episodes average duration (in minutes). DU improvement definition: a favorable change in all physician- and patient-related domains: patient's domains: a) pain (VAS) b) function (VAS); physician′s domains: a) ulcer activity (VAS) b) horizontal and transverse DU diameter (in mm). Systematic literature review was performed independently by 5 EP members and guided by the moderator. All articles in English were eligible. Data bases included PuBmed and Cochrane. The search strategy included all relevant terms: bosentan, iloprost, sildenafil, trepostinil, RP, DU, combined in different sets of keywords. The summary report of the scientific evidence included 25 articles. Ranking of papers according to the strength of evidence showed: 1a (1 paper), 1b (7), 2b (2), 3b (2), 4(8), 5(5). After second scoring round consensus was reached: 1st appropriate indication Iloprost; 2nd bosentan, 3rd sildenafil; 4th trepostinil.

Conclusion: The EP reached a consensus on vasodilator drugs, providing direction for common dilemmas in the pharmacologic treatment of RP and DU in refractory patients.

Disclosure: M. M. Katsicas, None; **M. Gonzalez**, None; **R. A. G. Russo**, None.

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Presentation, Diagnosis, and Treatment Of Chronic Recurrent Multifocal Osteomyelitis. Colin Anderson[1], Erin Wylie[2], Travis Heare[2], Jamie Stewart[2], Kelley Capocelli[2], Shelley Dell'Orfano[2] and Jennifer Soep[2]. [1]The University of Colorado, Aurora, CO, [2]Children's Hospital Colorado, Aurora, CO.

Background/Purpose: Chronic recurrent multifocal osteomyelitis (CRMO) is a rare, non-infectious inflammatory bone disorder in children. Knowledge about the disorder is limited secondary to its rare prevalence, often resulting in delayed diagnosis and unnecessary treatments. The purpose of this study is to report on one of the largest cohorts yet gathered for CRMO in order to provide more information about the presentation, diagnosis, and treatment.

Methods: Retrospective chart review was performed in 57 patients diagnosed with suspected CRMO (n = 32) or biopsy-confirmed (n = 25) at our institution over a 2-year period at a single tertiary referral center. Collected outcome measures included: gender, age at symptom onset, age at CRMO diagnosis, prior diagnosis, secondary diagnosis, antibiotic use, radiographic, laboratory and histology findings, treatment type and outcome, complications, duration of symptoms, and follow-up.

Results: The average age at symptom onset was 6.1 years (Range: 0.7–12.3 years). The average delay in diagnosis was 13.4 months (Range: 0.8–62.5 months). Incorrect initial diagnoses occurred in 56% of cases, resulting in 44% of patients unnecessarily treated with antibiotics prior to CRMO diagnosis. In 63% of cases, normal radiographs at presentation were observed. However, abnormal MRI findings were present in 100% of patients, with multifocal involvement in 75% of those studies. Average white blood cell count, erythrocyte sedimentation rate, and C-reactive protein at presentation were 11,600 /μL, 40.1 mm/hr, and 2.4 mg/dL, respectively. All biopsy

cultures were negative. Non-steroidal anti-inflammatory drugs (NSAIDs) provided complete symptomatic relief in 66% of patients, while 33% of patients required further treatment with methotrexate, steroids and/or TNF inhibitors.

Conclusion: Awareness of defining features of CRMO such as indolent onset of pain, multifocal involvement, presence of early MRI findings, inflammatory pathologic findings with sterile cultures, and marked clinical response to NSAIDs may assist with earlier diagnosis. Understanding of the clinical presentation of CRMO will assist healthcare providers in avoiding unnecessary treatments and lead to a quicker resolution of symptoms in patients diagnosed with this rare disease.

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Methotrexate and Infliximab With Or Without Zoledronic Acid Improve Disease Activity and Prevent Damage Progression In Chronic Nonbacterial Osteomyelitis. Yongdong (Dan) Zhao[1], Nancy Chauvin[1], Diego Jaramillo[1] and Jon Burnham[2]. [1]Children's Hospital of Philadelphia, PHILADELPHIA, PA, [2]The Children's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Chronic nonbacterial osteomyelitis (CNO) is an inflammatory bone disease that causes pain, disability, and sometimes permanent skeletal damage. MRI allows for visualization of bone edema, soft tissue inflammation (STI), periosteal reaction (PR), and characteristics of bone damage, such as growth plate bony bar formation and vertebral collapse. However, no standard MRI-based outcomes have been validated in CNO. This retrospective study aimed to assess changes in CNO activity and damage after tumor necrosis factor alpha inhibitor (TNFi) and methotrexate therapy using a standard MRI scoring method.

Methods: Children 2–18 years of age with CNO were included if paired MRI scans were performed $\leq$ 2 months prior to and $\geq$ 2 months after TNFi initiation. Clinical and laboratory data before and after TNFi therapy were recorded. Unique inflammatory lesions, bone edema severity, STI severity, total lesion number with PR, total lesion number with hyperostosis, bony bar severity, vertebral compression severity, and the number of inflamed joints were recorded by a single radiologist (NC). The Wilcoxon matched pairs signed-ranks test was used to compare changes after TNFi.

Results: Nine CNO patients treated with TNFi met inclusion criteria. All received infliximab (IFX) and concomitant methotrexate (MTX). All nine (6 females) were Caucasian. Mean age was 12 $\pm$ 4 years. Seven patients previously received antibiotics, NSAIDs, prednisone, bisphosphonate, and/or MTX. The median duration between diagnosis and initiation of IFX was 6.8 months (range: 0.5–19.3). Baseline MRI was obtained 1.0 $\pm$ 0.7 months prior to IFX and the follow up MRI was obtained 6.7 $\pm$ 3.7 months later. Paired site-specific scans were obtained in 6, and whole body scans in 3 patients. The mean dose of IFX was 8.1 $\pm$ 1.9 mg/kg, every 4–8 weeks. Five of six patients received zoledronic acid for vertebral lesions. The numbers of patients with lesions at specific sites were: spine (5), pelvis (6), clavicle (2), long bone (4), and mandible (1). At the visit closest to the follow up MRI, significant reductions were seen in the median pain score (4 to 0, $p<0.01$), patient global assessment (3 to 0, $p<0.01$), physician global assessment (2 to 0, $p<0.01$), and Childhood Health Assessment Questionnaire (0.25 to 0, $p=0.02$). There were significant reductions in the erythrocyte sedimentation rate (15 to 5 mm/hour, $p=0.01$) and C reactive protein levels (0.8 to 0.5 mg/dL, $p=0.03$). Significant decreases in the median total inflammatory lesion number (5 to 2, $p=0.03$) and maximum bone edema score (2.2 to 1.3, $p=0.02$) were observed. Maximum STI score and inflamed joint count decreased, but not significantly. Periosteal reaction ($n=2$) and hyperostosis ($n=1$) resolved. Skeletal damage severity, including bony bar formation and vertebral compression, did not progress.

Conclusion: In this retrospective study, IFX and MTX with or without zoledronic acid for CNO resulted in significant clinical and radiographic improvement. Standard MRI assessment demonstrated reductions in active bone lesions and bone edema severity without worsening of spine or growth plate damage. Prospective studies are needed to assess the reliability and validity of standardized MRI protocols.

Disclosure: Y. Zhao, None; **N. Chauvin**, None; **D. Jaramillo**, None; **J. Burnham**, None.

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Spectrum Of Musculoskeletal Inpatient Diagnoses At The Largest Pediatric Center In East Africa In 2011. Angela Migowa[1], Ines Colmegna[2], Evelyne Ng'ang'a[3], John Wachira[4], Thomas Ngwiri[4], Carol A. Hitchon[5], Sasha Bernatsky[6] and Rosie Scuccimarri[7]. [1]Aga Khan University Hospital, Nairobi, Kenya, [2]McGill University Health Centre, Montreal, QC, [3]University of Nairobi, Nairobi, Kenya, [4]Gertrude's Children Hospital, Nairobi, Kenya, [5]University of Manitoba, Winnipeg, MB, [6]McGill University Health Center, Montreal, QC, [7]Montreal Children's Hospital and McGill University, Montréal, QC.

Background/Purpose: Pediatric rheumatic diseases are among the most common chronic illnesses of childhood and can cause considerable disease burden and disability. The frequency and outcomes of pediatric rheumatic conditions in East Africa are unknown. Defining the spectrum of inpatient diagnoses is critical to designing a context-specific educational program targeting African pediatricians and pediatric trainees to improve diagnosis and treatment of children with these conditions.

Methods: In order to assess the spectrum of diseases seen on the inpatient service from January to December 2011 at Gertrude's Children Hospital, the largest pediatric center in East-Africa, patients identified as having diseases of the musculoskeletal (MSK) system and connective tissues (CT) by ICD-10 diagnostic codes ('M-codes') at discharge were included. After IRB approval, the admission records of these patients were reviewed locally and the de-identified information sent to the McGill investigators. Diagnoses were validated by two independent rheumatologists using information gathered from the medical records as well as laboratory and microbiology investigations. True cases were defined as those with recorded clinical evidence corresponding to the standard definition of the 'M-code' assigned by the local physician. Frequencies of each 'M-code' identified were then calculated.

Results: The total number of admissions to Gertrude's Hospital during 2011 was 8,011. Among those, 35 patients were identified as having an 'M-code' diagnosis at discharge. When the records were reviewed, non-MSK conditions accounted for 20% (7 cases) of all 'M-code' admissions. Minor surgical procedures made up 14.3% (5 cases). When both of these were excluded, diseases of the MSK system and CT represented 0.28% of the total admissions in 2011. Validated diagnoses were classified as inflammatory arthropathies (39.1% or 9 cases), septic arthritis (30.4% or 7 cases); soft tissue and muscle infections (17.4% or 4 cases) and Kawasaki disease (KD) (13.1 % or 3 cases).

Conclusion: Following the exclusion of misclassified patients and the validation of true diagnoses, diseases of the MSK and CT represented 0.28% of the total admissions to the largest pediatric referral center during 2011. The spectrum of rheumatic conditions requiring admissions included inflammatory and infectious arthropathies, soft tissue and muscle infections, and KD. Surprisingly, there were no admissions for lupus and other systemic vasculitides beyond KD during the studied time interval. This may indicate under-diagnosis of these conditions, poor sensitivity of 'M-codes' to identify these diseases or a true low frequency of these diagnoses. Although using 'M-codes' to identify rheumatic conditions may have its limitations, this study was the first step at identifying the frequency of these conditions in this inpatient population.

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Spectrum Of Outpatient Musculoskeletal Visits At The Largest Pediatric Center In East Africa In 2011. Laurel Broten[1], Angela Migowa[2], Rosie Scuccimarri[3], Evelyne Ng'ang'a[4], John Wachira[5], Thomas Ngwiri[5], Sasha Bernatsky[6], Carol A. Hitchon[7] and Ines Colmegna[8]. [1]McGill University, Montreal, QC, [2]Aga Khan University Hospital, Nairobi, Kenya, [3]Montreal Children's Hospital and McGill University, Montréal, QC, [4]University of Nairobi, Nairobi, Kenya, [5]Gertrude's Children Hospital, Nairobi, Kenya, [6]McGill University Health Center, Montreal, QC, [7]University of Manitoba, Winnipeg, MB, [8]McGill University Health Centre, Montreal, QC.

Background/Purpose: Pediatric rheumatic diseases are a major cause of morbidity, frequently leading to permanent disability, impaired functional status and quality of life, and significant direct and indirect costs to patients

and society. The prevalence and burden of pediatric rheumatic diseases in Sub-Saharan Africa are largely unknown. As a first step to design and promote policies to improve rheumatic patients' outcomes, we performed a cross-sectional study to evaluate the frequency and validity of the use of musculoskeletal ICD-10 diagnostic codes among outpatients at the largest pediatric center in East-Africa and its outreach clinics.

Methods: Using the Kranium database, the electronic medical record system containing all billing data for Gertrude's Children's Hospital System (GHS), we extracted all diagnoses classified under the ICD-10 codes for musculoskeletal (MSK) conditions (M00-M99) from pediatric outpatient visits recorded between January and December 2011. Frequencies were calculated for each disease category and subcategory within these ICD-10 categories. For cases coded in the category 'arthropathies' (M00-M25), the assigned ICD-10 diagnosis was verified against the patient's history, physical examination and investigations by two independent rheumatologists. True cases were defined as those with recorded clinical evidence corresponding to the ICD-10 code assigned by the local physician.

Results: Out of the 22 categories of all diseases in ICD-10, MSK conditions (M00-M99) were the 11th most commonly billed category at GHS, and more frequent than neoplasms and cardiovascular codes. The period prevalence of M-code diagnoses for outpatient consults at GH was 0.52% (1,197 total M-code consults / 232,273 total consults). The most frequent M-code categories assigned by local physicians corresponded to 'soft tissue disorders' (M60-M79) (57% of all M-code diagnoses) and 'arthropathies' (31%). Among the arthropathies an over-all diagnosis agreement of 36% was found between the M-code used and the verified clinical evidence recorded with 0% of agreement for the category of 'arthrosis' (M15-M19), 40% for the category of 'inflammatory arthropathies' (M05-M14) and 31% for 'other joint disorders' (M20-M25). Misclassification of patients with potential inflammatory and/or infectious diagnoses occurred in 50 out of 333 visits. After re-assigning diagnoses whose initial ICD-10 M code was found to be inaccurate, the most frequent MSK conditions seen were trauma (M12.5) (29%), inflammatory arthropathies (M05-M14) (20%) and pain in joint (M25.5) (15%).

Conclusion: Musculoskeletal conditions captured by M-codes are frequent among outpatient consults at the largest pediatric center in East-Africa. Trauma, inflammatory arthropathies and arthralgias all-together accounted for two-thirds of all MSK diagnoses. The lack of representation of systemic autoimmune diseases raises concern regarding their potential under-diagnosis or misclassification. Training local clinicians to recognize potential inflammatory conditions may help to improve the outcome of pediatric rheumatic disorders in Africa.

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Application Of The Bonexpert Method For Bone Age and Bone Health Assessment In Patients With Juvenile Idiopathic Arthritis. Charlotte M. Nusman[1], Janneke Anink[2], Lisette W.A. van Suijlekom-Smit[2], Marion A.J. van Rossum[3], Mario Maas[1] and Rick R. van Rijn[1]. [1]Academic Medical Center, Amsterdam, Netherlands, [2]Erasmus MC Sophia Children's Hospital, Rotterdam, Netherlands, [3]Emma Children's Hospital / Academic Medical Center and Reade Institute, Amsterdam, Netherlands.

Background/Purpose: Both the maturation of bone and its mineral density are affected by chronic inflammation in juvenile idiopathic arthritis (JIA). Bone age is in most cases assessed by a pediatric radiologist using a bone age standard atlas, usually the 'Radiographic Atlas of Skeletal Development of the Hand and Wrist' by Greulich and Pyle. Dual-energy X-ray densitometry (DXA) is the most commonly used method to assess bone density. Recently however, the old method of radiogrammetry has regained attention with the development of BoneXpert, an automated method of assessing bone age (BA) and bone density expressed in the Bone Health Index (BHI), using conventional hand X-rays. The objective of this study was to apply BoneXpert, measuring BA and BHI, in JIA patients prior to starting etanercept.

Methods: Radiographs of both right and left hand were collected for 63 patients (2 systemic JIA, 20 polyarthritis RF negative, 7 polyarthritis RF positive, 15 extendend oligoarthritis, 1 enthesitis related arthritis, 4 psoriatic arthritis) included in the Dutch Arthritis and Biologics in Children Register at start of etanercept. Because BoneXpert is developed for the use in children and has a bone age range of 2.5–17 years for boys and 2–15 years for girls, patients were selected within these age ranges. BA (Greulich and Pyle) and BHI were reported as standard deviations (SDS) from the reference population. Reproducibility of BoneXpert was assessed in all patients by calculating the BA and BHI twice for the left hand radiograph. Intraclass correlation coefficient (ICC) was used to determine the agreement between the two repeated measurements. Differences between patients and the reference population were tested with a one sample t-test. Patients for whom BoneXpert was not able to calculate BA or BHI were analysed separately.

Results: For 52 patients (median age 10.0 IQR 6.5–11.3, 56% female), BoneXpert was able to calculate both BA and BHI. BA SDS (mean -0.47 ± 1.32) and BHI SDS (mean -0.70 ± 1.10) differed significantly ($P<0.01$) from the reference population. For 11 patients BoneXpert was not able to calculate either BA, BHI or both, most likely caused by a bone age close to the outer limits of BoneXpert. Reproducibility was excellent with an ICC ranging from 1.00 (for BA, BA SDS, BHI) to 0.84 (for BHI SDS).

Conclusion: BoneXpert is an easy to use and reproducible method for assessing BA and BHI in patients with JIA starting etanercept, provided that radiographs are of reasonable quality and patients' BA is well within the age ranges of the program. The population investigated had a delayed bone maturation and lower bone density than healthy children as indicated by BoneXpert.

Disclosure: C. M. Nusman, None; **J. Anink**, None; **L. W. A. van Suijlekom-Smit**, Dutch Board of Health Insurances, Dutch Arthritis Association, Pfizer, Abbott, 2, Roche, Novartis, 5; **M. A. J. van Rossum**, None; **M. Maas**, None; **R. R. van Rijn**, None.

2185

Three Middle Finger Width Correlates With Maximum Mouth Opening and Is a New Reliable Parameter To Identify Joint Hypermobility In Schoolchildren. Francesca Sperotto[1], Gabriella La Falce[2], Fabio Vittadello[1], Lorenzo Favero[2] and Francesco Zulian[1]. [1]University of Padua, Padua, Italy, [2]Gnatology Unit, Department of Dentistry, Padua, Italy.

Background/Purpose: Maximum mouth opening (MMO) is a useful parameter to identify common temporomandibular joint (TMJ) disorders. Up to now, a few studies addressed the issue on MMO normal values in pediatric population, according to age and/or presence of generalized joint hypermobility (GJH), therefore it is not widely used in general medical practice.

Aim of the study was to evaluate the MMO in a cohort of healthy schoolchildren and to propose a new parameter, the *three middle finger width* (TMFW), the distance between 2nd and 4th fingers of the right hand at the level of the lowest nail bed, to evaluate the TMJ hypermobility in children. We also analyzed the relationship between GJH and TMJ hypermobility.

Methods: We conducted a cross sectional study in a cohort of healthy schoolchildren, aged 8–13 years. Information on family history of GJH and history of TMJ involvement were collected. Physical examination included height, weight, body surface area (BSA), body mass index (BMI) and musculoskeletal evaluation focused on the presence of GJH according to the Beighton criteria (BS≥4/9). TMJ evaluation included a complete gnathological visit, aimed to investigate the presence of TMJ disorders and to measure the MMO. The evaluation of TMFW was also performed and the Mouth Opening Ratio (MOR) was then calculated by the formula [(MMO-TMFW)/MMO]x100, adopting a 10% cut-off value to define the TMJ hypermobility.

Results: Two hundred and eighty-eight schoolchildren, 143 females and 145 males, entered the study. Mean MMO was 45.57 mm (± 5.12) for males and 44.87 mm (± 4.98) for females. Mean TMFW was 43.03 mm (± 4.09) for males and 41.71 mm (± 3.84) for females. Both MMO and TMFW significantly correlated with all growth parameters (height, weight, BMI and BSA). 89 subjects (30.9%) showed TMJ hypermobility (MOR>10%). In these subjects and in those with normal MOR, MMO correlated with TMFW ($r= 0.761$, $p<0.001$ and $r= 0.786$, $p<0.001$ respectively) although in the first group MMO showed an higher level distribution. The prevalence of subjects with GJH was significantly higher in the group with TMJ hypermobility than in the other (44.8% vs 21.5% $p<0.001$).

Conclusion: TMFW correlates with MMO in schoolchildren and may represent a simple and reliable method to evaluate TMJ abnormalities. MOR, as an index to identify TMJ hypermobility, correlates with the presence of GJH and could be reasonably included, as an adjunctive feature, to the Beighton Criteria.

Disclosure: F. Sperotto, None; **G. La Falce**, None; **F. Vittadello**, None; **L. Favero**, None; **F. Zulian**, None.

2186

Lower Extremity Strength Is Related To Diminished Quality Of Life In Obese Children. Sharon M. Bout-Tabaku[1], Matt Briggs[1], Tom Best[1], Colleen Spees[1], Ajit Chaudhari[1] and Laura Schmitt[2]. [1]The Ohio State University, Columbus, OH, [2]The Ohio State Universtiy, Columbus, OH.

Background/Purpose: Obese children have a higher prevalence of lower extremity (LE) pain, with associated diminished quality of life, greater knee malalignment, generate less knee extensor force, and are less physically active compared to healthy weight (HW) children, putting them at risk to be obese adults. In adults, obesity is one major risk factor in developing osteoarthritis (OA) that negatively affects quality of life. Obese children may have "adult" risk factors, which may confer a risk of developing OA. We explored the relationships between knee alignment, LE strength and quality of life in obese adolescents. We compared 1) knee alignment and lower extremity strength in OB and HW adolescents and 2) evaluated the relationship of BMI and LE strength, and LE strength and QOL.

Methods: Adolescents (ages 11–18) recruited from pediatric community and tertiary centers were enrolled into two age and sex matched groups based on obesity status. Body mass index (BMI= kg/m^2) was calculated to determine BMI Z-scores from CDC US 2002 data. QOL was assessed using the Pediatric Quality of Life™(PedsQL) physical function score. Frontal plane knee alignment was measured using umbilicus, knee and ankle landmarks. LE strength was measured bothisokinetically: quadricep peak torque (QPT) and hamstring peak torque (HSPT) and isometrically: hip abductor peak torque (AbdPT) and hip extensor peak torque (ExtPT). Peak torque was normalized to body weight and right side data were analyzed as all subjects were right leg dominant. Means and standard deviations described the data. Paired t-tests and Pearson's correlations coefficients evaluated group differences and associations among variables of interest.

Results: 12 males and 10 females were enrolled. They were divided into 2 groups: OB and HW based on mean BMI and BMI z-scores are reported in Table 1. Mean PedsQL physical function scores differ by group. (Table 1).

Mean right knee alignment did not differ between the OB and HW adolescents. (Table 1) The OB group had significantly lower QPT, HSPT, AbdPT, and ExtPT (Table 1).

BMI Z-scores were negatively correlated with LE strength (QPT $r = -0.443$, $p<0.05$, HSPT $r = -0.527$, $p< 0.05$, AbdPT $r = -0.394$, $p> 0.05$, ExtPT $r = -0.513$, $p< 0.05$). LE strength measures were positively correlated with physical function scores (QPT $r = 0.551$, $p< 0.05$, HSPT $r = 0.692$, $p< 0.001$, AbdPT $r = 0.538$, $p< 0.05$, ExtPT $r = 0.555$, $p< 0.05$).

Table 1. Clinical and serologic features, and mortality in comparison with adult onset disease

	Obese (n-11)	Non-obese (n=11)	p value
Age (years, sd)	13.9 ± 2.12	14.0 ± 2	p>0.05
BMI, (mean, sd)	29.56 ± 2.24	20.36 ± 2.94	p>0.001
BMI Z-score	1.96	0.19	p<0.001
PedsQL(mean, sd)	82.67 ± 10.59	91.76 ± 10.01	p<0.05
Right knee alignment (mean degrees, sd)	173.82 ± 6.23	170.82 ± 2.09	p>0.05
QPT (Nm/kg, sd)	1.44 ± 0.29	1.97 ± 0.32	p<0.001
HSPT (Nm/kg, sd)	0.77 ± 0.24	1.15 ± 0.22	p<0.001
AbdPT (Nm/kg, sd)	0.71 ± 0.38	1.08 ± 0.27	p<0.05
ExtPT (Nm/kg, sd)	0.94 ± 0.43	1.58 ± 0.44	p<0.05

Table 1. $p<0.05$ level of significance, sd= standard deviation

Conclusion: OB adolescents have diminished LE strength compared to HW counterparts. Higher BMI Z-scores correlated with lower LE strength while lower LE strength correlated with reduced physical function. LE strength may limit appropriate physical activity participation in obese adolescents further contributing to obesity and other risk factors that may lead to the development of knee OA. Future research need to explore why the muscles in obese children are not responding as expected to excess load by increasing muscular strength.

Disclosure: S. M. Bout-Tabaku, None; **M. Briggs**, None; **T. Best**, Abbott Immunology Pharmaceuticals, 5; **C. Spees**, None; **A. Chaudhari**, None; **L. Schmitt**, None.

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Inter-Rater Reliability Of Jumping Mechanography In Healthy Children and Adults. Johannes Roth[1], Ciaran M. Duffy[2], Tania Bennett[1], Marta Erlandson[3], Michele Gibbon[1], Heather Macdonald[4], Douglas Race[5], Leanne M. Ward[1] and Lori B. Tucker[5]. [1]University of Ottawa, Ottawa, ON, [2]Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa, ON, [3]University of Toronto, Toronto, ON, [4]The University of British Columbia, Vancouver, BC, [5]University of British Columbia, Vancouver, BC.

Background/Purpose: Muscle function can be affected by many chronic disorders of childhood including Juvenile Idiopathic Arthritis (JIA). Whereas the term "muscle strength" is often used to describe muscle function, it does not provide an objective assessment. Instead, the various components of muscle function including muscle force and power need to be measured precisely. Portable ground reaction force plates have been used to assess dynamic muscle function in clinical settings and for clinical studies and this method is commonly referred to as jumping mechanography. While **intra**-rater reliability has been published, no data is available for **inter**-rater reliability which is particularly important for multi-centre and longer-term prospective studies. The aim of this study was to determine inter-rater reliability for muscle function assessments using Leonardo™ Jumping Mechanography.

Methods: As part of the trans-Canadian, prospective study "Linking Exercise, Activity and Pathophysiology in Juvenile Idiopathic Arthritis (The LEAP Study)", inter-rater reliability of the Single Two-Legged Jump (S2LJ) and the Multiple One-Legged Jump (M1LJ) on the Leonardo™Jumping Mechanography was assessed between three raters.

14 healthy subjects were recruited among them 6 adults (3 males, mean age [SD] of 33.2 years[12.42]) and 8 children (3 males, mean age [SD] of 9.0 years[2.27]).

Each participant performed a set of three different jump types, a S2LJ followed by right and left M1LH with each one of three operators. Three trials were completed per jump type and participants had 15 minutes of rest in between jumps.

For the S2LJ, maximum Power was the primary outcome. Efficiency, Maximum Velocity, Maximum Force, Maximum Force and Maximum Height were also captured. For the M1LH, right and left Maximum Force was the primary outcome.

All of these measures were recorded relative to body weight and as absolute measurements. Reliabilty was determined using the interclass correlation coefficient (ICC) and coefficients of variation (%CV).

Results: For the S2LJ, CV and ICC (95% CI) for maximum power were 3.82% and 0.997 (0.992–0.999) respectively for the whole group and 5.09 % and 0.987 (0.958–0.997) for the children only. All other parameters assessed in the S2LJ were in the same range with the maximum variation observed for maximum force with a CV of 5.80% and ICC of 0.997 (0.945–0.992) for all and 6.75% and 0.932 (0.800–0.984) for the children only.

For the M1LH, the CV for maximum force was up to 8.96% and ICC 0.865 (0.704–0.949) for all and 3.69% and 0.851 (0.592–0.965) for the children only. Maximum force relative to body weight showed a maximum CV of 4.04% and ICC of 0.813 (0.615–0.929) in the entire group and 4.24% and 0.752 (0.412–0.938) for the children only.

Conclusion: Leonardo™ Jumping Mechanography is a suitable test for objective assessment of muscle function for clinical use and multi-centre trials, with very good inter-rater reliability across multiple parameters of muscle function. We found that maximum force calculation in children may need to be adjusted for body weight to increase accuracy. This method is currently in use in the LEAP study across Canada.

Disclosure: J. Roth, None; **C. M. Duffy**, None; **T. Bennett**, None; **M. Erlandson**, None; **M. Gibbon**, None; **H. Macdonald**, None; **D. Race**, None; **L. M. Ward**, None; **L. B. Tucker**, None.

ACR/ARHP Poster Session C
Pediatric Rheumatology - Pathogenesis and Genetics
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

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Role of Interleukin-1 in Abnormal Monocyte Phenotype in Systemic Onset Juvenile Idiopathic Arthritis. Yujuan Zhang[1], Claudia Macaubas[1], Clarissa Klein[1], M. Virginia Pascual[2], Arielle Hay[3], Susan D. Thompson[4], Christy I. Sandborg[1], Norman T. Ilowite[3] and Elizabeth D. Mellins[1]. [1]Stanford University Med Ctr, Stanford, CA, [2]Baylor Institue for Immunology Research, Dallas, TX, [3]The Children's Hospital at Montefiore, Bronx, NY, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Background/Purpose: Monocytes undergo phenotype changes when exposed to different microenvironments: the classic proinflammatory M1 phenotype, alternative regulatory M2 phenotype and M2-like phenotype,

are each regulated by specific transcriptional factors. Here, we investigate whether monocyte phenotypes change with interlukin-1 (IL-1) blockade in systemic onset juvenile idiopathic arthritis (sJIA). We took samples from RAPPORT (**RA**ndomized **P**lacebo **P**hase study **O**f **R**ilonacept in the **T**reatment of sJIA) to study the phenotype in monocytes by measuring level of transcriptional factors involved in monocyte polarization before and after treatment with Rilonacept, an IL-1 trap.

Methods: Subjects on the Rilonacept arm receive active drug from week 0 for a total of 24 weeks; subjects on Placebo arm receive placebo for 4 weeks then receive active drug Rilonacept for a total of 20 weeks. Blood samples are obtained at week 0, week 2, week 4, week 14 and week 24. RNA extracted from isolated monocytes is analyzed by real time PCR to measure M1 associated genes: Interferon Regulatory factor (IRF) family IRF5, Signal transducers and activators of transcription (STAT) family STAT1; M2 associated genes IRF4, STAT6, Kruppel-Like Factor 4 (KLF4) and peroxisome proliferator-activated receptor-γ (PPAR-γ). All transcript levels are normalized by the levels of 3 housekeeping genes.

Results: 30 RAPPORT samples from 15 subjects were tested. Samples from subjects treated with Rilonacept for 6 weeks or more ("Late RAPPORT") showed decreased expression of M2 genes except for PPAR-γ, compared to those treated for less than 6 weeks ("Early RAPPORT") (see Figure 1). KLF4 showed the most significant decrease in "Late RAPPORT"; in addition, KLF4 is persistently lower in those clinically improved by different measures, including PediACR30 (P=0.0006), joint count (P=0.0024), clinical lab values (P=0.02) or functional state (P=0.0015), but not by improvement in range of motion (ROM) (see Figure 2).

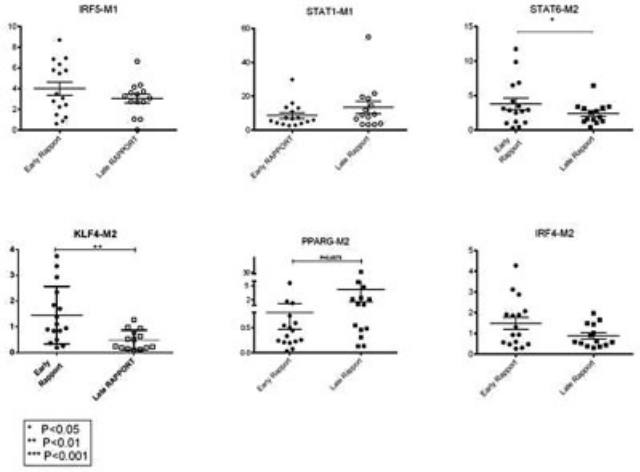

Figure 1.

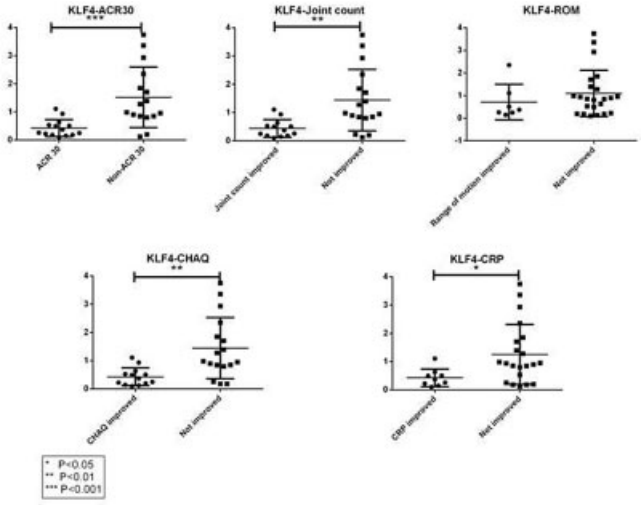

Figure 2.

Conclusion: Regulatory M2 genes (KLF4, IRF4 and STAT6) tend to decrease in sJIA monocytes after IL-1 blockade while M2-like gene PPAR-γ appears to increase. There is measurable impact of IL-1 blockade on monocyte phenotype at the transcription factor level.

Disclosure: Y. Zhang, None; **C. Macaubas**, None; **C. Klein**, None; **M. V. Pascual**, Novartis Pharmaceutical Corporation, 5, US Patent, 9, Novartis Pharmaceutical Corporation, 6; **A. Hay**, None; **S. D. Thompson**, None; **C. I. Sandborg**, None; **N. T. Ilowite**, Novartis Pharmaceutical Corporation, 5, Novartis Pharmaceutical Corporation, 6, Janssen Pharmaceutica Product, L.P., 6; **E. D. Mellins**, None.

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TLR 4 Endogenous Ligand MRP8/14 Levels in Enthesitis Related Arthritis (ERA) and Its Association With Disease Activity and TLR 4 Expression. Amita Aggarwal, Mujeeb Rahman, Arpita Myles, Priyanka Gaur and Ramnath Misra. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background/Purpose: Enthesitis related arthritis (ERA) is an inflammatory disease of childhood that lacks autoreactive T and B cells. We have previously shown that surface expressed Toll Like receptors (TLRs) are over-expressed in ERA. Myeloid related proteins (MRP)8/14 are calcium binding proteins that act as an endogenous ligand of TLR-4. MRP8/14 levels are elevated in patients with systemic onset arthritis. Thus we studied its role in ERA.

Methods: The study enrolled patients with ERA (fulfilling ILAR criteria) less than 18 years of age. Plasma and synovial fluid levels of MRP8/14 were measured by ELISA and TLR-4 expression on peripheral blood and synovial fluid monocytes was measured by 2 color flow-cytometry. Control plasma samples were collected from 48 blood bank donors. Follow up samples were obtained from 26 patients after 3–4 months of first sample collection

Results: Among 69 patients 67 were males. Mean age was 15.2±2.7 years, disease duration was 5±3 years. Median plasma levels of MRP8/14 were higher in patients than controls (10862.31,4426.13 ng/ml; $p<0.0001$) was higher in those with active disease (11669.54, 4421.76 ng/ml, $p<0.0001$.

Patients with follow up were not different from other patients with respect to duration of disease and treatment received. Plasma MRP8/14 levels reduced on follow up after 3 months only in patients who responded to treatment (10862.31, 3784.41ng/ml, p=0.012). MRP8/14 levels negatively correlated with frequency of CD14+TLR4 positive cells (r=−0.372, p=0.02)

MRP8/14 levels were higher in synovial fluid as compared to plasma (15858.45, 10862.31ng/ml, p=0.024). SFMC showed significantly higher MFI than PBMC (1409.49 ± 890.60 vs. 946.11± 798.92, p=0.005) as well as higher percentage of CD14+TLR-4 positive cells (18.69 ± 4.51 vs. 5.96 ± 3.99, $p<0.0001$).

Conclusion: MRP814 levels are increased in plasma of ERA patients, are higher in those with active disease and levels decrease in patient who respond to treatment suggesting that it may be a good biomarker during follow up.

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2190

Clinical and Immunologic Description Of Pediatric Conditions With Interferon-Regulated Gene Signatures (Chronic Atypical Neutrophilic Dermatosis Lipodystrophy Elevated Tempature, Aicardi Goutieres Syndrome, Juvenile Dermatomyositis, Juvenile Systemic Lupus Erythematosus). Hanna Kim[1], Adriana Almeida de Jesus[2], Yin Liu[2], Yan Huang[1], Gina Montealegre[2], Dawn Chapelle[2], Nicole Plass[1], Wanxia Tsai[2], Massimo Gadina[3], Lisa G. Rider[4], Adeline Vanderver[5] and Raphaela Goldbach-Mansky[1]. [1]National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD, [2]NIAMS / NIH, Bethesda, MD, [3]National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD, [4]NIEHS, NIH, Bethesda, MD, [5]Children's National Medical Center, Washington, DC.

Background/Purpose: Increased interferon (IFN) regulated gene (IRG) expression has been reported in juvenile systemic lupus (JSLE)[1] and juvenile dermatomyositis (JDM)[2]. Recently, two monogenic conditions chronic atypical neutrophilic dermatosis lipodystrophy elevated temperature (CANDLE) syndrome[3] and Aicardi Goutieres syndrome (AGS)[4] have demonstrated IRG signatures. The goal of this study is to characterize their phenotypic and immunologic features versus neonatal-onset multiple inflammatory disease

(NOMID), IL-1 mediated disease control and healthy controls, and identify potential disease activity biomarkers.

Methods: History, physical, and laboratory evaluation performed on 9 CANDLE, 7 AGS, 4 JSLE, 5 JDM, and 5 NOMID disease control patients (prior to IL-1 blocking therapy). Cytokine profile done on serum (ratios of means versus 3 pediatric controls) and CSF (CSF:serum ratios compared to non-inflammatory neurologic diseases)[5] using Luminex (Austin, TX) assay. Gene expression analyzed with RNA-seq. Data analyzed with Partek 6.6 and Ingenuity Pathway Analysis.

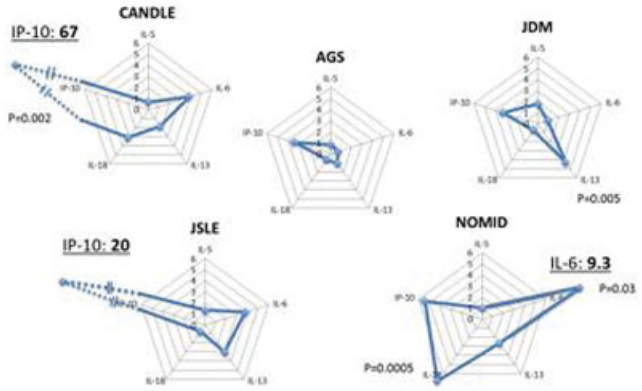
Results: A. Table of Clinical Characteristics

Systemic inflammatory markers were highest in NOMID and CANDLE patients. AGS, JDM and SLE patients were only mildly clinically active at time ofsampling. Systemic inflammatory markers were highest in NOMID and CANDLE patients. AGS, JDM and SLE patients were only mildly clinically active at time of sampling.

	With Type 1 Interferon-Regulated Gene Signature				IL-1 mediated
	CANDLE	AGS	JDM	JSLE	NOMID
rash	+++	++	+++	+++	+++
lipodystrophy	+++	−	+	−	−
myositis	++	−	+++	+	−
CNS	++ (L)	+++ (L)	−	++	+++ (N)
basal ganglia calcification	++	+++	−	−	−
autoantibodies	intermittent	intermittent	common	always	uncommon

+++: always or characteristic
++: sometimes or only with onset/flares
+: uncommon (L): lymphocytic
−: not described (N): neutrophilic

B. Serum/Plasma Cytokine Profiles



5 most distinguishing serum cytokines (Panel B, radar plots) show IP-10 was highly elevated in CANDLE and JSLE and IL-13 elevated in JDM. IP-10 and MCP-1 CSF/serum ratios were elevated for AGS. Gene expression identified upregulated IRGs for the 4 interferonpathies not present in the healthy controls or NOMID. There was a difference in disease-specific IFN signatures, with subsets uniquely upregulated and downregulated in each condition. IRGs were most upregulated in CANDLE, with greatest similarity to JSLE. AGS and JDM had other pathways higher-ranked than IFN pathways.

Conclusion: There are specific areas of phenotypic overlap such as basal ganglia calcifications (CANDLE, AGS), lipodystrophy (CANDLE, JDM), and myositis (CANDLE, JDM, less common JSLE). Disease-specific cytokine patterns included increased serum IP-10 (CANDLE, p=0.002), increased serum IL-13 (JDM, p=0.005), and increased CSF IP-10 and MCP-1 (AGS). These differences may indicate distinct and potentially organ-specific inflammatory pathways. Disease-specific differential gene expression patterns within the IFN response signature may reflect different pathogenesis, which may be due to differing triggers of IFN response.

[1]Bennett L, 2003; [2]Baechler E, 2007; [3]Liu Y, 2012; [4]Rice G, 2012; [5]Pranzatelli J, 2013.

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Intestinal Microbiome In Polyarticular Juvenile Idiopathic Arthritis: A PILOT Study. Petra C.E. Hissink Muller[1], A.E. Budding[2], Cornelia F. Allaart[3], Danielle M.C. Brinkman[3], Taco W. Kuijpers[4], Michiel Westedt[3], J. Merlijn van den Berg[5], Lisette W.A. Van Suijlekom-Smit[6], Marion A.J. Van Rossum[7], Tim G.J. de Meij[2] and Rebecca Ten Cate[3]. [1]Reade Institute, Amsterdam, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Emma Children's Hospital/Academic Medical Center (AMC), Amsterdam, Netherlands, [5]Emma Children's Hospital / Academic Medical Center (AMC), Amsterdam, Netherlands, [6]Erasmus MC Sophia Children's Hospital, Rotterdam, Netherlands, [7]Emma Children's Hospital/Academic Medical Center and Reade Institute, Amsterdam, Netherlands.

Background/Purpose: The intestinal microbiome may play a role in the pathogenesis of Juvenile Idiopathic Arthritis (JIA). In IBD patients an overall decrease in microbial diversity of the intestinal microbiota has been observed. Studies comparing intestinal microbiome in children with JIA and healthy controls have not been conducted to date. Therefore we analyzed and compared the composition and diversity of the distal colon associated microbiome between children with Disease-Modyfying-Anti-Rheumatic-Drug (DMARD) naive JIA and healthy controls and tried to identify specific gut bacteria associated with polyarticular JIA before initiation of a DMARD.

Methods: Total microbiome profile in stools of 8 children with DMARD naive polyarticular JIA were analyzed by means of IS-pro, a 16S-23S interspacer (IS) region-based profiling method and compared to stools of 24 age-matched healthy controls.

Results: Faeces of 8 (6 girls, 2 boys) children with polyarticular JIA, all rheumatoid factor negative were investigated and compared to 24 healthy controls. Anti-Nuclear Antibodies were positive in 3 patients. Median age at evaluation was 11.1 years (7.3–13.1), median period from start complaints to diagnosis was 7.1 months (4.4–13.2). Median ACR pedi scores were: VAS physician 47mm(32–58), VAS patient well-being 32mm(27–52), ESR 8mm(2–9), active joint count 10(7–14), limited joint count 2 (0–4), CHAQ score 1.2 (0.4–1.7).

One intra-articular steroid injection was given to each of two patients respectively 1 and 4 months prior to stool collection. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) were used by all patients at the time of evaluation. Median age of the healthy controls was 10.6 years (8.4–12.9).

Median Simpson reciprocal index within phylum of Firmicutes is significantly lower in children with JIA (6.0) compared to controls (8.0) ($p<0{,}012$). (figure 1). Diversity within the phyla Bacteriodetes and Proteobacteria did not differ between the 2 subgroups. By constructing a Pearson-correlation dendogram, no clustering was seen between the JIA group and the healthy controls on species-level (figure 2), a specific JIA associated microbiotal signature could not be identified.

Conclusion: Intestinal microbiome diversity within the phylum Firmicutes was significantly lower between children with DMARD naive polyarticular JIA and healthy controls. An overall decrease in microbial diversity of the intestinal microbiota has also been observed in IBD patients. Whether intestinal dysbiosis plays a role in the pathogenesis of JIA remains subject of further studies.

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Vitamin D Receptor Polymorphisms In A Cohort Of Italian Patients With Juvenile Idiopathic Arthritis. Fernanda Falcini[1], Francesca Marini[2], Donato Rigante[3], Federico Bertini[4], Gemma Lepri[5], Stefano Stagi[2], Marco Matucci Cerinic[5] and Maria Luisa Brandi[5]. [1]Department of Biomedicine, Division of Rheumatology AOUC, Excellence Centre for Research, Florence, Italy, [2]University of Florence, Firenze, Italy, [3]Università Cattolica Sacro Cuore, Rome, Italy, [4]Department of Internal Medicine, Rheumatology Section, University of Florence, Florence, Italy, [5]University of Florence, Florence, Italy.

Background/Purpose: A role for vitamin D has been hypothesized in generating disease activity for patients with juvenile idiopathic arthritis (JIA): specific polymorphisms of vitamin D receptor (*VDR*) gene have recently been associated with different biologic response to vitamin D itself.

To evaluate *VDR* polymorphisms in patients with JIA in comparison with unrelated healthy controls.

Methods: We recruited 81 Italian children, adolescents and young adults with JIA (mean age 20.21 + 7.11 SD, 67 female and 14 males, female/male ratio 4.79). After informed consent, during routine laboratory tests their genomic DNA was extracted from peripheral blood leukocytes, to analyze *VDR* polymorphisms by PCR-based sequencing (*CDX2* in the promoter region) and PCR-based enzymatic digestions (*FokI* in exon 2, *BsmI* and *ApaI* in intron 8, and *TaqI* in exon 9). An Italian population of 2221 unrelated individuals without JIA was used as healthy controls.

Results: The distribution of *FokI, BsmI, ApaI*, and *TaqI* polymorphisms did not show significant differences between children with JIA and controls. Regarding the *CDX2* polymorphism, we observed a statistical difference in the distribution of GG and GA genotypes, with the GG genotype more frequent in JIA subjects (Yates-corrected chi-square 6.64; Odds ratio=1.87; p=0.01) and the GA genotype in healthy controls (Yates-corrected chi-square 4.47; Odds ratio=0.58; p=0.035). Data about AA genotype were not significant due to their very low number (five) within the JIA population. G allele resulted to be more frequent in JIA subjects (Yates-corrected chi-square 5,64; Odds ratio=1.61; p=0.017).

Conclusion: Pathogenetic mechanisms influencing the predisposition to JIA are poorly elucidated. Our analysis of *CDX2* polymorphisms (located in the promoter region of the *VDR* gene) has revealed that both GG genotype and G allele are more represented in patients with JIA. We can speculate that the G allele decreases *VDR* transcriptional activity with respect to the A allele, as well as the presence of GG genotype could explain a reduction of *VDR* activity, with subsequent decreased response to vitamin D and potential immunity deregulation leading to JIA.

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Altered Apoptosis Profile and Associated Soluble Factors In Patients With Juvenile-Onset Systemic Lupus Erythematosus. Bernadete Liphaus[1], Maria H. B. Kiss[1], Solange Carrasco[2] and Cláudia Goldenstein-Schainberg[3]. [1]Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, [2]University of Sao Paulo School of Medicine, São Paulo, Brazil, [3]Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: Apoptosis has been demonstrated to be involved in immune dysregulation and development of adult systemic lupus erythematosus (SLE) but less is known about its relevance in juvenile-onset SLE (JSLE). Therefore we aimed to assess a panel of apoptosis related proteins in patients with JSLE and their possible relationship with disease activity.

Methods: Forty-three JSLE patients (36F:7M, mean age=14.3 yrs, revised ACR criteria), 30 with active disease (SLEDAI score ^{3} 4), and 35 age and gender matched healthy controls were studied. After staining with specific moAbs, Fas and Bcl-2 expressions in peripheral B and T lymphocytes and monocytes were analyzed by flow cytometry. Soluble sera molecules (sFas, sFasL, sTRAIL and sBcl-2) were measured by commercial ELISA kits. Statistical analysis used Kruskal-Wallis test and Spearman's rank, with P value $<$ 0.05 considered significant.

Results: JSLE patients compared to controls had significant increased Fas expression on CD3+ (43.7±10.3 vs. 28.9±9.4%, p<0.01), CD4+ (20.3±6.7 vs. 16.2±6.2%, p<0.05) and CD8+ (21.5±9.6 vs. 12.3±5.8%, p<0.01) T cells, and on CD19+ B cells (2.1±1.4 vs. 1.4±0.7%, p<0.05), whereas, it was decreased on CD14+ monocytes (93.6±6.9 vs. 96.7±2.5%, p=0.01). Percentages of CD19+Fas+ cells were positively correlated with SLEDAI (r=0.38, p=0.02) and an inverse correlation was observed for percentages of CD14+Fas+ cells and SLEDAI (r= −0.55, p=0.01). Mean fluorescence intensity (MFI) of Bcl-2-positive cells from JSLE patients was significantly increased in CD3+ (28.8±8.4 vs. 22.9±4.2%, p<0.01), CD4+ (28.6±8.2 vs. 22.9±4.4%, p<0.01) and CD8+ (29.4±9.4 vs. 22.8±3.6%, p<0.01) T cells, and also in CD19+ B cells (25.5±9.6 vs. 21.5±3.6%, p=0.06). Bcl-2 expression in CD14+ monocytes was lower in JSLE compared to controls (25.2±18.2 vs. 34.5±16.6%, p=0.006). Direct correlation between percentages of CD19+Bcl-2+ cells and SLEDAI (r=0.47, p=0.04) was shown. JSLE patients had significantly increased sFas (188.1±69.2 vs. 133.2±80.6pg/ml, P<0.05) and sTRAIL (691.3±631.8 vs 346.6±251.1pg/ml, P<0.05), decreased sFasL (0.08±0.1 vs. 0.36±0.4ng/ml, P<0.05), and similar sBcl-2 (7.4±8.6 vs. 9.3±9.6mg/ml, P<0.05) levels compared to healthy controls. SLEDAI score directly correlated with sFas (r=0.52; p=0.001).

Conclusion: The present study demonstrated that dysregulation of apoptosis pathways and associated soluble factors underlie JSLE pathogenesis, particularly during active disease. A role for CD19+Bcl-2+ cells and/or sFas as a marker of disease acitivity in children deserves further investigation in prospective studies.

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RNA-Sequencing In Peripheral Blood Mononuclear Cells Identifies Novel Differentially Expressed Coding and Non-Coding Transcripts In Juvenile Idiopathic Arthritis. Kaiyu Jiang[1], Xiaoyun Sun[2], Yanmin Chen[1], Yufeng Shen[2] and James N. Jarvis[1]. [1]The University at Buffalo, Buffalo, NY, [2]Columbia University, New York, NY.

Background/Purpose: Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood. The aetiology of JIA remains largely unknown, but the interplay between genes and environment is likely to be important. Recent genetic studies in complex disease have shown that 80% of disease-associated SNPs map to non-protein coding DNA sequences that comprise 80% of the human genome. However, data from projects like NIH's ENCODE consortium suggest that much of the genome is transcriptionally active. We used RNA-sequencing (RNA-seq) to identify differentially expressed (DE) protein-coding and non- coding transcripts in 3 JIA patients with active disease (AD), 3 patients at clinical remission on medicine (CRM), and 3 healthy controls.

Methods: RNA samples were isolated from peripheral blood mononuclear cells and prepared for sequencing using the Illumina TruSeq RNA prep kit. Sequencing was performed using the Illumina HiSeq 2000. The pass filter reads were mapped to the genome (Enseml/GRch37) using Tophat (version 1.3.3). Probable transcripts were assembled using CUFFLINKS, and DE transcripts were determined using CUFFDIFF using an adjusted P-value of 0.01. Fold change (FC) calculations were obtained using the log2 (FPKM) ratio,

Results: The average number of reads per sample was 42.95 million, and average number of mapped to genome was 32.9 million. Of the protein-coding regions, there are 119 DE genes (83 down-regulated, 36 up-regulated) in fold change 1.2 or greater when AD compared to HC, 83 DE genes (62 down-regulated, 21 up-regulated) in the AD vs CRM comparison and 19 DE (11 up-regulated, 7 down-regulated) in CRM vs HC. DE genes in AD vs HC and AD vs CRM predictably included those associated with connective tissue disorders, immunological disease and inflammatory disease (e.g. CCR5, IL3RA, IL8 etc.). Among non-protein coding transcripts, we observed DE of two long non-coding RNA (lncRNA) at 10p12.1 (p=0.001, FC= −3.73 and −4.74) and one lncRNA at 5q33.3 (p=0.023, FC=3.99) when AD compared to HC. Biological functions of these LncRNAs are unclear.

Conclusion: In this RNA-seq study in JIA, we identified DE genes in different disease states in JIA. These data also confirmed our previous observations using microarray technology. Three DE lncRNAs were observed in JIA. Future studies in JIA are warranted to further elucidate the functional consequences of these novel lncRNA associations.

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Expanding The Spectrum Of Recombination Activating Gene-1 Deficiency To Include Early Onset Autoimmunity. Lauren A. Henderson[1], Francesco Frugoni[1], Gregory Hopkins[1], Helen de Boer[1], Sung-Yun Pai[2], Yu Nee Lee[1], Jolan E. Walter[3], Melissa M. Hazen[1] and Luigi D Notarangelo[1]. [1]Boston Children's Hospital, Boston, MA, [2]Dana-Farber Cancer Institute, Boston, MA, [3]Massachusetts General Hospital for Children, Boston, MA.

Background/Purpose: We sought to identify the etiology of early onset autoimmunity and T cell lymphopenia in two siblings through genetic and functional studies. Newborn screening identified a full term infant (Patient B) with undetectable T-cell receptor excision circles, raising a concern for severe combined immunodeficiency (SCID). A female sibling (Patient A) had died at 2 years of age secondary to complications from autoimmunity. At 6 months, Patient A had developed vasculitis leading to digital necrosis, myositis, autoimmune cytopenias, positive autoantibodies (ANA, anti-cardiolipin, thyroid peroxidase, and thryroglobulin), elevated inflammatory markers, and hypocomplementia. Both children were severely T cell lym-

phopenic with poor lymphocyte proliferation to mitogens, although natural killer cells, B lymphocytes, and immunoglobulin levels were preserved. Due to the sibling's ultimate fatality, Patient B received prophylactic antibiotics and IVIG; the child never developed autoimmunity and underwent a successful bone marrow transplant at 3 months of age.

Methods: Genomic analysis was done on DNA extracted from whole blood. Recombinase activity was explored using Abelson-immortalized murine *Rag1*$^{-/-}$ pro-B cells with an intrachromosomal inverted GFP cassette flanked by recombination signal sequences. The Abelson pro-B cells were transduced with vectors encoding either wild type or mutant *RAG1* alleles. Recombination-dependent expression of GFP served as an indicator of RAG1 activity. The Abelson system was also used to assess RAG1 protein expression through immunoblotting. Expression of TCRVβ families in CD3+ cells was detected using monoclonal antibodies conjugated to fluorochromes. The B cell repertoire was evaluated by pyrosequencing.

Results: Testing in Patient A for mutations classically associated with T$^-$B$^+$SCID was unrevealing. Patient B had compound heterozygous missense mutations in *RAG1* (c.2522 G>A, p.R841Q; c.2920 T>C, p.F974L). Analysis of frozen genomic DNA from Patient A confirmed identical *RAG1*mutations. The parents were carriers (paternal allele: p.R841Q; maternal allele: p.F974L). In the Abelson system, the R841 mutant lacked protein expression and recombinase activity while the F974L mutant demonstrated normal protein expression but reduced activity (56.5% of wild type). In Patient B, the T cell repertoire was oligoclonal with 8/24 TCRVβ families falling in normal range. The restricted T cell diversity corrected after transplant. By pyrosequencing, the usage of variable, diversity, and joining (V(D)J) segments was skewed in the B cells.

Conclusion: Lymphocyte receptor diversity is generated by the activity of RAG1 and 2, which create DNA breaks that allow recombination of V(D)J gene segments. The clinical presentation of RAG deficiency ranges from T$^-$B$^-$SCID to isolated CD4$^+$ lymphopenia with the variability partially explained by the residual activity of RAG1. We describe a novel presentation of hypomorphic RAG deficiency characterized by early onset autoimmunity in the presence of B cells, highlighting the importance of considering immunodeficiencies in children who present with immune dysregulation, as prompt treatment can be lifesaving.

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Aberrant IgG Glycosylation Is Associated With Active Disease In Juvenile Idiopathic Arthritis Patients. Esperanza Cleland, Brooke Gilliam and Terry L. Moore. Saint Louis University, Saint Louis, MO.

Background/Purpose: Aberrant glycosylation of IgG is an abnormality of humoral immunity in patients with rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) that is not well understood. We examined the association between aberrant IgG glycosylation and clinical and laboratory parameters in JIA.

Methods: Sera from 100 JIA patients (32 IgM rheumatoid factor (RF)-negative polyarticular, 31 oligoarticular, 23 IgM RF-positive polyarticular, 11 systemic-onset, 3 psoriatic), 29 RA patients, and 27 healthy individuals were collected. Aberrant serum IgG glycan content was measured by ELISA in all sera samples. The positive cut-off point was OD>0.31 for aberrant IgG glycan levels. Anti-cyclic citrullinated peptide (anti-CCP) antibody and RF isotypes were also measured by ELISA. Patient records were evaluated for clinical and laboratory associations, including disease activity, erythrocyte sedimentation rate (ESR) and C-reactive proteins (CRP) levels.

Results: Forty-six (46%) JIA patients, 16 (55.2%) RA patients and 4 (14.8%) healthy individuals had elevated aberrant IgG glycan levels. Aberrant glycosylation of IgG was confirmed in JIA patients as compared with healthy individuals (OD=0.342 ± 0.213 versus OD=0.179 ± 0.110; p<0.001). Systemic-onset JIA patients demonstrated higher levels of aglycosylated IgG (OD=0.395 ±0.218) than other JIA subtypes and occurred more frequently in this subtype (54.5%). No significant difference in aberrant glycosylation of IgG was noted between JIA and RA patients (OD=0.319 ± 0.159; p=0.588). A significant correlation between aberrant IgG glycosylation and disease activity was noted in JIA patients (r=0.32, p=0.001), with aberrant IgG glycan levels significantly increased in patients with active disease (OD=0.35 ± 0.17) compared with asymptomatic patients (OD=0.23 ± 0.07) (p=0.024). This correlation was also present when looking at only the female JIA population (r=0.31, p=0.004), while no significant correlation was found in the male JIA population. Aglycosylated IgG correlated significantly with disease activity markers (ESR: r=0.47, p<0.001 and CRP: r=0.46, p<0.001) in JIA. Levels of ESR and CRP were significantly raised in JIA patients with increased aberrant IgG glycan levels (35±29 mm/hr and 2.2±2.4 mg/dl, respectively) compared to patients with normal levels (18±26 mm/hr and 0.91±1.45 mg/dl, respectively) (p<0.05). No association was found between anti-CCP antibody and RF isotypes and aberrant IgG glycosylation in JIA.

Conclusion: Aberrant IgG glycosylation was evident in all JIA subtypes included in this study, with the highest frequency and levels found in systemic-onset JIA patients. We have shown that IgG glycan aberrancy is strongly associated with disease activity in JIA patients. This correlation was also significant when only evaluating the female JIA patients, indicating a possible hormonal influence in IgG glycosylation regulation.

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High Titer IgG Anti-Cyclic Citrullinated Peptide Antibodies Are Associated With Joint Destruction In Juvenile Idiopathic Arthritis Patients. Brooke Gilliam, Lance Feller and Terry L. Moore. Saint Louis University, Saint Louis, MO.

Background/Purpose: IgG anti-cyclic citrullinated peptide (anti-CCP) antibodies have been identified as an important indicator of destructive disease in juvenile idiopathic arthritis (JIA), as is the case in rheumatoid arthritis (RA). We evaluated sera from patients with three subtypes of JIA, in addition to RA patients and healthy individuals to investigate the significance of anti-CCP titers in relation to disease severity.

Methods: Sera from 90 JIA patients were collected, including 30 IgM RF-positive polyarthritis, 30 IgM RF-negative polyarthritis, and 30 oligoarthritis. Sera were collected from 30 patients with RA and 30 healthy individuals. All sera were measured for IgG anti-CCP antibodies and IgM RF by ELISA. IgG anti-CCP antibody serum levels more than three times the cut-off (>60 Units) were considered high titer (HT) antibody levels. Patient records were evaluated for clinical and laboratory associations, including joint damage.

Results: Fifteen IgM RF-positive polyarthritis patients had HT IgG anti-CCP antibodies, 5 had low titer (LT) anti-CCP antibodies, and 10 were considered negative. Two IgM RF-negative polyarthritis were positive for IgG anti-CCP antibodies, one with HT and one with LT. None of the oligoarthritis patients were positive for IgG anti-CCP antibodies, while 2 healthy children had LT IgG anti-CCP antibodies. Eighteen RA patients had HT IgG anti-CCP antibodies, one LT, and 11 were considered negative. IgM RF-positive polyarthritis patients demonstrated significantly elevated levels of IgG anti-CCP antibodies (85±80 Units) compared to IgM RF-negative polyarthritis (14±38 Units), oligoarthritis (5±5 Units), and healthy children (6±7 Units) (p<0.001). When IgM RF-positive polyarthritis levels were compared with levels in RA patients (102±85 Units), the difference was not significant (p=0.436). Nine of 16 (56.3%) JIA patients with HT IgG anti-CCP antibodies and 2/6 (33.3%) with LT IgG anti-CCP antibodies had joint damage. JIA patients with joint damage had significantly higher levels of IgG anti-CCP antibodies (83±84 Units) compared to those with no joint damage (23±49 Units) (p=0.008). Thirteen of 18 (72.2%) RA patients with HT, 1 LT, and 6/11 (54.5%) negative for IgG anti-CCP antibodies had joint damage. The difference in IgG anti-CCP antibody levels did not differ significantly in RA patients with or without joint damage (p=0.17). IgM RF levels were also significantly higher in JIA patients with joint damage (54±56 Units) compared to those with no joint damage (20±30 Units; p=0.026). Regression analysis showed that HT anti-CCP antibodies were the strongest independent determinant of joint damage in JIA (OR 8.13 [95% CI: 2.37–27.84], p=0.001).

Conclusion: IgM RF-positive polyarticular JIA and adult RA patients demonstrated similar mean levels of IgG anti-CCP antibodies, both greater than the HT cut-off of >60 Units. HT anti-CCP antibodies were strongly associated with joint damage in JIA. Measurement of IgG anti-CCP antibody serum levels was found to be useful in identifying JIA patients with destructive disease and would be useful in management of JIA, particularly patients with IgM RF-positive polyarthritis and overall in JIA patients exhibiting HTs.

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Genome Wide Association Meta-Analysis Implicates *HLA-DRB1*, The *BTNL2/HLA-DRA* region, and a Novel Susceptibility Locus On Chromosome 1 In Systemic Juvenile Idiopathic Arthritis. Michael J. Ombrello[1], Elaine F. Remmers[2], Ioanna Tachmazidou[3], Alexei A. Grom[4], Dirk Föll[5], Alberto Martini[6], Marco Gattorno[7], Seza Ozen[8], Sampath Prahalad[9], John F. Bohnsack[10], Norman T. Ilowite[11], Elizabeth D. Mellins[12], Ricardo A. G. Russo[13], Claudio A. Len[14], Sheila K. Oliveira[15], Rae SM Yeung[16], Lucy R. Wedderburn[17], Jordi Anton[18], Carl D. Langefeld[19], Susan D. Thompson[4], Eleftheria Zeggini[3], Wendy Thomson[20], Daniel L. Kastner[2], Patricia Woo[21] and on Behalf Of the International Childhood Arthritis Genetics Consortium[22]. [1]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [2]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [3]The Wellcome Trust Sanger Institute, Cambridge, United Kingdom, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]University of Muenster, Muenster, Germany, [6]Istituto Giannina Gaslini, Genova, Italy, [7]G. Gaslini Institute, Genova, Italy, [8]Hacettepe University, Ankara, Turkey, [9]Emory Children's Center, Atlanta, GA, [10]University of Utah, Salt Lake City, UT, [11]Albert Einstein College of Medicine, Bronx, NY, [12]Stanford University Med Ctr, Stanford, CA, [13]Hospital de Pediatria Garrahan, Buenos Aires, Argentina, [14]Universidade Federal de São Paulo/UNIFESP, São Paulo, Brazil, [15]Instituto de Pediatria e Puericultura Martagão Gesteira (IPPMG) da Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil, [16]The Hospital for Sick Children and University of Toronto, Toronto, ON, [17]Arthritis Research UK Centre for Adolescent Rheumatology at University College London, Great Ormond Street Hospital and UCLH, University College London, London, United Kingdom, [18]Hospital Sant Joan de Deu, Barcelona, Spain, [19]Wake Forest School of Medicine, Winston-Salem, NC, [20]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Sciences Centre, Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom, [21]University College London, London, United Kingdom, [22]INCHARGE, London, United Kingdom.

Background/Purpose: Systemic juvenile idiopathic arthritis (sJIA) is a severe inflammatory disease of childhood characterized by periods of daily spiking fever, evanescent skin rash, arthritis, serositis, lymphoid hyperplasia, and in up to half of cases, macrophage activation syndrome. The causes of sJIA are unknown, and the rare nature and complex inheritance of sJIA have together stymied the investigation of sJIA genetics.

Methods: To identify genetic factors contributing to sJIA susceptibility, we generated single nucleotide polymorphism (SNP) genotypes in 988 children with sJIA and 514 healthy control subjects using a commercially available SNP array. These data were combined with SNP genotypes, *in silico,* from 7370 additional healthy control subjects. After dividing the dataset into 9 strata by country of origin, we excluded samples and markers that failed to meet strict quality standards. Haplotype phasing, SNP imputation, and association testing were performed independently in each stratum, and we then subjected the association results from > 1.6M SNPs to fixed- and random-effects meta-analyses. A second round of more intensive imputation employing a more densely genotyped set of reference haplotypes was performed in each region with $p_{min} < 1.0E-7$. Regions with association signals exceeding genomewide significance ($p < 1.7E-8$) were further evaluated with logistic regression and conditional analysis.

Results: Genome wide meta-analysis of sJIA identified associations between sJIA and two regions, the major histocompatibility complex (MHC) locus and an intergenic region on chromosome 1, each of which were subjected to a second round of SNP imputation. In both regions, meta-analysis of the second round of imputation data identified significant associations. Meta-analyses of the MHC locus identified two strong association signals, the first centered around *HLA-DRB1* ($p_{min} = 1.6E-10$, OR 1.5) and the second located between *BTNL2* and *HLA-DRA* ($p_{min} = 7.1E-15$, OR 2.2). Reciprocal univariate regression demonstrated that these two markers likely represent independent sources of sJIA risk. On chromosome 1, we identified an sJIA-associated cluster of 9 SNPs ($p_{min} = 5.4E-9$, OR 2.0) that was nearest to *LOC284661*, encoding a long, intergenic noncoding RNA. By cross referencing data from the ENCODE project with the 9 sJIA associated SNPs, we found evidence of transcriptional activity across the sJIA-associated region and in close proximity to many of the sJIA-associated SNPs. Furthermore, several of the sJIA-associated SNPs were located within known histone marks or transcription factor binding sites.

Conclusion: Our data implicate the class II MHC molecule, HLA-DR, in the pathogenesis of sJIA. The intergenic location of the most strongly associated variants raises the possibility that an alteration of HLA-DR regulation or expression may underlie its role in sJIA. Additionally, we have identified a novel genomic region on chromosome 1 as an sJIA susceptibility locus. Interestingly, the nearest gene encodes an uncharacterized long, intergenic noncoding RNA, a type of transcriptional regulator whose importance has only recently come to light.

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Analysis Of The MHC Region In a Large Cohort Of Juvenile Idiopathic Arthritis Cases Identifies Independent Effects At HLA-DRB1. Anne Hinks[1], Joanna Cobb[1], Buhm Han[2], Miranda C. Marion[3], Marc Sudman[4], Paul Martin[1], John F. Bohnsack[5], Lucy R. Wedderburn[6], Johannes Peter Haas[7], Paul de Bakker[2], Carl D. Langefeld[3], Soumya Raychaudhuri[2], Sampath Prahalad[8], Susan D. Thompson[4] and Wendy Thomson[1]. [1]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Sciences Centre, Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom, [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [3]Wake Forest University Health Sciences, Winston-Salem, NC, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]University of Utah, Salt Lake City, UT, [6]Arthritis Research UK Centre for Adolescent Rheumatology at University College London, Great Ormond Street Hospital and UCLH, University College London, London, United Kingdom, [7]German Centre for Rheumatology in Children and Young People, Garmisch-Partenkirchen, Germany, [8]Emory Children's Center, Atlanta, GA.

Background/Purpose: Juvenile idiopathic arthritis (JIA) is the most common arthritic disease of childhood and is caused by a combination of genes and environment. In the last few years great advances have been made in dissecting the genetic basis of JIA with now 17 confirmed susceptibility loci identified. One of these loci, the MHC region, has been established for many years but the complexity and the broad linkage disequilibrium (LD) across the region has rendered fine-mapping associations challenging. Novel imputation strategies can now be utilized to impute HLA classical alleles and amino acids across the region. The aim of this work was to gain a greater understanding of the associations across the HLA region in the 2 most common subtypes of JIA, oligoarthritis and rheumatoid factor-negative polyarthritis.

Methods: Using the dense genotype data obtained from the analysis of the custom-designed Illumina ImmunoChip in 2816 JIA cases and 13056 controls, we imputed HLA classical alleles (2-digit and 4-digit resolution) and amino acids across the MHC region (Chr6:29–34Mb) using the SNP2HLA algorithm and a large reference panel of 5225 individuals from the T1DGC consortium. We performed logistic regression for all markers across the region and tested all amino acids in HLA-DRB1 performing an omnibus test of amino acid residues for each position. Conditional analysis to identify potential independent effects was performed.

Results: We observed high correlation (0.99) between imputed and classically typed actual allele frequencies for HLA-DRB1 2-digit and 4-digit alleles for a subset of JIA cases (n=394). The most significant association across the HLA region was for the phenylalanine residue at amino acid 67 of HLA-DRB1, OR=3.03, $p=1 \times 10^{-179}$. The omnibus test for all amino acids across HLA-DRB1 showed most significant association at HLA-DRB1 amino acid 13 and conditioning on all residues at amino acid 13 found significant association remaining at HLA-DRB1 amino acid 67, suggesting two independent effects in HLA-DRB1.

Conclusion: Analysis of the MHC region in the largest cohort of JIA cases and controls studied to date has found the strongest association with the HLA-DRB1 region. Two independent effects have been identified,

amino acid 67 and 13. Interestingly, amino acid 13 has previously been associated with adult rheumatoid arthritis (RA) whereas amino acid 67 has not. Further analysis to look for independent effects across the rest of the HLA region is now underway.

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2200

Fatty Acid Profiling In Juvenile Idiopathic Arthritis: The Balance Between Pro-Inflammatory and Pro-Resolving Prostanoids. Weng Tarng Cham[1], Enzo Ranieri[2], Janice Fletcher[2] and Christina A. Boros[3]. [1]Women's and Children's Hospital, North Adelaide, SA 5006, Australia, [2]SA Pathology, North Adelaide, SA 5006, Australia, [3]University of Adelaide/Women's and Children's Hospital, Adelaide, Australia.

Background/Purpose: The prostanoids are a family of biologically active lipids derived from the 20-carbon essential fatty acids (LCPUFA) and are involved in all aspects of the immune response. Omega −3 (ω3) fatty acids, Eicosapentaenoic acid (EPA) and Docosapentaenoic acid (DPA), Docosahexanoic acid (DHA) and Lipoxin A4 (LPA4) are anti-inflammatory, whilst the ω6-fatty acids Arachidonic acid (AA), 13-(S)hydroxy-octadecadienoic acid [13(S)HODE], 12(S)-hydroxyeicosatetraenoic acid(12(S)HETE), Thromboxane B2 (TXB2), Prostaglandin F2α (PGF2α) and 6-Keto-Prostaglandin F1α (6kPGF1α) are pro-inflammatory. Liquid Chromatography Tandem Mass Spectrometry (LC-MSMS) allows contemporaneous analyses of multiple prostanoids by stable isotope determination from 3mm dried whole blood spots. This method is novel in JIA and may find biomarkers which can help predict disease activity and treatment response with greater accuracy than current methods.

Methods: Samples of whole blood from 115 JIA patients and 6 healthy siblings (HC) were collected onto specially prepared filter papers and analysed using LC-MSMS.

Results: The JIA M:F ratio was 1:1.4, the average age at study entry (9.4 ± 5.0 y), average disease duration (56.1 ± 46.1 m). None of the participants was taking fish oil.

Cross-sectional analysis

- 13(S)HODE and DHA levels were significantly different between JIA patient groups (p=0.05 for both)
- In general, there were significantly lower levels of pro-inflammatory prostanoids in JIA than in HC, particularly in polyarthritis
- JADAS correlated positively with PGB2 in all JIA sub-groups (p=0.046).

Longitudinal analysis

- Within subject comparisons
  - o Levels of AA (p=0.03), Leukotriene B4 (LTB4, p=0.003) and TBX2 (p=0.02) were all significantly lower in patients with active vs inactive disease (JADAS ≥1 vs <1)
  - o LPA4 levels were higher in patients with active disease (p=0.004)
- Between subject comparisons
  - o 13-S-HODE was reduced in patients with active disease (p=0.004)
- Correlations between changes in prostanoid levels, irrespective of disease activity (within subjects), showed combined changes in pro-and anti-inflammatory prostanoids:
  - o Increases in EPA correlated positively with higher levels of 13(S)HODE, 12(S)HETE, LTB4, TBX2, 6κPGF1α, (p<0.05 for all) as well as with increased LPA4 (p<0.0001)
  - o Increases in LPA4 correlated positively with DPA, and 6κPGF1α and negatively with AA, 15(S) HETE and TBX2 (p<0.0001 for all)
  - o There were no correlations between changes in ESR or CRP and those in prostanoids.

Conclusion: In our cohort, we found that pro-inflammatory prostanoids were, in general, decreased in patients with active disease and in comparison to healthy controls. Increased EPA and LPA4 production were strongly associated with these changes. These are novel findings and likely reflect the degree to which pro-resolving prostanoids are produced to control the inflammatory response in JIA over time. Prostanoid levels appear more sensitive to change than traditional laboratory markers of inflammation. Future analyses will include more detailed investigation of the prostanoids involved in the active resolution of inflammation.

Disclosure: W. T. Cham, None; **E. Ranieri**, None; **J. Fletcher**, None; **C. A. Boros**, None.

2201

Exon and miRNA Arrays Reveal Complexity and Specificity Of The Juvenile Idiopathic Arthritis Neutrophil Transcriptome. Zihua Hu[1], Kaiyu Jiang[2], Mark B. Frank[3], Yanmin Chen[2] and James N. Jarvis[2]. [1]University at Buffalo, Buffalo, NY, [2]The University at Buffalo, Buffalo, NY, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: Data from the NIH Roadmap Epigenomics and ENCODE projects have revealed unexpected richness in mammalian transcriptomes. Large regions the genome that do not encode proteins have now been shown to be functional. These studies were performed to examine the JIA neutrophil transcriptome in detail.

Methods: We studied neutrophils in 35 children with newly-diagnosed, untreated polyarticular, RF-negative JIA using Affymetrix exon and miRNA arrays. Labeling, hybridization, and scanning were undertaken using standard procedures. Patients were compared with 43 healthy controls (HC) and 15 children with cystic fibrosis (CF), a control group added to distinguish transcriptional features specific to JIA and those generic to chronic inflammation in soft tissues. Both exon and miRNA expression data were processed using RMA software in the Affy package of Bioconductor and analyzed using t-tests to detect differentially expressed genes (DEGs) between JIA and HC as well as between CF and HC. Exon arrays were also processed using APT program for Exon-level analysis. Splicing analyses were performed using APT program MiDAS and in-house developed PERL scripts.

Results: We found significant differences in the transcriptomes of children with JIA compared with children with CF, which was evidenced by the number of DEGs from JIA and CF when compared to HC. Whereas the analyses detected 5965 DEGs from CF and 216 DEGs from JIA, 148 of them are common to both groups (p = 7.5E-28). Similar results were obtained from both exon-level and miRNA gene expression data analysis. While 159 and 73 differentially expressed miRNA genes were detected in CF and JIA, respectively, 27 of them are common to both groups (p <0.001). At the isoform level, we found 5617 isoforms from CF and 446 isoforms from JIA displaying differential exon splicing, 169 of them are common to both groups (p=1.56E-129). Functional analyses indicated that those 148 common DEGs were enriched for lysosome and proteasomal ubiquitin-dependent protein catabolic processes, while those DEGs unique to JIA (68) are involved in intracellular signaling cascades, hormone-mediated signaling, and cell motion. DEGs to unique to JIA were able to clearly separate JIA from healthy controls in a clustering analysis, and therefore these DEGs could serve as a gene expression signature for the disease. Functional associations from differential exon splicing analyses indicated that the common 169 isoforms were enriched in functions that included actin cytoskeleton organization, regulation of transcription, ceramide metabolic process, leukocyte activation, and cell activation during immune response. Those DEGs unique to JIA (277) were associated with functions that included as spliceosome regulation, B and T cell receptor signaling pathways, and apoptosis and MAPK signaling pathways.

Conclusion: These findings reveal the complexity and specificity of the JIA neutrophil transcriptome. Furthermore, they demonstrate the importance of filtering JIA transcriptome results with controls that include other chronic inflammatory conditions. Finally these results indicate that a set of DEGs unique to JIA can serve as gene expression signature for the disease.

Disclosure: Z. Hu, None; **K. Jiang**, None; **M. B. Frank**, None; **Y. Chen**, None; **J. N. Jarvis**, None.

2202

TNF-α Is Associated With Cognitive Impairment In Childhood-Onset Systemic Lupus Erythematosus. Mariana Postal[1], Nailu A. Sinicato[1], Aline T. Lapa[1], Karina Peliçari[1], Bruna Bellini[1], Paula T Fernandes[1], Roberto Marini[1] and Simone Appenzeller[2]. [1]State University of Campinas, Campinas, Brazil, [2]Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil.

Background/Purpose: Cognitive impairment is common in over 50% of SLE patients with active neurological and psychiatric disorders. Cytokine dysregulation and in flammation are mechanisms that may underlie cognitive

impairment. TNF-α leading to inflammatory brain disease may result in cognitive impairment in childhood-onset systemic lupus erythematosus (cSLE).

Objective: To determine if increased sera TNF-α levels are associated with cognitive impairment in cSLE.

Methods: We included 57 SLE patients (women 52; mean age 17.51±4.37; range 9–30) and 65 healthy (women 60; mean age 18.93±65.95; range 6–32) age and sex matched controls. Cognitive evaluation was performed in all participants using Wechsler Intelligence Scale for children (WISC-III) and Wechsler Intelligence Scale for adults (WAIS), according to age and validated in Portuguese. Mood disorders were determined through Becks Depression and Anxiety Inventory in all participants. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current drug exposures. Total dose of corticosteroids and other immunosuppressant medications used since the onset of disease were calculated by data obtained by careful review of the medical charts. Sera samples were obtained from all participants in the absence of infections. TNF-α levels were measured by enzyme-linked immunosorbent assay using commercial kits from R&D Systems. Mann-Whitney Test was used to compare TNF-α concentrations between groups. Multivariate analysis was performed including sex, age, SLE duration, disease activity, and cumulative damage, cognitive impairment and current drug exposures. A P value of <0.05 was considered statistically significant.

Results: Sera TNF-α levels were increased in cSLE (3.39±5.57pg/mL) when compared to healthy controls (1.54±0.92pg/mL) ($p=0.015$). Cognitive impairment was identified in 28 (49.12%) cSLE and in 6 (9.23%) healthy controls. Sera TNF-α levels were increased in cSLE patients (4.64±1.52pg/mL) with cognitive impairment compared to cSLE patients without cognitive impairment (1.52±0.75pg/mL) ($p=0.03$). No significant difference in TNF-α levels between cSLE patients without cognitive impairment and controls was observed ($p=0.76$). No association between TNF-α levels and other clinical, laboratory variable, SLEDAI and SDI scores was observed. In the multivariate analysis, sera TNF-α levels were independently associated with cognitive impairment (OR=3.84; 95%CI 2.39–5.71).

Conclusion: Sera TNF-α levels are elevated in cSLE patients with cognitive impairment. TNF-α were independently associated with cognitive impairment. Our findings support the neuromodulator role of TNF-α in brain activity.

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2203

DEK's Autoantigenicity In Juvenile Idiopathic Arthritis Resides In Its C-Terminal 25 Amino Acids. Barbara S. Adams, Miguel Rivas, Yuanfan Ye, Lili Zhao, Maureen Legendre and Nirit Mor-Vaknin. University of Michigan, Ann Arbor, MI.

Background/Purpose: The nuclear oncoprotein DEK is a known autoantigen associated with juvenile idiopathic arthritis (JIA) and other autoimmune diseases. DEK is actively secreted by human macrophages and is a chemoattractant for neutrophils and T cells. We have previously demonstrated that DEK and DEK autoantibodies are abundant in inflamed synovia of JIA patients. Posttranslational modification, especially acetylation, increases DEK's antigenicity substantially. In agreement with previous observations by Szer et al., our studies of the nature of DEK autoantibodies have shown that autoantibodies from JIA patients recognize the DEK C-terminal region. By screening 69 serum samples, including those from 38 patients with JIA, 20 patients with other inflammatory conditions, and 11 samples from healthy controls, we show that the C-terminal 25 amino acids (aa) alone is the most essential site for DEK antigenicity.

Methods: Sera were collected from patients being treated for JIA and other rheumatologic diseases in the Pediatric Rheumatology Division at the University of Michigan. Samples were analyzed by a specific ELISA developed in our laboratory for the detection of DEK antibodies. Recombinant DEK His-tagged proteins, including full length(1–375aa), and partial length (187–375aa and 1–350aa) proteins were made in a baculovirus system, and were used as the antigen for ELISA and immunoblotting. In addition, we inserted DEK's C-terminal 25aa domain into a GST vector to be expressed by E. coli with subsequent purification. ELISA results were calculated as area under the curve (AUC) by Simpson Rule.

Results: ELISA results showed significantly higher levels of DEK autoantibodies in sera of JIA patients compared to patients without JIA ($p=0.01$) or healthy controls ($p=0.001$). Immunoblot screening against full length DEK (1–375aa), the DEK C-terminus 25aa (position 350–375), and full-length DEK minus the last 25 amino acids (1–350aa) confirms that DEK's most immunogenic portion consists of the C-terminal 25aa. These results were also corroborated by expression of DEK's C-terminal 25aa alone.

Conclusion: We have previously demonstrated presence of DEK and DEK autoantibodies in joints of JIA patients, resulting in development of immune complexes that contribute to joint inflammation. In addition, DEK plays an active role in recruiting neutrophils to joints, as well as in formation of neutrophil extracellular traps (NETs). Our current data suggests that the C-terminal 25aa is the most immunogenic portion of DEK. This finding has significant importance with respect to future development of specific diagnostic tools for JIA, as well as for new strategies to eliminate DEK autoantibodies.

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2204

Early Treatment With Methotrexate Is Associated With Extensive Re-Ordering Of The Neutrophil Transcriptome In Juvenile Idiopathic Arthritis. Zihua Hu[1], Kaiyu Jiang[2], Mark B. Frank[3], Yanmin Chen[2] and James N. Jarvis[2]. [1]University at Buffalo, Buffalo, NY, [2]The University at Buffalo, Buffalo, NY, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: We have previously demonstrated a role for neutrophils in polyarticulartar juvenile idiopathic arthritis (JIA) disease pathogenesis. For example, JIA neutrophils show specific abnormalities in gene expression that do not correct when children reach remission. The studies here were intended to gain insights into mechanisms of therapeutic response in JIA by examining molecular events in neutrophils early in therapy

Methods: We examined 35 children with JIA who had active, untreated disease (ADU) and 26 children with active disease (ADM) who had been on therapy with methotrexate (MTX) for periods ranging from 2 weeks to 2 months. We also studied 15 healthy control children (HC) for comparison. We performed transcriptome analysis using Affymetrix exon and miRNA hybridization-based microarrays. Exon gene expression data were processed using RMA software in the Affy package of Bioconductor and analyzed using t-tests to detect differentially expressed genes (DEGs) between JIA and HC as well as between ADM individuals and healthy controls. Enrichment analyses to determine the associated functions for DEGs were performedd using by DAVID Functional Annotation Tools (http://david.abcc.ncifcrf.gov/).

Results: 216 genes were detected showing differential expression between JIA and HC. More than half of these genes (51%) are involved in regulating gene/exon splicing. Treatment with MTX was found to have substantial impact on JIA transcriptome, even while children still maintained active disease status. Of the 216 genes that were differentially expressed between HC and ADU, 112 of them (52%) reverted to normal expression levels. However, early treatment with MTX was associated with extensive re-ordering of the neutrophil transcriptome, as shown by the large number of DEGs. A total of 1271 DEGs were detected between ADM and HC, of which 1167 (92%) are unique to ADM when compared to ADU. These DEGs are associated with a broad range of functions, including more than 20 biological processes and 40 gene groups. Similar results were obtained from both isoform-level and miRNA expression data analysis. While 193 and 73 differentially expressed miRNAs were detected in ADM and ADU, respectively, 53 of them are common to both groups ($p = 1.3E-22$). At the isoform level, we found 2808 isoforms from ADM and 446 isoforms from ADU displaying differential exon splicing, 275 of them are common to both groups ($p < 6.5E-322$). Functional analysis indicated that the 446 isoforms were associated with pathways of spliceosome, apoptosis, endocytosis, B and T cell receptor signaling pathways. On the other hand, the 275 common isoforms display enrichment in the pathways of spliceosome and endocytosis.

Conclusion: Upon initiation of therapy with methotrexate, substantial re-ordering of the neutrophil transcriptome occurs. How these changes relate to eventual therapeutic response, and whether and how they relate to or lead to changes in adaptive immune function are ongoing areas of investigation in our research groups.

Disclosure: Z. Hu, None; **K. Jiang**, None; **M. B. Frank**, None; **Y. Chen**, None; **J. N. Jarvis**, None.

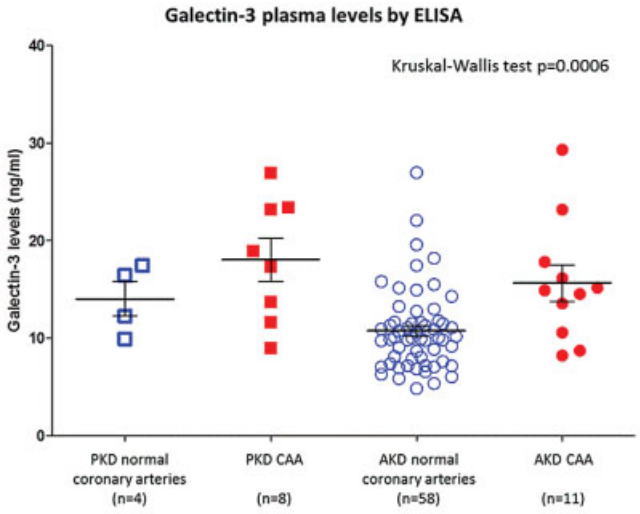
2205

Galectin-3 and Transforming Growth Factor-β Signaling In The Pathogenesis Of Coronary Artery Aneurysms In Kawasaki Disease. Fujito Numano, Matthew Vejar, Chisato Shimizu, Susan Jimenez-Fernandez, Adriana H. Tremoulet, Jane C. Burns and Lori B. Daniels. UC San Diego, School of Medicine, La Jolla, CA.

Background/Purpose: Kawasaki disease (KD) is a self-limited acute vasculitis of young children, and coronary artery aneurysms (CAA) are the most significant complication. Despite appropriate treatment (intravenous immunoglobulin and aspirin), CAA will develop in 5–9% of cases. The etiology of the vascular inflammation is still unknown. We previously reported that the transforming growth factor-β (TGF-β) signaling pathway plays an important role in the development of CAA. Galectin-3 (Gal-3) is a novel cardiac fibrosis marker associated with cardiovascular events, and also regulates tissue inflammation and fibrogenesis, which is mediated through the TGF-β pathway. However, the association of Gal-3 with CAA in KD patients has not been previously reported.

Methods: We measured Gal-3 levels in the plasma of 69 young adults with a history of KD (AKD) and 12 acute (pre-treatment) pediatric KD patients (PKD) by enzyme-linked immunosorbent assay (ELISA). AKD subjects were classified as having CAA or normal coronary arteries (CA), based on coronary artery diameter measured by CT or standard coronary angiography. Classification of PKD subjects was based on coronary artery internal diameter measured by transthoracic echocardiography normalized for body surface area and expressed as standard deviation units for the mean (Z-scores). Z-max was defined as the largest Z-score of either the right or left anterior descending coronary artery during the first 8 weeks after disease onset. Data were analyzed by the Kruskal-Wallis test using Prism software, $p<0.05$ was considered to be statistically significant.

Results: AKD subjects with normal CA had significantly lower Gal-3 levels (median 10.0ng/ml, n=58) compared to PKD subjects with CAA (18.1ng/ml, n=8), PKD subjects with normal CA (14.4ng/ml, n=4), and AKD subjects with CAA (14.9ng/ml, n=11) (p=0.0006). Overall, there was a trend toward higher Gal-3 levels in PKD vs AKD subjects, and in subjects with CAA vs normal CA (Figure).



PKD: pediatric Kawasaki disease, AKD: young adults with a past history of KD, CAA: coronary artery aneurysms

Conclusion: Gal-3 levels in both PKD and AKD CAA subjects tended to be higher than in normal CA subjects. Gal-3 tethers the TGF-β receptor on the cell surface, and leads to increased TGF-β signaling resulting in endothelial/epithelial to mesenchymal transition (EMT). Increased TGF-β signaling and EMT are implicated in CAA formation based on KD autopsy studies. In addition, secreted Gal-3 binds to extracellular matrix proteins and acts as a cell adhesion molecule that promotes inflammation. Thus, Gal-3 may participate in the pathogenesis of CAA formation but whether higher Gal-3 levels are causal remains to be determined. Further investigation with larger numbers of PKD subjects is in progress.

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2206

Detection Of State-Specific RNA Transcripts In Juvenile Idiopathic Arthritis Neutrophils Using RNA Sequencing. Kaiyu Jiang[1], Xiaoyun Sun[2], Yanmin Chen[1], Yufeng Shen[2] and James N. Jarvis[1]. [1]The University at Buffalo, Buffalo, NY, [2]Columbia University, New York, NY.

Background/Purpose: Once considered non-functional, the vast regions of the human genome that do not contain protein-coding genes are now known to contain important regulatory elements. These regulatory elements include both enhancer regions and regions encoding regulatory RNA transcripts such as long non-coding RNA (lncRNA). These studies were undertaken to examine in detail the transcriptome of neutrophils in children with polyarticular juvenile idiopathic arthritis (JIA).

Methods: We isolated RNA from neutrophils of children with 3 different phenotypes: children with active, untreated disease (AD, n=3), children on medication who fit criteria for remission by the Wallace criteria (CRM, n=3), and children with cystic fibrosis (CF, n=3), a control group designed to distinguish those transcriptome features specific to JIA and those common to other forms of chronic, soft tissue inflammation. RNA samples were prepared for sequencing using the Illumina TruSeq RNA prep kit. Sequencing was performed using the Illumina HiSeq 2000. The pass filter reads were mapped to the genome (NCBI/build 37.2) using TopHat (version 2.0.4). Probable transcripts were assembled using Cufflinks (version 2.0.2), and differential expressed transcripts were determined using DESeq. Fold change (FC) calculations were obtained using the log2(FPKM) ratio, where FPKM is the fragments per kilobase of exon model per million mapped fragments.

Results: For all phenotypes, we detected between 8,000–9,000 expressed genes, with children in CRM showing the highest number of expressed genes (n=8,668). Of these, 7,734 were common to all 3 phenotypes. Multiple isoforms of known genes were expressed in the 3 phenotypes, most of which were common to all 3. Of the protein-coding regions, there are 62 differentially expressed genes (29 down-regulated, 33 up-regulated) in fold change 1.2 or greater when AD compared to CRM, 64 DE genes (6 down-regulated, 58 up-regulated) in the AD vs CF comparison and 90 DE (40 down-regulated, 50 up-regulated,) in CRM vs CF. Principle component analysis (PCA) and hierarchical cluster analysis of DE genes showed clear separation between AD, CRM and CF. The functional enrichment analysis using DAVID for the DE genes shows they are associated with immune response (IFIH1, C4A, IFITM3, TNFSF15, APOBEC3G, OAS1, C4BPA, TRIM22, NOD2, FCGR2C, P2RY14, HLA-DRB5, ODZ1, CFD), innate immune response (IFIH1, NOD2, C4A, APOBEC3G, C4BPA, CFD), and inflammatory response (ORM1, TNFAIP6, C4A, IDO1, C4BPA, CFD, SPP1), etc. Finally, novel, previously uncharacterized transcripts were seen in each of the 3 phenotypes (n=5 for AD, n=11 for CRM, and n=9 for CF). These transcripts may represent previously-unknown lncRNA transcripts.

Conclusion: The sensitivity and dynamic range of RNAseq allow a much more detailed view of the neutrophil transcriptome. The finding of state-specific transcripts is expected to lead to new insights into JIA pathogenesis, response to therapy, and the development of diagnostic and prognostic biomarkers.

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2207

Plasma Cytokine Concentrations Are Associated With Folate Perturbations and Methotrexate Polyglutamate Accumulation In The Peripheral Blood Of Juvenile Idiopathic Arthritis Patients Treated With Low-Dose Methotrexate. Ryan S. Funk, Leon van Haandel, Marcia Chan, Lanny J. Rosenwasser, Andrew Lasky, Maria F. Ibarra, Mark F. Hoeltzel, J.S. Leeder and Mara L. Becker. Children's Mercy Hospital, Kansas City, MO.

Background/Purpose: Methotrexate inhibits the production of inflammatory cytokines, but is also an antifolate. The activity of MTX is thought to depend on the formation of polyglutamate metabolites ($MTXGlu_n$) traditionally measured in erythrocytes (RBCs). Therefore, this study evaluates the relationship between cytokines, folate homeostasis and methotrexate polyglutamates in a cohort of JIA patients treated with low-dose MTX.

Methods: Blood samples from JIA patients between 3 and 17 years of age (n=32) were evaluated. Samples were collected prior to and 3 months after the initiation of MTX therapy. IL-1α, IL-1β, IL-1RA, IL-6, TNFα and NAMPT in the plasma were measured by immunoassay. Concentrations of MTX and its polyglutamate metabolites were measured in patient RBCs and a subset of patient PBMCs (n=10). Whole blood, plasma and RBC levels of

folic acid, tetrahydrofolate, 5-formyl tetrahydrofolate and 5-methyl tetrahydrofolate (5mTHF) were measured. MTX and folate analyses were conducted by previously established UPLC/MS/MS methods. Statistical analyses were conducted by simple linear regression and Wilcoxon signed rank tests using analyte measurements at each time point (0 and 3 month) and the change in analyte from 0–3 months.

Results: Consistent with folic acid supplementation and the inhibition of intracellular reduced folate formation by MTX, post-treatment concentrations [median (IQR)] of plasma folic acid increased [0.85 (0.6, 2.35) to 27 (0.83, 58.2) nM ($p<0.01$)] and RBC 5mTHF levels decreased [750.1 (513.7, 968.8) to 560.8 (376.3, 707.2) nM, ($p<0.001$)]. An increase in plasma folic acid from 0–3 months was associated with a reduction in IL-1α ($p<0.01$), IL-1β ($p<0.05$), IL-1RA ($p<0.01$) and IL-6 ($p<0.01$), and a reduction in RBC 5mTHF concentrations from 0–3 months was associated with a reduction in TNFα ($p<0.05$).

Reduced concentrations of RBC 5mTHF at 3 months were associated with an increase in short chain RBC $MTXGlu_{1-2}$ ($p<0.05$), and a reduction in long chain RBC MTX_{3-5} ($p<0.05$). Accumulation of RBC $MTXGlu_{3-5}$ was associated with increased IL-1β ($p<0.05$), IL-6 ($p=0.05$) and NAMPT ($p<0.01$) concentrations at 3 months. There were no changes in cytokine concentrations associated with short chain RBC $MTXGlu_{1-2}$ accumulation at 3 months.

In contrast, short chain PBMC $MTXGlu_1$ ($p<0.05$) and PMBC $MTXGlu_2$ ($p<0.05$) were inversely associated with 3 month IL-1α concentrations, and PBMC $MTXGlu_4$ ($p<0.01$) was inversely associated with 3 month TNFα concentrations.

Conclusion: The accumulation of folic acid and depletion of RBC 5mTHF following the initiation of low-dose MTX therapy are associated with reduced concentrations of several cytokines implicated in inflammatory arthritis. Furthermore, an accumulation of short-chain, but not long-chain, MTX polyglutamates in RBCs was observed to associate with the depletion of RBC 5mTHF at 3 months after therapy initiation. At this early time point after MTX initiation, long-chain RBC $MTXGlu_{3-5}$ were associated with *higher* concentrations of inflammatory cytokines, while short chain PBMC-$MTXGlu_{1+2}$ were associated with reduction of cytokines, suggesting perhaps PBMCs may be a more reliable cell type to investigate $MTXGlu_n$.

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ACR/ARHP Poster Session C
ARHP Pediatrics
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

2208

Psychological Condition Of JIA Patients Treated With Biologic Agents. - A Nation-Wide Survey In Japan. Yuki Osako[1], Yukiko Nonaka[2], Harumi Akaike[2], Tomohiro Kubota[2], Tsuyoshi Yamatou[2], Tomokazu Nagakura[3], Junko Yasumura[4], Hiroyuki Imanaka[2] and Syuji Takei[2]. [1]Kagoshima University, Kagoshima city, Japan, [2]Kagoshima University, Kagoshima, Japan, [3]House of Meguminoseibo, Usuki, Japan, [4]Hiroshima University, Hiroshima City, Japan.

Background/Purpose: Biologic agents, newly developed medications targeting for inflammatory cytokines such as TNF-alpha or IL-6, have been drastically improving the disease course of JIA who were resistant to conventional therapy. However, there are very few studies examined whether the biologic agents had also improved the quality of life (QOL) of patients. Focusing on their both physical and psychological condition, therefore, we examined QOL of JIA patients treated with biologic agents.

Methods: Nation-wide survey was conducted for 8–18 years old JIA patients treated with biologic agents. To the family members of the JIA patients, both PedsQL™ Generic Core Scales[1]) evaluating for QOL and questionnaires evaluating for medical condition were handed from medical doctors who had registered the patient for the Governmental Medical Support Program for Chronic Pediatric Diseases in Japan. Statistical analysis was performed by Spearman rank correlation coefficient or Kruskal-Wallis test by using SPSS ver.19.

Results: A total of 201 JIA patients (77 boys and 124 girls) were involved in the study. The biologic agent was initiated at mean 3 years from onset. Functional daily activities of JIA patients were classified from Class 1 to Class 4 according to the Steinbrocker's functional class health assessment questionnaire score[2]).

The incidence of patient who had no difficulty in daily activities (Class 1) increased from 25 % to 75 % after mean 3 years of biologic therapy. On the contrary, the incidence of patients with Class 3 difficulty in daily activities decreased from 34 % to 3 % during the treatment period.

PedsQL™ Generic Core Scalesindicate that total psychological health score statistically correlated with total physical health score in JIA patients treated with biologic agents ($P=0.559$, $p<0.001$) (Figure 1).

However, there were some JIA patients whose psychological health score were relatively low for their physical health score as seen in figure 1 (below −1SD correlation line).

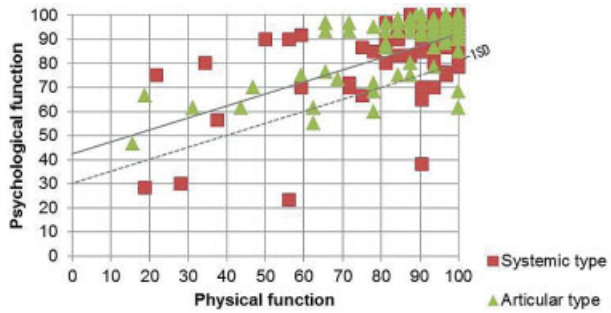


Figure 1 Correlation between physical and psychological health conditions

In such patients with relatively lower psychological health score, there were more patients who were systemic onset, treated with tocilizumab that forces to frequent refer to the hospital (every 2week), and, as the result, frequently absent from school.

Conclusion: In JIA patients treated with biologic agents, the psychological health condition improved in accordance with their physical health condition. However, we should aware that there are still patients who need psychological health support even if their physical function has improved, especially in systemic JIA patients treated with tocilizumab.

References:
1) Kobayashi K, et al. Pediatr Int 2010, 52: 80–8.
2) Steinbrocker O, et al. JAMA1949;140:659–62.

Disclosure: Y. Osako, None; **Y. Nonaka**, None; **H. Akaike**, None; **T. Kubota**, None; **T. Yamatou**, None; **T. Nagakura**, None; **J. Yasumura**, None; **H. Imanaka**, None; **S. Takei**, Caugai, Eisai, Takeda, Bristol-Myers, 2, Chugai, Eisai, Takeda, Abbvie, Astellas, Teijin, Novartis, Pfizer, Asahi Kasei, 8.

2209

Transition From The Pediatric Rheumatologist To The Adult Rheumatologist: Outcomes Of 5 Years Of Experience Between Two Institutions. Elizabeth C. Ortiz[1], Agarwal Arunima[2], Sandra Mintz[3] and Bracha Shaham[4]. [1]University of Southern California, Los Angeles, CA, [2]Childrens Hospital Los Angeles, Los Angeles, CA, [3]Children's Hospital of LA, Los Angeles, CA, [4]Children's Hospital Los Angeles, Los Angeles, CA.

Background/Purpose: It is well documented that children with rheumatologic conditions are living into adulthood and require transition of care into the adult medical center. This process is frequently met with a number of barriers that require programs and processes to address the issues for successful transfer of care. Children's Hospital Los Angeles (CHLA) and the Los Angeles County+University of Southern California Medical Center (LAC+USC MC) decided to collaborate to meet this need. The objective of this study is to evaluate the transfer success rate and length of time from last pediatric appointment to the adult setting. In addition, whether the adherence rates prior to transition correlated with the attendnce rate in the adult setting and identify trends between diagnosis and compliance history while at CHLA.

Methods: Retrospective review of charts from patients scheduled to transfer care from 2008–2013 were reviewed. Patients identified were either without medical coverage or with state-funded Medi-Cal, as these patients require transfer of care to the LAC+USC MC. Demographic data, diagnosis, adherence to pediatric appointments and adherence to adult appointments were noted.

Results: 131 patients were to transfer care from CHLA to USC+LAC MC from fall 2008-spring 2013. There were 103 women, 28 men. Diagnosis included SLE (58), JIA (36), AS (10), MCTD (6), Dermatomyositis (4),

Scleroderma (4), Psoriatic arthritis (3), Vasculitis (5), FMF and Sjogrens (1 each) and other (3). Fifty-nine patients (45%) were never seen at LAC+USC MC, while 72 (55%) attended their provided appointment. The mean time from the last CHLA appointment to the first LAC+USC MC appointment was 179.7 days (range: −12 to 1614 days). Adherence with pediatric appointments within the last year of treatment was defined as good (no missed appointments), fair (1–2 missed appointments), or poor (3+ missed appointments). Thirty-two (41.6%) of the 77 patients with good adherence to pediatric appointments were not seen at LAC+USC MC, 26 (55.3%) of 47 patients with fair adherence, and 1 (14.3%) patient of 6 patients with poor adherence. Mean time from last CHLA appointment to first LAC+USC MC appointment for those with good, fair or poor adherence was 97.2 days, 289.5 days, 359.8 days, respectively. Seventeen (47.2%) of 36 patients with JIA did not transfer care to LAC+USC MC, 25 (43.1%) of 58 patients with SLE. The mean time from last CHLA appointment to first LAC+USC MC appointment for those with JIA and SLE were 206.2 days and 217.4 days, respectively.

Conclusion: There are many obstacles to a successful transition from the pediatric to the adult rheumatologist. This data shows, despite having an identified appointment, only 55% of patients successfully transferred care. In addition, of those who demonstrated poor appointment compliance at CHLA, most attended their LAC+USC MC. From our data, it is clear there is work to be done as only half of those requiring transfer of care to LAC+USC MC are seen and many of those after a substantial gap in their care. A large-scale, prospective study of patients during this time period could further elucidate the reasons for these observations and identify areas for improvment.

Disclosure: E. C. Ortiz, None; **A. Arunima**, None; **S. Mintz**, None; **B. Shaham**, None.

2210

Involvement In Leisure Activities Among Children and Youth With Juvenile Idiopathic Arthritis. Sabrina Cavallo[1], Annette Majnemer[2], Ciaran M. Duffy[3] and Debbie Ehrmann Feldman[1]. [1]Université de Montréal, Montreal, QC, [2]McGill university, Montreal, QC, [3]Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa, ON.

Background/Purpose: Children with arthritis may be at greater risk for adopting a more sedentary lifestyle compared to their healthy peers in part due to disease related factors such as pain, joint stiffness and tenderness. The patterns of leisure participation and the identification of potential determinants of inactivity may guide the development of therapeutic strategies.

Objectives: To describe leisure activities in terms of diversity, intensity and enjoyment, as well as to identify potential socio-demographic and disease-related determinants.

Methods: Ninety three children and youth aged 8 to 18 years diagnosed with juvenile idiopathic arthritis (JIA) and their families participated in this cross-sectional study. Children and youth were administered the Children's Assessment of Participation and Enjoyment (CAPE), which measures involvement in leisure activities (recreation, physical, social, skill-based, self-improvement). The disease characteristics were abstracted from the child's medical file (JIA sub-type, active joint count, age of diagnosis), pain perception and functional status were obtained through self-report. Parents completed questionnaires on socio-demographic data.

Results: The most popular activities (>90%) were playing computer/video games, watching television, hanging out with friends and doing homework. Least popular activities were (<10%) martial arts, gymnastics and horseback riding. The level of enjoyment was highest for social activities (mean: 4.2 ±0.5). Involvement in informal leisure activities showed a significant negative association with functional limitations ($\beta = -0.266$; 95% CI= −0.589, −0.059; p=0.017).

Conclusion: Greater functional limitations may dissuade children and youth from participating in more active pursuits, which places them at greater risk for adopting sedentary lifestyles. The identification of determinants of leisure activities in children and youth with arthritis may allow healthcare professionals to assess children's health needs with more precision and promote a healthier lifestyle.

Disclosure: S. Cavallo, None; **A. Majnemer**, None; **C. M. Duffy**, None; **D. E. Feldman**, None.

2211

Hospital For Special Surgery's Charla De Lupus (Lupus Chat)® Teen/Young Adult/ Parent Group: Holistic Support For Lupus Patients and Their Families. Erica Sandoval[1], Lillian Mendez[2], Roberta Horton[3], Josephine Isgro[4] and Jillian A. Rose[3]. [1]Hospital For Special Surgery, New York, NY, [2]Hospital for Speical Surgery, New York, NY, [3]Hospital for Special Surgery, New York, NY, [4]Morgan Stanley Children's Hospital of New-York Presbyterian, Columbia University Medical Center, New York, NY.

Background/Purpose: Teens with chronic illnesses are faced with challenges to their identity, peer relationships, self-esteem, and developmental milestones, which can have a lasting impact on their psychosocial development; underscoring the need for a holistic approach when intervening with this population. Our lupus support and education group for teens/young adults and parents have been meeting monthly for 12 years at an urban medical center in collaboration with pediatric rheumatologists. Facilitated by social workers and bilingual/bicultural health educators, the group provides peer sharing, guest speakers, and recreational activities to improve and address the understanding and impact lupus has on families, medical adherence, self-image, and peer related concerns. We report on evaluations from our support group participants from 2011–2012, focused on the satisfaction and impact of our psychoeducational programs and special events.

Methods: There were 26 activities for teens/parents (16 programs, 10 special events). Derived from participants' expressed needs, programs focused on topics that directly affect teen health such as, "Lupus and Your Kidneys," "Taking Control of your Lupus", "Preparing for Transition," and "Depression and Lupus." Special events included plays, Thanksgiving Dinner, Holiday Party /Talent Show, Prom Night for Teens, and Spa Day for parents. After each program, a 9-item anonymous evaluation was self- administered(with mixed Likert scale and opened ended questions).

Results: 393 participants attended programs (254 teens, 139 parents); 247 completed evaluations. When asked overall satisfaction with the presentation 89% indicated they were "very much" satisfied; 82% both reported the presentations "very much" contributed to their understanding of lupus-related issues, and " very much" met their expectations; 60% reported that the presentation "very much" helped them to cope with their lupus.

In our annual satisfaction survey, when asked about the impact and satisfaction of special events, themes emphasized the importance of community and sense of family, i.e "this helps bring people closer." When asked for their favorite special event, respondents shared," Holiday Party because everyone meets and it's like a big holiday dinner," "Thanksgiving dinner because we were one big family." When asked what do you find most valuable, respondents shared, "it gives lupus patients a forum in which they can share their unique experiences"; "support in dealing with their chronic illness."

Conclusion: These programs address the many psychosocial, educational, and recreational needs of a culturally diverse lupus population. This model allows patients to gain practical knowledge about how to manage their illness while developing trusting relationships with practitioners in less formal settings, helping us learn how lupus impacts the family and how best to intervene to optimize outcomes.

Disclosure: E. Sandoval, None; **L. Mendez**, None; **R. Horton**, None; **J. Isgro**, None; **J. A. Rose**, None.

2212

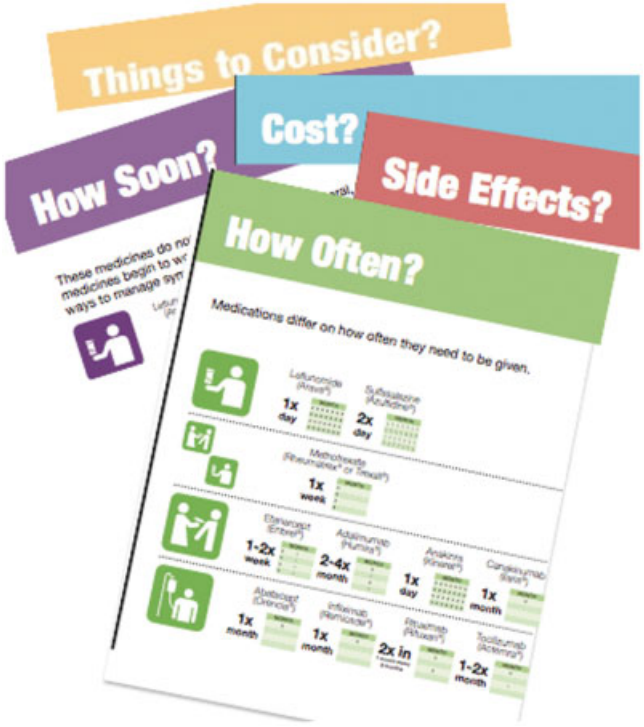
Development Of Tools To Facilitate Shared Decision Making About Medications For Juvenile Idiopathic Arthritis – A Project Of The Pediatric Rheumatology Care and Outcomes Improvement Network. Esi Morgan DeWitt[1], Ellen A. Lipstein[1], Katie Staun[2], Linda Scherer[1], Janalee Taylor[1], Carole M. Lannon[1] and William B. Brinkman[1]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]University of Cincinnati, Cincinnati, OH.

Background/Purpose: Medication options for juvenile idiopathic arthritis (JIA) are increasing. Medications differ on a variety of attributes, including mechanisms of action, dosing intervals, modes of administration, safety profiles, and cost. Some parents of children with JIA are left with questions and concerns about medications suggesting a need for improved clinician-parent communication. Decisions like this, with multiple reasonable options that differ in ways that matter to families, are conducive to "Shared Decision Making" (SDM). SDM is a process whereby clinicians share information about the options and patients/parents share information about their goals and preferences. Together, a treatment plan is developed that is the best fit for the individual patient and their family. We conducted a project to develop tools to facilitate SDM within the Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN). PR-

COIN is a learning network designed to improve outcomes of JIA care using quality improvement (QI) approaches.

Methods: Development of issue cards to facilitate SDM involved multiple steps including qualitative interviews with clinicians and care providers, direct observation of clinical encounters, and an iterative design process involving a graphic designer and a stakeholder panel of clinicians, allied health professionals and parents. We introduced the prototype issue cards for use in clinics using Plan-Do-Study-Act (PDSA) cycles. We elicited feedback to guide card revisions from PR-COIN members via weekly electronic surveys and discussions during monthly webinars and following direct observation of encounters using the cards.

Results: We identified the medication attributes deemed most important to discuss by our stakeholders, including "How Soon" will therapies take effect, "How Often" are they given, "Side Effects", "Cost", "How Long" will need to stay on the medication, and "Other Considerations." We used these attributes to organize the issue cards and symbols to convey key concepts (see Figure). Intended use of the cards involves clinicians showing the cards to patient and parent and asking which card they would like to discuss first. By selecting a card, the family reveals what is important to them. After 18 revisions, PR-COIN stakeholders at 6 sites found the issue cards to be acceptable for regular use.



Conclusion: PR-COIN issue cards are well accepted by clinicians and families within network sites. PDSA cycles continue as we seek to implement the issue cards in routine clinical care to facilitate SDM across the network. Our ultimate goal is to drive improvement in child JIA outcomes by reliably engaging patients/parents in SDM to select a medication that is a good fit.

Disclosure: E. Morgan DeWitt, None, 2; **E. A. Lipstein**, None, 2; **K. Staun**, None; **L. Scherer**, None; **J. Taylor**, None; **C. M. Lannon**, None, 2; **W. B. Brinkman**, None, 2.

ACR/ARHP Poster Session C
Rheumatoid Arthritis - Animal Models II
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

2213

Anti-IL-6 Receptor Antibody Normalizes Both DKK-1 and Sclerostin As Wnt Inhibitors In a Mouse Model Of Collagen-Induced Arthritis. Hiroto Yoshida[1], Mika Yagoto[1], Miho Suzuki[1], Keisuke Tanaka[1], Isao Matsumoto[2], Takayuki Sumida[2] and Yoshihiro Matsumoto[1]. [1]Chugai Pharmaceutical Co., Ltd., Gotemba, Japan, [2]University of Tsukuba, Tsukuba, Japan.

Background/Purpose: The Wnt pathway plays an important role in bone formation and regeneration. This pathway is regulated by several soluble inhibitors such as Dickkopf-1 (DKK-1) and sclerostin. However, it is not fully understood how development of arthritis affects DKK-1 and sclerostin production, or if levels of DKK-1 and sclerostin are improved by blockade of interleukin-6 (IL-6) or tumor necrosis factor-α (TNF-α). The purpose of this study was to examine DKK-1 and sclerostin production in inflammatory arthritis and how it is affected by blockade of IL-6 or TNF-α, using a mouse model of collagen-induced arthritis (CIA).

Methods: CIA in DBA/1J mice was triggered by intradermal injection of bovine type II collagen on Days 0 and 21. Mice were injected intraperitoneally with either anti-mouse IL-6 receptor antibody (MR16-1) on Days 0 and 21 or with TNF receptor-Fc (TNFR-Fc) 3 times per week from the first immunization. Serum was sampled on Days 14 (before swelling), 35 (peak of swelling), and 56 (after swelling subsides). Serum Wnt signalling inhibitors (DKK-1 and sclerostin) were measured by ELISA. Hind limb bones (periarticular bone) and the lumbar spine (systemic bone) were excised on Day 56. Bone volume (BV/TV) of the hind limb (cuboid bone) and the lumbar spine (trabecular bone of L6) was analysed by micro-computed tomography (μCT).

Results: In CIA mice, BV/TV of the hind limb and lumbar spine on Day 56 were significantly decreased to 72.6% ($p<0.0001$) and 62.1% ($p<0.0001$) of the respective values in non-immunized mice. MR16-1 and TNFR-Fc each significantly suppressed the development of arthritis ($p<0.001$ and $p<0.05$) and bone loss in the hind limb ($p<0.0001$ and $p<0.01$) compared with untreated CIA mice. On the other hand, bone loss in the lumbar spine was significantly suppressed by only MR16-1 ($p<0.0001$) and not by TNFR-Fc ($p=0.367$). On Days 14, 35, and 56, DKK-1 levels were significantly higher in CIA mice than in non-immunized mice ($p<0.0001$). Sclerostin levels were significantly lower on Days 14 and 35 in CIA mice than in non-immunized mice ($p<0.0001$). In MR16-1-treated CIA mice, DKK-1 was significantly lower than in untreated CIA mice on Days 35 and 56 ($p<0.0001$ and $p<0.01$), and sclerostin was significantly higher on Days 14 and 35 ($p<0.0001$). In TNFR-Fc-treated CIA mice, on the other hand, although DKK-1 on Day 35 was as significantly decreased as it was in MR16-1-treated mice ($p<0.0001$), sclerostin levels on Day 35 were similar to those of untreated CIA mice ($p=0.988$).

Conclusion: The high DKK-1 level in CIA mice was suppressed by blockade of not only TNF-α but also IL-6. This result indicates one mechanism through which blockade of TNF-α and IL-6 suppresses periarticular bone loss. However, DKK-1 might not affect systemic bone loss because TNFR-Fc treatment did not suppress bone loss in the lumbar spine. On the other hand, although sclerostin levels were significantly lower in CIA mice than in non-immunized mice, sclerostin levels were normalized only by blockade of IL-6. Our findings suggested that anti-IL-6 receptor antibody would have a beneficial effect on both periarticular and systemic bone loss by normalizing the Wnt pathway in inflammatory arthritis.

Disclosure: H. Yoshida, None; **M. Yagoto**, None; **M. Suzuki**, None; **K. Tanaka**, None; **I. Matsumoto**, None; **T. Sumida**, None; **Y. Matsumoto**, None.

2214

STAT3 Blockade Suppresses Autoimmune Arthritis In Mice Via The Reciprocal Regulation Of Treg and Th17 Cells. Jennifer Lee[1], Jae Ho Lee[1], Seung Min Jung[1], Young Sun Suh[1], Jung Hee Koh[1], Soo Young Lee[2], Dae Chul Jeong[1], Mi-La Cho[3], Seung-Ki Kwok[1], Ji Hyeon Ju[1], Kyung-Su Park[1] and Sung-Hwan Park[1]. [1]The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea, [2]The Catholic University of Korea, Incheon St. Mary's Hospital, Incheon, South Korea, [3]Catholic University of Korea, Seoul, South Korea.

Background/Purpose: IL-6-mediated STAT3 signaling which is essential to Th17 differentiation plays the central role in the pathogenesis of rheumatoid arthritis. To investigate the molecular mechanism underlying the anti-rheumatic effects and the T cell regulatory effects of STAT3 inhibition, we studied the effects of JAK2 inhibitor, AG490, on Th17/Treg balance and osteoclastogenesis.

Methods: AG490, inhibitor of Jak2, was administered via intraperitoneal injection in collagen-induced arthritis (CIA) model and the *in vivo* effects of AG490 were determined. The differential expressions of proinflammatory cytokines including IL-17, IL-1β and IL-6 were analyzed by immunohistochemistry. The levels of phosphorylated STAT3 and STAT5, the differentiation of Th17 and Treg after the treatment of AG490 in CIA model were analyzed by immunostaining. In vitro development of Th17 and Treg was analyzed by flowcytometry and real-time polymerase chain reaction.

Results: AG490 administration ameliorated the arthritic phenotype of CIA and increased the proportion of Foxp3-positive Treg cells. In contrast, the proportion of IL-17-producing T cells and the levels of inflammatory markers were reduced in AG490-treated group. The pSTAT3-positive CD4 T cells were reduced, whereas pSTAT5-positve CD4 T cells were elevated with treatment of

AG490. Further, AG490 markedly enhanced the expression of molecules associated with Treg development (ICOS, PD-1, ICAM-1 and CD103) as well as Foxp3. The development and the function of osteoclast were also suppressed with AG490 treatment.

Conclusion: Our results suggest that AG490 which specifically regulates JAK2/STAT3 pathway may be the promising treatment strategy for rheumatoid arthritis.

Disclosure: J. Lee, None; **J. H. Lee**, None; **S. M. Jung**, None; **Y. S. Suh**, None; **J. H. Koh**, None; **S. Y. Lee**, None; **D. C. Jeong**, None; **M. L. Cho**, None; **S. K. Kwok**, None; **J. H. Ju**, None; **K. S. Park**, None; **S. H. Park**, None.

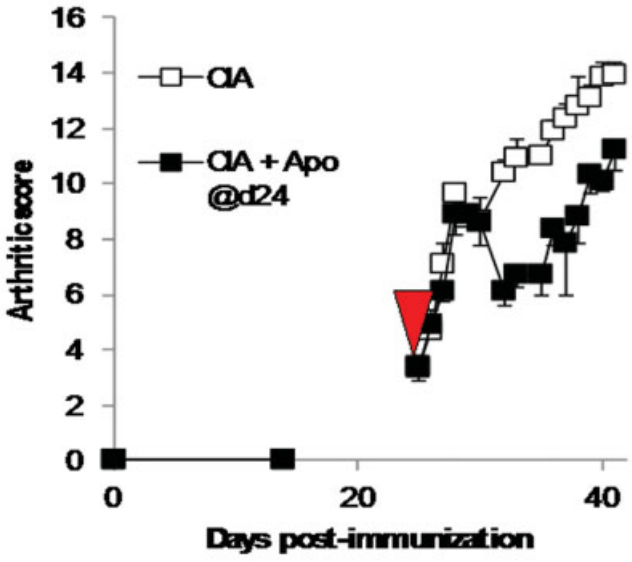
2215

Apoptotic Cell-Based Therapy To Treat Collagen-Induced Experimental Arthritis. Rationale For The Use Of Apoptotic Cells In The Treatment Of Rheumatoid Arthritis. Sylvain Perruche[1], Amandine Clauzon[1], Francis Bonnefoy[1], Eric Toussirot[2] and Philippe Saas[3]. [1]EFS Bourgogne Franche Comté, Besançon, France, [2]CIC Biotherapy 506 and Rheumatology and EA 4266 Pathogens and Inflammation, Besançon, France, [3]INSERM UMR1098 / Plateforme de Biomonitoring, Besançon, France.

Background/Purpose: Most of the currently available biological agents used in the treatment of rheumatoid arthritis (RA) target a cellular or soluble factor involved in the physiopathology of the disease. Alternatively, cellular therapies are scarce in the therapeutic management of RA. Apoptotic cells display immunologic properties that have been used to resolve inflammation in various experimental models of autoimmune diseases (diabetes, demyelinating diseases) as well as in bone marrow transplantation to favour engraftment and prevent graft versus host disease. Apoptotic cell approach has been successfully assessed to prevent arthritis development in experimental rat model. Here we evaluated a cell-based therapeutic approach based on the immuno-modulatory properties of apoptotic cells to treat RA. In this study, we thus investigated the effects apoptotic cell injection to treat arthritis in a mouse model of collagen-induced arthritis (CIA).

Methods: CIA was induced in susceptible DBA/1 mice using type II bovine collagen immunization. Four to 8 days after arthritis development (d20 post-immunization) mice presenting arthritic symptoms were treated with apoptotic cells (5.10e6 cell/mouse). As control, methotrexate was used (MTX, 15 mg/kg, twice) alone or with apoptotic cells. Regulatory T cells (Treg) were assessed by FACS at time of sacrifice (day 40/45).

Results: Apoptotic cell injection demonstrated a significant decrease of arthritis score ($p>0.01$; 4 independent experiments), associated with an increased percentage of Treg in the spleen at time of sacrifice (Figure: Apoptotic cell injection in collagen induced arthritis attenuates arthritis score either after early or late injection. Data are obtained in DBA1 mice immunized with bovine type II collagen). In addition, MTX was sufficient to decrease arthritis as well and apoptotic cell injection did not influence MTX efficiency and *vice-et-versa*. Whereas MTX did not affect the percentage of Treg, MTX + apoptotic cell treatment induced a strong increase of Treg in the spleen and draining lymph nodes.



Conclusion: Apoptotic cell injection is an effective treatment to reduce arthritis severity and should be consider in clinic as an alternative method for the treatment of patients with RA. A phase I/II clinical trial using this therapeutic approach is currently planned by our group in patients with RA refractory to biological agents.

Disclosure: S. Perruche, None; **A. Clauzon**, None; **F. Bonnefoy**, None; **E. Toussirot**, None; **P. Saas**, None.

2216

Tubastatin A, a Selective Histone Deacetylase-6 Inhibitor, Suppresses Synovial Inflammation and Joint Destruction In a Collagen Antibody-Induced Arthritis Mouse Model. Joong Kyong Ahn[1], Jaejoon Lee[2], Hyemin Jeong[3], Jiwon Hwang[3], Seulkee Lee[3], Ji Young Chai[4], Inyoung Kim[3], Eun Chung Hong[5], Eun-Kyung Bae[5], Hoon-Suk Cha[2] and Eun-Mi Koh[3]. [1]Kangbuk Samsung hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea, [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [4]Jesang Hospital, Seongnam-si Gyeonggi-do, South Korea, [5]Samsung Biomedical Research Institute, Seoul, South Korea.

Background/Purpose: Histone deacetylases (HDAC) play a key role in regulating gene expression by deacetylasing histones, and HDAC inhibitors induce various cellular effects, including apoptosis, cell cycle arrest and inhibition of angiogenesis. Tubastatin A is a potent and selective HDAC-6 inhibitor and its anti-rheumatic effect has not been determined. This study was undertaken to investigate the effect of Tubastatin A on synovial inflammation and joint destruction in collagen antibody-induced arthritis (CAIA) mouse model.

Methods: CAIA mice were given daily intraperitonial injections of various concentration of Tubastatin A (0, 10, 50, 100mg/kg, n=6 each). Clinical score, paw thickness, and body weight were measured for 14 days. On day 15, mice were sacrificed and the expression of TNF-α, IL-1, IL-6 from the serum was analyzed using ELISA. Hind foot was examined histologically and synovitis was scored by 2 independent pathologists. Micro CT of the joints was performed and joint destruction was quantified. Cell viability and the expression of inflammatory cytokines in human fibroblast-like synoviocytes (FLS) after incubation with various doses of Tubastatin A (0, 0.75, 1.5, 3μM) were measured using MTT assay and ELISA, respectively.

Results: In the Tubastatin A-treated group, clinical arthritis was attenuated and paw thickness was lower and this effect was statistically significant in the Tubastatin 100mg/kg group compared to control ($p<0.01$). All mice lost a small amount of weight but the difference was not statistically significant between groups. In the Tubastatin A 100mg/kg group, the histological severity of synovial inflammation as measured by synovial hypertrophy, density of resident cells, and inflammatory cell infiltrates was significantly lower compared with control ($p<0.01$, each). In addition, micro CT showed that joint destructions as measured by bone volume/tissue volume and bone surface area/bone volume were significantly less in the Tubastatin 100mg/kg group compared with control ($p<0.05$). Among pro-inflammatory cytokines, expression of IL-6 in the serum was significantly lower in the Tubastatin A 50mg/kg group compared with control ($p<0.05$). The expression of IL-6 from human FLS after incubation with Tubastatin A decreased in a dose-dependent manner without affecting the cell viability.

Conclusion: Our data demonstrated that Tubastatin A, a selective HDAC6 inhibitor, ameliorates synovial inflammation and protects against joint destruction in CAIA mice, and reduced expression of IL-6. Our data suggest that Tubastatin A warrant further investigation as a potential therapeutic agent in rheumatoid arthritis.

Disclosure: J. K. Ahn, None; **J. Lee**, None; **H. Jeong**, None; **J. Hwang**, None; **S. Lee**, None; **J. Y. Chai**, None; **I. Kim**, None; **E. C. Hong**, None; **E. K. Bae**, None; **H. S. Cha**, None; **E. M. Koh**, None.

2217

Experimental Arthritis Exacerbates Periodontal Disease But Periodontal Infection Does Not Exacerbated Experimental Arthritis. John Butcher[1], Jessica Oliver-Bell[1], Robert Benson[1], James Brewer[1], Paul Garside[1], Iain B. McInnes[1] and Shauna Culshaw[2]. [1]Institute of Infection, Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, United Kingdom, [2]Dental School, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, United Kingdom.

Background/Purpose: There is a proposed link between periodontal disease (PD) and rheumatoid arthritis (RA). A substantial, although not unanimous, body of epidemiological evidence indicates a bidirectional link, with patients with PD

more likely to suffer RA and vice versa. Several mechanisms have been proposed to explain the relationship between PD and RA, including i) periodontal bacterial generating autoantigens, ii) local periodontal inflammation generating autoantigens, ii) direct bacterial insult to the joint, iv) systemic inflammation associated with periodontitis exacerbating inflammation at distant sites, and v) shared risk factors. Previous studies, using experimental models of later stages of arthritis and joint destruction, suggest that periodontal infection may exacerbate arthritis and vice versa. We sought to investigate whether periodontal infection may impact on the initiation of arthritis and therefore used an experimental model of breach of immune tolerance, generation of autoantibodies and synovitis.

Methods: Mice were orally infected with *P. gingivalis* to initiate alveolar bone destruction, modeling human periodontal disease. Animals subsequently received Th1 polarized ovalbumin specific T cells by adoptive transfer, and were immunized, and then challenged in the footpad with ovalbumin. Paw swelling, joint histology, periodontal bone loss, responses of T cells from the draining lymph nodes, and serum antibody were assessed.

Results: Animals developed footpad swelling and histological evidence of synovitis. Circulating anti-CCP antibodies were significantly elevated in experimental arthritis compared with control animals (arthritis: 1189 ± 25.56 ELISA units (EU), control: 934.1 ± 99.39 EU; $p<0.05$), and a similar trend was observed for circulating anti-collagen antibodies, although this did not reach statistical significance (arthritis: 439.5 ± 124.2 EU, control: 224.0 ± 68.8 EU; $p=0.19$). Periodontal infection had no impact on any measures of this model of early arthritis. However, animals with periodontal infection and arthritis showed significantly more periodontal bone destruction (periodontal infection+arthritis: 0.44 ± 0.01 mm, periodontal infection: 0.40 ± 0.01 mm; $p<0.05$) compared with animals with periodontal infection alone.

Conclusion: These data suggest that periodontal infection may not be responsible for initiating the breach of tolerance associated with the initiation of arthritis. In this model system of breach of tolerance, oral infection made no impact on articular or autoantibody outcomes. Nonetheless, established periodontal inflammation may be detrimental to patients with RA and therefore further human and animal studies are required to unravel the mechanisms mediating the PD/RA relationship as understanding such a relationship offers potentially improved therapeutic strategies – for both PD and RA independently and in combination. *This project was supported by EUFP7 'Gums and Joints' Grant number 261460*

Disclosure: J. Butcher, None; **J. Oliver-Bell**, None; **R. Benson**, None; **J. Brewer**, None; **P. Garside**, None; **I. B. McInnes**, Roche Pharmaceuticals, 2; **S. Culshaw**, None.

2218

Gingival Stem Cells Suppress Osteoclast Formation and Bone Erosion In CIA Through CD39 Signal. Song Guo Zheng[1], Jian Gu[1], Maogeng Chen[1] and Yi Shen[2]. [1]University of Southern California Keck School of Medicine, Los Angeles, CA, [2]Shanghai East Hospital at Tongji University, Shanghai, China.

Background/Purpose: We recently have reported that human-derived gingival mesenchymal stem cells (GMSC) have strong capacity to suppress immune responses and T cell-mediated collagen-induced arthritis, however, the precise role and functions of GMSC in bone homeostasis are still unknown. This study was undertaken to determine the effects of GMSCs on osteoclastogenesis *in vitro* and on bone erosion *in vivo* in collagen-induced arthritis (CIA).

Methods: Human gingival tissues were gained from discard samples from suffers who underwent dental operation, GMSC were isolated from gingival tissues and cultured in α-MEM with 10% FBS. GMSC and mouse bone marrow derived-CD11b+ cells or human CD14+ cells were co-cultured with various ratios in the presence of 20ng/ml m-CSF and 30ng/ml RANKL. Fibroblast cells have been used for negative control. The osteoclast formation was determined by TRIP staining and numbers of osteoclast formation were calculated in microscope. In addition, GMSCs were adoptively transferred to mice with CIA to assess *in vivo* effects on disease development and bone erosion, the latter determined by CT scanning. To determine the molecular mechanisms, various inhibitors and antibodies have been added to cell cultures and administrated to CIA mice that had been infused with GMSC.

Results: We showed that GMSCs potently suppressed the genesis and proliferation of osteoclast cells from either mouse CD11b+ cells or human CD14+ cells. We also observed that that GMSC suppress osteoclast cell genesis via CD39 signal *in vitro*. Adoptive transfer of GMSCs reduced the severity of arthritis and bone erosion in CIA mice. Finally, we show that GMSCs are capable of preventing severity of CIA model via CD39 signals.

Conclusion: Use of GMSCs can treat rheumatoid arthritis and prevent bone erosion.

Disclosure: S. G. Zheng, None; **J. Gu**, None; **M. Chen**, None; **Y. Shen**, None.

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Active Immunization Against VEGF-Derived Oligopeptides Improves Joint Inflammation and Destruction In Collagen-Induced Arthritis. Emilie Duvallet[1], Laure Foulboeuf[1], Luca Semerano[2], Nadia Belmellat[1], Marc Lecouvey[3], Eric Assier[1], Sylviane Muller[4] and Marie-Christophe Boissier[2]. [1]EA4222, Li2P, University Paris 13, Sorbonne Paris Cité, Bobigny, France, [2]EA4222, Li2P, University Paris 13, Sorbonne Paris Cité and Rheumatology Department, Avicenne Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Bobigny, 93009, France, Bobigny, France, [3]CSPBAT Paris 13 University, Bobigny, France, [4]CNRS, Strasbourg, France.

Background/Purpose: We have demonstrated in experimental models the efficacy of vaccination against cytokines, using a heterocomplex of keyhole limpet hemocyanin (KLH) and human TNF, called TNF kinoid (-K). VEGF plays a key role in the development of rheumatoid arthritis (RA), allowing hypertrophy of the pannus by neovascularisation, articular inflammation and destruction. Thus, VEGF is a potential target in RA.

We aimed at demonstrating an inhibitory effect of a sustained inhibition of VEGF by vaccines based on VEGF-derived peptides linked to KLH (Vpep-K) in collagen-induced-arthritis (CIA).

Methods: Anti-murine VEGF immunization was performed by injecting intra-muscularly Vpep1-K and Vpep2-K formulated in incomplete Freund adjuvant (IFA) in DBA/1 mice (at days −36, −22, −8, 7 and 37). Control groups received KLH or PBS on the same schedule. Arthritides were induced by two subcutaneous injections of bovine type II collagen, the first at day 0 in complete Freund adjuvant, the second at day 21 in IFA. Clinical scores of arthritis were evaluated twice per week. Histological scores of joint inflammation and destruction after Hematoxylin/Eosin staining were quantified at sacrifice. Anti-peptide, anti-VEGF and anti-KLH antibody (Ab) levels were assessed by ELISA.

Results: Vpep1-K group showed lower arthritic scores as compared to KLH and PBS groups ($p<0.05$). At histological analysis, inflammation and destruction scores of the paws were lower in Vpep1-K group versus KLH and PBS group ($p<0.005$). Vpep1-K and Vpep2-K groups induced anti-VEGF Ab production as assessed by ELISA at day −2 and sacrifice.

Conclusion: These data show that Vpep1-K induces anti-VEGF Abs and improves arthritis in a murine model of RA.

Disclosure: E. Duvallet, None; **L. Foulboeuf**, None; **L. Semerano**, None; **N. Belmellat**, None; **M. Lecouvey**, None; **E. Assier**, None; **S. Muller**, None; **M. C. Boissier**, None.

2220

The Role Of CD11c+ Dendritic Cells In Inflammatory Arthritis. Antonia Puchner, Stephan Blüml, Victoria Saferding, Harald Leiss, Josef S. Smolen and Kurt Redlich. Medical University of Vienna, Vienna, Austria.

Background/Purpose: Dendritic cells (DCs) play an important role in bridging the innate and the adaptive immune response by serving as antigen presenting cells and are therefore implicated in the initiation of chronic autoimmune diseases, including rheumatoid arthritis.

Using the K/BxN serum transfer arthritis, a model of human rheumatoid arthritis, which depends only on the innate immune system, we investigated the innate role role of dendritic cells in inflammatory arthritis.

Methods: KBxN serum transfer arthritis was induced in CD11c-diphteria toxin receptor (DTR) transgenic mice, which express the human diphtheria-toxin receptor under the CD11c promoter. This allows for specific depletion of CD11c+ cells by administration of diphtheria toxin (DT). DT or PBS was given on day −1, 3, 6 and 9 and the severity of arthritis was determined clinically and histologically. In addition, serum transfer arthritis was induced in wild type animals, which also received DT.

Results: Efficient depletion of DCs from the spleen after injection of DT was confirmed by flow cytometry and histological analysis. Clinical scores of arthritis showed that CD11c-DTR transgenic mice had significantly reduced paw swelling and loss of grip strength compared to PBS treated animals. In contrast, wild type animals receiving DT showed identical clinical signs of arthritis as PBS treated animals, excluding unspecific effects of DT in mice. Histological analysis found that CD11c-DTR transgenic mice that had received DT displayed decreased synovial inflammation, local bone destruction and reduced the number of osteoclasts. In addition the number of CD115+ CD11b+ GR neg/low osteoclast precursors was significantly reduced in the peripheral blood of CD11c-DTR transgenic mice that had received DT, suggesting a role of CD11c+ cells for osteoclast precursor generation.

Conclusion: These data show that dendritic cells are involved in innate reactions leading to inflammatory arthritis and suggest that dendritic cells could be an important target for rheumatoid arthritis therapy.

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The Histamine H_4 Receptor Drives Inflammation In Preclinical Models Of Arthritis. Paul J. Dunford, Jeffery Cowden, Fuqu Yu, Homayon Banie, Mandana Farahani, Ping Ling, Steven Nguyen, Jason Riley, Mai Zhang, Jian Zhu and Robin L. Thurmond. Janssen R&D, LLC, San Diego, CA.

Background/Purpose: The histamine H_4 receptor (H_4R) has been shown to drive inflammatory responses in models of asthma, colitis and dermatitis and in these models it appears to impact both innate and adaptive immune responses. In this study we utilized both H_4R-deficient mice and specific H_4R antagonists, to investigate the involvement of the H_4R in mouse arthritis models and in toll-like receptor (TLR) driven events in vitro and in vivo.

Methods: H_4R-deficient mice and wild-type mice administered the H_4R antagonist, JNJ 28307474, were studied in models of collagen antibody-induced arthritis (CAIA) and collagen-induced arthritis (CIA). The impact on Th17 cells was assessed by restimulation of inguinal lymphocytes in the disease or immunization models and upon in vitro stimulation of whole blood. The impact of H4R antagonists, JNJ 7777120 and 28307474, on innate immunity were also examined in LPS challenge of mice, and of in vitro mast cells and dendritic cells.

Results: Both H_4R-deficient mice and mice treated with the H_4R antagonist exhibited reduced arthritis disease severity in both CAIA and CIA models. This was evident from the reduction in disease score and in joint histology. In the CIA model treatment with the H_4R antagonist reduced the number of IL-17 positive cells in the lymph node and the total production of IL-17. Th17 cell development in vivo was reduced in H_4R-deficient mice or in mice treated with an H_4R antagonist. In human blood an H_4R antagonist reduced the production of IL-17 when cells were stimulated in vitro. Additionally, H4R antagonists were able to inhibit TNF production in response to LPS challenge in mice, and to decrease IL-6 and multiple cytokine and chemokine production from TLR stimulated mast cells and dendritic cells, respectively

Conclusion: These results implicate the H_4R in disease progression in arthritis, in innate driven, proarthritic inflammatory events and in the production of IL-17 from Th17 cells. This work supports future clinical exploration of H_4R antagonists for the treatment of rheumatoid arthritis and other autoimmune diseases.

Disclosure: P. J. Dunford, Johnson & Johnson, 3, Johnson & Johnson, 1; **J. Cowden**, Johnson & Johnson, 3; **F. Yu**, Johnson & Johnson, 3; **H. Banie**, Johnson & Johnson, 3; **M. Farahani**, Johnson & Johnson, 3; **P. Ling**, Johnson & Johnson, 3; **S. Nguyen**, Johnson & Johnson, 3; **J. Riley**, Johnson & Johnson, 3; **M. Zhang**, None; **J. Zhu**, Johnson & Johnson, 3; **R. L. Thurmond**, Johnson & Johnson, 1, Johnson & Johnson, 3.

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Positive Allosteric Modulation Of The Adenosine A_{2a} Receptor Alters Inflammatory Cytokine Production and Alleviates Chronic Arthritis In Rats. Ajith A. Welihinda, Jordan A. Mechanic and Edward P. Amento. Molecular Medicine Research Institute, Sunnyvale, CA.

Background/Purpose: Rheumatoid arthritis is a chronic systemic autoimmune disease characterized by inflammation and joint destruction; a consequence of which is the high local concentration of adenosine. Adenosine, acting primarily through a member of the G-protein coupled receptor (GPCR) family of transmembrane receptors, the A_{2a} receptor ($A_{2a}R$), mediates anti-inflammatory and immunomodulatory activity. High affinity $A_{2a}R$ agonists have demonstrated therapeutic efficacy, however, their utility is hindered by lack of adenosine receptor subtype selectivity and inadvertent activation of the $A_{2a}R$ at non-disease sites. In light of the high concentrations of adenosine found at sites of chronic inflammation we explored the hypothesis that diminished receptor responsiveness to adenosine may play a role in disease expression. GPCR's are amenable to an agonist-independent mode of activity enhancement known as positive allosteric modulation (PAM). Positive allosteric modulators have no intrinsic agonist activity, yet enhance the activity of the receptor to its agonist. Using a positive allosteric modulator unique to the $A_{2a}R$, AEA061, we examined the effects of PAM of the $A_{2a}R$ on inflammatory cytokine production and chronic arthritis.

Methods: To assess the effect of PAM of the $A_{2a}R$ on cytokine production in vitro, mouse splenocytes were stimulated with LPS in the presence of AEA061. To determine whether PAM of the $A_{2a}R$ inhibits inflammation in vivo, control and $A_{2a}R$ deficient mice received vehicle or AEA061 i.v. 10 min prior to i.p. injection of LPS. The role of PAM of the $A_{2a}R$ on progression of chronic arthritis was evaluated in adjuvant-induced arthritis (AIA). Male Lewis rats were immunized by i.d. injection at the base of the tail with *M. tuberculosis* H37Ra in Freund's incomplete adjuvant. Paw volumes and clinical severity were assessed for 26 days. When the mean clinical score = 2, AEA061 was administered i.p. once daily. Splenocytes were cultured and cytokine in culture supernatants and in plasma were quantified using multiplex immunoassays.

Results: PAM of the $A_{2a}R$ inhibited LPS-stimulated production of TNF-α, MIP-1α, MIP-1β, MIP-2, IL-1α, RANTES and CXCL1 by mouse splenocytes in a dose-dependent manner in vitro ($p < 0.05$). AEA061 also reduced plasma TNF-α and MCP-1 levels while increasing IL-10 levels ($p < 0.05$) in control but not in $A_{2a}R$-deficient mice. In AIA rats, AEA061 reduced paw volumes ($p<0.01$) as well as reduced clinical scores ($p<0.01$). Splenocytes from AEA061-treated animals produced decreased IL-1 (45%) and increased IL-10 (341%) ex-vivo.

Conclusion: PAM of the $A_{2a}R$ to endogenous adenosine inhibits cytokine production in vitro and in vivo in models of acute inflammation and chronic arthritis. This is the first demonstration of the therapeutic utility of PAM of the $A_{2a}R$ and supports the notion that impaired receptor responsive to adenosine may contribute to the dysregulation of chronic inflammation. PAM of the $A_{2a}R$ presents a novel, unique and safe approach that focuses the therapeutic benefit at the site of disease, does not employ exogenous agonists and preserves the natural pattern of $A_{2a}R$ activation by endogenous adenosine while enhancing receptor responsiveness.

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Monitoring Of Active Matrix Metalloproteinase-3 Using. Sung Jae Choi[1], Young Ho Seo[2], Young Ho Lee[1], Jong Dae Ji[1], Gwan Gyu Song[3], Aeju Lee[2] and Jae-Hoon Kim[3]. [1]Korea University Medical Center, Seoul, South Korea, [2]Korea University Medical center, Seoul, South Korea, [3]Korea Univ College of Med, Seoul, South Korea.

Background/Purpose: Active matrix metalloproteinase-3 (MMP-3) is a prognostic marker of rheumatoid arthritis (RA). Recently, we developed the MMP-3 probe which can specifically detect an active MMP-3.

Methods: The aim of this study was to investigate whether detecting and monitoring of active MMP-3 using the MMP-3 probe will be useful to predict therapeutic drug responses in collagen-induced arthritis (CIA) mice. During the period of drug treatments such as methotrexate (MTX) or infliximab (IFX), fluorescence signals in arthritic joint tissues and in serum of CIA mice were monitored using the MMP-3 probe to correlate with MMP-3 mRNA and protein levels. Also, micro-computed tomography (micro-CT), X-ray and histology were performed to confirm drug responses.

Results: Strong fluorescence signals observed in joint tissues and serum of CIA mice were significantly decreased when drugs were treated (Fig. 1.). The decrease of RA scores in drug-treated CIA mice leads to the fluorescence reductions, which is mainly due to down-regulation of MMP-3 mRNA or protein levels. The results that micro-CT, X-ray (Fig. 2.) and histology clearly showed the markedly decrease of bone and cartilage destruction were consistent with the fluorescence reduction by down-regulation of active MMP-3 in drug-treated CIA mice.

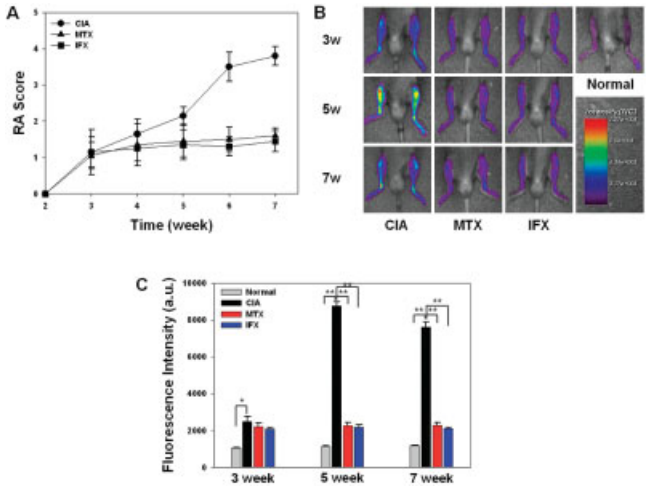

Figure 1. *In vivo* monitoring of RA activities and active MMP-3 levels using "smart probe" in arthritic joints of CIA mice with or without MTX or IFX treatment.

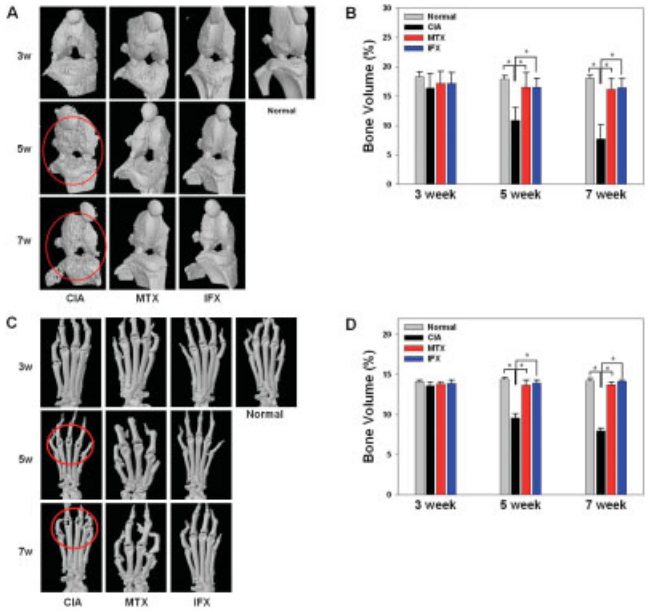

Figure 2. Three-dimensional reconstructions of micro-CT images and bone volume analysis using micro-CT in the knee joints and the paws of normal (n=5), CIA (n=5), and MTX (n=5) or IFX (n=5)-treated CIA mice at 3, 5, and 7 weeks after the first immunization.

Conclusion: We suggested that the MMP-3 probe could detect and monitor active MMP-3 of CIA mice serum in treatment course, and thereby predicting the drug response or resistance to RA therapies at an earlier stage. We hope that the MMP-3 probe will be a promising tool for drug discovery, development and drug responses in RA therapy.

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Tumor Necrosis Factor Alpha Induces Anti-Citrullinated Protein Antibodies and Arthritis In Part Through Peptidyl Arginine Deiminase 4. Miriam A. Shelef[1], Jeremy Sokolove[2], Catriona Wagner[3], Eric Sackmann[4], Thomas Warner[4], David Beebe[4], William H. Robinson[5] and Anna Huttenlocher[1]. [1]Univ of Wisconsin Schl of Med, Madison, WI, [2]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [3]VA Palo Alto Heatlh Care System and Stanford University, Palo Alto, CA, [4]University of Wisconsin, Madison, WI, [5]Stanford University, Palo Alto, CA.

Background/Purpose: Rheumatoid arthritis is an autoimmune, destructive arthritis characterized by anti-citrullinated protein antibodies (ACPAs) and high levels of inflammatory cytokines like tumor necrosis factor alpha (TNFalpha). Citrullinated proteins may be a trigger for the development of rheumatoid arthritis since ACPA immune complexes can stimulate TNFalpha production, which promotes inflammation and arthritis. Inflammation appears to induce protein citrullination, but it is not known if TNFalpha can lead to citrullination with resultant ACPAs. We hypothesized that TNFalpha could augment ACPA production with a role for the citrullinating enzyme peptidyl arginine deiminase 4 (PAD4) as part of a feedback loop to accelerate arthritis development.

Methods: We measured ACPA levels by multiplex array in mice with chronic inflammatory arthritis due to overexpression of TNFalpha. We then crossed mice that overexpress TNFalpha with mice that lack PAD4. We compared ACPA levels by multiplex array, lymphocyte activation by flow cytometry, arthritis by clinical score, and systemic inflammation using microfluidics devices in TNF+PAD4+/+ versus TNF+PAD4−/− mice.

Results: Mice that overexpress TNFalpha have increased serum ACPAs, suggesting that high levels of TNFalpha, as is seen in human rheumatoid arthritis, can amplify ACPA production. Further, mice with TNFalpha induced arthritis that lack PAD4 have decreased ACPAs, reduced T cell activation, and less inflammation and arthritis, suggesting that PAD4 makes key contributions to TNFalpha driven, chronic inflammatory arthritis.

Conclusion: These data support a positive feedback loop in which ACPAs, TNFalpha, and PAD4 synergize to enhance inflammation and the development of rheumatoid arthritis.

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COVA322: A Novel, Bispecific Tumor-Necrosis-Factor-Alpha/Interleukin-17A (TNF/IL-17A) Inhibitor With Excellent Pharmacokinetic Properties In Mice and Cynomolgus Monkeys. Mathias Locher, Dragan Grabulovski, Isabella Attinger-Toller, Susann Koenig-Friedrich, Ulrike von der Bey and Julian Bertschinger. Covagen AG, Schlieren, Switzerland.

Background/Purpose: The generation of bispecific antibody molecules with excellent biophysical and pharmacokinetic properties has been a challenging task in the past. We present here COVA322, a bispecific anti-TNF/IL-17A drug candidate moving towards the clinic that shows IgG-like pharmacokinetic properties.

Methods: Using phage display technology we have isolated Fynomers inhibiting human IL-17A. Fynomers are small binding proteins (7 kDa) derived from the human Fyn SH3 domain which can be engineered to bind to essentially any target of interest with high affinity and specificity. After genetic fusion of the anti-IL-17A Fynomer to a commercially validated anti-TNF antibody, the resulting bispecific molecule COVA322 was injected in mice and cynomolgus monkeys to determine its pharmacokinetic parameters. As controls, the commercially available antibodies adalimumab and golimumab were also injected into animals.

Results: The fusion of the anti-IL-17A Fynomer to the fully human anti-TNF antibody did not alter the favorable pharmacokinetic parameters of the parental anti-TNF antibody. COVA322 demonstrated comparable pharmacokinetic properties in mice and cynomolgus monkeys as adalimumab and golimumab. In addition, we could demonstrate that COVA322 stays fully functional and intact for at least ten days in cynomolgus monkeys, indicating that the Fynomer is not cleaved from the antibody.

Conclusion: These encouraging preclinical results indicate that COVA322 has highly promising pharmacokinetic properties. Through its unique mode-of-action of inhibiting simultaneously TNF and the IL-17A/A homodimer, COVA322 has game changing potential in the treatment of inflammatory diseases.

Disclosure: M. Locher, Covagen AG, 1, Covagen AG, 3; **D. Grabulovski**, Covagen AG, 1, Covagen AG, 3, Covagen AG, 4; **I. Attinger-Toller**, Covagen AG, 1, Covagen AG, 3; **S. Koenig-Friedrich**, Covagen AG, 3; **U. von der Bey**, Covagen AG, 3; **J. Bertschinger**, Covagen AG, 1, Covagen AG, 3, Covagen AG, 4.

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Involvement Of Suppressor Of Cytokine Signaling In Anti-Arthritic Effect Induced By Anti-IL-6 Receptor Antibody. Miho Suzuki[1], Hiroto Yoshida[1], Keisuke Tanaka[1], Isao Matsumoto[2], Takayuki Sumida[2] and Yoshihiro Matsumoto[1]. [1]Chugai Pharmaceutical Co., Ltd., Gotemba, Japan, [2]University of Tsukuba, Tsukuba, Japan.

Background/Purpose: In the treatment of rheumatoid arthritis (RA), biologics such as IL-6 and TNF inhibitors have high therapeutic efficacy with extended duration of effect ["LITHE study" J Rheumatol. 2013; 40: 113–26, "ATTEST study" Ann Rheum Dis. 2008; 67: 1096–103]. Among RA patients treated with anti-IL-6 receptor antibody (anti-IL-6R), in particular, it is reported that 10% were able to suspend the biologic for an extended period without relapse/flare ["DREAM study" Mod Rheumatol. 2013 May 3. [Epub ahead of print] DOI:10.1007/s10165-013-0894-z]. Although not yet fully clarified, this is thought to be causally related to a sustained anti-inflammatory effect of anti-IL-6R. It was reported that levels of suppressor of cytokine signaling (SOCS)-1 and -3, well-known feedback inhibitors of the JAK/STAT pathway, are high in RA [Rheumatology (Oxford). 2007; 46: 1538–46] and should be considered when allowing a drug-holiday in RA. In this study, we investigated the efficacy of anti-IL-6R on SOCS-1 and -3 levels, using a mouse model of arthritis.

Methods: Glucose-6-phosphate isomerase (GPI)-induced arthritis was triggered in DBA/1J mice by intradermal injection of recombinant GPI. We used anti-IL-6R to inhibit IL-6. Anti-IL-6R was intraperitoneally administered once at a dose of 4 mg 5 days after immunization (Day 5). Clinical symptoms of arthritis were evaluated by observation and expressed as an arthritis score on a scale of 0–3 for each limb. Expression levels of IL-6, SOCS-1 and -3 mRNA in the hind limbs

of mice were measured by real-time PCR, and IL-6, SOCS-1 and -3 levels in blood were measured by ELISA on Days 0, 7, 14, 21, 28 and 35.

Results: The mouse model used here is a transient arthritis model: arthritis starts to develop from about Day 5 and reaches peak swelling on Day 14. Blood levels of IL-6 and SOCS-3 reached their peaks on Day 7. SOCS-1 level in blood reached the plateau level on Day 7. Expression levels of IL-6 and SOCS-3 mRNA in hind limbs reached their peaks on Day 14 in line with the arthritis score. Expression level of SOCS-1 mRNA in hind limbs reached the plateau level on Day 14. Anti-IL-6R significantly suppressed the arthritis score and SOCS-3 levels both in blood and hind limbs on Day 14. On the other hand, anti-IL-6R suppressed expression level of SOCS-1 mRNA in hind limbs on Day 14 but did not suppress SOCS-1 level in blood.

Conclusion: We demonstrated that, though each peak time was different, IL-6 and SOCS-3 changed similarly both in blood and the hind limbs, with the changes in hind limbs well associated with changes in the arthritis scores, and that anti-IL-6R inhibited both SOCS-1 and -3 in the hind limbs in line with arthritis scores and inhibited only SOCS-3 but not SOCS-1 in blood. These results suggest that a possible mechanism of the anti-arthritic effect of anti-IL-6R is a reduction in SOCS-3. However, if reduced arthritis scores were caused by an increase in SOCS-1 in blood, it would also be important to consider blood levels of SOCS-1 maintained by anti-IL-6R. Furtherconsideration is needed to explain why SOCS-1 levels in blood and hind limbs respond differently to anti-IL-6R. Therefore, further studies for investigating the effect of anti-IL-6R on SOCS-1 and -3 may help to make a drug-holiday in RA possible.

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The Anti-Proliferative Function of RSK2 in Synovial Fibroblasts Protects Against TNF-á-Induced Joint Destruction in Inflammatory Arthritis. Anja Derer[1], Christina Boehm[1], Bettina Groetsch[1], Michael Stock[1], Kirsten Neubert[1], Sybille Boehm[1], Bettina Sehnert[1], Georg Schett[1], Axel J. Hueber[1] and Jean-Pierre David[2]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Background/Purpose: The pro-inflammatory cytokine Tumor Necrosis Factor alpha (TNF-α) directly activates the ribosomal S6 kinase RSK2 *in vitro*. We recently demonstrated the protective effect of RSK2 against TNF-induced bone loss. Interestingly, we found an increased activation of RSK2 in the inlfamed joints of arthritis patients as well as mice overexpressing the human TNF-α (*hTNF*tg). This prompted us to investigate the function of RSK2 in the development of TNF-α-induced inflammatory arthritis.

Methods: *hTNF*tg mice were crossed with RSK2-deficient ($Rsk2^{y/-}$) mice. Clinical scoring and histomorphometry of the joints were assessed. Levels of circulating pro-inflammatory cytokines as well as the cellularity of myeloid lineages in the spleen were compared. The expression of cytokines and mesenchymal markers in the joints was determined via QPCR. Bone marrow transfer of $Rsk2^{y/-}$ and wild-type littermates into *hTNF*tg mice was performed and clinical scoring as well as histomorphometry of the joints was assessed. Primary fibroblast-like synoviocytes (FLS) from *hTNF*tg and *hTNF*tg;$Rsk2^{y/}$ mice were isolated to analyze their expression of inflammatory cytokines and metalloproteinases as well as their proliferation and apoptosis *in vitro*.

Results: RSK2 deficiency in *hTNF*tg mice resulted in an early onset of clinical signs of arthritis as well as a drastic exacerbation of inflammation, increased cartilage destruction and increased local bone destruction. Increased levels of circulating pro-inflammatory cytokines and the increased proportion of all myeloid lineages in the spleen confirmed the enhanced inflammation in the *hTNF*tg mice lacking RSK2. Increased activation of synovial fibroblasts and macrophages in the joints of *hTNF*tg;$Rsk2^{y/-}$ mice was demonstrated by the locally increased expression of pro-inflammatory cytokines and matrix metalloproteinases (MMPs). Importantly, the phenotype could not be transmitted by the transfer of $Rsk2^{y/-}$ bone marrow into *hTNF*tg mice that demonstrated the essential role for RSK2 expression in mesenchymal cells driving the pathogenesis. In agreement, although no difference in the expression of pro-inflammatory cytokines or MMPs nor a change in apoptosis was detected in synovial fibroblasts isolated from *hTNF*tg;$Rsk2^{y/-}$, these cells displayed an increased proliferation rate.

Conclusion: The anti-proliferative function of RSK2 controls a cell autonomous negative feed-back against the activation of synovial fibroblasts by TNF-α, therefore limiting joint destruction in arthritis. Thus, activation of RSK2 is a potential target for the treatment of both local and systemic bone destruction in RA.

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FMS-Like Tyrosine Kinase 3 Ligand -Dependent CD103+DC Are Crucial For The Initiation Of Collagen-Induced Arthritis. Maria Ines Ramos, Samuel Garcia, Saïda Aarrass, Boy Helder, Kris A. Reedquist, Paul-Peter Tak and Maria C. Lebre. Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands.

Background/Purpose: Dendritic cells (DCs) are a heterogeneous cell population that plays an important role for the initiation of protective and pathogenic immunity. Flt3L is a growth factor that drives DC development from bone marrow (BM) progenitors and it is crucial for maintenance of DCsin the steady-state. The objective of this study was to address the role of Flt3L-dependent DCs in the initiation of collagen-induced arthritis (CIA).

Methods: CIA was induced in Flt3L−/− and WT C57/BL6 littermates. In vitro and in vivo uptake and migration was performed using BM-DCs and dermal DCs. Antigen presentation was studied in vivo by adoptive transfer of CFSE-labeled OT-I or OT-II T cells + OVA in Flt3L−/− and WT mice and in vitro by culturing BM-DCs with OT-I and OT-II cells. T cell proliferation was analyzed by CFSE dilution. To study BM-DC function qPCR array (Dendritic and Antigen Presenting Cell PCR Array- Qiagen) for 84 genes was performed. To test the potential of a Flt3 inhibitor (CEP701) in the prevention of CIA, an in vivo study was performed injecting CEP701 before the onset of disease in DBA-1 mice.

Results: We showed that Flt3L−/− mice are protected from CIA. In Flt3L−/− mice CD103+ DCs are almost absent. The amount of DCs carrying antigen reaching the LN in Flt3L−/− mice was reduced compared with WT. Uptake and migratory capacity was similar in Flt3L−/− BM-DCs compared to WT BM-DCs. Adoptive transfer of OT-I and OT-II T cells + OVA in Flt3L−/− mice resulted in a dramatic reduction of total cell proliferation and more importantly less divisions compared with WT animals. No intrinsic defects on DC function were observed by qPCR array. Mice treated with CEP701 before the onset of disease were protected from CIA and that correlated with the disappearance of $CD103^+$ migratory DCs. Synovial T cells were reduced and correlated with disease severity.

Conclusion: Antigen presentation in Flt3L−/− mice is impaired. As CD103+ DCs are absent in Flt3L−/− mice and are important in (cross)-presenting antigens our data reveals a crucial role for CD103+ DCs in the induction of CIA. As a consequence of CD103+ DC absence Flt3L−/− mice showed a reduction in T cell activation in particularly reduced CD8 T cell responses. Targeting this DC subset might be of interest in individuals at risk of developing autoimmune disorders.

Disclosure: M. I. Ramos, None; **S. Garcia**, None; **S. Aarrass**, None; **B. Helder**, None; **K. A. Reedquist**, Hoffmann-La Roche, Inc.; MedImmune/AstraZeneca; Five Prime Therapeutics, Inc.; GlaxoSmithKline, 2; **P. P. Tak**, None; **M. C. Lebre**, None.

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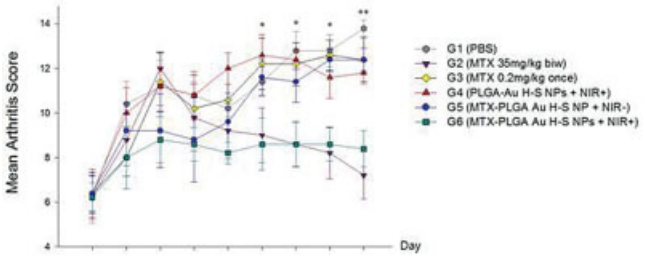
Alleviation Of Collagen-Induced Arthritis By Multifunctional Nanoparticle Containing Methotrexate. You-Jung Ha[1], Sun-Mi Lee[2], Ji-Hee Lim[1], Hyung-Joon Kim[2], Sang-Won Lee[1], Soo Kon Lee[1], Kyung-Hwa Yoo[2] and Yong-Beom Park[1]. [1]Yonsei University College of Medicine, Seoul, South Korea, [2]Yonsei University, Seoul, South Korea.

Background/Purpose: Methotrexate (MTX) is the most widely used disease-modifying anti-rheumatic drugs for the treatment of rheumatoid arthritis (RA). Despite of its efficacy, the continuous use of MTX is often accompanied by several adverse effects, especially in high-dosage MTX. We developed the multifunctional nanoparticle (MNP; Poly($_{DL}$-lactic-*co*-glycolic acid)-Au half-shell coated nanoparticles) containing 0.2mg/kg of MTX. Upon near-infrared (NIR) irradiation, these MNP can enhance the drug release and generate heat by Au half-shells. This study aimed to investigate the therapeutic efficacy of MNP containing MTX in a murine model of arthritis.

Methods: Collagen-induced arthritis (CIA) was induced in male DBA/1J mice by immunization with bovine type II collagen. Thirty CIA mice were divided into 6 groups (untreated, conventional MTX (35 mg/kg × 8 times intraperitoneal), MTX 0.2mg/kg once intravenous (IV), MTX-unloaded MNP

IV with NIR, MTX-loaded MNP IV, and MTX-loaded MNP IV with NIR). The clinical scores and hind paw thickness were evaluated. Histopathologic assessment of joint sections was performed. The serum levels of pro-inflammatory cytokines were measured by enzyme-linked immunosorbent assay.

Results: Treatment of MTX-loaded MNP with NIR significantly alleviated the severity of the arthritis, based on the reduced hind paw swelling and clinical scores, compared with untreated CIA mice. The treatment efficacy of MTX-loaded MNP with NIR group was comparable to that of conventional MTX-treated group. However, arthritis was not ameliorated in the mice treated with MTX 0.2mg/kg once or MTX-unloaded MNP with NIR. Treatment of MTX-loaded MNP without NIR showed partial treatment response only in an early treatment period. Histopathologic analyses and serum pro-inflammatory cytokines showed the similar pattern.



Conclusion: Treatment efficacy of MTX-loaded MNP with NIR was similar with conventional treatment in a much smaller dosage of MTX (about 1/1000 of MTX). Our results showed that this novel drug delivery system using MNP can be a new therapeutic tool for treatment of RA.

Disclosure: Y. J. Ha, None; **S. M. Lee**, None; **J. H. Lim**, None; **H. J. Kim**, None; **S. W. Lee**, None; **S. K. Lee**, None; **K. H. Yoo**, None; **Y. B. Park**, None.

2230

Specific Angiotensin Type II Receptor Stimulation Attenuates Collagen-Induced Arthritis Via Enhancement Of FoxP3 Regulatory T Cells. Bettina Sehnert[1], Veronica Valero-Esquitino[2], Georg Schett[3], Ulrika Muscha Steckelings[2] and Reinhard E. Voll[1]. [1]University Hospital Freiburg, Freiburg, Germany, [2]Medical Faculty Berlin, Berlin, Germany, [3]University of Erlangen-Nuremberg, Erlangen, Germany.

Background/Purpose: The renin-angiotensin system (RAS) is known to play an important role in inflammation, fibrosis, and end-organ damage. Moreover, AT2R signalling exerts anti-inflammatory and anti-apoptotic actions. Specific AT2R stimulation exhibits also neuroprotective characteristics. Compound 21 (C21) is the first non-peptide AT2 receptor agonist that stimulates selectively the AT2 receptor without affecting the AT1 receptor.

In the present study we examine the therapeutic potential of C21 in collagen-induced arthritis (CIA) and assess the role of Th1, Th17, and Treg subsets.

Methods: Collagen-induced arthritis was induced according standard protocols. Daily C21 treatment (0.1 mg/kg/i.p.) was started at day 20 after immunization. Etanercept was used as positive control. Disease activity was assessed by clinical scoring to a graded scale (0–4). At day 48 hind paws were removed for histological analysis. The stained sections (Hematoxylin/eosin, toluidine blue and tartrate-resistant acid phosphatase) were graded on a scale from 0–3. Serum cytokine profile (Th1) and splenic FoxP3+ regulatory T cells of arthritic mice were analysed by flow cytometry. *In vitro* differentiation of Th0, Th1, Th17, and Treg cells in the presence of C21 (1μM) was investigated using quantitative RT-PCR analysis of sorted naive T-cells isolated from spleen and lymph nodes of C57BL/6 mice.

Results: Systemic treatment with C21 attenuated the clinical severity of established CIA compared to the PBS group ($p<0.005$). The therapeutic efficacy of C21 was comparable to Etanercept which we used as a positive control. C21 administration reduced the cumulative incidence in CIA. Histological evaluation of C21 sections showed a well preserved articular cartilage and minor inflammatory infiltrates correlating with a reduction in disease severity. No significant difference between the groups was detectable on bone destruction. C21 did not suppress CIA by inhibition of anti-CII antibody production. Furthermore, the number of $CD4^+Foxp3^+$ cells was significantly increased after *in vivo* C21 treatment ($p<0.05$) compared to the PBS group. *In vitro* we detected decreased IFNγ mRNA expression in Th1, respectively a decrease in IL-17 mRNA expression in Th17 polarized T cells. Moreover, *in vitro* treatment of naïve T-cells with C21 significantly upregulated $FoxP3^+$Treg cells in the presence of polarizing factors.

Conclusion: C21-mediated AT2R-stimulation suppresses clinical severity, incidence and histological signs of established CIA. The regulation of IL-17-producing Th17 cells towards regulatory T cells (*Treg*) might explain the observed anti-inflammatory effect. Due to the absence of severe side-effects, C21 treatment presents an attractive concept in arthritis therapy.

Disclosure: B. Sehnert, None; **V. Valero-Esquitino**, None; **G. Schett**, None; **U. M. Steckelings**, None; **R. E. Voll**, None.

2231

The Actin-Crosslinking Protein Lasp-1 Regulates Synovial Fibroblast Migration and Cartilage Destruction In Arthritis. Denise Beckmann[1], Jan Hillen[1], Marianne Heitzmann[1], Catherine S. Chew[2], Stefan Butz[3], Dietmar Vestweber[3], Hermann Pavenstädt[1], Thomas Pap[4] and Adelheid Korb-Pap[1]. [1]University Hospital Muenster, Muenster, Germany, [2]Medical College of Georgia, Augusta, GA, [3]Max Planck Institute of Molecular Biomedicine, Muenster, Germany, [4]University Hospital Münster, Münster, Germany.

Background/Purpose: Lasp-1 localizes at focal adhesions along stress fibres and leading edges of migrating cells and regulates the metastatic dissemination of tumors. Although rheumatoid arthritis synovial fibroblasts (RASF) have been shown to contribute to the spreading of disease by leaving cartilage destruction sites, migrating via the bloodstream and re-initiating the destructive process at distant articular cartilage surfaces, the underlying mechanisms are not yet understood. Therefore, we investigated the role of Lasp-1 in SF migration and in a mouse model of RA.

Methods: We used Western blot analyses and immunofluorescence stainings of cells grown on different extracellular matrices (ECM) including fibronectin, laminin and in vitro reconstituted cartilage collagen fibrils to study the expression of Lasp-1 and its sub-cellular distribution in RASF as well as in SF isolated from the hind paws of wild type (wt) and human TNFalpha transgenic (hTNFtg) mice, an established animal model of human RA. To investigate the effects of a Lasp-1 deficiency on RA-like arthritis *in vivo*, we interbred Lasp-$1^{-/-}$ mice with hTNFtg mice. Wt, Lasp-$1^{-/-}$, hTNFtg and Lasp-$1^{-/-}$/hTNFtg mice were scored for clinical parameters such as paw swelling, grip strength and weight once weekly for 14 weeks. Hind paws of 14 weeks old mice of all genotypes were harvested, embedded into paraffin, and tissue sections were stained with toluidin-blue and analyzed using AxioVision software. The migration characteristics of SF derived from all genotypes were studied in a modified scratch assay as well as in live cell imaging studies.

Results: Western blot analyses showed a significantly increased expression of Lasp-1 in RASF and in hTNFtg SF compared to healthy and wt controls. Using immunofluorescence, Lasp-1 was localized to structures of cell adhesion and invasion especially when *in vitro* reconstituted cartilage collagen fibrils were used as ECM. Quantification of scratch assay data showed a significantly reduced migration of Lasp-$1^{-/-}$ SF compared to wt cells (-43.7%, $p<0.05$) and even more prominently of Lasp-$1^{-/-}$/hTNFtg SF compared to hTNFtg cells (-69.11%, $p<0.05$). Live cell imaging demonstrated striking differences both in the migration velocity and in migration edge formation of Lasp-$1^{-/-}$/hTNFtg SF compared to hTNFtg SF *in vitro*. Lasp-$1^{-/-}$/hTNFtg mice presented milder clinical symptoms compared to hTNFtg animals *in vivo*. Histopathologic analyses showed less cartilage damage in Lasp-$1^{-/-}$/hTNFtg compared to hTNFtg mice (5.2% vs. 33.6%, $p<0.05$) and attachment of synovial tissue to the cartilage (0.4 μm vs. 1.4μm, $p<0.05$) at an age of 14 weeks.

Conclusion: We conclude that Lasp-1 modulates SF migration and influences cartilage degradation and SF attachment to cartilage in hTNFtg mice. SF - when activated - migrate through the formation of invasive and adhesive membrane structures, where Lasp-1 is prominently localized. Thus, targeting Lasp-1 may be a promising strategy to reduce the invasive and migratory behaviour of RASF.

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Neutralization of Angiopoietin-2 Enhances the Efficacy of Anti-Tumor Necrosis Factor-Alpha Treatment in a Mouse Model of Rheumatoid Arthritis by Decreasing Cellular Infiltration into the Joint and Protecting Bone. Brian Naiman, Sean Turman, William Iverson, Ronald Herbst, Tomas Mustelin and Jane Connor. MedImmune, LLC, Gaithersburg, MD.

Background/Purpose: It has recently been established that >75% of patients on methotrexate and a biologic do not achieve complete remission based on the new definition set by ACR/EULAR in 2011. These findings aresupported by recent studies utilizing imaging technology such as PDUS or MRI that have detected "subclinical inflammation" in low disease activity patients that correlates with subsequent radiographic progression. Importantly, while anti-TNF-α therapies reduce neovascularization to some extent, the effect is incomplete. Our hypothesis is that inhibiting angiogenesis beyond that provided by anti-TNF-α therapy will provide tighter control of inflammation leading to greater impact on inhibiting disease progression. The key mediators of angiogenesis are members of the vascular endothelium growth factor (VEGF) and angiopoietin (Ang) families. Several investigators have reported increased expression of these mediators in the RA and PsA joint when compared to normal or osteoarthritis biopsies. Based on previous work demonstrating efficacy of anti-Ang2 therapy in models of RA, we chose to utilize a combination of anti-Ang2 along with anti-TNF-α to explore this hypothesis.

Methods: Arthritis was induced by immunization of DBA/1 mice with glucose-6-phosphate isomerase. Animals were treated with either 10 mg/kg anti-Ang2 antibody, 10 mg/kg anti-TNF-α antibody or a combination of the two beginning 7 days following immunization. Clinical scores were assessed daily. Animals were terminated 15 days following immunization and joints were evaluated for histological changes (H&E), CD31 staining for endothelial cells, F4/80 staining for macrophages and Cathepsin K for osteoclasts. In addition, selected joints were evaluated for bone cortical roughness around the joints using magnetic resonance imaging.

Results: Treatment with an anti-Ang2 antibody in addition to an anti-TNF-α antibody resulted in improved activity on clinical scores as well as protection from pathological changes in the joints compared to anti-TNF-α or anti-Ang2 treatment alone. Combination treatment provided a greater effect on inflammation/pannus formation and inflammatory cell infiltrates as well as on osteolysis and periosteal proliferation. CD31 staining revealed decreased vascularity in the synovium of combination treated mice with a concomitant decrease in macrophage and ostoeclast infiltration. MRI analysis of the bone surface of the joints revealed augmented protection from damage (cortical bone roughness) that is observed in this model as a result of the ongoing tenosynovitis.

Conclusion: These data suggest that the enhanced activity of combined anti-Ang2 and anti-TNF-α treatment is due to a greater effect in decreasing vascularity in the synovium which results in decreased infiltrating inflammatory cells, as well as osteoclasts, leading to decreased bone damage in the joint.

Disclosure: B. Naiman, MedImmune, LLC, 3; **S. Turman**, MedImmune, LLC, 3; **W. Iverson**, MedImmune, LLC, 3; **R. Herbst**, MedImmune, LLC, 3; **T. Mustelin**, MedImmune, LLC, 3; **J. Connor**, MedImmune, LLC, 3.

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Porphyromonas Gingivalis **peptidylarginine Deiminase Exacerbates Collagen-Induced Arthritis In C57BL/6 mice.** Saba Alzabin[1], Anne-Marie Quirke[2], Elena B. Lugli[2], Muslima Choudhury[2], Peter J. Charles[2], Richard O. Williams[2] and Patrick Venables[2]. [1]Epistem Ltd., Manchester, United Kingdom, [2]Kennedy Institute of Rheumatology, Oxford, United Kingdom.

Background/Purpose: There is increasing molecular and epidemiological evidence linking *Porphyromonas gingivalis* to RA. *P. gingivalis* is unique amongst periodontal pathogens in possessing a citrullinating enzyme peptidylarginine deiminase (PPAD) with the potential to generate citrullinated antigens driving the autoimmune response in RA. To examine the effect of PPAD on collagen induced arthritis (CIA), we co-immunised C57BL/6 mice with PPAD and collagen and measured disease outcome by clinical scores, histology and antibody responses.

Methods: Male C57BL/6 animals (8–10 weeks, n=15/group) were immunised with 200ug type II collagen (cII) in CFA alone, or cII emulsified in 50ug PPAD or emulsified in 50ug of an enzymatically inactive PPAD mutant control (C531A) in CFA at the base of the tail. Mice were monitored daily for the first appearance of peripheral joint oedema. Clinical scores and paw swelling measurements were recorded daily and mice were culled after 10 days of disease onset. Their joints were fixed in 10% buffered formalin and decalcified with 10%EDTA for histological analysis, and serum was collected by terminal cardiac puncture for antibody titres. Antibodies to collagen, CCP2 and recombinant PPAD were measured by ELISA.

Results: Between days 5–10 post disease onset, PPAD immunised mice had a significantly increased clinical score of arthritis (mean = 6.83, p=0.0126) compared to cII alone immunised mice (mean= 3.40). There was a minor increase in the clinical scores when C351A immunised mice (mean=4.77) were compared to mice immunised with cII alone, but this did not reach statistical significance (p=0.290). This correlated with an increase in PPAD-specific antibodies ($p< 0.0001$) in PPAD immunised mice when compared to the mutant C531A or cII immunised mice. There was no increase in anti-collagen antibodies in the PPAD immunised mice and anti-CCP2 antibodies where negative in all 3 groups. Histological analysis showed that PPAD immunisation resulted in increased synovitis and joint erosion (p=0.021) when compared to cII controls.

Conclusion: PPAD immunisation exacerbated both clinical and histological parameters of CIA. There was no significant difference between the mice immunised with cII alone and the mice co-immunised with the enzymatically inactive mutant (C351A), supporting the hypothesis that enzymatic activity of PPAD is necessary to drive its arthritogenic effect. These data indicate a molecular mechanism that explains the link between periodontitis and RA and suggests potential therapeutic benefit by targeting PPAD.

Disclosure: S. Alzabin, None; **A. M. Quirke**, None; **E. B. Lugli**, None; **M. Choudhury**, None; **P. J. Charles**, None; **R. O. Williams**, None; **P. Venables**, None.

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Targeting Therapy Of Citrullinated Antigen-Specific B Cells Ameliorates Collagen-Induced Arthritis. Kazuya Michishita[1], Kimito Kawahata[1], Takeyuki Kanzaki[2], Lisa Akahira[1], Toshiki Eri[1] and Kazuhiko Yamamoto[1]. [1]Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [2]Yamanashi Prefectural Central Hospital, Yamanashi, Japan.

Background/Purpose: The clinical benefit of B-cell depletion therapy in rheumatoid arthritis(RA) is a well-known fact, but problems such as relapse of tuberculosis and reactivation of hepatitis B are reported. We thought that these problems were resolved by focusing on depletion of pathogenic antigen-specific B cells using a B cell epitope tetramer conjugated with immunotoxin. We treated collagen-induced arthritis (CIA) mice by the peptide-tetramer method.

Methods: Arthritis was induced by immunizing DBA/1J mice with Bovine Type II collagen. Toxin-conjugated peptide tetramers, which had the ability to deplete peptide-specific B cells, were intravenously administered to CIA mice. After first immunization (day0), tetramers were administrated in day10 and day20 and boost immunization was carried out in day 21. We used three kinds of peptides for preparing tetramers. One (CIA1), which has citrullinated arginine residue of C1 domain, is a major epitope of type II collagen. The second (CIAC) has non-citrullinated arginine residue of C1 domain. The third has the lysine residue-rich peptide (LKP) as a control. We conjugated immunotoxin to these peptide tetramers in order to deplete peptide-specific B cells. We chose saporin which was class I ribosome-inactivating proteins as a immunotoxin. Non-cytotoxic tetramer using CIA1, anti-CD20 antibody, the anti-CD79β antibody and PBS were also injected mice as a comparison. The incidence, arthritis score and antibodies to peptide were evaluated.

Results: In mice administered CIA1 tetramer, anti-CIA antibody completely dissapeared as compared with PBS group ($P = 0.01$) and the onset of arthritis was delayed. Because the antibody titers for U1 epitope of the type II collagen did not have the significant difference between CIA1 and PBS group, it was shown that we depleted the B cells which were an antigen-specific. In mice administered tetramers using CIAC or LKP, anti-CD20 antibody, antiCD79 antibody and non-cytotoxic tetramer using CIA1, the antibody titers for CIA1 have increased and the onset of the arthritis was delayed.

Conclusion: By the depletion of citrullinated antigen-specific B cells using a B cell-epitope tetramer, the onset of the arthritis was delayed. It was necessary for the tetramer to have the cytotoxicity and the citrullinated peptide in order to improve clinical and pathological score. Targeting of citrullinated antigen-specific B cells might be a new strategy of RA treatment.

Disclosure: K. Michishita, None; **K. Kawahata**, None; **T. Kanzaki**, None; **L. Akahira**, None; **T. Eri**, None; **K. Yamamoto**, None.

2235

Fas Signaling In Macrophages Promotes Chronicity In K/BxN Serum Transfer Induced Arthritis. Qi Quan Huang[1], Robert Birkett[2], Renee E. Koessler[1], Carla M. Cuda[3], J.-P. Jin[4], Harris R. Perlman[1] and Richard M. Pope[5]. [1]Northwestern University, Chicago, IL, [2]Northwestern University Medical School, Chicago, IL, [3]Northwestern University Feinberg School of Medicine, Chicago, IL, [4]Wayne State University, Detroit, MI, [5]Northwestern Univ Med School, Chicago, IL.

Background/Purpose: A non-apoptotic role for Fas signaling has been implicated in the regulation of inflammation and innate immunity. These studies were performed to elucidate the role of Fas signaling on macrophages in the development of arthritis.

Methods: K/BxN serum transfer arthritis was induced in a mouse line with Fas conditionally deleted in the myeloid lineage ($Fas^{f/f}$, $LyzM^{cre}$). The arthritis was assessed clinically and histologically. IL-1b, CXCL5, IL-10, IL-6 and gp96 expression was determined by ELISA. Bone marrow derived macrophages were activated by IL-1b and gp96. Cells were analyzed for phenotype and apoptosis by flow cytometry.

Results: The onset of arthritis in $Fas^{f/f}$, $LyzM^{cre}$ mice was comparable to that observed in control mice, however, resolution was accelerated during the chronic phase. The attenuated arthritis was associated with reduced articular expression of the endogenous TLR2 ligand gp96 and the neutrophil chemokine CXCL5, and the enhanced expression of IL-10. Activation with IL-1b or gp96 induced increased IL-10 in Fas deficient, compared with control, macrophages. IL-10 suppressed IL-1b plus gp96 induced IL-6 and CXCL5. IL-1b-mediated activation of ERK, which regulates IL-10 expression, was increased in Fas-deficient macrophages.

Conclusion: Together, our observations suggest that impaired Fas signaling results in the enhanced expression of anti-inflammatory IL-10 and reduced gp96, which are associated with accelerated resolution of inflammation in the chronic phase of arthritis. These observations suggest that strategies to reduce endogenous TLR ligands and increase IL-10 may be beneficial in patients with RA.

Disclosure: Q. Q. Huang, None; **R. Birkett**, None; **R. E. Koessler**, None; **C. M. Cuda**, None; **J. P. Jin**, None; **H. R. Perlman**, None; **R. M. Pope**, None.

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Articular Inflammation Is Protected By Fat-1 During The Acute Phase Of Arthritis In Mice. Sang-Il Lee[1], Yun-Hong Cheon[1], Ji-Min Kim[2] and Won Seok Lee[3]. [1]Gyeongsang National University School of Medicine, Jinju, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Keimyung University School of Medicine, Daegu, South Korea, [3]Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea.

Background/Purpose: Omega-3 polyunsaturated fatty acids (n-3 PUFA) are well known to exert anti-inflammatory effects. The Fat-1 transgenic (Fat-1 TG) mice are capable of producing n-3 PUFA from the n-6 type and are emerging as a new tool for studying the role of n-3 PUFA without the interference of the potential confounding factors of diet. Therefore, this study was carried out to evaluate whether Fat-1 over-expression attenuate arthritis severity in passive K/BxN murine arthritis.

Methods: K/BxN serum transfer arthritis was induced in Fat-1 TG and age-matched wild type (WT) mice. Arthritis severity was assessed by clinical and histopathologic scoring. The levels of inflammatory cytokines in the joints and serum were measured by quantitative PCR and ELISA. The effect of Fat-1 on osteoclastogenesis was assessed using bone marrow monocytes (BMMs) and cytokine expression was assessed using fibroblast-like synoviocytes (FLS) from Fat-1 TG or WT mice.

Results: In the K/BxN serum transfer model, Fat-1 TG mice had significantly less severe arthritis than WT until day 6. The clinical scores were: 3.3 ± 0.5 in Fat-1 TG and 5.7 ± 0.3 in WT; $p < 0.01$) and the ankle diameter were: 2.17 ± 0.03 mm in Fat-1 TG and 2.35 ± 0.03 mm in WT; $p < 0.01$). The ankle joints from Fat-1 TG mice showed significantly decreased inflammation and bone erosion than WT (scores $= 0.75 \pm 0.2$ and 2.21 ± 0.4, for Fat-1 TG and WT, respectively; $p < 0.05$). These effects were paralleled by decreased levels of IL-1β, IL-6, MCP-1, and MMP-3. The BMMs of Fat-1 TG mice resulted in reduced osteoclastogenesis than WT. TNF-α stimulated FLS of Fat-1 TG mice displayed lower NF-kB activity than WT, resulting in decreased transcriptional activation of proinflammatory target genes.

Conclusion: These results suggest that Fat-1 plays a critical regulatory role in the NF-kB pathway and the expression of target genes and controls articular inflammation during the acute phase of K/BxN serum transfer-induced arthritis.

Disclosure: S. I. Lee, None; **Y. H. Cheon**, None; **J. M. Kim**, None; **W. S. Lee**, None.

ACR/ARHP Poster Session C
Rheumatoid Arthritis - Clinical Aspects III: Outcome Measures, Socioeconomy, Screening, Biomarkers in Rheumatoid Arthritis
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

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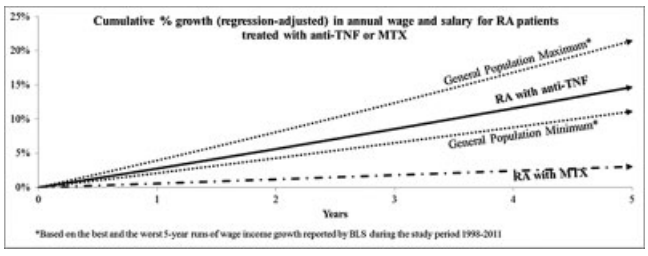
Assessment Of Wage and Salary Growth In Patients With Rheumatoid Arthritis (RA). Martin J. Bergman[1], Gourab De[2], Arijit Ganguli[3], James Signorovitch[4] and Yanjun Bao[5]. [1]Taylor Hospital, Ridley Park, PA, [2]Analysis Group, Inc., New York, NY, [3]AbbVie, Inc., North Chicago, IL, [4]Analysis Group, Inc., Boston, MA, [5]AbbVie Inc., North Chicago, IL.

Background/Purpose: RA negatively impacts patients' work outcomes. Treatment with tumor necrosis factor inhibitors (anti-TNFs) has been associated with improved work productivity and stability in RA. However, no studies have assessed the impact of anti-TNF treatment on changes in RA patients' income over time. Our study aims to compare growth of wage and salary income over time between employees with RA treated with anti-TNFs and those treated with methotrexate (MTX).

Methods: Adults with ≥ 1 RA diagnosis (ICD-9 CM: 714.0) were identified in a large-scale U.S. claims database (OptumInsight, 1998–2011). Patients were stratified into the following two groups: 1) those who filled ≥1 prescriptions for anti-TNFs, either with or without MTX (index date defined as the date of the first anti-TNF prescription) and (2) those who filled prescriptions for MTX monotherapy (index date randomly selected). During the 6-month baseline period preceding their index prescription, patients in both groups were required to have continuous health plan enrollment and to be free of anti-TNF prescriptions. The primary study outcome was annual wage or salary income (US dollars) observed from index year up to five years of follow-up (more than 90% of patients were lost to follow-up after five years). The effect of treatment on wage and salary income growth over time, starting from the same initial annual income, was assessed using a multivariable generalized linear model with adjustment for index year, age, region, gender, Charlson Comorbidity Index, health plan and total RA-related cost in the baseline period. Based on this regression model, income growth was compared to expected wage growth for the general population based on the best and worst 5-year runs of national wage data reported by Bureau of Labor Statistics during 1998–2011.

Results: The study included 1,866 patients in the MTX cohort and 1,848 patients in the anti-TNF cohort. At the index date, the MTX and anti-TNF cohorts had, respectively, average ages of 48.4 and 46.1 years, 64.8% and 62.0% females and average annual wage and salary income of $51,554 and $56,674. After adjusting for baseline characteristics, wage and salary incomes for patients in the anti-TNF cohort increased by 2.8% (CI: 1.9% – 3.6%) per year, significantly greater ($p<0.05$) than the 0.6% (CI: −0.2% – 1.4%) per year increase estimated for the MTX group. Based on this regression analysis, the average growth in wage and salary income for an RA patient treated with anti-TNF was consistent with that of the general population. In contrast, wage and salary growth for an RA patient treated with MTX was significantly lower than expected in the general population ($p<0.05$).



Conclusion: Compared to MTX monotherapy, anti-TNF treatment is associated with a greater rate of annual income growth among employees

with RA. In the anti-TNF group, income growth rate is comparable to the general employed population norm.

Disclosure: M. J. Bergman, AbbVie, 5; **G. De**, AbbVie, 5; **A. Ganguli**, AbbVie, Inc., 1, AbbVie, Inc., 3; **J. Signorovitch**, AbbVie, 5; **Y. Bao**, AbbVie, Inc., 1, AbbVie, Inc., 3.

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Comparison Of The Long-Term Outcome For Rheumatoid Arthritis Patients With persistent Moderate Disease Activity Or Disease Remission During The First Year After Diagnosis: Data From The Espoir Cohort. Bernard Combe[1], Isabelle Logeart[2], M. Belkacemi[3], S Dadoun[4], Jean-Pierre Daurès[5] and Maxime Dougados[6]. [1]Lapeyronie Hospital, Montpellier I university, Montpellier, France, [2]Pfizer, Paris, France, [3]CHRU Montpellier, Montpellier, France, [4]Paris-Pitié Salpêtrière University Hospital, Paris, France, [5]CHU, Nimes, France, [6]Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France.

Background/Purpose: The Treat to Target and EULAR recommendations highlighted the need for achieving and maintaining remission in patients with early RA. We investigated if early RA patients with persistent moderate disease activity during the first year have in daily life a worst 3 to 5 year outcome than patients who achieved clinical remission.

Methods: The ESPOIR cohort included 813 patients with early arthritis in at least 2 joints of less than 6 months disease duration. They were treated according to standard of care. Within the 573 patients who had a 5 year follow-up, 93 % fulfilled the ACR/EULAR criteria for RA. This study compared patients who were in persistent moderate disease activity (DAS28>3.2 and ≤ 5.1) at both month 6 and month 12 visits (group.1) versus those who were in sustained DAS28 remission at both M6 and M12 visits (group.2). The primary outcome measure was radiographic progression ((modified Total Sharp Score (mTSS)) at month 36. Secondary endpoints were clinical remission (DAS28, SDAI, ACR/EULAR), HAQ-DI, number of missed workdays at month 36 and 60. Fisher exact test was used to compare categorical variables and Kruskal-Wallis test for quantitative variables. Logistic regression analysis was performed to determine confounding factors of outcome.

Results: Baseline characteristics were not significantly different between groups. Patients with persistent moderate disease activity during the first year, had greater radiographic progression, higher HAQ disability and number of missed workdays and lower rate of remission at 3 to 5 years than those who achieved early sustained remission (table).

3-year Outcome variable	Group 1 n=107	Group 2 n=155
mTSS	**16.1±14.9****	**11.2±11.8**
r mTSS from day 0	**10.8±6.5~**	**6.5±8.9**
rmTSS >5 (%)	**56.0°**	**39.2**
DAS28 remission (%)	**27.4***	**81.0**
SDAI remission (%)	**13.8***	**56.0**
ACR/EULAR remission (%)	**10.3***	**50.4**
HAQ-DI	**0.68±0.61***	**0.21±0.38**
Missed workdays (n)	**157.3±226.2***	**30.9±75.9**
5-year outcome variable	**Group 1 n=107**	**Group 2 n=155**
DAS28 remission (%)	**39.2***	**80.7**
SDAI remission (%)	**24.0***	**59.6**
HAQ-DI<0.5	**51.6***	**80.7**
Missed workdays (n)	**272.2±338.9~**	**45.2±90.2**

Data are mean±SD unless indicated; Group2 vs group 1: * p<0.0001; ** p=0.019; ~p=0.006; °p=0.021
By logistic regression, anti-CCP antibodies, baseline ESR, age and moderate disease activity during the first year were significant independent risk factors of 3-year radiographic progression Persistent moderate disease activity during the first year was the most significant risk factor for not achieving clinical remission and for worst disability at 3 and 5 years

Conclusion: Early RA patients with persistent moderate disease activity during the first year showed worst outcome than patients who achieved sustained clinical remission. Persistent moderate disease activity affects long-term structure, remission rate and functional and work disability. Such patients may benefit from an intensive therapeutic strategy.

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2239

Validation Of a Patient Reported Experience Measure In Patients With Rheumatoid Arthritis. Marwan Bukhari[1], Peter Jones[2], Ifeanyi Sargeant[3], Maureen Cox[4], Alison Elliott[5], Suzanne Bullock[6], Anne O'Brien[2] and Ailsa Bosworth[7]. [1]Royal Lancaster Infirmary, Lancaster, United Kingdom, [2]Keele University, Keele, United Kingdom, [3]IS medical communications, Stafford, United Kingdom, [4]Nuffield Orthopaedic centre, Oxford, United Kingdom, [5]Roche Pharmaceuticals, Welwyn Garden City, United Kingdom, [6]Lancaster University, Lancaster, United Kingdom, [7]National Rheumatoid Arthritis Society, Maidenhead, United Kingdom.

Background/Purpose: Improving patient experience is important in all diseases, but most important in patients with chronic rheumatic diseases like rheumatoid arthritis. To date there have been no specific patient reported experience measures (PREMs) in rheumatology. A multi-disciplinary group, commisioning for quality in rheumatoid arthritis (CQRA) was established to develop the first PREM in RA, this group was supported under the terms of a joint working agreement with Roche Products Ltd. Firstly, a series of focus groups was held with patients from the UK National Rheumatoid Arthritis Society to determine which elements of the patient experience was deemed most important and this was mapped against UK Department of Health Patient Experience Framework. This framework comprises 8 domains. A questionnaire was developed using the same 8 domains, but with questions developed specifically relating to RA and Rheumatology Services and these were piloted across ten UK sites. The final question asked respondents to evaluate their overall level of care. All questions were graded from very satisfied to very unsatisfied on a five point scale.

Aim: To determine the construct validity of the PREM questionnaire developed by the CQRA group.

Methods: Cronbachs alpha was used to check internal consistency within groups of scores in each domain if it contained more than one question and whether it was reasonable to combine scores within groups into a numerical scale. Additionally for each question the percentage agreement with the overall assessment on the five point scale was calculated, in case of multiple questions per domain, the responses are shown as a range.

Results: 524 patients were included in the analysis, median age was 65 years (IQR 55,80 years). 377 (72%) were female. Median disease duration was 8 years (IQR 3.5, 15 years). The Cronbach alpha co-efficients within the multi-question domains and their percentage agreement with the question on overall care are shown in table1 below.

Table 1. Result of Cronbach's alpha analysis and their agreement with overall care

Domain	Number of questions	Alpha within domain	%Agreement with overall care
Needs and preferences	5	0.90	64.5–67.2
Co-ordination of care	4	0.87	59.1–69.1
Information about care	4	0.75	22.5–66.4
Daily living	2	0.61	33.2–53.4
Emotional support	2	0.84	53.5–68.9
Family and friends	1	–	61.8
Access to care	1	-	70.4

Conclusion: The PREM has good construct validity and is a valid tool for measuring RA patient experience. Some domains have higher agreement with overall patient experience. This could provide a useful future tool for measuring patient experience. Modification of the tool to use in other rheumatic conditions is underway.

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2240

Correlative Analysis Of Swollen Joints Between Clinical Examination and Musculoskeletal Ultrasound For Rheumatoid Arthritis. Kenta Misaki[1], Takashi Nakazawa[2], Shunichi Fujita[1], Hirotaka Yamada[1] and Toshihiko Yokota[1]. [1]Kurashiki Central Hospital, Kurashiki, Japan, [2]Osaka Saiseikai Nakatsu Hospital, Osaka, Japan.

Background/Purpose: The disease activity score 28 (DAS28), clinical disease activity index (CDAI) and simplified disease activity index (SDAI) are all used in the clinical assessment of rheumatoid arthritis (RA). A consensus concerning the appropriate assessment method of swollen joints

has yet to be reached and standardized grading criteria are yet to be created. For our study we selected handy rheumatoid activity score, with 38 joints (HRAS38) *(Mod Rheumatol (2006) 16:381–388)* due to the recent attention it has gathered and performed a correlative analysis between HRAS38 assessment and musculoskeletal ultrasound by semi-quantitative grading assessment (MSKUS) for the purpose of evaluation.

Methods: One hundred and eighty patients who satisfied either the 1987 American College of Rheumatology (ACR) or 2010 ACR/European League Against Rheumatism (EULAR) rheumatoid arthritis (RA) criteria were enrolled in this study (mean age: 62.8±14.4 years, mean DAS28-C-reactive protein (CRP): 3.06±1.43, female: 123 cases, male: 57 cases, respectively). Ten joints of the left hand (metacarpophalangeal [MCP] 1–5 joints, metaphalangeal (MP) 1 and proximal interphalangeal [PIP] 2–5 joints) were validated both with HRAS38 and MSKUS semi-quantitative grading. The 38 joints included in the evaluation were 26 joints of DAS28 except for bilateral shoulder joints, as well as 10 metatarsophalangeal (MTP) joints and the bilateral ankle joints. Each joint was scored as follows: 0 = none; 1 = mild (not convincing by observation and confirmed by palpation); 2 = moderate (convincing by observation, but not tense); 3 = severe (tense).

The MSKUS estimation was divided into gray scale (GS) (grade 0–3) and power Doppler examination (PD) (grade 0–3). The agreement between HRAS38 and MSKUS (GS and PD) was calculated using Cohen's Kappa values. The Kappa tests for Inter-Observer variation were as follows (MCP2 = 0.77, MCP3 = 0.82, MCP4 = 0.89, PIP2 = 0.75, PIP3 = 0.87, PIP4 = 0.88, PIP5 = 0.82).

Results: The median Kappa Value for GS examination was 0.221 and for PD examination was 0.268, respectively. Fair agreement was observed for GS of the PIP 4 (Kappa =0.505) and PD of the MCP 3 (Kappa=0.420), respectively. For the total patients who scored 0 for HRAS38, indicating no swollen joints, positive GS (GS≥a1) was observed in 25.6 % of patients (387 joints/1494 joints) and PD (PD≥a1) was observed in 13.7 % of patients (205 joints/1494 joints).

Conclusion: According to our correlative analysis, agreement was fair between HRAS38 and MSKUS. Furthermore, analysis suggested that MSKUS is more significant in the assessment of RA, with swollen joints which were not revealed according to HRAS 38 being revealed as active synovitis by MSKUS. The authors recommend that MSKUS is used as the principal method of RA assessment.

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2241

Assessing Significant Flares In Rheumatoid Arthritis: Validity Of The Outcome Measures In Rheumatology Preliminary Flare Questions In The Canadian Early Arthritis Cohort. Susan J. Bartlett[1], Clifton O. Bingham III[1], Ernest Choy[2], Juan Xiong[3], Gilles Boire[4], Boulos Haraoui[5], Janet E. Pope[6], J. Carter Thorne[7], Carol A. Hitchon[8], Diane Tin[7], Edward C. Keystone[9] and Vivian P. Bykerk[9]. [1]Johns Hopkins University, Baltimore, MD, [2]Cardiff University, Institute of Infection and Immunity, Cardiff, United Kingdom, [3]Mount Sinai Hospital, University of Toronto, Toronto, ON, [4]Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, [5]Centre Hospitalier de l'Université de Montréal, Montreal, QC, [6]St Joseph Health Care, London, ON, [7]Southlake Regional Health Centre, Newmarket, ON, [8]University of Manitoba, Winnipeg, MB, [9]Mount Sinai Hospital/University of Toronto, Toronto, ON.

Background/Purpose: Rheumatoid arthritis (RA) flares are common, poorly defined, and understudied. A tool is needed to measure significant RA flares that may signal need for evaluation for treatment change. Qualitative and quantitative research by the OMERACT RA Flare Group with patients and providers has identified an RA Flare Core Domain Set, ratified by OM 2012 attendees. Next, we identified preliminary flare questions (PFQs) to assess core domains. Here, we report evidence of discriminant validity of PFQs between patients who report flaring and those not in flare and convergent validity among PFQs and validated RA measures in a cohort of patients with early RA (ERA).

Methods: 1190 patients in the Canadian early ArThritis CoHort (CATCH) completed PFQs at visits from 11–2011 through 5–2013. Both patients and MDs independently rated if patient was in flare. Patients completed PFQs for pain, physical function (PF), fatigue, stiffness, participation and coping over 1 week prior to visit using 11-point scales, as well as HAQ, SF12, RADAI, WPAI and Patient Global. Wilcoxon rank sum and χ^2 were used to compare groups. Correlations (Spearman, polychoric, polyserial) were calculated between PFQs and relevant HAQ, SF12, WPAI, RADAI items and other scales.

Results: Participants were mostly female (74%), white (81%), and 55% had > high school education. Mean (SD) age was 53 (15) years and RA duration 6 (3) months. 33% of patients and 38% of MDs classified patient as being in flare; agreement for being in flare was 62% and not in flare 73% (kappa =.33; 95% CI.28-.39). Scores were significantly higher across all domains in patients reporting flare (Table). Correlations were strongest between PFQ pain and other pain scales (r's=.84-.88). Moderate-strong correlations were evident among PFQ with other measures of PF (r's=.63-.75), fatigue (r's=.52-.85), stiffness (r=.66), participation (r's=.60-.77) and coping (r's=.30-.55).

Comparison of OMERACT PFQ domain scores in patients reporting and not reporting being in RA flare (N=1190).

	Not in Flare	Flare	Significance
Reported RA as worse* in past week	43%	17%	<.001
OM PFQs†			
Pain	2.5 + 2.5	6.0 + 2.6	<.0001
Physical Function	2.2 + 2.5	5.5 + 3.0	<.0001
Fatigue	2.7 + 2.8	5.3 + 3.1	<.0001
Stiffness	2.4 + 2.5	5.6 + 2.9	<.0001
Participation	2.0 + 2.5	5.1 + 3.1	<.0001
Coping	1.8 + 2.3	4.3 + 2.8	<.0001

†Higher scores reflect great impairment; *slightly worse, worse or much worse.

Conclusion: In ERA patients who report being in flare, PFQ scores were significantly higher across all domains. There was substantial agreement among single item PFQs and other validated RA measures. Results provide evidence of the validity of OMERACT PFQs to assess flares in RA patients. Additional psychometric evaluation is needed to establish the reliability, validity, and responsiveness of items and relevant thresholds across a range of RA populations and settings prior to widespread use.

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2242

Patient Versus Physician Joint Counts In Rheumatoid Arthritis Utilizing a Unique Self-Joint Examination Tool. Daisy Bang[1], Yomei Shaw[2], Christine L. Amity[3], Kelly A. Reckley[4], Ilinca D. Metes[1] and Marc C. Levesque[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, [3]Univ of Pittsburgh, Pittsburgh, PA, [4]University of Pittsburgh School of Medicine, Pittsburgh, PA.

Background/Purpose: The quantitative assessment of disease activity has been endorsed by the American College of Rheumatology (ACR) to improve rheumatoid arthritis (RA) outcomes. To facilitate more quantitative assessments of disease activity, we created a unique self-joint examination tool and compared patient and physician joint assessments in RA subjects using this tool.

Methods: Subjects were part of the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry. Subjects performed a self-joint count on a computer tablet utilizing line-drawings of human figures incorporating both audio and written instructions on assessment of 28 joints (bilateral shoulders, elbows, wrists, knees, and first through fifth PIP and MCP joints) for tenderness and swelling. Physicians performed independent joint counts at each visit and serum C-reactive protein (CRP) concentrations were measured. Comparisons between patient and physician individual and total swollen and tender joint counts and between patient and physician DAS28-CRP scores were made using t tests and Cohen's kappa statistic.

Results: There were 516 paired patient and physician joint counts for RA subjects completing the self-joint exam for the first time. CRP was measured in 364 patients. Patient vs. physician total swollen (mean ± SD, 5.94 ± 7.28 vs. 2.40 ± 3.96; p<0.0001) joint counts were significantly higher. Mean patient vs. physician DAS28-CRP scores were also significantly higher (mean ± SD, 3.49 ± 1.50 vs. 3.02 ± 1.25; p<0.0001). Cohen's kappa statistic of interrater reliability between patients and physicians for individual tender joint counts ranged from 0.10 to 0.39; for swollen joints it ranged from 0.12 to 0.36. Interrater reliability was greatest for the knees, wrists and the second and third MCP joints. DAS28-CRP scores calculated from the patient and physician joint counts were used to categorize patients into remission,

low, moderate or high disease activity. Cohen's kappa for patient versus physician categorization into remission/low disease activity or moderate/high disease activity based on DAS28-CRP scores was 0.60. In 291 cases (88%), the categorizations agreed. In 73 cases (18%), the categorizations differed. In 52 (13%) of the discrepant cases, the patient's joint count indicated moderate/high disease activity while the physician's did not; in 21 (5%) of the discrepant cases the reverse was noted.

Conclusion: On average, patients reported significantly higher tender and swollen joint counts with greater differences in tender joint counts between patients and physicians. The difference in joint counts resulted in significantly higher DAS28-CRP scores and higher DAS28-CRP disease activity categorization in some cases with discrepancies large enough to potentially alter treatment decisions. These findings suggest that despite the use of a self-joint count tool that incorporates training, mannequin-formats, and a computer tablet interface, patient and physician joint counts still differ. Analysis of the factors that characterize discordant patient-physician pairs will help to inform next steps.

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2243

How Well Do The Three Generic Patient Reported Outcomes Measurement Information System Fatigue Instruments Perform In Rheumatoid Arthritis? Susan J. Bartlett, Ana-Maria Orbai, Trisha Duncan and Clifton O. Bingham III. Johns Hopkins University, Baltimore, MD.

Background/Purpose: NIH Patient-Reported Outcomes Measurement Information System (PROMIS) has created highly precise and efficient instruments to measure patient-reported outcomes across health domains relevant to chronic medical conditions. PROMIS is available without charge, and many domains offer item banks for computer adaptive testing (CAT) through Assessment Center, a secure online management tool, in addition to paper-based short forms (SF) and single domain items that form the Global Health measure. **PROMIS Fatigue item bank** assesses both the experience of fatigue from mild tiredness to an overwhelming, debilitating, and sustained sense of exhaustion as well as impact on physical, mental and social activities. However, the feasibility, validity and psychometric performance of the three PROMIS measures has not been reported in persons with rheumatoid arthritis (RA) where fatigue is highly prevalent and disabling.

Methods: Data are from the baseline visit of the first 125 RA patients enrolled in an ongoing study integrating PROs into routine care at an academic RA clinic. Three PROMIS fatigue measures (CAT [average 5–8 items], 7-item SF and Global Health single item of fatigue) were administered in random order along with other legacy measures immediately before a routine clinic visit. Spearman correlations were used to evaluate convergent validity.

Results: Participants were mostly female (79%) and white (86%) with a mean (SD) age of 56 (13) and RA duration of 12 (9) yr; 10% were diagnosed ≤ 2 yr. In general, PROMIS fatigue measures correlated highly with VAS of fatigue, pain and patient global, moderately with mHAQ, morning stiffness, CDAI and MD global and weakly with joint counts (see Table). A dose response relationship across CDAI levels was evident in all measures.

	Fatigue VAS	PROMIS CAT	PROMIS Short Form	Fatigue Item*
Mean (SEM)	**39.9 (2.8)**	**54.3 (0.9)**	**53.6 (0.8)**	**2.6 (0.1)**
Median (IQR)	35.0 [61]	53.5 [15]	53.7 [13]	3 [1]
Range	0–97	26.3–76.0	29.4–71.1	1–5
Floor/Ceiling	11%/1%	2%/1%	1%/0%	12%/3.2%
Correlations†				
Fatigue VAS	–	.856	.787	.812
Pain VAS	.749	.677	.596	.591
Patient Global	.779	.707	.661	.604
MHAQ	.496	.497	.563	.497
AM Stiff (min)	.430	.320	.323	.339
CDAI	.641	.620	.558	.557
MD Global	.436	.408	.398	.383
Swollen Joint (28)	.220	.247	.146 (NS)	.195
Tender Joints (28)	.337	.398	.366	.372
Health Rating	−.586	−.541	−.636	−.547
CDAI (Mean SD)				
Remission	12.7 (17.2)[a]	46.1 (8.5)[a]	47.4 (7.5)[a]	1.9 (0.7)[a]
Low	45.3 (29.0)[b]	55.6 (8.8)[b]	54.8 (9.2)[b]	2.7 (0.9)[b]
Moderate	57.5 (27.9)[c**]	59.5 (6.9)[c*]	58.0 (5.0)[b,c]	3.0 (0.7)[b,c]
High	64.3 (21.4)[c]	62.3 (9.4)[c]	58.8 (7.3)[c]	3.4 (0.9)[c]

*From Global Health SF. †Different superscripts reflect significantly different values ($p<.05$); **$p<.06$.

Conclusion: Our study contributes preliminary evidence of the feasibility of the 3 PROMIS fatigue instruments as part of routine RA visits and of construct validity with legacy measures and clinical indicators. All PROMIS fatigue measures correlated highly with the fatigue VAS; while the Fatigue CAT was most strongly associated with legacy measures and offers greater precision, the 7-item short form and single Fatigue item also performed adequately and are useful when paper-based or briefer versions are needed. PROMIS scores can be compared against population norms. Further evaluation of responsiveness and validity across diverse groups of patients and settings is warranted.

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2244

Diagnostic Accuracy Of Anti-Ccp Testing For Detecting Prevalent Rheumatoid Arthritis: Results From Screening a Population Based Cohort. Aase Haj Hensvold[1], Patrik KE Magnusson[2], Lena Israelsson[3], Monika Hansson[4], Vijay Joshua[3], Rikard Holmdahl[5], Per-Johan Jakobsson[3], Johan Askling[5], Vivianne Malmström[6], Lars Klareskog[3] and Anca I Catrina[3]. [1]Rheumatology unit, Karolinska University Hospital, Karolinska Institut, Stockholm, Sweden, [2]Swedish Twin Registry Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [4]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [5]Karolinska Institutet, Stockholm, Sweden, [6]Rheumatology unit, Karolinska University Hospital, Karolinska Institutet, STockholm, Sweden, Stockholm, Sweden.

Background/Purpose: Anti-CCP testing is a part of the clinical routine investigations for rheumatoid arthritis (RA). Previous studies have relative few included controls per patients. We therefor aimed to screen a large population-based cohort and investigate the diagnostic accuracy of testing anti-CCP, in high concentration, and testing of other ACPAs, for detecting RA.

Methods: We used a subset of the Swedish twin registry, which includes 12 590 monozygotic and dizygotic twins born 1958 or earlier (median age 65, range 48–93). Cases of RA were identified by linkage to the Swedish National Patient Register and by this way we defined clinical RA as the reference standard when analyzing the diagnostic accuracy. Blood samples were analyzed for Anti-CCP2 using Immunscan CCPlus (Eurodiagnostica). Cut off set by the manufacture were used to define positive (≥cut off), and high positive (>3x cut off) CCP was defined in accordance to EULAR criteria for RA. All Anti-CCP positive samples were further investigated by ELISA for the presence of antibodies against autoantigen-derived citrullinated peptides (alpha-enolase: aa5–21; collagen type II: aa359–369; fibrinogen: aa563–583 and vimentin: aa60–75). Sensitivity and specificity as well as the positive (PPV) and negative (NPV) predictive values of Anti-CCP testing for detecting prevalent RA were estimated.

Results: 350 out of 12 590 tested individuals (2.8%) were positive for Anti-CCP. 1.5% (192/12590) had prevalent RA with in median 5 years from first occurring RA diagnosis in register to blood donation. Of these RA cases, 65% (124/192) were positive for Anti-CCP and a majority had high concentrations (93%). The rest of those positive for Anti-CCP were without RA diagnosis and fewer had high positive anti-CCP (39%).

The sensitivity and specificity for high positive Anti-CCP testing were 60% (95% CI: 53–67%) and 99% (95% CI: 99%), respectively. Both high positive Anti-CCP and Anti-CCP had a good predictive value for detecting RA (PPV 57%, 95% CI 50–64% for high positive Anti-CCP and 35%, 95% CI 30–40% for Anti-CCP) and a negative predictive values close to 100%.

Anti-CEP1 antibodies were the most common ACPA among Anti-CCP positive RA patients and Anti-CCP positive without RA. There was a correlation between anti-ccp concentration and occurrence other ACPAs (Spearman Correlation Coefficient $r= 0.75$ $p <0.0001$). In accordance we found 52% sensitivity for positive anti-CCP2 test and ≥1 other ACPA test positive and 99% specificity, PPV was 56% and the NPV was 99%

Conclusion: Anti-CCP testing has a good diagnostic accuracy for RA in a large population based cohort. Anti-CCP in high concentration is correlated with presence of other ACPAs in population based cohort. A follow up study to identify new incident cases of RA among tested individuals will allow more accurate estimates in the future.

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2245

Predictive Validity Of Low Disease Activity Using Patient Reported Measures On Long-Term Outcomes In Early Rheumatoid Arthritis-Results From Study Of New Onset Rheumatoid Arthritis and Ontario Best Practices Initiative. Pooneh Akhavan[1], Binu Jacob[2], Paul R. Fortin[3], George A. Tomlinson[4] and Claire Bombardier[5]. [1]Mount Sinai Hospital/ University of Toronto, Toronto, ON, [2]University of Toronto, Toronto, ON, [3]University of Laval, Quebec, QC, [4]Toronto General Hospital, Toronto, ON, [5]University Health Network, Toronto, ON.

Background/Purpose: Patient reported outcome measures (PROM) are used in routine practice for assessment of disease activity. They have been shown to correlate well with other composite measures. Current guidelines suggest remission or low disease activity (LDA) as the target of therapy in rheumatoid arthritis (RA). Our objective was to assess the predictive validity of early LDA defined by PROMs on future joint damage and disability in patients with early RA.

Methods: We studied patients included in the Study of New Onset Rheumatoid Arthritis (SONORA), a multicenter early RA cohort and Ontario Best Practices Research Initiative (OBRI), a current clinical registry of RA patients followed in routine care. Patients with symptom duration ≤ 12 months at enrollment were included. In SONORA analysis, the main predictors were LDA (RADAI<2.2) at 4mo and 12 mo. Multivariate linear regression analysis was used for assessment of LDA predicting HAQ at 3 years and mutivariate logistic regression models were used for assessment of the impact of LDA on x-ray progression over 2 years adjusting for potential confounders. In OBRI analysis, the predictive validity of LDA at6 months (RADAI<2.2 and RAPID3<2) on HAQ at 2 years was estimated using multiple linear regression analysis..

Results: There were 984 early RA patients in SONORA. Baseline (BSL) mean(sd) HAQ was 1.0 (0.7) that improved to 0.7 (0.7) at 3 years. At 2 years, 116(17%) patients developed radiographic progression. At 4 mo 25% achieved LDA and it increased to 37% at 1 year. LDA at both 4mo and 1 year was a significant predictor of lower future HAQ (p<0.0001). LDA at 4 mo was associated with less radiographic progression (OR, 95% CI: 0.49, 0.25–0.95, p=0.03) in complete cases. Other significant factors associated with higher HAQ included higher BSL HAQ, older age and female sex and factors associated with future joint damage were BSL damage and positive RF and anti-CCP. There were 118 patients from the OBRI cohort who had at least 2-year follow-up with available outcome. At BSL 13(11%) were in LDA defined by RADAI that improved to 43(36%) at 6 mo. Mean (sd) HAQ 1.31 (0.8) at BSL improved to 0.78 (0.7) at 2 years. Based on RAPID3, 11% were determined to be in LDA at BSL which increased to 22 (22%) at 6 mo. LDA at 6 mo, defined by either PROM, was significantly associated with lower HAQ at 2 years (p=0.03 for RADAI, p=0.05 for RAPID3 criteria). Other significant factors associated with higher HAQ included older age, BSL HAQ and gender (female).

Conclusion: Achieving LDA as early as 4–6 months is associated with improved long-term outcomes in early RA. Disease status using PROMs seems to have significant predictive validity for future outcomes.

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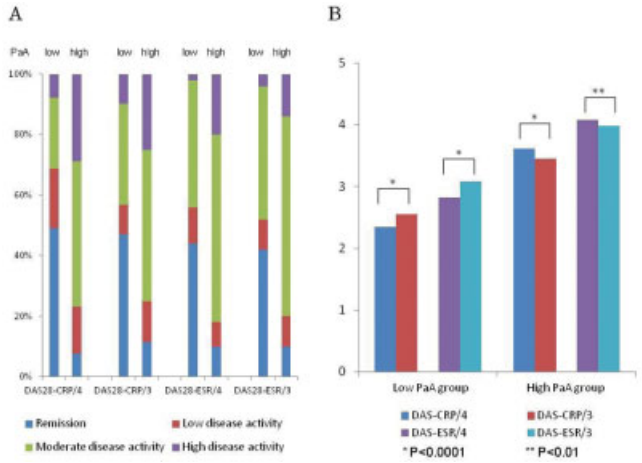
2246

Patients' Assessment of the Disease Greatly Influences the Determination of Disease Activity and Remission in Rheumatoid Arthritis. Kenrin Shi[1], Kenji Miki[2], Masao Yukioka[2], Kosuke Ebina[1], Shoichi Kaneshiro[1] and Hideki Yoshikawa[1]. [1]Osaka University Graduate School of Medicine, Suita, Japan, [2]Yukioka Hospital, Osaka, Japan.

Background/Purpose: Recently defined remission criteria of rheumatoid arthritis (RA), Boolean criteria or Simplified Disease Activity Index (SDAI) <3.3, requires considerably low rating not only of physicians' assessment (PhA) but also of patients' assessment (PaA) of the disease. However, it is very often that remission cannot be achieved or maintained because PaA does not fulfill the requisite. Also, PhA and PaA often differ largely from each other, and it has been reported that patients tend to assess the state of disease mostly by pain.

Methods: One hundred and four patients with RA were studied. Tender joint counts (TJC), swelling joint counts (SJC), and PaA as well as PhA by 100mm of Visual Analogue Scale were clinically evaluated. After the patients were divided into two groups according to PaA, either lower or higher than the median value, the two groups were compared in terms of age, duration, functional status, history of joint surgeries, comorbidities, prescribed medications, and laboratory data such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and matrix metalloproteinase-3. Other clinical data as well as disease activity were also compared by SDAI and four types of Disease Activity Score 28 (DAS28) formula; either including CRP or ESR, with or without PaA. Moreover, the correlation between PaA and PhA was examined, and clinical and functional remission was evaluated by Boolean criteria and Modified Health Assessment Questionnaire <0.5, respectively.

Results: The average and median value of PaA was 23.9mm and 17.5mm, respectively. In high PaA group (>17.5mm), functional status was significantly poorer (Steinbrocker Class III and IV, 23% vs 7.7%) and comorbidities were significantly more (32.7% vs 13.5%), whereas age, duration, history of joint surgeries showed no differences. Prescription of non-steroidal anti-inflammatory drugs and corticosteroid was significantly more often in high PaA group (67.3% vs 36.5% and 63.5% vs 28.8%, respectively), but there was no difference in that of methotrexate and biologics. TJC, SJC and PhA were significantly more in high PaA group (5.0 vs 2.4, 3.1 vs 1.3 and 30.4mm vs 16.2mm, respectively), whereas all laboratory data studied exhibited no differences. PaA and PhA significantly correlated with each other (r=0.57). All indices of disease activity were significantly higher in high PaA group (DAS28, Figure-A), among which DAS28, either including CRP or ESR, was significantly higher in low PaA group whereas lower in high PaA group, when PaA was excluded from the formula (Figure-B). Both Boolean and functional remission rate were significantly low in high PaA group (0% vs 35.3% and 55.6% vs 80%, respectively), but 19.2% of the patients in high PaA group would have achieved Boolean remission only if PaA had fulfilled the requisite.



Conclusion: Since PaA greatly influences the determination of disease activity as well as remission, it is very important to properly control the pain in RA.

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2247

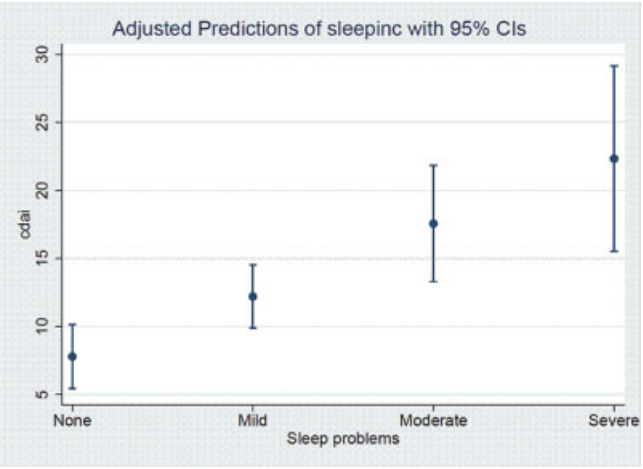
Response To a Sleep Query On The Multi-Dimensional Health Assessment Questionnaire (MDHAQ) Is Related To Levels Of Disease Activity. Martin J. Bergman[1], Sapna Sangani[2], Isabel Castrejón[3] and Theodore Pincus[3]. [1]Taylor Hospital, Ridley Park, PA, [2]Mercy Catholic Medical Center, Lansdowne, PA, [3]NYU Hospital for Joint Diseases and New York University School of Medicine, New York, NY.

Background/Purpose: Patients with rheumatoid arthritis (RA) often report fatigue, but a possible impact of disease on sleep and/or on disease activity are poorly characterized. We examined possible relationships between sleep and disease activity.

Methods: All patients with any diagnosis complete an MDHAQ at each visit to a single rheumatology practice. The MDHAQ includes sections regarding function, pain, patient global estimate, a patient self-reported joint

count, fatigue, exercise, AM stiffness and a brief psychological profile. The MDHAQ includes 3 "psychological profile" queries including "Over the past week, were you able to get a good night's sleep?" ("sleep"). The responses are 0–3 (without difficulty=0, with some difficulty=1, with much difficulty=2, unable to do=3). Each patient with RA also is assessed with an ESR and CRP, 28 tender and swollen joint counts, and a physician global estimate (0–10). From these values, multiple composite indices are calculated, including the DAS28(ESR), CDAI, SDAI and RAPID3. Patients are then characterized into disease activity categories ("remission", "low disease activity", "moderate disease activity", "high disease activity"), according to established criteria. Using a random visit for each patient, linear regression models were determined using the composite score value as the dependent variable, and "sleep" as the independent variable, to determine possible interactions between "sleep"score and disease activity scores. All statistical analyses were performed using Stata v12.

Results: 200 patients with RA had completed responses to "sleep". The median value for "sleep"=1 (with some difficulty). A patient with sleep=0 has a 95% chance of being in low CDAI, whereas a patient with sleep=1 has a 95% chance of not being in low CDAI. A "linear" worsening of CDAI was seen with each increment of "sleep" (fig.1). Similar findings were also seen in comparisons of sleep scores with DAS28, SDAI and RAPID3. (data not shown) Even if the patient global score is excluded from this calculation-("mdai"), a similar "linear" result is seen.



Conclusion: The response to a single question regarding having a good night sleep, explains variation in disease activity according to CDAI in patients with RA. Patients who report significant sleep disturbances are unlikely to be in a low disease state, whereas patients with no sleep disturbances are highly likely to be in a low disease state.

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2248

Difference Between The Two Versions Of Disease Activity Score Based On C-Reactive Protein and Erythrocyte Sedimentation Rate. Pinar Cetin[1], Dilek Solmaz[1], Hacer Gulluoglu[2], Ismail Sari[1], Merih Birlik[3], Servet Akar[1], Fatos Onen[1] and Nurullah Akkoc[1]. [1]Dokuz Eylul University School of Medicine, Izmir, Turkey, [2]Dokuz Eylul University School of Medicine, Yzmir, Turkey, [3]Dokuz Eylul University School of Medicine, izmir, Turkey.

Background/Purpose: In some countries reimbursement criteria require a DAS28 score of >5.1 for initiating anti-TNF therapy in patients with rheumatoid arthritis. DAS28 score can be calculated based on C-reactive protein (CRP) levels (DAS28-CRP) or erythrocyte sedimentation rate (DAS28-ESR). The results of a recent mini-survey suggest that Turkish rheumatologists use DAS28-CRP more frequent. The aim of this study was to assess the agreement between the ESR and CRP based DAS28 scores in Turkish patients with RA.

Methods: 84 RA patients from one center with full data for both DAS28-ESR and DAS28-CRP were identified in our biological therapy database (TURKBIO). We compared their DAS28-CRP and DAS-ESR scores obtained from baseline and following visits. Mean DAS28-ESR and DAS28-CRP values were compared by Spearman correlation and linear regression analysis. Bland-Altman analysis and kappa statistics were used to assess the agreement between the two DAS definitions in the whole group as well as in different gender and age groups.

Results: Of the 84 patients 71 were females (85%) with a mean age (±SD) of 52.5 (± 14.2). Disease duration was 10.5 years (±6.2) RF and CCP positivity was 58 % and 63%. DAS28-CRP and DAS28-ESR scores were available for 364visits. Mean DAS28-CRP and DAS-ESR values were 3.3 (±1.4) and 4.0 (±1.4)showing a strong correlation with each other [(Spearman correlation coefficient: 0.947, $p<0.001$) and linear regression analysis ($R^2=0.909$, $p<0.001$)]. The agreement between the two DAS versions was good for both genders and all age groups with weighted kappa values ranging from 0.695 to 0.809 The number of visits with high disease activity based on DAS28-ESR was greater than that based on DAS28-CRP ($p=0.08$). 47 (49%) visits with moderate disease activity according to DAS28-CRP were classified as high according to DAS28-ESR (Table1). Bland-Altman plot analysis showed a mean difference (95% CI) of 0.69 (0.63 – 0.75) between the two methods (DAS28-ESR – DAS28-CRP), which was quite consistent in different gender and age categories (Table 2).

Table 1. Agreement between DAS28-ESR and DAS28-CRP on the classification of the patient visits into different categories of disease activity

		DAS 28 ESR			
		≤3.2	3.21–5.10	≥5.11	Total
DAS 28 CRP	≤3.2	128	64	0	192
	3.21–5.10	0	74	47	121
	≥5.11	0	2	49	51
	Total	128	140	96	364

Table 2. Summary of Bland-Altman plot data for comparison of DAS-ESR and DAS-CRP in different gender and age categories

Patients (# of patients, # of visits)	Mean difference (95% CI)	Lower Limit (95% CI)	Upper Limit (95% CI)
Females (n=71, n=308)	0.735 (0.688–0.783)	0.097 (0.179–0.015)	1.569 (1.487–1.651)
Males (n=13, n=56)	0.471 (0.357–0.589)	0.377 (0.576–0.177)	1.324 (1.124–1.524)
≤40 years old (n=17, n=65)	0.481 (0.377–0.588)	0.369 (0.533–0.184)	1.331 (1.147–1.516)
41–60 years old (n=42, n=182)	0.791 (0.667–0.795)	0.094 (0.200–0.011)	1.553 (1.447–1.659)
≥61 years old (n=25, n=117)	0.761 (0.683–0.840)	0.080 (0.215–0.054)	1.603 (1.468–1.738)
Overall (n= 84, n=364)	0.695 (0.650–0.740)	0.160 (0.237–0.083)	1.551 (1.473–1.628)

Conclusion: The results suggest that DAS28-CRP may underestimate disease activity in RA patients, as compared to DAS28-ESR for both genders and different age groups. A significant proportion of patients, who would not qualify for reimbursement of anti-TNF therapy according to DAS28-CRP would be classified as having high disease activity according to DAS28-ESR.

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2249

What Proportion Of Patients With Rheumatoid Arthritis Fail To Achieve Remission Based On The Patient Global? An Analysis From The Prospective, Observational Biologic Treatment Registry Across Canada. Andrew Chow[1], Philip Baer[2], William G. Bensen[3], Isabelle Fortin[4], Majed M. Khraishi[5], Dalton E. Sholter[6], May Shawi[7], Allen J. Lehman[7], Susan M. Otawa[7], Emmanouil Rampakakis[8] and John S. Sampalis[8]. [1]Credit Valley Rheumatology, Mississauga, ON, [2]Rheumatology, Scarborough, ON, [3]St. Joseph's Hospital and McMaster University, Hamilton, ON, [4]Centre de Rhumatologie de l'Est du Québec, Rimouski, QC, [5]MD, Memorial University of Newfoundland, Nexus Clinical Research, St Johns, NF, [6]Rheumatology Associates, Edmonton, AB, [7]Janssen Canada Inc, Toronto, ON, [8]McGill University, Montreal, QC.

Background/Purpose: According to the latest ACR/EULAR guidelines, Boolean remission in RA is defined as achievement of patient global assessment (PtGA) ≤1, 28-swollen joint count (SJC) ≤1, 28-tender joint count (TJC) ≤1, and C-reactive protein (CRP) ≤1 mg/dL. Recently, PtGA has been criticized for not accurately assessing RA disease activity, as it may reflect aspects not directly related to RA disease activity such as fibromyalgia, low back pain, depression or other conditions. The aim of this analysis was to assess the proportion of patients failing to achieve remission based on PtGA in a real-world, routine clinical care setting in Canada.

Methods: Biologic Treatment Registry Across Canada (BioTRAC) is an ongoing, prospective registry of patients initiating treatment for RA, AS, or PsA with infliximab or golimumab as first biologics or after having been treated with a biologic for less than six months. In this analysis, data from RA patients who were treated with infliximab between January 2002 and June 2011 were used. Correlation of PtGA with other clinical outcome measures was assessed with general linear models.

Results: Eight hundred and thirty-eight RA patients who had 4,582 assessments were included in the analysis. Mean (SD) age was 55.6 (13.5) years and mean (SD) duration since diagnosis was 10.5 (19.8) years. A total of 2,015 instances of non-remission were identified, of which 620 (30.8%) were near-remission cases. Near-remission is defined as attainment of three of the four Boolean criteria (CRP, SJC, TJC and PtGA). Among these, PtGA was the most common reason of non-remission (54.0%), followed by 28-tender joint count (TJC28; 27.7%), C-reactive protein (CRP; 10.0%), and 28-swollen joint count (SJC28; 8.2%). General linear models using PtGA as the dependent variable showed a statistically significant ($P<0.001$) positive association with HAQ-DI (mean (95%CI) estimate = 2.57 (2.47, 2.67), TJC28 (0.21 (0.20, 0.22), SJC28 (0.24 (0.23, 0.26)), physician global assessment (0.67 (0.64, 0.70), and pain (0.940 (0.93, 0.95).

Conclusion: The results of this analysis have shown that PtGA is the most common limiting factor in achieving Boolean ACR/EULAR remission, accounting for as many as 54% of the near-remission cases. However, a positive association was observed between PtGA and clinical outcomes, functional activity, and pain. Further analyses are required to identify the determinants of patient global assessment.

Disclosure: A. Chow, JNJ, Amgen, Pfizer, Abbvie, UCB, Eli Lilly, Celgene, Takeda, Astra Zeneca, BMS, Roche, 5; **P. Baer**, Janssen Pharmaceutica Product, L.P., 5; **W. G. Bensen**, None; **I. Fortin**, None; **M. M. Khraishi**, Hoffman-La Roche Canada, Amgen and Pfizer Canada, and Abbott Canada., 2; **D. E. Sholter**, None; **M. Shawi**, Janssen Canada, 3; **A. J. Lehman**, Janssen Canada, 3; **S. M. Otawa**, Janssen Canada, 3; **E. Rampakakis**, None; **J. S. Sampalis**, None.

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What Is The Real World Relationship Between Patient-Reported Pain Or Patient Global Assessment and Disease Activity Indices In Rheumatoid Arthritis? An Analysis From The Prospective, Observational, Biologic Treatment Registry Across Canada.

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Background/Purpose: Patient-reported outcomes such as pain and patient global assessment of disease activity (PtGA) have been critiqued for not accurately assessing rheumatoid arthritis (RA) disease activity as they may reflect aspects not directly related to RA disease activity (e.g. fibromyalgia, low back pain, depression, etc.) or related to non-RA conditions. The aim of this analysis is to describe the relationship between patient-reported pain and disease activity levels, as measured with DAS28-ESR, CDAI, and SDAI, in a real-world, routine clinical care setting. An additional aim is to assess the occurrence of non-remission driven solely by pain using PtGA as a proxy for pain.

Methods: Biologic Treatment Registry Across Canada (BioTRAC) is an ongoing, Canadian prospective registry of rheumatology patients initiating treatment with infliximab or golimumab. In this analysis, data from RA patients who were treated with infliximab between January 2002 and June 2011 were used. Correlation of pain (VAS mm) with DAS28-ESR, CDAI and SDAI in a continuous or binary (low disease activity: yes vs. no; remission: yes vs. no) scale was assessed with linear regression and logistic regression, respectively. For the assessment of non-remission due to PtGA, DAS28-ESR, CDAI, and SDAI remission rates were compared to "non-PtGA" remission rates, calculated by subtracting the relative contribution of PtGA to the index.

Results: Eight hundred thirty eight RA patients who had 4,582 assessments were included in the analysis. A significant ($P<0.001$) positive linear relationship was found between pain and DAS28-ESR (standardized coefficient (β) = 0.662), CDAI (β = 0.660), and SDAI (β = 0.659). Increased pain was associated with reduced odds of achieving remission or low disease activity as defined by DAS28-ESR, CDAI, and SDAI (Table 1). Correlation analysis showed that a strong positive linear correlation existed between pain and PtGA (r = 0.914), supporting the use of PtGA as a proxy for pain. Cross-tabulation of remission achievement with "non-PtGA" remission achievement revealed that omission of PtGA from the DAS28-ESR, CDAI, and SDAI indices would result in the re-classification of an additional 2.0%, 9.3%, and 9.6% of the cases as remission.

Table 1. Relationship Between Pain (VAS mm) and Low Disease Activity or Remission

Disease Activity	Threshold	OR	95% CI	P-Value
Low Disease Activity	DAS28-ESR	0.950	0.946, 0.954	<0.001
	CDAI	0.943	0.940, 0.947	<0.001
	SDAI	0.940	0.936, 0.944	<0.001
Remission	DAS28-ESR	0.946	0.941, 0.951	<0.001
	CDAI	0.890	0.880, 0.901	<0.001
	SDAI	0.892	0.881, 0.904	<0.001

Conclusion: The results of this analysis show that increased pain is associated with higher disease activity as measured by the DAS28-ESR, CDAI and SDAI, which may be due to the strong correlation of pain with PtGA. Omission of PtGA from these disease activity indices resulted in the classification of additional cases as remission cases to an extent that paralleled the strictness of the remission criteria (i.e., from the less "strict" DAS28-ESR index to the more "strict" SDAI). Therefore, the CDAI and SDAI might be more sensitive to pain not directly related to RA.

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2251

Variability in the Classification of Remission Among Disease Activity Indices and Their Correlation: An Analysis From a Prospective, Observational Registry.

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Background/Purpose: In recent years, disease remission in rheumatoid arthritis (RA) has been assessed using various disease activity indices such as the DAS28-CRP, SDAI, CDAI, ACR/EULAR-recommended Boolean definition and the Patient Activity Scale (PAS).

The aim of this analysis is to describe the agreement between these five indices in classifying remission as well as to assess their correlation in a routine clinical care setting.

Methods: BioTRAC is an ongoing, prospective Canadian registry of rheumatology patients initiating treatment with infliximab or golimumab. In this analysis, data from RA patients who were treated with infliximab between January 2002 and June 2011 and had available information in all indices were used. The definitions for remission were as follows: DAS28 <2.6; SDAI ≤ 3.3, CDAI ≤ 2.8; PAS ≤ 1.0. Factor analysis was used to assess the variability due to each of the indices while inter-item correlation was measured with the Pearson correlation coefficient.

Results: Seven hundred thirty four RA patients who had 3,035 complete assessments were included in the analysis. Non-remission was classified by all indices in 63.1% of the cases, while 36.9% achieved remission in one (13.1%), two (7.8%), three (1.9%), four (4.9%) and all five types (9.1%) of indices. Factor analysis showed that PAS accounted for 70.4% of the matrix variance, followed by DAS28-CRP (13.4%), SDAI (9.0%), CDAI (5.6%),

and Boolean remission (1.6%), suggesting that PAS may reflect different aspects than the clinical indices. PAS remission revealed the lowest correlation with remission classified by the remaining indices (Table 1) and removal of any index, except PAS, would result in a lower overall Cronbach's alpha.

Table 1. Inter-Item Correlation Matrix of Disease Activity Indices

	PAS	DAS28-CRP	SDAI	CDAI	Boolean
PAS	N/A	0.466	0.520	0.521	0.381
DAS28-CRP	0.466	N/A	0.653	0.626	0.661
SDAI	0.520	0.653	N/A	0.918	0.739
CDAI	0.521	0.626	0.918	N/A	0.718
Boolean	0.381	0.661	0.739	0.718	N/A

Conclusion: The results of this analysis show that variability exists in the classification of remission by various disease activity indices. This variability was found to be predominantly due to the Patient Activity Scale, a patient-driven composite tool, suggesting that the patient perception of disease activity may differ from that captured by clinical outcome measures.

Disclosure: W. G. Bensen, None; **A. V. Jovaisas**, None; **J. C. Thorne**, None; **P. Baer**, None; **M. M. Khraishi**, Hoffman-La Roche Canada, Amgen and Pfizer Canada, and Abbott Canada., 2; **S. Dixit**, None; **D. Choquette**, None; **M. Starr**, None; **I. Fortin**, None; **D. E. Sholter**, None; **E. Rampakakis**, None; **J. S. Sampalis**, None; **F. Nantel**, None; **A. J. Lehman**, Janssen Canada, 3; **M. Shawi**, Janssen Canada, 3; **S. M. Otawa**, Janssen Canada, 3.

2252

Assessment Of Rheumatoid Arthritis Disease Activity By Patients and Physicians: Do Physicians Detect Improvement Before The Patient Does?

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Background/Purpose: Patient (PtGA) and physician (MDGA) global assessment of disease activity measure the same construct from two different perspectives. The objective of this study was to assess the agreement between these two measures over time as ascertained in Canadian routine clinical practice in patients with RA treated with infliximab or golimumab.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis (RA), ankylosing spondylitis (AS), or psoriatic arthritis (PsA) with infliximab or golimumab as first biologics or after having been treated with a biologic for less than six months. In this analysis, people with RA treated with infliximab who were enrolled between 2002 and 2012 and had at least one follow-up assessment and up to 60 months of follow up were included. PtGA and MDGA were measured on a 10-point numerical rating scale (NRS) and 10 cm visual analog scale (VAS), respectively. The association between treatment duration and difference between MDGA and PtGA was assessed with linear regression. Internal consistency was assessed with the intra-class correlation coefficient (ICC) and Cronbach's alpha (CA).

Results: A total of 675 patients assessed over 4193 visits during a mean follow up time of 20 months were included in the analyses. The overall mean (SD) PtGA and MDGA was 3.73 (2.89) and 3.38 (2.67), respectively ($P<0.001$). At baseline the mean difference between the MDGA and PtGA was +0.41 ($P<0.001$). However, during all the follow up assessments, this was reversed, with PtGA being significantly higher (worse) when compared to MDGA. The mean difference changed by −0.012 per month ($P<0.001$) indicating progressively higher scores by patients over time compared to physicians. The overall ICC and CA were 0.767 and 0.770, respectively, indicating moderate agreement. Both ICC and CA decreased over time. The mean difference between MDGA and PtGA assessments was non-significantly higher for females (−0.37) when compared to males (−0.29) and significantly higher for patients with history of MTX use (−0.43 vs. −0.18; $P=0.002$). TJC, SJC, CDAI and SDAI had positive and significant ($P<0.001$) associations with increased difference between MDGA and PtGA. Slope analysis showed that MD assessments declined by −0.265/month and Pt assessments declined by −0.189/month ($P<0.001$).

Conclusion: The results of this Canadian longitudinal observational registry have shown that there is poor agreement between physician-based and patient-based assessments of disease activity. In addition, the rate of reduction in disease activity over time is considerably higher when rated by physicians when compared to patients. In this chronic condition, physicians should be aware of this increasing discordance between the patient and physician global when making treatment decisions and managing patient expectations over time.

Disclosure: W. G. Bensen, None; **J. C. Thorne**, None; **P. Baer**, Janssen Pharmaceutica Product, L.P., 5; **A. Chow**, None; **R. Arendse**, None; **I. Fortin**, None; **M. F. Baker**, None; **B. Haraoui**, None; **A. Jovaisas**, Janssen Pharmaceutica Product, L.P, 5; **J. S. Sampalis**, None; **E. Rampakakis**, None; **A. J. Lehman**, Janssen Canada, 3; **F. Nantel**, None; **M. Shawi**, Janssen Canada, 3; **S. M. Otawa**, Janssen Canada, 3.

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How Often Are Core Variables Reported To Calculate Common Disease Activity Scores Measured In Routine Care Of Rheumatoid Arthritis Patients?

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Background/Purpose: Treat-to-target (T2T) is a therapeutic strategy in rheumatoid arthritis (RA) that has been associated with improved outcomes. T2T relies on objective measurement of disease activity at regular intervals with escalation of treatment until remission or low disease activity is achieved. In clinical trials, variables needed to assess disease activity are routinely collected but the ability to do the same in clinical practice is uncertain. The objective of this study was to determine the frequency by which core variables needed to calculate common disease activity scores are collected in a cohort of RA patients followed in routine care.

Methods: All patients (N=2018) enrolled in the Ontario Best Practices Research Initiative since its inception in 2009 were included in this study. OBRI is a clinical registry of RA patients with both early and established disease and are treated according to the discretion of the rheumatologist. We determined the frequency by which components required to calculate common composite disease activity scores (DAS28, SDAI, CDAI) were collected and documented during the first 6 consecutive visits: physician global health assessment (MDGA), patient global health assessment (PtGA), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), tender joint count-28 (TJC) and swollen joint count-28 (SJC).

Results are reported as the % of measured variables, expressed as the number of measured components divided by the number of patients at each visit.

Results: At entry into the cohort, 77% of patients were female with mean (SD) age 57 (13) years, and the majority (85%) was Caucasian. Patients had moderate disease activity according to both mean (SD) DAS28 4.5 (1.5) and CDAI scores 21(14). Over time, the % measurement was consistent for most variables with the exception of ESR and CRP, which had a higher frequency of measurement at cohort entry (visit 1) than subsequent visits. Documentation of TJC and SJC assessment was universally high at each visit and ranged from 92–96%. Global health assessment reported by physicians (MDGA range 85–89%) and patients (PtGA range 88–90%) were similar. Missing data was greatest for values of CRP (missing range 29–40%) (Table).

Table. Frequency (%) of core component measurement in the OBRI cohort.

	Visit 1 (N=2081)	Visit 2 (N=1811)	Visit 3 (N=1530)	Visit 4 (N=1185)	Visit 5 (N=873)	Visit 6 (N=670)
MDGA	87	85	86	87	89	87
PtGA	89	88	88	89	90	90
ESR	85	76	76	77	77	77
CRP	71	60	66	69	67	68
TJC	94	92	92	93	93	94
SJC	96	95	95	95	96	96

Conclusion: Measurement of core variables required to assess RA disease activity are collected in a majority of RA patients followed in routine clinical practice. Objective measures such as TJC and SJC have near perfect collection. MDGA and PtGA are missing in ~15% of visits and measurement

of inflammatory markers are sub-optimal which may limit calculation of composite scores that drive T2T strategies and comparison of disease activity to other cohorts. Further work determining potential barriers to collection of these variables is needed.

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Complementary and Alternative Medicine in Rheumatoid Arthritis - Persistently High Use Over the Past Decade Despite Advent of Biologics.

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Background/Purpose: Complementary and Alternative Medicine (CAM) is commonly used when traditional medicine cannot reliably alter the disease. Over the past decade, rheumatoid arthritis (RA) treatment has improved dramatically whereas osteoarthritis (OA) treatment has not. Accordingly, CAM use should be trending downward in RA relative to OA. Previous studies of CAM use by RA and OA patients have been limited by inaccurate diagnosis of arthritis and lack of long term trending. The purpose of this study was to evaluate the use of CAM in a well-defined population of RA and OA patients now and compared with a similar population 12 years previously.

Methods: 104 OA patients and 102 RA patients attending a Rheumatology clinic twice between May 1, 2011 and June 30, 2012 returned an 84 item questionnaire assessing their CAM use in the past 6 months. Inclusion criteria were met with ICD-9 codes; patients with other co-existing rheumatologic conditions were excluded. This survey was compared to survey results previously reported in 2000 assessing CAM use.

Results: In 2012, most participants were female (OA, 84%; RA, 74%). RA patients were younger and reported less pain than OA patients (57.9 vs. 70.1 years old, $p<0.001$; 3.5 vs. 4.9 on a 0–10 cm pain scale, $p<0.001$). Only 25% of OA and 20% of RA patients reported that their rheumatologist asked about CAM use. Likewise, only 30% of OA and 26% of RA patients reported that they told their rheumatologist about their CAM use.

In 2012, prayer was the most popular form of CAM for both OA and RA patients (63% and 61%) followed by glucosamine/chondroitin, green tea, fish oil, massage, and chiropracty (Figure 1). Additionally, glucosamine, chondroitin, fish oil, and water therapy were tried more commonly by OA patients than RA patients.

No significant decreases were found overtime in CAM use by RA patients compared with trends observed in OA patients for CAM use overall or by CAM category. Compared to 2000, RA patients in 2012 reported having tried several forms of CAM for specific treatment of their arthritis more often including cartilage, flaxseed, green tea, and melatonin ($p=0.049$, 0.049, 0.046, 0.014). Chiropracty, fish oil, and yoga were also tried more often by RA patients in 2012 ($p=0.078$, 0.007, 0.008).

Figure 1: Selected CAM Use	OA: 2012 survey (n=104)	RA: 2012 survey (n=102)	p value
Alternative Healing Systems	27.88%	22.55%	0.378
Chiropracty	**24.51%**	**20.00%**	0.441
Mind, Body & Spirit	65.38%	59.80%	0.408
Meditation	11.76%	14.29%	0.596
Prayer	**63.00%**	**61.22%**	0.797
Massage & Bodywork	27.88%	24.51%	0.582
Massage	**26.73%**	**24.00%**	0.656
Diets	43.27%	30.39%	0.056
Fish Oil	**36.54%**	**23.47%**	**0.043**
Herbs & Supplements	67.31%	57.84%	0.160
Chondroitin	**42.86%**	**15.84%**	**<0.001**
Glucosamine	**50.51%**	**21.78%**	**<0.001**
Green Tea	**33.00%**	**28.00%**	0.443
Miscellaneous	14.42%	21.57%	0.182
Copper Bracelets	7.84%	11.88%	0.334
Magnets	9.80%	11.00%	0.781
Moving Medicine	42.57%	18.18%	**<0.001**
Yoga	8.08%	10.20%	0.605
Water Exercise	36.00%	12.24%	**<0.001**

Conclusion: Despite pharmacologic advances for RA compared to OA over the past decade, there was not a decline in the use of CAM among RA patients. Prayer remains the most common CAM for both OA and RA patients in 2012. Increased use of certain individual therapies may reflect current cultural/market trends or possible immunologically active properties. A gap in communication between patient and physician about CAM use was identified, which is concerning due to the undetermined efficacies of the majority of CAM therapies. This may serve as an opportunity to change current practice and to improve shared medical decision making.

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Threshold Analysis of Patient Reported Morning Stiffness Where Delayed-Release (DR) Prednisone Was Compared to, and Replaced, Immediate Release Prednisone in Rheumatoid Arthritis (RA) Patients Receiving Conventional Disease-Modifying Antirheumatic Drugs (DMARDs) Over 1 Year.

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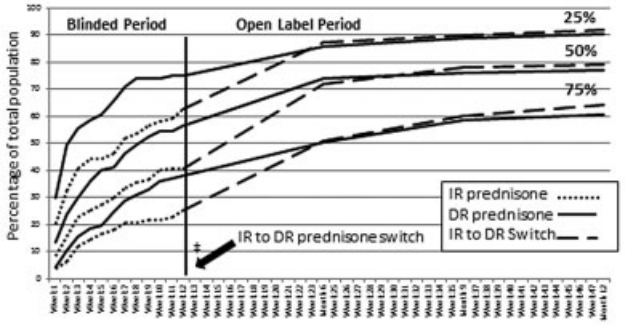
Background/Purpose: RA patients typically present with pain and morning stiffness (MS) in addition to joint swelling and tenderness. Nocturnal inflammatory cytokines are assumed to be associated with MS. DR prednisone given at bedtime has previously shown significant absolute and relative reduction in MS and early morning cytokines compared to both conventional (IR) prednisone and placebo in well controlled studies.(1–3) Studies of categorical and comparative MS responses to DR and IR prednisone are lacking. In this new analysis of Phase 3 study data, we completed a time-to-event analysis of morning stiffness.

Methods: CAPRA-1, a 12-week, double-blind, controlled study, randomized patients to IR-prednisone taken in the morning or DR-prednisone taken once daily at bedtime (eg, 10pm) in addition to standard DMARD treatment.(1) In the following open label phase, patients previously receiving IR prednisone (N=110) were then switched to DR-prednisone and followed at 3, 6, and 9 months.(2) Patients previously on DR-prednisone (N=97) continued on therapy. Patients completed diary entries at least 7 days prior to each visit including waking time, stiffness (yes/no), time of resolution and intensity of pain (VAS) during the day. In a novel analysis, all diary entries +/− 4 weeks of each scheduled visit were analyzed over 1 year for threshold response (see Figure 1). Weekly data was available during the DB study. Chi-square tests for category treatment differences were completed at end of DB and months 6, 9, and 12. Kaplan-Meier estimates and p-values were computed using a Cox proportional model. The response categories were not mutually exclusive.

Figure 1. Percentage Threshold Improvement* in Morning Stiffness Before and After Switch



*Thresholds for improvement represent % of patients achieving 25, 50, and 75% improvement in morning stiffness ‡ $p \le 0.05$ for all categories favoring DR prednisone

Results: The DR prednisone arm had statistically significantly more responders in each of the 3 MS response categories at the end of the DB period as compared to IR prednisone ($p \le 0.05$). DR prednisone had higher percentages of responders in the 3 response categories at each 12 week evaluation. The separation started after 1 week of therapy. Of those who had responses in the DB study, it took longer for the IR prednisone group to reach

the same level of response. The IR prednisone group, when switched to DR prednisone, had comparable responses in all categories within 3 months and significantly shorter time to response when compared to patients already receiving DR prednisone ($p \leq 0.008$).

Conclusion: DR prednisone, as compared to IR prednisone, produces significantly higher MS response rates as defined by 25/50/75% improvement thresholds. The time to reach these thresholds is quicker with DR prednisone and patients switched to DR prednisone from IR prednisone quickly "catch up" and manifest comparable responses. Patients treated with DR prednisone maintained their response with no evidence of tachyphylaxis up to 1 year.

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Analysis of the Factors That Contribute to the Differences Between DAS28-ESR and DAS28-CRP. Toshihiro Matsui[1], Hirotaka Tsuno[1], Jinju Nishino[2], Yoshiaki Kuga[3], Atsushi Hashimoto[1] and Shigeto Tohma[4]. [1]National Hospital Organization Sagamihara Hospital, Kanagawa, Japan, [2]Nishino Clinic, Orthopedics and Rheumatology, Tokyo, Japan, [3]Wakaba Hospital, Saitama, Japan, [4]Sagamihara Hospital, National Hospital Organization, Sagamihara, Japan.

Background/Purpose: It is widely accepted that the remission rate of DAS28-CRP is larger than that of DAS28-ESR, SDAI, and CDAI in patients with rheumatoid arthritis. DAS28-CRP was introduced to be comparable to DAS28-ESR and the same cut-off values of disease activity category were generally used for both DAS28. However, it had been reported that DAS28-CRP underestimates the disease activity compared with DAS28-ESR (Matsui T, et al. Ann Rheum Dis 2007;66:1221) and that the differences between DAS28-ESR and DAS28-CRP (DAS28DIF) were affected by gender and disease duration (Castrejon I, et al. Clin Exp Rheumatol 2008;26:769). It is very important to know the factors which affect DAS28DIF for evaluating the data by DAS28-CRP.The purpose of this study is to analyze the factors which have an influence on DAS28DIF.

Methods: We analyzed the data from 5987 patients with rheumatoid arthritis (RA) registered in NinJa (National Database of Rheumatic Diseases by iR-net in Japan) 2011. The mean age was 63.1 ± 12.9 years old, disease duration was 12.1 ± 10.8 years, and 80.7% of the patients were female. The mean DAS28-ESR and DAS28-CRP was 3.24 ± 1.28 and 2.58 ± 1.10, respectively (mean DAS28DIF$=0.659$). Multivariate linear regression analyses were conducted. Variables that were significant at $p<0.01$ on the univariate analysis were entered into the multivariate model.

Results: A univatiate analysis showed that several variables (gender, age, disease duration, stage, class, mHAQ, ESR, CRP, PtPainVAS, PtGVAS, DrVAS, artificial joint, TJC28, SJC28) were associated with DAS28DIF with $p<0.01$. A multivariate linear regression analysis demonstrated that ESR (standard partial regression coefficient:0.633), female gender (0.194), age (0.119), mHAQ (-0.087), and BMI (-0.037) were associated with DAS28DIF (coefficient of determination:0.474). Category analysis also revealed that value of DAS28DIF was significantly higher with increasing ESR, age, disease duration, class, mHAQ, DAS28-ESR, DAS28-CRP, and with decreasing BMI (Jonckheere-Tepstra trend test, $p<0.001$). There was significant difference in DAS28DIF between male (0.41) and female (0.72) (Wilcoxon signed-rank test, $p<0.001$). Mean DAS28DIF was -0.002 in patients whose ESR was 11 mm/hr or less. Cut-off value for DAS28-CRP calculated by regression analysis between DAS28-ESR and DAS28-CRP was 2.1 for remission, 2.5 for low disease activity and 4.0 for high disease activity, respectively.

Conclusion: This study showed that DAS28DIF can be affected by many kinds of valuables. We should pay attention to the background of the patients when analyzing the data by using DAS28-CRP and evaluating the cut-off value of remission for DAS28-CRP based on that of DAS28-ESR.

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Symptom Complexes At The Beginning Of Rheumatoid Arthritis: A Qualitative Exploration In At Risk Individuals and In New Patients Prior To Diagnosis. Rebecca J Stack[1], Lilian H.D. van Tuyl[2], Maurits Sloots[3], Lotte A. van de Stadt[3], Wijnanda Hoogland[3], Bertha Matt[3], Christian D Mallen[4], Rumandeep Tiwana[1], Karim Raza[1] and Dirkjan van Schaardenburg[3]. [1]University of Birmingham, Birmingham, United Kingdom, [2]VU University Medical Center, Amsterdam, Netherlands, [3]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [4]University of Keele, Keele, United Kingdom.

Background/Purpose: To achieve better prediction of the development of rheumatoid arthritis (RA) a EULAR study group recommended identification and assessment of symptoms in those with arthralgia and during the earliest phases of clinical arthritis as a research priority. The aim of this study was to explore early symptom experiences in individuals with arthralgia at risk of RA and in individuals with new onset RA.

Methods: Focus groups with fifteen arthralgia patients (positive anti-CCP) and in-depth interviews with eleven newly presenting RA patients (2010 criteria) were conducted. An active feedback procedure was used to share experiences of arthralgia patients with early RA patients and vice versa. When saturation was reached transcripts were analysed using thematic analysis and major themes were identified. The analyses were merged to explore similarities and differences in themes between groups.

Results: Themes common to arthralgia and early RA patients included: pain (described in the joints and also in muscles and tendons); tingling sensations; loss of strength and weakness; fatigue and sleeping difficulties; self-reported swelling, redness and warmth; joint stiffness and intermittent symptoms. However, some differences were noted. Arthralgia patients described pain that was often concentrated in their hands and feet as bothersome and annoying. Early RA patients described pain that had intensified to excruciating levels before diagnosis; in some cases pain was likened to a broken bone. Arthralgia patients reported short episodes of intermittent swelling which often involved feelings of pain and fatigue. RA patients recalled that changes in their experience of swelling marked a significant change in the course of their illness, with the nature and pattern of swelling (such as intensification, development of symmetry, translocation) changing shortly before being diagnosed. Such changes were reported to be triggers for patient consultation and physician referral. Fatigue and sleeping difficulties were a dominant problem for arthralgia patients, they noted intense and troubling pain at night. RA patients also reported that night pain was one of the first symptoms they recalled.

Conclusion: Understanding the features and patterns of symptoms characterising the earliest stages of RA is important if patients are to be identified and started on treatment early. Arthralgia and early RA patients shared symptoms which characterised the onset of disease, however, this detailed exploration of symptoms highlighted how the intensity (e.g. pain), and the pattern (e.g. changes in the pattern of swelling) differ between the two groups. Further research to develop measures of symptom patterns and clusters which occur in arthralgia patients and may signal the emergence of RA is required. This research should be followed by quantitative explorations of symptom clusters and their associated features.

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2258

Less Than 5% Of Ethnic Minority Rheumatoid Arthritis Patients Meet Inclusion Criteria For Randomized Controlled Clinical Trials. Gail S. Kerr[1], Yusuf Yazici[2], Christopher Swearingen[3], Chunqiao Luo[3], Yvonne R. S. Sherrer[4], Edward L. Treadwell[5], Angelia D. Mosley-Williams[6], Luis R. Espinoza[7], Rodolfo Perez Alamino[8], Sharon Dowell[9], Ignacio Garcia-Vallardes[10], Theresa Lawrence-Ford[11], Adrian Godoy[9], Akgun Ince[12] and Cindy Flower[13]. [1]Washington DC VAMC, Georgetown and Howard University, Washington, DC, [2]New York University Hospital for Joint Diseases, New York, NY, [3]University of Arkansas for Medical Sciences, Little Rock, AR, [4]Centre Rheum Immunol Arthritis, Fort Lauderdale, FL, [5]East Carolina University, Greenville, NC, [6]John Dingell VAMC, Detroit, MI, [7]LSU Medical Center, New Orleans, LA, [8]Lousiana State University and LSU Medical Center, New Orleans, LA, [9]Howard University, Washington, DC, [10]Guadalajara, Gaudalajara, Mexico, [11]North Georgia Rheumatology Group, PC, Lawrenceville, GA, [12]Saint Louis University, St. Louis, MO, [13]University of the West Indies, Bridgetown, Barbados.

Background/Purpose: RCT are the gold standard for therapeutic efficacy, yet many studies indicate most patients seen in routine clinical care do

not meet inclusion criteria. Apart from cultural challenges to the enrollment of ethnic minorities in clinical studies, decreased access and care, and late presentation in disease course may preclude inclusion in RA RCT. However, eligibility of ethnic minorities for RA RCT, to the best of our knowledge, has not been reported. EMRAC is a prospective clinical registry that collects data reflective of routine clinical care. In this study, we evaluated the applicability of standard RCT inclusion criteria in a cohort of ethnic minority RA patients.

Methods: Enrollment data collected on EMRAC patients include socio-demographic parameters (age, gender, tobacco use), RA disease status variables (disease duration, serology [RF, ACPA], nodules, erosions, MD-HAQ, TJC, SJC, ESR, CRP, CDAI, DAS28, RAPID3), treatments (prednisone, DMARD, Biologic therapies) and comorbidities (HTN, DM, HLD). RA related disease measures were evaluated for the following standard, high disease activity, RCT inclusion criteria: swollen joints (28) >= 6, tender joints (28) >= 6, ESR >= 28, morning stiffness >= 45 min. We also evaluated the cohort for low disease activity, defined as swollen (28) <= 1, tender (28) <= 1, ESR <= 10, morning stiffness <= 15 min. Comparisons were made of each individual criteria, high (RCT eligible) versus low disease activity, and overall RCT eligibility by Race (Caucasian, African American) using Chi-square test.

Results: 242 EMRAC patients had complete datasets available for analysis: 81 (33%) were Caucasian and 161 (67%) were African American (AA). The mean age was 62.5 years and the mean disease duration was 13.2 years. Only 4% AA and 4% Caucasians met standard RCT inclusion criteria, despite only 4% AA and 7% of Caucasians meeting criteria for low disease activity. The most stringent criterion was swollen joint count, with only 17% of AA and 15% of Caucasians meeting criteria, followed by tender joint counts (24% of AA and 32% of Caucasians). 52% AA and 40% Caucasian patients, respectively, met ESR criteria, while 38% AA and 37% Caucasians met morning stiffness thresholds. Caucasians were more likely to have low disease activity ESR than AA (27% vs 11%, p=0.002), while AA had low disease activity tender (28) compared to Caucasians (58% vs 43%, p=0.032).

Conclusion: In addition to reported socio-economic and cultural hurdles that preclude enrollment of ethnic minorities in RCT, African Americans, like their Caucasian counterparts, also fail to meet eligibility for RCT despite active disease, despite half as many African Americans as Caucasians achieving low disease status. These data may suggest reconsideration of current entry criteria for RCT in all patients with RA.

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2259

Does a Ratingen Score Of ≥ 3 At Disease Onset Define RA In ACR/EULAR 2010 Criteria Negative Patients? Ruediger Mueller, Toni Kaegi, Sarah Haile and Johannes von Kempis. Kantonsspital St. Gallen, St. Gallen, Switzerland.

Background/Purpose: A EULAR task force has recently selected an evidence and consensus based definition of erosive disease defining rheumatoid arthritis (RA) in patients who do otherwise not fulfil the 2010 ACR/EULAR criteria for classification of the disease. Erosive disease was defined as a minimum of 3 erosions in particular joints.

Methods: For this observational cohort study within the RA cohort of the Swiss registry SCQM, we included patients suffering from early RA or undifferentiated arthritis (disease duration ≤1 year), as defined by the treating rheumatologist, who had not received any previous DMARDs. Baseline diagnosis of RA/UA was reassessed according to the 2010 ACR/EULAR criteria at baseline. 2010 ACR/EULAR criteria negative patients were separated into 2 groups depending on whether or not they had more than two erosions in the Ratingen score (Ratingen positive: >2; Ratingen negative <3). The primary outcome measures were the radiological progression. HAQ and DAS 28 were used as secondary outcome measures. The average observation period was 4 years.

Results: A total number of 592 patients was analysed. 240 were not classifiable as RA according to the new criteria at baseline. 133 patients were Ratingen positive and 50 patients were Ratingen negative, 57 patients were not classifiable. Treatment was initiated in all patients with DMARDs, mostly MTX. There were no significant differences in the therapeutic strategies between Ratingen positive and negative patients. No differences in DAS 28 and HAQ scores were found during follow up over 4 years. Average radiographic progression was higher among Ratingen positive as compared to Ratingen negative patients (6.6 erosions/year vs. 0.4, resp., p=0.0004).

Conclusion: The presence of more than 2 erosions in the Ratingen score selected RA patients not fulfilling the 2010 ACR/EULAR criteria who will suffer from a radiographic progressive disease. This indicates that the propose definition of erosive disease is, indeed, selecting patients, who will develop definite RA.

Disclosure: R. Mueller, None; **T. Kaegi**, None; **S. Haile**, None; **J. von Kempis**, None.

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Smoking and Antibodies To Cyclic Citrullinated Peptides Predict Persistently High Levels Of Survivin In Early Rheumatoid Arthritis. Bjorn Svensson[1], Ingiäld Hafström[2], Malin Erlandsson[3], Kristina Forslind[4] and Maria Bokarewa[5]. [1]Lund University, Lund, Sweden, [2]Karolinska University Hospital, Stockholm, Sweden, [3]Göteborgs University, Göteborg, Sweden, [4]Section of Rheumatology, Department of Medicine, Helsingborg General Hospital, Helsingborg, Sweden, [5]University of Gothenburg, Gothenburg, Sweden.

Background/Purpose: High levels of the oncoprotein survivin may be detected in the majority of patients with early rheumatoid arthritis (RA). Survivin is a sensitive predictor of joint damage and persistent disease activity. Survivin-positive patients are often poor responders to anti-rheumatic and biological treatment. Present study investigates the reproducibility of survivin status in paired samples from RA patients.

Methods: Survivin levels were measured in 339 patients from the BARFOT cohort of early RA at baseline and after 24 months. The association of survivin status with joint damage (total Sharp-vd Heide score), disease activity (DAS28), functional disability (HAQ), and pain perception (VAS) was calculated in the groups positive and negative for survivin on both occasions, and for the positive-negative and negative-positive groups.

Results: In 268 patients (79%) the levels of survivin were similar at baseline and after 24 months, 15% converted from survivin-positive to being negative, and 5% from survivin-negative to being positive. A combination of smoking and aCCP antibodies predicted high levels of survivin on both test occasions (OR4.5 [95%CI: 7.54–2.74], p<0.001, PPV 0.67 and specificity 0.84). Survivin positivity on both test occasions was associated with the progression of joint damage, significantly higher DAS28 and lower rate of remission at 24 and 60 months compared to negative-negative patients. Survivin status was less associated with changes in HAQ and VAS.

Conclusion: Survivin status in RA patients may be predicted by smoking and aCCP and is highly reproducible at 24 months follow-up. Survivin is a relevant marker to use in predictive models and on which to base treatment decisions.

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Motivations For Inadequate Persistence With Disease Modifying Anti-Rheumatic Drugs In Early Rheumatoid Arthritis: *The Patient's Perspective.* Virginia Pascual-Ramos and Irazú Contreras-Yáñez. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

Background/Purpose: Knowledge of factors that contribute to non-persistence with disease modifying anti-rheumatic drugs (NP-DMARDs) is essential to improve rheumatoid arthritis (RA) outcomes. Aims of the study were to investigate patient's motivations and risk factors for NP-DMARDs in a cohort of early Mexican Mestizos patients with RA and traditional DMARDs.

Methods: Up to September 2012, data from 149 patients (93% of the entire cohort), who had at least 1 year of follow-up, and one DMARD indication, and 2 consecutive six-months-apart rheumatic evaluations that included assessment of compliance with treatment were reviewed. Compliance was evaluated according to a 22-items questionnaire locally designed that evaluates among others NP-DMARDs and patient's motivations of NP-DMARDs. Patients had partial health coverage and pay for their medication.

Descriptive statistics and logistic regression models were used. All statistical tests were 2-sided and evaluated at the 0.05 significance level. The

study was approved by the internal review board. Written informed consent was obtained.

Results: Up to cut-off, 715 questionnaires were applied to 149 patients, who had (mean ± SD) follow-up of 58.7 ± 27.9 months and were indicated (mean±SD) DMARDs/patient/follow-up of 2.4±0.7.

Patients were most frequently female (88.6%), middle-aged ([mean±SD] age of 38.5±12.8 years) with lower-middle/lower socio-economic status (87.9%) and (mean±SD) scholarship of 11±3.9 years.

Ninety-nine (66.4%) patients were NP-DMARDs and filled 330 questionnaires. Multivariate analysis showed that years of formal education (OR: 1.12, 95% CI: 1.1–1.24, p=0.03), perception of at least some difficulty to find arthritis medication (OR: 5.68, 95% CI: 2.48–13, p=0.000) and perception that arthritis medication is expensive (OR: 5.27, 95% CI: 2.1–13.84, p=0.001) at the first evaluation of patient′s compliance were all predictor of NP-DMARDs.

Among the 99 NP-DMARDs patients, 25 (25.3%) were recurrent-NP-DMARDs and accumulated more disease activity than their counterparts ([mean±SD cumulative DAS28] 3.7±2 vs. 2.9±1.7, p=0.04). Also, DAS28 remission was lower among recurrent-NP patients (8 vs. 45, p=0.002).

Combination of both reasons of NP-DMARDs ("Because it was not available at the drugstore" and "Because the medication is very expensive") when selected by the patient at the first evaluation of compliance was the only variable to predict recurrent NP-DMARD, OR: 4.8, 95%CI: 1.1–20.8, p=0.04.

Conclusion: Health systems should provide (first line) treatment for RA as a strategy to improve compliance with therapy and clinical outcomes, particularly in vulnerable populations.

Disclosure: V. Pascual-Ramos, None; **I. Contreras-Yáñez**, None.

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Antibody To Malondialdehyde-Acetaldehyde Adducts (MAA) Is a Biomarker Of Inflammation and Is Correlated With The Disease Activity In Rheumatoid Arthritis. Kathleen Young[1], Dathe Benissan-Messan[2], Michael J. Duryee[2], Daniel Anderson[2], Liron Caplan[3], Lisa A. Davis[4], Harlan Sayles[2], Carlos D. Hunter[2], Lynell W. Klassen[5], James R. O'Dell[2], Ted R. Mikuls[6] and Geoffrey M Thiele[5]. [1]Univ of Nebraska Med Ctr, Omaha, NE, [2]University of Nebraska Medical Center, Omaha, NE, [3]Denver Veterans Affairs Medical Center, Denver, CO, [4]Denver Health and Hospital Authority, Denver, CO, [5]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [6]Omaha VA and University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with rheumatoid arthritis (RA). While there are many markers used for evaluating the development and/or progression of CVD, the recent use of pro-inflammatory macromolecules (CRP, IL-6, TNF-α) has become increasingly helpful in the diagnosis and evaluation of CVD. Our laboratory has been evaluating antibody isotypes and concentrations to a unique malondialdehyde (MAA) adduct that appear to correlate with both systemic inflammation and cardiovascular events. We have hypothesized that inflammation directed against MAA could serve as a link between systemic inflammation and the excess CVD burden that both characterize RA. Thus, as a first step in addressing our overarching hypothesis, we sought to evaluate whether associations existed between anti-MAA antibodies and measures of RA disease activity and severity.

Methods: Serum samples from 704 RA patients from the Veterans Affairs RA (VARA) registry were evaluated for the presence and concentration of IgM, IgA and IgG antibodies to the MAA epitope using ELISA. Associations of these antibody concentrations with traditional markers of RA (RF, ESR, CRP, ACPA, DAS28, etc.) were performed using non-parametric Spearman Rank Correlation statistics. Additionally, antibody isotype concentrations to MAA were compared for patients with radiographic bone erosions to those without erosions using a two-sample t-test.

Results: Statistically significant correlations were observed between anti-MAA antibody concentrations and multiple RA measures (Table) including RF isotypes, ACPA, ESR, and CRP. Isotype variability was observed with measures including RF (by nephelometry) and swollen joint count, while no associations were observed between anti-MAA concentrations and tender joints, MD-HAQ, and DAS28. Finally, patients with radiographic erosions demonstrated higher concentrations of IgA anti-MAA compared to patients without erosions (p = 0.043), a difference that was not observed for IgG or IgM anti-MAA isotypes.

Table 1. Correlations of anti-MAA antibody concentration and measures of RA disease actvity/severity; top number in each cell represents the correlation coefficient while the bottom number represents the p-value.

	Isotypes of Anti-MAA Antibodies		
RA Measure	**IgG**	**IgA**	**IgM**
RF IgG	R = 0.2065	0.269	0.3634
	p <0.0001	**<0.0001**	**<0.0001**
RF IgA	0.1244	0.2951	0.4022
	0.0064	**<0.0001**	**<0.0001**
RF IgM	0.12	0.2516	0.4666
	0.0085	**<0.0001**	**<0.0001**
ESR	0.0961	0.1081	0.1424
	0.017	**0.0074**	**0.0004**
CRP	0.1415	0.1264	0.082
	0.0003	**0.0011**	**0.0344**
RF Nephelometry	0.0621	0.1943	0.4203
	0.1099	**<0.0001**	**<0.0001**
ACPA (anti-CCP)	0.1796	0.1393	0.1837
	<0.0001	**0.0003**	**<0.0001**
DAS28	0.0176	−0.0236	0.0498
	0.6801	0.5801	0.2416
Tender Joint Count	−0.0061	−0.0413	0.0387
	0.8751	0.2918	0.3244
Swollen Joint Count	0.1016	0.0178	0.0678
	0.0092	0.6499	0.0824
MD-HAQ	−0.0506	−0.0504	−0.0489
	0.2322	0.2341	0.2474

Conclusion: These results show there is a relationship between anti-MAA antibody levels and several traditional measures of disease activity and/or severity in RA. Although we have previously shown that both MAA and anti-MAA may play a role in CVD pathogenesis in patients without RA, further investigation will be needed to better elucidate whether MAA-related inflammation could serve as a mechanistic link between RA and CVD burden.

Disclosure: K. Young, None; **D. Benissan-Messan**, None; **M. J. Duryee**, None; **D. Anderson**, None; **L. Caplan**, None; **L. A. Davis**, None; **H. Sayles**, None; **C. D. Hunter**, None; **L. W. Klassen**, None; **J. R. O'Dell**, None; **T. R. Mikuls**, Roche/Genentech and Biogen IDEC Inc., 2; **G. M. Thiele**, None.

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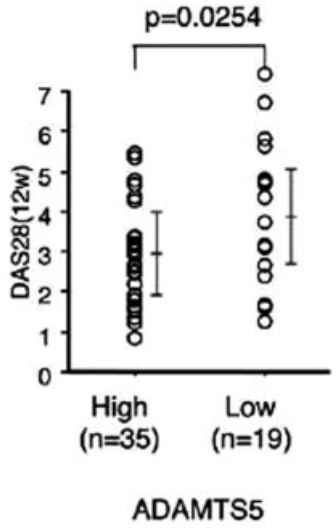
ADAMTS5 Is a Biomarker For The Efficacy Prediction Of Tocilizumab In Rheumatoid Arthritis. Kensei Tsuzaka, Masako Takao and Jiro Nishida. Ichikawa General Hospital, TDC, Ichikawa, Chiba, Japan.

Background/Purpose: We have previously (2009ACR, 2010ACR) reported that the efficacy of biologics, infliximab and adalimumab can be predictable using baseline blood a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5) mRNA level. In this study presented here, we investigated whether the efficacy of tocilizumab (TCZ) for the treatment of rheumatoid arthritis (RA) can be predicted by the baseline blood ADAMTS5 mRNA level because recently IL-6 has been reported to suppress ADAMTS5 expression.

Methods: Fifty-four randomly selected active RA patients were treated with TCZ. Peripheral blood samples were collected at baseline and ADAMTS5 mRNA was quantified using real-time PCR (BiologicMate®). Baseline IL-6 mRNA was also estimated using real-time PCR.

Results: Baseline ADAMTS5 mRNA levels (□L 10^{-4}) in the responder (2.85 ± 2.37 Index) was significantly (p=0.049) higher than that in the non-responder (1.56 ± 0.80 Index) at 12 wks' treatment with TCZ. Area under curve (AUC) of the ROC curve for predicting the clinical remission (DAS28<2.6) using the baseline ADAMTS5 mRNA at 12 wks was 0.75, and the cut-off value of ADAMTS5 mRNA was calculated as 1.70 Index. There observed no difference in the general patient backgrounds (average age, disease duration, dose of MTX, dose of steroid, baseline DAS28, etc) between the High-ADAMTS5 (^{3} 1.70 Index) group and the Low-ADAMTS5 group. However, DAS28 at 12 wks after treatment was significantly (p=0.0254) lower in the High-ADAMTS5 group (3.09 ± 1.29) than in the Low-ADAMTS5 group (3.88 ± 1.08) (Fig.1). The accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of

the baseline High-ADAMTS5 (^{3}1.7 Index) for predicting the clinical remission at 12 wks with TCZ was 75.0%, 94.1%, 48.7%, 45.7%, and 94.7%, respectively. Interestingly, we observed negative correlation between baseline IL-6 and ADAMTS5 mRNA expression.



Conclusion: The baseline ADAMTS5 mRNA level, which might be related to baseline IL-6, is a candidate biomarker for prediction of the response to TCZ in RA patients.

Disclosure: K. Tsuzaka, Kaytee Bio, 4; **M. Takao**, None; **J. Nishida**, None.

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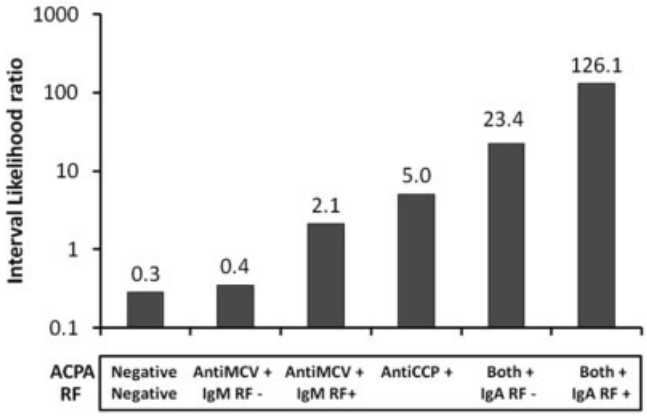
An Assay Panel Combining Anticitrullinated Peptide Autoantibodies and Rheumatoid Factor Isotypes Has High Yield In The Diagnosis Of Rheumatoid Arthritis. Nirupa J. Patel[1], Ignacio Garcia-Valladares[2], Derren Barken[3], Luis R. Espinoza[4], Heena Sheth[5] and Thierry Dervieux[3]. [1]LSU Health Sciences Ctr, New Orleans, LA, [2]Guadalajara, Guadalajara, Mexico, [3]Exagen Diagnostics, Vista, CA, [4]LSU Medical Center, New Orleans, LA, [5]University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: We sought to establish the diagnostic performances of rheumatoid factor isotypes (IgM and IgA) and anti-citrullinated peptide antibodies (ACPAs: anti-mutated citrullinated vimentin [anti-MCV] and anti-cyclic citrullinated peptide antibodies [antiCCP]) in a large population of patients with rheumatoid arthritis (RA) and other rheumatic diseases.

Methods: 1140 subjects were from the United States and informed consent was obtained from all patients. The group of 703 RA patients (78% females, age was 60.0±14 yrs) consisted of 452 patients diagnosed using the 1987 ACR criteria and 251 patients diagnosed using the 2010 ACR criteria. A total of 113 RA patients (16.1%) presented with disease duration lower than 2 years. Alternatively, the group of 387 patients with other diseases (83% females, age 44.6±15.0, mean±SD) consisted of 271 patients with Systemic lupus erythematosus and 116 patients with other autoimmune diseases. An additional 50 normal healthy volunteers were also enrolled. IgM RF, IgA RF, anti-CCP were measured using fluoroenzyme immunoassays (Phadia, Uppsala, Sweden) and anti-MCV was determined using enzyme linked immunosorbent assays (Orgentec, Mainz, Germany). Statistical analyses utilized area under receiver operating characteristic (ROC) curves, and calculations of diagnostic sensitivity, specificity, positive likelihood ratio (LR+) and interval LR. Cutoffs used for positivity were 5 U/ml for IgM RF, 20 U/ml for IgA RF, 10 U/ml for anti-CCP and 35 U/ml for anti-MCV.

Results: The area under the ROC curve was 0.857±0.022 for IgM RF, 0.724±0.031 for IgA RF, 0.828±0.025 for anti-CCP and 0.805±0.025 for anti-MCV. Sensitivity and specificity against other rheumatic diseases were 71% and 85% for IgM RF (positive LR=4.8), 41% and 90% for IgA RF (LR+=4.1), 70% and 96% for anti-CCP (LR+=18.0) and 62% and 92% for anti-MCV (LR=7.3). Specificity ranged from 94–100% against normal healthy individuals for all markers. A scoring system combining positivity for ACPA (anti-CCP and anti-MCV) and RF isotypes was calculated. Interval likelihood ratio increased from 0.3 among ACPA negative patients, to 126.1 among patients positive for both ACPAs and IgA RF (Figure). Interval LR differences when compared by disease duration and diagnostic criteria were not statistically significant.



Conclusion: An assay panel combining ACPAs (anti-CCP with anti-MCV) with RF isotopes can help in differentiating RA from other rheumatic diseases.

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Switching From Immediate Release (IR) Prednisone To Delayed Release (DR) Prednisone Improves Patient Reported Outcomes In Rheumatoid Arthritis (RA) Patients On Conventional Disease-Modifying Antirheumatic Drugs (DMARDs). Rieke Alten[1], Robert Holt[2], Amy Grahn[2], Patricia Rice[3], Jeffery Kent[2], Frank Buttgereit[4] and Allan Gibofsky[5]. [1]University of Berlin, Berlin, Germany, [2]Horizon Pharma, Inc, Deerfield, IL, [3]CliniRx Research, Naperville, IL, [4]Charité - Universitätsmedizin Berlin, Berlin, Germany, [5]Hospital for Special Surgery, New York, NY.

Background/Purpose: A surge in nocturnal inflammatory cytokines causing morning stiffness (MS) is recognized as a therapeutic target in RA. MS has been underappreciated in impacting the quality of life (QOL) of RA patients. Along with renewed interest in glucocorticoids (GCs) as an option for targeting these circadian disease fluctuations, ACR is updating its practice guidelines. Optimal timing for glucocorticoid administration will be a new and important topic to address. DR prednisone administered at bedtime produces significant absolute and relative reduction in morning symptoms. Inflammatory cytokines are also reduced significantly. In this analysis of patients with RA, we evaluated the reduction of symptoms that impact QOL. This assessment examined 9 months of patient reported diary data from the CAPRA I trial who were switched from IR-prednisone to DR-prednisone after 3 months of previous therapy.

Methods: RA patients previously randomized to IR prednisone (N=110) were switched to DR-prednisone open label and evaluated at 3, 6, and 9 months to measure median absolute (paired t-test) and relative changes (Wilcoxon Rank Sum Test) in pain, patient's global, and MS as the primary outcome. Patients completed diary entries at least 7 days prior to each of the 3 month visits including waking time, stiffness (yes/no), time of resolution and intensity of pain (VAS) during the day. In an analysis not previously performed, all patient diary entries +/− 4 weeks of each visit were compared to Baseline at Switch in addition to other disease measures.

Results: There was a statistically significant and clinically meaningful reduction in morning stiffness during the first 3 months after the switch and the response was maintained over the entire study period of 9 months (Figure 1). Absolute reduction of MS was approximately 50 min from 143.5 min and there was a > 40% relative reduction in MS at each visit. IL-6 levels were reduced concomitantly by the same amount. The mean reduction in MS was over 60 minutes at each of the three visits (Figure 2).

Figure 1. Switching from IR prednisone to DR prednisone produces Sustained Morning Stiffness Reduction

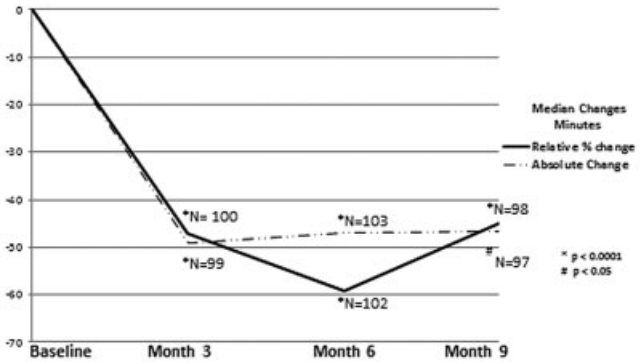
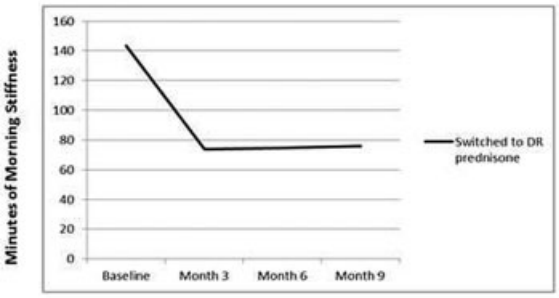


Figure 2. Observed Reduction in Morning Stiffness after switching to DR prednisone from IR Prednisone



Conclusion: This analysis demonstrates that RA patients on stable DMARD therapy, who have not adequately responded to IR-prednisone with respect to morning stiffness, showed statistically significant and clinically meaningful improvement in this symptom when switched to DR prednisone which markedly impacts quality of life. This beneficial effect was maintained over the 9 month study duration.

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Disclosure: R. Alten, Horizon Pharma, Inc, 5; **R. Holt**, Horizon Pharma, Inc, 5; **A. Grahn**, Horizon Pharma, Inc, 3; **P. Rice**, Horizon Pharma, Inc, 5; **J. Kent**, Horizon Pharma, Inc, 3; **F. Buttgereit**, Horizon Pharma, Inc, 2; **A. Gibofsky**, GlaxoSmithKline plc, 1, Bristol-Myers Squibb, 1, Johnson & Johnson, 1, Horizon Phartmaceuticals, 5, Iroko Pharmaceuticals, 5, Abbott Laboratories, 9, Amgen, Inc, 9, Genentech, Inc, 9.

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Research On Factors Influenced For Bone Metabolic Markers In Rheumatoid Arthritis Patients From Prospective Cohort Study. Masahiro Tada, Tatsuya Koike, Tadashi Okano, Yuko Sugioka, Kenji Mamoto, Kentaro Inui and Hiroaki Nakamura. Osaka City University Graduate School of Medicine, Osaka, Japan.

Background/Purpose: Patients with rheumatoid arthritis (RA) develop osteoporosis more frequently than healthy individuals. Bone resorption and formation are respectively increased and inhibited in patients with RA, and steroids negatively affect bone metabolism in both patients with RA and healthy individuals. The effect of reducing the steroid dose on bone metabolic markers in patients with RA has remained unknown. We aimed to investigate the factors influenced for bone metabolic markers in RA patients using multivariate analysis technique.

Methods: We started the 10-year prospective cohort TOMORROW (TOtal Management Of Risk factors in Rheumatoid arthritis patients to lOWer morbidity and mortality clinical trial (registration number, UMIN000003876)) in 2010. We compared changes in urinary crosslinked N-telopeptide of type I collagen (NTx) and serum osteocalcin (OC), which are markers of bone resorption and formation, respectively, in a total of 404 age- and sex-matched RA patients and volunteers between 2010 and 2011 (delta NTx = NTx during 2011 – NTx during 2010; delta OC = OC during 2011 – OC during 2010). We also investigated the factors influenced for delta NTx and delta OC in RA patients using multivariate analysis technique.

Results: Baseline demographics were showed in Table 1. There were no significant differences in all parameters between groups. The delta NTx values were significantly lower in the patients than in the volunteers (-0.51 ± 29.4 vs. 7.41 ± 18.7 nmol; $p = 0.0013$), whereas the delta OC values were significantly higher in the patients (0.94 ± 2.47 vs. 0.37 ± 1.62; $p = 0.0065$). The change of prednisolone (PSL) dosage negatively correlated with delta OC ($\beta = -0.229$, $p = 0.001$), whereas change of disease activity score (DAS28), bisphosphonate therapy, and period of biologics therapy did not significantly correlate with delta OC (Table 2).

Table 1. Baseline demographics

	Volunteers (n = 202)	RA patients (n = 202)
Age, years	58.8 ± 12.8	59.3 ± 12.5
Height, cm	157.7 ± 7.8	155.5 ± 9.0
Weight, kg	56.3 ± 10.5	54.8 ± 10.4
BMI, kg/m^2	22.6 ± 3.2	22.6 ± 3.6

BMI: body mass index

Table 2. The factors influenced for delta OC in RA patients

	β value	P value
delta PSL dosage	**−0.229**	**0.001**
delta DAS28-ESR	−0.007	0.918
Bisphosphonate therapy	−0.033	0.673
Period of biologics therapy	0.018	0.802
Age	0.155	0.054
Sex (female)	0.013	0.855
Disease duration	0.037	0.601
Steinbrocker class	−0.059	0.456

PSL: prednisolone, DAS: disease activity score

Conclusion: A decrease in the dose of PSL respectively decreased and increased markers of bone resorption and formation among patients with RA. That is, bone metabolic makers were improved. However, disease activity, bisphosphonate therapy, and period of biologics therapy did not influence for bone metabolic makers. Thus, bone metabolic markers might degenerate even when disease activity is under good control. Decreasing the PSL dosage is important for bone metabolism in patients with RA.

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The Diagnostic Accuracy Of Rheumatoid Factor Testing In Primary Care. Anne Miller[1], Alison L Nightingale[2], Cormac J Sammon[2], Tim Holt[3], Kamal R Mahtani[3], Neil McHugh[4], Corinne S de Vries[2] and Raashid A. Luqmani[1]. [1]Nuffield Orthopaedic Centre, Oxford, United Kingdom, [2]University of Bath, Bath, United Kingdom, [3]University of Oxford, Oxford, United Kingdom, [4]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom.

Background/Purpose: Studies of the diagnostic utility of rheumatoid factor (RF) testing for rheumatoid arthritis (RA) conducted in early arthritis clinics in secondary care have reported sensitivity and specificity of 69% and 85% respectively. However, few studies have been conducted in primary care where the pre-test probability of RA is low. We investigated the utility of RF in primary care using the Clinical Practice Research Datalink (CPRD), a large primary care electronic database representing 8.4% of the UK population.

Methods: The CPRD was searched for patients who had a first RF test between 1st January 2000 and 31stDecember 2008 and had at least 2 years of follow-up data or who died within 2 years of the test date. We excluded practice-years where there was evidence for preferential recording of positive RF tests. Patients diagnosed with RA within 2 years of their first test were identified using a validated algorithm; we then calculated the sensitivity, specificity and positive and negative likelihood ratios (LR+, LR-) for a diagnosis of RA. We calculated the relative risks (RRs) of positive compared

with negative RF results for patient characteristics and musculoskeletal symptoms recorded in the 6 months before the test using Poisson regression models.

Results: We found that 63,539 RF tests fulfilled the inclusion criteria; 92.3 % were negative and 68.4% were requested in females. There were 1753 incident cases of RA in patients undergoing RF testing giving an incidence rate of 1.4/100 /year (CI_{95} 1.3, 1.5) and 1013 RA cases (57.8%) had a positive RF test. The RR of RA diagnosis increased with RF titre from RR 5.0 (CI_{95} 4.0, 6.3) with titres of 1–9 IU/ml above the laboratory upper normal range (UNR) to RR 15.0 (CI_{95} 11.2, 20.0) at titres 40–50 IU/ml above UNR and RR 38.8 (CI_{95} 31.0, 48.4) at tires 500–999 IU/ml above UNR. The sensitivity and specificity of the RF test was 57.2% (CI_{95} 54.8%, 59.6%) and 93.8% (CI_{95} 93.6%, 94.0%) respectively. The LR+ was 9.3 (CI_{95} 8.8, 9.8) and the LR- was 0.5 (CI_{95} 0.4, 0.5). Patients were more likely to have a positive RF test when presenting with hand, shoulder or knee symptoms (RR 1.3 (CI_{95} 1.2, 1.4), 1.2 (CI_{95} 1.0, 1.3) and 1.1 (CI_{95} 1.0, 1.2) respectively), tenosynovitis (RR 1.5, CI_{95} 1.1, 2.0) or a history of connective tissue disease (RR 1.4, CI_{95} 1.2, 1.7). Those presenting with neck (RR 0.8, CI_{95} 0.7, 1.0) or back pain (RR 0.8, CI_{95} 0.7, 0.9) were less likely to have a positive RF test. Positive RF tests were associated with an increased risk of death in the 2 years following the test (RR 1.5 (CI_{95} 1.3, 1.7).

Conclusion: Whilst RF tests perform moderately well for identifying RA (LR+ 9.27), they do not perform well for ruling out disease if the result is negative (LR- 0.46). Forty two per cent of patients with an eventual diagnosis of RA had a negative initial RF test. We caution against the use of RF as screening tool to rule out RA in patients with symptoms consistent with RA and its indiscriminate use in patients with less specific musculoskeletal problems such as neck or back pain.

Disclosure: A. Miller, None; **A. L. Nightingale**, None; **C. J. Sammon**, None; **T. Holt**, None; **K. R. Mahtani**, None; **N. McHugh**, None; **C. S. de Vries**, None; **R. A. Luqmani**, None.

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Patient-Reported Outcome Measures For Rheumatoid Arthritis: Minimal Important Differences Review. Helen Kitchen[1], Brian Bekker Hansen[2], Linda Abetz[1], Lise Højbjerre[2] and Martin Strandberg-Larsen[2]. [1]Adelphi Values Ltd, Cheshire, United Kingdom, [2]Novo Nordisk A/S, Søborg, Denmark.

Background/Purpose: Rheumatoid Arthritis (RA) is a chronic autoimmune disease, affecting around 1.3 million people in the US. A patient-centred focus is increasingly advocated by healthcare authorities, making assessments of the impact of novel treatments on patient-reported outcomes (PRO) important. PRO data should be interpreted in context of whether it represents a clinically meaningful change. Minimal important difference/ minimal clinically important difference (MID/MCID) provide the benchmarks to define responders in clinical trials. The objective of the study was to review MIDs/MCIDs for PROs commonly applied in clinical trials in patients with RA.

Methods: Articles were identified in MEDLINE, EMBASE, and PsycINFO databases using pre-defined search terms related to RA, differential diagnosis, key PROs and MIDs/MCIDs. Reference lists of identified papers were manually searched. FDA/EMA regulatory guidance and reports, PRO user manuals, PRO Labels and PROQOLID were searched to identify information on MIDs/MCIDs. The following PROs in RA were included in the review: Health Assessment Questionnaire Disability Index (HAQ-DI), 0–100mm pain visual analogue scale (VAS), 0–100mm patient global assessment of disease activity (PtGA), Medical Outcomes Study Short-Form Health Survey (SF-36v2), EuroQol (EQ-5D-3L), Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue), and Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis (WPAI:RA). MIDs/MCIDs were prioritised as follows: Available in: 1) RA, 2) related inflammatory conditions, 3) general population. If MIDs/MCIDs were sparse, the next approach was taken.

Results: The search identified 1019 abstracts; 32 abstracts met inclusion and exclusion criteria. From the reference list search, an additional 17 abstracts met the criteria, totalling 49 articles for in-depth review. MIDs/ MCIDs were identified for an RA population for the HAQ-DI (≥0.22 units), Pain (VAS) (−11.9 mm for minimal improvement), PtGA (−9.1mm for minimal improvement), SF-36v2 (change of 2.0 to 3.8 points for Physical Component Summary (PCS) score and 2.7 to 4.6 points for Mental Component Summary (MCS) score), EQ-5D-3L (0.06 to 0.20 [improvement]), FACIT-Fatigue (3.5 to 4.1 points). No MID/MCID information for the WPAI:RA was identified. Most articles focused on the MIDs/MCID's for change over time within a treatment group. MID's/MCID's used in clinical trials in RA were not always consistent with the literature: often applied responder definitions for HAQ-DI ranged from 0.22 to 0.3 units, was 10mm for Pain (VAS) and PtGA, was 3 to 4 points for FACIT-Fatigue, and was a change of 2.5 points for the PCS and MCS of the SF-36v2.

Conclusion: MID/MCID information is available for the core PRO measures in RA. However, some gaps in information remains for the newer PRO measures in RA. Further research to explore patients' perspectives of what constitutes important differences in symptoms, Health-Related Quality of Life, and functioning, and information on important differences between treatment groups, may be beneficial to extrapolate meaning from clinical trial data to the real-world experience of patients.

Disclosure: H. Kitchen, Adelphi Values Ltd – paid consultant to conduct literature review, 5; **B. B. Hansen**, Novo Nordisk A/S, 3; **L. Abetz**, Adelphi Values Ltd – paid consultant to conduct literature review, 5; **L. Højbjerre**, Novo Nordisk A/S, 3; **M. Strandberg-Larsen**, Novo Nordisk A/S, 3.

2269

Patient Reported Pain: A Predictor Of Outcomes In Rheumatoid Arthritis From The Consortium Of Rheumatology Researchers Of North America Registry. Dimitrios A. Pappas[1], Chitra K. Karki[2], Chin Lee[3], George W. Reed[2], Ping He[4] and Sarah Al Sawah[3]. [1]Columbia University, New York, NY, [2]CORRONA, Inc., Southborough, MA, [3]Eli Lilly and Company, Indianapolis, IN, [4]UMASS Medical School, Worcester, MA.

Background/Purpose: Pain is a hallmark of rheumatoid arthritis (RA). The extent to which patient reported pain in RA is related to patterns of biologic treatment switching, change in physical function or work productivity has not been adequately explored. Understanding the impact of patient reported pain on these parameters has clinical relevance in the management of RA.

Objective: To investigate the impact of patient reported pain on biologic treatment switching, change in physical function and work productivity in patients with RA participating in the CORRONA registry.

Methods: The CORRONA registry is a network of rheumatology practices across the U.S. with patient and physician reported data on more than 30,000 patients with RA. To be included in the analysis, patients with RA had to initiate a biologic agent and remain on stable background RA therapy (no dose adjustments, discontinuations, additions or switching) for 6 months. Pain was assessed using a numeric rating scale from 0–10 with 10 defined as "pain as bad as it could be". Pain levels reported at the visit following 6 months of stable RA therapy served as the baseline visit for the analysis. Outcomes assessed during the 12 month follow up period or at the 12 month follow up visit included: 1) frequency of biologic treatment switching; 2) frequency of biologic treatment switching due to inefficacy; 3) change from baseline in physical function as measured by the modified health assessment questionnaire (mHAQ); and 4) days lost from work due to RA. Separate multivariate analyses were performed for each outcome. Covariates considered for adjustment were age, gender, race, education status, smoking status, insurance status, baseline clinical disease activity index (CDAI), disease duration, baseline mHAQ, and comorbidities. Covariates were included in the model if they were biologically plausible and significantly associated with the outcome of interest in bivariate evaluations.

Results: 1180 patients with RA met the eligibility criteria and had a 12 month follow up visit after baseline. The majority were females (77.9%) and Caucasian (84.7%) with a mean age of 57.4 (SD ±12.4) years, mean pain 3.1 (SD ±2.5); mean disease duration 11.5 (SD ±9.9) years, mean CDAI 11.45 (SD ±10.7), and mean mHAQ score 0.4 (SD ±0.5). More than half had a college or university education while a small percentage reported smoking (16.8%). The most common comorbidities reported were history of malignancies (16.5%), cardiovascular disease (7.7%), peptic ulcer (7.3%) and diabetes (7.2%).

The adjusted association between patient reported pain and outcomes of interest are shown in Table 1. Odds Ratios (OR), Relative Risk Ratios (RRR) and Coefficients refer to change in outcome associated with a one unit increase in patient reported pain.

Conclusion: Patient reported pain in RA patients is associated with biologic treatment switches, reduction in function, and days lost from work.

Disclosure: D. A. Pappas, CORRONA Inc, 3, Novartis Pharmaceutical Corporation, 5, Columbia University, 6; **C. K. Karki**, Corrona, Inc., 3; **C. Lee**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **G. W. Reed**, CORRONA, Inc., 3; **P. He**, UMASS Medical School, 3; **S. Al Sawah**, Eli Lilly and Company, 3.

2270

US Guided Treat-To-Target Approach In Early RA: Implications For Uncoupling Of Disease Activity and Structural Damage. Yasser El Miedany[1], Maha El Gaafary[2], Sally Youssef[2] and Annie Nasr[2]. [1]Medway Hospital, Gillingham, United Kingdom, [2]Ain Shams University, Cairo, Egypt.

Background/Purpose: To assess the relationship between inflammation and joint destruction in RA patients who have not responded clinically to treatment using Musculoskeletal US as a sensitive tool to evaluate structural damage as well as residual synovial inflammation.

Methods: Changes from baseline to week 54 in clinical variables and measures of radiographic progression were compared between RA patients who received anti-TNF biologic therapy (Treat-to-Target approach), and those who received DMARDs therapy (standard protocol). Musculoskeletal US was used to assess for underlying radiographic progression and inflammatory status. Patients were divided into: in remission, low (LDA), moderate (MDA) and high (HDA) disease activity at 1-year of treatment according to DAS-28 score. Radiographic progression in both hands and feet was scored at base line and at 54 weeks using the modified total Sharp score (MSS). In addition, US examination of individual joints, both hands and feet, was carried out and scores for, number of erosions as well as synovial hypertrophy and PD using a validated semi-quantitative method (0–3) were recorded.

Results: At week 54, the progression of MSS, US-GS as well as US-PD scores in MDA and HDA cohorts were significantly lower in the biologic therapy than the DMARDs group: ($P < 0.01$). On comparing the MSS scores, the biologic therapy cohort who showed LDA (DAS-28: 2.6–3.1) exhibited no significant difference from the DMARDs cohort showing the same LDA status; whereas there was significant difference on comparing US-GS and US-PD scores ($P < 0.001$) between both groups of patients. On the other hand, the biologic therapy cohort showing DAS-28 score > 3.2 had significantly less number of erosions and joint space narrowing ($P < 0.001$) as well as US-GS and US-PD scores in comparison to the DMARDs therapy cohort.

In the DMARDs group, 1-year MSS progression in LDA, MDA and HDA was 0.40 ± 0.88, 1.04 ± 1.73, and 1.31 ± 3.02, respectively, whilst in the remission group, it was $0.1 + 0.64$. Analysis using US revealed: LDA: $0.86+0.65$, MDA: $2.15+1.82$, HAD: $2.73+1.94$ whilst in the remission group it was $0.12+0.57$. In contrast, in the biologic therapy cohort, MSS progression was 0.32 ± 0.26, 0.57 ± 0.42, and 0.63 ± 0.44, (for LDA, MDA and HDA respectively). Similar findings were found on comparing US scores for the inflamed joints: 0.31 ± 1.06, 0.93 ± 0.42, and 1.05 ± 0.37, (for LDA, MDA and HDA respectively) whereas in remission there was no significant difference between the 2 patients groups.

US-GS synovial score and/or US-PD score ≥ 2 increased the risk of structural progression: OR= (1.36–2.98) $p<0.001$.

Conclusion: The combination of biologic therapy and DMARDs retards damage independently of its effects on disease activity, contrasting DMARDs therapy. This indicates that beyond cytokine blockade, biologic therapy conveys profound anti-destructive effects and dissociates the link between disease activity and joint damage.

This study confirms the validity of the presence of US determined synovial thickness and PD signal for predicting subsequent structural deterioration and that US joint examinations may be relevant to optimally evaluate the risk of subsequent structural deterioration.

Disclosure: Y. El Miedany, None; **M. El Gaafary**, None; **S. Youssef**, None; **A. Nasr**, None.

2271

Dietary Sodium Increases The Risk For Rheumatoid Arthritis Among Smokers – Results From a Nested Case-Control Study. Björn Sundström[1], Ingegerd Johansson[2] and Solbritt Rantapää Dahlqvist[3]. [1]Umeå University, Umeå, Sweden, [2]Umeå Universitet, Umeå, Sweden, [3]Umeå University Hospital, Umeå, Sweden.

Background/Purpose: Recent studies using animal models and human cells *ex vivo* have indicated that sodium chloride may affect the immune system by the inducting of pathogenic Th17 cells mediated through a salt–sensing kinase (SGK1) leading to autoimmune disease. Since Th17 cells may play a role in the early stages of disease development in rheumatoid arthritis (RA), the dietary intake of sodium is of interest to analyse as a risk factor for the development of RA.

Methods: A nested case–control study was performed using the population based prospective data from the Västerbotten Intervention Programme collected between 1991 and 2011. The study included 386 individuals who later developed RA according to the 1987 ACR criteria. These 386 individuals (271 women, 115 men) had stated their dietary habits in a food frequency questionnaire (FFQ) as part of the community intervention programme before the onset of symptoms of RA (pre–symptomatic individuals). The pre-symptomatic individuals were compared using conditional logistic regression analyses with 1886 controls – matched for age, sex, time point of examination and version of the FFQ – drawn from the same database.

Results: Among current smokers with higher sodium consumption an increased odds ratio (OR) for developing RA was observed (OR) 2.26 (95% CI 1.06–4.81). Restriction of analyses to current smokers examined within the tertile closest to the onset of symptoms, the OR increased to 7.82 (95% CI 1.48–41.3). These associations were not found among non-smokers. Among current smokers with the lowest consumption of sodium, no significantly increased risk for developing RA could be identified. An interaction between high sodium intake and being current smoker was found.

Conclusion: Higher sodium consumption among smokers yielded an increased OR for development of RA. An interaction between smoking and sodium was found. These results provide new insights into the pathogenesis of RA. Furthermore, since sodium intake is related to the consumption of foods that are suggested to have an impact on health, *i.e.* meat, fruit, and vegetables, these results may have implications for studies of the effect of diet in RA, as well as in other diseases.

Disclosure: B. Sundström, None; **I. Johansson**, None; **S. Rantapää Dahlqvist**, None.

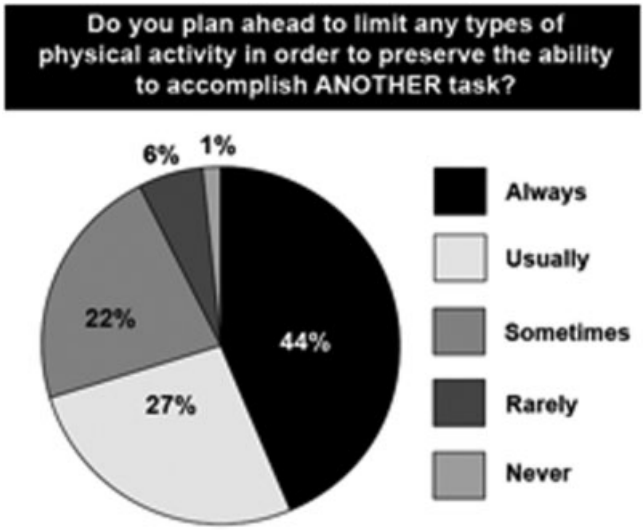
2272

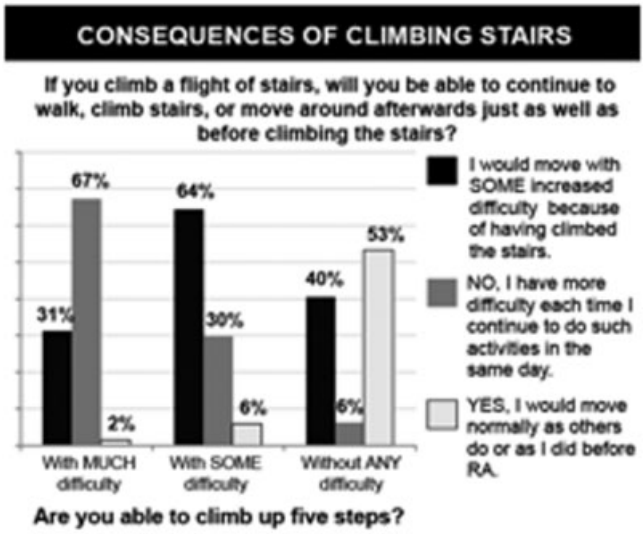
Patient Survey Regarding Utility Of The Health Assessment Questionnaire Reveals An Unrecognized Aspect Of Disease Activity In Rheumatoid Arthritis: Consequences Of Physical Activity. Kelly O'Neill Young[1], Dana M. Symons[1], Andrew T. Lumpe[2] and Cynthia S. Crowson[3]. [1]Rheumatoid Patient Foundation, Cocoa, FL, [2]Seattle Pacific University, Seattle, WA, [3]Mayo Clinic, Rochester, MN.

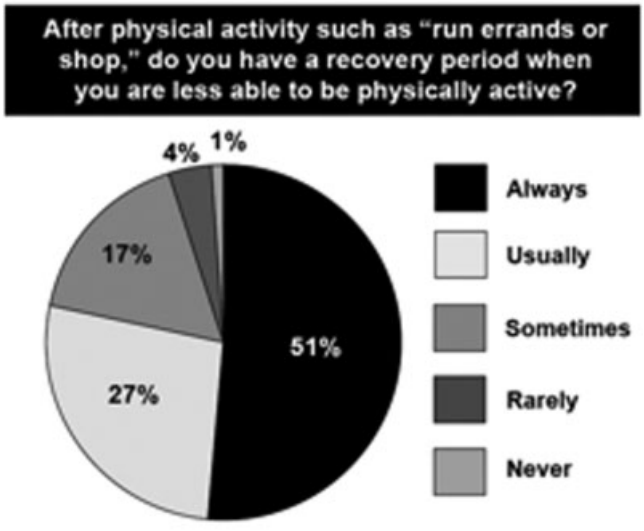
Background/Purpose: The Health Assessment Questionnaire (HAQ) has been used to assess disability in people with rheumatoid arthritis (RA) for over 30 years. However, the HAQ may not measure essential aspects of disease impact on ability to perform tasks because it does not consider real world context or consequences of performing particular tasks. The purpose of this study was to examine whether typical HAQ questions may miss fundamental information about functional status.

Methods: A web-based questionnaire was presented over 11 days in 2012 on a secure survey system preventing multiple entries. The questionnaire included 8 questions about consequences of performing certain physical tasks and whether a recovery period followed, and some questions directly from the HAQ. Analysis methods included reporting percentages, Pearson correlations and two-sample tests.

Results: The questionnaire was completed by 2,179 patients with self-reported RA (1997 women and 182 men; 72% seropositive) and a wide range of disease duration (< 2 years: 26%, 2–5 years: 29%, 5–10 years: 18% and >10 years: 26%). Of these, 71% reported often (44% "always" and 27% "usually") planning ahead to limit physical activities to preserve the ability to accomplish another task. Also 78% reported often (51% "always" and 27% "usually") having a recovery period when they are less able to be physically active after physical activity. The majority reported being unable to do chores such as vacuuming or yard work on the same day as running errands or shopping (24% "never", 33% "rarely", 28% "sometimes", 9% "usually" and 6% "always"). Comparing men and women, there were no significant differences in the responses to the consequence questions ($p=0.3$), but for the HAQ items men had significantly higher disease activity ($p<0.001$). Conversely, seropositive patients had higher levels of activity on the consequence questions than seronegative patients ($p=0.027$), but no differences in the HAQ items ($p=0.5$). The questions regarding consequences of physical activities for patients with RA were only moderately correlated with standard HAQ questions regarding shampooing and step climbing (correlation coefficients: 0.3–0.4; $p<0.01$), indicating these questions may be measuring similar but different aspects of RA disease activity than the HAQ.







Conclusion: Within the context of real-life, patients have lower functional capacity after performing tasks described in the HAQ, and may not be able to repeat such tasks with the same level of difficulty. Patients also modify tasks, which may not be detected by HAQ responses. Further investigation is needed to develop ways patient outcome measures can more accurately assess RA disease activity.

Disclosure: K. O. Young, None; **D. M. Symons**, None; **A. T. Lumpe**, None; **C. S. Crowson**, None.

2273

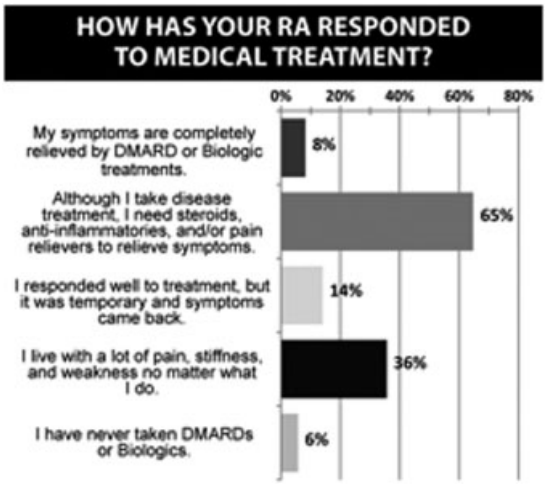
Patient Survey Challenges Conventional Notions Regarding Symptoms and Experiences Of People Living With Rheumatoid Arthritis.

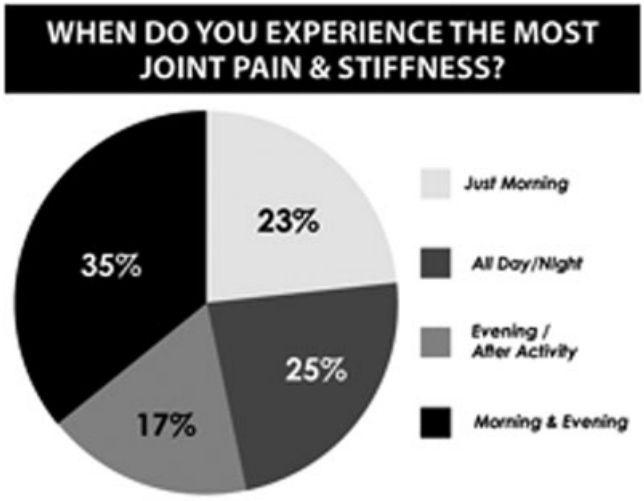
Kelly O'Neill Young[1], Cynthia S. Crowson[2] and Dana M. Symons[1]. [1]Rheumatoid Patient Foundation, Cocoa, FL, [2]Mayo Clinic, Rochester, MN.

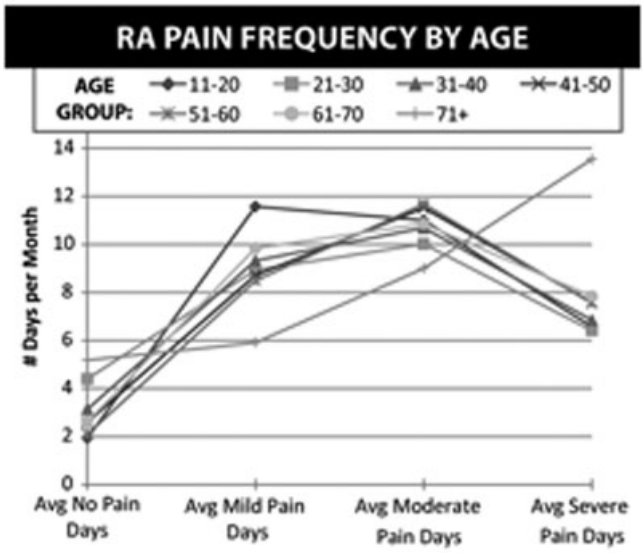
Background/Purpose: While rheumatoid arthritis (RA) has been studied for decades, many aspects of the disease are not well understood. Like systemic lupus erythematosus, RA manifests with a spectrum of symptoms that vary between patients and may not be accurately reflected in current literature. The goal of this study was to obtain greater understanding of the nature of RA as experienced by patients.

Methods: A 29-item web-based questionnaire was conducted in 2011 by a secure survey system preventing multiple entries. The questionnaire included questions about RA symptoms and treatments. Percentages and averages were used to summarize the data. 320 patients responded to an online poll with a follow-up question on morning stiffness.

Results: The questionnaire was completed by 1,465 self-reported RA patients (93% women and 7% men); 69% were seropositive (31% were seronegative or were unknown). Time since RA diagnosis varied with a mean of 6.6 years, 25% of respondents diagnosed within the past year, and 52% reported having RA symptoms for longer than a year prior to diagnosis. Low-grade fevers were common (80% reported experiencing sometimes) and most (99%) reported sometimes experiencing fatigue. On average, respondents experienced only 2 pain-free days per month with 68% having zero pain-free days in an average month. Pain levels were not affected by length of time since diagnosis and were similar across age groups, except for higher pain levels reported by those ≥ 71 years. Physical activity increased pain for 67%, and decreased pain for 18%. The top 3 factors cited as reducing pain were medications, rest and heat. Medications were reported to reduce pain by 80% of respondents, the majority stating that added medications (i.e., steroids, anti-inflammatories and/or pain relievers) were needed beyond disease treatments to address residual RA symptoms. Symptoms were completely controlled by treatments in only 8% of patients with 36% stating they continue to have a lot of symptoms "no matter what." While 23% of respondents reported they experience the most joint pain and stiffness in the morning, 25% have joint pain and stiffness all day and night; 52% experience some or most pain and stiffness in the evening or after activity. One-third said they always (12%) or usually (21%) have RA symptoms that their rheumatologists "do not believe or understand." 75% of respondents reported experiencing either joint damage without obvious swelling or having obvious joint swelling with no resulting damage, indicating the two are frequently unassociated.







Conclusion: The data in this survey indicate patient experiences and symptoms do not always reflect what is traditionally presented in the literature concerning RA pain, morning stiffness, the relationship between swelling and damage, and what worsens or improves symptoms. Additional research should seek a broader understanding of the disease experience of RA.

Disclosure: K. O. Young, None; **C. S. Crowson**, None; **D. M. Symons**, None.

2274

Assessment Of The Diagnostic Accuracy Of Different Strategies For Health Fair Case-Finding For Undiagnosed Inflammatory Arthritis. Kaylynn Aiona[1], Christopher C. Striebich[2], M. Kristen Demoruelle[3], Julia J. Rhiannon[3], Stuart M. Weisman[4], Marie L. Feser[4], Lezlie A. Derber[4], James H. Goddard[5], Stacey Brake[5], Jill Lysengen[6], Laura Rosseisen[6], John E. Hokanson[1], Anna E. Baron[1], Jill M. Norris[1], V. Michael Holers[3] and Kevin D. Deane[3]. [1]Colorado School of Public Health, Aurora, CO, [2]University of Colorado Denver, Aurora, CO, [3]University of Colorado School of Medicine, Aurora, CO, [4]University of Colorado School of Medicine, Division of Rheumatology, Aurora, CO, [5]9Health Fair, Denver, CO, [6]Arthritis Foundation, Great West Region, Denver Office, Denver, CO.

Background/Purpose: Early treatment of inflammatory arthritis (IA), and especially rheumatoid arthritis (RA), leads to improved outcomes, although diagnostic delays may impede timely treatment. We hypothesized that case finding in a community based health fair may improve the timing of diagnosis and treatment of IA. However, the diagnostic accuracy of this approach in a health fair where IA is likely rare is largely unknown. Therefore, we developed and tested the diagnostic accuracy of a case-finding strategy for IA in a Colorado-based health fair.

Methods: Volunteers were evaluated between 2009–2012 at 18 health fair sites using a self-reported joint symptom questionnaire and CCP3 (INOVA; ≥20 units positive) and RF (Roche RFII; >14 units positive) testing. IA was defined as synovitis identified by a trained clinician on examination of the wrists, elbows, and PIP and MCP joints performed at the same time as the questionnaire and blood testing.

Results: 3260 volunteers completed a questionnaire, joint examination and blood testing; 164 (5%) were identified with active, previously undiagnosed IA, of whom 33/164 (20%) were classified as RA by 2010 ACR/EULAR criteria. After modifications of an initial questionnaire to improve its ease of use and sensitivity for IA, the optimal prediction model for IA (multiple regression; bootstrap validated AUC of 0.73) included 4 items that each contributed similarly to the model: CCP positivity and self-reported: a) morning stiffness ≥1 hour, b) nodules, and c) joint pain, stiffness or swelling present the day of questionnaire completion. The maximal sensitivity (SENS) for IA was with ≥1 item positive (96%; corresponding specificity (SPEC) of 24%); ≥2 positive items resulted in the highest combination of SENS and SPEC (85% and 52%, respectively). In 2012 we piloted a questionnaire with a figure for subjects to identify symptom location, and symptoms in PIPs and MCPs were 93% SENS and 65% SPEC for IA, although there were too few cases of IA (N=15 out of 338 subjects) to evaluate adequately the diagnostic accuracy of additional factors. CCP and/or RF were positive in 279/3260 (9%) of subjects, and both autoantibodies (Abs) were independently significantly associated with IA ($p<0.01$ and 0.03, respectively). In evaluation of the diagnostic accuracy of Abs alone for IA, CCP and/or RF positivity was 11% SENS and 92% SPEC for IA, reflecting that most IA was seronegative. Additionally, CCP and RF levels >3 times normal were each highly specific for IA (CCP: SENS 5%, SPEC 99%; RF: SENS 5%, SPEC 99%).

Conclusion: Assessing self-reported symptoms and Abs in a health fair may identify previously undiagnosed IA/RA. As such, these items may be used initially independently of a clinician thus broadening the applicability of this approach to settings where trained joint examiners are absent. Further testing is necessary to validate these findings and to determine whether case-finding accuracy may be improved by ascertaining specific locations of joint symptoms. Additionally, determining final formal diagnoses, timing of treatment for IA, and post-health fair costs (including costs of evaluating false-positive results) will help determine the overall impact of this approach in arthritis care.

Disclosure: K. Aiona, None; **C. C. Striebich**, None; **M. K. Demoruelle**, None; **J. J. Rhiannon**, None; **S. M. Weisman**, None; **M. L. Feser**, None; **L. A. Derber**, None; **J. H. Goddard**, None; **S. Brake**, None; **J. Lysengen**, None; **L. Rosseisen**, None; **J. E. Hokanson**, None; **A. E. Baron**, None; **J. M. Norris**, None; **V. M. Holers**, None; **K. D. Deane**, AbbVie, 2.

2275

Responsiveness Of The Outcomes Measures In Rheumatology Clinical Trials Initiative's Preliminary Flare Questions To Detect Flares Within Patients In The Canadian Early Arthritis Cohort. Vivian P. Bykerk[1], Karen Visser[2], Ernest Choy[3], Clifton O. Bingham III[4], Daming Lin[1], Juan Xiong[1], Gilles Boire[5], Boulos Haraoui[6], Carol A. Hitchon[7], Janet E. Pope[8], J. Carter Thorne[9], Diane Tin[9], Edward C. Keystone[1], Susan J. Bartlett[10], - CATCH Investigators[11] and - OMERACT Flare Working Group[12]. [1]Mount Sinai Hospital, University of Toronto, Toronto, ON, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Cardiff University, Institute of Infection and Immunity, Cardiff, United Kingdom, [4]Johns Hopkins University, Baltimore, MD, [5]Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, [6]Institut de Rhumatologie de Montréal, Montreal, QC, [7]University of Manitoba, Winnipeg, MB, [8]St Joseph Health Care, London, ON, [9]Southlake Regional Health Centre, Newmarket, ON, [10]McGill University, Montreal, QC, [11]Canadian Collaboration, Toronto, ON, [12]International Collaboration, Baltimore, MD.

Background/Purpose: OMERACT (OM) recently developed preliminary flare questions (PFQs) that capture domains important to patients (pts) to identify a flare of RA[1]. Whether these change in pts who flare is unknown.

Objectives: To study responsiveness to change of the PFQs' 9 domains within early RA (ERA) pts who have a flare.

Methods: Paired data from CATCH (Canadian early arthritis cohort) pts who prospectively answered the PFQs twice in 3 months between 12/2011-5/2013 were used. The PFQs comprise 7 pt reported outcomes (PROs) assessing pt global, pain, physical function, stiffness, fatigue, coping, and participation as questions scored from 0–10 (best-worst) and pt reported tender and swollen joint counts (PtTJC40, PtSJC40). The median change (IQR) and effect size (ES) for each domain was compared in pts who flared based on a worsening of DAS28 of 1.2 (or 0.6 if DAS28> 3.2)[2] (DASdef) or by answering "Are you having a flare at this time?" with a flare defined as changing from no to yes (Fdef). Using the last pairs of 3-month interval PFQs, changes in PROs were analyzed by the Wilcoxon signed rank test. Responsiveness to change in each of the PFQs for flare vs. no-flare was assessed by non-parametric effect sizes (ES) calculated for both definitions.

Results: Of 115 eligible pts 79% were female, 85% Caucasian, 90% met ACR/EULAR 2010 criteria, 17% smoked, 24% had erosions, 69/73% were ACPA/RF+ve. Pts had a mean (SD) age of 55 (15) years, symptom duration 5.4 (3.0) months; Pts' initial DAS28 was 3.03 (1.34), HAQ-DI 0.52 (0.55); 46%/15% were in DAS28 remission/low disease activity. 23% reported a flare with a mean (SD) intensity of 6.3 (2.4) and duration ≥ 8 days in 59%. Median (IQR) increases in DAS28 using DASdef and Fdef was 1.8(1.–1.2) and 0.6(.4-.35). Changes in PtGlobal, pain, function, fatigue, stiffness, coping, PtTJC40 and PtSJC40 all changed significantly for flare vs. non-flare pts (Table). Responsiveness to change differed according to flare definitions (Figure).

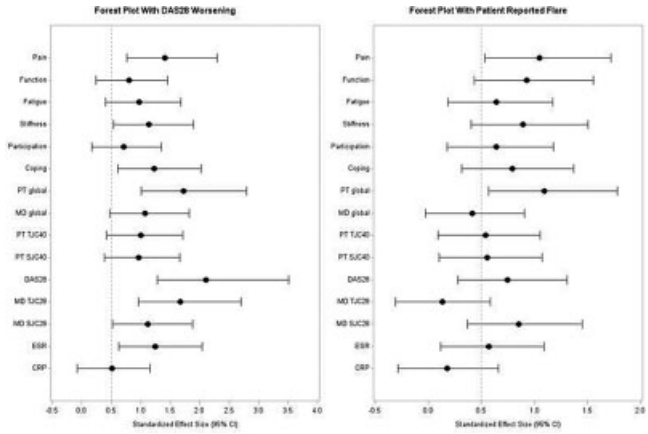


Figure. Effect Size (adjusted 95% CI) for each domain in the PFQs according to two definitions of RA flare.

Table. Responsiveness of OMERACT PFQ Domains and Physician/Lab based variables reported as median change (IQR) and effect size (p-value) in flare and non-flare groups using 2 flare definitions.

	DAS definition (increase of 1.2 or >.6 if 3.2)			Patient Flare definition (No to Yes)		
Variables	Flare* N = 16	Non-flare* N = 99	Effect Size** (p-value)***	Flare* N = 26	Non-flare* N = 89	Effect Size** (p-value)***
Pain	2 (2.5)	0 (2)	1.41 (<0.0001)	2 (2)	0 (2)	1.05 (<0.0001)
Function	1.5 (3.5)	0 (2)	0.8 (0.0043)	1.5 (3)	0 (1)	0.93 (0.0001)
Fatigue	1.5 (3.0)	0 (2)	0.97 (0.0006)	1 (3)	0 (2)	0.64 (0.0056)
Stiffness	3.0 (4.5)	0 (2)	1.14 (<0.0001)	1.5 (4)	0 (1)	0.89 (0.0002)
Participation	1.5 (4.5)	0 (1)	0.71 (0.0103)	0 (3)	0 (1)	0.64 (0.0057)
Coping	3.0 (3.0)	0 (1)	1.22 (<0.0001	1 (3)	0 (1)	0.79 (0.0008)
Pt global	3.0 (3.0)	0 (2)	1.72 (<0.0001)	1.5 (3)	0 (1)	1.09 (<0.0001)
PT TJC40	4.0 (12.0)	0 (5)	1 (0.0004)	1 (6)	0 (5)	0.54 (0.0179)
PT SJC40	2.0 (7.0)	0 (2)	0.96 (0.0007)	0 (4)	0 (2)	0.55 (0.0154)
Physician global	0.1 (2)	0 (1.5)	1.08 (0.0003)	0 (2)	0 (1.4)	0.41 (0.0677)
DAS28	1.5 (1)	−0.2 (1.3)	2.11 (<0.0001)	0.6 (1.6)	−0.2 (1.3)	0.75 (0.0014)
CRP	0.2 (3)	0 (2.9)	0.51 (0.0881)	0 (3.7)	0 (2.9)	0.18 (0.4544)
MD TJC28	3 (5.5)	0 (2)	1.67 (<0.0001)	0 (4)	0 (2)	0.13 (0.5563)
MD SJC28	0.5 (2)	0 (1)	1.12 (0.0001)	0 (1)	0 (1)	0.85 (0.0003)
ESR	6.5 (6.6)	−2 (7)	1.24 (<0.0001)	4 (8)	−2 (7)	0.57 (0.0129)

Responsiveness of PFQ Domains & Physician/Lab based variables (*Median change (IQR), **Effect Size (ES) (non-parametric), ***p-value using Wilcoxin Rank Sum Test. This analysis did not incorporate the self-management domain.

Conclusion: The OM PFQs are responsive to change with worsening of disease activity within ERA pts over time but the magnitude of change varies with flare definition. Studies are needed to understand the relative contributions of each domain to identify RA flares that necessitate treatment increases.

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2276

Does Socioeconomic Status Affect Outcomes In Early Rheumatoid Arthritis? Data From An Inception Cohort.

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Background/Purpose: Assess the impact of socioeconomic status (SES) on outcomes in patients with early inflammatory arthritis using data from the Canadian Early Arthritis Cohort (CATCH) study.

Methods: 2023 patients were recruited into a prospective cohort study, and allocated to low- or high-SES groups based on education and income. Outcomes at baseline and 12 months analyzed against SES include the Disease Activity Score (DAS28), pain, patient global assessment scale, the Health Assessment Questionnaire Disability Index (HAQ), and the SF12-v2 Health Survey. Correlations and regression analyses were performed.

Results: Forty-four % had education of high school or less and 38% were in the lowest income group (<$50,000/year). The low-education group presented with higher DAS28 (p=0.045) at baseline; DAS28 and education were not correlated at 12 months. Low education was also associated with lower physical component score on SF12-v2 at baseline (p=0.018) and 12 months (p=0.024). Patients from the low-income group presented with higher HAQ (p=0.017), pain (p=0.035), patient global assessment (p=0.004), and Simplified Disease Activity Index (SDAI) (p=0.022). Comparing baseline low to high income groups was associated with an odds ratio (OR) for above-median: HAQ 1.220 (95% CI 1.013–1.470), patient global assessment 1.284 (95% CI 1.067–1.546), and SDAI 1.240 (95% CI 1.018–1.509). The predictive value of low income for HAQ remained at 12 months, OR 1.304 (95% CI 1.018–1.669) but the other variables were non-significant.

Conclusion: Low SES is associated at baseline with higher disease activity, poorer physical function, more pain, higher patient global assessment, and higher HAQ. Physical function and HAQ remain worse at one-year follow-up. This could be due to an effect of SES on health related behaviors or confounding (such as older patients having lower SES and more comorbidities).

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2277

Midcarpal Joint Effusion Is As Common As Radiocarpal Joint Effusion In Swollen Wrists Of Patients With Rheumatoid Arthritis.

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Background/Purpose: Wrist joint is most commonly involved in rheumatoid arthritis (RA) and consists of multiple compartments; radiocarpal, midcarpal, and carpometacarpal joints. Intraarticular corticosteroid injection is usually done into radiocarpal joint for wrist joint swelling. However, it is hard to expect that drug injected into the radiocarpal joint spread to other compartments of wrist joint. To identify the distribution of joint effusions in swollen wrist joints of patients with RA and examine the effect of intraarticular corticosteroid injection into multiple compartments of wrist joints.

Methods: In RA patients with wrist joint swelling, we examined the distribution of joint effusion (radiocarpal, midcarpal, and carpometacarpal joints and extensor digitorum tendons) using musculoskeletal ultrasound.

Results: Twenty-seven patients presented with wrist joint swelling including 3 patients with both wrists involved and total of 30 wrist joints were examined. Twenty patients were female (74%), mean age was 55.8 ± 11.8 years, and mean disease duration was 62.5 ± 61.22 months. Twenty-four patients (88.9%) were seropositive and 9 patients (33.3%) had been treated with anti-TNF agents. Radio-carpal joint effusion was present in all 30 swollen wrist joints. Of note, effusion was found in midcarpal joints of 28 swollen wrists (93.3%). Among midcarpal joints, lunate-capitate joint was most commonly involved (n=28), followed by lunate-hamate joint (n=26), scaphoid-trapezoid joint (n=25), and triquetrum-hamate joint (n=25). In 15 wrists, effusion was also found in carpometacarpal joints (CMC); 4th CMC joint (n=10), 5th CMC joint (n=9), 3rd CMC joint (n=6), and 2nd CMC joint (n=2). Extensor digitorum tendons were involved in 3 wrists. We injected corticosteroid into both radiocarpal and midcarpal joints in 7 wrists and 6 of them (85.7%) showed marked improvement in pain and swelling at the next visit.

Conclusion: Midcarpal joint effusion is as common as radiocarpal joint effusion in swollen wrists of patients with RA. This suggests that, in patients with wrist joint swelling, not only radicarpal joint but also midcarpal joint should be considered for intraarticular corticosteroid injection.

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2278

Ordering Of Serologic Markers Of Rheumatoid Arthritis Among Primary Care and Subspecialty Providers: Under-Utilization Of Anti-Citrullinated Peptide Antibody Tests By Non-Rheumatologists. Emily H. Glynn[1], Mark H. Wener[1] and Michael Astion[2]. [1]University of Washington, Seattle, WA, [2]Seattle Children's Hospital, Seattle, WA.

Background/Purpose: Anti-citrullinated peptide antibodies (ACPA) are more specific and have a superior positive predictive value for diagnosis of rheumatoid arthritis (RA) compared to RF. The American College of Rheumatology revised the RA classification criteria to include ACPA in addition to RF in 2010 (Arthr Rheum. 2010; 62:2569–2581). This study's aim is to characterize utilization of RF and ACPA among primary care, non-rheumatology subspecialty, and rheumatology providers 2 years before and 2 years after the new criteria were published. The expectation is that the 2 tests will be ordered in a 1:1 ratio after the new criteria, whereas RF would be ordered more than ACPA before 2010.

Methods: The study was performed at an academic medical center in the western United States. All orders for RF and ACPA (ordered as anti-CCP) placed in 2008 and 2012 were retrieved and the medical records from outpatient encounters were reviewed. Orders meeting the following criteria were included: (1) RA was in the differential diagnosis, (2) patient endorsed musculoskeletal complaints, and/or (3) the provider noted tests were ordered for an "inflammatory," "rheumatologic," or "autoimmune" indication. Orders placed on patients with a previous history of RA or who were being evaluated only for extra-articular manifestations of RA or cryoglobulinemia were excluded. Included orders were sorted by provider type (primary care, non-rheumatology subspecialty, rheumatology), and the ratio of RF to anti-CCP orders for each type was calculated.

Results: Out of 765 RF & antiCCP orders reviewed, 463 orders (238 from 2008 and 225 from 2012) met the inclusion criteria. Of these, 297 (64%) were ordered by primary care providers, 80 (17%) by non-rheumatology subspecialty providers, and 86 (17%) by rheumatology providers. The RF/anti-CCP ratios by provider type comparing 2008 to 2012 were as follows: primary care providers 2.7 vs. 3.1, non-rheumatology subspecialty providers 12.5 vs. 3.5, and rheumatologists 0.85 vs. 0.96. Isolated RF orders represented the majority of orders placed by non-rheumatologists (primary care and subspecialty providers) comprising 72% and 70% of total orders placed in 2008 and 2012, respectively. Among rheumatologists, RF in isolation represented only 4% and 11% of orders, while the combination of RF and anti-CCP comprised 66% and 88% of orders placed in 2008 and 2012, respectively.

Conclusion: Our results indicate that 2 years after revision of the RA classification criteria, anti-CCP remains a vastly underutilized test among non-rheumatology providers considering the diagnosis of RA.

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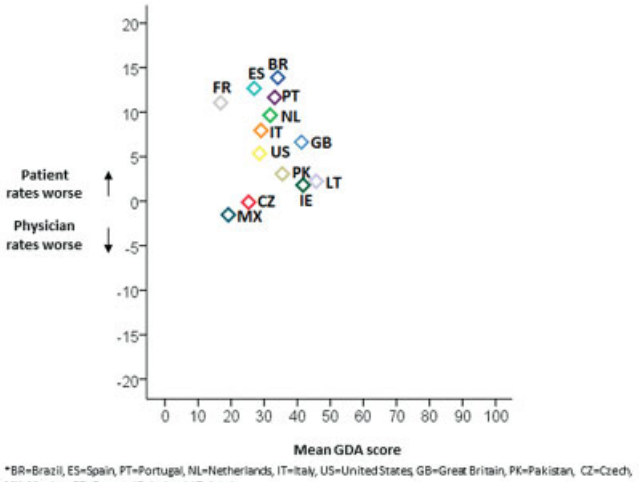
2279

Assessment Of Global Disease Activity In Rheumatoid Arthritis By Patients and Physicians: Cultural Differences Among Countries In The Meteor Database. E. Gvozdenovic[1], R. Wolterbeek[1], C.F. Allaart[1], Claiton Brenol[2], Arvind Chopra[3], Maxime Dougados[4], Paul Emery[5], D. van der Heijde[1], T.W.J. Huizinga[1], Jonathan Kay[6], Emilio Martín Mola[7], Robert J. Moots[8], José A. P. Da Silva[9], Josef S. Smolen[10], Douglas J. Veale[11] and R. Landewe[12]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Universidade Federal do Rio Grande do Sul, Porto Alegre RS, Brazil, [3]Center for Rheumatic Diseases, Pune, India, [4]Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France, [5]Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [6]UMass Memorial Medical Center and University of Massachusetts Medical School, Worcester, MA, [7]Rheumatology. La Paz Hospital. IdiPaz, Madrid, Spain, [8]University of Liverpool, Liverpool, United Kingdom, [9]Centro Hospitalar e Universitário de Coimbra – Hospitais da Universidade de Coimbra, E.P.E., Coimbra, Portugal, [10]Medical University of Vienna, Vienna, Austria, [11]St. Vincent's University Hospital, Dublin 4, Ireland, [12]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands.

Background/Purpose: Dissonant perceptions of disease activity between rheumatoid arthritis (RA) patients and their rheumatologists may influence treatment decisions. The discordance between patient's and physician's global disease activity assessment (PtGDA and PhGDA, respectively) may vary by country because of cultural differences. Our aim is to compare the differences between PtGDA and PhGDA among 13 countries in the METEOR database.

Methods: The Measurement of efficacy of Treatment in the Era of Rheumatology (METEOR) database, a worldwide online tool for disease monitoring in RA, was used to anonymously select 14,020 patients during the period between 2008 and 2012. PtGDA and PhGDA were scored independently on a 100 mm visual analogue scale (VAS) with 0 and 100 as extremes. Linear Mixed Models (LMM) were used to estimate the mean differences between PtGDA and PhGDA score in13 countries (Brazil, Czech Republic, Spain, France, United Kingdom, Ireland, Italy, Latvia, Mexico, Pakistan, Portugal, United States, and the Netherlands), adjusted for DAS. Generalized Estimated Equation (GEE) was used to model differences (>20mm) between PtGDA and PhGDA score as the outcome and countries as determinants, corrected for DAS.

Results: Mean difference between PtGDA and PhGDA score differs by country, varying from −2 mm (physician scores higher) in Mexico to 14 mm (patient scores higher) in Brazil (Figure 1), independent of DAS. GEE indicated that 'country' was a significant determinant of the difference between PtGDA and PhGDA score, independent of differences in DAS. With the Netherlands as a reference, PtGDA and PhGDA scores differ significantly within the same patient in almost all countries (Brazil, Czech Republic, Great Britain, Ireland, Italy, Latvia, Mexico, Pakistan, Portugal and United States).



*BR=Brazil, ES=Spain, PT=Portugal, NL=Netherlands, IT=Italy, US=United States, GB=Great Britain, PK=Pakistan, CZ=Czech, MX=Mexico, FR=France, IE=Ireland, LT=Latvia.

Conclusion: We find differences between patients' and physicians' assessment of global disease activity, the magnitude of which varies depending upon the country in which the patient and the physician both reside. Cultural influences must be taken into account when interpreting discordances between the patient's and the physician's assessment of global disease activity

in RA. Although the magnitude differs across countries, patients nearly always assess global disease activity to be worse than do their physicians.

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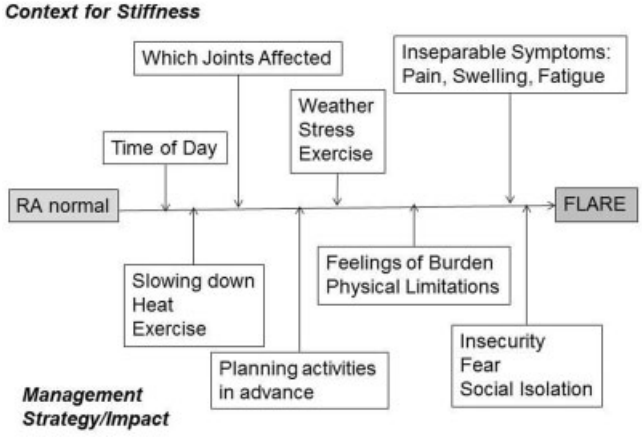
Stiffness From The Perspective Of People Living With Rheumatoid Arthritis. Ana-Maria Orbai[1], Katherine Clegg-Smith[2], Susan J. Bartlett[3], Elaine De Leon[4], Michelle Jones[1] and Clifton O. Bingham III[1]. [1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins University School of Public Health, Baltimore, MD, [3]McGill University, Montreal, QC, [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

Background/Purpose: Stiffness was included in the 1961 and 1987 Rheumatoid Arthritis (RA) classification criteria and continues to be commonly queried in clinical care. Its relative contribution to disease activity levels is controversial possibly due to limited knowledge of how people with RA experience stiffness and its impact on daily life.

Methods: We held focus groups (FG) with people with RA recruited from an academic clinic and private practice setting to explore stiffness experiences. Inductive thematic analysis was conducted by a team of clinical and behavioral scientists to identify themes.

Results: FGs (N=20 people) were held 2 – 11/2012. Most (75%) were female, mean (SD) age 57 (13) yrs and RA duration 16 (8) yrs. Mean patient global scores were 44 (27), pain (100 mm VAS) 47 (30) and mHAQ 0.48 (0.55). Five themes were identified: 1. People with RA outlined a hierarchical and relational conceptualization of symptoms (stiffness, pain, swelling, fatigue) 2. Stiffness was associated with management strategies and symptom alleviation 3. Stiffness was described in temporal terms 4. Stiffness had individual meanings 5. Stiffness had impact on physical, emotional and social well-being. Stiffness, pain and swelling were difficult to distinguish between as they co-occurred or as pain increased. Strategies to alleviate or reduce stiffness were common (warmth, slow down, stretch, swim). Stiffness was primarily characterized by onset (morning, evening) and key exacerbating factors (weather, stress, exercise). Participants related their current level of stiffness to the usual for them since developing RA and independently introduced "RA normal" as their reference state. The spectrum of stiffness intensity spanned from "RA normal" to flare ("I went into total lock up"). Stiffness impacted physical, emotional, and social health and was poorly understood by people without RA in comparison to pain. Unexpected or overwhelming stiffness caused feelings of anxiety, fear and vulnerability.



Conclusion: Stiffness is an integral part of RA and may be more heterogeneous in presentation than previously recognized. People living with RA report stiffness can have a significant impact on daily life, often underappreciated by family and others. The current model of morning stiffness duration, used in clinical practice and clinical trials, poorly reflects the experiential descriptions of stiffness which encompass temporal patterns, location, intensity, and impact on life activities. Individuals' use of "RA normal" as the new reference point for change in disease states might affect how insightful our clinical questions are, when we probe disease activity and impact on health and health related quality of life. The diversity of stiffness experiences, adaptations, and life impact suggest that a more individualized assessment may be needed to effectively monitor stiffness and ultimately enhance clinical care.

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2281

An Analysis Of Highly Discordant Erythrocyte Sedimentation and C Reactive Protein Levels In Rheumatoid Arthritis. Micha Abeles[1], Manuel Gomez-Ramirez[2] and Aryeh M. Abeles[1]. [1]University of Connecticut Health Center, Farmington, CT, [2]Johns Hopkins University, Baltimore, MD.

Background/Purpose: Discordance between the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) exists in a significant minority of rheumatoid arthritis (RA) patients. Interpretation of studies exploring the phenomenon is problematic for a number of reasons including: the dichotomization of continuous variables, failure to consider potential influence of none acute phase factors and common co-morbid conditions. To assess discordant values between the ESR and CRP we did a prospective case control study by establishing deciles of CRP and ESR values and evaluating the highest decile (i.e. the one having the most discrepant values).

Methods: Data on individual RA patients consecutively seen over a 6 month period were prospectively obtained. Serologic data included complete blood counts, albumin, liver and renal function, and serum protein electrophoresis. All co-morbid conditions and medications used were noted. Weight, sex, age, and length of time from diagnosis were recorded. The clinical disease activity index (CDAI) was used as a measure of disease activity. We established deciles and categorized participants into separate groups based on their ESR/CRP ratios (stratifying by ESR; age and gender were accounted for). The discordant group comprised participants with the top 10% elevated ESR and normal CRP values and vice versa. Each patient was matched to a non-discordant patient seen most closely to that visit and matched for age and sex (and when possible, weight). Data was consequently de-identified and evaluated. We computed between-subject (discordant vs. controls) univariate analyses of variance (ANOVA) on the above variables using age as a covariate.

Results: 251 individual RA patients were seen in the 6 month period. Of 26 patients meeting criteria 22 were in the high ESR normal CRP category. We elected not to include participants with high CRP normal ESR values because of low sample number (N = 4). Age, sex, ethnicity and weight were similar between groups, The most common co-morbid conditions included hypertension, gastric reflux disease and hyperlipidemia equally seen in each group. The only significant difference our data revealed was of hematocrit ($p < 0.01$), with the discordant group having significant lower mean values as compared to controls (36.30 vs. 40.15).The ANOVA failed to reveal an effect on CDAI ($p > 0.05$)

Conclusion: No previous study has looked at extreme discordance between CRP and ESR values in RA. We prospectively evaluated RA patients and compared those in the highest decile of discordance with matched controls (accounting for sex, weight, and ethnicity), analyzing multiple variables and found that aside from hematocrit values, there was no difference between groups.

Disclosure: M. Abeles, None; **M. Gomez-Ramirez**, None; **A. M. Abeles**, None.

2282

Performance Of The 2010 ACR/EULAR Classification Criteria For Rheumatoid Arthritis In a Group Of Elderly Onset Patients. Pierluigi Macchioni[1], Giovanni Barausse[2], Luigi Boiardi[1], Giulia Pazzola[1], Roberto Bortolotti[2], Giovanna Restuccia[1], Maria Grazia Catanoso[1], Giuseppe Paolazzi[3] and Carlo Salvarani[4]. [1]Arcispedale S Maria Nuova, IRCCS, Reggio Emilia, Italy, [2]Ospedale di Trento, Trento, Italy, [3]Ospedale Santa Chiara, Trento, Italy, [4]Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy.

Background/Purpose: To evaluate the diagnostic ability of the 2010 ACR/EULAR classification criteria for Rheumatoid arthritis (RA) in a consecutive series of elderly onset (> 50y) RA (EORA) in comparison with a group of new onset polymyalgia rheumatica (PMR) patients.

Methods: All patients with early arthritis seen at our two centres are followed according to a standardized protocol which include clinical examination (including 66 joint count), determination of laboratory parameters, QOL questionnaire, X-ray examination of hands and feet. Consecutive patients seen in our rheumatological centres with recent onset arthritis and

followed for at least 12 months were included prospectively during a 5 year period. Patients entered the study if diagnosis of RA or PMR were confirmed at 12 month follow-up period according to rheumatologist opinion (PM, GB). Diagnostic performance of ACR/EULAR 2010 classification criteria were evaluated and compared in the two groups of patients

Results: 144 new EORA and 137 new onset PMR patients entered the study. Table 1 compare demographic, clinical and laboratory data between the two populations.

Table 1. Demographic, clinical and laboratory characteristics of the patients at first examination.

	EORA	PMR	p	Difference (95%CI)
Mean Age (y)	64.6+9.2	74.5+7.4	<0.001	9.4 (7.5–11.4)
Male/female	27/73	29/71	ns	
Mean Disease duration (Weeks)	13+12	13+19	ns	0.7 (−4.6–3.2)
ESR (mm/first hour)	41+26	60+24	<0.001	18 (12–24)
CRP (mg/dl)	2.5+3.2	5.1+4.3	<0.001	2.5 (1.6–3.4)
RF/ACPA +	49%	1%	<0.001	
Mean large joint involved	1.6+1.7	3.38+1	<0.001	1.7 (1.5–2)
Mean small Joint Involved	7.4+5.6	1+1	<0.001	6.5 (7.5–5.5)
Mean ACR/EULAR points	6.3+1.9	3.4+1	<0.001	3 (3.3–2.4)
ACR/EULAR positivity	66.2%	3.2%	<0.001	OR 48.9 (14–163)

Conclusion: In a group of new onset EORA patients ACR/EULAR 2010 RA classification criteria have 66.2% sensitivity. ACR/EULAR 2010 criteria have high specificity and could be used to exclude RA in a new onset PMR patients.

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2283

The Evolving Use Of Biologic Monotherapy In Rheumatoid Arthritis and Its Impact On Patient Outcomes. Laurent Chanroux, Katrina Johnson and Joan Casellas. The Research Partnership, London, United Kingdom.

Background/Purpose: The aim of our study is to understand whether the use of biologic monotherapy among rheumatoid arthritis (RA) patients is increasing and whether this has any impact on their potential outcomes when compared to combination therapy with traditional disease-modifying anti-rheumatic drugs (DMARDs).

Methods: We used data collected as part of an online treatment survey conducted among a panel of rheumatologists between May 2008 and December 2012 across the five largest EU countries (France, Germany, Italy, Spain and the UK). We selected a sub-sample of 43,193 patient records from this data set. Patient cases were selected if a patient was currently prescribed his or her first ever biologic. This limited any confounding effects due to patients' previous biologic experience. No other screening criteria or quotas were applied to the data to ensure a natural fall-out of monotherapy patients. Patient demographics and key indicators of current health and quality of life were analysed including: disease activity score (DAS), overall joint count, perceived disease severity at diagnosis and latest consultation (assessed by physician), ability to work and current co-morbidities.

Results: In Q4 2012, 24% of reported biologic patients were currently treated without the concomitant use of traditional DMARDs, a non-significant increase over the level observed in Q2 2008 (23%). The use of biologic monotherapy was most common for patients treated with tocilizumab (42%) and was most frequently seen among our Italian and UK patients (26%). Monotherapy patients were on average significantly older (> 60 years old) and were perceived to have milder disease at diagnosis when compared to patients simultaneously treated with biologics and DMARDs. In addition, monotherapy patients were significantly more likely to have inflammatory back pain, ankylosing spondylitis, congestive heart failure and wider cardiovascular disease, whereas fibromyalgia and dactylitis were more common in patients receiving combination therapy. There were no differences in patients' gender, time since diagnosis and ability to work or the number of DMARDs patients had tried prior to initiating their biologic. However, when adjusting for disease severity at diagnosis, we saw no difference in physicians' perceptions of the current disease severity of patients from both groups, although a significantly higher proportion of monotherapy patients had a DAS < 2.6 (51%) while a significantly greater proportion of combination therapy patients has a DAS > 5.1 (7%).

Conclusion: Our data show that the use of biologic monotherapy has remained steady over the last four years and has been concentrated primarily among tocilizumab patients. Biologic monotherapy appears to be reserved for older, potentially more fragile patients with milder disease whereas combination therapy may still be preferred for patients with more severe forms of RA. Moreover, use of biologic monotherapy does not seem to negatively impact on patient outcomes with a significantly higher proportion of these patients achieving disease remission.

Disclosure: L. Chanroux, None; **K. Johnson**, None; **J. Casellas**, None.

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How Well Do Generic Patient Reported Outcomes Measurement Information System Instruments Capture Health Status In Rheumatoid Arthritis? Susan J. Bartlett, Ana-Maria Orbai, Trisha Duncan and Clifton O. Bingham III. Johns Hopkins University, Baltimore, MD.

Background/Purpose: PROMIS offers precise, reliable generic measurement of physical, mental and social health across chronic conditions. However, little is known about the validity and performance of PROMIS instruments in rheumatoid arthritis (RA), where high levels of pain and fatigue and low physical function and mood are common.

Methods: Data are from the baseline visit of the first 125 RA patients enrolled in an ongoing study to evaluate systematically integrating patient reported outcomes (PROs) into arthritis care. Patients completed PROMIS computerized adaptive tests (CATs) assessing pain, fatigue, physical function, mood, sleep and social roles/activities using a tablet computer linked to Assessment Center in the waiting room immediately prior to the visit. Legacy measures (100 mm VAS for pain and fatigue, MHAQ) were also obtained as well as traditional clinical indicators of disease activity. PROMIS and legacy measures were compared using Spearman correlations and regression and across CDAI disease activity levels with ANOVA.

Results: Patients were mostly female (79%) and white (86%) with a mean (SD) age of 56 (13) and disease duration of 12 (9) yr; 10% were diagnosed <= 2 yr. PROMIS CATs included an average 63 (12) items requiring 12 (5–32) minutes to complete. PROMIS CATs for pain (intensity, impact), fatigue, physical function, anxiety, depression, anger, sleep (disturbance, impairment) and social roles/activities (participation, satisfaction) correlated highly with pain VAS (r's=.82-.83), fatigue VAS (r=.86) and mHAQ (r=-.74) (p's<.001). A dose-response relationship was evident in PROMIS measures across remission, low and moderate disease activity levels (except anger; see Table). Floor effects were common in legacy measures (16%, 11% and 43% for pain VAS, fatigue VAS and MHAQ, respectively) and were not common in PROMIS instruments.

Estimates of Impact and Mean Values across CDAI Disease Activity Levels on Legacy and PROMIS Measures in Rheumatoid Arthritis.

Variable	B	Effect Size (β/SE)	Remission N=33	Low N=50	Moderate N=23	High N=12
Pain 100 mm VAS	18.3	8.0	5.9 ± 7.8[a]	33.8 ± 25.2[b]	52.4 ± 28.2[c]	54.1 ± 26.0[c]
PROMIS Pain Intensity	4.6	6.6	38.0 ± 7.1[a]	46.0 ± 6.1[b]	48.1 ± 7.4[b,c]	51.7 ± 8.2[c]
PROMIS Pain Interference	5.6	7.0	45.9 ± 7.7[a]	55.4 ± 8.5[b]	58.2 ± 6.2[b,c]	62.1 ± 8.5[c]
Fatigue 100 mm VAS	18.4	7.1	12.7 ± 17.2[a]	45.3 ± 29.0[b,c]	57.5 ± 27.9[c*]	64.3 ± 21.7[c]
PROMIS Fatigue	5.7	6.7	46.1 ± 8.5[a]	55.6 ± 8.8[b]	59.5 ± 6.9[c*]	62.3 ± 9.4[c]
mHAQ	.19	5.1	0.1 ± 0.4[a]	0.3 ± 0.3[a]	0.5 ± 0.4[b]	0.7 ± 0.4[b]
PROMIS Physical Function[‡]	−5.6	−7.8	50.3 ± 8.7[a]	42.7 ± 7.1[b]	38.2 ± 5.7[c]	33.7 ± 5.6[d**]
PROMIS Anxiety	2.6	3.6	47.5 ± 7.6[a]	52.1 ± 8.9[b]	51.0 ± 8.0[a,b]	57.4 ± 8.3[c]
PROMIS Depression	3.0	3.5	46.4 ± 8.5[a]	49.8 ± 9.3[a]	50.9 ± 9.4[b*]	57.1 ± 8.6[c*]
PROMIS Anger	2.6	2.9	45.2 ± 7.9[a]	46.8 ± 9.7[a]	48.9 ± 10.9[a]	54.2 ± 8.8[b]
PROMIS Sleep Disturbance	3.2	3.6	46.6 + 9.1[a]	52.6 + 8.0[b]	54.3 + 10.2[b]	55.7 + 8.3[c]
PROMIS Sleep Impairment	3.8	4.2	46.3 + 9.3[a]	52.7 + 9.6[b]	53.7 + 9.1[b]	58.7 + 6.6[c]
PROMIS Social[†] - Participation	−4.7	−5.9	55.2 ± 9.5[a]	49.9 ± 8.2[b]	46.7 ± 6.1[b]	40.1 ± 6.4[c]
PROMIS Social[†] - Satisfaction	−5.5	−6.1	55.7 ± 9.6[a]	47.0 ± 9.6[b]	44.9 ± 6.6[b]	38.4 ± 7.1[c]

[†]Social Roles and Activities. Differing superscripts denote significantly different groups (p<.05). *p=.06; **p=.08

Conclusion: These data contribute preliminary evidence of convergent and known groups validity and demonstrate robust psychometric performance of PROMIS instruments to assess PROs in people receiving routine RA care. PROMIS CATs can be completed relatively quickly and appear to address some of the well-recognized limitations (non-linearity, floor effects) of existing legacy measures in RA.

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Correlation Of Individual Health Assessment Questionnaire (HAQ) Questions With Outcome Measures In Rheumatoid Arthritis: Implications For Instrument Reduction. J. Carter Thorne[1], Majed M. Khraishi[2], Boulos Haraoui[3], Jude F. Rodrigues[4], Algis Jovaisas[5], Denis Choquette[3], Sanjay Dixit[6], Dalton E. Sholter[7], Philip Baer[8], Maqbool K. Sheriff[9], Emmanouil Rampakakis[10], John S. Sampalis[10], Francois Nantel[11], Allen J. Lehman[11], May Shawi[11] and Susan M. Otawa[11]. [1]Southlake Regional Health Centre, Newmarket, ON, [2]MD, Memorial University of Newfoundland, Nexus Clinical Research, St Johns, NF, [3]Institut de Rhumatologie de Montréal, Montreal, QC, [4]Rheumatology, Windsor, ON, [5]University of Ottawa, Ottawa, ON, [6]McMaster University, Burlington, ON, [7]Rheumatology Associates, Edmonton, AB, [8]Rheumatology, Scarborough, ON, [9]Nanaimo Regional General Hospital, Nanaimo, BC, [10]McGill University, Montreal, QC, [11]Janssen Canada Inc, Toronto, ON.

Background/Purpose: Despite the importance of the Health Assessment Questionnaire (HAQ) in assessing patient-reported functional status, it was originally developed primarily for research studies. As a result, HAQ has been critiqued for being time-consuming, not easily scored, and, thus, not contributing to decisions made in routine clinical care as well as for assessing general health and not specifically the clinical status of Rheumatoid Arthritis (RA).

The aim of this analysis is to describe the correlation of the individual HAQ questions with other outcome measures used in RA as well as to examine whether the instrument could be reduced to better reflect routine clinical practice.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, AS, or PsA with infliximab or golimumab as first biologics or after having been treated with a biologic for less than 6 months. In this analysis, data from RA patients who were treated with infliximab between January 2002 and June 2011 were used. Parameter correlation was described with the Pearson's correlation coefficient and the impact of each question on the use of aids/devices/help was assessed with logistic regression. Factor analysis was used to assess variability in HAQ score due to each of the individual questions.

Results: 877 RA patients who had 4,180 complete HAQ assessments were included in the analysis. Higher pain score, patient assessment of global disease activity (PtGA), 28-tender joint count (TJC-28) and, to a lesser extent, 28-swollen joint count (SJC-28) were associated with increased functional impairment. Correlation analysis showed that individual HAQ questions correlated at different extents with each outcome measure (SJC-28) (Table 1). Notably, Q5B showed the lowest correlation with patient outcome measures while the two questions related to "Rising" (Q2A, Q2B) showed the highest overall correlation.

Logistic regression showed that all individual questions were significantly associated with the use of aids/devices/help within their corresponding category with the exception of Q3B and Q8B. In factor analysis, "Dressing and Grooming" was found to account for 66.5% of the matrix variance (Q1A: 60.5%; Q1B: 6.0%) suggesting that the ability to dress/groom alone may be the main driver of the HAQ score.

Table 1. Correlation between individual HAQ Questions and Outcome Measures

HAQ Question	Pain	PtGA	TJC-28	SJC-28
Q1A: Dress alone	0.58	0.58	0.40	0.35
Q1B: Shampoo hair	0.48	0.48	0.36	0.29
Q2A: Stand up from chair	0.61	0.61	0.42	0.36
Q2B: Get in/out of bed	0.62	0.61	0.43	0.36
Q3A: Cut meat	0.50	0.50	0.37	0.31
Q3B: Lift a full cup/glass	0.49	0.48	0.35	0.33
Q3C: Open milk carton	0.52	0.53	0.40	0.35
Q4A: Walk outdoor on flat ground	0.56	0.55	0.36	0.31
Q4B: Climb up five steps	0.58	0.58	0.39	0.31
Q5A: Wash/dry body	0.55	0.54	0.40	0.33
Q5B: Take a tub bath	0.42	0.41	0.29	0.26
Q5C: Get on/off toilet	0.55	0.54	0.39	0.34
Q6A: Reach and get down object	0.53	0.52	0.38	0.32
Q6B: Pick clothing from floor	0.57	0.56	0.40	0.30
Q7A: Open car door	0.48	0.49	0.41	0.34
Q7B: Open jar	0.52	0.53	0.40	0.36
Q7C: Turn faucet on/off	0.47	0.48	0.40	0.35
Q8A: Run errands/shop	0.55	0.54	0.40	0.30
Q8B: Get in/out of car	0.60	0.59	0.43	0.36
Q8C: Do chores	0.52	0.51	0.37	0.29

* Weak: r < 0.30; Moderate: r = 0.30–0.39; Strong: 0.40–0.69; Very Strong: ≥0.70

Conclusion: Results of this analysis show that variability exists in the correlation of individual HAQ questions with patient-reported and clinical outcome measures. Pain and joint tenderness are significantly associated with the individual functions of the HAQ while the number of swollen joints appears to be of minor importance. Furthermore, the ability to dress/groom alone was the main driver of the variability in HAQ which may have implications from an occupational health perspective and in the design of self-report instruments assessing the (dis)ability to perform daily activities.

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2286

Reliability and Smallest Detectable Difference Of The Patient Global Assessment, Pain and Fatigue In Rheumatoid Arthritis Patients. Paul Studenic[1], Josef S. Smolen[2] and Daniel Aletaha[1]. [1]Medical University Vienna, Vienna, Austria, [2]Medical University of Vienna, Vienna, Austria.

Background/Purpose: Patient reported outcomes (PRO) represent an important part of outcomes assessment in rheumatoid arthritis (RA) patients. The Patient Global Assessment (PGA) is an essential PRO; pain and fatigue can also be assessed by visual analogue scales. Since RA disease activity fluctuates, it is unclear how estimates of the smallest detectable difference (SDD) are influenced by the time elapsed between assessments, and if SDD differs in relation to disease activity. Thus we investigated if reliability estimates of PROs change when using different test-retest intervals, and if they can be better specified based on patients' disease activity.

Methods: Forty RA patients were asked to report their PGA, pain and fatigue daily over 28 days in this prospective observational study. We calculated variability of PROs comparing the initial measurement to ones performed 1–27 days thereafter. We calculated reliability using the intra-class correlation coefficient (ICC), which determines the amount of measurement variability attributable to true scores. The SDD was calculated as the standard deviation of the difference between two measurements multiplied by 1.95. We finally divided patients into tertiles by baseline simplified disease activity index (SDAI) and investigated the differences in SDD based on starting points.

Results: Data of forty patients (85% female, 60% rheumatoid factor positive, mean SDAI: 12.8±8.4, mean disease duration 11.3±8.3yrs) was used. Mean ICC between day 1 and each consecutive day was 0.63±0.13 for PGA, 0.56±0.14 for pain and 0.48±0.15 for fatigue. The mean SDDs of PGA, pain and fatigue were 26.5±5.7, 27.2±6.4 and 42.1±5.7mm, respectively (Figure). As expected, higher reliability (ICC) coincides with a smaller SDD, but no temporal trend was found for any PRO.

Ranges for the tertiles by baseline SDAI were 3.2–8.1 (mean=5.3), 8.3–16.8 (mean=12.5), and 17.4–37.7 (mean=23.9). For PGA, higher SDAI coincided with higher SDD ($p<0.001$), resulting in (mean, 95% confidence intervals) 18.2 (14.9–21.4), 27.14 (23.4–30.9), and 30.1 (26.1–34.1) mm, respectively. The same trend could be found for SDDs of pain ($p=0.002$): 22.5 (19.7–25.4), 28.1 (24.3–32.1), 29.9 (26.1–33.7). For SDDs of fatigue the trend was inverse, so that patients with higher SDAI had lower SDDs ($p<0.001$): 45.6 (39.5–51.7), 39.7 (34.8–44.5), 18.7 (16.6–20.8).

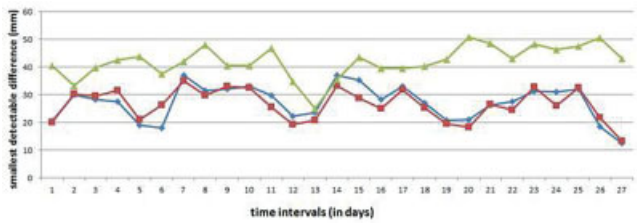

Figure. Smallest detectable differences (SDD) between day 1 and consecutive 27 days. Blue line: development of SDD for pain; the red line: for patient global assessment; the green line: for fatigue.

Conclusion: We demonstrated here, that reliability and SDDs of neither PGA, pain nor fatigue are dependent on the time between assessments. PGA showed the best reliability of all tested PROs. Cut-offs to identify true changes seem to be dependent on disease activity. Much lower SDDs of pain and PGA can be applied in patients with low disease activity.

Disclosure: P. Studenic, None; **J. S. Smolen**, None; **D. Aletaha**, None.

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What Is The Internal Consistency Of The Disease Activity Score (DAS)-28 In Rheumatoid Arthritis Patients Treated In a Real–World Setting? Andrew Chow[1], J. Carter Thorne[2], Regan Arendse[3], Dalton E. Sholter[4], Denis Choquette[5], Isabelle Fortin[6], Boulos Haraoui[5], Emmanouil Rampakakis[7], John S. Sampalis[7], Francois Nantel[8], Allen J. Lehman[8], May Shawi[8] and Susan M. Otawa[8]. [1]Credit Valley Rheumatology, Mississauga, ON, [2]Southlake Regional Health Centre, Newmarket, ON, [3]University of Saskatchewan, Saskatoon, SK, [4]Rheumatology Associates, Edmonton, AB, [5]Institut de Rhumatologie de Montréal, Montreal, QC, [6]Centre de Rhumatologie de l'Est du Québec, Rimouski, QC, [7]McGill University, Montreal, QC, [8]Janssen Canada Inc, Toronto, ON.

Background/Purpose: The DAS-28 is used in clinical decision making and research as an outcome assessment for patients with RA. The tool measures clinical, patient centric and inflammatory components of disease activity. Simplification or improvement of the tool would be important in facilitating its use in real–world settings. The objective of this analysis was to assess the internal consistency of the DAS-28 components and contrast these upon replacing patient global assessment (PtGA) with HAQ-DI in RA patients treated with infliximab or golimumab in a Canadian real-world setting.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis (RA), ankylosing spondylitis (AS), or psoriatic arthritis (PsA) with infliximab or golimumab as first biologics or after having been treated with a biologic for less than six months. Patients with RA treated with infliximab or golimumab who were enrolled between January 2002 and June 2012 and had a maximum of 60 months of follow-up were included in this analysis.

Results: A total of 510 patients evaluated over 3,817 visits were included in this analysis. Mean follow up was approximately 20 months. The overall correlation between TJC and SJC was high (r = 0.746), whereas the correlations of ESR with TJC (r = 0.187) and SJC (r = 0.212) were poor. The correlation between patient assessment of disease activity (PtGA) was poor with ESR (r = 0.190) and modest for TJC (r = 0.519) and SJC (r = 0.487). Internal consistency was low [Cronbach's alpha (CA) = 0.482) and Intra-Class Correlation Coefficient (ICC) = 0.205]. All item-item correlations, ICC and CA deteriorated with time over the 60-month follow up period. The correlations of TJC (r = 0.454) and SJC (r = 0.367) with HAQ-DI were lower when compared to those with PtGA while the correlation of ESR (r = 0.260) was higher with HAQ-DI. Replacement of PtGA with HAQ-DI would result in lower internal consistency (CA = 0.337) suggesting modest improvement in validity.

The slopes measuring rate of change over time for the DAS-28 items showed acceptable internal consistency (ICC = 0.638). Item-item correlations were low for the ESR-slope with PtGA-Slope (r = 0.262), TJC-Slope (r = 0.240) and SJC-Slope (r = 0.300); PtGA-slope had moderate correlation with SJC-Slope (r = 0.512) and TJC-Slope (r = 0.570). When compared to PtGA, HAQ-DI-Slope had comparable correlations with the slopes of the DAS-28 components.

Conclusion: There is poor cross sectional and longitudinal correlation between the DAS-28 components indicating that they are measuring related but discriminating concepts of disease activity. The exception being SJC and TJC and therefore exclusion of one of these measures may be considered. Replacement of PtGA with HAQ within the DAS-28 would not provide any significant statistical benefits however it could offer practical benefits (i.e. reduce measurement workload) without loss of the validity of DAS-28.

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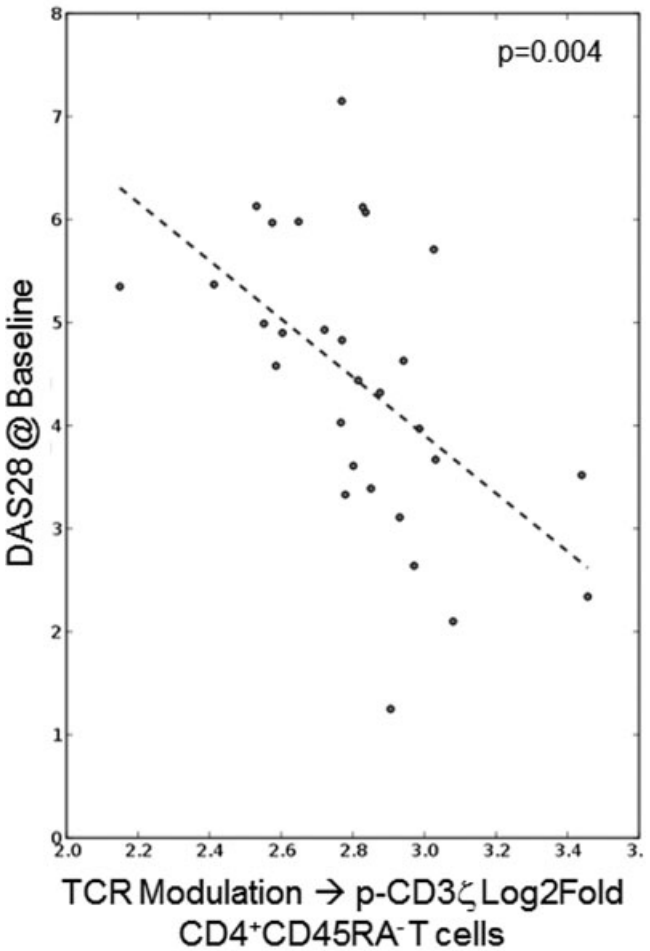
Novel Biomarkers From Peripheral Blood Mononuclear Cells Indicate Disease Activity In Rheumatoid Arthritis Patients. Jason Ptacek[1], Rachael Hawtin[1], Brent Louie[1], Erik Evensen[1], James Cordeiro[1], Barbara Mittleman[1], Michelle Atallah[1], Alessandra Cesano[1], Clifton O. Bingham III[2], Stacey Cofield[3], Jeffrey R. Curtis[4], Maria I. Danila[3], Richard A. Furie[5], Mark C. Genovese[6], Marc C. Levesque[7], Larry W. Moreland[7], Peter A. Nigrovic[8], James R. O'Dell[9], William H. Robinson[6], Nancy A. Shadick[8], E. William St Clair[10], Christopher C. Striebich[11], Geoffrey M Thiele[9], Peter K. Gregersen[5] and S. Louis Bridges Jr.[3]. [1]Nodality, Inc., South San Francisco, CA, [2]Johns Hopkins University, Baltimore, MD, [3]University of Alabama at Birmingham, Birmingham, AL, [4]University of Alabama at Birmingham, School of Public Health, Birmingham, AL, [5]The Feinstein Institute for Medical Research and North Shore-Long Island Jewish Health System, Lake Success, NY, [6]Stanford University, Palo Alto, CA, [7]University of Pittsburgh, Pittsburgh, PA, [8]Brigham and Women's Hospital/Harvard University, Cambridge, MA, [9]Omaha VA and the University of Nebraska Medical Center, Omaha, NE, [10]Duke Unversity Medical Center, Durham, NC, [11]University of Colorado Denver, Aurora, CO.

Background/Purpose: Biomarkers reflecting immune function and associating with disease activity can help stratify rheumatoid arthritis (RA) patients (pts) in practice and in clinical trials. Single cell network profiling (SCNP) is a multiparametric flow cytometry-based assay that measures induced changes in intracellular signaling proteins, providing a functional measure of pathway activity and immune networking in multiple cell subsets. In this study the association between disease activity as measured by DAS28 and signaling profiles in specific subsets of monocytes, B, and T cells from RA pts were assessed in an effort to identify biomarkers for immune monitoring.



Methods: SCNP of 42 nodes (combinations of modulator and intracellular readout) within 21 immune cell subsets was performed on PBMCs from 181 RA pts collected before initiating treatment with either metho-

trexate or a biologic agent for clinical indications and 10 age- and gender-matched healthy donors. RA pts were from the Treatment Efficacy and Toxicity in Rheumatoid Arthritis Database and Repository (TETRAD). Clinical data included DAS28 at enrollment (prior to starting the index drug). Statistical analyses, including Wilcoxon test and linear regression as appropriate, were performed using data from the 117 evaluable donors with no recent use of a biologic to identify signaling that associated with baseline disease activity, after controlling for age.

Results: This systems biology study identified several candidate signaling biomarkers associated with disease activity. As expected in donors with high disease activity (DAS28 $>$ 5.1), unmodulated cells had significantly elevated levels of p-S6, p-AKT, and p-p38 compared to donors with lower disease activity. Specific modulated signaling pathways responsive to IFNa (p-STAT5 in B cells, p=0.03) and T cell receptor modulation (p-LCK, p-ZAP70, p-PLCg2, and p-CD3z; e.g. p-CD3z in $CD4^+CD45RA^-$ T cells, p=0.004) showed signaling inversely correlated to the continuum of disease activity. The reduced signaling associated with higher disease activity potentially reflects disease processes including negative feedback from prior *in vivo* exposure or alterations in components necessary for signaling pathway integrity. Interestingly, signaling induced by TNFa (monocytes, p=0.0004) and IL-6 (central memory $CD4^-$ T cells, p=0.01) was higher in donors with high disease activity, which is consistent with these established treatment modalities.

Conclusion: Characterization of intracellular signaling within immune cells from RA patients provides insights into disease pathology and possible therapeutic targets. Functional pathway analysis of RA pts PBMCs has revealed potential predictive biomarkers that, once validated in future studies, may enable novel means for immune monitoring and therapeutic selection for the individual patient.

Disclosure: J. Ptacek, Nodality, Inc., 3; **R. Hawtin**, Nodality, Inc., 3; **B. Louie**, Nodality, Inc., 3; **E. Evensen**, Nodality, Inc., 3; **J. Cordeiro**, Nodality, Inc., 3; **B. Mittleman**, Nodality, Inc., 3; **M. Atallah**, Nodality, Inc., 3; **A. Cesano**, Nodality, Inc., 3; **C. O. Bingham III**, None; **S. Cofield**, None; **J. R. Curtis**, None; **M. I. Danila**, None; **R. A. Furie**, None; **M. C. Genovese**, None; **M. C. Levesque**, None; **L. W. Moreland**, None; **P. A. Nigrovic**, None; **J. R. O'Dell**, None; **W. H. Robinson**, None; **N. A. Shadick**, Crescendo Biosciences, Medimmune, BMS, Genentech, Abbott and AMGEN, 2; **E. W. St Clair**, None; **C. C. Striebich**, None; **G. M. Thiele**, None; **P. K. Gregersen**, None; **S. L. Bridges Jr.**, None.

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Correlation Of Anti-Citrullinated Protein and Anti-Carp Antibodies With Disease Duration and Activity In Rheumatoid Arthritis. Michael Mahler[1], Gabriella Lakos[1], Tyler Webb[1], Alvin Yee[1], Leendert A. Trouw[2] and Pier-Luigi Meroni[3]. [1]INOVA Diagnostics, San Diego, CA, [2]Leiden University Medical Center, Leiden, Netherlands, [3]University of Milan, Milano, Italy.

Background/Purpose: Anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) are important serological markers in the diagnosis of rheumatoid arthritis (RA) and are part of the recent disease criteria. However, in early RA the sensitivities of ACPA and RF are low underlining the need for additional biomarkers. Additionally, there is a strong need for reliable markers for monitoring of disease activity and treatment response. Recently, antibodies directed against carbamylated antigens were identified. Those anti-CarP antibodies recognize antigens containing homocitrulline which is generated from lysine through chemical modification. This study analyzes the correlation of ACPA fine specificities and of anti-CarP antibodies with disease activity and disease duration.

Methods: A total of 80 RA patients were tested for anti-CCP2 (CCPlus® Immunoscan, Eurodiagnostica) and anti-CCP3 antibodies (QUANTA Lite CCP3, INOVA), for ACPA fine specificities (to three citrullinated peptides, ACPA 1 – 3) and for anti-CarP antibodies by ELISA using fetal calf serum as the antigen as previously described (Shi et al.). In addition RF (IgM) was determined. Disease activity was accessed using the disease activity score 28 (DAS28).

Results: ACPA, including anti-CCP2 (p=0.0050) and anti-CCP3 (p=0.0128) antibodies, as well as the ACPA fine specificities showed significant association with disease duration. In contrast, RF and anti-CarP antibodies did not show association with disease duration. Although no correlation between any of the autoantibodies and disease activity (DAS28) reached statistical significance, one ACPA peptide showed some degree of positive (p=0.0734) and anti-CarP antibodies negative correlation (p=0.0734). When those two biomarkers were combined in a score (ACPA peptide 1 divided by anti-CarP) a statistically relevant correlation was found (p=0.0264).

Assay/antibody	Correlation with disease duration	Correlation with DAS28
CCP2	**p=0.0050**	p=0.1058
CCP3	**p=0.0128**	p=0.2839
ACPA 1	**p=0.0051**	p=0.0734
ACPA 2	**p=0.0280**	p=0.1458
ACPA 3	p=0.0741	p=0.1814
RF	p=0.8178	p=0.1370
CarP	p=0.8700	p=0.0751
ACPA 1/CarP Score	**p=0.0128**	**p=0.0264**

Conclusion: We confirmed the presence of anti-CarP antibodies in RA using an independent cohort of RA patients from Italy. ACPA, but not RF IgM and anti-CarP antibodies are significantly correlated with disease duration. Combining one ACPA peptide with anti-CarP antibodies in an activity score showed association with DAS28. This score might represent a promising biomarker to measure disease activity, but further studies are needed to verify and validate those preliminary findings.

Disclosure: M. Mahler, Inova Diagnostics, Inc., 3; **G. Lakos**, Inova Diagnostics, Inc., 3; **T. Webb**, Inova Diagnostics, Inc., 3; **A. Yee**, Inova Diagnostics, Inc., 3; **L. A. Trouw**, Janssen Biologics, 9; **P. L. Meroni**, Inova Diagnostics, Inc., 5.

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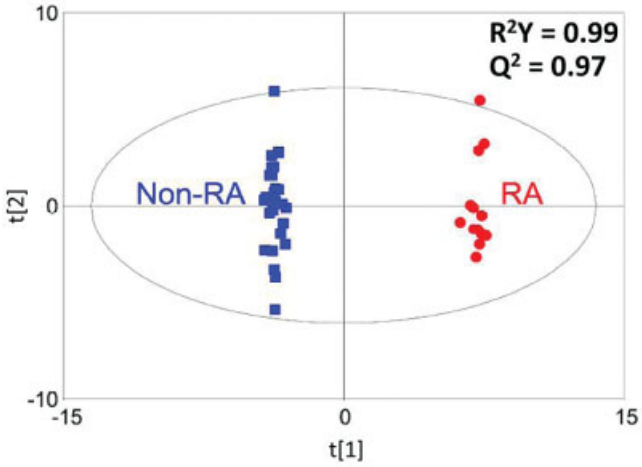
Global Metabolite Profiling Of Synovial Fluids From Different Forms Of Inflammatory Arthritis For The Identification Of Putative Biomarker In Rheumatoid Arthritis. Jiwon Hwang[1], Joong Kyong Ahn[2], Jaejoon Lee[3], Inyoung Kim[1], Seulkee Lee[1], Chan Hong Jeon[4], Eun-Mi Koh[1] and Hoon-Suk Cha[3]. [1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Kangbuk Samsung hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [3]Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea, [4]Soonchunhyang University College of Medicine, Bucheon, South Korea.

Background/Purpose: Metabolomics is the study of unique chemical fingerprints of specific cellular processes. Metabolite profiling is recently applied in identifying biomarkers in medical research including rheumatologic diseases. The aim of this study is to assess the metabolite profiling of synovial fluid in patients with different forms of inflammatory arthritis and to identify putative biomarker for rheumatoid arthritis (RA) compared to the other inflammatory arthritis.

Methods: Synovial fluid samples were obtained from patients with RA (n = 13, mean age 44.2 ± 10.7 yr), ankylosing spondylitis (AS) (n = 7, mean age 35.4 ± 10.7 yr), Behcet's disease (BD) (n = 5, mean age 41.6 ± 12.5 yr) and gout (n = 13, mean age 45.9 ± 7.9 yr). To identify putative biomarkers for RA, the synovial fluid samples were divided into two groups; RA versus non-RA (NRA) which included AS, BD and gout. The metabolites of synovial fluid were analyzed using gas chromatography/time-of-flight mass spectrometry (GC/TOF MS). The multivariate statistical analyses by orthogonal partial least squares discriminant analysis (OPLS-DA) were conducted for the comparison between two groups. The potential biomarkers in RA patients were identified and evaluated by variable importance for projection (VIP) values, nonparametric Wilcoxon-Mann-Whitney test and one-way ANOVA test. Chemometric model validation was finally carried out using receiver operating characteristic (ROC) curve and area under the ROC curve (AUC).

Results: A total of 119 metabolites were identified from 38 samples. The metabolite profiling between RA and NRA were clearly discriminated by OPLS-DA (Figure 1). Candidates of biomarkers in RA were determined by VIP values extracted from OPLS-DA and 41 metabolites were selected by VIP scores of greater than 1.0, of which 29 metabolites were elevated in RA and 12 metabolites in NRA. After eliminating variables with no significant difference using Wilcoxon-Mann-Whitney test and one-way ANOVA test, 23 of 41 metabolites were selected as putative biomarkers for RA compared to NRA. Fifteen metabolites were higher level in RA (succinic acid, octadecanol, asparagines, terephtalic acid, salicylaldehyde, glutamine, citrulline, tyrosine, uracil, lysine, phenylalanine, ribitol, tryptophan, xylose and pyrophosphate) and 8 metabolites in NRA (isopalmitic acid, glycerol, myristic acid, palmitoleic acid, hydroxylamine, ethanolamine, alanine and serine). These metabolites were validated by AUC, all of which had AUC $>$ 0.8. ROC curve analysis for the power of discrimination of RA from NRA showed a sensitivity of 69.2% and a specificity of 84.0%.



Conclusion: Our study suggests that the synovial fluid metabolomic profiling can be a novel approach in differentiating RA from AS, BD and gout. A set of validated metabolites could be a putative biomarker in synovial fluid of RA patients.

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Only Rheumatoid Factor-Positive Subset Of Anti-Citrullinated Peptide/Protein Antibody-Negative Rheumatoid Arthritis Seroconverts To Anti-Citrullinated Peptide/Protein Antibody-Positive. Ryosuke Hiwa, Koichiro Ohmura, Shuichiro Nakabo, Chikashi Terao, Ran Nakashima, Yoshitaka Imura, Naoichiro Yukawa, Hajime Yoshifuji, Motomu Hashimoto, Moritoshi Furu, Hiromu Ito, Takao Fujii and Tsuneyo Mimori. Graduate School of Medicine, Kyoto University, Kyoto, Japan.

Background/Purpose: Sensitivity of anti-citrullinated peptide/protein antibody (ACPA) in early rheumatoid arthritis (RA) has been reported to be as low as 50%, whereas that in established RA is ~80%. The discrepancy of these figures has been explained by the seroconversion from ACPA-negative RA to ACPA-positive RA, but the seroconversion of ACPA seems to be rare in the previous reports. We investigated the precise proportion of seroconversion of ACPA retrospectively.

Methods: RA patients were recruited from January 2007 through November 2011 at Kyoto University Hospital and all the patients were Japanese. Titer of ACPA in sera or plasma was measured with the 2nd generation anti-CCP antibody ELISA kit. The ACPA-negative RA patients who were measured ACPA more than once with the interval of 3 months or longer were investigated for seroconversion of ACPA. The clinical characteristics of patients who turned into ACPA-positive were also assessed. Student's t-test and Fisher's exact probability test were used in statistical analysis.

Results: 216 (17.3%) out of 1,246 RA patients were negative for ACPA. In 149 cases of the ACPA-negative RA whose ACPA were measured more than once, only 8 patients (5.4%) turned into ACPA-positive during follow up. When we investigated the clinical characteristics of the 8 seroconverted cases (Table 1), we found all of them were positive for rheumatoid factor (RF) and showed bone erosions by X-ray. None of the ACPA-negative RF-negative RA turned into ACPA-positive. Since there were 56 ACPA-negative RF-positive RA, 14.3% of them seroconverted to ACPA-positive. The comparison of the basic clinical information of seroconverted and non-seroconverted RA patients were shown in Table 2.

Table 1. Clinical characteristics of each patient who turned into ACPA-positive

Pt No.	Age & Sex	Disease duration* (Y)	ACPA titer (U/ml) 1st	ACPA titer (U/ml) 2nd**	Interval of seroconversion (Y)	RF (IU/ml)	Stage	Treatment
1	76, W	0.2	3.3	20.4	0.8	104.9	II	MTX, SSZ
2	60, W	0.3	3.2	180.0	4	18.9	II	SSZ, PSL
3	39, M	1	3.0	10.8	0.4	420.8	II	MTX
4	36, W	4	2.6	8.4	3.3	79.2	II	LEF
5	64, W	6	3.2	8.3	2.4	942.0	IV	TCZ
6	63, W	18	3.7	6.1	0.7	55.5	IV	IFX, MTX
7	64, W	19	4.0	11.7	5	49.1	IV	TCZ, PSL
8	64, W	26	<0.6	14.2	5	23.0	IV	TCZ, SSZ, PSL

MTX; methotrexate, SSZ; sulfasalazine, PSL; prednisolone, LEF; leflunomide, TCZ; tocilizumab, IFX; infliximab
*Duration from disease onset to the first ACPA measured
**ACPA titer when ACPA was seroconverted.

Table 2. Basic cinical information of seroconverted RA and non-seroconverted RA

	ACPA(−)->(+)RA	ACPA(−)->(−)RA	P value
N	8	141	
Age	58.25 ± 13.66	65.64 ± 13.44	0.066
Women	7 (87.5%)	109 (77.3%)	0.44
RF positive	8 (100%)	48 (34.0%)	0.00029
RF titer (IU/ml)	211.68 ± 322.85	97.56 ± 244.26	0.88
Bone erosions	8 (100%)	72 (51.1%)	0.00058
ANA≥1:80	4 (50.0%)	40 (28.4%)	0.18
MTX administration	3 (37.5%)	78 (55.3%)	0.27
Biologic DMARDs	4 (50.0%)	23 (16.3%)	0.14
Onset to 1st ACPA (Y)	9.30 ± 10.15	5.24 ± 7.73	0.92
1st ACPA to 2nd ACPA (Y)	2.69 ± 1.92	2.27 ± 1.94	0.72

Conclusion: The proportion of seroconversion from ACPA-negative to ACPA-positive RA was as total 5.4%. This result is consistent with the previous report in an early arthritis cohort in Europe, in which only 0.8% was seroconverted from ACPA-negative to ACPA-positive. When we subdivided ACPA-negative RA into RF-negative and RF-positive, only RF-positive subset seroconverted to ACPA-positive. These results imply that ACPA-negative RF-negative RA and ACPA-negative RF-positive RA may be different subsets.

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Factors Affecting The Discrepancy Between Physician and Patient Global Assessment Of Disease Activity In Early and Established Rheumatoid Arthritis Patients- Results From The Ontario Best Practices Initiative. Pooneh Akhavan[1], Binu Jacob[2], Edward C. Keystone[3], Xiuying Li[4], J. Carter Thorne[5] and Claire Bombardier[2]. [1]Early Rheumatoid Arthritis Program, Mount Sinai Hospital and University of Toronto, Toronto, ON, [2]University of Toronto, Toronto, ON, [3]University of Toronto/Mount Sinai Hospital, Toronto, ON, [4]University Health Network, Toronto, ON, [5]Southlake Regional Health Centre, Newmarket, ON.

Background/Purpose: Discrepancy between patient (PGA) and physician (MDGA) global assessments in Rheumatoid Arthritis (RA) can adversely affect therapeutic decisions. The pattern of PGA and MDGA, factors influencing each and the discrepancy between the two may be different in patients with established disease compare to patients with early disease. The objective of this study was to assess the pattern of PGA-MDGA discrepancy in early and established RA and to identify predictors of this discrepancy in the two patient populations.

Methods: Patients with RA were recruited from the Ontario Best Practice Initiative (OBRI), a clinical registry of RA patients followed in routine care. PGA and MDGA were scored from 0–100. PGA-MDGA discrepancy was calculated by subtracting MDGA from PGA at baseline. A clinically meaningful discrepancy was considered a difference of ≥30 (PGA-MDGA > 30: Positive (Pos) and PGA-MDGA < −30: Negative (Neg)). The rate of discrepancy was determined in patients with disease duration of less than or equal to 12 months (early RA) and disease duration of greater than 5 years (established RA) at baseline. Linear regression analysis was used to evaluate factors associated with MDGA, PGA and the PGA-MDGA discrepancy when adjusted for potential confounders including patient demographics, ESR, swollen joint count (SJC), tender joint count (TJC), pain, RF and anti-CCP and joint damage in both early and established disease.

Results: 439 early and 737 established RA patients were analyzed with the mean age of 57.0 and 59.0 years and DAS28 of 4.7 and 4.5 respectively. Mean PGA was 50.0 and 53.0 and MDGA was 48.0 and 43.0 in early and established groups respectively. A meaningful PGA-MDG discrepancy was found in182 (41%) early (101 positive and 81 negative) and 309 (42%) established (229 positive and 80 negative) RA. Regression analysis showed that there was a significant association between MDGA and pain, TJC, SJC and ESR at baseline in both groups and pain score was the only predictor of PGA. PGA-MDGA discrepancy was associated with pain ($p<.0001$), TJC ($p=0.0014$), SJC ($p=0.004$) and ESR ($p=0.01$) in early RA and was associated with pain ($p<.0001$), TJC ($p=0.002$), SJC($p<.0001$) and age ($p=0.05$) in patients with established disease (Table). In both groups higher pain score, SJC or TJC would increase the discrepancy. Higher pain score would increase the positive discrepancy (PGA>MDGA) whereas SJC, TJC and ESR (only in early RA) would increase the negative discrepancy (MDGA>PGA).

Table. Multivariate analysis assessing predictors of PGA- MDGA discrepancy in patient with early and established RA Predictors Early RA Established RA

	Early RA		Established RA	
Predictors	**β**	**p-value**	**β**	**p-value**
Age	0.07	0.51	0.17	0.05
Female	−2.83	0.38	−2.75	0.25
TJC	−0.90	0.001	−0.63	0.002
SJC	−1.00	0.004	−1.85	<0.0001
ESR	−0.15	0.01	−0.05	0.23
Pain score	6.68	<.0001	6.03	<.0001
RF positive	−0.10	0.29	−0.03	0.35
Anti-CCP positive	−0.03	0.33	−0.02	0.40
Joint damage	−2.26	0.33	−0.03	0.98
Education	0.89	0.68	2.21	0.17

Conclusion: PGA-MDGA discrepancy exists in a significant portion of RA patients irrespective of their disease duration. Pain score and active joints are the main clinical factors affecting this discrepancy in patients with either early or established disease.

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Anti-Citrullinated Peptide/Protein Antibody Specificities and Subclinical Synovitis In Palindromic Rheumatism: Towards a Better Understanding Of The Relationship With Rheumatoid Arthritis. Sonia Cabrera-Villalba[1], Julio Ramirez[1], Georgina Salvador[2], Virginia Ruiz-Esquide[1], M. Victoria Hernández[1], José Inciarte[1], Celia Saura[1], J. D. Cañete[1] and Raimon Sanmarti[1]. [1]Hospital Clinic, Barcelona, Spain, [2]Hospital Mutua de Terrassa. Barcelona, Barcelona, Spain.

Background/Purpose: Palindromic rheumatism (PR) may evolve to rheumatoid arthritis (RA), especially in anti-citrullinated peptide/protein antibody (ACPA) positive patients, although many do not evolve to RA after long-term follow-up. It is unclear whether ACPA-positive patients have more subclinical synovitis during the intercritical phase and whether this is a risk factor for progression to RA. There are no data on different ACPA specificities in PR compared with RA.

Objectives: To analyze differences in the presence of subclinical synovitis in PR patients according to ACPA status and determine whether fine specificities of citrullinated peptides differ between PR and RA.

Methods: Patients with pure PR (**Guerne et al* criteria) with no progression to chronic rheumatic disease at study entry were included. Clinical, demographic, serological and therapeutic variables were collected. Subclinical synovitis (grade≥ 2 synovial hyperplasia plus Doppler signal) in the intercritical period was analyzed by ultrasound of both hands. ACPA specificities were assayed by home-made ELISA tests using chimeric fibrin/filaggrin (CFFCP1), fibrin/vimentin (CFVCP), and vimentin/fibrin (CVFCP) citrullinated chimeric synthetic peptides in pure PR patients who were positive for commercial CCP2 tests: results were compared with controls with established RA (1987 ACR criteria).

Results: Fifty-seven patients (64.9% female, mean age 51.6±11.2 years and mean disease duration 11.9±10.5 years) with pure PR were included: 39 (68.4%) were ACPA+ (CCP2 test). No significant clinical differences were observed between ACPA+ and ACPA- patients except for a shorter duration of attacks and greater DMARD use (mainly hydroxychloroquine) in ACPA+ patients. RF was most-frequently found in ACPA positive patients. Subclinical synovitis by ultrasound was observed in 16 patients (28.1%), most-frequently in the metacarpal joints and wrists, without significant differences between ACPA+ and ACPA+ PR patients (30.8 vs. 22.2% p=0.51).

Citrullinated peptide specificities did not significantly differ between CCP2+ PR patients (n=39) and control patients (n=39) with established CCP2+ RA (66.7% female, mean disease duration 7.2±4.4 years), although there was a trend to a higher number of specificities and a higher titer of ACPAS in RA patients (Table 1).

Table 1. Frequency of citrullinated peptide specificities in CCP2-positive PR and RA patients.

	PR-CCP2 positive n=39	RA-CCP2 positive n=39	p value
CCP2 levels(IU/L)	467.72 ± 513.6	761.74 ± 595.7	0.09
CFFCP1 n (%)	29 (74.4%)	35 (89.7%)	0.24
CFVCP n (%)	24 (61.5%)	26 (66.7%)	0.6
CVFCP n (%)	29 (74.4%)	34 (87.2%)	0.43
CFFCP1 levels (ODU)	1.01 ± 0.97	1.25 ± 0.88	0.24
CFVCP levels (ODU)	0.59 ± 0.54	0.65 ± 0.60	0.25
CVFCP levels (ODU)	0.82 ± 0.80	0.89 ± 0.66	0.24
≥2 Specificities	28 (71.7%)	35 (89.7%)	0.2
3 Specificities	23 (59%)	25 (64.1%)	0.7

ODW: optic density units

Conclusion: ACPA are frequently found in patients with PR. Most PR patients do not have subclinical synovitis (by ultrasound), which is not associated with ACPA status, in the intercritical period. No significant differences in the different specificities of ACPAS were observed between PR and RA, suggesting that chronic PR might be considered an abortive form of RA

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The Role Of Patient Global Disease Activity Score In The Definition Of American College Of Rheumatology/European League Against Rheumatism Remission In Very Early Rheumatoid Arthritis From The Norwegian Very Early Arthritis Clinic. Maria Dahl Mjaavatten[1], Anne Julsrud Haugen[2], Halvor Nygaard[3], Olav Bjørneboe[4], Patrik Stolt[5], Cathrine Thunem[6] and Tore Kristian Kvien[7]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Østfold Hospital Trust, Fredrikstad, Norway, [3]Revmatismesykehuset Lillehammer, Lillehammer, Norway, [4]Martina Hansens Hospital, Gjettum, Norway, [5]Innlandet Hospital Trust, Brumunddal, Norway, [6]Betanien Hospital, Skien, Norway, [7]University of Oslo, Oslo, Norway.

Background/Purpose: In the ACR/EULAR criteria remission can be defined in two ways, either by fulfilment of 4 Boolean criteria or by a Simplified Disease Activity Index (SDAI) score ≤ 3.3. Failure to fulfill the patient global disease activity (PGA) score < 1 cm criterion in the Boolean version has been shown to be the major determinant of "near misses" of remission in established RA. It is not known if this factor is of the same importance when RA patients are identified and treated at a very early stage. The purpose of this study was to investigate the role of PGA in fulfilment of the ACR/EULAR remission criteria after 2 years in patients with RA in a very early arthritis clinic.

Methods: Patients with arthritis of <16 weeks' duration were included in an early arthritis cohort from 2004–2010 and followed for 2 years with a comprehensive data collection. Patients were treated according to current clinical practice and not with a structured treat-to-target approach. Patients with RA according to the 2010 classification criteria with 2 years follow-up time were included in the present analysis. Frequency of 2-year remission was calculated according to both versions of the criteria, as well as which criterion was not fulfilled in patients fulfilling 3/4 Boolean criteria.

Results: Of 1086 very early arthritis patients included, 185 (17.0 %) had RA according to the 2010 criteria at inclusion and had 2-year data on Boolean remission (mean (SD) age 52.5 (13.8) years, n (%) females 112 (60.5), median (25–75 percentile) duration of symptoms at inclusion 63 (40–83)). 171 of these patients had data on SDAI remission. After 2 years, 41/185 (22.2 %) were in Boolean remission, while 65/171 (38.0 %) were in SDAI remission. 63 patients (34.5 %) fulfilled 3 of the Boolean criteria (criterion not fulfilled: PGA n=52, CRP n=5, TJC n=3, SJC n=1, missing data n=2). If the PGA cut-off was raised to ≤2, the remission rate increased to 61/185 (33.0 %). A PGA cut-off of ≤ 3 gave a remission rate of 72/185 (38.9 %). Omitting the PGA criterion, the remission rate was 93/185 (50.3 %). Mean (range) PGA score in the 52 patients failing to fulfill the criteria due to elevated PGA was 3.5 (1.1–8.9). 44/52 (84.6 %) of patients with PGA > 1 had evaluator's global disease activity (EGA) ≤ 1; 25 of these 44 (56.8 %) were in SDAI remission. 13 patients who were not in ACR/EULAR Boolean remission fulfilled the PGA criterion.

Conclusion: In this very early arthritis clinic only 22% of early RA patients were in ACR/EULAR Boolean remission after 2 years of follow-up, while 38 % were in remission according to SDAI. Elevated PGA was the major reason for not being in remission in patients fulfilling 3/4 of the Boolean remission criteria, and in the majority of these patients EGA was ≤ 1. A PGA cut off of ≤ 3 resulted in a similiar remission rate (38.9 %) as with the index based (SDAI) remission definition.

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Mortality In Early Rheumatoid Arthritis Comparing Lithuania and Finland. A 13-Year Follow Up. Tuulikki Sokka[1], Sigita Stropuviene[2], Hannu Kautiainen[3], Tuomas Rannio[4] and Jolanta Dadoniene[2]. [1]Jyvaskyla Central Hospital, Jyvaskyla, Finland, [2]Vilnius Univ, Vilnius, Lithuania, [3]Unit of Primary Health Care, Helsinki University Central Hospital, Helsinki, Finland, [4]Jyvaskyla Central Hospital, Jyväskylä, Finland.

Background/Purpose: Life span of patients with rheumatoid arthritis (RA) is reduced by 3–10 years compared to non-RA population. Only recent reports indicate improvements in survival outcomes in RA in a few countries. The QUEST-RA study indicated that RA continues to be an active and severe disease especially in countries with lower gross domestic product (ARD 2009;68:1666–7). Therefore, it is of interest to compare survival outcomes of patient with RA in different countries. Our objective was to study long-term survival of patients with early RA in Vilnius (VIL), Lithuania, and Jyväskylä (JYV), Finland, and predictors of vital status as well as comparison to the population.

Methods: A cohort of 191 patients with early RA (disease duration <4 years) was established in VIL in 1998 – 2003. A comparison cohort was drawn from the JYV RA database that includes all incident and prevalent patients with RA since 1982. To each VIL patient, a control subject was identified in JYV, matched for gender, year of birth, starting year of arthritis, and RF status (negative, positive). Vital status of the patients was acquired from the central statistics office in each country. Regression analyses for mortality included nation, baseline disease activity(DAS28_esr3), patient self-report of function(HAQ), early continuous use of DMARDs and systemic steroids(SS), presence of a life threatening disease(LTD), smoking, and a type of work (white vs blue collar) as a proxy of wealth. Patients were followed until December 2012 or death, which ever happened first. Standard Mortality Ratio (SMR) was calculated.

Results: A total of 186 patients and controls (age at diagnosis 52 years, 78%F, 85% RF+) were included in analyses. Over a median (IQR) follow-up of 13 (11, 15) years, 55 and 32 patients died in VIL and JYV, respectively, including 16(40%) and 11(28%) of men (p=0.24) and 39(27%) and 21(15%) of women (p=0.009) [HR=1.83 (95% CI: 1.18 to 2.83), p<0.001]. In multivariate analysis, age and country were the only independently significant variables for mortality. SMR (95%CI) was similar to that of the population in each country (VIL: 1.3, 1.0 to 1.7; JYV: 1.4, 1.0 to 1.9).

Conclusion: In this analysis of patients with early RA over a median of 13 years, higher mortality was seen in VIL compared to JYV patients but SMR was similar to the general population in each country indicating improved outcomes of RA in these countries.

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2296

Are SDAI50 and DAS28 Response Measures Comparable In Early Rheumatoid Arthritis Patients? Mohammed Omair[1], Edward C. Keystone[1], Juan Xiong[2], Gilles Boire[3], Janet E. Pope[4], J. Carter Thorne[5], Carol A. Hitchon[6], Boulos Haraoui[7], Diane Tin[5], Deborah Weber[2], Vivian P. Bykerk[1] and Pooneh Akhavan[1]. [1]Mount Sinai Hospital/University of Toronto, Toronto, ON, [2]Mount Sinai Hospital, Toronto, ON, [3]Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, [4]St Joseph Health Care, London, ON, [5]Southlake Regional Health Centre, Newmarket, ON, [6]University of Manitoba, Winnipeg, MB, [7]Institut de Rhumatologie de Montréal, Montreal, QC.

Background/Purpose: An essential element of treat to target strategy is adjusting therapy in the absence of achieving a target response by 12 wk. A ΔDAS28 of 1.2 and Simplified Disease Activity Index of 50% (SDAI50) are used as response measures (RM). Our objective was to assess the relationship between the 2 RM and to characterize patients failing to respond based on either RM.

Methods: Data from the Canadian early ArThritis CoHort (CATCH), an early arthritis cohort of patients with symptoms duration of ≤ 12 mo were used. Among patients with RA, we assessed biologic naive patients with available data to calculate DAS28 and SDAI at baseline (BSL) and 12 wk. We included patients on stable DMARD (no Δ in therapy) during the first 3 mo of f/u. Response to treatment was evaluated at 12 wk.

Correlation and agreement between 2 criteria was assessed by kappa statistics and Spearman correlation. BSL characteristics and median change from BSL were compared in patients with discordant RM. Probability plots of achieving each RM against BSL DAS28 score were evaluated.

Results: In total, 419 patients were included. Most were women (75%) with mean age of 52.6 years. Other BSL variables (mean): disease duration 5.7 months, tender joint count (TJC) 9.0, swollen joint count (SJC) 8.2, DAS28 5.2, SDAI 29.7 and CRP 14.4.

198 (47%) patients failed to achieve a DAS28Δ and 206 (49%) failed to achieve SDAI50. There was a significant agreement between DAS28 and SDAI50 RM (Kappa 0.66) with a Spearman Correlation of 0.66 (p<0001). Of patients failing SDAI50, 19.2% achieved a DAS28Δ, of patients failing a DAS28Δ, 16.6% patients achieved SDAI50. In patients with discordant RM, BSL disease activity measures were higher in DAS28 responders (Table). The probability of achieving the DAS28Δwas higher patients in higher disease activity and it was the opposite in the lower activity range (Figure). Median change of activity measures was higher in patient who achieved DAS28Δ (Table).

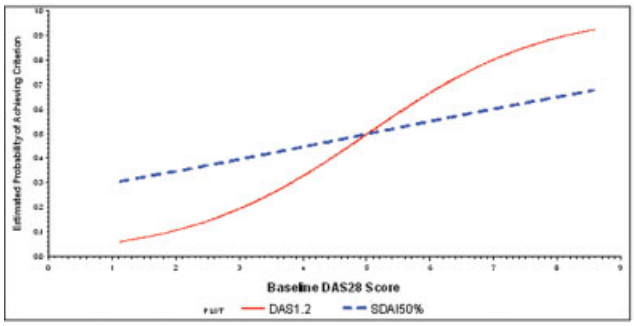

Figure. Plot of the predicted probability of achieving criterion DAS1.2 and SDAI50 against baseline DAS28 score.

Table. Comparing baseline characteristics and change in individual disease activity measures from baseline to 3 months in two patients with discordant RM

	Baseline characteristics			Median Δ in individual activity measures		
Baseline variables	SDAI50-No DAS1.2-Yes N=40	SDAI50-Yes DAS1.2-No N=32	p-value	SDAI50-No DAS1.2-Yes N=40	SDAI50-Yes DAS1.2-No N=32	p-value
Age (years)*	54.2 ± 13.4	52.7 ± 16.6	0.507	–	–	–
Female n (%)	29 (73)	27 (71)	0.266	–	–	–
SJC28*	10.3 ± 5.9	4.7 ± 5.26	<.0001	−3.0	−2.0	0.227
TJC28*	12.7 ± 7.0	4.5 ± 5.5	<.0001	−4.0	−2.0	0.012
PHGA*	59.5 ± 23.3	38.9 ± 26.6	0.002	−20.0	−30.0	0.083
HAQ *	1.2 ± 0.6	0.9 ± 0.7	0.061	−0.44	−0.44	1.000
PTGA*	72.6 ± 25.8	36.8 ±27.1	<.0001	−40.0	−10.0	0.005
Pain*	70.7 ± 23.6	45.0 ±29.5	<.0001	−40.0	−17.5	0.005
CRP*	23.9 ± 20.9	9.3 ±14.5	<.0001	−8.3	−0.3	<0.0001
DAS28*	6.1 ± 1.1	3.8 ± 1.0	<.0001	−1.7	−0.9	<0.0001
SDAI*	38.7 ± 14.8	17.6 ± 12.2	<.0001	−13.8	−10.7	0.158

* mean (sd)

Conclusion: SDAI50 and DAS28 RM are well correlated although in patients in high disease activity states the likelihood of achieving an SDAI50 is lower than achieving a DAS28Δ, while the reverse is true at lower disease activity states.

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2297

Evaluating Depression Questionnaires In German Rheumatoid Arthritis Patients – Preliminary Results From a Validation Study. Matthias Englbrecht[1], Rieke Alten[2], Martin Aringer[3], Christoph G. Baerwald[4], Harald Burkhardt[5], Nancy Eby[6], Gerhard Fliedner[7], Bettina Gauger[8], Ulf Henkemeier[9], Michael Hofmann[10], Stefan Kleinert[11], Christian Kneitz[12], Christoph Pohl[13], Georg Schett[1], Marc Schmalzing[11], Anne-Kathrin Tausche[14], Hans Peter Tony[15] and Joerg Wendler[16]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]University of Berlin, Berlin, Germany, [3]University Clinical Center Technical University of Dresden, Dresden, Germany, [4]University Hospital Leipzig, Leipzig, Germany, [5]CIRI /Div. of Rheumatology, Goethe-University, Frankfurt/Main, Germany, [6]AMS-Advanced Medical Services, Mannheim, Germany, [7]Praxis Osnabrück, Germany, Germany, Osnabrück, Germany, [8]Roche Pharma AG, Grenzach, Germany, [9]University Hospital Frankfurt, Frankfurt, Germany, [10]Chugai Pharma, Frankfurt, Germany, [11]University Hospital Würzburg, Würzburg, Germany, [12]Hospital Südstadt, Rostock, Germany, [13]Schlosspark Klinik, Berlin, Germany, [14]Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Dresden, Germany, [15]University of Würzburg, Würzburg, Germany, [16]Schwerpunktpraxis Rheumatologie, Erlangen, Germany.

Background/Purpose: To date, only a few studies have discussed the prevalence of depression in RA patients in Germany and depression ques-

tionnaires have not been validated for use in RA patients in the German language. This was the aim of the first part of the Validation of Depression Questionnaires for Patients with Rheumatoid Arthritis (VADERA) study presented in this abstract.

To evaluate the construct validity, retest reliability and sensitivity to change of the following four tools measuring depressiveness: the WHO five well-being index (WHO-5), the patient health questionnaire (PHQ-9), the Beck Depression Inventory (BDI-II), and Montgomery-Åsberg Depression Rating Scale (MADRS).

Methods: A patients with no previous history of depressive disorders were asked to complete the WHO-5, PHQ-9 and BDI-II questionnaires and a subsequent structured interview (MADRS) at 2 time-points with a 10–14 week interval between assessments. Additional information on demography (e.g. age, sex, disease duration) and disease activity (e.g. CRP, ESR, disease activity score 28 [DAS28]) was collected.

In order to evaluate convergent and discriminant validity as subsets of construct validity, we calculated Pearson correlations of the PHQ-9, WHO-5, BDI-II, and MADRS at both time-points (= convergent) followed by Pearson correlation of the depression scores with age and DAS28 (= discriminant). Results from patients who had no psychotherapeutic intervention for depression and who had a change of < 0.6 in DAS28 between the first and second time-point were evaluated for the retest reliability of the instruments (i.e. a Pearson correlation). Sensitivity to change was evaluated among patients who had received psychotherapeutic intervention between the first and second time-point using the standardized response mean (SRM).

Results: 277 RA patients from 9 centers in Germany were evaluated in VADERA I. Baseline characteristics were: mean (±SD) age 60 (±13.0) years, 79% female, mean duration of disease 12.4 (± 9.4) years, 61% anti-citrullinated protein antibody positive and a mean DAS28 score 3.5 (± 1.6). 10.0% of the patients were undergoing anti-depressive therapy.

All Pearson correlations for convergent validity showed statistically significant correlations at both time-points. Corresponding coefficients ranged from r=0.63 (p<0.001) (PHQ-9 with BDI-II) to r= 0.79 (p<0.001) (BDI-II with MADRS) and from r= −0.36 (p<0.001) (WHO-5 with MADRS) to r=−0.54 (p<0.001) (WHO-5 with PHQ-9).

Correlations of discriminant validity ranged from r= −0.14 (p=0.05) (PHQ-9) to r= 0.17 (p=0.01) (WHO-5) for age and from r= −0.22 (p=0.002) (WHO-5) to r=0.43 (p<0.001) (MADRS) for disease activity.

All questionnaires showed good retest reliability which ranged from r= 0.68 (p<0.001) for the PHQ-9 to r= 0.85 (p<0.001) for the WHO-5.

The SRMs were rather small and ranging from −0.37 (n=12, BDI-II) to 0.13 (n=14, PHQ-9), suggesting the BDI-II to be most sensitive to changes in depression status.

Conclusion: Especially the PHQ-9, the BDI-II, and the MADRS may be assumed to be construct valid and retest reliable. SRMs were rather small and suggesting the BDI-II to be most sensitive.

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2298

Upper-Half Serum IgA (20+ TU/ml) and IgM (10+ IU/ml) Levels Significantly Predicted The Long-Term (mean 12 yrs) Onset Of Rheumatoid Arthritis When Combined, But Neither test Individually In Their Respective Full Ranges Of Values. Alfonse T. Masi[1], Azeem A. Rehman[1], Jean C. Aldag[1], Huaping Wang[1], Ned J. Goertzen[1] and Marius C. Teodorescu[2]. [1]University of Illinois College of Medicine at Peoria, Peoria, IL, [2]TheraTest Laboratories Inc, Lombard, IL.

Background/Purpose: Serum rheumatoid factor (RF) is a major predictor of the new onset of rheumatoid arthritis (RA). In very early arthritis patients, higher titers of both IgA and IgM RF isotypes predicted bone erosions at 2 years (A&R 2010; 62:1739–47). However, no data have been reported on efficacy of IgA or IgM RF isotypes to predict new onset of RA. This cohort study analyzed baseline IgA and IgM RF isotype levels as predictors of new onset of RA, and searched for factors associated with baseline levels of these biomarkers.

Methods: In 1974, baseline sera were obtained from a community-based cohort (n=21,061 adults) enrolled in the CLUE 1 follow up study. In 1994, baseline pre-RA cases were identified, who subsequently developed ACR-positive RA, 3 to 20 (median 12) years *after* entry. Four non-RA control (CN) cohort subjects were matched to each case on age, sex, and Caucasian race. The RF isotype assays were performed by ELISA concurrently and without identification, on stored (−70°C) baseline sera of 32 pre-RA and 119 CN subjects. Median (Md) levels were determined for IgA (20 TU/ml) and IgM (10 IU/ml) RF isotypes from total subject sample values, which were then stratified into 4 gradient subgroups (1 = both < Md, 4 = both ≥ Md). The subgroup with both RF isotypes lower than Md values (1) was used as baseline in odds ratio (OR, 95% CIs) prediction of RA for the other 3 subgroups (Table):

Mds: IgA = 20, IgM = 10	Means		Females (n)		Males (n)		Both Genders [n, ORs (95% CIs)]		
Isotype Subgroups	IgA	IgM	CN	pre-RA	CN	pre-RA	CN	pre-RA	ORs (95% CIs)
(1) IgA & IgM < Md	9.9	4.7	12	4	23	3	35	7	1.0
(2) Only IgA ≥ Md	32.1	5.5	14	2	13	2	27	4	0.74 (0.196–2.793)
(3) Only IgM ≥ Md	11.1	17.1	9	2	17	2	26	4	0.77 (0.204–2.906)
(4) Both RFs ≥ Md	50.4	25.5	16	7	15	10†	31	17†	2.74 (1.004–7.485)
Total Subgroups	21.5	10.8	51	15	68	17	119	32	(† = p < 0.010)

Results: Expected random frequencies were found for the CN in each of the 4 gradient categories, 31 (26%) of 119 in the highest subgroup, whereas pre-RA predominated in that subgroup, 17 (53%) of 32 (p = 0.005). In univariate analyses (Table), category 4 predicted RA onset in total subjects, OR 2.74 (1.004 – 7.485). In males, category 4 also predicted RA onset, 5.05 (1.642–15.520), but not in females, 1.91 (0.593–6.193). In a logistic regression (LR) model, the higher combined IgA/IgM RF category 4 was included as a dichotomous, independent factor (0 = no, 1 = yes), and predicted (p = 0.006) the dependent RA outcome, OR 3.16 (1.381 – 7.225). The model included other baseline variables: cohort entry age; sex; a 7-category cigarette smoking history score, and years from entry to RA onset. The smoking variable also independently predicted RA outcome, OR 1.28 (1.008 – 1.626). Unlike category 4, neither RF isotype alone in full-range values predicted RA in LR models. In other LR models, using the higher IgA/IgM RF category 4 as the dependent outcome variable, neither the cigarette gradient scores, nor individually-entered serum levels of acute phase proteins (CRP, ASAA, IL-1ra), inflammatory cytokines (IL-1B, IL-6, TNF-α), or selected receptors (sTNF-R1 and sIL-2Rα) were independent predictors.

Conclusion: The combination of upper-half IgA and IgM RF levels was a significant predictor of long-term development of RA in total subjects and males. Factors which influence the combined higher IgA/IgM RF isotype levels, as was found in pre-RA, deserve further study.

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2299

Disease Activity Scoring: Comparing Patient and Physician Global Assessment Of Disease Activity In Rhumatoid Arthritis Patients Starting a First Biologic Agent. Boulos Haraoui[1], Louis Bessette[2], Diane Sauvageau[1], Jean Pierre Pelletier[1], Jean-Pierre Raynauld[1], Edith Villeneuve[1], Louis Coupal[1] and Denis Choquette[1]. [1]Institut de Rhumatologie de Montréal, Montreal, QC, [2]Centre Hospitalier Universitaire de Québec, pavillon CHUL, Sainte-Foy, QC.

Background/Purpose: Visual analogue scales (VAS) are routinely used in daily clinical practice and are part of the different composite outcome measures such as the DAS, CDAI and SDAI. Studies often report weak to moderate positive correlations between physician and patient global assessment of disease activity. It is thought that they are driven by different considerations such as pain, fatigue and mental status for patients and more objective measures such as the swollen joint count and acute phase reactants for physicians. We hypothesized that while absolute values of patient and physician global disease activity do not always correlate, changes in these measures may offer a better correlation. To this end, we looked at global evaluation changes before and after introduction of a first biologic agent in patient with RA.

Methods: We included patients treated for at least 6 months with a first anti-TNF agent (adalimumab, etanercept or infliximab) starting in January 2005.The patient and physician global assessments of disease activity of RA patients were extracted from the RHUMADATA® clinical database and registry. Pearson correlations coefficients between pre, post and pre-post changes in patient and physician assessments were computed (SAS v 9.13) and compared.

Results: The global disease activity scores from 83 patient-physician pairs were available for this analysis. The pre-treatment assessments were

made within 0 and 176 days (mean 33 days) of biologic initiation while the post treatment assessments occurred between 182 and 799 days (mean 268 days). The patient and physician pre, post, and pre-minus-post global assessment means and standard deviations are presented below. The pre and post treatment Pearson correlations coefficients between patient and physician assessments are respectively $r^2=0.34$ ($p=0.001$) and $r^2=0.19$ ($p=0.08$). The correlation coefficient between patient and physician change in global assessment is 0.15 ($p=0.19$).

Physician and patient global disease activity assessment

	Physician Mean (StD)	Patient Mean (StD)	Difference (Patient-physician) Mean (StD)
Pre-treatment	5.27 (1.19)	5.58 (2.96)	0.31 (2.94)
Post-treatment	1.42 (1.78)	3.79 (2.81)	2.37 (3.02)
Difference (post-pre)	−3.85 (2.31)	−1.79 (2.95)	

Conclusion: While the pre treatment initiation global disease activity assessments showed moderate correlation, the change in these assessments exhibited a weak relationship. Both physicians and patients agree on disease activity improvement although their magnitudes differ. Reasons for this difference are being explored.

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Rheumatologists Who Are Consistently Using An Objective Outcome Instrument Do Not "Treat To Target" In a Real World Setting. Gary Craig[1], Howard Kenney[2], Keith Knapp[2] and Sergio Schwartzman[3]. [1]Arthritis Northwest PLLC., Spokane, WA, [2]T3 JointMan LLC., Spokane, WA, [3]Hosp for Special Surgery, New York, NY.

Background/Purpose: The public database JointMan™ was launched January 2012 with a mission to provide a practical outcome tool to manage patients with RA in a clinical setting. This was not constructed as a research registry. The rheumatology community has been educated on the importance of measurement in patients with RA, but has not yet adopted the strict concept of treating to target; rather, in a real world setting rheumatologists may be measuring but not acting on their measurements.

In this observational study, the stated hypothesis is that rheumatologists who are consistently measuring are not yet treating to target and therefore not utilizing the obtained outcome measurements to attain a specific therapeutic goal.

Methods: JointMan™captures RA diagnostic criteria and selected disease features, formal joint counts, MDHAQ, DAS 28, CDAI, SDAI, RAPID3, CRP and ESR, medication use, toxicities and reason for discontinuation. This was a descriptive observational study.

Results: To date 16 national providers have entered patients. A total of 2465 unique RA patients and 6860 encounters were recorded between January 1, 2012 and December 31, 2012. Of the 2465 unique RA patients, 1862 patients had greater than one encounter reported. Only patients with greater than one encounter were evaluated. Demographic characteristics of this group revealed that 72 % were female, mean age was 62, 55 % were RF positive, 41 % were CCP positive, 34 % had documented erosions noted on radiographic studies.

CDAI and RAPID3 scores were available for 83.4% and 91.73% respectively. The mean initial CDAI score was 14.01 at the time of first encounter and a mean CDAI score of 12.05 was noted at the time of the last encounter for a 1.96 improvement (13.98% improvement). The mean initial RAPID3 score was 11.28 at the time of first and 10.94 was noted at the time of the last encounter for a 0.34 improvement (3.01% improvement). The mean number of encounters per patient where CDAI and RAPID3 were recorded was 4.71 and 4.38 respectively.

Conclusion: Utilizing a new database, JointMan™, constructed to easily enter patient data in a clinical setting, it was demonstrated that physicians in a real world setting consistently determine outcome measurements. However, although there is a definite mean improvement in chosen outcome measurements, a mean low disease state is not achieved for this group of patients.

The primary purpose of objective measurement is quality improvement. The optimal method to achieve this goal is to provide feedback through a real time data visualization tool. Having succeeded in educating physicians to actually obtain an outcome measurement consistently, there is now a need to more formally teach rheumatologist as to how to use the measurement to attain a desired disease state.

Disclosure: G. Craig, Genentech and Biogen IDEC Inc., 8, Genentech and Biogen IDEC Inc., 5, Abbott Immunology Pharmaceuticals, 8, BMS, 2, T3 JointMan LLC., 4; **H. Kenney**, BMS, 2, T3 JointMan LLC., 4; **K. Knapp**, BMS, 2, T3 JointMan LLC., 3; **S. Schwartzman**, Abbvie, Pfizer, Janssen, UCB, Genentech, 8, Abbvie, Pfizer, Janssen, UCB, Genentech, Hospira, Crecendo, 5.

2301

T Cell Proliferative Response To Type II Collagen In Patients With Rheumatoid Arthritis. Nida Saleem[1], Tahir Aziz Ahmed[2], Javaid Mahmood Malik[3], Mushtaq Ahmed[4] and Mukarram Bashir[5]. [1]Armed Forces Institute Of Pathology, RAWALPINDI, Pakistan, [2]Armed Forces Institute of Pathology, Rawalpindi, Pakistan, [3]Rahmat Noor Clinic and Arthritis Research Centre, Rawalpindi, Pakistan, [4]Military Hospital Rawalpindi, rawalpindi, Pakistan, [5]Armed Forces Institute Of Pathology, rawalpindi, Pakistan.

Background/Purpose: To compare the frequency of Collagen II reactive T cells in RA patients and healthy control and evaluating the relationship of Collagen II reactive T cells with disease activity in RA patients.

Materials and Methods: Patients with a clinical diagnosis of Rheumatoid arthritis on fulfilling 1987 ACR criteria were included in the study. Patients were compared with a group of age and gender matched healthy subjects. T cell proliferative response was assessed against Bovine Collagen II, PHA (positive control) and RPMI (negative control) by measuring incorporation of the 5-bromo-2- deoxyuridine (BrdU) into DNA of proliferating cells and expression of CD25 on proliferating cells and was subsequently detected with monoclonal antibodies (BrdU-moAb and CD25-moAb) as percentage of CD3+/BrdU+ and CD3+/CD25+ T-cells, respectively.

RA patients were classified into three groups of mild, moderate and severe disease activity as per Simplified disease activity index for RA. Four parameters, frequency of CD3+/BrdU+, frequency of CD3+/CD25+ T-cells, Mean Fluorescent Intensity (MFI) of BrdU-FITC and MFI of CD25-FITC were compared in mild, moderate and severe disease activity groups.

Results: Five male and twenty five female RA patients with an age range of 28–60 years (mean 42 years) and 25–58 years (mean 36 years) respectively were studied. Percentages of CD3+/CD25+ cells and CD3+/BrdU+ cells in T lymphocytes from RA patients induced by Collagen II were much higher (45.22% and 53.45%) than those observed for T lymphocytes in control group (33.51% and 45.22%). The difference was statistically significant ($p<0.05$).

Statistically significant differences were observed when frequency of CD3+/BrdU+ cells and CD3+/CD25+ cells along with MFI of BrdU-FITC and CD25-FITC was compared between the three disease activity groups, mild, moderate and severe in patients ($p<0.05$).

Conclusion: These observations suggest that Collagen II is an important auto antigen in joints of RA patients with Collagen II reactive T cells playing a critical role in pathogenesis of RA and Collagen II reactive T lymphocytes may be used as a specific prognostic laboratory marker for assessment of disease activity in RA.

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2302

Anti-Carbamylated Protein Antibody In Japanese Patients With Rheumatoid Arthritis. Shunichi Shiozawa[1], Leendert A. Trouw[2] and Kazuko Shiozawa[3]. [1]Kyushu University Beppu Hospital, Beppu, Japan, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Konan Kakogawa Hospital, Kakogawa, Japan.

Background/Purpose: Serology represents a powerful tool for the identification and sub-classification of patients with rheumatoid arthritis (RA). IgM-rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibodies are now part of the 2010 EULAR/ACR criteria for RA. Recently, anti-carbamylated protein (anti-CarP) antibodies have been described to be present over 40% of European patients with RA and to predict joint damage (Shi J et al. PNAS 108:17372, 2011). Here, we have characterized this antibody in Japanese patients with RA.

Methods: Sera of the patients fulfilling ACR diagnostic criteria who visited hospital within 2 yrs after disease onset between April 2003 and March 2006 were obtained. Anti-CarP fetal calf serum (CarP FCS) and anti-CarP fibrinogen (CarP Fib) were measured by using ELISA as before. Anti-CCP2 and anti-CCP3 were detected using commercial assays. Radiographic evaluation was done using van der Heijde-modified Sharp score (SHS), with a range of 0–306 (narrowing + erosion) and expressed as annual change from baseline. Statistical analyses were done using Student's t-test.

Results: Anti-CarP FCS and anti-CarP Fib antibodies were found in 82/ 258 (31.78%) and 87/ 258 (33.72%) of Japanese patients with RA. Anti-CCP2 and anti-CCP3 antibodies were found in 197/ 258 (76.36%) and 210/ 258 (81.40%) patients, respectively. Among anti-CCP2-positive patients, anti-CarP FCS and anti-CarP Fib were also positive in 78/ 197 (39.59%) and 87/ 197 (44.16%) patients, respectively. Likewise, among anti-CCP3-positive patients, they were positive in 82/ 202 (40.59%) and 87/ 202 (43.07%) of the patients, respectively. Several patients were negative for anti-CCP but positive for anti-CarP: 4/ 258 (1.55%) of the patients were anti-CCP2-negative but anti-CarPFCS-positive; 1/ 258 (0.39%) and 1/ 258 (0.39%) of the patients were anti-CCP3-negative but anti-CarP FCS-positive and anti-CarP Fib-positive, respectively. Radiographic progression as measured by using SHS in the patients positive for anti-CCP3 antibody alone was 10.02±11.48 (n=88), those positive for anti-CCP3 and for either anti-CarP FCS or anti-CarP Fib was 9.45±10.80 (n=61), and those positive for anti-CCP3 and both anti-CarP FCS and anti-CarP Fib antibodies was 36.55±9.25 (n=53); the values statistically significant as compared with 4.57±8.97 of those all negative for anti-CCP3 and anti-CarP antibodies (n=66) at p=0.001, 0.006 and 0.0007, respectively. Radiographic progression depended on the presence, but not the titer, of anti-CCP2, anti-CCP3, anti-CarP FCS and anti-CarP Fib antibodies at baseline.

Conclusion: Anti-CarP antibodies are present in a substantial fraction of Japanese patients with RA to the extent similar to previous findings in Europe.

Disclosure: S. Shiozawa, None; **L. A. Trouw**, None; **K. Shiozawa**, None.

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Clinical Characteristics Of Rheumatoid Factor-Positive Or Negative Subsets Of Anti-Citrullinated Peptide/Protein Antibody-Negative Rheumatoid Arthritis. Ryosuke Hiwa, Koichiro Ohmura, Noriyuki Yamakawa, Moritoshi Furu, Chikashi Terao, Ran Nakashima, Yoshitaka Imura, Naoichiro Yukawa, Hajime Yoshifuji, Motomu Hashimoto, Hiromu Ito, Takao Fujii and Tsuneyo Mimori. Graduate School of Medicine, Kyoto University, Kyoto, Japan.

Background/Purpose: Although anti-citrullinated peptide/protein antibody (ACPA) is a specific autoantibody for rheumatoid arthritis (RA), ~20% of RA are ACPA negative. It has been reported that ACPA(−) RA is a distinct subset clinically and genetically; radiographic progression is more severe in ACPA(+) RA and HLA-DR shared epitope is not associated with ACPA(−) RA. Recently we further subdivided ACPA(−) RA into rheumatoid factor (RF) positive and negative subsets and showed that HLA usage is different between ACPA(−)RF(+) RA and ACPA(−)RF(−) RA. Here we investigated the clinical characteristics of each subset.

Methods: RA patients were registered in the KURAMA cohort from May 2011 through May 2013 at Kyoto University Hospital and all the patients were Japanese. Titer of ACPA in sera or plasma was measured with the 2nd generation anti-CCP antibody ELISA kit. RF were measured with latex agglutination turbidimetric immunoassay. A patient was considered to be RF-negative when all the available tests were negative for RF. Age, sex, distribution of affected joints, positivity of anti-nuclear antibody (ANA), disease activity and treatment were assessed. Van der Heijde modified Sharp score (mTSS) of hands & feet X-ray films were scored by two evaluators.

Results: 84 out of 451 RA patients were negative for ACPA. In the ACPA negative group, 43 were positive for RF and 41 were RF-negative. There were significantly more women in RF-positive subset compared to RF-negative (88.4% and 70.7%, respectively). Distribution of affected joints and positivity of ANA, disease activity (DAS28-ESR, SDAI) were similar among the two subsets. Administration of methotrexate, oral glucocorticoid and biologic DMARDs were also similar. The mean of mTSS divided by the disease duration (mTSS/Y) of RF-positive subset were greater than RF-negative subset although there was no statistically significant difference (9.81±1.00 and 8.88±9.62, respectively). The other results were shown in table 1.

Table 1. Clinical characteristics of ACPA(−)RF(+) RA and ACPA(−)RF(−) RA

	ACPA(−)RF(+)	ACPA(−)RF(−)	P value
N	43	41	
Age	62.67 ± 12.85	65.20 ± 13.80	0.19
Women	38 (88.4%)	29 (70.7%)	0.044
Disease duration (M)	152.98 ± 175.93	111.02 ± 146.39	0.88
ANA ≥ 1:80	17 (39.5%)	12 (29.3%)	0.32
DAS28-ESR	4.02 ± 1.44	3.50 ± 1.17	0.62
SDAI	12.83 ± 9.77	13.80 ± 10.15	0.34
MTX dose (mg/w)	6.09 ± 2.27	6.24 ± 2.91	0.43
PSL dose (mg/d)	4.56 ± 2.72	5.73 ± 3.39	0.15
Biologic DMARDs	2 (4.65%)	2 (4.88%)	0.67
mTSS/Y*	9.81 ± 1.00	8.88 ± 9.62	0.65

*mTSS were evaluated for 35 ACPA(−)RF(+) and 28 ACPA(−)RF(−) RA patients.

Conclusion: Although ACPA(−)RF(+) RA and ACPA(−)RF(−) RA are genetically distinct, there seems to be no substantial clinical differences between those two subsets.

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Follow-Up Of Patients With Preclinical Rheumatoid Arthritis – Results Of a Telephone Survey. Pascal Klaus, Vivien Köhler, Hans Bastian, Tanja Braun, Eva Gremmelsbacher, Vera Höhne-Zimmer, Frank Buttgereit, Gerd R. Burmester and Jacqueline Detert. Charité - Universitätsmedizin Berlin, Berlin, Germany.

Background/Purpose: Preclinical rheumatoid arthritis (pre-RA) describes a subset of patients with arthralgia (but no synovitis) where either anti-citrullinated peptide antibodies (ACPA) and/or rheumatoid factor (RF) can be found, but without clinical synovitis, where there was no evidence of clinical RA, and no disease-modifying anti-rheumatic drug (DMARD) therapy was initiated. Recent data indicate that 35% of these patients develop arthritis after 12 months (van de Stadt et al, 2012). The objective of this investigation was to follow the course of disease in patients with pre-RA by means of a telephone survey, and evaluate how many patients develop clinical RA.

Methods: In a retrospective analysis, we identified patients with pre-RA who presented in the early arthritis clinic (EAC) of the Department for Rheumatology and Clinical Immunology of Charité – Universitätsmedizin Berlin between 2004 and 2011. All patient had given written consent to be contacted in the future. Approval from the local ethics committee was present. All patients were called who were in our EAC at least 12 months ago. The follow-up questionnaire included questions about tender and swollen joints, overall pain, current antirheumatic therapy, and whether a diagnosis of RA has been established. Descriptive statistical analysis was performed using SPSS.

Results: 47 patients (pts) with pre-RA out of 1,400 pts of our EAC (3.4%) were identified. 23 of these pts (49%) agreed to participate in the telephone survey. 14 (61%) pts were female. The mean age was 54 (standard deviation (SD) ± 15) years. Mean duration between first contact in EAC and follow-up was 6 (SD ± 2) years. RF >20 U/ml was present in 20 pts (87%) with a mean serum level of 86 ± 144 U/ml in RF positive pts, ACPA >20 U/ml ± were present in 7 pts (30%) with a mean serum level of 28 ± 68 U/ml. RF and ACPA were simultaneously present in 4 pts (17%).

When asked about the course of their symptoms including joint pain and joint swelling, 5 pts (22%) stated that they were now free of complaints, in 10 pts (44%) complaints were improved, in 5 (22%) they were unchanged, in 3 (13%) they had reappeared, and in none of the pts (0%) had complaints deteriorated.

3 pts (13%) developed clinical RA after a duration of 1, 3, and 6 years, respectively. These 3 pts are currently taking DMARD therapy (2 Methotrexate, 1 Leflunomide). 2 of these patients are RF positive (serum level 33 and 74 U/ml, respectively), 1 patient is ACPA positive (70 U/ml). None of the patients are double positive.

Conclusion: The overall risk of developing clinical RA in this cohort of pre-RA patients was low (13%). Serum levels of RF or ACPA were not predictive for the development of RA, and neither was double positive antibody status associated with a higher risk for RA. Large prospective cohorts are needed to confirm these findings.

Disclosure: P. Klaus, None; **V. Köhler**, None; **H. Bastian**, None; **T. Braun**, None; **E. Gremmelsbacher**, None; **V. Höhne-Zimmer**, None; **F. Buttgereit**, None; **G. R. Burmester**, AbbVie Inc., BMS, Merck, Roche, Pfizer, and UCB, 2, AbbVie Inc., BMS, Merck, Roche, Pfizer, and UCB, 5, AbbVie Inc., BMS, Merck, Roche, Pfizer, and UCB, 8; **J. Detert**, Abbott Immunology Pharmaceuticals, 2.

2305

Influence Of Disease Activity On The Physical Activity Of Rheumatoid Arthritis Patients. Vanesa Hernández-Hernández, Ivan Ferraz-Amaro, Esmeralda Delgado-Frías, Sagrario Bustabad-Reyes and Federico Diaz-Gonzalez. Hospital Universitario de Canarias, La Laguna, Spain.

Background/Purpose: It is generally assumed that rheumatoid arthritis (RA) patients tend to exercise less than what is currently recommended. However, there is little data on the level of daily PA in RA patients vs. to healthy controls, using objective procedures, such as accelerometry. Moreover, there remain two important unanswered questions concerning PA vis-à-vis RA: 1) Do patients who are sufficiently physically active suffer from less severe disease? and viceversa, 2) Does disease activity influence PA in RA patients?. With regard to the former, there is considerably more evidence in favor of prescribing PA for RA patients than there is against. However, there is currently no evidence that decisively answers the latter.

The purposes of this study were to compare PA in a group of RA patients versus healthy controls through both objective (triaxial accelerometry) and subjective (International Physical Activity Questionnaire- IPAQ) methods, and to explore the impact of disease levels on PA in these patients. We also sought to determine the potential role of PA assessment as a measure of RA disease activity.

Methods: A group of 50 RA patients and 50 age-and sex-matched healthy controls were included in this cross-sectional study. PA was assessed by accelerometry and with the IPAQ. We performed multiple regression analysis not only to compare PA between groups, but also to explore the relation between RA features, including disease activity and cardiovascular risk parameters, and PA. In a randomized group of 30 RA patients a test/re-test study was carried out in order to determine the correlation between variations in disease activity and PA.

Results: The number of minutes of moderate and vigorous activity/day, as evaluated by accelerometry and adjusted for sex, age, work activity was significantly lower in RA patients than in healthy controls (23±16 vs 33±27 min/day, p=0.02). In RA patients, accelerometry and IPAQ demonstrated concordance to a moderate degree (quadratic weighed Kappa index of 0.27 [0.06–0.48], p=0.02). HAQ negatively correlated with both IPAQ and accelerometry data (beta coef. −1623 (−2742– −503) MET/min/week, p=0.00; beta coef −43 (−81– −6.46) counts/min, p 0.02). DAS28-CRP was also inversely related with IPAQ. Framinghan score and metabolic syndrome were inversely associated with PA in RA patients. Interestingly, variations in PA, as measured by accelerometry, inversely correlated with RA disease activity (r:−0.42, p= 0.02), particularly in the patient group that exhibited changes in DAS28 consistent with an RA flare or improvement.

Conclusion: In RA patients, accelerometry is a reliable technique to evaluate PA. Not only showed that RA patients spend less time doing moderate and vigorous PA than healthy controls, but also PA, as assessed by accelerometry, was sensitive to any changes in disease activity.

Disclosure: V. Hernández-Hernández, None; **I. Ferraz-Amaro**, None; **E. Delgado-Frías**, None; **S. Bustabad-Reyes**, None; **F. Diaz-Gonzalez**, None.

ACR/ARHP Poster Session C
ARHP Rheumatoid Arthritis - Clinical Aspects: Clinical Practice/Patient Care
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

2306

Comparative Study Of Patients With Peripheral Psoriatic Arthritis, Axial Psoriatic Arthritis and Axial Spondyloarthritis Without Psoriasis. Abhijeet Danve[1], Neha Garg[2] and Atul Deodhar[1]. [1]Oregon Health and Science University, Portland, OR, [2]Oregon Health and Sciences University, Portland, OR.

Background/Purpose: Axial involvement in Psoriatic Arthritis (PsA) is reported to be between 40 –70%. Both, axial and peripheral arthritis in patients with PsA can cause unique functional challenges and can reduce quality of life substantially. We aimed to compare the disease characteristics and quality of life (QoL) in three groups of patients: PsA with axial involvement (PsAax), PsA with only peripheral disease (PsApr), and axial spondyloarthritis patients without psoriasis (axSpA).

Methods: Patients with new diagnosis of PsAax seen at Oregon Health & Sciences University between 2007 and 2012 were identified by searching electronic medical records. Age and sex matched patients with PsApr and axSpA without psoriasis were identified. Demographic and clinical data was collected retrospectively. Disease activity and QoL was measured using validated measures such as RAPID 3 and BASDAI. Statistical significance was calculated using Mann-Whitney, Chi square and Fisher's exact tests as applicable.

Results: We found 28 patients with PsAax, who were compared with age and sex matched patients with PsApr (n=26) and axSpA without psoriasis (n=29) respectively. Disease duration, BMI, BASDAI and RAPID 3 scores were similar among three groups (see Table). Smokers were more prevalent in PsAPr than axSpA patients (p = 0.05). PsAax patients had more peripheral arthritis and uveitis compared to axSpA patients (p = 0.01 for both). Prevalence of depression was more in patients with psoriasis (PsAax and PsApr (about 40%) compared to axSpA (24%) but did not reach statistical significance. Prevalence of fibromyalgia, inflammatory bowel disease, mean ESR and CRP were similar in all three groups. More patients in axSpA group used NSAIDs compared to PsAax group (p = 0.05). DMARDs were used more often in patients with PsAax (p = 0.01) and PsApr (p = 0.01) than in axSpA. TNF blockers were used more often in PsAax than in axSpA group (p = 0.03).

	PsA with axial disease (PsAax) N =28 Mean (SD) or %	PsA peripheral (PsApr) N=26 Mean (SD) or %	Axial spondyloarthritis without psoriasis (axSpA) N=29 Mean (SD) or %
Age (years)	48 (14)	45 (14)	45 (13)
Females	57	62	55
Disease duration (years)	13 (13)	8 (9)	13 (13)
BMI (kg/m2)	29 (7)	31 (10)	30 (10)
Smoking	32	12*	34*
Peripheral arthritis	50∞	100	10∞
Uveitis	4∞	0*	31*∞
Depression	39	42	24
RAPID3	4 (2)	5 (2)	5 (2)
BASDAI	4 (1)	NA	5 (5)
NSAID use	17*	21	26*
DMARD use	68∞	85	17∞
Anti-TNF use	82*	77	55*

* $p < 0.05$
∞ $p = 0.01$
NA= Not applicable

Conclusion: In this comparative analysis of PsA patients with axial and peripheral disease and axSpA patients without psoriasis, PsAax patients had higher prevalence of peripheral arthritis compared to those with axSpA alone. Uveitis was less prevalent in PsAax and PsApr compared to axSpA patients. Depression was more prevalent in patients with psoriasis suggesting an important impact on QoL related to skin disease.

Disclosure: A. Danve, None; **N. Garg**, None; **A. Deodhar**, AbbVie, Merck-Sharp-Dohme, Pfizer and UCB, 5, AbbVie, Merck-Sharp-Dohme, Pfizer and UCB, 8, AbbVie, Amgen, Novartis, UCB, 2.

2307

Lifestyle Factors Were Seldom Discussed With Patients Visiting a Rheumatology Clinic. Ann B. I. Bremander and Stefan Bergman. Spenshult Research and Development Center, Halmstad, Sweden.

Background/Purpose: There is increasing evidence that lifestyle factors are of importance for outcome of rheumatic diseases, and lifestyle interventions should be a natural part of management.

The aim was to study if lifestyle factors (diet, physical activity, smoking and alcohol use) were discussed with patients on a regular visit to a specialized rheumatology clinic.

Methods: A questionnaire was distributed to 318 patients visiting an outpatient clinic, and 223 (70%) responded. The questionnaire assessed if lifestyle factors (diet, physical activity, smoking and alcohol use) were discussed at the visit. If not, it also assessed if the patients themselves felt that this discussion would have been desirable.

Results: The questionnaire was answered by 69 (31%) men and 154 (69%) women, and 69% were younger than 65 years. Diet was more frequently discussed with men (14.7% vs. 4.8%) although more women (11.6% vs 4.4%) would have desired it to be discussed. 83% of the patients did not consider that it was needed to discuss at all. Physical activity was discussed with 28% of the patients, without any significant difference between men and women. Only 8% of those not having this discussion thought that they needed it. Smoking was discussed with 15%, without any significant difference between men and women. Alcohol use was discussed

with more men than women (15.9% vs. 4.0%). Of those not having this discussion 3% of the women but none of the men thought that they needed it.

Conclusion: Although recommended as part of management, lifestyle factors are seldom discussed with the patients, and this discussion is not actively thought for by the patients. Lifestyle factors are more frequently discussed with men although women would have desired to have this discussion to a higher extent. There is a need for health care to actively take the initiative and discuss lifestyle as part of regular care.

Disclosure: A. B. I. Bremander, None; **S. Bergman**, Pfizer Inc, 8.

2308

Rheumatoid Arthritis Flares: Inflammatory Or Avalanche? Caroline A. Flurey[1], Marianne Morris[1], Jon Pollock[1], Rodney A. Hughes[2], Pamela Richards[3] and Sarah Hewlett[1]. [1]University of the West of England, Bristol, United Kingdom, [2]St. Peters Hospital, Chertsey Surrey, United Kingdom, [3]University of Bristol, Bristol, United Kingdom.

Background/Purpose: Previous research has not addressed how RA patients' symptoms change daily. The aim of this study was to explore symptom patterns during daily life and flare.

Methods: RA patients completed self-reported NRS (0–10) of pain, fatigue, swollen joints, stiffness, anger, frustration, worry and flare status (yes/no) daily for 3 months either on paper or online. This was an exploratory study and therefore not powered for statistical significance. Data were analysed for descriptive statistics and visually analysed with the use of graphs to identify symptom patterns.

Results: 28 patients took part: 5 withdrew, 6 had missing data for >10/91 days. The 17 patients included in the analysis were 15 female, mean age: 62.9yrs, disease duration: 18.6yrs, HAQ: 1.86.

On plotting the symptoms onto graphs, 3 patients reported constant flare for 91 days (constant flare group), 6 patients self-reported ≥1 flare with periods of non-flare (intermittent flare group) and 8 patients did not report being in a flare (daily life group).

As expected, the group means of the individual symptoms were highest in the constant flare group and lowest in the daily life group. In the daily life group, patients' individual mean pain scores ranged from 0.2 to 5.8, whereas in the intermittent flare group patients' individual mean pain scores ranged from 2.5 to 7.0 and in the constant flare group patients' individual mean pain scores ranged from 2.4 to 9.3. Thus some individual patients reported lower mean pain in flare than other patients reported on non-flare days, this was also the case with the other self-reported measures (see Table 1).

Table 1. Mean symptom scores for the three different trajectories

		Pain	Fatigue	Stiffness	Swollen Joints	Frustration	Anger	Worry
Constant Flare Group	Group Mean (SD)	4.3 (2.7)	4.7 (2.7)	3.6 (2.6)	3.9 (2.6)	3.7 (2.9)	3.1 (3.3)	3.7 (3.1)
	Lowest Individual Patient Mean	2.4 (1.3)	4.4 (2.1)	2.3 (1.5	2.2 (1.4)	1.1 (1.3)	0.7 (0.9)	0.6 (0.9)
	Highest Individual Patient Mean	9.3 (0.8)	9.3 (0.7)	9.5 (0.8)	9.5 (0.7)	9.0 (0.7)	8.9 (0.7)	8.9 (0.7)
Intermittent Flare Group	Group Mean	4.8 (2.3)	4.9 (2.0)	4.0 (2.1)	4.4 (2.1)	4.1 (2.2)	3.1 (2.6)	4.3 (2.4)
	Lowest Individual Patient Mean	2.5 (1.2)	2.7 (1.2)	1.7 (0.7)	2.3 (0.8)	2.1 (0.7)	0.0 (0.1)	1.9 (0.8)
	Highest Individual Patient Mean	7.0 (0.6)	7.4 (1.0)	6.2 (1.1)	6.5 (0.9)	6.3 (1.2)	5.7 (1.3)	7.8 (1.2)
Daily Life Group	Group Mean	3.1 (2.3)	3.6 (2.6)	2.4 (1.5)	2.7 (1.9)	2.8 (2.9)	2.2 (3.3)	2.7 (3.1)
	Lowest Individual Patient Mean	0.2 (0.5)	0.4 (0.9)	0.3 (0.7)	0.5 (0.9)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
	Highest Individual Patient Mean	5.8 (2.2)	7.6 (2.0)	4.8 (1.6)	6.5 (1.6)	8.7 (0.7)	9.2 (0.7)	9.4 (0.6)

Further 5/6 patients in the intermittent flare group rated their symptoms as more severe on non-flare days than on days in flare. Thus patients may be using different criteria other than symptoms to decide whether they are in a flare.

Whilst many patients report traditional 'Inflammatory Flare' of symptoms, other patients may be reporting flare based on experiencing overall loss of control in their lives and thus defining their overall disease activity as more severe (in flare) despite individual symptoms being less severe. The term 'Avalanche Flare' is proposed for this cascading effect of life.

Conclusion: Definitions of flare vary within and between patients and may not be defined by symptom severity alone. Clinicians need to be aware that patients use 'flare' to explain a range of experiences. Understanding the terminology is necessary to improve communication and inform treatment decisions.

Disclosure: C. A. Flurey, Arthritis Research UK, 2; **M. Morris**, None; **J. Pollock**, None; **R. A. Hughes**, None; **P. Richards**, None; **S. Hewlett**, Arthritis Research UK, 2.

2309

Quantifying The Gap Between General Population Guidelines and Expert Opinion For Cardiovascular Risk Management In Rheumatic Disease Patients. Katherine P. Liao[1], Jonathan Brown[1], Jonathan S. Coblyn[1], Paul Cohen[1], Jorge Plutzky[1] and Daniel H. Solomon[2]. [1]Brigham and Women's Hospital, Boston, MA, [2]Harvard Medical School, Brigham and Women's Hospital, Division of Rheumatology, Division of Pharmacoepidemiology, Boston, MA.

Background/Purpose: Cardiovascular (CV) risk is higher among rheumatic disease patients than the general population. However, CV risk management guidelines calibrated for the rheumatic disease population do not currently exist. At our academic medical center, we recently established an interdisciplinary Cardiovascular Rheumatology clinic aimed at optimizing CV care. The objective of this study was to characterize and quantify the change in management recommended for rheumatic disease patients after formal evaluation by cardiologists.

Methods: We studied patients referred to the CV Rheumatology clinic for cardiovascular risk assessment from January 2012 when the clinic began to April 2013. The clinic is held once a month in the rheumatology clinic with patients referred from the rheumatology practice, staffed by 3 board certified cardiologists. Patient demographic information was obtained from the medical record. CV risk factors and change in management was assessed by manual chart review of cardiologists' notes. The following were considered changes in management: (1) change in medication therapy (defined as starting, increasing dose, or switching CV related medications); or (2) further work-up to assess risk (e.g. further laboratory studies to stratify CV risk, stress testing or referral to a cardiac subspecialty). The Adult Treatment Panel III (ATP III) Guidelines were applied to the subset of subjects who were recommended to start or increase statin dose. The ATP III Guidelines specifies low density lipoprotein (LDL) goal levels for patients based on number of traditional CV risk factors and 10 year risk for heart disease according to the Framingham Risk Score.

Results: We studied 31 patients referred for CV risk assessment. The mean age was 57 yrs and 77% were female. The most common underlying rheumatic diseases in the CVR clinic were RA (38.7%) and SLE (25.8%). Hypertension (51.6%) was the most prevalent CV risk factor at presentation, followed by hyperlipidemia (45.2%). Of the patients seen, 83.9% were recommended a change in their current CV management. The most commonly recommended change or intervention was starting or increasing statin therapy (35.5%), change in anti-HTN therapy (16.1%) or stress testing (12.9%). Among the subjects recommended to start or intensify statin therapy, 63.6% would have been considered already at target LDL according to ATP III Guidelines.

Conclusion: We observed that the majority of rheumatic disease patients referred to the CV Rheumatology clinic had a change in CV risk management after evaluation by a cardiologist. Recommended LDL targets by cardiologists at our center were lower than ATP III guidelines, leading to intensification of statin therapy. These data suggest a need for CV risk management optimization in patients with rheumatic diseases.

Disclosure: K. P. Liao, None; **J. Brown**, None; **J. S. Coblyn**, CVS, 5; **P. Cohen**, None; **J. Plutzky**, None; **D. H. Solomon**, Lilly, Amgen, CORRONA, 2, Lilly, Novartis, BMS, Pfizer, 6, Lilly, BMS, Novartis, 9.

2310

Nurse Training; Confidence and Competence For Educating Patients Commencing *Methotrexate* Therapy. Sandra M. Robinson[1], Andrew Hassell[2], Sarah Ryan[3], Nicola Adams[4], Peta S. Heslop[1] and David Walker[5]. [1]North Tyneside General Hospital, North Shields, United Kingdom, [2]School of Medicine (Keele Campus), Keele, United Kingdom, [3]Keele University, Staffordshire, United Kingdom, [4]Northumbria University, Newcastle Upon Tyne, United Kingdom, [5]Freeman Hospital, Newcastle Upon Tyne, United Kingdom.

Background/Purpose: The education of patients is a central part of the nursing role in the UK. Nowhere is it more important than in relation to drugs such as methotrexate, where the effect is delayed and side effects are anticipated. Nurses had expressed variable confidence in educating patients starting *Methotrexate* and training for this varied from none, some training and observing other nurses to being observed. We were interested to explore this with a survey of nurses who educate patients starting *Methotrexate*. These are the results from the respondents.

Methods: A survey was designed using an online survey tool around questions about their role; training; confidence and we used multiple choice questions on clinical situations testing knowledge. A web link to the survey was sent to possible participants with encouragement to spread the link to colleagues.

Results: 44 nurses completed the online questionnaire. 70% were nurse specialists and 30% monitoring nurses. 62% had been counselling for more than 5 years.

Training: 17% had no training prior to starting this role. 66% described it as some training and 17% as a lot. For those who had training, 55% described it as very helpful and 45% as less than helpful. 61% expressed that they would have liked more training. Ranking training requirements, respondents rated knowledge highest followed by communication then consultation skills and finally experience.

Confidence: 60% of respondents described themselves as very confident in this role, with 23% confident and 15% somewhat confident. One person was not confident at all. 43% reported that their education of patients had changed a lot and 50% reported that this had changed somewhat while they had been performing the role. The time it took to become confident in the role was variable with 10% confident in 1–2months, 53% in 3–6 months and a further 20% by a year.

Competence: This was tested with MCQs on clinical situations. There was 90–100% accurate response to questions about vaccinations, antibiotics and liver function. Questions on pregnancy and alcohol, however, scored approximately 50% for complete accuracy. A question on Shingles was not well understood. A variety of written information was used in the education processs, this information was often used together. The Arthritis Research UK information sheet was used by 80% and judged to be very helpful.

Conclusion: The nurses included in this survey show a great variation in the training they had prior to starting this role with those nurses performing the role for the longest period of time having had the least training. The majority would like more training. Most respondents took 3–12 months to feel confident in this role. A training package aimed at satisfying these aspirations could shorten this period and result in better and more consistent education for patients. This should result in improved concordance and safety of treatment.

Disclosure: S. M. Robinson, None; **A. Hassell**, None; **S. Ryan**, None; **N. Adams**, None; **P. S. Heslop**, None; **D. Walker**, None.

2311

Impact Of Healing Architecture In a Rheumatology Outpatient Clinic. Gunhild Bukh[1], Erik Kehn Jensen[2], Anne Marie Munk Tommerup[3] and Ole Rintek Madsen[4]. [1]Copenhagen University Hospital Gentofte, Hellerup, Denmark, [2]Kehn & Warnøe, Copenhagen, Denmark, [3]Danish Architecture Centre, Copenhagen, Denmark, [4]Copenhagen University Hospital Gentofte, Copenhagen, Denmark.

Background/Purpose: Healing Architecture (HA) is a design concept primarily aimed at reducing factors of stress in the physical environment both for the patient and for the medical staff. HA works through modifications of the physical environment and the practical functionality of the room. HA has the long term goal of achieving measurable improvements on economy, ressources, productivity and user/staff satisfaction. The study objective was to examine whether the application of HA principles in an outpatient infusion room for treatment with biologic agents used in treatments of rheumatologic diseases would impact patient experience and ultimately improve patient satisfaction as well as work satisfaction of attending nurses.

Methods: A water wall making silent bobbles were installed in the infusion room in order to increase the stimulation of the senses and to improve relaxation. Artificial plants were introduced. Decorative art paintings substituted existing disease information related wall posters. The functionality of the room was improved by changing the layout of the seating and arrangement of infusion pumps. New ergonomic chairs were installed and for each chair a small table dedicated to the individual patient was provided. Furthermore, individual reading lamps were mounted for the allowing each patient to individually regulate the light. A high table was positioned in the center of the room with coffee, tea and water. In order to de-hospitalize the room all new furniture were similar in appearance and quality to what would be used at home. A questionnaire was designed to quantify the experience of the attending patients on 16 different parameters before and after application of HA modifications. The questionnaire, administered before and after the HA intervention recorded two sets of scores for each parameter: One set scored the perceived patient experience of each parameter. The other set scored the perceived importance of each parameter. A calculated combination of the two scores provided a composite score of the satisfaction with each parameter experienced (range 0–130). The change in the total composite patient satisfaction score before and after re-modeling of the treatment room was evaluated. In addition to this quantitative research, a total of four patients and nurses underwent a qualitative interview before and after the HA intervention.

Results: 43 patients completed a questionnaire before and after the HA intervention. Mean age was 54 $\pm$ 12 years, mean disease duration 13 $\pm$ 10 years, mean treatment duration 23 $\pm$ 8 months. The total score before and after the intervention was 56.6 $\pm$ 16.5 and 71.8 $\pm$ 19.2, respectively ($p<0.001$). Both nurses and patients reported highly positive attitudes regarding the HA modifications.

Conclusion: The study confirmed that the principles of HA significantly can increase patient satisfaction. The quantitative findings were supported by qualitative research, which demonstrated both increased patient satisfaction and increased satisfaction for the attending nurses.

Disclosure: G. Bukh, None; **E. K. Jensen**, None; **A. M. M. Tommerup**, None; **O. R. Madsen**, None.

2312

Experiences Of Older People Living With Ankylosing Spondylitis. Jane Martindale, Elham Kashefi and Lynne Goodacre. Lancaster University, Lancaster, United Kingdom.

Background/Purpose: With an increasing demographic of ageing, more people may be living longer with a long-term health condition. There may be implications in terms of the knowledge, skills and expertise patients living with AS need to develop to manage their symptoms as they age. Our aim was to develop a greater understanding of the experience of ageing with AS and the needs of older people living with this condition.

Methods: Ethical approval was obtained for a qualitative study embedded within a longitudinal cohort study exploring the needs of people living with AS throughout the life course. Patients over 60 years were recruited from two Rheumatology outpatient clinics in the UK. Six focus groups were conducted to explore participants' experiences through peer group discussion. The groups were recorded and transcribed. Transcripts were coded and a thematic analysis was conducted using NVIVO 10.

Results: Four women and 28 men consented to participate; average age 68 years (range 60–83). Eight participants were on biologics. Six participants were still in employment. Analysis identified 5 key themes: 1. 'It doesn't go away" describes how AS remains active as people age with continuing functional and symptomatic challenges. Positive and negative aspects of the tendency to normalise symptoms were identified. 2. 'Wheels fall off after 60' describes participants' perceptions of their disease progression within the context of 'normal ageing'. Additionally, they describe how they no longer felt out of place in comparison to their peers. 3. 'Keep on pushing, keep on going' describes the challenges of maintaining motivation to remain active and the importance of a positive mental attitude. Monitoring, trust and support from health care professionals is seen as being an integral part of this theme. 4. 'Living a fulfilling life' describes how participants developed 'learnt expertise' and made active choices about how they managed their AS with its imposed restrictions. 5. 'Paying a price' describes the significant psychological, physical and financial consequences associated with living with AS on participants and their families.

Conclusion: As people living with AS make the transition into retirement, many aspire to live active lives whilst facing new challenges in relation to their lifestyles and priorities. However, ageing is often seen as a time of decline in physical and mental function. This coupled with a tendency to normalise symptoms highlights a continuing clinical need to monitor symptoms with an appreciation that the 'older person' faces some additional challenges. As well as monitoring, there is a need to offer tailored interventions to enable older people to remain active and to continue to lead the lives they choose within the context of an active and often debilitating condition.

Disclosure: J. Martindale, None; **E. Kashefi**, None; **L. Goodacre**, None.

2313

Pain-Related Anxiety As a Barrier To Use Of Methotrexate In Rheumatoid Arthritis: Comparing Conventional Vial, Needles, and Syringe With An Investigational Auto-Injector In Healthy Volunteers. Victoria L. Ruffing[1] and Kaushik J. Dave[2]. [1]Johns Hopkins University, Baltimore, MD, [2]Antares Pharma Inc, Ewing, NJ.

Background/Purpose: Methotrexate (MTX) is the cornerstone of rheumatoid arthritis (RA) treatment. Limitations of systemic exposure of oral MTX can affect its efficacy. Subcutaneous (SC) MTX improves bioavailability, which may result in better efficacy, and tolerability. Self-administration of SC MTX via conventional vial, needle, syringe (VNS) is challenging for some patients due to functional limitations, injection-site adverse events (AEs), and especially anxiety associated with pain. Use of SC MTX is limited to <5% of patients in the U.S. An analysis of literature from 1982–2012 on patient perception and experiences with self-administered medication for multiple diseases (RA, diabetes, hepatitis, multiple sclerosis) also suggests that anxiety associated with pain when using conventional VNS is often a barrier to use. Improvements in the delivery of SC MTX may alleviate anxiety associated with pain. In this study, the prototype of an investigational, first-in-class auto-injector (AI) for MTX is evaluated.

Methods: This study compares administration-related pain and bleeding in healthy volunteers using conventional VNS and AI. 21 volunteers received 12 injections (6 with AI; 6 with VNS) of 1.0 mL saline administered by study personnel according to a randomized schedule. Pain was measured on a 20-point scale ranging from 0 (no pain) to 19 (extremely intense pain). Injection site bleeding was also assessed.

Results: Pain was rated as none or faint for 78.4% of 125 AI administrations and 59.7% for 129 injections with VNS (Fishers Exact Text, P=0.0017). In addition, no pain was reported for 56.0% of AI administrations vs. 34.9% with VNS (P=0.0010) (Table). No pain scores >10 were reported for either treatment. No bleeding was observed in 89.7% of AI administrations vs. 79.2% of those with VNS (P=0.0069).

Table. Pain scores

Pain Score	Auto-injector (n=125) %	VNS (n=129) %
0	56.0	34.9
1	22.4	24.8
2	6.4	6.2
3	5.6	17.0
4	3.2	6.2
5	2.4	3.9
6	0.8	1.5
7	2.4	2.3
8	0	2.3
9	0	0.8
10	0.8	0
>10	0	0

Conclusion: Pain-related patient anxiety often associated with SC administration of medications is a potential cause for underutilization of SC MTX in the treatment of RA. By decreasing pain associated with self-injection, an AI may address issues of needle phobia and improve rates of utilization of SC MTX in patients who may benefit from this method of delivery.

Disclosure: V. L. Ruffing, None; **K. J. Dave**, Antares Pharma, 3.

2314 WITHDRAWN

2315

Reducing The Need For Total Knee Arthroplasty: The Experience Of a Multidisciplinary Osteoarthritis Clinic. Caroline Jones[1], Angelo Papachristos[1] and Laurence A. Rubin[2]. [1]St Michael's Hospital, Toronto, ON, [2]St. Michael Hospital, Toronto, ON.

Background/Purpose: St. Michael's Hospital (SMH) is a tertiary care facility located in Toronto, serving a diverse social, economic and cultural urban population. In 2008, a multidisciplinary osteoarthritis (MOA) clinic was established at SMH. The majority of referrals are received in the clinic from orthopaedic surgeons in patients contemplating knee replacement surgery. The team (Rheumatologist, Advanced Practitioner) designs and implements a comprehensive treatment plan.

Purpose: To complete a qualitative review of all of the patients who attended clinic and who subsequently went on to require a total knee arthroplasty.

Methods: A retrospective chart review was completed on all patients who attended the OA clinic between January 2011 and April 2012. During this time period there were 329 patients who attended clinic of which 24 went on to require a total knee arthroplasty (TKA). The charts of the patients who went on to a TKA were reviewed in detail and analyzed to determine if there are key criteria that determine who will subsequently elect to have a joint replacement. This project is designed as part of a continuous quality improvement initiative.

Results: In the 16 months that this data was obtained there was 329 patients who attended clinic of which 24 went on to require a total knee arthroplasty. All of the patients completed a WOMAC, an MDHAQ, x-rays as well as a complete physical exam. All of the patients had x-rays that demonstrated OA. The majority of patients had x-ray evidence of moderate to severe arthritis. Table showing the mean of results:

	General Cohort	Arthroplasty Group
WOMAC total, mean	41.3	49.8
MDHAQ pain	5.9	8
Global health	4.9	7
fatigue	4.8	5.4
ACR function	2	3

Discussion: The results from this project provide information with respect to actual clinical situations. A significant number of patients that attended the clinic had x-ray evidence of moderate to severe arthritis yet less than 10% went on to require an arthroplasty. There were some subtle differences between the two patient groups and it was the intent of this review to examine in more detail the criteria that patients feel is crucial in opting for surgical intervention.

Conclusion: The results show that the decision to proceed to surgery is multifactorial with pain and decreased function being the key criteria in patients' decision making process. Interestingly, patients who perceived their general health as negatively impacted were more likely to proceed with surgery.

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ACR/ARHP Poster Session C
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy III
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

2316

Anti-Human TNF-Alpha Domain Antibody Construct, CEP-37247/ Placulumab, Is As Efficacious As Other Leading TNF-Alpha-Blockade Therapies in a Humanized Mouse Model of Rheumatoid Arthritis. Matthew M. Seavey[1], Linglong Zou[2], Adam Clarke[3], Anthony G. Doyle[3], Roberta Weiss[4], Aric Orbach[5], Brad McIntyre[6] and Merav Bassan[5]. [1]Teva Pharmaceuticals, Inc., West Chester, PA, [2]Teva Biopharmaceuticals, Rockville, MD, [3]Teva Pharmaceuticals, Inc., Sydney, Australia, [4]Teva Pharmaceuticals, Inc., Frazer, PA, [5]Teva Pharmaceuticals, Inc., Netanya, Israel, [6]Teva Pharmaceuticals, Inc., West Cheater, PA.

Background/Purpose: The cytokine tumor necrosis factor (TNF) alpha is a potent pro-inflammatory mediator involved in several autoimmune diseases including rheumatic arthritis and for over a decade has been a target of numerous biological therapies. CEP-37247 is a bivalent anti-TNF-alpha domain antibody (dAb) construct combining the antigen-recognition function of a dAb with the pharmacological advantages of human immunoglobulin-G Fc region. In order to assess

the therapeutic applicability of CEP-37247 in comparison to other marketed anti-TNF-alpha biologics, we performed head-to-head comparisons to approved reference agents in the well established human-TNF-alpha over expressing transgenic mouse model (Tg197) that develops spontaneous rheumatoid arthritis.

Methods: Symptomatic, arthritic animals were treated in a semi-therapeutic manner starting from week-3, at disease onset. Animals (N=8/group, male and female combined) were treated ip, twice weekly with either CEP-37247 at 30, 10, 3 or 0.3 mg/kg or reference agent Remicade at 10 or 3 mg/kg, Enbrel or Humira both at 10 mg/kg; untreated control included isotype Ab IgG_1at 10 mg/kg. Animals were monitored for changes in body weight and clinical disease score; end measurements included serum PK/PD and histopathology.

Results: CEP-37247 provided a dose dependent, and significant ($p<0.01$), effect on mean arthritic scores by week 10 of disease with 0.3 mg/kg providing an effect similar to isotype control. CEP-37247 at 30 mg/kg significantly reduced (85%, $p<0.001$) arthritic disease score of treated animals from onset until week 10 of age as compared to isotype control with no significant difference between dose matched groups of Remicade, Humira or Enbrel ($p>0.05$). Histopathology of blinded scored H+E stained sections revealed that the isotype control had extensive cartilage destruction, bone erosion and synovial infiltrates as expected from an untreated animal; CEP-37247 impact on joint pathology mirrored that of the disease score with 30, 10 and 3 mg/kg all providing significant reduction in damage and inflammation ($p<0.01$) below that of isotype control, however no difference in dose matched groups compared to reference agents. Serum CEP-37247 levels correlated with in vivo efficacy and ex vivo cytokine responses (e.g., reduction in IL-1-beta).

Conclusion: These data demonstrate the clear efficacy of a potent anti-human TNF-alpha domain antibody construct to suppress active disease in a humanized mouse model of rheumatoid arthritis as compared head-to-head against available anti-TNF-alpha therapies on the market. At half the size of a conventional Ab but with full functionality CEP-37247 may provide the benefits of lower cost of production, immunogenicity and improved tissue distribution.

Disclosure: M. M. Seavey, None; **L. Zou**, None; **A. Clarke**, None; **A. G. Doyle**, None; **R. Weiss**, None; **A. Orbach**, None; **B. McIntyre**, None; **M. Bassan**, None.

2317

Impact of PVA Coated Nanoparticles On Cellular Viability and Functionality of Immune Cells Obtained From Healthy Donors and Patients With Rheumatoid Arthritis Or Osteoarthritis. Cindy Strehl[1], Timo Gaber[1], Manuela Jakstadt[1], Martin Hahne[1], Saskia Schellmann[1], Barbara Szostak[1], Géraldine Coullerez[2], Heinrich Hofmann[2], Gerd-Rüdiger Burmester[3] and Frank Buttgereit[4]. [1]Charité University Medicine, Berlin, Germany, [2]École polytechnique fédérale de Lausanne, Lausanne, Switzerland, [3]Charite University Hospital, Berlin, Germany, [4]Charité - Universitätsmedizin Berlin, Berlin, Germany.

Background/Purpose: Nanotechnology has developed into a key technology of the 21st century. Over the recent years, the number of nanotechnical products has received an enormous boost. More and more efforts are currently being done to use this technology also in rheumatology for diagnostic and therapeutic purposes (see www.nanodiara.eu). Therefore, crucial questions concern the safety aspects. Thus, the focus of our work here was to identify putative effects of nanoparticles on human immune cell function. We analysed interactions between PVA coated super paramagnetic iron oxide nanoparticles (SPIONS) and human immune cells in the presence or absence of dexamethasone.

Methods: PBMCs were isolated from blood samples obtained from healthy donors, RA and OA patients, and CD4 positive T cells were separated via MACS-Sort. Cells were incubated in fully supplemented RPMI 1640 with/without dexamethasone treatment at the clinical relevant concentration 10^–8M. Functionalised amino-PVA-SPIONS were added at varying concentrations, and cells were incubated for 24h. Apoptosis was analysed by measuring the caspase-3/7-activity via luminescence. Caspase-3 and -7 are members of the cysteine aspartic acid-specific protease family, which play a key effector role in apoptosis in mammalian cells. Furthermore, CD4 positive T cells were incubated with/without PHA, with/without 10^–8M dexamethasone and/or with/without PVA-SPIONS at different concentrations. Functionality was determined via proliferation measurements of CFSE (carboxyfluorescein diacetatesuccinimidyl ester) labeled T cells after 72h under normoxic (5% CO_2 and 18% O_2) or hypoxic (5% CO_2 and <1% O_2) conditions by flow cytometry.

Results: Caspase measurements to investigate cellular toxicity of amino-PVA-SPIONS did not show any measurable effects on the survival of isolated CD4+ T cells (as already observed for whole blood assays) at concentrations less than 1000μg/ml. Interestingly, SPION-treatment with increasing concentrations in the presence of dexamethasone even resulted in a decrease of caspase activity indicating a diminished apoptosis of the CD4+ T cells in RA patients. Also in healthy donors a decrease of caspase activity with increasing SPION concentrations could be observed. Dexamethasone itself did not have any effects on caspase activity.

As expected, there was less proliferation under hypoxia than under normoxia; and treatment with dexamethasone decreased the percentage of divided cells for both RA patients and HD under normoxia and hypoxia. Focusing on the influence of dexamethasone on the T cell proliferation in the presence of PVA-SPIONS, we observed no difference in the impact of dexamethasone on proliferation.

Conclusion: PVA coated nanoparticles at concentrations up to 1000μg/ml do not interfere with effects of dexamethasone on proliferation and caspase-3/7-activity of human T cells. The impact of PVA-SPIONS on other human immune cells and on effects of glucocorticoids on these cells need to be further analyzed. This represents a critical need prior to the clinical use of nanoparticles in rheumatology.

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2318

Disease Activity in Moderate and Severe Rheumatoid Arthritis At Discontinuation in 10-Year Open-Label Extension Studies With Etanercept. Michael E. Weinblatt[1], Joan M. Bathon[2], Michele Hooper[3], Bojena Bitman[3], Yue Yang[4], David H. Collier[3], James Chung[5] and Mark C. Genovese[6]. [1]Brigham and Women's Hospital, Boston, MA, [2]Columbia University, New York, NY, [3]Amgen Inc., Thousand Oaks, CA, [4]Assent Consulting, South San Francisco, CA, [5]Amgen, Thousand Oaks, CA, [6]Stanford University, Palo Alto, CA.

Background/Purpose: Retention rates may be used as a surrogate of long-term effectiveness of drug therapy in open-label studies. Studies have reported that patients (pts) with moderate rheumatoid arthritis (RA) are more likely to achieve low disease activity or remission than pts with severe disease. We examined disease activity in pts who withdrew from long-term open-label extension (OLE) studies of etanercept (ETN) for reasons other than loss of efficacy (LOE) to see if they had lost drug response and whether response rates differed by baseline disease activity.

Methods: Data from pts with early RA (ERA) and long-standing RA (LRA) enrolled in OLE studies were analyzed. Using disease activity score with 28 joint count with CRP (DAS28-CRP) criteria, pts were categorized at baseline of the original study as having moderate (DAS28-CRP $\geq$3.2 and $\leq$5.1) or severe (DAS28-CRP >5.1) disease. In the original studies, ERA pts received methotrexate (MTX) or ETN monotherapy and LRA pts received ETN, MTX, ETN+MTX, or placebo. All pts received ETN in the OLE studies. For this analysis, DAS28-CRP was evaluated at the time of first efficacy measurement after patients initiated ETN (either parent study or OLE) as baseline and at study withdrawal. We compared DAS28-CRP in moderate and severe pts who had withdrawn for LOE or other reasons with pts who completed the OLE studies.

Results: Overall, 65.2% of ERA pts and 69.6% of LRA pts withdrew over the 10 years of the OLE studies. More pts withdrew for reasons other than LOE as listed by the investigator. Pts who withdrew for LOE showed no improvement in DAS28-CRP from baseline until last DAS28-CRP measurement (Table). Pts who withdrew for other reasons (eg, physician decision, protocol issues, patient refusal, others) had improved DAS28-CRP from baseline, but not as low as pts who completed the study. While DAS28-CRP scores in pts who withdrew for LOE were similar between moderate and severe pt groups, mean DAS28-CRP was lower in pts with moderate RA compared with pts with severe RA in both ERA and LRA pts at the time of withdrawal for reasons other than LOE and in the completer group.

Baseline and Last DAS28-CRP in Patients who Withdrew and Patients who Continued in Etanercept Clinical Trials by Withdrawal Category

	Moderate RA		Severe RA	
	n	Mean (SD)	n	Mean (SD)
ERA Patients				
MTX in original study, ETN in OLE				
Withdrew for LOE				
Baseline DAS28-CRP	4	4.81 (1.73)	7	4.48 (0.49)
Last DAS28-CRP	4	5.97 (0.98)	7	5.84 (1.14)
Withdrew for other reason (not AE)				
Baseline DAS28-CRP	13	3.50 (1.50)	47	4.39 (1.38)
Last DAS28-CRP	13	2.97 (0.91)	44	4.02 (1.64)
Continued to study closure				
Baseline DAS28-CRP	10	3.52 (1.72)	42	3.69 (1.37)
Last DAS28-CRP	10	2.55 (1.46)	42	2.73 (1.03)
ETN in original study, ETN in OLE				
Withdrew for LOE				
Baseline DAS28	6	4.63 (0.30)	29	6.37 (0.68)
Last DAS28	5	5.15 (1.70)	29	5.63 (1.52)
Withdrew for other reason (not AE)				
Baseline DAS28	34	4.50 (0.51)	118	6.45 (0.78)
Last DAS28	34	3.27 (1.43)	118	3.80 (1.50)
Continued to study closure				
Baseline DAS28-CRP	32	4.41 (0.46)	109	6.30 (0.74)
Last DAS28-CRP	31	2.50 (1.02)	108	2.79 (1.13)
LRA Patients				
Withdrew for LOE				
Baseline DAS28	8	4.61 (0.37)	69	6.66 (0.72)
Last DAS28	8	4.99 (1.30)	69	5.71 (1.27)
Withdrew for other reason (not AE)				
Baseline DAS28-CRP	35	4.59 (0.40)	143	6.55 (0.79)
Last DAS28-CRP	34	3.25 (1.35)	141	4.58 (1.44)
Continued to study closure				
Baseline DAS28-CRP	42	4.20 (0.98)	151	5.57 (1.51)
Last DAS28-CRP	41	2.51 (1.12)	149	2.77 (1.10)

ERA, early rheumatoid arthritis; LRA, long-standing rheumatoid arthritis; LOE, lack of efficacy; DAS28-CRP, Disease Activity Score using 28 joint count with CRP; AE, adverse events

Funded by Immunex, a wholly owned subsidiary of Amgen Inc. and by Wyeth.

Conclusion: ERA and LRA pts with moderate or severe disease who withdrew from ETN OLE studies for reasons other than LOE (the majority of pts) had a positive clinical response at the time of withdrawal so the overall withdrawal rate did not reflect lack of drug efficacy. Pts who withdraw from long-term studies for reasons other than LOE generally still demonstrate improvement over their baseline DAS28-CRP. Also, while ETN treatment is effective in ERA and LRA pts with moderate and severe disease, pts with moderate disease at baseline achieved lower DAS 28-scores than pts with severe disease.

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2319

Comparative Safety Of Biological Agents Among Medicare Rheumatoid Arthritis Patients. Huifeng Yun[1], Fenglong Xie[1], Elizabeth S. Delzell[1], Lang Chen[1], Emily Levitan[1], James Lewis[2], Kenneth G. Saag[1], Timothy Beukelman[1], Kevin L. Winthrop[3], John Baddley[1], Paul M. Muntner[1] and Jeffrey R. Curtis[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Pennsylvania, Philadelphia, PA, [3]Oregon Health & Science University, Portland, OR.

Background/Purpose: Several new biologic disease-modifying antirheumatic drugs (DMARDs) have been approved for treatment of rheumatoid arthritis (RA) in United States. However, their comparative risks of serious infections are unclear. The objective of the current study is to determine if the risks of hospitalized infections associated with various biologics used for RA differs.

Methods: Using Medicare data from 2006–2011 for 100% of patients with RA, we identified new biologic users of etanercept, adalimumab, certolizumab, golimumab, infliximab, abatacept, rituximab and tocilizumab. New users were defined specific to each drug as no use of that therapy in the prior 12 month 'baseline' period. To increase homogeneity of patients for biologics typically not used as first line agents, patients were required to have used another biologic during baseline (i.e. they were 'switchers'). Eligible subjects were continuously enrolled in Medicare Parts A, B and D in baseline and throughout follow up. Follow up started from the drug initiation date and ended at the earliest date of: a hospitalized infection, 12 months after biologic initiation, a 30 day gap in current exposure, death, or loss of Medicare coverage. We identified hospitalized infection using inpatient physician diagnosis codes in primary or secondary position. Confounding was controlled through a person-specific infection risk score that was separately derived among biologic-naïve new users of anti-TNF and non-biologic DMARDs. We calculated the incidence rate of hospitalized infection for each biologic and compared their hospitalized infection risks during follow-up using Cox regression adjusting for infection risk score decile, disability status, glucocorticoids use during baseline, methotrexate use during baseline, most recent biologic during baseline and Medicaid eligibility.

Results: Of 29,776 new biologic switchers, 11.9% were exposed to etanercept, 15.0% adalimumab, 5.9% certolizumab, 4.3% golimumab, 12.3% infliximab, 29.0% abatacept, 14.9% rituximab and 6.4% tocilizumab. During follow-up, we identified 2,224 hospitalized infections yielding infection incidence rates from a low of 12.3 (abatacept) to a high of 17.4 (infliximab) per 100 person years across different biologics. After adjustment for potential cofounders, etanercept, infliximab and rituximab users had significantly higher hazard ratios of hospitalized infection compared to abatacept users. Adjusted HRs for all other drug-outcome comparisons were not significantly different from abatacept (table).

Table. Events, absolute incidence rate and adjusted hazard rate of hospitalized infection by different types of biologic exposures during follow-up

Biologic Exposures	Events	Incidence rate per 100 person years	Adjusted Hazard Ratio* (95% CI)
Abatacept	624	12.3	1.00 (Ref)
Adalimumab	278	13.8	1.10 (0.94 – 1.29)
Certolizumab	93	13.2	1.08 (0.86 – 1.35)
Etanercept	238	14.8	1.26 (1.08 – 1.48)
Golimumab	77	13.5	1.17 (0.91 – 1.49)
Infliximab	325	16.1	1.39 (1.19 – 1.61)
Rituximab	477	17.4	1.37 (1.20 – 1.55)
Tocilizumab	112	13.8	1.10 (0.89 – 1.36)

* Adjusted for infection risk score decile, steroid use during baseline, methotrexate use during baseline, recent biologic use during baseline, original reason for Medicare coverage and Medicaid eligibility.

Conclusion: Among RA patients with exposure to biologic therapies, etanercept, infliximab and rituximab were associated with a higher one year risk of serious infection compared to abatacept.

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2320

Ultrasonographic Monitoring Of Response To Infliximab In Patients With Rheumatoid Arthritis. Xiaomei Leng[1], Weiguo Xiao[2], Xiaochun Zhu[3], Zhonghui Xu[1], Wei Yu[1], Jing Lu[2], Jiakai Wang[2], Xiaoru Xia[3], Yongji Li[3], Yi Liu[4], Yi Zhao[4], Honghao Tang[4], Dongbao Zhao[5], Yeqing Shi[5], Huji Xu[6], Jun Bao[6], Lin Chen[6], Ling Lin[6], Ling Zhou[6], Guoqiang Chen[7], Weihong Zhang[7] and Yan Zhao[1]. [1]Peking Union Medical College Hospital, Beijing, China, [2]The First Hospital of China Medical University, Shenyang, China, [3]The First Hospital of Wenzhou Medical College, Wenzhou, China, [4]West China Hospital of Sichuan University, Chengdu, China, [5]Changhai Hospital of Shanghai, Shanghai, China, [6]Shanghai Changzheng Hospital, Shanghai, China, [7]The First People's Hospital of Foshan, Foshan, China.

Background/Purpose: To evaluate the efficacy of treatment with infliximab on joint inflammation and bone erosion in rheumatoid arthritis (RA) patients using ultrasonography.

Methods: 80 eligible subjects were enrolled from 7 sites. Subjects received infliximab 3 mg/kg IV infusion at 0, 2, 6 weeks, repeated every 8 weeks until 22 weeks. Endpoints included 7-joint and 12-joint ultrasound (US) synovitis scores at 22 weeks, and correlations between US scores and DAS28 (using CRP)/radiography (modified Sharp score (MSS)/van der Heijde scoring)/HAQ outcome. The 7 joints included those of the clinically dominant hand and foot: wrist, second and third metacarpophalangeal and proximal interphalangeal, and second and fifth metatarsophalangeal joints.

Results: The patients (81.25% women) had a mean age of 47.22Â± 14.27 years (meanÂ±SD). Baseline 7-joint and 12-joint synovitis scores were 22.35Â±11.67 and 42.09Â±29.64 in grayscale and power Doppler (GS+PD) US, 15.45Â±5.54 and 29.41Â±16.12 in GS US, and 6.90Â± 7.26 and 12.68Â±15.65 in PD US. At baseline, DAS28 was 5.73Â±1.05, MSS was 17.75Â±25.27, SDAI was 187.29Â±55.68, CDAI was 152.16Â±45.82, and HAQ score was 1.36Â±0.79. 64 patients (80.00%) completed all visits and 66 patients (82.50%) completed treatment for 22 weeks. After 22 weeks of therapy, 7-joint GS+PD US scores significantly decreased to 18.97Â±10.81 and the GS US and PD US scores significantly decreased to 11.98Â±6.42 (P<0.01) and 3.34Â±4.59 (P<0.01), respectively **(Figure)**. There were significant decreases in scores for 12-joint GS+PD US (28.47Â±20.93), GS US (22.65Â±15.19, P<0.01), PD US (5.82Â±8.17, P<0.01), DAS28 (3.20Â±1.31, P<0.01), SDAI (77.73Â±54.27), and CDAI (62.13Â±41.95). MSS increased (18.04Â±23.91, P>0.05) and HAQ score significantly decreased (0.56Â±0.61, P<0.01). There was a positive correlation between US scores and RA activity evaluation indexes, including DAS28, SDAI and CDAI (correlation coefficients 0.5535, 0.6364 and 0.5532) **(Table)**. 14 patients experienced an adverse event and 2 patients experienced a serious adverse event.

Figure. Ultrasonic total score contrast.

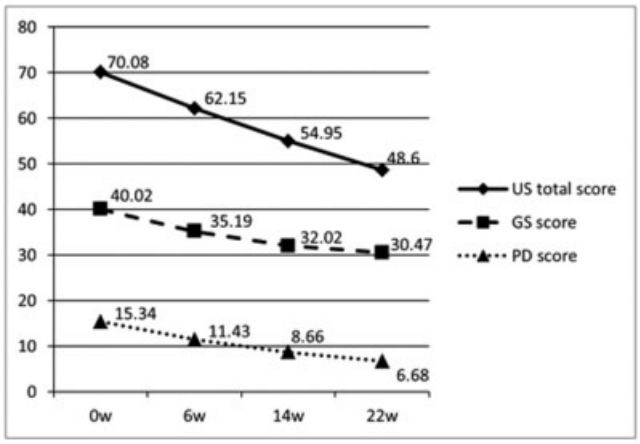

Table. Correlation between ultrasonic total score and DAS28.

Items	Correlation coefficient*	P-value
Baseline (0w)	0.3994	0.0005
6w	0.3975	0.0013
14W	0.4245	0.0007
22w	0.5535	0.0000

* Spearman rank correlation

Conclusion: In this study, treatment with TNF inhibitors relieved synovitis in patients with moderate to severe RA. US is a viable tool for examining patients with RA in daily practice because it significantly reflects therapeutic response. The 7-joint US synovitis score can be used for the evaluation of clinical efficacy in the clinic, instead of the 12-joint method. This trial showed that there is a positive correlation between US scores and DAS28. Large multicenter, prospective, randomized controlled studies are needed to confirm this preliminary observation.

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2321

Long-Term Safety and Efficacy Of Certolizumab Pegol In Combination With Methotrexate In The Treatment Of Rheumatoid Arthritis: 5-Year Results From a 24-Week Randomized Controlled Trial and Open-Label Extension Study.

Josef S. Smolen[1], Ronald van Vollenhoven[2], Arthur Kavanaugh[3], Vibeke Strand[4], Jiri Vencovsky[5], Michael H. Schiff[6], Robert Landewé[7], Boulos Haraoui[8], Susan Walker[9] and Désirée van der Heijde[10]. [1]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [2]The Karolinska Institute, Stockholm, Sweden, [3]University of California San Diego, San Diego, CA, [4]Stanford University, Palo Alto, CA, [5]Institute of Rheumatology, Department of Clinical and Experimental Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [6]University of Colorado, Denver, CO, [7]Academic Medical Center Amsterdam & Atrium Medical Center, Heerlen, Netherlands, [8]Centre Hospitalier de l'Université de Montréal, Montreal, QC, [9]UCB Pharma, Raleigh, NC, [10]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: In the RAPID2 randomized controlled trial (RCT; NCT00160602), certolizumab pegol (CZP) +MTX every 2 weeks (Q2W) improved signs and symptoms of rheumatoid arthritis (RA) over 24 weeks (wks). Previous results demonstrated long-term safety and efficacy of CZP+MTX over 3 yrs in RAPID2 open-label extension (OLE).[2] We present the final report on long-term safety and efficacy of CZP+MTX over 5 yrs.

Methods: Eligible patients (pts) from RAPID2 RCT were treated in OLE (NCT00160641) with CZP 400mg Q2W, reduced to 200mg Q2W after ≥6 months, +MTX. Combined safety data from RCT and OLE are reported for all pts treated with ≥1 dose of CZP (N=612). AEs and SAEs were assessed at each visit following first dose of CZP. DAS28(ESR), HAQ-DI and ACR20/50/70 are presented to Wk232 for CZP Completers (pts who completed RCT and enrolled onto OLE [N=342]) and CZP ITT population (all pts randomized to CZP in RCT [N=492]). Change from baseline in modified Total Sharp Score (mTSS) and % of pts with radiographic non-progression (mTSS change from RCT baseline ≤0.5) are reported to Wk128 for CZP Completers. Dose reduction efficacy data is presented for all Wk24 CZP Completers who received CZP 400mg Q2W +MTX for ≥6 months in OLE, following which the CZP dose was reduced to 200mg Q2W over 132 wks of CZP exposure. Modified non-responder imputation (mNRI) was used for ACR responses; LOCF for continuous efficacy measures; mTSS data imputed by linear extrapolation.

Results: Of 492 pts treated with CZP+MTX, 355 (72%) completed the RCT and 342 entered OLE, of which 215 remained after 232 wks from RCT baseline. Safety profile was consistent with previous reports. Most frequent AEs (preferred terms) are reported (Table). 19 pts (3.1%) died (IR=0.82) (including 5 malignancies, 4 cardiac disorders, 4 nervous system disorders, 4 injuries). No new safety signals were identified. Clinical improvements from RCT were maintained to Wk232 in CZP Completers and ITT Population, respectively: mean DAS28(ESR), 3.7 and 3.9; mean HAQ-DI, 0.96 and 1.06; ACR20/50/70, 68.4%/47.1%/25.1% and 65.9%/45.4%/24.2%. Radiographic progression in CZP-treated pts was minimal (mean mTSS change from RCT baseline to Wk24: 0.62, from RCT baseline to Wk128: 0.79; % of pts with radiographic non-progression at Wk24: 84.6%, Wk128: 73.2%). Clinical improvements were maintained in the dose reduction population (400mg to 200mg Q2W +MTX; N=288) from the first CZP 200mg treatment (DAS28[ESR]=3.5) through 132 wks of CZP 200mg Q2W (DAS28[ESR]=3.6).

Table. Summary of AEs and SAEs in the RAPID 2 RCT and OLE (Safety Population; N = 612)

Adverse Event	No. of Pts (%)	Total number of events	Event rate per 100 pt-years	Incidence rate per 100 pt-years
Total AEs	546 (89.2)	3789	162.7	100.5
Infections and Infestations [a]	420 (68.6)	1257	54.0	38.7
Malignancies	18 (2.9)	19	0.8	0.8
Most frequent adverse events by preferred term (ER > 4.0 per 100 pt-yrs)				
Upper respiratory tract	93 (15.2)	154	6.6	4.4
Nasopharyngitis	67 (10.9)	101	4.3	3.1
Urinary tract infections	65 (10.6)	94	4.0	3.0
AEs leading to withdrawal	119 (19.4)	157	–	5.2
AEs leading to death	19 (3.1)	25	–	0.8
Total SAEs	219 (35.8)	364	15.6	11.3
Serious infections/ infestations [a]	90 (14.7)	105	4.5	4.1

[a] MedDRA system organ class. AE: Adverse Event; ER: Event Rate; SAE: Serious Adverse Event.

Conclusion: In pts with active RA despite MTX, CZP+MTX maintained reduction in signs and symptoms of RA with a favorable long-term risk-benefit ratio.

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Post–Hoc Analysis Showing Better Clinical Response With The Loading Dose Of Certolizumab Pegol In Japanese Patients With Active Rheumatoid Arthritis. Tsutomu Takeuchi[1], Kazuhiko Yamamoto[2], Hisashi Yamanaka[3], Naoki Ishiguro[4], Yoshiya Tanaka[5], Katsumi Eguchi[6], Akira Watanabe[7], Hideki Origasa[8], Mariko Kobayashi[9], Toshiharu Shoji[9], Nobuyuki Miyasaka[10] and Takao Koike[11]. [1]Department of Rheumatology, Keio University, Tokyo, Japan, [2]Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [3]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [4]Nagoya Univeristy Graduate School of Medicine, Nagoya, Japan, [5]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [6]Sasebo City General Hospital, Sasebo, Nagasaki, Japan, [7]Tohoku University, Sendai, Japan, [8]University of Toyama School of Medicine, Toyama, Toyama, Japan, [9]UCB Pharma, Tokyo, Japan, [10]Tokyo Medical and Dental University, Tokyo, Japan, [11]NTT Sapporo Medical Center, Sapporo, Japan.

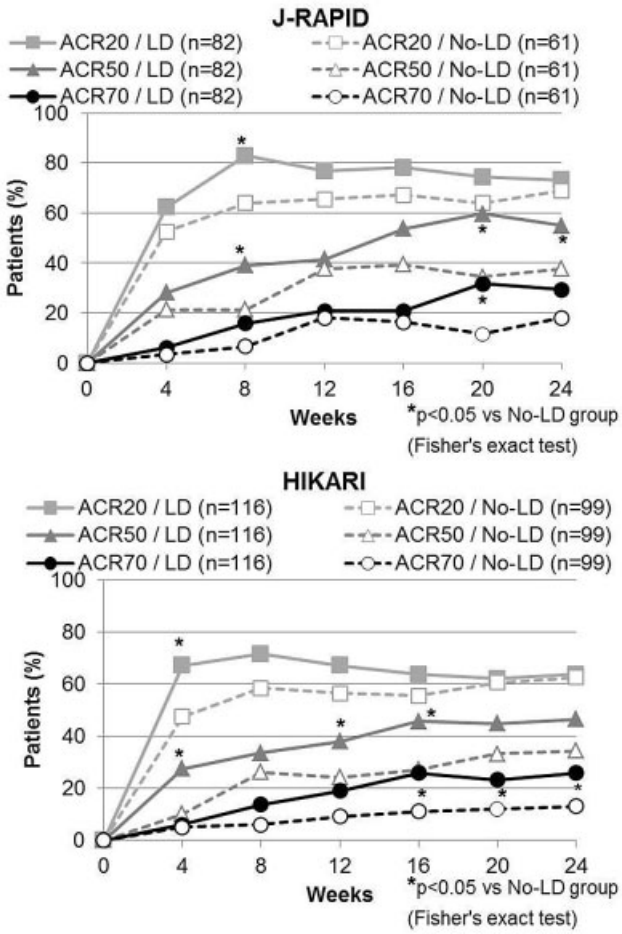
Background/Purpose: Certolizumab pegol (CZP) with MTX (J-RAPID; NCT00791999) and without MTX (HIKARI; NCT00791921) has demonstrated rapid and sustained improvements in disease activity in Japanese patients (pts) with active rheumatoid arthritis (RA) in placebo-controlled, double-blind (DB), randomized studies[1,2]. Based on these and previous studies, the recommended dose of CZP includes subcutaneous initial loading dose (LD) of 400mg at Weeks (wks) 0, 2 and 4 followed by 200mg every 2 wks (Q2W). Nevertheless, benefits of LD have never been directly demonstrated in a clinical study. We hereby report safety and efficacy of CZP, with and without LD, from two Japanese studies.

Methods: Data from J-RAPID and HIKARI were used for this analysis; pts eligible to enter open-label extension (OLE) studies at Wk16 or Wk24 received CZP 200mg Q2W or CZP 400mg Q4W without LD (label dose). In J-RAPID DB study, 316 pts were randomized to CZP 100, 200 or 400mg + MTX with initial LD or placebo + MTX Q2W for 24 wks. In HIKARI DB study, 230 pts were randomized to CZP 200mg with LD or placebo Q2W for 24 wks.

Safety and efficacy in pts who received CZP 200mg Q2W with LD during DB phases (LD group: n=82 J-RAPID; n=116 HIKARI) and pts who received CZP 200mg Q2W without LD during OLE phases after being assigned to placebo in DB phase (No-LD group: n=61 in J-RAPID; n=99 in HIKARI) were directly compared. Mean DAS28(ESR) in No-LD groups at OLE baseline were slightly lower than DB baseline (5.8 vs 6.5 J-RAPID; 6.2 vs 6.3 HIKARI). ACR response rates, DAS responses and development of anti-CZP antibodies (Abs) were assessed during 24 wks after initiating CZP. ACR responses were determined using non-responder imputation. Safety population consisted of 1) all pts who received CZP in DB (n=239), 2) LD group and 3) No-LD group. Adverse events were reported both within DB and OLE.

Results: No-LD group showed delayed initial kinetics of ACR20/50/70 responses and sustained lower response to Wk24 (ACR50/70) compared to LD group (Figure). Development of anti-CZP Abs was observed more frequently in No-LD group than LD group (J-RAPID: n=4 [6.6%] vs n=1 [1.2%]; HIKARI: n=27 [27.3%] vs n=18 [15.5%]). Similar safety profiles were reported between No-LD and LD groups during CZP administration period (incidence rates per 100 pt-years; any AEs: 299.2 vs 310.5 J-RAPID, 312.9 vs 308.6 HIKARI; any serious AEs: 17.9 vs 13.4 J-RAPID, 23.0 vs 21.5 HIKARI).

Figure: ACR20/50/70 response rates after CZP initiation



Conclusion: While comparison of DB and OLE data has limitations, administration of CZP loading dose over the first 24 wks is associated with more rapid onset of efficacy, development of lower Ab levels and sustained response compared with initiating CZP without loading dose. These results suggest administration of CZP loading dose improves clinical response in active RA pts with similar safety profile.

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Comprehensive Disease Remission Achieved By Certolizumab Pegol Treatment, and Factors Associated With Certolizumab Pegol Comprehensive Disease Remission, In Rheumatoid Arthritis Patients With Predominantly High Disease Activity. Yoshiya Tanaka[1], Kazuhiko Yamamoto[2], Tsutomu Takeuchi[3], Hisashi Yamanaka[4], Naoki Ishiguro[5], Katsumi Eguchi[6], Akira Watanabe[7], Hideki Origasa[8], Tadao Okamoto[9], Yumiko Wada[9], Toshiharu Shoji[9], Nobuyuki Miyasaka[10] and Takao Koike[11]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]The University of Tokyo, Tokyo, Japan, [3]Keio University, Tokyo, Japan, [4]Tokyo Women's Medical University, Tokyo, Japan, [5]Nagoya University, Nagoya, Japan, [6]Sasebo City General Hospital, Sasebo, Japan, [7]Tohoku University, Sendai, Japan, [8]University of Toyama School of Medicine, Toyama, Toyama, Japan, [9]UCB Pharma, Tokyo, Japan, [10]Tokyo Medical and Dental University, Tokyo, Japan, [11]NTT Sapporo Medical Center, Sapporo, Japan.

Background/Purpose: The therapeutic goals of treating rheumatoid arthritis (RA) are clinical, structural and functional remissions.[1,2] Simultaneously achieving all three has been referred to as comprehensive disease remission (CDR). Certolizumab pegol (CZP) has demonstrated rapid and sustained improvement in disease activity and inhibition of structural damage in 2 double-blind (DB) trials, J-RAPID[3] (with MTX; NCT00791999) and HIKARI[4] (without MTX; NCT00791921), and in subsequent open-label extensions (OLE; NCT00851318 and NCT00850343, respectively) in Japanese patients (pts). This post-hoc analysis evaluated CDR achievement in RA pts with high baseline disease activity treated with CZP. Factors associated with CZP CDR at OLE Wk52 were also investigated.

Methods: CDR was defined as simultaneous achievement of DAS28 (ESR) ≤2.6 (DAS remission), HAQ-DI ≤0.5 (HAQ remission) and yearly change in (Δ) mTSS ≤0.5 (radiographic non-progression), while comprehensive disease control (CDC) was defined by substituting DAS28(ESR) <3.2 in CDR. CDC/CDR of CZP vs placebo (PBO), with and without MTX, were evaluated at Wk24 of DB trials on the full analysis set (FAS) population of CZP (200mg every 2 weeks [Q2W]; approved dose) and PBO groups in J-RAPID (CZP n=82, PBO n=77) and HIKARI (CZP n=116, PBO n=114). Additionally, CZP CDC/CDR were evaluated at OLE entry and Wk52 for DB CZP 200mg Q2W pts who entered OLE studies (J-RAPID n=74, HIKARI n=105; FAS). Factors associated with CZP CDC/CDR at OLE Wk52 were analyzed for all DB CZP pts, regardless of dose, who entered OLE (J-RAPID n=215, HIKARI n=105; FAS), using several Wk12 clinical response measures eg. DAS28(ESR) disease activity and HAQ.

Results: CDC and CDR at Wk24 of J-RAPID were 28.0% and 13.4% for CZP, and 5.2% and 0% fo PBO, respectively (Table). In HIKARI, 25.0% and 15.5% CZP pts achieved CDC and CDR at Wk24 vs 0% and 0% PBO pts, respectively. In HIKARI, CZP was shown to be similarly effective in attaining CDR as monotherapy (9/54, 16.7%) or with concomitant non-MTX DMARDs (9/62, 14.5%). CDC and CDR at OLE Wk52 were 37.8% and 24.3% in J-RAPID, and 28.6% and 21.9% in HIKARI, respectively (Table). Of pts with DAS remission at Wk12, 50% (14/28) and 50% (8/16) achieved CDR at OLE Wk52 in J-RAPID and HIKARI, respectively. Similarly, 35% (J-RAPID 43/124) and 31% (HIKARI 19/62) of pts with Wk12 HAQ remission achieved CDR at OLE Wk52.

Table Comprehensive Disease Remission (CDR) achieved by CZP With and Without MTX at Week 24 in DB and at Week 52 in OLE

	CZP vs PBO at DB 24 week [a]				at OLE entry and at OLE 52 week [b]			
Study	J-RAPID (with MTX)		HIKARI (without MTX)		J-RAPID (with MTX)		HIKARI (without MTX)	
Outcomes, % (n)	CZP	PBO	CZP	PBO	OLE entry	OLE 52 wk	OLE entry	OLE 52 wk
DAS28-ESR [c]								
≤3.2 (LDA)	37.8% (31)	6.5% (5)	32.8% (38)	1.8% (2)	44.6% (33)	54.1% (40)	33.3% (35)	45.7% (48)
<2.6 (remission)	17.1% (14)	0.0% (0)	16.4% (19)	0.9% (1)	21.6% (16)	31.1% (23)	21.9% (23)	32.4% (34)
HAQ-DI≤0.5[c] (remission)	61.0% (50)	33.8% (26)	55.2% (64)	17.5% (20)	64.9% (48)	74.3% (55)	54.3% (57)	66.7% (70)
ΔmTSS ≤ 0.5 [d] (remission)	66.7% (54)	40.8% (31)	65.8% (75)	43.0% (49)	69.2% (45)	71.0% (44)	59.8% (55)	66.7% (58)
	N = 82	N = 77	N = 116	N = 114	N = 74	N = 74	N = 105	N = 105
CDC [e,f]	28.0% (23)	5.2% (4)	25.0% (29)	0.0% (0)	29.7% (22)	37.8% (28)	17.1% (18)	28.6% (30)
CDR [f,g]	13.4% (11)	0.0% (0)	15.5% (18)	0.0% (0)	17.6% (13)	24.3% (18)	13.3% (14)	21.9% (23)

[a] The analysis was performed on the FAS, which included pts who were originally assigned to CZP 200mg Q2W group and PBO group in the DB phase of J-RAPID (CZP n = 82 and PBO n = 77)and HIKARI (CZP n = 116 and PBO n = 114), respectively.
[b] The analysis was performed on the FAS, which included pts who entered the OLE studies, and were originally assigned to CZP 200mg Q2W group in the DB phase (excluding pts who were in the placebo group during the DB phase) of J-RAPID (n = 74) and HIKARI (n = 105), respectively. During OLE, the pts were treated with CZP 200mg Q2W or CZP 400mg Q4W.
[c] Last observation carried forward.
[d] Yearly ΔmTSS from baseline: FAS-Linear extrapolation.
[e] CDC: DAS28(ESR)≤3.2, ΔmTSS≤0.5 and HAQ-DI≤0.5.
[f] For CDC and CDR, yearly ΔmTSS from baseline (Linear extrapolation, with NRI for patients with no data) was used.
[g] CDR: DAS28(ESR)<2.6, ΔmTSS≤0.5 and HAQ-DI≤0.5.

Conclusion: CZP treatment demonstrated high rates of CDC/CDR at Wk24 and OLE Wk52 in RA pts with high baseline disease activity. CZP treatment, regardless of concomitant MTX or as monotherapy, was effective in achieving CDC/CDR. Wk12 DAS or HAQ remission with CZP was associated with high achievement of CDR at OLE Wk52.

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Persistence On Biologics Is Associated With Concomitant Methotrexate Use Among Rheumatoid Arthritis Patient. Jie Zhang[1], Fenglong Xie[1], Elizabeth S. Delzell[1], Huifeng Yun[1], James Lewis[2], Kevin Haynes[3], Lang Chen[1] and Jeffrey R. Curtis[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Pennsylvania, Philadelphia, PA, [3]University of Pennsylvania., Philadelphia, PA.

Background/Purpose: Concomitant methotrexate (MTX) is associated with improved treatment efficacy in randomized controlled trials of biologic agents to treat rheumatoid arthritis (RA), yet many patients receive biologics without MTX. The present study compared persistence among RA patients who initiated a biologic alone vs. with MTX in routine clinical practice. We also examined if the association differed by type of biologic initiated.

Methods: We conducted a retrospective cohort study among RA patients using national Medicare administrative claims data from 2006 to 2010. Eligible patients were new users (no use of specific agent in 12 months prior) of etanercept, infliximab, adalimumab, or abatacept and were required to have ≥ 12 months continuous Medicare coverage before (baseline) and after treatment initiation. Exposure groups were biologic monotherapy (no MTX or any other non-biologic disease modifying anti-rheumatic drugs [NB-DMARDs]) versus biologic with MTX (with or without other NB-DMARD). The outcome was non-persistence with biologics, which included discontinuation or switching to a different biologic. Patients were censored if they changed from monotherapy to combination therapy or vice versa. We generated Kaplan-Meier curves to compare biologic non-persistence across different exposure groups. We also calculated the hazard ratio (HR) for biologic non-persistence comparing monotherapy to combination therapy overall and for each biologic agent separately adjusting for demographics, receipt of state subsidy, reason for Medicare enrollment, Charlson comorbidities, and any hospitalization during baseline.

Results: Of 22,073 eligible RA patients, 8,755 initiated biologic monotherapy and 13,318 initiated a biologic in combination with MTX. At treatment initiation, mean age (standard deviation) was 65.6 (12.6) and 82.0% were women. Patients who initiated a biologic without concomitant MTX were 1.7 (95% CI: 1.6–1.8) times more likely to be non-persistent. The magnitude of the association between concomitant MTX use and biologic non-persistence differed significantly by biologic agent ($p < .0001$); the strongest association was observed among infliximab users (HR: 2.1; 95% CI: 1.9–2.3) and the smallest among abatacept users (HR: 1.5; 95% CI: 1.3–1.6).

Kaplan-Meier figure presents detailed data.

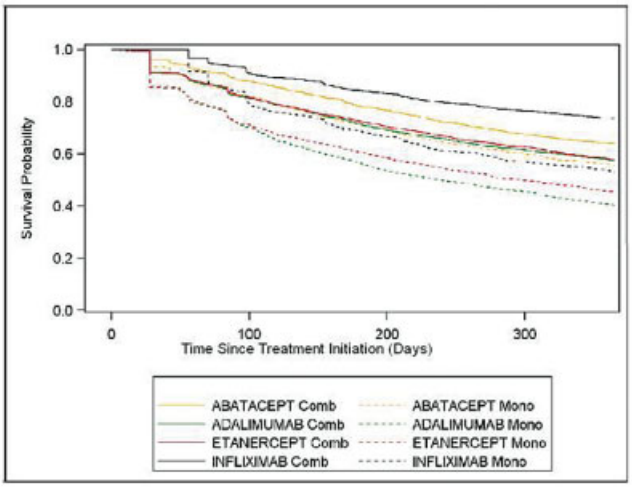

Figure. Kaplan-Meier curves of time to non-persistence by type of biologic therapy and use of concomitant methotrexate

Conclusion: Concomitant MTX was associated with better persistence on biologic therapy; the largest impact was observed among infliximab users.

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Final 5-Year Safety and Efficacy Results Of a Phase 3, Randomized, Placebo-Controlled Trial Of Golimumab In Patients With Active Rheumatoid Arthritis Despite Previous Anti-Tumor Necrosis Factor Therapy. Josef S. Smolen[1], Jonathan Kay[2], Robert Landewé[3], Eric L. Matteson[4], Norman B. Gaylis[5], Jürgen Wollenhaupt[6], Frederick T. Murphy[7], Chenglong Han[8], Timothy A. Gathany[8], Stephen Xu[9], Yiying Zhou[9], Elizabeth C. Hsia[10] and Mittie K. Doyle[9]. [1]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [2]University of Massachusetts Medical School, Worcester, MA, [3]Academic Medical Center, University of Amsterdam and Atrium Medical Center, Heerlen, Netherlands, [4]Mayo Clinic, Rochester, MN, [5]Arthritis & Rheumatic Disease Specialties, Aventura, FL, [6]Schön Klinik Hamburg Eilbek, Hamburg, Germany, [7]Altoona Ctr for Clinical Research, Duncansville, PA, [8]Janssen Global Services, LLC., Malvern, PA, [9]Janssen Research & Development, LLC., Spring House, PA, [10]Janssen Research & Development, LLC./U of Penn, Spring House/Philadelphia, PA.

Background/Purpose: GO-AFTER was the first multicenter, randomized, placebo (PBO)-controlled trial of the safety/efficacy of an anti-TNFα agent, GLM, in pts with active RA despite prior anti-TNFα therapy.

Objective: Final safety and efficacy results through 5yrs are reported.

Methods: Pts were randomized (1:1:1) to PBO, GLM 50mg, or GLM 100mg q4w. At wk16, pts with inadequate treatment response entered double-blind early escape: PBO to GLM 50mg or GLM 50mg to 100mg. At wk24 (start of long-term extension), pts still receiving PBO switched to GLM 50mg, all other pts continued current treatment. After the last pt completed the wk24 visit, unblinding occurred, and a one-time GLM dose increase (50 to 100mg) or decrease (100 to 50mg) was permitted at investigator's discretion. The last GLM injection was at wk252. Observed efficacy results (ACR20/50/70, DAS28-CRP, CDAI) by randomized treatment group and cumulative safety data are reported through wks 256 and 268, respectively. Efficacy data from 1 site (16 pts) were excluded (protocol violations).

Results: 461 pts were randomized, and 459 received study agent; 183 pts continued treatment through wk252, and 276 pts withdrew (86 for AE, 107 for lack of efficacy, 9 lost to follow-up, 69 for other reasons, 5 deaths). 178 completed the safety follow-up through wk268. Efficacy results are shown in the table. Of pts with available data at wk256, 60.3% had an ACR20, 42.3% had an ACR50, 21.7% had an ACR70, 84.3% had DAS28-CRP EULAR response, 29.0% had DAS28-CRP <2.6, and 16.0% had CDAI$\leq$2.8. The most common AEs were upper respiratory tract infection(27.1%), sinusitis(17.1%), and nasopharyngitis(16.9%). Through wk268, 151/431 pts had an SAE, with similar rates among dose groups (50mg only, 50 and 100mg, 100mg only) Rates of serious infections, malignancies, and death were 13.9%, 4.6%, and 2.1%, respectively. 12.3% of pts had $\geq$1 injection-site reaction. Of 388 pts with available samples, 31 (8.0%) tested positive for antibodies to GLM.

Table. Efficacy results at wk256.

	PBO/GLM[a]	GLM 50mg[b]	GLM 100mg[c]	Total
ACR20	37/57 (64.9%)	39/65 (60.0%)	38/67 (56.7%)	114/189 (60.3%)
ACR50	24/57 (42.1%)	26/65 (40.0%)	30/67 (44.8%)	80/189 (42.3%)
ACR70	10/57 (17.5%)	16/65 (24.6%)	15/67 (22.4%)	41/189 (21.7%)
DAS28-CRP EULAR Response	50/55 (90.9%)	53/65 (81.5%)	53/65 (81.5%)	156/185 (84.3%)
DAS28-ESR EULAR Response	48/56 (85.7%)	47/65 (72.3%)	49/64 (76.6%)	144/185 (77.8%)
DAS28-CRP <2.6	18/55 (32.7%)	16/65 (24.6%)	20/66 (30.3%)	54/186 (29.0%)
DAS28-ESR <2.6	13/56 (23.2%)	14/65 (21.5%)	13/66 (19.7%)	40/187 (21.4%)
CDAI $\leq$2.8	7/56 (12.5%)	10/65 (15.4%)	13/67 (19.4%)	30/188 (16.0%)

[a]Pts randomized to PBO who switched to GLM 50mg at wk16 or 24; after wk24 pts could receive GLM50 or 100mg.
[b]After wk 24 pts could receive GLM50 or 100mg.
[c]After wk 24 pts could receive GLM100 or 50mg.

Conclusion: GLM efficacy was maintained through 5yrs among pts with refractory RA who continued treatment. The long-term safety of GLM is consistent with other anti-TNFα agents.

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Head-To-Head Comparison Of Subcutaneous Abatacept Versus Adalimumab On Background Methotrexate In RA: Blinded Two Year Results From The Ample (Abatacept Versus Adalimumab Comparison in Biologic-Naive RA Subjectswith Background Methotrexate) study. Michael E. Weinblatt[1], Michael H Schiff[2], Robert Valente[3], Désirée M. van der Heijde[4], Gustavo Citera[5], Ayanbola Elegbe[6], Michael A Maldonado[6] and Roy M. Fleischmann[7]. [1]Brigham and Women's Hospital, Boston, MA, [2]University of Colorado, Denver, CO, [3]Arthritis Center of Nebraska, Lincoln, NE, [4]Leiden University Medical Center, Leiden, Netherlands, [5]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [6]Bristol-Myers Squibb, Princeton, NJ, [7]University of Texas Southwestern Medical Center, Dallas, TX.

Background/Purpose: AMPLE (**A**batacept Versus Adali**m**umab Com**p**arison in Bio**l**ogic-Naiv**e** RA Subjects with Background Methotrexate) is the first 2 year, active comparator study in RA patients utilizing biologic agents on a background of MTX. At Year 1, SC abatacept (ABA)

and adalimumab (ADA) demonstrated comparable efficacy, including radiographic outcomes, with similar safety.[1] Here we report 2 year study results including radiographic outcomes.

Methods: AMPLE is a phase IIIb randomized, investigator-blinded study of 2 years duration with a primary efficacy endpoint at Day 365. Biologic-naïve patients with active RA and an inadequate response to MTX were randomized 1:1 to receive 125 mg ABA weekly (without an IV load) or 40 mg ADA bi-weekly, with a stable dose of MTX.[1] Study conduct continued unchanged from Year 1, including investigator blinding; all clinical efficacy endpoints were captured through Day 729 including radiographs assessed using the van der Heijde modified Total Sharp score (mTSS). All efficacy analyses were done using the intent-to-treat population with non-responder imputation where appropriate. All radiographs were read through Day 729, including re-reading Year 1 images, by readers blinded to treatment allocation and sequence.

Results: Baseline characteristics of the 646 patients, equally randomized to each group, were similar as previously reported.[1] 79.2% (252 of 318) ABA patients and 74.7% (245 of 328) ADA patients completed Day 729. At Year 1, 64.8% ABA and 63.4% ADA patients were ACR20 responders. Consistent with Year 1, clinical efficacy measures and inhibition of radiographic progression were comparable between groups at Year 2 (Table). There were similar rates of AEs, SAEs (13.8% vs. 16.5%), and malignancies (2.2% vs. 2.1%). More autoimmune AEs occurred in the ABA arm (3.8% vs. 1.8%); none were SAEs. Fewer infections (3.8% vs 5.8%) and opportunistic infections (in 3 vs. 5 patients) occurred with ABA including 2 cases of tuberculosis in the ADA arm that led to discontinuation (DC). There were fewer DC due to AEs (3.8% vs. 9.5%), SAEs (1.6% vs. 4.9%), and serious infections (in 0/12 vs. 9/19 patients) in the ABA arm. Injection site reactions (ISR) occurred less frequently in the ABA arm (4.1% vs. 10.4%).

	ACR Responses ABA = 318 ADA = 328				DAS Responses				Radiographic score, mean ABA=257 ADA=260		
	ACR 20	ACR 50	ACR 70	ACR 90	Mean Change* ABA = 318 ADA = 327	<2.6 (%)** ABA = 251 ADA =244	HAQ (≥0.3 U) ABA = 318 ADA = 328	X ray non progression (SDC≤2.2; %) ABA = 257 ADA = 260	mTSS	Erosion	JSN
ABA	59.7	44.7	31.1	14.5	−2.35	50.6	54.1	84.8	0.89	0.41	0.48
ADA	60.1	46.6	29.3	8.2	−2.33	53.3	48.8	83.8	1.13	0.41	0.72

*LOCF **As-observed

Conclusion: Through 2 years of treatment, in this first active comparator study between biologic agents in RA patients with an inadequate response to MTX, this robust data set demonstrates that SC abatacept and adalimumab were equally efficacious in clinical, functional and radiographic outcomes. Overall, the frequency of AEs was similar in both groups but there were less discontinuations due to AEs, SAEs, serious infections, and fewer local ISR in patients treated with SC abatacept.

[1] Weinblatt et al. Arthritis Rheum. January, 2013; 65(1): 28–38

Disclosure: M. E. Weinblatt, Bristol-Myers, AbbVie, 2, Bristol-Myers Squibb, AbbVie, 5, AbbVie, 9; **M. H. Schiff**, Bristol-Myers Squibb, AbbVie Inc., 5, Bristol-Myers Squibb, AbbVie Inc., 8; **R. Valente**, UCB, Pfizer, Novartis, Eli Lilly, Takeda, Bristol-Myers Squibb, and Centocor, 5; **D. M. van der Heijde**, Abbott, Bristol-Myers Squibb, Amgen, AstraZeneca, Centocor, Chugai, Eli-Lilly, GSK, Merck, Novartis, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, and Wyeth,, 5; **G. Citera**, Bristol-Myers Squibb, Pfizer, Abbott, 5, Pfizer Inc, 2; **A. Elegbe**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **M. A. Maldonado**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 1; **R. M. Fleischmann**, Bristol-Myers Squibb, AbbVie Inc., Amgen, Pfizer, UCB, Jansen, Roche, Eli-Lilly, Sanofi-Aventis, Novartis, Lexicon, Vertex, and GSK, 5, Bristol-Myers Squibb and AbbVie Inc., 2.

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Dose Reduction Of Tocilizumab In Rheumatoid Arthritis Patients With Low Disease Activity Is Feasible. Noortje van Herwaarden[1], Susan Herfkens-Hol[1], Aatke van der Maas[1], Bart J.F. van Den Bemt[1], Ronald F. van Vollenhoven[2], Johannes W.J. Bijlsma[3] and Alfons A. den Broeder[1]. [1]Sint Maartenskliniek, Nijmegen, Netherlands, [2]Karolinska Institute, Stockholm, Sweden, [3]University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: Tocilizumab, at a registered dose of 8mg/kg, has proven to be effective in the treatment of rheumatoid arthritis. Clinical trial data show that a large proportion of patients achieve low disease activity on a lower than registered starting dose.[1] A lower dose might reduce dose-dependent side effects and costs. We investigated the feasibility of dose reduction to 4 mg/kg in patients who reached low disease activity at a registered dose of 8 mg/kg.

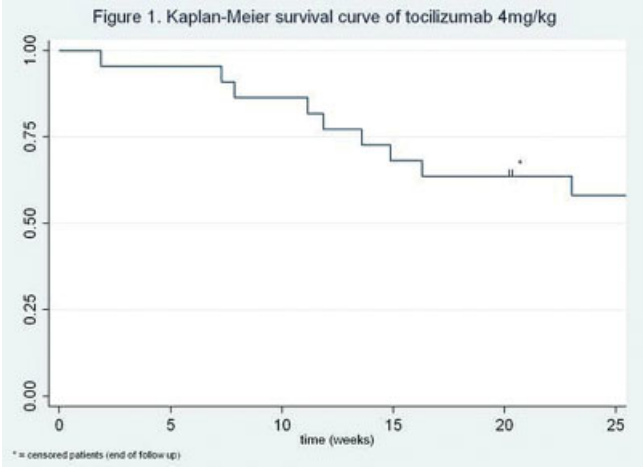
Methods: According to the local treatment protocol, rheumatoid arthritis patients start with tocilizumab 8mg/kg every 4 weeks. After about 6 months, the dose is reduced to 4 mg/kg if patients have low disease activity (DAS28<3.2 and/or judgement of rheumatologist). In case of loss of disease control (DAS28>3.2 and/or judgement rheumatologist), the dose could be increased again to 8mg/kg. In this retrospective study, baseline patient-, disease- and treatment characteristics were collected as well as data on disease activity before and 3 and 6 months after dose reduction and when applicable 3 and 6 months after dose escalation.

Results: In 22 patients tocilizumab dose was reduced because of low disease activity (table 1). After 3 and 6 months follow up, 77% (95% CI 54–91) and 55% (95% CI 32–76) of patients still had low disease activity, respectively (figure 1). Seven out of 9 flares after dose reduction (78%), occurred within the first 16 weeks. The mean DAS28 at time of dose reduction was 2.3 (SD 0.9). The DAS28 at 3 and 6 months was somewhat higher than baseline, 2.7 (SD 1.2) and 2.5 (SD 1.0) respectively. All patients who experienced worsening of disease activity after dose reduction regained low disease activity after dose escalation.

Table 1. Baseline characteristics (start tocilizumab 8 mg/kg)

	n = 22
Age, years (SD)	61 (12)
Woman, n (%)	20 (91)
Disease duration, years median [p25-p75]	10 [5–17]
Rheumatoid factor positive, n (%)	14 (64)
Anti-CCP positive, n (%)	14/19 (74)
Erosive disease, n (%)	13 (59)
DAS28 before start tocilizumab (SD)	4.9 (0.9)
Previous DMARDs, n median [p25-p75]	3 [2–5]
Previous biologicals n, median [p25-p75]	3 [2–5]
Concomitant DMARD, n (%)	9 (41)
Concomitant corticosteroid, n (%)	14 (64)

anti-CCP= anti-cyclic citrullinated peptide; DAS28 = 28 joints disease activity score; DMARD = disease-modifying antirheumatic drug



Conclusion: In this proof of principle study, dose reduction of tocilizumab to 4 mg/kg seems feasible in the majority of rheumatoid arthritis patients who had achieved low disease activity at a 8 mg/kg dose. Dose escalation after flare was effective in all patients.

Reference:
1. Kremer JM, et al. Arthritis Rheum 2011;63(3):609–21.

Disclosure: N. van Herwaarden, None; **S. Herfkens-Hol**, None; **A. van der Maas**, None; **B. J. F. van Den Bemt**, None; **R. F. van Vollenhoven**, Abbott Immunology Pharmaceuticals, 2, BMS, 2, GSK, 2, MSD, 2, Pfizer Inc, 2, Roche Pharmaceuticals, 2, UCB, 2, Abbott Immunology Pharmaceuticals, 5, BMS, 5, GSK, 5, MSD, 5, Pfizer Inc, 5, Roche Pharmaceuticals, 5, UCB, 5; **J. W. J. Bijlsma**, Abbott Immunology Pharmaceuticals, 5, Roche Pharmaceuticals, 5, BMS, 5, UCB, 5, Pfizer Inc, 5, Merck Pharmaceuticals, 2, Pfizer Inc, 2, UCB, 2, BMS, 2, Roche Pharmaceuticals, 2, Abbott Immunology Pharmaceuticals, 2; **A. A. den Broeder**, None.

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Tofacitinib, An Oral Janus Kinase Inhibitor, In The Treatment Of Rheumatoid Arthritis: Open-Label, Long-Term Extension Safety and Efficacy Up To 5 Years. Jürgen Wollenhaupt[1], Joel Silverfield[2], Eun Bong Lee[3], Susan P. Wood[4], Ketti K. Terry[4], Hiroyuki Nakamura[5], Yukako Ohno[5], David Gruben[4], Birgitta Benda[6], Lisy Wang[4] and Richard Riese[4]. [1]Schoen-Klinik Hamburg-Eilbek Teaching Hospital of the University of Hamburg, Hamburg, Germany, [2]Healthpoint Medical Group, Tampa, FL, [3]Seoul National University, Seoul, South Korea, [4]Pfizer Inc, Groton, CT, [5]Pfizer Japan Inc, Tokyo, Japan, [6]Pfizer Inc, Collegeville, PA.

Background/Purpose: Tofacitinib is a novel, oral JAK inhibitor for the treatment of rheumatoid arthritis (RA). Here we report tofacitinib safety, tolerability, and durability of response up to 60 months (mo) in long-term extension (LTE) studies.

Methods: Data were pooled from two open-label studies (A3921024 [NCT00413699], A3921041 [NCT00661661]) of patients (pts) who previously participated in randomized Phase (P)2 or P3 tofacitinib studies. Treatment was initiated with tofacitinib 5 or 10 mg BID as monotherapy or with background disease-modifying antirheumatic drugs (DMARDs); data from both doses ± background DMARDs were pooled. Baseline was that of the P2 or P3 study for pts enrolling within 7 (A3921041) or 14 (A3921024) days of participation; if enrollment was >7 or >14 days after participation, baseline was the start of the LTE study. Primary endpoints were AEs and confirmed (2 sequential) laboratory safety data. Secondary endpoints included ACR responses, DAS28-4(ESR) (DAS28), and HAQ-DI. Safety data were included over 72 mo of observation and efficacy data up to Mo 60 (limited pt numbers [n=39] post-Mo 60).

Results: Overall, 4827 pts were treated for a total duration of 9196 pt-years (pt-y); mean (maximum) treatment duration was 687 (2187) days; 1246 pts (25.8%) discontinued (AEs: 616 [12.8%]; lack of efficacy: 110 [2.3%]; other: 520 [10.8%]). The most commonly reported AE classes were infections and infestations (55.8%), GI disorders (25.4%), and musculoskeletal/connective tissue disorders (27.8%). The most frequent investigator-reported AEs were nasopharyngitis (14.3%), upper respiratory tract infection (11.9%), and urinary tract infection (8.3%). Serious AEs (SAEs) were reported in 18.2% of pts with an incidence rate (IR) of 10.3 per 100 pt-y (95% CI 9.6, 11.0). Serious infection events (SIEs) were reported in 5.5% of pts with an IR of 2.9 per 100 pt-y (95% CI 2.6, 3.3). IRs for SAEs and SIEs did not increase between 48-[1]and 60-mo observations. All malignancies excluding NMSC were reported in 1.7% of pts with an IR of 0.9 per 100 pt-y (95% CI 0.7, 1.1).

Decreased hemoglobin (Hgb; ≥2 g/dL change from baseline, or Hgb <8 g/dL) was observed in 4.6% of pts. Raised aminotransferases (>3 × ULN) were observed in 2.0% (ALT) and 0.9% (AST) of pts. Moderate to severe neutropenia (absolute neutrophil count [ANC] 0.5–1.5 × 10^3/mm^3) was reported in 1.0% of pts; there were no cases of ANC <0.5 × 10^3/mm^3. Absolute lymphocyte counts <0.5 × 10^3/mm^3 were reported in <1.0% of pts. Increases >50% from baseline in creatinine were noted in 3.6% of pts. Mean values for laboratory safety measures were consistent with findings in P2 and P3 studies and stable over time.

Efficacy was maintained for tofacitinib ± background DMARDs between Mo 1 and Mo 60: ACR20, 60.2% and 77.9%; ACR50, 39.8% and 56.7%; ACR70, 22.7% and 40.4%, respectively. Mean DAS28 was 6.2 at baseline, 3.7 at Mo 1, and 3.6 at Mo 60. Mean HAQ-DI score was 1.4 at baseline, 0.8 at Mo 1, and 0.7 at Mo 60.

Safety and efficacy were similar for pts receiving tofacitinib as monotherapy or with background DMARDs.

Conclusion: Tofacitinib 5 or 10 mg BID in pts with RA showed a consistent safety profile and sustained efficacy over 5 years in LTE studies.

Reference:

1. Wollenhaupt J et al. Arthritis Rheum 2012; 64: S548.

Disclosure: J. Wollenhaupt, Roche Pharmaceuticals, Chugai Pharma, Pfizer Inc, Abbott, UCB, 5, Roche Pharmaceuticals, Chugai Pharma, Pfizer Inc, Abbott, UCB, 8; **J. Silverfield**, Pfizer Inc, 2, Pfizer Inc, Novartis, Takeda, 8; **E. B. Lee**, Pfizer Inc, 5; **S. P. Wood**, Pfizer Inc, 1, Pfizer Inc, 3; **K. K. Terry**, Pfizer Inc, 1, Pfizer Inc, 3; **H. Nakamura**, Pfizer Inc, 1, Pfizer Inc, 3; **Y. Ohno**, Pfizer Inc, 1, Pfizer Inc, 3; **D. Gruben**, Pfizer Inc, 1, Pfizer Inc, 3; **B. Benda**, Pfizer Inc, 1, Pfizer Inc, 3; **L. Wang**, Pfizer Inc, 1, Pfizer Inc, 3; **R. Riese**, Pfizer Inc, 1, Pfizer Inc, 3.

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Improvements In Physical Function Correlate With Improvements In Health Related Quality Of Life: Reported Outcomes In Rheumatoid Arthritis Patients Treated With Tofacitinib: Results From 3 Randomized Phase 3 Trials. V. Strand[1], R. E. Alten[2], C. I. Nduaka[3], R. Riese[3], D. Gruben[3], S. H. Zwillich[3], J. Andrews[3] and G. Wallenstein[3]. [1]Stanford University, Palo Alto, CA, [2]Schlosspark-Klinik, University Medicine, Berlin, Germany, [3]Pfizer Inc, Groton, CT.

Background/Purpose: Tofacitinib is a novel, oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). RA affects all domains of health-related quality of life (HR-QoL), which patients report being more important to them than the joint counts and laboratory tests favored by many physicians.[1]

Objectives: To compare improvements in HR-QoL using the Medical Outcomes Survey Short Form-36 (SF-36) by Health Assessment Questionnaire-Disability Index (HAQ-DI) responders (based on improvement ≥0.3) and non-responders in the tofacitinib database at Month 3, by treatment.

Methods: Data are reported from 3 double-blind randomized controlled Phase 3 trials of tofacitinib: a) 6-month tofacitinib monotherapy in patients with an inadequate response (IR) to nonbiologic or biologic disease-modifying antirheumatic drugs (DMARDs) (ORAL Solo, NCT00814307); b) 12-month tofacitinib with methotrexate (MTX) combination in MTX-IR patients (ORAL Standard, NCT00853385); and c) 6-month tofacitinib with MTX combination in tumor necrosis factor inhibitors (TNFi)-IR patients (ORAL Step, NCT00960440). Patients were randomized to tofacitinib 5 mg or 10 mg BID, placebo or adalimumab (ADA; in ORAL Standard only).

Results: For each treatment group in ORAL Solo, regardless of HAQ-DI responder status, there were significant correlations between changes from baseline in HAQ-DI and SF-36 Physical Component Scores [PCS] at Month 3: tofacitinib 5 mg, r = −0.55 (N= 230; P<0.0001); 10 mg, r = −0.56 (N= 222; P<0.0001) placebo, r = −0.51 (N= 107; P<0.0001). HAQ-DI responders reported consistently greater improvements in all 8 domains of SF-36 compared with non-responders, all of which exceeded MCID (Table). This was similarly true when analyzed by treatment group, where HAQ-DI responders reported large improvements in BP and VT as well as PF, RP and GH domains (Table). Results from ORAL Standard and ORAL Step were similar.

Mean changes (SD) from baseline in domains and component summary scales of SF-36 by HAQ-DI responses (based on improvements ≥0.3) at Month 3 in ORAL Solo (monotherapy)

	HAQ-DI Responder N=294			HAQ-DI Non-Responder N=272		
SF-36, Mean (SD)	Tofacitinib 5 mg BID N=127	Tofacitinib 10 mg BID N=129	Placebo N=38	Tofacitinib 5 mg BID N=106	Tofacitinib 10 mg BID N=96	Placebo N=70
Physical function	9.01 (10.30)			1.55 (8.15)		
	10.29 (10.57)	8.98 (10.33)	4.79 (8.18)	0.91 (8.16)	3.69 (7.29)	−0.41 (8.69)
Role physical	8.49 (10.16)*			2.47 (8.12)†		
	8.47 (10.04)	9.58 (9.95)	4.77 (10.70)b	2.45 (7.29)c	4.55 (8.58)	−0.37 (7.89)
Bodily pain	12.68 (9.91)			3.21 (8.60)		
	12.41 (9.56)	14.12 (10.02)	8.71 (9.77)	2.79 (7.55)	5.76 (9.35)	0.33 (8.10)
General health	7.27 (8.90)			1.77 (7.34)		
	6.70 (8.72)	8.60 (9.09)	4.61 (8.25)	2.03 (8.07)	2.17 (7.31)	0.84 (6.12)
Vitality	9.17 (9.84)			2.56 (8.23)		
	8.60 (9.39)	10.58 (10.25)	6.30 (9.31)	2.94 (8.27)	4.52 (7.62)	−0.68 (8.09)
Social functioning	9.00 (11.96)			1.03 (9.35)		
	7.83 (11.89)	11.13 (12.18)	5.66 (10.31)	0.91 (9.25)	2.91 (9.06)	−1.38 (9.46)
Role emotional	6.20 (13.90)*			0.99 (12.07)†		
	6.13 (13.34)*	6.98 (14.29)	3.68 (14.46)b	1.87 (11.66)*	1.22 (11.79)	−0.65 (13.05)
Mental health	6.15 (10.98)			1.90 (9.77)		
	5.67 (11.39)	7.15 (11.11)	4.37 (8.87)	2.46 (9.63)	1.70 (9.80)	1.35 (10.04)
Physical component score	10.26 (8.69)*			2.45 (7.38)†		
	10.67 (8.71)a	11.11 (8.60)	5.93 (7.81)b	1.84 (6.76)c	5.03 (7.63)	−0.17 (6.90)
Mental component score	5.81 (11.35)*			1.27 (9.66)†		
	4.86 (11.51)a	7.23 (11.45)	4.11 (10.09)b	2.21 (8.99)c	1.20 (9.92)	−0.07 (10.23)

*N=292; †N=271
[a]N=126; [b]N=37; [c]N=105
BID, twice daily; HAQ-DI, health assessment questionnaire-disability index; SD, standard deviation; SF-36, short-form 36

Conclusion: In 3 Phase 3 trials of tofacitinib as monotherapy or in combination with MTX, there were positive correlations between improvements in physical function by HAQ-DI and all domains of HR-QoL by SF-36 - particularly physical, pain and vitality domains.

Reference:

1. Kirwan JR et al. J Rheumatol 2005; 32: 2250–2256.

Disclosure: V. Strand, UCB Pharma, 5; **R. E. Alten**, Abbott, BMS, Horizon, Novartis, Pfizer, UCB, Roche, 2; **C. I. Nduaka**, Pfizer Inc, 1, Pfizer Inc, 3; **R. Riese**, Pfizer Inc, 1, Pfizer Inc, 3; **D. Gruben**, Pfizer Inc, 1, Pfizer Inc, 3; **S. H. Zwillich**, Pfizer Inc, 1, Pfizer Inc, 3; **J. Andrews**, Pfizer Inc, 1, Pfizer Inc, 3; **G. Wallenstein**, Pfizer Inc, 1, Pfizer Inc, 3.

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Relationship Between Lymphocyte Count and Risk Of Infection In Rheumatoid Arthritis Patients Treated With Tofacitinib. R. F. van Vollenhoven[1], R. Riese[2], S. Krishnaswami[2], T. Kawabata[2], C. Fosser[2], S. Rottinghaus[2], M. Lamba[2] and S. H. Zwillich[2]. [1]The Karolinska Institute, Stockholm, Sweden, [2]Pfizer Inc, Groton, CT.

Background/Purpose: Tofacitinib is a novel oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). Cytokines involved in lymphocyte development, function and homeostasis are known to signal through JAK. Here we characterize changes in absolute lymphocyte counts (ALC) following tofacitinib treatment and evaluate the relationship between ALC and rates of infection. These data were presented previously.[1]

Methods: ALC and adverse event data of treated (requiring antimicrobial therapy or surgical intervention; TIs), serious (SIs), and opportunistic infections (OIs) were analyzed from 5 randomized controlled Phase 3 (P3), and 2 open-label long-term extension (LTE) studies in patients (pts) with RA. Lymphopenia was defined by OMERACT criteria (ALC $\times 1000/mm^3$) as mild, ≥ 1.5 to <2; moderate to severe, <1.5 to ≥ 0.5; and potentially life threatening, <0.5. Confirmed lymphopenia was defined as lymphopenia in 2 consecutive measurements. Cox analysis was applied to evaluate the relationship between "time-varying" ALC and rates of infection. Threshold values of ALC were evaluated by calculating the percentage of correct decisions (POCD), based on the sum of pts falling below a specific threshold (e.g. 0.5 or 1.0) and experiencing an SI, and those with ALC above threshold and without an SI.

Results: Across treatment groups, at baseline 35–39% of pts in P3 (N = 3252) had ALC of <1.5. Pooled analysis of P3 data showed mean increases in ALC from baseline with tofacitinib at Month (Mo) 1 followed by a gradual decrease of approximately 10% from baseline after 12-mo of therapy. Further decreases in mean ALC were not seen in the LTE studies. Lymphopenia frequency in the P3 studies was similar between tofacitinib and placebo pts at Mo 3 and 6; all placebo pts were advanced to tofacitinib at Mo 6. Lymphocyte subset analyses from P2 dose-ranging studies (6 and 24 weeks [wks]) showed increases in B cell counts (~40%; 1–24 wks), decreases in NK cell counts (~40%; Wks 2–24) and a transient increase in T cell counts (Wks 1–2). Subset analyses from LTE studies (median exposure 22 mo) showed that NK cell counts were similar to baseline counts, B cell counts remained elevated and T cell counts decreased slightly ($<20\%$). For pts with ALC ≥ 0.5, there was no increase in the frequency of TI, SI or OI. Although confirmed lymphopenia of <0.5 was infrequent (5/2430 pts (0.2%) in P3; 10/3219 (0.3%) in the LTE), 11, 4, and 1 of these pts experienced a TI, SI, and OI, respectively. The SI in this group included 1 case each of pneumonia, cellulitis, tuberculosis (an OI), and pyelonephritis. Cox analysis using all available P2, P3 and LTE data showed a significant trend ($p<0.05$) for increased risk for infection (SI and OI) with decreased ALC. The POCD decreased from ~94% for an ALC threshold of 0.5 $\times 1000/mm^3$ to 66% for 1.0 $\times 1000/mm^3$.

Conclusion: Tofacitinib treatment in patients with moderate to severe RA is associated with modest mean decreases in ALC over 12-mo of therapy. Confirmed ALC $<0.5 \times 1000/mm^3$ occurred rarely and may be the optimum threshold for defining increased risk of SI. These data could inform appropriate risk mitigation strategies.

Reference:

1. van Vollenhoven RF et al. Ann Rheum Dis 2013; 72: 250–251.

Disclosure: R. F. van Vollenhoven, AbbVie, BMS, GSK, MSD, Pfizer Inc, Roche, UCB, 2, AbbVie, BMS, GSK, MSD, Pfizer Inc, Roche, UCB, 5; **R. Riese**, Pfizer Inc, 1, Pfizer Inc, 3; **S. Krishnaswami**, Pfizer Inc, 1, Pfizer Inc, 3; **T. Kawabata**, Pfizer Inc, 1, Pfizer Inc, 3; **C. Fosser**, Pfizer Inc, 1, Pfizer Inc, 3; **S. Rottinghaus**, Pfizer Inc, 1, Pfizer Inc, 3; **M. Lamba**, Pfizer Inc, 1, Pfizer Inc, 3; **S. H. Zwillich**, Pfizer Inc, 1, Pfizer Inc, 3.

2331

Efficacy and Safety Of Tofacitinib In Older and Younger Patients With Rheumatoid Arthritis. J. R. Curtis[1], H. Schulze-Koops[2], L Takiya[3], C. A. Mebus[4], K. Terry[4], R. Chew[4] and T. V. Jones[3]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Munich, Munich, Germany, [3]Pfizer Inc, Collegeville, PA, [4]Pfizer Inc, Groton, CT.

Background/Purpose: Tofacitinib is a novel, oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). The clinical development program for tofacitinib in RA enrolled □500 patients (pts) aged ≥65 years (yrs). Rates of infection and other conditions seen in pts with RA typically increase with age. This analysis evaluated the efficacy and safety of tofacitinib in older (≥65 yrs) and younger pts (<65 yrs).

Methods: Efficacy was evaluated in a post-hoc, pooled analysis of four Phase (P) 2 and five P3 studies (ORAL Solo, ORAL Sync, ORAL Scan, ORAL Standard and ORAL Step). Efficacy results for rates of ACR20/50/70 and improvement from baseline in HAQ-DI ≥0.22 were reported as probability ratios (PRs; proportion of responders in tofacitinib group divided by placebo [PBO] at Month 3) with 95% confidence intervals. Pts randomized to PBO advanced to tofacitinib beginning at Month 3. Safety was evaluated in a post-hoc pooled analysis of five P3 studies (Month 0–12) and a pooled analysis of two ongoing long-term extension (LTE) studies. Incidence rates for safety endpoints were compared in older vs younger pts.

Results: A total of 3439 pts received tofacitinib 5 mg, tofacitinib 10 mg, or PBO, twice daily (BID), and 520 were aged ≥ 65 years. PRs for rates of ACR20/50/70 and HAQ-DI improvement in older pts treated with tofacitinib 5 mg BID (N=196) vs PBO (N=122) were 1.86 (1.42–2.42), 2.84 (1.72–4.70), 3.32 (1.49–7.42) and 1.23 (1.02–1.50) respectively, which were similar to, or slightly lower than, the PRs for other age groups (not shown). PRs for tofacitinib 10 mg BID vs PBO were numerically slightly higher for all outcomes. The rate of serious adverse events (SAEs) and discontinuations due to adverse events (AEs) was generally higher in older than in younger pts irrespective of treatment group. The rate of serious infection events (SIE) was greater by 6.2/100 pt yrs in older pts who received tofacitinib vs PBO; the corresponding rate difference in younger pts was 0.9/100 pt yrs (Table). Herpes zoster (HZ) rates were higher in tofacitinib pts vs PBO, and HZ rates for tofacitinib-treated pts were similar irrespective of age. MACE, or malignancies, did not occur in older pts receiving PBO in any of the P3 studies and were infrequent in both age groups of tofacitinib-treated pts (Table). Safety results for older and younger pts in LTE studies were generally consistent with P3 study results.

Table. Incidence rates for key safety endpoints by age group and treatment in five tofacitinib Phase 3 studies

Age group (yrs)	Younger pts (<65)			Older pts (≥65)		
Treatment group	PBO	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	PBO	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID
Number of patients	580	1026	1030	101	190	184
Serious adverse events						
N	23	76	67	7	28	20
Exposure (pt-yrs)	171.4	748.2	766.4	28.3	124.4	124.8
Incidence rate/100 pt yrs (CI)	13.4 (8.9–20.2)	10.1 (8.1–12.7)	8.7 (6.9–11.1)	24.7 (11.8–51.9)	22.5 (15.5–32.5)	16 (10.4–25.0)
Discontinuations due to adverse events						
N	21	76	74	4	19	25
Exposure (pt-yrs)	172.7	767.3	778.8	28.8	130.6	126.6
Incidence rate/100 pt yrs (CI)	12.2 (7.9–18.6)	9.9 (7.9–12.4)	9.5 (7.6–11.9)	13.9 (5.2–37.0)	14.5 (9.3–22.8)	19.7 (13.3–29.2)
Serious infections						
N	3	19	21	0	10	6
Exposure (pt-yrs)	173.6	769.9	781.7	28.9	131	127.3
Incidence rate/100 pt yrs (CI)	1.7 (0.6–5.4)	2.5 (1.6–3.9)	2.7 (1.8–4.1)	0	7.6 (4.1–14.2)	4.7 (2.1–10.5)
Herpes zoster						
N	3	35	31	0	4	7
Exposure (pt-yrs)	172.8	756	768.7	28.9	129.7	126.6
Incidence rate/100 pt yrs (CI)	1.7 (0.6–5.4)	4.6 (3.3–6.4)	4 (2.8–5.7)	0	3.1 (1.2–8.2)	5.5 (2.6–11.6)
Opportunistic infections						
N	0	2	7	0	1	3
MACE						
N	2	2	2	0	2	4
All malignancies (excluding NMSC)						
N	0	3	7	0	2	1

BID, twice daily; CI, 95% confidence interval; MACE, major adverse cardiovascular events; N, number of cases; NMSC, non-melanoma skin cancer; PBO, placebo; pt, patient; yrs, years

Conclusion: Older pts (≥65 yrs) treated with tofacitinib were observed to be at increased risk of SIEs vs older pts treated with PBO, consistent with reports from multiple RA pt databases of biologic DMARDs (Listing et al 2013). Older pts generally were at increased risk of SAEs and discontinuations due to AEs vs younger pts (<65 yrs). The benefit-risk profile of tofacitinib must be taken into account when considering treatment of older pts with RA.

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Assessment of Lipid Changes and Infection Risk In Diabetic and Nondiabetic Patients With Rheumatoid Arthritis Treated With Tofacitinib.

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Background/Purpose: Tofacitinib is a novel, oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Studies have shown an increased prevalence of diabetes mellitus (DM) in patients (pts) with RA. Nearly 9% of pts enrolled into Phase 3 (P3) studies of tofacitinib in RA also had DM. Both RA and DM are associated with lipid changes and an increased risk of infection. This analysis evaluated selected safety endpoints in pts with and without DM receiving tofacitinib for RA.

Methods: Safety endpoints, including changes in fasting blood glucose (FBG), lipids and risk of all infections (regardless of severity), were evaluated in a post-hoc pooled analysis of five tofacitinib P3 studies in DMARD inadequate responders. Baseline (BL) clinical characteristics and lab data, and follow-up lipid data at Month (Mo) 3, were available for all studies. Follow-up FBG data were available for four studies of tofacitinib with background nonbiologic DMARDs. Categorical changes (defined by the American Diabetes Association [ADA]) in FBG vs BL were compared using shift analyses.

Results: Of 2430 pts who received tofacitinib, 8.7% (211) had DM: 8.9% (108/1216) 5 mg BID; 8.5% (103/1214) 10 mg BID. Additionally, 7.0% (48/681) of pts receiving placebo (PBO) had DM. At BL, 49.1% (tofacitinib 5 mg BID), 46.6% (tofacitinib 10 mg BID), and 50% (PBO) of pts with DM used glucocorticoids.

Mean BL FBG in pts with DM was 138 mg/dL, 129.8 mg/dL and 138.9 mg/dL in the tofacitinib 5 mg BID, 10 mg BID and PBO groups, respectively. Corresponding values at Mo 3 were 126.1 mg/dL, 124.0 mg/dL and 129.5 mg/dL. The shift analysis of FGB data from 82 tofacitinib 5 mg BID pts with DM showed 10 pts moved from lower to higher ADA category at BL at Mo 1 or 3, while 19 pts moved from higher to lower category (53 with no change, see Table). For tofacitinib 10 mg BID pts with DM, numbers moving to higher, lower, or no change in category were 19, 13, and 46, respectively. Corresponding numbers for PBO pts with DM were 9, 9, and 25 (not shown).

Increases in mean low density lipoprotein (LDL) and triglyceride (TG) levels were observed at Mo 3 in pts treated with tofacitinib, as reported previously, although the same pattern was seen in pts with and without DM. During 3 Mo of follow-up 23.1%, 21.4% and 25.0% of pts with DM in the tofacitinib 5 mg BID, 10 mg BID and PBO groups, respectively, had ≥1 infection. Corresponding proportions in pts without DM were 21.0%, 21.8% and 18.6%.

Table. Shift analysis of maximum fasting blood glucose levels from baseline to Month 1 or Month 3 in patients with rheumatoid arthritis and diabetes mellitus receiving tofacitinib 5 mg or 10 mg twice daily

		Maximum on-treatment FBG (mg/dL at Month 1 or Month 3)			
		<100 n (%)	100–125 n (%)	≥126 n (%)	Total n (%)
Tofacitinib 5 mg BID	**<100 n (%)**	15 (63)	5 (21)	4 (17)	24 (100)
	100–125 n (%)	7 (41)	9 (53)	1 (6)	17 (100)
Baseline FBG (mg/dL)	**≥126** n (%)	2 (5)	10 (24)	29 (71)	41 (100)
	Total n (%)	24 (29)	24 (29)	34 (41)	82 (100)
Tofacitinib 10 mg BID	**<100 n (%)**	8 (10.3)	6 (7.7)	4 (5.1)	18 (23.1)
	100–125 n (%)	5 (6.4)	12 (15.4)	9 (11.5)	26 (33.3)
Baseline FBG (mg/dL)	**≥126 n (%)**	1 (1.3)	7 (9.0)	26 (33.3)	34 (43.6)
	Total n (%)	14 (17.9)	25 (32.1)	39 (50.0)	78 (100.0)

BID, twice daily; FBG, fasting blood glucose
Only patients with valid fasting blood glucose measurements at baseline and an on-treatment value at Month 1 or Month 3 are included

Conclusion: In the P3 studies evaluated, pts with RA and DM showed no increase in mean FBG levels after 3 Mo of tofacitinib therapy; the number of pts with DM whose FBG increased to ≥126 mg/dL was limited and similar to that observed in pts receiving PBO. Mean increases in LDL and TG were numerically similar in pts with and without DM. The proportion of tofacitinib-treated pts who experienced ≥1 infection, regardless of severity, was numerically similar between pts with and without DM.

Disclosure: W. F. C. Rigby, Roche Pharmaceuticals, 5; **L. Takiya**, Pfizer Inc., 1, Pfizer Inc., 3; **S. P. Wood**, Pfizer Inc, 1, Pfizer Inc, 3; **H. Fan**, Pfizer Inc, 1, Pfizer Inc., 3; **T. V. Jones**, Pfizer Inc., 1, Pfizer Inc,, 3.

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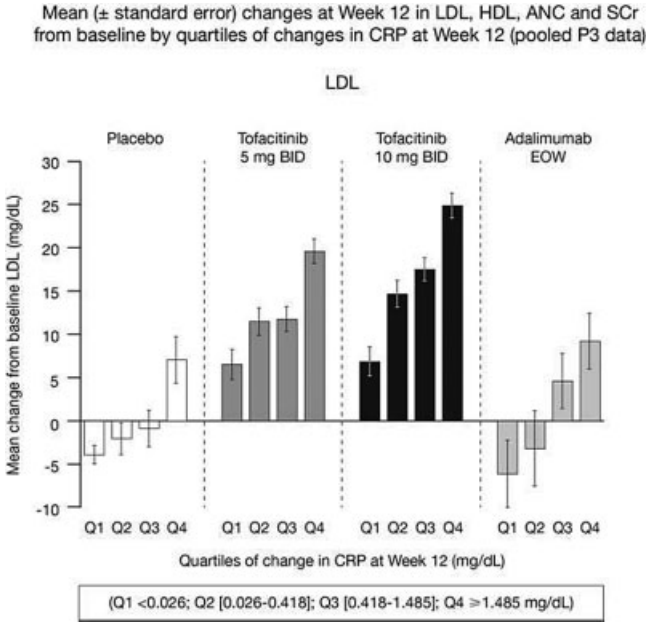
Association Of Mean Changes In Laboratory Safety Parameters With C-Reactive Protein At Baseline and Week 12 In Rheumatoid Arthritis Patients Treated With Tofacitinib.

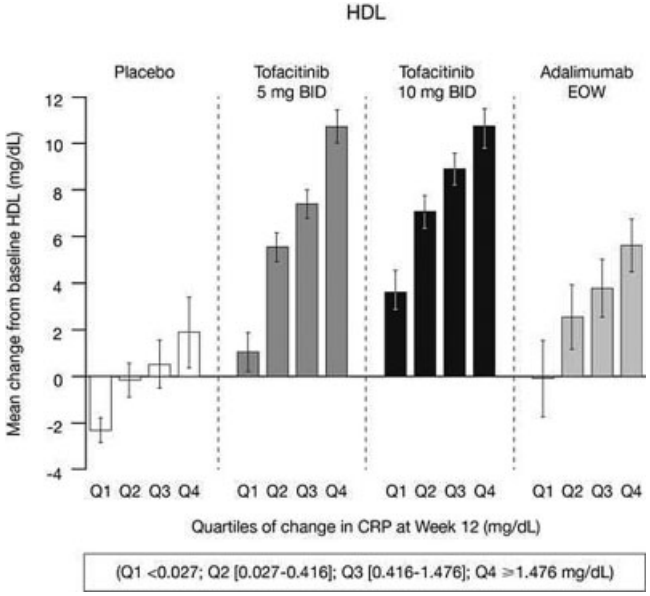
V. Strand[1], J. D. Isaacs[2], S. Menon[3], J. Beal[4], C. I. Nduaka[3], S. Krishnaswami[3], R. Riese[3] and M.G. Boy[3]. [1]Stanford University, Palo Alto, CA, [2]Newcastle University, Newcastle-upon-Tyne, United Kingdom, [3]Pfizer Inc, Groton, CT, [4]Pfizer Inc, Collegeville, PA.

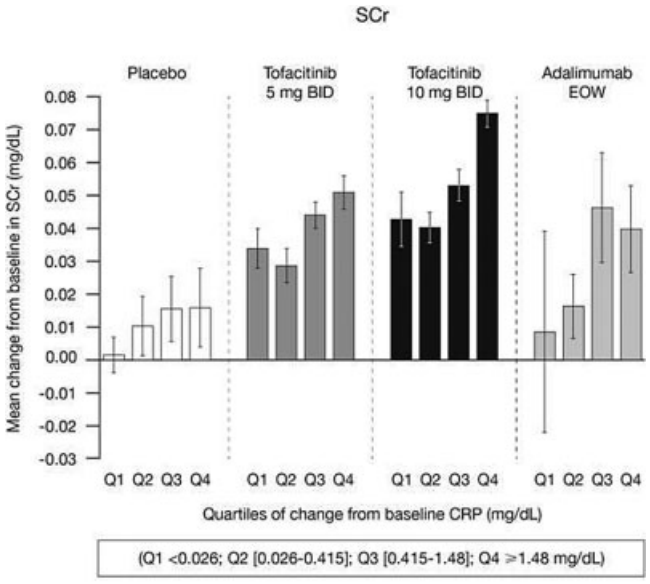
Background/Purpose: Tofacitinib is a novel, oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). Changes in laboratory parameters observed during tofacitinib treatment included mean increases in low (LDL) and high (HDL) density lipoproteins, serum creatinine (SCr) and mean decreases in neutrophils (ANC). Potential explanatory mechanisms were investigated.

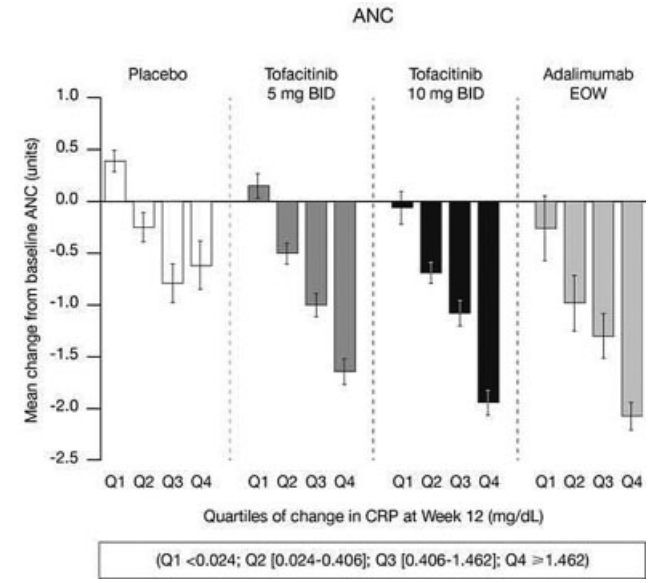
Methods: Baseline and Week 12 data from five Phase 3 (P3) traditional or biologic disease-modifying anti-rheumatic drug (DMARD)-inadequate responder (IR) trials were pooled for each treatment arm: placebo, tofacitinib 5 mg and 10 mg twice daily, and adalimumab 40 mg every other week. The defined laboratory parameters were explored with C-reactive protein (CRP) as a marker of inflammation. Mean changes at Week 12 were compared with quartile levels of CRP at baseline and quartiles of change in CRP at Week 12.

Results: Across the defined laboratory parameters, the smallest mean changes from baseline were observed in the quartile of patients with the smallest reductions in CRP (Figure, 1st quartile) and the greatest changes were observed with the greatest reductions in CRP (Figure, 4th quartile). A similar pattern of association was evident with baseline CRP, where the greatest mean changes in laboratory parameters occurred in patients with highest levels of baseline CRP. Numerical differences in the magnitude of changes across the treatment arms were observed, but no statistical comparisons were performed.









Conclusion: A consistent pattern of association between mean changes in each of the laboratory parameters and CRP was observed. The precise mechanism behind these laboratory changes is unknown. Based upon these analyses, the lowering of inflammation, as measured by CRP, may partly explain some of the observed mean changes in laboratory parameters during clinical studies.

Disclosure: V. Strand, Abbott Immunology Pharmaceuticals, Amgen Inc, AstraZeneca, Biogen Idec, Canfite Pharma, Centocor Inc, Cypress Biosciences Inc, Euro-Diagnostica Inc, Fibrogen, Forest Laboratories, Genentech, Human Genome Sciences Inc, Incyte, Novartis Pharmaceuticals Corp, 5; **J. D. Isaacs**, Pfizer Inc, 2, Pfizer Inc, 5, Pfizer Inc, 8; **S. Menon**, Pfizer Inc., 1, Pfizer Inc., 3; **J. Beal**, Pfizer Inc, 1, Pfizer Inc, 3; **C. I. Nduaka**, Pfizer Inc, 1, Pfizer Inc, 3; **S. Krishnaswami**, Pfizer Inc., 1, Pfizer Inc., 3; **R. Riese**, Pfizer Inc, 1, Pfizer Inc, 3; **M. G. Boy**, Pfizer Inc, 1, Pfizer Inc, 3.

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ORAL SCAN: Effects Of The Oral JAK Inhibitor Tofacitinib In Combination With Methotrexate On Patient Reported Outcomes In a 24-Month Phase 3 Trial Of Active Rheumatoid Arthritis. V. Strand[1], D. van der Heijde[2], C. A. F. Zerbini[3], C. A. Connell[4], D. Gruben[4], R. Riese[4] and G. Wallenstein[4]. [1]Stanford University, Palo Alto, CA, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Centro Paulista de Investigação Clinica, Sao Paulo, Brazil, [4]Pfizer Inc, Groton, CT.

Background/Purpose: Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). Efficacy, inhibition of structural damage, and safety of tofacitinib versus placebo (PBO) were reported previously from the tofacitinib Phase 3 ORAL Scan trial (NCT00847613) in patients with active RA with an inadequate response (IR) to methotrexate (MTX).[1,2] Here we report 24-month patient-reported outcomes (PRO) data from this study.

Methods: Patients on stable-dose MTX were randomized 4:4:1:1 to: tofacitinib 5 mg twice daily (BID), 10 mg BID, or PBO advanced to 5 or 10 mg BID. Patients receiving PBO advanced at Month 3 if non-responders (<20% reduction in swollen or tender joint counts) or at Month 6. Mean changes from baseline in PROs were secondary endpoints, including: Patient Global Assessment (PtGA) of disease activity (visual analog scale [VAS]); patient-reported pain (VAS); Health Assessment Questionnaire-Disability Index (HAQ-DI; mean change from baseline at Month 3 was a co-primary endpoint); and health-related quality of life (HR-QoL; Short Form-36 version 2, acute; SF-36). Analyses used a longitudinal linear mixed-effect model that included all post-baseline visits and accounted for repeated measures on patients, the randomized sequences and baseline values as covariates, on all patients who received ≥1 study drug dose and had both a baseline and ≥1 post-baseline value (full analysis set). Least squares mean changes from baseline at Month 24 are presented. No imputation was used for percentage of patients reporting improvements ≥minimum clinically important differences (MCIDs). Statistical significance at $p \leqq 0.05$, two-sided testing, no adjustment for multiple testing.

Results: 797 patients were randomized and treated; 535 (67.1%) completed 24-months treatment. Baseline characteristics were similar across groups. At Month 3, patients receiving tofacitinib reported statistically significant mean changes versus placebo in all PROs, exceeding MCID; NNTs ranged from 3.7–7.8 and 3.1–5.7 in 5 and 10 mg BID groups, respectively. At Month 24, tofacitinib treatment resulted in statistically significant improvements versus baseline in all PROs (Table), similar to those reported at Month 3. Mean changes across all PROs were numerically greater in patients receiving tofacitinib 10 mg BID, more of whom reported improvements ≥MCID (Table).

Table. PROs at Month 24; least squares mean changes (standard error) from baseline (FAS, longitudinal model) and rate of patients achieving ≥minimally clinically important difference (MCID; FAS, no imputation)

	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Placebo to 5 mg BID		Placebo to 10 mg BID	
PRO	Δ score at Mo 24	% ≥MCID at Mo 24	% ≥MCID at Mo 3 (NNT)	Δ score at Mo 24	% ≥MCID at Mo 24	% ≥MCID at Mo 3 (NNT)	Δ score at Mo 24	% ≥MCID at Mo 24	Δ score at Mo 24	% ≥MCID at Mo 24
PtGA (VAS) [MCID=10]	−24.45 (1.43)***	70.0	67.1 (4.2)	−29.97 (1.41)***	78.3	75.9 (3.1)	−22.46 (2.80)***	70.4	−27.62 (2.85)***	73.1
Pain (VAS) [MCID=10]	−26.72 (1.43)***	74.8	69.2 (3.7)	−31.57 (1.41)***	78.9	73.7 (3.1)	−25.21 (2.80)***	81.5	−27.69 (2.86)***	69.2
Physical function (HAQ-DI) [MCID=−0.22]	−0.50 (0.03)***	69.1	62.6% (5.1)	−0.65 (0.03)***	80.3	74.0 (3.2)	−0.56 (0.06)***	79.6	−0.59 (0.06)***	69.2
HR-QoL (SF-36)										
Physical component score [MCID=2.5]	6.42 (0.46)***	69.7	67.6 (4.2)	8.11 (0.45)***	76.2	71.7 (3.6)	7.32 (0.90)***	75.9	7.14 (0.92)***	67.3
Mental component score [MCID=2.5]	3.33 (0.61)***	53.9	51.9 (7.8)	5.00 (0.60)***	56.0	56.7 (5.7)	3.07 (1.20)*	57.4	4.31 (1.22)**	50.0

*p<0.05; **p<0.001; ***p<0.0001 versus baseline
BID, twice daily; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-Disability Index; HR-QoL, health-related quality of life; MCID, minimally clinically important difference; PRO, patient-reported outcome; PtGA, Patient Global Assessment of disease activity; SF-36, Short Form-36; VAS, visual analog scale

Conclusion: In this Phase 3 trial, MTX-IR patients receiving tofacitinib 5 or 10 mg BID in combination with MTX reported continued clinically meaningful improvements in PROs from Month 3 to 24, which were statistically significant versus baseline. After rescue at Month 3 or 6, placebo patients reported changes of similar magnitude at Month 24, also significant versus baseline.

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1. Burmester G et al. Arthritis and Rheumatism 2012; 64: S10: 549.
2. van der Heijde D et al. Arthritis Rheum 2013; 65: 559–570.

Disclosure: V. Strand, Pfizer Inc, 5; **D. van der Heijde**, Pfizer Inc, 5, Pfizer Inc, 4; **C. A. F. Zerbini**, Novartis, Pfizer, Bristol. Lilly, Amgen, MSD, 2, Pfizer, Bristol, Lilly, MSD, 5, MSD, Sanofi, 6; **C. A. Connell**, Pfizer Inc, 1, Pfizer Inc, 3; **D. Gruben**, Pfizer Inc, 1, Pfizer Inc, 3; **R. Riese**, Pfizer Inc, 1, Pfizer Inc, 3; **G. Wallenstein**, Pfizer Inc, 1, Pfizer Inc, 3.

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Epstein-Barr Virus In Peripheral Blood Of Rheumatoid Arthritis Patients Predicts Response To Rituximab Therapy. Heikki Valleala[1], Markku Korpela[2], Markku J. Kauppi[3] and Yrjo T. Konttinen[4]. [1]Helsinki University Central Hospital, Helsinki, Finland, [2]Tampere University Hospital, Tampere, Finland, [3]Department of Internal Medicine, Päijät-Häme Central Hospital, Lahti, Finland, [4]Helsinki Univ Central Hospital, Helsinki, Finland.

Background/Purpose: Autoreactive B-cells infected by Epstein-Barr virus (EBV) are suspected to be involved in the aetiology of various human chronic autoimmune diseases. The aim of this study was to determine whether EBV load in the peripheral blood of rheumatoid arthritis (RA) patients predicts response to B-cell depleting therapy with rituximab (RTX).

Methods: 35 RA patients who started treatment with RTX in a routine clinical setting were recruited to this observational study between February 2010 and August 2011. At baseline, disease activity was assessed using DAS28 (ESR) and whole blood (WB) samples were collected to be stored at −70°C. Treatment response was evaluated 3 – 7 months after RTX and if the patient had more than one visit the lowest DAS28 value was used for efficacy analysis. EBV viral load was assessed using quantitative PCR. Quantitative data are reported as median and range, and were compared using Mann-Whitney test. For qualitative data analysis Fisher's exact test was used.

Results: The median disease duration was 16.0 (3–38) years. The number of prior biologicals was 2 (0–4) and the median number of failed synthetic DMARDs was 6 (2–9). 34/35 (97.1%) of the patients were RF positive and 26/27 (96.3%) anti-CCP positive. EBV DNA was detected in 16/35 (45.7%) of the WB samples collected prior to RTX treatment. In the 16 EBV positive patients the median viral load was 3.15 (2.68 – 4.00) log copies/ml. Good/moderate EULAR response was observed in 16/16 of the EBV DNA positive *vs* 13/19 EBV DNA negative patients, $p = 0.022$. Significant response (DAS28 change >1.2) was observed in 14/16 of the EBV DNA positive *vs* 10/19 EBV DNA negative patients, $p = 0.035$. The decline in DAS28 after RTX was 2.10 (1.03 – 4. 78) in the EBV DNA positive *vs* 1.47 (−0.7 – 4.70) in the EBV DNA negative patients, $p = 0.13$.

Conclusion: Our results suggest that presence of EBV genome in WB predicts clinical response to B-cell depleting therapy with RTX. The results also putatively suggest that EBV may have an aetiopathogenic role in a subpopulation of RA patients. However, over 50 % of the EBV negative patients had a clinically significant response to RTX suggesting that, in addition to EBV, also other environmental triggers may be involved in the development of autoreactive B-cell clones.

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Phase 2 Evaluation Of PF-04171327, a Dissociated Agonist Of The Glucocorticoid Receptor, For The Treatment Of Rheumatoid Arthritis In Patients With An Inadequate Response To Methotrexate. Thomas Stock[1], Dona Fleishaker[2], Xin Wang[2], Arnab Mukherjee[2] and Charles Mebus[2]. [1]Pfizer Inc., Collegeville, PA, [2]Pfizer Inc., Groton, CT.

Background/Purpose: PF-04171327, a pro drug of PF-00251802, is under investigation as a potential dissociated agonist of the glucocorticoid receptor (DAGR). PF-00251802 is a selective high-affinity partial agonist of the glucocorticoid receptor (GR). It manifests potent anti-inflammatory activity in preclinical in vivo models, at exposures that provide lower adverse effects on bone and glucose metabolism relative to prednisolone, a full GR agonist. If this dissociation is present clinically, PF-04171327 represents a therapeutic improvement relative to current glucocorticoids (GC). The purpose of this study was to evaluate efficacy and safety of PF-04171327, relative to placebo (PBO) and low-dose prednisone, in subjects with active rheumatoid arthritis (RA) and an inadequate response to methotrexate (MTX).

Methods: Adult subjects (>18 years) with active RA and receiving concomitant MTX were randomized to receive oral doses of either PF-04171327 10 mg (n=21) or 25 mg (n=22), prednisone 5 mg (n=21), or PBO (n=22) once daily for 2 weeks in a blinded fashion. Diagnosis of active RA was based on the ACR 1987 Revised Criteria (including at least 6 tender and 6 swollen joints plus elevated CRP of 0.7 mg/dL or higher). Subjects with prior use of GC within six weeks of baseline were excluded. The primary efficacy endpoint was the change from baseline on DAS28-4 (CRP) at Week 2. Secondary efficacy variables included: ACR20/50/70 response rates; individual components of ACR response; DAS28-3 (CRP) and DAS28-4 (CRP), and SF-36. Adverse events (AEs) and safety laboratory tests were recorded throughout. Blood samples were collected for pharmacokinetic and biomarker analyses.

Results: At Week 2, PF-04171327 10 mg and 25 mg showed a statistically significantly greater improvement in the mean change from baseline in DAS28 over PBO by −0.73 ($p=0.0141$) and −1.26 ($p<0.0001$), respectively. In addition, both doses of PF-04171327 demonstrated a greater reduction in DAS28 than prednisone 5 mg at Week 2. Prednisone did not show statistically significant differences in the mean change from baseline in DAS28 over PBO. The effects of PF-04171327 on secondary efficacy variables were generally consistent with those observed for the primary endpoint. Treatment-emergent all causality AEs were reported for 8 (38%), 3 (14%), 11 (19%), and 12 (55%) subjects in the PF-04171327 10 mg, 25 mg, prednisone 5 mg, and PBO groups, respectively. The majority of AEs were mild in severity, with headache the most frequently reported. Four subjects discontinued the study due to an AE (two subjects from the PF-04171327 10 mg group and 2 subjects from the PBO group). There were no SAEs during the study.

Conclusion: PF-04171327 10 mg and 25 mg demonstrated robust and rapid onset of efficacy relative to PBO and prednisone. Both doses were well tolerated. These results support ongoing evaluation of PF-04171327 as a treatment for RA.

Disclosure: T. Stock, Pfizer Inc, 1, Pfizer Inc, 3; **D. Fleishaker**, Pfizer Inc, 1, Pfizer Inc, 3; **X. Wang**, Pfizer Inc, 9; **A. Mukherjee**, Pfizer Inc, 1, Pfizer Inc, 3; **C. Mebus**, Pfizer Inc, 1, Pfizer Inc, 3.

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Serious Adverse Events Associated With Using Biological Agents To Treat Rheumatic Diseases: Network Meta-Analysis From a National Guideline Panel. Simon Tarp[1], Ulrik Tarp[2], Lis S. Andersen[3], Tove Lorenzen[4], Hanne M. Lindegaard[5], Michael Stoltenberg[6], Hanne S. Jensen[7], Birgitte Brock[8], Camilla M. Mikkelsen[9], Dorte V. Jensen[10], Karsten Asmussen[7], Troels Herlin[11] and Robin Christensen[1]. [1]Musculoskeletal Statistics Unit, The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, [2]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [3]Department of Rheumatology, Copenhagen University Hospital, Gentofte, Denmark, [4]Department of Rheumatology, Region Hospital Silkeborg, Silkeborg, Denmark, [5]Odense University Hospital, Odense, Denmark, [6]Department of Rheumatology, Copenhagen University Hospital, Køge, Denmark, [7]Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, [8]Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark, [9]The Capital Region of Denmark Hospital Pharmacy, Medicine Information Centre, Copenhagen NV, Denmark, [10]The Danish Rheumatologic Database (DANBIO), Center of Rheumatology and Spine Diseases VRR, Copenhagen University Hospital, Glostrup, Denmark, [11]Aarhus University Hospital, Aarhus, Denmark.

Background/Purpose: Clinical guidelines are needed to help clinicians provide optimal medical treatment and advise patients about the potential hazards associated with certain drugs.

Our objective was to compare the number of serious adverse events (SAEs) for the biologics available for inflammatory arthritis (i.e., rheumatoid arthritis, psoriatic arthritis, and spondylarthritis), enabling a national consensus on safety associated with using these drugs.

Methods: A national guideline panel consisting of clinical experts and methodologists conducted systematic literature searches, identifying random-

ized controlled trials (RCTs) and inviting all pharmaceutical companies marketing the biologics in question. Eligible RCTs included patients with rheumatoid arthritis, psoriatic arthritis, or spondylarthritis, where approved biologics in standard dose were compared with another biologic or placebo. One reviewer extracted data on the number of patients with an SAE from included trials, and a second reviewer confirmed data, which also entailed inviting the respective pharmaceutical companies to verify extracted data regarding their own drug(s). The network meta-analysis was based on mixed-effects logistic regression (modeled in SAS) [1] combining statistical inference from both direct and indirect comparisons of the treatment effects of among the biologics.

Results were reported as odds ratios (OR [95%CI]). For sensitivity, we explored trial duration using weeks as a covariate in the model.

Results: From the 94 identified RCTs complying with our eligibility criteria, 7 did not report data on SAEs. Thus, the meta-analysis included 87 trials (27,333 patients) comprising 85 placebo and 90 biologic trial arms: abatacept (8), adalimumab (22), anakinra (2), certolizumab (8), etanercept (15), golimumab (8), infliximab (14), rituximab (5), and tocilizumab (8). The odds for SAEs were statistically higher ($P < 0.05$) for certolizumab and tocilizumab compared with the placebo (1.60 [1.19;2.16]; $P = 0.0022$ and 1.33 [1.03;1.70]; $P = 0.028$ respectively). Certolizumab was statistically more likely to result in SAEs compared with all of the following: golimumab (2.02[1.26;3.25]; $P = 0.0042$), etanercept (1.70[1.15;2.51]; $P = 0.0084$), rituximab (1.68[1.06;2.66]; $P = 0.027$), abatacept (1.53 [1.05;2.25]; $P = 0.028$), and adalimumab (1.44[1.02;2.02]; $P = 0.037$). Further, tocilizumab was statistically more likely to result in SAEs than golimumab (1.67[1.07; 2.62]; $P = 0.025$). All other comparisons showed no statistically significant differences ($P > 0.05$).

Conclusion: This network meta-analysis of RCTs provides empirical evidence that certolizumab and tocilizumab both present an increased likelihood of SAEs compared with placebo. Supported by a recent Cochrane review [2] the Danish guideline panel concluded that certolizumab was more likely to cause SAEs compared with several other biologics and thus made a weak recommendation against its use.

References:

[1] Singh JA, et al. CMAJ. 2009;181(11):787–96.

[2] Singh JA, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev. 2011;2:CD008794

Disclosure: S. Tarp, None; **U. Tarp**, None; **L. S. Andersen**, None; **T. Lorenzen**, Roche and Pfizer, 6; **H. M. Lindegaard**, Lilly, MSD, Nordpharma, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, MSD, 5; **M. Stoltenberg**, Abbvie, BMS, MSD, Pfizer, Roche, and UCB, 8, BMS and UCB, 6, Roche Pharmaceuticals, 5; **H. S. Jensen**, None; **B. Brock**, AstraZeneca, GSK, and Novartis, 8; **C. M. Mikkelsen**, None; **D. V. Jensen**, AbbVie, 2; **K. Asmussen**, MSD, abbvie, Pfizer, BMS and UCB, 5, MSD, abbvie, Pfizer, BMS and UCB, 8; **T. Herlin**, None; **R. Christensen**, Abbott, Axellus A/S, Bristol-Myers Squibb, Cambridge Weight Plan, Norpharma, Pfizer, and Roche, 5, Axellus A/S, Cambridge Weight Plan, Mundipharma, and Roche, 2, Abbott, Axellus, Bayer HealthCare Pharmaceuticals, Biogen Idec, Bristol-Myers Squibb, Cambridge Weight Plan, Ipsen, Laboratoires Expanscience, MSD, Mundipharma, Norpharma, Pfizer, Roche, and Wyeth, 8.

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Biologic Switching Rates Among Patients With Rheumatoid Arthritis.

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Background/Purpose: Treatment guidelines for the management of RA recommend sequential use of biologic therapies, and the majority of patients switch from one anti-TNF agent to another. Previous data from commercial claims databases have shown that patients on a second-line anti-TNF agent are more likely to switch biologic treatment than those on second-line abatacept, a biologic with a different mechanism of action.[1] We assessed treatment switching in a Medicare population of patients with RA, who had received a first- or second-line biologic DMARD (bDMARD; abatacept, adalimumab, etanercept, infliximab).

Methods: A retrospective, observational analysis using Medicare claims data (January 2006–December 2010) was conducted in patients with RA newly initiated on a bDMARD (first-line cohort). Further analysis in a subgroup compared first-line anti-TNF patients who switched to another anti-TNF (adalimumab, etanercept, infliximab) with first-line anti-TNF patients who switched to abatacept (second-line cohort). Patients in the first- and second-line cohorts were required to have a minimum of 6-month pre-index, and 12-month post-index, eligibility. Patients were defined as switchers if they had a claim for a new bDMARD within 200% days' supply of the last claim for index bDMARD during the post-index period. Switch rates in first- and second-line cohorts were determined. Patients who discontinued index bDMARD (and did not switch) in the post-index period were excluded from the analyses. Logistic regression determined the odds of switching for patients on abatacept compared with those on anti-TNFs, while controlling for covariates.

Results: Of the 18,148 first-line bDMARD patients with RA included in the analyses (81.5% anti-TNF and 18.5% abatacept), switch rates were 11.7% and 10.6% for those taking anti-TNFs and abatacept, respectively ($p=0.0174$). For the second-line analyses, 777 bDMARD patients were included (45.4% anti-TNF and 54.6% abatacept). Subsequent switch to a third bDMARD occurred in 12.7% of those who had previously switched to abatacept and 28.6% of those who had previously switched to an anti-TNF ($p<0.001$). Logistic regression demonstrated that, after adjusting for covariates, patients who switched to abatacept had significantly lower odds of switching again than anti-TNF switchers (odds ratio=0.33, 95% CI: 0.22, 0.51).

	Total, n (%)	Switchers, n (%)
First-line analysis (n=18,148)		
Anti-TNF	14,794 (81.5)	1728 (11.7)
Abatacept	3354 (18.5)	357 (10.6)
Second-line analysis (n = 777)		
Anti-TNF to anti-TNF	353 (45.4)	101 (28.6)
Anti-TNF to abatacept	424 (54.6)	54 (12.7)

Conclusion: In a Medicare population, patients with RA who switch between anti-TNFs have significantly higher rates of subsequent bDMARD switch compared with those who switch from an anti-TNF to abatacept. It is hypothesized that treatment pathways that include switching to a different class of bDMARD may reduce subsequent overall bDMARD switch rates and therefore reduce costs in the management of patients with RA.

Reference:

1. Meissner B, et al. *Arthritis Rheum* 2011;**63**(Suppl 10): 2198.

Disclosure: L. Rosenblatt, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **F. Lobo**, Bristol-Myers Squibb, 3; **P. Cockrum**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **L. Wang**, Bristol-Myers Squibb, 5; **E. Alemao**, Bristol-Myers Squibb, 3; **O. Baser**, Bristol-Myers Squibb, 5; **H. Yuce**, None.

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Patient Evaluations Of Subcutaneous Golimumab Delivery By Autoinjector (SmartJect®) For Treatment Of Rheumatoid Arthritis.

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Background/Purpose: Self-injection of subcutaneous (SC) golimumab (GLM) using an autoinjector device may be useful for patients with rheumatoid arthritis (RA), especially if they have functional impairment in the joints of the hand and fingers. An autoinjector designed to account for RA patient disability may improve patient satisfaction. The purpose of this study was to measure the acceptability, ease of use, and preferences for use of an autoinjector for SC GLM administration; effects of patient age and functional impairment were evaluated.

Methods: GO-MORE was an open-label, multinational, prospective study in biologic-naïve patients with active RA (DAS28-ESR ≥3.2). Patients self-injected 50-mg SC GLM once monthly for 6 months. At months 4 and 6, patients reported their use preferences and opinions of the autoinjector device on a questionnaire. Responses were analyzed descriptively. Effects of patient age and functional impairment on responses were evaluated.

Results: Overall, the vast majority of patients found the autoinjector to be easy to use, to cause mild or no discomfort, and to cause mild or no pain (table). At month 6, most of the efficacy-evaluable patients reported they preferred to self-inject in the thigh (75.2%; 1563/2077), followed by the abdomen (17.5%; 363/2077) and the upper arm (7.3%; 151/2077). More than 85% of patients indicated that they used their right hand for self-injection. More than 95% of patients were sure or very sure that when they used the

autoinjector, the treatment had been fully injected; and 92.1% were satisfied or very satisfied with the monthly autoinjection frequency. Responses did not differ by patient age group. Patients with minimal or no functional impairment (HAQ-DI ≤0.5) at baseline tended to have more favorable responses, including greater ease of injection and less pain with injection, than those with functional impairment. At month 6, the overall self-injection experience was considered extremely favorable by 53.7% and favorable by 39.5% of patients without impairment and extremely favorable by 42.5% and favorable by 49.1% of patients with impairment.

Table. Patient Assessments of Autoinjector Use for SC GLM Delivery at Month 6

Overall Impression	n (%)	Impressions of Pain	n (%)
Ease of autoinjector use	N=2089	Overall injection discomfort	N=2090
Extremely easy/easy	1744 (83.5)	None/mild	1983 (94.9)
Neither easy nor difficult	274 (13.1)	Moderate	96 (4.6)
Difficult/extremely difficult	71 (3.4)	Severe/prohibitive	11 (0.5)
Overall impression of self-injection	N=2094	Pain/stinging upon injection	N=2092
Extremely favorable/favorable	1922 (91.8)	None/mild	1977 (94.5)
Neither favorable nor unfavorable	151 (7.2)	Moderate	107 (5.1)
Unfavorable/extremely unfavorable	21 (1.0)	Severe/prohibitive	8 (0.4)

Conclusion: Most patients had very favorable evaluations of the autoinjector device for GLM, reporting it to be easy to use, with minimal pain or discomfort upon injection and satisfactory administration frequency.

Disclosure: H. Schulze-Koops, Abbott, Actelion, Biotest, BMS, Chugai, Essex, GSK, MSD, Medac, Merck, Mundai Pharma, Novartis, Nycomed, Pfizer, Roche, UCB, 5, Abbott, Actelion, Biotest, BMS, Chugai, Essex, GSK, MSD, Medac, Merck, Mundai Pharma, Novartis, Nycomed, Pfizer, Roche, UCB, 2, Abbott, Actelion, Biotest, BMS, Chugai, Essex, GSK, MSD, Medac, Merck, Mundai Pharma, Novartis, Nycomed, Pfizer, Roche, UCB, 8; **R. Giacomelli**, None; **W. Samborski**, None; **S. Rednic**, None; **M. Herold**, None; **R. Yao**, Merck Sharp & Dohme, 3; **M. Govoni**, Merck Sharp & Dohme, 3; **N. Vastesaeger**, Merck Sharp & Dohme, 3; **H. Weng**, Merck Sharp & Dohme, 3.

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Persistent Use Of Biologic Therapies At Lower Than Recommended Dosing Among Rheumatoid Arthritis Patients Enrolled In The US Medicare Program. Jie Zhang[1], Fenglong Xie[1], Elizabeth S. Delzell[1], Huifeng Yun[1], James Lewis[2], Kevin Haynes[3], Lang Chen[1], Kenneth G. Saag[1] and Jeffrey R. Curtis[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Pennsylvania, Philadelphia, PA, [3]University of Pennsylvania., Philadelphia, PA.

Background/Purpose: Biologic therapy is associated with significant personal and societal costs. One possible strategy to reduce such cost is the use of reduced dose biologic whenever possible and the appropriateness of such an approach has been shown in a randomized clinical trial. The objective of the study is to examine the use of self-injectable biologics at reduced dose compared to the recommended dose in real world clinical practice.

Methods: We conducted a retrospective cohort study among patients with rheumatoid arthritis who were enrolled in the Medicare fee for service program with prescription drug coverage from 2006 to 2010. Eligible patients were required to have initiated either etanercept or adalimumab after a 12-month period with continuous coverage free of that agent. Follow-up started at treatment initiation and ended when a patient discontinued their biologic (> 90 day gap since end of days supply), switched to a different biologic, lost coverage, or died. For each patient, we calculated the number of days covered under each filled prescription assuming a constant rate of use (etanercept: 50 mg/week; adalimumab: 40 mg/2 weeks). We divided the follow-up time into 6-month intervals in which a patient remained under follow-up at the end of the interval; within each interval we calculated the proportion of days covered by the medications out of the total number of days. We defined reduced-dose biologic as having < 80% of the days covered and calculated the proportion of patients who continuously used reduced-dose biologic for 18 months, 24 months, and 30 months.

Results: We identified 3943 RA patients who were eligible to be included in this analysis, mean age 62 (standard deviation: 13); 83% were women; 2,541 initiated etanercept; and 2,389 initiated adalimumab. Among etanercept users, 11.4% of the patients received reduced-dose etanercept continuously for 18 months during their follow-up; 7.0% and 4.4% of the patient received reduced-dose etanercept continuously for at least 24 and 30 months, respectively. Among adalimumab users, the corresponding proportions were lower with 7.6%, 4.5%, and 1.9% of the persistent users received reduced-dose adalimumab for a continuous period of 18, 24, and 30 months. Data are also presented in the figure below.

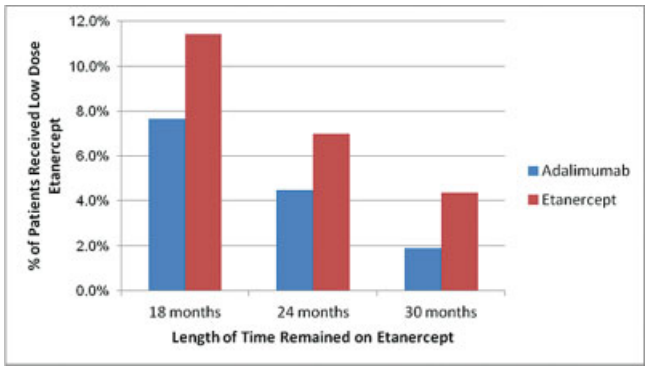

Figure. Proportion of RA Patients who Continuously Used Reduced Dose Injectable Etanercept or Adalimumab

Conclusion: In real-world clinical practice, up to 11% of RA patients received self-injectable biologics at a lower than the recommended dose for an extended period of time.

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Efficacy Of Adalimumab Plus Methotrexate Therapy In Rheumatoid Arthritis Non-Responders Receiving Methotrexate Monotherapy Or Adalimumab Combination Therapy: Results From The Optima Trial. Josef S. Smolen[1], Ronald F. van Vollenhoven[2], Roy Fleischmann[3], Paul Emery[4], Stefan Florentinus[5], Suchitrita S. Rathmann[6], Anabela Cardoso[7], Hartmut Kupper[8] and Arthur Kavanaugh[9]. [1]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [2]The Karolinska Institute, Stockholm, Sweden, [3]University of Texas Southwestern Medical Center, Dallas, TX, [4]Leeds Teaching Hospital, Leeds, United Kingdom, [5]AbbVie, Rungis, France, [6]AbbVie Inc., North Chicago, IL, [7]AbbVie, Amadora, Portugal, [8]AbbVie Deutschland GmbH & Co KG, Ludwigshafen, Germany, [9]University of California, San Diego, La Jolla, CA.

Background/Purpose: EULAR recommendations advocate Methotrexate (MTX) as first line therapy. For patients (pts) who fail to attain remission or low disease activity (LDA) after 6 months of MTX treatment, TNF inhibitors should be added to the therapeutic regimen in pts with high risk of bad outcome. This *post hoc* analysis examined outcomes following open label (OL) adalimumab (ADA) +MTX in rheumatoid arthritis (RA) pts who did not achieve a stable LDA target at 22 and 26 weeks (wks) either from ADA+MTX or MTX monotherapy. Consequences of optimizing or not optimizing therapy were assessed.

Methods: OPTIMA was a 78 wk, randomized, double-blind, double-treatment period study designed to compare safety and efficacy of ADA+MTX with placebo (PBO) +MTX in early RA pts. Following ADA+MTX or PBO+MTX treatment for 26 wks (Period 1), non-responders (NR) were defined as pts failing to achieve a stable LDA target of DAS28(CRP) <3.2 at wks 22 and 26 and given OL ADA+MTX for an additional 52 wks, (Period 2) (OL ADA Carry On and Rescue ADA arms, respectively). Period 2 responders were defined as those achieving LDA at wk78 following OL ADA+MTX therapy. Logistic regression analysis was conducted with baseline and wk26 disease characteristics as variables.

Results: Compared with responders, Period 1 NR began the study with higher overall disease activity. Among these, 78/259 (30%) OL ADA Carry On and 157/348 (45%) Rescue ADA pts achieved DAS28(CRP) <3.2 following 26 wks of OL ADA+MTX therapy; 33/259 (13%) and 49/348 (14%) OL ADA Carry On and Rescue ADA pts, respectively, had DAS28(CRP) ≥3.2 at wk52 and achieved DAS28(CRP) <3.2 at wk78. Mean values of responders' clinical, radiographic, and functional outcomes

were much lower than those of NR and were similar to those seen for pts who achieved the treatment target within the first period. This indicates that starting with MTX followed by ADA in insufficient responders to MTX is an appropriate strategy; a small subset of pts responds more slowly to MTX/ADA combination from start (**Table**). ACR20/50/70 scores for the Rescue ADA arm from wk26 to wk78 were sizeable (51%, 34%, and 19%, respectively). OL ADA Carry On arm achieved ACR20/50/70 from wk26 baseline in 27%, 15%, and 8% of pts, respectively, at wk78. Age, patient and physician's global assessment of disease, and tender/swollen joint counts were all predictors of achieving DAS28(CRP) <3.2 at wk78.

Table. Period 2 Responder vs. Non-Responder Outcomes

	DAS28(CRP)				mTSS				HAQ-DI			
	Responders		Non-Responders		Responders		Non-Responders		Responders		Non-Responders	
	CO[a] n=106	RES[b] n=175	CO[a] n=121	RES[b] n=142	CO[a] n=106	RES[b] n=175	CO[a] n=120	RES[b] n=142	CO[a] n=106	RES[b] n=175	CO[a] n=121	RES[b] n=142
Baseline	6.13[c]	5.98[d]	6.32[e]	6.34[f]	10.16[c]	11.15	11.98	13.44	1.75[c]	1.59[g]	1.71	1.73
Week 26	3.73	4.13	4.41	4.88	10.34	12.75	12.27	14.14	0.82	0.94	1.10	1.20
Week 52	2.38	2.29	4.34	4.25	10.38	12.76	12.32	14.18	0.62	0.53	1.10	1.02
Week 78	2.71	2.28	4.02	3.81	10.66	12.65	12.41	14.51	0.60	0.50	1.08	1.01

[a]ADA Carry On arm; [b]Rescue ADA arm; [c]n=105; [d]n=169; [e]n=118; [f]n=141; [g]n=174; DAS28(CRP), 28-joint disease activity score with C-reactive protein; mTSS, modified total Sharp score; HAQ-DI, disability index of the health assessment questionnaire.

Conclusion: When advanced to OL ADA+MTX therapy, pts initially not achieving stable LDA target at wk26 following MTX monotherapy demonstrated improvements in clinical and functional outcomes at wk52 and wk78. In addition, structural progression was minimal. Some improvement was also seen among pts who did not yet attain stable LDA at wk26 on ADA+MTX but continued this treatment; however, it remains unknown whether pts who were not in LDA at wk78 might have benefited from earlier treatment adjustment in an attempt to further improve outcomes.

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Long-Term Safety Of Rituximab: Pooled Analysis Of The Rheumatoid Arthritis Global Clinical Trial Program Over 11 Years. Ronald van Vollenhoven[1], Paul Emery[2], Clifton O. Bingham III[3], Edward Keystone[4], Roy M. Fleischmann[5], Daniel E. Furst[6], Eva W. Hessey[7], Abdul Mehbob[7] and Patricia B. Lehane[7]. [1]Karolinska Institute, Stockholm, Sweden, [2]Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [3]Johns Hopkins University, Baltimore, MD, [4]University of Toronto, Toronto, ON, [5]University of Texas Southwestern Medical Center, Dallas, TX, [6]University of California, Los Angeles, Los Angeles, CA, [7]Roche Products Ltd., Welwyn Garden City, United Kingdom.

Background/Purpose: This analysis evaluated the long-term safety of rituximab (RTX) in rheumatoid arthritis (RA) patients in a global clinical trial program.

Methods: Pooled observed case analysis of safety data from patients with moderate to severe active RA treated with RTX+MTX. Patients were re-treated based on physician's determination of clinical need and evidence of active disease (defined as either SJC and TJC ≥8 or DAS28 ≥2.6). Subgroup analysis of patients with follow-up >5 years was undertaken. Pooled data from patients who received placebo during placebo-controlled study periods were also analyzed.

Results: As of Sep 2012, 3595 patients (All-Exposure population) had received up to 20 courses of RTX over the 11-year observation period (14 816 pt-yrs). Of these patients, 1246 had >5 years follow-up. The placebo population comprised 818 patients (1107 pt-yrs) with a mean follow-up of 1–1.5 years. In the All-Exposure population, infusion-related reaction (IRR) was the most frequent adverse event (AE); most were grade 1 or 2, were rarely serious (0.5%), and primarily occurred following the 1st infusion of the 1st course (799/3595 patients; 22%). Rates per 100 pt-yrs for AEs, serious AEs (SAEs), and infections were not increased when compared to placebo (Table). Overall serious infection rates in RTX-treated patients were comparable to those observed in the placebo population. Pneumonia was the most frequently reported serious infection (2% of RTX patients). There were no cases of hepatitis B reactivation. Serious opportunistic infections were rare (0.05/100 pt-yrs in RTX patients vs 0.09/100 pt-yrs in placebo). One confirmed case of PML in the RA clinical trial program has been reported, as previously described.[1] Following RTX treatment, low immunoglobulin (Ig) concentrations (particularly IgM, less often IgG) were observed. For both Ig classes, serious infection rates were similar before and during/after development of low Ig. No increased risk of malignancy over time or course was evident, and MI rates (0.39/100 pt-yrs) were consistent with rates in the general RA population (0.48–0.59/100 pt-yrs).[2]

Table 1. Summary of AE rates per 100 patient-years (95% CI)

	RTX All-Exposure (n=3595) 14 816 pt-yrs	RTX Long-Term (>5 yrs) (n=1246) 8970 pt-yrs	Pooled placebo (n=818) 1107 pt-yrs
AEs	239.11 (236.63–241.61)	219.36 (216.31–222.44)	315.43 (305.14–326.06)
SAEs	13.82 (13.24–14.43)	11.88 (11.19–12.62)	13.82 (11.79–16.19)
Infections	75.70 (74.31–77.11)	70.52 (68.81–72.28)	90.39 (84.96–96.17)
Serious infections	3.76 (3.46–4.09)	2.71 (2.39–3.07)	3.79 (2.80–5.13)

AEs, adverse events; CI, confidence interval; pt-yrs, patient-years; RTX, rituximab; SAEs, serious adverse events.

Conclusion: These long-term data from 3595 patients treated with RTX over 11 years (14 816 pt-yrs) of follow-up in clinical trials confirm that RTX remains well tolerated over time and multiple courses, with a consistent safety profile. No new safety signals were observed with increasing duration of exposure. Apart from IRRs and low Ig (where there was a lack of placebo comparator), the overall safety profile of RTX remains similar to that for the pooled placebo population and is consistent with published data for moderate to severe RA and with previous analyses of this patient cohort.[3]

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2. British Society for Rheumatology Biologics Register, 2007.
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Assessment Of Subclinical Atherosclerosis (Flow Mediated Dilatation and arterial stiffness) After 24 Weeks Of a Tocilizumab Therapy In 22 Patients With Rheumatoid Arthritis. Martin Soubrier[1], Thomas Frayssac[2], Bruno Pereira[3], Marion Couderc Sr.[4], Coline Daron[2], Jean Jacques Dubost[5], Sandrine Malochet-Guinamand[4], Anne Tournadre[4] and Sylvain Mathieu[4]. [1]CHU CLERMONT-FERRAND, Clermont-Ferrand, France, [2]CHU CLERMONT-FERRAND, Clermont-ferrand, France, [3]Clinical research department, Clermont-Ferrand, France, [4]Rheumatology CHU Gabriel Montpied, Clermont-Ferrand, France, [5]CHU G.-Montpied, Clermont-Ferrand, France.

Background/Purpose: Increased incidence of cardiovascular diseases and sub-clinical atherosclerosis have been observed in rheumatoid arthritis (RA). Inflammation and traditional risk factors could be involved in the pathogenesis. As Tocilizumab inhibits the IL6 pathway, it decreases inflammation and then could improved the cardiovascular risk. However, this positive effect could be counterbalanced by the induced dyslipidemia. Objectives: To investigate the effects of Tocilizumab treatment on flow mediated dilatation (FMD) and arterial stiffness (i.e augmentation index AIx and pulse wave velocity PWV), two markers of sub-clinical atherosclerosis in active RA.

Methods: Sub-clinical atherosclerosis was assessed in 22 RA patients at baseline and after 24 weeks of Tocilizumab therapy.

Results: 22 RA patients, including 18 women (81%) with a mean age of 58.2 ± 11.6 years were included. Of these 22 patients, 18 (81%) had positive rheumatoid factors, 16 (72%) had positive anti-CCP antibodies, 20 (90%) were erosive. 18 patients (81%) were refractory to TNF alpha inhibitors treatments, 2 (9%) to rituximab treatment, 4 (18%) to abatacept treatment. No changes in FMD (N = 9 patients) (6,63±4,68 at 6 month vs. 5,21±2,54 at baseline, p=0,59) or arterial stiffness (N = 22) (PWV: 7,95±3,59 vs. 7,96±2,98, p=0,93; AIX: 29,57±11,7 vs. 29,89±12,83, p=0,92) were detected after 6 months of treatment with Tocilizumab. DAS28 ESR and DAS28 CRP were significantly improved (2,67±1,1 vs. 5,03±0,84, p<0,001 and 3,11±0,95 vs. 4,78±0,66, p<0,001, respectively). Among the DAS28 parameters, a significant improvement in patient global score (41,33±25,88 vs. 64,18±15,29, p=0,003), and number of tender and swollen joints (respectively 4,54±6,42 vs. 7,63±5,63, p=0,01 and 2,5±2,61 vs. 6,63±4,47, p<0,001) was observed. After 6 months of Tocilizumab therapy, CRP (4,28±8,98 vs. 23,93±32,20 mg/l, p=0,015) and ESR (4,19±3,02 vs. 29,19±24,12 mm/h, p<0.001) significantly decreased. There was no change in systolic and diastolic blood pressure (SBP: 130.79±17.21 vs 131.32±22.96 mm Hg; p=0.87/DBP: 78.47±11.58 vs 74±12.29 mm Hg; p=0.16). Total cholesterol (2,26±0,45 vs. 1,97±0,48 g/l, p<0,001), LDL cholesterol (1,66±0,4 vs. 1,13±0,30 g/l, p=0,004), atherogenic index (3,62±1,18 vs. 3,07±1,11, p=0,026) and triglycerides (1,22±0,61 vs 1,04±0,48 g/l, p = 0,047) were significantly increased whereas no significant modification in HDL cholesterol (0,66±0,19 vs. 0,71±0,26 g/l, p=0,40) was detected. There was significant increase in hip circumference (99,43±13.14 vs. 96,68±13,99 cm; p=0,02).

Conclusion: Unlike Protogerou[1] and Kume[2], our results suggest that sub-clinical atherosclerosis observed in RA, was not improved after 6 months of Tocilizumab therapy. This lack of improvement might be due to the induced proatherogenic lipid profile. Further studies are needed.

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Effect Of Tocilizumab On Treatment Patterns, Effectiveness and Safety With Laboratory Values For Patients With Rheumatoid Arthritis: Analyses From The Corrona-Certain Study.

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Background/Purpose: Data from randomized clinical trials (RCTs) and their open-label extensions in patients (pts) with rheumatoid arthritis (RA) indicate that tocilizumab (TCZ) may be associated with treatment-related decreases in neutrophils and platelets and increases in lipids and liver enzymes1; however, analyses of treatment effects on laboratory parameters in real-world pt populations are limited. The objective of this study was to assess changes in laboratory measures with TCZ treatment over 6 months in pts with RA from the prospective CORRONA CERTAIN substudy.

Methods: Pts with at least moderate disease activity (CDAI >10) initiating TCZ were eligible for the ongoing biologic agent comparative effectiveness study (CERTAIN) nested within CORRONA. The decision to start TCZ was made by the physician prior to enrollment. Efficacy outcomes (CDAI and HAQ) and laboratory measures (CRP, hemoglobin, cell counts, lipids and liver enzymes) were assessed at baseline (BL) and every 3 months for a year. Cutoff values for laboratory normals were based on US Prescribing Information, where applicable.2 Data for pts who have completed a 6-month visit are presented.

Results: Of 1620 pts with RA enrolled in CERTAIN, 244 pts initiated TCZ therapy between November 2010, and February 2013. At the time of analysis, 65 pts had not yet completed 6 months of follow-up and 43 pts had exited the CERTAIN study prior to 6 months; available reasons for TCZ discontinuation include 8 safety (1 serious side effect), 11 efficacy and 4 other reasons. Of the 136 pts who completed a 6-month follow-up visit, 109 (80.1%) were female, 120 (88.2%) were Caucasian and 72/128 (56.3%) were seropositive at BL; the mean ± SD age and RA duration were 57.9 ± 12.9 years and 11.9 ± 9.4 years, respectively. A total of 41 (30.1%) pts received TCZ as monotherapy; of the pts initiating TCZ in combination with nonbiologic DMARDs, 72 (75.8%) received concurrent MTX. After 6 months of TCZ treatment, median (IQR) CDAI improved from 31.0 (23.0–41.7) to 15.0 (8.0–26.3). Median (IQR) HAQ improved from 1.25 (0.5–1.75) to 1.00 (0.5–1.63). Changes in laboratory values of interest over 6 months are shown in Table 1. The proportion of pts with anemia decreased from 19.5% at BL to 11.0% and 1.7% of pts developed neutropenia at 6 months. Median lipid values increased at 6 months and 15.5% and 17.9% of pts respectively had AST and ALT above the upper limit of normal at 6 months vs 2.7% and 6.5% at BL.

Table 1. Laboratory Measures for Patients Initiating TCZ Therapy Within CERTAIN at Baseline and After 6 Months Follow-up

Laboratory Measurements	Baseline	6-Month Follow-up
CRP, median (IQR), n=120	3.88 (1.64–12.50)	0.57 (0.23–1.42)
Hemoglobin (g/dL), median (IQR), n=118	13.1 (12.1–14.0)	13.4 (12.4–14.2)
Anemia, n (%)[a]	23 (19.5)	13 (11.0)
Neutrophils (/μL), median (IQR), n=118	4490 (3280–6310)	3785 (2310–5430)
<500, n (%)	0 (0.0)	0 (0.0)
500 to 1000, n (%)	0 (0.0)	2 (1.7)
>1000, n (%)	118 (100.0)	116 (98.3)
Neutropenia (%)[b]	0 (0.0)	2 (1.7)
Platelets (/μL ×1000), median (IQR), n=115	278 (232–328)	227 (192–284)
<50,000, n (%)	0 (0.0)	0 (0.0)
50,000 to 100,000, n (%)	0 (0.0)	0 (0.0)
>100,000, n (%)	115 (100.0)	115 (100.0)
Thrombocytopenia (%)[c]	0 (0.0)	0 (0.0)
TC (mg/dL), median (IQR), n=123	195.0 (171.0–221.0)	210.0 (184.0–240.0)
<200, n (%)	69 (56.1)	52 (42.3)
≥200, n (%)	54 (43.9)	71 (57.7)
HDL (mg/dL), median (IQR), n=123	60 (49.0–73.0)	61.0 (48.0–71.0)
<40, n (%)	13 (10.6)	12 (9.8)
≥40, n (%)	110 (89.4)	111 (90.2)
LDL (mg/dL), median (IQR), n=122	114.5 (94.0–132.0)	124.5 (101.0–151.0)
<100, n (%)	36 (29.5)	29 (23.8)
≥100, n (%)	86 (70.5)	93 (76.2)
TG (mg/dL), median (IQR), n=123	138.0 (94.0–190.0)	152.0 (106.0–232.0)
<150, n (%)	71 (57.7)	61 (49.6)
≥150, n (%)	52 (42.3)	62 (50.4)
AST (U/L), median (IQR), n=110	21.0 (17.0–26.0)	24.0 (20.0–31.0)
Normal (ULN), n (%)	107 (97.3)	93 (84.6)
>1 to 3x ULN, n (%)	3 (2.7)	17 (15.5)
>3 to 5x ULN, n (%)	0 (0.0)	0 (0.0)
>5x ULN, n (%)	0 (0.0)	0 (0.0)
ALT (U/L), median (IQR), n=123	21.0 (16.0–29.0)	26.0 (20.0–42.0)
Normal (ULN), n (%)	115 (93.5)	101 (82.1)
>1 to 3x ULN, n (%)	8 (6.5)	20 (16.3)
>3 to 5x ULN, n (%)	0 (0.0)	2 (1.6)
>5x ULN, n (%)	0 (0.0)	0 (0.0)

[a]Anemia defined as <11.5 g/dL for females, <13.2 g/dL for males.
[b]Neutropenia defined as <1000 neutrophils/μL.
[c]Thrombocytopenia defined as <50,000 platelets/μL.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDAI, clinical disease activity index; CRP, C-reactive protein; HAQ, health assessment questionnaire; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TCZ, tocilizumab; TG, triglycerides; ULN, upper limit of normal; WBC, white blood cells.

Conclusion: TCZ improved clinical outcomes and was associated with alteration of specific laboratory parameters in pts with RA. The interim analyses of laboratory changes are similar with observations from RCTs for 6 months. Continued enrollments and longer follow-up in CERTAIN are needed to further assess clinical relevance of these laboratory changes.

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2. Actemra REMS. http://www.fda.gov. Accessed June 2013.

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Long-Term Targeted Safety Event Rates In RA Patients Following Initiation Of Rituximab: Interim Analysis From Sunstone Registry. Kenneth G. Saag[1], Kevin L. Winthrop[2], Kimberly Alexander[3], Steven Francom[3] and Daniel E. Furst[4]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Oregon Health & Science University, Portland, OR, [3]Genentech, Inc., South San Francisco, CA, [4]UCLA, Los Angeles, CA.

Background/Purpose: Rituximab (RTX) is used for the treatment of rheumatoid arthritis (RA) in patients (pts) with an inadequate response to anti-TNF therapy (TNF-IR). Long-term safety data on real world RTX use in RA are limited. The objective of this study is to describe the frequency of targeted safety events in an observational cohort of RA pts initiating RTX in the US.

Methods: SUNSTONE is a prospective observational cohort study designed to evaluate the safety of RTX in RA pts in the real-world setting. Pts are evaluated and treated according to their physician's standard practice and followed at standard of care visits every 6 mo. All pts were required to receive ≥1 RTX course but could subsequently receive other RA therapies including biologic DMARDs. Pts are assessed at baseline and at follow-up visits every ≤6 mo. Data collection focuses on targeted adverse events (AEs) (significant infections [infections that meet serious AE criteria or require IV antibiotics], cardiovascular [CV] thrombotic events, seizures, deaths, and pregnancies. Pts are followed for 5 y (regardless of time of RTX discontinuation or start of another biologic therapy), until death, withdrawal of consent or loss to follow-up. Interim analysis results (Apr 1, 2013) are presented (study completion expected 2014). Baseline demographic and disease characteristics, and safety events captured during follow-up are summarized. For calculating incidence rates (IR), patients were censored at the time of first event[1–3]. Crude IR per 100 pt-yrs (PY) are reported.

Results: Overall, 994 pts (3800 PY) received RTX (82% female; median age 58 y; median disease duration 9 y; 72% RF+). Mean follow-up was 3.8 y; mean number of RTX courses was 4; 72% received ≥2 courses. Significant infections were reported in 195 pts (20%), with a corresponding IR of 5.8 (95% CI: 5.0–6.7) per 100 PY. Respiratory (n=75), skin/soft tissue (n=32) and genitourinary infections (n=24) were the most common infections observed. IR per 100 PY (95% CI) of other safety events were: myocardial infarction 0.6 (0.4–0.9), stroke 0.5 (0.3–0.8), pulmonary embolism 0.3 (0.1–0.5), deep vein thrombosis 0.4 (0.2–0.7) and seizures 0.1 (0.1–0.3). Eight pregnancies were reported. No cases of progressive multifocal leukoencephalopathy or tuberculosis were reported. Overall, 62 deaths were reported (1.6/100 PY; 95% CI 1.3–2.1). CV disease (n = 14), malignancy (n = 12) and infection (n = 15) were the most common causes of death.

Conclusion: This interim analysis provides a preliminary summary of the frequency of targeted safety events from the SUNSTONE registry of RA pts who were TNF-IR and initiated RTX treatment. Although there are important limitations when comparing the results of the SUNSTONE registry with similarly designed observational studies, these results are consistent with registries of aTNF's and provide real-world data for rituximab.[1–3]

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3. Thyagarajan V, et al. *Semin Arthritis Rheum* 2012;42(3):223–33.

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Effects Of Tofacitinib, An Oral Janus Kinase Inhibitor, On Work Limitations In Patients With Rheumatoid Arthritis. Vibeke Strand[1], Keith S. Kanik[2], Carol Connell[2], Bethanie Wilkinson[2], David Gruben[2] and Gene Wallenstein[2]. [1]Stanford University, Palo Alto, CA, [2]Pfizer Inc, Groton, CT.

Background/Purpose: Tofacitinib is a novel, oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Participation, in particular work productivity, is increasingly recognized as an important outcome in RA. Here we describe workplace limitations in patients (pts) with RA treated with tofacitinib.

Methods: Data were reviewed from five, Phase 3, double-blind, randomized controlled trials of 6–24 months' duration in pts with 7–13 years' mean disease duration, having failed various disease-modifying antirheumatic drugs (DMARDs). Tofacitinib was dosed at 5 or 10 mg twice daily (BID) as either monotherapy (ORAL Solo, NCT00814307) or in combination with non-biologic DMARDs (mainly methotrexate) in pts with inadequate responses to ≥1 non-biologic or biologic DMARD, including tumor necrosis factor inhibitors (ORAL Scan, NCT00847613 [1-year data]; ORAL Sync, NCT00856544; ORAL Standard, NCT00853385; ORAL Step, NCT00960440). The 25-item Work Limitations Questionnaire (WLQ) was used to assess the impact of RA on job performance and productivity. Responses are combined into 4 scales ranging from 0 (no limitation) to 100 (limited all of the time): time management, physical, mental/interpersonal, and output demands.

Results: Proportions of pts working at the baseline visit were: 49% (302/611; ORAL Solo), 50% (394/792; ORAL Sync), 49% (387/797; ORAL Scan), 39% (278/717; ORAL Standard), 38% (153/399; ORAL Step). Least squares mean changes from baseline at Month 3 are presented in the Table.

		LSM change from baseline at Month 3				
Scale	Treatment	ORAL Solo	ORAL Sync	ORAL Scan	ORAL Standard	ORAL Step
Time Management Demands	Tofacitinib 5 mg BID	11.43	−11.31	−4.01	−9.83	−10.96*
	Tofacitinib 10 mg BID	11.55	−14.58	−9.43	−16.01**	−11.03*
	Placebo	5.67	−8.26	−5.64	−0.52	4.09
Physical Demands	Tofacitinib 5 mg BID	0.99	−5.60**	0.30	−0.10	−0.17
	Tofacitinib 10 mg BID	−3.75	−4.06*	−4.41	−5.84	−2.89
	Placebo	−2.47	6.17	−0.98	3.67	−9.42
Mental/Interpersonal Demands	Tofacitinib 5 mg BID	5.03	−9.29	−2.94	−3.37	−2.69
	Tofacitinib 10 mg BID	6.18	−9.67	−5.32	−7.99	−5.29*
	Placebo	4.52	−8.15	1.24	−0.48	7.11
Output Demands	Tofacitinib 5 mg BID	9.52	−9.71	−6.15	−8.29	−11.36**
	Tofacitinib 10 mg BID	9.80	−13.10	−11.40**	−13.49*	−8.15*
	Placebo	4.54	−8.89	−0.64	−3.82	6.25

*p<0.05; **p<0.01 versus placebo; no correction for multiple comparisons
P-values are for LSM change from baseline versus placebo. Negative values imply improvement
BID, twice daily; LSM, least squares mean

Conclusion: Across the five Phase 3 studies reviewed, pts receiving tofacitinib reported significant effects in at least one scale of the WLQ, but not across all scales. These pt populations had long disease duration having failed multiple DMARDs, including biologics, and only 38–50% of pts were working at the baseline visit. Taken together, these data indicate an overall positive effect of tofacitinib on work productivity in pts with RA.

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Functional Single Nucleotide Polymorphisms In The Interferon-γ and The NLRP3 (Cryopyrin) Genes Associated With Anti-TNF Response In Danish Rheumatoid Arthritis Patients. Jacob Sode[1], Niels H. H. Heegaard[2], Henning Locht[3], Ulla Vogel[4], Steffen Bank[5], Merete Lund Hetland[6] and Vibeke Andersen[7]. [1]University of Southern Denmark, Odense, Denmark, [2]Statens Serum Institut, Copenhagen, Denmark, [3]Frederiksberg Hospital, Frederiksberg, Denmark, [4]National Research Centre for the Working Environment, Copenhagen, Denmark, [5]University of Aarhus, Aarhus, Denmark, [6]The Danish Rheumatologic Database (DANBIO), Glostrup Hospital., Copenhagen, Denmark, [7]OPEN (Odense Patient data Explorative Network), Odense, Denmark.

Background/Purpose: Most patients with rheumatoid arthritis (RA) benefit from tumor necrosis factor-a blocking treatment (anti-TNF). About 1/3, however, do not respond to this costly and potentially harmful treatment. The objective of this study was to determine whether polymorphisms of inflammatory pathway genes may predict the variation in response to anti-TNF treatment in RA patients.

Methods: Forty-one single nucleotide polymorphisms (SNPs), including 34 functional, in 28 genes involved in inflammatory pathways were assessed in 538 anti-TNF naive Danish RA patients. Prospectively collected clinical data including functional status (HAQ), patient global score, lifestyle factors (smoking), tender and swollen joint counts, treatments, rheumatoid factor status and CRP were obtained from the DANBIO registry. Multivariable logistic regression analyses were performed to test associations between genotypes and EULAR response at 3–6 months. ACR50 response and relative change in DAS28 were secondary outcomes. Subgroup analyses were stratified by smoking status, type of anti-TNF drug, and rheumatoid factor status.

Results: Statistically significant associations with EULAR response were found for two SNPs in the total cohort (*NLRP3* (rs4612666) and *INFG* (rs2430561), for seropositive RA patients (407) in *TNFRS1A* (rs4149570), and for seronegative RA patients (131) in *IL17A* (rs2275913), *TLR2* (rs1816702), *NFKB1* (rs28362491), *LY96* (rs11465996), *TGFB1* (rs1800469) and *IL10* (rs1800872) (Table 1). Significant associations with ACR50-response were present for six SNPs (*TLR4* (rs5030728), *IL1B* (rs1143623), *TLR4* (rs12377632), *IL17A* (rs2275913), *NFKB1* (rs28362491), *TLR2* (rs1816702)). Baseline HAQ-score (OR=0.72 (0.53–0.96), p=0.025) and CRP>10 mg/L (OR=1.91 (1.27–2.86), p=0.002) were significant clinical predictors of EULAR good/moderate response, whereas smoking status, type of anti-TNF drug and rheumatoid factor status were not.

Table 1. Genotypes in Danish patients with Rheumatoid Arthritis. Odds ratio (OR) for associations between gene variants and EULAR response to anti-TNF treatment.

						GOOD/ MODERATE			GOOD		
GENE (SNP)	GENOTYPE	NO.	NONE	MODERATE	GOOD	ADJ. OR	95% CI	P-VALUE	ADJ. OR	95% CI	P-VALUE
IFNG	TT	137	34	37	66	Ref.			Ref.		
rs2430561	TA	263	74	71	118	0.81	(0.50–1.31)	0.395	0.75	(0.45–1.27)	0.285
	AA	114	40	38	36	0.59	(0.34–1.02)	0.059	0.40	(0.21–0.76)	**0.005****
	TA/AA	377	114	109	154	0.73	(0.47–1.15)	0.177	0.63	(0.38–1.03)	0.067
	TT/TA	400	108	108	184	Ref.			Ref.		
	AA	114	40	38	36	0.67	(0.43–1.06)	0.084	0.48	(0.29–0.82)	**0.007****
NLRP3	CC	275	69	84	122	Ref.			Ref.		
rs4612666	CT	210	73	54	83	0.62	(0.42–0.92)	**0.018***	0.62	(0.40–0.97)	**0.037***
	TT	31	9	8	14	0.85	(0.37–1.96)	0.707	0.89	(0.36–2.24)	0.808
	CT/TT	241	82	62	97	0.64	0.44–0.95)	**0.025***	0.65	(0.43–1.00)	**0.050***
SEROPOSITIVE RA											
IFNG	TT	106	26	30	50	Ref.			Ref.		
rs2430561	TA	205	56	55	94	0.85	(0.49–1.46)	0.547	0.83	(0.43–1.51)	0.544
	AA	78	30	21	27	0.51	(0.26–0.96)	**0.038***	0.42	(0.20–0.87)	**0.020***
	TA/AA	283	86	76	121	0.73	(0.43–1.22)	0.229	0.69	(0.39–1.21)	0.196
	TT/TA	311				Ref.			Ref.		
	AA	78	30	21	27	0.57	(0.33–0.96)	**0.034***	0.48	(0.26–0.87)	**0.016***
NLRP3	CC	212	51	62	99	Ref.			Ref.		
rs4612666	CT	156	55	39	62	0.58	(0.37–0.92)	**0.020***	0.58	(0.35–0.96)	**0.035***
	TT	25	9	5	11	0.59	(0.24–1.43)	0.241	0.64	(0.24–1.71)	0.375
	CT/TT	181	64	44	73	0.58	(0.37–0.90)	**0.016***	0.59	(0.36–0.96)	**0.032***
TNFRSF1A	GG	137	33	40	64	Ref.			Ref.		
rs4149570	GT	196	68	47	81	0.59	(0.36–0.98)	**0.040***	0.63	(0.37–1.09)	0.102
	TT	56	15	18	23	0.89	(0.43–1.85)	0.76	0.82	(0.37–1.82)	0.619
	GT/TT	252	83	65	104	0.65	(0.40–1.04)	0.074	0.67	(0.39–1.13)	0.13
SERONEGATIVE RA											
IL10	CC	76	28	19	29	Ref.			Ref.		
rs1800872	CA	45	7	19	19	2.99	(1.14–7.85)	**0.026***	2.47	(0.85–7.16)	0.097
	AA	5	2	2	1	0.67	(0.09–4.77)	0.692	0.33	(0.03–4.16)	0.39
	CA/AA	50	9	21	20	2.48	(1.01–6.07)	**0.047***	1.93	(0.72–5.22)	0.192
IL17A	GG	58	11	20	27	Ref.			Ref.		
rs2275913	GA	56	23	16	17	0.37	(0.16–0.90)	**0.028***	0.29	(0.11–0.78)	**0.014***
	AA	11	3	3	5	0.56	(0.12–2.74)	0.478	0.59	(0.11–3.29)	0.551
	GA/AA	67	26	19	22	0.4	(0.17–0.93)	**0.033***	0.32	(0.12–0.84)	**0.020***
NFKB1	WW	56	12	18	26	Ref.			Ref.		
rs28362491	WM	46	18	13	15	0.34	(0.14–0.88)	**0.026***	0.31	(0.10–0.89)	**0.030***
	MM	22	5	9	8	0.87	(0.25–2.97)	0.819	0.69	(0.17–2.76)	0.6
	WM/MM	68	23	22	23	0.46	(0.19–1.09)	0.076	0.39	(0.15–1.04)	0.059
TGFB1	CC	57	21	18	18	Ref.			Ref.		
rs1800469	CT	57	10	19	28	2.74	(1.11–6.76)	**0.029***	2.87	(1.04–7.88)	**0.041***
	TT	11	5	3	3	0.65	(0.16–2.59)	0.544	0.68	(0.13–3.55)	0.65
	CT/TT	68	15	22	31	2.05	(0.90–4.64)	0.087	2.17	(0.85–5.56)	0.107
TLR2	CC	100	23	32	45	Ref.			Ref.		
rs1816702	CT	25	13	8	4	0.25	(0.09–0.68)	**0.006****	0.13	(0.03–0.50)	**0.003****
	TT	0	0	0	0	–		–	–		
	CT/TT	25	13	8	4	0.25	(0.09–0.68)	**0.006****	0.13	(0.03–0.50)	**0.003****

Logistic regression, adjusted for gender, age, HAQ-, DMARD at baseline, CRP, presence of RF/ACPA under assumption of a dominant model.

Conclusion: Danish RA patients with genetically determined higher *NLRP3*– and *IFNG* (IFN-γ) expression were more likely to respond to anti-TNF treatment. Further, the data suggest a difference in pathophysiology between seropositive and seronegative RA patients and validate HAQ-score and CRP as clinical predictors of anti-TNF responses. These findings should be replicated in independent cohorts and augmented by assessing cytokine levels and activity of the relevant gene products.

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Long Term Safety Of Intravenous Golimumab and Comparisons With Subcutaneous Golimumab In Rheumatologic Conditions: Results From The 120-Day Safety Report Of a Phase 3 Trial Of Intravenous Golimumab.

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Background/Purpose: To describe safety profile of IV GLM in RA from the Ph3 GLM IV program. AE rates of interest are indirectly compared to those observed in the GLM SC clinical program across rheumatologic indications.

Methods: 2 multicenter, randomized, double-blind, PBO-controlled studies were included in the integrated IV data safety analysis. GO-LIVE evaluated IV PBO or GLM 2mg/kg or 4mg/kg, ± MTX q12wks in pts with active RA despite MTX. GO-FURTHER is evaluating GLM 2mg/kg IV at wks 0, 4, and q8wks +MTX in active RA despite MTX. In the SC GLM program (GO-FORWARD, GO-BEFORE, GO-AFTER [RA], GO-REVEAL [PsA], GO-RAISE [AS]), PBO or GLM (50mg/100mg) was administered SC q4wks in Ph3 studies and q2 or 4 wks in Ph2 study. Approx. half of pts received MTX. Safety findings for the Ph3 GLM IV RA studies combined through the IV dosing period of GO-LIVE (median 60wks exposure) and through the August 15, 2012 cut-off for GO-FURTHER (median 92wks exposure) are reported; for the ongoing SC studies the data cut was through wk160. Comparison of targeted safety events between IV and SC GLM are reported. Pts who received ≥1administration were analyzed.

Results: 1210 pts were treated with IV GLM in the integrated Ph3 RA IV studies with median duration of follow-up of 72.7 wks. Overall AEs observed in the integrated Ph3 RA IV program are summarized(Table). Since follow-up was longer for the SC rheumatology program, more overall events were observed; however when corrected for events/100 pt yrs, no difference in AE rates or significant SAEs were observed between GLM IV and SC. Incidence of non-serious infusion reactions (median 30 minute infusions) remained low regardless of infusion length, and no serious infusion reactions, requiring study discontinuation, were reported. NMSC (incidence/100 pt-yrs of f/u: 0.49 [95%CI: 0.33,0.71] vs 0.14[95% CI: 0.03,0.42] for GLM SC vs GLM IV) and lymphoma rates were numerically higher in the GLM SC grp vs. the GLM IV grp.

Overall AE summary: Phase 3 GLM IV RA studies combined through 120 day safety update

	PBO	GLM
Pts treated/Avg duration of f/u (wks)	326/22.3	1210*/74.0
AE/Serious AE/ D/c due to AE	58.6% /4.0%/1.8%	82.2%/16.3%//7.2%
Overall infection/Serious infection	29.8%/0.9%	51.3%/5.8%
Infusion reactions	2.5%	4.5%

AEs of interest in pts receiving IV or SC GLM: Incidence per 100 pt-years of follow-up (95% CI)

	Integrated RA GLM IV studies[a] (n= 1213)*	Rheumatologic GLM SC studies[b](n=2363)
Total pt/yrs of follow-up	2103	5714
Deaths	0.62 (0.33, 1.06)	0.37 (0.23, 0.56)
Sepsis	0.38 (0.16, 0.75)	0.37 (0.23, 0.56)
Tuberculosis	0.29 (0.10, 0.62)	0.32 (0.19, 0.50)
Opportunistic Infections	0.33 (0.13, 0.69)	0.25 (0.13, 0.41)
Cellulitis	2.76 (2.09, 3.57)	2.24 (1.87, 2.66)
Postbaseline ALT ↑ (>1to<3xULN)	83.84 (79.97, 87.85)	85.82 (83.44, 88.26)
Lymphoma: Total pt yrs f/u	2103	5713
Observed # of pts with event/Incidence/ 100pt yrs (95% CI)	0/0.00 (0.00, 0.14)	7/0.12 (0.05, 0.25)
Other malignancies: Total pt yrs f/u	2101	5707
Observed # of pts with event/Incidence/ 100pt yrs(95% CI)	9/0.48 (0.23, 0.88)	32/0.56 (0.38, 0.79)
All malignancies: Total pt yrs of f/u	2101	5706
Observed # of pts with event/Expected #of pts with event/SIR (95% CI)	9/12.81/0.70 (0.32, 1.33)	39/33.04/1.18 (0.84, 1.61)

[a]Based on data cut off as of Aug 15, 2012; includes Phase 3 studies of IV GLM in RA pts: GO-LIVE(n=643), GO-FURTHER (n=592).[b]Includes C0524T02 (completed Ph2 PK study of SC GLM). Through Wk 160 for ongoing Phase 3 SC studies in rheumatologic indications: (RA: GO-FORWARD, GO-BEFORE, GO-AFTER, PsA: GO-REVEAL, AS: GO-RAISE); *3 PBO+MTX pts in GO-LIVE did not receive IV GLM during the double-blinded phase of the study, but received SC GLM during the LTE of the study.

Conclusion: Overall safety of IV GLM in RA pts observed through Aug 15, 2012 continue to demonstrate an acceptable safety profile. Rates for events of interest such as malignancies and serious infections in the IV studies are comparable with or lower than rates in the SC studies in RA pts, AS, and PsA.Follow-up through 2yrs will provide information regarding long-term safety of IV GLM.

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Abatacept and Anti-Tumor Necrosis Factor Monoclonal Antibodies: Efficacy and Safety Comparisons. M Schiff[1], M Dougados[2], R Fleischmann[3], J Fay[4] and M Maldonado[4]. [1]University of Colorado, Denver, CO, [2]Hopital Cochin, Descartes University, Paris, France, [3]University of Texas Southwestern Medical Center, Dallas, TX, [4]Bristol-Myers Squibb, Princeton, NJ.

Background/Purpose: A paucity of clinical trial data exists comparing the efficacy and safety of biologic therapies for RA. This study evaluated remission rates and safety for patients (pts) treated with SC or IV abatacept compared with the anti-TNF monoclonal antibodies, adalimumab and infliximab, in a *post hoc*, cross-trial comparison.

Methods: In the head-to-head AMPLE study,[1] pts were randomized to SC abatacept (125 mg weekly) or SC adalimumab (40 mg biweekly), plus background MTX. In the double-blind, double-dummy, placebo- and active-controlled ATTEST study,[2] pts were randomized 3:3:2 to IV abatacept (~10 mg/kg every 4 weeks), infliximab (3 mg/kg every 8 weeks), or placebo, plus background MTX. Pts in both trials had active RA with inadequate response to MTX and were biologic naïve. Remission according to DAS28 (CRP) and SDAI was evaluated *post hoc* over 12 months of treatment for all randomized and treated pts with data available at the visit of interest. Safety was evaluated for all pts who received ≥1 dose of study drug.

Results: In AMPLE, 318 and 328 pts received SC abatacept and adalimumab, respectively; in ATTEST, 156 pts received IV abatacept and 165 received infliximab. Baseline DAS28 (CRP) scores (mean±SD) were 5.5±1.1 in AMPLE and 6.4±0.9 in ATTEST. Duration of RA was 1.9±1.4 and 1.7±1.4 years for SC abatacept and adalimumab in AMPLE, and 7.9±8.5 and 7.3±6.2 years for IV abatacept and infliximab in ATTEST. Remission rates over 12 months were similar for treatment groups in each trial (Table). Over 12 months, 11 (3.5%) vs 20 (6.1%) SC abatacept- vs adalimumab-treated pts, and 4 (2.6%) vs 12 (7.3%) IV abatacept- vs infliximab-treated pts discontinued due to adverse events (AEs); 32 (10.1%) vs 30 (9.1%) and 15 (9.6%) vs 30 (18.2%) experienced SAEs; 5 (1.6%) vs 4 (1.2%) and 1 (0.6%) vs 2 (1.2%) had malignancy; 10 (3.1%) vs 4 (1.2%) and 2 (1.3%) vs 1 (0.6%) experienced autoimmune events. Serious infections were reported in 7 (2.2%) vs 9 (2.7%) and 3 (1.9%) vs 14 (8.5%) pts treated with SC abatacept vs adalimumab in AMPLE and IV abatacept vs infliximab in ATTEST, respectively, with 0/7 vs 5/9 and 0/3 vs 4/14 serious infections leading to discontinuation, and opportunistic infections for 1 (0.3%) vs 1 (0.3%) and 0 vs 5 (3.0%).

		AMPLE		ATTEST	
	Month	SC abatacept	Adalimumab	IV abatacept	Infliximab
DAS28 remission	3	26.8	26.0	11.8	19.0
	6	30.6	38.1	20.0	25.2
	9	39.6	43.1	30.8	23.0
	12	43.3	41.9	29.9	21.4
SDAI remission	3	10.4	10.7	4.6	6.3
	6	13.2	16.6	9.0	10.6
	9	17.6	23.9	11.9	12.8
	12	23.3	24.8	13.1	11.4

Conclusion: Greater proportions of pts in the AMPLE trial achieved remission outcomes vs ATTEST; however, pts in AMPLE had shorter disease duration and lower disease activity at baseline. Over time both routes of abatacept administration provided similar remission rates to the anti-TNF therapies, regardless of disease duration. Safety outcomes were mostly balanced, with increased SAEs and serious infections for infliximab vs abatacept, and increased discontinuations due to AEs and serious infections in both anti-TNF groups vs abatacept. This analysis provides comparative insight into the efficacy and safety of these biologic agents.

1. Weinblatt ME. *Arthritis Rheum* 2013;**65:**28–38;
2. Schiff M. *Ann Rheum Dis* 2008;**67:**1096–103.

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Effects Of VX-509, An Investigational Oral Selective Janus Kinase 3 (JAK3) Inhibitor, On Patient-Reported Outcomes In a Phase 2A Study Of Patients With Active Rheumatoid Arthritis. Vibeke Strand[1], Ellison Suthoff[2], Roy M. Fleischmann[3], Montserrat Vera-Llonch[4], John Jiang[2], Yanqiong Zhang[2] and Nils Kinnman[5]. [1]Stanford University, Palo Alto, CA, [2]Vertex Pharmaceuticals Incorporated, Cambridge, MA, [3]Metroplex Clinical Research Center, University of Texas Southwestern Medical Center, Dallas, TX, [4]Vertex Pharamceuticals Incorporated, Cambridge, MA, [5]Vertex Pharmaceuticals Incorporated, Geneva, Switzerland.

Background/Purpose: VX-509 is an oral JAK3 inhibitor being evaluated as a treatment for RA. Safety and efficacy results from a phase 2a, 12-week, randomized placebo-controlled trial (RCT) in patients with active rheumatoid arthritis (RA) who had failed ≥ 1 DMARD have been reported previously. The objective was to assess impact of treatment with VX-509 on patient-reported outcomes (PRO) during the RCT.

Methods: Patients were randomized to treatment groups that received 1 of 4 doses of VX-509 (25, 50, 100, or 150 mg BID) or placebo BID as monotherapy for 12 weeks. PRO assessments included the Health Assessment Questionnaire-Disability Index (HAQ-DI), visual analog scale (VAS) assessments of patient's general health (subject general health; PtGH) and pain, and the Short Form 36 Health Survey (SF-36). Least squares (LS) mean changes from baseline (BL) were obtained for each group and significance testing versus placebo was conducted using a mixed-effects model for repeated measures analysis. The percentages of patients reporting clinically meaningful improvements (Minimal Clinically Important Differences; MCID) for each PRO are reported, using non-responder imputation for early terminations or incomplete data. In addition, the Cochran-Armitage test was conducted to assess trends in the MCID data across dose groups.

Results: 204 patients were randomized to treatment groups and received at least 1 dose of study drug. Patients receiving 50, 100, and 150 mg BID VX-509 reported significant (all $p<0.01$) and clinically meaningful improvements in PtGH, pain, HAQ-DI, and SF-36 Physical Component Score (PCS) at week 12 (Table).

	Placebo (N=41)	VX-509 25 mg BID (N=41)	VX-509 50 mg BID (N=41)	VX-509 100 mg BID (N=40)	VX-509 150 mg BID (N=41)
Baseline Scores, mean (SD)					
Age (years)	54.9 (10.6)	56.8 (9.5)	55.6 (11.3)	56.5 (8.9)	57.0 (9.3)
Duration of RA (years)	10.0	8.5	6.3	6.7	7.1
PtGH (VAS)	63.5 (19.9)	66.6 (18.7)	64.9 (18.3)	62.2 (19.8)	63.9 (23.3)
Pain (VAS)	64.4 (19.6)	68.3 (21.2)	65.5 (18.3)	66.1 (19.2)	66.2 (21.9)
HAQ-DI	1.61 (0.6)	1.70 (0.6)	1.58 (0.5)	1.64 (0.6)	1.70 (0.6)
SF-36 PCS	30.75 (7.1)	30.54 (6.9)	30.61 (8.0)	29.49 (6.6)	29.26 (7.1)
SF-36 MCS	39.19 (11.2)	38.02 (11.7)	40.43 (12.8)	39.03 (11.7)	38.54 (11.1)
Week 12					
PtGH (VAS)					
LS mean change from BL (SE)	−9.7 (3.4)	−16.2 (3.3)	−29.3 (3.3)***	−27.1 (3.3)***	−34.2 (3.3)***
% MCID [−10][a]	34.1	46.3	65.9	57.5	61.0
Pain (VAS)					
LS mean change from BL (SE)	−10.6 (3.5)	−16.6 (3.4)	−30.6 (3.4)***	−34.4 (3.4)***	−37.6 (3.4)***
% MCID [−10][b]	39.0	53.7	58.5	67.5	68.3
HAQ-DI					
LS mean change from BL (SE)	−0.12 (0.08)	−0.24 (0.08)	−0.50 (0.08)***	−0.52 (0.08)***	−0.64 (0.08)***
% MCID [−0.22][b]	29.3	36.6	53.7	65.0	58.5
SF-36 PCS					
LS mean change from BL (SE)	3.27 (1.3)	2.96 (1.3)	8.11 (1.2)**	9.25 (1.2)***	8.90 (1.2)**
% MCID [2.5][b]	34.1	41.5	58.5	67.5	61.0
SF-36 MCS					
LS mean change from BL (SE)	3.14 (1.8)	4.75 (1.7)	4.42 (1.7)	3.09 (1.7)	7.83 (1.7)
% MCID [2.5][a]	29.3	48.8	29.3	42.5	56.1

SD = standard deviation; SE = standard error
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared with placebo, according to the mixed-effects model for repeated measures
[a] $p < 0.05$, [b] $p < 0.01$ according to the Cochrane-Armitage trend test

Conclusion: In this phase 2a clinical study of patients with RA, VX-509 administered as monotherapy resulted in meaningful improvements in PROs, suggesting that VX-509 treatment may result in benefits to patients beyond traditional efficacy measures.

Disclosure: V. Strand, Vertex Pharmaceuticals Incorporated, 5; **E. Suthoff**, Vertex Pharmaceuticals Incorporated, 3; **R. M. Fleischmann**, Vertex Pharmaceuticals Incorporated, 2, Vertex Pharmaceuticals Incorporated, 5; **M. Vera-Llonch**, Vertex Pharmaceuticals Incorporated, 3; **J. Jiang**, Vertex Pharmaceuticals Incorporated, 3; **Y. Zhang**, Vertex Pharmaceuticals Incorporated, 3; **N. Kinnman**, Vertex Pharmaceuticals Incorporated, 3.

2351

Tocilizumab In Patients With Rheumatoid Arthritis and Rates Of Malignancy: Results From Long-Term Extension Clinical Trials. Ronald F. van Vollenhoven[1], Andrea Rubbert-Roth[2], Anthony Sebba[3], Benjamin Porter-Brown[4], Lucy Rowell[4], Pavel Napalkov[5] and Devi Smart[4]. [1]Karolinska Institute, Stockholm, Sweden, [2]University of Cologne, Cologne, Germany, [3]University of South Florida, Tampa, FL, [4]Roche, Welwyn Garden City, United Kingdom, [5]Genentech, South San Francisco, CA.

Background/Purpose: Malignancy is a potential risk of immunomodulatory treatments and may be increased in patients (pts) with rheumatoid arthritis (RA). The risk of malignancy was analyzed over long-term treatment with tocilizumab (TCZ) in clinical trials in adults with RA.

Methods: Assessment of malignancies was performed in all pts who received ≥1 dose of intravenous TCZ in 1 of 5 phase 3 placebo-controlled studies (OPTION, TOWARD, RADIATE, AMBITION, LITHE), a clinical pharmacology study, or long-term extension studies. In addition, 6-month data were included from the phase 4 TCZ monotherapy study (ADACTA). Data were pooled and analyzed from initial TCZ exposure to May 2, 2012 (cutoff). The indirect method of standardization was used to calculate age- and sex-adjusted standardized incidence ratio (SIR=ratio of observed to expected malignancies). The Surveillance Epidemiology and End Results (SEER) program of the US National Cancer Institute was used to calculate expected cases based on malignancy rates in a general population.

Results: In total, 4171 pts were included. Mean (median [range]) duration was 3.9 y (5.1 [0.0–6.8]); total observation time was 16,204.8 pt-y (PY). In addition to routine study monitoring for potential malignancy, investigators were queried via targeted questionnaire to ascertain details such as tissue diagnosis and biopsy results. Events with confirmed malignancy and those in which malignancy was not confirmed but could not be excluded were considered malignant for this analysis. The malignancy rate described above, including nonmelanoma skin cancer (NMSC), was 1.26/100 PY (95% CI: 1.09, 1.44) and remained stable over time. SIR for all malignancies combined (excluding NMSCs, which are not collected by SEER) and for individual tumor types showed that, with the exception of lung and cervical cancer, the observed number of malignancies was not statistically different (95% CI for SIR include 1.00)[1] from that expected in the general population (Table). Meta-analysis of the incidence of malignancy in RA pts suggests that RA pts have a 63% increase in lung malignancy risk versus the general population.[2] The observed cases of cervical cancer occurred in South America and Eastern Europe, regions with disproportionately high burdens of cervical cancer and underserved by national cervical cancer screening programs.[3] As in other RA studies, the most frequent malignancy was NMSC: 42 basal cell carcinomas and 26 squamous cell carcinomas.

Table. Standardized Incidence Ratios for Malignancy (All TCZ Population)

Organ Class	Observed Cases*	Expected Cases	SIR (95% CI)
All sites	136†	117.36	1.16 (0.97, 1.37)
Lung and bronchus	29	13.24	2.19 (1.47, 3.15)§
Female breast	21	31.35	0.67 (0.41, 1.02)
Prostate	12	9.57	1.25 (0.65, 2.19)
Colon, excluding rectum	7	6.56	1.07 (0.43, 2.20)
Corpus uteri	6	7.14	0.84 (0.31, 1.83)
Cervix uteri	5	1.42	3.51 (1.13, 8.19)§
Non-Hodgkin lymphoma	5	4.27	1.17 (0.38, 2.74)
Stomach	4	1.36	2.94 (0.79, 7.53)
Ovary	4	2.83	1.41 (0.38, 3.62)
Urinary bladder	4	2.98	1.34 (0.36, 3.44)
Melanoma of the skin	4	5.29	0.76 (0.20, 1.94)
Oral cavity and pharynx	4‡	2.34	1.71 (0.46, 4.38)
Rectum	3	2.27	1.32 (0.27, 3.86)
Thyroid	4	4.84	0.83 (0.22, 2.12)
Esophagus	2	0.81	2.45 (0.28, 8.86)
Brain	2	1.18	1.70 (0.19, 6.13)
Leukemia	2	2.21	0.91 (0.10, 3.27)
Pancreas	3	2.66	1.13 (0.23, 3.29)
Kidney and renal pelvis	2	3.37	0.59 (0.07, 2.14)

*Excludes NMSCs (because they are not collected by SEER) and nonmalignant tumors.
†Includes 13 malignant cases (anal cancer, bone and joint, larynx, skin excluding basal and squamous, soft tissue including heart, other endocrine and thymus, and other) not listed in a site- specific category.
‡Includes 1 malignant case of nasopharynx, 2 malignant cases of tongue, and 1 case of pharyngeal cancer.
§Statistically significant (ie, SIR >1 and 95% CIs exclude 1.00).

Conclusion: The rate of all malignancies in RA pts receiving long-term TCZ treatment has remained stable over time. To date, there is no evidence of higher than expected malignancy risk in RA pts treated with TCZ versus the general population.

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2352

Evaluation and Management Of Laboratory Abnormalities During Tocilizumab Treatment Either As Monotherapy Or In Combination With Dmards In RA Patients: Findings From The ACT-STAR Study. Michael Weinblatt[1], Dennis Preston[2], Josh Friedman[2], Natasha Singh[2], Jenny Devenport[2] and Joel M. Kremer[3]. [1]Division of Rheumatology, Brigham & Women's Hospital, Boston, MA, [2]Genentech, Inc., South San Francisco, CA, [3]Albany Medical College and The Center for Rheumatology, Albany, NY.

Background/Purpose: Laboratory values from phase III clinical trials of tocilizumab (TCZ) in patients with RA were the basis of the recommendations for monitoring and managing the potential risks associated with laboratory abnormalities. In order to further evaluate and understand the extent and impact of lab abnormalities and their outcomes, additional analyses of the open-label phase IIIB ACT-STAR study, were undertaken.

Methods: ACT-STAR was a prospective, open-label phase IIIB study that evaluated safety, tolerability and efficacy of TCZ monotherapy (Mono) and TCZ + DMARDs in adults with moderate to severe, active RA who were inadequate responders or had safety/tolerability related issues with stable doses of their current DMARDs or biologic based regimens. All patients exposed to TCZ in ACT-STAR were included in this analysis. Scheduled labs were collected and analyzed centrally every 4 weeks during the core study

(24 wks + 8wks follow-up) and every 8 wks during the long term extension (eligible patients completing the core study could receive TCZ until ≥3 months after commercial availability). AEs were collected on an ongoing basis. Laboratory abnormalities of interest (LFTs, neutrophils, platelets) were assessed and subsequent AEs, study medication changes and outcomes were evaluated for possible associations.

Results: 883 patients received TCZ treatment in ACT-STAR (TCZ 8 mg/kg Mono, n=138; TCZ 4 mg/kg + DMARD with option to escalate to 8 mg/kg at or after week 8, n=364; TCZ 8 mg/kg + DMARD, n=381). Of the 142 (16.2%) patients with ALT > ULN (55 U/L) or 77 (8.8%) with AST > ULN (40 U/L) for ≥ 2 consecutive scheduled visits, > 50% normalized during the study and most completed the planned treatment and observation period. No cases of drug induced liver injury were reported for either group. Of the 26 (3%) patients with ANC ≤ 1000 cells/mm^3 at any point, 81% normalized during study and none experienced serious infections. Similarly, of the 24 (2.7%) patients with platelets ≤ 100,000 cells/mm^3 at any point, 75% normalized during study and no serious bleeding events were observed.

		Resolution		
Parameter	**Rate n/N (%)**	**Normalized n/N (%)**	**Did not normalize n/N (%)**	**Associations***
ALT†	142/876 (16.2)	73/142 (51)	69/142 (48.6)	No reports of drug-induced liver injury observed at any time point
Sustained‡ ALT> ULN (55 U/L)		· 43/73 normalized with medication changes after 2nd consecutive elevation	· 18/69 had no follow-up labs after 2nd consecutive abnormal lab finding (eg., at last visit)	
		· 30/73 normalized without medication changes after 2nd consecutive elevation	· 51/69 had labs after 2nd consecutive elevation [20 had no medication changes; 31 had medication changes]	
AST†	77/876 (8.8)	46/77 (60)	31/77 (40)	No reports of drug-induced liver injury observed at any time point
Sustained‡		· 28/46 normalized with medication changes after 2nd consecutive elevation	· 11/31 had no follow-up labs after 2nd consecutive abnormal lab finding (eg., at last visit)	
AST > ULN (40 U/L)		· 18/46 normalized without medication changes after 2nd consecutive elevation	· 20/31 had labs after 2nd consecutive elevation [10 had medication changes; 10 had no medication changes]	
Neutrophils	26/876 (3.0)	21/26 (81)	5/26 (19)	No serious infections observed at any time point
ANC ≤ 1000 cells/mm^3 on at least 1 occasion			· 5/5 had no follow-up labs after abnormal lab finding (eg., at last visit)	
Platelets	24/876 (2.7)	18/24 (75)	6/24 (25)	No serious bleeding events observed at any time point
≤ 100,000 cells/mm^3 on at least 1 occasion	2/876 (< 1)		· 6/6 had no follow-up labs after abnormal lab finding (eg., at last visit)	
Platelets < 50,000–25,000 cells/mm^3 on at least 1 occasion				

* Associations apply to all patients with the abnormality regardless of normalization status.
† LFT parameters were analyzed separately for events or resolution. However, 154 patients had either ALT or AST sustained elevations (12 AST only, 77 ALT only, 65 both).
‡ Sustained is defined as an abnormal value at ≥ 2 consecutive visits.

Conclusion: Management of patients with RA who receive tocilizumab requires periodic examinations and laboratory monitoring to assess potential risks. In ACT-STAR, no association between lab abnormalities and clinical consequences was observed. Results from this study support the current monitoring guidelines in place in the USPI for TCZ.

Disclosure: M. Weinblatt, Amgen, Abbott, Astra Zeneca, Bristol Myers Squibb, Janssen, UCB, Abbott, Merck, Pfizer and Roche/Genentech, 5; **D. Preston**, Roche/Genetech, 3; **J. Friedman**, Genentech, Inc., 3; **N. Singh**, Genentech, Inc., 4; **J. Devenport**, Genentech, Inc., 3; **J. M. Kremer**, Genentech, Pfizer, Lilly, UCB, Novartis, 2, Genentech, Pfizer, Lilly, UCB, Novartis, 5.

2353

Evaluation Of An Irreversible Dual Target Inhibitor (AC0025) Of Bruton's Tryosine Kinase and Janus Kinase 3 As a Therapeutic Agent For Rheumatoid Arthritis. Xiao Xu, Long Mao, Biao Xi, Xiaoying Zhang, Che Fang, Jia Liu and Wanhong Xu. ACEA Biosciences Inc., San Diego, CA.

Background/Purpose: Bruton's Tryosine Kinase (BTK) and Janus Kinase 3 (JAK3) are intimately involved in the signaling pathways regulating B cell and T cell functions. Perturbing either pathway leads to immune disorders and diseases such as rheumatoid arthritis (RA). The purpose of the study is to develop a small molecule inhibitor targeting BTK and JAK3.

Methods: A novel small molecular inhibitor (AC0025) was rationally designed to selectively target BTK and JAK3 using computer-aided design. The inhibitory activity and selectivity were evaluated at enzymatic, molecular and cellular levels, and in rat CIA animal models. The pharmacological properties and safety were evaluated both in vitro AMEDT assays and in PK/PD/TOX animal models.

Results: AC0025 inhibited BTK and JAK3 enzyme activity with IC_{50} values of 0.9 nM for BTK and 0.1 nM for JAK3. AC0025 does not inhibit other JAK family members including JAK1 and JAK2 with the IC50 values of 10.5 μM and 2.16 μM, respectively. AC0025 covalently binds to Cys481 in BTK and Cys909 in JAK3 resulting in irreversible blockage of the ATP binding site of both kinases, and therefore silences BTK and JAK3 activities. The inhibitory potency and selectivity of AC0025 were further evaluated and confirmed in the cell lines either stably expressing BTK and JAK3, or activated by cytokines. In rat collagen-induced arthritis (CIA) model, AC0025 significantly reduced paw edema and the disease severity by oral administration. Pharmacologic properties of AC0025 as a therapeutic agent for RA were assessed using in vitro ADMET assays and PK/PD/Tox animal models.

Conclusion: AC0025 as a novel irreversible dual target inhibitor showed potent inhibitory activities against BTK and JAK3 and further studies to develop AC0025 as a therapeutic agent for RA are warranted.

Disclosure: X. Xu, ACEA Biosciences, 3; **L. Mao**, ACEA Biosciences Inc., 3; **B. Xi**, ACEA Biosciences Inc., 3; **X. Zhang**, ACEA Biosciences Inc., 3; **C. Fang**, ACEA Biosciences Inc., 3; **J. Liu**, ACEA Biosciences Inc., 3; **W. Xu**, ACEA Biosciences Inc., 3.

2354

Drug Survival Rates Of Anti-Tumor Necrosis Factor Therapies In Patients With Rheumatoid Arthritis and Ankylosing Spondylitis. Dong-Jin Park[1], Kyung-Eun Lee[1], Ji-Hyoun Kang[1], Jeong-Won Lee[1], Tae-Jong Kim[2], Yong-Wook Park[1] and Shin-Seok Lee[1]. [1]Chonnam National University Medical School, Gwangju, South Korea, [2]Chonnam National University Medical School and Hospital, Gwangju, South Korea.

Background/Purpose: We investigated the compliance of Korean patients using anti-tumor necrosis factor (TNF) agents to treat rheumatoid arthritis (RA) and anklyosing spondylitis (AS), and identified potential predictors associated with treatment discontinuation.

Methods: The study population comprised 114 RA and 310 AS patients treated with anti-TNF agents at a single tertiary center for at least 1 year from December 2002 to November 2011. Demographic, clinical, laboratory, and treatment-related data at the time of initiation of anti-TNF agents were collected, and the cause of discontinuation was also determined by reviewing patients' charts. Survival curves were plotted to compare the drug survival between three different anti-TNF agents; life-table analysis and multivariate Cox proportional hazard models were used to identify predictors of treatment discontinuation of anti-TNF therapy.

Results: Of the 114 RA patients, 64 (56.1%) discontinued their first anti-TNF agents with a mean duration of 18.1 months. In constrast, 65 of 310 patients (21.0%) with AS discontinued their first anti-TNF agents, with a mean duration of 84 months. Over a mean follow-up of 33.8 months (range, 10–77 months), the 1-year and 4-year drug survival rates were 44% and 37% in RA patients and 79% and 67% in AS patients, respectively. Although the survival rate did not differ among the three anti-TNF agents in the AS patients, the etanercept group had a lower discontinuation rate than the infliximab group in the RA patients. The most common cause of discontinuation of anti-TFF agents in RA patients was inefficacy, which was reported by 43 (67.2%) patients for all anti-TNF agents, whereas the reasons for discontinuation in AS patients were adverse events (39.7%), inefficacy (33.3%), intention of paitents (9.5%), economic status (11.1%), hospitalization (3.2%), and lost to follow-up (3.2%). In addition, RA patients who received corticosteroids in combination with anti-TNF agents were more likely to discontinue their anti-TNF therapies. The independent predictors of drug discontinuation in AS patients were male gender and complete ankylosis on radiographs of the sacroiliac joint.

Conclusion: We found that AS patients had a higher continuation rate of anti-TNF agent treatment compared to RA paitents and identified predictive variables for drug discontinuation in these paitents. Our results provide further evidence that real-life treatment outcomes of RA and AS patients may be different from those observed in randomized clinical trials.

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2355

Sarilumab, a Subcutaneously-Administered, Fully-Human Monoclonal Antibody Against The IL-6 Receptor Alpha: Using Acute Phase Reactants, Efficacy and Safety Parameters To Inform Phase 3 Dose Selection. Janet van Adelsberg[1], Steven P. Weinstein[2], Neil Graham[3], Tanya Momtahen[4], Chunpeng Fan[4] and Stefano Fiore[4]. [1]Regeneron Pharmaceutials, Inc., Tarrytown, NY, [2]Regeneron Pharmaceuticals Inc, Tarrytown, NY, [3]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [4]Sanofi, Bridgewater, NJ.

Background/Purpose: Sarilumab (SAR) is a fully human mAb directed against IL-6Rα. In phase 2 MOBILITY Part A (NCT01061736), SAR administered SC plus MTX (methotrexate 10–25 mg/wk) achieved primary endpoint of ACR20 at wk 12. Sensitivity analyses for several pharmacodynamic (PD) parameters, modification of disease activity scores, and safety parameters guided selection of 2 doses for Phase 3 studies. These post hoc analyses evaluated the relationship between SAR doses and change from baseline in serum levels of 3 acute phase reactants (APRs): C reactive protein [hs-CRP], serum amyloid A [SAA] and fibrinogen.

Methods: Pts were randomized to 6 groups: placebo (PBO), SAR 100, 150, 200 mg every other wk (q2w), and 100, 150 mg every wk (qw). Disease characteristics, including systemic inflammation (hs-CRP, SAA and fibrinogen) were collected at baseline and every 2 wks. ANCOVA models were used to analyze treatment effects on change from baseline at each visit to wk 12.

Results: Baseline characteristics were similar across all groups (n=306): mean age 52.2±12.3 yrs; 79% women; mean disease duration 7.8±8.1 yrs; RF+ 79.7%; mean hs-CRP 2.8±3.0 mg/dL. CRP results by dose group are shown (Figure). After the first dose, all SAR groups >100 mg q2w had robust and sustained suppression of hs-CRP, maintained throughout the dosing intervals. Similar responses were observed with SAA and fibrinogen and were accompanied by an increase of serum albumin levels. The 150 and 200 mg q2w doses had a response rate at wk 12 comparable to doses of 100 and 150 mg qw for PD parameters and clinical response measures, although the 150 mg q2w dose trended toward more favorable outcomes for some safety parameters. Comparisons of 150 and 200 mg q2w doses show that the 200 mg q2w had a greater and earlier suppression of APRs (at wk 2) but the difference was not significant over time. The most common TEAEs reported in all SAR groups were non-serious infections 12–26%, neutropenia 0–20%, and ALT increase 0–6%. Eight pts (none in the PBO and the 150 and 200 mg q2w groups) experienced at least 1 treatment emergent SAE; of these 6 led to permanent treatment discontinuation. There were no infection-related SAEs in pts with grade 3 or 4 neutropenia and total infection rates were similar to PBO. There was 1 death due to respiratory distress syndrome/cerebrovascular accident in 100 mg q2w group.

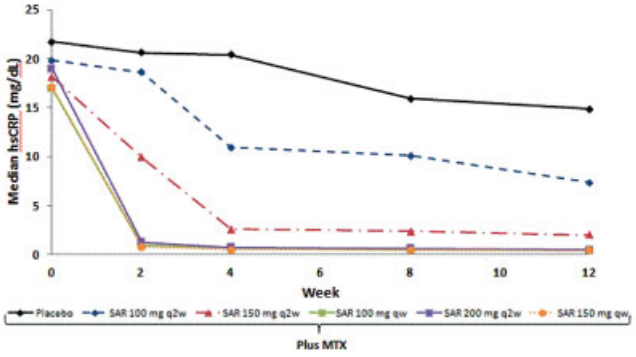

Figure. Change in hs-CRP concentration over time

Conclusion: SAR 150 and 200 mg q2w doses resulted in a significant suppression of APRs, evident at wk 2, maintained throughout the dosing intervals, and comparable to suppression achieved with qw dosing. These doses also demonstrated comparable ACR results to qw dosing. In consideration for a less frequent dosing, and potential for better safety profiles, the 150 and 200 mg q2w doses were selected for further Phase 3 studies.

Disclosure: J. van Adelsberg, Regeneron, 3, Regeneron, 1; **S. P. Weinstein**, Regeneron, 3, Regeneron, 1; **N. Graham**, Regeneron, 3, Regeneron, 1; **T. Momtahen**, Sanofi-Aventis Pharmaceutical, 3, Sanofi-Aventis Pharmaceutical, 1; **C. Fan**, Sanofi-Aventis Pharmaceutical, 3, Sanofi-Aventis Pharmaceutical, 1; **S. Fiore**, Sanofi-Aventis Pharmaceutical, 3.

2356

Soluble Interleukin-2 Receptor Levels and The CD4/CD8 Ratio As Predictors Of The Efficacy Of Abatacept In Biologics-naïve Rheumatoid Arthritis Patients. Hajime Sano[1], Masahiro Sekiguchi[1], Masayasu Kitano[1], Naoto Azuma[1], Shinichiro Tsunoda[1], Kiyoshi Matsui[1] and Tsuyoshi Iwasaki[2]. [1]Hyogo College of Medicine, Nishinomiya-city, Japan, [2]Hyogo University of Health Sciences, Kobe, Japan.

Background/Purpose: Abatacept (ABT) is a recombinant fusion protein consisting of the extracellular domain of human CTLA-4, binding to CD80/86 on antigen presenting cells and thereby inhibits the interaction between these molecules and CD28 on T cells. ABT suppresses T cell activation and has been reported to have the therapeutic benefit for patients with rheumatoid arthritis (RA). However, there are limited data to compare the efficacy of ABT and biomarkers of T cell activation. Soluble IL-2 receptor (sIL-2R) is a marker of T-cell activation in diseases including RA and various cancers. The aim of this study was to investigate the relationship between the efficacy of ABT and biomarkers of T cell activation such as sIL-2R and CD4/CD8 ratio in biologics-naïve RA patients.

Methods: We analyzed 24 biologic-naïve RA patients treated with ABT from January 2010 to May 2012. (Patients received 10 mg/kg abatacept plus MTX during 24 weeks). To evaluate the efficacy of the treatment, we measured DAS28-CRP (DAS), CRP and MMP-3 levels at week 0, 4, 12 and 24 after treatment. We also examined serum levels of sIL-2R and peripheral blood CD4/CD8 ratio before and after treatment with ABT. sIL-2R and peripheral blood CD4+/CD8+ lymphocytes were analyzed using ELISA and flow cytometry.

Results: At week 0, 4 and 24 after ABT treatment, the mean DAS score and serum CRP/ MMP-3/sIL-2R levels were DAS (4.5→3.5→2.8), CRP (2.1→1.1→0.8 mg/dl), MMP-3 (219.1→169.7→114.1 ng/dl), and sIL-2R (441→259→232 U/ml), respectively. We observed statistically significant reduction of DAS scores and serum CRP/MMP-3/sIL-2R levels at week 4 after ABT treatment. The reduction of DAS scores was higher in patients who reduced more than 50% of sIL-2R than in patients who reduced less than 50% at week 4 after treatment (1.18 vs 0.61, p=0.023). At week 0 and 4 after ABT treatment, the mean CD4/CD8 ratio was not statistically different (2.00 vs 2.05). However, the reduction of DAS scores was higher in patients who reduced CD4/CD8 ratio after treatment than in patients who increased CD4/CD8 ratio (1.09 vs 0.60, p=0.014).

Conclusion: We observed the efficacy of ABT at week 4 after treatment of biologic-naïve RA patients. We also observed that the reduction of sIL-2R and CD4/CD8 ratio after treatment correlated with improvement of DAS scores. These results indicate that the decreased serum sIL-2R levels and peripheral blood lymphocyte CD4/CD8 ratio after treatment is a predictor of the efficacy of ABT in biologics-naïve RA patients.

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2357

Confounding By Indication Distorts The Relationship Between Steroid Use and Cardiovascular Disease In Rheumatoid Arthritis. Alper M. van Sijl, Maarten Boers, Alexandre E. Voskuyl and Mike T. Nurmohamed. VU University Medical Center, Amsterdam, Netherlands.

Background/Purpose: Glucocorticoids (GC) are among the most effective drugs in rheumatoid arthritis (RA), but concerns over long-term side effects have not been resolved. Recent studies indicate that cumulative exposure to GC is associated with an increased risk of cardiovascular (CV) disease, perhaps in part through worsening of the CV risk profile. However, GC also strongly decrease inflammation in RA, and inflammation also has an etiological role in the increased CV risk in this group. The net effect of GC use on CV risk in RA therefore remains unknown.

Methods: RA patients aged 50–75 years were followed for approximately 10 years to study the development of CV disease in the Cardiovascular Risk in RhEumatoid arthritis (CARRE) study. This study was the first to report that CV disease incidence in RA was equal to diabetes mellitus. For the current study, GC exposure was characterized by duration, last exposure by date, the mean dose of GC and cumulative exposure in grams. Data collection included traditional CV risk factors and RA-related parameters and disease activity. Cox proportional hazard analysed the association between GC exposure and incident CV disease, with adjustment for confounders.

Results: The study comprised 353 individuals of whom 59 (17%) were exposed to GC at the time of inclusion, with a median (interquartile range) the cumulative exposure was 8.7 (2.5–25.4) grams. After a total follow-up experience of 2361 years, 58 (17%) participants developed incident CV disease, yielding an incidence rate of 24.6/1.000 patient years. Incident cases were more frequently treated with GC at baseline than RA patients without CV disease (22 vs. 16%, p-value 0.089), were treated with GC for a longer period (4.1 vs. 1.9 years, p-value 0.090) and cumulatively used more GC (31.9 vs. 8.5 grams, p-value 0.046). These differences remained after adjustment for demographics and CV risk. However, additional adjustment for at baseline measured 28-joint disease activity score (DAS28) and disability (Health Assessment Questionnaire, HAQ) completely erased the associations of GC with incident CV disease. These observations appear robust and unaffected by power constraints, as the standard errors of the beta estimates remained essentially similar after adjustment.

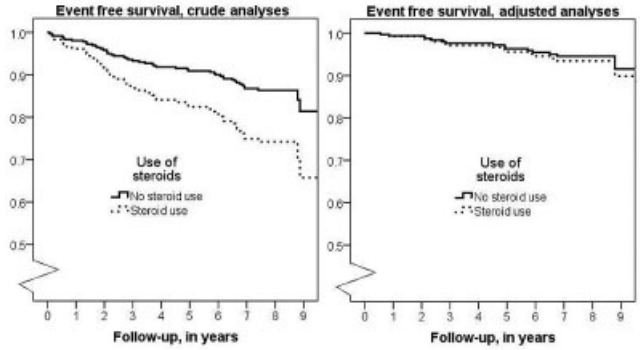

Figure. Kaplan-Meier survival curves

Conclusion: It appears that GC use in uncontrolled populations represents a marker of high RA disease activity; high disease activity itself represents an increased risk of CV disease. Thus the observed relationship of GC with CV disease in RA patients is strongly confounded by indication, as suggested by the adjusted analyses. In this setting, it is possible that the adverse CV effects of GC are balanced by positive effects working through inflammation control.

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2358

Sarilumab, a Subcutaneously Administered, Fully Human Monoclonal Antibody Inhibitor Of The IL-6 Receptor Alpha: 12 Week Infection Rates By Level Of Circulating Neutrophils In Rheumatoid Arthritis and Ankylosing Spondylitis. Kevin L. Winthrop[1], Tanya Momtahen[2], Stefano Fiore[2], Steven P. Weinstein[3], Janet van Adelsberg[4], Richard Wu[5] and Neil Graham[5]. [1]Oregon Health & Science University, Portland, OR, [2]Sanofi, Bridgewater, NJ, [3]Regeneron Pharmaceuticals Inc, Tarrytown, NY, [4]Regeneron Pharmaceutials, Inc., Tarrytown, NY, [5]Regeneron Pharmaceuticals, Inc., Tarrytown, NY.

Background/Purpose: Sarilumab is a human monoclonal antibody directed against the alpha subunit of the IL-6 receptor (IL-6Rα). IL-6 blockade is associated with a reduction in circulating neutrophil levels (CNL). It has been suggested that changes in CNL with IL-6 blockade may be due to margination of neutrophils or other mechanisms. The relationship between decrease in CNL and risk of infection is unclear.

Methods: To evaluate the risk of neutropenia and infection with sarilumab, we retrospectively assessed clinical trial data from two 12-week Phase 2b studies in patients with RA (MOBILITY Part A [NCT01061736]) and with AS (ALIGN [NCT NCT01061723]). In these studies, patients were randomized to 6 groups: placebo (PBO), sarilumab 100 mg, 150 mg, 200 mg every other week (q2w) and 100 mg, 150 mg weekly (qw). CNL were determined q2w and incidence of total, serious, viral, fungal and bacterial infections were recorded. Data were analyzed across the PBO and sarilumab groups, with a focus on the 150 mg and 200 mg q2w dose regimens that were subsequently chosen for study in phase 3.

Results: Three hundred six patients were enrolled in MOBILITY Part A (80% female; median age, 54 yrs [19:74]). 300 patients were enrolled in ALIGN (30% female; median age, 40 yrs [18:72]). One serious infection was reported in the 100 mg qw group of the ALIGN study. All other reported infections in both studies were non serious. Percent of patients with reported infections in the 6 dose groups above were 14, 12, 23, 26, 24, and 20% in MOBILITY and 18, 27, 22, 25, 18, and 29% in ALIGN. Infection rates in the Pbo groups and according to CNL in the pooled 150 mg (n = 103) and 200 mg (n = 100) q2w dose groups are presented in the Table. Infections in patients on sarilumab were most often observed among patients with normal CNL.

Number (%) of Patients With Infection From Baseline to Week 12 in MOBILITY Part A (RA) and ALIGN (AS): in Placebo Group; in Pooled Sarilumab 150mg q2w and 200mg q2w Dose Groups by Lowest Post-Baseline Circulating Neutrophil Level (CNL)

MOBILITY (150 mg q2w and 200 mg q2w	Normal CNL N=69	Grade 1 CNL (≥1500/mm^3 LLN) N=13	Grade 2 CNL (≥1000–1500/mm^3) N=12	Grade 3 & 4 CNL (<1000/mm^3) N=7	Pbo N=51
Any Infection	20 (29%)	2 (15%)	1 (8%)	1 (14%)	7 (14%)
Viral*	4 (6%)	0	0	0	0
Fungal*	1 (2%)	0	0	0	0
Bacterial*	1 (2%)	1 (8%)	0	1 (14%)	0
ALIGN (150 mg q2w and 200 mg q2w)	**Normal CNL N=55**	**Grade 1 CNL (≥1500/mm^3-LLN) N=16**	**Grade 2 CNL (≥1000–1500/mm^3) N=18**	**Grade 3 & 4 CNL (<1000/mm^3) N=11**	**Pbo N=50**
Any Infection	15 (27%)	2 (13%)	2 (11%)	2 (18%)	9 (18%)
Viral*	5 (9%)	0	0	1 (9%)	3 (6%)
Fungal*	0	1 (6%)	0	0	0
Bacterial*	0	0	0	0	1 (2%)

* Coded by etiology when provided à infections by etiology do not sum to total number of infections

Conclusion: In these 12 week studies, decreases in CNL did not appear to be associated with infection risk. This may be due to CNL margination or other mechanisms. These preliminary results warrant further exploration in the larger, longer phase 3 studies with sarilumab in patients with RA currently in progress.

Disclosure: K. L. Winthrop, Pfizer Inc, 2, Genentech Inc., Pfizer, UCB, Regeneron, 5; **T. Momtahen**, Sanofi-Aventis Pharmaceutical, 3, Sanofi-Aventis Pharmaceutical, 1; **S. Fiore**, Sanofi-Aventis Pharmaceutical, 3; **S. P. Weinstein**, Regeneron, 3, Regeneron, 1; **J. van Adelsberg**, Regeneron, 3, Regeneron, 1; **R. Wu**, Regeneron, 3, Regeneron, 1; **N. Graham**, Regeneron, 3, Regeneron, 1.

2359

Impact Of Etanercept-Methotrexate Treatment Withdrawal On Patient-Reported Outcomes In Patients With Early Rheumatoid Arthritis (PRIZE Trial). Piotr Wiland[1], B Combe[2], Oliver M. FitzGerald[3], Hasan Tahir[4], Stefanie Gaylord[5], Theresa Williams[5], Ronald Pedersen[6], Jack Bukowski[6], Bonnie Vlahos[5] and Sameer Kotak[7]. [1]Medical University of Wroclaw, Wroclaw, Poland, [2]Hôpital Lapeyronie, Montpellier, France, [3]St. Vincent's University Hospital, Dublin, Ireland, [4]Barts Health NHS Trust, London, United Kingdom, [5]Pfizer Inc., Collegeville, PA, [6]Pfizer Inc, Collegeville, PA, [7]Pfizer Inc., New York, NY.

Background/Purpose: Active rheumatoid arthritis (RA) is commonly associated with impairment of physical function and health-related quality of life (QoL), as well as work disability. The importance of patient-reported outcomes (PROs) in evaluating the impact of RA treatment on function, QoL, and the ability to work is well recognized. Patients with early (mean symptom duration, 6 months), moderate-to-severe RA who previously received induction therapy and achieved DAS28 remission with etanercept (ETN) 50 mg/methotrexate (MTX) in the 52-week, open-label Phase 1 of the PRIZE study received ETN 25 mg/MTX, MTX alone, or no treatment in the 39-week, randomized, double-blind Phase 2. The results of Phase 1/2 demonstrated a statistically significant and clinically meaningful favorable impact/sustained effect of biologic therapy on PROs.[1] Patients were subsequently included in a 26-week, observational, treatment-free Phase 3 if they had DAS28 ≤3.2 to assess the impact of complete therapy withdrawal.

Methods: Patients achieving response at end of Phase 2 (week 91: DAS28 ≤3.2) to treatment with ETN/MTX, MTX/placebo (PBO) injection, or PBO capsules/PBO injection continued to 26-week drug-free Phase 3. MTX was tapered to 0 by 5-mg weekly decrements. At week 117, the following PROs were assessed: the Health Assessment Questionnaire disability index (HAQ-DI); EuroQol-5 Dimensions utility score (EQ-5D); Short Form Health Survey Physical/Mental Component Summary (SF-36 PCS/MCS); Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue); Work Productivity and Activity Impairment Questionnaire (WPAI: RA); and Work Instability Scale for Rheumatoid Arthritis (RA-WIS).

Results: After withdrawal of treatment in patients who responded to ETN/MTX and MTX/PBO therapy at week 91, worsening of most PROs was observed (Table 1). At week 117, the proportions of patients who achieved the following endpoints were not significantly different between the ETN/MTX and MTX/PBO groups after treatment withdrawal: normal HAQ-DI or

EQ-5D VAS; clinically relevant improvements in EQ-5D utility and SF-36 PCS; and low risk of work disability. Whereas worsening of most PROs plateaued among patients who were treatment free in both Phases 2 and 3, sharper declines were observed among patients withdrawn from ETN/MTX and MTX/PBO treatment in Phase 3.

Table 1. Effects of Biologic Treatment Withdrawal on PROs in PRIZE Phase 3 (LOCF)

		Patients, %			Pairwise Comparison *P* value§		
		ETN/MTX (n=63)	MTX/PBO (n=65)	PBO (n=65)	ETN/MTX vs MTX/PBO	ETN/MTX vs PBO/PBO	MTX/PBO vs PBO/PBO
HAQ-DI ≤0.5*	Wk 91	77.8	72.3	44.6	0.543	0.0001	0.002
	Wk 117	66.7	58.5	40.0	0.366	0.003	0.053
EQ-5D utility improvement ≥0.05†	Wk 91	76.2	73.8	53.8	0.839	0.010	0.028
	Wk 117	68.3	67.7	52.3	1.000	0.073	0.107
EQ-5D VAS >82*	Wk 91	71.4	58.5	32.3	0.142	<0.0001	0.005
	Wk 117	55.6	38.5	32.3	0.076	0.012	0.582
SF-36 PCS improvement ≥5†	Wk 91	79.4	76.6	42.2	0.831	<0.0001	0.0001
	Wk 117	58.7	62.5	34.4	0.718	0.008	0.003
SF-36 MCS improvement ≥5†	Wk 91	58.7	46.9	35.9	0.215	0.013	0.282
	Wk 117	60.3	39.1	39.1	0.021	0.021	1.000
Low risk RA-WIS ≤9‡	Wk 91	86.1	84.4	62.1	1.000	0.041	0.050
	Wk 117	80.6	71.1	58.6	0.438	0.062	0.319

*"Normal" value, data shown for mITT population; †improvement from Phase 1 baseline mITT population (LOCF), representing clinically relevant improvement; ‡low risk of work disability; §based on 2-sided pairwise Fishers' exact tests.

Conclusion: Withdrawal of ETN/MTX therapy in Phase 3 of the PRIZE study resulted in loss of favorable impact on PROs.

Reference:
1. Emery P, et al. Ann Rheum Dis 2013;72(Suppls3):765.

Disclosure: P. Wiland, Pfizer, Roche, UCB, Abbvie, MSD, 5; **B. Combe**, Pfizer, Roche-Chugai, 2, Merck, Pfizer, Roche-Chugai, and UCB, 5; **O. M. FitzGerald**, Abbott, BMS, Pfizer, MSD, 2, Abbott, UCB, Pfizer, 5, Abbott, Pfizer, MSD; Janssen and Cellgene, 8; **H. Tahir**, None; **S. Gaylord**, Pfizer Inc, 1, Pfizer Inc, 3; **T. Williams**, Pfizer Inc, 1, Pfizer Inc, 3; **R. Pedersen**, Pfizer Inc, 1, Pfizer Inc, 3; **J. Bukowski**, Pfizer Inc, 1, Pfizer Inc, 3; **B. Vlahos**, Pfizer Inc, 1, Pfizer Inc, 3; **S. Kotak**, Pfizer Inc, 1, Pfizer Inc, 3.

2360

Incidence Of Diabetes and Effect Of Etanercept and Adalimumab On HbA1c Over 1 Year: Data From a Randomised Trial In Patients With Rheumatoid Arthritis. Paola de Pablo[1], Fiona M. Maggs[2], David Carruthers[3], Abdul A. Faizal[4], Mark T. Pugh[5] and Paresh Jobanputra[6]. [1]University of Birmingham, College of Medical & Dental Sciences, Queen Elizabeth Hospital Birmingham, UK, Birmingham, United Kingdom, [2]Queen Elizabeth Hospital Birmingham, UK, Birmingham, United Kingdom, [3]Sandwell and West Birmingham Hospitals NHS Trust, UK, Birmingham, United Kingdom, [4]Heart of England NHS Foundation Trust, UK, Solihull, United Kingdom, [5]Saint Mary's Hospital, UK, Isle of Wight, United Kingdom, [6]Queen Elizabeth Hospital Birmingham, UK., Birmingham, United Kingdom.

Background/Purpose: Inflammation such as that which occurs in rheumatoid arthritis (RA) is associated with insulin resistance and risk of diabetes mellitus (DM). Some DMARDs including TNF inhibitors (TNFi) may improve insulin resistance and DM risk. However, it is unknown whether TNFi improve HbA1c in patients with RA with or without DM. Data on HbA1c was collected in a randomised trial comparing drug continuation rates for etanercept and adalimumab (BMJ Open 2012;2:e001395). We estimated the incidence of DM from this data and studied the impact of therapy on HbA1c.

Methods: Participants with active RA, who had previously failed to respond to 2 non-biologic DMARDs including methotrexate, were randomised to etanercept or adalimumab and followed 3-monthly over 1 year. Data collected included co-morbidities, clinical and laboratory parameters, and medications at each visit. The primary endpoint was newly recorded diabetes defined as HbA1c >48mmol/mol at any time point. Predictors of HbA1c and HbA1c change were determined with univariate and multivariate analyses.

Results: Of the 125 patients with active RA randomised to etanercept or adalimumab, 6 (4.8%) were known diabetics and 88% were RF/ACPA positive. Of the 119 without DM, 7 (5.9%) were diagnosed with DM (HbA1c >48mmol/mol) at baseline. 73 participants (73% female) completed 1 year of TNFi therapy: mean age 54 yrs (SD±12), mean BMI 27.8, mean HbA1c 38 mmol/mol. Of these, 4 (5%) patients had DM at baseline. A majority of patients were on methotrexate (67%) and 33% on prednisolone. Baseline characteristics were similar for patients' allocated to adalimumab (52%) or etanercept (48%), except more patients on etanercept were on prednisolone (49% vs. 18%; p=0.006); and more patients on adalimumab were on hydroxycloroquine (24% vs. 3%; p=0.01). After excluding those with known DM at baseline, among those completing one year of TNFi (n=69), 3 (4.4%) patients had an HbA1c >48 mmol/mol at baseline, 1 (1.5%) at 3 months, 1 (1.5%) at 6 months, and 2 (2.9%) at 12 months of follow-up. 2 (3%) cases had a HbA1c >48 mmol/mol at 2 follow-up visits. The incidence of DM was 29 new cases per 1000-person years (95% CI 3.51–105). Those on adalimumab tended to have higher levels of HbA1c than those on etanercept but the differences between groups at each time point were non-significant. However, there was a significant rise in HbA1c levels after 1 year of adalimumab therapy (37.27 mmol/mol and 38.80 mmol/mol; p=0.01). Etanercept therapy did not influence HbA1c levels over time.

Conclusion: Incidence of diabetes in patients entering a randomised trial of etanercept and adalimumab was considerably higher than other recent data. Treatment with a TNFi did not improve HbA1c levels with either agent in diabetics and non-diabetics. After excluding those with diabetes, those on adalimumab had higher mean HbA1c levels after 1 year of therapy.

Disclosure: P. de Pablo, None; **F. M. Maggs**, None; **D. Carruthers**, None; **A. A. Faizal**, None; **M. T. Pugh**, None; **P. Jobanputra**, None.

2361

Pharmacokinetic and Pharmacodynamic Characterization Of a Dissociated Agonist Of Glucocorticoid Receptor, Following Multiple Dose Administration In Healthy Japanese Adult Subjects. Brinda Tammara[1], Sou Miyoshi[2] and Judith Hey-Hadavi[3]. [1]Pfizer, Collegeville, PA, [2]Pfizer, Tokyo, Japan, [3]Pfizer, NewYork, NY.

Background/Purpose: PF-04171327 is a prodrug of PF-00251802, a dissociated agonist of the glucocorticoid receptor (DAGR) and being developed as treatment for Rheumatoid Arthritis. The objective of the study was to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of PF-00251802 following multiple doses of PF-04171327.

Methods: This was a randomized, placebo-controlled Phase 1 study of multiple doses of PF-04171327 in healthy adult Japanese subjects (N=8). PF-04171327 tablet (20 mg) or matching placebo once daily were administered in the morning for 12 days in a fasted state. The subjects were randomized in a 3:1 ratio to PF-04171327 or placebo, respectively. Blood samples for PK and PD analysis were collected at pre specified time points and analyzed using validated assay methods. Standard non-compartmental analyses methods were used to estimate PK parameters. PD effects were assessed using bone biomarkers (serum P1NP, serum CTX, osteocalcin, urine NTX), carbohydrate markers (fasting glucose, insulin, adiponectin) and HPA axis marker (plasma cortisol).

Results: The geometric mean summary of the plasma PK parameters of PF-00251802 and its metabolite PF-04015475 on Day 1 and Day 12 are shown in Table 1. The median percent change from baseline on Day 12 for the bone PD markers are shown in Table 2.

Table 1.

PK parameter (Units)		PF-00251802 N=6	PF-04015475 N=6
C_{max} (ng/mL)	Day 1	154	33.9
	Day 12	256	85
AUC_T (ng · h/mL)	Day 1	1430	610
	Day 12	3170	1520
$t_{1/2}$*(h)	Day 1	NA	NA
	Day 12	29	30

*Arithmetic mean, C_{max}: maximum observed concentration; AUC; area under the plasma concentration-time profile over the dosing interval; $t_{1/2}$, half-life

Table 2.

% Change from baseline	Placebo N=2	PF-04171327 N=6
P1NP	−19	−22
Osteocalcin	−11	−35
sCTX	6	11
uNTX	−4	31

P1NP: procollagen type 1 N-terminal propeptide.
sCTX: serum C-terminal telopeptide of type 1 collagen.
uNTX: urine N-telopeptide of type 1 collagen.

The mean observed accumulation ratios of exposure were 2.23 and 2.50 for PF-00251802 and PF-04015475, respectively. There was no change in the carbohydrate markers with treatment and complete suppression of cortisol levels was observed. There were no deaths, serious adverse events, severe AEs, subject discontinuations, in this multiple dose part of the study.

Conclusion: Following multiple dosing steady state concentrations of PF-00251802 were achieved by Day 9. There was a trend for greater suppression of bone formation markers osteocalcin and P1NP compared to placebo and increase in bone resorption marker urine-NTX, but not serum CTx. Overall, the treatments administered in this study were well tolerated with an acceptable safety profile.

Disclosure: B. Tammara, Pfizer Inc, 3; **S. Miyoshi**, Pfizer Inc, 3; **J. Hey-Hadavi**, Pfizer Inc, 3.

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Incidence Of Adverse Events In Patients With Rheumatoid Arthritis and Spondyloarthritis Exposed To Anti-TNF Therapy. Data From The Brazilian Registry For Monitoring Of Biologic Therapies In Rheumatic Diseases (BiobadaBrasil). Roberto Ranza[1], David C Titton[2], Valeria Vallim[3], Ines Silveira[4], Aline Ranzolin[5], Andre Hayata[6], Mirhelen M. Abreu[7], Paulo Louzada-Jr[8], Angela LBP Duarte[5], Claiton Brenol[9], Geraldo C Pinheiro[10], Glaucio R Castro[11], Hellen M Carvalho[12], Isaias Costa[13], Jose C Macieira[14], Jose R Miranda[15], Julio CM Bertacini[16], Luis SG Barbosa[17], Manoel B Bertolo[18], Marcelo M. Pinheiro[12], Maria F Sauma[19], Marilia B Silva[20], Marlene Freire[21], Roberto A Toledo[22] and Vander Fernandes[23]. [1]Universidade Federal de Uberlandia, Uberlandia MG, Brazil, [2]Hospital de Clínicas da UFPR, Curitiba PR, Brazil, [3]Universidade Federal do Espirito Santo, Vitoria ES, Brazil, [4]PUCRS, Porto Alegre RS, Brazil, [5]Universidade Federal de Pernambuco, Recife PE, Brazil, [6]CRO Osasco, Osasco SP, Brazil, [7]Universidade Federal de São Carlos, São Carlos SP, Brazil, [8]USP RP, Ribeirão Preto SP, Brazil, [9]Universidade Federal do Rio Grande do Sul, Porto Alegre RS, Brazil, [10]UERJ, Rio de Janeiro RJ, Brazil, [11]Hospital Governador Celso Ramos, Florianopolis SC, Brazil, [12]Brazilian Registry of Spondyloarthritis, São Paulo, Brazil, [13]Universidade Federal MS, Campo Grande MS, Brazil, [14]UFS Aracaju, Aracaju SE, Brazil, [15]Artrocenter Clinica Medica, Taubate SP, Brazil, [16]USP SP CDMAC, São Paulo SP, Brazil, [17]Universidade Federal Mato Grosso, Cuiabá MT, Brazil, [18]UNICAMP, Campinas SP, Brazil, [19]UFPA, Belem PA, Brazil, [20]Hospital Universitario Evangelico, Curitiba PR, Brazil, [21]UFTM, Uberaba MG, Brazil, [22]FUNFARP, São José do Rio Preto SP, Brazil, [23]Universidade de Cuiabá, Cuiaba MT, Brazil.

Background/Purpose: The safety profile of a-TNF biologic drugs might have substantial regional differences due to geographic and socio economic factors and to epidemiology of infectious diseases. Registries are the best way to monitor drugs safety in the real world. In 2009, the Brazilian Society of Rheumatology started BiobadaBrasil, as part of a Latin America project (BiobadaAmerica) developed with the methodological support of the Spanish Society of Rheumatology and of the Biobadaser Study Group. Purpose:To report the incidence of adverse events (AE) in patients exposed to a-TNF drugs in Brazil.

Methods: Since January 2009 a growing number of centers from almost all Brazilian states (32 at 12/31/2012 when data were downloaded) included patients with active rheumatic diseases who started a biologic drug or a synthetic DMARD as a parallel control group. A constant three level monitory of data quality has been performed (online, by phone and in situ). The present study focuses on serious AE (SAE) and serious infectious AE (SIAE) (for SAE and SIAE definition: Protocolo 1.1 in https://biobadaser.ser.es/biobadamerica/Brasil/cgi-bin/upload/documentacion.aspx) in patients with Rheumatoid Arthritis (RA) and Spondyloarthritis (SpA = Ankylosing Spondylitis and Psoriatic Arthritis) exposed to a-TNFs. Time of exposure is considered from the beginning of therapy to the date of the last administration plus twice the half-life of the drug. Continuous variables were expressed as mean with standard deviation (SD). The AE incidence rate per 1000 patients per year of exposure and its 95% confidence level (95%CI) were calculated.

Results: 1372 subjects with RA (877) and SpA (495) exposed to a-TNF drugs were included in BiobadaBrasil, 3202 patient/yrs, mean age at baseline of 47 (SD12) yrs, mean disease duration of 9 (SD8) yrs, 65% females. Controls were 486 (RA 452, SpA 34), 1210 patient/yrs, mean age 50 (SD12) yrs, mean disease duration 6 (SD7), 82% females. The incidence rates of AE for 1000 patient/yrs [95%CI] in the a-TNF vs the control group were: SAE 58 [50,67] vs 19 [13,29] (ratio 3.04 [1.97,4.69] p=0.000), SIAE 26 [21,32] vs 4 [2,10] (ratio 6.2 [2.51,15.29] p=0.000). The incidence rates for the three more prescribed a-TNFs were: for SAE = ADAlimumab 50 [39,65], ETAnercept 58 [44,77], IFliXimab 64 [52,80] (ADA vs IFX p=0.35) and for SIAE = ADA 17 [11,26], ETA 30 [20,44], IFX 31 [23,43] (ADA vs IFX p=0.07). The first a-TNF was associated with a lower incidence of SAE and SIAE when compared with the subsequent but with no statistical significance. No significant difference of AE incidence rates has been found between RA and SpA patients.

Conclusion: In the BiobadaBrasil registry the incidence rate of SAE and SIAE in patients exposed to a-TNF drugs is similar to that reported by other registries. The comparison with the incidence rates of the internal control group showed a 3-fold risk for SAE and a 6-fold risk for SIAE.

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Positivity Of Rheumatoid Factor and Anti-Cyclic Citrullinated Peptide Is Associated With The Response Rate Of Infliximab, But Not Tocilizumab, In Treatment Of Rheumatoid Arthritis. Masao Sato[1], Masao Takemura[1], Ryuki Shinohe[1], Yasuko Yamamoto[2] and Kuniaki Saito[2]. [1]Gifu University, Gifu, Japan, [2]Kyoto University, Kyoto, Japan.

Background/Purpose: Recent reports have shown that positivity for rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) can influence the efficacy of rheumatoid arthritis (RA) treatment. Additionally, RF^+ and $ACPA^+$ statuses were emphasized in the revised ACR–EULAR Classification Criteria for Rheumatoid Arthritis. This study examined whether RF^+ and $ACPA^+$ statuses in patients with RA impacted the clinical efficacy of anti-TNF-α or anti-IL-6 therapy.

Methods: We retrospectively evaluated 235 patients with RA who were observed through 52 weeks of follow-up after infliximab (IFX) or tocilizumab (TCZ) treatment at our hospital and related facilities (IFX, n = 142; TCZ, n = 93). Clinical efficacy was assessed based on a 28-joint disease activity score using erythrocyte sedimentation rate (DAS28-ESR) remission and achievement of Boolean-based remission criteria and its components ($\leq$1) at 52 weeks after initiating treatment.

Results: Before treatment, DAS28-ESR score in IFX and TCZ groups was 6.6 $\pm$ 1.5 and 6.5 $\pm$ 1.3, respectively. The proportion of RF^+ and $ACPA^+$ patients was 79.6% and 81.7% in the IFX group and 79.6%, and 87.1% in the TCZ group, respectively. The proportion of patients concomitantly treated with MTX was 100% in the IFX group and 55% in the TCZ group ($p < 0.0001$); the proportion of patients previously treated with biological products was 0% in the IFX group and 56% in the TCZ group ($p < 0.0001$). Among patients who achieved remission at 52 weeks in the IFX group, DAS28-ESR remission was seen in 36% and 59% RF^+ and RF^- patients ($p = 0.02$), respectively, and in 36% and 62% $ACPA^+$ and $ACPA^-$ patients, respectively ($p = 0.01$). TJC $\leq$1 was seen in 60% and 89% $ACPA^+$ and $ACPA^-$ patients, respectively ($p = 0.005$) and SJC $\leq$1 was seen in 60% and 85% $ACPA^+$ and $ACPA^-$ patients, respectively ($p = 0.01$). The proportion of patients who achieved remission was significantly lower in RF^+ and $ACPA^+$ patients. In the TCZ group, no efficacy index between RF^+ and RF^- patients or between $ACPA^+$ and $ACPA^-$ patients significantly correlated with remission. Correlations between pretreatment patient demographics and achievement of DAS28 remission at 52 weeks were evaluated. In the IFX group, patients who achieved no remission had higher CRP levels (3.0 vs. 1.9 mg/dL; $p = 0.0007$), higher disease activity by DAS28-ESR (6.8 vs. 6.2; $p = 0.01$), and a significantly higher RF^+ (86% vs. 71%; $p = 0.02$) and $ACPA^+$ rates (88% vs. 72%; $p = 0.01$) than those who achieved remission. However, similar differences were not observed in the TCZ group. A multivariate logistic regression analysis was performed to identify factors related to non-remission at 52 weeks after initiating treatment. DAS28-ESR (OR, 2.24; 95% CI, 1.52–3.47; $p = 0.0001$) and $ACPA^+$ (OR, 2.82; 95% CI, 1.19–6.97; $p = 0.04$) were identified as related factors in the IFX group; however, no factors were identified for the TCZ group.

Conclusion: RF^+ and $ACPA^+$ statuses are likely to be risk factors that affect the clinical efficacy of IFX treatment but not TCZ treatment.

Disclosure: M. Sato, None; **M. Takemura**, None; **R. Shinohe**, None; **Y. Yamamoto**, None; **K. Saito**, None.

2364

Baseline Procalcitonin Levels Are Predictive Marker Of Remission In Biologic naïve Patients With Rheumatoid Arthritis Treated With Tocilizumab: Result From 24 Weeks Of Follow-Up. Soichiro Tsuji[1], Akiko Yura[2], Michihito Katayama[1], Satoru Teshigawara[1], Maiko Yoshimura[1], Eriko Tanaka[1], Yoshinori Harada[2], Yoshinori Katada[2], Masato Matsushita[1], Shiro Ohshima[3], Jun Hashimoto[1] and Yukihiko Saeki[3]. [1]Rheumatology, Osaka-Minami Medical Center, Kawachinagano City, Japan, [2]Allergology, Osaka-Minami Medical Center, Kawachinagano City, Japan, [3]Clinical Research, Osaka-Minami Medical Center, Kawachinagano City, Japan.

Background/Purpose: Procalcitonin (PCT) is a useful marker of infection. PCT-mRNA increases expression from peripheral blood mononuclear cells by stimulation of a pro inflammatory cytokine, IL-6 and TNF-α. Of the 216 Rheumatoid arthritis(RA) patients who started tocilizumab(TCZ) treatment until September 2012 at our center, about half of the patients did not attain remission after 24 weeks, and therefore, predictive marker will be useful for patient care. To purpose of this study is to investigate whether the levels of PCT, modified HAQ(mHAQ), MMP-3, RF, ESR, CRP, and ACPA at baseline(BL) of TCZ treatment can be used to predict remission at 24 weeks after the start of TCZ treatment (Week 24).

Methods: Biologic (Bio) naïve RA patients treated with TCZ for more than 24 weeks were enrolled in this study. PCT(n=30), mHAQ(n=71), MMP-3(n=98), RF(n=89), ESR(n=94), CRP(n=101) and ACPA(n=81) were identified at BL. The patients were divided into 2 groups, based on DAS28ESR remission (DAS28ESR<2.6) at Week 24. For each variable, there was a significant difference between the remission and non-remission group; ROC analysis was performed and cut-off values (COV) were analyzed. For each of these variables, 2 groups were formed by dividing the Bio naïve RA at the COV: the under COV (U) group and over COV (O) group, and the Week 24 remission rate in each group was found.

Results: The variables with significant difference between the remission and non-remission group were PCT(p=0.013), mHAQ(p<0.000), MMP-3(p=0.028), RF(p<0.000), ESR(p<0.000) and CRP(p<0.000). The COVs were 0.026ng/ml for PCT, 0.5 for mHAQ, 85mg/dl for MMP-3, 94U/ml for RF, 56mm/hr for ESR, and 1.09mg/dl for CRP. For each variable, the remission rate in the U group (PCT 91.7%, mHAQ 82.2%, MMP-3 68.8%, RF 72.3%, ESR 63.2% and CRP 65.2%) was significantly higher than in the O group. For PCT at BL, DAS28ESR was no different between the U group and O group and no correlation with DAS28ESR was observed. But the BL DAS28ESR was significantly lower in the U groups for other variables.

Conclusion: Baseline PCT level is a useful marker of predictive remission at week 24 in Bio naïve RA patients treated with TCZ. Moreover, unlike the other variables, it is not affected by the BL disease activity level.

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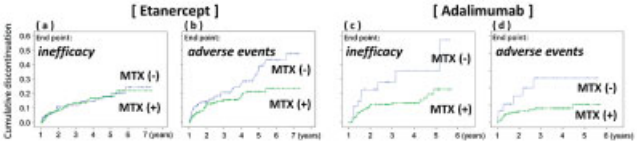
2365

Concomitant Methotrexate Did Not Affect Discontinuation Rate Of Etanercept Due To Ineffectiveness: Six-Year Results From Japanese Multicenter Registry System. Nobunori Takahashi[1], Toshihisa Kojima[1], Atsushi Kaneko[2], Yuji Hirano[3] and Naoki Ishiguro[4]. [1]Nagoya University Hospital, Nagoya, Japan, [2]Nagoya Medical Center, Nagoya, Japan, [3]Toyohashi Municipal Hospital, Toyohashi, Japan, [4]Nagoya Univeristy Graduate School of Medicine, Nagoya, Japan.

Background/Purpose: In the last decade, treatment with tumor necrosis factor (TNF) inhibitors has significantly improved the outcome in patients with rheumatoid arthritis (RA). Recent studies have highlighted drug immunogenicity as a mechanism behind treatment failure. Concomitant immunosupressors, such as methotrexate (MTX), can reduce the production of anti-drug anitibodies (ADA) which might reduce drug efficacy and result in drug discontinuation. We investigated the effect of concomitant use of MTX on the long-term adherence of etanercept and adalimumab.

Methods: All eligible patients were registered in the Tsurumai Biologics Communication Registry (TBCR), an RA research consortium that consists of Nagoya University Hospital and 12 affiliated institutes. As of September 2011, 2,176 RA patients treated with biologics are registered in this registry. Seven hundred ninety four RA patients previously unexposed to biological DMARDs were treated with etanercept (n = 560) or adalimumab (n = 234). Drug discontinuation rates were calculated by Kaplan-Meier method using the end-point of inefficacy or adverse events. Statistical difference between two groups was tested by Log-rank test. Statistical significance was defined as p-value < 0.05.

Results: Among the etanercept group, the discontinuation rate due to inefficacy were quite similar between the patients with concomitant MTX (n = 385) and those without (n = 175) (16.8 vs 14.8% at 3 years and 22.2 vs 24.5% at 6 years, p = 0.936, Fig. a). Conversely among the adalimumab group, the patients with concomitant MTX demonstrated significantly lower discontinuation rate due to inefficacy (13.5 vs 36.2% at 3 years, p = 0.014, Fig. c). The patients without MTX demonstrated significantly higher discontinuation rate due to adverse events both in the etanercept (p = 0.011, Fig. b) and adalimumab group (p = 0.016, Fig. d). The reason for this difference would have included the patients' background complications for which they could not take MTX therapy. Unfortunately, such information was not available in the registry data.



Conclusion: It was quite interesting that the concomitant MTX usage did not improve the discontinuation rate due to inefficacy in the patients with etanercept therapy. Production of anti-drug antibodies (ADA) reduces the biological DMARDs effect that can be attenuated by concomitant methotrexate, which reduces ADA frequency. In the case of adalimumab, some previous reports demonstrated that the long-term clinical outcome is strongly dependent on the presence or absence of anti-adalimumab antibodies. On the other hand, some report showed that anti-etanercept antibody is hardly detected. Our current data clearly support these previous data that showed less immunogenicity of etanercept. Thus, we would conclude that the drug immunogenicity should be considered especially for the patients that cannot take concomitant MTX.

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Economic Impact Of Adalimumab Treatment In Japanese Patients With Rheumatoid Arthritis: Analysis Of 24 Weeks Data From The Anouveau Study. Yoshiya Tanaka[1], Yasuhiko Shinmura[2], Ryo Nakajima[2], Takahiro Muramatsu[2], Shuichi Komatsu[2], Tadamichi Kubo[2], Aki Kuroki[2], Ataru Igarashi[3], Toshiro Tango[4] and Tsutomu Takeuchi[5]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]AbbVie GK, Tokyo, Japan, [3]The University of Tokyo, Tokyo, Japan, [4]Center for Medical Statistics, Tokyo, Japan, [5]Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: Patients with rheumatoid arthritis (RA) incur higher costs owing to missed work days and short-time disability. Although methotrexate combined with adalimumab (ADA) provides comprehensive disease control in patients with RA, its impact in aspect of economic burden is less well understood. The purpose of this study is to assess the economic benefit of ADA treatment in Japanese patients with RA.

Methods: Data were taken from the first 24 weeks of a 48-week, multicenter, prospective, single-cohort study of self-reported work productivity and activity impairment in 512 Japanese patients with RA receiving ADA. Work-related outcomes were measured using the Work Productivity and Activity Impairment questionnaire for rheumatoid arthritis (WPAI/RA), including employment status (paid worker [PW] employed for ≥35hours/week, n=160, part time worker [PTW] employed for <35hours/week, n=80, or home worker [HW] non-employed, n=272), absenteeism (percentage of work time missed due to RA), presenteeism (percentage of impairment while working due to RA),

percentage of overall work impairment (OWI) due to RA, and percentage of activity impairment (AI) due to RA. The Health Assessment Questionnaire-Disability Index (HAQ-DI), EuroQol-5 Dimensions (EQ-5D), and disease activity score based on 28 joints count erythrocyte sedimentation rate (DAS28 ESR) were used to assess clinical response. Annually productivity loss was estimated using WPAI/RA scores and basic wages in Japanese workers 2012 by the Ministry of Health, Labor and Welfare.

Results: At week 24, disease activity measures were significantly improved. There were significant improvements in presenteeism of PWs and PTWs, in OWI of PWs, and in AI of all employment status. Changes in WPAI/RA domain scores correlated strongly with measures of clinical response. The saved productivity losses due to OWI and AI through week 24 were 7,400 USD for PWs, 1,300 USD for PTWs, and 4,700 USD for HWs. Improvements 2 in DAS28 ESR score, 0.5 in HAQ-DI score, and 0.2 in EQ-5D through one year were estimated to save 10,000 USD annually from productivity loss due to OWI in PWs (1 USD = 100 JPY in 2013).

Conclusion: ADA treatment reduced indirect cost due to work impairment in Japanese RA patients in different employment status.

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Discontinuation Of Biological Therapy Due To Adverse Drug Reactions In Rheumatoid Arthritis Patients: 12 Years Follow-Up. Luis Rodriguez-Rodriguez, Leticia Leon, Zulema Rosales, Cristina Lajas, Lucía Arietti, Ana B. Rodríguez-Cambrón, Cristina Martínez-Prada, Jose María Leal, Pilar Macarrón, Gloria Candelas, Juan A. Jover and Lydia Abásolo. Hospital Clínico San Carlos, Madrid, Spain.

Background/Purpose: To describe in a cohort of rheumatoid arthritis (RA) patients followed up to 12 years, in standard clinical practice, the rate of biological agents (BAs) discontinuation due to adverse drug reactions (ADRs). Also, to analyze which factors influence the rate of severe ADRs (defined as those that required hospital admission or resulted in patient death), paying special attention on the comparison between BAs.

Methods: Observational retrospective longitudinal study, that included RA patients attending the rheumatology outpatient clinic of our center, whom started treatment with any BA [including etanercept (ETN), golimumab, certolizumab, infliximab (IFX), adalimumab (ADA), rituximab (RTX), abatacept (ABA), or tozilizumab], between January 1st, 2000, and January 1st, 2012. Clinical records were examined until withdrawal of the drug, loss of follow up, or December 18th, 2012. Survival techniques were used to estimate the incidence ratio (IR) of BA withdrawal due to ADRs, expressed per 100 patient-years with 95% confidence interval (95%CI). Cox bivariate and multivariate regression models (adjusted by age, gender and calendar time) were used to examine risk factors for BAs discontinuation due to severe.

Results: 405 patients were included, whom began 744 different courses of BA treatments, with a total follow up of 1,612 patient-years. 81% were women, with a mean [standard deviation (SD)] age at diagnosis of 52.5 (13) years and a mean (SD) elapsed time to the first BA of 5 (4.8) years. The most frequently used BAs were ADA (32%), ETN (25%), IFX (20.7%), and RTX (13.5%). There were 198 discontinuations due to ADRs, mostly due to infections (46%), mucocutaneous (14%), and infusion reactions (10%). 18% of the BAs therapies were discontinued during the first year due to ADRs, with a mean survival time of 5 years (95% CI 4.3–7.6). The IR was estimated in 12.8 (95%CI 10.7–14.1). 77 (39%) were severe ADRs, with an IR of 4.8 (95% CI 3.8–6.0). The most frequent types of severe ADRs were infections (51%) [IFX (55%), ADA (30%), RTX (7.5%) and ETN (2.5%)], cancer (13%) [IFX (30%), ADA (30%), and ETN (30%)], and congestive heart failure (9%) [IFX (58%), and RTX (42%)]. 50% were lower respiratory tract infections and 11% tuberculosis. 20% were lung and 20% were pancreatic cancers. 6 ADRs resulted in death [IFX (n=3), ADA (n=1), RTX (n=1), ABA (n=1)] with an IR of 0.4 (95% CI 0.2–0.8).

Both in the bivariate and multivariate regression analysis, age (HR: 1.04, 95%CI: 1.02–1.06), maximum rheumatoid factor (HR: 1.0001, 95%CI: 1.00006– 1.0002, p=0.002), and, compared with ETN, treatment with IFX or RTX (HR:5.7, 95%CI: 2.2–14.8, p=0.001; HR:3.3 95% CI: 1.2–9.8, p=0.02, respectively) were significantly associated to a higher risk of BAs discontinuation due to severe ADRs. Treatment with ADA did not achieve statistical signification (HR:2.4, 95%CI: 0.96–6.3, p=0.06).

Conclusion: This study describes the incidence of ADRs (50% related to infections) in RA patients taking BA in real life conditions. 39% resulted in hospital admissions and even in death, thus close monitoring is required in these patients. Within the BA more widely used in our setting, it seems that ETN generates less hospital admissions due to ADRs.

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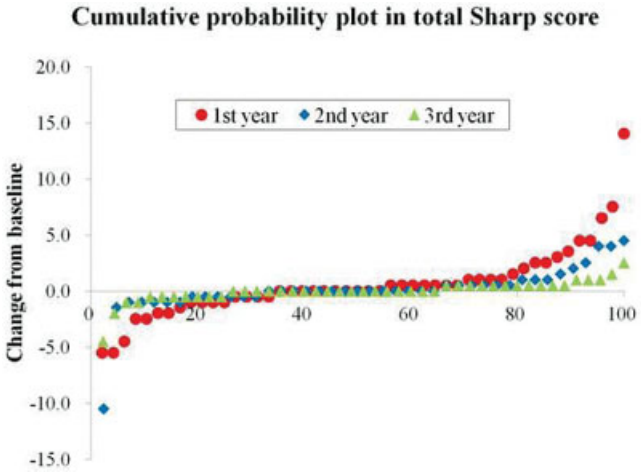
Tocilizumab Efficiently Halts Radiographic Progression In Patients With Rheumatoid Arthritis and Swollen Joint Counts Within a Year Predict Long-Term Radiographic Outcomes: Three Year Results From Michinoku Tocilizumab Study Group. Ryu Watanabe[1], Hiroshi Okuno[2], Tomonori Ishii[1], Yasuhiko Hirabayashi[3] and Hideo Harigae[1]. [1]Tohoku University, Sendai, Japan, [2]Tohoku University Graduate School of Medicine, Sendai, Japan, [3]Hikarigaoka Spellman Hospital, Sendai, Japan.

Background/Purpose: One of the important therapeutic goals in patients with rheumatoid arthritis (RA) is to halt radiographic progression. Tocilizumab (TCZ), an IL-6 receptor antibody, has been demonstrated that it efficiently improves clinical signs and inhibits structural damages in RA patients. However, it remains unknown what the predictive factor is for long-term radiographic outcomes in RA patients receiving TCZ. The objectives of this study are to assess the structural remission rate and to clarify the predictive factor for long-term radiographic outcomes in patients receiving TCZ under daily clinical practice.

Methods: Michinoku Tocilizumab Study Group comprised 34 institutions in the Northeast region of Japan. RA patients who received 8 mg/kg TCZ every 4 weeks were registered from June 2008 to December 2010 [1]. The clinical and radiographic outcomes were evaluated in 130 patients at 1 year, including 50 patients who received TCZ for 3 years.

Results: Baseline characteristics of patients who received TCZ for 1 year and 3 years, respectively, were as follows: mean age of 59.7/ 58.0 years, the mean disease duration of 10.8/ 10.9 years, the mean DAS28-ESR of 4.8/ 4.8, and 37.7/ 36.0% of patients were taking MTX. Mean change from baseline in van der Heijde-modified total Sharp score (mTSS) was 0.79 at 1 year, and the structural remission rate (ΔmTSS$\leq$0.5) was 69.2%. In the 50 patients who received TCZ for 3 years, the structural remission rate for 3 years (ΔmTSS$\leq$1.5) was 66%. Radiographic benefit gradually increased as the structural remission rate at the first, second, third year was 68.6%/78.6%/88.9%, respectively (Figure 1). At baseline, not tender joint counts (p=0.58), but swollen joint counts (SJC, p=0.04) predicted the structural remission at 3 years. Receiver Operating Characteristic (ROC) analysis showed that the cut-off value of SJC at baseline for structural remission at 3 years was 5. Even when SJC at baseline were above 5, SJC at 9 months (p=0.02) and at 12 months (p=0.004) were good predictors for structural remission at 3 years.



Conclusion: TCZ continuously inhibited radiographic progression in RA patients. SJC within a year could predict long-term radiographic outcomes irrespective of baseline disease activity in patients receiving TCZ.

Reference:

[1] Hirabayashi Y, Ishii T, and the Michinoku Tocilizumab Study Group. The DAS28-ESR cutoff value necessary to achieve remission under the new Boolean-based remission criteria in patients receiving tocilizumab. Clin Rheumatol. DOI 10.1007/s10067-012-2103-4.

Disclosure: R. Watanabe, None; **H. Okuno**, None; **T. Ishii**, None; **Y. Hirabayashi**, None; **H. Harigae**, None.

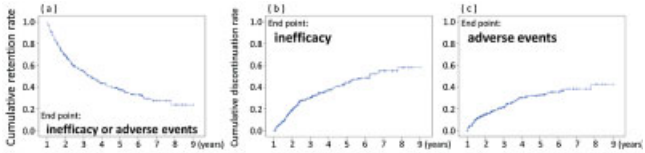
2369

Long-Term Outcome Of Infliximab Therapy In Rheumatoid Arthritis Patients: Results From Japanese Multicenter Registry System. Nobunori Takahashi[1], Toshihisa Kojima[1], Atsushi Kaneko[2], Yuji Hirano[3] and Naoki Ishiguro[4]. [1]Nagoya University Hospital, Nagoya, Japan, [2]Nagoya Medical Center, Nagoya, Japan, [3]Toyohashi Municipal Hospital, Toyohashi, Japan, [4]Nagoya Univeristy Graduate School of Medicine, Nagoya, Japan.

Background/Purpose: After demonstration of effectiveness of anti-tumor necrosis factor (TNF) agents in patients with rheumatoid arthritis (RA), their use has become common practice in treating patients not responding to classical disease modifying anti-rheumatic drugs (DMARDs). In this paper, we studied the long-term clinical outcome of infliximab, which is first biological DMARD for RA in Japan, to demonstrate the 'the real-world' data using our registry system. To accumulate the data from daily clinical practice is quite important to improve the treatment strategy for RA.

Methods: All eligible patients were registered in the Tsurumai Biologics Communication Registry (TBCR), an RA research consortium that consists of Nagoya University Hospital and 12 affiliated institutes. As of September 2011, 2,176 RA patients treated with biologics are registered in this registry system. Four hundred forty seven RA patients previously unexposed to biological DMARDs were treated with infliximab (IFX). Drug retention rates were calculated by Kaplan-Meier method using endpoint of inefficacy or adverse events.

Results: As baseline characteristics, mean age was 56.6 years, disease duration was 14.9 years, proportion of patients with methotrexate was 99.6%, MTX dose was 7.2 mg/week, proportion of patients with prednisolone (PSL) was 76.1%, PSL dose was 5.2 mg, serum C-reactive protein was 3.8 mg/dL, and DAS28 was 5.7. IFX retention rate was 67.5% at 1 year, 31.0% at 5 years, and 22.5% at 8 years (Fig. a). IFX discontinuation rate due to inefficacy was 58.1% (Fig. b). Primary inefficacy was seen in 6.9% and secondary inefficacy was seen in 27.1% of patients. Discontinuation rate due to adverse events was 42.7% at 8 years (Fig. c). Most frequent adverse events resulted in IFX discontinuation was pulmonary complication (9.8%) including interstitial pneumonia (IP, 2.5%), bacterial pneumonia (4.3%), pulmonary tuberculosis (1.1%), pneumocystis pneumonia (0.7%), and organizing pneumonia (0.4%). The second most frequent was infusion reaction seen in 7.8%. The incidence of malignant neoplasm was seen in 1.8%.



Conclusion: We observed quite high discontinuation rate due to secondary inefficacy. This is probably dependent on the relatively low MTX dose, because of the Japanese regulation of public health insurance coverage. We are convinced of improved discontinuation rate if only with higher dose of concomitant MTX, which would reduce the production of anti-IFX antibodies resulting in secondary inefficacy and infusion reaction. It was the important data that the most frequent adverse events resulting in discontinuation was pulmonary complications. Putting all our results together, we would suggest that the most suitable patients for IFX treatment, expecting long-tern adherence, would be ones using sufficient dosage of concomitant MTX treatment and do not have baseline comorbidity of pulmonary diseases.

Disclosure: N. Takahashi, None; **T. Kojima**, None; **A. Kaneko**, None; **Y. Hirano**, None; **N. Ishiguro**, Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, BMS, Eisai, Janssen, Kaken and Pfizer, 2, Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, BMS, Eisai, Janssen, Kaken, Pfizer, Taisho-Toyama and Otsuka, 8.

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The Effectiveness Of Biological Agents Concomitant With Tacrolimus In Rheumatoid Arthritis. Kenya Terabe[1], Toshihisa Kojima[2], Nobunori Takahashi[2], Koji Funahashi[2], Atsushi Kaneko[3], Daihei Kida[3], Yuichiro Yabe[4], Yuji Hirano[5], Masatoshi Hayashi[6] and Naoki Ishiguro[1]. [1]Nagoya Univeristy Graduate School of Medicine, Nagoya, Japan, [2]Nagoya University Hospital, Nagoya, Japan, [3]Nagoya Medical Center, Nagoya, Japan, [4]Tokyo Kosei Nenkin Hospital, Tokyo, Japan, [5]Toyohashi Municipal Hospital, Toyohashi, Japan, [6]Nagano Red Cross Hospital, Nagano, Japan.

Background/Purpose: In Japan, oral tacrolimus (TAC) was approved for the treatment of RA in 2005 and the improvement of symptoms thorough the use concomitant with disease modifying antirheumatic drugs (DMARDs), including MTX has been reported. On the other hand, the efficacy and tolerance of biological agents therapy concomitant with TAC are unknown. The objective of this study was to investigate the efficacy and tolerance of biological agents concomitant with TAC in Japanese patients with RA using retention rate analysis.

Methods: Total patients (n=1541) who underwent 4 biological agents (etanercept: ETN, adalimumab: ADA, tocilizumab: TCZ, abatacept: ABT) treatment between 2003 and 2011 at Nagoya University Hospital and 12 other institutes (Tsurumai Biologics Communication Study Group) were enrolled. In each biologics analysis, patients were divided into three groups: (1) concomitant only MTX (MTX group) (2) concomitant only TAC (TAC group) (3) monotherary (mono group). In TAC or MTX group, these drugs were only ones which concomitant with biologics. Patients who underwent biologics combined with other DMARDs were excluded. Kaplan-Meier analysis was used to estimate retention rate in each biologics group. To estimate the tolerance of concomitant biologics with TAC, cumulative hazard function was performed in each biologics group.

Results: In total 1541 patients, 91 patients (5.9%) administered each biologics concomitant with TAC (ETN: n=38, 101.0 patient-years (PY) ADA: n=13, 12.8 PY TCZ: n=24, 40.8 PY ABT: n=17, 16.2 PY). Average dosages of TAC at starting were ETN: 2.1±0.9mg ABT: 2.4±0.9mg. With comparison of retention rate in each biologics concomitant with TAC, ADA was significantly lower rate than other 3 biologics (fig1). Each biologics agent's number was ETN (MTX: n=641, 1473.0 PY mono: n=194, 469.1PY), ADA (MTX: n=641, 1473.0 PY mono: n=34, 35.2PY), TCZ (MTX: n=181, 247.5 PY mono: n=85, 120.0PY), ABT (MTX: n=85, 89.6 PY mono: n=38, 35.1PY). In only ETN analysis, the retention rate of TAC group was higher than mono group (fig2). In ADA, that of MTX group was higher than TAC and mono group. There was no difference of comparison that of other 2 biologics analysis. Comparison of incidence of adverse event between TAC and mono group using cumulative hazard function in each biologics analysis, in only ETN analysis incident rate of mono group was higher than TAC group and there was no difference in other 3 biologics analysis.

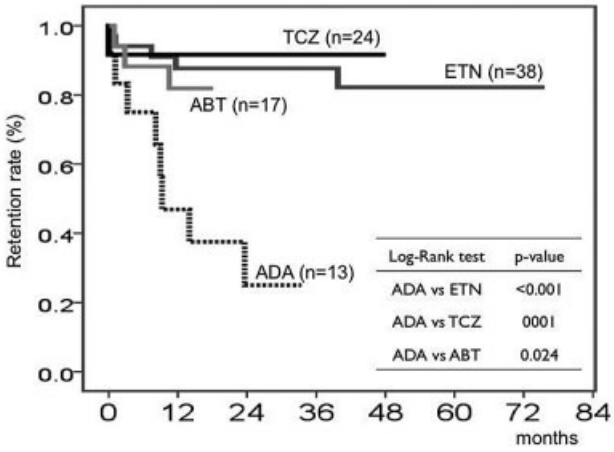

fig1: the retention rate of each biologics concomitant withTAC tretment (n=91)

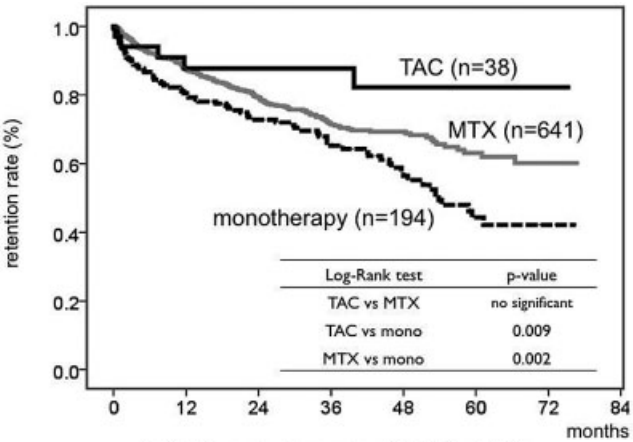

fig2: the retention rate of ETN (n=873)

Conclusion: We suspected that combination therapy ETN and TAC are subsequent options for treatment to RA patient, especially in whom MTX cannot be administration.

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2371

Is a Single Variable, The Swollen Joint Count, Valid As An Outcome Measure Separate From Being In An Index Measure? An Analysis From The Prospective, Biologic Treatment Registry Across Canada. J. Carter Thorne[1], Boulos Haraoui[2], William G. Bensen[3], Algis Jovaisas[4], Jude F. Rodrigues[5], Denis Choquette[2], Alice V. Klinkhoff[6], Emmanouil Rampakakis[7], John S. Sampalis[7], Francois Nantel[8], Allen J. Lehman[8], May Shawi[8] and Susan M. Otawa[8]. [1]Southlake Regional Health Centre, Newmarket, ON, [2]Institut de Rhumatologie de Montréal, Montreal, QC, [3]St. Joseph's Hospital and McMaster University, Hamilton, ON, [4]University of Ottawa, Ottawa, ON, [5]Rheumatology, Windsor, ON, [6]The Mary Pack Arthritis Ctr, Vancouver, BC, [7]McGill University, Montreal, QC, [8]Janssen Canada Inc, Toronto, ON.

Background/Purpose: The importance of joint counts as measures of synovitis is reflected in their prominence in all major clinical composite indices, the Disease Activity Score (DAS), the Clinical Disease Activity Index (CDAI) and the Simplified Disease Activity Index (SDAI). The twenty eight swollen joint count (SJC28) contributes numerically to approximately 16% of DAS28, 37% of CDAI and 33% of SDAI. The aim of this analysis was to examine whether SJC28 could be used as a stand-alone measure of disease remission.

Methods: Biologic Treatment Registry Across Canada (BioTRAC) is an ongoing, prospective registry of patients initiating treatment for RA, AS, or PsA with infliximab or golimumab as first biologics or after having been treated with a biologic for less than six months. In this analysis, data from RA patients treated with infliximab who were enrolled between January 2002 and June 2011 were used. Agreement between SJC28≤1 and remission or low disease activity as defined by the DAS28, CDAI, and SDAI criteria was assessed with the sensitivity, specificity, as well as the positive (PPV) and negative (NPV) predictive value.

Results: A total of 838 RA patients with mean (SD) age of 55.6 (13.5) years and mean (SD) duration since diagnosis of 10.5 (19.8) years were included in this analysis, providing information from 4,582 assessments. Using DAS28, CDAI, SDAI, and Boolean remission as reference standards, SJC28 sensitivity was 91.0%, 99.1%, 98.3%, and 100.0%, respectively. In addition, SJC28 correctly classified non-remission (NPV of 94.9%, 99.8%, 99.5%, and 100.0% for DAS28, CDAI, SDAI, and Boolean definition, respectively). However, specificity was only moderate (DAS28: 72.6%, CDAI: 64.0%, SDAI: 63.0%, Boolean: 61.8%), and SJC28 yielded a considerable proportion of false positives as indicated by the low PPV observed (DAS28: 58.9%, CDAI: 32.1%, SDAI: 33.0%, Boolean: 29.3%). When looking at low disease activity, SJC28≤1 showed lower sensitivity (DAS28: 83.2%, CDAI: 83.8%, SDAI: 85.0%) and NPV (DAS28: 85.8%, CDAI: 86.9%, SDAI: 87.5%) but higher specificity (DAS28: 83.2%, CDAI: 85.2%, SDAI: 84.2%) and PPV (DAS28: 80.1%, CDAI: 82.2%, SDAI: 81.1%).

Conclusion: The results of this analysis have shown that SJC28≤1 has high discriminatory power for low disease activity and moderate discriminatory power for remission as defined by the DAS28, CDAI and SDAI criteria. The more rigorous ACR/EULAR Boolean remission criteria were associated with increased sensitivity and NPV but decreased specificity and PPV.

Disclosure: J. C. Thorne, None; **B. Haraoui**, None; **W. G. Bensen**, None; **A. Jovaisas**, Janssen Pharmaceutica Product, L.P, 5; **J. F. Rodrigues**, None; **D. Choquette**, None; **A. V. Klinkhoff**, None; **E. Rampakakis**, None; **J. S. Sampalis**, None; **F. Nantel**, None; **A. J. Lehman**, Janssen Canada, 3; **M. Shawi**, Janssen Canada, 3; **S. M. Otawa**, Janssen Canada, 3.

2372

Comparison Of Proposed Biosimilar PF-05280586 With Rituximab: Nonclinical and Phase I Clinical Assessments. Dolca Thomas[1], Jean-Claude P. Becker[1] and Chee-Keng Ng[2]. [1]Pfizer Inc., New York, NY, [2]Pfizer Inc., Andover, MA.

Background/Purpose: PF-05280586 is being developed as a potential biosimilar to rituximab, a monoclonal antibody (mAb) approved for the treatment of moderate-to-severe rheumatoid arthritis and lymphomas. The purpose is to present data demonstrating the structural and functional similarity of PF-05280586 to rituximab in nonclinical studies and pharmacokinetic (PK) and pharmacodynamic (PD) similarity in the first clinical study that has completed recruitment and dosing.

Methods: Nonclinical Studies: Structural similarity of PF-05280586 and rituximab-EU (MabThera®) was determined by side-by-side comparisons of peptide maps. In vitro functional similarity was determined with complement-dependent cytotoxicity (CDC) and antibody-dependent cell cytotoxicity (ADCC) assays using the Ramos B lymphoblastoid cell line as the target. Similarity of interaction with receptors was determined using SPR system.

Clinical Trial: A phase1/2 clinical trial (NCT 01526057) in patients with active rheumatoid arthritis (RA) is in progress to determine PK and PD similarity between PF-05280586 and the two marketed formulations of rituximab from the US (rituximab-US; Rituxan®) and the EU (rituximab-EU; MabThera®).

Results: Nonclinical Studies: The peptide map of PF-05280586 was similar to that of rituximab-EU indicating amino acid identity between the two mAbs. The dose-response curves of the 2 mAbs in the CDC and ADCC assays were essentially superimposable indicating similar in vitro function. Similarly, the binding to FcγRIIIa (158V) of PF-05280586 coincided with that of rituximab-EU, indicating similar mechanisms of actions of the two mAbs.

Clinical Trial: A total of 220 patients with active RA have been randomized into 3 arms and dosed. Monitoring for safety by an independent committee has shown no safety signals. The anticipated trial completion is Q42013.

Conclusion: PF-05280586 showed in vitro structural and functional similarity to rituximab-EU. PF-05280586 and rituximab appear to be well tolerated in nonclinical and clinical studies. These results support the development of PF-05280586 as a proposed biosimilar to rituximab.

Disclosure: D. Thomas, Pfizer Inc, 1, Pfizer Inc, 3; **J. C. P. Becker**, Pfizer Inc, 1, Pfizer Inc., 3; **C. K. Ng**, Pfizer Inc, 1, Pfizer Inc, 3.

2373

UK Clinical Practice Use Of Biologics In Monotherapy For The Treatment Of Patients With Rheumatoid Arthritis. Andrew J. Ostor[1], G. Chelliah[2], Theodoros Dimitroulas[3], Margaret-Mary Gordon[4], Nicola Hewson[5], JA Mitchell[5], Senam Beckley-Kartey[6], Hok Pang[6] and Jose Saraiva-Ribeiro[6]. [1]Department of Rheumatology, Addenbrookes Hospital, Cambridge, United Kingdom, [2]Clinical Trials Unit, Wrightington Hospital, Wigan, United Kingdom, [3]Department of Rheumatology, Research and Development, Dudley Group NHS Foundation Trust, Russell's Hall Hospital, Dudley, United Kingdom, [4]Rheumatology Department, Gartnavel General Hospital, Glasgow, United Kingdom, [5]Syne Qua Non Ltd., Diss, United Kingdom, [6]Medical Department, Roche, Welwyn Garden City, United Kingdom.

Background/Purpose: NICE guidelines recommend that patients with severe active rheumatoid arthritis (RA) be treated with a biologic disease-modifying anti-rheumatic drug as monotherapy (bDMARD mono) if they respond inadequately to 2 traditional DMARDs and are intolerant to methotrexate (MTX). Registry and healthcare utilisation data have shown that around one-third of RA patients receive their biologic treatment as monotherapy. We intended to better understand the current management of RA patients with biologics in monotherapy, particularly why patients receive monotherapy and how effective this is in daily practice.

Methods: This UK wide chart review was conducted in 26 Rheumatology Hospitals between September 2012 and May 2013 and data from 309 RA patients, who had been prescribed a bDMARD mono, were collected retrospectively. We present data from an interim analysis of 150 patients.

Results: Mean age was 62.4 yrs. and mean duration of disease was 16.3 yrs. The majority of patients were female (109). 102 (74.4%) patients were Rheumatoid factor positive (n=137) and 34 (36.6%) anti-CCP positive (n=93). With regards to past RA treatment (prior to switch to monotherapy, n=61), the most frequently used bDMARDs mono (at any time prior to switch) were etanercept (ETN; 19.3%),adalimumab (ADA; 14%), certolizumab pegol (CZP, 7.3%), rituximab (RTX, 4.7%) and tocilizumab (TCZ, 2.7%). 55 (36.7%) patients had used two or more bDMARD mono. The most frequently used traditional DMARDs (n=146) were methotrexate (MTX; 92%), sulfasalazine (74.7%) and hydroxychloroquine (42.7%).With regards to current RA treatment (all patients receiving bDMARD mono), the most frequently used bDMARDs were ETN (42.7%), ADA (26%), TCZ (10.7%), RTX (9.3%) and CZP (8%). The main reason for prescribing bDMARD mono (n=150) was unknown (88%, assumed clinician decision). Others were patient preference (6.7%) and contra-indication (7.3%). Nearly a quarter of patients were on non-NICE approved monotherapy drug and only 10.7% were in DAS28 ESR remission.

Conclusion: Registry and healthcare utilisation data have shown that around one-third of RA patients receive their biologic treatment as monotherapy. The results of this audit draws attention to a patient population where treatment outcomes with bDMARD monotherapy are still not optimal (only 10.7% were in DAS28 ESR remission). 76.7% of the patients were treated with the above NICE approved TNF inhibitor. 55 (36.7%) patients had used two or more bDMARD monotherapies indicating that there are a significant number of patients where combination therapy with traditional DMARDs is not an option. As remission is the treatment goal and only 10.7% of patients were in remission there is an unmet medical need and therefore alternative treatment options should be explored to ensure better treatment outcomes for patients with this debilitating disease.

Disclosure: A. J. Ostor, None; **G. Chelliah**, Roche Pharmaceuticals, 2; **T. Dimitroulas**, Roche Pharmaceuticals, 2; **M. M. Gordon**, Roche Pharmaceuticals, 2; **N. Hewson**, Roche Pharmaceuticals, 5; **J. Mitchell**, Roche Pharmaceuticals, 5; **S. Beckley-Kartey**, Roche Pharmaceuticals, 3; **H. Pang**, Roche Pharmaceuticals, 3; **J. Saraiva-Ribeiro**, Roche Pharmaceuticals, 3.

2374

Pharmacodynamics Of a Novel Jak1 Selective Inhibitor In Rat Arthritis and Anemia Models and In Healthy Human Subjects. Jeffrey Voss[1], Candace Graff[2], Annette Schwartz[2], Deborah Hyland[2], Maria Argiriadi[2], Heidi Camp[3], Lori Dowding[2], Michael Friedman[2], Kristine Frank[3], Jonathon George[2], Eric Goedken[2], Gloria Lo Schiavo[2], Michael Morytko[2], Robert o'Brien[2], Robert Padley[3], Matthew Rosebraugh[3], Michael Rozema[3], Kent Stewart[3], Grier Wallace[2], Neil Wishart[2], Anwar Murtaza[4] and Lisa Olson[1]. [1]AbbVie Pharmaceuticals, Worcester, MA, [2]Abbvie Pharmaceuticals, worcester, MA, [3]abbvie pharmaceuticals, north chicago, IL, [4]Broad Institute, Cambridge, MA.

Background/Purpose: Anti-cytokine therapies have become the mainstay of treatment for rheumatoid arthritis (RA) disease symptoms and can arrest disease progression. Despite numerous treatment options there are still many RA patients who fail to experience substantial decreases in disease activity. Recently, Jak kinase blockade was shown clinically to be effective in managing disease and in some cases achieving remission. However, these first generation Jak inhibitors have failed to meet expectations due to dose-limiting tolerability and safety issues. ABT-494 is a second generation Jak kinase inhibitor with high selectivity for Jak1 thereby minimizing the potential for side effects related to Jak2 and Jak3 inhibition. Here we describe preclinical and early clinical data that suggest ABT-494 has potential to address some of the current unmet medical needs of RA patients.

Methods: ABT-494 was engineered for increased selectivity for Jak1 using structural predictions that indicated the potential for differential binding interactions outside the ATP-binding active site of Jak1 but not Jak2. The efficacy and selectivity of ABT-494 were tested in a battery of relevant cellular *and in vivo* pharmacology assays including bone marrow colony formation, adjuvant induced arthritis (AIA), erythropoietin induced reticulocyte deployment and NK/NKT cell suppression. The potency of ABT-494 in a variety of complementary pharmacodynamic assays was also assessed at multiple dosages in healthy human subjects administered orally for 14 days.

Results: ABT-494 demonstrates approximately 74 fold selectivity for Jak1 over Jak2 in cellular assays dependent on specific, relevant cytokines. ABT-494 is a potent inhibitor of inflammation and bone loss in rat AIA and, compared to Tofacitinib, spares relevant essential physiological processes such as erythropoietin signaling and peripheral NK cell counts at similarly efficacious doses in rats. When dosed orally for 14 days in healthy human subjects ABT-494 did not decrease reticulocyte or NK cell counts at predicted efficacious doses consistent with its pharmacodynamic properties in rats.

Conclusion: ABT-494 is a Jak1-selective inhibitor that demonstrates efficacy in rat arthritis models. Preliminary evidence suggests that pharmacodynamic properties of ABT-494 are consistent between those observed in rodent models and in healthy human subjects. Taken together, these encouraging observations support further testing of ABT-494 in RA patients in Phase II randomized placebo controlled trials and indicate it may have increased potential to address patient needs over existing agents.

The design, study, conduct and financial support for the clinical trial and research was provided by AbbVie. AbbVie participated in the interpretation of data, review and approval of this disclosure. AM was an employee of AbbVie at the time of data collection and analysis.

Disclosure: J. Voss, Abbott Immunology Pharmaceuticals, 3; **C. Graff**, Abbott Immunology Pharmaceuticals, 3; **A. Schwartz**, Abbott Immunology Pharmaceuticals, 3; **D. Hyland**, Abbott Immunology Pharmaceuticals, 3; **M. Argiriadi**, Abbott Immunology Pharmaceuticals, 3; **H. Camp**, Abbott Immunology Pharmaceuticals, 3; **L. Dowding**, Abbott Immunology Pharmaceuticals, 3; **M. Friedman**, Abbott Immunology Pharmaceuticals, 3; **K. Frank**, Abbott Immunology Pharmaceuticals, 3; **J. George**, Abbott Immunology Pharmaceuticals, 3; **E. Goedken**, Abbott Immunology Pharmaceuticals, 3; **G. Lo Schiavo**, Abbott Immunology Pharmaceuticals, 3; **M. Morytko**, Abbott Immunology Pharmaceuticals, 3; **R. o'Brien**, Abbott Immunology Pharmaceuticals, 3; **R. Padley**, Abbott Immunology Pharmaceuticals, 3; **M. Rosebraugh**, Abbott Immunology Pharmaceuticals, 3; **M. Rozema**, Abbott Immunology Pharmaceuticals, 3; **K. Stewart**, Abbott Immunology Pharmaceuticals, 3; **G. Wallace**, Abbott Immunology Pharmaceuticals, 3; **N. Wishart**, Abbott Immunology Pharmaceuticals, 3; **A. Murtaza**, Abbott Immunology Pharmaceuticals, 1; **L. Olson**, Abbott Immunology Pharmaceuticals, 3.

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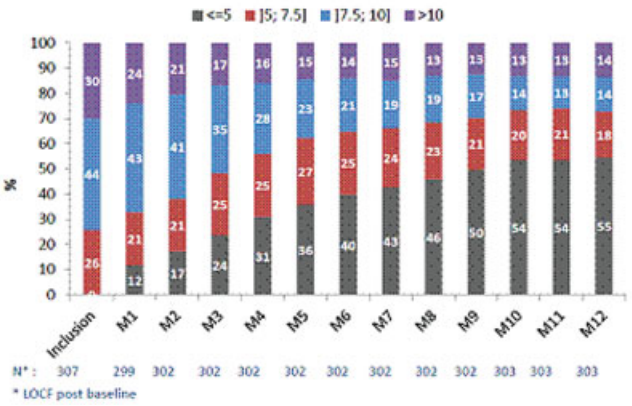
Tocilizumab Glucocorticoids Sparing Effect: The Spare-1 Study. Alain Saraux[1], Stephanie Rouanet[2], Rene-Marc Flipo[3], Jean-Cyril Poncet[4], Patrice Fardellone[5], Pascal Hilliquin[6], Isabelle Idier[7] and Alain G. Cantagrel[8]. [1]CHU Brest et Université Bretagne Occidentale, Brest, France, [2]Roche, Boulogne-Billancourt, France, [3]Hopital R Salengro CHRU Lille, Lille, France, [4]General Hospital Gap, Gap, France, [5]Hôpital Nord, C.H.U. d'Amiens, Amiens, France, [6]General Hospital Corbeil, Corbeil-Essonnes, France, [7]Chugai Pharma France, La Defense, France, [8]Purpan University Hospital Toulouse, Toulouse Cedex 9, France.

Background/Purpose: Although glucocorticoids (GCs) may be appropriate in rheumatoid arthritis (RA), there is general agreement that GCs sparing is desirable. The safety of GCs is duration and dose dependent and the risk has been demonstrated for a dose ≥ 5 mg/day. Tocilizumab (TCZ) is an effective biologic therapy in RA, even without concomitant methotrexate. The aim of this study is to describe the GCs sparing effect in patients treated with TCZ in real life clinical setting.

Methods: Multicenter, prospective, non-interventional 12-month study. Patients had active RA, were treated with more than 5 mg daily of prednisone for at least 3 months and initiated TCZ. No instructions were given regarding TCZ or GCs doses. Patient's characteristics were collected at baseline. After TCZ initiation, monthly disease activity components and RA treatments doses were collected. HAQ-DI and RAID were completed every 6 months. Primary endpoint: proportion of patients treated by 5mg/day or less of prednisone at M12 without intensification of synthetic DMARDs. Analysis: patients fulfilling inclusion/non-inclusion criteria and with at least one TCZ infusion. For primary endpoint, patients with missing GCs dose at M12 or with missing data on DMARDs intensification were considered as "non-responders". Last Observation Carried Forward (LOCF) method was used for missing cortisone dose value.

Results: 321 patients were selected and 307 analyzed. Baseline characteristics were: mean age 57±14 years, 249 females (78%), disease duration 10±9 years, RF or anti-CCP positive: 249 (82%); DAS 28-ESR: 5.1±1.3; CDAI: 27±12; SDAI: 29±13; HAQ: 1.6±0.7; RAID: 6.2±2.0; 216 (71%) previously treated by biologic DMARD. TCZ was initiated as monotherapy in 116 (38%) patients. At TCZ initiation, 92 (30%) patients received more than 10 mg of prednisone daily, 136 (44%) 7.5 to 10 mg, 79 (26%) 5 to 7.5 mg with a mean dose of 12±7 mg/day. At M12, 185 (66%) patients completed the study. 105 (34%) patients prematurely withdrew for: adverse event (AE) (n=38), TCZ discontinuation (n=47), lost-to-follow-up/move/refusal to continue the study (n=19). One 82-year old patient died after osteoporotic fracture. At M12, 124 patients (40%, 95%CI [35%; 46%]) received 5 mg or less of prednisone/day without DMARD intensification and 20% have stopped GCs. 33 % were in DAS28 remission and 42% had low disease activity. Mean DAS 28-ESR, CDAI and SDAI were 2.3±1.2, 9.3±8.4 and 9.7±8.5 respectively. At M12, 14% received prednisone daily dose>10 mg, 14% 7.5 to 10 mg, 18% 5 to 7.5 mg and 55% received 5 mg or less (Fig.1). No new safety signal was reported. 211 (67%) patients had at least one AE, 44 (14%) had at least one serious AE.

Fig.1.Evolution of prednisone daily dose (mg/day)



Conclusion: This study is the first large prospective study evaluating TCZ GCs sparing effect in RA in real life. 40% of patients were able to decrease their prednisone dose to 5 mg or below at 12 months without increasing disease activity.

Disclosure: A. Saraux, Roche Pharmaceuticals, 2, Chugai Pharma, 5, Merck Sharp Dohme-Chibret, 5, Bristol-Myers Squibb, 5, Abbvie, 5, UCB Pharma, 5; **S. Rouanet**, Roche Pharmaceuticals, 3; **R. M. Flipo**, Roche Pharmaceuticals, 5, Chugai Pharma, 5, Merck Sharp & Dohme-Chibret, 5, Abbvie, 5, UCB Pharma, 5; **J. C. Poncet**, Roche Pharmaceuticals, 2, Chugai Pharma, 2; **P. Fardellone**, Roche Pharmaceuticals, 2, Chugai Pharma, 2; **P. Hilliquin**, Roche Pharmaceuticals, 5, Chugai Pharma, 5, Bristol-Myers Squibb, 5, Merck Sharp & Dohme-Chibret, 5, UCB Pharma, 5, Pfizer Inc, 5, Expanscience, 5; **I. Idier**, Chugai, 3; **A. G. Cantagrel**, Roche Pharmaceuticals, 5, Chugai Pharma, 5, Merck Sharp & Dohme-Chibret, 5, Bristol-Myers Squibb, 5, Abbvie, 5, UCB Pharma, 5.

2376

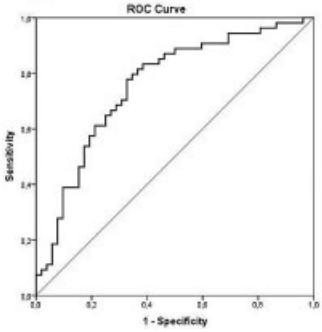
A Novel and Effective Prediction Model Of Response To Rituximab In Rheumatoid Arthritis. Alper M. van Sijl, Michel W.P. Tsang-A-Sjoe, Hennie G. Raterman, Michael T. Nurmohamed and Alexandre E. Voskuyl. VU University Medical Center, Amsterdam, Netherlands.

Background/Purpose: For patients with rheumatoid arthritis (RA) who are refractory to tumor necrosis factor (TNF)-inhibitors, it is still not clear which determinants are associated with response when switching to rituximab (RTX). Prior studies have shown anti-CCP positivity and a lower number of previously-failed TNF inhibitors to be associated with good-to-moderate response. We developed a prediction model for response to rituximab with widely available clinical and laboratory parameters.

Methods: RTX treated RA patients (n=115) were assessed prospectively for the following variables at baseline: demographic and disease characteristics, number of previous biologicals, co-morbidities, basic laboratory data, rheumatoid factor levels, anti-CCP levels and immunoglobulin levels (IgA, IgM and IgG). Clinical response was determined at 6 months after RTX initiation, using the European League Against Rheumatism (EULAR) response criteria for RA. Variables with $p < 0.10$ in univariate analyses were selected as candidate variables and entered into a forward and backward logistic regression analyses. A prediction model was constructed using backward logistic regression and an area under the curve (AUC) was calculated for the new prediction model.

Results: Mean disease activity score 28 (DAS28) was 5.34 at baseline and 4.44 at 6 months ($p<0.001$). A good-to-moderate response was achieved in 57 patients (49.6%). 101 patients (87.8%) used at least 1 biological prior to RTX treatment. RTX was re-administered in 70.9% of patients. The prediction model (see figure) consisted of age (in years), number of swollen joints, hydroxychloroquine use at baseline, steroid use at baseline and IgM level at baseline. The AUC (95% confidence interval) was 0.756 (0.663–0.850). When only using clinical variables (excluding IgM levels), the AUC was 0.714 (0.621–0.808).

A



B

	No response	Moderate response
Age, in years	58.6 ± 12.1	54.3 ± 13.8
Current use of HCQ, %	10	23
Current use of steroids, %	69	53
Swollen joint count, n	7 (4-11)	9 (5-14)
IgM level, gram/L	1.3 ± 0.8	1.8 ± 1.6

Results presented as mean ± standard deviation, median (interquartile range) or percentages, when appropriate

	Odds ratio (95%-Confidence Interval)
Age, in years	0.98 (0.95-1.00) *
Current use of HCQ, %	0.39 (0.14-1.11) *
Current use of steroids, %	2.00 (0.93-4.28) *
Swollen joint count, n	1.11 (1.03-1.20) *
IgM level, gram/L	1.44 (0.96-2.16) *

* p < 0.10 for associations between clinical determinants and EULAR response

Figure. Area Under the Receiver Operating Characteristic (AUROC) of a predictive model of EULAR response at 6 months after RTX treatment (A) and the clinical determinants comprising the model (B)

Conclusion: We developed a prediction model for response to rituximab with simple clinical and laboratory parameters. This model is easy to use and accurate in the prediction of response to treatment. Further validation of this model could make the implementation of this model cost-effective and patient friendly.

Disclosure: A. M. van Sijl, None; **M. W. P. Tsang-A-Sjoe**, None; **H. G. Raterman**, None; **M. T. Nurmohamed**, None; **A. E. Voskuyl**, None.

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Biomarkers Associated With Rheumatoid Arthritis Disease Activity Including Joint Damage Correlate With Changes In Clinical Response In Subjects Treated With Mavrilimumab At Doses Above 10 Mg. Wendy White[1], Patricia Ryan[1], Xiang Guo[1], Dominic Sinibaldi[1], Gopi Ranganna[2], Alex Godwood[3], Didier Saurigny[3], David Close[3], Steve Eck[1], Dee Wilkins[4], Lorin Roskos[4], Matthew A. Sleeman[2], Wanying Li[5], Guy Cavet[5] and Nadine A. Defranoux[5]. [1]MedImmune, LLC, Gaithersburg, MD, [2]MedImmune, LLC, Cambridge, United Kingdom, [3]MedImmune, Ltd, Cambridge, United Kingdom, [4]MedImmune, Gaithersburg, MD, [5]Crescendo Bioscience Inc., South San Francisco, CA.

Background/Purpose: GM-CSF plays a central role in the pathogenesis of rheumatoid arthritis (RA) through effects on macrophages and neutrophils. Mavrilimumab (CAM-3001) is a human monoclonal antibody targeting the alpha subunit of GM-CSF receptor. Marvrilimumab was recently evaluated in RA subjects in a phase 2a study (EARTH). Results reported from the European (EU) cohort demonstrated that mavrilimumab may provide clinical benefit to patients with moderate to severe RA (Burmester GR, et al. ARD 2012). Here, we describe final data from EARTH comparing results in the EU

and Japanese (JA) cohorts. Biomarker (BM) assessments were also performed to elucidate mechanistic aspects of mavrilimumab.

Methods: Mavrilimumab (10, 30, 50 or 100 mg) or placebo was administered SC every other week to subjects with moderate/severe RA (DAS28 > 3.2) on stable methotrexate for 12 weeks followed by a 12 week drug free follow up period. A multi-biomarker disease activity (MBDA) score was calculated using the validated Vectra ®DA algorithm and used to track the effect of the drug on disease activity over time. An additional multi-BM-based algorithm (MBSD) was used to assess the impact of mavrilimumab on markers known to be associated with progressive joint damage. The relative ability of different mavrilimumab doses, over time, to saturate GM-CSF receptors in whole blood was examined by flow cytometry using receptor occupancy assay (ROA) in the EU cohorts.

Results: In the EARTH study, mavrilimumab demonstrated good clinical activity with generally similar responses in the EU and JA cohorts. In the overall population, the primary endpoint (DAS28-CRP reduction ≥1.2 at Week 12) was met. Improvements were seen as early as week 2 and persisted through the 12 week follow up especially in the 100 mg dose group. The MBDA score decreased significantly as early as day 8 ($p<0.05$) and remained suppressed during the entire treatment period in cohorts from both EU and JA. Additional samples from the 100 mg EU cohort showed that suppression of the MBDA was maintained for a minimum of 4 weeks after the last dose. Individual components of the MBDA score, as well as additional BMs in the EU cohort showed that CRP, SAA, IL-6, IL-2RA and MDC were significantly decreased on days 8, 15, 88 and 113 in the 100 mg cohort compared to placebo. Lesser or no changes were observed with the 10 mg cohort. There was an early and sustained dose-related inhibition of the joint damage composite index MBSD observed in the EU cohort. In the JA cohort a significant decrease was also observed when comparing treatment group to placebo group. The ROA results showed the 10 mg dose was sub-optimal in its ability to saturate GM-CSF receptor. This sub-optimal effect was reflected in the BM analysis and in the clinical efficacy endpoints.

Conclusion: Promising clinical safety and efficacy results of mavrilimumab support further clinical development at doses greater than 10 mg. Mechanistically, the drug suppressed both acute phase and inflammatory blood markers. Tracking of disease activity by MBDA showed a clear biomarker-based dose-response relationship. The association of MBSD decline with radiographic damage will be assessed in an on-going phase 2b study.

Disclosure: W. White, AstraZeneca, 3, AstraZeneca, 1; **P. Ryan**, AstraZeneca, 3, AstraZeneca, 1; **X. Guo**, AstraZeneca, 3, AstraZeneca, 1; **D. Sinibaldi**, AstraZeneca, 3, AstraZeneca, 1; **G. Ranganna**, AstraZeneca, 3, AstraZeneca, 1; **A. Godwood**, AstraZeneca, 1, Medimmune, 3; **D. Saurigny**, AstraZeneca, 1, MedImmune, 3; **D. Close**, AstraZeneca, 1, Medimmune, 3; **S. Eck**, AstraZeneca, 3, AstraZeneca, 1; **D. Wilkins**, AstraZeneca, 3, AstraZeneca, 1; **L. Roskos**, AstraZeneca, 3, AstraZeneca, 1; **M. A. Sleeman**, AstraZeneca, 3, AstraZeneca, 1; **W. Li**, Crescendo Bioscience Inc., 1, Crescendo Bioscience Inc., 3; **G. Cavet**, crescendo bioscience, 3, Crescendo Bioscience, 1; **N. A. Defranoux**, Crescendo Bioscience Inc., 1, Crescendo Bioscience Inc., 3.

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Safety Of Mavrilimumab In Cynomolgus Monkeys: Relevance Of Non-clinical Findings In Lung To Human Safety. Patricia C. Ryan[1], Matthew A. Sleeman[2], Marlon Rebelatto[1], Bing Wang[3], Hong Lu[3], Chi-Yuan Wu[3], Dee Wilkins[1], Susan Spitz[1], Gopi Ranganna[2], Alex Godwood[4], Alex Michaels[1], Didier Saurigny[4], Lorin Roskos[1], David Close[4], Heidi Towers[2], Kathleen McKeever[1] and Rakesh Dixit[1]. [1]MedImmune, Gaithersburg, MD, [2]MedImmune, LLC, Cambridge, United Kingdom, [3]MedImmune, Hayward, CA, [4]MedImmune, Ltd, Cambridge, United Kingdom.

Background/Purpose: GM-CSF plays a central role in the pathogenesis of rheumatoid arthritis (RA) through the activation, differentiation, and survival of macrophages and neutrophils. Mavrilimumab (CAM-3001) is a human monoclonal antibody targeting the alpha subunit of GM-CSF receptor which MedImmune is developing as a novel treatment for RA. Because GM-CSF plays a role in the regulation of pulmonary surfactant homeostasis (Trapnell and Whitsett, Ann Rev Physiology, 2002:775–802), lung toxicity is a potential concern for biologics such as mavrilimumab which inhibit GM-CSF receptor signaling. As a result, additional attention was given to the potential impact of lung toxicity during the development of mavrilimumab.

Methods: Nonclinical safety of mavrilimumab was evaluated in several repeat dose studies in cynomolgus monkeys. Comprehensive toxicity parameters were assessed in each study, and treatment duration ranged from 4 to 26 weeks. All animal studies were performed under approved protocols at AAALAC-accredited labs. In the recently completed Ph2a clinical study EARTH (Burmester et al., ARD 2012) intensive respiratory monitoring included chest X-rays, forced expiratory volume (FEV1), forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (DLCO) and dyspnea scores. Serum biomarkers of lung damage, surfactant protein D (SP-D) and Krebs von den Lungen-6 (KL-6) were measured using commercially available immunoassays (BioVendor, LLC; Candler, NC).

Results: Mavrilimumab has an acceptable safety profile in monkeys with no changes in any parameters other than microscopic findings in lung. In several studies, minimal accumulation of foamy alveolar macrophages was observed. This finding was reversible following a dose-free recovery period and was considered non-adverse. At very high dose levels (≥30 mg/kg), in a 26-week repeat IV dose study, the presence of lung foreign material, cholesterol clefts, and granulomatous inflammation was also observed in a few animals and was considered adverse. These dose and time related changes in lung were consistent with mavrilimumab inhibitory effects on lung macrophage function arising from exaggerated pharmacology. Overall, a clean no-observed-adverse-effect-level (NOAEL) without any effects in lung was established and provided adequate clinical safety margins. In EARTH, mavrilimumab demonstrated good clinical activity with no clinically significant or persistent changes in the lung function tests performed. Likewise, the serum biomarkers of lung damage, SP-D and KL-6, showed no clinically significant changes following mavrilimumab treatment.

Conclusion: These results suggest that suppressing macrophage activity by targeting GM-CSF receptor alpha may be a novel approach with an acceptable safety profile for the treatment of RA.

Disclosure: P. C. Ryan, MedImmune, 3, AstraZeneca, 1; **M. A. Sleeman**, AstraZeneca, 3, AstraZeneca, 1; **M. Rebelatto**, MedImmune, 3, AstraZeneca, 1; **B. Wang**, MedImmune, 3, AstraZeneca, 1; **H. Lu**, MedImmune, 3, AstraZeneca, 1; **C. Y. Wu**, MedImmune, 3, AstraZeneca, 1; **D. Wilkins**, AstraZeneca, 3, AstraZeneca, 1; **S. Spitz**, MedImmune, 3, AstraZeneca, 1; **G. Ranganna**, AstraZeneca, 3, AstraZeneca, 1; **A. Godwood**, AstraZeneca, 1, Medimmune, 3; **A. Michaels**, MedImmune, 3, AstraZeneca, 1; **D. Saurigny**, AstraZeneca, 1, MedImmune, 3; **L. Roskos**, AstraZeneca, 3, AstraZeneca, 1; **D. Close**, AstraZeneca, 1, Medimmune, 3; **H. Towers**, Heidi Towers, 3, AstraZeneca, 1; **K. McKeever**, MedImmune, 3, AstraZeneca, 1; **R. Dixit**, MedImmune, 3, AstraZeneca, 1.

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In Rheumatoid Arthritis Patients With Stable Low Disease Activity On Methotrexate Plus Etanercept, Continuation Of Etanercept Is Superior Both Clinically and Radiographically To Discontinuation: Results From a Randomized, 3-Armed, Double-Blind Clinical Trial. Mikkel Østergaard[1], Marjatta Leirisalo-Repo[2], Till Uhlig[3], Marita Jansson[4], Esbjörn Larsson[4], Fiona Brock[5] and Ronald F. van Vollenhoven[6]. [1]Copenhagen University Hospital Glostrup, Copenhagen, Denmark, [2]Helsinki University Central Hospital, Helsinki, Finland, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]Pfizer AB, Sollentuna, Sweden, [5]Quanticate, Hitchin, Hertfordshire, United Kingdom, [6]The Karolinska Institute, Stockholm, Sweden.

Background/Purpose: The randomized clinical trial "DOSERA" has shown that in patients receiving concomitant methotrexate (MTX) therapy, continuation of etanercept (ETN) at 50 mg wkly is clinically superior to placebo, as is continuation at 25 mg wkly. The aim of this post hoc analysis was to investigate differences in radiographic progression between these treatment groups.

Methods: RA patients on stable ETN 50 mg/wk plus MTX (stable dose 7.5–25 mg/wk) and documented low disease activity/remission (LDA/REM; DAS28 ≤3.2) for ≥11 mths based on retrospective data were included. Additional key inclusion criteria were: age ≥18 y, stable MTX, no prior non-anti-TNF therapy and no prior attempt to discontinue ETN due to stable disease. Patients were followed for 2 mths on ETN 50 mg/wk plus MTX to ensure stable LDA/REM, and stratified based on LDA/REM status, and randomly assigned 1:1:1 to ETN50 mg/wk (ETN50), ETN 25 mg/wk (ETN25), or placebo (PBO) while continuing MTX. Failure was defined as DAS28 >3.2 on ≥1 occasion or disease progression as determined by investigator or patient. In cases of failure, patients received open-label ETN 50 mg/wk. Radiographs of hands and feet were obtained at baseline and at 48 wks and scored double-blindly by two investigators using the van der Heijde modified Sharp method (SHS). Radiographic progression was assessed from week 0 to week 48 on an intent-to-treat basis and independent of whether patients entered open-label ETN50 mg/wk.

Results: Of 106 patients screened, 91 were enrolled, and 73 randomized. The groups were demographically and clinically well-balanced at baseline,

but a higher baseline SHS was seen in the ETN25 group. The average age (SD) was 57 (11) y and disease duration was 13.6 (8.8) y. After 48 wks the % of non-failures was 52% for ETN50, 44% for ETN25, and 13% for PBO ($p=0.007$ and 0.044 for the two doses vs. PBO, respectively). Sixty-four patients had radiographs at baseline and at 40–48 wk follow-up. SHS (mean±SD) at baseline was 51.0±53.4 and at follow-up was 51.2±53.4. The mean progression in all patients was 0.13 (median 0) and was numerically highest for PBO (0.43) and lower for ETN50 (–0.13), and ETN25 (0.10). The number of patients with progression (SHS change >0) was 9/20 (45%) for PBO, 6/24 (25%) for ETN25, and 2/20 (10%) for ETN50. Radiographic progression was limited to ≤2 points in all but one patient in the PBO group (SHS change 3). Adverse events were similar between the groups; no unexpected safety signals were noted.

Conclusion: For RA patients with stable LDA/REM on ETN 50 mg/wk + MTX, continued treatment with ETN at 50 mg/wk or 25 mg/wk provides a significantly higher likelihood of non-failure of treatment over 48 wks than PBO. More patients in the PBO group had radiographic progression than those in the ETN50 and ETN25 groups. These radiographic data plus the clinical findings suggest that discontinuing ETN after achieving a stable LDA/REM state may lead to clinical worsening and radiographic damage, and should therefore not be recommended. In addition, the results from the reduced ETN dosage used in this trial provide further evidence that an "induction-maintenance" strategy may be feasible even in some patients with established RA.

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Is Isoniazid Treatment For LTBI Safe For RA Patients With TNF Inhibitor Therapy? Yoon-Kyoung Sung[1], Soo-Kyung Cho[2], Soyoung Won[2], Jeeseon Shim[2], Dam Kim[1], Ji-Young Choi[1], Chan-Nam Son[1], Chan-Bum Choi[1], Tae-Hwan Kim[1], Jae-Bum Jun[1], Dae-Hyun Yoo[1] and Sang-Cheol Bae[2]. [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea.

Background/Purpose: Isoniazid (INH) is increasingly used in RA patients with evidence of latent tuberculosis infection (LTBI) for whom TNF inhibitor therapy is planned. The potential for hepatotoxicity of INH has been concerned in RA patients treated with DMARDs including methotrexate (MTX). However, the safety and impact of INH for RA patients on persistency of TNF inhibitors has not been known. We aimed to study the safety of INH treatment for LTBI and its impact on the persistency of TNF inhibitors.

Methods: Data were extracted from medical records of RA patients who had treated with TNF inhibitor at our university hospital from December 2000 to November 2011 (REtrospective study for Safety and Efficacy of Anti-RA treatment with biologiCs, RESEARCh). Comprehensive chart reviews were undertaken on all patients, and the data for each patient consists of two components: demographic and clinical characteristics (age, sex, disease duration, disease activity, comorbidity and laboratory finding) and information related with TNF inhibitors (type of drug, history of DMARDs before starting TNF inhibitor, concomitant medication andtreatment period).

A total 312 patients aged 18 years old or older were enrolled in this study, and among them 96 patients (30.9%) experienced INH treatment for LTBI. The occurrences of LFT abnormality were evaluated in both patients with and without INH treatment. Then Kaplan-Meier curve and Cox proportional hazard analysis were used to evaluate its impact on persistency of TNF inhibitors

Results: There was no difference in demographic and clinical features in both groups except the frequency of MTX use (83.3% in INH treatment group and 72.2% in INH non-user group, $P=0.049$). The LFT abnormality was more commonly happened in patients treated with INH than those without INH treatment (20.8% vs. 8.8%, $P=0.005$). This increased risk for hepatotoxicity by INH treatment was persistent after adjusting covariates including MTX use in multivariate regression analysis (OR 3.18, 95% CI 1.48–6.84). However, the persistent rate of TNF inhibitors during 5 years using Kaplan-Meier curve was not different between two groups with and without INH treatment (49.4% vs. 54.6%, $p=0.79$ in log-rank test). INH treatment for LTBI was not associated with discontinuation of TNF inhibitors in Cox proportional hazard model (HR 1.02, 95%CI 0.66–1.58).

Conclusion: INH treatment for LTBI in RA patients who started TNF inhibitors is associated with the occurrence of LFT abnormality. However, it does not affect the persistency of TNF inhibitors.

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The JAK1-Selective Inhibitor GLPG0634 Is Safe and Rapidly Reduces Disease Activity In Patients With Moderate To Severe Rheumatoid Arthritis; Results Of a 4-Week Dose Ranging Study. Chantal Tasset, Pille Harrison, Annegret Van der Aa, Luc Meuleners, Frédéric Vanhoutte and Gerben van 't Klooster. Galapagos NV, Mechelen, Belgium.

Background/Purpose: GLPG0634 is an oral, selective inhibitor of Janus kinase 1 (JAK1). JAKs signal for cytokines and growth factors, including those involved in rheumatoid arthritis (RA). Non-selective JAK inhibitors have demonstrated efficacy in patients with RA, but also dose-limiting toxicity. In a prior 4-week Proof-of-Concept (PoC) study, GLPG0634 showed promising efficacy and safety at a daily dose of 200 mg.

The objective of this study is to evaluate short-term safety and efficacy of a dose range of GLPG0634 administered as once-daily regimen in RA patients with insufficient response to methotrexate (MTX) alone.

Methods: 4-week, double-blind Phase IIA study, comparing GLPG0634 at 30, 75, 150 and 300 mg once-daily (QD) versus placebo in a total of 91 patients. Patients had active RA (mean DAS28 of 6.0) with insufficient response to MTX and naïve to biological therapies, and continued their stable background therapy of MTX.

Results: GLPG0634 treatment was generally well tolerated; most adverse events (AEs) were mild and no serious AEs were reported. No patient discontinued due to AEs. No anemia was observed but rather a dose related improvement in hemoglobin. There was a limited decrease in absolute neutrophil count, no neutropenia, and no impact on lymphocyte subsets. No consistent changes in LDL were observed. ALT/AST was stable with no elevations >1.5 times ULN.

After 4 weeks treatment	Once-daily GLPG0634				
	Placebo	30 mg	75 mg	150 mg	300 mg
CRP: mean change (mg/L)	−5.7	−13.3	−15.1	−20.5	−17.4
- CRP shift high to normal (% pts)	0	24	32	47	60
Mean change DAS28(CRP)	−1.2	−1.1	−1.7	−1.8	−2.3
- Low disease, <3.2 (% pts)*	18	12	32	13	45

* includes patients achieving remission (<2.6).

Within 4 weeks, GLPG0634 showed an encouraging dose trend in efficacy. There was a limited improvement with the 30 mg dose whereas good anti-inflammatory (CRP) response and change in disease activity (DAS28) was apparent for doses of 75 through 300 mg QD (table). The results achieved at 300 mg are similar to those with 200 mg QD in the prior PoC study (DAS28: −2.2, with 33% <3.2 at week 4). The improvement in RA disease parameters was similar for doses of 75 mg through 300 mg, with highest response rates (at 150 or 300mg) for TJC68: -15, SJC: -11, physician's global: -29, patient's global: -26, patient's pain: -30, and HAQ-DI: -0.7. A high response rate in the placebo group may be related to a lower disease activity at baseline. For the 150 mg group, having the highest level of disease, 4 weeks treatment was too short to obtain good patient-reported outcomes. For ACR scores, best results were obtained for the 300mg group (65% ACR20, 45% ACR50). In spite of the small study, statistically significant improvements were obtained for CRP, DAS28, HAQ-DI and ACR50 at the high dose.

Conclusion: These early clinical results demonstrate that selective JAK1 inhibition by GLPG0634 at daily doses of 75 to 300 mg QD is efficacious and generally well tolerated after 4 weeks in patients with RA. Safety and efficacy findings were consistent for two Phase IIA studies. A dose trend was found and current data suggest that a maximum level of efficacy is attained at 200 mg/day. Larger 24-week studies in RA patients are ongoing to evaluate optimal doses for efficacy and safety.

Disclosure: C. Tasset, GALAPAGOS NV, 3; **P. Harrison**, GALAPAGOS NV, 3; **A. Van der Aa**, Galapagos NV, 3; **L. Meuleners**, GALAPAGOS NV, 3; **F. Vanhoutte**, Galapagos NV, 3; **G. van 't Klooster**, Galapagos NV, 3.

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B Cell Analysis Is An Essential Tool To Anticipate Clinical Relapse In Rheumatoid Arthritis Patients Treated With Rituximab. Anne-Priscille Trouvin[1], Serge Jacquot[2], Sébastien Grigioni[1], Hélène Boulard[1], Ingrid Dutot[2], Olivier Vittecoq[3], Xavier Le Loët[3], Olivier Boyer[2] and Vincent Goëb[4]. [1]Rouen University Hospital, Rouen, France, [2]INSERM U905, University of Rouen, Rouen, France, [3]Rouen University Hospital & Inserm905, University of Rouen, Rouen, France, [4]Amiens University Hospital, Amiens, France.

Background/Purpose: Rituximab is a safe and effective treatment in rheumatoid arthritis (RA), however the current treatment regimen requires to wait for a clinical relapse before a new course of treatment. The interval between two courses of treatment varies from one patient to another and remains unknown prior to the treatment. Our aim was to evaluate the utility of following-up different B cells subtypes depletion as a tool to foresee RA clinical relapse. Our aim was to assess the usefulness of periodical B cell analysis to determine if it may predict clinical relapse of RA in patients treated with rituximab.

Methods: Prospective single-center observational study of 39 patients with RA treated with rituximab 1g twice 15 days apart. Patients were monitored clinically and biologically every 2 months until retreatment. Clinical assessment consisted of RA activity and report of adverse event, biological assessment consisted of inflammatory parameters, antibodies, gammaglobulins titres and B cell analysis. The clinician was blinded of the B cell analysis results.

Results: 39 patients were included from March 2010 to December 2011 with a follow-up until January 2013. 7 patients had two courses of treatment and a total of 46 cycles of rituximab were analysed. At baseline mean DAS 28 was 5,44; 33 patients were RF and/or ACPA positive. At 6 months, 44 patients (96%) had a good-to-moderate clinical response according to the EULAR criteria. The mean treatment duration was 13 months.

After the two infusions, total number of CD19+ cells decreased (0.155G/l vs 0.0002G/l, p=0.006) with a complete depletion for all patients in the memory (CD19+27+) and transitional subtypes (CD19+CD38++ CD24++) (p<0.0001). At relapse B cells were detected in all but 1 patient. Significant majority of patients relapsed within the 4 months that follows B cell CD19+ increase (p=0,04). Looking at B cell subtypes, significant majority of patients relapsed within the 4 months that follows increase in CD19+CD27+ (p=0,01) and increase in CD19+CD38++CD24++ (p=0,007).

Conclusion: Increase in peripheral B lymphocytes after initial depletion appeared to be predictive of a clinical relapse in the next four months, providing objective elements on a forthcoming clinical relapse.

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A Useful Mathematical Model Able To Predict The Early Response To Tocilizumab In Rheumatoid Arthritis. Chiara Stagnaro, Claudia Ferrari, Rosaria Talarico, Camillo Giacomelli, Stefano Bombardieri and Laura Bazzichi. Rheumatology Unit, Pisa, Italy.

Background/Purpose: In the last few year the introduction of biological agents has radically changed the clinical outcome of patients with Rheumatoid Arthritis (RA). However, no single drug is able to control all patients with RA and it is known that each drug may be poorly effective in a sizable proportion of the treated patients. For these reasons the early identification of clinical responder patients may represent a crucial advantage for either clinical and socioeconomic reasons. Recently, mathematic algorithms, based on classical clinical parameters, have been proposed to predict the clinical response to anti TNF and DMARDs. In the present study we have applied the mathematic algorithm proposed to predict early response to anti TNF on our cohort of RA patients treated with tocilizumab (TCZ).

Methods: We collected the data of 61 RA patients (male: female= 52:9; mean age ± SD 50.0 ± 16.0; DAS28 at the onset:5.2±0.7; DAS28 at 1 year: 1.5±0.35) followed in our unit and treated with TCZ from Jan 2010 to Jan 2013, with a follow up of at least 12 months. The mathematic algorithm was based on the following parameters: Tender Joint, Swollen Joint, Illness activity VAS by Physician and patient, Pain VAS, ESR and CRP. It was applied to calculate the putative responders at one month of treatment and this value was compared with the DAS 28 at one month and at one year of therapy. The patients were classified as good responders if they had a delta DAS28> 1.2.

Results: The mathematical model allows to predict 90% of the final responders for all treated patients, with the occurrence of 3 false negative patients. Moreover, after 1 month of therapy a delta DAS 28>1.2 was recorded in 30% of patients, while at one it was found in 88% of cases.

Conclusion: these data suggest that the mathematical algorithm proposed to predict the clinical response to anti TNF, may be apply in the routine clinical practice also to RA patients treated with TCZ. Although we need further results from ongoing prospective clinical studies, it is desirable that this simple mathematical model will use to predict at one month the response in almost RA patients.

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Variability In Patient Characteristics and Outcomes In Rheumatoid Arthritis Upon Infliximab Treatment Based On The Size Of Biologic Treatment Registry Site. J. Carter Thorne[1], William G. Bensen[2], Sanjay Dixit[3], Rafat Y. Faraawi[4], Dalton E. Sholter[5], Maqbool K. Sheriff[6], Philip Baer[7], Denis Choquette[8], Boulos Haraoui[8], Algis Jovaisas[9], Emmanouil Rampakakis[10], John S. Sampalis[10], May Shawi[11], Francois Nantel[11], Allen J. Lehman[11] and Susan M. Otawa[11]. [1]Southlake Regional Health Centre, Newmarket, ON, [2]St. Joseph's Hospital and McMaster University, Hamilton, ON, [3]McMaster University, Burlington, ON, [4]Rheumatologist, KW Musculoskeletal Research Inc., Kitchener, ON, [5]Rheumatology Associates, Edmonton, AB, [6]Nanaimo Regional General Hospital, Nanaimo, BC, [7]Rheumatology, Scarborough, ON, [8]Institut de Rhumatologie de Montréal, Montreal, QC, [9]University of Ottawa, Ottawa, ON, [10]McGill University, Montreal, QC, [11]Janssen Canada Inc, Toronto, ON.

Background/Purpose: Efficacy of TNFi agents in the management of rheumatoid arthritis (RA) has been demonstrated in numerous controlled clinical trials. Variations with respect to patient (pt) profile, extent of physician familiarization with TNFi agents, and pt management may affect real-world outcomes. The aim of this analysis is to compare the pt profile and outcomes of RA patients (pts) treated with infliximab under routine clinical practice in biologic treatment registry sites of different sizes.

Methods: BioTRAC is an ongoing, prospective registry of pts initiating treatment for RA with infliximab or golimumab as first biologics or treated with a biologic for <6 mons. Pts with RA treated with infliximab who were enrolled between 2002–2012 were included in the analysis (N=832). The number of pts enrolled in BioTRAC at each site was used as the measure for the size of the registry site, resulting in the classification of 3 sizes of registry sites - Group A: sites enrolling 1–15 pts; Group B: sites enrolling 16–35 pts; Group C: sites enrolling >35 pts. The total number of pts enrolled in each type of rheumatology practice site was; Group A: n=324, Group B: n=239, Group C: n=269.

Results: Mean (SD) age of the cohort was 55.8 (13.4) years with the majority of pts being female (76.0%) and rheumatoid factor (RF) positive (74.2%). No significant differences in demographic characteristics and RF status were observed between the three pt subgroups. Pts seen at larger sites had significantly shorter disease duration (Group A: 11.9 years, Group B: 10.9 years, Group C: 7.5 years; P<0.001) and had been treated with a smaller number of previous DMARDs (2.5, 2.5, 1.6, respectively; P<0.001). Furthermore, a trend towards lower disease activity at infliximab initiation was observed in larger sites as indicated by the decreased physician global assessment (7.0 vs. 6.4 vs. 6.2; P<0.001), DAS28-CRP (5.6 vs. 5.3 vs. 5.3; P=0.023), CDAI (38.1 vs. 34.5 vs. 35.0; P=0.019), and SDAI (40.9 vs. 36.3 vs. 36.9; P=0.009). Significant differences were also observed with respect to pt management with a significantly greater proportion of pts in the larger sites being treated with concomitant DMARD (87.3% vs. 89.5% vs. 95.2%; P=0.004) and lower proportion being treated with a corticosteroid (23.5% vs. 22.6% vs. 15.6%; P=0.044).

Upon adjusting for baseline disease activity, DAS28-CRP remission (P=0.013) and minimal clinically meaningful improvement in HAQ-DI (Δ≥0.25; P=0.025) over 24 mons of treatment was significantly greater among pts seen in larger sites. Achievement of CDAI and SDAI remission was numerically higher without reaching statistically significance.

Conclusion: Consistent with findings from a Canadian early RA registry[1], results of this real-world observational study demonstrate that significant variation in disease characteristics, pt management and outcomes exist within the BioTRAC registry based on the size of the site. A trend towards earlier

infliximab initiation and improved outcomes was observed with larger enrolment sites.

Reference:

Harris J, et al. Improving outcomes in early RA by determining best practices: Does site size matter or is best treatment early? An analysis of the Canadian ERA cohort. CRA 2013.

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2385

Anti-IL-6 Antibody Clazakizumab Is More Potent Than Tocilizumab In Blocking *In Vitro* and *Ex Vivo* IL-6-Induced Functions. Q Zhao, J Pang, D Shuster, C Hung, S Baglino, R Dodge, H Sun, W Trigona and L Salter-Cid. Bristol-Myers Squibb Research and Development, Princeton, NJ.

Background/Purpose: Interleukin-6 (IL-6), a pleiotropic cytokine, drives cell functions by binding to membrane-bound IL-6 receptor (IL-6R, classical signaling) or to soluble IL-6R (sIL-6R, trans-signaling) and is a key player in the pathogenesis of chronic inflammatory diseases including RA. Tocilizumab, an antibody targeting the IL-6 pathway via the IL-6R, is the only agent currently available for the treatment of RA and juvenile idiopathic arthritis. The objective of this study was to compare the potency of clazakizumab (BMS-945429), an antibody against the IL-6 cytokine that is in clinical development for several auto-immune conditions, with that of tocilizumab in blocking IL-6-induced cell functions.

Methods: Multiple *in vitro* assays for IL-6-induced functions (classical signaling) and IL-6/sIL-6R-mediated functions (trans-signaling) were used to compare the potential of clazakizumab and tocilizumab for inhibiting signaling, proliferation, activation, antibody production and secretion of acute phase protein (Table). Pharmacokinetic/pharmacodynamic (PK/PD) studies of clazakizumab and tocilizumab were also conducted using monkey and human IL-6R knock-in (hIL-6R KI) mouse models to examine pSTAT3 and serum amyloid A blockade, respectively.

Results: In multiple cell function assays, clazakizumab and tocilizumab inhibited both classical signaling and trans-signaling; clazakizumab was between 3 and 120 times more potent than tocilizumab (Table). Furthermore, PK/PD studies confirmed that clazakizumab is a potent blocker of *ex vivo* IL-6-induced pSTAT3 in cynomolgus monkey and of serum amyloid A protein induction in hIL-6R KI mice injected with human IL-6.

Cell function assay		Stimulus	Clazakizumab IC50, nM (SD)	Tocilizumab IC50,nM (SD)	Fold tocilizumab/ clazakizumab
Signaling	pSTAT3 in human whole blood	IL-6 (0.7 nM)	0.07 (0.04)	4.8 (0.08)	~66
Proliferation	TF-1 erythroleukemic cell line (classical)	IL-6 (0.1 nM)	0.007 (0.007)	0.23 (0.23)	~33
	PHA-activated blood T cell (classical)	IL-6 (0.1 nM)	0.005 (0.002)	0.6	120
Activation	Endothelial cell secretion of MCP-1 (trans)	IL-6 (1 nM)/sIL-6R (1 nM)	0.1 (0.05)	0.3 (0.2)	~3
	JURKAT T-cell line expression of JAK3 (trans)	IL-6 (1 nM)/sIL-6R (10 nM)	0.1 (0.05)	4.8 (0.2)	~44
Antibody production	SKW B-cell line secretion of IgM (classical)	IL-6 (0.1 nM)	0.007 (0.005)	0.3 (0.1)	~43
Secretion of acute phase protein	PLC/PRF/5 hepatocyte line secretion of CRP (classical)	IL-6 (0.1 nM)	0.008 (0.004)	0.7 (0.5)	~88

Conclusion: Both *in vitro* and *ex vivo*/*in vivo* studies have shown that clazakizumab is a potent blocker of IL-6-induced functions. Evidence collected thus far has demonstrated that clazakizumab is more potent than tocilizumab in blocking IL-6-induced functions.

Disclosure: Q. Zhao, Bristol-Myers Squibb, 3; **J. Pang**, Bristol-Myers Squibb, 3; **D. Shuster**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **C. Hung**, Bristol-Myers Squibb, 3; **S. Baglino**, Bristol-Myers Squibb, 3; **R. Dodge**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **H. Sun**, Bristol-Myers Squibb, 3; **W. Trigona**, Bristol-Myers Squibb, 3; **L. Salter-Cid**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3.

2386

Survival Of Biological Therapy In Rheumatoid Arthritis: 12 Years Follow-Up Cohort. Zulema Rosales, Cristina Vadillo, Leticia León, Rayma Peña, Margarita Blanco, Esperanza Pato, J.L. Fernández Rueda, Luis Rodriguez-Rodriguez, Benjamin Fernández-Gutiérrez, Lydia Abásolo and Juan A. Jover. Hospital Clínico San Carlos, Madrid, Spain.

Background/Purpose: After more than a decade of biological agents (BA) use for the treatment of rheumatoid arthritis (RA), it is necessary a thorough knowledge of their long-term use in real life conditions, with a special emphasis in the causes leading to treatment discontinuation, in order to improve and optimize the prescription and withdrawal of these medications. To evaluate the survival of BA and the causes of discontinuation in a cohort of patients diagnosed with RA.

Methods: We performed an observational retrospective longitudinal study from January 1st, 2000, until December 18th, 2012. We included subjects followed up in our outpatient clinic, diagnosed with RA, whom started treatment with a BA [etanercept (ETN), golimumab (GOLI), certolizumab (CTZ), infliximab (IFX), adalimumab (ADA), rituximab (RTX), abatacept (ABA), or tozilizumab (TZL)]. Our primary endpoint was BA discontinuation due to: a) adverse drug reaction (ADR) (including those that required hospital admission and those that resulted in patient death), b) inefficacy c) patient decision d) remission or improvement, e) other causes. Kaplan Meier curves were set to account for all drugs discontinuation. To estimate the incidence of BA suspension we used survival techniques, expressing the incidence rate (IR) per 100 patients-year with their respective 95% confidence interval (95% CI).

Results: 405 patients were included in the study, whom began 744 different courses of BA treatment, with a total follow up time of 1,612 patients-year. Of these, 81% were women with a mean age [standard deviation (SD)] at diagnosis of 52.5 (13) years and the mean time (SD) to the first BA of 5 (4.8) years. The drug most frequently used was ADA (32%), followed by ETN (25%), IFX (20.7%), RTX (13.5%), ABA (4.3%), CTZ (1.8%), TZL (1, 6%), and GOLI (1.1%). 61.3% of the BA were discontinued during the follow-up (456 suspensions in 248 patients): 45% due to inefficacy, 43.4% to ADR (including 17% of those that required hospital admission and 1.3% deaths) and 11.6% other (3.5% improvement, 5.4% patient decision and 2.7 due to other medical decision). In the first year of therapy 68% of the patients continued on BA, and the mean survival time was 2 years (95%CI 1.6–2.3). The IR of discontinuation, regardless the cause, was 28.3 per 100 patient-years (95% CI: 25–31). The IRs depending on the causes of withdrawal were 12.6 (95%CI 11.0–14.5; inefficacy); 12.3 (95%CI 10.7–14.1; all ADR); 4.8 (95%CI 3.8–6.0; severe ADR); 0.6 (95%CI 0.3–1.1; death); 0.9 (95%CI 0.6–1.6; improvement); and 1.5 (95%CI 0.9–2.2; patient decision).

Conclusion: The IR for BA suspension in RA patients was 28 per 100 patients-year, being the most common cause inefficiency, and ADR. This study contributes to increasing knowledge of the long-term survival of these drugs in real life.

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2387

Change of serum Amyloid a predict The Effect Of Biological Treatment In Rheumatoid Arthritis Patient. Chisa Okura[1], Yukio Yonemoto[1], Koichi Okamura[1], Tetsuya Kaneko[2], Tsutomu Kobayashi[1] and Kenji Takagishi[1]. [1]Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan, [2]Inoue Hospital, Takasaki, Gunma, Japan.

Background/Purpose: The C-reactive protein (CRP) level and the erythrocyte sedimentation rate (ESR) are common markers of inflammation in patients with rheumatoid arthritis (RA). The serum amyloid A (SAA) level is also a sensitive inflammatory marker, and biologic medications, especially tocilizumab (TCZ), an inhibitor of IL-6, have been reported to decrease the SAA levels. However, thus far, few reports have compared the SAA level, disease activity, other inflammatory markers and future outcomes following treatment with biologics. The aim of this study was to assess the SAA level, the levels of other inflammatory markers and the disease activity in patients with RA who are receiving biologics.

Methods: The subjects included 32 RA patients who started to receive biologic treatment in or after July 2008 (17 patients received TNF inhibitors and 15 patients received TCZ). The swollen joint count, the tender joint count, the DAS28-ESR score and the levels of SAA, ESR, CRP and MMP-3 were assessed before treatment and at two, four and six months after treatment.

Results: No significant differences were found among the groups at baseline. At two, four and six months after treatment, the SAA, ESR and CRP levels in the TCZ group were significantly lower than those in the TNF inhibitor group. The DAS28-ESR scores obtained six months after treatment were significantly correlated with the SAA, ESR and CRP levels obtained two and four months after treatment in the TNF inhibitor group and with only the SAA levels obtained two and four months after treatment in the TCZ group.

Conclusion: We used the DAS28-ESR score as an endpoint in this study. It has been reported that comparatively high values may be obtained for both efficacy and remission rates, particularly in patients treated with TCZ, which directly inhibits inflammatory responses. Furthermore, there are also reports of relationships having been found between the DAS28-ESR and the CDAI and SDAI, thus indicating that DAS28 assessments are sufficiently useful. In our study, the DAS28-ESR scores obtained six months after treatment significantly correlated with only the SAA levels obtained after two and four months in the TCZ group. These results suggest that it may be possible to use the SAA level as a predictive factor of the therapeutic effects for not only TNF inhibitor therapy, but also for TCZ therapy.

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2388

Predictive Factors Of Relapse Or Persistent Stable Remission For Rheumatoid Arthritis (RA) Patients In Remission in a TNF Blocker-Spacing Strategy Trial (STRASS Trial). Thao Pham[1], Jacques Morel[2], Toni Alfaiate[3], Emmanuelle Dernis[4], Philippe Gaudin[5], Olivier Brocq[6], Elisabeth Solau-Gervais[7], Jean-Marie Berthelot[8], Jean-Charles Balblanc[9], Xavier Mariette[10], Florence Tubach[11] and Bruno Fautrel[12]. [1]Sainte Marguerite Hospital, Marseille, France, [2]Lapeyronie Hospital, Montpellier, France, [3]AP-HP, Paris, France, [4]Le Mans Hospital, Le Mans, France, [5]CHU Hôpital Sud, Grenoble Teaching Hospital, Echirolles, France, [6]Hospital of Princesse Grâce de Monaco, Monaco, France, [7]University Hospital of Poitiers, Poitiers, France, [8]Nantes University Hospital, Nantes, France, [9]Centre Hospitalier Général de Belfort, Belfort, France, [10]Bicêtre University Hospital, Le Kremlin Bicetre, France, [11]Universite Paris Diderot, Paris, France, [12]Paris 6 – Pierre et Marie Curie University; AP-HP, Rheumatology, Pitié-Salpêtrière Hospital, - GRC-UPMC 08 – EEMOIS, Paris, France.

Background/Purpose: The STRASS trial was a 18-month randomized controlled trial, conducted in established RA patients in DAS28 remission with etanercept (ETA) or adalimumab (ADA), comparing the impact of a DAS28-driven step-down strategy based on TNF-blocker injection spacing (S arm) to a maintenance strategy (M arm). We aimed to identify baseline characteristics predicting relapse (DAS28 $>$ 2.6 and ΔDAS28 $>$ 0.6) or persistent stable remission (DAS28 constantly $\leq$ 2.6) during the 18-month follow-up.

Methods: Inclusion criteria were: ETA or ADA $>$ 1 year, DAS28 remission $>$ 6 months, stable damage on X-rays. Patients were randomized and followed every 3 months for 18 months. In the S arm, the inter-injection interval was increased every 3 months up to complete interruption at 4th step. Relapse was defined by DAS28 $>$2.6 and ΔDAS28 $>$0.6 (Cox model). Predictive factors for relapse or persistent remission were identified by univariate then multivariate analysis using logistic regression. Optimal cut-off was determined with ROC curves analysis.

Results: 137 patients were included, 64 and 73 in the S and M arm (mean/%: age 55 yrs, female 78%, RA duration 9.5 yrs, ACPA+ 78%, erosive 88%, DAS28 1.8, ETA 54 %, ADA 46 %).

In the S arm, 46 (71.9%) patients were able to space out their injections, among which 17 (14.1%) completely stopped the TNF-blocker. Although mean DAS28 was not statistically different between the 2 strategy arms, RA relapse occurred in both arms more frequently in the S arm (81% vs. 56% in the M arm)[1] (see Table). By univariate analyses, predictors of relapse were HAQ score (p=0.05), treatment strategy arm (p=0.001), morning stiffness duration (p=0.04) and patient global assessment (PGA) (p=0.02). Baseline DAS score, Sharp score and smoking status were not associated with later relapse. Baseline factors predicting persistent remission were DAS28 score (p=0.003), HAQ score (p=0.01), treatment strategy arm (p=0.001), morning stiffness duration (p=0.008) and patient global assessment (PGA) (p=0.03). By multivariate analysis, predictors of relapse were spacing strategy – S arm – (OR=3.45; CI95%: 1.51–7.92, p=0.003) and HAQ score (OR=2.84; CI95%: 1.07–7.54, p=0.03). Predictors of persistent remission were strategy treatment arm (OR=0.30; CI95%: 0.13–0.70, p=0.005) and DAS28 score (OR=0.41; CI95%: 0.20–0.83, p=0,01). Receiver-operator characteristics of HAQ and DAS scores plotted as predictors of relapse and remission, respectively, resulted in no meaningful thresholds identified.

Table. Percentage of relapse according to assessment schedule and strategy treatment group.

N (%)	Visit (months)	Total (N=137)	M arm (N=73)	S arm (N=64)	Predictors OR (95% CI)
Time of 1st relapse	M0	0 (0.0%)	0 (0.0%)	0 (0.0%)	Spacing 3.45 (1.51, 7.92) HAQ 2.84 (1.07, 7.54)
	M3	25 (27.2%)	11 (27.5%)	14 (26.9%)	
	M6	19 (20.6%)	8 (20.0%)	11 (21.1%)	
	M9	10 (10.9%)	2 (5.0%)	8 (15.3%)	
	M12	15 (16.3%)	5 (12.5%)	10 (19.2%)	
	M15	8 (8.7%)	5 (12.5%)	3 (5.7%)	
	M18	15 (16.3%)	9 (22.5%)	6 (11.5%)	
Stable remission i.e., DAS28≤2.6	M0 thru M18	39 (28.5%)	28 (38.3%)	11 (17.2%)	Spacing 0.30 (0.13, 0.70) DAS28 0.41 (0.20, 0.83)

Conclusion: TNF-blocker injection spacing and HAQ/DAS28 were the main predictors of relapse/persistent stable remission in these established RA patients.

[1]Fautrel B et al. EULAR 2013. OP0066.

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Tocilizumab Survives Introducing The Hemadialysis Longer Than Oral Medicine In AA Amyloidosis Patients With Rheumatoid Arthritis Of Renal Insufficiency. Osamu Saiki, Hiroshi Uda, Ayumi Matsumoto, Aya Mizumoto, Tamaki Harada and Toshirou Takama. Higashiosaka City General Hospital, Higashiosaka, Japan.

Background/Purpose: In AA amyloidosis patients with RA taking oral medicines such as methotrexate and prednisolone, it is generally accepted that the renal function deteriorates gradually and finally most of the patients will receive hemodialysis in five years, even the disease activity is in good control. However, the effect of biologics therapy on renal insufficiency is not clarified. The main focus of the present study is to compare the effect of tocilizumab and oral medicines on clinical course of the renal function of AA amyloidosis patients with severe renal insufficiency.

Methods: RA patients with amyloidosis who had high disease activity and renal dysfunction (creatinine clearance $<$ 20 ml/min/1.73m^2) were enrolled in the present study. The patients were treated with prednisolone and low dose of methotrexate (group 1) or tocilizumab monotherapy (group 2) and we followed up for more than three years prospectively. In those patients who had obtained DAS28 remission, we compared the clinical course of renal function and the disease activity between two groups.

Results: The mean creatinine levels of the group 1 patients and the group 2 patients were 2.2 and 2.4 mg/dl respectively at the entry. The mean CRP levels of the group 1 patients and the group 2 patients were 3.2 and 2.8 mg/dl respectively at the entry. After treated with either oral medicine or tocilizumab, the levels of CRP were decreased to normal levels in less than one year and DAS28 were improved significantly in both groups. The renal functions of group 1 patients were deteriorated rapidly and were introduced hemodialysis in 2.1 years. Typical clinical course was shown in figure 1A. However, the patients of group 2 did not progress renal insufficiency rapidly and were not introduced hemodialysis for more than three years. In a typical case, hemodialysis was not introduced for more than five years (figure 1B).

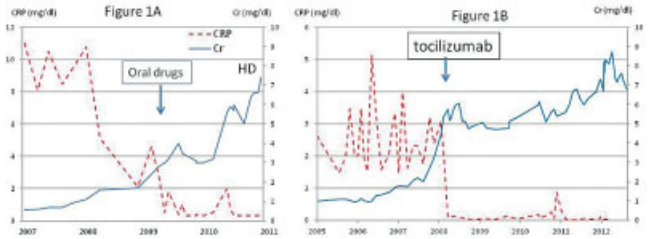

Figure 1. The typical clinical courses of CRP and Creatinine in amyloidosis patients treated with oral drugs (A) or tocilizumab (B).

Conclusion: Both oral medicines and tocilizumab monotherapy introduced clinical remission, however, tocilizumab but not oral medicines survives introducing the hemodialysis for more than three years in AA amyloidosis patients with renal insufficiency. This result shows the different effects on progression of renal insufficiency between tocilizumab and oral medicine, and suggests that we should select tocilizumab rather than oral medicine in these patients.

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Low Dose Of Tocilizumab Can Be Effective In RA Patients Who Achieve Remission.. Cecilia Prieto- Candau[1], Virginia Moreira- Navarrete[2], Carmen Vargas-Lebrón[2], Juan M Prieto-Martinez[2], Dolores Ruiz-Montesinos[2], Javier Toyos-Saenz de Miera[2] and Federico Navarro-Sarabia[3]. [1]Hospital Virgen Macarena, SEVILLE, Spain, [2]Hospital Virgen Macarena, Seville, Spain, [3]Hospital Virgen Macarena, Serv. de Reumatología, Sevilla, Spain.

Background/Purpose: Tocilizumab (TCZ), an anti-IL-6-receptor antibody, is used for the treatment of moderate to severe rheumatoid arthritis (RA) in adults with inadequate response or intolerance to previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs) or anti-tumor necrosis factor (anti-TNF). The approved dose in EU is 8 mg/kg every four weeks. The reduction of these dose is recommended in selected cases for security reasons. There are studies that assess dose reduction with other biologic therapies in patients with clinical remission. However, no studies evaluate the effectiveness of reducing the dose, either for safety or low disease activity, in patients treated with TCZ. Our objective was to evaluate the effectiveness of reducing the dose of TCZ in a serie of patients with RA.

Methods: A retrospective longitudinal observational study that included RA patients receiving reduced doses of tocilizumab. The demographics and disease characteristics were recorded in all patients. The dose reduction was based clinical practice. For qualitative variables percentages were obtained and for quantitative variables means were calculated with confidence intervals. Comparison between disease activity before and after dose reduction was performed with a t- student test.

Results: A total of 67 RA patients treated with an initial dose of TCZ of 8 mg/kg were included in this study. A dose reduction was started in 25 of them - 22 patients reduced the dose due to clinical remission of the disease (DAS 28 < 2,6) and 3 aditional patients due to leukopenia. Initial dose reduction was 6 mg/kg of TCZ and afterwards in 8 patients the dose was reduced to 4mg/kg. All the patients with reductions due leukopenia received 4mg/kg. The mean follow-up before the dose reduction was 25 months (SD 22.4). At the end of the follow-up, 24 patients remained in dose reduction and 1patients had to discontinue because of severe leukopenia. The DAS28 mean at the begining of the dose reduction was 2.20 (SD 1.45) and at the end 1.59 (0.78) with a median follow-up of 14 months. There was no statistically significant difference regarding disease activity before and after dose reduction (p = 0.36).

Women n(%)	**26 (92,9)**
Age mean(SD)	**57,9 (12,1)**
RF positive n(%)	**25 (89.3)**
ACPA positive n(%)	**17 (60.7)**
RA duration mean(SD)	**13,7 (9.8)**
Erosive disease n(%)	**19 (67,9)**
Rheumatoid nodules n(%)	**4 (14,3)**
Previous treatment n(%)	**28 (100)**
Methotrexate	9 (32,1)
Leflunomide	7 (25,0)
Hidroxicloroquine	7 (25)
Anti TNF	
RA duration until Tocilizumab, mean (SD)	**6,5 (6,68)**

Conclusion: In RA patients treated with Tocilizumab who achieve clinical remission this condition can be mantained with a lower dose of the drug. The economic consequences may be relevant. Further studies are needed to verify these results.

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Pathogenic Pro-Inflammatory Cytokine Production Induced By Synovial Fluid From RA Patients Is Related To Levels Of Endogenous TLR4 Ligands and Is Blocked By a Novel Therapeutic Anti-Human TLR4 Monoclonal Antibody, NI-0101. Limin Shang[1], Greg Elson[1], Jeremy Sokolove[2], Prof Iain B. McInnes[3], James Reilly[3], Eric Hatterer[1], Marie Kosco-Vilbois[4], Walter Ferlin[4], Emmanuel Monnet[4] and Cristina de Min[4]. [1]NovImmune S.A., Plan-Les-Ouates, Geneva, Switzerland, [2]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [3]University of Glasgow, Glasgow, United Kingdom, [4]NovImmune S.A., Geneva, Switzerland.

Background/Purpose: Deregulation of Toll-Like Receptor 4 (TLR4) signaling is thought to play a role in the pathogenesis of certain autoimmune diseases. In rheumatoid arthritis (RA), increased expression of several endogenous TLR4 ligands has been reported in both blood and synovial fluids. We first confirmed that macrophages can be activated by immune complexes containing citrullinated fibrinogen (cFb-IC) via TLR4 and then demonstrated that this activation is inhibited by NI-0101, a new therapeutic anti-human TLR4 monoclonal antibody (mAb). The purpose of this study was 1) to investigate the ability of RA synovial fluids to induce cytokine production by fibroblasts and monocytes obtained from RA patients, 2) to analyze its relation with levels of endogenous TLR4 ligands and finally 3) to demonstrate the ability of NI-0101 to inhibit RA synovial fluids induced cytokine production.

Methods: cFb-IC were incubated with blood derived macrophages from healthy subjects and cytokine release determined by ELISA. The capacity of pooled and individual RA synovial fluids to stimulated cytokine production from RA blood-derived monocytes and RA joint-derived fibroblasts was analyzed by ELISA and multiplex analyses. The expression levels of S100A8/A9, High-mobility group protein B1 (HMGB1), tenascin C were measured by commercially available ELISA kits and anti-citrullinated protein antibodies (ACPA) were measured in RA synovial fluid samples by ELISA method developed for purpose. TLR4 antagonism was assessed using NI-0101.

Results: cFb-IC stimulated TNFα production in blood-derived macrophages was significantly inhibited by NI-0101 ($p<0.001$), confirming that the ability of cFb-IC to induce cytokine production is realized through TLR4-activation. Eleven out of fifteen individual RA synovial fluids stimulated IL-6 production from patient-derived synovial fibroblasts and 10 out of 14 from monocytes. NI-0101 significantly reduced the individual RA synovial fluids induced response (5/11 RA synovial fluids on fibroblasts and 10/10 RA synovial fluids on monocytes). Analysis of RA synovial fluids composition demonstrated variable patterns of ACPA, S100A8/A9, High-mobility group protein B1 (HMGB1), tenascin C and cFb-IC levels. These synovial fluids containing the highest combined level of ACPA, cFb-IC, HMBG1, S100A8/A9 were found to induce the more robust IL-6 response. Furthermore, the NI-0101 inhibitory response of IL-6 induction was also correlated with the combined presence of the afore mentioned TLR4 ligands.

Conclusion: The ability of RA synovial fluids to induce *ex vivo* inflammatory cytokine production is directly correlated to the levels of endogenous TLR4 ligands in RA synovial fluids (including S100A8/A9, HMGB1, ACPA and cFb-IC). NI-0101 effectively abrogates RA synovial fluids induced cytokine release in those samples with high levels of endogenous TLR4 ligands. These results indicate that TLR4 blockade by NI-0101, currently in late Phase I of clinical development, is a promising strategy in RA treatment and endogenous TLR4 ligand levels might be used as a biomarker to identify patients for anti-TLR4 therapy.

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Impact Of CT-P13 and Originator Infliximab Treatment On Quality Of Life Derived From The Health Assessment Questionnaire (HAQ) and Short-Form 36 (SF-36) From a Randomized, Double-Blind Trial In Patients With Active RA. Dae-Hyun Yoo[1], Andriy Yagensky[2], Antoaneta Toncheva[3], Osca Ruiz Santacruz[4], Fidencio Cons Molina[5], Yunju Bae[6], Taek Kwon[6], SinHye Kim[6], Peter Lacouture[7], Teresa Kok[8] and Won Park[9]. [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Lutsk City Hospital, Lutsk, Ukraine, [3]National Multiprofile Transport Hospital, Sofia, Bulgaria, [4]Centro Integral de Reumatología e Inmunología - CIREI S.A.S, Bogotá, Colombia, [5]Centro de Investigacion en Artritis y Osteoporosis SC, Mexicali, Mexico, [6]Celltrion Inc., Incheon, South Korea, [7]Hospira Inc, Lake forest, IL, [8]Hospira Inc., Lake Forest, IL, [9]Inha University Hospital, Incheon, South Korea.

Background/Purpose: Quality of life and functionality are important outcome metrics in understanding the value of therapeutic interventions in RA. Biological products have become an established therapeutic modality in rheumatic conditions and the development of biosimilar products that offer therapeutic equivalence are in development. One such biologic treatment in clinical development currently approved in Korea is a biosimilar monoclonal antibody to infliximab which has been in clinical use for the treatment of RA.

Methods: As part of the development program for a biosimilar infliximab, in a phase 3, randomized, double-blind, active-controlled trial, 606 patients with RA were treated for up to 1 year with either biosimilar infliximab (CT-P13) or Originator infliximab (INX). Treatment was initiated with 3mg/kg doses infused IV over 2 hours at Week 0, Week 2, Week 6 and then every 8 weeks up to Week 54. The primary endpoint (ACR20) previously reported, achieved therapeutic equivalence. Key secondary endpoints were captured; one such endpoint evaluated quality of life based on the standard HAQ-disability index and SF-36. The HAQ assessment of physical function measures 20 items in eight categories on a scale from 0 (without any difficulty) to 3 (unable to do). SF-36 assesses eight subscales, a low score representing poor health status. Baseline measurement was determined at the initiation of treatment and on treatment at Week 14, Week 30 and Week 54.

Results: Adjusted HAQ and SF-36 outcomes in study patients with RA (mean ± standard deviation; per protocol population) are shown below in Table 1 and Table 2 respectively.

Table 1. Adjusted HAQ Outcomes

Index	Baseline		Week 14		Week 30		Week 54	
	CT-P13 (n=246)	INX (n=250)	CT-P13 (n=246)	INX (n=250)	CT-P13 (n=246)	INX (n=250)	CT-P13 (n=226)	INX (n=220)
Overall HAQ	1.60 + 0.56	1.53 + 0.58	1.02 + 0.61	1.04 + 0.64	1.00 + 0.65	1.03 + 0.66	0.99 + 0.61	1.02 + 0.64
P-value	0.183	0.674	0.679	0.657				
Components of the adjusted HAQ								
Dressing and Grooming	1.52 + 0.72	1.42 + 0.76	0.87 + 0.84	0.87 + 0.82	0.85 + 0.83	0.88 + 0.82	0.88 + 0.83	0.93 + 0.82
Arising	1.37 + 0.77	1.29 + 0.78	0.76 + 0.74	0.82 + 0.77	0.82 + 0.75	0.89 + 0.79	0.79 + 0.74	0.83 + 0.74
Eating	1.58 + 0.80	1.52 + 0.83	0.95 + 0.75	0.90 + 0.80	0.90 + 0.77	0.92 + 0.81	0.84 + 0.76	0.90 + 0.82
Walking	1.28 + 0.75	1.28 + 0.75	0.82 + 0.80	0.82 + 0.79	0.84 + 0.81	0.78 + 0.82	0.77 + 0.79	0.79 + 0.78
Hygiene	1.69 + 0.83	1.59 + 0.85	1.11 + 0.97	1.21 + 0.93	1.14 + 0.96	1.19 + 0.92	1.14 + 0.94	1.20 + 0.90
Reach	1.89 + 0.69	1.77 + 0.78	1.24 + 0.81	1.31 + 0.84	1.15 + 0.86	1.20 + 0.87	1.17 + 0.81	1.15 + 0.83
Grip	1.79 + 0.71	1.73 + 0.74	1.16 + 0.85	1.21 + 0.87	1.18 + 0.88	1.16 + 0.91	1.13 + 0.88	1.13 + 0.90
Activities	1.71 + 0.76	1.66 + 0.78	1.20 + 0.81	1.17 + 0.83	1.16 + 0.83	1.20 + 0.82	1.21 + 0.76	1.20 + 0.82

Table 2. SF36 Outcomes

Index	Baseline		Week 14		Week 30		Week 54	
	CT-P13 (n=246)	INX (n=250)	CT-P13 (n=246)	INX (n=250)	CT-P13 (n=246)	INX (n=250)	CT-P13 (n=226)	INX (n=220)
Physical Component Summary	31.44 + 6.08	31.84 + 7.21	38.94 + 7.61	37.64 + 7.94	38.66 + 7.88	38.34 + 8.00	39.22 + 7.52	38.57 + 8.71
P-value	0.5085	0.0641	0.6572	0.4036				
Mental Component Summary	36.80 + 10.44	38.41 + 11.29	43.44 + 10.76	44.88 + 9.66	43.89 + 10.12	45.01 + 10.32	43.93 + 9.90	45.09 + 10.02
P-value	0.1005	0.1172	0.2218	0.2200				
Scales of the SF-36								
Physical Function	29.48 + 8.76	30.39 + 9.23	36.91 + 10.03	36.30 + 9.64	37.11 + 10.20	37.26 + 10.21	37.55 + 9.92	37.07 + 10.93
Role-Physical	31.69 + 7.87	32.29 + 8.18	38.45 + 8.67	38.12 + 8.69	38.56 + 8.87	39.19 + 8.88	39.19 + 8.47	39.42 + 9.17
Bodily Pain	31.39 + 5.78	32.81 + 7.03	41.55 + 8.14	40.96 + 8.11	40.85 + 8.59	41.08 + 8.52	41.06 + 8.14	40.95 + 8.89
General Health	33.44 + 7.53	33.00 + 7.89	38.95 + 8.94	37.99 + 8.29	38.94 + 8.75	38.26 + 8.33	39.52 + 8.49	38.76 + 8.68
Vitality	39.76 + 8.70	41.08 + 9.24	47.46 + 9.51	47.62 + 8.71	47.12 + 8.78	47.68 + 9.02	47.37 + 8.64	48.12 + 8.74
Social Functioning	32.86 + 9.57	34.18 + 10.18	40.82 + 9.81	40.99 + 10.07	41.35 + 10.02	41.21 + 9.78	41.50 + 9.36	42.17 + 10.18
Role-Emotional	30.32 + 11.51	31.73 + 11.99	37.52 + 11.79	38.29 + 11.12	38.14 + 11.57	38.79 + 11.23	38.20 + 10.90	38.55 + 11.39
Mental Health	36.36 + 10.23	37.76 + 10.91	42.78 + 10.74	44.37 + 10.00	43.01 + 10.56	44.78 + 10.03	43.26 + 10.00	44.38 + 10.05

Baselines were similar between treatment groups. Scores between 1 and 2 generally represent moderate to severe disability reflected in this population. Early overall improvement as measured by a reduction in the HAQ scores was evident and similar in magnitude between biosimilar infliximab and originator infliximab by Week 14. Changes over time were similar between the two treatments. Effectiveness of CT-P13 and INX was sustained over the 1 year interval. The agents were generally well tolerated in RA patients in this study. In addition, there were clear correlations between HAQ and physical or mental component summary of SF-36 from Pearson's test.

Conclusion: Treatment with infliximab improved physical function as assessed by HAQ in patients with moderate to severe physical disability which was sustained over a one year interval. These data support the comparability with respect to improvement in physical function of CT-P13 and INX in patients with active RA.

Disclosure: D. H. Yoo, None; **A. Yagensky**, Celltrion, 2; **A. Toncheva**, Celltrion, 2; **O. Ruiz Santacruz**, Celltrion, 2; **F. Cons Molina**, CELLTRION, Inc., 2; **Y. Bae**, Celltrion, 3; **T. Kwon**, Celltrion Inc., 3; **S. Kim**, Celltrion Inc., 3; **P. Lacouture**, Hospira Inc., 3; **T. Kok**, Hospira Inc., 3; **W. Park**, CELLTRION, Inc., 5.

ACR/ARHP Poster Session C
Rheumatoid Arthritis: Human Etiology and Pathogenesis II
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

2393

Involvement Of Transitional T Follicular Like Helper Cells Bearing Triple Phenotypes Of Tfh/Th1/Th17 In The Pathogenesis Of Rheumatoid Arthritis. Shingo Nakayamada, Satoshi Kubo, Naoki Yunoue, Maiko Yoshikawa, Shunsuke Fukuyo, Kazuyoshi Saito and Yoshiya Tanaka. University of Occupational and Environmental Health, Japan, Kitakyushu, Japan.

Background/Purpose: T follicular helper (Tfh) cells are a new subset of T helper cells that regulate B cell function and promote autoantibody production. We previously reported that T helper cell differentiation exhibits Tfh-like transitional stage which is regulated by dynamic balance of transcription factors. However, the role of this subset in the pathogenesis of rheumatoid arthritis (RA) remains unclear. The purpose of this study was to assess the characteristic and pathological role of Tfh cells in patients with RA.

Methods: Peripheral blood mononuclear cell (PBMC) was obtained from patients with 49 RA and 35 other autoimmune diseases including systemic lupus erythematosus (SLE) and Sjogren's syndrome (SS), as well as from 10 healthy donors (HD). PBMCs were analyzed by 8 color staining multiparameter flow cytometry. The proportion of T cell subsets was determined by expression of chemokine receptors and the results were correlated with patient characteristics, including the titer of autoantibodies (RF, ACPA), CRP, ESR, MMP-3 and simplified disease activity index (SDAI).

Results: The number of effector memory T cells has increased in RA patients compared with HD. The proportion of $CD4^+CXCR3^+$ Th1 cells, $CD4^+CCR6^+$ Th17 cells, and $CD4^+CXCR5^+$ Tfh cells was not different among HD, RA, and other autoimmune diseases including SLE and SS. The frequency of activated Tfh cells was significantly correlated with the presence of ACPA in RA patients. The proportion of the $CD4^+CXCR3^+CXCR5^+$ (Th1/Tfh) cells and $CD4^+CCR6^+CXCR5^+$ (Th17/Tfh) cells was increased in patients with RA and SLE compared to HD. We found that the subpopulation of Tfh cells which express intermediate levels of CXCR5, CXCR3 and CCR6 all together has characteristically increased in patients with RA compared to both HD and other autoimmune diseases. Those cells also expressed surface activation markers such as CD38 and CD69. The frequency of those cells was closely correlated with CRP, ESR, MMP-3, and SDAI, whereas those of Th1 cells and Th17 cells showed no correlation.

Conclusion: The new population of T helper cells, which shares triple phenotypes of Th1/Th17/Tfh (transitional Tfh like: tTfh) cells, was identified. These findings have shown that the increased frequency of tTfh cells is correlated with disease activity of RA, indicating the possible involvement of tTfh cells in the disease progression of RA. Our findings also provided the concept that Tfh cells are most plastic and flexible T helper subsets in human and support the relevance of tTfh cells as a potential therapeutic target for RA.

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In Rheumatoid Arthritis, Smoking Is Not Primarily Associated With Anti-Citrullinated Protein Antibodies, But With The Presence Of Multiple Autoantibodies. Ammar Muhammad[1], Tineke van Wesemael[1], Yuta Kochi[2], Maria Mjaavatten[3], Kirsten Wevers-de-Boer[1], Cornelia F. Allaart[1], Leendert A. Trouw[1], Akari Suzuki[2], Kazuhiko Yamamoto[4], Annette H.M. van der Helm-van Mil[1], Tom W.J. Huizinga[1], René E.M. Toes[1] and Diane van der Woude[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]RIKEN, Yokohama, Japan, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.

Background/Purpose: Smoking is associated with the presence of several autoantibodies in various autoimmune diseases. In rheumatoid arthritis (RA), smoking has been described to be specifically associated with the presence of anti-citrullinated protein antibodies (ACPA). We investigated whether smoking is specifically associated with ACPA-positive RA, or with autoantibody-positive RA in general.

Methods: A meta-analysis was performed using RA patients from 5 countries: Norway, Sweden, the United Kingdom, the Netherlands and Japan. Complete data on rheumatoid factor (RF)-, ACPA-status and tobacco exposure were available for 6320 RA patients. The odds ratios (ORs) and 95% confidence intervals (95% CIs) associated with the presence of RF, ACPA or both were calculated by logistic regression comparing ever smokers with never smokers, and using the RF-negative ACPA-negative RA patients as the reference category.

Results: There was no significant association between tobacco exposure and seropositive RA in patients who were positive for only one antibody, being either RF (OR 1.04, 0.76 – 1.42) or ACPA (OR 1.00, 0.82 – 1.22). However, smoking was significantly associated with double-positive (RF-positive and ACPA-positive) RA (OR 1.55, 1.20 – 2.00). When double-positive patients were compared to single-positive patients, the effect of the additional presence of RF or ACPA was comparable; OR for RF: 1.42 (1.20 – 1.67), OR for ACPA: 1.50 (1.26 – 1.79).

Conclusion: Smoking is not associated with ACPA-positive RA, but rather with the concurrent presence of RF and ACPA in RA patients. These data indicate that smoking predisposes to the development of multiple autoantibodies, and not exclusively to ACPA-positive RA.

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2395

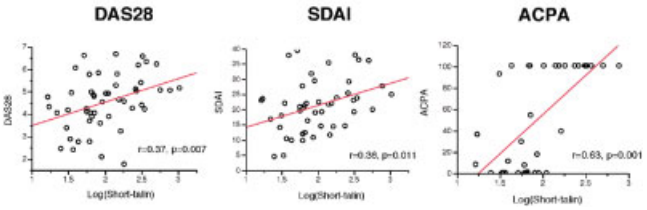
Plasma Short-Talin Is a New Rheumatoid Arthritis Monitoring Biomarker Independent Of The Inflammatory Markers. Kensei Tsuzaka, Masako Takao and Jiro Nishida. Ichikawa General Hospital, TDC, Ichikawa, Chiba, Japan.

Background/Purpose: Talin has been known as a cytoskeletal protein, which, by binding to integrin beta-subunit, enhances the inside-out signaling from intracellular to extracellular of integrins, cell adhesion, cell migration, and causes chronic inflammation and angiogenesis. Last 2012ACR meeting, we have reported that intracellular talin in RA patients is cleaved into short-talin and expressed predominantly in plasma. In 2011ACR meeting, we have demonstrated higher sensitivity and specificity of the plasma short-talin than those of anti-CCP antibody (ACPA). Although several RA biomarkers have been reported, some of them are not independent of the inflammatory markers like CRP and ESR due to the usage of the algorithm combined with them. In this paper, we investigated whether the plasma short-talin can be an RA biomarker independent of the inflammatory markers.

Methods: RA was diagnosed as the 2010 Rheumatoid Arthritis Classification Criteria. Plasma and sera were obtained simultaneously from 51 RA patients (Age, 60.9±14.4 y/o; DAS28, 4.54 ± 1.20). Sixteen (31.4 %) of these 51 patients were untreated, and 18 patients (35.3%) were treated with biologics DMARD at the time of collecting blood samples. Plasma short-talin was quantified using a sandwich ELISA with anti-short talin capture and detecting antibodies. Serum ACPA was measured using a commercial ELISA kit. RA activity at the time of collecting blood samples was estimated using DAS28, SDAI, and CDAI.

Results: The expression of the plasma short-talin was significantly correlated with DAS28 (r=0.37, p=0.0070), SDAI (r=0.36, p=0.011), CDAI (r=0.32, p=0.030), and ACPA (r=0.63, p=0.001) (Fig.1). However, plasma short-talin level was not correlated with ESR, CRP, and MMP-3.

Fig.1



Conclusion: The expression of the plasma short-talin could reveal the RA activity and can not only be an RA diagnostic marker, but also an RA monitoring biomarker independent of the inflammatory markers like ESR and CRP.

Disclosure: K. Tsuzaka, Kaytee Bio, 4; **M. Takao**, None; **J. Nishida**, None.

2396

PI3Kdelta Regulates Invadosome Formation and Invasiveness Of Fibroblast-Like Synoviocyte In Rheumatoid Arthritis. Beatrix Bartok and G. S. Firestein. UCSD School of Medicine, La Jolla, CA.

Background/Purpose: Fibroblast-like synoviocytes (FLS) in the intimal lining are major effectors of cartilage damage in rheumatoid arthritis (RA). PI3Kdelta, a member of the Class IA phosphoinositide 3-kinases (PI3K), was recently identified as a regulator of aggressive behavior by RA FLS. Invasive migration requires dynamic interactions between the extracellular matrix (ECM), the actin cytoskeleton and the capacity for matrix degradation. The specialized ECM-degrading membrane protrusions like invadopodia in cancer cells or podosomes in macrophages are known to facilitate invasive migration. Therefore, we investigated the role of PI3Kdelta in formation of invadosomes and matrix degradation.

Methods: To visualize invadosomes, RA FLS were cultured in fluorescent labeled gelatin coated dishes for 16 h. Invadosomes were identified with anti-cortactin, anti-TKS5, anti-MT1-MMP and phalloidin staining and observed with confocal microscopy. To quantify the gelatin degradation, we measured the degradation area and normalized it to total cell surface area using Image J software. Co-localization analysis was performed for PI3Kdelta and Akt with cortactin, TKS5, MT1-MMP or F-actin. MMP expression was analyzed with qPCR following TNF stimulation for 24 h in the presence or absence PI3Kdelta inhibitors (INK007, CAL101) or a PI3Kdelta/gamma inhibitor (IPI145).

Results: The collective term invadosomes includes podosomes that form in monocytic cells and invadopodia that are associated with cancer cells. First, we examined whether RA synoviocytes spontaneously form extracellular matrix degrading invadosomes. 25–40% of the cells spontaneously formed invadosomes, which was increased by 2.5 fold in presence of TNF or IL-1 ($n=5$, $p<0.04$). Because TNF regulates expression and activity of PI3Kdelta in FLS, we next examined cellular distribution of p110delta using confocal microscopy. Immunofluorescence staining revealed colocalization of p110delta with invadopodia markers cortactin, TKS5 and MT1-MMP in TNF treated and control cells. To determine whether PI3Kdelta activity is required for invadosome formation and matrix degradation, cells were plated onto fluorescent gelatin coated dishes in the presence or absence of PI3Kdelta inhibitors INK007, CAL101, IPI145 (0.1–3 uM) or vehicle control. PI3Kdelta inhibition significantly decreased gelatin degradation in a concentration dependent manner, with 65±6% inhibition at 1 uM for INK007 ($p< 0.035$; similar results for other inhibitors). Furthermore, the percentage of cells with invadosomes was reduced by PI3Kdelta inhibition. Consistent with these findings, phosphorylation and accumulation of Akt, a downstream target of PI3Kdelta, was decreased by PI3Kdelta inhibition at the invadopodia-mediated gelatin degradation site. PI3Kdelta inhibition had no effect on MMP1, 2, 3 and MT1-MMP gene expression in TNF-treated RA FLS.

Conclusion: PI3Kdelta plays a critical role in invasive matrix degradation by RA FLS by regulating spontaneous and TNF-induced invadosome formation. These observations, together with previous findings that PI3Kdelta regulates FLS migration, growth and survival, suggest that PI3Kdelta inhibition could protect cartilage in RA.

Disclosure: B. Bartok, None; **G. S. Firestein**, Infinity Pharmaceuticals, 2.

2397

To Which Extent May The Familial Risk Of Rheumatoid Arthritis Be Explained By Established Risk Factors? Xia Jiang[1], Thomas Frisell[1], Johan Askling[1], Lars Klareskog[2], Lars Alfredsson[1] and Henrik Källberg[1]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Rheumatoid arthritis (RA) is a complex inflammatory disease known to aggregate within families, implicating the crucial role of shared genetic and/or environmental factors in its etiology. Despite the many advances from genome-wide association studies, family history is an easily obtained aggregate of an individual's complete genetic risk, and is accepted to be important in clinical diagnosis. Our study is aimed to explore how much of the RA familial risk can be explained by established genetic and environmental risk factors; and to find out whether identified genetic markers enough to explain the burden of familial risk.

Methods: We used data from two Swedish population registers and the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) project. First degree relatives (FDRs) of the index person (EIRA cases and controls) were identified through the Swedish Multi-Generation register. The index individual was considered 'exposed' to familial risk if any FDRs had a RA diagnosis from the Swedish Patient Register. Analysis was run divided by ACPA status in cases and by RF status in relatives. Established genetic risk factors (45 SNPs according to GWAS catalog and the shared epitope) were selected. Environmental risk factors (smoking, drinking, BMI, socio-economic status, silica exposure, fish consumption) were determined based on previous publications. Due to missingness for individual risk factors, the complete case analysis was followed by Multiple Imputation. All analysis was adjusted for age, gender and residential area.

Results: We found a stronger aggregation pattern in APCA/RF positive RA (OR=4.09) than ACPA/RF negative RA (OR=2.30); while the ORs for cross-phenotype familial risk was 3.18 in ACPA positive cases/RF negative relatives, and 1.62 in ACPA negative cases/RF positive relatives. Further, we found that established non-genetic risk factors do not visibly explain anything of the familial risk, while SE and the identified 45 SNPs only explain a small proportion for ACPA positive RA (ACPA+ cases/RF+ relatives: $OR_{Crude}=4.09$, $OR_{adjust\ for\ SE}=3.85$, $OR_{adjust\ for\ 45SNPs}=3.66$, $OR_{adjust\ for\ both}=3.55$; ACPA+ cases/RF- relatives: $OR_{Crude}=3.18$, $OR_{adjust\ for\ SE}=2.45$, $OR_{adjust\ for\ 45\ SNPs}=2.29$, $OR_{adjust\ for\ both}=2.07$) but not for ACPA negative RA.

Conclusion: We found that established genetic and environmental risk factor do not explain much of the familial aggregation of RA, suggesting that most heritability remain to be elucidated. It is likely that a large amount of additional loci with individually extremely small magnitude remain to be identified. In particular for ACPA negative RA, it seems that we have only found factors for a very minor (or no) part of the familial aggregation. This suggests a need for studies focusing specifically on ACPA negative RA, trying to find genetic risk factors or identify disease subtypes with a stronger familial risk.

Disclosure: X. Jiang, None; **T. Frisell**, None; **J. Askling**, None; **L. Klareskog**, No own commercial interests, 2; **L. Alfredsson**, None; **H. Källberg**, None.

2398

Redox Mediated Angiogenesis In The Hypoxic Joint Of Inflammatory Arthritis. Monika Biniecka[1], Chin Teck Ng[1], Emese Balogh[1], Douglas J. Veale[2] and Ursula Fearon[2]. [1]Translation Research Group, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [2]St. Vincent's University Hospital, Dublin 4, Ireland.

Background/Purpose: To investigate whether *in vivo* synovial hypoxia and TNF blocking therapy determine expression of Nicotinamide Adenine Dinucleotide Phosphate Oxidase (Nox2) - a key source of Reactive Oxygen Species (ROS) in vasculature - and its relationship with macroscopic and microscopic markers of angiogenesis in inflammatory arthritis.

Methods: Fifty four patients with active inflammatory arthritis (RA n=33 and PsA n=21) were recruited prior to starting biological treatment and underwent arthroscopy, clinical assessment and synovial tissue oxygen (tpO_2) measurements. A subgroup of 16 patients pre/post-TNFi therapy was also recruited. Synovial tissue biopsies were obtained for immunohistochemical and *ex vivo* explant cultures. Paired peripheral blood samples were collected and peripheral blood mononuclear cells (PBMCs) were isolated for mRNA Nox2 analysis. Macroscopic synovitis/vascularity was measured by visual analogue scale. Synovial levels of Nox2, angiogenic markers (VEGF, Ang2, Factor VIII, NCAM and α-SMA), proinflammatory cytokine (TNF-α) and redox signaling factors (NF-κB) were quantified by immunohistology/immunofluorescence. Using RA synovial explant cultures *ex-vivo*, the effect of the Nox2 activators (4-HNE and TNF-α) and inhibitor (DPI) on IL-8 release was measured by ELISA.

Results: The median tpO_2 was 26.59 mmHg (range 3.2–63 mmHg), equivalent to an ambient oxygen tension 3.5% (range 0.42–8.28%). Nox2 was expressed both in lining layer (LL), sublining layer (SL) and vascular region (BV) of synovial tissue with a cytoplasmic pattern of staining. Microscopic Nox2 synovial levels and Nox2 mRNA expression in PBMC were increased in patients with tpO_2< 20mmHg compared to patients with tpO_2 >20mmHg (in LL, BV and PBMC $p<0.05$; in SL $p=0.07$). High synovial Nox2 expression correlated with greater macroscopic vascularity, synovitis, and angiogenic markers: VEGF, Ang2, Factor VIII, NCAM, and α-SMA (all $p<0.05$) and was co-localized with VEGF, Ang2, Factor VIII, TNF-α and NFκB. In biologic responders there was a significant reduction in cytoplasmic Nox2 positivity in synovial tissue ($p<0.05$), which was paralleled by a significant increase in tpO_2 levels ($p<0.05$) before and after starting TNFi. In contrast, in patients whose tpO_2levels remained the same or reduced after TNFi, no significant change in Nox2 expression was observed. 4-HNE and TNF-α significantly increased IL-8 spontaneous release from synovial tissue explants compared to unstimulated ($p<0.05$) and DPI inhibited TNF-α induced IL-8 secretion ($p<0.001$).

Conclusion: Synovial tissue hypoxia activates expression of Nox2 protein and Nox2-derived ROS may promote angiogenic processes in the inflamed joint. Following successful TNFi biologic therapy, a significant decrease in synovial Nox2 expression was coupled with higher *in vivo* tpO_2. These effects may in part be mediated through hypoxic activation of downstream redox sensitive signaling events.

Disclosure: M. Biniecka, None; **C. T. Ng**, None; **E. Balogh**, AbbVie, Pfizer, MSD, Roche, 2; **D. J. Veale**, AbbVie, Pfizer, MSD, Roche, 2, Pfizer, Roche, 5, Abbott, Pfizer, MSD, Roche, 8; **U. Fearon**, AbbVie, Pfizer, MSD, Roche, 2.

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Altered Histone Methylation Is Associated With IL-6 Dependent Matrix Metalloproteinases Gene Transcriptional Activation In Rheumatoid Arthritis Synovial Fibroblasts. Yasuto Araki[1], Takuma Tsuzuki Wada[1], Kojiro Sato[2], Kazuhiro Yokota[2], Fumihiko Miyoshi[2], Yu F. Asanuma[2], Yuji Akiyama[2] and Toshihide Mimura[1]. [1]Research Center for Genomic Medicine, Saitama Medical University, Saitama, Japan, [2]Saitama Medical University, Saitama, Japan.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease which causes progressive joint destruction. In spite of the modern medications including biologic reagents, it is still hard to cure RA completely. A line of evidence suggests that synovial fibroblasts (SFs) play an important role in the pathogenesis of RA. RASFs produce matrix-degrading enzymes and promote bone and cartilage destruction. Recent advances have revealed that epigenetic mechanisms including histone modifications are important regulators in gene transcription. We have hypothesized that aberrant epigenetic regulations might cause long-lasting synovitis in RA.

Methods: Human SFs were enzymatically isolated from knee articular synovial tissues removed at the time of joint replacement from patients with RA or osteoarthritis (OA) as a control. We compared matrix metalloproteinases (MMPs) gene expression by quantitative RT-PCR (qRT-PCR) and histone methylation in their promoters by chromatin immunoprecipitation (ChIP) assay in RASFs and OASFs. Interleukin-6 (IL-6) is an inflammatory cytokine and has been proved to be involved in the pathogenesis of RA. It was unknown whether IL-6 affected MMPs gene transcription, so we stimulated SFs with IL-6 and/or soluble IL-6 receptor α (sIL-6Rα) and examined the change in MMPs gene expression by qRT-PCR. IL-6 induces Signal Transducer and Activator of Transcription 3 (STAT3) activation. To elucidate the mechanisms of IL-6 dependent MMPs gene transcriptional activation in RASFs, we investigated cell surface expressions of IL-6 receptor (gp130 and IL-6Rα) by flow cytometry, phospho-STAT3 (p-STAT3) expression by immunoblotting, and STAT3 binding to the MMP1, 3, 9, and 13 promoters by ChIP assay.

Results: MMP1, 3, 9, and 13 mRNA levels were significantly higher in RASFs than in OASFs. Tri-methylation of histone 3 lysine 4 (H3K4me3) is associated with active gene transcription and tri-methylation of histone 3 lysine 27 (H3K27me3) with gene silencing. The amounts of H3K4me3 significantly increased whereas those of H3K27me3 substantially decreased in the MMP1, 3, 9, and 13 promoters in RASFs. These data showed that

histone methylation was correlated with MMP1, 3, 9, and 13 gene transcriptional activation in RASFs. Then, MMP1, 3, and 13 but not MMP9 mRNA levels significantly increased at 24 hr after stimulation with IL-6 (100 ng/ml) and sIL6Rα (100 ng/ml) in RASFs. Cell surface expressions of gp130 and IL-6Rα were comparable and STAT3 was similarly phosphorylated after stimulation with IL-6 and sIL-6Rα in RASFs and OASFs. STAT3 strongly associated with the MMP1, 3, and 13 promoters but not the MMP9 promoter in RASFs. Together, it was suggested that STAT3 binding to their promoters resulted in MMP1, 3, and 13 gene transcriptional activation after stimulation with IL-6 and sIL-6Rα in RASFs.

Conclusion: Characteristic histone methylation is associated with IL-6 dependent MMPs gene transcriptional activation and possibly arthritogenic properties of RASFs.

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2400

Targeted Exon Resequencing For Korean Rheumatoid Arthritis. So-Young Bang[1], Kwangwoo Kim[2], Young-Ji Na[2], Jaemoon Lee[3], Youngho Park[3], Sun Young Lee[4], Adnan Ahmad Ansari[4], Chan-Bum Choi[2], Yoon-Kyoung Sung[2], Tae-Hwan Kim[2], Jae-Bum Jun[2], Dae-Hyun Yoo[2], Junghee Jung[5], Hwanseok Rhee[6], Jong-Young Lee[7], Bok-Ghee Han[7], Sung-Min Ahn[4], Sungho Won[3], Hye-Soon Lee[1] and Sang-Cheol Bae[2]. [1]Hanyang University Guri Hospital, Guri, South Korea, [2]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [3]Chung-Ang University, Seoul, South Korea, [4]Gachon University, Incheon, South Korea, [5]Bioinfomatics Center, Macrogen Inc, Seoul, South Korea, [6]Bioinfomatics Center, Macrogen Inc, Seoul, South Korea, [7]Korea National Institute of Health, Osong, South Korea.

Background/Purpose: Rheumatoid arthritis (RA) is a systemic autoimmune disorder with heritability estimated at 65% characterized by arthritis and autoantibodies formation against citrullinated peptides (ACPA). Although there have been many efforts to identify underlying genetic causes of RA by common variants from genome-wide association studies (GWAS), most of around 60 loci identified have modest effect sizes and explained fully little of missing heritability. To discover functional and causal rare variants, we targeted genes outside of MHC region by for which there was reasonable evidence for involvement in Korean RA.

Methods: We performed targeted exon resequencing for 402 candidate genes in non-HLA region for 1,997 Korean RA cases-controls with Agilent's SureSelect kit (target region = 1.36Mb) on the HiSeq2000 platform. The sequencing data was filtered by our quality control criteria. RA association was assessed by a logistic regression for common markers and by a gene-based analysis using both Score-Seq and SKAT-O for rare coding variants.

Results: A total of 10,590 high-quality single-nucleotide variants (SNVs) was found in 1,217 cases and 717 healthy controls after applying the quality criteria (minimal depth coverage = 20x). The majority of the variants had low or rare frequency (90.6%) and 7,208 SNV was not reported in public databases like the 1000 genome project data. There were no novel loci associated with RA susceptibility in a single-marker level but we identified a significant accumulation of rare nonsynonymous variants in *gene A* associated with RA (Score-Seq: $P = 3.5 \times 10^{-4}$, SKAT-O: $P = 7.0 \times 10^{-3}$).

Conclusion: The *gene A* involved in the differentiation and activation Th17 was associated with RA risk by gene-based approaches of rare coding variants.

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2401

Disease Activity (DAS-28CRP) In Rheumatoid Arthritis Correlates With Synovial Expression Of Tumor-Associated and IL-6-Dependent Genes. Bernard Lauwerys[1], Julie Ducreux[1], Adrien Nzeusseu Toukap[1], Valérie Badot[2], Frédéric A. Houssiau[1] and Patrick Durez[1]. [1]Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium, [2]Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium.

Background/Purpose: The molecular mechanisms that regulate disease activity in rheumatoid arthritis (RA) are unknown. Using high-throughput transcriptomic data sets generated in knee synovial biopsies from patients with RA, we wanted to identify which probe sets display the highest levels of correlation with disease activity (DAS-28CRP values), and whether they cluster in specific molecular pathways.

Methods: We retrieved gene expression data obtained after hybridization of 65 synovial biopsy samples using GeneChip HGU133Plus2.0 microarrays. 21 of them originated from untreated RA patients. Paired samples were obtained in 12 of these patients, 3 months after initiation of tocilizumab therapy, and in another 8 patients, 3 months after initiation of methotrexate therapy. The last samples were obtained in methotrexate- and TNF blockade-resistant patients before (n=12) and 3 months (n=12) after administration of rituximab therapy. Correlation coefficients were calculated between normalized expression values of each probe set (n = 51,452) and DAS28-CRP among the samples.

Results: When the analyses were performed on all samples, we found that 1,304 probe sets display a >0.50 correlation coefficient with DAS-28CRP values. Strikingly, almost the totality of these probe sets are IL-6 dependent, since they are down-regulated in synovial tissue after administration of tocilizumab.

In a previous study, we found that tocilizumab, rituximab and methotrexate therapies preferentially target IL-6-dependent genes in the synovium. Therefore, correlation studies between gene expression and DAS-28CRP values, performed before and after administration of these treatments, presumably result in a bias favorable to these genes. We therefore performed our correlation study on 21 synovial biopsy samples from untreated patients with RA and active disease. In this case, we found that 393 probe sets display a > 0.50 correlation coefficient with DAS-28CRP values. 15% of them are significantly down-regulated by tocilizumab therapy in the synovium, however, the probe sets with the highest correlation coefficients (between 0.65 and 0.75: GADD45B, TACSTD2, PDE4D, . . .) are associated with chromatin remodeling, regulation of cell cycle and tumor progression in cancer tissues.

Conclusion: Our data indicate that two distinct sets of transcripts are associated with disease activity (expressed as DAS-28CRP values) in the RA synovium. Immunohistochemistry experiments are ongoing in order to identify which synovial cells express these IL-6-dependent- versus tumor progression-associated transcripts.

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2402

Association Between Life Events and Rheumatoid Arthritis, Results From The EIRA Case Control Study. Annmarie Wesley[1], Camilla Camilla Bengtsson[1], Marie Holmqvist[2], Töres Theorell[3], Saedis Saevarsdottir[4], Eva Skillgate[1], Lars Klareskog[4], Lars Alfredsson[1] and Sara Wedrén[4]. [1]Karolinska Insitutet, Stockholm, Sweden, [2]Karolinska Institutet, Stockholm, Sweden, [3]Public Health Sciences, Karolinska Insitutet, Stockholm, Sweden, [4]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: The association between life events and rheumatoid arthritis (RA) has previously been studied with contradicting results. No previous study have investigated the impact of life events on risk of developing RA in the two major subsets of RA defined by the presence or absence of anti-citrullinated protein antibodies (ACPA) (Klareskog, Catrina et al. 2009). We aimed to investigate the association between life events and the risk for RA with and without ACPAs.

Methods: We used a population based case-control study of individuals aged 18 to 70 years, living in geographically defined parts of Sweden between May 1996 and November 2009. We included incident cases (n=2774) diagnosed by rheumatologists according to the American College of Rheumatology 1987 criteria for RA and randomly selected controls (n=3911) matched to cases by age, sex, and area of residence. All answered a questionnaire, including questions about 15 life events. We calculated odds ratios (OR) and 95% confidence intervals (CI) from unconditional logistic regression models adjusted for matching variables and confounding factors.

Results: Having experienced a life event was weakly associated with ACPA positive as well as ACPA negative RA, OR 1.1, 95%CI 1.0–1.2, and 1.2 95%CI 1.0–1.4, respectively. The association with ACPA negative RA was stronger with increasing number of events (OR 1.4 95%CI 1.1–1.7 for having experienced 3 or more events vs. none). Several particular life events were associated with RA (e.g., "conflict at work", "change of residence", "change of workplace", and "increased responsibility at work"). The results were more consistent in women than in men.

Conclusion: Our study lends support to the concept that stress, here measured as life events, is associated with an increased risk of developing RA.

Klareskog, L., A. I. Catrina, et al. (2009). "Rheumatoid arthritis." Lancet **373**(9664): 659–672.

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2403

The Incidence Of Factor V Leiden A1691G, Methylene Tetrahydrofolate Reductase C677T, and Prothrombin G20210A Mutation In Patients With Rheumatoid Arthritis. Taskin Senturk[1], Zahit Bolaman[1], Sabri Batun[2], Irfan Yavasoglu[3] and Gurhan Kadikoylu[1]. [1]Professor, Aydin, Turkey, [2]Professor, Diyarbakır, Turkey, [3]Associated Professor, Aydin, Turkey.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic, systemic and inflammatory disease. Thromboembolic phenomenas are more frequent in patients with RA than healthy individuals and several hemostatic factors increase in these patients with RA. The knowledge about FV Leiden A1691G, methylenetetrahydrofolate reductase (MTHFR) C677T, and prothrombin G20210A mutation in RA is very limited. We aimed to evaluate the incidence of factor V Leiden A1691G, MTHFR C677T, and prothrombin G20210 mutation in patients with RA.

Methods: Forty-seven patients with RA and 53 healthy individuals as control group are included to the study. The DNA of patients and control group were obtained from blood in tubes with EDTA by using pure polymerase chain kit. Then factor V Leiden A1691G, prothrombin G20210A, and MTHFR C677T mutation were investigated in DNA by using LightCycler-Factor V A1691G, prothrombin G20210A, and MTHFR C677T estimate kits. Yates chi-square and students t test for comparison of groups were used.

Results: The mean age of patients and control groups were 48.8 ±12.2 and 48.8 ± 7.9 years, respectively. There is no history or physical finding of venous thrombosis in patients and control group. The heterozygote FV Leiden A1691G point mutation was estimated in 9 patients with RA (6.3%) and 2 patients (3.7%) in control group ($p<0.001$). The homozygote FV Leiden and A1691G mutation were not determined among patients and control group. Heterozygote prothrombin G20210A mutation was estimated in 9 patients with RA (15%). There was no heterozygote prothrombin G20210A mutation in control group ($p<0.001$). Homozygote prothrombin G20210A mutation was not estimated among the patients and the control group. Heterozygote MTHFR C677T mutation was found in 40 patients (85%) with RA while in 13 patients (24%) of the control group ($p<0.001$). There was no homozygote MTHFR C677T mutation in patients with RA, while homozygote MTHFR C677T mutation was determinated in 2 patients of the control group ($p>0.05$).

Conclusion: The incidences of heterozygote prothrombin G20210A and MTHFR C677T are higher in patients with RA than healthy individuals. We do not know the importance of heterozygote prothrombin G20210A, and MTHFR C677T in patients with RA. It may be useful to follow up closely in respect of further thromboembolic events in RA patients with heterozygote prothrombin G20210A, and/or MTHFR C677T mutations.

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2404

CXCL13-Producing CD4 T-Cells In Rheumatoid Synovitis Are a Distinct Subset. Shio Kobayashi[1], Koichi Murata[1], Hideyuki Shibuya[1], Masahiro Ishikawa[1], Moritoshi Furu[2], Hiromu Ito[2], Shuichi Matsuda[1], Takeshi Watanabe[1] and Hiroyuki Yoshitomi[1]. [1]Kyoto University Graduate School of Medicine, Kyoto, Japan, [2]Graduate School of Medicine, Kyoto University, Kyoto, Japan.

Background/Purpose: Ectopic lymphoid structures are frequently formed in synovial tissues of patients with rheumatoid arthritis (RA). Several reports suggested that CD4 T-cells have a crucial role in pathogenesis of RA. Although Th1 and Th17 cells are key subsets in mouse arthritis models, roles of those subsets in RA patients are still controversial. In this study, we examined an involvement of other T-cell subsets in the pathogenesis of RA. Previous report showed CD4 T-cells in synovial tissues and synovial fluid of RA produced CXCL13 which was crucial for formation of germinal center. We examined whether these cells were related to known Th subset.

Methods: We analyzed CD4 T-cells of RA synovitis by flow cytometry and immunohistofluoresecence.

Results: CD4 T-cells of rheumatoid synovitis produced CXCL13 ex vivo without exogenous stimulation of TCR or cytokines and flow cytometric analyses showed that the CXCL13+ CD4 T-cells were a population independent of IFN-γ^+ Th1, IL-4^+ Th2, and IL-17^+ Th17 cells. Although human follicular helper T-cells, which express CXCR5 as a crucial marker, produce CXCL13, CXCR5 was not expressed in RA synovial CXCL13+ CD4 T-cells. CXCL13+ CD4 T-cells were limited in the local inflamed site but not in blood nor non-inflammatory joints. Moreover, we revealed that TCR stimulation and inflammatory cytokine were important for the maintenance of CXCL13 production and for the induction of CXCL13+ CD4 T-cells from blood CD4+T-cells of healthy volunteer.

Conclusion: Our results showed that CXCL13-producing CD4 T-cells were a newly identified Th subset and distinct from other known Th subsets. The CXCL13+ CD4 T-cells in RA are thought to recruit circulating Tfh cells and B-cells, which express CXCR5, to inflamed joint, to participate in the neogenesis of ectopic lymphoid organ, and to maintain inflammation.

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2405

Respiratory Diseases As Risk Factors For Rheumatoid Arthritis. Marie Holmqvist[1], Johan Askling[1], Lars Alfredsson[1], Camilla Bengtsson[1], Fredrik Nyberg[2] and Göran Tornling[3]. [1]Karolinska Institutet, Stockholm, Sweden, [2]AstraZeneca R&D, Mölndal, Sweden, [3]Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden.

Background/Purpose: The etiology of rheumatoid arthritis (RA) is only partly understood. In addition to smoking, other airway exposures, e.g. silica dust and traffic pollution, have been positively associated with RA. Inflammatory events in the lungs may thus be of pivotal importance in the pathogenesis of RA, in particular for anti-citrullinated protein antibody (ACPA) positive RA. The potential role for respiratory tract diseases (RTD) in RA pathogenesis has not been systematically explored. We aimed to explore the hypothesis that RTD may initiate the development of RA, with a specific focus on ACPA subtype.

Methods: Cases and controls included 1996–2009 in the population-based case-control study of incident RA, EIRA (2880 cases/4069 controls), were linked to the National Patient Register to detect hospitalizations and outpatient visits listing RTDs (exposures) that occurred prior to first symptom of RA (corresponding date in matched controls). The exposures were analysed overall (any RTD), and subdivided into chronic lower (CL), acute lower (AL), chronic upper (CU) and acute upper (AU) RTD. Asthma, chronic obstructive pulmonary disease (COPD), and interstitial lung disease (ILD) were also assessed separately. Using unconditional logistic regression models with RA as the dependent variable and RTDs as the independent variables, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. Models were adjusted for smoking (ever vs. never smoking). Subgroup analyses based on smoking history (never, former, non-regular, or current smoking) were performed.

Results: Overall (irrespective of ACPA status), subjects with a history of any RTD were at increased risk of developing RA (all ORs are found in the table). Individuals with a history of CU RTDs and asthma were at significantly increased risk. ACPA positive RA was not associated with a history of any RTD. However, there was a suggestive increased risk of ACPA positive RA following a history of interstitial lung disease. For ACPA negative RA, a history of a RTD conferred significantly increased risks. This was particularly true for chronic lower RTD and for asthma. When these associations were stratified by smoking status, the increased risk was most prominent in never or non-regular smokers (data not shown).

Table. Odds ratios (OR) and 95% confidence intervals (CI) assessing the relationship between respiratory tract diseases and rheumatoid arthritis. All models adjusted for smoking

	ACPA status	N exposed cases/controls	OR (95% CI)
Any respiratory tract disease	All	410/503	1.18 (1.02–1.36)
	Positive	251/503	1.08 (0.92–1.28)
	Negative	159/503	1.32 (1.09–1.61)
Chronic lower diseases	All	77/88	1.26 (0.92–1.71)
	Positive	43/88	1.03 (0.71–1.50)
	Negative	34/88	1.55 (1.03–2.32)
Acute lower diseases	All	99/128	1.07 (0.82–1.40)
	Positive	54/128	0.90 (0.65–1.25)
	Negative	45/128	1.40 (0.98–1.98)
Chronic upper diseases	All	190/217	1.27 (1.04–1.55)
	Positive	126/217	1.26 (1.00–1.59)
	Negative	64/217	1.23 (0.92–1.64)
Acute upper diseases	All	98/126	1.13 (0.86–1.48)
	Positive	56/126	0.98 (0.71–1.36)
	Negative	42/126	1.41 (0.98–2.02)
Asthma	All	54/57	1.46 (1.00–2.12)
	Positive	29/57	1.14 (0.72–1.80)
	Negative	25/57	1.85 (1.14–2.98)
Chronic obstructive pulmonary disease	All	11/21	0.63 (0.30–1.32)
	Positive	6/21	0.53 (0.21–1.32)
	Negative	5/21	0.86 (0.32–2.31)
Interstitial lung disease	All	5/4	1.74 (0.46–6.56)
	Positive	4/4	2.34 (0.57–9.61)
	Negative	1/4	0.92 (0.10–8.26)

Conclusion: In contrast to our hypothesis, RTD seems to be associated with ACPA negative, and not ACPA positive, RA.

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2406

The Relationship Between Anti-Citrullinated Protein Antibodies and Radiographic Damage In African-Americans With Rheumatoid Arthritis. Maria I. Danila[1], Richard J. Reynolds[2], Stella Aslibekyan[2], Ashutosh Tamhane[2], Laura B. Hughes[2], Jeremy Sokolove[3], William H. Robinson[4], Doyt L. Conn[5], Beth L. Jonas[6], Leigh F. Callahan[7], Larry W. Moreland[8], Richard D. Brasington[9], Edwin A. Smith[10], Ted R. Mikuls[11], Désirée van der Heijde[12] and S. Louis Bridges Jr.[2]. [1]Univ of Alabama-Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [4]Stanford University School of Medicine, Stanford, CA, [5]Emory Univ School of Medicine, Atlanta, GA, [6]University of North Carolina at Chapel Hill, Chapel Hill, NC, [7]University of North Carolina, Chapel Hill, NC, [8]University of Pittsburgh, Pittsburgh, PA, [9]Washington Univ School of Med, St. Louis, MO, [10]Med Univ of South Carolina, Charleston, SC, [11]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [12]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Joint erosions and joint space narrowing may lead to impaired functional status and disability in rheumatoid arthritis (RA). Autoantibodies to citrullinated proteins (ACPA) are present in RA sera, but the contribution of different specificities of ACPA to radiographic damage has not been studied. The objectives of this cross-sectional study were: to test the hypothesis that particular ACPA specificities are associated with radiographic damage in African-Americans with RA.

Methods: Using a custom Bio-Plex™ bead-based autoantibody assay platform, we measured serum (N = 730 RA patients) concentration of antibodies targeting putative RA associated hyper-citrullinated autoantigens [vimentin, fibrinogen, histone 2A (H2A), histone 2B (H2B), and apolipoprotein A1 (Apo A1)] and their constitutively citrullinated forms. Radiographic severity was defined as total Sharp/van der Heijde scores of hands/feet. Three negative binomial regression models of radiographic severity were fit: 1) conditional on sex, smoking, disease duration, BMI and ln(CCP), 2) Model 1 + each autoantibody, and 3) Model 2 without ln(CCP). A highly conservative Bonferroni corrected alpha level of 0.005 for testing the autoantibodies was used.

Results: Significant covariates from Model 1 included positive association of radiographic damage with disease duration and ln(CCP) (Table). In addition there was a weaker negative association of joint damage and body mass index (BMI). Results for model 2 demonstrated significant associations of antibodies against native H2A, while antibodies against vimentin and histone 2B were nearly significant. There were no statistically significant associations between total radiographic score and antibodies to the hyper-citrullinated proteins. Results from Model 3 demonstrated that the associations between joint damage and the antibodies against native and hyper-citrullinated proteins were slightly stronger if anti-CCP antibodies were not taken into account. The antibodies against native H2A, H2B, and vimentin remained statistically significantly associated with radiographic severity, but none of the antibodies against hyper-citrullinated proteins attained significance.

Table. Estimated parameters and negative binomial model fit statistics for the covariates and the natural logarithm of antibody concentrations given the covariates.

Model 1

Variable	Estimate	p
Intercept	1.3	**0.00073**
Sex(Male)	0.19	0.39
Smoking(Never)	0.25	0.09
Disease duration	0.095	**2.00E–16**
BMI	−0.019	0.043
ln(CCP)	0.14	**6.60E–07**

Model 2

Constitutive	Estimate	p	Citrullinated	Estimate	p
Fibrinogen	0.29	0.082	Fibrinogen	−0.028	0.65
Vimentin	0.27	0.0067	Vimentin	0.014	0.77
Histone 2B	0.32	0.0073	Histone 2B	−0.079	0.17
Apolipoprotein A1	0.34	0.11	Apolipoprotein A1	0.022	0.71
Histone 2A	0.49	**0.0018**	Histone 2A	−0.085	0.11

Model 3

Constitutive	Estimate	p	Citrullinated	Estimate	p
Fibrinogen	0.37	0.029	Fibrinogen	0.07	0.2111
Vimentin	0.31	**0.00256**	Vimentin	0.087	**0.033**
Histone 2B	0.4	**0.00057**	Histone 2B	0.064	0.14
Apolipoprotein A1	0.44	0.042	Apolipoprotein A1	0.098	0.064
Histone 2A	0.58	**0.00019**	Histone 2A	0.051	0.2

Conclusion: Autoantibodies against hyper- citrullinated proteins vimentin, fibrinogen, ApoA1, H2A and H2B were not associated with joint damage. However, for African-Americans with established RA, antibodies to constitutively citrullinated proteins are most strongly associated with radiographic damage.

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2407

Rheumatoid Arthritis-Related Autoantibodies In The Lung Evolve Over Time In Subjects At Elevated Risk For Future Rheumatoid Arthritis. M. Kristen Demoruelle[1], Patrick R. Wood[1], Michael H. Weisman[2], Mark C. Parish[1], Isabel F. Pedraza[2], Jill M. Norris[3], V. Michael Holers[1] and Kevin D. Deane[1]. [1]University of Colorado School of Medicine, Aurora, CO, [2]Cedars-Sinai Medical Center, Los Angeles, CA, [3]Colorado School of Public Health, Aurora, CO.

Background/Purpose: Recent data from our group have demonstrated that RA-related autoantibodies (Abs), including anti-CCP and RF, are detectable in sputum from subjects with early Classified RA (1987 criteria; <1 year from diagnosis) as well as those at elevated risk for future RA (Willis and Demoruelle 2013, in press). In this cross-sectional study, 71% of 49 subjects at elevated risk for future RA (At-Risk) had ≥1 RA-related Ab in sputa. By comparing the ratio of RA-related Ab to total immunoglobulin (Ig) levels in sputa and sera, a subset of these At-Risk subjects appeared to generate RA-related Abs in the lung. These findings support a hypothesis that the lung is a site of initial generation of RA-related autoimmunity; however, the stability and evolution of lung RA-related Abs in subjects at elevated risk for future RA is unknown.

Methods: From the 49 At-Risk subjects previously tested in cross-section, we studied 11 that had follow-up sputum testing (median 19 months from initial testing). These At-Risk subjects were from the Studies of the Etiology of RA (SERA) cohort and at elevated risk for future RA based on family history of RA, or seropositivity for RA-related Abs in absence of synovitis identified through community healthy screenings. All subjects had no history of RA and were without synovitis at the time of sputum testing based on 68-joint examination. Induced sputum was collected using nebulized 5% saline and a protocol designed to minimize salivary contamination. Sputa samples were homogenized with mechanical disruption, and tested for RA-related Abs using ELISAs: CCP2 (IgG, Axis-Shield), CCP3.1 (IgA/IgG, INOVA), and RF isotypes (IgM/A/G, INOVA). Sputum positivity for each RA-related Ab was determined based on previously established cut-off levels (2 standard deviations above the mean level in 21 healthy controls).

Results: In these 11 At-Risk subjects, the median number of RA-related Abs positive in sputa at initial testing was 1.0 (range 0–4). At follow-up, 6/11 (55%) had a net change in the number of positive sputa RA-related Abs. These changes included both gain (N=3) and loss (N=3) of ≥1 RA-related Ab. RF-IgA was the most likely Ab to become positive: 3 of 9 (33%) subjects initially sputa RF-IgA negative were RF-IgA positive in sputa at follow-up. CCP3.1 also detects IgA, and 4/11 (36%) subjects had a change in sputum CCP3.1 status (2 gained positivity, 2 lost positivity). Changes were not associated with smoking status. Additionally, in 4 subjects with Classified RA who had 2 sputa samples collected (median 8 months apart), 1 subject lost positivity for a single RA-related Ab (CCP2), and all other sputa RA-related Abs remained stable on repeat testing.

Conclusion: Sputum RA-related Abs are elevated and fluctuate over time in subjects at elevated risk for future RA. These results may represent evolving immune responses in the lung, and in particular mucosal IgA responses, that may be associated with generation and regulation of RA-related autoimmunity during the development of RA. Going forward, extended longitudinal study of these and additional subjects will be performed to evaluate the relationship between evolution in lung RA-related Abs and the development of serum RA-related Abs and/or incident clinically classifiable RA.

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2408

Secretory Leukocyte Protease Inhibitor Released By Rheumatoid Synovial Fibroblasts Exerts a Negative Control Of BAFF-Dependent B Cell Activation In Vitro and In Vivo In The Collagen-Induced and Chimeric RA/SCID Arthritis Models. Yvonne NW Kam[1], Andrew Filer[2], Christopher D. Buckley[3], Costantino Pitzalis[4] and Michele Bombardieri[4]. [1]Centre for Experimental Medicine and Rheumatology, QMUL, London, United Kingdom, [2]Rheumatology Department, Birmingham, United Kingdom, [3]University of Birmingham, Birmingham, United Kingdom, [4]William Harvey Research Institute, QMUL, London, United Kingdom.

Background/Purpose: Rheumatoid arthritis (RA) is characterized by the formation of synovial niches of autoreactive B cells which are favored by the autocrine production of B cell survival factor BAFF by RA synovial fibroblasts (RASF). Secretory leukocyte protease inhibitor (SLPI) is a serine protease inhibitor which also acts as a potent immune-regulator. Here we investigated whether i) SLPI is expressed by RASF and is modulated by Toll-like receptors (TLR) ligands; ii) it can regulates BAFF expression by RASF and downstream B cell activation; iii) exerts immunoregulatory effects in vivo in the collagen induced arthritis (CIA) and the chimeric RA synovium/SCID models of arthritis.

Methods: mRNA and protein expression of SLPI in RASF and RADF (dermal) stimulated with TLR2/TLR3/TLR4 ligands was assessed by QT-PCR and ELISA. RASF were treated with/without recombinant SLPI to study: i) BAFF mRNA/protein expression; ii) AID expression and Ig class-switching in IgD+ B cells stimulated with BAFF/IL-4 or in co-culture with RASF. Furthermore, severity of arthritis, production of anti-CII antibodies, and joint histopathology were studied in CIA mice treated with rSLPI after arthritis onset. Finally, BAFF expression and antibody production were examined in rSLPI-treated RA/SCID mice.

Results: RASF expressed significantly higher baseline SLPI mRNA compared to RADF. Stimulation of RASF with TLR3-ligands led to a 15-fold induction of SLPI mRNA. SLPI protein was time-dependently released from TLR3-stimulated RASF, but not RADF. SLPI restrained the production of BAFF mRNA/protein in TLR3-treated RASF. Furthermore, SLPI down-modulated AID expression and IgA, IgG and IgM production in IgD+ B cells stimulated with BAFF/IL-4 or in co-culture with RASF. SLPI reduced BAFF expression and IgG/IgM production in RA/SCID mice while severity of arthritis, cartilage damage and anti-CII-IgG2a were significantly reduced in CIA mice by rSLPI administered after arthritis onset.

Conclusion: RASF release high levels of SLPI constitutively and upon TLR3 stimulation. SLPI directly modulates BAFF and B cell activation in vitro/in vivo and reduces joint inflammation and damage in animal models of arthritis, highlighting a novel endogenous anti-inflammatory pathway which could be exploited for therapeutic purposes in RA.

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2409

Association Of High Serum Interleukin-23 Levels With *Porphyromonas Gingivalis* Antibodies In Patients With Early Rheumatoid Arthritis. Sheila L. Arvikar[1], Klemen Strle[1], Deborah S. Collier[1], Mark C. Fisher[1], Toshihisa Kawai[2], Jose U. Scher[3] and Allen C. Steere[1]. [1]Massachusetts General Hospital, Boston, MA, [2]Forsyth Institute, Cambridge, MA, [3]NYU Hospital for Joint Diseases, New York, NY.

Background/Purpose: Rheumatoid arthritis (RA) is associated with an increased frequency of periodontal disease (PD) and antibodies to *P. gingivalis* (*Pg*), a major periodontal pathogen. Both Th1 and Th17 immune responses are thought to be important in RA, and a Th17 polarizing milieu has been demonstrated in periodontitis. Here we examined the association of *Pg* antibodies with specific cytokine and chemokine responses in early RA patients, prior to and during DMARD therapy.

Methods: Sera were obtained from 48 early RA patients, 36 from our cohort and 12 from NYU, who were enrolled prior to initiation of DMARDs, and from 24 healthy control subjects. Sera were tested for *Pg* IgG antibodies by ELISA using whole *Pg* sonicate (ATCC 33277). Protein levels of 20 cytokines and chemokines, including those associated with Th1 and Th17 immune responses, were quantified by Luminex in serum and, when available, in synovial fluid (SF).

Results: Prior to DMARD therapy, 23 of the 48 patients (48%) had positive IgG antibody responses to *Pg*. These patients more often had elevated anti-CCP antibodies than those who were *Pg*-negative (91% vs. 64%, P=0.06) and tended to have higher serum levels of most cytokines and chemokines tested. The differences between *Pg*-positive and *Pg*-negative patients were most striking for the Th17-associated cytokine, IL-23, the levels of which were at least 8-fold higher in serum than the other mediators. In the 7 patients in whom SF was available, IL-23 levels were 4-fold higher in serum than in SF, and serum levels of IL-23 were significantly higher in *Pg*-positive versus *Pg*-negative patients (P=0.04). In contrast, the levels of Th1-associated chemokines were more concentrated (>10X) in SF than in serum (CXCL9, P =0.1; CXCL10, P=0.02) of both *Pg*-positive and *Pg*-negative patients.

In *Pg*-positive patients, the levels of anti-CCP antibodies and most inflammatory mediators correlated directly with disease activity (DAS-28-CRP), whereas these correlations were not seen in *Pg*-negative patients (P≤0.05). Moreover, there was a trend towards a correlation between DAS-28 and the Th17-associated cytokines, IL-23 and IL-17α, in *Pg*-positive patients (P≤0.1), but not in *Pg*-negative patients (P≤0.8). During the 12 months of DMARD therapy, disease activity measures and inflammatory mediators declined, whereas the *Pg* antibody levels did not change significantly. Of the inflammatory mediators and biomarkers studied, *Pg* antibody levels were the strongest predictor of DAS-non-remission at 12 months (P=0.02) and a similar trend was observed for IL-23.

Conclusion: The levels of IL-23 were higher in serum than in SF of *Pg*-positive early RA patients, whereas Th1-associated mediators were concentrated in SF of both *Pg*-positive and *Pg*-negative patients. This suggests that in *Pg*-positive patients, IL-23 production may occur in extra-articular sites such as the oral mucosa. Moreover, *Pg* antibody positivity and high IL-23 levels were associated with a higher frequency of DAS-non-remission at 12 months. Thus, *Pg* infection is one factor that may contribute to Th17 immune responses and greater inflammation in a subset of early RA patients who may benefit from more aggressive initial therapy.

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2410

Effects Of Leptin and Adiponectin On Proliferation and Activation Were Are Significantly Increased In CD4$^+$ T Cells From Rheumatoid Arthritis Patients. Daniel Xibille-Friedmann[1], Carolina Bustos-Rivera Bahena[2], Marisol Sandoval-Rios[3] and Jose Luis Montiel-Hernandez[3]. [1]Hospital General de Cuernavaca, Cuernavaca, Mexico, [2]Facultad de Ciencias, Cuernavaca, Mexico, [3]Facultad de Farmacia, Cuernavaca, Mexico.

Background/Purpose: *In vitro* and *in vivo* studies suggest that leptin and adiponectin are involved in the development of inflammation in RA patients. Previous findings by our group have shown that levels of these adipokines are significantly higher in RA in comparison with healthy patients, and correlate with variations in DAS28 after two years of follow-up. We have observed that high levels of adiponectin at baseline predict a positive response to DMARD treatment after 6–12 months. However, the biological mechanism of leptin and adiponectin on T cell physiology is still poorly understood.

Objective: To compare the *in vitro* proliferative and activation effects of leptin and adiponectin on mononuclear (MN) and CD4$^+$ T cells from healthy donors and RA patients.

Methods: All RA patients included in the present study fulfilled the ACR 2010 criteria and were followed at the rheumatology clinic. Healthy donors samples were obtained from a local blood bank. Mononuclear cells were obtained by Ficoll Paque the same day the blood was obtained. CD4$^+$T cells were magnetically purified (Miltengy). *In vitro* assays were done employing recombinant human leptin and adiponectin (Peprotech). Proliferation was evaluated by MTT technique. Activation was evaluated by flow cytometry (CD25, CD69) and by ELISA (IL-1b, IL-2, IL-6, TNF-a). Th17 differentiation was evaluated by ELISA/cytometry (IL-17A) and western blot (RORγT). Descriptive statistics were employed to evaluate differences between groups and Spearman correlation was used to associate them with clinical parameters. A p-value <0.05 was considered as statistically significant.

Results: MN and CD4$^+$T cells from RA patients showed a significantly higher proliferative effect when exposed to leptin and adiponectin in comparison with healthy donors. According with these, leptin and adiponectin treatment were able to rescue MN cells from apoptosis induced by etoposide by an IL-2-related mechanism. Interestingly, the level of proliferation correlated with the DAS28 of patients. Similarly, cells from patients were more sensitive to leptin and adiponectin treatment when evaluating CD25$^+$/CD69$^+$ cell expression and IL-2, TNF-a secretion, in comparison to healthy donor cells. Comparatively, adiponectin treatment was significantly more effective in inducing the expression of CD25, CD69 and IL-6, whereas leptin was a better inductor of IL-2 and TNF-a on RA patient cells. Comparing this with the clinical activity of patients, we only observed a significant correlation between the DAS28 and IL-2 induction when exposed to leptin. On the other hand, CD4$^+$T cells from RA patients incubated for several days with leptin induced an increase of IL-6 and IL-17A in the cell culture supernatant and cell expression of RORgT, suggesting a direct mechanism by which high levels of leptin could favor inflammation during the progression of RA.

Conclusion: MN and CD4$^+$ T cells derived from RA patients were more sensitive to leptin/adiponectin treatment, in comparison to healthy donor cells with respect to their effects on proliferation, activation and Th17 differentiation. Additionally, clinical activity correlated with the proliferative effect and IL-2 secretion induced by treatment with leptin.

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2411

The Peripheral Blood T Cell Repertoire Before The Clinical Onset Of Rheumatoid Arthritis – a Study Of Incident Cases and Controls. Carl Turesson[1], Ulf Bergström[1], Edgars Grins[2], Olle Melander[1], Lennart Truedsson[2], Lennart Jacobsson[1] and Stefan Jovinge[2]. [1]Lund University, Malmö, Sweden, [2]Lund University, Lund, Sweden.

Background/Purpose: Previous studies indicate that circulating antibodies may be detected in individuals who later develop rheumatoid arthritis (RA) years before onset, and T cells have been implicated in the pathogenesis of RA. The purpose of this study was to investigate peripheral blood T cell phenotypes before the onset of RA.

Methods: Incident cases of RA were identified among participants (n=30447) in a community based health survey, which was linked to local and national registers, followed by a structured review of the medical records. One control, matched for age, sex and year of inclusion in the health survey, was selected for each validated case. Peripheral blood cells from a subset of participants in the health survey had been frozen according to a specified protocol and stored at −140° C. Phenotypes of peripheral blood T cells were determined by direct immunofluorescence staining and multicolor flow cytometry. Th1 cells were defined as CD4+ IFN-g+ cells, Th2 cells as CD4+ IL-4+ cells, Th17 cells as CD4+ IL-17+ cells, and regulatory T cells (Tregs) as CD25+ FoxP3+ cells. Anti-CCP2 antibodies (Euro-Diagnostica; reference interval <20 U/L) were measured in sera collected at the same time as the cell samples. Analyses were stratified by time from inclusion in the health survey to RA diagnosis and by anti-CCP2 status.

Results: Peripheral blood cell samples were available from 78 matched pairs of pre-RA cases and controls (mean age 57 years, 82 % women). The median time from inclusion in the health survey to RA diagnosis in the cases was 6 years [interquartile range (IQR) 3–8; range 1–13]. Twelve pre-RA cases (15 %) were anti-CCP2 positive. There were no major differences in lymphocyte counts or the proportions of CD3+, CD4+ or CD8+ cells among lymphocytes between cases and controls. Pre-RA cases and controls had similar proportions of Th1, Th2 and Th17 cells in the CD4+ population. The distribution of Tregs was skewed among pre-RA cases, with a reduced number of cases with high Treg counts compared to controls [median 0.50 % of CD3+ cells (IQR 0.22–1.03) vs. median 0.49 % (IQR 0.32–1.91)], although the difference did not reach significance (p=0.18). This trend was more pronounced in the subset of anti-CCP negative cases included 1–6 years before RA diagnosis and their controls [median 0.51 % (IQR 0.21–1.27) vs. 0.80 % (IQR 0.41–2.86); p=0.15]. Pre-RA cases had significantly lower proportions of CD4+ CD28null cells compared to controls [median 1.58 % of CD4+ cells (IQR 1.18–2.99) vs. 2.24 % (IQR 1.33–3.97); p=0.047]. Anti-CCP positive cases tended to have lower counts of Th1 cells [median 24.2 % of CD4+ cells (IQR 14.8–51.2) vs. 47.7 % (IQR 19.1–73.9); p=0.15] compared to controls.

Conclusion: In this study of a unique resource, we did not find any major abnormalities in the peripheral blood T cell repertoire before the clinical onset of RA. Given the limited sample, we can't exclude a downregulation of Tregs in anti-CCP negative pre-RA cases and a down-regulation of Th1 cells in anti-CCP positive cases. The lower levels of CD4+ CD28null cells in the pre-RA cases suggest that the demonstrated expansion of such cells in established RA is a consequence of chronic inflammation, rather than an inherent part of the immune phenotype of the disease.

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Anti-CCP Antibodies and Increased Cartilage Turnover In Patients Developing Rheumatoid Arthritis. Carl Turesson[1], Christina Book[1], Ulf Bergström[1], Lennart Truedsson[2], Lennart Jacobsson[1] and Tore Saxne[2]. [1]Lund University, Malmö, Sweden, [2]Lund University, Lund, Sweden.

Background/Purpose: Autoantibodies may be detected years before the onset of rheumatoid arthritis (RA). We have previously shown that levels of Cartilage oligomeric matrix protein (COMP), a marker of cartilage turnover, are elevated in particular in individuals who are negative for anti-CCP antibodies before RA diagnosis. A similar pattern has been reported in early RA (Christensen J Rheumatol 2011; 38:1563–8). Our purpose was to investigate changes in COMP from the pre-clinical phase to early RA, and their relation to anti-CCP status.

Methods: Between 1991 and 1996, 30 447 subjects from a defined catchment area were included in a health survey. From this population, individuals who developed RA after inclusion were identified by linking the health survey database to a community based RA register and local and national patient administrative databases. In a structured review of the medical records, patients were classified according to the 1987 ACR criteria for RA. The identified sample of incident cases of RA was linked to an inception cohort of early RA patients (symptom duration <12 months) from the same area. Serum COMP at baseline and at inclusion as early RA was measured with a sandwich ELISA (AnaMar Medical) among those diagnosed with RA 1–5 years after inclusion in the health

survey. Based on previous studies, 12 U/L was used as a cut off for elevated COMP. Anti-CCP2 antibodies were determined by standard methods (Euro-Diagnostica).

Results: Among a total of 172 incident cases of RA, data on COMP were available from the pre-RA inclusion in the health survey (baseline) and from inclusion in the early RA cohort in 30 cases (22 females/8 males; mean age at RA diagnosis 62 years). The median duration of symptoms was 9 months [interquartile range (IQR) 6–11]. The median time from baseline to inclusion in the early RA cohort was 4.2 years (IQR 3.2–5.2). The proportion of anti-CCP positive individuals increased from 24 % at baseline to 63 % in early RA ($p<0.001$), and the proportion with elevated COMP levels increased from 20 % to 67 % ($p=0.006$). The median COMP levels were 10.1 U/L (IQR 8.0–11.9) at baseline and 12.7 U/L (IQR 11.2–14.2) in early RA ($p<0.001$). The increase in COMP tended to be less pronounced in the subset that was anti-CCP positive at baseline [median change 1.3 U/L (IQR – 1.0 to 3.8) vs 3.6 U/L (IQR 0.6 to 6.3) in anti-CCP negative pre-RA cases; $p=0.16$]. COMP levels increased among those who converted from anti-CCP negative to anti-CCP positive ($n=12$; median change 2.8 U/L) as well as among those who remained anti-CCP negative in early RA ($n=10$; median change 4.5 U/L). The proportion with elevated COMP levels in early RA was greater among those who were anti-CCP negative at baseline (77 % compared to 43 % in anti-CCP positive pre-RA cases; $p=0.16$), whereas there was no such difference by anti-CCP status in early RA (anti-CCP negative patients: 73 %; anti-CCP-positive patients: 63%; $p=0.70$).

Conclusion: The clinical onset of RA was associated with development of anti-CCP antibodies and increased COMP levels. The increase in COMP was greater among individuals lacking anti-CCP antibodies before the onset of RA. This suggests that RA-specific autoimmunity and increased cartilage turnover may represent distinct pathways in the pre-clinical phase of RA.

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2413

Expression and Function Of a YAP, a Novel Pathway In Fibroblast-Like Synoviocyte In Rheumatoid Arthritis. Beatrix Bartok, UCSD School of Medicine, La Jolla, CA.

Background/Purpose: Modulating molecular pathways that regulate pathogenic behavior fibroblast-like synoviocytes (FLS) could lead to new therapies for rheumatoid arthritis (RA). Targeting transcription factors are especially interesting, because they regulate the expression of multiple genes and therefore regulate diverse pathways that contribute to disease. The transcriptional coactivator YAP is emerging as a major regulator of proliferation. organ size and oncogenesis. Several downstream targets of YAP such as surviving and CTGF are implicated in different aspect of RA; however the YAP pathway itself has not been characterized yet in inflammatory synovitis. Therefore, we explored expression and function of YAP in RA synoviocytes.

Methods: For confocal microscopy cells were starved overnight, fixed and stained for YAP, DAPI, and with phalloidin for F-actin. For quantification, YAP signal was scored as nuclear/nuclear+cytoplasmic versus cytoplasmic only by analyzing 150–200 cells for each cell line. For qPCR analysis the relative abundance of mRNA was calculated by normalizing to GAPDH. For siRNA knockdown, YAP and control siRNA weretransfected using AMAXA technology. To quantify cell proliferation, 5 days following transfection cell were plated in 1% FBS containing media in the presence of absence of TNF (10 ng/ml) and cell number was assayed with MTT on day 0, 2, 4 and 6.

Results: Using Western blot analysis, YAP protein was abundant and levels were similar in RA and OA FLS ($n=4$). Next we assayed the subcellular localization of YAP in RA and OA FLS using confocal microscopy. 80% of the RA FLS had nuclear YAP compared with only 40% of OA cells ($n=4$, $p<0.035$). These observations suggested that YAP is constitutively active in RA FLS and is increased compared with OA. To confirm YAP transcriptional activity, qPCR was performed for YAP target genes survivin, CTGF and CCN1. mRNA levels for all three were significantly greater in RA compared with OA ($n=3$, $P<0.04$ for each). When RA FLS were stimulated with TNF, YAP was dephosphorylated (S473) and underwent nuclear translocation. This was followed by a 2.5 fold ($P<0.04$) increase in survivin and 1.5 fold ($P<0.03$) in CTGF mRNA levels ($n=3$). To determine critical role of YAP in TNF signaling, YAP was knocked down by siRNA and cells were stimulated with TNF. Proliferation increased 1.8 fold in control siRNA treated cells but not in YAP deficient cells ($n=3$, $P<0.03$).

Conclusion: This is the first study to demonstrate that YAP is expressed in FLS and that YAP activity is dysregulated in RA compared with OA FLS. Increased YAP activity might contribute to persistent activation and pathogenic behavior of RA FLS, especially TNF-regulated functions. Therefore, reprogramming RA FLS by modulating the YAP pathway represents a novel therapeutic approach for RA.

Disclosure: B. Bartok, None.

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Elevated Serum Resistin Levels In Rheumatoid Arthritis With Periodontitis. Byoong Yong Choi[1], Jin-Hee Kim[2], Kyung Hwa Kim[2], Kyong Rok Kim[1], Sang Hyun Joo[3], Myeong Jae Yoon[4], Hye Jin Oh[5], Hye Won Kim[1], Sung Hae Chang[1], Eun Young Lee[1], Eun Bong Lee[1], Yong-Moo Lee[2] and Yeong Wook Song[1]. [1]Seoul National University College of Medicine, Seoul, South Korea, [2]Department of Periodontology, School of Dentistry, Seoul National University, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Seoul National University, Seoul, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea, [5]Seoul National University, Seoul, South Korea.

Background/Purpose: Epidemiological relationships between rheumatoid arthritis (RA) and periodontitis (PD) have been revealed recently. However, the pathologic link between RA and periodontitis has remained unclear. Resistin is adipokine which has been involved in insulin resistance in rodents but its pro-inflammatory properties are known to be superior to insulin resistance-inducing effects in human. Previous studies suggested that resistin may play a role in RA and periodontitis.

Methods: Serum resistin levels were determined by enzyme-linked immunosorbent assay (ELISA). Ninety RA patients and 45 healthy subjects (2:1 age and gender matched). Serum samples were analysed for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), anti-cyclic citrullinated peptide (anti-CCP), IgM rheumatoid factor. The disease activity was determined using the Disease Activity Score in 28 joints (DAS28). We divided the subjects into high (DAS28 $\geq$ 3.2) and low (DAS28 $<$ 3.2) disease activity groups. Clinical measurement for PD such as plaque index (PI), gingival index (GI), probing pocket depth (PPD) and clinical attachment levels (CAL) were performed in total subjects.

Results: Serum resistin levels were significantly increased in active RA patients (DAS28 $\geq$ 3.2; n = 49, median 11.5 ng/mL) compared to inactive RA patients (DAS28 $<$ 3.2; n = 41, 7.3 ng/mL) or healthy control group ($p < 0.01$ and $p < 0.05$ respectively). In total RA patients, serum resistin levels were positively correlated with ESR ($r = 0.25$, $p < 0.05$), CRP ($r = 0.48$, $p < 0.01$) and DAS28 ($r = 0.26$, $p < 0.05$) as well as the severity of PD such as PI ($r = 0.36$, $p < 0.001$) and CAL ($r = 0.29$, $p < 0.01$). Active RA subgroup had more patients with clinically significant PD (n = 40/49, 81.6%) than inactive RA subgroup (n = 22/41, 53.7%; $p < 0.01$) and healthy controls (n = 14/45, 31.1%; $p < 0.001$). Serum resistin levels were also elevated in RA patients with anti-CCP antibody compared to those without (11.28 vs. 8.00 ng/mL, $p < 0.05$).

Conclusion: Serum resistin levels were elevated in active RA patients compared to inactive RA patients or healthy controls, and associated with the severity of PD and the presence of anti-CCP. The present study suggests that resistin may play a role of pathologic cross-link between RA and PD.

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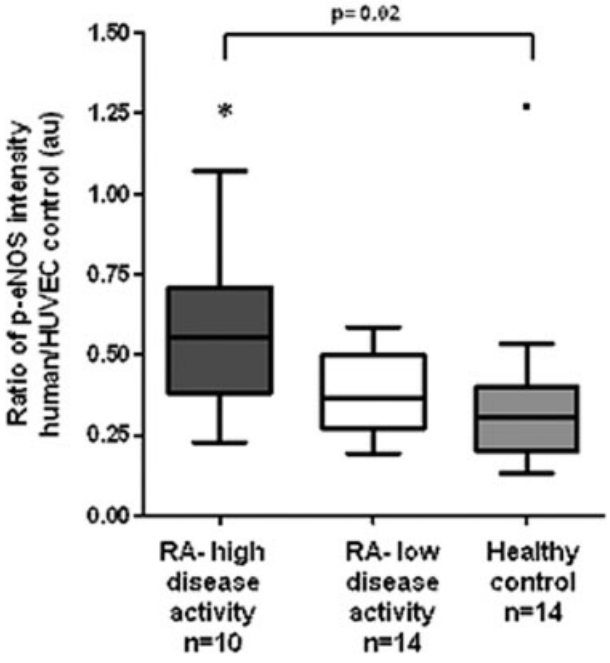
Phosphorylated Venous Endothelial Nitric Oxide Synthase Is Elevated In Rheumatoid Arthritis Subjects With High Disease Activity. Elizabeth Blair Solow, Wanpen Vongpatanasin and David R. Karp. UT Southwestern Medical Center, Dallas, TX.

Background/Purpose: Endothelial dysfunction is present in arthritis animal models and rheumatoid arthritis (RA), a population known to develop premature cardiovascular disease. Previous studies indicate inflammation modulates phosphorylation of endothelial nitric oxide synthase (eNOS) at the S1177 residue leading to endothelial impairment. The expression of eNOS in the RA vasculature has not been assessed. We investigated the hypothesis that subjects with high disease activity RA, defined by an abnormal C-reactive protein and disease activity score (DAS) >3.2, will have reduced levels of eNOS expression as compared to low disease activity RA patients and healthy controls.

Methods: We assessed endothelial function in 10 high disease activity RA, 14 low disease activity RA, and 14 healthy control (HC) subjects by brachial artery flow mediated dilation (FMD) and extracted venous endothelial cells by soft tipped J-wires from forearm catheters. RA subjects met the 1987 ACR diagnostic criteria and were either rheumatoid factor or anti-citrullinated peptide antibody positive. Expression of eNOS and phosphorylated eNOS (p-eNOS) was captured by digital immunofluorescence microscopy using human umbilical vein endothelial cell (HUVEC) controls.

Results: High disease activity RA subjects (mean age 44 years, 86% female) were significantly different from low disease activity (mean age 48 years, 91% female) for DAS (5.55±0.32 vs 2.36±0.16 au p=0.0001) and health assessment questionnaire (0.94±0.14 vs 0.34±0.10 au p=0.002). HC subjects (mean age of 43 years, 79% female) were found to have lower systolic blood pressure compared to high and low disease activity RA subjects (107±1.8 vs 119±3.6 vs 121±2.7 mmHg p=0.004). Body mass index was greater in high disease activity RA compared to low disease activity and HC (32±1.8 vs 26±1.5 vs 25±1.2 au respectively, p=0.008). Methotrexate and biologic medications were used with similar frequencies between RA subject groups (p=0.8 and p=0.7 respectively).

Despite higher levels of C-reactive protein in high disease activity RA (1.9±0.5 mg/dL vs 0.27±0.05, p=0.0001), we found the expression of p-eNOS to be significantly greater as compared to low disease activity RA and HC (0.58±0.08 vs 0.38±0.03 vs 0.36±0.08 au, respectively, p=0.02, see figure). eNOS expression was similar between high and low disease activity RA and HC (0.47±0.05 vs 0.54±0.06 vs 0.35±0.05 au, respectively, p=0.24). FMD percent change in dilation over baseline was similar between high and low disease activity RA and HC (8.5±1.12 vs 9.2±1.65 vs 9.3±1.10 au, respectively, p=0.99).



Conclusion: In conclusion, we show upregulation of p-eNOS expression in high disease activity RA subjects with elevated C-reactive protein. Further studies are required to better understand the molecular mechanisms of endothelial dysfunction in RA that lead to premature cardiovascular disease.

Disclosure: E. B. Solow, None; **W. Vongpatanasin**, None; **D. R. Karp**, None.

2416

Discovery Of Novel Biomarkers In Rheumatoid Urine: Significance Of Urinary CD14. Yune-Jung Park[1], Hyun-Sook Kim[2], Seung-Ah Yoo[3], Susanna Choi[3], Dong-Ho Kim[4], Chul-Soo Cho[5] and Wan-Uk Kim[5]. [1]Division of Rheumatology, Department of Internal Medicine, The Catholic University of Korea, School of Medicine, Seoul, Korea, Suwon, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Soonchunhyang University of Korea, Seoul, Korea, Seoul, South Korea, [3]Research Institute of Immunobiology, The Catholic University of Korea, Seoul, South Korea, [4]Research Institute of Immunobiology, Catholic Research Institute of Medical Science, Seoul, Korea., Seoul, South Korea, [5]College of Medicine, The Catholic University of Korea, Seoul, South Korea.

Background/Purpose: Current serum measures for assessing rheumatoid arthritis (RA) are invasive and are not highly sensitive to changes in disease activity. Thus, there is a need for the discovery of additional non-invasive biomarkers for RA through an un-biased approach. Here, we postulated that urine may serve as a source of biomarkers that can reflect rheumatoid inflammation.

Methods: We found 134 novel, differentially expressed proteins (DEPs) between RA and osteoarthritis urine samples via proteomics analysis. Cellular processes enriched by DEPs were associated with cell adhesion, immune response, and proteolysis, suggesting that RA patients have inflammatory urine. After integrating the urinary DEPs with gene expression profiles in the joints and mononuclear cells, we identified 12 secretory DEPs that reflect joint pathology.

Results: Of the 12 candidates, we confirmed the increased expression of gelsolin, orosomucoid 1 and 2, and soluble CD14 (sCD14), in the RA urine via immunoassay. Moreover, urinary sCD14 had comparable diagnostic value to conventional serum biomarkers, even higher predictive power for RA activity when combined with serum C-reactive protein (CRP). Finally, we proposed a ratio of serum CRP to urinary sCD14 as a new measure for RA activity and determined a cutoff value (0.06) of the measure that minimizes false positive and negative errors.

Conclusion: This work defines the pro-inflammatory nature of rheumatoid urine, and suggests that urinary proteome profiles in RA offer new diagnostic dimensions beyond current serum parameters for disease activity.

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Disclosure: Y. J. Park, None; **H. S. Kim**, None; **S. A. Yoo**, None; **S. Choi**, None; **D. H. Kim**, None; **C. S. Cho**, None; **W. U. Kim**, Korea Healthcare technology R&D Project, 2.

2417

Antibodies To *Porphyromonas Gingivalis* Peptidylarginine Deiminase In Rheumatoid Arthritis Are Not Directed Against The Autocitrullinated Enzyme. Maximilian F. Konig[1], Alizay Paracha[2], Malini Moni[1], Clifton O. Bingham III[1] and Felipe Andrade[1]. [1]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [2]The University of Oklahoma, Norman, OK.

Background/Purpose: *Porphyromonas gingivalis* (*Pg*) has received considerable attention by investigators trying to explain the striking association of periodontal disease (PD) and rheumatoid arthritis (RA). Bacterial *Pg* peptidylarginine deiminase (PPAD) has provided an exciting model to mechanistically link bacterial-induced citrullination and loss of tolerance to citrullinated proteins observed in RA. The recent finding that autocitrullinated GST-His-tagged PPAD is preferentially

recognized by antibodies in RA has focused interest on PPAD as a bacterial target of anti-citrullinated protein antibody (ACPA) initiation. This observation would have significant implications on our understanding of RA pathogenesis.

Methods: PPAD was cloned from *Pg strain W83* (ATCC) into pET-28a(+). Mutant PPAD^{C351S} lacking the capacity to autocitrullinate was generated by site-directed mutagenesis. PPAD and PPAD^{C351S} containing only His-tags were purified by affinity chromatography. Patients with RA (n=77) and healthy controls (n=39) were assayed for IgG antibodies to autocitrullinated PPAD (citPPAD) and PPAD^{C351S} by ELISA. To minimize error, antibodies to both citPPAD and PPAD^{C351S} were assayed on the same plate. Arbitrary units were corrected for background from individual sera given by PBS-coated wells. Radiolabeled PPAD generated by in vitro transcription/translation was immunoprecipitated by RA sera. Antibodies to cyclic citrullinated peptides (CCP) were assayed by QUANTA Lite CCP3 IgG ELISA (INOVA). Correlation between anti-CCP3 units and anti-PPAD levels was analyzed using Spearman's correlation. Statistical analysis of PPAD ELISA groups was performed using the Wilcoxon and Mann-Whitney test, when appropriate.

Results: PPAD, but not PPAD^{C351S}, demonstrated prominent autocitrullination when expressed in *E. coli* BL21(DE3). Antibodies to citPPAD and PPAD^{C351S} did not differ significantly among patients with RA (p=0.89; Fig. 1A). Correlation of citPPAD and PPAD^{C351S} antibody levels was highly significant (r=0.99, p<0.0001; Fig. 1B). Anti- citPPAD and anti-PPAD^{C351S} levels were not significantly different in RA compared to controls (p=0.16). Anti-CCP3 antibodies were found in 74% of RA patients (57/77), and levels were not correlated with anti-citPPAD or anti-PPAD^{C351S} (r=0.04, p=ns; r=0.07, p=ns). Sera from RA patients with high titer anti-CCP3 did not immunoprecipitate radiolabeled PPAD.

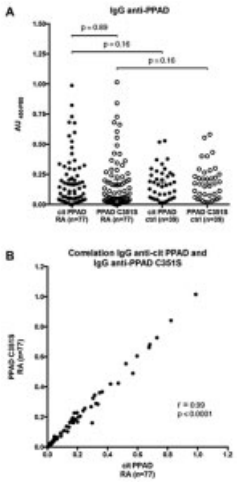

Fig. 1. Antibodies to citPPAD and PPAD^{C351S} in RA and healthy controls.

Conclusion: Anti-PPAD antibodies are present in RA, but demonstrate no preferential reactivity to autocitrullinated PPAD. Levels of anti-PPAD do not differ significantly between RA and controls. Anti-CCP antibodies do not correlate with anti-PPAD levels in RA, and do not cross-react with PPAD. Our findings suggest that PPAD autocitrullination is not the underlying mechanism linking *Pg*-associated PD and RA.

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2418

The Transmembrane Protein Tyrosine Phosphatase Kappa Promotes Aggressiveness Of Rheumatoid Arthritis Fibroblast-Like Synoviocytes. Stephanie M. Stanford[1], William B. Kiosses[2], Amanda M. Campbell[1], Michael F. Maestre[1], David L. Boyle[3], Gary S. Firestein[3] and Nunzio Bottini[1]. [1]La Jolla Institute for Allergy and Immunology, La Jolla, CA, [2]The Scripps Research Institute, La Jolla, CA, [3]UCSD School of Medicine, La Jolla, CA.

Background/Purpose: Fibroblast-like synoviocytes (FLS) in the synovial intimal lining are key mediators of inflammation and joint destruction in rheumatoid arthritis (RA). In RA these cells assume a tumor-like phenotype, aggressively invading the extracellular matrix and producing cartilage-degrading proteases and inflammatory cytokines. The behavior of synovial fibroblasts is controlled by multiple interconnected signal transduction pathways involving reversible protein phosphorylation. However, little is known about the role of protein tyrosine phosphatases (PTPs) in FLS function. The objective of this study was to identify PTPs involved in the aggressive phenotype of RA FLS.

Methods: Comparative screening was conducted of PTP expression in FLS from patients with RA or osteoarthritis (OA) by quantitative polymerase chain reaction (PCR). The functional effect on RA FLS of protein tyrosine phosphatase kappa (RPTPκ), a transmembrane PTP that was up-regulated in RA, was then analyzed by knockdown using cell-permeable antisense oligonucleotides (ASO). Transwell FLS invasion assays were performed with Matrigel-coated inserts, using fetal bovine serum or platelet-derived growth factor as chemoattractants. FLS adhesion and spreading was assessed by F-actin staining with phalloidin and visualized by immunofluorescence microscopy. Expression levels of matrix metalloproteinases (MMPs) were quantified by qPCR. Western blotting of cell lysates using phosphospecific antibodies was used to assess activation of signaling pathways. Cell survival was measured by flow cytometry following staining with propidium iodide and Annexin V.

Results: Expression of *PTPRK*, encoding the protein tyrosine phosphatase RPTPκ, was increased in RA (n=16) compared to OA (n=15) FLS (1.99±0.68 fold increase, p<0.05). RPTPκ, a proposed transforming growth factor β (TGFβ) dependent gene, belongs to a family of PTPs that mediate cell-cell adhesion through homophilic interaction between their extracellular domains. We found that *PTPRK* expression is induced by stimulation of RA FLS with 50 ng/ml TGFβ1 for 24 hours (1.91±0.45 fold increase, p<0.05). Subsequent studies focused on the functional role of RPTPκ in RA FLS. Knockdown of this PTP with ASO led to impaired cell invasion (67.8±16.5% decrease, p<0.05). Although cell adhesion to an extracellular matrix was unaffected, RPTPκ deficiency disrupted cell spreading (40.2±12.7% decrease, p<0.05). RPTPκ-deficient RA FLS displayed more than 2-fold decreased TNF (50 ng/ml) or TGFβ-mediated induction of *MMP1*, *MMP8*, *MMP10*, *MMP13* and *MMP14*, which correlated with reduced induction of JNK phosphorylation.

Conclusion: These findings indicate a novel role for RPTPκ as a key mediator of FLS function. RPTPκ promotes the invasiveness of RA FLS and, due to its higher expression in RA compared with OA FLS, could contribute to the unique "transformed" phenotype of rheumatoid cells. Therefore RPTPκ could be a novel therapeutic target for RA.

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2419

CDK6 Transcripts Expression Control By The Synoviocyte Proliferation Gene, SPACIA1. Rie Komatsu[1], Ryoji Fujii[1], Tomoo Sato[1], Yoshihisa Yamano[1], Kazuo Yudoh[1], Moroe Beppu[1], Kusuki Nishioka[2] and Toshihiro Nakajima[3]. [1]St. Marianna University School of Medicine, Kanagawa, Japan, [2]Tokyo Medical University, Tokyo, Japan, [3]Misato Marine Hospital, Kohchi, Japan.

Background/Purpose: SPACIA1 is a novel gene associated with abnormal synovial proliferation. We have already shown that SPACIA1 could be involved in the progression of synovitis *in vivo*. We previously reported that *SPACIA1* siRNA inhibited the proliferation of rheumatoid arthritis synovial fibroblasts (RASFs) and delayed the cell cycle at the G1 phase. These findings indicate that SPACIA1 is tightly linked to functional genes at the G1 phase; however, the molecular mechanism is still unclear. In particular, *CDK6* was found by transcriptome analysis to be downregulated in RASFs that were transfected with *SPACIA1* siRNA **(Fig. 1.)**. In the present study we investigated the mechanisms involved in the SPACIA1-related regulation of CDK6 gene expression *in vitro*.

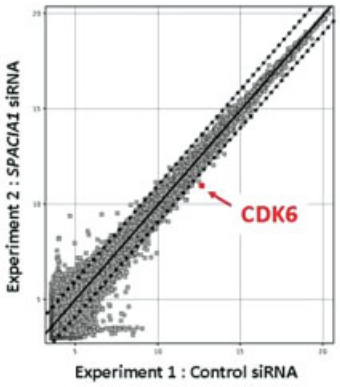

Fig. 1. Expression profiling reveals downregulation of *CDK6* by SPACIA1 siRNA in RASFs. Linear scatter plot of gene expression measured by transcriptome analysis.

Methods: RASFs were transfected with control siRNA or *SPACIA1* siRNA. Seventy-two hours after transfection, we examined the expression of several key regulators of G1 phase mRNA and protein production by qRT-PCR and Western blot analysis, respectively. To determine the processes responsible for SPACIA1 down-regulation of CDK6 expression, the basal luciferase activity of pGV-basic2 luciferase reporter-containing the *CDK6* 5'-upstream region was analyzed by luciferase assay in cells treated with control siRNA or *SPACIA1* siRNA. To determine whether the stability of *CDK6* mRNA is regulated by *SPACIA1*, we compared mRNA decay rates of *CDK6* transcripts analyzed by qRT-PCR at different time points following control/*SPACIA1* siRNA- and actinomycin D (Act-D)-treatment.

Results: Among the key regulators of the G1 phase, the only gene to be significantly reduced by *SPACIA1* siRNA was *CDK6,* which was reduced to half of its control expression. The basal luciferase activity of the reporter containing the Cdk6 5'-upstream region averaged 8 to 10-fold higher activity than the promoter-less pGV-basic2 luciferase vector. The *Cdk6* 5'-upstream region could function as a promoter, however, CDK6 promoter activity was not affected by *SPACIA1* knockdown. Knockdown of *SPACIA1* accelerated the degradation of *CDK6* mRNA in the presence of Act-D relative to control siRNA. After 60min of Act-D treatment, 40% of *CDK6* mRNA was reduced by *SPACIA1* siRNA, but, not control siRNA. This indicates that SPACIA1 is involved in regulation of *CDK6* mRNA decay.

Conclusion: We identified that SPACIA1 regulates the functional gene, *CDK6*, at the G1 phase, and found that the presence of SPACIA1 is due to alterations in *CDK6* mRNA turnover.

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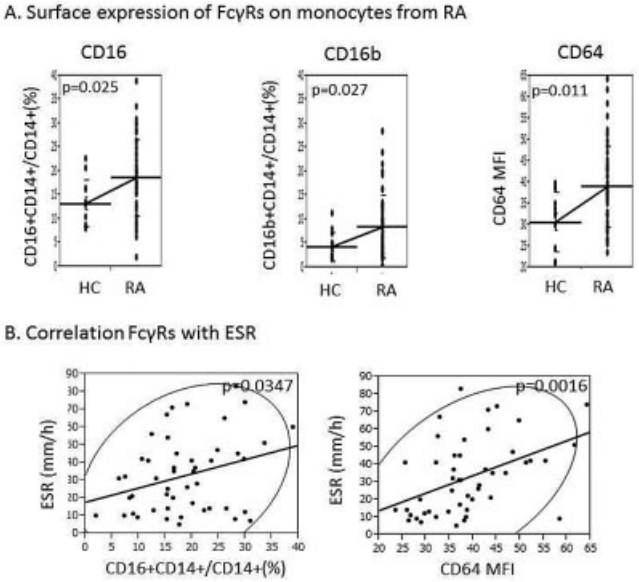
2420

Pleiotropic Roles Of Fcγ Receptors Upregulated On Circulating Monocytes In Rheumatoid Arthritis Patients. Masako Tsukamoto, Katsuya Suzuki, Keiko Yoshimoto, Hideto Kameda and Tsutomu Takeuchi. Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: We have previously demonstrated that Fc gamma receptor (FcγR) IIIb(CD16b) polymorphisms were associated with infusion reaction in rheumatoid arthritis(RA) patients. While CD16b is mainly expressed on the surface of neutrophils, mast cells, role of FcγRs on monocytes in RA patients has not been fully elucidated. We hypothesized that FcγRs might play important roles in the interaction between immune complexes and monocytes. Aim of this study is to elucidate role of FcγRs expressed on monocytes and determine their clinical significance in RA patients.

Methods: Heparinized venous blood was obtained from 48 RA patients and 12 healthy controls (HC). Surface expression of CD16 (FcγR III), CD16b, CD32(FcγRII) and CD64(FcγRI) molecules on CD14+ cells were measured by flow cytometry FcγR.

Conclusion: We found CD16 and CD64 were aberrantly upregulated on CD14+ monocytes in RA patients. Clinically, CD16b upregulation together with its functional polymorphism may participate in adverse reaction such as infusion reaction, and CD64 and CD16a rather may relate to inflammation and autoantibody production in RA.



Disclosure: M. Tsukamoto, None; **K. Suzuki**, None; **K. Yoshimoto**, None; **H. Kameda**, None; **T. Takeuchi**, Astra Zeneca K.K., Eli Lilly Japan K.K., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Co., and Asahi Kasei Medical K.K, 5, AbbVie GK., Bristol–Myers K.K., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., and Takeda Pharmaceutical Co., Ltd., 8, AbbVie GK., Astellas Pharma, Bristol–Myers K.K., Chugai Pharmaceutical Co, Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Nippon Shinyaku Co., Ltd., Pfizer Japan Inc., Sanofi–Aventis K.K., 2, Santen Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Teijin Pharma Ltd., 2.

2421

Association Between Physical Work Load and Rheumatoid Arthritis, Results From The EIRA Case Control Study. Annmarie Wesley[1], Henrik Källberg[2], Camilla Bengtsson[2], Eva Skillgate[1], Johan Rönnelid[3], Mohammed Mullazehi[3], Lars Klareskog[4], Lars Alfredsson[2], Saedis Saevarsdottir[4] and Sara Wedren[5]. [1]Karolinska Insitutet, Stockholm, Sweden, [2]Karolinska Institutet, Stockholm, Sweden, [3]Uppsala University, Uppsala, Sweden, [4]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [5]Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden.

Background/Purpose: The association between occupation and RA has previously been investigated where occupations associated with a physical work load (quarry workers, construction workers, assistant nurses, freight, and transport workers) have shown association with risk of developing RA. From a biological standpoint physical challenges to the joint and ensuing tissue injury may expose antigenic molecules that could trigger and /or perpetuate local activation of the immune system.

The aim of present study was to investigate the association between physical work load and the risk of developing rheumatoid arthritis (RA) with and without antibodies against cyclic citrullinated peptide (anti-CCP) and against native type II collagen (anti-CII).

Methods: A population based case-control study of individuals aged 18 to 70 years, living in geographically defined parts of Sweden between May 1996 and November 2009. We included incident cases (n=2268) diagnosed by rheumatologists according to the American College of Rheumatology 1987 criteria for RA and controls, matched to cases by age, sex, and area of residence (n=3176). All answered an extensive questionnaire, including questions about physical work load five years prior to study inclusion. In addition, we classified the individuals with regard to physical work load using Nordic Occupational Classification Code (NYK). We calculated odds ratios (OR) and 95% confidence intervals (CI) associated with physical work load by means of unconditional logistic regression models adjusted for matching factors, smoking, and education. Anti-CCP and anti-CII were measured by ELISA.

Results: Perceived physical work load was significantly associated with RA independent of anti-CCP-status OR 1.3 (95% CI 1.2–1.5) for anti-CCP positive RA and OR 1.5 (95% CI 1.3–1.8) for anti-CCP negative RA. The association was more pronounced in men. The occurrence of anti-CII showed no association to physical work load among RA patients.

Conclusion: Physical work load is associated with an increased risk to developing RA irrespective of anti-CCP status.

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2422

Anti-*P. Gingivalis* antibody Is Correlated With Severity Of Periodontitis But Not With Rheumatoid Arthritis Disease Activity In RA. Joo Youn Lee[1], In Ah Choi[2], Jin-Hee Kim[3], Kyung-Hwa Kim[4], Hye Jin Oh[5], Myeong Jae Yoon[6], Eun Young Lee[2], Eun Bong Lee[2], Yong-Moo Lee[3] and Young Wook Song[1]. [1]Department of Molecular Medicine and Biopharmaceutical Sciences, Seoul National University, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul National University, Seoul, South Korea, [3]Department of Periodontology, School of Dentistry, Seoul National University, Seoul, South Korea, [4]Department of Periodontology and Dental Research Institute, School of Dentistry, Seoul National University, Seoul, South Korea, [5]Seoul National University, Seoul, South Korea, [6]Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea.

Background/Purpose: Periodontitis (PD) has been suggested to be one of risk factors for rheumatoid arthritis (RA). *Porphyromonas gingivalis* (*P. ginvivalis, Pg*) is a gram-negative anaerobic bacterium that is recognized as a major pathogenic organism in periodontitis (PD). Anti-enolase 1 (ENO1) antibody is one of the autoantibodies in RA./This study examined the relationship between serum levels of anti-*Pg* and anti-ENO1 antibodies and PD severity and RA disease activity in patients with RA.

Methods: 248 Patients with RA and 85 age-, sex- matched non-RA controls were enrolled in this study. After rheumatologic and periodontal examination, serum levels of anti-*Pg* antibodies and anti-ENO1 antibodies were measured by enzyme-linked immunosorbent assay (ELISA).

Results: Patients with RA showed significantly higher levels of anti-*Pg* antibodies and, anti-ENO1 antibodies than controls ($P = 0.0082$, $P < 0.0001$). Anti-*Pg* antibodies were strongly correlated with anti-ENO1 antibodies in RA patients ($p<0.0001$). In active RA, there were significant correlations between anti-*Pg* antibodies with probing pocket depth (PPD), bleeding on probing (BOP) and clinical attachment level (CAL) ($P = 0.0015$, $P=0.006$, $P=0.0004$). However, there were no correlations of anti-*Pg* antibodies and periodontal parameters in controls and inactive RA. Anti-ENO1 titer did not correlate with periodontal parameters except bleeding on probing (BOP) in RA. Anti-*Pg* antibodies were not correlated with RA disease activity except ESR ($p= 0.0175$). However anti-ENO1 antibodies were significantly correlated with ESR, DAS28-ESR, anti-CCP titer ($P= 0.0008$, $P= 0.0092$, $P= 0.0129$).

Conclusion: Anti-*Pg* antibodies and anti-ENO1 antibodies were elevated in RA patients than controls. Anti- *Pg* antibodies were correlated with severity of PD and anti-ENO1 antibodies were correlated with RA disease activity in RA patients.

Disclosure: J. Y. Lee, None; **I. A. Choi**, None; **J. H. Kim**, None; **K. H. Kim**, None; **H. J. Oh**, None; **M. J. Yoon**, None; **E. Y. Lee**, None; **E. B. Lee**, None; **Y. M. Lee**, None; **Y. W. Song**, None.

2423

Mir-27b As Biomarker and Regulator Of IL-6R Pathway In Resistant Rheumatoid Arthritis Monocyte. Marina Frleta, Ashleigh-Ann Rainey, Derek S. Gilchrist, Lynn Crawford, Derek Baxter, Mariola Kurowska-Stolarska and Prof Iain B. McInnes. University of Glasgow, Glasgow, United Kingdom.

Background/Purpose: Whereas molecular mechanisms mediating treatment responses to biologic DMARDS in Rheumatoid Arthritis (RA) are emerging, those pathways that subserve treatment resistance are poorly explored. MicroRNAs (miRs) post-transcriptionally regulate different elements of given signal pathways, and as such capture a 'snapshot' of the cell state. We previously assembled a cross-sectional cohort of RA patients with distinct therapy response characteristics including rapid sustained response to conventional (c)DMARD, cDMARD failure and recurrent DMARD (conventional and biologic) resistance. We sought herein to identify dysregulated miR species in therapy resistant patients.

Methods: Peripheral blood (PB) CD14+ monocytes were isolated from three groups of RA patients meeting ACR 2010 criteria: good responders to cDMARD (n=20), failing cDMARDs (n=17) or resistant to biologic agents (n=30). Comparative samples from age-matched healthy volunteers (n=23) were obtained. Candidate miR profiling (based on cytokine receptor targeting miRs) was performed using real-time quantitative PCR. Potential miR-27a/b targets were identified using TargetScan with transcriptional pathway analysis data from PB RA CD14+ cells and functionally validated by Luciferase reporter assay. THP-1 cells were transfected with control or miRNA-27a/b antagomiR and membrane IL-6R expression evaluated by flow cytometry.

Results: We identified that miR-27b was significantly down-regulated in sorted CD14+ monocytes obtained from cDMARD failure and biologic treatment resistant, compared to cells from patients responding well to cDMARD and HV ($p<0.03$). Elevated levels of serum IL-6 were evident in both therapy resistant groups ($p<0.001$). TargetScan identified several potential miR-27 targets in the IL-6R signal pathway, including soluble and membrane bound variants of IL-6 receptor (IL-6R). Both IL-6R isoforms were confirmed as direct targets of miR-27a/b by luciferase reporter assay. Inhibition of endogenous miR-27a/b via antagomiR in THP-1 cells (myeloid line) significantly increased surface levels of Il-6R ($p=0.05$, n=4), demonstrating that miR-27a/b actively regulates membrane IL-6R expression.

Conclusion: Together our data uncover a previously unrecognized miR-27:IL-6R pathway interaction that operates particularly in monocytes of RA patients with active or treatment refractory disease. Our study thereby identifies a potential new biomarker and functional mechanism associated with disease chronicity.

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2424

Investigation Of The Role Of Histone Deacetylases In Rheumatoid Arthritis Synovial Fibroblasts. Sarah Hawtree, Munitta Muthana, Sarah Aynsley, J. Mark Wilkinson and Anthony G. Wilson. University of Sheffield, Sheffield, United Kingdom.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic, autoimmune, inflammatory disease that affects synovial joints. A key characteristic of RA is hyperplasia of fibroblast-like synoviocytes (FLS). These FLS develop an aggressive phenotype that augments tissue destruction and it is not currently known how their phenotype is stably maintained, however epigenetic changes have been implicated. Histone deacetylases (HDACs) are key enzymes that contribute to the epigenetic signature through changes in the acetylation status of histones. Recent studies have reported conflicting evidence of HDAC activity in RA synovium and FLS; however promising results were obtained using HDAC inhibitors in murine arthritis models and human juvenile arthritis. Further investigations into the specific role of individual HDACs in RA are required and may allow discovery of more specific therapeutic targets. Our aim is to determine the role of HDACs in maintaining the autoaggressive phenotype of RA FLS.

Methods: Fresh synovial biopsies obtained from RA and osteoarthritis (OA) patients were used to isolate FLS following digestion with collagenase-1. Real time-qPCR (RT-qPCR) was used to assess the levels of HDAC1–11 in RA FLS compared to OA FLS. To determine the cellular localization of HDACs, sections from patient arthroscopies were co-stained with anti-HDACs and anti-fibroblast antibody. In addition, HDACs and a non-targeting control (NTC) were knocked down in FLS using siRNA transfection; this was confirmed by RT-qPCR and western blotting. Cell viability after knockdown was assessed by flow cytometry using annexin V/propidium iodide dual staining. Cell invasion and migration after knock down were assessed using a matrigel invasion assay and a scratch assay, respectively.

Results: The mRNA levels of HDACs 1–11 are higher in RA compared to OA, with HDAC1 levels showing the greatest difference (4.3-fold higher). A 65% knockdown of HDAC1 ($HDAC1^{KD}$) mRNA was achieved using siRNA compared to a NTC (n=3 patients) and this did not affect cell viability (n=6) (>95.5% viable $HDAC^{KD}$ cells vs. >95% viable NTC cells). Using the matrigel invasion assay we found that $HDAC1^{KD}$ reduced the number of FLS invading the Matrigel ($p=0.02$) compared to the NTC (n=6). Also $HDAC^{KD}$ reduced the number of FLS migrating ($p=0.01$) compared to the NTC (n=6).

Conclusion: HDAC1 expression is increased in RA FLS compared to OA FLS. Knocking down HDAC1 in RA FLS does not affect cell viability but does reduce their ability to invade and migrate, suggesting that HDAC1 may contribute to the invasiveness and migration potential of RA FLS. Further

work will determine the effects of HDAC1 knockdown in FLS on proliferation and the expressed genome.

Disclosure: S. Hawtree, None; **M. Muthana**, None; **S. Aynsley**, None; **J. M. Wilkinson**, None; **A. G. Wilson**, None.

2425

Impaired TNFá Production By Dendritic Cells From Rheumatoid Arthritis Patients Upon Contact With Porphyromonas Gingivalis. Kim CM Santegoets, Mark H. Wenink, Wim B van den Berg and Timothy RDJ Radstake. Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.

Background/Purpose: The prevalence of periodontitis is increased in patients with rheumatoid arthritis (RA) and the severity of periodontitis can affect the level of arthritis. Porphyromonas gingivalis is one of the main bacteria causing periodontitis, it can citrullinate proteins and DNA from this bacterium is present in RA synovium. Our aim was to determine if there are differences in the innate immune response against P. gingivalis between healthy controls and RA patients.

Methods: We isolated monocytes from healthy controls, RA patients and psoriatic arthritis (PsA) patients and cultured them into monocyte-derived dendritic cells (DCs). DCs were stimulated with a set of bacteria possibly involved in RA (range of gram-negative and positive bacteria) including the periodontal bacteria P. gingivalis and Prevotella intermedia and single Toll-Like receptor (TLR) agonists (e.g. Pam3CSK4 and LPS). To determine which pathways could be involved in the different response between RA patients and healthy controls, P. gingivalis stimulation was performed in the presence of CXCR4 or CR3 blocking antibodies.

Results: TNFα production was significantly decreased by DCs from RA patients as compared to healthy controls upon stimulation with P. gingivalis, but not with any of the other bacteria tested. PsA patients were included as a diseased control group and did not differ from healthy controls, suggesting a RA specific deregulated response to P. gingivalis. The TNFα production upon P. gingivalis stimulation was similar in all medication groups and was not correlated with the presence of autoantibodies, disease activity or erosions. P gingivalis is mainly recognized via TLR2 and TLR4, of which the signaling pathways can be affected by simultaneous binding of the bacterium to CXCR4 or CR3. All these receptors were not differentially expressed between RA patients and healthy controls. Cytokine production upon specific TLR2 and TLR4 stimulation were not different between patients and controls and P. gingivalis stimulation was not affected by blocking of CXCR4. Blocking of CR3 however decreased the TNFα production by DCs from healthy controls to the level of the RA patients. The TNFα production in RA patients was not significantly decreased further by blocking of CR3, indicating that decreased signaling via CR3 is involved in the aberrant TNFα response towards P. gingialis by DCs from RA patients.

Conclusion: DCs from RA patients produce less pro-inflammatory cytokines upon P. gingivalis stimulation, which may be caused by defective CR3 signaling. The decreased cytokine response to P. gingivalis could facilitate its survival subsequently leading to a chronic systemic inflammatory status and the breakthrough of tolerance thereby facilitating RA onset.

Disclosure: K. C. Santegoets, None; **M. H. Wenink**, None; **W. B. van den Berg**, None; **T. R. Radstake**, None.

2426

Signaling Abnormalities In Neutrophil Granulocytes Of Rheumatoid Arthritis Patients Are Associated With Increased Extracellular Trap Formation and Provide a Basis For The Induction Of Anti-Citrullinated Peptide Antibodies. Chanchal Sur Chowdhury[1], Stavros Giaglis[1], Ulrich A. Walker[1], Andreas Buser[1], Paul Hasler[2] and Sinuhe Hahn[1]. [1]University Hospital Basel, Basel, Switzerland, [2]Kantonsspital Aarau, Aarau, Switzerland.

Background/Purpose: Rheumatoid arthritis (RA) is often associated with anti-citrullinated peptide antibodies (ACPAs) in the serum. While ACPAs have been associated with increased inflammation, joint destruction and reduced response to therapy, the mechanisms leading to the citrullination of arginine residues by peptidyl arginine deiminase (PAD) isozymes 2 and 4 on ACPA target antigens have remained unclear. PAD2 and PAD4 are present in polymorphonuclear granulocytes (PMNs), which represent the primary part of the leukocyteinfiltrate in the RA joint. Citrullination of histone by PAD4 is critical for neutrophil extracellular trap (NET) formation[1,2].

In the present study, we sought to investigate the signaling pathway leading to histone modification and NET extrusion in RA neutrophils.

Methods: Peripheral blood neutrophils from active RA patients and control subjects were isolated. Reactive oxygen species (ROS) production was evaluated by FACS utilizing a DCFH-DA assay. Spontaneous NET formation from RA and control neutrophils was observed by scanning electron (SEM) and SytoxGreen fluoresence microscopy. Combined immunostaining with anti-myeloperoxidase (MPO), anti-neutrophil elastase (NE), anti-PAD2, anti-PAD4, anti-citH3, anti-H1-core histones antibodies and staining with DAPI were applied for detailed characterization of the process. Protein translocation was confirmed by Western blotting.

Results: Peripheral blood PMNs from RA cases exhibited increased spontaneous NET formation *in vitro* assessed by fluorescence and SEM. This was associated with enhanced NE and MPO message and protein expression, elevated ROS production and translocation of PAD4 from the cytoplasm to the nucleus. Moreover, nuclear morphology and lobulation status indicated that RA PMN were in a significantly higher activation state from baseline. PAD4, together with PAD2, was found extruded and co-localized on NETs along with citrullinated histone (citH3) and DNA.

Conclusion: Altered signalling leading to NETosis and the extracellular presence of PAD4 and PAD2 could provide a mechanism for aberrant citrullination of relevant intra- and extracellular proteins and peptides. These findings suggest a novel explanation for *in vivo* autoantigen citrullination as a basis for ACPA induction, and implicate PMNs as key upstream factors in the pathogenesis of RA.

Disclosure: C. Sur Chowdhury, None; **S. Giaglis**, None; **U. A. Walker**, None; **A. Buser**, None; **P. Hasler**, None; **S. Hahn**, None.

2427

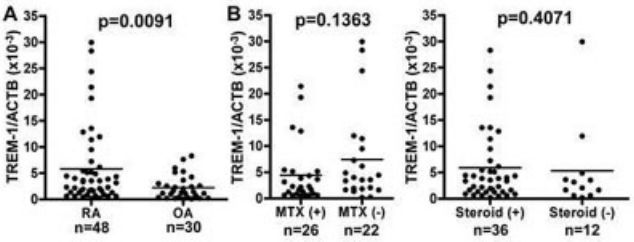
Enhanced Expression Of mRNA For Triggering Receptor Expressed On Myeloid Cells 1 In CD34+ Cells Of The Bone Marrow In Rheumatoid Arthritis. Tatsuo Nagai[1], Tetsuya Tomita[2], Hideki Yoshikawa[2] and Shunsei Hirohata[1]. [1]Kitasato University School of Medicine, Sagamihara, Japan, [2]Osaka University Graduate School of Medicine, Suita, Japan.

Background/Purpose: We previously showed that bone marrow (BM) CD34+ cells from rheumatoid arthritis (RA) patients have abnormal capacities to respond to tumor necrosis factor alpha and to differentiate into fibroblast-like cells producing MMP-1, resembling type B synoviocyte. In addition, we have recently demonstrated that the mRNA expression of nuclear factor kappa B1 (NFkB1) (p50), Krüppel-like factor 5 (KLF-5) and FK506-binding protein 5 (FKBP5) in BM CD34+ cells is significantly higher in RA patients than osteoarthritis (OA) patients. Triggering receptor expressed on myeloid cells 1 (TREM-1) is a recently identified cell surface receptor that is inducible mainly on monocytes and neutrophils, and plays an important role as amplifier of inflammatory response in acute and chronic inflammatory conditions. Recent studies have disclosed increased TREM-1 expression in rheumatoid synovial tissue, and have suggested that TREM-1 ligation contributes to the pathogenesis of RA. The current study therefore examined the mRNA expression of TREM-1 in BM CD34+ cells from RA patients.

Methods: BM samples were obtained from 48 patients with RA (6 males and 42 females: mean age 58.8 years) and 30 patients with OA (3 males and 27 females: mean age 71.1 years), who gave informed consent, during joint operations via aspiration from iliac crest. CD34+ cells were purified from the BM mononuclear cells by positive selection with magnetic beads. The expression of mRNA for TREM-1 was examined by quantitative reverse transcription PCR and is shown as the ratio of the copy numbers to those of beta-actin mRNA.

Results: The expression of mRNA for TREM-1 was significantly higher in RA BM CD34+ cells than OA BM CD34+ cells (Fig. A). The TREM-1 mRNA expression level was not correlated with serum C-reactive protein or with the administration of methotrexate or oral steroid (Fig. B). TREM-1 mRNA expression was significantly correlated with NFkB1 ($r=0.56$, $p<0.0001$), KLF-5 ($r=0.75$, $p<0.0001$) and FKBP5 ($r=0.62$, $p<0.0001$) mRNA expression in RA BM CD34+

cells.



Conclusion: These results indicate that the enhanced expression of TREM-1 mRNA in BM CD34+ cells plays a pivotal role in the pathogenesis of RA, and might be secondary to the enhanced mRNA expression of NFkB1, KLF-5 or FKBP5.

Disclosure: T. Nagai, None; **T. Tomita**, None; **H. Yoshikawa**, None; **S. Hirohata**, None.

2428

Suppression Of Tumor Necrosis Factor Receptor Associated Factor (TRAF) 6 Attenuates The Proinflammatory Effect Of Rheumatoid Arthritis Fibroblast-Like Synoviocytes. Lang Jing Zhu, Jing Jing Zhou, Chan Juan Zou, Dong Hui Zheng, Xiu Ning Wei, Jian Da Ma, Ying Qian Mo and Lie Dai. Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by chronic inflammatory synovitis, leading to invasion of synovial tissue into the adjacent cartilage matrix with degradation of articular cartilage and bone. Fibroblast-like synoviocyte (FLS) in RA synovium plays a key role by producing cytokines that perpetuate inflammation and proteases that contribute to cartilage destruction. Tumor necrosis factor receptor-associated factor 6 (TRAF6) is essential for signaling downstream of IL-1R/TLR superfamily which plays critical roles in the activation and proinflammatory effect of RA-FLS. We have reported that elevated synovial TRAF6 expression in RA correlated significantly with histological synovitis severity and cell density of subintimal mononuclear inflammatory cells. Here we aimed to investigate the TRAF6 expression and its role in the proinflammatory effect of RA-FLS.

Methods: Synovium from inflamed knees of active RA patients, and osteoarthritis (OA) as "less inflamed" disease control was collected by closed needle biopsy, and double immunofluorescence staining of TRAF6 and CD55 were tested. FLS were isolated from active RA synovium or OA synovium by modified tissue culture method. TRAF6 expression in primary cultured RA-FLS or OA-FLS was detected by immunofluorescence staining. TRAF6 in RA-FLS was depleted by Lentiviral-TRAF6-RNAi. The mRNA expression of proinflammatory cytokines, including TNF-a, IL-1β, IL-6 and IL-8, as well as MMP 3 and MMP13, was evaluated by Real-time PCR.

Results:(1) Double immunofluorescence staining showed TRAF6 was obviously expressed in CD55+ cells as well as some other CD55- cells in intimal and subintimal area of RA synovium (Fig 1). (2) Immunofluorescence staining showed obviously higher expression of TRAF6 in RA-FLS than in OA-FLS (Fig 2). (3) Lentiviral-TRAF6-RNAi infection effectively suppressed the expression of TRAF6 in RA-FLS. Suppression of TRAF6 attenuates the mRNA expression of proinflammatory cytokines, including TNF-a, IL-1β, IL-6 and IL-8, as well as MMP3 and MMP13 in RA-FLS.

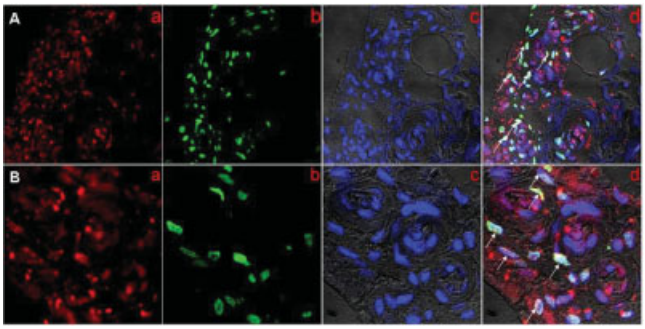


Fig 1. Representative confocal microscopic images showed TRAF6 and CD55 by indirect double immunofluorescence staining in RA synovium (A, original magnification *400; B, original magnification *1200. a, TRAF6 (red); b, CD55 (green); c, DAPI (blue); d, merged a, b with c. The white arrows point to intimal and subintimal CD55/TRAF6 double+ cells).

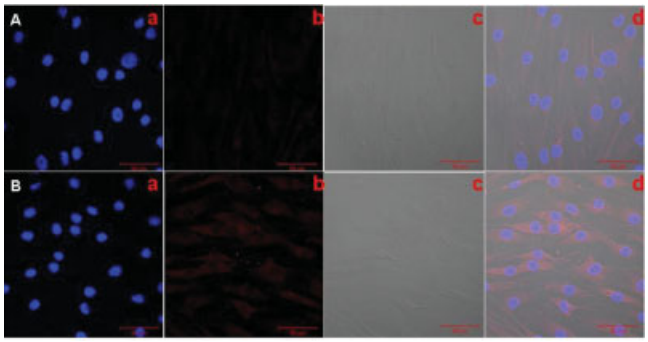


Fig 2. Immunofluorescence staining of TRAF6 in primary cultures of FLS from OA and RA patients. RA-FLS stained significantly positive with TRAF6 than OA-FLS (A: OA-FLS, B: RA-FLS; original magnification *400. a, DAPI (blue); b, TRAF6 (red); c, neutral light; d, merged a, b with c).

Conclusion: Elevated TRAF6 was involved in the pathogenesis of synovial inflammation and the proinflammatory effect of RA-FLS. TRAF6-blocking might provide novel target for the treatment of RA.

Disclosure: L. J. Zhu, None; **J. J. Zhou**, None; **C. J. Zou**, None; **D. H. Zheng**, None; **X. N. Wei**, None; **J. D. Ma**, None; **Y. Q. Mo**, None; **L. Dai**, None.

2429

Enhanced Responsiveness To Stimulation and Increased Extrusion Of Extracellular Traps By Rheumatoid Arthritis Neutrophil Granulocytes and of Healthy Control Neutrophils to Serum and Synovial Fluid From Rheumatoid Arthritis Patients. Stavros Giaglis[1], Chanchal Sur Chowdhury[1], Ulrich A. Walker[1], Andreas Buser[1], Sinuhe Hahn[1] and Paul Hasler[2]. [1]University Hospital Basel, Basel, Switzerland, [2]Kantonsspital Aarau, Aarau, Switzerland.

Background/Purpose: Polymorphonuclear granulocytes (PMNs) are the most abundant immune cell population in the synovial fluid in the joints of patients with rheumatoid arthritis (RA) and appear to play a central role in the inflammatory process leading to destruction of the cartilage.

Upon certain types of activation, PMNs extrude their nuclear content in the form of nucleoprotein threads, known as extracellular traps (NETs), which have extensive pro-inflammatory and immune-stimulatory activities[2].

The focus of the present study was to investigate the responsiveness of RA neutrophils to PMA and of healthy control neutrophils to RA serum and joint fluid.

Methods: Peripheral blood neutrophils from RA patients and control subjects were isolated and cultured with and without the addition of PMA, an established chemical trigger of NET formation. Cl-amidine, a chemical PAD4 inhibitor, was applied for inhibition studies. Spontaneous NET formation was evaluated with simultaneous immunostaining for myeloperoxidase (MPO), neutrophil elastase (NE) and DAPI, immunofluorescence microscopy and morphometry. PMNs from healthy donors were incubated with sera and synovial fluid from RA patients. NET formation by RA and control neutrophils was assessed by combined immunostainings with anti-PAD4, anti-cit-H3 and anti-H1-core histone antibodies, and DAPI. Cell-free nucleosomes were measured by ELISA, and PAD4 protein translocation from the cytoplasm to the nucleus was confirmed by Western blotting.

Results: Freshly isolated neutrophils from patients with RA showed enhanced spontaneous NET release after 3 hours compared to the healthy controls. Intriguingly, the population of neutrophils with delobulated/diffused nuclear phenotype was also remarkably higher in RA from the outset. Moreover, neutrophils derived from RA patients exhibited even higher rates of NETosis and PAD4 nuclear translocation after chemical stimulation with PMA. The effect of PMA was practically abolished by pre-treatment with Cl-amidine, a chemical PAD4 inhibitor, which plays a key role in modifying histones and triggering NETosis. Treatment of control neutrophils with either RA serum or RA synovial fluid augmented the release of NETs significantly compared to cells treated with normal serum or synovial fluid from OA patients, respectively.

Conclusion: RA neutrophils show enhanced NET formation that is mediated by PAD4 and is driven by factors present in the serum and synovial fluid from RA patients. Further investigations will more clearly define the role of NET formation in the innate and adaptive immune responses in RA.

Disclosure: S. Giaglis, None; **C. Sur Chowdhury**, None; **U. A. Walker**, None; **A. Buser**, None; **S. Hahn**, None; **P. Hasler**, None.

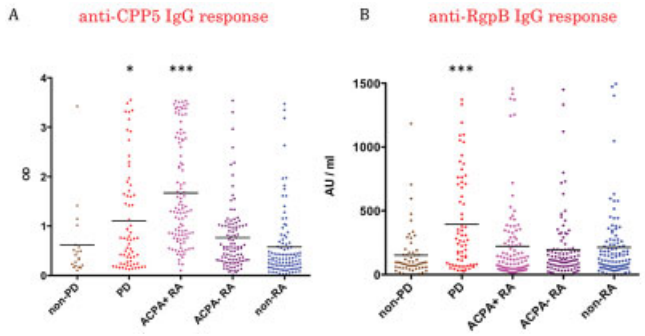
2430

Antibodies To *Porphyromonas Gingivalis* as An Etiological Clue To The Development Of Anti-Citrullinated Protein Antibody Positive Rheumatoid Arthritis. Nastya Kharlamova[1], Natalia Sherina[1], Anne-Marie Quirke[2], Kaja Eriksson[3], Lena Israelsson[4], Jan Potempa[5], Patrick Venables[2], Tulay Yucel-Lindberg[3] and Karin Lundberg[6]. [1]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Kennedy Institute of Rheumatology, Oxford, United Kingdom, [3]Department of Dentistry, Karolinska Institutet, Stockholm, Sweden, [4]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [5]Jagiellonian University, Krakow, Poland, [6]Rheumatology unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Rheumatoid arthritis (RA) is characterized by the production of autoantibodies to citrullinated proteins (ACPA). Citrullinated proteins are generated by the actions of peptidyl arginine deminase (PAD) enzymes during inflammation. Since ACPA can be detected prior to joint symptoms develop, it has been suggested that citrullination and break of tolerance to citrullinated proteins may be triggered outside the joint, potentially at mucosal surfaces. We hypothesize that *Porphyromonas gingivalis*, a major cause of chronic periodontitis (PD) and the only known pathogen to express PAD (*P.*PAD), is etiologically involved in the development of ACPA+ RA. We (Quirke, Potempa and Venables) have recently shown that autocitrullinated *P.*PAD is targeted by antibodies in RA, while arginine gingipain (another *P. gingivalis*-specific protein) is not. We have now investigated these antibody responses in more detail, with an aim to develop a serological test for diagnosing PD and to elucidate the potential link between PD and RA.

Methods: In-house ELISA assays, based on five different citrullinated *P.*PAD peptides (CPP3, 5, 6, 8 and 10), one arginine-containing control peptide (RPP3) and recombinant arginine gingipain protein (RgpB) were used to examine IgG responses in serum from: 102 ACPA+ RA cases; 98 ACPA- RA cases; 100 non-RA controls; 66 patients with confirmed PD; and 60 non-PD controls (confirmed by dentist). Mann-Whitney U-test for independent groups was used to determine statistical differences.

Results: The anti-CPP3 IgG response associated only, strongly and significantly with ACPA+ RA, while no antibody response was recorded towards RPP3. Also anti-CPP6 and 8 IgG showed similar association with ACPA+ RA, while the anti-CPP5 response also associated with confirmed PD (fig 1A). No anti-CPP10 IgG response could be detected in any subgroup. The antibody response towards RgpB associated mainly and significantly with confirmed PD. Compared to non-PD controls, anti-RgpB IgG levels were also increased in ACPA+ RA, ACPA- RA and non-RA controls, although no statistical significance could be detected between the groups (fig 1B).



Conclusion: Based on these results, anti-RgpB IgG could potentially be used as a serological marker to identify PD-cases retrospectively. This would be of great help when investigating the etiological link between PD and RA, or PD and other inflammatory diseases, since validated information on periodontal status is often lacking, while serum cohorts are available. The antibody-response to citrullinated *P.*PAD in RA could be confirmed and evaluated in more detail. This antibody response was confined to ACPA+ RA and specific epitopes, where CPP5 was particularly interesting as antibodies associated with both ACPA+ RA and PD, supporting the hypothesis that PD/*P. gingivalis* may be causatively linked to the development of ACPA+ RA.

Disclosure: N. Kharlamova, None; **N. Sherina**, None; **A. M. Quirke**, None; **K. Eriksson**, None; **L. Israelsson**, None; **J. Potempa**, None; **P. Venables**, None; **T. Yucel-Lindberg**, None; **K. Lundberg**, None.

2431

Association Of T Follicular Helper / Th17 T Cell and Memory B Cell Populations In Rheumatoid Arthritis With Disease Activity and Therapy With TNF Antagonists. Marc C. Levesque[1], Camilla Macedo[1], Lisa Boyette[1], Kevin Hadi[2], Erich R Wilkerson[1], Diana Metes[1], Larry W. Moreland[1] and Mandy J. McGeachy[2]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Univeristy of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Autoreactive memory B cells and T cells contribute to the pathogenesis of rheumatoid arthritis (RA) through production of antibodies and cytokines that activate monocytes and joint stromal cells. Memory B cells and T cells react to similar citrullinated joint proteins, and have been shown to decrease in response to therapy with TNF inhibitors. However, interactions between these cells have not been interrogated in the same RA patients in relation to disease activity and therapy response.

Methods: We obtained RA PBMC samples from the Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry. 26 subjects were selected based on disease activity (19 patients with active disease (Clinical Disease Activity Index (CDAI) > 2.8) and 7 patients in remission (CDAI ≤ 2.8)). Subjects were treated with methotrexate (MTX) ($n = 14$) or with a TNF inhibitor plus MTX ($n = 12$). Nine healthy subjects served as controls. We performed flow cytometry on PBMC to analyze monocyte and T and B cell subsets. Mann-Whitney tests were used for unpaired comparisons of T and B cell populations from RA subjects and healthy controls. Spearman's rho was determined for correlations of T and B cell populations with disease activity.

Results: The frequencies of peripheral blood classical, non-classical and intermediate monocytes were not different between RA subjects and healthy controls, and were not associated with disease activity or therapy. Of CD4+ T helper (Th) subsets, $CXCR5^{high}$ T follicular helper (TFh)-like cell subsets that co-expressed CCR6 ($CXCR5^{high}$ Th17) were increased in RA compared to healthy controls ($p = 0.0082$), and there was a trend towards increased frequencies of $CXCR5^{high}$ Th17 cells in patients with active disease compared to remission. In contrast, $CXCR3^{+}$TFh cells ($CXCR5^{high}$Th1) showed the opposite pattern, and were decreased in RA patients with active disease ($p < 0.0004$), but unchanged between those in remission and healthy controls. This resulted in significantly higher $CXCR5^{+}$Th17:$CXCR5^{+}$Th1 ratios in active RA patients compared to healthy controls ($p < 0.01$) or to patients in remission ($p < 0.05$). For these T cell populations, there was no association with treatment or between T helper subsets and memory B cell subsets. However, the proportion of isotype-switched memory B cells was positively correlated with disease activity in the MTX group (rho $= 0.54$, $p = 0.05$) but not TNF inhibitor plus MTX group (rho $= 0.37$, $p = 0.24$).

Conclusion: TFh/Th17 cells and memory B cells were both increased in RA while TFh/Th1 cells were decreased in active RA. Disease activity correlated with class-switched memory B cells in subjects treated with MTX but not with TNF antagonists. Although TNF inhibitors have been reported to decrease Th17 cell populations, our results suggest that disease activity rather than therapy may have a greater effect on frequencies of TFh/Th17 and TFh/Th1 cells.

Disclosure: M. C. Levesque, Genentech and Biogen IDEC Inc., 2, Genentech and Biogen IDEC Inc., 5; **C. Macedo**, None; **L. Boyette**, None; **K. Hadi**, None; **E. R. Wilkerson**, Genentech and Biogen IDEC Inc., 2; **D. Metes**, None; **L. W. Moreland**, Genentech and Biogen IDEC Inc., 2; **M. J. McGeachy**, None.

2432

Characterization Of Lung Inflammation and Identification Of Shared Citrullinated Targets In The Lungs and Joints Of Early RA. Vijay Joshua[1], Gudrun Reynisdottir[1], Jimmy Ytterberg[2], Marianne Engström[1], Anders Eklund[3], Magnus Skold[3], Per-Johan Jakobsson[1], Johan Rönnelid[4], Vivianne Malmström[5], Lars Klareskog[1], Johan Grunewald[3] and Anca I Catrina[1]. [1]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [2]Rheumatology Unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [3]Division of Respiratory Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [4]Uppsala University, Uppsala, Sweden, [5]Rheumatology unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden.

Background/Purpose: To investigate if lung changes are present in rheumatoid arthritis (RA) patients early in the disease process and to address the contribution of these changes to disease initiation.

Methods: 24 RA patients with patient-reported symptom duration less than 1 year and naive to DMARD treatment and 9 healthy individuals were subjected to bronchoscopy and mucosal large bronchial biopsies were retrieved. Histological analysis for identification of inducible bronchia associated lymphoid tissues (iBALT) and lymphocyte infiltration, as well as immunohistochemistry for PAD enzymes, CD3, HLA-DQ and HLA-DR were performed. Presence of citrullinated targets were detected by immunohistochemistry using biotinylated ACPA isolated from synovial fluid of RA patients. Mass spectrometry was used for identification of citrullinated epitopes in 6 of the lung biopsies and additional 8 synovial RA biopsies. An in house ELISA was set-up to measure reactivity against new identified citrullinated targets in the blood of RA patients in two distinct cohorts (in total 250 individuals).

Results: Bronchial lymphocyte infiltration and iBALT formation was observed in half of the ACPA+ RA patients but only 1 out of 6 ACPA- patients (17%) and 1 out of 9 healthy volunteers (10%). Higher expression of CD3, HLA-DQ, HLA-DR and citrullinated targets was observed in bronchial biopsies of ACPA+ as compare to ACPA- RA. BAL fluids were enriched in both IgG and IgA ACPA as compared to paired serum samples. Mass spectometry identified 5 proteins in the synovium (in total 8 sites) and 4 in the lungs (in total 6 sites) containing citrullinated residues. Two vimentin derived citrullinated peptides were present in a majority of both synovial and lung biopsies with slightly higher citrullinated/unmodified peptides ratios in the smokers as compared to non-smokers. An average of 15% of the RA patients tested by ELISA showed antibody reactivity against one of the new identified citrullinated target.

Conclusion: Signs of inflammation and local ACPA enrichment are present early in bronchial tissues of ACPA+ RA patients. Shared citrullinated targets in the lung and joints as well as systemic reactivity against these targets are present in RA patients. Our findings support the notion that early inflammatory events in the lungs may represent a critical initiating factor in the development of ACPA+ RA.

Disclosure: V. Joshua, None; **G. Reynisdottir**, None; **J. Ytterberg**, None; **M. Engström**, None; **A. Eklund**, None; **M. Skold**, None; **P. J. Jakobsson**, None; **J. Rönnelid**, None; **V. Malmström**, None; **L. Klareskog**, None; **J. Grunewald**, None; **A. I. Catrina**, None.

ACR/ARHP Poster Session C
Spondylarthropathies and Psoriatic Arthritis: Clinical Aspects and Treatment III
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

2433

Evaluation Of The Two-Step Referral Strategy For Axial Spondyloarthritis In The Spondyloarthritis Caught Early Cohort. Ozair Abawi[1], Rosaline van den Berg[1], Désirée van der Heijde[1], Manouk de Hooge[1], Pauline Bakker[1], Monique Reijnierse[1], Tom Huizinga[1], Juergen Braun[2] and Floris van Gaalen[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Rheumazentrum Ruhrgebiet, Herne, Germany.

Background/Purpose: Currently, in primary care no satisfactory referral model exists for referral to the rheumatologist of patients with chronic back pain (CBP) with possible axial spondyloarthritis (axSpA). Recently, a non-invasive, inexpensive and easily applicable two-step referral strategy was developed, based on a computer-generated model.[1]The aim of our study was to validate this two-step referral strategy in the SPondyloArthritis Caught Early (SPACE)-cohort.

Methods: In the first step of the referral strategy, the presence of psoriasis, alternating buttock pain (ABP) and improvement of back pain by exercise (IBPE) were registered. If ≥2 of these anamnestic features are present, the patient is referred to a rheumatologist. In the second step, if ≤1 anamnestic feature is present, HLA-B27 testing is performed; if the result is positive, the patient is also referred. The required data was obtained from the SPACE-cohort, in which patients with CBP (≥3 months, ≤2 years, onset <45 years) were included (n=192). The model was tested in this cohort; the performance of the model was evaluated by calculating sensitivity, specificity and likelihood ratios (LR) using classification by ASAS axSpA criteria as external standard.[2] For the patients which were erroneously referred or erroneously not referred, post-test probabilities for axSpA were calculated based on LR products for the presence of SpA features[3], with a LR product of ≥78 which equals a probability of ≥80% defined as cut-off value for probable axSpA.

Results: A total of 74/192 patients had axSpA (ASAS), 61 of which would have been referred according to the strategy, yielding a sensitivity of 82.4%. The 13 false negatives are obligatory HLA-B27 negatives, have ≥1 SpA feature and sacroiliitis on imaging, 3/13 (23%) of which on X-ray. The referral strategy would have referred a total of 93/192 patients, yielding a specificity of 72.9%. Out of the false positive patients, 8/32 (25%) would have been referred erroneously due to HLA-B27 positivity in absence of ≥2 SpA features. Half of these 32 patients (n=16; 50%) had a combination of ABP and IPBE, which are features of inflammatory back pain, which itself is not specific for axSpA. Although none of these false positives fulfil the ASAS axSpA criteria, 6/32 (19%) had probable axSpA (probability ≥80%) (table).

Referred to rheumatologist by referral strategy	axSpA by ASAS criteria Yes	No		
Yes	61	32		
No	13	86		
Sensitivity: 82.4%	Specificity: 72.9%	LR+: 3.04	LR-: 0.24	

Number of anamnestic features present in false positive patients (n=32)	Post-test probability for axSpA 0–20% n (%)	20–50% n (%)	50–80% n (%)	≥80% (probable axSpA) n (%)
3: ABP, IBPE and psoriasis (n=2)	1 (3)	0 (0)	0 (0)	1 (3)
2: ABP and IBPE (n=16)	8 (25)	3 (9)	3 (9)	2 (6)
Psoriasis and IBPE (n=5)	2 (6)	2 (6)	0 (0)	1 (3)
ABP and psoriasis (n=1)	1 (3)	0 (0)	0 (0)	0 (0)
1*: ABP (n=2)	0 (0)	0 (0)	0 (0)	2 (6)
IBPE (n=3)	0 (0)	0 (0)	3 (9)	0 (0)
Psoriasis (n=0)	n/a	n/a	n/a	n/a
0* (n=3)	0 (0)	1 (3)	2 (6)	0 (0)

Number of anamnestic features present in false negative patients (n=13)	Post-test probability for axSpA 0–20% n (%)	20–50% n (%)	50–80% n (%)	≥80% (probable axSpA) n (%)
1: ABP (n=2)	0 (0)	1 (8)	0 (0)	1 (8)
IBPE (n=7)	3 (23)	2 (15)	0 (0)	2 (15)
Psoriasis (n=2)	0 (0)	1 (8)	1 (8)	0 (0)
0 (n=2)	0 (0)	0 (0)	0 (0)	2 (15)

Anamnestic features: ABP=alternating buttock pain; IBPE=improvement of back pain by exercise; psoriasis.
*: These patients are referred due to HLA-B27 positivity, not anamnestic features.

Conclusion: The two-step referral strategy performed well in the SPACE-cohort. These results show the potential of simple referral strategies for the early recognition of axSpA. However, all patients in this study had already been referred to the rheumatologist. Thus, the performance of this model in its target population (i.e. primary care) remains to be addressed in further studies.

References:
(1) Braun A et al. Rheumatology (Oxford), 2013 Apr 4 [Epub] doi: 10.1093/rheumatology/ket115
(2) Rudwaleit M et al. Ann Rheum Dis, 2009;68:777–783
(3) Rudwaleit M et al. Ann Rheum Dis, 2004;63:535–543

Disclosure: O. Abawi, None; **R. van den Berg**, None; **D. van der Heijde**, None; **M. de Hooge**, None; **P. Bakker**, None; **M. Reijnierse**, None; **T. Huizinga**, None; **J. Braun**, None; **F. van Gaalen**, None.

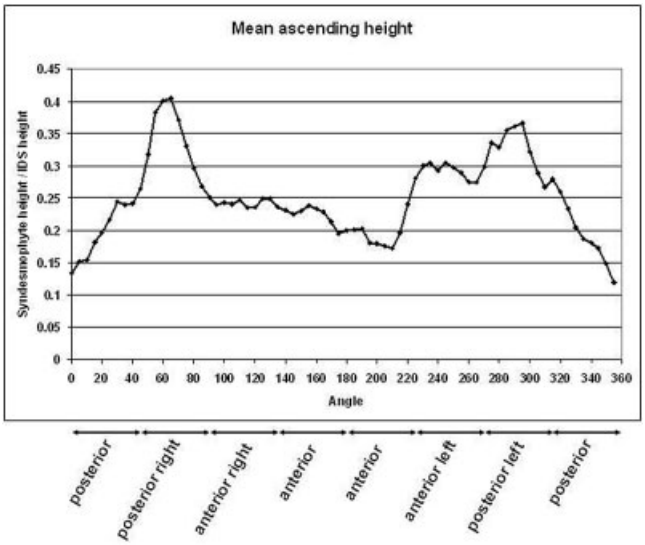
2434

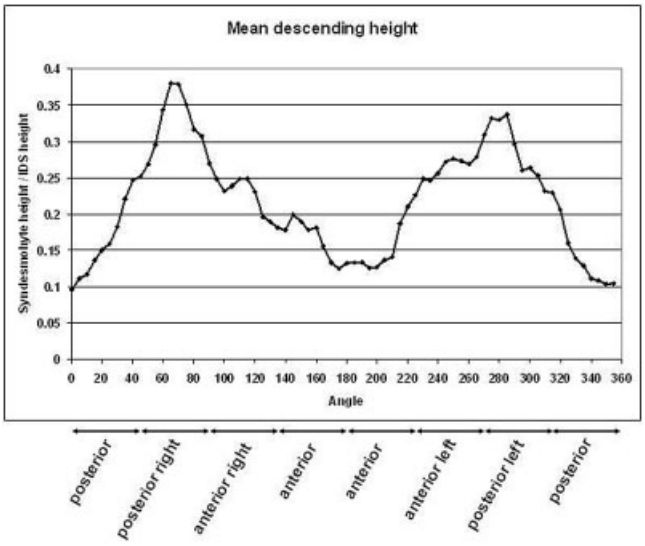
Syndesmophyte Distribution Along The Vertebral Rim In Ankylosing Spondylitis Is Non-Random. Sovira Tan[1], Abhijit Dasgupta[1], Jianhua Yao[2], John A. Flynn[3], Lawrence Yao[2] and Michael M. Ward[1]. [1]NIAMS/NIH, Bethesda, MD, [2]NIH Clinical Center, Bethesda, MD, [3]Johns Hopkins University, Baltimore, MD.

Background/Purpose: Syndesmophytes, the hallmark of structural damage in ankylosing spondylitis (AS), are typically visualized 2-dimensionally by radiographs. However, these projections only allow a limited view of syndesmophytes and their locations along the vertebral rim. With computed tomography (CT), a clear and complete view of syndesmophytes and their precise location is possible. The question immediately arises whether the distribution of syndesmophytes along the vertebral rim is random, as might be suspected if due to inflammation alone, or if they occur more commonly at particular locations. The radial distribution of syndesmophytes along the vertebral rim, if not random, could provide clues about the drivers of syndesmophyte development.

Methods: We scanned 38 patients (31 men and 7 women, mean age of 46.1 years) at the thoracolumbar junction (T10 to L4) using CT, providing 4 intervertebral disk spaces (IDS) per patient for analysis. Syndesmophytes were identified by a computer algorithm that detects them as bone projecting from the periphery of vertebral endplates. We divided the vertebral rim into angular sectors and measured syndesmophyte height every five degrees. We standardized syndesmophyte height by dividing by the height of the disk so that a value of 1 indicated bridging. We plotted radial heights for both ascending and descending syndesmophytes. Bridged syndesmophytes were counted as both ascending and descending. We used the permutation testing for correlated angular data devised by Follmann and Proschan to assess whether the distribution around the rim was uniform or not.

Results: Of 152 IDSs processed, 95 had syndesmophytes. For both ascending and descending syndesmophytes, the mean height distribution along the vertebral rim was non-random ($p<.0001$ for both). The mean radial height plots show that the most common location for syndesmophytes was posterolateral (Figure). The second most common location was anterior left. Ascending syndesmophytes were more frequent and taller than descending syndesmophytes. In a separate analysis, we sorted the 95 IDSs in rank order of increasing fusion. Isolated syndesmophytes and small (early) syndesmophytes were most common in the posterolateral left and posterolateral right locations, suggesting that syndesmophyte growth most often begins at these locations.





Conclusion: The distribution of syndesmophytes along the vertebral rim is strongly non-random, with posterolateral the most common location. The non-random distribution suggests that mechanical factors may be a driver of syndesmophyte growth.

Disclosure: S. Tan, None; **A. Dasgupta**, None; **J. Yao**, None; **J. A. Flynn**, None; **L. Yao**, None; **M. M. Ward**, None.

2435

Prevalence Of Inflammatory Lesions MRI-Spine In Patients With Chronic Back Pain Of ≤2 Years Duration Included In The SPACE-Cohort. Manouk de Hooge[1], Rosaline van den Berg[1], Monique Reijnierse[1], Victoria Navarro-Compán[1], Floris van Gaalen[1], Karen Fagerli[2], Maureen C. Turina[3], Maikel van Oosterhout[4], Roberta Ramonda[5], Tom Huizinga[1] and Désirée van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [4]GHZ Hospital, Gouda, Netherlands, [5]University of Padova, Padova, Italy.

Background/Purpose: Inflammatory lesions of the spine are not included in the ASAS definition of a positive MRI for fulfilment of the ASAS axial spondyloarthritis (axSpA) criteria[1]. However, inflammatory lesions in the spine on MRI (MRI-spine) may occur in the absence of affected sacroiliac joints (SIJ). Therefore the aim of this study is to determine the prevalence of inflammatory lesions on MRI-spine and to investigate if axSpA patients with inflammatory lesions in the spine only exist.

Methods: The SPondyloArthritis Caught Early (SPACE)-cohort includes patients with chronic back pain (≥3 months, ≤2 years, onset <45 years) recruited from 5 participating centres in Europe. All patients underwent MRI of the SIJ (MRI-SI) and MRI-spine scored by 3 well-calibrated readers independently. MRI-SI were scored according to the ASAS definition[1] (the presence of ≥1 lesion on ≥2 consecutive slices or the presence of >1 lesion on a single slice). Inflammatory lesions on MRI-spine suggestive of spondylitis were scored when visible on ≥2 consecutive slices and according to the ASAS/OMERACT consensus definition[2] (the presence of ≥3 lesions on ≥2 consecutive slices). Lesions were considered present if 2/3 readers agreed.

Results: All patients with MRI-spine (n=306) were included to determine the prevalence of BME lesions in patients grouped according to the ASAS axSpA criteria (radiographic, non-radiographic (imaging & clinical arm), possible SpA (presence of ≥1 SpA features with a Likelihood Ratio (LR+) of ≥6 or ≥2 SpA features with a LR+ <6) and no-SpA (see table). In 292 patients MRI-SI and MRI-spine data were both available. There were 51 patients with a positive MRI-spine, of which 30 patients (58.8%) had a negative MRI-SI. Nine of these 30 patients fulfilled the ASAS axSpA criteria via the clinical-arm. Of the remaining 21 patients, 3 patients had no SpA features at all, 7 patients had 1 SpA feature, 8 patients had 2 SpA features, 1 patient had 3 SpA features and 2 patients had 4 SpA features. Only the sole patient with 4 SpA features had a probability (calculated from the LR+) ≥80%. When using the ASAS consensus definition of a positive MRI-spine in post-test probability calculations, another 6 patients would reach a probability ≥80% of having axSpA.

MRI-Spine	AxSpA (ASAS axSpA) n=126		Possible axSpA (≥1 SpA features with LR+ ≥6 or 2 with LR+ <6)		No-SpA n=64
	Imaging-arm n=72				
	mNY+ n=26	mNY− n=46	Clinical-arm, n=54	n=116	
BME lesion >1	12 (46.2%)	23 (50%)	17 (31.5%)	29 (25%)	17 (26.6%)
BME lesion >2	10 (38.5%)	16 (34.8%)	11 (20.4%)	21 (18.1%)	9 (14.1%)
BME lesion >3	8 (30.8%)	11 (23.9%)	3 (5.6%)	12 (10.3%)	4 (6.3%)
BME lesion >4	7 (26.9%)	7 (15.2%)	2 (3.7%)	5 (4.3%)	3 (4.7%)
BME lesion >5	6 (23.1%)	4 (8.7%)	1 (1.9%)	3 (2.6%)	2 (3.1%)
BME lesion >6	4 (15.4%)	3 (6.5%)	1 (1.9%)	2 (1.7%)	1 (1.6%)
BME lesion >7	4 (15.4%)	2 (4.3%)	1 (1.9%)	2 (1.7%)	0

Conclusion: A cut-off of ≥3 BME lesions discriminates well between patients with and without axSpA. A positive MRI-spine can be present in patients without inflammation on MRI-SI. MRI-spine might have (limited) additional value to MRI-SI in a group of patients with a certain level of suspicion of axSpA.

Reference:
[1]Rudwaleit ARD 2009;68:1520–7 [2]Hermann ARD 2012;71:1278–88

Disclosure: M. de Hooge, None; **R. van den Berg**, None; **M. Reijnierse**, None; **V. Navarro-Compán**, None; **F. van Gaalen**, None; **K. Fagerli**, None; **M. C. Turina**, None; **M. van Oosterhout**, None; **R. Ramonda**, None; **T. Huizinga**, None; **D. van der Heijde**, None.

2436

Classification Of Axspa Based On Positive Imaging (Radiographs and/or MRI of the Sacroiliac Joints) By Local Rheumatologists Or Radiologists Versus Central Trained Readers In The DESIR-Cohort. Rosaline van den Berg[1], Grégory Lenczner[2], Fabrice Thévenin[3], Pascal Claudepierre[2], Antoine Feydy[3], Monique Reijnierse[1], Alain Saraux[4] and Désirée van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Henri Mondor Teaching Hospital, AP-HP, Créteil, France, [3]Paris Descartes University, Côchin Hospital, APHP, Paris, France, [4]Université Brest Occidentale, Brest, France.

Background/Purpose: Sacroiliitis on MRI and X-rays play an important role in the ASAS axial spondyloarthritis (axSpA) criteria[1]. Though, recognition of sacroiliitis on X-rays (X-SI) and MRI of the sacroiliac joints (MRI-SI) can be challenging, resulting in misinterpretations. Usually the reading in clinical trials is done by ≥1 trained readers. In cohorts it varies and in the DEvenir des Spondylarthropathies Indifferenciées Récentes (DESIR)-cohort, X-SI and MRI-SI at inclusion are read by a local radiologist/rheumatologist. The impact on classification of patients (pts) by local read (LocR) instead of centralized read (CentR) is unknown. We investigated the difference in classification of pts (ASAS axSpA) using LocR versus CentR as external standard.

Methods: In the DESIR-cohort, pts aged 18–50 with inflammatory back pain (IBP; ≥3 months, ≤3 years) were included (n=708). Local radiologists/rheumatologists read all baseline X-SI and MRI-SI; X-SI according to a method derived from the modified New York (mNY) criteria[2] (grade 2 and 3 pooled in one combined grade 'DESIR-2'). Sacroiliitis was defined by at least unilateral ≥DESIR-2. Sacroiliitis on MRI was defined as definite inflammatory lesions in ≥1 SI-joint. Next, 2 well-calibrated central readers independently read all X-SI (original mNY) and MRI-SI (ASAS[3]). An experienced radiologist was adjudicator in case the 2 readers disagreed. An image was marked positive if 2/3 readers agreed. Subsequently, LocR was compared to CentR and to the reads by the central readers separately; pts were classified (ASAS axSpA), using both LocR and CentR (external standard).

Results: Pts with onset IBP <45 and complete X-SI and MRI-SI (n=582) were included. LocR and CentR differed in 163/582 pts (28%; 91 X-SI; 59 MRI-SI; 13 both X-SI and MRI-SI). In 46/582 pts (7.9%), a different read resulted in a different classification; 18 no-SpA pts (3.1%) based on CentR were classified as axSpA using LocR (14 with positive X-SI); 28 axSpA pts (4.8%; 13 mNY+) based on CentR were classified as no-SpA using LocR (table). Among the patients classified as axSpA, additional discrepancies occurred if fulfilling the imaging arm was considered; 16 axSpA/582 pts (2.7%; 8 mNY+) fulfilled the imaging arm based on CentR but fulfilled the clinical arm based on LocR, and 29 axSpA pts (5.0%) fulfilled the clinical arm based on CentR but fulfilled the imaging arm based on LocR (table). Comparisons of LocR versus the separate readers show very similar results (table).

Patients in which the local and centralized read (2/3 readers) differed, n=163			Centralizedread(2/3readers)		
			axSpA (ASAS+)		No SpA (ASAS−)
			Imaging+	Imaging−	
Local reads	axSpA (ASAS+)	Imaging+	72	29	*18*
		Imaging−	16	–	–
	No SpA (ASAS−)		*28*	–	–
Patients in which the local read and central reader 1 differed, n=189			**Central reader 1**		
			axSpA (ASAS+)		No SpA (ASAS−)
			Imaging+	Imaging−	
Local reads	axSpA (ASAS+)	Imaging+	74	28	*18*
		Imaging−	26	–	–
	No SpA (ASAS−)		*43*	–	–
Patients in which the local read and central reader 2 differed, n=170			**Central reader 2**		
			axSpA (ASAS+)		No SpA (ASAS−)
			Imaging+	Imaging−	
Local reads	axSpA (ASAS+)	Imaging+	68	28	*23*
		Imaging−	26	–	–
	No SpA (ASAS−)		*30*	–	–

Only patients in which the local and centralized reads (either X-SI or MRI-SI, or both) differed are selected.
Imaging+ could be either a positive X-SI or a positive MRI-SI, or both positive.
Imaging- indicates that patients fulfil the clinical-arm only.
In the upper part the centralized read (2/3; CentR) is used as external standard to compare the local reads (LocR).
In the lower part the separate readers are used as external standard to compare the local reads (LocR).

Conclusion: Looking at the complete ASAS axSpA criteria, the classification changed in 7.9% of the pts when using LocR instead of CentR. However, when interested in whether pts fulfil the imaging arm or not, changes are seen in an additional 8.2% of the pts resulting in 15.6% of the pts classified differently.

References:
[1]Rudwaleit ARD 2009;68:777–83. [2]van der Linden A&R 1984;27:361–8.
[3]Rudwaleit ARD 2009;68:1520–7

Disclosure: R. van den Berg, None; **G. Lenczner**, None; **F. Thévenin**, None; **P. Claudepierre**, None; **A. Feydy**, None; **M. Reijnierse**, None; **A. Saraux**, None; **D. van der Heijde**, None.

2437

Prevalence Of Axial Spondyloarthritis In The United States Among Patients With Chronic Back Pain and Other Spondyloarthritis-Related Features. Atul Deodhar[1], Philip J. Mease[2], Jeffrey R. Curtis[3], Piyalal M. Karunaratne[4], Kailash Malhotra[4] and Aileen L. Pangan[4]. [1]Oregon Health & Science University, Portland, OR, [2]University of Washington and Swedish Medical Center, Seattle, WA, [3]University of Alabama at Birmingham, Birmingham, AL, [4]AbbVie Inc., North Chicago, IL.

Background/Purpose: The age-adjusted prevalence of spondyloarthritis (SpA) has been estimated to be 0.9–1.4% of the US population using the Amor and ESSG criteria. The objective of this study was to determine the prevalence of non-radiographic axial SpA (nr-axSpA) based on the Assessment of Spondyloarthritis International Society (ASAS) axial SpA criteria among undiagnosed patients (pts) with chronic back pain.

Methods: This is an ongoing, non-drug, multicenter study in the US. Pts previously undiagnosed with SpA, who have had chronic back pain for ≥3 months, with age at onset of <45 years, and at least 1 of the following: 1) positive HLA-B27, 2) current inflammatory back pain, or 3) imaging (MRI or x-ray) evidence of sacroiliitis were included. Pts were either new referrals from other physicians, self-referred, or existing pts in the rheumatologist's clinic. Medical history, physical exam findings, disease activity measures, and laboratory and imaging test results were collected. The rheumatologist was asked if a diagnosis of axial SpA could be made based on this information and the level of confidence with the diagnosis. Data collected were then analyzed independently to determine which patients are classified as nr-axSpA based on fulfillment of the ASAS criteria for axial SpA, but not modified New York (modNY) criteria for ankylosing spondylitis (AS).

Results: As of February 2013, 459 pts have been enrolled (31.6% new referrals, 6.5% self-referred, and 61.9% existing pts at the site). 210 (46%) pts fulfilled ASAS criteria, of whom 146 (32%) were classified as nr-axSpA (fulfilled ASAS but not modNY criteria), 59 (13%) classified as AS (fulfilled ASAS and modNY criteria), and 5 (1%) had missing data that did not allow for evaluation of fulfillment of the modNY criteria. Of those who fulfilled ASAS criteria and had available data, 74% were also given a diagnosis of axial SpA by the investigator (95% of those classified as AS and 64% of those classified as nr-axSpA). In addition, 20% of pts who did not fulfill ASAS criteria were given a diagnosis of axial SpA by the investigator, although the overall level of confidence in the diagnosis was lower for these pts. Demographics and disease characteristics for pts classified as nr-axSpA are presented in the Table.

Table. Baseline Demographics and Disease Characteristics of Patients Classified as nr-axSpA*

Characteristic	nr-axSpA N=146
Gender, n (%)	
Female	76 (52.1)
Age (years)	
Mean (SD)	40 (12.3)
Duration of chronic back pain (months)	
Mean (SD)	166 (145.7)[a]
Age at onset of chronic back pain (years)	
Mean (SD)	27 (9.3)[a]
Human leukocyte antigen-B27 (HLA-B27), n (%)	
Positive	110 (75.3)
Bath AS functional index (BASFI)	
Mean (SD)	4.4 (2.6)
Bath AS disease activity index (BASDAI)	
Mean (SD)	5.9 (2.1)
AS Disease Activity Score (ASDAS)	
Mean (SD)	2.3 (0.8)[b]
hs-CRP or CRP, category	
Elevated	48 (34.3)[b]
Missing	6

*fulfilled ASAS but not modNY criteria
[a]n=144. [b]n=140

Conclusion: Almost half of pts enrolled with chronic back pain and at least 1 SpA-related feature were classified as having axial SpA based on ASAS criteria. Two-thirds of these axial SpA pts had nr-axSpA, with an average of 14 years of symptoms, indicating a substantial delay in diagnosis. The majority of pts who fulfilled ASAS criteria were also diagnosed as having axial SpA by US rheumatologists, but a quarter of these patients were not.

Disclosure: A. Deodhar, AbbVie, Merck-Sharp-Dohme, Pfizer and UCB, 5, AbbVie, Merck-Sharp-Dohme, Pfizer and UCB, 8, AbbVie, Amgen, Novartis, UCB, 2; **P. J. Mease**, AbbVie, Amgen, BiogenIdec, Bristol-Myers Squibb, Genentech, GlaxoSmith-Kline, Janssen Lilly, Merck, Merck-Serono, Novartis, Novo-Nordisk, Pfizer, Roche, UCB, and Vertex, 2, AbbVie, Amgen, BiogenIdec, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, Janssen Lilly, Merck, Merck-Serono, Novartis, Novo-Nordisk, Pfizer, Roche, UCB, and Vertex, 5, AbbVie, Amgen, BiogenIdec, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, Janssen Lilly, Merck, Merck-Serono, Novartis, Novo-Nordisk, Pfizer, Roche, UCB, and Vertex, 8; **J. R. Curtis**, from Janssen, Amgen, Abbvie, UCB, CORRONA, Crescendo, BMS, Roche/Genentech, Pfizer, Celgene, Medimmune, 2, from Janssen, Amgen, Abbvie, UCB, CORRONA, Crescendo, BMS, Roche/Genentech, Pfizer, Celgene, Medimmune, 5; **P. M. Karunaratne**, AbbVie, 1, AbbVie, 3; **K. Malhotra**, AbbVie, 1, AbbVie, 3; **A. L. Pangan**, AbbVie, 1, AbbVie, 3.

2438

Effectiveness Of Exercise Program in Ankylosing Spondylitis: Meta-Analysis Of Randomized Controlled Trials. Virginie Pécourneau[1], Arnaud L. Constantin[2] and Alain G. Cantagrel[3]. [1]CHU Toulouse, Toulouse, France, [2]Purpan University Hospital, Toulouse Cedex 9, France, [3]Hopital Purpan, Toulouse CEDEX 9, France.

Background/Purpose: Current recommendations for management of ankylosing spondylitis (AS) encompass appropriate medication and exercises as the cornerstones of treatment. The aim of our study is to assess the efficacy of exercise programs on disease activity and function in AS patients through a meta-analysis of randomized controlled trials.

Methods: A systematic literature search was performed on Medline and Cochrane databases up to February 2013. Randomized controlled trials examining the effectiveness of exercise programs for AS patients were included. Outcomes analyzed were evolution of BASDAI and BASFI after the completion of exercise programs. Modalities of exercise were compared and the use of biotherapy reported. Efficacy was assessed by weighted mean differences (WMDs) of exercise program versus control groups. Heterogeneity was assessed with Cochran's Q-test and I^2. Standardized mean differences (SMDs) were pooled through meta-analysis using the inverse variance model.

Results: After screening of 167 abstracts, a total of 23 trials were selected for detailed evaluation and 7 trials were finally included, assessing home based exercise programs (2/7), swimming (1/7), Pilates training (1/7) or supervised exercises (2/7), with a total of 275 AS patients. Two trials included patients with anti-TNF therapy. All trials except one showed a decrease of BASDAI and BASFI in exercise groups. The WMDs (95% CI) were −0.73 (−1.15, −0.30) (I^2=4%, p=0.0007) for BASDAI and −0.73 (−1.22, −0.23) (I^2= 2%, p=0.004) for BASFI in favor of exercise programs.

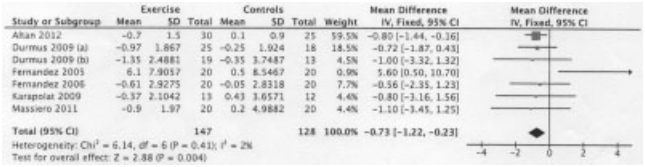


Fig. 1. Meta-analysis of randomized controlled trials assessing the impact of exercise program on BASDAI in AS patients.

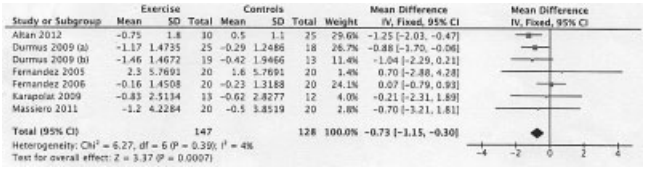


Fig. 2. Meta-analysis of randomized controlled trials assessing the impact of exercise program on BASFI in AS patients.

Conclusion: Even if the small numbers of patients and the quality of exercise programs constitute potential limitations of the randomized clinical trials included in this meta-analysis, its results support the potential of exercise programs to improve disease activity and function in AS.

Disclosure: V. Pécourneau, None; **A. L. Constantin**, None; **A. G. Cantagrel**, None.

2439

Smoking Was Not Associated With Response To Adalimumab Therapy In Patients With Non-Radiographic Axial Spondyloarthritis. Joachim Sieper[1], Denis Poddubnyy[2], Aileen L. Pangan[3], Suchitrita S. Rathmann[3] and Jaclyn K. Anderson[4]. [1]Charité Universitätesmedizin, Berlin, Germany, [2]Charité Universitätsmedizin Berlin, Berlin, Germany, [3]AbbVie Inc., North Chicago, IL, [4]AbbVie, North Chicago, IL.

Background/Purpose: Cigarette smoking has been reported as a risk factor for early disease onset, higher disease activity, and poor function in patients (pts) with axial spondyloarthritis (SpA). Adalimumab (ADA), approved for treating ankylosing spondylitis (AS), was recently approved in the EU for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS, but with objective signs of inflammation by elevated CRP and/or MRI who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs. The objective of this analysis was to examine the association of smoking with baseline pt characteristics, disease activity, and clinical outcome after treatment with adalimumab in pts with non-radiographic axial SpA (nr-axSpA).

Methods: ABILITY-1 is an ongoing phase 3, double blind (DB), randomized, controlled trial in pts with nr-axSpA fulfilling ASAS classification criteria for axial SpA but not modified New York criteria for AS who had an inadequate response, intolerance, or contraindication to NSAIDs. A 12-wk DB period of ADA 40 mg every other week (eow) or placebo was followed by an open-label (OL) extension phase in which pts could receive OL ADA 40 mg eow for up to an additional 144 wks. This post hoc analysis of data through wk 68 evaluated the differences in baseline characteristics and disease activity and response to treatment in current smokers vs. past smokers vs. nonsmokers in a subpopulation with positive MRI or elevated CRP (MRI+/CRP+) using a chi-square test or one-way analysis of variance (depending on categorical/continuous variables). Kaplan–Meier analysis was performed for time to first ASAS40 response using smoking status as strata.

Results: 142 pts were in the MRI+/CRP+ subpopulation; 63 (44%) were smokers [34 (24%) current smokers, 29 (20%) past smokers] and 79 (56%) were nonsmokers. Few differences were observed between current smokers, past smokers and nonsmokers at baseline (BL) and no differences were observed in age at SpA symptom onset or diagnosis. At BL more nonsmokers 43/79 (54%) than smokers [past smokers 13/29 (45%), current smokers 10/34 (29%)] had elevated CRP levels. Smoking status did not predict response to ADA therapy with no differences observed in ASAS20, ASAS40, ASAS PR, ASAS5/6, BASDADI50, ASDAS, BASFI, $BASMI_{lin}$, PGA, PtGA, HAQ-S or SF-36 PCS responses at wks 12 and 68. There was also no difference in the percentage of patients who had SPARCC scores of the SI joint or spine ≥2 at weeks 12 and 52 based on smoking status. Additionally, the time to reach ASAS40 response was not different between past smokers, current smokers and nonsmokers (figure).

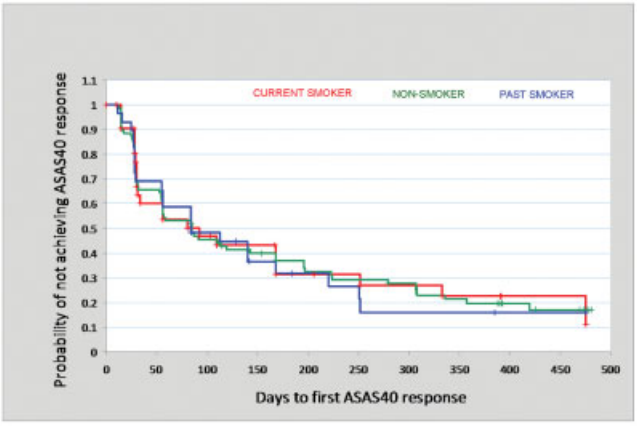


Figure.

Conclusion: In this MRI+/CRP+ nr-axSpA subpopulation of ABILITY-1, smoking status was not associated with age of symptom onset, disease activity, functional status, response to adalimumab therapy, or time to ASAS40 clinical response.

Disclosure: J. Sieper, AbbVie, Merck, Pfizer, UCB, 2, AbbVie, Merck, Pfizer, UCB, 5, AbbVie, Merck, Pfizer, UCB, 8; **D. Poddubnyy**, MSD, 5, AbbVie, MSD, Pfizer, and USB, 8; **A. L. Pangan**, AbbVie, 1, AbbVie, 3; **S. S. Rathmann**, AbbVie, 1, AbbVie, 3; **J. K. Anderson**, AbbVie, 1, AbbVie, 3.

2440

Is There a Role For Etoricoxib In Patients With Axial Ankylosing spondylitis Refractory To Traditional NSAID? Maria García Manrique[1], Pilar Font[2], Joan Calvet[3], María Cruz Fernandez[4], Carlos Montilla[5], Luis Linares[6], Elia Brito[7], Xavier Juanola[8], Juan Mulero[9], Rubén Queiro[10], Rosa M. Morla[11], Rosario Garcia-Vicuña[12], Alba Erra[13], Mireia Moreno[14], Marta Larrosa[15], Eduardo Collantes[16] and Jordi Gratacos[17]. [1]Hospital Parc Taulí, Sabadell, Spain, [2]IMIBIC-Reina Sofia Hospital, Cordoba, Spain, [3]Corporació Sanitària Parc Taulí, Sabadell, Spain, [4]Hospital General de Móstoles, Mostoles, Spain, [5]Hospital Universitario de Salamanca, Salamanca, Spain, [6]Hospital Universitario Virgen de la Arrixaca, Murcia, Spain, [7]Hospital Ramón y Cajal, Madrid, Spain, [8]Hospital Universitari de Bellvitge, Barcelona, Spain, [9]Hospital Universitario Puerta de Hierro Majadahonda, Majadahonda (Madrid), Spain, [10]Rheumatology Department. Hospital Universitario Central de Asturias, Oviedo, Spain, [11]Hospital Sta Tecla, Tarragona, Spain, [12]Hospital Universitario de La Princesa, Madrid, Spain, [13]Hospital de Sant Rafael, Barcelona, Spain, [14]Hospital Universitari Parc Taulí, Sabadell, Spain, [15]Hospital Universitari Parc Tauli, Sabadell, Spain, [16]Hospital Reina Sofia, Cordoba, Spain, [17]Hospital Universitari Parc Taulí, Sabadell (Barcelona), Spain.

Background/Purpose: Anti-TNF treatment has demonstrated its effectiveness in axial ankylosing spondylitis (AS) patients with inadecuate response to traditional NSAIDs (tNSAIDs) therapy (>=2 tNSAIDs), but also aspects such as potential adverse events and cost must be considered. Etoricoxib(a selective COX-2 NSAID) has proved more efficacy than naproxen in these patients, and in an open label study up to 40% of patients refractory to tNSAIDs achieved a good clinical response with etoricoxib.

Objective: To evaluate the proportion of patients with axial AS with inadecuate response to tNSAIDs which achieve a good clinical response to etoricoxib after 4 weeks of treatment. To assess the proportion of these patients that mantain the good clinical response at 6 months follow-up. To analyze the effect of etoricoxib on the different clinical and biological parameters determined at 4 weeks and 6 months.

Methods: Open label, multicentric (12 centers) randomized, prospective (4 weeks with a 6-month open extension), non-controlled study, with inclusion period of approximately 2 years (mid 2010–2012). 57 axial AS patients with inadequate response to tNSAID following the consensus and guidelines previously published for the initiation of anti-TNF treatment were included. Patients who achieved a good clinical response at week 4 were followed in an open extension study for 6 moths. Variables analyzed at baseline, 2, 4 weeks and 6 months included: BASDAI, clinical symptoms such as back and nocturnal back pain, global patient and physician assessment of disease (VAS score), disability (BASFI), and biological parameters (CRP mg/dl). We also evaluated both the proportion of patients who achieved good clinical response defined as patients who did not fulfill anti-TNF therapy criteria after etoricoxib treatment, and ASASBIO response (50% in BASDAI and VAS physician global assessment improvements).

Results: 26/57 patients (46%, CI 34–58) achieved a good clinical response and 11/57 patients (19%, CI 8–31) achieved an ASASBIO response. 17/26 (65%) of patients included in the extension study maintaned the good clinical response and did not fulfill criteria of anti-TNF treatment at the end of 6 moths follow-up, representing 30% (CI 18–43) of the total of patients included. Moreover, 13/57 (23%,CI 11–36) achieved an ASASBIO response at 6-months follow-up. Only 17/57 (30%) showed a good clinical response at week 2. A discordant good clinical response between week 2 and 4 was observed in 9 patients, one of them losing response and the remaining 8 achieving response at week 4. All individual clinical variables analyzed improved significatively after 2 wks achieving around 30% of mean reduction after 4 wks of treatment ($p<0.001$ in all variables). The mean BASFI score significatively improved in the same range that clinical variables, however the improvement of CRP did not reach statistical significance (1.1 to 0.83 p=ns), although about 30% of patients with a good clinical response were showed with CPR normalization.

Conclusion: Etoricoxib treatment should be tried in axial AS patients before prescription of antiTNF treatment because around a third of patients achieved a good 6-months clinical response. Response at week 2 did not appear to predict response at week 4.

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2441

Do Postural Deformities In Patients With Ankylosing Spondylitis Cause Balance Problems? M. Ece Cinar, Yesim Akkoc, Hale Karapolat and Gokhan Keser. Ege University School of Medicine, Izmir, Turkey.

Background/Purpose: In this study, we assessed the impact of postural deformities caused by ankylosing spondylitis (AS) on balance.

Methods: 29 AS patients and 21 healthy controls were enrolled. Control group consisted of healthy hospital staff. Demographic data (age, sex, body mass index, treatment regimes, comorbidities, symptom and disease durations, smoking and alcohol use) were recorded. Physical examination, timed up-and-go test, 5 times sit-to-stand test, gait speed, functional reach test, 6 minute walk test, Romberg tests (eyes open and closed-feet together, tandem and on a soft surface), Dynamic Gait Index (DGI), Functional Gait Assessment (FGA), Berg Balance Scale (BBS) and for the AS group Bath Ankylosing Spondylitis Metrology Index (BASMI) were scored. Subjects were asked to fill out questionnaires for Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Back Depression Inventory (BDI), Activity Specific Balance Confidence Scale (ABC) and Dizziness Handicap Inventory (DHI).BASDAI, BASFI, and BASMI were only used in the AS group. The AS patients were then subgrouped according to their BASMI scores. Patients with scores ranging between 0–4 were assigned to subgroup AS1 while those with scores between 5–10 were assigned to subgroup AS2. These two subgroups were then compared with each other and with healthy controls.

Results: AS1 patients had higher Berg Balance Scores compared to AS2 patients($p<0.05$), while no significant difference was found between AS1 and AS2 groups in 5 times sit-to-stand test, timed up and go test, gait speed, Romberg tests, 6 min. walk test, functional reach test, DGI, FGA, BDI or ABC scales ($p>0.05$).

AS and control subjects were found to have significant differences in 5 times sit-to-stand test, tandem Romberg test with eyes closed, BDI, BBS and ABC scores ($p<0.05$).

The control and the AS2 group differed significantly in 5 times sit-to-stand test, timed up and go test, tandem romberg with eyes closed, 6 min. walk test, functional reach test, FGA, BBS, BDI, DHI and ABC scores ($p<0.05$), these differences were not observed in the AS1 group.

Conclusion: Our study results support the concept that ankylosing spondylitis patients have poorer static and dynamic balance compared to healthy subjects. Poor balance and resulting falls may increase disease morbidity and should be assessed in patients with AS.The chronic nature of the disease and slow progression of postural deformities may explain why poor balance is not a more common symptom of AS. Still, especially in patients with fracture risk factors such as osteoporosis and immobilisation, it is important to assess balance and take the necessary precautions.

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2442

[18F]-Fluoride PET/CT Assessment In Patients Responding To The ASAS Criteria For Spondyloarthritis Despite Negative Sacroiliac Joint MRI. Cecile Caoduro[1], Orland Angoue[1], Hatem Boulahdour[1] and Eric Toussirot[2]. [1]University Hospital, Besançon, France, [2]CIC Biotherapy 506 and Rheumatology and EA 4266 Pathogens and Inflammation, Besançon, France.

Background/Purpose: The ASAS group has defined criteria for the diagnosis of axial or peripheral spondyloarthritis (SpA). Sacroiliac joint MRI is included in these criteria and is a pivotal tool in daily practice to evaluate the patients with suspected early and non radiographic SpA. A substantial proportion of patient responds to the ASAS criteria (i.e. the clinical arm) despite negative MRI. Positron emission tomography/computed tomography (PET/CT) is a new imaging technique of potential interest in inflammatory rheumatic diseases. PET/CT has been rarely evaluated in patients with SpA and mainly used [18 F] fluorodeoxyglucose, a marker of inflammation. [18 F] fluoride is a specific bone tracer that may have potential in SpA imaging, a condition associated with spinal ossifications and sacroiliac ankylosis.

Objectives: to evaluate the clinical utility of [18 F] fluoride PET/CT in patients with negative sacroiliac joint MRI but fulfilling the ASAS criteria for SpA.

Methods: consecutive outpatients seen for inflammatory back pain and responding to the ASAS criteria for SpA were included. Patients were previously evaluated by sacroiliac joint MRI (STIR) which must be normal (no bone marrow edema). Whole body [18 F] PET/CT was performed using a SIEMENS Biograph device. Areas of interest (spine, entheseal structures and sacroiliac joints) were examined on whole body scan for the detection of increased uptake. Increased activity was defined as an activity greater than the activity of an adjacent normal bone. Patients with defined ankylosing spondylitis (AS) and positive sacroiliac joint MRI were used as positive controls.

Results: 10 patients were evaluated (8F, 2 M, mean age: 41.8, symptom duration: 3.2 years, HLA B27 positive 9/10; mean BASDAI: 5.6, mean ASDAS: 2.3). 9 responded to axial SpA ASAS criteria and I to peripheral SpA ASAS criteria. They all received or had received NSAIDs. No patients had DMARD or TNF inhibitors. All the patients had normal sacroiliac joint MRI. [18 F] fluoride PET/CT did not show increase activity for any patients. 5 patients with radiographic AS and positive MRI were also evaluated: for 4 patients, active lesions were detected with [18 F] fluoride PET/CT showing increased uptake in the sacroiliac joints, the spine and sternoclavicular joints.

Conclusion: [18 F] fluoride PET/CT does not seem useful in patients with inflammatory back pain, negative MRI and responding to the ASAS criteria. Thus, using this bone tracer, PET/CT does not give additional information relevant for the diagnosis of SpA. Conversely, this imaging technique using [18 F] fluoride may be able to detect active lesions in patients with defined disease and positive MRI. Measurement and quantification of maximal standard uptake value may be useful for improving the sensibility of this imaging modality in the diagnosis of SpA.

Disclosure: C. Caoduro, None; **O. Angoue**, None; **H. Boulahdour**, None; **E. Toussirot**, None.

2443

Prevalence Of Coronary Heart Disease In Spondyloarthopathies may Be Increased Due To Higher Prevalence Of Risk Factors As Well As The Disease Itself- A Retrospective Analysis At Single VA Medical Center. Trayton Mains[1] and Vikas Majithia[2]. [1]University of Mississippi Medical Center, Jackson, MS, [2]G.V. "Sonny" Montogomery VA Medical Center, Jackson, MS.

Background/Purpose: An increased prevalence of cardiovascular disease (CVD) and coronary heart disease (CHD) has been reported in patients with spondyloarthritides (SpA). This study investigated the prevalence of CVD risk factors, CVD including CHD and stroke in veterans with SpA (including PsA, Ankylosing Spondylitis (AS), and reactive arthritis (ReA) at the Jackson VAMC.

Methods: A retrospective chart review using ICD-9 codes for PsA, AS, and ReA was performed at Jackson, VAMC. Data including age, race, gender, medications, ESR, CRP, lipid panel, HbA1c, 25-OH Vitamin D level, hypertension (HTN), smoking, statin use, and CVD events were tabulated. Age, sex and race matched controls were selected from VA clinics with a 2:1 ratio. Comparisons of CHD, stroke, and CVD risk factors were made to a matched population from the American Heart Association data, as well as the CDC's 2003–2004 evaluation of chronic disease in Male veterans. Risk factors included smoking, dyslipidemia (DLD), HTN, and diabetes Mellitus (DM). Prevalence ration and odds ratio were calculated by standard method. Statistical significant (alpha <0.05) was calculated using Chi-square and Fisher's exact test.

Results: There were 81 patients, 79 were male and 2 female. With a mean age of patients with PsA, AS, and ReA being 61,8, 60.4, and 56, respectively. There was a significant increase in the prevalence of CHD and its risk factors in the SpA, PsA, and AS patients when compared with the AHA data, and General Male vets from the 2003–04-control population. When compared to the matched controls, prevalence was increased in the overall SpA, PsA and AS patients but did not achieve statistical significance suggesting increased an risk despite having slightly lower prevalence of risk factors. Also, in both SpA and matched controls population there was an increased prevalence of these risk factors, when compared to the AHA and national data. There was insufficient number of black patients in the cohort to assess effect of ethnicity.

Table 1. CHD comparison among spondyloarthropathies and 3 controls.

CHD	%	SpA	PsA	AS	ReA
%		26.9	29.3	30.4	14.2
AHA Controls	9.1	PR= 2.96 OR= 3.72 p-value= 0.002	PR= 3.21 OR= 4.18 p-value=0.003	PR= 3.34 OR= 4.42 p-value= 0.01	PR= 1.56
General Male Veterans	11.5	PR= 2.34 OR= 2.83 p-value=0.01	PR= 2.55 OR= 3.18 p-value= 0.04	PR= 2.64 OR= 3.36 p-value=0.05	PR= 1.23
Matched Controls	18.6	PR= 1.45 OR= 2.83 p-value - NS	PR= 1.57 OR= 3.18 p-value- NS	PR= 1.63 OR= 3.36 p-value- NS	PR= 0.76

Table 2. CHD Risk Factors

	AHA Controls (1) (%)	General Male Veterans (2) %	Matched Controls (3) %	SpA (%)	PsA (%)	AS (%)	ReA (%)
DM	7.6	13.6	29.5	24.7	22.7	26.1	28.6
PR				3.25	2.99	3.43	3.76
				1.81	1.67	1.92	2.1
				0.84	0.77	0.88	0.97
HTN	34.4	41.2	66	70.4	70.5	73.9	64.3
PR				2.05	2.05	2.15	1.87
				1.71	1.71	1.79	1.56
				1.07	1.07	1.12	0.97
DLD	45.2	44.6	69	60.5	69.8	56.5	42.5
PR				1.34	1.54	1.25	0.95
				1.36	1.57	1.27	0.96
				0.88	1.01	0.82	0.62
Smoking	23.1	22.8	63.1	62.7	62.5	56.5	75
PR				2.71	2.71	2.45	3.25
				1.5	1.54	0.87	1.83
				0.99	0.99	0.9	1.19
Family Hx			34.1	27.8	25	36.4	21.4
PR				0.87	0.73	1.07	0.63

Conclusion: Our results suggest that patients with SpA have an increased risk of developing CHD as well its risk factors. Our study is unique as increased risk and it quantification have not been previously reported in the U.S. veteran population. The increased CHD risk attributable to the increased prevalence of risk factors cannot be determined in this study but has been suggested to be over and above them.

Disclosure: T. Mains, None; **V. Majithia**, None.

2444

The Contribution Of Disease Activity On Function and Quality Of Life In Patients With Ankylosing Spondylitis; Investigating Causality By Using Structural Equation Model. Servet Akar[1], Sabri Erdem[2], Kivanc Akat[1], Dilek Solmaz[1] and Ismail Sari[1]. [1]Dokuz Eylul University School of Medicine, Izmir, Turkey, [2]Dokuz Eylul University Faculty of Business, Izmir, Turkey.

Background/Purpose: It has been demonstrated that patient reported questionnaires including disease activity, functional impairment, anxiety and depression were correlated each other. However the causal relationships among activity, function and quality of life (QoL) in AS patients has never been evaluated before. Therefore we aimed to investigate the causal relationships among factor structures (A*ctivity*, *Function* and *QoL*) in AS patients by using Structural Equations Modeling (SEM) approach.

Methods: BASDAI, BASFI and Short Form 36 (SF 36) were used for the assessment of disease activity, function and QoL. All questionnaires simultaneously employed. BASDAI and BASFI were answered by both 10-cm VAS and numeric rating scale (NRS) format. Data analysis presented here was performed by VAS scores. Activity, Function and QoL were our latent variables (i.e. factor structures). A latent model was created that demonstrating the causality among these three factor structures by means of SEM approach in Lisrel 8.8 medium. Besides, Function was also tested for mediating role between Activity and QoL. Both model fit and parameter fit values were assessed against statistical significance of the proposed model.

Results: A total 114 consecutive patients with AS (87 [76%] male, mean age was 39.8 ± 10.9 years) according to the modified NY criteria were included in the study. Mean (±SD) BASDAI, BASFI, SF-36 physical component summary, and SF-36 mental health component summary score were 3.6 ± 2.6, 3.3 ± 3.0, 53.1 ± 25, and 59.2 ± 19.9 respectively. Significance of parameters of about relationships between factor structures, factor loadings of latent variables by observed variables, error terms of observed variables are all tested by t-test and results are found as significant ($p<0.05$). Proposed model is demonstrated in Figure 1. According to that model, *QoL* can be significantly ($|t|>1.96$ and $P<0.05$) explained by both *Activity* and *Function*. Additionally, *Function* plays a mediating role that reflects the indirect effect of Activity on *QoL*. Direct and indirect effects are shown in Equation Model (RMSEA=0.089, c^2/df =1.9, RMR=0.055, GFI=0.74, AGFI=0.69, NFI=0.95 and NNFI=0.97) and parameter fit (for all parameters $|t|>1.96$ and $P<0.05$) results satisfied allowable limits. NRS answering formats of BASDAI and BASFI were also produced similar results.

Conclusion: Our results show that proposed model is significant and both disease activity and function can explain the QoL in patients with AS. Function has also a mediating role as indirect effect of disease activity on QoL. This model can be utilized for the estimation of quality of life in AS patients in clinical practice or clinical trials.

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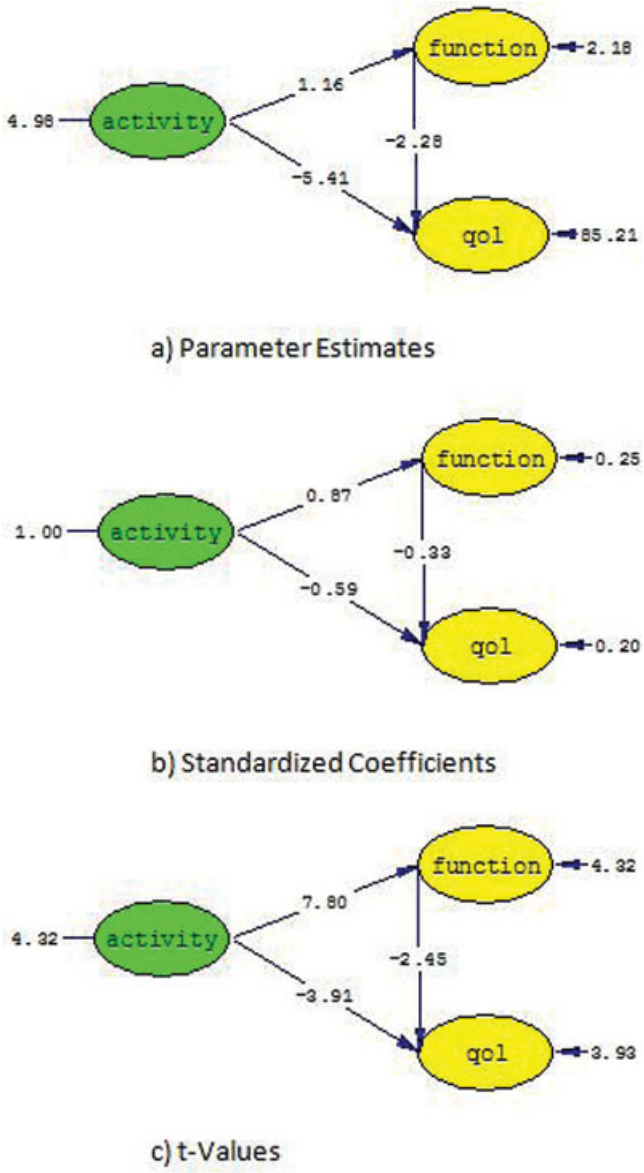

Figure 1. Structural equations model

2445

Acute Phase Reactant As a Marker Of Anti-Drug Antibody Formation In Ankylosing Spondylitis. Seokchan Hong[1], Eun-Ju Lee[1], You Jae Kim[1], Bon San Koo[1], Wook Jang Seo[2], Kyung joo Ahn[3], Yong-Gil Kim[1], Chang-Keun Lee[1] and Bin Yoo[1]. [1]University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [2]Seoul Veterans Hospital, Seoul, South Korea, [3]KEPCO medical center, Seoul, South Korea.

Background/Purpose: The development of antibodies to biologics is one of the main mechanisms of treatment failure in inflammatory arthritis, including rheumatoid arthritis (RA) and ankylosing spondylitis (AS). However, assessment of anti-drug antibodies (ADA) is not available in routine clinical practice. To address whether acute phase reactants (CRP and ESR) are useful to predict the ADA formation in AS, we analyzed the association between several disease parameters, including the levels of acute phase reactants and the presence of ADA.

Methods: In a cohort of 21 AS patients treated with TNF-blockers, ADA levels were measured in the serum using an enzyme-linked immunosorbent assay. All except one patient, serial samples were available before (baseline) and after 3 months of TNF-blockers therapy. We evaluated the levels of acute phase reactants and disease activity, as assessed by BASDAI, BASFI and patient global assessment at baseline and at 3 months after TNF-blocker treatment.

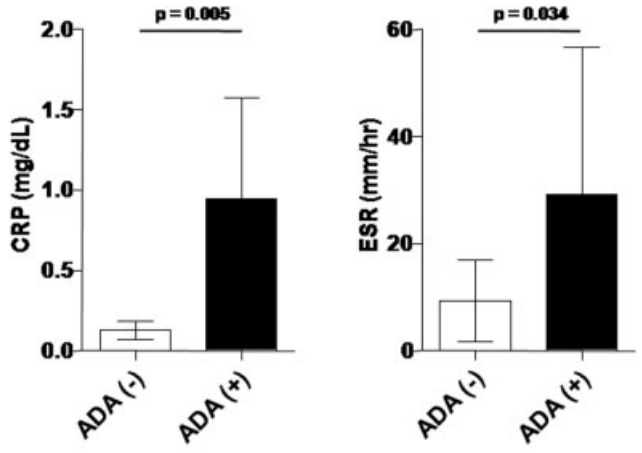

Figure 1. Differences in levels of acute phase reactants between patient with and without ADA at 3 months after TNF-blocker treatment.

Results: Among 21 patients (adalimumab n=16, infliximab n=5), ADA were detected in 5 (23.8%) patients (adalimumab n=2, infliximab n=3). At baseline, there was no significant difference in laboratory data and clinical activity scores between patients with and without ADA. After 3 months of TNF-blockers, ADA-positive patients had higher CRP levels in serum (0.9 +/− 0.6 ADA-positive vs. 0.1 +/− 0.1 ADA-negative, p=0.005). In addition, ESR levels in serum of patients with ADA were significantly higher than that of patients without ADA (29.2 +/− 27.5 ADA-positive vs. 9.4 +/− 7.6 ADA-negative, p=0.034) (Figure 1). However, we found no significant difference at 3 months in disease activity index according to the presence of ADA. The number of patients who received concomitant treatment with DMARDs or NSAIDs was not significantly different in both groups.

Conclusion: Patients who developed ADA had significant higher levels of acute phase reactants (CRP and ESR) in their serum after 3 months treatment with TNF-blockers. Acute phase reactant might be useful marker for early detection as well as for evaluation of drug immunogenicity in AS during TNF-blocker treatment.

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2446

Opiate Use In Patients With Ankylosing Spondylitis. John D. Reveille[1], Michael M. Ward[2], MinJae Lee[3], Mohammad Rahbar[3], Manouchehr Ardjomand-Hessabi[3], Laura A. Diekman[3], Matthew A. Brown[4], Lianne S. Gensler[5] and Michael H. Weisman[6]. [1]University of Texas Health Science Center at Houston, Houston, TX, [2]NIAMS/NIH, Bethesda, MD, [3]The University of Texas Health Science Center at Houston, Houston, TX, [4]University of Queensland Diamantina Institute, Brisbane, Australia, [5]University of California, San Francisco, San Francisco, CA, [6]Cedars-Sinai Medical Center, Los Angeles, CA.

Background/Purpose: Prescription opiates are commonly prescribed in patients with chronic pain, yet there is no evidence that these drugs ameliorate disease progression, and are associated with numerous side effects, including dependence and overdosage. The purpose of this study was to assess factors associated with narcotics usage in AS patients.

Methods: 611 AS patients, meeting the modified New York criteria followed up to 4 years and enrolled in a longitudinal outcome study were assessed. Demographic, clinical and self-reported outcomes were collected every 4–6 months. Usage of medications since last visit was collected every visit, including daily dosage, how many days in the prior month taken and how many months since the previous visit. Disease activity was defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), functional outcomes by the Bath Ankylosing Spondylitis Functional Index (BASFI) and radiographic severity by the Bath Ankylosing Spondylitis Radiographic Index (BASRI) and the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). Depression was gauged by self-report, by the use of anti-depressant medications, and by Center for Epidemiologic Studies Depression Scale (CES-D) testing. Univariable mixed models were used to identify factors associated with narcotic usage accounting for correlation of repeated measures over time. Final longitudinal multivariable models were developed that identified independent factors associated with narcotic usage.

Results: The cohort was 71% male and 76% of patients were white, having a mean age 41.1 years (SD= 13.6). Mean disease duration was 17.6 years (SD=13.5). Opiate usage was reported in 87 (14.3%) of patients (9.36% taking continuously, 4.96% intermittently). Table 1 shows the univariable associations between narcotics usage and each independent variable from longitudinal model. Independent factors associated with narcotic usage in the multivariable analysis included subjective disease activity (measured by the BASDAI, OR=2.9, 95% CI=(1.8, 4.7), p<0.0001), functional impairment (measured by the BASFI, OR=1.9, 95% CI=(1.1, 3.15), p=0.023), depression (OR=2.3, 95% CI=(1.12 4.7), p=0.015) and the use of muscle relaxants (OR=5.3, 95% CI=(2.6, 10.7), p<0.0001). Complex interrelationships were encountered between depression, anti-depressives and other medications (anxiolytics and muscle relaxants).

Table 1. Univariable Association Between Narcotics Usage And Other Selected Variables

Variable	OR	95% CI	P
Male gender	0.647	(0.389, 1.075)	0.093
White	2.010	(1.113, 3.63)	0.021
Smoking (present or prior)	2.125	(1.324, 3.409)	0.0018
Age >40 years	1.853	(1.154, 2.974)	0.011
Patient employed	3.352	(1.999, 5.622)	<0.0001
Depression (self report)	5.907	(3.33, 10.478)	<0.0001
High blood pressure	2.186	(1.23, 3.885)	0.0077
Elevated ESR	1.285	(0.89, 1.855)	0.18
Patient Global Pain assessment	4.240	(2.866, 6.274)	<0.0001
Concomitant use of Prednisone	2.996	(1.345, 6.675)	0.0073
Concomitant use of TNFi Agents	1.526	(0.997, 2.336)	0.0514
Concomitant use of anti-depressants	2.601	(1.504, 4.498)	0.0006
Concomitant use of anxiolytics	8.042	(3.384, 19.114)	<0.0001
Concomitant use of muscle relaxants	8.458	(4.913, 14.562)	<0.0001
Radiographic severity (mSASSS)	1.236	(0.747, 2.043)	0.41
Depression (Elevated CES-D)	3.071	(2.078, 4.539)	<0.0001
Disease activity (BASDAI < 4)	5.460	(3.707, 8.043)	<0.0001
Impaired function (BASFI)	4.323	(2.857, 6.543)	<0.0001
Exercise 3 times or more per week	0.805	(0.569, 1.14)	0.22

Conclusion: AS patients using opiates have significantly greater subjective disease activity, report greater functional impairment, exhibit more depression and are more likely to take muscle relaxants than those that do not.

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2447

Disease Activity Is Associated With Development Of Inflammatory Bowel Disease In Ankylosing Spondylitis: 12-Year Results From OASIS. Ivette Essers[1], Sofia Ramiro[2], Carmen Stolwijk[3], Robert Landewé[4], Désirée van der Heijde[5], Filip van Den Bosch[6], Maxime Dougados[7] and Astrid Van Tubergen[3]. [1]Maastricht University Medical Center, Maastricht, Netherlands, [2]Hospital Garcia de Orta, Almada, Portugal, [3]Maastricht University, Maastricht, Netherlands, [4]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [5]Leiden University Medical Center, Leiden, Netherlands, [6]Department of Rheumatology Ghent University Hospital, Ghent, Belgium, [7]Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France.

Background/Purpose: Ankylosing spondylitis (AS) is associated with extra-articular manifestations (EAMs) such as acute anterior uveitis (AAU), inflammatory bowel disease (IBD), and psoriasis. Little is known about the characteristics of patients who develop any EAM. We aimed to identify characteristics associated with the development of EAMs in a prevalence cohort of patients with AS.

Methods: Twelve year follow-up data from patients included in the Outcome in AS International Study (OASIS) were used. Additionally, medical charts were checked for the presence of AAU, IBD or psoriasis, by two independent extractors. Baseline demographic, clinical and radiographic characteristics of patients with and without uveitis, IBD or psoriasis were compared. Logistic regression was performed to identify characteristics associated with the presence of any EAM. Furthermore, Cox regression and survival analyses were performed to identify characteristics associated with development of any EAM over time. Analysis were performed with baseline characteristics as well as with time-varying characteristics.

Results: 216 patients were included (mean age 43.6 years (SD 12.7), 154 (71%) men, mean symptom duration 20.5 years (SD 11.7), 174 (85%) HLA-B27 positive and mean follow-up period 8.3 years (SD 4.3)). At baseline, 59 (27%) patients had any EAM, of which 39 (18%) AAU, 15 (7%) IBD, and 9 (4%) psoriasis. Four patients (2%) had more than one EAM. At baseline, patients with AAU compared with patients without AAU were older (49.1 vs 42.4 years, p<0.01), had a longer symptom duration (25.9 vs 19.3 years, p<0.01), and more radiographic damage (modified Stoke AS Spinal Score 16.9 vs 10.6, p=0.03). Patients with psoriasis compared with patients without psoriasis were older (51.3 vs 43.3 years, p=0.05). There were no differences between patients with and without IBD. During follow-up 27 patients developed a new EAM; 19 AAU, 9 IBD, and 5 psoriasis with incidence rates of 0.9%, 0.4%, and 0.02% per year, respectively. The following time-varying characteristics were associated with the development of IBD in univariable analysis: AS Disease Activity Score (HR 2.81, 95%-CI 1.43–5.53), Bath Ankylosing Disease Activity Index (HR 1.47 95%-CI 1.09–1.98), C-reactive protein (HR 1.02, 95%-CI 1.00–1.05) Bath AS Functional index (HR 1.40, 95%-CI 1.09–1.80) and Bath AS Global Score (HR 1.46, 95%-CI 1.10–1.96). CRP was also weakly associated with the development of AAU (HR 1.02, 95%-CI 1.01–1.04) in time-varying analysis. No significant associations with development of psoriasis were found.

Conclusion: At baseline, a substantial number of patients already had an EAM in this prevalence cohort with relatively long symptom duration. Development of new EAMs was infrequently observed. In particular disease activity, but also physical function and patient global assessment, were associated with development of IBD. CRP was associated with the development of AAU. Characteristics associated with the development of psoriasis were not found.

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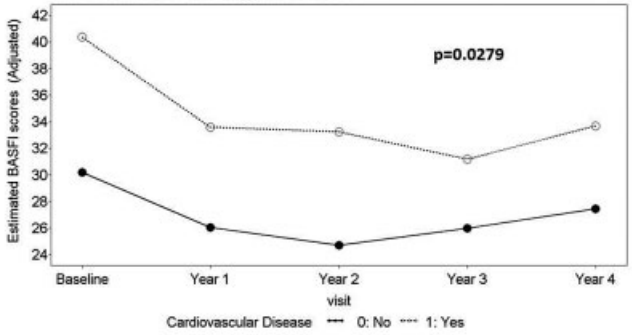
Cardiovascular Disease Is Associated With Worse Functional Outcomes In Ankylosing Spondylitis. Lianne S. Gensler[1], Michael M. Ward[2], MinJae Lee[3], Mohammad Rahbar[3], Matthew A. Brown[4], John D. Reveille[5] and Michael H. Weisman[6]. [1]University of California, San Francisco, San Francisco, CA, [2]NIAMS/NIH, Bethesda, MD, [3]The University of Texas Health Science Center at Houston, Houston, TX, [4]University of Queensland Diamantina Institute, Brisbane, Australia, [5]University of Texas Health Science Center at Houston, Houston, TX, [6]Cedars-Sinai Med Ctr, Los Angeles, CA.

Background/Purpose: Cardiovascular disease is an important comorbidity in inflammatory arthritis. There is evidence that AS patients have a significant burden of cardiovascular comorbidity. This appears to correlate well with disease activity. To date, there is very little evidence of how cardiovascular disease impacts function in AS. The purpose of this study was to assess the impact of cardiovascular disease, including hypertension, ischemic heart disease and valvular heart disease on long-term functional outcomes in AS.

Methods: This is a prospective cohort of 611 AS patients, meeting the modified New York criteria followed up to 4 years. We collected cardiovascular medical history (including hypertension, angina, coronary artery disease, myocardial infarction, stent or angioplasty, bypass surgery and valvular disease, including valve replacement) in addition to other comorbidities at baseline. We also collected clinical and self-reported outcomes every 6 months. Functional outcomes were assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI). Tracer comorbidities (such as pulmonary disease) were included as controls. Using mixed models, we assessed univariable associations between independent variables and function that accounted for correlation of repeated measures over time. Potential confounding and effect modifications were addressed while developing a final longitudinal multivariable model.

Results: There were 611 patients included with a mean age of 41.1 ± 13.6 years. The cohort comprised 71% males and 76% of patients were white. The mean disease duration was 17.6 ± 13.5 years. The mean baseline modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) was 15.2 ± 21.1. At baseline, 24% of patients had any cardiovascular disease, including 4% with ischemic heart disease, 4% with valvular heart disease and 19% with hypertension. In the univariable analysis, composite cardiovascular disease ($p < 0.0001$), ischemic heart disease ($p = 0.011$) and hypertension ($p < 0.0001$), but not valvular heart disease were associated with BASFI longitudinally. Gastrointestinal disease was also significant ($p < 0.0001$), but pulmonary disease and diabetes were not associated with BASFI over time. The final model also adjusted for age, gender, prior joint surgery, smoking, erythrocyte sedimentation rate, education, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), mSASSS and depression (by the Center for Epidemiologic Studies Depression Scale [CES-D]). Figure 1 shows the adjusted means of BASFI by the cardiovascular disease status which was found to be statistically significant over time ($p = 0.0279$).

Figure 1. Longitudinal Association of Cardiovascular Disease with Function from the multivariable longitudinal model



p-value for Cardiovascular Disease group (yes vs. no)

Adjusted with potential confounders including: age, sex, race, past AS-related joint surgery, Smoked more than 100 cigarettes, ESR, disease activity (by BASDAI), disease damage (by baseline mSASSS), depression (by CES-D), gastrointestinal disease, pulmonary disease, diabetes.

Conclusion: AS patients with cardiovascular comorbidities have significantly worse function over time than those without cardiovascular disease.

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Patient-Reported Disease Activity and Outcome In Male Versus Female Patients Of The Groningen Leeuwarden Axial Spondyloarthritis (GLAS) Cohort. Suzanne Arends[1], Fiona Maas[2], Eveline van der Veer[2], Reinhard Bos[1], Monique Efde[1], Martha K. Leijsma[2], Hendrika Bootsma[2], Elisabeth Brouwer[2] and Anneke Spoorenberg[2]. [1]Medical Center Leeuwarden, Leeuwarden, Netherlands, [2]University Medical Center Groningen, Groningen, Netherlands.

Background/Purpose: Ankylosing Spondylitis (AS) occurs more often in males than in females. Most women tend to have milder disease and may therefore be underdiagnosed. Male AS patients are more likely to develop radiographic spinal damage. The aim of the present study was to investigate whether there are differences in patient-reported assessments of disease activity, physical function, and quality of life between male and female patients with axial spondyloarthritis (SpA).

Methods: All consecutive patients from the Groningen Leeuwarden Axial SpA (GLAS) cohort who visited the outpatient clinic between January 2011 and December 2012 were included in this cross-sectional analysis. All patients fulfilled the modified New York criteria for AS (>90%) or the ASAS criteria for axial SpA. Disease activity was assessed using Bath AS Disease Activity Index (BASDAI), AS Disease Activity Score (ASDAS; calculated from BASDAI questions 2, 3 and 6, patient global assessment of disease activity (GDA), and, C-reactive protein (CRP)), swollen joint index (range 0–44), and tender joint index (range 0–46). Physical function was assessed using Bath AS Functional Index (BASFI) and quality of life using AS Quality of Life (ASQoL) questionnaire.

Results: Of the 469 included patients, mean age was 45 years (SD±13), mean duration of symptoms was 17 years (range 0–61), 66% were male, and 80% were HLA-B27+. Males were significantly older, had longer disease duration, and were more frequently HLA-B27+ compared to females. Extra-articular manifestations, comorbidity, and current use of NSAID, DMARD, and anti-TNF were comparable between both groups.

Patient-reported measures of disease activity (BASDAI, patient GDA, and tender joints) and outcome (BASFI and ASQoL) were significantly higher in female compared to male patients. ASDAS, capturing both subjective and objective aspects of disease activity, was also significantly higher in females. This difference can be explained by patient-reported aspects of the ASDAS, since CRP levels were comparable between male and female patients (Table 1). Differences remained statistically significant after correcting for age, disease duration, and HLA-B27 status.

Table 1. Clinical assessments in male and female patients with axial SpA

	All patients (n = 469)	Males (n = 310)	Females (n = 159)	P-value
BASDAI	3.6 (0.0–9.6)	3.4 (0.0–9.4)	4.2 (0.2–9.6)	0.000
ASDAS(CRP)	2.3 (0.0–5.7)	2.2 (0.0–5.2)	2.5 (0.6–5.7)	0.004
Patient GDA	4 (0–10)	3 (0–10)	5 (0–10)	0.001
CRP (mg/L)	3 (0–94)	3 (0–94)	3 (0–82)	0.415
CRP ≥5	176 (38%)	115 (38%)	61 (39%)	0.731
Swollen joints	0 (0–9)	0 (0–9)	0 (0–2)	0.576
≥1 swollen joint	18 (4%)	13 (4%)	5 (3%)	0.575
Tender joints	0 (0–22)	0 (0–22)	0 (0–19)	0.018
≥1 tender joint	108 (23%)	61 (20%)	47 (30%)	0.020
BASFI	3.3 (0.0–9.9)	3.0 (0.0–9.7)	4.0 (0.0–9.9)	0.030
ASQoL	6 (0–18)	4 (0–18)	7 (0–18)	0.000

Values are presented as median (range) or number of patients (%).

Conclusion: This cross-sectional study shows that patient-reported measures of disease activity and outcome as well as ASDAS were significantly worse in female axial SpA patients. It is important to be aware of these differences when interpreting patient-reported measures in research and clinical practice. These findings underline the importance of research into more balanced and objective markers of disease activity and outcome including biomarkers in axial SpA.

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Differences and Similarities Of Spondyloarthritis Classification Subgroups Defined By The Assessment Of Spondyloarthritis International Society (ASAS). Jacqueline E. Paramarta[1], Maud Van de Schoot[2], Maureen C. Turina[1], Carmen A. Ambarus[1], Johannes W.J. Bijlsma[2], Leen de Rycke[1] and Dominique L. Baeten[1]. [1]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: Since the Assessment of SpondyloArthritis international Society (ASAS) developed new classification criteria, spondyloarthritis (SpA) is no longer divided into different phenotypic subtypes such as ankylosing spondylitis and psoriatic arthritis, but into axial and peripheral SpA. This study aimed to compare the clinical characteristics and disease activity of the different SpA subpopulations according to the new ASAS criteria.

Methods: 389 patients presenting on two dedicated SpA outpatient clinics fulfilling the European Spondyloarthropathy Study Group (ESSG) criteria were included in a prospective observational cohort. Baseline characteristics were collected and patient's and physician's global assessment of disease activity, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), 68 swollen and tender joint count, Schober, ESR and CRP were measured every 3 months. Data were analyzed with Mann Whitney U and chi square tests.

Results: 314 of the 389 SpA patients (81%) fulfilled the ASAS classification criteria. Patients fulfilling the ASAS criteria had a younger age at disease onset (median 34.1 vs 38.2), were more often male (61.8 vs 36.0%) and HLA-B27 positive (65.1 vs 2.9%), and had more often sacroiliitis on imaging (53.4 vs 1.4%) than those who did not fulfil the ASAS criteria. Strikingly, most disease activity parameters were similar between the two groups and the median BASDAI (4.6 vs 5.3) and TJC (0 vs 3) was even higher in the latter group.

Of the patients fulfilling the ASAS criteria, 230 (59% of the total population) fulfilled the axial and 84 (22%) the peripheral SpA criteria. ASAS peripheral SpA had an older age at disease onset (32.3 vs 38.2) and were less often HLA-B27 positive (76.2 vs 27.3%) than ASAS axial SpA. The parameters of global disease activity (patient's and physician's global assessment and ASDAS) were higher in axial than peripheral SpA, whereas CRP and ESR were similar.

As the ASAS criteria exclude patients with active axial symptoms from the peripheral SpA group but do not exclude patients with peripheral disease from the axial SpA group, we additionally subdivided patients who fulfilled the ASAS axial SpA criteria into pure axial and combined disease (back pain plus arthritis, enthesitis or dactylitis). The combined group was intermediate between pure axial SpA and peripheral SpA in terms of clinical characteristics such as disease symptoms and age at disease onset. Most importantly, the combined group had the highest disease activity compared to the other two groups (eg. ASDAS 3.0 vs 2.6 and 2.0, respectively).

Conclusion: The ASAS criteria fail to classify a subgroup of 20% of the patients fulfilling the ESSG criteria and having high disease activity. Within the patients fulfilling the ASAS axial SpA criteria, we discriminate two separate groups corresponding to exclusive axial disease versus combined axial and peripheral disease. These data support a classification into axial, combined, or peripheral disease rather than just axial versus peripheral disease. The combined group could enter the classification through either the axial or peripheral SpA criteria.

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Work Instability Scores In Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis Are Equal and Higher Than In Psoriatic Arthritis. Sherry Rohekar[1], Robert D. Inman[2] and Dafna D. Gladman[3]. [1]St. Joseph's Hospital, London, ON, [2]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON, [3]University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Clinical subsets of spondyloarthitis (SpA), such as ankylosing spondylitis (AS) and psoriatic arthritis (PsA) may be associated with significant impact on work performance and attendance. Prior to becoming completely work disabled, patients will commonly experience a state of work instability (WI). Our purpose was to determine the characteristics of WI in a large population of patients with SpA.

Methods: Patients were recruited from two large, prospective longitudinal cohorts of AS and PsA. WI was evaluated using a validated questionnaire, the AS-WIS. Standard protocols were completed at the time of completion of the AS-WIS which included a detailed history, physical examination, physician-ascertained outcome measures and patient-reported outcomes.

Results: 718 respondents completed the questionnaire, 505 of which were employed at the time and included in the analysis. Mean age was 45.5 years (SD 11.8) and 69.3% were male. 60.4% had completed university. 63.3% were being treated with NSAIDs, 33.6% DMARDs and 54.1% TNF inhibitors. Mean swollen joint count was 0.08 (SD 0.40), tender joint count 0.85 (SD 2.76) and damaged joint count 3.47 (SD8.44). Mean AS-WIS score was 7.0 (SD 6.0), corresponding to low risk of work instability. AS-WIS scores were equally low in AS, non-radiographic axial SpA (nr-axSpA) and undifferentiated SpA (uSpA). AS-WIS scores in PsA were significantly lower than in AS, nr-axSpA and uSpA ($p<0.01$ for each). Higher AS-WIS were significantly associated with female gender, lower education level, higher tender joint count, current NSAID use, history of GI disease, history of CNS disease, and history of peripheral arthritis, enthesitis or dactylitis. TNF inhibitor use was not associated with higher WIS scores. Multinomial logistic regression showed that the groups at the highest risk of WI were those with GI history, peripheral arthritis, enthesitis and dactylitis history. All patient-reported outcome measures correlated highly with AS-WIS.

Conclusion: In axSpA, WI was low, and was comparable for AS, nr-axSpA and uSpA. PsA was found to have significantly lower WI than these subsets of ax-SpA, however, in this cohort, PsA was well controlled with low joint counts, which may have impacted the WIS scores. Female gender, history of GI, CNS or peripheral disease and NSAID use was associated with greater WI.

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Effects Of Smoking In Patients With Axial Spondyloarthritis - Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis - Receiving Anti-TNF therapy. Ozlem Pehlivan, Yasemin Yalcinkaya, Nihat Huseyinsinoglu, Nilufer Alpay Kanitez, Burak Erer, Sevil Kamali, Murat Inanç, Orhan Aral, Ahmet Gul and Lale Ocal. Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey.

Background/Purpose: Ankylosing spondylitis (AS) is a systemic disease characterized by sacroiliitis and inflammatory back pain. The radiological findings of AS appear late causing delay in diagnosis, therefore axial spondyloarthritis (axSpA) which includes AS and nonradiographic axSpA (nr-axSpA) have been defined.

The objective of this study is to identify the potential impacts of smoking on disease activity markers, physical examination and laboratory findings in severe AS and nr-axSpA receiving anti-tnf therapy.

Methods: In this study, 211 patients treated with Anti-TNF diagnosed as axSpA based on ASAS criteria (of which 142 AS according to modified New York criteria and 69 as nr-axSpA) between 2000 and 2013 were included. Patients were evaluated retrospectively. Smoking intensity has been evaluated as per pack-year. Patients were separated into groups according to smoking habits and intensity. Acute phase reactants and functional indexes - erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Bath AS Metrology Index (BASMI), Bath AS Functional Index (BASFI), Bath AS Disease Activity Index (BASDAI) and AS Quality of Life (ASQoL)- were compared between groups. Physical examination including Schober's test (ST), chest expansion (CE), fingertip-to-floor distance (FFD), tragus wall distance (TWD), lateral lumbar flexion (LLF), cervical rotation (CR), occiput-to-wall distance (OWD), inter-malleolar distance (IMD), chin-sternum distance (CSD) was performed. Independent sample t, paired t test, one-way Anova were used to compare values.

Results: Based on comparison betweeen smokers (n:121) and non-smokers (n:90), physical mobility indicators ST (p:0.03), FFD ($p<0.001$) and LLF (p: 0.035) were found significantly more restricted in smokers and BASDAI (p: 0.011) values were significantly improved after anti-TNFα treatment in non-smokers. If smoking period is >20 years, LLF (p:0.004), CR (p:0.004), CE (p:0.005), OWD (p:0.021), TWD (p: 0.001), IMD (p: 0.015), BASFI (p: 0.019) and BASMI ($p< 0.001$) were significantly deteriorated. When effects of smoking were evaluated between AS (n:142) and nr-axSpA

(n: 69) groups, significant restriction of ST (p:0.04) and FFD ($p<0.001$) in AS group within smokers, restriction of FFD (p:0.02), CR(p:0.04), OWD (p:0.02), TWD (p:0.003), CSD (p: 0.02) and LLF (p:0.002) in AS group among smokers >10 years or more and significant restriction of ST (p: 0.04), FFD ($p<0.001$), LLF (p: 0.01) in AS group who had quit smoking compared to non-smokers were found. Among currently smoking patients (n:46) comparison between who smoke >20 pack-year (n:23) and who smoke <20 pack-year (n:46) showed significant deterioration of ST (p: 0.007), CR (p:0.01), CE (p:0.002), TWD (p:0.01), IMM (p: 0.007), BASFI (p: 0.004), BASDAI (p:0.005), BASMI (p: 0.005) and ASQoL (p:0.04) only in nr-axSpA group.

Conclusion: Our study showed that smoking and especially heavy smoking had negative effects on all stages of axSpA. In nr-axSpA, considered as early axSpA, to quit smoking would be more important for significant differences were seen in spinal mobility, functional situation, disease activity and quality of life in this group of patients.

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Identification Of Determinants Of The Functional Outcome In Patients With Early Axial Spondyloarthritis: Results From The German Spondyloarthritis Inception Cohort. Denis Poddubnyy[1], Hildrun Haibel[1], Joachim Listing[2], Jürgen Braun[3], Martin Rudwaleit[4] and Joachim Sieper[1]. [1]Charité Universitätsmedizin Berlin, Berlin, Germany, [2]German Rheumatism Research Center, Berlin, Germany, [3]Rheumazentrum Ruhrgebiet, Herne, Germany, [4]Endokrinologikum Berlin, Berlin, Germany.

Background/Purpose: In cross-sectional studies it has been shown already that functional status in ankylosing spondylitis (AS), which represents probably the most important long-term outcome in this disease, is related to both the presence of structural damage in the spine and to disease activity. Nonetheless, studies investigating the clinical relevance of radiographic progression in the spine prospectively, especially early in the course of the disease, are lacking. The aim of the current study was to investigate the relationship between worsening of functional status, clinical disease parameters and radiographic spinal progression over two years in patients with axial spondyloarthritis (axSpA).

Methods: In total, 160 patients with early axSpA (91 with AS and symptom duration ≤10 years, and 69 with non-radiographic axSpA (nr-axSpA) and symptom duration ≤5 years) from the German Spondyloarthritis Inception Cohort (GESPIC) were included in the current analysis based on the availability of radiographic data and data on the functional status at baseline and after 2 years of follow-up. Spinal radiographs were scored according to the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) independently by two trained readers who were blinded for time point and all clinical data. Functional status was assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI, 0–10 points), and clinical disease activity by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI, 0–10 points).

Results: In total, 44 patients (27.5%) of the patients demonstrated worsening of the BASFI by at least one point after 2 years as compared to baseline, and 20 patients (12%) experiences BASFI worsening in 2 points and more, which was considered to be clinically relevant. BASFI worsening by ≥1 point was significantly associated only with higher BASDAI worsening over 2 years in comparison to those without functional worsening: 1.2 ± 1.4 vs -0.6 ± 1.6, $p<0.001$. BASFI worsening by ≥2 points was, however, associated not only with increased disease activity (as reflected by BASDAI), but also with a higher rate of radiographic spinal progression - table. Importantly, in the multivariate analysis both BASDAI increase and progression of structural damage in the spine remained statistically significantly associated with BASFI worsening. No other disease-related parameters were found to be significantly associated with BASFI worsening over two years.

Table Association of disease-related parameters with worsening of BASFI (≥2 units) over two years in patients with axial spondyloarthritis.

Parameter	BASFI worsening (n = 20)	No BASFI worsening (n = 140)	p	OR (95% CI) for the BASFI worsening
BASDAI change	1.5 ± 1.6	−0.3 ± 1.6	<0.001	-
mSASSS change	2.6 ± 5.6	0.5 ± 1.7	0.20	-
mSASSS worsening by ≥2 points	35.0%	13.6%		3.4 (1.2–9.7)
mSASSS worsening by ≥4 points	25.0%	5.7%	0.012	5.5 (1.6–19.0)
New syndesmophytes formation/progression	30%	10%	0.022	3.9 (1.3–11.6)
HLA-B27 (+)	70%	78%	0.41	0.7 (0.2–1.9)
Male sex	65%	51%	0.34	1.8 (0.7–4.7)
Smoking	55%	36%	0.14	2.1 (0.8–5.5)
Elevated (>20 mm/h) time-averaged ESR	45%	25%	0.11	2.5 (0.9–6.4)
Elevated (>6 mg/l) time-averaged CRP	55%	39%	0.22	2.0 (0.8–5.0)

Conclusion: In this prospective study we could demonstrate that only 2 factors were significantly associated with worse functional outcome over two years in patients with early axSpA: 1) increase of disease activity (BASDAI) and 2) progression of structural damage. It seems that even a relatively small progression of structural damage such as an mSASSS worsening by 2 units or formation of a new syndesmophyte might have an impact on the functional status, even early in the course of the disease.

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High Prevalence Of Left Ventricular Diastolic Dysfunction In Patients With Ankylosing Spondylitis. Sjoerd C. Heslinga[1], Thelma C. Konings[1], Irene E. Van der Horst-Bruinsma[2] and Michael T. Nurmohamed[2]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands.

Background/Purpose: Patients with ankylosing spondylitis (AS) have an increased cardiovascular risk leading to decreased life expectancy. This is due to both accelerated atherosclerotic disease as well as cardiac morbidity such as valvular disease and congestive heart failure. In this study we investigated the prevalence of cardiac disease with echocardiography in patients with AS who were eligible for TNF-blocking therapy.

Methods: We performed a cross sectional study on consecutive patients with AS starting treatment with a TNF-blocker. Patients were screened for cardiac disease using standard transthoracic echocardiography that included two-dimensional, three-dimensional and M-mode echocardiography, spectral Doppler, color Doppler and tissue Doppler imaging. The ejection fraction (EF) was used to describe systolic function, with systolic dysfunction defined as EF<50%. For diastolic function a combination of echocardiographic measurements, namely peak early diastolic filling velocity (E), late diastolic filling velocity (A), E/A ratio, early diastolic mitral annular velocity (E'), deceleration time (DT) and isovolumetric relaxation time (IVRT) were used. Based on these parameters diastolic dysfunction is graded into three categories: mild (grade I), pseudonormal (grade II) and restrictive (grade III). Valvular abnormalities were evaluated according to the current echocardiographic guidelines. Disease activity was measured using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Blood pressure, serum glucose, total cholesterol, triglycerides, low density lipoprotein (LDL), high density lipoprotein (HDL), c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured. Data was compared with data from literature using one-sample t-test.

Results: 17 AS patients were included with a mean age of 44 ± 11 years and a disease duration of 18 ± 10 years (Tabel1). In total, 5 out of 17 (29%) patients had diastolic dysfunction grade I, of which one was female. This was significantly higher compared to literature, in which the prevalence of diastolic dysfunction grade I is approximately 5% in an age and sex-matched control group ($p=0.046$). One patient had systolic dysfunction, with an EF of 49%, but had suffered from a myocardial infarction in the past. Two patients had mild aortic regurgitation and two other patients had mild mitral regurgitation (23.5%). Overall, 7 out of 17 (41.1%) patients had some form of cardiac dysfunction or disease.

Conclusion: Patients with AS have an increased prevalence of diastolic dysfunction compared with the general population. This may be attributable to the general inflammation process that results in a decreased relaxation ability of the left ventricle as well as compromised valve cups function. As diastolic heart failure is associated with increased mortality, diastolic dysfunction in AS patients might have an important role in the increased cardiovascular risk.

Disclosure: S. C. Heslinga, None; **T. C. Konings**, None; **I. E. Van der Horst-Bruinsma**, MSD, 2; **M. T. Nurmohamed**, Roche, Abbvie, Pfizer, Janssen, 5, Roche, Abbvie, Pfizer, 8, Roche, Abbvie, Pfizer, MSD, UCB, BMS, 2.

2455

The Lipid Profile Improves In Patients With Ankylosing Spondylitis Responding To TNF Blocking Therapy. Sjoerd C. Heslinga[1], Irene E. Van der Horst-Bruinsma[1], Alper M. van Sijl[2] and Michael T Nurmohamed[1]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands.

Background/Purpose: Patients with ankylosing spondylitis (AS) have a decreased life expectancy due to an increased cardiovascular risk. Cardiovascular risk factors such as smoking, dyslipidemia, overweight, male gender and hypertension are implicated in atherogenesis. However, atherogenesis is also amplified by inflammation. Anti-inflammatory treatment with tumor-necrosis factor (TNF) inhibitors decreases the incidence of cardiovascular disease, which could be due to an improvement of cardiovascular risk factors, such as atheroprotective changes in the lipid profile. Therefore, the effect of treatment with TNF inhibitors on the lipid profile in patients with AS was investigated.

Methods: We evaluated all consecutive AS patients, who fulfilled New York 1984 criteria for AS, starting either with adalimumab or etanercept at our clinic Reade, Amsterdam. A total of 107 patients started adalimumab, and 183 patients started etanercept. Clinical data and blood samples were collected at baseline, at 24 and at 52 weeks of follow-up. A response to TNF blocking therapy was defined as a decrease in C-reactive protein (CRP) levels from >10 mg/L at baseline to <10 mg/L at 24 weeks, or a decrease in erythrocyte sedimentation rate (ESR) from >20 mm/h at baseline to < 20 mm/h at 24 weeks. Systolic and diastolic blood pressure, serum glucose, CRP, ESR, total cholesterol, triglycerides, low density lipoprotein (LDL), high density lipoprotein (HDL), apolipoprotein A (ApoA) and apolipoprotein B (ApoB) were measured. The students t-test was used to calculate changes.

Results: Patients with high disease activity (CRP >10 mg/L) had decreased lipid levels compared with patients with low disease activity. Seventy-four out of 206 (35,9%) patients showed a response to anti TNF therapy within 24 weeks. Total cholesterol levels increased significantly in responding patients (figure 1). In addition, triglycerides, HDL, LDL and ApoA levels also increased significantly. After one year of treatment this effect was still present. In non responding patients only HDL levels increased significantly after 24 weeks, but this effect disappeared after a year.

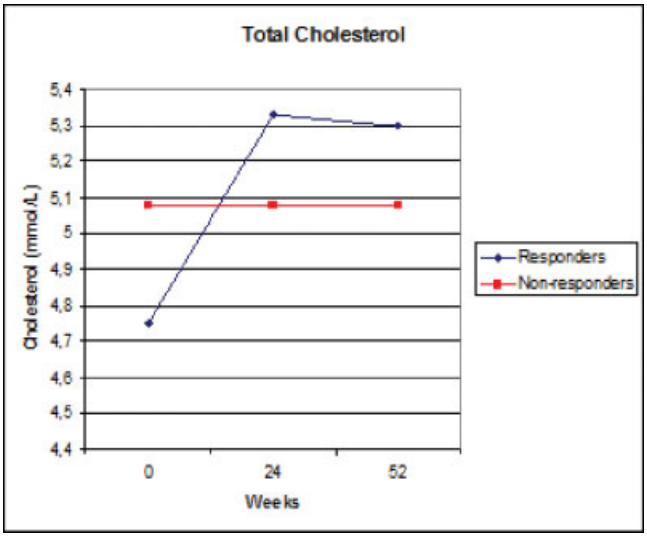

Figure 1. Changes in total cholesterol levels in responding and non-responding patients (n=292).

Conclusion: In AS patients with high disease activity lipid levels are depressed to a similar extent as observed in rheumatoid arthritis. Lipid levels normalized in responding AS patients. This effect was still present after one year of therapy. Anti-inflammatory therapy with TNF-blockers normalizes lipid levels and could potentially decrease the cardiovascular risk.

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2456

Prevalence Of Overweight and Obesity and The Relation To Disease Activity, Physical Function and Quality Of Life In Patients With Axial Spondyloarthritis. Fiona Maas[1], Anneke Spoorenberg[1], Eveline van der Veer[1], Reinhard Bos[2], Monique Efde[2], Hendrika Bootsma[1], Elisabeth Brouwer[1] and Suzanne Arends[1]. [1]University Medical Center Groningen, Groningen, Netherlands, [2]Medical Center Leeuwarden, Leeuwarden, Netherlands.

Background/Purpose: Obesity is a growing problem in Western society. It is associated with an increased risk for many disorders, impaired functional capacity, and impaired quality of life (QoL). The aim of the present study was to evaluate the prevalence of overweight and obesity and the relation with clinical assessments of disease activity, physical function, and QoL in patients with axial spondyloarthritis (SpA).

Methods: 465 consecutive patients from the Groningen Leeuwarden Axial SpA (GLAS) cohort who visited the outpatient clinic between January 2011 and December 2012 were included in this cross-sectional analysis. All patients fulfilled the modified New York criteria for ankylosing spondylitis (AS) (>90%) or the ASAS criteria for axial SpA. Body mass index (BMI) was calculated and patients were divided into groups according to the WHO criteria: low BMI (BMI <18.5 kg/m^2), normal BMI (BMI 18.5–25 kg/m^2), overweight (BMI 25–30 kg/m^2), and obesity (BMI >30 kg/m^2). Disease activity was assessed by Bath AS Disease Activity Index (BASDAI), AS Disease Activity Score (ASDAS), and C-reactive protein (CRP), physical function by Bath AS Functional Index (BASFI), and quality of life by ASQoL questionnaire.

Results: Mean age of the 465 patients was 45 years (SD±13), median symptom duration was 17 years (range 0–61), 65% were male, and median BMI was 26.0 kg/m^2 (range 17.0–45.4). In total, 8 (2%) patients had low BMI, 183 (39%) had normal BMI, 174 (37%) were overweight, and 100 (22%) were obese. Of the 100 obese patients, 19 had BMI between 35–40 kg/m^2 and 3 had BMI >40 kg/m^2. In comparison, the general Dutch population aged 30–70 years and matched for gender had an estimated prevalence of 1% low BMI, 44% normal BMI, 42% overweight, and 13% obesity.[1]

Obese axial SpA patients were significantly older, had longer disease duration, and more comorbidity than patients with normal BMI. Disease activity of obese patients was significantly higher and physical function and QoL were significantly worse compared to patients with normal BMI (Table 1). These differences remained statistically significant after correcting for age, disease duration, and comorbidity. No significant differences in clinical assessments were found between patients with overweight and normal BMI (Table 1).

Table 1. Disease activity, physical function, and QoL of axial SpA patients with overweight and obesity compared to those with normal BMI.

	Normal BMI [18.5–25] (n = 183)	Overweight BMI [25–30] (n = 174)	P-value*	Obesity BMI [>30] (n = 100)	P-value*
BASDAI (range 0–10)	3.4 (0–9.2)	3.5 (0–9.6)	0.235	4.4 (0.6–9.4)	0.029
ASDAS(CRP)	2.1 (0–5.2)	2.1 (0.3–5.1)	0.983	2.7 (0.5–5.7)	0.000
CRP (mg/L)	3.0 (0–73)	3.0 (0–94)	0.372	5.0 (0–82)	0.000
CRP ≥5 mg/L	62 (34)	56 (32)	0.795	53 (53)	0.001
BASFI (range 0–10)	2.9 (0–9.1)	2.7 (0–9.9)	0.635	5.1 (0.1–9.7)	0.000
ASQoL (range 0–18)	5.0 (0–17)	4.0 (0–18)	0.077	8.0 (0–18)	0.002

Values are presented as median (range) or number of patients (%). *P-values compared to patients with normal BMI.

Conclusion: In this large cohort of axial SpA patients with relatively longstanding disease, almost a quarter of the patients were obese. Cross-sectional analysis shows that the presence of obesity was associated with higher disease activity and worse physical function and QoL.

References:

1. Rijksinstituut voor Volksgezondheid en Milieu (2012). Available at: www.rivm.nl.

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Ankylosing Spondylitis and a Diagnostic Dilemma: Coccydynia. Rabia Deniz[1], Gülsen Ozen[1], Sibel Yilmaz-Oner[1], Sibel Z. Aydin[2], Can Erzik[1], Osman Hakan Gunduz[1], Nevsun Inanc[3], Haner Direskeneli[1] and Pamir Atagunduz[1]. [1]Marmara University School of Medicine, Istanbul, Turkey, [2]Medeniyet University, Goztepe Training and Research Hospital, Istanbul, Turkey, [3]Marmara University, School of Medicine, Istanbul, Turkey.

Background/Purpose: Coccydynia is defined as pain in or around the tail bone area. The most common cause of coccydynia is either a trauma such as a fall directly on to the coccyx or repetitive minor trauma. The etiology remains obscure in up to 30% of patients as idiopathic. The literature on the contribution of rheumatic diseases to coccydynia is scarce. In this study, our aim was investigating the prevalence of coccydynia in Ankylosing spondylitis (AS) patients.

Methods: One hundered and seven consecutive patients with AS were evaluated for coccydynia were enrolled between January and November 2012 for a cross-sectional analysis. Seventy four consecutive patients followed for mechanical back pain as controls and the AS patients were interviewed for the presence of coccydynia. In AS patients, disease activity assessed by Bath AS disease activity index (BASDAI) and treatment with biologic agents. Collected data was evaluated on SPSS® version 11.5 and Microsoft Excel® Programmes.

Results: Prevalence of coccydynia in AS (38.3%) was significantly higher than the control group ($p<0.0001$) in both female and male AS patients (Female AS vs. control=40.9% vs. 18.4%, $p=0.015$ and male AS vs. control=36.5% vs. 8.0%, $p=0.005$). Both genders were affected equally in the AS group whereas coccydynia was slightly more frequent in female patients in the control group. In AS patients; when each individual domain of BASDAI was evaluated for the affect of coccydynia, the question about the neck, back or hip pain had significantly higher score (p:0.019) in patients with coccydynia. Overall BASDAI score was also higher in this subset of patients (p:0.020). Although not significant, the need for anti-tumour necrosis factor α (Anti-TNF α) therapy seemed also higher in patients with coccydynia, suggesting a higher disease severity (31.8 % vs. 22.2%, $p=0.20$).

Conclusion: Coccydynia is a previously neglected symptom of AS and it is almost three times more common in AS than in non-specific chronic low back pain. Our observation may implicate that inflammatory diseases have a role in the etiology of coccydynia, especially in those without a history of recent or past trauma and coccydynia may be a factor associated with the severity of AS as well.

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Change Over Time In The Profile Of Ankylosing Spondylitis Patients Treated With Infliximab In Canadian Routine Care. Denis Choquette[1], Michael Starr[2], Majed M. Khraishi[3], William G. Bensen[4], Saeed A. Shaikh[5], Jude F. Rodrigues[6], Dalton E. Sholter[7], Maqbool K. Sheriff[8], Julie Vaillancourt[9], John S. Sampalis[10], Allen J. Lehman[11], Susan M. Otawa[11], Francois Nantel[11] and May Shawi[11]. [1]Institut de Rhumatologie de Montréal, Montreal, QC, [2]Montreal General Hospital, Montreal, QC, [3]MD, Memorial University of Newfoundland, Nexus Clinical Research, St Johns, NF, [4]St. Joseph's Hospital and McMaster University, Hamilton, ON, [5]McMaster University, St Catharines, ON, [6]Rheumatology, Windsor, ON, [7]Rheumatology Associates, Edmonton, AB, [8]Nanaimo Regional General Hospital, Nanaimo, BC, [9]JSS Medical Research, Montreal, QC, [10]JSS Medical Research, St-Laurent, QC, [11]Janssen Canada Inc, Toronto, ON.

Background/Purpose: Canadian provincial reimbursement policies in regards with infliximab coverage status have evolved in the last decade. The objective of this study was to describe and compare over time the demographics and disease parameters at infliximab treatment initiation and to assess the effectiveness of treatment at 6 and 12 months in Canadian AS patients.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis (RA), ankylosing spondylitis (AS), or psoriatic arthritis (PsA) with infliximab or golimumab as first biologics or after having been treated with a biologic for less than six months. People with AS treated with infliximab who were enrolled between 2002 and 2013 were included in this analysis (N=303) and stratified to two groups (2005–2007: n=135; 2008–2013: n=168) based on the year of enrolment in the registry.

Results: Table 1 summarizes the patient characteristics at infliximab initiation by period of enrolment in BioTRAC. Patient demographics were comparable in the two cohorts with a mean (SD) age of 45.72 (11.74) years and the majority being males (62.4%). A significant change in the geographic distribution of patients enrolled in the BioTRAC registry was observed ($P=0.001$) and more patients with provincial coverage were enrolled in 2008–2013 compared to 2005–2007 ($P=0.012$). A trend towards earlier initiation of infliximab was observed in more recent years as indicated by the shorter disease duration (11.12 vs. 8.24 years; $P=0.013$) and the lower number of prior traditional DMARDs used (0.83 vs. 0.59; $P=0.078$). Furthermore, overall, patients recruited in 2008–2013 had lower disease activity compared to those enrolled in 2005–2007. ESR (29.96 vs. 19.91 mm/hr; $P<0.001$), physician global assessment (MDGA; 6.99 vs. 6.26; $P=0.001$) were significantly lower in the 2008–2013 cohort while a statistical trend was observed in morning stiffness (78.96 vs. 70.11 minutes; $P=0.064$) and ASDAS (3.90 vs. 3.70; $P=0.103$).

Treatment for 6 months resulted in a greater proportion of patients in the 2008–2013 cohort achieving inactive disease (ASDAS<1.3) without reaching statistical significance (20.7% vs. 34.9%; $P=0.140$).

Table 1. Demographics and Patient Characteristics at IFX Initiation by Enrolment Period

	Enrolment Period		
Parameter	2005–2007 (N = 135)	2008–2013 (N = 168)	P-Value
Age (years), mean (SD)	45.58 (11.61)	45.65 (11.89)	0.958
Male gender, n (%)	82 (60.7%)	107 (63.7%)	0.634
Disease duration (years), mean (SD)	11.12 (10.77)	8.24 (9.18)	0.013
Province			
Maritime	4 (3.0%)	9 (5.4%)	0.001
Quebec	53 (39.3%)	53 (31.5%)	
Ontario	50 (37.0%)	96 (57.1%)	
Manitoba	3 (2.2%)	0 (0.0%)	
Saskatchewan	2 (1.5%)	1 (0.6%)	
Alberta	3 (2.2%)	1 (0.6%)	
British-Colombia	20 (14.8%)	8 (4.8%)	
Coverage	n = 135	n = 160	
Provincial	38 (28.1%)	67 (41.9%)	0.012
Private	71 (52.6%)	70 (43.8%)	
Provincial and private	10 (7.4%)	16 (10.0%)	
Other	16 (11.9%)	7 (4.4%)	
Infliximab dose (mg/kg), mean (SD)	4.31 (1.02)	4.43 (1.19)	0.372
Previous use of DMARD, n (%)	56 (41.5%)	56 (33.3%)	0.144
Number of previous DMARDs, mean (SD)	0.83 (1.12)	0.59 (0.86)	0.078
Concomitant use of DMARDs, n (%)	37 (27.4%)	50 (29.8%)	0.653
Morning stiffness (minutes), mean (SD)	78.96 (38.86)	70.11 (42.42)	0.064
HAQ-DI, mean (SD)	1.26 (0.58)	1.19 (0.59)	0.318
ESR (mm/hr), mean (SD)	29.96 (23.07)	19.91 (18.09)	<0.001
CRP (mg/L), mean (SD)	20.43 (23.85)	16.68 (25.66)	0.243
MDGA (NRS: 0–10), mean (SD)	6.99 (1.56)	6.26 (2.05)	0.001
ASDAS, mean (SD)	3.90 (0.87)	3.70 (1.06)	0.103
ASDAS Disease Activity, n (%)	*n = 103*	*n = 130*	
Inactive (ASDAS <1.3)	0 (0.0%)	4 (3.1%)	0.160
Moderate (1.3 ≤ ASDAS <2.1)	1 (1.0%)	3 (2.3%)	
High (2.1 ≤ ASDAS ≤ 3.5)	34 (33.0%)	50 (38.5%)	
Very High (ASDAS >3.5)	68 (66.0%)	73 (56.2%)	
BASDAI, mean (SD)	6.54 (1.90)	6.37 (2.16)	0.490
BASFI, mean (SD)	6.30 (2.23)	6.09 (2.48)	0.447

Conclusion: The results of this analysis show that the profile of the AS patient population in the BioTRAC registry has changed over time towards lower disease activity and earlier initiation in the patient management process. These results may reflect differences in patient management over time or may be related to earlier access to care. Irrespective of enrolment period, 6-month treatment with infliximab was effective in reducing disease activity in Canadian AS patients.

Disclosure: D. Choquette, None; **M. Starr**, None; **M. M. Khraishi**, Hoffman-La Roche Canada, Amgen and Pfizer Canada, and Abbott Canada., 2; **W. G. Bensen**, None; **S. A. Shaikh**, None; **J. F. Rodrigues**, None; **D. E. Sholter**, None; **M. K. Sheriff**, None; **J. Vaillancourt**, JSS, 3; **J. S. Sampalis**, None; **A. J. Lehman**, Janssen Canada, 3; **S. M. Otawa**, Janssen Canada, 3; **F. Nantel**, None; **M. Shawi**, Janssen Canada, 3.

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Improvement In Physical Function, Health-Related Quality Of Life, and Work Productivity With Adalimumab Treatment In Non-Radiographic Axial Spondyloarthritis. Désirée M. van Der Heijde[1], Philip J. Mease[2], Aileen L. Pangan[3], Sumati A Rao[3], Naijun Chen[3] and Mary Cifaldi[3]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA, [3]AbbVie Inc., North Chicago, IL.

Background/Purpose: Adalimumab (ADA) was approved in the European Union for the treatment of severe non-radiographic axial spondyloarthritis (nr-axSpA) in patients with objective signs of inflammation (elevated C-reactive protein (CRP) or positive MRI) and inadequate response or intolerance to NSAIDs. We aimed to evaluate effects of long-term ADA treatment on patient-reported outcomes (PROs) and work productivity in nr-axSpA patients with elevated CRP or positive MRI.

Methods: ABILITY-1 is an ongoing Phase III, multicenter, randomized, controlled trial of ADA vs. placebo (PBO) in patients with nr-axSpA (fulfilling Assessment of Spondyloarthritis international Society axial SpA criteria but not modified New York criteria for ankylosing spondylitis). After the 12-week double-blind phase, all patients switched to open-label ADA (represented as ADA/ADA and PBO/ADA groups) for 144 weeks. This *post-hoc* analysis evaluated productivity and PROs until Week 52 among 142 patients with elevated CRP or MRI evidence of inflammation (spine or SI joints) at baseline. Physical function was assessed using the disability index of the Health Assessment Questionnaire for Spondyloarthropathies (HAQ-S) and health-related quality of life using the Short Form 36 Health Survey (SF-36) Physical Component Summary (PCS) score. Productivity was assessed using the Work Productivity and Activity Impairment Questionnaire (WPAI). Changes from baseline to Week 12 were compared between groups using ANCOVA with adjustment for baseline scores and with treatment as a factor.

Results: No significant differences between treatment groups were observed in baseline HAQ-S, SF-36 PCS, or WPAI domain scores. After 12 weeks of therapy in the double-blind period, the ADA group experienced significant improvements from baseline compared with PBO in mean HAQ-S (P=.007) and SF-36 PCS (P<.001) scores, and in 3 of 4 WPAI domain scores (P=.017, 0.041, 0.128, and 0.005, for absenteeism, presenteeism, overall work impairment, and activity impairment, respectively). By Week 52, PBO patients who switched to open-label ADA demonstrated improvements comparable to those in patients who received ADA during the double-blind period. Patients in both groups achieved SF-36 scores (43.2 and 44.3 for the PBO/ADA and ADA/ADA groups, respectively) approaching the US general population norm of 50 at Week 52.

Baseline Scores and Mean Change From Baseline Through Week 52 in HAQ-S, SF-36 PCS, and WPAI Domain Scores Among nr-axSpA Patients With Positive MRI or Elevated CRP Levels, Mean ± SD (n)[a]

Double-Blind Phase	HAQ-S[b]		SF-36 PCS[c]		WPAI Presenteeism[d]		WPAI Activity Impairment[d]	
	PBO	ADA	PBO	ADA	PBO	ADA	PBO	ADA
Baseline Score	1.02 ± 0.53 (n = 73)	1.01 ± 0.56 (n = 69)	33.2 ± 8.16 (n = 73)	33.3 ± 7.78 (n = 69)	44.2 ± 26.48 (n = 48)	38.5 ± 23.41 (n = 41)	55.7 ± 25.33 (n = 72)	56.4 ± 24.13 (n = 69)
Week 12	−0.13 ± 0.35 (n = 69)	−0.33 ± 0.52 (n = 68)	2.3 ± 6.81 (n = 72)	6.9 ± 9.32 (n = 69)	−7.6 ± 27.12 (n = 42)	−14.4 ± 26.93 (n = 39)	−4.6 ± 26.34 (n = 68)	−16.2 ± 24.02 (n = 69)
Open-Label Phase	**HAQ-S[b]**		**SF-36 PCS[c]**		**WPAI Presenteeism[d]**		**WPAI Activity Impairment[d]**	
	PBO/ADA	ADA/ADA	PBO/ADA	ADA/ADA	PBO/ADA	ADA/ADA	PBO/ADA	ADA/ADA
Week 36	−0.41 ± 0.46 (n = 64)	−0.45 ± 0.52 (n = 60)	8.4 ± 10.01 (n = 64)	9.9 ± 10.66 (n = 59)	−18.8 ± 30.76 (n = 41)	−19.7 ± 27.47 (n = 34)	−23.2 ± 30.52 (n = 63)	−22.2 ± 25.80 (n = 59)
Week 52	−0.45 ± 0.48 (n = 60)	−0.46 ± 0.46 (n = 56)	10.0 ± 9.91 (n = 61)	11.0 ± 9.93 (n = 55)	−23.1 ± 30.96 (n = 39)	−27.3 ± 24.34 (n = 30)	−26.1 ± 33.32 (n = 59)	−31.5 ± 24.45 (n = 55)

[a]n = number of subjects with nonmissing values for both baseline and the respective visit.
[b–d]MID = −0.26, 3.0, and −7.0%, respectively.

Conclusion: Among patients with elevated CRP or positive MRI, ADA therapy was associated with significant improvement in PROs and productivity compared with PBO during the double-blind phase of the ABILITY-1 trial. Patients who continued on ADA therapy and those who switched to ADA in the open-label period experienced comparable meaningful improvements in PROs and productivity through Week 52.

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Spondyloarthritis Epidemiology and Burden Phase 2 [SPEED 2] Study: Disease Progression In Axial Spondyloarthropathy (SpA). Eric Ruderman[1], Vibeke Strand[2], Avani Joshi[3], Yanjun Bao[3], Keith Betts[4], Pooja Chopra[4], Michael B. McGuire[5] and Sumati A Rao[3]. [1]Northwestern University, Chicago, IL, [2]Stanford University, Palo Alto, CA, [3]AbbVie Inc., North Chicago, IL, [4]Analysis Group, Inc., Boston, MA, [5]Medical Data Analytics, Parsippany, NJ.

Background/Purpose: Limited information is available on progression of non-radiographic axial spondyloarthropathy (nr-axSpA) to ankylosing spondylitis (AS) in patients with SpA meeting the Assessment of Spondyloarthritis International Society (ASAS) criteria in the US. We assessed disease progression from nr-axSpA to AS and numbers of remissions and flares in this population in rheumatology practices.

Methods: SPEED-2 was a retrospective, multicenter, observational cohort study based on medical chart review. For inclusion, individuals met the following criteria (from 2000 to 2005): ≥18 years old; rheumatologists' diagnoses or suspected diagnoses of SpA (axial SpA, nr-axSpA, AS, or undifferentiated SpA); fulfilled ASAS criteria for axial SpA; with a minimum follow up of ≥7 years with ≥1 documented radiographic assessment of sacroiliac joints (SIJ). An index date was defined as the earliest date between 2000–2005 when subjects had SIJ radiographs after having retrospectively fulfilled ASAS criteria. Their disease course, from 7–12 years following the index date (follow-up period), was reviewed. Stratified analyses included patients with AS and nr-axSpA in an approximate 1:1 ratio. Rate of progression from nr-axSpA to AS over time was determined by Kaplan-Meier analysis according to SIJ radiographs. Number of rheumatologist-reported "remissions" (defined as symptom- and treatment-free periods) and "flares" (defined as periods with increased symptoms requiring treatment during follow-up) were summarized.

Results: Of 286 patients fulfilling ASAS criteria for axial SpA, 166 were classified as AS and 120 as nr-axSpA. Patients with AS or nr-axSpA were predominantly white, male, with a mean age of 45 and 43 years, respectively. Approximately 89% and 85%, respectively, had an original diagnosis of axial SpA, AS, or nr-axSpA. Of 120 patients with nr-axSpA, 51 had a repeat SIJ radiographs during follow-up: approximately 2% of these 51 patients progressed to AS in the first 2 years and 27.6% over a period of 11 years after the index date. The majority of patients with nr-axSpA did not have spontaneous (91%) or treatment-related (73%) remissions reported. During follow-up, 66% with nr-axSpA had ≥1 flare, with an average duration of 18 days, suggesting ongoing disease activity.

Patient Demographics and Disease Characteristics at Index Date and Outcomes During Follow-Up

Characteristic	AS N = 166	nr-axSpA N = 120
Age (years), mean ± SD	44.8 ± 10.18	43.4 ± 8.84
Male, n (%)	139 (83.7)	91 (75.8)
White, n (%)	128 (77.1)	100 (83.3)
Rheumatologists' Diagnoses at Index Date[a]		
Axial SpA, n (%)	38 (22.9)	25 (20.8)
Ankylosing spondylitis, n (%)	109 (65.7)	52 (43.3)
Non-radiographic axial SpA, n (%)	1 (0.6)	25 (20.8)
Undifferentiated SpA, n (%)	14 (8.4)	16 (13.3)
Inflammatory back pain, n (%)	12 (7.2)	5 (4.2)
Psoriatic arthritis, n (%)	3 (1.8)	3 (2.5)
Progression from nr-axSpA to AS[b]		
AS classification at 2 years, n (%)		1 (2.0)
AS classification at 11 years, n (%)		12 (27.6)
Remissions and Flares[c]		
Patients with ≥1 spontaneous remission, n (%)		11 (9.2)
Patients with ≥1 treatment-related remission, n (%)		33 (27.5)
Patients with ≥1 flare, n (%)		79 (65.8)
Average flare duration in days, mean ± SD		18.2 ± 26.05

[a]Rheumatologists' diagnoses or suspected diagnoses were determined from charts provided retrospectively. More than 1 clinical diagnosis was reported for some subjects.
[b]Patients fulfilling modified New York criteria for AS among 51 with follow-up radiographs.
[c]Reported by rheumatologists.

Conclusion: This observational cohort study demonstrated that few patients with nr-axSpA progressed to AS. Few spontaneous or treatment related remissions were reported among both nr-axSpA and AS patients, and

the majority experienced disease flares during the follow-up period, indicative of disease activity.

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2461

Quality Of Life, Physical Function and Symptoms In Non-Radiographic Axial Spondyloarthritis:The Patient Perspective. Philip J. Mease[1], Sumati A Rao[2], Avani D. Joshi[2], Sarah Clifford[3], Christina Vernon[3] and Mary A. Cifaldi[2]. [1]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA, [2]AbbVie Inc., North Chicago, IL, [3]United BioSource Corporation, Bethesda, MD.

Background/Purpose: Pain, physical function impairment, and health-related quality of life (HRQoL) impact are substantial for patients with non-radiographic axial spondyloarthritis (nr-axSpA).[1] Understanding the most important aspects of nr-axSpA from the patient's perspective may offer insights regarding the relevance of the disease specific patient-reported outcome (PRO) instruments and lead to better disease assessment and management in this patient population. We explored the impact of nr-axSpA on patients' physical function and other HRQoL outcomes and assessed content validity for 3 commonly used PROs.

Methods: In this cross-sectional cognitive interview study, participants ≥18 years old with chronic back pain and physician-diagnosed nr-axSpA were interviewed at 4 US sites in the Midwest/West. Participants were asked open-ended questions regarding their nr-axSpA symptoms including frequency, severity, and effect on their lives. Participants then completed and were interviewed with the Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and Health Assessment Questionnaire–Spondyloarthropathies (HAQ-S).

Results: Among the 20 participants, mean age was 42.8 years, 45% were women, 85% were white, and mean duration of nr-axSpA was 3.5 years. The majority (90%) reported pain (**table**), which tended to increase in intensity during flares and as patients aged. Other symptoms—most notably stiffness, weakness, swollen joints, problems with the sacroiliac (SI) joints, and aches—were also mentioned. The most common physical functioning and HRQoL impacts were associated with sleeping, walking, athletic activity, bending, sitting for long periods, and household chores. Mean scores on the PRO measures were 4.7 (range of 0.52–8.85) for BASFI, 4.85 (range of 1.13–8.31) for BASDAI, and 1.09 (range of 0–2) for HAQ-S. The cognitive interviews suggested that HAQ-S covers key symptoms and effects of nr-axSpA and the majority of the participants found the items clear and relatable to their condition. The interviews also suggested overall relevance of the BASFI and BASDAI in nr-axSpA, but symptoms and difficulties such as swollen joints, SI joint problems, aches, and sexual/emotional aspects may not be addressed fully.

Table 1. Summary of Patient-Reported nr-axSpA Symptoms[a]

		n (%)
Typical SpA symptoms	Pain (hurt)	18 (90)
	Stiffness (body joints)	11 (55)
	Weakness	6 (30)
	Fatigue (drained)	3 (15)
Other symptoms[b]	Swelling in joints	8 (40)
	SI joint fusing	5 (25)
	Aches/achy/aching/sore	5 (25)
	Lack of flexibility (eg, in hands, knees)	3 (15)
	Tightness	2 (10)
	Hands go numb/numbness	2 (10)

[a]Symptoms reported in the patient's own language
[b]Anemia, fever, tender, wrist gets warm, hand turns purple, eyesight worsening, like a knot, stabbing, and burning each were reported by 1 patient.

Conclusion: This study highlights patients' perspectives of their nr-axSpA symptoms. Pain and other symptoms such as stiffness and joint problems often caused significant impairment in the participants' daily lives. The findings strongly support the relevance of the HAQ-S, BASFI, and BASDAI in the nr-axSpA population. Future studies could explore whether additional items or modification to wording and response options, as suggested by the participants, could enhance the measures or lead to the development of new measures.

Reference:
[1]Sieper J, et al. doi:10.1136/annrheumdis-2012–201766.

Disclosure: P. J. Mease, AbbVie, Amgen, BMS, Celgene, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, UCB, 5; **S. A. Rao**, AbbVie, 1, AbbVie, 3; **A. D. Joshi**, AbbVie, 3, AbbVie, 1; **S. Clifford**, United BioSource Corporation, 3; **C. Vernon**, United BioSource Corporation, 3; **M. A. Cifaldi**, AbbVie, 3, AbbVie, 1.

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Comparison Of Tumor Necrosis Factor Inhibitor Use For Ankylosing Spondylitis At University Rheumatology Clinics In Scotland and Oregon. Anusha Reddy[1], Abhijeet Danve[2], Kiana Vakil-Gilani[2], Jennifer H. Ku[2], Sanjay Ganhasan[1], Alison Black[1] and Atul Deodhar[2]. [1]Aberdeen Royal Infirmary, Aberdeen, United Kingdom, [2]Oregon Health and Science University, Portland, OR.

Background/Purpose: Use of tumor necrosis factor inhibitors (TNFi) for ankylosing spondylitis (AS) is directed by national guidelines in the UK. However in the US, in the absence of treatment recommendations, the use of TNFi is dictated by local practice patterns. We compared the use of TNFi in the treatment of AS at Aberdeen Royal Infirmary (ARI) in Scotland, and Oregon Health & Science University (OHSU) in Oregon.

Methods: This was a retrospective analysis of patients who were newly started on TNFi for treatment of AS between 2007 and 2012 at OHSU, and between 2004 and 2011 at ARI. Data on patient demographics, clinical characteristics and treatment were collected from electronic medical records. Descriptive analysis, Mann-Whitney U test and chi-square test (Fisher's exact test if N <5) was used to compare the two groups of patients.

Results: There were significant differences between the 2 groups regarding age, HLA B27 positivity, NSAID use, physical function and presence of depression, (see Table). Time to start TNFi after the symptom onset was median 10 (11.5) years at ARI compared to 6 (8) years at OHSU. The baseline BASDAI at the time of initiation of TNFi at ARI was 7 (2.2) compared to 6 (3.9) at OHSU (p=0.04). Adalimumab was the most frequently prescribed TNFi in both places (67% of ARI and 51% of OHSU patients). Percentage reduction in BASDAI in 1 year from baseline was significantly higher at ARI (64%) as compared to OHSU (17%). According to the NICE guidelines followed in the UK, AS patients are not allowed to switch the TNFi for inefficacy. In OHSU, 22% patients switched TNFi once and 12% switched TNFi more than once, for either allergic reaction or inefficacy. These patients had mean BASDAI score of 3.45 (2.6) and 3.97 (3) respectively after one year.

	OHSU (2007–2012) N = 41 N, median (iqr) Or N (%)	ARI 2004–2011 N=67 N, median (iqr) Or N (%)	P value
Age years	45 (12)	40.5 (17.5)	0.048*
Female	14 (34.2)	14 (21.9)	0.17
Symptom onset to time of starting TNFi in years	30, 6 (8)	20, 10 (11.5)	0.16
Positive HLA-B27	20 (64.5)	15 (100)	<0.01*
NSAID use	31 (75.6)	64 (100)	<0.01*
Baseline BASDAI	16, 6.0 (3.9)	61, 7.0 (2.2)	0.04*
Baseline RAPID 3	26, 5.2 (2.2)	N/A	N/A
Pain	26, 7 (2.5)	59, 7.4 (2.4)	0.97
Function	26, 2.7 (2.3)	60, 6.2 (3.3)	<0.01*
BASMI	N/A	58, 3.7 (3.2)	N/A
Uveitis	4 (9.8)	11 (17.2)	0.40
Psoriasis	5 (12.2)	5 (7.8)	0.51
Inflammatory bowel disease (IBD)	6 (14.6)	4 (6.4)	0.18
Depression	13 (32.5)%	4 (6.3)	<0.01*
Fibromyalgia	5 (12.2)	N/A	N/A
Ischemic heart disease	2 (4.9)%	1 (1.6)	0.32
% change in BASDAI at 1 year	17.6%	64.7%	<0.01

* statistical significanceN/A "not applicable"

Conclusion: Patients at ARI had higher baseline BASDAI and longer time to start TNFi after symptom onset as compared to OHSU. Higher prevalence of depression in OHSU patients may have affected the change in BASDAI, which is a subjective measure. OHSU patients who switched TNFi due to inadequate response had a good outcome suggesting that switching TNFi is a valid strategy, which is currently not available to patients in the UK.

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2463

Tomosynthesis As a New Diagnostic Tool For Evaluation Of Ankylosing Spondylitis With Modified Stoke Ankylosing Spondylitis Spinal Score: A Comparison With Plain Radiographs. Seunghun Lee[1], Tae-Hwan Kim[2], Jae-Bum Jun[2], Kyung-Bin Joo[3], Young Bin Joo[2] and Jina Park[4]. [1]Hanyang University College of Medicine, Seoul, South Korea, [2]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [3]Hanynag University, Seoul, South Korea, [4]Hanyang University Hospital, Seoul, South Korea.

Background/Purpose: In assessment of ankylosing spondylitis (AS), accurate scoring of modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) is important to evaluate the treatment effects or follow-up results. Until now, lateral plain radiographs of cervical and lumbar spine were used for the assessment of mSASSS. We assessed the potential of tomosynthesis in evaluation of AS with mSASSS.

This study aimed to demonstrate the benefit of tomosynthesis in assessment of mSASSS, compared with plain radiographs.

Methods: The study group comprised 68 (55 men and 13 women; mean age, 32 years) patients with AS who underwent tomosynthesis and plain radiographs of cervical and lumbar spine on the same day. Two experienced radiologists (reader 1 and 2) independently assessed mSASSS with tomosynthesis and reader 1 assessed mSASSS with plain radiographs. Reader 1 also assessed the presence of facet narrowing or ankylosis on each level with tomosynthesis. Statistical agreements between tomosynthesis and plain radiographs in assessing total mSASSS score and scores on each spinal level were analyzed. And we analyzed the interobserver reliability between reader 1 and 2 in the interpretation of tomosynthesis.

Results: In scoring the anterior corner lesions, tomosynthesis and plain radiographs showed fair agreement in upper border of C3, upper border of C5 and upper border of L1 (kappa value of 0.324, 0.358 and 0.391, respectively). In lower border of C4, lower border of T12, lower border of L1 and upper border of L3, tomosynthesis and plain radiographs showed moderate agreement (kappa value of 0.584, 0.43, 0.573 and 0.541). 44 of 68 patients (64.7%) showed higher total mSASSS score on tomographic evaluation as compared with radiographic studies. The mean mSASSS with tomography and plain radiographs were 13 and 11.6, respectively. On tomosynthesis, cervical facet arthropathies were detected in 15 of 68 patients (22%) and lumbar facet arthropathies were detected in 23 of 68 patients (33.8%). Interobserver agreement between two readers in tomographic evaluation of total mSASSS score and scores on C-spine and L-spine levels showed excellent agreement (kappa values of 0.974, 0.924 and 0.969, respectively).

Conclusion: We suggest that tomosynthesis is an excellent method for evaluation of AS with mSASSS. Tomosynthesis is superior to plain films in detecting and assessing anterior corner lesions. And also, it is good method to evaluate facet joint involvement in AS patients.

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2464

Late-Onset Ankylosing Spondylitis Has Distinctive Presenting Symptoms and a Higher Inflammatory Burden. Yeon-Ah Lee[1], Sang-Hoon Lee[2], Ran Song[2], Hyung-In Yang[2] and Seung-Jae Hong[1]. [1]Kyung Hee University, Seoul, South Korea, [2]Hospital at GANGDONG, Kyung Hee University, Seoul, South Korea.

Background/Purpose: Most ankylosing spondylitis (AS) patients experience their first symptoms prior to age 45. However, symptoms of AS can develop after the age 45 and the initial manifestations may vary according to the different onset-age subsets. This study was performed to investigate whether there are characteristic clinical features and more inflammatory burdens in the late-onset AS patients compared to adult-onset AS.

Methods: We retrospectively studied the clinical and laboratory features of 499 AS patients. These patients was fulfilled the modified New York criteria for AS and were classified into 2 groups based on their age at symptom onset: adult-onset AS (>16 but < 45 years; AOAS); and late-onset AS (≥45 years; LOAS). The onset of disease was defined by the day of appearance of the first manifestation of AS. In both groups, the following data were compared:(1) epidemiological variables (sex, age at symptom onset, and duration of disease); (2) laboratory results (HLA-B27, ESR and CRP); (3) clinical manifestations, including signs and symptoms at diagnosis and during follow-up, involvement of the cervical spine, shoulder and hip, and extra-articular manifestations; (4) BASDAI and BASMI; (5) radiographic data (BASRI total and BASRI spine); (6) use of anti-TNF-α agent and time to start anti-TNF-α therapy.

Results: There were 29 patients (5.8%) with LOAS. LOAS group had more female patients (44.8% vs. 21.5%, p=0.004), shorter disease duration (6.2±4.9 vs.11.3±6.8 years, p<0.001) and less HLA-B27 positivity (69.0% vs. 82.6%, p=0.037) than AOAS group. As an initial manifestation, the patients with LOAS more often presented cervical pain (40.0% vs. 18.8%, p=0.005), shoulder pain (30.0% vs. 6.6%, p<0.001), lower extremity arthritis (56.7% vs. 36.5%, p=0.027), and the anterior chest wall pain (30.0 % vs. 6.6%, p<0.001) than AOAS. Clinical symptoms during follow-up and the radiological scores did not differ between the two groups. The most notable findings of the LOAS group were higher initial ESR (47.8±29.8 vs. 29.6±23.8 mm/hr, p< 0.001) and more frequent use of TNF-α inhibitors during the course of the disease (58.6% vs. 38.5%, p< 0.001). Among the all anti-TNF-α users, LOAS patients tended to show higher BASDAI score and higher ESR at the start of the therapy compared to AOAS.

Conclusion: Our results suggest that LOAS has distinctive presenting symptoms and a higher inflammatory burden. With increased clinical attention to LOAS as a cause of inflammatory arthritis in elderly patients, a timely initiation of disease-specific treatment can be provided.

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2465

Prevelance Of Inflammatory Back Pain and Axial Spondyloarthritis Among University Employees In Izmir, Turkey. Fatos Onen[1], Dilek Solmaz[1], Pinar Cetin[1], Ali Balci[2], Servet Akar[1] and Nurullah Akkoc[1]. [1]Dokuz Eylul University School of Medicine, Izmir, Turkey, [2]Dokuz Eylul University School of Medicine, izmir, Turkey.

Background/Purpose: The prevalence of axial spondyloarthritis (SpA) has not yet been investigated in a population based survey by using new ASAS classification criteria. The aim of this study was to determine the prevalence of axial SpA among university employees in Izmir, Turkey.

Methods: The study was conducted in the Health Sciences Campus with a population of 2894 medical and non-medical staff at Dokuz Eylul University in Izmir. A sample size of 395 subjects was calculated by assuming that the inflammatory back pain (IBP) prevalence of 5% in the general population (1) using OpenEpi (version 2.3 Atlanta, GA, USA), based on a confidence interval of ±2%. Six trained medical students using a standard questionnaire performed a face-to-face interview with participants. The subjects who were classified as having IBP based on ASAS Experts' criteria and other IBP criteria sets were invited to the Rheumatology out-patient clinic to participate in the study. They were evaluated for axial SpA by two rheumatologists using ASAS classification criteria. The patients with IBP were also evaluated to determine whether they met the modified New York (mNY) criteria for ankylosing spondylitis (AS) and both the ESSG and the Amor criteria for SpA.

Results: A total of 381 subjects (131 male, 250 female; mean age: 38.0 ± 9.4) were contacted with an acceptance rate of 96.5%. Twenty five subjects (6.5 %; CI 95% 4.0–9.0) with back pain lasting ≥ 3 months were classified as having IBP according to ASAS Experts' criteria. The prevalence of IBP according to Berlin and Calin criteria was found to be 7.0% (CI 95% 4.0–10.0) and 21.5% (CI 95% 17.0–25.0), respectively (Table).

Three subjects with IBP (0.78%) were classified as having axial SpA according to ASAS classification criteria. Two of these patients (0.52%) had radiographic sacroiliitis and they met the mNY criteria for AS. There were 8 patients (2.0%) who fulfilled both the Amor and ESSG criteria for whole group of SpA (Table). One of them had psoriasis.

Table. Prevalence of IBP and SpA according to various classification criteria in the university employees

	Total % (CI 95%)	Female % (CI 95%)	Male % (CI 95%)
IBP Criteria			
ASAS Experts'	6.5 (4.0–9.0)	8.0 (5.0–12.0)	3.0 (1.0–8.0)
Berlin	7.0 (4.0–10.0)	8.0 (5.0–12.0)	3.0 (1.0–8.0)
Calin	21.5 (17.0–25.0)	24.2 (19.0–29.0)	16.0 (11.0–24.0)
ASAS Criteria for Axial SpA	0.78 (0.16–2.30)	0.80 (0.097–2.89)	0.70 (0.02–4.25)
MNY Criteria for AS	0.52 (0.06–1.80)	0.40 (0.01–2.20)	0.70 (0.02–4.25)
Amor Criteria for SpA	2.00 (0.90–4.00)	2.40 (0.88–5.22)	1.40 (0.18–5.50)
ESSG Criteria for SpA	2.00 (0.90–4.00)	2.40 (0.88–5.22)	1.40 (0.18–5.50)

IBP: inflammatory back pain; SpA: spondyloarthritis; MNY: modified New York; ESSG: European Spondyloarthropathy Study Group

Conclusion: This is the first population-based survey of axial SpA using ASAS classification criteria. The prevalence estimates of IBP and SpA/axial SpA reported in this study are within the upper range of other studies in European countries and US.

Reference:

1. Weismann MH et al. The prevalence of inflammatory back pain: population-based estimates from the US National Health and Nutrition Examination Survey, 2009–10. Ann Rheum Dis 2013 Mar;72(3):369–73

Disclosure: F. Onen, None; **D. Solmaz**, None; **P. Cetin**, None; **A. Balci**, None; **S. Akar**, None; **N. Akkoc**, None.

2466

Long Term Efficacy Over Five Years Of Adalimumab In Patients With Active Non - Radiographic Axial Spondyloarthritis. Hildrun Haibel[1], Xenofon Baraliakos[2], Joachim Listing[3], Juergen Braun[2] and Joachim Sieper[1]. [1]Charité Universitätsmedizin Berlin, Berlin, Germany, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, [3]German Rheumatism Research Center, Berlin, Germany.

Background/Purpose: Adalimumab had demonstrated good efficacy in 46 patients with active non-radiographic axial SpA in a 12-weeks, placebo-controlled trial with a 40-weeks, open-label extension.[1,2]In 19 patients who flared after drug withdrawal therapy was restarted and patients were followed-up. The purpose of the study was to evaluate the long term efficacy over 5 years after re-treatment with adalimumab in patients whose disease flared after treatment was stopped at week 52.

Methods: Of 46 patients originally enrolled, all patients were stopped and 23 (52% male; mean age 32 years [range 24–45]; mean disease duration before treatment 4 years [range 1–10]; 74% HLA-B27+) had reached a major response defined as reaching an 40% improvement according to the ASsessments in SpondyloArthritis international Society (ASAS40). In case of a flare (defined as <ASAS40 response compared to baseline), adalimumab therapy (40 mg eow) was re-started and patients were treated continuously for up to 5 years (week R264). ASAS response criteria and Bath AS disease activity score were (BASDAI) were calculated using a completer analysis.

Results: 19 out of these 23 patients had to be retreated: 16/19 (84%) patients were still in the study at year 3 and 4. 12/19 (63%) patients completed year 5 of retreatment. After 3 years of adalimumab re-treatment, 13/16 (81%) again reached ASAS 40 and 11 of 16 (69%) achieved ASAS partial remission. After 4 years ASAS 40 was reached in 69% (11/ 16 patients) and after 5 years in 75% (9/ 12 patients). ASAS partial remission was reached in 56% (9/16) of patients after 4 years and in 58% (7/12) of patients at the end of year 5. The mean BASDAI for the completers at the different time points decreased from 5.1±1.8 at R-Baseline to 1.6±1.6 at year 3 ($p < 0.001$), to 2.2±2.1 at year 4 ($p = 0.001$) and 1.5±1.8 at year 5 ($p = 0.001$) of retreatment.

Conclusion: In this group of 19 patients with early axial SpA who had achieved a good response after 52 weeks of adalimumab therapy, and who had to be retrated because of a flare, the majority of patients who remained in the study had a good and sustained clinical response.

(1) Haibel H, et al, A&R, 2008, 58(7):1981–91.
(2) Haibel H et al, A&R, 2013 May 17.[epub ahead of print]

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Response to Tumor Necrosis Factor inhibitors In Axial Spondyloarthritis: Does Sacroiliitis Make Any Difference? Julien Girodon[1], Vianney Jouhet[2] and Elisabeth Solau-Gervais[1]. [1]University Hospital of Poitiers, Poitiers, France, [2]University hospital Bordeaux, Bordeaux, France.

Background/Purpose: Axial spondyloarthritis (SpA) are characterized by sacroiliitis. The TNF inhibitors (TNFi) have been proven to be highly effective in ankylosing spondylitis. Recently, adalimumab demonstrate clinical efficacy in patients with axial SpA without radiographically defined sacroiliitis (SI). The objectives of the study are to compare patient's characteristics and response to treatment according to the presence of SI.

Methods: 162 records of patients with axial SpA treated with TNFi were analyzed. These patients were out and in patients followed in an university hospital in year 2009–2011. Patients have to fulfilled ASAS criteria and treated by at least one TNFi (infliximab, adalimumab, etanercept) to be included. Three groups of patients were designed: group 1: SpA with SI on X-Rays, group 2: SpA without SI on X-Rays and with SI on magnetic resonance analysis (MRI) and group 3: SpA without sacroiliitis on X-Rays and MRI. Statistical analysis used univariate, multivariate and survival analysis with GraphPad software.

Results: Characteristics of the patients and results of univariate analysis have been detailed in table 1:

	Group 1	Group 2	Group 3	1 versus 3	1 versus 2	2 versus 3
N	105	26	31			
Sex (M/F) (%)	64,7/35,3	38,46/61,54	38,7/61,3	0,01	0,014	0,98
Age	44,38 +/− 13,32	44,69 +/−9,18	40,93 +/− 11,97	0,22	0,7	0,17
HLA B27 (%)	83,8	65,38	87,1	0,65	0,035	0,052
Age at diagnostic	30,64 +/− 11,9	37,38 +/−8,1	33,03 +/− 9,9	0,136	0,001	0,088
Increased CRP (%)	77,1	50	51,6	0,006	0,006	0,9
CRP (mg/l)	31,27 +/− 32,07	13,92+/−13,77	20,38 +/− 31,88	0,013	0,007	0,96
TNFi n	1,33+/− 0,63	1,73+/−0,77	1,71+/−0,82	0,009	0,005	0,86

In multivariate analysis, factors associated statistically with the absence of radiological X-Rays sacroiliitis were (ORs; 95% confidence intervals): number of TNFi used (4,154; 1,41–12,1; p = 0,0032), age at diagnosis (0,89; 0,83–0,96; p = 0,0012) and increased of CRP (0,31; 0,14–0,69; p = 0,0045). At least the rate of the first TNFi maintenance was significantly (p=0.009) higher in the group 1 (68,5%) compared to group 2 (54.5%) and group 3 (34.6%).

Conclusion: Presence of sacroiliitis in axial SpA is associated with an earlier diagnosis and more frequent increased CRP as well as a greater maintenance rate of the first TNFi

Disclosure: J. Girodon, None; **V. Jouhet**, None; **E. Solau-Gervais**, None.

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The Prevalence Of Sjogren's Syndrome In Patients With Ankylosing Spondylitis. Ayse Balkarli[1], Adem Kucuk[2], Sahin Temel[3], Tayfun Gungor[4], Ramazan Ucar[5] and Veli Cobankara[6]. [1]Pamukkale University, Division of Rheumatology, Denizli, Turkey, [2]Necmettin Erbakan University, Division of Rheumatology, Konya, Turkey, [3]Department of Internal Medicine, Pamukkale University, Denizli, Turkey, [4]Department of Physical medicine and Rehabilitation, Necmettin Erbakan University, Konya, Turkey, [5]Konya Education and Research Hospital, Department ofInternal Medicine, Konya, Turkey, [6]Division of Rheumatology, Pamukkale University, Denizli, Turkey.

Background/Purpose: Sjögren's syndrome (SS) is a chronic autoimmune inflammatory disease that primarily affects exocrine glands with a prevalence of 1% to 4.8. SS mainly affects middle-aged women with a female-male ratio of 9:1. Ankylosing spondylitis (AS) is the prototype of spondyloarthropathy that is characterized by sacro-ileitis, inflammation, enthesitis and also involves peripheral joints, eye and aorta. The prevalence of AS is about 0.5% with a similar female-male ratio. We aimed to evaluate the SS prevalence in patients with AS.

Methods: 143 patients with the diagnosis of AS according to Modified New York Criteria were included in the study. Sicca questionnaire that includes sicca symptoms for SS was performed in all patients. Schirmer test was performed for xerophthalmia and unstimulated salivation test for xerostomia. Rheumatoid factor (RF), antinuclear antibody (ANA), anti-Ro and anti-La antibodies were measured as laboratory tests. Minor salivary gland biopsy was performed in patients with positive xerophthalmia and xerostomia tests and Sicca questionnaire. The presence of SS was assessed according to classification criteria of American-European Consensus Group.

Results: The mean age of patients was 39.6 years old and 73 of them were male. Fourteen (10%) of the patients were diagnosed as SS according to American-European Consensus Group classification criteria. Twenty-three of the patients were undergone minor salivary gland biopsy those fulfilled the three criteria. Fourteen biopsies of the patients were evaluated as pathologically. Three of them were reported as grade IV and 11 of them as grade III sialadenitis according to the criteria of Mason Chisholm. Seven of these 14 patients were male and there was no difference in terms of sex. Only one patient has a positive anti-Ro and anti-La antibodies. However, 13 of patients (except 1 patient) had ANA positivity (> 1/80). There was bilateral sacro-ileitis in MRI of all patients diagnosed as SS.

Table 1. General characteristics of the patients

	n(%)
Age (years)	39.6
Sex(F/M)	73/70
Duration of disease (years)	6.6±5.3
Drugs	89 (62.2%)
SLZ	13 (9.1%)
IFX ADA	19 (13.3%)
ETA	20 (14%)
Xerostomia	51 (35.7%)
Xerophthalmia	24 (16.8%)

Conclusion: In our study, we found a high prevalence of SS in patients with AS. ANA positivity was higher in co-existence of SS and AS and it may be a risk factor for SS.

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Radiographic Sacroiliitis Progression In An Early Spondyloarthritis Cohort. Concepcion Castillo-Gallego[1], Eugenio de Miguel[1], Carmen Martin-Hervas[1], Diana Peiteado[2], Leticia Lojo[2] and Emilio Martin-Mola[1]. [1]Hospital Universitario La Paz, Madrid, Spain, [2]Hospital Universitario La Paz, Spain, Spain.

Background/Purpose: The improvement of treatment in axial Spondyloarthritis (axSpA) and the development of the ASAS classification criteria have facilitated the early diagnosis and management of this disease. It is important to know what are the more relevant predictors of radiographic progression in early SpA to take clinical decision.

The aim of this study was to assess predictive factors for radiographic sacroiliitis progression in a cohort of early axSpA.

Methods: Patients included in the study came from the early SpA unit at our hospital, as part of the ESPERANZA programme, a nationwide health management programme designed to provide excellence in care for early SpA. One of the inclusion criteria was symptom duration between 3 and 24 months. Every patient had a complete examination at baseline that included ESR, CRP, ASDAS-CRP, ASDAS-ESR, BASDAI, HLA-B27, radiographs of pelvis and Magnetic resonance (MRI) of sacroiliac joints (SIJ). MRI of SIJ were assessed according to ASAS definition for bone marrow oedema. Radiographs of pelvis at baseline and at follow up were done for every patient. These x-Rays were centrally digitized and the SIJ were scored according to the grading system of the modified New York criteria (mNYc). SPSS program version 17.0 was used for Statistical analysis. Paired-sample t test was used for comparison of radiographic sacroiliitis progression.

Results: Forty-one consecutive patients from the early axial Spondyloarhtritis cohort of the Esperanza program were analyzed, 39% of them were female. The average evolution time since onset of symptoms until baseline clinic visit was 10.9±7.1 months. All patients fulfilled ASAS criteria for axSpA and three of them had Ankylosing Spondytitis (AS) according to mNYc at baseline. The mean follow up time was 3.51 years (range: 2–5years; SD±1.03). Progression of sacroiliitis over follow up by at least one grade at one side was found in 61% (25/41). Among the 38 non radiographic axSpA patients at baseline, 5 of them (13.16%) progressed to AS according to mNYc. Statistically significant radiographic progression was observed in all the variables analyzed (see table 1).

Table 1.

	Baseline SIJ x-Ray score (mean±SD)	Follow up SIJ x-Ray score (mean±SD)	P	n
HLA-B27 positive	0.84 ± 0.91	1.48 ± 1.07	<0.001	23
HLA-B27 negative	0.25 ± 0.55	0.58 ± 0.73	<0.01	18
BASDAI<4	0.57 ± 0.96	1.18 ± 1.06	<0.001	14
BASDAI≥4	0.56 ± 0.75	1.04 ± 1.04	<0.001	26
CRP<5	0.47 ± 0.75	0.97 ± 0.90	<0.001	30
CRP≥5	0.82 ± 0.96	1.41 ± 1.30	<0.01	11
ESR<10	0.50 ± 0.78	1.03 ± 0.92	<0.001	29
ESR≥10	0.71 ± 0.91	1.21 ± 1.28	<0.01	12
ASDAS-CRP<2.1	0.35 ± 0.73	0.76 ± 0.85	<0.01	17
ASDAS-CRP≥2.1	0.72 ± 0.86	1.33 ± 1.12	<0.001	23
ASDAS-CRP<3.5	0.53 ± 0.82	1.00 ± 0.94	<0.001	31
ASDAS-CRP≥3.5	0.67 ± 0.84	1.39 ± 1.33	<0.01	8
ASDAS-ESR<2.1	0.34 ± 0.70	0.69 ± 0.82	<0.01	16
ASDAS-ESR≥2.1	0.71 ± 0.87	1.35 ± 1.10	<0.001	24
ASDAS-ESR<3.5	0.50 ± 0.78	0.95 ± 0.88	<0.001	31
ASDAS-ESR≥3.5	0.78 ± 0.94	1.55 ± 1.42	<0.01	9
MRI positive	1.11 ± 0.92	1.58 ± 0.99	<0.001	14
MRI negative	0.17 ± 0.38	0.67 ± 0.73	<0.001	20

Conclusion: Every patient of this early axSpA cohort had radiographic sacroiliitis progression independently of the outcome assessed. Patients HLA-B27 positive, with MRI positive, higher values of CRP or ESR and higher scores of BASDAI and ASDAS not only presented higher radiographic scores at baseline and but also more radiographic progression at follow up.

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Combined Axial and Peripheral Involvement Is Associated With Miscegenation In A Large and Heterogeneous Brazilian Cohort Of 1505 Patients With Spondyloarthritis. Percival D Sampaio-Barros, Mittermayer Santiago, Adriana B. Bortoluzzo, Antonio Carlos Ximenes, José Antonio Braga da Silva, Manoel B Bértolo, Sandra Lúcia Ribeiro, Mauro Keisermann, Rita Menin, Thelma L. Skare, Sueli Carneiro, Valderilio F. Azevedo, Walber P. Vieira, Elisa Albuquerque, Washington A. Bianchi, Rubens Bonfiglioli, Cristiano Campanholo, Hellen M Carvalho, Izaias P. Costa, Angela Luzia B. P. Duarte, Charles Kohem, Nocy Leite, Sonia Lima, Eduardo S. Meirelles, Ivânio A. Pereira, Marcelo M. Pinheiro, Elizandra Polito, Gustavo G. Resende, Francisco AC Rocha, Maria de Fátima L. C. Sauma, Valéria Valim and Celio R. Gonçalves. Brazilian Registry of Spondyloarthritis, São Paulo, Brazil.

Background/Purpose: Spondyloarthritides (SpA) constitute a group of diseases that can present different patterns according to the genetic background. Brazilis a large country with a heterogeneous population, constituted by 48.7% of whites, 50.6% African-Brazilians (43.6% Mulatos, originated from the miscegenation of whites and blacks, and 7.0% blacks of pure origin), and 0.7% of Asian ancestry (predominantly Japanese) and Indians (National Census, 2010). This ethnic distribution varies a lot among the different geographic regions in the country. The objective of this study is to analyze disease patterns in a large cohort of patients with SpA, according to the five main geographic regions.

Methods: Brazilian multicentric cross-sectional study of 1505 SpA patients according to the European Spondyloarthropathy Study Group (ESSG), evaluated by a standardized protocol. There were 762 patients from the Southeast (68% whites and 20.1% African-Brazilians), 272 from the Midwest (49.4% whites and 43.7% African-Brazilians), 258 from the South (84% whites and 12% African-Brazilians), 126 from the North (66.7% whites, 16.7% African-Brazilians, and 16.6% mixed, including Indians), and 87 from the Northeast (32.1% whites and 56% African-Brazilians).

Results: Patients from the South region presented higher frequency of axial involvement ($p < 0.001$) and uveitis ($p = 0.001$), whereas patients from the more miscegenated regions (Northeast and North) presented higher frequencies of combined axial and peripheral involvement ($p < 0.001$), and higher mean values of erythrocyte sedimentation rate (ESR) ($p < 0.001$) and C-reactive protein (CRP) ($p < 0.001$). Patients from the Northeast region were characterized by a higher frequency of male patients ($p = 0.002$), hip involvement ($p < 0.001$) and work incapacity ($p = 0.001$), with higher scores of Maastricht Ankylosing Spondylitis Enthesitis Score (MASES; $p < 0.001$), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; $p < 0.001$), Bath Ankylosing Spondylitis Functional Index (BASFI; $p < 0.001$), and Ankylosing Spondylitis Quality of Life (ASQoL; $p < 0.001$).

Conclusion: The present study provides evidence that miscegenation in the Northeast of Brazil may underlie the clinical presentation of SpA in this region with a distinct clinical pattern characterized by combined axial and peripheral involvement and a more aggressive disease.

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Prevalence Of Inflammatory Back Pain In Psoriatic Arthritis: The Prepare Study. Majed Khraishi[1], Dafna D. Gladman[2], Javier Coindreau[3], Lotus Mallbris[3], Annette Szumski[3], Eustratios Bananis[3] and Heather Jones[3]. [1]Nexus Clinical Research, St John's, NF, [2]University of Toronto, Toronto Western Hospital, Toronto, ON, [3]Pfizer Inc., Collegeville, PA.

Background/Purpose: Up to 30% of patients with psoriasis (Ps) may develop psoriatic arthritis (PsA); ranging from mild and non-destructive disease to severe and erosive arthritis.[1] Spondylitis prevalence in PsA is approximately 25–30%. PREPARE, an international, multicenter, non-interventional study assessed PsA prevalence in patients presenting to dermatologists with Ps (285/949 had PsA, 117/285 = newly diagnosed; the Toronto Psoriatic Arthritis Screen [ToPAS] and Psoriasis and Arthritis Screening Questionnaire [PASQi] detected probable PsA in 42.9% and 45.1% of patients).[2] Since no formal assessment of inflammatory back pain (IBP) formed part of the PREPARE study, the focus of these post-hoc analyses was to determine if positive IBP correlated with PsA diagnosis as a useful screening tool.

Methods: Our analyses included patients with Ps who received either the PASQi or ToPAS screening questionnaires during their dermatologist's visit. Patients were subsequently evaluated by a rheumatologist to establish/exclude a clinical diagnosis of PsA. The prevalence of IBP was identified by the PASQi and ToPAS questionnaires: PASQi back pain was defined by patients who "ever had back troubles" with stiffness lasting >30 minutes and IBP total score>4; ToPAS had 1 question addressing back pain occurrence lasting >3 months that was not injury related (although this was not included in the scoring of ToPAS). *Cochran–Mantel–Haenszel* (CMH) tests were used to analyze differences in proportions of positive IBP between PsA vs non-PsA groups. Kappa coefficients determined the agreement between PsA diagnosis and positive IBP.

Results: Of the patients, 85/341 (24.9%) had positive PASQi defined IBP while 146/337 (43.3%) had positive ToPAS defined IBP. Patients with PsA detected by a rheumatologist/PASQi/ToPAS/a combination had higher IBP prevalence than Ps patients with no indication of PsA (32.6%-55.2% vs 17.6%-38.9%; Table). Of the patients with detected PsA or IBP, there was a higher extent of activity impairment in patients with IBP than those without IBP (PsA: 22.4% vs 15.75%, P=0.003; PASQi: 19.1% vs 16.2% P=0.3651 and ToPAS 23.5% vs 13.4% P=0.0003). Work productivity impairment was significantly higher in patients with PsA vs non-PsA (16.5% vs 10.9%, P=0.012) and positive vs negative IBP as detected by the ToPAS screen (19.1% vs 9.3%, P=0.003). All κ coefficients were <0.2 indicating slight agreement between IBP and PsA as defined by PASQi, ToPAS or a rheumatologist (Table).

IBP defined by:	PsA defined by:	PsA Proportion with IBP (%)	Non-PsA Proportion with IBP (%)	CMH P-value	Kappa coefficient
PASQi	PASQi	52/153 (34.0)	33/188 (17.6)	0.0005	0.171*
PASQi	Rheumatologist	30/92 (32.6)	50/225 (22.2)	0.0537	0.108
PASQi	PASQi and Rheumatologist†	26/62 (41.9)	27/144 (18.8)	–	–
ToPAS	ToPAS	76/141 (53.9)	70/196 (35.7)	0.0009	0.181**
ToPAS	Rheumatologist	53/96 (55.2)	86/221 (38.9)	0.0073	0.145***
ToPAS	ToPAS and Rheumatologist†	39/73 (53.4)	50/158 (31.7)	–	–

†PsA defined by both a questionnaire and by rheumatologist. PsA present if positive for both; PsA not present if negative for both.
*P<0.0001; **P<0.001; ***P<0.01

Conclusion: In this study, Ps patients with PsA had increased IBP incidence compared to those without PsA. Kappa coefficients indicate that IBP is not a good marker for PsA diagnosis in patients with Ps. However, the high incidence of IBP detected in Ps patients warrants further investigation.

1. Haroon, M *et al. Ann Rheum Dis*. 2013; 72:736–40
2. Mease, PJ *et al.* Presented at EADV 2012, Prague, Czech Republic

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Disease Burden Is Similar Between Non-Radiographic Axial Spondyloarthritis and Ankylosing Spondylitis and Independent Of Gender Influences. Salih Ozgocmen, Erkan Kilic, Gamze Kilic and Ozgur Akgul. Erciyes University, Faculty of Medicine, Kayseri, Turkey.

Disease Burden is Similar between Non-Radiographic Axial Spondyloarthritis and Ankylosing Spondylitis and Independent of Gender Influences

Background/Purpose: Axial spondyloarthritis (SpA) covers both ankylosing spondylitis (AS) with established radiographic changes and non-radiographic axial SpA (nr-axSpA) without definite radiographic sacroiliitis. Clinical characteristics and differences between women and men with nr-axSpA or AS have been documented; however comparison of patients with nr-axSpA and AS within the same genders may provide more data. Registry data revealed similar burden of disease, however baseline characteristics regarding gender distribution and HLA-B27 differ in nr-axSpA from AS. We compared nr-axSpA and AS within the same genders regarding the clinical characteristics in a cohort of patients with axial SpA.

Methods: A total of 170 consecutive patients diagnosed with axial SpA were studied and clinical and laboratory results were compared between male and female patients in subgroups of nr-axSpA and AS. Standard clinical assessment tools (VAS-pain, global assessment, BASDAI, BASFI, ASQoL and SF-36, ASDAS), laboratory data, existence of inflammation on the sacroiliac and lower-thoracic and lumbar spine MR (blindly assessed), SpA features and comorbidities were used in the analysis.

Results: Patients with AS (n=96) were predominantly male (79.2%) whereas patients with nr-axSpA (n=74) were predominantly female (55.4%) (p=0.0001). Women with nr-axSpA and AS did not differ in clinical variables except family history for SpA and spinal inflammation on MR (16.7% vs 68.8%, p=0.0001, respectively). Men with nr-axSpA and AS did not differ in clinical variables, except HLA B27, peripheral arthritis, younger age and spinal inflammation of MR (25.0% vs 52.1%, p=0.014, respectively).

Table 1. Comparison between groups for the measured parameters

	Women			Men		
	nr-axSpA (n=41)	AS (n=20)	p	nr-axSpA (n=33)	AS (n=76)	p
Age, y	34.7±9.6	38.3±7.1	0.142	29.7±7.6	37.5±8.7	0.0001
Age at symptom onset, y	29.5±7.8	28.1±8.2	0.454	24.1±7.7	26.9±7.4	0.07
VAS-pain	4.7±2.5	5.2±2.8	0.336	4.4±3.0	3.8±2.7	0.334
Physician's global	3.7±1.3	4.4±1.8	0.195	3.5±2.3	3.4±2.0	0.728
Patient's global	4.6±2.4	5.6±2.1	0.066	4.0±2.8	3.9±2.5	0.779
BASDAI	3.9±1.9	4.3±2.2	0.634	3.8±2.2	3.2±2.3	0.255
BASFI	2.2±1.9	3.5±2.8	0.122	1.8±1.9	2.6±2.3	0.085
SF-36 MCS	51.6±23.3	40.2±17.2	0.072	56.0±22.4	58.7±23.2	0.575
SF-36 PCS	49.9±22.1	42.1±19.9	0.213	54.7±21.6	55.5±23.2	0.869
ASQoL	7.7±4.7	10.1±6.0	0.118	5.7±4.9	6.6±5.4	0.399
ASDAS-CRP	2.7±0.9	2.9±0.9	0.509	2.5±0.9	2.7±1.0	0.452
HLA B27+ve, %	48.8	60.0	0.430	51.5	72.3	0.047
Smoking, %	29.3	15.0	0.224	54.5	44.7	0.346
Inflammation-SIJ MR, %	82.1	89.5	0.703	78.8	61.8	0.084
Uveitis, %	9.8	15.0	0.546	15.1	19.7	0.570
Psoriasis, %	2.4	10.0	0.248	9.1	3.9	0.261
Family history,%	12.2	35.0	0.035	18.8	26.7	0.382
Peripheral arthritis	24.4	15.0	0.400	28.1	11.8	0.038
Preceding infection, %	19.5	5.0	0.134	18.8	6.6	0.056

Conclusion: Results of our cohort confirm the earlier data showing that the burden of disease is similar between nr-axSpA and AS. Although disease burden seem to be independent of gender, men or women with nr-axSpA differ from AS in several clinical aspects including HLA B27, peripheral arthritis, positive family history for SpA and more prevalent inflammation on spinal MR.

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Comparison Of The Two Subtypes Of Axial Spondyloarthritis Patients Fulfilling The Imaging Arm Based On Radiographic and MRI Findings. Dilek Solmaz, Servet Akar, Ismail Sari, Pinar Cetin, Fatos Onen and Nurullah Akkoc. Dokuz Eylul University School of Medicine, Izmir, Turkey.

Background/Purpose: New Axial Spondyloarthritis Classification Criteria include an imaging arm and a clinical arm. The imaging arm includes radiographic ax-SpA patients who have radiographic sacroilitis according to modified New York criteria and non-radiographic (nr) ax-SpA patients who have sacroiliitis only by MRI. Although there is no doubt that radiographic and non-radiographic axSpA have many overlapping features, it is now one of the hot topics of discussion whether they are different entities.

The aim of this study was to compare the demographics and clinical characteristics between the radiographic and nr-axSpA patients fulfilling the criteria of the imaging arm.

Methods: A local database has been used since December 2008 to register all patients fulfilling the imaging arm of AxSpA classification criteria.

Data related to demographics, clinical features, disease activity, functional status, treatment were recorded.

Results: 720 patients who met the study criteria were identified. Radiographic sacroiliitis according to modified New York criteria was present in 533 patients. The remaining 187 patients were classified as nr-axSpA based on MRI findings. Demographics and clinical characteristics are summarized in Table 1. Patients with nr-axSpA had an earlier onset of symptoms and were more often females. Prevalence of extraspinal manifestations was similar in both groups, except for anterior uveitis, which was more frequently reported by the patients with radiographic axSpA. C-reactive protein levels were significantly higher in patients with radiographic sacroiliitis as compared to those with nr-AxSpA. HLA-B27 prevalence was numerically greater among patients with radiographic axSpA, but was not statistically significant. Disease activity measured by BASDAI, but not by ASDAS, was higher in the nr-axSpA group; BASFI scores were similar in both groups. BASMI score was higher in radiographic ax-SpA patients. While anti-TNF therapy was used more frequently by patients with radiographic sacroiliitis, DMARD use was similar in both groups.

Table 1. Demographics and clinical characteristics of the radiographic and non-radiographic axSpA patients.

Demographic and clinical features	Radiographic sacroiliitis (n:533)	Non-radiographic sacroiliitis (n:187)	*P*
Age, mean ± SD	43 ± 12.0	42 ± 13.2	0.232
Male sex n,%	395, 74.1	72, 38.5	<0.001
Age at beginning of the symptoms, mean ± SD	25 ± 9.1	28 ± 10.3	0.010
Diagnostic delay, mean ± SD	8 ± 8.5	7 ± 8.0	0.023
Arthritis n,(%)	195, (36.6)	42, (22.5)	0.491
Hip replacement n,(%)	23, (4.3)	0	0.023
Anterior uveitis n,%	97, (18.2)	10, (5.3)	0.007
Psoriasis n,%	16, (3.0)	4, (2.1)	0.399
IBD n,%	16, (3.0)	2, (1.0)	0.082
HLA B27 positivity n1/n2 (%)	166/243 (68.3)	46.3 % (36/78)	0.146
CRP mg/dl, mean ± SD	19.0 ± 25.6	9.5 ±17.1	<0.001
BASDAI, mean ± SD	3.5 ± 2.2	4.3 ± 2.5	<0.001
ASDAS-CRP, mean ± SD	2.9 ±1.1	2.1 ±1.1	0.223
BASFI, mean ± SD	2.9 ±2.6	2.7 ±2.5	0.346
BASMI, mean ± SD	3.9 ±1.9	2.3 ±1.0	<0.001
SSZ, n, (%)	132, (24.2)	21, (11.2)	0.316
MTX, n, (%)	34, (6.3)	4, (2.1)	0.317
Anti TNF, n,(%)	103, (19.3)	8, (4.2)	<0.001

Conclusion: Although many demographic and clinical features are similar between the ax-SpA patients with and without radiographic sacroiliitis classified with the imaging arm, differences such as higher prevalence of females and numerically lower prevalence of HLA-B27 among patients with nr-axSpA are of interest.

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Fat Mass and Resistin: Predictive Factors For Anti-TNF Therapy Response In Ankylosing Spondylitis Patients. Carla G.S. Saad, Andressa Silva Abreu, Ana Cristina Medeiros Ribeiro, Julio C. B. Moraes, Luiz A. Perandini, Thalita Dassouki, Rosa M. R. Pereira, Eloisa Bonfa and Ana Lucia S. Pinto. Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: The adipose tissue immune properties and pharmacokinetic consequences can contribute to the pathogenesis of inflammatory conditions. The hole of fat tissue in active Ankylosing Spondylitis (AS) patients and its influence on response to anti-TNF therapy has not been widely investigated. The purpose of this study was to evaluate the fat tissue in active AS patients and the influence on clinical response to TNF blockade therapy.

Methods: 37 patients with active AS referred to receive anti-TNF therapy with high/very high disease activity according to AS Disease Activity Score (ASDAS > 2.1) and have completed 6 months of treatment were included. At baseline patients were evaluated for weight, height, body mass index (BMI), waist circumference, body composition (DXA) including total fat and trunk fat. Factors related to adipocytokines and inflammation (leptin, resistin, adiponectin, TNFα and IL-6) were also evaluated at baseline. Disease parameters and inflammatory markers [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] were assessed at baseline and after 6 months of treatment. Responders to anti-TNF therapy were defined according to ASDAS improvement criteria with Δ ASDAS $\geq$ 2.0.

Results: Patients had a mean age of 37.0 ± 12.1 years, 75.7% were male with a mean of 9.0 ± 9.8 years of disease duration. At baseline patients had [mean (SD)]: weight 70.4(11.9)kg, BMI 26.1(4.3)kg/m2, waist circumference 89.0(10.4)cm, total fat 18.9(6.6)kg and trunk fat mass 19.5(6.7)kg. Regarding disease parameters, the mean ASDAS value was 3.2(0.9), BASFI 4.4(2.4) and BASMI 4.4(2.7). After 6 months of anti-TNF treatment 12 (32.4%) patients reached major improvement by ASDAS criteria. Comparing responders and non-responders groups we observed that the patients with good response had lower BMI ($p=0.01$), waist circumference ($p=0.005$), trunk fat mass (0.03) and higher resistin ($p=0.02$) serum levels and infflmmatory parameters [CRP ($p=0.02$) and ESR ($p=0.01$)]. Resistin serum levels at baseline correlated with CRP ($r=0.58$, $p<0.01$) and ESR ($r=0.37$, $p=0.02$).

Conclusion: This study provides evidence that fat mass and resistin serum levels may predict the anti-TNF response in AS patients. Further studies are necessary to elucidate the mechanism by which adipose tissue affects inflammatory condition in AS.

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Relationship Between Extra-Articular Manifestations and Disease Activity In Patients Diagnosed With New-Onset Spondyloarthropathy In a Cohort In Spain. César Antonio Egües Dubuc[1], Maria Martin Martinez[2], Joaquin Belzunegui Otano[1], Miren Uriarte Ecenarro[1], Juan Mulero[3], Eugenio de Miguel[4], Santiago Muñoz[5], Pedro Zarco[6], Eduardo Collantes[7], Sabina Perez Vicente[2] and Milena Gobbo[2]. [1]Donostia University Hospital, San Sebastián, Spain, [2]Research Unit, Spanish Society of Rheumatology., Madrid, Spain, [3]Hospital Universitario Puerta de Hierro Majadahonda, Majadahonda (Madrid), Spain, [4]Hospital Universitario La Paz, Madrid, Spain, [5]Hospital Infanta Sofia, Madrid, Spain, [6]Fundación Hospital Alcorcon, Alcorcon, Madrid, Spain, [7]Hospital Reina Sofia, Cordoba, Spain.

Background/Purpose: The Spondyloarthropathy (SpA) that affect in many aspects of life of the patients, either for their musculoskeletal or extra-articular manifestations (EAM). EAM vary in frequency and severity, the most common are: uveitis, inflammatory bowel disease and skin diseases. Some epidemiological studies have found increased incidence of EAM as a consequence of disease activity. This study aims to analyze the relationship between the EAM with disease activity in patients with new onset SpA.

Methods: This is a longitudinal study, for which the ESPERANZA Program database from Spanish Society of Rheumatology was analyzed. Database includes SpA patients with aged between 18 and 45 years, with duration of disease between 3 and 25 months, belonging to 25 health centers in Spain. The primary endpoint were all the EAM analyzed together and by themselves. The independent variables were: demographics; disease activity parameters as BASDAI, at least one painful and swollen joints, at least one enthesitis, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR); metrological parameter (BASMI), quality parameter (ASQoL) and functionality parameter (BASFI); HLA-B27, duration of disease at the diagnoses and the presence of sacroiliitis on magnetic resonance. The quantitative variables were described as mean and standard deviation (SD) if distributed symmetrically and if distributed asymmetrically by the median and interquartile ranges (IR), qualitative were described with percentages accompanied by absolute value. The Pearson or Spearman correlation, Student t test, analysis of variance and chi square test were used for bivariate analysis according to the variables to be analyzed. For multivariate analysis the variables analyzed were those that had $P<0.20$, or those that had clinical relevance for the study, we used multiple linear regression analysis or logistic regression model.

Results: 698 patients [426 men (61%)] with median age of 32.9 years (CI: 27.5–38.9) were studied. Table 1 shows the EAM studied. Table 2 shows the independent variables, which were analyzed with the EAM (table 3).

Table 1. Extra-articular manifestations in patients diagnosed with new-onset spondyloarthropathy (n=698).

	Patient without EAM	Patient with EAM
At least one EAM	406 (41.8%)	292 (58.2%)
Psoriasis	577 (82,7%)	121 (17.3%)
Urethritis	685 (98.1%)	13 (1.9%)
Uveitis/Iritis	656 (94%)	42 (6%)
Pustulosis	694 (99.4%)	4 (6%)
Acne	692 (99.1%)	6 (0.9%)
Inflammatory bowel disease	654 (93.7%)	44 (6.3%)
Nail psoriasis	670 (96%)	28 (4%)
Dactylitis	625 (89.5%)	73 (10.5%)
Enthesopathy	634 (90.8%)	64 (9.2%)

Table 2. Demographic, measurement parameters, markers of activity, presence of sacroiliitis on MRI, presence of HLA B27, according to the presence of extra-articular manifestations in patients diagnosed with new-onset spondyloarthropathy (n=698).

	Total Spa patients (n = 698)				Spa patients with at least one EAM (n=292)				Spa patients without EAM (n=406)			
	N	Lost	Mean (SD)	Median (IR)	N	Lost	Mean (SD)	Median (IR)	N	Lost	Mean (SD)	Median (IR)
Men	426 (61%)				180 (61.6%)				246 (60.6%)			
Women	272 (39%)				112 (38.4%)				160 (39.4%)			
Age at diagnosis of Spa	698	0		32.92 (27.6–38.8)	292	0	-	34.14 (28.66–39.75)	406	0	-	31.98 (26.61–38.27)
BASDAI	597	101	-	4.7 (2.8–6.2)	252	40	-	4.8 (3–6.38)	345	61	-	4.4 (2.75–6.05)
BASMI	698	0	1.09 (1.06)	-	292	0	1.05 (1.02)	-	406	0	1.12 (1.09)	-
BASFI	574	124	2.65 (2.22)	-	244	48	2.57 (2.21)	-	330	76	2.58 (2.21)	-
ASQoL	519	179	6.96 (2.22)	-	231	61	7.14 (4.92)	-	288	118	6.74 (4.83)	-
ESR	578	120	16.98 (7.42)	-	237	55	19.25 (18.9)	-	341	65	15.4 (16.15)	-
CRP (mg/dl)	633	65	10.08 (18.36)	-	262	30	11.9 (18.6)	-	371	35	-	3 (1–9)
Evolution of the disease (month)	698	0	11.77 (6.67)	-	292	0	11.02 (6.46)	-	406	0	-	12.17 (6–17.7)
Presence of swollen joint	181 (25.9%)	0			120 (41.1%)				61 (15%)			
Absence of swollen joint	517 (74.1%)	0			172 (58.9%)				345 (85%)			
Presence of painful joint	165 (23.6%)	0			108 (37%)				349 (86%)			
Absence of painful joint	533 (76.4%)	0			184 (63%)				57 (14%)			
Presence of enthesitis	253 (36.2%)	0			124 (42.5%)				129 (31.8%)			
Absence of enthesitis	445 (63.8%)	0			168 (57.5%)				277 (68.2%)			
Positive HLA B27	363 (52%)	51			112 (38.4%)				251 (61.8%)			
Negative HLA B27	284 (40.7%)				149 (51%)				135 (33.3%)			
Sacroiliitis on MRI	159 (22.8%)	397			37 (12.7%)				122 (30%)			
Absence of sacroiliitis on MRI	142 (20.3%)				62 (21.2%)				80 (19.7%)			

Table 3. Relationship of the appearance of extra-articular manifestations with: disease activity parameters; metrological, functionality and quality parameters; HLA-B27, duration of disease at the diagnoses and the presence of sacroiliitis on magnetic resonance.

		C.I. 95%		
	OR	Lower limit	Upper Limit	p value
Age	1.036	1.013	1.058	0.002
BASDAI	1.067	0.991	1.148	0.084
BASMI	0.937	0.812	1.082	0.376
BASFI	0.973	0.902	1.048	0.467
ASQoL	0.983	0.949	1.019	0.349
ESR	1.013	1.003	1.022	0.01
CRP	1.01	1	1.019	0.045
Evolution of the disease (month)	0.971	0.949	0.994	0.012
Woman	0.957	0.703	1.303	0.778
Positive HLA B27	0.404	0.293	0.558	0
Sacroiliitis on MRI	0.391	0.238	0.642	0
Presence of swollen joint	3.946	2.757	5.647	0
Presence of painful joint	3.564	2.489	5.188	0
Presence of enthesitis	1.585	1.16	2.166	0.004

Conclusion: The presence of enthesitis, tender and swollen joint favors the appearance of EAM. The presence of HLA B27 and sacroiliitis are protective factors of occurrence of EAM. These are raw data, to be wanting to adjust for covariates and potential confounders.

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Periodontal Disease Is Not Associated With Ankylosing Spondylitis and TNF-Alpha Blockers Usage In Korea. Sung Hae Chang[1], Jung Tae Lee[1], Byoung Youg Choi[1], Hyon Joung Cho[1], Jong Jin Yoo[2], Hye Jin Oh[3], Eun Ha Kang[1], Yeong Wook Song[3], Hyo Jung Lee[1] and Yun Jong Lee[4]. [1]Seoul National University Bundang Hospital, Seongnam-si, South Korea, [2]Armed Forces Capital Hospital Seongnam Republic of Korea, Seongnam si, South Korea, [3]Seoul National University Hospital, Seoul, South Korea, [4]Seoul National University College of Medicine, Seoul, South Korea.

Background/Purpose: Periodontal disease (PD) is a chronic inflammatory disease, which has been reported to be associated with rheumatoid arthritis (RA). But, a few studies on an association between ankylosing spondylitis (AS) and PD showed inconsistent results. Thus, we performed a prospective and longitudinal study on the prevalence and course of PD and the effects of TNF-α blockers on PD in AS patients.

Methods: A total of 75 AS patients and 73 age- and gender-matched healthy controls (HC) were prospectively recruited. Full-mouth periodontal probing, 6 sites per tooth, was performed at the baseline and, if a subject had PD, 12 week after periodontal scaling. Periodontal status was assessed using the plaque index (PI), bleeding on probing (BOP), probing pocket depth (PPD), and clinical attachment loss (CAL). PD was defined using clinical case definitions proposed by the Centers for Disease Control and Prevention (CDC). AS disease activity, spinal mobility, and radiographic status were evaluated using the Bath ankylosing spondylitis disease activity score (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Metrology Index (BASMI), and the modified Stoke AS Spinal Score (mSASSS).

Results: The prevalence of PD was comparable between subjects with HC and AS (58.9% versus 68.0%, p = 0.250). There was no significant difference in PI, BOP, PPD and CAL between the two groups. In AS patients, male gender (p = 0.009) was significantly associated with PD at the baseline examination, whereas the other variables including current use of TNF-α blockers (17/51 versus 4/24, p = 0.288) was not. Periodontal status 12 weeks after periodontal scaling was not different between AS (n = 29) and HC (n = 14, p = 0.317). In addition, among AS patients with PD, current use of TNF-α blockers did not affect periodontal treatment outcomes.

Table 1. The prevalence and severity of periodontal disease in AS patients and healthy controls at the baseline.

Characteristics	AS	HC	P-value
Periodontal disease prevalence	51 (68.0%)	43 (58.9%)	0.314
Periodontal disease severity			0.607
Mild	0 (0.0%)	2 (2.7%)	
Moderate	44 (58.7%)	33 (44.6%)	
Severe	7 (9.3%)	10 (13.5%)	
Plaque index (%)	25.0 [13.4–41.7]*	23.2 [10.7–36.6]	0.521
Probing pocket depth (mm)	2.54 [2.30–2.77]	2.54 [2.38–2.77]	0.950
Bleeding on probing (%)	11.8 [7.14–22.6]	6.5 [6.35–17.6]	0.231
Clinical attachment loss (mm)	2.58 [2.38–2.86]	2.58 [2.39–2.92]	0.934

AS, ankylosing spondylitis; HC, healthy control; *, median [interquartile range]

Conclusion: Contrast to RA patients, the prevalence and severity of PD was not increased in AS patients. Furthermore, TNF-α blocker usage in AS patients was associated with neither the prevalence of PD nor the outcome of treatment in our interim analyses.

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Impact Of Stressful Life Events On Disease Activity In Spondyloarthritis: Results Of The Coenv-2 Prospective Cohort Study. Guanguan Luo[1], Pierre Yves Boelle[1], Clément Turbelin[1], Roula Said Nahal[2], Nadine Zeboulon[2], Maria-Antonietta D'Agostino[3], Solen Kerneis[1], Thomas Hanslik[3] and Maxime A. Breban[3]. [1]Faculté de Médecine Pierre et Marie Curie, Paris, France, [2]Ambroise Paré Hospital, Boulogne-Billancourt, France, [3]Ambroise Paré Hospital, and Versailles Saint Quentin en Yvelines University, Boulogne-Billancourt, France.

Background/Purpose: The relative contribution of environmental factors to triggering and/or progression of spondyloarthritis (SpA) remains poorly characterized. A link between disease activity and stressful life events and vaccination has been shown previously (J Rheumatol 2013,40:469). The

objective of this study was to specify the types of vaccine and life event related to disease activity.

Methods: Adult spondyloarthritis patients were enrolled in the dedicated cohort, CoEnv-2, which was prospectively followed for 2 years. Patients logged on to a secured website every month to complete an auto-questionnaire. They reported whether they had been exposed to stressful life events, vaccinations or other environmental factors through a detailed standardized questionnaire. Patients were asked to rate the impact of a potential exposure to life events occurring since the previous connection, on a visual numeric scale (VNS) from 0 (no impact) to 10 (worst impact). The main outcome variable was the difference of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) measured on two consecutive connections. Months with occurring event(s) were compared to those without such event.

Results: Three hundred and one patients participated and returned 3,896 monthly questionnaires. Months when an abrupt and unexpected traumatic event (such as natural disaster, robbery, physical abuse. . .) occurred were associated with an increase in BASDAI of 0.58 [95%CI: 0.50;0.66], as compared to months without such occurrence ($p<0.001$). The events with the highest rating on the VNS had the largest impact (0.66 [0.40;0.92] for a VNS $\geq$5, and 0.96 [0.33;1.59] for a VNS $\geq$9). Among non-abrupt stressful life events, only work-related events were followed by an increased BASDAI (0.40 [0.13;0.67]). Seasonal influenza vaccination was associated with a more moderate increase in BASDAI (0.35 [0.06;0.34], $p<0.05$).

Conclusion: Among stressful life events, abrupt and unexpected traumatic events had a clear-cut measurable impact on disease activity in patients with SpA. The link between vaccination and disease activity appeared as limited to influenza immunisation. Ongoing analyses will allow us to determine the duration of such effects.

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Clinical Characteristics Of Patients With Early Spondyloarthritis. Results From a Specialized Consultation In a Clinical Hospital. Juan Jose Aznar Sánchez, Eugenio Chamizo Carmona, Adela Gallego Flores, Raul Veroz Gonzalez and Tamara Libertad Rodriguez Araya. Hospital de Mérida, Mérida, Spain.

Background/Purpose: The classification criteria for spondyloarthritis (SpA) intend to identify patients with this disease from the initial stages. The nonspecific characteristics, symptoms, signs, and additional tests found in many patients at the onset of SpA, and the limitations of the classification criteria explain the delayed diagnosis. In Spain, the delay for the diagnosis is about 6 years[1]. Recently, the Assessment of SpA international Society (ASAS) has developed new criteria that try to reduce the time to diagnosis for axial SpA[2] and peripheral SpA[3]. In 2008 a SpA unit of recent onset was created in the General Hospital of Mérida (Spain) in order to establish an early diagnosis of this pathology. We describe the demographic and clinical characteristics of this population.

Methods: Between 2008 and 2013, we included patients aged from 18 to 45 years with symptoms for more than 3 months and less than 2 years including inflammatory back pain, asymmetric arthritis and/or mechanical low back pain (LBP) or arthralgias accompanied by at least one of the following: psoriasis, uveitis, inflammatory bowel disease, enthesitis, sacroiliitis imaging, positive HLAB27 or family history of SpA. Patients with previous diagnosis of SpA were excluded.

Results: The most common reason for consultation was LBP (76%). We studied 121 patients: 54 patients (45%) met ASAS criteria for SpA, 31 patients had axial SpA, and 23 patients had peripheral SpA. The gender distribution was similar in both groups. In axial SpA, 25.8% met NY criteria and most of these patients were men, the other 74,2% were non-radiological SpA with a female predominance. In the peripheral SpA, the most frequent was Psoriatic arthritis (PsA) (56.5%). The mean age at diagnosis was lower for axial SpA (30 years), undifferentiated SpA (uSpA 27.9 years) and AS (29 years) compared to peripheral SpA (35.7 years). HLA B27 was positive in 63% of patients with SpA and in 10.4% of no-SpA subjects. HLAB27 was more prevalent in axial SpA (84%), especially in AS (100%), compared to peripheral SpA (34%). It should be noted that 87.5% of the peripheral uSpA were positive HLAB27. The 39% of patients with SpA had family history, being more frequent in axial (55.5%) and peripheral (57%) uSpA and PsA (30%). Arthritis was present in 37% of SpA and 100% of PsA. Enthesitis was observed in 38% of SpA, in 50% of axial uSpA and 100% of the peripheral uSpA. There was one Dactylitis in a patient with peripheral uSpA and 5 cases of uveitis, all in axial SpA.

Conclusion: The creation of units of recent onset could help us to select patients fulfilling ASAS criteria. We achieved a diagnostic rate of 45% of patients referred. Axial SpA was more frequent (57.4%) and especially the non-radiological (74.2% of the axial). The most frequent peripheral SpA presentation was PsA (24%). Axial SpA, and especially axial uSpA, appears at a younger age than peripheral SpA. The gender distribution was similar for SpA, but non-radiographic axial SpA were more common in women. We found a family history of SpA more frequently in both axial and peripheral uSpA and a strong association between HLA B27 and AS (100%) and both axial and peripheral uSpA. In contrast, we found no association between HLA B27 and PsA or enteropathic arthritis.

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Adalimumab Significantly Reduces Inflammation In Active Ankylosing Spondylitis: An Ultrasound Study. Zaiying Hu[1], Manlong Xu[2], Zetao Liao[1], Zhiming Lin[3] and Jieruo Gu[4]. [1]THIRD AFFILIATED HOSPITAL OF SUN YAT-SEN UNIVERSIT, Guangzhou, China, [2]THIRD AFFILIATED HOSPITAL OF SUN YAT-SEN UNIVERSIT, Guangzho, China, [3]third affiliated hospital of Sun Yat-sen Universtiy, Guangzhou, China, [4]Third Affiliated Hospital of Sun Yat-sen University, GuangZhou, China.

Background/Purpose: To evaluate the feasibility of using power Doppler ultrasound (PDUS) to detect inflammation in sacroiliac joints and entheses after adalimumab (a TNF-alpha antagonist) treatment in active ankylosing spondylitis (AS) patients.

Methods: This was a randomized, double-blind, placebo-controlled study. Active AS patients received 40 mg adalimumab ($n = 21$) or placebo ($n = 20$) every other week during an initial 12-week double-blind period, and all switched to adalimumab treatment for another 12 weeks. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Function Index (BASFI), C-reactive protein (CRP), Ankylosing Spondylitis Disease Activity Scores (ASDAS) were measured and inflammation in sacroiliac joints and entheses were detected by PDUS at baseline, week 12 and week 24. The regions of enthesitis we detected including sternoclavicular joint, thoracic rib joints, lumbar spinous process, anterior superior iliac spine, posterior superior iliac spine, patellar tendon, and achilles tendon. The color flow signals of PDUS were scored on a 0–4 semi-quantitative scale.

Results: The total PDUS scores of active AS patients decreased significantly after 24 weeks treatment of adalimumab (4.95 ± 4.07 vs. 3.33 ± 3.12, $p=0.033$). And obvious improvements in clinical assessments (BASDAI, BASFI, CRP and ASDAS reduced, all $P < 0.05$) were also observed after 24 weeks of adalimumab. But the total PDUS scores of AS patients did not change statistically after 12 weeks treatment of adalimumab (4.67 ± 4.10 vs. 4.27 ± 3.20, $p=0.416$) or placebo (4.75 ± 3.63 vs. 4.35 ± 4.22, $p>0.05$). And the total PDUS score did not correlate with clinical assessments (all $p=0.494$).

Conclusion: Our study found that adalimumab was highly effective in reducing inflammation in active AS patients as detected by power Doppler ultrasound.

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Predicting Progression Of Non-Radiographic Axial Spondyloarthritis. Nigil Haroon[1], Lianne S. Gensler[2], Dinny Wallis[3], Ammepa Anton[1], Grace Yoon[4] and Robert Inman[5]. [1]Toronto Western Research Institute, Toronto, ON, [2]University of California, San Francisco, San Francisco, CA, [3]Toronto Western Hospital, University of Toronto, Toronto, ON, [4]UCSF, San Franciscao, CA, [5]University of Toronto and Toronto Western Hospital, Toronto, ON.

Background/Purpose: A proportion of patients with non-radiographic axial spondyloarthritis (NR-AxSpA) progress to AS but the predictors of progression have not been well established. We studied the predictors of progression of NR-AxSpA.

Methods: Patients with NR-AxSpA who were followed in two major SpA centers were enrolled in this study. Patients are classified as NR-AxSpA if they do not satisfy the modified New York Criteria for AS but satisfied the ASAS criteria for axial SpA. All patients had two X-rays of the pelvis

separated by at least 1.5 years. All patients were followed with a standardized protocol and were assessed on an annual basis. Disease activity was assessed by Bath AS Disease Activity Index (BASDAI), ESR and CRP. Markers of inflammation were averaged over the period of follow-up to estimate the ongoing level of inflammation. HLA-B27 was done in all patients and MRI of the spine was done as clinically indicated. Smoking pack-year history was collected. Three readers, blinded to patient details scored the pelvis radiographs using the New York grading system for sacroiliitis. Progressors were defined as those who had significant increase in SI joint score (2 grades). Logistic regression analysis was done to identify predictors of progression.

Results: Fifty-one patients (51% females and 75% HLA-B27 positive) qualified for the study and were followed for a mean (± SD) duration of 3.6 ± 2.1 years. The mean disease duration was 9.5 ± 7.7 years. The baseline and time averaged BASDAI were 5.1 ± 2.0 and 4.8 ± 2.1 respectively. Iritis, inflammatory bowel disease (IBD) and Psoriasis were present in 29.4%, 7.8% and 13.7% respectively. Except for one patient, all others had inflammatory back pain (IBP). Only 14 patients were smokers with 2.1 ± 6.5 pack-years history. Only 6 patients had significant progression and 4 patients satisfied the Modified New York criteria at last follow-up. Except for one patient who progressed at 2.5 years, all others did so after 6 years of follow-up.

Progressors are compared to non-progressors in Table 1. All patients who progressed were HLA-B27 positive. Patients with iritis had a relative risk of progression of 4.8 (1.0, 23.5; p=0.053). Progressors had significantly higher baseline BASDAI (p=0.04, Median Test). Those who progressed had longer follow-up and after correction for this, logistic regression analysis showed significant association of progression with smoking pack years with an OR of 1.2 (1.03–1.4, p=0.02). In multivariate logistic regression analysis including all baseline parameters, the only significant variable associated with progression was the duration of follow up.

Table 1. Comparison of progressors with non-progressors

Variable	Progressors (N=6)	Non-progressors (N=45)	p
Median Age of Onset (IQR, years)	29 (18, 42)	28 (22, 36)	ns
HLA-B27 (%)	6 (100)	32 (71)	0.051
Female (%)	3 (50)	23 (51)	ns
Median Disease Duration (IQR, years)	14 (11, 17)	7 (2, 16)	ns
Baseline Median ESR (IQR, mm per hour)	8 (5, 12)	7 (3, 19)	ns
Baseline Median CRP (IQR mg/L)	3 (3, 4)	3 (3, 5)	ns
Average Median ESR (IQR, mm per hour)	5 (3, 8)	7 (3, 18)	ns
Average Median CRP (IQR mg/L)	3 (2, 4)	3 (2, 4)	ns
Baseline Median BASDAI (IQR)	6.2 (6, 7)	5 (3, 7)	0.04
Average Median BASDAI (IQR)	6 (5, 7)	5 (3, 7)	ns
Iritis (%)	4 (67)	11 (24)	0.054
IBD (%)	1 (17)	3 (7)	ns
Psoriasis (%)	2 (33)	5 (11)	ns
Peripheral Arthritis (%)	4 (67)	33 (73)	ns
Enthesitis (%)	4 (67)	30 (67)	ns
Dactylitis (%)	0	3 (7)	ns
IBP (%)	6 (100)	44 (98)	ns
Smoking (%)	3 (50)	11 (24)	ns
Smoking (Median, IQR Pack Years)	1 (0, 10)	0 (0, 0)	ns
Biologics (%)	2 (33)	25 (56)	ns
Biologics Median Duration (IQR, Yrs)	3 (0, 7)	3 (0, 4)	ns
Median Gap between X-rays (IQR, Yrs)	7 (4, 9)	3 (2, 4)	ns

Conclusion: Over a mean follow up of 3.6 years, 8% of patients with NR-AxSpA progressed to AS. Smoking appears to be a risk factor for significant progression of SI joint scores. HLA-B27, higher baseline BASDAI and iritis were more common in progressors.

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External Validation Of The Spondyloarthritis Radiography Online Reference Module For Training Readers To Score The Modified Stoke Ankylosing Spondylitis Score. Praveena Chiowchanwisawakit[1], Susanne Juhl Pedersen[2] and Walter P. Maksymowych[3]. [1]Mahidol University, Bangkok, Thailand, [2]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [3]University of Alberta, Edmonton, AB.

Background/Purpose: The modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) is commonly used to assess disease severity and progression in patients with AS; however, the reliability of scoring change in mSASSS is still challenging. The SpondyloArthritis Radiography (SPAR) online training module is aimed at providing explicit instructions for scoring the mSASSS, reference cases in DICOM format, and raw expert reader scores aimed at training and calibration of readers for detecting change in mSASSS[1]. However, it has not been validated beyond the group of experts that originally developed the module.

Methods: The SPAR module is comprised of 4 parts: 1) slide review of mSASSS scoring methodology, 2) reference DICOM image set of 34 cases with pairs of radiographs with two year time frames and a schematic of the spine for direct online data entry, 3) raw data scores for reference DICOM image set from two expert readers and unblinding data, and 4) schematic of the spine illustrating the mSASSS scoring module for calibrated reviewers to conduct direct online data entry for test cases. The details are available at http://tools.carearthritis.com/spar/. In exercise 1, 2 inexperienced readers independently assessed the 34 pairs of cervical and lumbar spine radiographs of the SPAR reference case DICOM image set blinded to time point (baseline, 2 years). Exercise 2 was conducted after review of the SPAR module that included assessment of expert reader raw scores for the 34 case reference image set. Exercise 2 included 21 pairs of scans from exercise 1 that were randomly scored with an additional 34 new pairs of scans to assess consistency of reliability. This nested study design addresses the limitation for assessment of reliability posed by differences in progression rates between different study samples, which may significantly impact ICC scores when between-patient variability in progression is small. Inter-observer reliability of mSASSS for status and change scores was assessed by intra-class correlation coefficient (ICC). Inter-observer reliability of each type of lesion was assessed by kappa and percentage of agreement.

Results: There was consistent reliability of mSASSS for status score and the reliability of the change score was improved in exercise 2 after reviewing the online module (Table 1). Improved reliability in detecting specific lesions was also observed.

Table 1.

	Exercise 1		Exercise 2		
	All cases (n = 34)	Ex 1 Subset (n = 21)	All cases (n = 55)	Ex 1Subset (n = 21)	New cases (n = 34)
Status ICC (95% CI)	0.94 (0.88, 0.97)	0.97 (0.92, 0.99)	0.96 (0.92, 0.97)	0.97 (0.93, 0.99)	0.94 (0.89, 0.97)
Change ICC (95% CI)	0.38 (0.04, 0.63)	0.53 (0.13, 0.78)	0.67 (0.50, 0.80)	0.56 (0.19, 0.79)	0.71 (0.50, 0.85)

Table 2. *Cases scored in both exercises

		Squaring		Sclerosis		Syndesmophyte		Ankylosis	
	Cases	Kappa	Agreement	Kappa	Agreement	Kappa	Agreement	Kappa	Agreement
Exercise 1 (N = 34)	All	0.17	84.9%	0.12	94.1%	0.49	92.0%	0.76	94.6%
	N = 21*	0.09	78.7%	0.11	91.2%	0.51	90.3%	0.83	95.0%
Exercise 2 (n = 55)	All	0.65	90.9%	0.47	97.6%	0.59	90.7%	0.87	97.0%
	N = 21*	0.64	91.4%	0.61	97.6%	0.63	90.2%	0.86	96.2%

Conclusion: The reliable scoring of the mSASSS by inexperienced readers can be improved by using the SPAR online training module.

1. Maksymowych et al. Ann Rheum Dis 2012. **71(Suppl3):** 405

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2482

Which Contextual Factors Have An Important Influence On Work Outcome In Patients With Ankylosing Spondylitis. A Systematic Literature Review. Jose Dionisio Castillo-Ortiz[1], Carmen Stolwijk[2] and Annelies Boonen[1]. [1]Maastricht University Medical Center, Maastricht, Netherlands, [2]Maastricht University, Maastricht, Netherlands.

Background/Purpose: It is increasingly recognized that contextual factors (either environmental or personal) play a role in the magnitude in which the disease influences work participation. However, no summary data exist on which factors might be relevant. Therefore, we reviewed the literature on contextual factors in relation to work outcomes in patients with Ankylosing Spondylitis (AS).

Methods: Medline, EMBASE, PsyINFO and Cinahl as well as references of selected articles were searched systematically up to June 2012. Articles were eligible if reporting original data on the influence of contextual factors (CF) on work disability, sick leave or presenteeism in patients with AS. Assessment of risk of bias and extraction of data were performed by two independent persons. CF were grouped in environmental and personal factors according to the framework proposed by OMERACT (1).. Analyses were

marked as 'high quality' if the CF was significantly contributing to work outcome in multivariable analyses, after adjustment for disease activity and physical function in a study that had a sufficient samples size for a multivariable analyses.

Results: Out of 1165 studies, 19 met the inclusion criteria of which one was added by hand search (seventeen cross-sectional and two longitudinal); 17 studies addressed employment/WD, three sick leave and 2 presenteeism. For work disability (n=11 studies), there was high quality evidence for the adverse influence of higher age (n= 4), (absence of) work accommodations (n=2), nature of work (n=1), (absence of) workplace support (n=1), (absence of) non-workplace support (n=1), avoidant coping (n=1) and being unmarried (n=1). Evidence was conflicting for gender and education. For sick leave and presenteeism there was no high level evidence for the role of any contextual variable.

Conclusion: Depending on the threshold used to decide whether evidence of the association between a CF and work-outcome can be considered as 'high quality', age, work accommodations, nature of work, workplace support and coping/ are candidate variables to be included as important contextual factors of work outcome in addition to disease related variables (function and disease activity). It should be noted all these studies reported cross-sectional associations.

Disclosure: J. D. Castillo-Ortiz, None; **C. Stolwijk**, None; **A. Boonen**, None.

2483

Periarticular Bone Gain In Early Psoriatic Arthritis But Not In Rheumatoid Arthritis Following Anti-Rheumatic Treatment As Measured By Digital X-Ray Radiogrammetry. Agnes Szentpetery, Muhammad Haroon, Phil Gallagher, Eric J. Heffernan and Oliver FitzGerald. Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland.

Background/Purpose: Hand bone loss is an early feature in both RA and PsA, but there is less data available on periarticular bone gain, in particular in PsA following treatment. Digital X-ray radiogrammetry (DXR) is a sensitive method for quantifying changes in periarticular bone mineral density (DXR-BMD) in the early phase of the disease.

The aim of this study was (1) to investigate DXR-BMD changes in early PsA and RA prior to and 3, 12 months after introducing an anti-rheumatic drug; and (2) to explore associations between disease-related variables and DXR-BMD.

Methods: Recent-onset (<12 months), active, treatment naïve PsA and RA patients were selected. Hand BMD was measured by DXR based on digitized hand radiographs (Sectra, Sweden) at baseline, 3 and 12 months. Mean DXR-BMD (mg/cm^2) values of both hands and changes in DXR-BMD (mg/cm^2/month) were calculated and compared between the two groups at all time points. Changes in hand BMD were further analysed by dividing PsA and RA into 3 subgroups based on cut-offs for the categories normal, elevated BMD loss (>−0.25 mg/cm^2/month) and highly elevated BMD loss (>−2.5 mg/cm^2/month). DXR-BMD was correlated with clinical parameters including ESR, CRP, DAS28-CRP4v and HAQ.

Results: 64 patients (32 PsA, 32 RA) were included with median age 43 years. 95% of the patients were commenced on a DMARD therapy at baseline and 11.7 % (12.5% RA; 10.7% PsA) were also started on a TNF inhibitor. There were no patients taking anti-resorptive medications, 17.2% were on oral glucocorticoids (15.6% RA; 18.7% PsA) less than 10 mg per day. At 12 months 94.8% of the patients were on a DMARD and 34.5% on a TNF inhibitor (33.3% RA; 35.7% PsA).

Mean DXR-BMD decreased in both diseases at 3 months and was significantly lower in RA at 12 months (p=0.004) compared to baseline. In contrast mean DXR-BMD increased in PsA over 12 months (p=0.07) and was higher at both 3 and 12 months compared to RA.

DXR-BMD loss were significantly higher in RA compared to PsA from baseline to 12 months (p=0.0005) and also from 3 to 12 months (p=0.0006). There were no bone loss in 91.7% of patients with PsA, but only in 40.7% of patients with RA between baseline and 12 months. Among all patients with elevated BMD loss, change in DXR-BMD was less marked in the PsA group compared to RA from baseline to 3 (p=0.018) and from 3 to 12 months (p=0.014). Highly elevated bone loss was present only in the RA cohort (7.5%) at 12 months.

Disease activity scores were significantly lower in PsA than in RA at baseline and 3 months. ESR, CRP, DAS28-CRP4v improved significantly in both diseases during the study. Mean DXR-BMD correlated negatively with ESR at 12 months in RA (r = −0.39; p= 0.038), however no other significant correlations between other clinical parameters and DXR-BMD were found.

Conclusion: To our knowledge this is the first prospective study showing hand bone loss as early as 3 months as measured by DXR in both PsA and RA despite intervention of appropriate anti-rheumatic drug. After 1 year of treatment we observed cortical bone gain in PsA but further bone loss in RA supporting the hypothesis of different pathomechanisms being involved in hand bone remodelling in PsA.

Disclosure: A. Szentpetery, None; **M. Haroon**, None; **P. Gallagher**, None; **E. J. Heffernan**, None; **O. FitzGerald**, Pfizer, Abbott, BMS, MSD, Roche, UCB, 2, Pfizer, Abbott, BMS, MSD, Janssen, Roche, 5, Pfizer, Abbott, Janssen, Roche, UCB, 8.

2484

Immunogenicity Of TNFα Blockers In Patients With Psoriatic Arthritis. Michael Zisapel Zisapel[1], Noa Madar-Balakirsi[2], Hagit Padova[3], Irena Wigler[3], Daphna Paran[4], Uri Arad[3], Dan Caspi[5] and Ori Elkayam[3]. [1]Tel Aviv Medical Centet, Tel Aviv, Israel, [2]Tel Aviv Medical Center, Tel Aviv, Israel, [3]Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [4]Tel Aviv Sourasky Medical Ctr, Tel-Aviv university, Tel Aviv, Israel, [5]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

Background/Purpose: TNFα blockers have been shown to produce immunogenecity in patients with rheumatoid arthritis, spondyloarthrritis and inflammatory bowel diseases. Data on the induction of anti-drug antibodies against TNF alpha blockers in psoriatic arthritis is scarce. The purpose of this study was to assess the prevalence of anti-drug antibodies (ADA) against infliximab, adalimumab and etanercept in a cohort of patients with psoriatic arthritis (PsA).

Methods: Patients with PsA treated for at least 3 months with adalimumab (n=48), infliximab (n=24) and etanercept (n=21) participated in this study. Clinical activity was assessed using the DAS 28, physician and patient global assessment using a VAS of 100 mm, psoriasis assessement of severity score (PASI), BASDAI, ESR and CRP.

Results: ADA were detected in 26 (55%) patients on adalimumab, 5 (28%) on infliximab and none of the patients on etanercept. A significant correlation was found between the presence of ADA and drug levels of adalimumab and infliximab. A significant correlation was found between drug levels of adalimumab and global physician and patient assessment, and the PASI. In patients treated with infliximab, ADA was associated with higher DAS and PASI, Twenty-six % of the patients were concomitantly treated with methotrexate (MTX). A significant correlation between the use of MTX and the absence of ADA was demonstrated in patients treated with infliximab and adalimumab.

Conclusion: A substantial proportion of patients with PsA develop anti drug antibodies to adalimumab and infliximab. The use of MTX seems to lower immunogenecity. The presence of ADA correlated with drug levels and several parameters of disease activity.

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2485

High Incidence Of Disease Recurrence After Discontinuation Of Disease Modifying Anti-Rheumatic Drug Treatment In Patients With Psoriatic Arthritis In Remission. Elizabeth Araujo, Stephanie Finzel, Dominik A. Schreiber, Matthias Englbrecht, Axel J. Hueber, Francesca Faustini, Juergen Rech and Georg Schett. University of Erlangen-Nuremberg, Erlangen, Germany.

Background/Purpose: In the era of modern anti-rheumatic therapy, it is now possible to contemplate the idea of clinical remission in patients with psoriatic arthritis (PsA). It is however unknown whether patients in clinical remission can stop methotrexate (MTX) or tumor necrosis factor inhibitor (TNFi) treatment. The objective of this study was to investigate drug-free remission in patients with PsA and potential predictors for flare

Methods: Patients with PsA in remission (no musculoskeletal symptoms, no or minimal skin/nail disease) for at least 6 months were included. At baseline the following parameters were assessed: age, sex, BMI, disease duration, duration of remission, swollen joint count, tender joint count, VAS-pain, VAS-global, NAPSI, PASI, MASES, LDI, HAQ-DI, SF-36, FACIT-F, anti-rheumatic therapy (MTX, TNFi), ESR and CRP. In addition, ultrasound of 30 joints and 20 enthesis was performed. After discontinuation of therapy at day 1, patients were followed for 6 months for the occurrence of flares.

Results: 26 patients (methotrexate monotherapy: N =14, tumor necrosis factor inhibitors: N = 12) with a mean age of 55.2 years, absence of musculoskeletal symptoms and minimal skin disease (mean PASI: 0.21) were enrolled. Incidence of recurrence of disease was high (N=20, 76.9%,) and occurred rapidly (74.50 ± 51.72 days) after treatment discontinuation. Male PsA patients were significantly more likely to lose remission. Long disease duration, more severe skin involvement, and the presence of synovial hypertrophy by ultrasonographic examination at baseline decreased the likelihood for drug-free remission. Re-initiation of DMARDs promptly restored remission in all PsA patients with recurrence of disease.

Conclusion: This study shows that the chance to reach drug-free remission in PsA patients is low. Discontinuation of DMARD therapy cannot be recommended in patients with PsA.

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2486

Clinical Performance Of 4 Methods For Detecting Latent Tuberculosis Infection (LTbI) In Patients With Active Chronic Inflammatory Arthritis Taking TNFα Blockers. Carina M F Gomes[1], Maria Teresa Terreri[2], Maria Isabel Pinto[1], Karen Oseki[1], Fernanda Spina[1] and Marcelo M. Pinheiro[3]. [1]Universidade Federal de São Paulo, Sao Paulo, Brazil, [2]Universidade Federal de São Paulo / UNIFESP, Sao Paulo, Brazil, [3]Brazilian Registry of Spondyloarthritis, São Paulo, Brazil.

Background/Purpose: About 5% of the Brazilian population has some chronic inflammatory arthropathy (CIA), including rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PA) and juvenile idiopathic arthritis (JIA), and 30 to 50% of them will need to use some TNFα inhibitor to control disease activity. However, several studies have shown greater rates of active mycobacterial infections after starting of these medications. According Brazilian database, the incidence of active cases of mycobacterial infection, especially tuberculosis, has increased in patients with CIA when compared to the adult (86.93/100.000 persons-year vs. 37.48/100.000 P-Y, respectively) and pediatric Brazilian population (22.53/100.000 P-Y vs. 15.91/100.000 P-Y, respectively). It is worthy emphasizing that all of them were negative for latent tuberculosis infection (LTbI) in the first medical evaluation. Purpose: To compare clinical performance of 4 methods for detecting LTbI in CIA patients taking TNFα blockers.

Methods: A total of 87 patients were included in this cross-sectional study, of whom 35 with RA, 35 with AS, 7 with PA and 10 JIA patients. Patients with active tuberculosis, hepatitis B or C and HIV infection were excluded. All participants answered a specific questionnaire, including details on epidemiologic data, medical history, and symptoms related to tuberculosis, as well as BCG vaccine history and socioeconomic status. Besides, they performed chest radiography and tuberculin skin test (PPD). In case of induration lower than 4 mm, the test was repeated in the contralateral forearm up to 3 weeks after the first reading (PPD-Booster). The interferon gamma specific release assays (IGRAs) were performed using Elispot (T-SPOT.*TB*) and Quantiferon (Quantiferon-TB GOLD).

Results: Fourteen new cases of LTBI were identified in CIA adult patients taking TNFα inhibitors (Table 1). All JIA children were negative for the 4 tests. Although the concordance between the 4 tests has been above 75%, the positivity was not associated with active tuberculosis.

Test for LTbI	Rheumatoid Arthritis (n=35)	Ankylosing Spondylitis (n=35)	Psoriatic Arthritis (n=7)
PPD before starting TNFα blockers	9 (25.7%)	8 (22.8%)	1 (14.2%)
PPD after starting TNFα blockers	13 (37.1%)	10 (28.5%)	3 (42.8%)
ELISPOT	12 (34.2%)	11 (31.4%)	3 (42.8%)
Quantiferon (QTF)	6 (17.1%)	7 (25.9%)	3 (42.8%)
PPD-Booster	2 (9%)	1 (4%)	0

Conclusion: Fourteen new cases of LTBI were identified in CIA adult patients taking TNFα inhibitors (Table 1). All JIA children were negative for the 4 tests. Although the concordance between the 4 tests has been above 75%, the positivity was not associated with active tuberculosis. Table 1. Clinical performance of 4 methods for detecting LTBI in patients taking TNFα blockers.

Disclosure: C. M. F. Gomes, None; **M. T. Terreri**, None; **M. I. Pinto**, None; **K. Oseki**, None; **F. Spina**, None; **M. M. Pinheiro**, None.

2487

Role Of IL-33 In The Development Of Premature Atherosclerosis In Psoriatic Arthritis Patients. Priscilla Ching-han Wong[1], Qing Shang[2], Cheuk-Man Yu[2] and Lai Shan Tam[2]. [1]Prince of Wales hospital, New Territories, Hong Kong, [2]The Chinese University of Hong Kong, Hong Kong, Hong Kong.

Background/Purpose: Interleukin 33 (IL-33) is a newly identified member of the IL-1 cytokine family. It involves in T-cell mediated immune responses through the activation of the ST2 receptor that are widely expressed by the T helper 2 cells and mast cells. Many previous studies have demonstrated the role of IL-33 in chronic autoimmune diseases. Whether this may play a role in the pathogenesis of inflammation and accelerating atherosclerosis in psoriatic arthritis (PsA) has never been addressed.

Methods: A prospective study of 89 PsA patients followed up by the Prince of Wale hospital were recruited with comprehensive measurements of the traditional and novel CV risk factors, markers of clinical disease activity and severity, laboratory markers of inflammation, intima-media thickness (IMT) and augmentation index (AIx). Frozen plasma was retrieved for the measurement of IL-33. 66 patients came back for follow-up after 5 years and vascular assessments were repeated. SPSS was used for statistical analysis

Results: Among the 89 patients, 50.6% were male and 49.4% were female. The mean age was 46.1.9 ± 11.8 years old and the mean disease duration was 9.2 ± 7.1. IL-33 was measurable in only 54 out of 89 patients. Among these 54 patients, the mean of the IL-33 was 3.97 ± 17.79 pg/ml. IL-33 was associated with the mean IMT ($r=0.273$, $p=0.011$) and the maximum IMT ($r=0.239$, $p=0.026$), but it was not associated with AIx ($r=-0.016$, $p=0.891$). IL-33 was also not associated with the traditional and novel CV risk factors, the markers of clinical disease activities and severity, as well as the laboratory markers of inflammation.

Conclusion: IL-33 could be a novel pathway in accelerating the progression of premature atherosclerosis in PsA patients affecting both structural (IMT) and functional (AIx) modification of the blood vessels, independent of the CV risk factors.

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ACR/ARHP Poster Session C
Spondyloarthropathies and Psoriatic Arthritis: Pathogenesis, Etiology, Animal Models II
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

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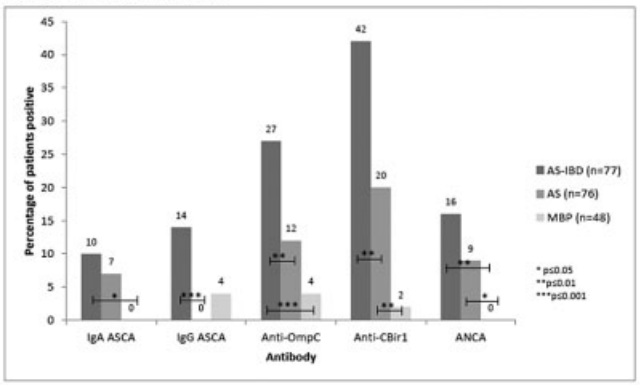
Elevated Serum Anti-Flagellin Antibodies Implicate Subclinical Bowel Inflammation in Ankylosing Spondylitis. Dinny Wallis[1], Arundip Asaduzzaman[1], Michael H. Weisman[2], Nigil Haroon[1], Ammepa Anton[3], Dermot P. B. McGovern[4], Stephan R. Targan[4] and Robert D. Inman[1]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]Cedars-Sinai Med Ctr, Los Angeles, CA, [3]Toronto Western Research Institute, Toronto, ON, [4]Cedars-Sinai Medical Center, Los Angeles, CA.

Background/Purpose: Ankylosing spondylitis (AS) and inflammatory bowel disease (IBD) share genetic and clinical features. IBD is associated with the presence of antibodies to a variety of commensal microorganisms including anti-Sacchoaromyces cerevesiae antibodies (ASCA), antineutrophil cytoplasmic antibodies (ANCA), anti-I2 (associated with anti-Pseudomonas activity), anti-E. coli outer membrane porin C (anti-OmpC) and anti-flagellin antibodies (anti-CBir1). Subclinical intestinal inflammation may be present in up to 65% of patients with AS. This study evaluated the presence of antimicrobial antibodies in patients with AS alone, patients with AS and concomitant IBD (AS-IBD) and a control group of patients with mechanical back pain (MBP).

Methods: Patients with AS-IBD were identified from a longitudinal prospective AS cohort and matched by age and disease duration to patients with AS alone. Sera were tested by ELISA for ASCA IgG and IgA, anti-OmpC, anti-CBir1 and ANCA in 76 patients with AS alone, 77 patients with AS-IBD and 48 patients with MBP (who underwent clinical, laboratory and radiological investigation to exclude spondyloarthritis). Antibody positivity rates, median quantitative antibody levels and the proportion of patients with antibody levels in the 4th quartile of a normal distribution were compared between the three groups of patients.

Results: Antibody positivity rates are shown in Figure 1. Patients with AS alone demonstrated higher anti-CBir1 antibody positivity rates (19.7% versus 2.1%, p=0.005) and median antibody levels (15.0 [10.0–23.8] EU versus 10.0 [7.0–15.0] EU, p=0.0007) than MBP patients. AS-IBD patients demonstrated elevated responses when compared to AS alone for ASCA, anti-OmpC and anti-CBir1. Quartile analysis confirmed the findings. Acute phase reactants were significantly elevated in anti-CBir1 positive patients compared to anti-CBir1 negative patients: median (IQR) CRP 11.5 (5.3–20.5)mg/L versus 6.0 (3.0–15.5)mg/L (p=0.006); median (IQR) ESR 19.0 (8.5–32.0)mm/h versus 8.0 (3.0–18.0)mm/h (p<0.001). Among patients with AS alone, acute phase reactants remained significantly elevated in anti-CBir1 positive patients compared to anti-CBir1 negative patients (median (IQR) CRP 14.0 (7.0–19.0)mg/L versus 3.0 (3.0–15.0)mg/L, p=0.033); median ESR (IQR) 26.0 (10.0–33.0)mm/h versus 5.0 (3.0–20.0)mm/h). No significant difference was seen in acute phase reactants between anti-CBir 1 positive and negative patients within the AS-IBD group.

Figure 1 Positivity rates of antibodies



Conclusion: These data suggest that adaptive immune responses to microbial antigens occur in AS patients without clinical IBD and support the theory of mucosal dysregulation as a mechanism underlying the pathophysiology of AS.

Disclosure: D. Wallis, None; **A. Asaduzzaman**, None; **M. H. Weisman**, None; **N. Haroon**, None; **A. Anton**, None; **D. P. B. McGovern**, None; **S. R. Targan**, None; **R. D. Inman**, None.

2489

Spondyloarthritis-Associated Polymorphisms Of ERAP1 Are Correlated With Gene Expression, Protein Level and Enzymatic Activity Of The Amino-Peptidase. Félicie Costantino[1], Alice Talpin[1], Irini Evnouchidou[2], Amir Kadi[1], Roula Said-Nahal[3], Ariane Leboime[3], Nelly Bonilla[1], Franck Letourneur[1], Tifenn Leturcq[1], Zeyna Ka[1], Peter van Endert[2], Henri-Jean Garchon[3], Gilles Chiocchia[3] and Maxime A. Breban[3]. [1]Institut Cochin - Université Paris Descartes - INSERM U1016 - CNRS (UMR 8104), Paris, France, [2]INSERM U1013 - Université Paris Descartes - Sorbonne Paris Cité, Paris, France, [3]Ambroise Paré Hospital (AP-HP), and Versailles Saint Quentin en Yvelines University, Boulogne-Billancourt, France.

Background/Purpose: Endoplasmic reticulum aminopeptidase 1 (ERAP1) exerts a central role in antigen presentation making it an attractive candidate gene for inflammatory diseases. Several polymorphisms in this gene have been associated with ankylosing spondylitis and then with the whole SpA group. A specific ERAP1 haplotype, rs17482078/rs10050860/rs30187-CCT, is strongly associated with increased risk of SpA, whereas the -TTC haplotype is associated with reduced risk. Because the linkage disequilibrium in the region is extensive, the causative polymorphism still remains to be determined. It has been suggested that rs30187, one of the polymorphisms of this haplotype may affect ERAP1 enzymatic activity. However, there is currently little data regarding the consequences of SpA-associated polymorphisms on gene expression level.

The aim of the present work was to determine whether SpA-associated ERAP1 polymorphisms might modify gene expression, protein level and enzymatic activity.

Methods: The discovery cohort included 9 HLA-B27+ SpA patients and 10 healthy controls. The replication cohort consisted of 13 SpA-discordant HLA-B27 positive sib-pairs and 18 additional independent controls (11 HLA-B27+ and 7 HLA-B27-). In both cohorts, we derived dendritic cells from monocytes (MD-DCs) and stimulated them or not with lipopolysaccharide (LPS). We also used Epstein-Barr virus (EBV) immortalized lymphoblastoid cell lines from HLA-B27+ individuals homozygous for risk, neutral or protective ERAP1 haplotype (7 patients, 1 control). In all the studied populations, we investigated the relation between ERAP1 haplotype and mRNA expression level (assessed by RT-PCR in the discovery cohort and in EBV cell lines and by microarray in the replication cohort) with a likelihood ratio test in Unphased software. Additionally, the relative protein expression of ERAP1 was measured in EBV cell lines by Western-blot and enzymatic activity was determined using a fluorogenic assay.

Results: In MD-DCs, there was a strong association between ERAP1 mRNA expression level and both rs30187 genotype and ERAP1 haplotype, at every time-point (table 1). This association was independent of the disease or HLA-B27 status. A similar trend was observed in EBV cell lines. Western-blot showed that ERAP1 protein level in cell lines harboring the risk haplotype was 2- and 1.5-fold higher than in those harboring the protective and the neutral ones, respectively. Moreover, ERAP1 enzymatic activity was higher in cell lines harboring increased risk haplotype, than in those harboring reduced risk haplotype.

Table 1. P-values of association tests between ERAP1 haplotype and mRNA expression

Stimulation time-point	Discovery	Replication	Pooled results
H0	0.04	4.56×10^{-5}	7.9×10^{-7}
H6	0.04	1.6×10^{-4}	1.2×10^{-6}
H24	0.09	9×10^{-4}	4.3×10^{-6}

Conclusion: Overall, these data provide strong evidence that SpA-associated ERAP1 polymorphisms affect the level of gene expression, protein production and aminopeptidase activity. How an increased production/activity of ERAP1 influences susceptibility to SpA remains to be determined.

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2490 WITHDRAWN

2491

Serum Levels Of Novel Noggin- and Sclerostin-Immune Complexes Are Elevated In Ankylosing Spondylitis. Florence W. Tsui[1], Hing Wo Tsui[2] and Robert D. Inman[3]. [1]Toronto Western Research Institute UHN and University of Toronto, Toronto, ON, [2]Toronto Western Research Institute UHN, Toronto, ON, [3]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON.

Background/Purpose: Unravelling the basis of joint inflammation and ankylosis represents a major challenge in ankylosing spondylitis (AS) research. As noggin (NOG) and sclerostin (SOST) have recently been associated with the disease process in mouse and human studies respectively, we explored the immune responses to these two molecules in AS.

Methods: Immune-complexes (ICs) comprised of IgG autoantibodies to NOG and SOST were detected by immunoprecipitation and Western blot analyses. Epitope-specific IgGs were measured using peptide-binding ELISAs. Serum samples were obtained from healthy controls and patients with AS, mechanical back pain (MBP) and inflammatory bowel disease (IBD) with or without concomitant AS.

Results: NOG- and SOST-IgG ICs were present in NOG-treated and untreated *ank/ank* (*progressive ankylosis*), but not in wild-type mice. Higher than normal levels of NOG- and SOST-IgG ICs are present in AS sera ($p<0.001$). We showed that a SOST peptide (SOST-S146, with homology to a bacterial glycotransferase peptide) binds to a NOG peptide (NOG-N54) which contains a N-glycosylation site. AS patients have higher levels of IgGs recognizing the NOG-N54 and SOST-S146 peptides compared to the levels in normal controls, IBD and MBP patients (1 way ANOVA: $p<0.0001$).

Conclusion: This is the first report showing IgG autoantibodies to NOG and SOST in normal individuals and higher levels of NOG- and/or SOST-IgG ICs likely contribute to neo-ossification in AS patients. These

novel findings implicate earlier diagnosis, better management of AS with comorbidities and new therapeutic approaches to modulate ankylosis in AS.

Disclosure: F. W. Tsui, PCT Patent Application NO. PCT/CA2012/000667 filed Jul 12, 2012.US Patent Application No. 61/758,940 filed Jan 31, 2013., 9; **H. W. Tsui**, None; **R. D. Inman**, PCT patent application No. PCT/CA2012/000667 filed Jul 12, 2012; US patent application No. 61/758,940 filed Jan 31, 2013., 9.

2492

Functionally Distinct ERAP1 Haplotype Combinations Distinguish Individuals With Ankylosing Spondylitis. Edward James[1], Emma Reeves[1], Alexandra Colebatch[2], Tim Elliott[1] and Christopher J. Edwards[3]. [1]University of Southampton, Southampton, United Kingdom, [2]University Hospital Southampton, Southampton, United Kingdom, [3]NIHR Wellcome Trust Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom.

Background/Purpose: The association of Ankylosing Spondylitis (AS) with HLA-B27 has been known for many years. Recent genetic linkage studies have identified polymorphisms within the aminopeptidase, *ERAP1*, associated with the disease. ERAP1 lies on the antigen processing pathway, generating peptide antigens for immune presentation by HLA. We examined the extent of polymorphism of *ERAP1* and the haplotype combinations present in affected and control individuals. In addition, we assessed the ability of the identified ERAP1 genotypes to trim peptides for presentation on MHC class I molecules.

Methods: Individual *ERAP1* haplotypes were cloned from patients with AS and control individuals recruited with informed consent and sequenced. ERAP1 trimming function was assessed by observing the ability of *Erap1* deficient cells, expressing the identified haplotype molecules, to trim and present peptide for stimulation of an antigen-specific T cell and also to reconstitute surface HLA-B27.

Results: We found that *ERAP1* from both AS cases (n=17) and controls (n=19) are highly polymorphic and comprise nine haplotypes that are predominantly made up of multiple SNPs. *ERAP1* haplotype combinations from AS cases were distinct from those found in controls. AS case ERAP1 haplotype combinations trimming capacity was significantly decreased as less than a third of the final epitope was generated from peptide precursors for presentation to T cells compared to controls. In addition, AS case ERAP1 combinations were unable to reconstitute HLA-B27 to normal levels recovering only 50% of that observed with control haplotype combinations.

Conclusion: These results demonstrate for the first time that ERAP1 from patients with AS is dysfunctional and provides strong evidence that ERAP1 variation predisposes to chronic inflammatory disease via its influence on the antigen processing pathway.

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Interleukin-17 Serum Levels Are Associated With Markers Of Systemic Inflammation In Patients With Active Ankylosing Spondylitis. Denis Poddubnyy[1], Alain Vicari[2], Hildrun Haibel[1], Jürgen Braun[3], Martin Rudwaleit[4] and Joachim Sieper[1]. [1]Charité Universitätsmedizin Berlin, Berlin, Germany, [2]EMD Serono, Geneva, Switzerland, [3]Rheumazentrum Ruhrgebiet, Herne, Germany, [4]Endokrinologikum Berlin, Berlin, Germany.

Background/Purpose: There is accumulating evidence that the Th17-signaling axis, particularly interleukin-17 (IL-17), plays an important role in the pathogenesis of ankylosing spondylitis (AS). Furthermore, biologics targeting IL-17 have shown clinical efficacy inactive AS. The purpose of the current study was to investigate the association of IL-17A and IL-17F serum levels with clinical, laboratory and radiographic parameters in patients with AS.

Methods: 50 anti-TNF-naïve patients with AS, as defined by the modified New York criteria, with symptom duration of ≤10 years and clinically active disease (BASDAI ≥4), were selected from German Spondyloarthritis Inception Cohort (GESPIC) for this study. Available spinal radiographs (baseline and after 2 years, n=28) were scored according to the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), by two independent blinded readers. Baseline serum levels of IL-17A and IL-17F were measured by the ultra-sensitive Erenna Immunoassay (Singulex, Almeda, CA).

Results: The mean (±SD) serum levels of IL-17A and IL-17F in the studied population were 0.87±1.48 pg/ml and 7.36±20.8 pg/ml, respectively. There was a significant correlation of serum cytokine levels with each other: Spearman's rho = 0.490, $p<0.001$. Serum level of IL-17A showed a significant correlation with the serum level of C-reactive protein: rho = 0.327, p = 0.020, while IL-17F correlated with erythrocyte sedimentation rate: rho = 0.331, p = 0.026. Also, there was a negative correlation of IL-17A with patients' age: −0.318, p = 0.025. Serum IL-17A level was significantly higher in HLA-B27 positive patients (n=39): 1.01±1.65 pg/ml vs. 0.36±0.24 pg/ml in negative ones, p = 0.021. Similar trend was observed also for IL-17F: 8.29±23.43 pg/ml vs. 4.08±3.80 pg/ml, respectively, p=0.29. A trend for a higher IL-17A serum level was found in patients with peripheral arthritis (n=7): 1.45±1.74 pg/ml vs. 0.79±1.44 pg/ml in patients without arthritis, p=0.37. No correlation between IL-17 serum levels and either symptom duration, sex, presence of enthesitis, levels of BASDAI and BASFI, smoking status, or presence and progression of structural damage in the spine was found.

Conclusion: IL-17 serum levels correlate with markers of systemic inflammation in patients with clinically active AS. IL-17A is significantly elevated in HLA-B27 positive patients.

Disclosure: D. Poddubnyy, None; **A. Vicari**, EMD Serono, 3; **H. Haibel**, None; **J. Braun**, None; **M. Rudwaleit**, None; **J. Sieper**, None.

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Ankylosing Spondylitis Associated Endoplasmic Reticulum Aminopaptidase 1 Variants In Antigen Presentaing Cells Affect HLA-B27 Free Heavy Chain Expression and Binding To NK-Cell Receptors. Nigil Haroon and Zhenbo Zhang. Toronto Western Research Institute, Toronto, ON.

Background/Purpose: ERAP1 and HLA-B27 are strongly associated with ankylosing spondylitis (AS). Using well-controlled tissue culture systems, we studied the effects of AS-associated ERAP1 variants on HLA-B27 expression and interaction with KIR receptors

Methods: C1R cells stably expressing HLA-B27 were transfected with ERAP1shRNA to silence the endogenous ERAP1 expression ($C1R^{ERAP1sh}$). The stable cells were confirmed by flow cytometry with GFP and western blot for ERAP1. We then transfected either the common variant ERAP1 ($ERAP1^{WT}$) or one of the two AS-associated ERAP1 variants, K528R or Q730E into the $C1R^{ERAP1sh}$cells. Lentivirus expression vector alone was used as control and the ERAP1 variants were tracked with the HA-tag.

The stable cell lines were tested by flow cytometry for intact HLA-B27 (ME1 antibody), MHC-I free heavy chain (FHC) expression (HC-10), MARB4 staining and binding to KIR-3DL1 and KIR-3DL2-Fc. Anti-Mouse IgG-PE was used as secondary antibody.

Results: Following antibiotic selection, nearly all cells were GFP positive indicating successful stable ERAP1 shRNA expression. We achieved more than 80% suppression of ERAP1. After introduction of ERAP1 into $C1R^{ERAP1sh}$ cells, Western Blot with anti-HA antibodies showed similar expression of $ERAP1^{WT}$. K528R and Q730E variants respectively.

There was significant increase in surface FHC, intracellular FHC and MARB4 staining with ERAP1 shRNA and subsequent normalization of levels with introduction of $ERAP1^{WT}$. C1R cells with AS-associated ERAP1 variants failed to completely normalize these levels.

KIR3DL1 and KIR3DL2 binding to target cells were assessed using the Fc-chimeric molecules of these receptors. As expected, KIR-3DL1 and KIR-3DL2 binding was increased in $C1R^{ERAP1sh}$ cells and C1R cells with ERAP1 variants known to have less peptide trimming function compared to C1R-$ERAP1^{WT}$ Cells. The percentage of cells with KIR3DL1-Fc binding increased from 40.1% of cells to 64.9% with ERAP1 suppression. KIR-3DL1-Fc binding dropped to 55.9% with introduction of $ERAP1^{WT}$but was higher at 70.4% and 57.3% in C1R cells with K528R and Q730E ERAP1 variants respectively.

Conclusion: Cells with stable ERAP1 knock down had higher intracellular FHC, surface FHC expression and MARB4 staining as well as higher KIR-3DL1 and KIR-3DL2 receptor binding. These changes were corrected with the introduction of the common ERAP1 variant but not with AS-associated K528R or Q730E variants. Decreased ERAP1 activity could be protective because higher surface FHC can interact with inhibitory receptors on NK cells. On the other hand, higher intracellular FHC seen with decreased ERAP1 activity could be pathogenic by triggering the unfolded protein response. Thus the effect of ERAP1 variants on AS pathogenesis may vary depending on the relative balance of these effects.

Disclosure: N. Haroon, None; **Z. Zhang**, None.

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Ankylosing Spondylitis Protective Endoplasmic Reticulum Aminopeptidase 1 Variants Lead To Decreased Natural Killer Cell Conjugation and Activation. Hasan Abdullah[1], Zhenbo Zhang[2], Robert Inman[3] and Nigil Haroon[4]. [1]University of Toronto, Toronto, ON, [2]Toronto Western Research Institute, Toronto, ON, [3]University of Toronto and Toronto Western Hospital, Toronto, ON, [4]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON.

Background/Purpose: Ankylosing Spondylitis (AS) is an inflammatory arthritis affecting the axial and peripheral joints. Human Leukocyte Antigen (HLA)-B27 and Endoplasmic Reticulum Aminopeptidase (ERAP) 1 genes are strongly associated with AS. An AS pathogenesis mechanism proposes that variant forms of HLA-B27 including B27 free heavy chains (FHC) can be recognized by Natural Killer (NK) cells through receptors like KIR3DL1and KIR3DL2, and could be pathogenic. ERAP1 variants K528R and Q730E with decreased function are protective in AS. Decreased function results in higher HLA-B27 (FHC) expression and can bind to the inhibitory receptors KIR3DL1 and KIR3DL2 altering NK cell activation.

Methods: C1R cells stably expressing HLA-B27 were transfected with ERAP1shRNA to silence the endogenous ERAP1 expression. These cells were transfected with either the common or one of the rare AS associated ERAP1 variants K528R/Q730E. The target cell line was co-cultured with both a KIR3DL1 expressing as well as a non-KIR3DL1 expressing YTS NK cell line for 9 hours. Supernatants were analyzed for 64 cytokines and chemokines using a bead based multiplex assay. Separately, co-cultured cells were stained for intracellular Macrophage Inflammatory Protein (MIP)-1α. NK cells and target cells were each labeled with separate surface staining fluorescent dyes before co-culture. Co-cultured cells were analyzed by flow cytometry at baseline and after 5 and 10 minutes of co-incubation, for NK cell-target cell conjugate formation. Activation of NK cells was also analyzed by flow cytometry after staining for the degranulation marker CD107a.

Results: Duplicate results of the multiplexing assay show MIP-1α is reduced when C1R-B2705 + wild type ERAP1, C1RB2705 + ERAP1 K528R, and C1RB2705 + ERAP1 Q730E cells were co-cultured with 3DL1 NK cells in comparison to YTS NK cells (60%, 45% and 40% reduction respectively). Conjugate formation with the passage of co-incubation time is also reduced in the variant co-cultures as a result of KIR3DL1 interaction (K528R: 27%, Q730E: 18% reduction). Intracellular staining for NK cell MIP-1α production in the above co-cultures revealed a corresponding inhibition of MIP-1α (K528R: 4.6%, Q730E: 28% reduction). YTS-3DL1 NK cell CD107a expression trends lower in the ERAP1 variants in comparison to wild type ERAP1.

Conclusion: Our results are a logical extension of our previous results that showed protective ERAP1 variants lead to increased surface HLA-B27 FHC in monocytes. Here we show that the protective ERAP1 variants, when expressed in C1R cells, result in decreased conjugate formation with KIR3DL1 expressing NK cells, in comparison to wild type ERAP1. A corresponding decrease in MIP-1α chemokine expression and NK cell activation was observed. Reduced function ERAP1 variants may be protective in AS because increased surface HLA-B27 FHC can interact with inhibitory NK cell receptors like KIR3DL1 and cause reduced conjugate formation and NK cell suppression.

Disclosure: H. Abdullah, None; **Z. Zhang**, None; **R. Inman**, None; **N. Haroon**, None.

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HLA-B27 Influence On The Gut Microbiome. Robert D. Inman[1], Aifeng Lin[2], Phillip Sherman[3] and Lee Pinnell[3]. [1]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON, [2]Toronto Western Research Institute and University Health Network, Toronto, ON, [3]Hospital for Sick Children, Toronto, ON.

Background/Purpose: The interrelationship between the gut microbiome and spondyloarthritis (SpA) has been highlighted by recent findings of (i) Subclinical bowel inflammation in SpA (ii) Antimicrobial serology in AS which is comparable to inflammatory bowel disease (IBD) (iii) The association of HLA-B27 with chronicity in post-Salmonella reactive arthritis. This has raised the important unanswered question whether the HLA-B27 may influence disease susceptibility by an influencing the gut microbiome.

Methods: MHC-I transgenic mice were generated on a background of deleted endogenous MHC-I (DKO) and are designated by the transgenic allele: B27tg, B7tg, and A2tg, and compared with C57BL6 (WT). Mice were challenged with *Salmonella typhimurium* (5×10^7 organisms) by gavage and followed to establish differential host responses. Selected mice were euthanized at 24, 48 and 72 hr after infection. Colons were collected for H&E staining. Spleen, liver and mesenteric lymph nodes were dissected and cytokine gene expression determined by real-time PCR. At baseline and at selected time points, colonic contents were collected for analysis of the gut microbioata with primer sets specific for universal bacteria, g-proteobacteria, β-proteobacteria, bacteroidetes, firmicutes, and actinobacteria.

Results: Survival curves after oral Salmonella challenge indicated that the B27tg mouse demonstrated improved survival compared with B7tg and A2tg mice (Fig. 1) (**No figure available**). Review of colon pathology, however, revealed no significant differences in the degree of colonic inflammation. Cytokine profiling in mesenteric lymph nodes at 72hr post-challenge showed that B7tg mice expressed less IFN-g and IL-10 and B27 expressed less Foxp3 than respective tg controls. Analysis of the gut microbioal composition at baseline *prior to* infectious challenge revealed differences related to the MHC-I profile of the mouse: colonization by b-Proteobacteria was enhanced in the B27tg mouse compared with B7tg and A2tg as well as with the DKO and WT control mice (Fig. 2) (**No figure available**).

Conclusion: Class I MHC expression influences survival and host immune response to oral *S. typhimurium* challenge in an allele-specific manner. The endogenous gut microbial profile was distinctively different in B7tg mice, suggesting that the HLA-B27 status directly influences the composition of the gut microbiome. This raises the possibility that the clinical interface between SpA and IBD could be mediated by an interplay between host MHC and the gut microflora.

Disclosure: R. D. Inman, None; **A. Lin**, None; **P. Sherman**, None; **L. Pinnell**, None.

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Evidence Of a Microbial Signature In The Intestinal Microbiome In Ankylosing Spondylitis. Mary-Ellen Costello[1], Francesco Ciccia[2], Brooke Gardiner[1], Mhairi Marshall[1], Dana Willner[3], Tony Kenna[1], Giovanni Triolo[2] and Matthew A. Brown[1]. [1]University of Queensland Diamantina Institute, Brisbane, Australia, [2]Rheumatology Unit, University of Palermo, Palermo, Italy, [3]Australian Centre for Ecogenomics, School of Chemistry and Molecular Biosciences, University of Queensland, Brisbane, Australia.

Background/Purpose: Ankylosing spondylitis (AS) occurs in genetically predisposed individuals exposed to an unknown but likely ubiquitous environmental trigger. In both AS and Crohn's disease (CD) interplay between host genetic factors and largely undefined environmental factors, most likely involving the gut microbiome, are thought to drive the disease. To date, no comprehensive characterization of intestinal microbiota in AS patients has been performed. Our objective was to characterize the intestinal microbiome of newly diagnosed TNF-antagonist naïve AS cases using next generation sequencing and to determine if the AS gut carries a distinct microbial signature. To explore the effect of host genotype on microbiome composition we also characterized the intestinal microbiome in stools of mice with knockouts of two major AS-susceptibility genes, *ERAP* and *IL23R*, in comparison with wild-type controls.

Methods: Terminal ileal (TI) biopsies from patients with AS, CD and healthy controls (HC) and mouse faecal samples were profiled using culture-independent high-throughput next generation sequencing of the 16S rRNA gene on an Illumina MiSeq.

Results: Our results show the TI microbial communities of AS patients differ significantly and are more diverse than the intestinal microbial communities from those with CD and HC. The AS microbial community is characterized by higher abundance of five families of bacteria, *Lachnospiraceae, Veillonellaceae, Prevotellaceae, Ruminococcusaceae* and *Porphyromonadaceae*. Increased abundances of the families *Lachnospiraceae* and *Prevotellaceae* have been strongly associated with colitis and CD. TI microbial composition was found to correlate with disease status ($P = < 0.001$) and greater differences were observed between disease groups than within disease groups. In mice, absence of either *ERAP* or *IL23R* alone was sufficient to significantly alter the microbiome. Absence of *ERAP* and *IL23R* caused an increase a member of the *Rikenellaceae* family bacteria, *Rikenella Alistipes spp.*, compared to wild type controls ($P = 0.001$). *Rikenella Alistipes spp.* is an indicator species found to be driving the AS TI microbiome signature ($P = 0.001$). In the *IL23R* $^{-/-}$ mice, there was an increase in the genus Parabacteroides ($P = 0.023$) (*Porphyromonadaceae* family). No clustering of mouse stool microbiome was noted in relationship to the cage mice were raised in, confirming that these differences are driven by the mouse genotype and not local environmental effects. In our AS cohort we also see an increase the same genus of bacteria.

Conclusion: AS case microbiomes are different from those of CD and HC, and knockout mouse studies show that AS-associated genes shape the intestinal microbiome. This is consistent with models for AS in which genetic effects lead to changes in the gut microbiome which in turn cause immunological effects which lead to AS.

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ERAP2 Functional Knockout In Humans Does Not Alter ER Stress Or Evidence Of HLA-B27 Misfolding In Ankylosing Spondylitis. Philip Robinson[1], Yang Wang[2], Eugene Lau[2], Patricia Keith[2], Tony Kenna[2] and Matthew A. Brown[2]. [1]University of Queensland Diamantina Insititute, Brisbane, Australia, [2]University of Queensland Diamantina Institute, Brisbane, Australia.

Background/Purpose: SNPs in *ERAP2* are strongly associated with ankylosing spondylitis (AS). One associated SNP is rs2248374 which changes the strength of the exon 10 donor splice site, with the G allele resulting in a truncated protein which is degraded by nonsense-mediated decay, resulting in a complete absence of ERAP2. This allele has a frequency of approximately 0.5 in the European descendent population, therefore 25% of the population (those who are GG homozygous) are natural ERAP2 knockouts. We investigated the effect of this associated variant on HLA class I allele presentation, HLA class I heavy chain presentation, ER stress markers and pro-inflammatory cytokine gene transcription in AS.

Methods: AS patients and healthy controls with either AA or GG homozygous status for rs2248374 were recruited. Ficoll gradient separated PBMCs were analysed with flow cytometry. Anti-CD14-Pacific Blue, anti-CD19-ECD, anti-HLA-A, B, C-PECy7, anti-V alpha7.2-PE, anti-CD161-PerCy5.5, anti-HC10 and anti-HLA-B27 were used to analyse the PBMCs. Cells were analysed as monocytes, B cells and mucosal associated invariant T (MAIT) cells. Expression levels of endoplasmic reticulum (ER) stress markers (GRP78 and CHOP) and pro-inflammatory genes (TNF, IL-6, IL-17 and IL-22) were assessed by RT-PCR in unsorted PBMCs, normalised to RPL32 housekeeping gene-expression.

Results: 7 AS cases and 8 controls with GG genotype, and 8 AS cases and 8 controls with the AA genotype (all HLA-B27 positive) were analysed. rtPCR patient numbers were: B27+*ERAP2* AA = 8; B27+ *ERAP2* GG = 12; B27-*ERAP2* AA = 16; B27-*ERAP2* GG = 15. Comparing rs2248374 AA and GG genotype carriers, there were no significant differences in HLA Class I expression or free HLA Class I heavy chain levels either intracellularly or extracellularly, ER stress as measured by expression of markers GRP78 and CHOP, or pro-inflammatory gene expression. Also, no difference in ER stress markers or free HLA Class I heavy chain levels was noted between AS cases and healthy controls in any cell type studied.

Conclusion: The study demonstrates that there are not large differences in surface expression of class I antigens or heavy chains, ER stress or pro-inflammatory cytokine gene expression between the two genotypes in AS cases. This suggests that *ERAP2* loss of function variants which are protective against AS do not operate by effects on ER stress or HLA Class I misfolding. Further, the absence of a difference between cases and controls in measures of either free HLA Class I heavy chain levels or ER stress markers is not consistent with HLA-B27 operating to cause AS through either misfolding or ER stress induction, at least in the cell types studied.

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Analysis Of Inflammatory Markers Within Facet Joints Of Patients Within Ankylosing Spondylitis. Uta Syrbe[1], Janine Bleil[2], Rene Maier[3], Heiner Appel[1] and Joachim Sieper[4]. [1]Charité Medical University, Campus Benjamin Franklin, Berlin, Germany, [2]Charité, Berlin, Germany, [3]Charite, Berlin, Germany, [4]Charitè Campus Benjamin Franklin, Berlin, Germany.

Background/Purpose: Inflammation within sacroiliac joints and within the spine is a hallmark of ankylosing spondylitis (AS). Apart from nonsteroidal anti-rheumatic drug (NSAID) treatment, inhibition of TNF, but not of IL-6, has been proven successful in the treatment of signs and symptoms of AS. In addition to its direct inflammatory role, some cytokines might particularly affect bone metabolism. For instance, IL-23 can induce bone formation involving IL-22 as a secondary mediator.

To determine the potential involvement of several inflammatory mediators such as cytokines like IL-23, IL-22, IL-12, IL-6, IL-10 and prostaglandins in the inflammation-driven joint remodeling process in AS, we determined their expression within the cartilage, the subchondral bone and within entheses in zygapophyseal joints of patients with ankylosing spondylitis. Furthermore, we determined their expression within the subchondral bone marrow and within fibrous tissue, which we find in joints undergoing joint remodeling.

Methods: Expression of IL-6, IL-10, IL-12, IL-22, IL-23 as well as of PGE2 and its receptor EP2 were determined by immunohistochemistry in zygapophyseal joints of patients with ankylosing spondylitis (n=13 patients with AS), and in 9 patients with osteoarthritis (OA) and in zygapophysel joints of 10 autopsy controls (CO). AS patients joints were obtained from patients undergoing polysegmental correction surgery because of hyperkyphosis.

Results: The number of IL-6-expressing cells within the cartilage and bone marrow were reduced in AS joints compared to controls ($p<0.005$). The number of IL-10+ cells was reduced within cartilage and the entheses in AS joints ($p<0.005$ and $p<0.01$), but increased in osteocytes found within the subchondral bone plate ($p<0.01$). Numbers of IL-12+ cells were not significantly different between AS and the control groups. IL-22 was reduced within the cartilage and entheses in AS joints compared to autopsy controls ($p<0.001$ and $p<0.01$). Numbers of IL-23+ cells were reduced at enthesial sites of AS joints ($p<0.05$) compared to autopsy controls but not within cartilage or subchondral bone. Prostaglandin E2 expression and expression of the receptor EP2 was high within cartilage in general and particularly high within the fibrous tissue (i.e. about 90% of cells were positive within subchondral fibrous tissue of AS joints), which is not present in healthy joints obtained from autopsy controls.

Conclusion: In contrast to IL-23 and IL-17 (Appel et al. ARD, 2011, 2013), which are highly expressed within the subchondral bone marrow of AS joints we found no increase in IL-6 expression.

Within cartilage and/or entheses we rather find a reduction in IL-10, IL-22 and IL-23 expression which might reflect the disturbed homeostasis of the cartilage in the AS joints undergoing joint remodeling, i.e. intraarticular ankylosis. The high prostaglandin E2 expression and EP2 expression within the fibrous tissue might indicate that prostaglandins are involved in the putative pathological role of this tissue promoting joints remodeling. NSAIDs, which seem to retard radiographic spinal progression might block the pathogenic activity of this subchondral fibrous tissue.

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Mast Cells Are a Major Source Of IL-17 In Synovium and Extra-Articular Tissues In Spondyloarthritis Related Diseases. T. Noordenbos[1], I. Gofita[1], M. Alsina[2], E.W.M. Vogels[3], A. A. te Velde[3], J. D. Cañete[4], D. Baeten[5] and N. Yeremenko[1]. [1]Department of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, [2]Department of Dermatology, Hospital Clinic de Barcelona, Barcelona, Spain, [3]Tytgat Institute for Liver and Intestinal Research, Academic Medical Centre/University of Amsterdam, the Netherlands, Amsterdam, Netherlands, [4]Hospital Clinic, Barcelona, Spain, [5]Department of Clinical Immunology and Rheumatology Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands.

Background/Purpose: IL-17 plays a key role in the pathogenesis of spondyloarthritis (SpA) as demonstrated by a recent proof-of-concept trial with the anti-IL17A mAb secukinumab. The cellular source of IL-17A in SpA remains incompletely defined and may vary between different target tissues of the disease.

As we previously demonstrated strong colocalization of IL-17 and mast cells in SpA synovitis, we aimed here to prove that synovial mast cells are an important source of IL-17 in synovitis and to explore whether this was also the case in other target tissues such as psoriasis skin and IBD-affected gut mucosa.

Methods: Mast cells were isolated by *fluorescence-activated cell sorting (FACS)* of *FceR+/ c-Kit+ cells* from synovial tissue (n=5) and *tonsil (n=6)* as the most readily available source of human mast cells. IL-17 expression was assessed directly ex vivo by Western blot or after stimulation with *PMA* and *ionomycin by quantitative real-time PCR*

(qPCR). The frequency of IL-17-positive mast cells was analyzed in the *paraffin-embedded* biopsies from *lesional psoriatic (n=10)* or normal human *skin (n=10),* colon and ileum from *Crohn's disease (n=7), ulcerative colitis (n=6) and control (n=3) by immunofluorescence (IF).*

Results: Because previous studies described mast cells and neutrophils as sources of IL-17A in the synovial tissue were performed with *polyclonal goat anti-human IL-17A antibody,* the question arose whether these immunostainings really detect intracellular IL-17A and not a cross-reactive protein. Western blot analysis of freshly isolated mast cells using both mouse monoclonal and goat polyclonal anti-human IL-17A antibodies revealed expression of IL-17A protein in synovial and tonsil mast cells. In order to investigate if mast cells do not only contain but also produce IL-17A, we accessed IL-17A mRNA levels in directly ex vivo sorted mast cells and after stimulation with *PMA* and *ionomycin. IL-17A mRNA was undetectable in unstimulated mast cells, however* we were able to detect IL-17A mRNA in mast cells stimulated 12 h with *PMA* and *ionomycin. As these data confirmed that mast cells can express and produce IL-17A,* we next investigated whether mast cells were also a major source of IL-17A in other tissues which can be affected by SpA. Double immunofluorescent staining of *psoriatic lesions* identified that IL-17 in the skin is predominantly produced by mast cells (median 94%; interquartile range 86–100%). Analysis of intestine biopsies from IBD patients revealed that the major source of IL-17 is different between lamina propria and submucosal layers. Similar to synovium and skin, mast cells were found to express IL-17 within the submucosa (median 75%; interquartile range 60–90%). In contrast, IL-17 was expressed by CD15+ polymorphonuclear cells (median 80%; interquartile range 60–90%) rather than mast cells (median 23%; interquartile range 6–30%) in the lamina propria.

Conclusion: Our data confirmed expression of IL17 protein by synovial and tonsil mast cells. Our results indicate that mast cells are a major source of IL-17 not only in SpA synovitis but also in psoriasis skin and IBD gut.

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Validation Of Gene Expression Biomarkers Of Psoriatic Arthritis. Fatima Abji[1], Remy Pollock[1], Fawnda Pellett[1], Kun Liang[2], Vinod Chandran[1] and Dafna Gladman[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Waterloo, Waterloo, ON.

Background/Purpose: Psoriatic arthritis (PsA) is a seronegative immune mediated arthritis that develops in about a third of patients with cutaneous psoriasis (PsC). The cellular pathways which distinguish the skin and joint manifestations in PsA are poorly understood. Through microarray and qPCR array studies, we have identified several genes which are dysregulated in PsA. The goal of this study was to validate the expression of these genes and associated signaling pathways in a large cohort of patients.

Methods: Total RNA was isolated from peripheral blood of PsA patients satisfying CASPAR criteria and PsC patients. All patients were Caucasian and were not receiving treatment with biological agents. Quantification of mRNA expression of 49 genes was completed using the Nanostring nCounter® system (NanoString Technologies). Fold change differences between PsA and PsC patients were determined from normalized results. Significance was determined by performing multivariate logistic regression analyses and controlling for clinical variables (FDR<0.05).

Results: Gene expression was computed in 48 PsA patients (mean age 46 years, 52% males, psoriasis duration 17 years, PASI 7.5, active joint count 6.3) and 48 PsC patients (mean age 46 years, 50% males, psoriasis duration 17 years, PASI 4.9). Twenty-nine genes were found to be significantly altered (FDR < 0.05) in PsA patients compared to PsC patients (Table 1), including several genes linking the innate immune system and chromatin modification. Downstream signaling molecules in the toll like receptor pathway, such as CXCL10, EZR, MyD88, and CD14, were upregulated in PsA. SMARCA4 is a component of the BAF complex linked to chromatin modification upon TLR4 activation which was also over-expressed in our PsA cohort. Out of these genes, 21 genes were upregulated and 8 genes were downregulated. No significant differences in clinical covariates for any gene were found. Cluster analysis revealed 19 PsA patients that grouped together.

Table 1. Significantly altered genes (FDR<0.05) in PsA patients compared to PsC

Gene	Description	Fold Change	OR (95% CI)	FDR
TLR7	Toll-like receptor 7	1.62	4.03 (1.82, 8.90)	0.0008
CXCL10 (IP10)	Chemokine (C-X-C motif) ligand 10	1.45	1.46 (0.95, 2.24)	0.0420
PARP1	Poly (ADP-ribose) polymerase 1	1.41	2.91 (1.44, 5.88)	0.0028
XRCC6	X-ray repair complementing defective repair in Chinese hamster cells 6	1.36	5.23 (2.37, 11.58)	0.0004
SMARCA4	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4	1.35	4.28 (2.03, 9.01)	0.0005
EZR	Ezrin	1.35	2.01 (1.07, 3.77)	0.0196
SYNCRIP	Synaptotagmin binding, cytoplasmic RNA interacting protein	1.34	4.10 (1.87, 9.03)	0.0007
EHMT2	Euchromatic histone-lysine N-methyltransferase 2	1.31	4.12 (1.95, 8.95)	0.0006
TICAM1 (TRIF)	Toll-like receptor adaptor molecule 1	1.31	3.36 (1.72, 6.53)	0.0006
SETD1A	SET domain containing 1A	1.31	2.28 (1.27, 4.09)	0.0049
RP11-94I2.2	NBPF11 neuroblastoma breakpoint family, member 11	1.30	2.33 (1.33, 4.10)	0.0028
IFNA1	Interferon, alpha 1	1.29	1.77 (1.02, 3.09)	0.0261
CD14	CD14 molecule	1.27	2.16 (1.21, 3.86)	0.0072
PRMT6	Protein arginine methyltransferase 6	1.24	2.13 (1.15, 3.96)	0.0120
TRAM1	Translocation associated membrane protein 1	1.22	3.23 (1.60, 6.51)	0.0011
PUM1	Pumilio homolog 1 Drosophila)	1.20	3.28 (1.66, 6.50)	0.0008
MSN	Moesin	1.16	2.02 (1.06, 3.85)	0.0201
IL15	Interleukin 15	1.16	1.81 (1.01, 3.26)	0.0278
SMYD3	SET and MYND domain containing 3	1.15	1.57 (0.96, 2.57)	0.0352
HAT1	Histone acetyltransferase 1	1.12	1.99 (1.08, 3.67)	0.0196
MyD88	Myeloid differentiation primary response 88	1.07	1.83 (0.95, 3.50)	0.0352
CXCL1	Chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)	0.61	0.27 (0.13, 0.54)	0.0006
LY96 (MD2)	Lymphocyte antigen 96	0.69	0.23 (0.11, 0.48)	0.0005
BCL2A1	BCL2-related protein A1	0.73	0.24 (0.11, 0.52)	0.0006
CD58	CD58 molecule	0.77	0.24 (0.12, 0.48)	0.0004
CLEC2B	C-type lectin domain family 2, member B	0.79	0.40 (0.22, 0.74)	0.0028
N2N	NOTCH2NL notch 2 N-terminal like	0.80	0.35 (0.19, 0.64)	0.0009
TLR2	Toll-like receptor 2	0.88	0.59 (0.33, 1.05)	0.0352
SETD2	SET domain containing 2	0.92	0.62 (0.38, 1.01)	0.0317

Conclusion: We validated genes involved in the regulation and activation of signaling pathways of the innate immune system that were dysregulated in PsA compared to PsC patients. Future studies will focus on understanding how expression of these genes is linked to clinical variables and progression of PsA, and distinguish whether these genes can serve as biomarkers of PsA susceptibility in patients with PsC.

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2502

Contributions Of Skin and Joint Manifestations To The Parent-Of-Origin Effect In Psoriatic Disease. Remy Pollock[1], Arane Thavaneswaran[1], Vinod Chandran[1], Art Petronis[2], Al Amin P. Rahman[3] and Dafna Gladman[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]Centre for Addiction and Mental Health, Toronto, ON, [3]Memorial University, St Johns, NE.

Background/Purpose: Excessive paternal transmission has been previously documented in psoriatic disease. Our objective is to delineate the differential contributions of skin and joint manifestations to this 'parent-of-origin' effect, and determine whether the effect is differentially associated with psoriasis or PsA.

Methods: Parental history of PsA and/or psoriasis without arthritis was ascertained by questionnaire or during clinical assessment of PsA and psoriasis patients from two large cohorts. Data was combined with previously-published data. Proportions of maternal and paternal transmissions were compared using a normal approximation to the binomial distribution. Parental and patient phenotypes were resolved where possible into psoriasis alone or PsA and compared by chi-square test and logistic regression. Patients with paternally and maternally-transmitted disease were compared with respect to demographic and clinical characteristics as well as carriage of risk alleles at *HLA-B*, -C, *-DR*, *-DQ*, and *MICA*, using Student's t-test or chi-square test.

Results: We found a preponderance of patients with affected fathers compared to affected mothers in the combined analysis (397 [56%] versus 313 [44%], p=0.002). There was a greater excess of paternal transmissions in

patients with a parental history of psoriasis (223 [58%] versus 162 [42%], p=0.002) compared to patients with a parental history of PsA (75 [54%] versus 65 [46%], p=0.45), but no difference in frequencies between these patients (p=0.37). Although the parent-of-origin effect also appeared to be stronger in PsA than in psoriasis patients, paternal history of psoriasis could not predict PsA. PsA patients with paternally-transmitted psoriasis had fewer damaged joints than patients with maternally-transmitted psoriasis (mean damaged joint count 6.3 compared to 12.9, p=0.04), and PsA patients with paternally-transmitted PsA had an earlier age of PsA diagnosis than patients with maternally-transmitted PsA (mean age 32.8 compared to 37.5 years, p=0.05). In one particular cohort, PsA patients with paternally-transmitted psoriasis had lower carriage rates of *HLA-B*38* (p=0.006), *HLA-C*06* (p=0.03), and *MICA-129*Met (p=0.01).

Conclusion: We have provided additional evidence of a parent-of-origin effect in psoriatic disease, which may be driven by paternal transmission of psoriasis without arthritis and may be characterized by an earlier-onset yet milder disease that is not associated with several known risk alleles in the MHC.

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2503

IL-17+ CD8+ T Cells Are Enriched In The Joints Of Patients With Psoriatic Arthritis and Correlate With Markers Of Disease Activity and Joint Damage Progression. Bina Menon[1], Nicola J. Gullick[2], Hayley G. Evans[3], Gina J. Walter[3], Megha Rajasekhar[3], Toby Garrood[1], Leonie S. Taams[3] and Bruce W. Kirkham[1]. [1]Guy's and St. Thomas' Foundation Hospital NHS Trust, London, United Kingdom, [2]King's College Hospital Foundation NHS Trust, London, United Kingdom, [3]King's College London, London, United Kingdom.

Background/Purpose: Psoriatic arthritis (PsA) and rheumatoid arthritis (RA) have clear differences in clinical, radiological and genetic features, suggesting that the immunopathology of the conditions may also differ. IL-17/Th17 cells are thought to contribute to inflammatory arthritis as well as psoriasis. Given the strong association between MHC class I and PsA, we hypothesized that IL-17+ CD8+ T cells are enriched in PsA and correlate with disease activity and synovitis.

Methods: Mononuclear cells from synovial fluid (SF) and peripheral blood (PB) compartments from 21 patients with PsA, 14 patients with RA and 14 healthy controls (PB only) were isolated and stimulated for three hours in vitro with PMA and ionomycin in the presence of GolgiStop. CD3+ T cells were investigated for expression of IL-17A by flow cytometry. Clinical measures and Power Doppler Ultrasound (PDUS) of the affected joint were assessed at the time of joint aspiration. PsA subjects were assessed by a blinded observer for erosive changes in hand and feet radiographs.

Results: Both patients with PsA and RA had a significant increase in IL-17+ CD4+ T cells in the synovial fluid compared to their peripheral blood. Notably, we also found a significant increase in IL-17 expressing cells in the CD4- compartment in SF from patients with PsA (SF vs. PB, median (IQR)%, 1.10 (0.46–2.29) vs. 0.18 (0.09–0.32), p=0.0002)) whilst this population was virtually absent in SF from patients with RA (p=0.83). The IL-17+ CD4- cells consisted predominantly of CD8+ T cells. No significant differences were found between IL-17+ T cell frequencies from the blood in patients with PsA vs. HC. SF IL-17+ CD4-(CD8+) T cells correlated significantly (Spearman's r) with CRP (r= 0.57, p=0.005), ESR (r=0.62, p=0.002) as well as PDUS score of the affected joint (n=16, r=0.49, p=0.05), whilst SF IL-17+ CD4+ T cell frequency correlated only with ESR (r=0.42, p=0.05). Interestingly, patients with erosive disease (n=13) had elevated levels of IL-17+ CD3+CD4-(CD8+) cell frequencies in SF vs. non erosive subjects (n=8) (1.91 (1.03–4.94) vs. 0.32 (0.11–1.12), p<0.05, One-way ANOVA, post test: Dunn's). IL-17+ CD8+ T cells expressed low levels of perforin, granzyme B and CD107a in PB and SF (n=3) when compared to IFNγ+ CD8+ T cells, indicating that these cells may have a different effector function than cytotoxic CD8+ T cells.

Conclusion: This is the first report documenting elevated IL-17+ CD3+CD4-(CD8+) cell frequencies in the PsA SF compartment with strong correlates with clinical and imaging measures of disease activity. We propose that IL-17+ CD8+ T cells may be a hitherto unrecognised population in PsA that may contribute to the immunopathology of this disease.

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2504

Male Children With Higher SLE Disease Activity In An US Cohort. Lakshmi N. Moorthy[1], Elizabeth Roy[2], Margaret Peterson[3], Afton L. Hassett[4], Alexa B. Adams[3], Laura V. Barinstein[5], Elizabeth C. Chalom[6], Karen Onel[7], Linda Ray[8], Jorge Lopez-Benitez[9], Kathleen A. Haines[10], Philip Hashkes[11], Daniel J. Kingsbury[12], Victoria Cartwright[12], Nora G. Singer[13], Ingrid Tomanova-Soltys[14], Andreas Reiff[15], Sandy D. Hong[16] and Thomas J. A. Lehman[3]. [1]Robert Wood Johnson Medical School-UMDNJ, New Brunswick, NJ, [2]RWJMS-UMDNJ, New Brunswick, NJ, [3]Hospital for Special Surgery, New York, NY, [4]University of Michigan, Ann Arbor, MI, [5]Mount Sinai Med Ctr, New York, NY, [6]St. Barnabas Medical Center, Livingston, NJ, [7]PRCSG, Cincinnati, OH, [8]University of Mississippi Medical Center, Jackson, MS, [9]Pediatric Rheumatology Program Centro Medico La Costa, Asuncion, Paraguay, [10]Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [11]Shaare Zedek Medical Center, Jerusalem, Israel, [12]Legacy Emanuel Children's Hospital, Portland, OR, [13]Director, Division of Rheumatology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH, [14]Winthrop University Hospital, Mineola, NY, [15]Children's Hospital Los Angeles, Los Angeles, CA, [16]U of Iowa Children's Hosp, Iowa City, IA.

Background/Purpose: Although systemic lupus erythematosus (SLE) is more common in females, males tend to have more severe disease. We compared age at SLE diagnosis, duration, activity, damage, and medication use in young males to that in young females in an expanded pediatric cohort from the US.

Methods: We examined age at SLE onset, and duration of pediatric SLE patients (≤18years) from a cross-sectional multicenter cohort. We determined use (current and past) of cyclophosphamide or rituximab, mycophenolate, and azathioprine. Physicians completed the SLE disease activity index (SLEDAI), Physicians Global Assessment of disease activity (PGA) and the Systemic Lupus International Collaborating Clinics/ACR damage index (SDI). We compared age at SLE diagnosis, duration, activity and damage in boys to that in girls. Depending on the data distribution, the independent samples t-tests (t) and/or Mann-Whitney U (MWU) tests were used to compare samples. We compared medication using the Chi-Square test.

Results: We identified 29 boys and 138 girls. Compared to girls, boys had a higher age of disease onset (p<0.01), lesser disease duration (p<0.01), and greater disease activity as assessed by SLEDAI and PGA (p<0.05) (Table 1). Differences in SDI and immunosuppressive medication use between the two groups were not statistically significant (Table 1).

Table 1. Comparison between young males and young females with SLE

Variables	Males (n=29 unless specified)	Females (n=138 unless specified)
Ethnicity (non-white, %)	23 (80%)	112 (81%)
Age at diagnosis in years (mean±SD)	13±3	11±4* (t)
Mean SLE duration in months (mean±SD)	18±20	40 ±41* (MWU)
PGA-none/mild SLE activity (n, %)	12 (45%)	86 (65%, n=133)
PGA-moderate-severe SLE activity (n, %)	17 (59%)	47 (33%, n=133)
PGA mean (mean±SD)	1.7±0.8	1.2±0.8* (n=133) (MWU)
SLEDAI mean (mean±SD)	7±6	5±6*(n=135) (MWU)
SDI mean (mean±SD)	0.9±1 (n=28)	0.8±1 (n=135)
Cyclophosphamide/ Rituximab (n, %)	10 (34%)	43 (31%)
Azathioprine (n, %)	5 (17%)	31 (22%)
Mycophenolate (n, %)	9 (31%)	44 (32%)

* p<0.05; Mann Whitney U test (MWU); Independent samples t test (t).

Conclusion: SLE activity was higher in boys compared to girls in our cohort. Boys had a later age at diagnosis and shorter disease duration when compared to the girls in our study. A higher index of suspicion is warranted to diagnose and detect worsening in young males with SLE, so that aggressive treatment can be instituted early.

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2505

Higher Disease Damage Among African Americans With Familial Versus Sporadic Systemic Lupus Erythematosus. April Barnado, Lee Wheless, Stephanie Slan, Gary S. Gilkeson and Diane L. Kamen. Medical University of South Carolina, Charleston, SC.

Background/Purpose: Studies in predominantly Caucasian cohorts have found no significant clinical or serologic differences in systemic lupus erythematosus (SLE) patients with a family history of SLE compared to those with no family history. Using a unique cohort of African Americans with SLE and a high prevalence of multipatient families, we examined whether having a family history of SLE would impact autoantibodies, age at SLE diagnosis, ACR criteria, and disease damage.

Methods: Utilizing data from a prospective longitudinal cohort of African Americans with SLE, familial SLE was defined as having a confirmed family history of SLE versus sporadic SLE defined as no known family history of SLE. SSA, SSB, ds-DNA, anticardiolipin, and lupus anticoagulant were all tested. A patient was considered to have a positive serology if the serology had ever been positive. Cumulative damage was measured using the Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index (SDI). Chi-square testing was used for comparing categorical and Student's t-test used for comparing continuous variables. The association between familial vs. sporadic SLE and SDI was modeled using Poisson regression adjusting for covariates. Two-sided p-values < 0.05 were significant.

Results: 400 African American females had SLE, 55 of who were familial SLE cases. Mean age of familial cases was 47.1 +13.9 years vs. 43.3 + 14.7 for sporadic cases ($p = 0.08$). Mean age at diagnosis was 28.1 +11.5 years for familial vs. 31.0 + 13.0 for sporadic ($p = 0.13$). Mean disease duration was 18.7 + 9.1 years for familial vs. 12.3 + 7.1 for sporadic ($p < 0.01$). Familial SLE cases had similar rates of dsDNA, SSA, SSB, anticardiolipin, and lupus anticoagulant positivity compared to sporadic cases. Familial cases had similar rates of being on dialysis as sporadic cases (19.2% vs. 12.2%, $p = 0.17$). There were similar rates of fulfilling ACR renal criterion (58.0% familial vs. 52.8% sporadic). Familial cases were significantly more likely to fulfill ACR criterion of photosensitivity (65.3% vs. 49.3%, $p = 0.04$) but no significant differences in the other ACR criteria. Familial cases had significantly higher SDI scores (2.8 + 2.6 vs. 1.6 + 1.8, $p = 0.02$) compared to sporadic cases. After adjustment for age at diagnosis and disease duration, familial SLE was still associated with a significantly higher SDI ($p < 0.01$).

Conclusion: Consistent with predominantly Caucasian SLE cohorts, we found African American SLE familial and sporadic cases had similar serologic and clinical profiles. However, familial SLE cases had significantly higher SDI scores compared to sporadic cases, even after adjusting for age at diagnosis and disease duration. Further studies are underway to elucidate the causes of higher disease damage in familial versus sporadic SLE.

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2506

Systemic LUPUS Erythematosus Patients Presenting With Immune Thrombocytopenia and The Association Between Two Diseases. Omer Nuri Pamuk, Gulsum Emel Pamuk and Mehmet Sevki Uyanik. Trakya University Medical Faculty, Edirne, Turkey.

Background/Purpose: We evaluated the features of our systemic lupus erythematosus (SLE) patients who presented with immune thrombocytopenia (ITP) and compared them to other SLE patients. In addition, we searched for the frequency of autoantibody positivity in our ITP series and evaluated ITP patients who developed SLE during follow-up.

Methods: Patients who were diagnosed with SLE at our university's rheumatology department and those diagnosed with ITP at the hematology department were retrospectively evaluated. The clinical features, autoantibody profiles and outcome of the patients were recorded down. SLE was diagnosed according to revised ACR criteria. ITP was diagnosed according to American Society of Hematology (ASH) 2011 guidelines and a platelet count <100000/mm3 was a prerequisite. Antiplatelet antibodies were not routinely evaluated. SLE presenting with ITP was diagnosed when the clinical symptoms of SLE and autoantibody positivity did develop within the first year after the diagnosis of ITP.

Results: Twelve (6.7%) of the 280 SLE patients who were diagnosed within this time period presented with isolated ITP. The median time for the development of SLE in these patients was 3 years. Two SLE patients presented with thrombotic thrombocytopenic purpura (TTP) and one SLE patient had TTP during follow-up. When the features of 14 SLE patients who presented with ITP or TTP were compared to others, it was seen that the mean age (31.8 ± 11.1 vs. 38.6 ± 12.1, $p=0.043$) and anti-ds-DNA positivity (21.4% vs. 47.3%, $p=0.05$) were lower in this group; and these patients tended to have more active disease during pregnancy or had a higher probability of initially presenting with pregnancy (35.7% vs. 15.8%, $p=0.067$).Fortyone SLE patients (14.6%) had thrombocytopenia during any time of their disease. SLE patients with thrombocytopenia had more frequently initially active SLE (SLEDAI score >6) (70.7% vs 37.3%, $p<0.001$); fever (26.8% vs 14%, $p=0.038$); neurologic involvement (34.1% vs. 18.5%, $p=0.022$); renal involvement (45% vs 25%, $p=0.009$); low C3 level (61% vs 30.6%, $p<0.001$); also, the frequency of patients whose disease started with pregnancy or become aggravated with pregnancy were significantly higher (31.6% vs. 14.3%, $p=0.009$). There was no association between antiphospholipid antibodies (APS) and thrombocytopenia in SLE patients. Of 216 patients with ITP, ANA was positive in 18.5% (28/151), and anti-DNA was present in 1.6% (2/121). None of the patients had findings of SLE or other autoimmune rheumatic diseases. After 2, 5, and 6 years of follow-up, however, 3 female patients developed SLE. APS antibodies were positive in 29.3% (24/82) of ITP patients in which they were available. Nevertheless, except one, all were IgM antibody positivity at low titers. None of the cases with positive APS antibodies had history of thrombosis or abortion.

Conclusion: Some patients with ITP might develop SLE during follow-up. Onset of SLE with pregnancy, renal or neurologic involvement, and initially active disease are risk factors for the development of ITP in SLE patients.

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2507

What Is The Risk Of Having a Total Hip Or Knee Replacement for Patients With Lupus? Sandeep Mukherjee[1], David Culliford[2], Nigel K. Arden[3] and Christopher J. Edwards[1]. [1]NIHR Wellcome Trust Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, [2]University of Southampton, Southampton, United Kingdom, [3]Oxford NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, United Kingdom.

Background/Purpose: Individuals with systemic lupus erythematosus (SLE) frequently have arthralgia, but joint damage leading to surgery is thought to be less common. In addition to inflammatory damage, other reasons like avascular necrosis (AVN), often associated with steroid use and antiphospholipid syndrome (APS), may increase the likelihood of large joint failure. Demonstrating the risk of joint replacement in lupus patients and factors contributing to this may allow preventative action.

Methods: We performed a retrospective matched case control study of all total hip replacements (THR) and total knee replacements (TKR) between 1991 and 2011 recorded in the General Practice Research Database (GPRD), a primary care database containing data on approximately 3.6 million patients from over 480 primary care practices. There were two controls for each case of primary THR or TKR, matched for age, sex and GP practice location (a proxy for socio-economic status). The odds of having THR or TKR for individuals with SLE were compared with those without lupus through Chi-squared analysis followed by conditional logistic regression taking account of the matching. Individuals with inflammatory arthritis due to any other cause were excluded and results adjusted for steroid use and APS.

Results: During the 20-year study period 63162 patients had a primary THR (123624 matched controls). Within this total sample size of 186786, 122 individuals with a previous diagnosis of SLE had a THR performed (see table). After excluding those who had an inflammatory arthritis other than lupus, there remained 181464 individuals without lupus and 60167 of them

underwent primary THR (see table). During the same period 54276 individuals had a primary TKR (106302 matched controls). Again out of this new total sample size of 160578, 124 individuals with a diagnosis of SLE had a TKR performed (see table). After exclusions for other inflammatory arthritis, there were 154850 individuals without lupus, 50658 of whom underwent primary TKR (see table). Overall, for individuals with a previous diagnosis of SLE, the unadjusted odds ratio (OR) of having a THR was 1.43 (95% confidence interval (CI): 1.13 to 1.81, p=0.0030) over those without lupus and that for having a TKR was 2.54 (95% CI: 1.94 to 3.33, p<0.0001). However, after adjustment the OR were 1.20 (95% CI: 0.94 to 1.52, p=0.1441) and 1.91 (95% CI: 1.44 to 2.53, p<0.0001) respectively.

	THR Without Lupus	THR With Lupus	TKR Without Lupus	TKR With Lupus
Number of individuals	60167	122	50658	124
Mean Age (years)	69.5	65.7	70.4	66.3
Male:Female	1:1.6	1:10	1:1.3	1:8
OR unadjusted		1.43 (p = 0.0030)		2.54 (p = <0.0001)
OR adjusted		1.20 (p = 0.1441)		1.91 (p = <0.0001)

Conclusion: Patients with lupus who have a THR or TKR tend to be younger than their peers without lupus. In addition, they appear to have a significantly increased risk of TKR but the increased risk of THR does not remain after adjustment for anti-phospholipid syndrome and steroid use.

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2508

Clinical and Serological Discordance In The Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) Cohort. Murray B. Urowitz[1], Dafna Gladman[1], Nicole Anderson[1] and Systemic Lupus Erythematosus International Collaborating Clinics SLICC[2]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]Toronto Western Hospital, Toronto, ON.

Background/Purpose: Anti-DNA antibodies and serum complement levels are considered important biomarkers for disease activity in SLE. Despite this many SLE patients present serologically active (positive antibody and or low complement) but clinically quiescent (SACQ). We aim to determine the frequency of SACQ in a multicentre, multinational cohort.

Methods: An inception cohort of SLE patients from 31 centres in 12 countries has been assembled according to a standardized protocol between 2000 and 2013 to study the risk factors for atherosclerosis. Patients enter the cohort within 15 months of SLE diagnosis (≥4 ACR criteria). Clinical and laboratory features of SLE and comorbidities are gathered in a standardized protocol at yearly intervals. SACQ was defined as at least two consecutive yearly visits with SLEDAI of 2 or 4 from serologic activity only (increased anti-double-stranded DNA and/or hypocomplementemia), during which patients could be taking antimalarials, but not steroids or immunosuppressives. We examined patients 1 year after the SACQ period and beyond. Flare was defined as any increase in clinical activity. Since patients were mandated to only be on antimalarials it is unlikely they had moderate to severe flares between yearly assessment visits. Serologically quiescent and clinically quiescent (SQCQ) was defined as SLEDAI-2K score of 0.

Results: 91 of 1837 (5%) patients met the criteria for SACQ. Of the 91 patients studied, 86.8% were female and the race/ethnicity distribution was 65.9% Caucasian, 9.9% Black, 13.2% Asian, 7.7% Hispanic and 3.3% other. The age at SLE diagnosis was 34.6 ± 11.9 years. Disease duration at last follow–up was 7.1± 3.0 years. Fifty-five patients did not retain SACQ status after the first year and 36 patients experienced a prolonged SACQ. Of the 55 patients that did not retain SACQ status, 25 (45.45%) flared, 14 (25.45%) became SQCQ and 16 (29.09%) were censored at the last visit. Of the 36 patients that went onto prolonged SACQ: 9 (25.00%) patients flared after 3 years of SACQ, 4 (11.11%) patients became SQCQ and 23 (63.89%) patients were censored at their last visit.

Conclusion: Sixty percent of the SACQ patients no longer retained SACQ status in the first year, while 40% experienced a prolonged SACQ period and 25% of those flared later. Therefore treatment decisions in these patients must be based on close clinical observation.

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2509

Long Term Natural History Of Asymptomatic Avascular Necrosis In a Cohort Of Patients With Systemic Lupus Erythematosus Treated With Corticosteroids. Eileen J. Lydon[1] and H. Michael Belmont[2]. [1]NYUHJD, New York, NY, [2]NYU School of Medicine, New York, NY.

Background/Purpose: Avascular necrosis (AVN) is cellular death of bone components due to interruption of the blood supply resulting in area of ischemic necrosis but may or may not progress to collapse and painful arthritis. The incidence of AVN in SLE patients is high although the natural history (e.g. prevalence of progression) has not been well characterized. In 2002, we initiated the APLLE (Avascular Necrosis Prevention with Lipitor in Lupus Erythematosus), trial to assess the effectiveness of statin therapy to prevent the incidence of AVN in any of 12 sites per patient (femoral heads, medial and lateral femoral condyle, tibeal plateau, distal tibia or talar domes) ascertained by comparing baseline to follow up MRI's at four and nine months. We could not demonstrate that atorvastatin prevented AVN and the study was terminated in 2008. We now report on the course of AVN sites that were identified by MRI during the course of the study emphasizing the development of symptomatic (sx) AVN in patients previously asymptomatic.

Methods: APLLE trial participants were contacted starting 1/2013. A questionnaire was used to identify sx AVN and a chart review was conducted to collect pertinent information. Sx was defined as interfering with ADL [daily pain and loss of function]. If patient verbalized symptoms, they were invited for an office visit with the nurse practitioner to complete a focused history and physical.

Results: 23 of 42 APLLE participants available for follow-up at mean of 7.35 years; 19F, 4M; 9AA,9H,2C,3A; 18/23(78%) completed 9 month MRI with 5/18(28%) new AVN, 13 sites out of 216. During intervention trial; 11/23(48%) atorvastatin, 22/23(96%) hydroxychloroquine; During follow up study; 19/23(83%) hydroxychloroquine,3/23(13%) statin, 3/23(13%)bisphosphonate, 0/23 teriparatide.

AVN Site Results: Interventional & Follow up Studies

	N	# of Patients with AVN	# Total AVN Sites	# Symptomatic	# Asymptomatic
Interventional: Baseline MRI	42	15/42 (36%)	48/180 (27%)	2/48 (4%)	46/48 (96%)
Interventional: 9 month MRI	28	12/28 (43%)	47/144 (33%)	3/47 (6%)	44/47 (94%)
Follow-up Study	23	8/23 (35%)	33/96 (34%)	7/33 (21%)	26/33 (79%)

Follow-up study new sx AVN in 3 patients. 1st patient-2 sites sx delayed 2.5 years requiring bilateral THR, 2nd patient-2 sites sx delayed 8 years, 3rdpatient-3 sites, delayed.75, 1 and 4 years. No sx AVN in the 18 of 23 in follow-up study without AVN in interventional trial.

Conclusion: Although AVN is a frequent complication of steroid treatment in SLE, MRI studies are sensitive and can overestimate clinically relevant episodes which should be a source of reassurance to patients. Both at baseline of interventional trial (4%) and in follow-up study (21%) AVN infrequently sx. Results did not demonstrate protective role for statins or medications intended to preserve bone density. Symptomatic progression, often delayed over years (range.75 – 8 years), occurred in 7/33(21%) arguing against need for aggressive intervention in all patients (e.g. bisphosphonates, teriparatide, core decompression). Future studies will need to identify risk factors for progression to justify randomized controlled trials.

Disclosure: E. J. Lydon, None; **H. M. Belmont**, None.

2510

The Epidemiology Of Systemic LUPUS Erythematosus and Clinical Features Of Patients At A Single Center In Northwestern Turkey. Omer Nuri Pamuk[1], Salim Dönmez[2], Gokce Busra Calayir[1] and Cigdem Mengus[1]. [1]Trakya University Medical Faculty, Edirne, Turkey, [2]Yüzüncü Yıl University Medical Faculty, Edirne, Turkey.

Background/Purpose: We evaluated the clinical features, treatment modalities, treatment responses and prognosis of patients diagnosed with systemic lupus erythematosus (SLE). We also estimated the prevalence and incidence of SLE in Thrace region of Turkey.

Methods: Twohundred-and-seventynine patients (260F, 19M, mean age: 38.7±11.6 years) diagnosed with SLE between 2003–2013 at our center were retrospectively evaluated. Clinical features, treatments and responses to various treatment modalities were recorded. In addition, the incidence and prevalence of SLE in our population were calculated. Our hospital has been the only tertiary referral center for rheumatological diseases for a mixed rural and urban population of 616000 people for >16 years (316000M, 300000F).

Our city, Edirne, is located in Thrace region in northwestern Turkey and makes borders with Greece and Bulgaria.

Results: The mean annual incidence of SLE was 4.5/100000 (8.7/100000 in females, 0.6/100000 in males). The overall prevalence of SLE was 45.3/100000 (86.7/100000 for females, 6.1/100000 for males). Malar rash was present in 37.9% of patients; photosensitivity, 72.4%; discoid rash, 15.6%; alopecia, 9.2%; raynaud phenomenon, 32.1%; pericarditis, 8%; pleural involvement, 16.1%; and livedo reticularis in 8.1%. The percentages for major organ involvement were as follows: neurologic involvement, 20.1%; renal involvement, 28.2%; autoimmune hemolytic anemia, 9.6%; and trombocytopenia, 14.7%. Results of positivity for autoimmune tests were ANA, 98.2%; anti-dsDNA, 46%; anti-Sm, 15.7%; anti-Ro, 31.3%; anti-nucleosome, 10.4%; anti-ribosomal P, 4.8%; RF, 15%; ANCA, 8.4%; and antiphospholipid antibody, 17.6%.

At a median follow-up of 49 months, 13 SLE patients (10F, 3M) died. The 5-year survival was 95%, and the 10-year survival was 92%. According to Kaplan-Meier survival analysis, being male (5-year survival 77% vs. 95%, p=0.015); having pleural involvement (5-year survival 95.4% vs. 87%, p=0.011); having renal involvement (5-year survival 88.4% vs. 98.5%, p=0.014); usage of cyclophosphamide (5-year survival 87.3% vs. 96.6%, p=0.004); and an initially high SLEDAI score (>6) (5-year survival 89% vs 97.8%, p=0.005) were poor prognostic factors.

Smoking (5-year survival 89% vs. 95.4%, p=0.07) and autoimmune hemolytic anemia (5-year survival 96.2%, 85%, p=0.058) tended to be associated with poor prognosis.

According to Cox regression analysis, pleural involvement (OR: 6.25, p=0.018), hemolytic anemia (OR: 4.1, p=0.05), renal involvement (OR: 4.8, p=0.045), and low C3 level at the time of initial diagnosis (OR: 5.1, p=0.038) were independent poor prognostic factors which influenced survival.

Conclusion: Our results revealed that the annual incidence and prevalence of SLE in northwestern Turkey were quite similar to western data. In our series, majority of patients were females. Survival was similar to data from western countries. Poor prognostic factors were renal involvement, pleural involvement, initially active disease and autoimmune hemolytic anemia.

Disclosure: O. N. Pamuk, None; **S. Dönmez**, None; **G. B. Calayir**, None; **C. Mengus**, None.

2511

Multicenter Validation Of The Lupus Activity Scoring Tool (LAST) As Compared To The Selena Sledai (SS) Modification. Majed M. Khraishi[1], Rana Aslanov[2], Sanjay Dixit[3], Krista Fudge[4], Vandana Ahluwalia[5] and Sarah Khraishi[6]. [1]MD, Memorial University of Newfoundland, Nexus Clinical Research, St Johns, NF, [2]MD, MSc, Memorial University of Newfoundland, St. John's, NF, [3]McMaster University, Burlington, ON, [4]Western Memorial Hospital, Corner Brook, NF, [5]Past President, Ontario Rheumatology Association, Brampton, ON, [6]Memorial University of Newfoundland, St. John's, NF.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a chronic immune modulated disease with variable clinical manifestations. New advances in the management of SLE mandated closer monitoring of the disease activity and its response to treatment. Current disease activity indices (e.g. SELENA SLEDAI, BILAG & SLAM) have their own limitations.

In our centre, a new tool for the assessment of SLE activity: the Lupus Activity Scoring Tool (LAST) was developed and validated. This tool simplifies the approach to quantifying SLE activity while maintaining high sensivity. This study was designed to validate this tool in different clinical settings. Apple iPad and Windows web-based applications were developed for the LAST.

We aimed: To validate the LAST in multiple clinical settings using its correlation to the SELENA SLEDAI modification. To test the usability and the accuracy of an electronic application of the same tool.

Methods: This multicenter study was initiated in four Canadian clinics: two in Newfoundland and two in Ontario. The LAST included patient global assessment of disease activity (PGA), physician global assessment of disease activity (PHGA), C3, C4 and Anti-ds Anti-DNA titer abnormalities, and a formula incorporating the current immunomodulating medication used as an indication of SLE activity. Patients who met the SLE ACR 1997 criteria update were recruited and evaluated in the study centres using LAST. Some of the patients were prospectively followed and evaluated by the same tool at each visit. The SS was also calculated for each visit. Descriptive statistics and correlation bivariates were conducted. The LAST scores of the disease activity of patients with multiple assessments were compared to the SS scores.

Results: Thirty two patients (91% females) with 66 assessments from four study centers were included in this analysis. The mean (SD) age was 46.3 (14.7) years and the mean (SD) of disease duration was 13.6 (6.1) years. Scores from the LAST were obtained at each visit in addition to the SLEDAI scores. The mean (SD) SLEDAI score was 6.6 (3.9). The mean (SD) LAST (with C3, C4 and Anti-ds Anti-DNA) score was 34.9 (18.2). The SLEDAI scores were consistent and strongly correlated (r=0.791; p<0.001) with the LAST scores at the baseline and follow-up visits: SS scores 0–4 corresponded to the LAST scores of 0–30 while SS scores of 8 or higher corresponded to 50 and higher, respectively. The electronic applications of the LAST were easy to use and no errors were found with their results as compared to the manually obtained scores.

Conclusion: The Lupus Activity Scoring Tool (LAST) is a new disease activity index that correlates well with the SELENA SLEDAI modification. The use of simple clinical variables as a measure of SLE activity seems to be valid under different clinical settings with different assessors. The development of easy to use electronic apps will make the use of these activity tracking tools simpler and can possibly be utilized in non-specialist settings.

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2512

Smoking Is Associated With More Severe Skin Disease In Subjects With Moderate To Severe Systemic Lupus Erythematosus (SLE). Victoria P. Werth[1], Munther A. Khamashta[2], Gabor G. Illei[3], Stephen Yoo[3], Liangwei Wang[3] and Warren Greth[3]. [1]Philadelphia Veterans Affairs Medical Center, Philadelphia, PA, [2]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [3]MedImmune, LLC, Gaithersburg, MD.

Background/Purpose: The influence of smoking on the severity of cutaneous manifestations in adults with moderate to severe SLE was assessed in an ongoing international, multi-center, double-blind, randomized, placebo-controlled study.

Methods: Adult subjects with SLE (n=431; 94.7% female; median disease duration 6.3 years; 59% white; 37% Hispanic; median age 40; mean SLEDAI 2K 11.3) were assessed for mucocutaneous disease activity and smoking history at baseline. Subjects were classified as Current (within 1 year) (n=61) or Past (stopped >1 year)/Never Smokers (n=365). The 426 subjects who had Cutaneous Lupus Activity and Severity Index (CLASI), SLEDAI 2K, and smoking history available at baseline are included in this analysis.

Results: Based on SLEDAI 2K scoring at baseline 79.4%, 67.1%, and 45.2% had an inflammatory rash, alopecia, or mucosal ulcers, respectively, with no significant differences between smokers and non-smokers. Current smokers had significantly higher CLASI scores and were more likely to have moderate or severe rash (CLASI ≥10) (Table 1). There was no significant difference in CLASI scores between Past/Never smokers (7.1±6.6/7.0±6.3 P=0.890).

Table 1.

	Smoking History				
	Current	N	Never/Past	N	Significance
CLASI activity score (mean ± SD)	13.1±10.6	61	7.0±6.3	365	P<0.001†
CLASI damage (mean ± SD)	3.7±6.2	61	2.2±4.5	365	P=0.087†
CLASI <10 (%)	44.3%	27	75.3%	275	P<0.001‡
CLASI ≥10 (%)	55.3%	34	24.7%	90	
SLEDAI Rash present	83.6%	51	78.9%	288	NS‡
SLEDAI Alopecia present	73.8%	45	65.8%	240	NS‡
SLEDAI Mucosal ulcers present	44.3%	27	45.5%	166	NS‡

†2 sample t-test; ‡Chi-square test
CLASI: Cutaneous Lupus Activity and Severity Index; NS: not significant; SD: standard deviation; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

This observation was consistent across geography, races, ethnicities, and SLE medications at baseline (Table 2). There was no relationship between smoking and cutaneous damage.

Table 2.

Smoking	Never/Past Mean CLASI	SD	N	Current Mean CLASI	SD	N
Race/Ethnicity						
American-Indian	5.4	5.1	20	NA	NA	0
Asian	9.5	7.0	65	NA	NA	0
Black	6.5	3.7	27	8.4	6.9	5
Other	5.0	3.6	56	20.0	1.4	2
White	6.9	6.8	197	13.3	10.9	54
Hispanic/Latino	5.5	4.4	148	9.3	7.2	11
Not Hispanic/Latino	7.9	7.2	217	14.0	11.1	50
Medications						
Antimalarials						
No	6.9	6.3	104	13.1	12.0	10
Yes	7.0	6.3	261	13.1	10.4	51
Immunosuppressive						
No	7.6	6.5	184	11.9	10.6	33
Yes	6.3	6.1	181	14.5	10.6	28
Corticosteroids						
No	6.7	5.9	53	11.0	9.4	10
Yes	7.0	6.4	312	13.5	10.8	51

CLASI: Cutaneous Lupus Activity and Severity Index; SD: standard deviation

Conclusion: Previous studies have shown that smoking is associated with an increased risk of cutaneous lupus. In agreement with a previous single center study, here we show in a large, multinational and multiethnic cohort that current smoker SLE subjects have higher CLASI activity scores than past or non-smokers. The CLASI seems more sensitive to detect these differences of inflammatory skin involvement in subjects with moderate to severe SLE than the SLEDAI 2K mucocutaneous descriptors (rash, alopecia, mucous ulcers). The lack of difference in the frequency of mucocutaneous manifestations based on SLEDAI 2K between current smokers and past/never smokers is in apparent contrast to published data but is a consequence of the study eligibility criteria enriching for patients with active mucocutaneous disease. The consistency of the relationship between smoking and higher CLASI activity but not chronicity scores in SLE subjects with skin involvement across geographies, races, ethnicities, and SLE medications suggest that smoking may actively worsen skin disease in SLE. As CLASI activity is similar in past smokers and never smokers, smoking cessation should be emphasized in the management of SLE with cutaneous involvement.

Disclosure: V. P. Werth, Medimmune, 5, University of Pennsylvania, 7; **M. A. Khamashta**, MedImmune, 9; **G. G. Illei**, AstraZeneca, 1, MedImmune, 3; **S. Yoo**, AstraZeneca, 1, MedImmune, 3; **L. Wang**, AstraZeneca, 1, MedImmune, 3; **W. Greth**, AstraZeneca, 1, MedImmune, 3.

2513

Anti-Mullerian Hormone In Patients With Systemic Lupus Erythematosus. Chiara Tani[1], Sabrina Vagnani[1], Linda Carli[2], Giovanni Gallo[2], Maria Rita Sessa[3], Chiara Baldini[2], Alessandra Della Rossa[2], Rosaria Talarico[2], Francesca Strigini[1], Marco Maccheroni[3], Stefano Bombardieri[1] and Marta Mosca[1]. [1]Rheumatology Unit, University of Pisa, Pisa, Italy, [2]Rheumatology Unit, Pisa, Italy, [3]S. Chiara Hospital, Pisa, Italy.

Background/Purpose: Systemic Lupus Erythematosus (SLE) frequently affects women in childbearing age; disease related factors and treatment can interfere with ovarian function. Anti-Mullerian-hormone (AMH) levels are considered a surrogate marker of the ovarian reserve in pre-menopausal women. In this study we aimed at evaluating AMH levels in SLE patients and at establishing possible correlations with disease variables, therapies and obstetrical history

Methods: AMH levels were assessed in pre-menopausal SLE patients with an enzymatically amplified two-site immunoassay (AMH Gen II ELISA; Beckman Coulter). According to the published literature in healthy subjects, values 1 to 8 ng/mL indicate normal, values $<$ 1ng/mL indicate reduced and $<$0.4 strongly reduced ovarian reserve. Demographic data, clinical variables, disease activity, ongoing therapies as well as cumulative glucocorticoids dosage (GC) and previous therapy with Cyclophsphamide (Cyc) at the time of AMH evaluation were collected from clinical charts. Obstetrical history and menopausal status at the end of follow up were also considered.

Results: Seventy-five SLE patients were examined (mean age and disease duration 32.9$\pm$7 and 9.4 $\pm$6 years respectively); 58 (77.3%) presented a history of renal involvement and 44 (58.6%) had received Cyc before AMH assay (mean cumulative dosage 7.31$\pm$6 g, intravenous in 33, oral in 8, both regimens in 3). The median time between the latest Cyc administration and AMH determination was 6.3 years ($\pm$5.5). At study entry, the mean GC dosage was 5.9 mg ($\pm$6.9) and the mean cumulative dosage was 14.9 ($\pm$11); 35 (46%) patients were receiving immunosuppressants. AMH values were within the normal ranges in 23 (30.6%) patients, reduced in 16 (21.3%) and strongly reduced in 36 (48%). AMH levels were inversely related to age ($p=0.0001$) and disease duration ($p=0.004$) and to previous therapy with Cyc ($p=0.03$). At the end of follow-up, 48 patients (64%) had at least one pregnancy and 4 (5%) were in menopause (2 premature ovarian failures). No relationships were observed between AMH levels and disease activity or cumulative GC. AMH levels were not correlated with the occurrence of pregnancy but were significantly associated with the number of pregnancies ($p=0.03$).

Conclusion: In our cohort, a high percentage of patients presented low or very low levels of AMH; as expected, a significant decrease with age progression have been observed and previous therapy with Cyc seem to be important contributors. The association of AMH levels and the number of subsequent pregnancies supports the significance of this testing to assess ovarian reserve in these patients.

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2514

The Brief Index of Lupus Damage, a Patient-Reported Measure of Lupus Damage, Is Sensitive to Change. Patricia P. Katz[1], Laura Trupin[2], Stephanie Rush[2] and Jinoos Yazdany[2]. [1]University of California San Francisco, San Francisco, CA, [2]University of California, San Francisco, San Francisco, CA.

Background/Purpose: Extending lupus research outside of the clinical setting remains a challenge, in part due to the complexity of measuring disease damage. Previously, we developed and validated a patient-reported measure of lupus damage (BILD) for research purposes. Here we report additional validation of the BILD, focusing on its ability to detect change.

Methods: Data were drawn from the UCSF Lupus Outcomes Study (LOS), in which participants are interviewed by phone annually. The BILD was administered in 2 waves, 5 years apart. Only participants who were interviewed in both years are included in the analysis (n=740). We calculated changes in BILD scores, and categorized increases in scores as 0, 1, 2, 3, or $>$3. (Only increases in scores are possible because, by definition, damage cannot be reversed.) We then examined changes in disease activity measured with the Systemic Lupus Activity Questionnaire (SLAQ), changes in the number of physician visits, and number of hospitalizations in the years between the two BILD administrations. These measures were chosen because the disease manifestations included in the BILD would likely give rise to increased symptoms or utilization at the time they occur. Increases in SLAQ and physician visits were defined by an increase of 0.5 standard deviation over baseline in at least one interview wave during the 5-year observation period, equivalent to an increase of 4 points on the SLAQ and 5 physician visits. For hospitalizations, we examined the occurrence of 2+ hospitalizations in at least one wave.

Results: BILD scores ranged from 0–13 with a median of 1 (IQR 0–3) in the first administration. At the second administration, scores ranged from 0–15 with a median of 2 (IQR 1–4). Changes in BILD ranged from 0–8 with a median of 1 (IQR 0–1). Of the 740 LOS participants, 369 had no increase in BILD score. Of the remaining participants, 210, 84, 41, and 36 had increases of 1, 2, 3, and $>$3 points, respectively (Table). Overall, 37% of LOS participants had an increase in SLAQ, 43% had an increase in physician visits, and 14% had 2+ hospitalizations in at least one interview wave. For SLAQ scores, the prevalence of an increase was highest among participants with changes in BILD $\geq$3. There was a greater prevalence of increased physician visits among participants with a change in BILD $>$0. Greater increases in BILD were associated with significantly greater likelihood of at least one year with 2+ hospitalizations.

Table. Increases in disease activity and physician visits and hospitalizations associated with increases in BILD scores

		Increase in BILD					
	Total (n=740)	0 (n=369)	1 (n=210)	2 (n=84)	3 (n=41)	>3 (n=36)	p*
SLAQ (at least 1 score > baseline by 0.5 SD)	37%	34%	40%	36%	39%	50%	.06
MD visits (at least 1 wave > baseline by 0.5 SD)	43%	36%	50%	44%	56%	47%	.0057
Hospitalizations (at least 1 wave with 2+)	14%	5%	19%	15%	29%	55%	<.0001

* p value from c^2 for trend

Conclusion: Change in BILD score corresponds with increases in disease activity and physician visits and with hospitalizations that are likely to reflect disease manifestations that could cause increases in disease damage. Previous cross-sectional examination of the BILD showed concurrent validity; this analysis provides evidence of the BILD's ability to detect change. While not intended to replace clinical evaluation of disease damage, the BILD does appear to be a useful tool for research.

Disclosure: P. P. Katz, None; **L. Trupin**, None; **S. Rush**, None; **J. Yazdany**, None.

2515

Social Capital: A Novel Platform For Understanding Social Determinants Of Health In Systemic Lupus Erythematosus. Susan Kim[1], Carol Mancuso[2], Wei-Ti Huang[1] and Doruk Erkan[1]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, NY, NY.

Background/Purpose: Social capital is the degree of connectedness, and the extent and quality of social relations, networks, and interactions in a given population. The objective of this study was to assess the relationship between social capital and health-related psychosocial variables in SLE patients.

Methods: In a cross-sectional study, SLE patients completed: a) Adapted Social Capital Assessment Tool (A-SCAT), which measures cognitive and structural domains of social capital (range: 0–71) (higher scores reflect higher social capital); and b) health-related psychosocial variables including Medical Outcomes Study (MOS)-Social Support Survey (range: 0–100), Center for Epidemiologic Studies Depression Scale (CES-D) (range: 0–60), and Self Efficacy for Managing Chronic Disease 6-item Scale (range: 1–10) (higher scores reflect higher social support, depression, and self-efficacy, respectively). Pearson correlation and analysis of variance were used to evaluate for any associations and significant differences, respectively, between social capital scores and the psychosocial variables.

Results: We recruited 89 SLE patients who met ACR SLE criteria (female: 83; Caucasian: 28 (31%); African American: 32 (36%); Asian: 6 (7%); other: 23 (26%); and Hispanic: 53 (60%)). Mean age was 39 ± 15 y; mean disease duration 11.6 ± 8.2y, mean SLEDAI 3.5 ± 3.0, and mean SLICC 1.3 ± 1.8. Selected socioeconomic features were: Medicaid 47 (53%), ≥ high school degree 69 (78%), annual household income <$40,000 53 (60%), employed 25 (28%), unemployed 31 (35%), and disability 30 (34%). The mean A-SCAT score was 34 ±15; the mean CES-D score was 22 ± 13; the mean MOS-SSS was 66 ± 27; the mean self efficacy score was 5 ± 2, and 56 (63%) had a positive screen (CES-D≥ 16) for depression. Social capital was not associated with self-efficacy or affectionate and interaction social support, but was associated with informational and tangible social support. Cognitive social capital domain was negatively associated with the depression scale (Table 1). There were no significant differences in the SLEDAI and SLICC scores according to social capital, social support, and depression measures.

	Social Capital (A-SCAT)		
	Overall	Structural Domain	Cognitive Domain
MOS-Social Support Survey			
Informational Subscale	0.39‡	0.33‡	0.35‡
Tangible Subscale	0.26†	0.16	0.30‡
Affectionate Subscale	0.17	0.13	0.19
Positive Social Interaction Subscale	0.19	0.17	0.17
Overall	0.31‡	0.25†	0.31‡
CES-D	−0.20	−0.09	−0.27†
Self-Efficacy	0.17	0.16	0.13

Pearson Correlation Coefficient; †P<0.02; ‡P<0.005

Conclusion: This is the first study to use social capital as a novel platform in a lupus population defined by the commonality of a chronic illness, on which ideas of social connectedness can broaden our understanding of health disparities and chronic illness. Our results show that social capital has features that overlap with social support, specifically in the informational and tangible (provision of material aid or behavioral assistance) subscales, but is distinct from traditional health-related psychosocial measures.

Disclosure: S. Kim, None; **C. Mancuso**, None; **W. T. Huang**, None; **D. Erkan**, None.

2516

Plasma Microparticles Are Associated With Venous Thrombosis In Systemic Lupus Erythematosus. Michelle Petri[1], Melissa Nastacio[1], Hong Fang[1], Thomas Kickler[1], Jayesh Jani[1] and Laurence S. Magder[2]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD.

Background/Purpose: Thrombosis in SLE is highly associated with antiphospholipid antibodies, yet the majority of those with antiphospholipid antibodies never have a thrombotic event. Plasma microparticles (PMP) have been identified as a risk factor for atherosclerosis. D-dimers are elevated in the setting of deep venous thrombosis. We investigated both as markers of thrombosis in SLE.

Methods: We measured plasma microparticles (by their capacity to generate thrombin) and D-dimer levels in 1044 SLE patients. The relationship between these biomarkers and history of, and future risk of, thrombosis was determined.

Results: The patients were 92% female, 37% African American, 54% Caucasian with mean age 48.1 ±13.1 years. Of the 1044 patients, 270 had at least one thrombotic event, including deep venous thrombosis (122), stroke (77), myocardial infarction (26), other venous (22), and other arterial thrombosis (13). Elevated levels of D-dimer were not associated with thrombosis. Thrombin generated microparticles were associated with history of a thrombotic event (Table 1). In subanalyses, we found that this association was only found with respect to venous (but not arterial) events (Table 2). There were 46 patients with a thrombotic event during prospective followup. The adjusted risk ratio for plasma microparticles (adjusted for presence of antiphospholipid antibodies) was 1,6,1.4,1.4 respectively for the 2nd 3rd and 4th quartiles.

Table 1. Life-time Rates of Thrombotic Events in SLE by Biomarker Levels

Group	# events	# of person-years at risk	Rate per 1000 person years	Risk Ratio (95% Confidence Interval)	P-value	Adjusted[1] Risk Ratio (95% Confidence Interval)	P-value
Everyone	270	45,480	5.9				
D-dimer							
1st quartile	76	11,035	6.9	1.0 (Ref. Group)	0.12	1.0 (Ref. Group)	0.12
2nd quartile	65	11,766	5.5	0.8 (0.6, 1.1)	0.029	0.8 (0.6, 1.1)	0.022
3rd quartile	58	11,712	5.0	0.7 (0.5, 1.0)	0.79	0.7 (0.5, 0.9)	0.41
4th quartile	71	10.967	6.5	1.0 (0.7, 1.3)		0.9 (0.6, 1.2)	
PMP							
1st quartile	54	10,826	5.0	1.0 (Ref. Group)	0.16	1.0 (Ref Group)	0.043
2nd quartile	63	10,523	6.0	1.3 (0.9, 1.9)	0.020	1.5 (1.0, 2.1)	0.0014
3rd quartile	68	10,233	6.6	1.5 (1.1, 2.2)	0.19	1.8 (1.3, 2.6)	0.028
4th quartile	62	10,460	5.9	1.3 (0.9, 1.9)		1.5 (1.0, 2.2)	

[1] Adjusting for ever having a positive anticardiolipin or lupus anticoagulant

Table 2. Life-time rates of Venous Thrombotic Events, by Biomarker Levels

Group	# events	# of person-years at risk	Rate per 1000 person years	Risk Ratio (95% Confidence Interval)	P-value	Adjusted[1] Risk Ratio (95% Confidence Interval)	P-value
Everyone	167	46,489	3.6				
D-dimer	40	11,403	3.5	1.0 (Ref. Group)	0.55	1.0 (Ref. Group)	0.59
1st quartile	48	11,946	4.0	1.1 (0.7, 1.7)	0.39	1.1 (0.7, 1.7)	0.34
2nd quartile	35	11,923	2.9	0.8 (0.5, 1.3)	0.50	0.8 (0.5, 1.3)	0.94
3rd quartile	44	11,216	3.9	1.2 (0.8, 1.8)	1.0 (0.7, 1.6)		
4th quartile							
PMP	32	11,085	2.9	1.0 (Ref. Group)	0.093	1.0 (Ref. Group)	0.028
1st quartile	42	10,758	3.9	1.5 (0.9, 2.4)	0.46	1.7 (1.1, 2.7)	0.14
2nd quartile	33	10,552	3.1	1.2 (0.7, 2.0)	0.059	1.5 (0.9, 2.4)	0.0072
3rd quartile	43	10,652	4.0	1.6 (1.0, 2.5)		1.9 (1.2, 3.0)	
4th quartile							

[1] Adjusting for ever having a positive anticardiolipin or lupus anticoagulant

Conclusion: Plasma microparticles that generate thrombin increase the risk of venous thrombosis. These data indicate that hypercoagulability in SLE can be further characterized beyond antiphospholipid antibodies, allowing prophylactic therapy to be given to the subset at greatest risk.

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2517

The Interferon-Alpha Signature In Patients With Serologically Active Clinically Quiescent Systemic Lupus Erythematosus. Amanda J. Steiman[1], Murray B. Urowitz[1], Dominique Ibanez[1], Carolina Landolt-Marticorena[2], Joan E. Wither[3] and Dafna D. Gladman[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON, [3]Toronto Western Research Institute, Toronto Western Hospital, University of Toronto, Toronto, ON.

Background/Purpose: Interferon-α (IFN-α) plays a prominent pro-inflammatory role in SLE. Studies suggest clinical/serologic discordance may illuminate systemic lupus erythematosus (SLE) pathophysiology, as peripheral IFN-α production is blunted in some autoantibody-producing, clinically quiescent SLE mice despite abundant IFN-α –producing plasmacytoid dendritic cells (pDCs). This goes against the current SLE paradigm which postulates that nucleic acid-containing immune complexes stimulate pDCs via Toll-like receptors to generate copious IFN-α, leading to upregulation of proinflammatory molecules and clinical disease. Thus serologically active clinically quiescent (SACQ) patients who, like these mice, exhibit persistent autoantibody production despite durable clinical quiescence, may provide unique insights. We investigated whether 5 IFN-associated genes and IFN-associated cyto/chemokines differed in SACQ patients compared to serologically and clinically active (SACA) and serologically and clinically quiescent (SQCQ) patients.

Methods: We defined SACQ and SQCQ as ≥2-year periods without clinical activity, with/without persistent serologic activity, respectively, by SLE Disease Activity Index 2000 (SLEDAI-2K), over which antimalarials were permissible but corticosteroids/immunosuppressives were not. SACA was defined as disease activity, by SLEDAI-2K, which compelled immunosuppression. Clinical and lab data were collected at each visit. Gene expression of *OAS1*, *IFT1*, *MX1*, *LY6E* and *ISG15* was measured by *q*RTPCR, and a composite IFN gene score was developed. Plasma cyto/chemokines were measured by 65-plex Luminex panel, with the 19 most relevant selected *a priori*for analysis. Non-parametric univariate and logistic regression analyses were conducted with Bonferroni correction applied.

Results: Twenty-two, 27 and 43 SACQ, SQCQ and SACA patients, respectively, were included in the analysis. There were no differences in gene expression, or in cyto/chemokine levels between SACQ and SQCQ. SACQ patients were older (43.7 ± 13.7 vs 28.7 ± 9.4, $p < 0.0001$) and had longer disease duration (18.5 ± 12.5 vs 7.4 ± 7.1 years, $p=0.0005$) at study start than did SACA patients. Anti-Ro (82% vs 46%, $p=0.007$) and anti-La (50% vs 13%, $p=0.002$), antibodies were significantly more prevalent in SACQ than in SACA patients. Anti-RNP antibodies were significantly more prevalent in SACA than in SACQ (74% vs 36%, $p=0.004$). The SACQ IFN gene score was significantly lower than that of SACA ($p=0.003$). Levels of GM-CSF, IL-6, IL-10, IP-10, MCP-1 and TNF-α were significantly lower in SACQ than SACA. Logistic regression analysis revealed that anti-La antibody positivity, and low levels of MCP-1 and *LY6E*were associated with SACQ status.

Conclusion: The SACQ interferon signature and cytokine/chemokine profile closely resemble those of patients who are in complete remission. Anti-La antibody positivity and low levels of MCP-1 and *LY6E* were associated with SACQ status in this small pilot study. The presence of this combination of factors may serve to reinforce the clinical impression of disease quiescence in SACQ patients.

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2518

Only BAFF mRNA, Not BAFF Protein Level In Blood, Is Associated With SLE Activity Over One Year. Eric Zollars[1], Hong Fang[1], Jadwiga Bienkowska[2], Julie Czerkowicz[3], Ann Ranger[3], Norm Allaire[2], Alice Thai[3], Jeff Browning[4], Laurence S. Magder[5] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Biogen Idec Inc., Cambridge, MA, [3]Biogen Idec Inc, Cambridge, MA, [4]Boston University School of Medicine, Boston, MA, [5]University of Maryland, Baltimore, MD.

Background/Purpose: B-cell–activating factor (BAFF; also known as B lymphocyte stimulator or BLyS) is a prominent factor in the selection and survival of B cells. BAFF has been demonstrated to be elevated in the blood of systemic lupus erythematosus (SLE) patients and is implicated in the pathogenesis of the disease. We have shown that BAFF gene expression level (mRNA) in whole blood associates with same day disease activity and predicts future activity in SLE patients. The concentration of the BAFF protein in serum has also been used as a marker of disease activity. In this study, we investigated the utility of BAFF mRNA versus protein level as a predictor of future global disease activity in SLE patients.

Methods: 292 patients (59% Caucasian, 34% African-American, 92% female, mean age 46 ±12 years) were enrolled in a prospective observational study. At baseline, BAFF gene expression level was measured in peripheral blood RNA (PAXgene) using microarray (Affymetrix) and confirmed with quantitative PCR. Serum BAFF (protein) levels were measured using the Rules Based Medicine platform. The number of visits per patient over the following year ranged from 1–9. Six patients had 1 visit, 46 patients had 2–3 visits, 159 patients had 4 visits, and 81 patients had more than 4 visits. P-values were calculated using generalized estimating equations as implemented in SAS 9.2. P-values were then adjusted for ethnicity.

Results: Table 1 shows the association of BAFF mRNA with SLE global activity (physician global assessment, PGA; and SLEDAI) over the next year, as well as renal activity, serologies and ESR over the next year. Table 2 shows the association of BAFF protein with the same disease parameters.

Table 1. Association of baseline BAFF mRNA level with percentage of visits with disease activity over the subsequent year

Variable	Low BAFF (<10.7) N visits=387	Med BAFF (10.7–11.4) N visits=476	High BAFF (>11.4) N visits=347	Adjusted P-value for ethnicity
Physician global assessment >1	8%	21%	24%	0.0041
SLEDAI ≥2	36%	57%	71%	<0.0001
Urine Protein/Creatinine Ratio (≥0.5)	3%	13%	13%	0.0096
Anti-dsDNA ≥10	9%	21%	35%	<0.0001
C3 <79 mg/dL	4%	11%	21%	0.0004
C4 <12 mg/dL	4%	11%	19%	0.0005
ESR >20	35%	55%	63%	0.0005

Table 2. Association of baseline BAFF protein level with percentage of visits with disease activity over the subsequent year

Variable	Low (>950 pg/ml) N patients = 96 N visits = 405	Med (950–1400 pg/ml) N patients = 98 N visits = 404	High (>1400 pg/ml) N patients = 98 N visits = 401	P-value	Adjusted P-value for ethnicity
Physician global assessment >1	17%	15%	21%	0.49	0.53
SLEDAI ≥2	51%	52%	60%	0.30	0.073
Urine Protein/Creatinine Ratio (≥0.5)	9%	7%	12%	0.39	0.38
Anti-dsDNA ≥ 10	18%	14%	32%	0.0036	0.0031
C3 <79 mg/dL	7%	10%	18%	0.052	0.090
C4 <12 mg/dL	9%	7%	16%	0.090	0.14
ESR >20	45%	51%	55%	0.25	0.11

Conclusion: BAFF mRNA at the baseline visit was strongly associated with global disease activity, urine protein/creatinine ≥0.5, serologies, and ESR over the next year. In contrast, BAFF protein level in the blood at baseline only correlated with anti-dsDNA over the next year. This study supports the use of BAFF mRNA level in peripheral blood rather than protein as a predictive biomarker of disease activity in SLE patients.

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A Systemic Lupus Erythematosus (SLE) Diagnostic Test Based On DNA Methylation Signatures From Peripheral Blood Mononuclear Cells. David W. Anderson, Robert Shoemaker, Kurt Krummel, Zachary Hornby and Jonathan E. Lim. IGNYTA, Inc., San Diego, CA.

Background/Purpose: The heterogeneous nature of SLE and a lack of reliable biomarkers make SLE a challenge to classify in patients. A differential diagnosis of SLE from other rheumatic and autoimmune diseases can be difficult due to lack of definitive tests with sufficient sensitivity and specificity. Genome-wide DNA methylation analysis of SLE patients' PBMCs was performed on *Illumina HumanMethyl450* BeadChips to assess whether SLE has a DNA methylation signature that outperforms current diagnostic tests.

Methods: PBMC Genomic DNA was isolated from 252 patients and evaluated with the Illumina *HumanMethylation450*chip. The 147 patient sample training set consisted of 15 SLE, 16 rheumatoid arthritis, (RA), 13 osteoarthritis (OA), 28 healthy control (HC), and 75 with undifferentiated arthritis (UA), but not SLE after one year of follow up. Differentially methylated loci (DML) were identified using a non-parametric statistical test

to rank CpG loci that were differentially methylated in SLE samples compared to non-SLE samples. An independent, blinded 105 patient PBMC sample test set: 17 SLE, 28 RA, 12 HC, 17 other rheumatic (ankylosing spondylitis, psoriatic arthritis, reactive arthritis, spondyloarthopathy), and 31 other autoimmune disease (Crohn's, Diabetes Type I, multiple sclerosis, psoriasis, ulcerative colitis) patients was used to confirm the model.

Results: Of 456,355 autosomal CpGs whose methylation frequencies were assessed, the top 25 DML were identified. These 25 DML were associated with 18 genes (10 kb upstream to 10 kb downstream of gene). 10 of these genes had previously been found to be differentially methylated or differentially expressed in published SLE studies. DML selection and model training were repeated on 258 CpGs associated with these 10 genes; a panel of the top 25-DML from the resultant list was selected. This 10 gene-based 25 DML panel was used to train a support vector machine model (radial basis function kernel, cost = 1). The model cut off for SLE/non-SLE classification was determined using leave one out cross validation on the training set. In a prospective study, our 25-DML SLE diagnostic model correctly classified 14 of 17 independent SLE samples (82% sensitivity) and 86 of 88 non-SLE samples (98% specificity), achieving overall accuracy of 95%. Disease severity and medication information did not explain the misclassification of 3 SLE samples. The 18 genes associated with the initial 25 DML were enriched in Ingenuity's pathways for 1) Interferon Signaling and 2) Activation of interferon regulatory factors by Cytosolic Pattern Recognition Receptors (Benjamini-Hochberg p-value < 0.01 for each). The Interferon Signaling pathway was also enriched in SLE patients for the selected 25 DML panel validated on the 105 prospective samples.

Conclusion: This study confirms that SLE can be distinguished with high accuracy from other rheumatic diseases using DNA methylation biomarkers from PBMCs. Expanded studies are warranted to improve the diagnosis of SLE based on DNA methylation signatures. Furthermore, these biomarkers could identify the underlying molecular pathways associated with SLE. This understanding might be used to select therapies for patients or to identify novel therapeutic targets.

Disclosure: D. W. Anderson, IGNYTA, Inc, 3; **R. Shoemaker**, IGNYTA, Inc., 3; **K. Krummel**, IGNYTA, Inc, 3; **Z. Hornby**, IGNYTA, Inc, 3; **J. E. Lim**, IGNYTA, Inc, 4.

2520

A Freely Accessible Toolbox For Patient-Reported Outcomes: Development and Systematic Literature Review For Lupus Instruments. Isabel Castrejón[1], Loreto Carmona[2], Robin Christensen[3], Till Uhlig[4], Birgit Prodinger[5], Francis Guillemin[6], Marieke Scholte-Voshaar[7] and Laure Gossec[8]. [1]NYU Hospital for Joint Diseases and New York University School of Medicine, New York, NY, [2]Institute for Musculoskeletal Health, Madrid, Spain, [3]Musculoskeletal Statistics Unit, The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, [4]Diakonhjemmet Hospital, Oslo, Norway, [5]Swiss Paraplegic Group, Nottwil, Switzerland, Notwill, Switzerland, [6]CHU Nancy, Clinical Epidemiology and Evaluation, Université de Lorraine, Paris Descartes University, APEMAC, EA 4360, Nancy, France, [7]EULAR Standing Committee of People with Arthritis/Rheumatism in Europe, Zurich, Switzerland, [8]Pitié-Salpêtrière Hospital, Pierre et Marie Curie University, Paris, France.

Background/Purpose: Patient self-report has become prominent in the assessment of rheumatic and musculoskeletal diseases (RMD). In a workshop on priorities in PROs in 2009 it was proposed to generate a catalogue with the available instruments. The main objective of this project was to develop a structured design for this catalogue freely available online which would include a comprehensive database of validated instruments.

Methods: The first work package was aimed to develop the toolbox with the participation of 15 methodological collaborators to decide the toolbox′s aims and scope, and basic requirements. In a second work package, the aim was to feed the toolbox using systematic reviews of the literature by target disease with a common strategy to identify validation of PRO. The systematic literature review for systematic lupus erythematous (SLE) is described here as a methodological example. A search strategy was run in MEDLINE, EMBASE, and the Cochrane Library. Validation studies, cohort studies, reviews and meta-analyses were included. Selection criteria were: a) studies on adult patients with SLE defined by the ACR criteria, and b) validation studies of PRO. A reviewer screened title/abstracts and the relevant information was collected using a standardized data collection form based on the COSMIN checklist. The third work package was to provide educational support.

Results: Two hundred thirty six instruments have been identified of which 106 are generic and the remaining ones RMD specific. In particular for SLE, from 704 initial studies captured, we identified 18 articles meeting the predefined criteria. Studies addressed validation of 10 PRO, 1 to evaluate disease activity, 1 to evaluate lupus symptoms, 3 to evaluate quality of life, 2 to evaluate damage and 3 to evaluate patient's needs, health and family functioning. Internal consistency was studied in all, with Cronbach's α ranging from 0.71 to 0.96. Validity, examined by means of convergence with other instruments, was generally similar between tools. Responsiveness was tested in SLAQ, SLEQoL, with a standardized response mean (SRM) ranging from 0.12 to 0.44. Interpretability was only tested in SLE QoL, Lupus QoL and Lupus PRO with similar floor/ceiling effect (Table). Information about construct being measured, recommendations for use, translated versions and validation have been uploaded in the catalogue website. A list and definition for each validation aspect was included for educational support

Table. Summary of the results of the validity of the 10 SLE patient report outcomes

SLE PROs	Domain	# Items & Range	Measurement Properties				
			Reliability	Cronbach	Validity	Responsiveness	Interpretability
SLAQ (Systemic Lupus Activity Questionnaire)	Disease Activity	Items: 3 Range: 0–44		$\alpha = 0.87$	+++	**SRM:** 0.12	—
SSC (SLE Symptom Checklist questionnaire)	Lupus Symptoms	Items: 38 Range: 0–152		$\alpha = 0.89$	+++	++	—
SLEQOL (SLE-specific quality-of-life instrument)	Quality of Life	Items: 49 Range: 40–280		$\alpha = 0.95$	+++	**SRM:** 0.44 **Effect Size:** 0.33	**Floor:**14.9% **Ceiling:**<2.6%
LupusQoL (Lupus quality of life)	Quality of Life	Items: 34 Range: 0–100		$\alpha = 0.88$–0.96	+++	—	**Floor:**<10.8% **Ceiling:** 4–21%
SLENQ (SLE needs questionnaire)	Needs	Items: 97 Range: –		$\alpha = 0.77$	+++	—	—
LDIQ (Lupus Damage Index Questionnaire)	Damage	Items: 56 Range: 0–22		$\alpha = 0.72$	+++	—	+
L-QoL (Lupus quality of life)	Quality of Life	Items: 25 Range: 0–22		$\alpha = 0.92$	+++	—	—
BILD (Brief Index of Lupus Damage)	Damage	Items: 28 Range: 0–33		—	+++	—	—
LupusPRO (Lupus Patient-Reported Outcome)	Health outcome	Items: 44 Range: 0–100		$\alpha = 0.72$–0.94	+++	++	**Floor:**22.3% **Ceiling:**1.2%
SLE-FAMILY	Family functioning	Items: 6 Range: 1–7		$\alpha = 0.71$	+++	—	—

SRM: Standardized Response Mean

Conclusion: A freely accessible toolbox for PROs has been designed. This toolbox employs scientific measurement properties and provides PROs with advice on their application in a user-friendly manner. This toolbox is an on-going process led by rheumatologists, related professionals, and patients that should help to better understand and use PRO in RMD.

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Correlation Of Anti Single and Double Stranded DNA Antibodies and Disease Activity In Systemic Lupus Erythematosus. Cecilia Catoggio, Cecilia Reimundes and Carlos Edgardo Perandones. CEMIC, Buenos Aires, Argentina.

Background/Purpose: Anti DNA antibodies are considered a hallmark of systemic lupus erythematosus (SLE). Anti double stranded DNA antibody (dsDNA) is part of the SLE classification and activity criteria due to its high specificity. However its sensitivity is moderate. On the other hand, the role of single stranded DNA antibodies (ssDNA) has not been fully addressed. The objective of this study is to correlate the presence of anti ssDNA and dsDNA antibodies with SLE activity, measured by ECLAM (*European Consensus Lupus Activity Measurement).*

Methods: We reviewed the charts of our SLE patients who had both anti ssDNA and dsDNA antibodies measured simultaneously between 2001 and 2011. Anti dsDNA was determined by *Crithidia luciliae* immunofluorescence assay and anti ssDNA was determined by a home-made ELISA. In each serologic determination, disease activity was established by ECLAM according to chart information from the previous 30 days. Finally, determinations were classified in 4 serologic groups for analysis: Group 1 (negative ssDNA and dsDNA), Group 2 (positive ssDNA and negative dsDNA), Group 3 (positive ssDNA and dsDNA) and Group 4 (negative ssDNA and positive dsDNA).

Results: Ninety patients were evaluated (80 female), with a median age (range) of 39 (23–77) years. There were 328 simultaneous serologic determinations of anti ssDNA and dsDNA. According to the ECLAM, activity was

found in 269 (82%) determinations and inactivity was found in 59 (18%) determinations.

Considering the ECLAM as the gold standard for activity, we calculated sensitivity, specificity, positive and negative predictive value (PPV, NPV) and positive likelihood ratio (+LHR) for anti ssDNA and dsDNA, using dicotomic variables.

	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+ LHR
Anti ssDNA	78 (73–82)	44 (39–49)	86 (83–90)	30 (25–35)	1.39
Anti dsDNA	28 (23–32)	92 (88–94)	94 (91–96)	22 (17–26)	3.29

When the serologic determinations were classified in groups, we calculated sensitivity, specificity, PPV, NPV and +LHR for anti ssDNA and dsDNA.

Serologic Groups	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+ LHR
Group 1 (n: 83)	21 (17–27)	56 (42–69)	69 (57–78)	14 (10–18)	0.47
Group 2 (n: 165)	52 (45–58)	53 (39–65)	83 (76–88)	19 (14–26)	1.11
Group 3 (n: 77)	27 (22–33)	92 (80–97)	94 (85–98)	22 (17–28)	3.38
Group 4 (n: 3)	—	—	—	—	—

Finally, the seropositive determinations were correlated with the following variables:

	Group 2			Group 3		
Variables	RR	95 % IC	*p*	RR	95 % IC	*p*
<50 years	2.65	1.47–4.77	***0.001***	19.18	6.9–53.21	***0.0001***
Joints	1.31	0.46–3.74	0.607	3.79	1.17–12.27	***0.026***
Skin	0.93	0.27–3.12	0.902	1.79	0.49–6.45	0.370
Renal	4.17	1.11–15.73	***0.035***	6.35	1.62–24.95	***0.008***
Hematologic	0.74	0.41–1.34	0.323	1.03	0.48–2.22	0.939
Erythrosedimentation rate	1.43	0.72–2.85	0.304	1.66	0.71–3.87	0.238
Hypocomplementemia	4.13	2.05–8.31	***0.0001***	6.31	2.83–14.06	***0.0001***

RR: relative risk

Conclusion: Anti ssDNA antibody shows a higher sensitivity and lower specificity than anti dsDNA antibody for SLE activity. The presence of anti ssDNA with or without anti dsDNA, was associated with younger age, hypocomplementemia and renal involvement.

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2522

Novel Autoantibody Against CAF-1 Is a Biomarker For CNS Manifestation in patients With SLE. Kentaro Doe, Kazuhisa Nozawa, Kaori Hiruma, Yusuke Yamada, Yuko Matsuki, Soichiro Nakano, Michihiro Ogasawara and Yoshinari Takasaki. Juntendo University School of Medicine, Tokyo, Japan.

Background/Purpose: Proliferating cell nuclear antigen (PCNA) is known to be an autoantigen specifically recognized by antibodies in sera from patients with systemic lupus erythematosus (SLE). Although a prevalence of anti-PCNA antibody among the patients with SLE is relatively rare (less than 5%), we have demonstrated that patients with SLE often elicit autoimmune response against multiple proteins consisting of PCNA complex even though immune response against PCNA itself is absent. Therefore, the autoimmune response to the consisting proteins of PCNA complex is a unique mechanism of autoantibody production specifically recognized in SLE. Chromatine assembly factor-1(CAF-1) is an essential molecule for DNA replication belonging to the constitutive proteins of PCNA complex. Therefore, we conducted this study to confirm whether the autoimmune response to CAF-1 occurred in patients with SLE.

Methods: Immunoreactivity against CAF-1 among sera with SLE, normal healthy controls (NHCs), and other disease controls (PM/DM, SSc, SjS, MCTD, and RA) was evaluated by ELISA and immunoblotting. The gene expression of CAF-1, interferon regulating factor-1 (IRF-1), and pro-apoptotic molecules (Fas, BID, and TNFRS10B) were measured by quantitative RT-PCR in peripheral mononuclear cells (PBMCs) of SLE patient in comparison with those of NHCs. Serum level of interferon gamma inducing protein-10 (IP-10) was measured by ELISA.

Results: Increased autoimmune response to CAF-1 was significantly observed in SLE compared to the disease controls and NHCs. CNS involvement and disease onset of younger age were significantly recognized in the anti-CAF-1 antibody positive lupus patients in comparison with those of anti-CAF-1 antibody negative lupus patients. In addition, increased gene expression of CAF-1 and proapoptotic molecules on PBMCs was observed in SLE compared to those of NHCs. Moreover, increased gene expression of IRF-1 in PBMCs along with serum level of IP-10 was significantly observed in SLE.

Conclusion: In the present study, we identified anti-CAF-1 antibody as a novel autoantibody specifically recognized in patients with SLE. Measurement of anti-CAF-1 antibody is useful for the diagnosis of SLE and could be a new biomarker for CNS lupus. Moreover, our results indicated that increased apoptosis and aberrant regulation of IFN-g in peripheral mononuclear cells (PBMCs) played an important role for a mechanism for anti-CAF-1 antibody production in SLE.

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Inflammatory Arthritis Activity During Pregnancy In Systemic Lupus Erythematosus. Sara K. Tedeschi, Bonnie L. Bermas and Karen H. Costenbader. Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: While overall SLE disease and lupus nephritis activity during pregnancy have been studied, the activity of inflammatory arthritis during SLE pregnancy has not been examined. Our goals were to evaluate the activity of inflammatory arthritis during pregnancy in SLE and its effects on pregnancy outcomes.

Methods: From our Registry of all patients seen in our Lupus Center with confirmed SLE by rheumatologist review for 1997 ACR Criteria for Classification, we identified women with >2 visits to our Center and ≥1 pregnancy between 1990–2013. From Registry and medical records, we collected data on: ages at SLE diagnosis and at pregnancy, history of inflammatory arthritis preceding and during pregnancy, SLE medications during pregnancy, and pregnancy outcomes. We analyzed the data using descriptive statistics and Fisher's exact tests.

Results: Of 1,127 women with SLE, 56% had a history of inflammatory arthritis and 134 had ≥1 pregnancy (184 pregnancies). Among women with pregnancies, mean age at SLE diagnosis was 23.1 (SD 6.8) years; 61% were White, 14% Hispanic and 13% Black. Mean age at conception was 30.8 (SD 5.3) years; average SLE duration prior to pregnancy was 7.1 (SD 5.8) years; 9% were diagnosed with SLE during pregnancy; 33% were primigravida. Of the women without a history of inflammatory arthritis (n=80), none experienced arthritis during pregnancy. Of the 104 pregnancies in women with a history of inflammatory arthritis, 16 had active arthritis in the 6 months prior to conception (**Table**). Five of these women received an immunosuppressant 6 months prior to conception and 13 had medication changes during pregnancy. In 4 of 16 pregnancies with active arthritis prior to pregnancy, arthritis flared during pregnancy (25%), whereas arthritis flared in 6 of 88 pregnancies with no active inflammatory arthritis within 6 months of pregnancy (7%, p 0.045). Overall, 83% of arthritis flares occurred in the 2nd trimester.

Of the 16 pregnancies in which the mother had recently active inflammatory arthritis, 62% were term deliveries, 19% were pre-term, and 19% 1st trimester abortions. Of the pregnancies with quiescent inflammatory arthritis 6 months prior to pregnancy, delivery outcomes were: 68% term, 17% preterm (p 0.73 vs. in those with arthritis), 10% 1st trimester abortions, and 5% 2nd or 3rd trimester fetal loss (p 0.71 vs. in those with arthritis).

Table. Arthritis Activity in 104 Pregnancies among Women with a History of SLE Arthritis, 1990–2013

				Medications 6 months prior to Pregnancy			
	Number of pregnancies	Age at pregnancy, mean (SD)	Arthritis during pregnancy, N (%)	Prednisone, N (%)	Immuno-suppressants*, N (%)	Hydroxy-chloroquine, N (%)	NSAID, N (%)
Arthritis active 6 months prior to pregnancy	16	29.8 (5.4)	4 (25)	8 (50)	5 (31)	10 (63)	7 (43)
History of arthritis, not active 6 months prior to pregnancy	88	30.9 (4.9)	6 (7)	31 (35)	11 (13)	44 (50)	12 (14)

* Immunosuppressants: azathioprine, mycophenylate mofetil, sulfasalazine, and rituximab. Not mutually exclusive categories.

Conclusion: Inflammatory arthritis activity during pregnancy was uncommon in this female SLE population. Among women with inflammatory arthritis symptoms 6 months prior to conception, a higher proportion had persistent or worsened symptoms during pregnancy than among women whose inflammatory arthritis was inactive 6 months prior to conception. Pregnancy outcomes were similar among those with and without active inflammatory arthritis prior to pregnancy.

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Application of The 2012 Systemic Lupus International Collaborating Clinics Classification Criteria On a Regional Swedish Systemic Lupus Erythematosus Register. Anna Ighe[1], Örjan Dahlström[2], Thomas Skogh[1] and Christopher Sjöwall[1]. [1]Linköping University, Linköping, Sweden, [2]Linneaus Centre HEAD, Swedish Institute for Disability Research, Linköping, Sweden.

Background/Purpose: In addition to the 1982 American College of Rheumatology criteria (ACR-82) for scientific classification of systemic lupus erythematosus (SLE), many clinicians find the 'Fries criteria' (requiring an abnormal ANA titer *plus* at least two typical organ manifestations) helpful for diagnostic purposes. Last year, the Systemic Lupus International Collaborating Clinics group proposed a new set of validated classification criteria (SLICC-12), claimed to being more sensitive for SLE. The aim of the present study was to analyze the performance of SLICC-12 compared to Fries criteria and ACR-82 among well-characterized SLE cases and controls in a regional Swedish register.

Methods: The study population consisted of 231 SLE cases (93% Caucasians; 203 women, 28 men; mean age at diagnosis 38.8 years, range 3–85) confirmed by Fries criteria and/or ACR-82. 53 controls (46 women, 7 men; mean age 40.8 years; range 12–83 years) were enrolled on the basis of referral to a rheumatology specialist based on at least one criterion regarding 'immunologic disorder' according to ACR-82 and a clinical suspicion of SLE. Sensitivity and specificity figures for SLE were calculated. All confirmed SLE cases took part in a prospective follow-up programme at the Rheumatology clinic, Linköping University hospital. Informed consent was obtained from all subjects and the research protocol was approved by the Regional Ethics Committee in Linköping (M75-08). The controls were eventually diagnosed with the following conditions: SLE, rheumatoid arthritis, palindromic rheumatism, undifferentiated arthritis, pleuritis, undifferentiated connective tissue disease, primary antiphospholipid syndrome, scleroderma, polymyositis, fibromyalgia, primary Sjögren's syndrome, psoriatic arthritis, PAPA syndrome, renal infarction, mixed connective tissue disease, Muckle-Wells syndrome, arthralgia, multiple sclerosis and overlap syndrome.

Results: Of the confirmed SLE cases, 98% fulfilled Fries criteria, 81% ACR-82 and 91% SLICC-12. The combinations of Fries and/or SLICC-12 identified 99%, compared to 93% of all confirmed SLE cases identified by ACR-82 and/or SLICC-12. The sensitivity was high for Fries (97%) and SLICC-12 (91%), but lower for ACR-82 (79%), whereas the specificity was superior for ACR-82 (98%) compared to Fries (83%) and SLICC-12 (75%).

Conclusion: We confirm that the ACR-82 criteria set offers a very high diagnostic specificity, but fail to reveal >20% of the SLE cases as defined here. The SLICC-12 criteria provide important additional sensitivity, whereas the specificity was mediocre in this comparison. To increase sensitivity and specificity figures, we advice a combination of the ACR-82 and SLICC-12 criteria for future SLE studies.

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An Assay Panel Combining Cell Bound Complement Activation Products With Autoantibodies To Extractable Nuclear Antigens and Mutated Citrullinated Vimentin Helps With The Differential Diagnosis Of Systemic Lupus Erythematosus. Chaim Putterman[1], Richard Furie[2], R. Ramsey-Goldman[3], Anca Askanase[4], Jill P. Buyon[4], Kenneth C. Kalunian[5], W. Winn Chatham[6], Elena M. Massarotti[7], Emily C. Somers[8], Irene Blanco[1], Puja Chitkara[9], Nicole Jordan[1], Kyriakos A. Kirou[10], Arthur Weinstein[11], Susan Manzi[12], Joseph M. Ahearn[12], Claudia Ibarra[13], Derren Barken[13] and Thierry Dervieux[13]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]North Shore-LIJ Health System, Lake Success, NY, [3]Northwestern University Feinberg School of Medicine, Chicago, IL, [4]NYU School of Medicine, New York, NY, [5]UCSD School of Medicine, La Jolla, CA, [6]University of Alabama at Birmingham, Birmingham, AL, [7]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [8]University of Michigan, Ann Arbor, MI, [9]SDAMC, San Diego, CA, [10]Hospital for Special Surgery, New York, NY, [11]Washington Hospital Center, Washington, DC, [12]West Penn Allegheny Health System, Pittsburgh, PA, [13]Exagen Diagnostics, Vista, CA.

Background/Purpose: We previously established the value of cell-bound complement activation products (CBCAPS) in the diagnosis of systemic lupus erythematosus (SLE) (CAPITAL study). The purpose of this study was to enhance the performance of this diagnostic method for SLE patients compared with non-SLE rheumatic disease patients. For this, we combined CBCAPs together with autoantibodies to extractable nuclear antigens (ENA: anti-Smith [Sm], SS-B, Centromere, Scl-70, Jo-1), and mutated citrullinated vimentin (MCV).

Methods: The study population consisted of 678 subjects (291 SLE, 272 other diseases and 115 healthy) enrolled in CAPITAL (n=503) and follow-up studies (n=175). All SLE patients met the 1982 ACR SLE classification criteria and presented with active and non-active disease. The group of non-SLE patients consisted of subjects with rheumatoid arthritis, systemic sclerosis, primary Sjogren's, polymyositis/dermatomyositis and various other rheumatic diseases. ANA, autoantibodies to ENA and MCV were measured using solid phase immunoassays. C4d fragment deposited on erythrocytes (EC4d) and B-lymphocytes (BC4d) were determined using flow cytometry. The analysis involved two consecutive "tiers" of analyses. In tier 1 the diagnosis of SLE relied on anti-dsDNA positivity (base model) with the addition of positivity for anti-Sm and elevated CB-CAPS (EC4d>35 units or BC4d>200 units). Tier 2 was determined among subjects negative in tier1 and consisted of a weighted index score of ANA positivity (base model), with the addition of EC4d/BC4d levels and positivity for antibodies to ENA/MCV. Positivity for the index score (>0) was indicative of SLE, and the two-tier combination resulted in the overall performance characteristics. Statistical analyses utilized area under receiver operating characteristic (ROC) curves (SLE vs. non-SLE patients), and calculations of diagnostic sensitivity and specificity.

Results: Positivity for ANA was sensitive for SLE (89%); specificity for non SLE subjects was low (54%). Conversely, anti-dsDNA and anti-Sm were less sensitive (32% and 11%, respectively) but highly specific (96% and 100%, respectively). EC4d and BC4d levels were 2.6 and 3.2-fold higher in SLE than in non SLE subjects ($p<0.01$). The model combining anti-dsDNA with ANA positivity (base model) yielded poor performances (AUC=0.689) (Table). However, the stepwise addition of antibodies to ENA/MCV and CBCAPs in two-tier analysis improved the overall specificity (AUC=0.887; $p<0.01$ vs. base model; $p<0.01$ vs. base model with ENA/MCV). The overall performance of the best model consisted of 80% sensitivity for SLE, and 85% specificity in distinguishing SLE from other rheumatic diseases. Specificity against healthy individuals was 97%.

	Base Model	Base Model with ENA/MCV	Base Model with ENA/MCV, CBCAPS	Difference From base model
Tier1	dsDNA/ANA	dsDNA; Sm	dsDNA; Sm; CBCAPS	
Tier2	ANA	ANA; ENA/MCV	ANA; ENA/MCV; CBCAPS	
Specificity primary Sjogren's (n = 31)	12.9%	61.3%	67.7%	+54.8%
Specificity systemic sclerosis (n = 34)	35.3%	73.5%	88.2%	+52.9%
Specificity PM/DM (n = 27)	25.9%	40.7%	70.4%	+44.5%
Specificity rheumatoid arthritis (n = 162)	68.5%	87.0%	91.4%	+22.9%
Specificity Other diseases (n = 18)	66.7%	66.7%	72.2%	+5.5%
Total Specificity (non-SLE) (n = 272)	53.7%	76.5%	84.9%	+31.2%
Total Sensitivity (SLE) (n = 291)	88.7%	82.8%	80.1%	-8.6%
AUC (n = 593)	0.689	0.806	0.887	+0.198

Conclusion: An assay panel combining CBCAPS with ANA, anti-dsDNA, and autoantibodies to ENA and MCV is sensitive and specific for SLE.

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An Autoantibody Profile for The Diagnosis Of Systemic Lupus Erythematosus Using the IMMUNARRAY iCHIP™. Chaim Putterman[1], Irene Blanco[1], Nicole Jordan[1], Yves Renaudineau[2], Vered Daniel Carmi[3], Rachel Sorek[3], Ornit Cohen-Gindi[3], Miriam Lerner[3], D. Scott Batty[3], Idan Tamir[3] and Irun R Cohen[4]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]Brest Occidentale University, Brest, France, [3]ImmunArray, Rehovot, Israel, [4]Weizmann Institute of Science, Rehovot, Israel.

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic, recurrent, and potentially fatal multisystem inflammatory disorder mainly affecting women. SLE patients produce antibodies to many different self-antigens, some of which play an important role in the pathogenesis of tissue injury in this disease. Accurate and timely diagnosis of SLE is important because early treatment can reduce morbidity and mortality, particularly from lupus nephritis. Nevertheless, currently used serological markers for SLE are lacking in specificity and/or sensitivity. The aim of this study was to develop

an improved diagnostic test by measuring and multiplexing specific autoantibody reactivities in SLE patients.

Methods: Autoantibody reactivity profiles in serum samples collected from 97 SLE patients within three years of the diagnosis were compared with those of 56 healthy controls. In addition, autoantibody profiles of SLE patients was compared with those of patients with progressive systemic sclerosis, primary Sjogren's syndrome, and primary anti-phospholipid antibody syndrome (APS). Autoantibody profiles were determined using the ImmunArray iCHIP™ - a proprietary protein microarray technology that allows the display of antigens representing a wide range of SLE-associated biochemical pathways on a single chip.

Results: Using this novel platform, SLE patients could be differentiated from healthy subjects and from patients with systemic sclerosis, Sjogren and APS by a relatively small subset of auto-antigens and Epstein Barr Virus (EBV) antigens. The autoantibody reactivity profile that allowed SLE diagnosis with high sensitivity and specificity displayed differential response to known SLE-specific antigens, such as single-stranded DNA and EBV, and to several novel ones. Validation of the autoantibody profile that differentiates SLE patients from healthy controls in additional patient samples showed good performance (75% sensitivity and 85% specificity).

Conclusion: We successfully developed a novel method of antibody profiling for SLE diagnosis, using a single multiplexed chip. The ImmunArray iCHIP™ was able to distinguish between lupus patients and healthy controls, as well as between lupus and other inflammatory rheumatic diseases.

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Association Of Nail Dystrophy With Capillaroscopic Abnormalities, Anti-Endothelial Cell Antibody, Endothelin-1, Activity and Chronicity In Systemic Lupus Erythematosus. Violeta Higuera[1], Luis M. Amezcua-Guerra[2], Felipe Massó[2], Mariana Patlan[1], Hugo Montoya[1], Araceli Paez[1] and Luis H. Silveira[3]. [1]Instituto Nacional de Cardiologia Ignacio Chavez, Mexico city, Mexico, [2]Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico, [3]Instituto Nacional Cardiología Ignacio Chávez, Mexico City, Mexico.

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown etiology, characterized by a broad spectrum of clinical manifestations. There is a large variety of nail abnormalities described in SLE; these abnormalities were detected with a frequency of 25–31% in different series of patients with SLE. Although nail changes have been rarely considered a specific sign of the disease, they have been associated with an increased disease activity, higher incidence of Raynaud's phenomenon and oral ulcerations. It has been postulated that vascular damage plays a crucial role in the pathogenesis of SLE, so many studies have focused on the role of angiogenesis activity markers and endothelial damage. We suggest that the nail dystrophy (ND) could be a reflection of the damage to the microvasculature in patients with SLE.

Objectives: To evaluate the possible association between nail dystrophy (ND) and disease activity, damage index, capillaroscopic abnormalities, autoantibody profile, and endothelial cell activation markers in systemic lupus erythematosus (SLE).

Methods: Analytical and transversal study of SLE patients from a Rheumatology Clinic in a tertiary care hospital. The patients have been divided in two groups, one with, and the other without ND (control group). Clinical, demographic, activity, chronicity, serologic, nailfold capillaroscopy (NFC) characteristics, serum levels of anti-endothelial cell antibodies (AECA), and plasma levels of endothelin-1 (ET-1), were compared between groups. Activity was determined by the SLEDAI-2K and damage by the SLICC/ACR Damage Index. The AECA and ET-1 were determined by an enzyme-linked immunosorbent assay (ELISA).

The probability of differences in the variables frequency distributions was determined by χ^2 test, and the significance of the differences between the means was determined using Mann-Whitney test. *P*-values less than 0.05 were considered statistically significant. The unpaired t-test was used to assess differences between SLE subgroups.

Results: Sixty one patients were included; 50 (82%) were female. Thirty two (52.5%) patients showed ND and 29 did not (control group). The sex, mean age and disease duration were similar in both groups. A significant association of ND with an increased damage index was found ($p=0.04$). Cyclophosphamide was more used in the ND group ($p=0.03$). Onycholysis was the most frequently nail change, it was reported in 40% of the patients. NFC changes were detected in 43% of the ND patients and in 13% of the controls ($p=0.02$). The most frequent NFC finding in the ND group was elongated capillaries (40%). There was not an association of autoantibody profile, ET-1, and AECA with ND.

Conclusion: ND is associated with a greater index of chronicity and with capillaroscopic abnormalities. This might suggest that ND is caused by microvascular damage.

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Pregnancy Outcome In 69 Pregnancies Of Multinational Population In Qatar With Systemic Lupus Erythematosus. Abdul Razzakh Poil[1], Mohammed Hammoudeh[1], Prem Chandra[2], Abdo Lutf[1] and Samar AL Emadi[3]. [1]Hamad General Hospital, Doha, Qatar, [2]Hamad Medical Corporation, Doha, Qatar, [3]ASSISTANT proffesor of clinical medicine weill cornell medical school Qatar, Doha, Qatar.

Background/Purpose: The aim of this study is to determine the frequencies of abnormal pregnancy outcomes in a cohort of patients in Qatar and to identify clinical and laboratory factors predicting adverse fetal and maternal outcomes with systemic lupus erythematosus (SLE) in multinational population in Qatar.

Methods: Data of 69 pregnancies of 36 SLE patients from January 2005 to July 2012 in Hamad General Hospital in Qatar were analyzed retrospectively. Associations between qualitative variables were assessed using Chi-square or Fisher exact tests. Quantitative variables means between the two groups were analyzed using unpaired t test. Lupus activity was assessed based on SLE Disease Activity Index (SLEDAI) criteria.

Results: Among 69 pregnancies (36 patients) 35 (50.7%) in Qatari and 34 (49.3%) were in non-Qatari national. Average numbers of pregnancies prior to and after onset of SLE were 3.73 ± 1.8 and 2.72 ± 1.5. Age at conception (years) and gestational age at delivery (weeks) were 34.5 ± 5.4 and 37.4 ± 2.8 respectively. Antiphospholipid (aPLs), Anti-Ro and Anti-La antibodies were present in 18 (26.1%), 23 (33.3%), 13 (18.8%) pregnancies respectively. There were 10 (14.5%) abortions, 5 (5.7%) stillbirths, 1 neonatal death and 54 (78.3%) live births including two twin gestations. Though, not statistically significant, baby weight at birth was found to be low (2.68 ± 0.64 vs. 2.87 ± 0.60, $p=0.360$) in active lupus patients compared to patients on remission. Pregnancy induced hypertension (PIH) (17.4% vs. 11.1%), intrauterine growth retardation (IUGR) (36.4% vs. 11.8%), preterm delivery (31.6 % vs. 11.8%), still birth (13% vs. 5.6%) and eclampsia (13% vs. 0%)were observed to be higher in active lupus patients compared to patients on remission. Compared with pregnancies without lupus nephritis ($n=44$), pregnancies with lupus nephritis ($n=7$) were associated with a higher risk of still birth (28.6% vs. 4.5%, $p=0.092$), higher rate of eclampsia (28.6% vs. 4.9%, $p=0.103$), IUGR (42.9% vs. 26.2%, $p=0.626$), and PIH (28.6% vs. 9.8%, $p=0.412$). The percentage of live births were higher in pregnancies without lupus nephritis compared to with lupus nephritis (42/44, 95.5% vs. 5/7, 71.4%, $p=0.092$), and live births were significantly higher in pregnancies without eclampsia compared to pregnancies with eclampsia (42/42, 100% vs. 2/7, 28.6%, $p<0.001$). Stillbirth and preterm delivery were found to be higher in pregnancies with proteinuria and presence of Anti-Ro antibody was significantly associated with IUGR (8/18, 44.4% vs. 6/37, 16.2%, $p=0.034$). One case of neonatal heart block was found in which Anti Ro/La antibody was positive. Low level of C3 was associated with higher rate of stillbirth, IUGR, preterm delivery, and PIH, however, the difference were not statistically significant ($p>0.05$).

Conclusion: SLE in pregnancies in Qatar population were associated with higher risk adverse pregnancy outcomes. Disease activity during pregnancy, proteinuria, lupus nephritis and eclampsia/preeclampsia were all negatively associated with pregnancy outcome such as IUGR, still births and preterm delivery. Anti-Ro/La antibodies and low level of C3 were also associated with adverse pregnancy outcomes.

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Improved Outcomes In High Risk Lupus Pregnancies: Usefulness Of a Protocol Based Multidisciplinary Approach In Kerala, India. Vinod Ravindran[1], S Bhadran[2], P Shyjus[3], M Divakaran[4] and V Reshma[5]. [1]MES Medical College, Kerala, INDIA, Perinthalmanna, India, [2]Department of Obstetrics, National Hospital, Calicut, India, [3]Department of Obstetrics, MES Medical College, Perinthalmanna, India, [4]Department of Obstetrics, PVS Hospital, Calicut, India, [5]Department of Obstetrics, Indira Gandhi Hospital, Thalassery, India.

Background/Purpose: In patients with SLE who had previous adverse obstetric outcome(s) the risk of an adverse outcome in subsequent pregnancy rises. The primary objective of this study was to assess the impact of a protocol based multidisciplinary care on pregnancy outcome(s) in a prospective cohort of patients with SLE who had previous adverse obstetric outcome(s).

Methods: Between March 2010 and March 2013 all patients with SLE fulfilling the ACR classification criteria with previous at least one adverse obstetric outcome (maternal; preterm labour, pre ecalampsia or previous medical termination of pregnancy (MTP) in view of SLE flare, foetal; miscarriage, IUGR, preterm birth, low birth weight (LBW), intrauterine death or still birth) desirous of having more children were prospectively enrolled. All patients had in-depth preconception counselling and were prospectively followed throughout the pregnancy as per the protocol with multidisciplinary team input. Therapeutic changes were made as necessary at each visit.

Results: Twenty-one patients (age mean±SD years; 28±3) were enrolled. Previous poor obstetric outcomes were: miscarriage(s) in 8, MTP in 7, preterm labour with IUGR in 3, intrauterine death, still birth and pre ecalapmsia in 1 each. Five patients had secondary APS and 8 had both or either Ro/La positive. Three had lupus nephritis (LN); >6months ago in 2. There were 15 (75%) live births (3 LBW; instrumentation or caesarean section in 5). Three patients had miscarriages (one had ongoing LN). One decided against becoming pregnant after the initial counselling. Seven patients (35%) had lupus flare (4 mild, 2 moderate and 1 severe based on SLEDAI).

Conclusion: Majority of patients in our prospective cohort had acceptable pregnancy outcome. This highlights that for high risk lupus pregnancies a multidisciplinary input with protocol based care offers a superior chance of improved pregnancy outcome.

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Sustained Improvements In Health-Related Quality Of Life In Patients With Systemic Lupus Erythematosus following Epratuzumab Treament: Results from a Phase IIb Trial and Its Open-Label Extension. Vibeke Strand[1], Joan T. Merrill[2], Enkeleida Nikai[3], Brian Kilgallen[4], Antoine Regnault[5] and Caroline Gordon[6]. [1]Stanford University, Palo Alto, CA, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]UCB Pharma, Brussels, Belgium, [4]UCB Pharma, Raleigh, NC, [5]Mapi HEOR & Strategic Market Access, Lyon, France, [6]University of Birmingham, Birmingham, United Kingdom.

Background/Purpose: Epratuzumab is a monoclonal antibody targeting CD22. Improvements in health-related quality of life (HRQoL) with epratuzumab in patients with systemic lupus erythematosus (SLE) have been reported in the ALLEVIATE trials from week 12 and sustained to 4 years.[1,2] In the EMBLEM™ study (dose-ranging phase IIb randomized controlled trial [RCT] in SLE), epratuzumab treatment resulted in clinically relevant improvements in SLE disease activity.[3] We report HRQoL data from EMBLEM™ and its open-label extension (OLE) (NCT00660881).

Methods: In EMBLEM™ patients with moderate-to-severely active SLE (≥1 BILAG 2004 A or ≥2 Bs) were randomized to 1 of 6 intravenous regimens over 12 weeks added to standard of care (SOC): placebo (PBO) or cumulative dose (cd) epratuzumab (200, 800, 2400 or 3600 mg in equal divided doses using 2 every other week [EOW] infusions or 2400 mg cd as 600 mg every week [QW]). Patients from any EMBLEM™ arm completing 12 weeks blinded treatment and those who discontinued due to lack of efficacy but completed ≥8 weeks were eligible to enter the OLE where all patients received 1200mg epratuzumab at weeks 0 and 2 of repeating 12-week cycles. Short Form-36 (SF-36) Version 2.0 was used to assess HRQoL. Data are reported to the end of EMBLEM™ and to weeks 48 and 108 of the OLE (week 108 is last time-point when ≥ 50% of patients reported SF-36 data). Mean changes and % pts reporting improvements ≥ minimum clinically important differences (MCID) (Increases from baseline ≥5.0-points in domain and ≥2.5-points in physical and mental component scores [PCS and MCS]) are presented. Observed case analyses are presented for the OLE.

Results: In EMBLEM™ mean SF-36 PCS, MCS and domain scores across epratuzumab and placebo groups (both receiving background SOC) generally increased over time from baseline through week 12, with greater increases in the PBO group. Longer treatment with epratuzumab during OLE resulted in clinically meaningful changes in HRQoL vs EMBLEM baseline (Table). At week 108 in the OLE 70.8% and 59.3% of patients reported improvements ≥ MCID in PCS and MCS scores.

Table. SF36 scores and MCID with epratuzumab in EMBLEM™ and EMBLEM™ OLE

	EMBLEM™ BL		EMBLEM™ OLE screening			Week 48 of the EMBLEM™ OLE			Week 108 of the EMBLEM™ OLE			
SF36 domain	N	Mean absolute Score	N	Mean absolute Score	Mean change from EMBLEM™ baseline	N	Mean absolute Score	Mean change from EMBLEM™ baseline	N	Mean absolute Score	Mean change from EMBLEM™ baseline	% pts with improvement ≥ MCID
Physical functioning	201	47.0	203	56.6	8.5	156	61.2	15.0	114	57.4	12.6	69.3
Role physical	201	37.9	203	51.1	13.3	156	53.5	15.1	113	54.7	16.5	73.5
Bodily pain	201	36.1	203	48.3	12.1	156	53.0	17.1	114	52.7	16.9	68.4
General health	201	32.6	203	41.3	8.7	156	46.5	13.6	114	47.8	16.2	82.5
Vitality	201	34.3	203	42.8	8.6	156	46.3	13.1	113	43.6	10.9	63.7
Social functioning	201	46.1	203	58.1	12.1	156	63.3	17.9	114	61.4	17.4	66.7
Role emotional	201	50.9	203	58.9	7.9	156	61.4	10.5	113	60.1	10.5	56.6
Mental health	201	50.8	203	57.8	7.1	156	61.5	11.6	113	60.5	11.4	66.4
PCS	201	34.2	203	38.7	4.5	156	40.1	6.4	113	40.5	6.4	70.8
MCS	201	36.1	203	40.0	3.9	156	41.6	6.0	113	40.9	5.7	59.3

Conclusion: In the 12 week EMBLEM™ study treatment period no differences in improvements in HRQoL were observed with epratuzumab, which may be attributed to short term treatment, small sample sizes and active background (SOC) therapy. Nonetheless, over a greater length of time sustained improvements were observed in the EMBLEM™ OLE, which are consistent with those in the ALLEVIATE RCTs.[1,2]

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Elevated Combined Serum Free Light Chains Are Associated With Active Disease In Systemic Lupus Erythematosus. Lakhvir Kaur Assi[1], Larissa Lisnevskaia[2], Emma Ross[3], Richard G Hughes[1], Anisur Rahman[3] and David A. Isenberg[3]. [1]The Binding Site Group Ltd, Birmingham, United Kingdom, [2]Oshawa Clinic, Oshawa, ON, [3]University College London, London, United Kingdom.

Background/Purpose: Chronic and hyper-stimulated B cells are characteristics commonly found in patients with systemic lupus erythematosus (SLE). Due to the complexity and variability observed during the course of the disease there is a paucity of suitable biomarkers and those available do not always reflect disease activity. Polyclonal serum free light chains (FLC), a marker of immune status and renal function, have been reported to be elevated in SLE. The aim here was to compare FLC levels with both routine biomarkers and the British Isles Lupus Assessment Group Index (BILAG) for disease activity in a prospectively collected SLE cohort.

Methods: Combined FLC (FLCκ + FLCλ= cFLC; Combylite; The Binding Site Group Ltd), IgG, IgA, IgM and Cystatin C (The Binding Site Group Ltd) were measured in sera from 62 patients who met the revised ACR criteria for the classification of SLE. Results were compared to conventional biomarkers of SLE disease activity, including anti-dsDNA antibodies, C3, lymphocyte count and erythrocyte sedimentation rate (ESR). Serologically active disease was defined as patients with elevated anti-dsDNA antibody levels (>50 IU/ml) and reduced C3 (<0.9g/L). BILAG was used to assess disease activity; clinically active disease was defined as an A or B score in any organ system. Statistical analysis (Mann Whitney U test and Spearman correlations) was performed using SPSS v21.

Results: The median age was 43 years (range: 21–86); 90% were female and 50% were Caucasian. The median cFLC concentration was 31.86mg/L (IQR: 22.27–58.17; median concentration in a healthy population: 20mg/L). Moderate correlations were observed between cFLC vs: ESR (r: 0.5, $p<0.001$), cystatin C (r: 0.41, $p=0.002$), IgG (r: 0.6, $p<0.001$) and IgA (r: 0.6, $p<0.001$). A weak correlation was seen between cFLC and anti-dsDNA antibodies (r: 0.3, $p=0.02$), but there was no association with C3 (r: −0.2, $p=0.15$), lymphocyte count (r: −0.1, $p=0.36$) or IgM (r: 0.03, $p=0.82$). In patients with serologically active disease (N=19, 32%), median cFLC levels were significantly elevated: 58.1mg/L (34.67–80.9) vs 28.9mg/L (20.56–45.09), $p=0.02$. Using the BILAG score, cFLC levels were elevated in patients with clinically active (N=26, 42%) vs inactive disease (N=36, 58%): 39.6mg/L (IQR: 25.3–80.9) vs 29.7mg/L (IQR: 19.3–49.3), $p=0.05$. Anti-dsDNA antibody levels were also elevated: 258 IU/ml (16–644.5) vs 45 IU/ml (10–181), $p=0.04$; however, there was no significant difference in the levels of C3 ($p=0.32$), ESR ($p=0.65$), IgG ($p=0.31$), IgA ($p=0.27$), IgM ($p=0.68$), or cystatin C ($p=0.09$) between the two groups.

Conclusion: cFLC concentrations are likely to reflect B cell activity and therefore represent attractive markers in SLE. In this study, elevated levels correlated with disease activity supporting this hypothesis, however further work is required to evaluate the usefulness of this observation and to determine how cFLC may be used to monitor disease progression.

Disclosure: L. K. Assi, The Binding Site Group Ltd, 3; **L. Lisnevskaia**, None; **E. Ross**, None; **R. G. Hughes**, The Binding Site Group Ltd, 3; **A. Rahman**, None; **D. A. Isenberg**, None.

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Changes In Quality Of Life In The First 5 Years Of Disease In The Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) Cohort. Murray B. Urowitz[1], Dominique Ibanez[1], Nicole Anderson[1], Dafna D. Gladman[1] and Systemic Lupus SLICC[2]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]Toronto Western Hospital, Toronto, ON.

Background/Purpose: The Medical Outcome Survey Short Form 36 (SF-36) is one of the most widely used tools for measuring patient reported outcomes. In cross-sectional studies, there has been no correlation between QoL and disease activity or damage. The aim of this study is to assess QoL over time in the first 5 years of a multinational multicenter cohort.

Methods: An inception cohort of SLE patients from 31 centres in 12 countries has been assembled according to a standardized protocol between 2000 and 2013 to study the risk factors for atherosclerosis. Patients enter the cohort within 15 months of SLE diagnosis (≥4 ACR criteria). Clinical and laboratory features of SLE and comorbidities are gathered in a standardized protocol at yearly intervals. In addition patients complete the SF-36 at yearly intervals. Only patients who had 5 years of follow up and who had a minimum of 5 completed questionnaires were included in this analysis. The outcomes assessed include the 8 health domains of SF-36, in addition to physical component scores (PSC) and mental component scores (MCS) for each patient. In order to test for change in SF-36 domains over the 5 year period, GEE models were run separately for each of the 8 domains and the 2 composite scores. Each model adjusted for repeated measures by patients. Domains were also compared for gender, age, ethnicity and active disease (SLEDAI-2K ≥ 6) at enrolment.

Results: 485 patients (90.1% female) with 5 or more SF-36 evaluations were included. The disease duration at enrolment was 5.3 ± 4.1 months and the mean age at diagnosis was 35.8 ± 13.2 years. The race/ethnicity distribution was as follows: 57% Caucasian, 15% Black, 16% Asian, 8% Hispanic and 4% other. All 8 domains, in addition to MCS and PCS showed improvement that was statistically significant in the first 2 years of follow-up. No significant improvement was noted in any of the 8 domains or composite scores from years 3–5.

	SLE	APS	Whole group
IUFD	2	3	5
Perinatal death	0	1	1
Preterm delivery	17	12	29
IUGR	7	1	8
Pre-eclampsia	7	4	11
HELLP	0	2	2
Maternal thrombotic manifestations	2	3	5

Baseline domain scores range from 44.2–70.7 and PCS and MCS scores were 39.4 and 44.9. In year 2 domain scores range from 52.4–71.6 and PCS and MCS scores were 42.8 and 47.7.

Generally higher values of SF-36 scores are associated with male gender, younger age and Hispanic and Asian ethnicities. Levels of disease activity were not associated with SF-36.

Conclusion: Unlike late stage lupus where QoL is stable, in patients with early disease (within the first 2 years) all domains improve. Therefore SF-36 may be used as an outcome measure for improvement in the first two years of SLE.

Disclosure: M. B. Urowitz, None; **D. Ibanez**, None; **N. Anderson**, None; **D. D. Gladman**, None; **S. L. SLICC**, None.

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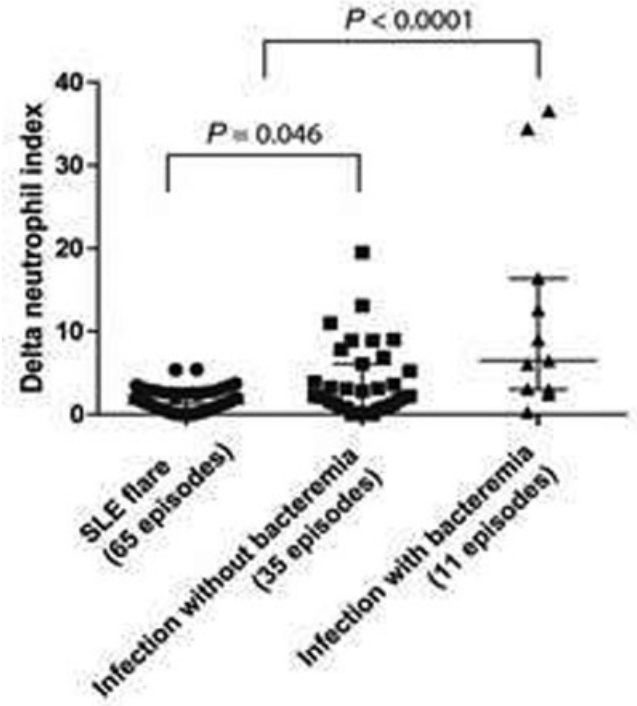
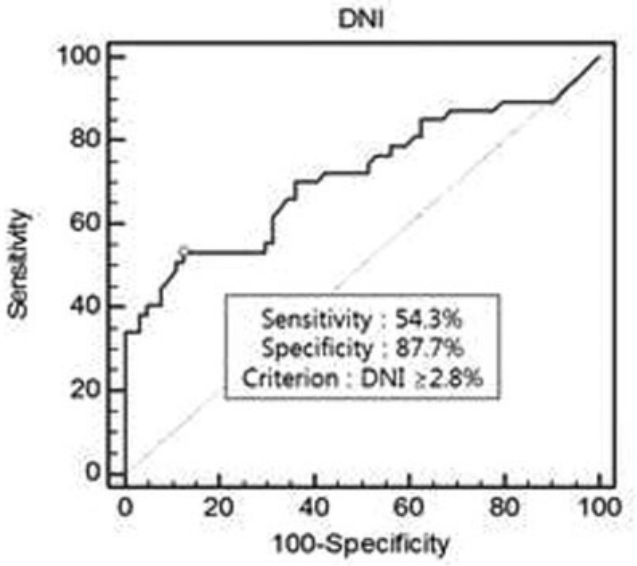
Delta Neutrophil Index As a Marker For Differential Diagnosis Between Flare and Infection In Febrile Systemic Lupus Erythematosus Patients. You-Jung Ha, Jung Yoon Pyo, Jin Su Park, Hee-Jin Park, Jason Jungsik Song, Yong-Beom Park, Soo-Kon Lee and Sang-Won Lee. Yonsei University College of Medicine, Seoul, South Korea.

Background/Purpose: The immature granulocyte count has been reported to be a marker of infection and sepsis. The difference in leukocyte subfractions (delta neutrophil index, DNI), automatically determined by the ADVIA 2120 electronic cell analyzer, reflect the fraction of circulating immature granulocytes in the blood. Because fever is a common symptom of systemic lupus erythematosus (SLE), it is difficult to discriminate between SLE flare and infection. In this study, we investigated the utility of DNI in discriminating infections from SLE flares in febrile SLE patients.

Methods: We included all consecutive SLE patients hospitalized due to febrile episodes at Severance Hospital, Yonsei University Health System, Seoul, South Korea, from January 2010 to February 2012. In total, 111 episodes in 92 febrile SLE patients were reviewed. All SLE patients were assigned to three groups: (1) patients with SLE flare, (2) patients with infection without bacteremia, and (3) patients with infection and bacteremia. DNI was determined using a specific blood cell analyzer.

Results: The infection group showed significantly higher white blood cell counts, neutrophil counts, C-reactive protein and procalcitonin than the SLE flare group. Complement (C)3 and C4 levels were decreased significantly in the SLE flare group. Patients in the SLE flare group had significantly lower DNI than those in both infection groups, with or without bacteremia. When we selected a DNI value of 2.8% as the cutoff for infection, SLE patients with DNI >= 2.8% were found to be at higher risk for infection than those with DNI < 2.8% (relative risk 8.48-fold). In a multivariate logistic regression analysis, only DNI >= 2.8% was a significant independent factor for the presence of infection (OR 18.9).





Conclusion: SLE patients with infection showed higher DNI than SLE flare group, and febrile SLE patients with DNI >= 2.8% are likely to have infection. Our findings suggest that DNI may be a useful marker to differentiate infections from SLE flares in febrile SLE patients.

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Pregnancy Complications In Lupus: Retrospective Observational Analysis From a US Health Claims Database. Michelle. A. Petri[1], Paola Daly[2], Daphnee S. Pushparajah[3], David Friesen[4] and Lydia Makaroff[3]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Lupus Foundation of America, Washington DC, DC, [3]UCB Pharma, Brussels, Belgium, [4]UCB Pharma, Slough, United Kingdom.

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune disease most frequently affecting women of childbearing age. Women with SLE are known to be at increased risk of miscarriage and other complications during pregnancy. This study used a large health claims database to quantify the reported incidence of maternal and fetal complications in pregnant women with SLE compared to pregnant women without SLE.

Methods: A retrospective observational analysis of the MarketScan US administrative healthcare claims database from 2006 to 2012 was conducted. Records of all women aged 12–54 years were reviewed. SLE patients were defined by ICD-9 codes for 710.0 on at least 2 different days. Pregnancies were identified by including codes for live birth, miscarriage, and either first-or second trimester ultrasound. Pregnant women with SLE were matched 1:5 by index year and quarter, age, geography, data type, insurance plan type, and employee relationship with pregnant women without SLE. Conditional logistic regression was used to calculate p values. Statistical tests were not corrected for multiple comparisons. P values are presented in the table.

Results: 1721 pregnancies in women with SLE were matched with 8605 pregnancies in women without SLE. Demographics were similar; mean (± SD) age of 31.5 (± 5.6) in the SLE group and 31.4 in (± 5.6) in controls. 23 in every 100 SLE pregnancies resulted in a miscarriage before 22 weeks gestation vs. 19 in every 100 control pregnancies. There was an increased risk of threatened abortion/premature labour without delivery in pregnancies with SLE vs. those without (46.0% vs. 39.8%). Hypertension was reported in 28.4% of SLE pregnancies vs. 12.4% of controls. Preeclampsia occurred in 1 in every 10 SLE pregnancies vs. 1 in every 22 non SLE pregnancies. Preterm delivery occurred in 1 in every 9 SLE pregnancies vs. 1 in every 17 non SLE pregnancies, with stillbirths reported in 2.4% of SLE pregnancies vs. 1.3% of subjects without SLE. There was a 7.5% increase in the risk of fetal complications in pregnancies with SLE vs. those without. A code for known/suspected fetal abnormality affecting management of the mother occurred in 39.7% of SLE pregnancies vs. 28.0% of controls.

Table. Obstetric features, complications and outcomes between pregnant women with SLE vs. pregnant women without SLE

	SLE Pregnancies N = 1721 N (%)	Control Pregnancies N = 8605 N (%)	P value
Hypertension	489 (28.4%)	1066 (12.4%)	<0.0001
Preeclampsia	170 (9.9%)	386 (4.5%)	<0.001
Eclampsia	6 (0.3%)	9 (0.1%)	0.0321
Nephritis	288 (16.7%)	100 (1.2%)	<0.0001
Primary hypercoagulable state	132 (7.7%)	54 (0.6%)	<0.0001
Obstetric infections	23 (1.3%)	65 (0.8%)	0.0244
Miscarriage before 22 weeks gestation	398 (23.1%)	1634 (19.0%)	<0.0001
Threatened abortion/premature labor without delivery	791 (46.0%)	3429 (39.8%)	<0.0001
Pre-term delivery between 22 to 37 weeks gestation	197 (11.4%)	510 (5.9%)	<0.0001
Induction of labor	154 (8.9%)	657 (7.6%)	0.0683
Caesarean delivery	515 (29.9%)	2090 (24.3%)	<0.0001
Stillbirth	41 (2.4%)	114 (1.3%)	0.0019
Gestational diabetes	169 (9.8%)	1006 (11.7%)	0.0228
Fetal complications	1185 (68.9%)	5518 (64.1%)	0.0001
Known or suspected fetal abnormality affecting the management of the mother	684 (39.7%)	2413 (28.0%)	<0.0001

Conclusion: In this large database analysis of over 10,000 pregnant women, those with SLE had a higher risk for suspected fetal abnormalities affecting care of the mother, and a doubling of risk for hypertension, preeclampsia, pre-term delivery and stillbirths. However, increased risk for earlier adverse pregnancy events, including miscarriage prior to 22 weeks and threatened abortion, appeared modest. These data highlight the need for regular physician-patient interaction, counseling and high quality education for women with SLE who are pregnant or looking to conceive to ensure possible complications are recognized early and managed appropriately.

Disclosure: M. A. Petri, UCB Pharma, 2, UCB Pharma, 5; **P. Daly**, None; **D. S. Pushparajah**, UCB Pharma, 3; **D. Friesen**, UCB Pharma, 3; **L. Makaroff**, UCB Pharma, 3.

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Rare Autoantibodies To Cellular Antigens In Systemic Lupus Erythematosous. Micaela Fredi[1], Ilaria Cavazzana[2], Marzia Quinzanini[2], Mara Taraborelli[1], Stefania Cartella[2], Angela Tincani[3] and Franco Franceschini[2]. [1]Rheumatology Chair, University of Brescia and Pavia, Brescia, Italy, [2]Rheumatology Unit, Spedali Civili, Brescia, Italy, [3]Rheumatology Unit, University of Brescia, Brescia, Italy.

Background/Purpose: a high number of antinuclear antibody specificities can be detected in Systemic Lupus Erythematosous (SLE). Some of them are related to a distinct clinical subset of disease, independently from their frequence. Aim of our study was investigate, in a cohort of SLE patients from a single Centre, the prevalence and the clinical relevance of autoantibodies to cellular antigens less frequently found in SLE.

Methods: antinuclear antibodies was detected by indirect immunofluorescence (IIF) on HEp-2 cells while counterimmunoelectrophoresis (CIE) was used to detect anti-ENA antibodies in 532 patients with SLE classified according to SLICC criteria[1]. Clinical and serological features about our cohort of SLE patients were collected from clinical charts. Categorical variables were analyzed with Chi-Squared test or Fisher's exact test. Multivarite analysis was conducted with a logistical regression model (Statview), $p<0.05$ was considered as significant.

Results: 311 (58.5%) of 532 sera were positive for anti-ENA antibodies. Anti-SSA/Ro was the most prevalent antibody found in 232 out of the 311 positive sera (74.5%), 50 of whom (16%) also contains anti-SSB/La. Anti-U1RNP were detected in 69 (22%) and anti-Sm in 45 (14.5%) patients. In a multivariate analysis anti-U1UNP and anti-SSA/Ro resulted to be associated with malar rash ($p= 0.010$ and $p=0.029$ respectively) while anti-U1RNP was also associated with leukopenia ($p=0.0065$). Other anti-ENA antibodies were found in 49 out of the 311 anti-ENA positive sera (15.8%). Anti-Ki/SL antibodies represented the most frequent between these rare antibodies and were detected in 31 sera, anti-Ku in 8 sera, anti-centromere in 4, isolated anti-SSB/La, PCNA and anti-Scl70 in 3 sera each and anti-Jo-1 in 2 sera. About half of these antibodies (26 out of 49; 53%) were detected as the single anti-ENA specificity in serum. Anti-Ki/SL was significantly associated with male gender ($p=0.0054$), being detected in 7 males and in 24 females; anti-Ku was significantly associated with African ethnicity (0.00031) being detected in 3 out of 11 patients of African origin. No sign of muscular or pulmonary involvement were found in the anti-Jo-1

positive patients while features of systemic sclerosis were detectable in 2 out of 3 anti-Scl70 and in one of the 4 anti-centromere positive patients.

Conclusion: our study shows that antibodies to cellular antigens more rarely found in SLE are detectable in more than 15% of patients with anti-ENA antibodies. The majority of them are found as a single anti-ENA specificity. Anti-Ki and anti-Ku appears to characterize a subset of disease with a prevalence of male and of patients from African origin respectively. Clinical features of scleroderma and/or myositis was found only in a minority of patients with antibodies to topoisomerase-1, Jo-1 or centromere. [1] Petri M, Orbai A-M, Alarcon G, et al. Derivation and Validation of the Systemic Lupus International Collabarating Clinics Classification Criteria fo Systemic Lupus Erithematosous. Arthritis Rheum 2012; 64:2677–86.

Disclosure: M. Fredi, None; **I. Cavazzana**, None; **M. Quinzanini**, None; **M. Taraborelli**, None; **S. Cartella**, None; **A. Tincani**, None; **F. Franceschini**, None.

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Lupus Impact Tracker Is Responsive To Changes In Physician Assessed Disease Status By Systemic Lupus Erythematosus Responder Index. Hervé Devilliers[1], Mark Kosinski[2], Cindy Garris[3] and Meenakshi Jolly[4]. [1]Internal medicine and systemic disease unit, Dijon University Hospital, Dijon, France, [2]QualityMetric Inc, Lincoln, RI, [3]GlaxoSmithKline R&D, Research Triangle Park, NC, [4]Rush University Medical Center, Chicago, IL.

Background/Purpose: Lupus Impact Tracker (LIT) is a 10-item patient reported outcome tool to measure the impact of Systemic Lupus Erythematosus (SLE) or its treatment on patients' daily lives. The transformed scores range from 0–100, where higher scores denote greater impact. The tool is responsive to self reported changes in SLE health status over time. Herein, we test the responsiveness of the LIT to changes in disease activity as judged by SLE responder index (SRI).

Methods: Adult SLE patients were prospectively recruited from 20 North American Rheumatology clinics for the LIT study- an observational, non-interventional prospective multi center study conducted across the US and Canada. Data (Demographics, LIT, BILAG, SELENA-SLEDAI) were obtained three months apart. Responders according to modified SRI were defined as (1) a decrease in SELENA-SLEDAI (4 points), (2) No new BILAG A and not more than 1 new B and (3) No increase in Physician Global Assessment (PGA). Latter definition was used as our PGA variable was categorical (0/1/2/3). Standardized response mean (SRM) and effect size (ES) for LIT was calculated among SRI responders and non-responders by taking the average difference divided by the standard deviation of the differences between the paired measurements, and baseline LIT, respectively. Difference in the LIT variation was compared among SRI responders and non responders using Kruskall Walis test.

Results: 325 patients participated (90% Female); 53% Whites, 33% Black and 17% Hispanic. Mean (SD) age and SELENA-SLEDAI at baseline were 42.3 (16.2) yrs and 4.3 (3.8), respectively. Mean (SD) LIT score at baseline was 39.4 (22.9). SRI data was available for 295 (40 R and 255 NR) at the 3 month timepoint. SRM and ES were −0.69 and −0.36 among SRI responders, −0.20 and −0.12 among non responders respectively. The mean LIT variation (SD) was −2.9 (14.4) and −7.9 (11.4) among non responder and responders, respectively (p=0.02). The mean difference in LIT variation between non-responders and responders was 5.0.

Conclusion: LIT was moderately responsive to changes in disease activity as assessed by SRI in patients with SLE in this study. The value of 5.0 seems to indicate a clinically important difference in LIT variation between two groups of patients

Disclosure: H. Devilliers, GlaxoSmithKline, 5; **M. Kosinski**, None; **C. Garris**, GlaxoSmithKline, 3, GlaxoSmithKline, 1; **M. Jolly**, GSK, 5, Medimmune, 5.

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Inactive Systemic Lupus Erythematosus: Cytokines and Soluble Tumor Necrosis Factor Receptors Response To Moderate/Intense Exercise. Luiz A. Perandini[1], Diego Sales-de-Oliveira[1], Suzana B.V. Mello[2], Niels O Camara[3], Fernanda R. Lima[1], Eduardo F. Borba[2], Eloisa Bonfa[2], Ana Lucia Sá-Pinto[1], Hamilton Roschel[4] and Bruno Gualano[5]. [1]University of Sao Paulo, Rheumatology Division, Sao Paulo, Brazil, [2]University of Sao Paulo, Rheumatology Division, São Paulo, Brazil, [3]University of Sao Paulo, Sao Paulo, Brazil, [4]Universidade de São Paulo, Faculdade de Educação Física e Esporte, São Paulo, Brazil, [5]University of Sao Paulo, School of Physical Education and Sport, Sao Paulo, Brazil.

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease characterized by a chronic inflammation associated with worse cardiovascular outcome. Although a few studies have investigated the safety of physical exercise in this disease, none of them have assessed the underlying cytokine response, an important marker of inflammation. Therefore, the aim of this study was to evaluate the cytokines (INF-γ, IL-6, IL-10, TNF-α) and soluble TNF receptors (sTNFR1 and sTNFR2) response to either a moderate or an intense acute exercise session in inactive SLE patients.

Methods: Twelve patients with SLE [age: 35.3 ± 5.7 yrs; body mass index (BMI): 25.6±3.4 kg/m^2; SLEDAI: 1.4±1.0] and 10 healthy age- and BMI-matched controls (age: 30.6±5.2 yrs, P=0.12; BMI: 24.1±2.3 kg/m^2, P=1.00) performed 30min of moderate (~50% of VO_2max) and intense (~70% of VO_2max) exercises in a treadmill, on separate occasions. Serum cytokines (INF-γ, IL-10, IL-6, TNF-α) and sTNFRs were assessed at baseline, immediately after exercise, every 30 min during three hours of recovery, and 24h after the end of exercise. Serum cytokines and sTNFRs were evaluated by the multiplex technique.

Results: At baseline, SLE had higher levels of TNF-α (P=0.001) and sTNFR2 (P=0.001) when compared with controls, whereas all other cytokines and sTNFR1 levels were comparable between groups (P>0.05). After the moderate exercise session, INF-γ, IL-10, IL-6, TNF-α, sTNFR1 and sTNFR2 levels remained stable in SLE when compared with baseline in all time points (P>0.05). Likewise, both the sTNFR2 and cytokines levels remained unchanged in healthy controls (P>0.05), except for the sTNFR1 levels, which showed a decrease at the 90th (P=0.038), 120th (P=0.028), 150th (P=0.005) and 180th (P=0.037) minute of recovery, returning to baseline levels 24h after the moderate exercise (P=0.093). After the intense exercise, only the sTNFR1 was altered in SLE patients, showing a decrease at the 150th (P=0.041) and 180th (P=0.034) minute of recovery, returning to baseline levels at the 24h time point. The sTNFR2 and all other cytokines remained unchanged (P>0.05). In healthy controls, IL-10, TNF-α, sTNFR1 and sTNFR2 did not change in response to the intense exercise session. Conversely, INF-γ decreased (P=0.05) and IL-6 increased at the end of exercise (P=0.028), with no differences observed at the post-24h time point (P>0.05).

Conclusion: This study demonstrates that both moderate and intense acute exercise sessions results in mild and transient changes in cytokine levels in SLE, providing novel evidence that exercise does not trigger inflammation in this disease. This finding supports the safety and recommendation of physical exercise for these patients.

Disclosure: L. A. Perandini, FAPESP 2011/24093-2, 2; **D. Sales-de-Oliveira**, None; **S. B. V. Mello**, FAPESP 2011/24093-2, 2; **N. O. Camara**, None; **F. R. Lima**, FAPESP 2011/24093-2, 2; **E. F. Borba**, FAPESP 2011/24093-2, 2; **E. Bonfa**, FAPESP 2011/24093-2, 2; **A. L. Sá-Pinto**, FAPESP 2011/24093-2, 2; **H. Roschel**, FAPESP 2011/24093-2, 2; **B. Gualano**, FAPESP 2011/24093-2, 2.

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Impact Of Omega-3 Fatty Acids On Quality Of Life In Systemic Lupus Erythematosus. Cristina Arriens[1], Chandra Mohan[2] and David R. Karp[3]. [1]University of Texas Southwestern Medical Center at Dallas, Dallas, TX, [2]University of Texas Southwestern Medical Center, Dallas, TX, [3]UT Southwestern Medical Center, Dallas, TX.

Background/Purpose: A comprehensive metabolomic screen of sera from patients with Systemic Lupus Erythematosus (SLE) has shown that the concentrations of many substrates for energy generation, as well as physiological antioxidants, are reduced when compared to sera from healthy controls. It is possible that these metabolic alterations underlie one of the most common patient reported features of SLE - fatigue. The metabolomic studies also noted reduced omega-3 fatty acids (omega-3 FAs). Given that omega-3 FAs are powerful anti-oxidants, the reduction in these FAs may be causally related to the tremendous degree of oxidative stress and lipid peroxidation seen in lupus. Supplementation with omega-3 FAs in SLE has been shown to increase anti-oxidants and reduce reactive oxygen species to more closely resemble healthy controls. The effect of omega-3 FA supplementation on the serum metabolome and clinical measures of fatigue are the subject of a randomized clinical trial.

Methods: Fifty SLE patients were recruited, 25 supplemented with omega-3 FAs and 25 with olive oil placebo. At baseline and after 6 months of FA supplementation, Short Form-36 (SF-36), Fatigue Severity Scale (FSS), SLE Disease Activity Index (SLEDAI), and Physician Global Assessment (PGA) were completed; serum was also collected to perform metabo-

lomic analysis. Demographic information and baseline clinical laboratory data were collected from the electronic medical record.

Results: Eighteen subjects receiving FA and 14 placebo patients completed the study. The FA patients were: 14 female, 4 male, 10 black and 8 Hispanic patients aged 43 ± 8 years. The placebo patients were: 11 female, 3 male, 1 white, 6 black, and 7 Hispanic patients aged 35 ± 11 years. Each group had an average of 6 ACR criteria for SLE. The SF-36 total scores pre- and post-treatment were compared using a paired t test and noted a significant improvement in the omega-3 patients (32.60 vs.42.19, p=0.0076), and no significant change in placebo patients (60.58 vs. 64.76, p=0.235). The SF-36 Vitality/Fatigue also yielded significant improvement in the omega-3 group (29.44 vs. 39.17, p=0.023) and no significant change in the placebo group (52.50 vs. 52.86, p=0.92). PGA improved significantly in the omega-3 group (1.21 vs. 0.56, p=0.0018), and did not significantly change in the placebo group (0.94 vs. 0.92, p=0.95). No significant changes were noted for FSS or SLEDAI in either group. Metabolomic data are currently being analyzed.

Conclusion: In this placebo-controlled 6-month trial of omega-3 FA supplementation in SLE, improvement was noted in both the total SF-36 quality of life measure as well as the Vitality/Fatigue sub-score. There were also two assessments of disease activity, but only the PGA noted significant improvement in the omega-3 group. Serum from the subjects in this cohort is now under analysis for markers of oxidative stress and antioxidant response and will be correlated with patient-reported outcomes as well as disease activity.

Disclosure: C. Arriens, None; **C. Mohan**, None; **D. R. Karp**, None.

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The Reliability Of a Novel Automated System For ANA Immunofluorescence Analysis In Daily Clinical Practice. Mohammed Alsuwaidi[1], Margit Dollinger[1], Martin Fleck[2] and Boris P. Ehrenstein[1]. [1]Asklepios Clinic Bad Abbach, Bad Abbach, Germany, [2]University Medical Center of Regensburg, Regensburg, Germany.

Background/Purpose: Recently, automated interpretation (AI) systems for anti-nuclear antibody (ANA) analysis have been introduced based on assessment of indirect immunofluorescence (IIF) patterns. However, the reliability of these systems has not been assessed in routine clinical practice. Therefore, the diagnostic performance of a novel automated IIF reading system was compared with visual interpretation (VI) of IIF in daily clinical practice.

Methods: ANA-IIF tests of consecutive serum samples from patients with suspected connective tissue disease were carried out using HEp-2 cells according to routine clinical care. VI was performed first by two laboratory experts independently; discrepant results were resolved by collegial discussion with a third expert. Afterwards, AI of IIF findings were obtained using a visual analyzer (Zenit G-sight, Menarini, Germany) utilizing novel automated pattern recognition algorithms. VI and AI readings were stratified as negative (serum dilution of 1:80 with no fluorescence), ambiguous (dilution of 1:80 with slight fluorescence, but no defined pattern) and positive (dilution of ≥ 1:80 with definite IIF pattern). Agreement rates between ANA results by AI and VI were calculated. IIF patterns were categorized as either being homogeneous, fine granular, coarse granular, nucleolar, centromeric, or mitochondrial by AI and VI, respectively.

Results: Of the 340 samples investigated, VI yielded 205 (60%) negative, 42 (12%) ambiguous and 93 (27%) positive results, whereas 82 (24%) were determined negative, 176 (52%) ambiguous and 82 (24%) positive by AI. Of the 82 negative samples by AI, 78 (95%) were also negative, 3 (4%) were ambiguous and 1 (1%) was positive as judged by VI. Of the 176 ambiguous samples by AI, 125 (71%) were negative, 30 (17%) also ambiguous and 21 (12%) positive by VI. Of the 82 positive samples by AI, 2 (2%) were negative, 9 (11%) ambiguous and 71 (87%) also positive by VI. AI displayed a diagnostic accuracy of 179/340 samples (53%) with a kappa-coefficient of 0.35 compared to VI as the gold standard. Solely relying on AI with VI only performed for all ambiguous samples by AI would have missed 1 of 93 (1%) positive results by VI, and misclassified 2 of 205 (1%) negative results by VI as positive. Of the 93 positive samples by VI, AI identified 36 (39%) IIF patterns correctly (18 (95%) of 19 homogeneous, 1 (3%) of 3 fine granular, 13 (65%) of 20 coarse granular, 2 (18%) of 11 nucleolar, 1 (33%) of 3 centromeric, and 1 (100%) of 1 mitochondrial patterns).

Conclusion: Utilizing novel algorithms, AI of ANA-IIF displayed reliable detection of positive and negative results as confirmed by VI. However, there were a substantial number of ambiguous results as well as inconsistencies in the identification of the correct pattern by AI requiring additional VI analysis. In contrast to previous studies utilizing well defined biobank samples, the use of AI in daily clinical practice resulted only in a moderate reduction of the VI workload (82 of 340 samples: 24%), which was predominantly due to a large proportion of ambiguous AI-results.

Disclosure: M. Alsuwaidi, None; **M. Dollinger**, None; **M. Fleck**, None; **B. P. Ehrenstein**, None.

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Serum Mercury Level and Disease Activity Of Systemic Lupus Erythematosus (SLE): A Case-Control Study. Chi Chiu Mok[1], Becky Fong[1] and Chris Wong[2]. [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Baptist University Hong Kong, Hong Kong, Hong Kong.

Background/Purpose: Environmental contamination with mercury (Hg) is linked to autoimmune diseases. Exposure to low-dose non-organic mercury has been reported to exacerbate murine SLE. The aim of this study is to evaluate the serum Hg levels in patients with SLE and their associated risk factors

Methods: Consecutive patients who fulfilled >=4 ACR criteria for SLE were recruited. An equal number of age and sex matched healthy controls was also recruited. Blood was taken in the morning for the assay of Hg level (atomic absorption spectrophotometry by a DMA80 direct Hg analyzer, Milestone, Italy) and other markers of disease activity (anti-dsDNA, complement C3 and C4) (for SLE patients). Disease activity of SLE patients was assessed by the SELENA-SLE disease activity index (SLEDAI) and organ damage was assessed by the SLICC/SLE damage index (SDI). Bivariate correlation between Hg level and various clinical and serological markers was studied by Pearson's correlation test. A linear regression model was established to study the clinical risk factors associated with higher serum Hg levels in SLE patients.

Results: 246 SLE patients (93% women) were studied. All were ethnic Chinese. The mean age during venepuncture was 40.7±12.5 years and SLE duration was 7.7±7.0 years. The mean SELENA-SLEDAI and SDI score was 5.8±6.5 and 0.97±1.5, respectively. 85(35%) patients had clinically active SLE, defined as a SELENA-SLEDAI score of >=6. 107 (43%) patients had organ damage (SDI>=1). The mean serum total mercury level of the SLE patients studied was 1.34±0.69 ng/mL (NR <3.85), which was significantly higher than that of 246 age and gender matched healthy subjects (N=246) (0.72±0.34 ng/mL; p<0.001). Only 2 (0.8%) SLE patients had Hg level ^{3}3.85ng/mL. Patients with clinically active SLE had significantly higher mercury level than those with SLEDAI<6 (1.50±0.57 vs 1.26±0.74 ng/mL; p=0.006). In addition, the levels of mercury in patients with clinically and serologically inactive disease (SLEDAI =0) were significantly higher than those with controls (1.15±0.56 vs 0.72±0.34 ng/mL; p<0.001) adjusted for age and sex (by ANCOVA test). Bivariate correlation study revealed that younger age (r −0.24; p<0.001), female sex (r 0.19; p=0.003), shorter SLE duration (r −0.16; p=0.01), anti-dsDNA titer (r 0.22; 0.001), SLEDAI score (r 0.24;<0.001) and physicians' global assessment (PGA) of disease activity (r 0.17;p=0.007) were significantly associated with higher mercury level. SDI damage score (r −0.06; p=0.33), C3 (r −0.06; p=0.36), C4 (r −0.07; p=0.28), photosensitivity, serum creatinine and other clinical manifestations were not significantly associated with mercury levels. In a linear regression model, the SLEDAI score (beta 0.14; p=0.04) and female sex (beta 0.18; p=0.006) were independently and significantly associated with higher Hg level, after adjustment for age, SLE duration and serum creatinine level.

Conclusion: In this cross-sectional study, the total serum mercury level was significantly elevated in patients with both active and inactive SLE than matched controls. Mercury level correlated independently with clinical disease activity and the female sex in a multivariate model, suggesting mercury may be an environmental trigger for SLE.

Disclosure: C. C. Mok, None; **B. Fong**, None; **C. Wong**, None.

2541

Disease Activity Does Not Improve Significantly In One System and Worsen In Another System. Zahi Touma, Dafna Gladman and Murray B. Urowitz. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Systemic Lupus Erythematous Disease Activity Index-2000 (SLEDAI-2K) is a global index that describes disease activity overall in 9 systems. The use of multiple measures is time consuming and physicians favor one measure, as long as the results are

robust. We aimed to determine if SLEDAI-2K is valid in identifying patients who had a clinically important overall improvement with no worsening in other systems.

Methods: This is an analysis of prospectively collected data on all active lupus patients who attended the Lupus Clinic from 2000–2012. Patients were included if at baseline visit: 1) SLEDAI-2K ≥6, 2) at least 1 of the 6 SLEDAI-2K clinical organ systems was active and for the renal system the presence of proteinuria was mandatory and 3) start or increase in the dose of prednisone. All patients had at least one follow-up at 9–12 months.

Based on the change in the total SLEDAI-2K scores on follow up visits, patients were grouped as: 1) improved (SLEDAI-2K decreased by ≥4), 2) flared/worsened (SLEDAI-2K increased by ≥4) and 3) unchanged.

Focusing on patients who improve, each organ system was defined as 1) **New Organ:** organ system inactive at start but active at study end 2) **Same:** no change in activity between start and end 3) **Improved:** lower activity in organ system at the end and 4) **worse:** higher activity in organ system at study end.

Results: 158 patients were analyzed (table 1). SLEDAI-2K was 12.25±5.27 at baseline and 6.65±4.88 at follow-up visits.

Sex F	97 (89%)
Age at diagnosis (years)	26±11
Age at 1st visit in the study (years)	39±13
Disease Duration at 1st visit in the study (years)	12±9
Race	
Caucasian	67 (61%)
Black	13 (12%)
Asian	14 (13%)
Others	15 (14%)
Medications at 1st visit in the study: patients number (%)	
Steroid	109 (100%)
Anti-malarial	82 (75%)
Immunosuppressants	69 (63%)

Of the 158 patients studied 109 patients had improved on SLEDAI-2K scoring on follow-up visit, 38 stayed the same and 11 worsened.

109 patients improved with a mean SLEDAI-2K score at baseline visit of 13.1±5.7 and at follow-up visit of 4.8±4.4. In this group, no one had a new system at study end. Worsening was identified in 5 patients at study end and this resulted from abnormal laboratory results: 1) one patient developed pyuria at follow up visit in addition to existing proteinuria and hematuria that were persistent from study start and 2) 4 patients had worsening in the immunological system (either a new anti-DNA positivity or low complements). In all 5 patients, this laboratory worsening was not clinically significant and did not require a change in the management (table 2).

Table 2. Activity of SLEDAI-2K systems' descriptors in patients who improved at study end

Global disease activity	Improvement n = 109			
Organ systems	**New organ**	**Same**	**Improved**	**Worsened**
CNS	0	95	14	0
Vascular	0	92	17	0
MSK	0	65	44	0
Renal	0	61	47	1
Dermal	0	75	34	0
Serosal	0	105	4	0
Immunological	4	71	30	4
Constitutional	0	102	7	0
Hematologic	0	102	6	0

Conclusion: SLEDAI-2K is valid to identify improvement in disease activity overall and we have now shown that no clinically important worsening occurs simultaneously. Therefore, SLEDAI-2K can be used as a single measure in the assessment of disease activity.

Disclosure: Z. Touma, None; **D. Gladman**, None; **M. B. Urowitz**, None.

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Validation Of The Revised Selena Flare Index In Systemic Lupus Erythematosus. Michelle Petri[1], Joan T. Merrill[2], R. Maciuca[3], John C. Davis Jr.[3] and William P. Kennedy[3]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Genentech, Inc, South San Francisco, CA.

Background/Purpose: The SELENA flare index (SFI) has been used in clinical and clinical trial settings since 2005 (1), but has the limitation that it classifies only severe versus combined mild/moderate flares. Since mild flares are often clinically insignificant, and it is useful to distinguish flares by organ system, a revision of the SELENA flare index (2) was carried out to define severe, moderate and mild flares separately, in terms of clinical and/or treatment variables, and by organ system. This revised flare index (rSFI) is independent of SLEDAI and was compared to the original SFI in the Phase 2 (ROSE) trial of rontalizumab (anti-interferon alpha) in extrarenal lupus (3).

Methods: The ROSE study enrolled patients with moderate to severe active SLE disease (3). Study investigators were trained on the use of the rSFI and other instruments before the start of the trial. rSFI was administered at scheduled study visits in the ROSE trial along the original SELENA flare index (SFI) and BILAG index. The new BILAG 2004 flare definition was used (severe = new or worse A, moderate = ≥2 B new or worse, mild = ≥1B or ≥3C new or worse). The proportion of patients with flares from week 4 to 24 was tabulated. Inter-instrument agreement between the different flare classifications was evaluated with Cohen's kappa/weighted kappa coefficient (4).

Results: A total of 235 efficacy-evaluable patients were included in the analysis. The assignment of no flare/ mild-moderate flare/ severe flare was compared for the rSFI versus SFI. In general, there was substantial agreement between the rSFI and SFI (kappa 0.70, weighted kappa 0.73). The agreement between rSFI and SFI was better for the clinical part of the rSFI (kappa 0.69) than the treatment part of rSFI (kappa 0.35). The SFI showed fair agreement (kappa 0.30; weighted 0.39) and the rSFI showed moderate agreement (kappa 0.31; weighted 0.51) with the BILAG flare index. Many of the significant discrepancies between instruments (e.g., mild flare by rSFI, but severe by the BILAG flare index) were determined, after further review, to be correctable data reporting errors.

Conclusion: The revised SFI (rSFI) has substantial agreement with the previously validated SFI, and the clinical portion of the rSFI, tested independently, showed the best agreement. The rSFI has better agreement with the BILAG flare index than the original SFI. Some discrepancies were due to data entry errors that can be avoided with improved site training. One possibility to improve flare endpoints would be to combine moderate and severe flares, as those are most likely to be clinically important.

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(3) ACR 2012 Abstract # 2622

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Patients' Perception Of Their Lupus Disease Activity, But Not Overall Health, Correlates With Physician Assessments. Anca Askanase[1], Samrawit Abraha[1], Ummara Shah[2], Aleks Merkovich[1] and Jill P. Buyon[3]. [1]New York University School of Medicine, New York, NY, [2]New York University School of Medicine, NYC, NY, [3]NYU School of Medicine, New York, NY.

Background/Purpose: The Physician Global Assessment represents the average assessment of a patient's disease activity based on physical examination and laboratory data while the Patient Global Assessment reflects the patient's perceived overall health and disease activity. The discordance between the physician and patient assessments has been previously observed. This current study investigates the influence of the specific question being asked in the questionnaire on the concordance between physician and patient assessments. This study will analyze the correlation between patient and physician assessments of disease activity in a longitudinal cohort.

Methods: Data was collected on a convenience sample of 43 patients with SLE enrolled in a subset of the NYU cohort. Each patient completed a questionnaire which included a Lupus Activity Patient Global Assessment (LA PtGA) on a visual analog scale (0–100) focusing on the patient's perceived SLE disease activity by asking the patient to indicate how active the patient thought her lupus was. Additionally, each patient

completed the Modified Health Assessment Questionnaire (MDHAQ), utilized in routine clinical care. This questionnaire contains a PtGA on a numerical rating scale (0–10) that specifically asks patients to evaluate how their illness and health conditions affect them. These two PtGAs values were compared to the physician global assessment (PGA) on a numerical rating scale (0–3) and SELENA-SLEDAI scores. Each patient had multiple visits included in the analysis. The level of correlation was determined by the Spearman rank order correlations.

Results: 43 patients seen on average of 2.3 visits were included in the study. The mean age was 42.1 years, 95% females, 34% were Caucasian, 24% Black, 30% Hispanic, 11% Asian, disease duration was 13.02 + 9.01 years, and 74% of patients had 3rdparty insurance. The mean SELENA-SLEDAI score (3.13±2.94), PGA (1.07±0.75), LA PtGA (25.68±24.66), and MDHAQ PtGA (3.04±2.80) reflect mild SLE activity. The correlation between PGA and SELENA-SLEDAI was 0.69 ($p<0.01$). The correlation between PGA and LA PtGA was 0.32 ($p<0.01$). In contrast, the correlation between the PGA and the MDHAQ PtGA was only 0.13 ($p=0.18$). The two PtGAs correlated well with each other with $r= 0.58$ ($p<0.01$).

Conclusion: As expected, the correlations between PGA and SLEDAI score as well as between LA PtGA and MDHAQ PtGA were high. The strength of association between LA PtGA and the physician measure were more modest. Given the absence of a statistically significant correlation between the MDHAQ PtGA and PGA, the data emphasizes the importance of the content of the questions being asked on patient instruments to ensure patients are evaluating lupus specific disease activity rather than overall health conditions. The latter may be misleading since it is less specifically focused on lupus per se. Understanding all the factors that influence patients' evaluation of their lupus disease activity is essential in creating an accurate SLE PtGA tool which can be used in clinical settings.

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Serum Mediated Phagocytosis Of Necrotic Material By Polymorphonuclear Leukocytes May Be Used As a Tool To Predict Clinical Manifestations In Systemic Lupus Erythematosus. Michele Compagno, Birgitta Gullstrand, Andreas Jönsen, Lennart Truedsson, Gunnar Sturfelt and Anders A. Bengtsson. Lund University, Lund, Sweden.

Background/Purpose: Polymorphonuclear (PMNs) leukocytes with engulfed necrotic cell material (NCM), as formerly used in the LE-cell test, are frequently seen in SLE and associated to severe clinical manifestations.

The aim of this study was to investigate if phagocytosis of NCM could predict or was associated with specific clinical phenotypes and/or disease activity in patients affected by SLE.

Methods: Sixty-nine SLE-patients were followed longitudinally for a median time of 2.1 years. A total of 1074 serum samples were taken approximately every 60 days together with registration of an extensive set of clinical and laboratory variables. NCM was generated by heat treatment of mononuclear cells from healthy donors, and PMNs from healthy donors were isolated by density gradient centrifugation. Sera from SLE-patients were incubated with PMNs and NCM, and phagocytosis was assessed by flow cytometry. Association and prediction of relevant clinical phenotypes were evaluated with logistic regression and odds ratio (OR) and 95% confidence intervals (CI) were calculated.

Results: In serum samples from 46 of the 69 SLE patients, phagocytosis of NCM by PMNs was seen at least once and totally 417 times. Significant association between phagocytosis of NCM by PMNs was found with clinical phenotypes such as lupus nephritis (OR=1.7, CI=1.2–2.5), mucocutaneous involvement (OR=1.45, CI=1.1–1.9) and also with increased disease activity (SLEDAI score) (OR=1.41, CI=1.0–2.0). Arthritis, though, was inversely associated with phagocytosis of NCM (OR=0.51, CI= 0.3 –0.8). Furthermore, phagocytosis of NCM by PMNs could predict alopecia (OR=2.22, CI=1.3–3.7) while arthritis was inversely related (OR=0.38, CI=0.1–1.0).

Conclusion: In SLE, high capacity of serum mediated phagocytosis of NCM by PMNs is commonly seen. It is associated with disease activity and certain clinical phenotypes and was a predictor for alopecia and inversely related to arthritis. The assessment of phagocytosis of NCM by PMNs may be used as a complementary laboratory tool in management of SLE-patients.

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Active Systemic Lupus Erythematosus: Cytokines and Soluble Tumor Necrosis Factor Receptors Response To Moderate/Intense Exercise. Luiz A. Perandini[1], Diego Sales-de-Oliveira[1], Suzana B.V. Mello[2], Niels O Camara[3], Fernanda R. Lima[1], Eduardo F. Borba[2], Eloisa Bonfa[2], Ana Lucia Sá-Pinto[1], Hamilton Roschel[4] and Bruno Gualano[5]. [1]University of Sao Paulo, Rheumatology Division, Sao Paulo, Brazil, [2]University of Sao Paulo, Rheumatology Division, São Paulo, Brazil, [3]University of Sao Paulo, Sao Paulo, Brazil, [4]Universidade de São Paulo, Faculdade de Educação Física e Esporte, São Paulo, Brazil, [5]University of Sao Paulo, School of Physical Education and Sport, Sao Paulo, Brazil.

Background/Purpose: Systemic lupus erythematosus (SLE) is a rheumatic autoimmune condition characterized by altered lipoprotein profile, physical dysfunction and increased risk of cardiovascular disease. Exercise is, therefore, a promising therapeutic strategy to counteract SLE disease outcomes. However, there are no studies evaluating exercise-induced inflammation in moderately active SLE patients, with some evidence of clinical safety in patients in remission. Therefore, the aim of the present study was to assess cytokines (INF-γ, IL-10, IL-6, TNF-α) and soluble TNF receptors (sTNFR) response to bouts of either moderate or intense exercises in patients with active SLE.

Methods: Eleven patients with active SLE (SLEDAI: 5.8±2.0) and 10 healthy controls with comparable age- and body mass index (BMI) performed 30 minutes of moderate and intense (~50% and ~70% of VO_2max, respectively) exercises in a treadmill. Serum cytokines (INF-γ, IL-10, IL-6, TNF-α) and sTNFR1 and sTNFR2 were assessed at baseline, immediately after the exercise, every 30 minutes of a 3-h recovery period and 24h after the end of exercise. Serum cytokines and sTNFRs were assessed by multiplex technique.

Results: SLE patients and controls had similar mean age (30.4 ± 4.5 vs. 30.6±5.2 yrs, $P=1.0$) and BMI (26.1±4.8 vs. 24.1±2.3 kg/m^2, $P=0.66$). At baseline, patients had a significant higher levels of IL-6 ($P=0.043$) and TNF-α ($P=0.020$) compared to controls. After moderate exercise, IL-6 decreased at the 60th (7.6±5.8 vs. 6.0±4.5 pg/mL; $P=0.035$) and 180th (7.6±5.8 vs. 5.2±3.9 pg/mL; $P=0.022$) minute of recovery compared to baseline whereas levels of IFN-γ, IL-10, TNF-α, sTNFR1, and sTNFR2 remained stable ($P>0.05$). Healthy controls showed solely a sTNFR1 decrease at 90th, 120th, 150th, 180th minute of exercise recovery ($P<0.05$) with no significant changes in the levels of IFN-γ, IL-10, TNF-α, IL-6, and sTNFR2 ($P>0.05$) when compared with baseline. In response to intense exercise, IL-6 at the end of exercise ($P=0.028$) and TNF-α at the 30th minute of recovery ($P=0.038$) increased transiently, followed by a decrease during late recovery [IL-6: 60th ($P=0.047$), 120th ($P=0.022$), and 180th ($P=0.028$) minute of recovery; TNF-α: 120th ($P=0.037$) minute of recovery]. IL-10 increased at the end of exercise ($P=0.034$) and at the 30th minute of recovery ($P=0.039$), whereas sTNFR1 decreased at the 180th minute of recovery ($P=0.05$) compared to baseline. IFN-γ and sTNFR2 did not change ($P>0.05$). Healthy controls showed no significant changes in IL-10, TNF-α, sTNFR1, and sTNFR2 after the intense exercise bout ($P>0.05$). INF-γ decreased at the end of the exercise ($P=0.05$), whereas IL-6 increased at the end of exercise ($P=0.028$) and at the 30th minute of recovery ($P=0.037$). Of note, cytokines and sTNFRs returned to baseline levels 24h after the end of the moderate and intense exercise bout ($P>0.05$) in active SLE and healthy controls.

Conclusion: In conclusion, the minor and transient change of cytokines and sTNFR with a complete recovery in 24h reinforces the safety of exercise in SLE patients with active disease. This finding opens a window of opportunity to develop interventions aimed to promote exercise in lupus patients in the course of treatment.

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Anti-Nucleosome Antibodies As a Predictor Factor For Relapses In Clinically Quiescent Systemic Lupus Erythematosus: Results Of a Prospective Cohort Study. Dalia Sanchez-Mosco[1], Nadia Alejandra Gandarilla-Martinez[2], Nicte Selene Fajardo-Robledo[3], Valeria Diaz-Rizo[4], Soraya Amali Zavaleta-Muñiz[5], Miguel Huerta[6], Xochitl Trujillo[6], Arnulfo Nava[7], Ernesto German Cardona-Muñoz[8], Jose Francisco Muñoz-Valle[9], Jorge Ivan Gamez-Nava[10] and Laura Gonzalez-Lopez[2]. [1]Centro Universitario de Investigación Biomédica, Universidad de Colima; Hospital General Regional 110 IMSS, Guadalajara, Jalisco, Mexico, [2]Hospital General Regional 110, Instituto Mexicano del Seguro Social (IMSS), Guadalajara, Jalisco, Mexico, [3]Doctorado en Farmacología, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Jalisco, Mexico, [4]Doctorado en Ciencias Médicas, Centro Universitario de Investigación Biomédica, Universidad de Colima; UMAE, Hospital de Especialidades, Centro Médico Nacional de Occidente, IMSS, Guadalajara, Jalisco, Mexico, [5]UMAE, Hospital de Especialidades Centro Médico Nacional de Occidente, IMSS; Doctorado en Ciencias con orientación en Inmunología, Guadalajara, Jalisco, Mexico, [6]Centro Universitario de Investigación Biomédica, Universidad de Colima, Colima, Mexico, [7]UMAE, Hospital de Especialidades Centro Médico Nacional de Occidente, IMSS, Guadalajara, Jalisco, Mexico, [8]Unidad de Investigación Cardiovascular, CUCS, Universidad de Guadalajara, Guadalajara, Jalisco, Mexico, [9]Doctorado en Ciencias Biomédicas. Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Jalisco, Mexico, [10]UMAE, Centro Médico Nacional de Occidente, IMSS; Doctorado en Farmacología, Universidad de Guadalajara, Jalisco, Mexico.

Background/Purpose: A significant number of studies have identified a correlation between anti-nucleosome antibodies (AN-ab) and disease activity in SLE; nevertheless, there is a lack of prospective cohort studies performed in clinically quiescent SLE directed to evaluate if these antibodies are associated with the increase in risk for relapses. The purpose of this study was to evaluate if serum anti-nucleosome antibodies (AN-ab) are predictor factor for the development of short-term relapses in patients with clinically quiescent systemic lupus erythematosus (SLE).

Methods: Patients with clinically quiescent SLE according to modified-SLEDAI (m-SLEDAI) and prednisone doses ≤15 mg/d were included. Baseline serum levels of (AN-ab), anti-DNA, C3 and C4 were determined. Patients were assessed at fixed times during 6 months by researchers blinded to serum levels of antibodies. A relapse was identified when the m-SLEDAI score increased to 3 or more points. Statistical analysis included Hazard risk (HR) and 95% confidence intervals (95%CI) for the development of relapses in presence of AN-ab. Survival curves were obtained for development of relapses in presence of different risk factors.

Results: Sixty-patients were followed. In patients with clinically quiescent SLE the frequency of AN-ab at the baseline was 15%. At six months 11/60 patients developed at least one relapse, 27% of the relapses achieved a m-SLEDAI store >8 points, involving mainly kidney or central nervous system. At 6-month was observed an increase in the development of relapses in patients with AN-ab at the baseline 4/9 (44%) compared with the relapses observed in SLE without these antibodies 7/51 (14%) HR=3.56 (IC95% 1.14–11.15, p=0.05). After the adjustment in the Cox regression analysis the presence of AN-ab and fewer time for inactive disease remained as predictors for relapses at short-term.

Conclusion: These results indicate that the identification of AN-ab is useful as marker to predict relapses in clinically quiescent patients in SLE, and this determination should be included in the clinical assessment of these patients in order to improve the tools for clinical decision-making.

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Anti-Ribosomal P Antibody Has a Protective Role In The Development Of Chronic Kidney Disease In Patients With Lupus Nephritis. Kyung-Eun Lee[1], Dong-Jin Park[1], Tae-Jong Kim[2], Yong-Wook Park[1] and Shin-Seok Lee[2]. [1]Chonnam National University Medical School, Gwangju, South Korea, [2]Chonnam National University Medical School and Hospital, Gwangju, South Korea.

Background/Purpose: Anti-ribosomal P antibody (anti-P) in patients with systemic lupus erythematosus (SLE) is associated with neuropsychiatric manifestation. Of interest, recent studies have suggested that anti-P is a marker for renal flare and disease activity and is associated with renal histopathologic findings in patients with lupus nephritis (LN). However, the clinical relevance and prognostic value of anti-P in patients with LN are not well characterized. Therefore, we examined the association of the presence of anti-P with the identification of clinical, histopathologic, and prognostic values in Korean patients with biopsy-proven LN.

Methods: Seventy-nine patients with LN were included in this study based on the availability of kidney biopsy specimens. Sociodemographic, clinical, laboratory, and treatment-related data at the time of kidney biopsy and during follow-up were obtained by reviewing patients' charts. Renal biopsy specimens were reclassified according to the ISN-RPS classification by two renal pathologists blinded to the previous classification. Anti-P was measured by immunoblot assay at the time of renal biopsy. Kaplan-Meier analysis was performed to estimate the probability of progression to chronic kidney disease (CKD) according to the presence of anti-P.

Results: Twenty-eight (35.4%) of 79 patients were positive for anti-P. Patients with anti-P had an earlier age at LN onset (26.6 ± 10.1 versus 34.7 ± 12.1, P = 0.005), higher SLEDAI 2000 score (12.7 ± 4.2 versus 10.5 ± 4.8, P = 0.029), and higher *e*GFR level (129.0 ± 47.6 versus 102.2 ± 41.5, P = 0.005) at the time of renal biopsy than those without. The autoantibody profiles in patients with anti-P were not different from those without; however, anti-Sm antibodies were more common in patients with anti-P (71.4% versus 37.3%, P = 0.004). The renal histopathologic findings showed that patients with anti-P had less interstitial inflammation (67.9% versus 94.1%, P = 0.003) in the activity index and less glomerular sclerosis (21.4% versus 45.1%, P = 0.037), less tubular atrophy (42.9% versus 66.7%, P = 0.040), and less interstitial fibrosis (57.1% versus 78.4%, P = 0.046) in the chronicity index. In addition, anti-P positivity was significantly associated with lower chronicity scores (1.29 ± 1.24 versus 2.25 ± 1.63, P = 0.006). Although 13 of 51 (25.5%) patients without anti-P progressed to CKD after a median follow-up of 47 (6–108) months, only 1 of 28 (3.6%) patients with anti-P developed CKD (P = 0.015).

Conclusion: Our findings have shown that although anti-P is associated with an earlier age of onset and higher disease activity at the time of LN diagnosis, anti-P has a protective role in the development of CKD in patients with LN.

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Assessment Of Worsening In Lupus Clinical Trials: Do The Endpoints Reflect Medical Judgement? Aikaterini Thanou[1], Eliza Chakravarty[1], Stan Kamp[2], Fredonna C. Carthen[1] and Joan T. Merrill[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma CIty, OK.

Background/Purpose: Discrimination between treatment and placebo is problematic in lupus trials. Recently, composite endpoints have evolved which define response by both improvement in baseline findings and lack of clinically significant deterioration in other features. The predominant endpoints, the SLE Responder Index (SRI) and BILAG-Based Composite Lupus Assessment (BICLA), do not preclude the designation of response if there is one new moderate organ score (BILAG B) vs baseline but do exclude **>/=2 new BILAG B scores**. The British Isles Lupus Assessment Group (BILAG) has reported a provisional definition of flares (1). Here a moderate flare is defined as **>/=2 B scores rated either new or worse.** We addressed this disparity in defining a moderate, clinically significant deterioration in a cohort study.

Methods: The BILAG 2004 index was prospectively scored at the time of 182 clinic encounters of 91 patients. Overall disease worsening was retrospectively judged by a clinician as either no worsening, mild, moderate, or severe flare.

		Physician-rated flares				
		No flare	Mild	Moderate	Severe	Total
BILAG 2004-defined flares (new or worse manifestations)	**No new/worse A or B**	**103**	**9**	**0**	**0**	**112**
	1 B	**1**	**20**	**16**	**2**	**39**
	>/= 2 B (wo A)	**0**	**2**	**11**	**3**	**16**
	2 B		2	9	2	
	>2 B			2	1	
	>/= 1 A	**2**	**0**	**5**	**8**	**15**
	No B	2		3	5	
	Plus 1B			2	1	
	Plus >/= 2 B				2	
	Total	**106**	**31**	**32**	**13**	**182**

		Physician-rated flares				
		No flare	Mild	Moderate	Severe	Total
BICLA and SRI-defined Worsening (only new scores counted)	**No new A or B**	**106**	**21**	**17**	**5**	**149**
	1 B	**0**	**9**	**10**	**1**	**20**
	>/= 2 B (wo A)	**0**	**1**	**3**	**4**	**8**
	2 B		1	2	3	
	>2 B			1	1	
	>/= 1 A	**0**	**0**	**2**	**3**	**5**
	No B			2	0	
	Plus 1B				1	
	Plus >/=2 B				2	
	Total	**106**	**31**	**32**	**13**	**182**

Results: Flares receiving one new BILAG B score or one new or worse B were usually considered mild by the clinician, confirming the approach by both constructs to discount increased disease at B level in only one organ as a moderate flare. Using the clinician's judgement as a standard to distinguish moderate flares, the sensitivity of the BILAG cutoff of >/= 2 B "new or worse" (detecting all flares that were as severe or more severe than the cutoff) was 60.0% as opposed to 26.7% for the SRI/BICLA definition of >/= 2 "new" B scores. Specificities were 97.1% and 99.3% respectively.

Conclusion: Whether worsening is defined by "new" or "new or worse" moderate disease, one BILAG B in isolation does not usually represent clinically significant deterioration by clinical judgement. Limiting the definition of moderate deterioration to 2 "new" B scores, which is now common practice in clinical trials for lupus, is a very insensitive measure for the degree of clinical deterioration considered moderate (or worse) by a physician. The concept of moderate flare defined by the BILAG group (>/= 2 "new or worse" B scores) might be a more helpful approach to define a threshold of moderate, clinically significant deterioration in composite endpoints for SLE trials.

1. Isenberg DA, Allen E, Farewell V, et al. An assessment of disease flare in patients with systemic lupus erythematosus: a comparison of BILAG 2004 and the flare version of SELENA. Annals of the Rheumatic Diseases. 2011;70:54–59.

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2549

Can Biomarkers Provide An Objective Standard Against Which To Assess Lupus Clinical Endpoint Measures? Aikaterini Thanou[1], Melissa E. Munroe[1], Stan Kamp[2], Joel M. Guthridge[1], Judith A. James[3] and Joan T. Merrill[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma CIty, OK, [3]Oklahoma Medical Research Foundation and University of Oklahoma Health Sciences Center, Oklahoma City, OK.

Background/Purpose: Despite the heterogeneity of SLE, specific pathways of immune dysregulation characterize significant subsets of patients. We examined cytokines reflecting IL6-TH17 pathology in lupus as an objective standard to test performance of clinical outcome measures.

Methods: 91 patients, all with active disease at baseline (SLEDAI >/= 6) participated in two visits at which BILAG and SLEDAI were prospectively scored. A clinician retrospectively assessed the second visit as overall worse, the same, or improved. Cytokines were measured by xmap multiplex bead-based assay.

Results: Using physician-rated improvement (PRI), 68 patients improved and 23 were same or worse at follow up. Cytokine changes were evaluated in patients who did or did not meet response criteria of PRI, SRI (SLE Responder Index) and BICLA (BILAG-based Composite Lupus Assessment). Of patients with detectable IL6 at baseline and/or follow up (IL6+) (n=51), those who improved by PRI, SRI or BICLA had a significant drop in IL6, not observed in patients who did not improve (Table 1). IL21 and IL23 decreased in those who improved by PRI, but did not track with SRI or BICLA. IL17 was only detected in 3 patients and could not be evaluated.

Table 1. P values of cytokine changes in patients with detectable cytokine levels at baseline and/or follow up

IL6 (n = 51)	PRI	SRI	BICLA	IL21 (n = 57)	PRI	SRI	BICLA	IL23 (n = 24)	PRI	SRI	BICLA
Endpoint met	n = 39 **p = 0.010**	n = 42 **p = 0.032**	n = 32 **p = 0.021**	Endpoint met	n = 45 **p = 0.008**	n = 43 **p = 0.042**	n = 41 p = 0.084	Endpoint met	n = 18 **p = 0.048**	n = 16 p = 0.252	n = 18 p = 0.08
Endpoint not met	n = 12 p = 0.569	n = 9 p = 0.82	n = 19 p = 0.141	Endpoint not met	n = 12 p = 0.266	n = 14 **p = 0.017**	n = 16 **p = 0.006**	Endpoint not met	n = 6 p = 0.625	n = 8 p = 0.195	n = 6 p = 0.313

IL21 and IL23 were detectable when IL6 was, both at baseline ($p<0.001$ and $p=0.002$ respectively) and at follow up ($p=0.032$ and $p=0.006$). In IL6+/IL21+ (double positive) patients (n=35), IL21 tracked well with IL6 ($p=0.0028$), driven by the patients who improved by PRI (n=26) ($p=0085$).

In IL6+ patients the PRI was tested as a standard to compare performance of SRI and BICLA (sensitivities 94.9% and 74.4%, specificities 58.3% and 75%). Using decrease in IL6 as an objective standard of improvement, sensitivities of SRI vs BICLA were 85.2% vs 66.7% and specificities were 35.9% vs 39.1%.

Conclusion: Decreases in IL6, IL21 and IL23 reflected improvements by SRI, BICLA and clinical judgement. IL21 and IL23 were detectable when IL6 was, consistent with expected relatedness in an IL6-TH17 pathway. The SRI was more sensitive than and as specific as the BICLA in detecting objective biologic change in this subset of IL6 producing patients. Low specificities underscore the multiple pathways of lupus pathology, but we speculate that a range of predictable cytokine changes in definable patient subsets could be formulated into objective standards for testing clinical outcome instruments.

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Predictive Markers Of Preeclampsia During Pregnancy In Patients With Systemic Erithematosus LUPUS and / Or Antiphospholipid Syndrome. Esther Rodriguez-Almaraz[1], Elena Gonzalo-Gil[1], Ignacio Herráiz[2], Paula I Gómez-Arriaga[2], Paloma Vallejo[2], Elena A López-Jiménez[3], María Galindo Izquierdo[1] and Alberto Galindo Izquierdo[2]. [1]Department of Rheumatology. Hospital Universitario 12 de Octubre, Madrid, Spain, [2]Fetal Medicine Unit, Department of Obstetrics and Gynecology. Hospital Universitario 12 de Octubre., Madrid, Spain, [3]Department of Biochemistry. Hospital Universitario 12 de Octubre., Madrid, Spain.

Background/Purpose: Patients with systemic lupus erythematosus (SLE) have an increased risk of preeclampsia (PE), which can be confused with lupus nephritis. Our objective was to evaluate the behaviour of mean pulsatility index in the uterine arteries (mPI-UtA), sFlt-1/PlGF ratio and endoglin levels in pregnant women with SLE and/or antiphospholipd syndrome (APS).

Methods: Pregnant women with SLE and/or APS attending our high-risk pregnancy unit were consecutively included. Clinical, analytical and sonographic evaluations were conducted at baseline, at different weeks (wk) of gestational age (10–13, 22, 28, 32), at delivery and postpartum. We collected demographic data, information regarding cardiovascular risk factors and toxic habits, the underlying disease, obstetrical history, last SLE flare, previous and current treatments, as well as usual blood tests including complement and a-dsDNA antibodies levels. Levels of sFlt-1, PlGF, and maternal serum endoglin were quantified by ELISA. PE and its severity were diagnosed according with the ISSSHP definition. Intrauterine growth restriction (IUGR) was defined as a small for gestational age newborn together with a Doppler PI in the umbilical artery above the 95th percentile.

Results: 34 consecutive patients were recruited, of whom 29 had SLE (4 with secondary APS), 3 had primary APS and 2 had antiphospholipid antibodies but without clinical criteria for APS. Five patients have not delivered at the time of writing and we missed 1 patient in the follow-up. Ten patients (36%) suffered an early pregnancy loss (<12 wks), being most frequent among patients with previous APS diagnosis ($p=0.03$),

high blood pressure ($p = 0.01$), arterial thrombosis related to APS ($p = 0.03$), and the presence of lupus anticoagulant ($p = 0.004$). In uneventful pregnancies the values of the studied markers were within normal limits for the gestational age throughout pregnancy. One SLE patient (5.6%) had mild PE after 32 wk together with IUGR. We observed a relationship between IUGR and higher SLEDAI both before and throughout pregnancy (baseline, $p = 0.01$; 10–13 wks, $p = 0.04$; 22 wk, $p = 0.02$; 28 wk, $p = 0.05$; 32 wk, $p = 0.01$). IUGR was also associated with higher mPI-UtA at 22 wk ($p = 0.05$). Endoglin levels (14.6 ng/ml vs <7.9, 26.9 vs <7.2, 49 vs <13.6, at 22 wk, 28 wk and 32 wk, respectively) and ratio curve sFlt1/PlGF (17 vs 14.8, 36.6 vs 16.9, 170.7 vs 86.4 at 22 wk, 28 wk and 32 wk, respectively) behaved abnormal in this case. Among remaining patients, 1 patient with SLE (5.6%) developed HBP before delivery, 1 SLE patient had premature rupture of membranes at term, and 3 SLE patients had a preterm delivery at 28, 32 and 36 wks, respectively. 12 patients (67%) had a mild exacerbation of SLE, and only 1 (8%) had moderate activity requiring high doses of corticosteroids and azathioprine.

Conclusion: Our preliminary results indicate that mPI-UtA, sFlt1/PlGF ratio and endoglin levels behave in patients with SLE and/or APS essentially as in the general population. Moreover, these markers may be useful to predict the onset of PE in women with SLE and to make the differential diagnosis between PE and an episode of lupus activity.

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Pharmacodynamics and Predictive Biomarkers In Patients Treated With Atacicept: Data From The APRIL-SLE Trial. David A. Isenberg[1], David Wofsy[2], Yong Li[3], Daiana Licu[4], Stephen D. Wax[3], Caroline Gordon[5] and Claudia Pena Rossi[4]. [1]University College London, London, United Kingdom, [2]University of California San Francisco and NIAID Autoimmunity Centers of Excellence, San Francisco, CA, [3]EMD Serono, Rockland, MA, [4]Merck Serono S.A., Geneva, Switzerland, [5]University of Birmingham, Birmingham, United Kingdom.

Background/Purpose: Atacicept is a fusion protein that inhibits B cell stimulating factors BLyS and APRIL. We examined the pharmacodynamic (PD) effects of atacicept in patients with SLE. We also investigated whether PD markers have the potential to function as predictors of flare and clinical response to atacicept.

Methods: APRIL-SLE was a double-blind, placebo-controlled study of subjects with active SLE that had become inactive during a 12-week course of tapered corticosteroids. Subjects were then randomized 1:1:1 to receive placebo or atacicept 75 or 150 mg twice weekly for 4 weeks, then weekly for 48 weeks. The primary outcome measure was the percent of subjects experiencing an SLE flare (BILAG A and/or B) during a 52-week treatment period. Patients also were followed during a 24-week follow-up period. PD analyses were conducted on the treatment completer population. Analyses of BLyS and APRIL levels as potential predictive biomarkers were performed on the potential completer population. Efficacy and safety results are reported separately.

Results: Atacicept induced substantial changes in PD and disease-related markers, including reductions in Ig levels, autoantibody levels, and both naïve and memory B cells, as well as increases in complement levels (Table). Except for memory B cells, which continued to decline, these effects lessened during the follow-up period but did not fully return to baseline over 24 weeks. The atacicept treatment effect (reduction in flares vs placebo) was observed in subjects with BLyS or APRIL levels ≥median, but not subjects with levels < median (except in the atacicept 150 mg arm). The difference was most pronounced in patients with both baseline BLyS and APRIL ≥median, with flare rates of 76, 53 and 23% in the placebo, 75 mg, and 150 mg groups, respectively. Atacicept-treated patients with the greatest absolute decrease in IgG experienced the fewest new flares (37.2% for patients in the bottom tertile [<–4 g/L] vs 61.5% for the upper tertile [≥–1.5 g/L]). This pattern was also observed for changes in IgM (47.5 vs 60.0%) and for naïve B cells (38.2 vs 57.1%). The incidence of infection was comparable regardless of BLyS or APRIL level at baseline, or the degree of decline in IgG or IgM levels.

Table. Median percent change from baseline; Treatment Completer population

	Placebo (n = 111)		Atacicept 75 mg (n = 112)		Atacicept 150 mg (n = 62)	
	Wk 52	24-wk FU	Wk 52	24-wk FU	Wk 52	24-wk FU
Total IgG	3.23	3.51	−30.40	−7.01	−37.62	−9.24
Total IgA	2.12	1.16	−52.61	−16.22	−57.89	−21.96
Total IgM	−1.44	−3.13	−65.74	−29.27	−68.75	−24.04
Naïve B cells*	−9.00	−5.63	−80.12	−66.67	−81.47	−66.67
Memory B cells*	−2.17	9.30	−12.50	−50.00	−28.21	−40.00
Plasma cells*	0.00	−34.85	−61.58	−55.00	−67.08	0.00
	Wk 52	**12-wk FU**	**Wk 52**	**12-wk FU**	**Wk 52**	**12-wk FU**
Anti-dsDNA (subjects +ve at screening)†	**13.89**	**41.42**	**−31.46**	**−20.85**	**−37.86**	**−11.78**
C3 (subj > normal at screening)‡	4.13	3.56	7.15	3.01	15.38	5.43
C4 (subj > normal at screening)§	−0.44	0.00	42.71	18.18	49.50	48.94

* Flow cytometry population: placebo, n = 37; atacicept 75 mg, n = 38; atacicept 150 mg, n = 25; †Anti-dsDNA > = 30 IU/ml; placebo, n = 71; atacicept 75 mg, n = 62; atacicept 150 mg, n = 43; ‡C3 <0.9 g/L; placebo, n = 33; atacicept 75 mg, n = 53; atacicept 150 mg, n = 28; §C4 <0.1 g/L; placebo, n = 28; atacicept 75 mg, n = 32; atacicept 150 mg, n = 17; Wk = week; FU = follow-up; IgG = immunoglobulin G; IgA = immunoglobulin A; IgM = immunoglobulin M.

Conclusion: Atacicept caused declines in IgG, IgA and IgM, as well as naïve and memory B cells. With the exception of memory B cells, these levels returned towards baseline after therapy. Atacicept also had favorable effects on anti-dsDNA and complement levels. The exploratory *post-hoc* analysis of potential predictive biomarkers identified a subgroup of patients with higher BLyS and APRIL levels at baseline who were more likely to benefit from treatment. In addition, patients with the largest decrease in Ig levels and/or naïve B cells demonstrated a greater clinical response. Further studies are required to clarify the associations between biomarkers and clinical response to atacicept.

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Predictive Significance Of ANTI-Prothrombin Antibodies For Second and Third Trimester Obstetric Complications In Patients With Systemic LUPUS Erythematosus and ANTI-Phospholipid Syndrome. Marta Mosca[1], Chiara Tani[1], Martina Fabris[2], Francesca Strigini[3], Linda Carli[4], Sabrina Vagnani[1], Rosaria Talarico[4], Chiara Baldini[4], Alessandra Della Rossa[4], Elio Tonutti[5] and Stefano Bombardieri[1]. [1]Rheumatology Unit, University of Pisa, Pisa, Italy, [2]Institute of Clinical Pathology, Udine, Italy, [3]University of Pisa, Pisa, Italy, [4]Rheumatology Unit, Pisa, Italy, [5]Santa Maria Hospital, Udine, Italy.

Background/Purpose: Anti-prothrombin antibodies (aPT) either alone or in association with other anti-phospholipid antibodies have been associated with an increased risk of thrombosis as well as of adverse obstetric outcomes particularly, recurrent early miscarriages. To assess whether anti-prothrombin antibodies have a predictive significance for the occurrence of late obstetric complications and maternal events in patients with SLE and APS.

Methods: Sera from pregnant patients with SLE and APS collected during the first trimester of pregnancy were examined for the presence of anti-prothrombin antibodies (aPT), anticardiolipin antibodies (aCL), anti-B2GPI antibodies, Lupus anticoagulant (LA). Pregnancies were prospectively followed. The following obstetric complications were considered: preterm delivery, pre-eclampsia, eclampsia, intrauterine growth retardation, intrauterine fetal death. In addition the occurrence of maternal thrombotic complications was recorded.

Results: Seventy six pregnancies in 60 patients (18 APS and 52 SLE) with a duration >10 weeks were included in the analysis. Anti-phospholipid antibodies were positive in 26 patients (aCL 25, LA 17, aPT 16, anti- B2GPI 6). Pregnancy outcomes are reported in the table 1.

A significant correlation was observed between the presence of anti-prothrombin antibodies and the occurrence of obstetric complications ($p<0.05$). The positivity of anti-prothrombin antibodies in addition to either positive aCL, anti-B2GPI and/or LA increased the risk of developing late obstetric complications ($p< 0.001$). No correlations were observed between the presence of anti-prothrombin antibodies alone or multiple anti-phospholipid antibodies and the occurrence of maternal thrombotic events.

	SLE	APS	Whole group
IUFD	2	3	5
Perinatal death	0	1	1
Preterm delivery	17	12	29
IUGR	7	1	8
Pre-eclampsia	7	4	11
HELLP	0	2	2
Maternal thrombotic manifestations	2	3	5

Conclusion: The presence of aPT antibodies appears associated with an increased risk for late obstetric complications in SLE and APS and therefore their assessment is suggested in these patients at the beginning of pregnancy.

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The Clinical Value Of Testing For Aphl, a New ELISA Kit With a Unique Phospholipid Mixture In Patients With Systemic Lupus Erythematosus (SLE). Savino Sciascia[1], Giovanni Sanna[2], Veronica Murru[3], Munther A. Khamashta[3] and Maria Laura Bertolaccini[3]. [1]Centro di Immunopatologia e Documentazione su Malattie rare, Torino, Italy, [2]Louise Coote Lupus Unit, St. Thomas' Hospital, London, United Kingdom, [3]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom.

Background/Purpose: Antibodies directed to APhL (a mixture of phospholipids) have been reported to predict APS more reliably than aCL tests. We designed this study to evaluate the performance characteristics of the IgG and IgM APhL ELISA, in an attempt to establish the diagnostic utility of these new aPL antibody tests in a wide cohort of SLE patients.

Methods: This study included 158 patients (152 women, mean age 41.8±11.6 years, mean disease duration 11.7±7.8years), all fulfilling the 1982 criteria for SLE. All the patients were tested for the routinely used aPL, including LA, aCL and ab2GPI. Data were compared with that obtained by the APhL ELISA (Louisville APL Diagnostic, Inc, Louisville, KY, USA). The diagnostic accuracy for each test was assessed by ROC and their area under the curve (AUC) analysis.

Results: APhL were found in 77% of the patients. IgG and IgM APhL were more frequently found along with routine aPL than in isolation ($p=0.007$ and $p=0.04$, respectively). APhL were more frequently found in patients with definite APS than in those without ($p=0.001$). aPhL were not only more frequent in patients with thrombosis than in those without ($p=0.02$) but their titres were also significantly higher in thrombosis, when compared to those without ($p=0.02$). APhL showed an OR for thrombosis of 1.46 [95%CI1.08–3.19] (AUC 0.533). Twenty-seven patients (17.09%) were positive for isolated APhL. Of those 8 (29.6%) had a thrombotic event (6 arterial, 1 venous, 1 both). No associations were found between the presence of APhL and pregnancy loss. The presence of aPhL did not correlate with that of any of the other aPL tested. Multivariate analysis confirmed the associations with APS, particularly with thrombosis.

Conclusion: APhL are frequent in patients with SLE. Their presence is associated with thrombosis, making these antibodies a novel marker for APS. The finding of isolated APhL in thrombosis (particularly arterial) deserves further investigation.

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In Vitro Fertilization In Systemic Lupus Erythematosus and Antiphospholipid Syndrome: A Series Of 82 Cycles. Pauline Orquevaux[1], Agathe Masseau[2], Véronique le Guern[3], Vanessa Gayet[3], Danièle Vauthier-Brouzes[4], Du Boutin[5], Bertrand Wechsler[6], Nathalie Morel[7], Jean Loup Pennaforte[1], Jean-Charles Piette[8] and Nathalie Costedoat-Chalumeau[9]. [1]CHU Reims, Reims, France, [2]Nantes University Hospital, Nantes, France, [3]Cochin Hospital, Paris, France, [4]Pitié Salpétrière Hospital, Paris, France, [5]Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Paris, France, [6]Hôpital Pitié-Salpêtrière, AP-HP, UPMC Univ Paris 06 & French National Reference Center For Systemic Lupus and Antiphospholipid Syndrome, Paris, France, [7]COCHIN, Paris, France, [8]CHU Pitié-Salpêtrière, Paris, France, [9]Hopital Cochin, Paris, France.

Background/Purpose: Patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) undergoing in vitro fertilization (IVF) are at increased risk of both hormone-associated flare and thrombosis. The literature is scarce with two series of IVF performed in 19 and 21 patients respectively [1; 2]. We report our experience with in vitro fertilization in 34 women with SLE and/or APS.

Methods: Retrospective study of women followed in four French centers (Pitié-Salpêtrière, Cochin, Nantes and Reims) who (1) had a diagnosis of SLE (ACR criteria) and/or APS (Sydney criteria), and (2) underwent at least one cycle of IVF between 2003 and 2012.

Results: The diagnosis of the 34 included women was: SLE alone (n=9, including one case diagnosed during the IVF), SLE associated with antiphospholipid antibodies (n=9), SLE associated with APS (n=5), and primary APS (n=11, including one case diagnosed during the IVF).

These women underwent 82 cycles of IVF. Underlying causes of infertility were of female origin (42%), male origin (33%), mixed (21%) or unexplained (4%). There was no premature ovarian insufficiency due to cyclophosphamide.

Median age at IVF was 34.7 years (range, 22–45). Median number of IVF cycles was 2.4 (1–7). 72 cycles (88%) of IVF were allowed and supervised by an internist. Women were treated with hydroxychloroquine (52%), steroids (61%), aspirin (79%) and/or low-molecular-weight heparin (67%). Ovulation induction protocols varied according to the centers.

Eight IVF cycles (10%) resulted in complications: SLE flare in 4 (three joint flares and one lupus enteritis) and thrombosis in 4. Interestingly, one SLE flare occurred in a patient with unknown SLE and 2 flares and 2 thromboses were explained by poor adherence to treatment. No ovarian hyperstimulation syndrome was observed.

24 pregnancies (29%) occurred, including four twin pregnancies, and lead to 22 live births (92% of pregnancies), 1 miscarriage and one medical termination for trisomy 13.

In addition, during the follow-up, eight spontaneous pregnancies occurred. Eventually, a total of 24 patients (70%) delivered at least one healthy child.

Conclusion: SLE flare and thrombosis were low (10%) and were often explained by poor adherence to treatment or absence of treatment. These preliminary results confirm that IVF can be successfully performed in SLE and/or APS women providing they have adequate treatment. The new protocols using GnRH antagonists may further decrease those risks.

[1] Le Thi Huong D et al. Semin Arthritis Rheum 2002; 32: 174–188
[2] Guballa N et al., Arthritis Rheum 2000; 43: 550–556

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Development and Validation Of a Questionnaire To Screen For The Presence Of Autoimmune Disease. Alan Boroway[1], Aileen M. Davis[2], Carolina Landolt-Marticorena[1] and Joan E. Wither[2]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]Toronto Western Research Institute, Toronto Western Hospital, University of Toronto, Toronto, ON.

Background/Purpose: Healthy family members of patients with systemic autoimmune rheumatic diseases (SARDs) are at higher risk of developing autoimmune disease than the general population. It is postulated that serological changes precede the onset of clinical autoimmune disease in affected individuals. Our aim is to determine if these serological changes are present in the relatives of patients with SARD, and if so, whether they can be used to predict the development of autoimmune disease. This would permit introduction of treatment early in the disease course thereby preventing damage. We have previously obtained blood for serologic testing and performed a cellular analysis on the first-degree relatives of patients with systemic lupus erythematosus. At the time of blood draw, a questionnaire was administered seeking evidence of autoimmune disease. In total 893 medical histories were obtained via questionnaire, with 178 reporting an autoimmune disease. However, less than 50% were able to be confirmed as accurate (Cooper et al, J Rheumatol. 2008 35 (10): 2001–4). In this study, we developed a validated questionnaire that more accurately reflects the presence of autoimmune disease, that can be used for a follow-up of the first-degree relatives of patients with SARDs.

Methods: A questionnaire was developed in consultation with an expert for distribution to patients for validation. In contrast to our previous questionnaire it incorporates questions that have been developed to confirm the

presence of disease through questions regarding specific clinical manifestions of disease and/or treatment. After obtaining informed consent, the questionnaire was administered to patients with each autoimmune disease of interest, with those having other autoimmune diseases or osteoarthritis serving as controls. Accuracy at identifying the presence or absence of a particular autoimmune disease was confirmed against data from patients' medical records. False positive (FP) and false negative (FN) rates were compared for each autoimmune disease.

Results: 63 patients were consented and completed the questionnaire, including at least 5 patients with each autoimmune disease of interest. Results are shown below:

Comparison of Accuracy of Original Questionnaire (Cooper et al) and New Questionnaire

	Cooper et al Questionnaire FP Rate N *(%)*	Questionnaire FP Rate (Screening Question) N *(%)*	Questionnaire FP Rate (Confirmatory Questions) N *(%)*	Questionnaire FN Rate (Confirmatory Questions) N *(%)*
Systemic Lupus Erythematosus	9/24 *(32.5%)*	0/18 *(0%)*	—	—
Rheumatoid Arthritis	45/60 *(75%)*	6/12 *(50%)*	1/12 *(8.3%)*	—
Systemic Sclerosis	1/4 *(25%)*	0/13 *(0%)*	—	—
Polymyositis/Dermatomyositis	2/2 *(100%)*	6/10 *(60%)*	1/10 *(10%)*	—
Sjogren's Syndrome	3/9 *(33.3%)*	3/9 *(33.3%)*	1/9 *(11.1%)*	—
Antiphospholipid Syndrome	4/5 *(80%)*	2/5 *(40%)*	1/5 *(20%)*	—
Hemolytic Anemia	12/13 *(92.3%)*	2/7 *(28.6%)*	2/7 *(28.6%)*	4/56 *(7.1%)*
Multiple Sclerosis	2/4 *(50%)*	1/6 *(16.7%)*	1/6 *(16.7%)*	1/57 *(1.8%)*
Thyroid Disease	45/96 *(46.9%)*	5/12 *(41.7%)*	0/12 *(0%)*	—
Type 1 Diabetes	N/A	0/10 *(0%)*	—	—
Idiopathic Thrombocytopenic Purpura	N/A	3/7 *(43%)*	1/7 *(14.3%)*	1/56 *(1.8%)*

There were no FP results in the general screening questions of both SLE and Type 1 DM. In those SARDs that had FP responses to the original screening question, accuracy was was improved in many by the confirmatory questions. In general FN rates were low.

Conclusion: The new questionnaire improved overall accuracy over our original questionniare in screening for most autoimmune diseases and can be used to more accurately identify family members with these conditions.

Disclosure: A. Boroway, None; **A. M. Davis**, None; **C. Landolt-Marticorena**, None; **J. E. Wither**, None.

2556

Concordance Of Indirect Immunofluorescence and Multiplex Immunoassay For Measurement Of Antinuclear Antibodies. Caroline D'Souza[1], Donald L. Kimpel[1], Walter Oliveira[2] and Janet E. Lewis[1]. [1]University of Virginia School of Medicine, Charlottesville, VA, [2]University of Virginia, Department of Pathology, Medical Laboratories, Charlottesville, VA.

Background/Purpose: The indirect immunofluorescence assay (IIF) is the gold standard for ANA testing. However, many laboratories now use multiplex assay as an ANA screening test. Multiplex ANA assay tests for a limited number of autoantibodies (antibodies to dsDNA, chromatin, ribosomal P, SSA-52, SSA-60, SSB, Sm, SmRNP, RNP-A, RNP-68, Scl-70, Jo-1, centromere B) while IIF allows the detection of antibodies to a much larger number of autoantigens. There is a concern that reliance on multiplex analysis as a screening test might lead to cases where a positive ANA, and hence a diagnosis, is missed. Our study aims to evaluate the concordance between IIF and multiplex assay for ANA screening.

Methods: ANA is tested by IIF at UVA. Samples are considered positive at a titer of 1:80. Thirteen specific autoantibodies are tested by an automated multiplex platform. For this study, samples with at least one autoantibody positive on multiplex analysis were considered ANA + by multiplex. A total of 545 blood samples sent to the UVA lab between June and November 2012 to be tested for ANA and specific autoantibodies were analyzed.

Results: About 25.3% are ANA positive by IIF and 24.7% are ANA positive by multiplex. Only 13.8% of samples are positive by both methods (concordant). Kappa coefficient of agreement is 0.39 (fair). The most common antibody in all multiplex+ samples is that to RNP followed by SSA and dsDNA. In the subset of multiplex + samples that were IIF negative, RNP was the most common antibody (40%). The most common pattern overall was homogenous. When the threshold for a positive ANA by IIF was increased to 1:160, the number of total samples that were IIF positive is reduced as expected (20.4%). Kappa coefficient of agreement was improved only to a value of 0.428 (moderate). A large number (74%) of the low titer (1:80) IFA assays were also multiplex negative. The majority (84.7%) of strongly positive IIF samples (1:640 and above) were also multiplex positive. However, 9 of the 59 high titer IIF samples were multiplex negative.

		Multiplex	
I		**−**	**+**
I	**−**	**347 (63.6%)**	**60 (11%)**
F	**+**	**63 (11.5%)**	**75 (13.8%)**

Fig 1: Concordance chart for ANA tested by IIF and Multiplex with a positive cutoff for IIF at a titer of 1:80.

Conclusion: We found a high rate of ANA positivity by both IIF and multiplex. Most of the discordant samples were either low titer IIF or had autoantibodies that might be less specific like anti-RNP. The agreement between the two tests as measured by a kappa co-efficient was only fair at a cutoff of 1:80 and improved to moderate at 1:160. This suggests that there is at best moderate agreement between the two tests. Also, in some cases, multiplex did not identify samples with high titer ANAs. We conclude that there is still a role for IIF to be used for ANA screening in patients suspected to have an autoimmune disease.

Disclosure: C. D'Souza, None; **D. L. Kimpel**, None; **W. Oliveira**, None; **J. E. Lewis**, None.

2557

Fluctuations In sVCAM-1 and Adiponectin Mirror Fluctuations In Disease Activity In Lupus, But Cannot Be Use To Accurately Predict Impending Changes In Disease State. Carolina landolt-Marticorena[1], Stephenie Prokopec[2], Stacey Morrison[3], Heather Reich[3], James Scholey[3], Dafna Gladman[4], Murray B. Urowitz[4], Paul Boutros[2], Paul R. Fortin[5] and Joan E. Wither[6]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]Ontario Institute for Cancer Research, Toronto, ON, [3]The Toronto Western Hospital, Toronto, ON, [4]University of Toronto, Toronto Western Hospital, Toronto, ON, [5]University of Laval, Quebec, QC, [6]Toronto Western Research Institute, Toronto Western Hospital, University of Toronto, Toronto, ON.

Background/Purpose: Previous reports have identified a number of pro-inflammatory cyto/chemokines as candidate activity-specific SLE biomarkers. In our preliminary studies we found that out of a panel of 20 common cyto/chemokines examined, only MCP-1, IP-10, sVCAM and adiponectin were preferentially elevated in patients with active as compared to inactive disease. In this study, the relationship between fluctuations in disease activity and these four cyto/chemokines was examined to determine their utility in predicting fluctuations (exacerbation or improvement) in disease activity.

Methods: SLE patients (n = 55) satisfying 4 or more ACR criteria were recruited and followed over a 14-month period with a minimum of 3 clinical and biochemical assessments over that time. The plasma concentration of the 4 analytes was determined by Luminex assay. Disease activity was determined by the SLEDAI-2K (S-2K). A modified SLEDAI-2K (mS-2K) was calculated by subtracting the contribution of anti-dsDNA antibodies and complement (C3) from the global score. Variation between visits was examined with a change in S-2K of $\pm$ 4 between two consecutive visits deemed a clinically significant event. Event classification was compared with analyte levels using a one-way ANOVA followed by visualization. The ability of analyte levels to forecast disease activity was evaluated using a leave-one-out cross-validation analysis.

Results: Analysis of all available assessments showed a statistically significant positive correlation between adiponectin (Spearman's rho (r) = 0.25, $p < 1 \times 10^{-3}$), VCAM (r = 0.24, $p < 1 \times 10^{-3}$) and IP-10 (r = 0.21, $p = 2 \times 10^{-3}$) and global disease activity as defined by the mS-2K. These correlations were comparable to the performance of traditional biomarkers; anti-dsDNA antibodies (r = 0.22, $p < 1 \times 10^{-3}$) and complement (C3, r = −0.24, $p < 1 \times 10^{-3}$). The relationship between meaningful fluctuations in disease status between consecutive visits and biomarker levels was examined. Changes in disease state were exclusively reflected in changes in sVCAM-1 ($p = 0.04$) and adiponectin ($p = 0.05$). Both traditional biomarkers (anti-dsDNA antibodies and C3) and other tested cytokines (MCP-1, IP-10) did not reflect fluctuations in disease state. The ability of these biomarkers to predict a clinically meaningful change in disease status within 3 to 6 months of assessment was also assessed. In our analysis < 10% of events were accurately predicted.

Conclusion: These results suggest that despite their early promise, and evidence that some of the selected cyto/chemokines fluctuate with disease activity, none of the analytes examined could accurately forecast clinically significant changes in disease state.

Disclosure: C. landolt-Marticorena, None; **S. Prokopec**, None; **S. Morrison**, None; **H. Reich**, None; **J. Scholey**, None; **D. Gladman**, Abbott, Bristol-Myers Squibb, Celgene, Johnson & Johnson, MSD, Novartis, Pfizer, UCB Pharma, 2, Abbott, Bristol-Myers Squibb, Celgene, Johnson & Johnson, MSD, Novartis, Pfizer, UCB Pharma, 5; **M. B. Urowitz**, None; **P. Boutros**, None; **P. R. Fortin**, None; **J. E. Wither**, None.

ACR/ARHP Poster Session C
Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's II
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

2558

Bone Morphogenic Protein Receptor 2 (BMPR2) Gene Mutations Are Associated To The Development Of Isolated Pulmonary Arterial Hypertension (PAH) In Systemic Sclerosis (SSc) Patients. Tatiana Sofia Rodriguez-Reyna[1], Jose Luis Hernandez-Oropeza[1], Tomas Rene Pulido-Zamudio[2], Felipe Massó[2], Jessica Gutierrez-Manjarrez[1], Alexandra Rueda de Leon-Aguirre[1], Julio Sandoval-Zarate[2] and Carlos Rodriguez-Osorio[1]. [1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico, [2]Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico.

Background/Purpose: Isolated pulmonary arterial hypertension (PAH) secondary to Systemic Sclerosis (SSc) is a severe life-threatening complication. Several pathogenic pathways have been implicated in its development. Bone morphogenic protein receptor 2 (BMPR2) is a protein of the TGF-beta receptor superfamily; mutations in this gene seem to be implicated in the proliferation of pulmonary artery smooth muscle cells, a major component of pulmonary arteriolar remodeling in PAH, and they have been associated to the susceptibility to develop idiopathic and familial PAH; exon 5 has higher frequency of mutations according to previous analyses. The aim of this study was to evaluate if BMPR2 gene exon 5 mutations are associated to isolated PAH in Mexican Mestizo SSc patients.

Methods: DNA samples from 38 Mexican Mestizo SSc patients with isolated PAH (mean resting pulmonary artery pressure (PAP) >25 mmHg, pulmonary wedge pressure < 15 mmHg and pulmonary vascular resistance > 3 Wood units by right side catheterization; or systolic PAP >40 mmHg, tricuspid annular plane systolic excursion <20 mmHg and dilatation and hypertrophy of right ventricle by transthoracic echocardiogram; patients were also required to have no or minimal interstitial lung disease by computed tomography) and 38 Mexican Mestizo SSc patients without PAH, matched by SSc subtype, age (+/− 5 years), gender, time of evolution of the disease and SSc-associated autoantibody were analyzed. High resolution melting analysis (HRMA) of exon 5 of the BMPR2 gene was performed in previously amplified DNA (sense primer: 5′TCA TGC TAT TCT GCA TTC ATC.3′, antisense primer: 5′CAG GTC TAG TAT CAC AGT AGA.3′). Aberrant curves were considered as positive for mutation in the exon 5 of the BMPR2 gene. Severity of the organ involvement was evaluated using the Medsger severity scale. Statistical analysis was performed using SPSS v.19 and Epi-Info 7.0. Chi square was used to compare mutation frequencies between groups; Student's t test and Wilcoxon rank test were used to compare numeric variables. Values were considered significant when two-tailed p values were <0.05.

Results: Mean age was 50 years, mean time of SSc evolution was 12.25 years, 80% of patients were female, with no differences between PAH and non-PAH patients. Mean PAP was 57 mmHg in PAH-SSc patients and 25 mmHg in non-PAH-SSc patients ($p<0.001$); BMPR2 gene exon 5 mutations were detected in 7 (18%) of PAH-SSc patients and in 1 (3%) non-PAH-SSc patient ($p=0.001$, OR: 31, 95% CI 5.1–1263). From the 7 patients with PAH that had a mutation, 6 were female, 6 had limited cutaneous SSc, 6 had severe vascular involvement (digital ulcers and/or gangrene at any time of the evolution of the disease), 1 had anti-Topoisomerase I and 2 had anti-U1-RNP antibody. Prevalence of BMPR2 gene exon 5 mutation in our sample was 11%.

Conclusion: Prevalence of BMPR2 gene exon 5 mutations in PAH-SSc patients is higher than in non-PAH-SSc patients; prevalence of BMPR2 gene exon 5 mutations in this SSc sample is similar to the prevalence reported in some idiopathic PAH studies; our results suggest that BMPR2 gene exon 5 mutations increase the risk to develop PAH in Mexican Mestizo SSc patients.

Disclosure: T. S. Rodriguez-Reyna, None; **J. L. Hernandez-Oropeza**, None; **T. R. Pulido-Zamudio**, None; **F. Massó**, None; **J. Gutierrez-Manjarrez**, None; **A. Rueda de Leon-Aguirre**, None; **J. Sandoval-Zarate**, None; **C. Rodriguez-Osorio**, None.

2559

Effect Of NOX4 Overexpression On The Levels Of Micro RNAs Relevant To Systemic Sclerosis Fibrotic Process. Sonsoles Piera-Velazquez, Alma Makul and Sergio A. Jimenez. Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center, Thomas Jefferson University, Philadelphia, PA.

Background/Purpose: Systemic sclerosis (SSc) is characterized by the excessive deposition of collagen and other connective tissue components in skin and multiple internal organs. Although transforming growth factor β (TGF-β) has been shown to play a crucial role in the development of tissue fibrosis in SSc, recently, other factors such as excessive oxidative stress have been implicated in the pathogenesis of the disease. Oxidative stress is caused by cellular overproduction of ROS (reactive oxidative species). NOX4 is one of seven NADPH isoforms which plays a crucial role in the generation of ROS. Numerous recent studies have described an important role of microRNAs (miRNA) in the pathogenesis of the fibrotic process in various fibrotic diseases including renal, pulmonary, and liver fibrosis as well as in SSc. The purpose of these studies was to induce overexpression of NOX4 in normal human dermal fibroblasts and to examine the effect of increased NOX4 levels on the expression of various miRNA that participate in the regulation of tissue fibrosis.

Methods: Two different cell lines of normal human dermal fibroblasts were isolated from skin biopsies, and were expanded in monolayer cultures to approximately 70% of confluence and then they were transiently transfected with either a NOX4 protein expression construct (pCI-NOX4) to induce in NOX4 expression or with the vector control pCI. The effects of NOX4 overexpression on global gene expression levels and on the expression of relevant miRNA were examined employing microarrays using Human gene 1.0 ST array Affymetrix gene chips.

Results: Induced NOX4 expression did not cause apparent morphological changes or cytotoxicity. Remarkable changes in the expression levels of numerous transcripts associated with the phenotypic activation of fibroblasts into myofibroblasts were observed. Also, NOX4 overexpression caused significant changes in the levels of several relevant miRNAs. It was of substantial interest that the predicted gene targets for these miRNA included highly relevant genes such as those encoding members of the TGF-β pathway, as well as genes encoding numerous ECM proteins, and several crucial regulatory/transcription factor genes including Fli1, Gli3, and Hif1A.

Conclusion: Induced NOX4 expression resulted in remarkable changes in the levels of expression of numerous transcripts associated with the phenotypic activation of myofibroblasts as well as changes in the levels of several miRNAs that exert important regulatory effects on various genes that participate in the fibrotic process. These observations provide strong support to the notion that targeting NOX4 expression may be a novel therapeutic approach for SSc and other systemic fibrotic disorders.

Disclosure: S. Piera-Velazquez, None; **A. Makul**, None; **S. A. Jimenez**, None.

2560

Analysis Of Global Gene Expression Of Pulmonary Endothelial Cells From Caveolin-1 Knock-Out Mice. Sonsoles Piera-Velazquez[1], Zhaodong Li[1], Sankar Addya[2], Peter J. Wermuth[1] and Sergio A. Jimenez[1]. [1]Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center, Thomas Jefferson University, Philadelphia, PA, [2]Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA.

Background/Purpose: Caveolin-1 (Cav-1) deficiency has recently been shown to participate in the pathogenesis of tissue fibrosis in Systemic Sclerosis (SSc). Although the mechanisms involved have not been fully elucidated, it has been shown that Cav-1 deficiency can induce the phenotypic conversion of quiescent fibroblasts into activated myofibroblasts, the effector cells responsible for the fibrotic process in SSc. It has also been shown that Cav-1 deficiency mediates the phenotypic conversion of endothelial cells (EC) into myofibroblasts through endothelial-mesenchymal transition (EndoMT). Furthermore, Cav-1 deficiency causes a synergistic stimulation of TGF-β-induced EndoMT. The objective of this study was to

examine the differences in global gene expression patterns of Cav-1 knockout (KO) and wild-type murine lung EC regarding genes participating in the EndoMT process.

Methods: Pulmonary EC were isolated from wild-type (WT) and cav-1 knockout (cav-1 KO) mice employing immunomagnetic methods with sequential anti-CD31 and anti-CD102 antibody selection followed by *in vitro*culture and treatment with TGF-β1. To assess the differences in gene expression we performed microarray analysis of RNA isolated from cultured early passage lung EC from wild-type and cav-1 KO mice, employing the Affymetrix mouse cDNA array. Pathway analysis was performed employing Ingenuity software.

Results: A large number of differentially expressed genes were identified in lung EC from cav-1 KO mouse in comparison to EC from wild-type controls, including several unexpected extracellular matrix proteins such as decorin (58-fold higher), dermatopontin (28-fold higher), and versican (17-fold higher), as well as fibroblast growth factor 7 (30-fold higher), and some metalloproteinases, such as, matrix metalloproteinase 3 which was increased 12-fold. Of interest was also the observation that podoplanin a small glycoprotein considered to be specifically expressed in EC of lymphatic origin and which is highly increased in a variety of malignant cells was elevated 17–20 fold in samples from the cav-1 KO mouse lung EC. Numerous genes involved in the EndoMT process were also found to be upregulated in the cav-1 KO mice lung EC compared with the wild-type (WT) controls. Cav-1 deficiency caused a synergistic stimulation of the TGF-β-induced gene expression patterns although some unique genes appeared to be induced by TGF-β treatment of the Cav-1 KO cells but not by treatment of the WT cells.

Conclusion: Cav-1 deficiency results in remarkable changes in the global gene expression patterns of murine lung EC and potentiates the stimulatory effects of TGB-β1 inducing the differential expression of numerous pro-fibrotic genes and of genes involved in EndoMT. These results provide novel information about the mechanisms responsible for the participation of Cav-1 in SSc pathogenesis and further suggest that modulation of Cav-1 expression or activity/function may be a novel therapeutic target for SSc.

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Disclosure: S. Piera-Velazquez, None; **Z. Li**, None; **S. Addya**, None; **P. J. Wermuth**, None; **S. A. Jimenez**, None.

2561

Multiplex Cytokine Analysis Of Dermal Interstitial Blister Fluid In Systemic Sclerosis Defines Potential Pathogenic Pathways and Differentiates Clinical Subsets. Kristina E.N. Clark[1], Henry Lopez[2], Joanna Nikotorowicz-Buniak[1], Xu Shiwen[1], Korsa Khan[1], George Martin[3], David J. Abraham[1], Christopher P. Denton[1] and Richard J. Stratton[1]. [1]UCL Medical School, London, United Kingdom, [2]Murigenics, Vallejo, CA, [3]Aero Dap, Vallejo, CA.

Background/Purpose: Clinical diversity in systemic sclerosis (SSc) is likely to reflect multifaceted pathogenesis and the effect of key growth factors or cytokines operating within a disease-specific microenvironment. Dermal interstial fluid sampling offers the potential to examine local biological mechanisms and define protein expression within lesional tissue. We propose multiplex cytokine analysis could be a pragmatic method to define the inflammatory and immune activity in the lesions of SSc patients.

Methods: Interstitial fluid samples from forearm skin of patients (n=25; DcSSc =19, LcSSc=6) and comparable sites on healthy controls (HC) (n=10) were collected using the dermal suction blister method. These were profiled by Luminex array for inflammatory cytokines, chemokines, and growth factors. Permutation analysis (SAM in EXCEL) was used to compare cytokine levels in SSc and HC samples.

Results: Luminex array profiling of the dermal blister fluid showed increased inflammatory cytokines (mean IL-6 in SSc 77.2 pg/ml versus 17.8 pg/ml in HC p=0.009, mean IL-17 in SSc 0.61 pg/ml versus 0 pg/ml, p=0.03), and vascular growth factors (VEGF 21.7 pg/ml in SSc, 13.5 pg/ml in HC (p=NS) and PDGF-aa 16.4 pg/ml in SSc versus 0.97 pg/ ml in HC, p=0.049). Additionally MCP-3 (CCL7), IL-15, and IFN-g were all found to be significantly increased in SSc compared to HC ($p<0.05$) (Figure 1).

Subanalysis highlighted a correlation between IL-6 and skin score (r=0.44, p=0.024) in SSc, and MCP-3 with disease duration (r=0.54, p=0.005). There was also a significant correlation between IL-6 and IL-10 (r=0.59, p=0.002)

IFN-g, IL-17, PDGF-bb were largely undetectable in the blister fluid of HC, but were present in a subgroup of SSc patients. IL-17 was only detectable in DcSSc (5/19), and in 0/6 LcSSc and 0/10 HC, while IFN-g was present in the blister fluid of 1/10 HC, and 15/25 SSc. IFN-g levels were higher in the diffuse subset compared to those with limited disease (mean 1.76 pg/ml and 0.67pg/ml respectively). IL-6 showed a trend towards increased concentrations in DcSSc compared to LcSSc, but this was not statistically significant (mean 71.7 pg/ml in DcSSc, 32.3 pg/ml in LcSSc, p=0.07).

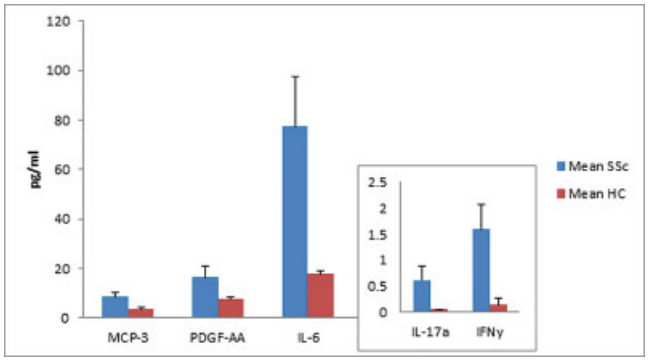

Figure 1. Graph to show mean concentration of MCP-3, PDGF-AA, IL-6, IL-17a and IFN-gamma in SSc patients and healthy controls.

Conclusion: Our results confirm the potential utility of dermal blister fluid to non-invasively define local biological processes in SSc, and identify profibrotic, angiogenic and T-cell derived factors expressed locally within the skin lesions. This technique of profiling patients using blister fluid has the potential to complement clinical and gene expression based classification to facilitate targeted therapy, as well as providing potential markers of disease activity or treatment effect.

Disclosure: K. E. N. Clark, None; **H. Lopez**, Murigenics, 4; **J. Nikotorowicz-Buniak**, None; **X. Shiwen**, None; **K. Khan**, None; **G. Martin**, Murigenics, 3; **D. J. Abraham**, None; **C. P. Denton**, None; **R. J. Stratton**, None.

2562

Inhibition Of SOX9 Phosphorylation Abrogates The Increased Expression Of Profibrotic Genes In Systemic Sclerosis Dermal Fibroblasts. Sonsoles Piera-Velazquez, Alma Makul and Sergio A. Jimenez. Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center, Thomas Jefferson University, Philadelphia, PA.

Background/Purpose: SOX9, a high mobility group transcription factor is a master regulator of chondrogenesis and plays a crucial role in the regulation of chondrocyte gene expression. However, recent studies on hepatic fibrosis and segmental glomerulosclerosis have suggested that SOX9 may participate in tissue fibrosis. Furthermore, we previously demonstrated that human normal dermal fibroblasts contained high levels of SOX9 phosphorylated at serine residue 181 and that TGFβ1 stimulates Ser181 SOX9 phosphorylation mediated by RhoA kinase and to a lesser extent by PI3K. We explored here the role of Ser181 phosphoSOX9 in the fibrotic process of Systemic Sclerosis (SSc) employing cultured SSc dermal fibroblasts treated *in vitro*with specific inhibitors of the kinases that may be responsible for Ser181 SOX9 phosphorylation and examined the effect of these inhibitors on the increased expression of profibrotic genes and exaggerated production of extracellular matrix proteins characteristics of SSc fibroblasts.

Methods: Dermal fibroblasts obtained from normal skin and from clinically affected forearm skin from patients with diffuse SSc of recent onset were studied. Ser181 phosphoSOX9 levels were assessed by Western blot analysis of cell lysates of confluent dermal fibroblast cultures employing a phospho-specific antibody that recognizes a SOX9 epitope containing a phosphorylated Ser 181 residue. Gene expression analyses were performed employing real time PCR. Collagen production was assessed by Western blots of fibroblast culture media. The effects of kinase inhibitor treatment on Ser181 phosphoSOX9 were assessed in confluent cultures in the presence or absence of TGF-β1 (10ng/mL) for 24h. The potential kinases involved were identified employing Kinexus phosphoproteome databases. The intracellular kinases PIM1, PIM2 and PKCδ were identified as being responsible for Ser181 SOX9 phosphorylation. The role of these kinases was examined by inhibition with specific small molecule kinase inhibitors. For PKCδ inhibition studies two novel specific inhibitors developed by CompleGen (CG1037 and CG1056) were employed.

Results: Previous results showed that dermal fibroblasts from SSc patients displayed marked elevation of Ser181 phosphoSOX9 levels in comparison with normal fibroblasts. Here, we show that TGF-β caused potent stimulation of Ser181 SOX9 phosphorylation which was abrogated at nM concentrations by the two small molecule inhibitors targeting PKCδ as well as the PIM1 and PIM2 specific kinase inhibitors. The kinase inhibitors did not cause morphological changes or detectable cytotoxicity at the concentrations employed. The levels of type I collagen production were reduced in parallel with the changes in Ser181 phosphoSOX9 levels.

Conclusion: The results indicate that Ser181 phosphoSOX9 participates in the molecular mechanisms responsible for the exaggerated fibrotic process in SSc and demonstrate that PKCδ and PIM1/2 kinases are responsible for Ser181 SOX9 phosphorylation. Thus, the kinases involved in Ser181 SOX9 phosphorylation provide novel therapeutic targets for SSc and other fibrotic disorders.

Disclosure: S. Piera-Velazquez, None; **A. Makul**, None; **S. A. Jimenez**, None.

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Modulating Myofibroblast Transition Of Human Scleroderma Fibroblasts Through Inhibition Of Rho Guanine Nucleotidase-Regulated Gene Transcription. Andrew Haak[1], Pei-Suen Tsou[2], Dinesh Khanna[2], David A. Fox[2], Scott D. Larsen[3] and Richard R. Neubig[4]. [1]Department of Pharmacology, University of Michigan Medical Center, Ann Arbor, MI, [2]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [3]Vahlteich Medicinal Chemistry Core, College of Pharmacy, University of Michigan, Ann Arbor, MI, [4]Department of Pharmacology & Toxicology, Michigan State University, East Lansing, MI.

Background/Purpose: Systemic sclerosis (SSc) or scleroderma, like many fibrotic disorders, has no effective therapy. Deposition of collagen and excess extracellular matrix depends on the transition of dermal fibroblasts into myofibroblasts. Current drug development has focused on targeting the initial inflammatory stimuli and specific receptors involved in fibrosis. Recent evidence, however, indicates that a transcriptional program regulated by Rho GTPase is critical for myofibroblast transition. This could be a more effective convergent target for interrupting pathological fibrosis regardless of the initial inflammatory or fibrotic stimulus. We recently identified novel inhibitors of this transcription mechanism including CCG-203971 (Bell et al, Bioorg Med Chem Lett. 23:3826, 2013). Here we assess their effectiveness in human SSc dermal fibroblasts.

Methods: Primary human dermal fibroblasts were obtained from normal individuals and patients with diffuse SSc. Cells were passaged three times in DMEM containing 10% fetal bovine serum prior to studies which were carried out at passage 4 or 5. mRNA for connective tissue growth factor (CTGF), alpha-smooth muscle actin (ACTA2) and collagen type 1 alpha 1 (COL1α1) were quantified by qRT-PCR. The fraction of cells positive for the myofibroblast maker alpha-smooth muscle actin (α-SMA) was determined by immunocytochemistry. Inhibitors of Rho/MRTF/SRF-regulated gene expression (CCG-203971) and pirfenidone, the only approved antifibrotic therapy, were tested for their ability to suppress these markers of myofibroblast transition and fibrosis.

Results: SSc dermal fibroblasts express significantly more mRNA for CTGF (3.7-fold) and ACTA2 (4.6-fold) than do normal control fibroblasts. Similarly the percentage of cells staining positively for α-SMA was significantly greater for SSc (77$\pm$9%) than for normal (27$\pm$18%) dermal fibroblasts ($p<0.001$, $n=6$). CTGF, ACTA2, and COL1α1 mRNA in SSc fibroblasts were inhibited at 24 hours by CCG-203971 with an IC_{50} of $\sim$10 μM. Treatment of SSc fibroblasts for 72 hours with 10 μM CCG-203971 reduced the percentage of α-SMA positive cells to control levels (26$\pm$18%) while pirfenidone at 300 μM was only marginally effective (41$\pm$16%).

Conclusion: Targeting the Rho/MRTF/SRF transcriptional pathway strongly suppresses myofibroblast activation and fibrosis-related gene expression in human SSc dermal fibroblasts. This could represent a novel targeted approach to disrupt a key genetic switch involved in fibrosis mechanisms and may provide a broad spectrum approach to treatment for systemic sclerosis and other disorders of fibrosis.

Disclosure: A. Haak, None; **P. S. Tsou**, Arthritis Foundation, 2; **D. Khanna**, NIH, 2, Scleroderma Foundation, 2; **D. A. Fox**, None; **S. D. Larsen**, None; **R. R. Neubig**, None.

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Functional Activation Of The TRPV1 and TRPV2 Non-Selective Cation Channels Potentiates TGF-β1-Induced Endothelial-To-Mesenchymal Transition In Murine Pulmonary Endothelial Cells Suggest a Potential Role Of Trpv Channels In The Pathogenesis Of Systemic Sclerosis. Peter J. Wermuth and Sergio A. Jimenez. Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center, Thomas Jefferson University, Philadelphia, PA.

Background/Purpose: Transient receptor potential (Trp) cation channel, subfamily V (TRPV) members can impact a diverse range of vascular functions, including vascular tone, vascular permeability, mechanosensing, angiogenesis and endothelial cell (EC) proliferation, apoptosis, and death. Recently, it has been shown that endothelial-to-mesenchymal transition (EndoMT) may play a role in generating myofibroblasts responsible for the uncontrolled production of extracellular matrix in many fibrotic diseases, including Systemic Sclerosis (SSc). Thus the purpose of these studies was to investigate the effect of TRPV1 and TRPV2 inhibition on the EndoMT process.

Methods: Pulmonary EC were isolated from three C57BL/6J mice employing sequential immunomagnetic selection with anti-CD31 and anti-
CD102 antibodies followed by *in vitro* culture and treatment with TRPV1 and TRPV2 agonists or antagonists in the presence and absence of TGF-β1. EndoMT was assessed by α-smooth muscle actin (α-SMA) immunofluorescence and by Western blot analysis for α-SMA and type I collagen. Induction of type I, type III and type IV collagens, α-SMA, fibronectin, as well as various mesenchymal cell specific genes, including the transcription factor Twist1, and the transcriptional repressors Snail1 and Snail2 as well as expression of EC-specific genes (Pecam1 and VE-cadherin) was assessed by semi-quantitative RT-PCR in triplicate for two replicates per cell line.

Results: Exposure of lung ECs to either the TRPV1 antagonist capsazepine or the TRPV2 antagonist tranilast caused downregulation of expression of EC-specific genes and upregulation of mesenchymal-specific genes. These agents did not induce noticeable changes in cell morphology. Treatment of cells with either capsazepine or tranilast in combination with TGF-β1 showed synergisitic stimulation of TGF-β1 effects on gene expression. Capsazepine in combination with TGF-β1 produced a pronounced morphological change from EC to fibroblast morphology cells which was of greater magnitude than those induced by TGF-β1 alone. In contrast, neither the TRPV1 agonist capsaicin nor the TRPV2 agonist probenecid alone or in combination with TGF-β1 induced EndoMT in murine lung ECs. Capsaicin and probenecid, however, abrogated TGF-β1-induced EndoMT, and reversed TGF-β1-induced morphological changes in the lung EC.

Conclusion: Functional downregulation of TRPV1 and TRPV2 causes strong synergistic potentiation of TGF-β1-induced EndoMT and may play a pathogenetic role in pulmonary fibrosis and other fibrotic diseases, including SSc. The abrogation of TGF-β1-induced EndoMT by capsaicin and probenecid suggests that induction or activation of TRPV1 and TRPV2 activation could represent an important and novel strategy to prevent EndoMT-mediated generation of activated myofibroblasts in fibrotic diseases.

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Disclosure: P. J. Wermuth, None; **S. A. Jimenez**, None.

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Synergistic Effects Of Endothelin-1 On Transforming Growth Factor-β1 (TGF-β1) Induced Endothelial-To-Mesenchymal Transition. A Novel Mechanism For The Fibrogenic Effects Of Endothelin. Peter J. Wermuth, Zhaodong Li and Sergio A. Jimenez. Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center, Thomas Jefferson University, Philadelphia, PA.

Background/Purpose: The process of endothelial-to-mesenchymal transition (EndoMT) may be a crucial pathway in the generation of activated myofibroblasts, cells that play a pivotal role in the development of tissue and organ fibrosis in fibrotic diseases such as Systemic Sclerosis

(SSc). It has been previously demonstrated that TGF-β1 induces EndoMT *in vitro* in murine lung endothelial cells (ECs). Since extensive previous studies demonstrated a potent profibrotic role for Endothelin-1 (ET-1), the role of ET-1 in the induction of EndoMT was investigated in cultured murine lung ECs.

Methods: Pulmonary EC were isolated from three C57Bl/6J mice employing trypsin/collagenase tissue digestion followed by sequential immunomagnetic selection with anti-CD31 and anti-CD102 antibodies. After *in vitro* culture, the purified EC were treated with ET-1 *in vitro* in the presence and absence of TGF-β1. EndoMT was assessed by immunofluorescence for α-smooth muscle actin (α-SMA) and by Western blot analysis for α-SMA and type I collagen. Induction of type I, type III and type IV collagens, α-SMA, fibronectin, as well as several mesenchymal specific genes, including the transcription factor Twist1 and the transcriptional repressors Snail1 and Snail2 was assessed by semi-quantitative RT-PCR triplicate assays for two replicates per cell line.

Results: Treatment of murine pulmonary ECs with TGF-β1 induced high levels of α-SMA expression in comparison to saline-treated control ECs. ET-1 alone did not affect α-SMA levels but produced a synergistic effect with TGF-β1 by potentiating TGF-β1-induced EndoMT as indicated by increased α-SMA production. A quantitative assessment of the number of α-SMA expressing EC in TGF-β1-treated cultures was 27% compared to 52% in cultures treated with both TGF-β1 and ET-1. These results were confirmed by Western blot analysis. Semi-quantitative RT-PCR analysis demonstrated that ET-1 synergistically potentiated TGF-β1-mediated increased expression levels of types I and III collagens, α-SMA, fibronectin, Twist1, Snail1 and Snail2. Expression of EC-specific VE-cadherin (Cdh5) was downregulated in TGF-β1-treated cultures compared to saline controls and ET-1 also synergistically potentiated this TGF-β1-mediated effect.

Conclusion: ET-1 plays an important role in regulating EndoMT by causing a synergistic potentiation of TGF-β1-induced EndoMT-mediated generation of activated myofibroblasts and of EndoMT-mediated increased expression of extracellular matrix components including Types I and III collagens. Furthermore, ET-1 also potentiated the TGF-β1-induced increase in expression of various genes involved in the phenotypic conversion of EC into myofibroblasts including Twist1, Snail1 and Snail2. Since ET-1 plays a crucial role in the pathogenesis of SSc-associated pulmonary arterial hypertension and may play a profibrotic role in skin and lung fibrosis, the results described here identify a novel mechanism supporting the concept that ET-1 plays a key pathogenetic role in SSc-associated pulmonary fibrosis.

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Nilotinib Treatment Effect In The Skin As Measured By DNA Microarray In Patients With Diffuse Systemic Sclerosis. Jessica K. Gordon[1], Tammara A. Wood[2], Robert F. Spiera[1] and Michael L. Whitfield[3]. [1]Hospital for Special Surgery, New York, NY, [2]Dartmouth Medical School, Hanover, NH, [3]Geisel School of Medicine at Dartmouth, Hanover, NH.

Background/Purpose: Gene expression profiling by DNA microarray is used to identify potential biomarkers in Systemic Sclerosis (SSc). Discrete gene expression signatures have been observed to subset patients and correlate with clinical parameters. We tested the hypothesis that treatment modulates gene expression in SSc skin in the context of an open label study of nilotinib to treat early diffuse cutaneous (dc)SSc.

Methods: Ten adult patients with early progressive dcSSc of $<$3 yrs since the initial SSc symptom were treated with nilotinib 400 mg PO twice daily. Three mm punch biopsies of lesional forearm skin were performed at baseline and after 6 and 12 mos of treatment, and the Modified Rodnan Skin Score (MRSS) was recorded. Clinical improvement was defined as improvement in MRSS by 20% from baseline. Using this criterion, we classified 4 patients as improvers and 4 patients as non-improvers. RNA was extracted from the whole skin, converted to cRNA, and hybridized to Agilent 8$\times$60K whole human genome microarrays. Significance Analysis of Microarrays (SAM) was used to identify genes differentially expressed between pre- and post-treatment skin biopsies for both improvers and non-improvers separately and together. Patients before and after 6 and 12 months of treatment were assigned to intrinsic subsets using a gene expression classifier algorithm.

Results: Eight out of 10 patients from the nilotinib trial had at least baseline and 6 month biopsies that were included in the gene expression analysis. Patient characteristics (n=8) were: 75% female; median age 48.5 (IQR 41,53); median disease duration from the first non-Raynaud's symptom of SSc: 0.67 (IQR 0.42, 0.71); baseline Modified Rodnan Skin Score (MRSS): 27.5 (IQR 22, 32); 62.5% RNA Pol3 positive; 25% Scl70 positive. SAM identified 185 genes with significantly decreased expression post treatment in improvers. These genes were significantly enriched for inflammatory response, hematopoiesis and cell-cell adhesion. In contrast, we did not find significant changes in gene expression post-treatment in non-improvers. Analysis of patient intrinsic subsets showed that 3 out of 4 non-improvers showed stable or increasing inflammatory signatures. Improvers showed either rapid decrease in the inflammatory signature or absence of the inflammatory signature with concomitant stable or increasing fibroproliferative signatures.

Conclusion: We observed modulation of gene expression in skin as measured by DNA microarray in improvers but not in non-improvers during the course of the nilotinib trial. Patients that did not show improvement had an inflammatory signature that was stable or increasing, whereas patients that improved show decreasing inflammatory and increasing fibroproliferative gene signatures. Whether these changes in gene-expression signify biological effect of nilotinib or natural history of scleroderma will require an untreated control group to determine.

Disclosure: J. K. Gordon, None; **T. A. Wood**, None; **R. F. Spiera**, Roche Pharmaceuticals, 2, Novartis Pharmaceutical Corporation, 2, GlaxoSmithKline, 2; **M. L. Whitfield**, None.

2567

Cadherin-11 Regulates Pulmonary Fibrosis In Bleomycin-Induced Lung Injury. Mesias Pedroza, Anuh T. George and Sandeep K. Agarwal. Baylor College of Medicine, Houston, TX.

Background/Purpose: Pulmonary fibrosis (PF) is the leading cause of death in systemic sclerosis. Pathologically, PF is characterized by an aberrant wound healing repair mechanism leading to excessive fibroblast proliferation, myofibroblast differentiation, and extensive matrix deposition in the alveolar airways. Epithelial-to-mesenchymal transition (EMT) is the differentiation of fibroblast-like phenotype from epithelial cells that results in myofibroblast accumulation. Cadherin-11 (Cad11), a mesenchymal, homophillic adhesion molecule, has been reported to be expressed on hyperplastic alveolar epithelial cells (AEC), a populations of cells postulated to be undergoing EMT during the development of fibrosis. However it is not known if Cad11 is a regulator of EMT and if this contributes to the development of PF. We hypothesized that Cad11 contributes to the development of pulmonary fibrosis through the regulation of EMT.

Methods: Cad11 deficient mice and neutralizing Cad11 monoclonal antibodies were used to determine the role of Cad11 in the intraperitoneal (IP) bleomycin (BLM) model of pulmonary fibrosis that exhibits EMT. AEC cell lines (A549, MLE-12) and primary murine AEC induced to undergo EMT by TGF-beta were used to determine if Cad11 regulates EMT in vitro.

Results: Cad11 deficient mice had reduced fibrosis in the IP BLM model as assessed by improved arterial oxygen saturation, decreased collagen deposition, diminished alpha-smooth muscle actin (aSMA) accumulation, decreased TGF-b production and reduced b-catenin expression. These findings were confirmed using neutralizing antiCad11 monoclonal antibodies in wild type mice. *In vitro*studies demonstrated that activation of Cad11 using immobilized Cad11-Fc fusion protein increased Col1a expression by A549 and MLE-12 AEC. In contrast, siRNA knockdown of Cad11 expression in A549 and MLE-12 AEC decreased the expression of fibrotic genes such as Col1a, aSMA, and CTGF. In addition, primary AECs from Cad11 deficient mice had decreased capacity to undergo EMT induced by TGF-beta relative to primary AECs from wild type mice. Finally, Cad11 inhibition with soluble Cad11-Fc fusion protein reduced EMT markers in wild type AECs treated with TGF-beta.

Conclusion: These findings demonstrate that Cad11 is an important mediator of EMT in vitro and pulmonary fibrosis in vivo. Furthermore, these data suggest that Cad11 may be a therapeutic target in the treatment of pulmonary fibrosis.

Disclosure: M. Pedroza, None; **A. T. George**, None; **S. K. Agarwal**, None.

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Involvement Of Collagen-Binding Heat Shock Protein 47 In The Scleroderma-Associated Fibrosis. Haiyan Chu[1], Ting Wu[1], Wenyu Wu[2], Wenzhen Tu[3], Yanyun Ma[1], Qingmei Liu[1], Hejian Zou[4], Li Jin[1] and Jiu-Cun Wang[1]. [1]Ministry of Education Key Laboratory of Contemporary Anthropology, School of Life Sciences, Fudan University, Shanghai, China, [2]Division of Dermatology, Huashan Hospital, Fudan University, Shanghai, Shanghai, China, [3]Shanghai Traditional Chinese Medicine-Integrated Hospital, Shang hai, China, [4]Huashan Hospital, Shanghai, China.

Background/Purpose: Scleroderma or systemic sclerosis (SSc) is characterized by the fibrosis of skin and visceral organs, especially the uncontrolled fibrosis of multiple organs. Collagen is a major extracellular matrix (ECM) protein that deposited in the fibrotic organs. Heat shock protein 47 (HSP47) has been identified as a collagen-specific chaperon, and plays an important role in the development of fibrosis. Our previous study demonstrated that HSP47 was significantly up-regulated in the skin of dermal sclerosis mice induced by bleomycin. The aim of the present study is to investigate the role of HSP47 in the pathogenesis of scleroderma.

Methods: For *in vivo* studies, C57BL/6 female mice of 6–8 weeks (n = 5 for each treatment) were injected with bleomycin subcutaneously into the same site of the shaved upper back daily for 3 weeks. The mRNA and protein level of HSP47 in the lesion skins from the mouse model was assessed by real-time PCR and western blot. In clinical study, skin biopsies and fibroblasts, peripheral blood mononuclear cells (PBMC) and plasma of SSc patients were obtained to study the role of HSP47 during the pathogenesis of SSc. Immunohistochemical staining was performed to identify the localization of HSP47 in the skin of SSc patients, real-time PCR and western blot were conducted to respectively test the gene and protein expression levels of HSP47 in the skin fibroblasts, and ELISA was used to detect the protein level of HSP47 in the plasma of SSc patients. For *in vitro* study, silencing and over-expression of HSP47 in NIH/3T3 fibroblast cells were performed using HSP47 siRNA and HSP47 expression plasmid respectively to investigate the effect of HSP47 on collagen production.

Results: For *in vivo* study, HSP47 was significantly up-regulated in the skin lesion of the mice treated by bleomycin. Meanwhile, the expression of α-SMA increased in the skin lesion of the mice in response to bleomycin. In clinical study, the level of HSP47 increased in the fibroblasts cultured from SSc patients' skin, the number of HSP47 positive cells increased in the skin of SSc patients, and the localization of HSP47-positive cells were observed in accordance with the α-SMA-positive cells. Additionally, the protein level of HSP47 in the plasma and the mRNA level of HSP47 in the peripheral blood mononuclear cells were both elevated in the SSc samples. *In vitro*study found that over-expression of HSP47 in the fibroblasts increased the level of collagen, whereas knockdown of HSP47 gene decreased its expression.

Conclusion: The production of collagen is affected by HSP47, and HSP47 might be involved in the pathogenesis of scleroderma. Further investigations may be necessary to test this collagen chaperone as an important therapeutic approach.

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Serum S100A4 Levels Correlate With Skin Fibrosis and Lung Involvement In Systemic Sclerosis. Michal Tomcik[1], Lucie Andres Cerezo[1], Simona Skacelova[1], Martin Komarc[2], Radim Becvar[1], Mariam Grigorian[3], Joerg HW Distler[4] and Ladislav Senolt[1]. [1]Institute of Rheumatology, Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [2]Institute of Biophysics and Informatics of the First Faculty of Medicine, Charles University, Prague, Czech Republic, [3]Institute of Cancer Biology, Danish Cancer Society, Copenhagen, Denmark, [4]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany.

Background/Purpose: Our previous study demonstrated that S100A4 is overexpressed in scleroderma (SSc) skin, fibroblasts and preclinical models of SSc in a TGF-β dependent manner. Furthermore, we showed that S100A4 is a new regulator of canonical TGF-β signalling and its inhibition prevents the stimulatory effects of TGF-β on collagen synthesis. Similarly, deficit of S100A4 prevented dermal fibrosis induced by bleomycin or in Tsk-1 mice. The aim of this study was to evaluate S100A4 in the circulation of SSc patients and characterize its potential association with skin changes and SSc-related features.

Methods: A total of 33 patients (29 females; mean age 52.8; disease duration 4.2 years; dcSSc/lcSSc = 8/25) who met the ACR classification criteria for SSc and 20 healthy individuals matched by age and sex were included in this study. Serum S100A4 levels were measured using ELISA (CycLex Co., Ltd., Nagano, Japan). CRP, ANA and ENA complex were evaluated. SSc-related manifestations were obtained from the Czech Registry Database of SSc patients. Interstitial lung disease, pulmonary arterial hypertension, oesophageal dysmotility, cardiac and renal involvement, nailfold capillaroscopy and Raynaud's phenomenon were recorded. Skin changes were assessed using the modified Rodnan skin score and EUSTAR SSc activity score was determined. Data are presented as mean ± SEM.

Results: S100A4 serum levels were significantly increased in SSc patients compared with healthy controls (119.2 ± 23.4 vs. 43.9 ± 3.3 ng/ml, $p = 0.011$). Patients with diffuse cutaneous SSc had significantly higher levels of serum S100A4 compared with patients with limited cutaneous SSc or healthy controls (201.8 ± 53.1 vs. 92.7 ± 24.0 ng/ml, $p = 0.017$ and 201.8 ± 53.1 vs. 43.9 ± 3.3 ng/ml, $p = 0.001$, respectively). The levels of S100A4 positively correlated with the modified Rodnan skin score ($r = 0.556$, $p = 0.001$). In addition, S100A4 levels negatively correlated with forced vital capacity (FVC) and saturation of peripheral oxygen (SpO2) ($r = -0.362$, $p = 0.038$ and $r = -0.414$, $p = 0.029$, respectively). Of particular interest, S100A4 levels positively correlated with EUSTAR SSc activity score ($r = 0.750$, $p = 0.0001$). However, only relations between S100A4 and the modified Rodnan skin score, and S100A4 and EUSTAR SSc activity score were approved at corrected level of statistical significance after Bonferroni's correction ($p = 0.001 < 0.01$, $p = 0.0001 < 0.01$, respectively). The presence of autoantibodies (ANA, anti-centromere, anti-Scl70), a pathological capillaroscopic pattern (early, active, late), the administration of low dose glucocorticoids (or immunosuppressive treatment) and exhibition of the main individual clinical symptoms of SSc did not significantly affect levels of serum S100A4.

Conclusion: We demonstrate that S100A4 serum levels are significantly increased in SSc patients compared with healthy controls. Higher levels of S100A4 are associated with dcSSc subset, skin involvement, deteriorated parameters of lung involvement and higher disease activity. These data support our previous findings on the role of S100A4 as a regulator of TGF-β induced fibroblast activation and dermal fibrosis in SSc.

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Tenofovir But Not Adefovir Prevents Liver and Skin Fibrosis In Two Models Of Adenosine-Mediated Injury. Jessica L. Feig[1], Doreen Tivon[1], Miguel perez Aso[2], Timothy Cardozo[1] and Bruce N. Cronstein[3]. [1]New York University School of Medicine, New York, NY, [2]NYU Univ Medical Center, New York, NY, [3]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Acyclic nucleoside phosphonates are a key class of antivirals commonly used in the treatment of both DNA and retroviral infections. Adefovir and tenofovir are AMP analogues that resemble substrates of CD73. We have previously reported that adenosine, generated by the CD73-mediated dephosphorylation of AMP, acting at A_{2A}receptors, plays a critical role in development of both hepatic and dermal fibrosis in murine models of cirrhosis and scleroderma, respectively. A recent clinical trial demonstrated that tenofovir, but not other antiviral agents, reverses hepatic fibrosis/cirrhosis in patients with hepatitis B. We therefore proposed the hypothesis that tenofovir's antifibrotic effects are mediated by inhibition of adenosine production by CD73-mediated dephosphorylation of AMP.

Methods: In silico modeling and docking studies were performed using an ICM-Browser www.molsoft.com. CD73 enzyme activity was quantitated by malachite green. Alkaline Phosphatase activity (Abcam) was performed. Thioacetamide(TAA,100 mg/kg IP)-treated mice were treated with vehicle, Adefovir, or Tenofovir (75mg/kg, SubQ) [n=5–10 per group]. Bleomycin (0.25 U, SubQ)-treated mice were treated with vehicle, Adefovir, or Tenofovir (75mg/kg, IP) [n=5–10 per group]. Adenosine levels were determined by HPLC. Skin breaking strength was via tensiometer. H&E or picrosirus red-stained slides were imaged, and pixel quantification was performed with SigmaScan software. Scar index was determined as the ratio of red/green pixels representing compact/filamentous fibers; higher numbers indicate more fibrosis.

Results: In silico modeling data suggested that both adefovir and tenofovir bound to the enzymatic pocket of CD73. Tenofovir (Sequoia), but not adefovir (Sequoia), inhibited CD73 activity of 293T cells overexpressing CD73 (38+7.4%, at 10 uM) and of recombinant enzyme (72+1.0%, at 10uM). Yet, the inhibition of CD73 by Tenofovir (Gilead) was not pharmacologically relevant with an IC50>100uM. Alkaline phosphatase activity wasn't modulated by Adefovir or Tenofovir. Adefovir decreased adenosine levels in the skin of bleomycin-challenged mice though this trend was not significant. Tenofovir significantly decreased adenosine levels in the skin of bleomycin-challenged mice (273.95+8.41 vs. 432.58+24.34nM adenosine/12mm punch biopsy, n=8–10, [$p<0.05$]). Tenofovir (75mg/kg), but not Adefovir (75mg/kg), diminished hepatic fibrosis in thioacetamide-treated mice (fibrotic area/hepatic slide area 1.00+0.04% vs 4.45+0.37%) Tenofovir (75mg/kg), but not Adefovir (75mg/kg), diminished bleomycin-induced dermal fibrosis in bleomycin-treated mice (73.7+3.1% reduction of hydroxyproline content [$p<0.05$]; 33.5+3.8% reduction of dermal thickness [$p<0.06$] and reduction of breaking tension by 66.8+1.4% [$p<0.05$]). Picrosirius red staining showed dramatic altering of dermal collagen quality (scar index of 1.2+0.1 vs 22.2+0.7 [$p<0.001$], normal skin is 2.5) in Tenofovir-treated mice.

Conclusion: Tenofovir reduces fibrosis via inhibition of adenosine production. Tenofovir may have therapeutic potential in treating fibrosis in patients suffering from non-viral fibrosing diseases such as scleroderma.

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Pigment Epithelium Derived Factor Secreted By Activated Fibroblasts Can Contribute To Impaired Angio and Vasculogenesis In Scleroderma. Vasiliki Liakouli[1], Georgia Mavria[2], Justin Gillespie[3], Margherita Scarcia[2], Paola Cipriani[1], Roberto Giacomelli[1], Paul Emery[4] and Francesco Del Galdo[4]. [1]Rheumatology Unit, University of Aquila, L'Aquila, IT, L'Aquila, Italy, [2]Signal Transduction and Angiogenesis group, Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, UK, Leeds, United Kingdom, [3]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [4]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

Background/Purpose: Systemic Sclerosis (SSc) is an autoimmune disorder characterized by tissue fibrosis and vasculopathy. This latter comprises both neointima proliferation and defective angio and vasculogenesis. Although some of the clinical manifestations of the vasculopathy often precede the onset of fibrosis, there is scanty of data investigating the molecular mechanisms eventually linking the profibrotic activation of fibroblasts (FBs) and the poor angio/vasculogenesis in Scleroderma. Recently, a proteomic analysis of the secretome of SSc dermal FBs (SSc FBs), identified among other proteins a consistent increased secretion of Pigment Epithelium Derived Factor (PEDF) associated with the profibrotic phenotype (AJP, 2010). PEDF has been described as produced by retinal-pigmented epithelium and melanocytes, and is a major endogenous inhibitor of intraocular angiogenesis. Here we aimed to validate the increased expression of PEDF in SSc and test the hypothesis that PEDF might play an important role in establishing or perpetuating SSc vasculopathy.

Methods: PEDF expression was investigated in the involved skin and FBs of 4 SSc patients in the early phase of the diffuse form of the disease and 4 healthy controls (HC) by immunohistochemistry (IHC) and real time-PCR analysis. Functional effects of PEDF on angio/vasculogenesis were examined by Matrigel assays. Organotypic co-culture assays were performed seeding HUVECs or microvascular endothelial cells (MVECs), on monolayers of either primary healthy FBs (HC FBs) or SSc FBs or HC FBS silenced for Caveolin-1 (Cav-1). Endothelial cells were evidenced by IHC staining for CD31 in organotypic co-culture assays. Vascular tubule number, length and junctions were identified and analyzed by Angiosys software *(TCS* CellWorks).

Results: Both Healthy and Scleroderma skin biopsies showed high PEDF protein expression on melanocytes, as expected. Nevertheless, in SSc skin 52% (+/−5.9) of the FBs showed a strong expression of PEDF whereas only 13% (+/−0.68) of the FBs in HC skin were positive *(*$p<0.0006$). Double IHC studies indicated that FBs positive for PEDF showed a decreased expression of Cav-1 in both HC and SSc skin. *In vitro* studies confirmed that SSc FBs showed on average a 5-fold increased in PEDF expression compared to HC FBs ($p<0.05$). Functional studies confirmed that recombinant PEDF protein had a direct inhibitory effect on vasculogenesis, suppressing both tubule length and number. Consistently, organotypic co-culture assays indicated that SSc FBs or HC FBs silenced for Cav-1 inhibited tubulogenesis both on MVECs or HUVECs, respectively.

Conclusion: PEDF expression is increased in SSc biopsies and SSc FBs. PEDF expression is associated with decreased Cav-1 expression *in vivo* and it is induced by silencing Cav-1 *in vitro*. Functionally, PEDF can suppress vasculogenesis both in Matrigel and co-culture assays. This suggests that the decreased expression of Cav-1 observed in SSc FBs may contribute to the vasculopathy of Scleroderma. Further studies unraveling the mechanisms of the antiangiogenic effect of PEDF may shed light in understanding the molecular events linking the profibrotic phenotype and SSc vasculopathy.

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An Atypical Cyclin-Dependent Kinase Mediates Fibrosis and Is a Novel Target In Scleroderma. Jun Wei[1], Roberta G. Marangoni[1], Wenxia Wang[1], Jingang Huang[2], Joerg H. W. Distler[2] and John Varga[3]. [1]Northwestern University, Chicago, IL, [2]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Northwestern University Medical School, Chicago, IL.

Background/Purpose: Cyclin-dependent kinase 5 (CDK5), expressed primarily in the central nervous system, plays important roles in axonal guidance, dopaminergic signaling, neuronal migration, and pain sensing. Aberrant CDK5 function is implicated in neurodegenerative diseases including Alzheimer's disease. In contrast to other cyclin-dependent kinases, binding of the non-cyclin activator p35 is sufficient to induce CDK5 activity. Recent studies reveal novel extra-neuronal role for in inflammation and metabolism. The nuclear receptor PPAR-γ, a master regulator of adipogenesis and adipokine production, is impaired in scleroderma. Since PPAR-γ is a novel CDK5 substrate, we hypothesized that the CDK5/p35 pathway might be responsible for impaired PPAR-γ function in SSc and play a role in the development and persistence of fibrosis.

Methods: Expression of p35 was examined in skin biopsies from bleomycin-injected mice and explanted scleroderma fibroblasts. Regulation of p35/CDK5 expression and activity in vitro was examined in human and mouse skin fibroblasts, progenitor cells and mature adipocytes by real-time qPCR, Western analysis and in vitro kinase assays. Effects of CDK5/p35 loss-of-function and gain-of-function were evaluated in normal and scleroderma skin fibroblasts using monolayer cultured fibroblasts and ex vivo using human skin organ cultures. CDK5 inhibition was examined in vivo using mouse models of fibrosis induced by bleomycin or constitutively active Type I TGF-β receptor.

Results: Levels of p35 mRNA were markedly elevated in explanted scleroderma fibroblasts (n=6, $p<0.005$). p35 was also elevated in lesional skin from mice with bleomycin-induced scleroderma. Both p35 expression and CDK5 activity were strongly stimulated by TGF-β in human and mouse skin fibroblasts, mesenchymal progenitor cells and mature adipocytes. Ectopic p35 and CDK5 caused suppression of adiponectin expression and simultaneous stimulation of collagen synthesis in these cells, whereas RNAi-mediated knockdown of p35/CDK5 abrogated TGF-β-induced fibrotic gene expression. Pharmacological inhibitors of CDK5 not only prevented but even reversed TGF-β-induced fibrotic responses in monolayer cultures and in skin organ cultures, and ameliorated collagen overproduction in scleroderma fibroblasts. Moreover, CDK5 inhibitor prevented and reversed skin fibrosis in complementary inflammatory and TGF-β-driven mouse models of scleroderma.

Conclusion: The CDK5/p35 axis has a previously unrecognized important non-neuronal function in modulating fibrotic responses. Elevated p35 expression and CDK5 activity is an unexpected feature of scleroderma that might contribute to development of fibrosis. Pharmacological targeting CDK5/p35 might be novel treatment for fibrosis.

Disclosure: J. Wei, None; **R. G. Marangoni**, None; **W. Wang**, None; **J. Huang**, None; **J. H. W. Distler**, None; **J. Varga**, None.

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The Role Of STAT-3 In The Development Of Pulmonary and Dermal Fibrosis. Mesias Pedroza, Sarah To, Anuh T. George, David J. Tweardy and Sandeep K. Agarwal. Baylor College of Medicine, Houston, TX.

Background/Purpose: Fibrosis is the accumulation of excessive extracellular matrix in tissues, leading to tissue damage. In systemic sclerosis, the trigger is postulated to be an autoimmune response that leads to tissue injury, production of growth factors, pro-inflammatory and profibrotic cytokines, and accumulation of myofibroblasts. Two potential sources of myofibroblasts are the differentiation of local fibroblasts and the process of epithelial-to-mesenchymal transition (EMT). IL-6 is a proinflammatory and profibrotic cytokine that is increasingly recognized as an important mediator of fibrosis and may contribute to the accumulation of myofibroblasts. After engaging its receptor, IL-6 signals through the STAT-3. STAT-3 has been shown to be elevated in skin and pulmonary fibrosis. The extent to which STAT-3 is involved in the development of fibrosis and the mechanisms by which it leads to fibrosis are not known. We hypothesizes that STAT-3 signaling contributes to the development of tissue fibrosis in the lung and skin in part through the modulation of EMT.

Methods: Fibrotic tissue from systemic sclerosis patients, idiopathic pulmonary fibrosis patients, and mouse models of lung and skin fibrosis was processed for phosphor-STAT-3 staining by immunohistology. To determine if STAT-3 signaling contributes to the development of fibrosis, C-188-9, a novel small molecule STAT-3 inhibitor, was administered to C57/Bl-6 mice in both the intraperitoneal (IP) bleomycin mouse model of lung fibrosis and the subcutaneous (SC) bleomycin mouse model of skin fibrosis. To determine the role of STAT-3 in EMT and myofibroblast differentiation, C-188-9 was used in tissue culture experiments with alveolar epithelial cells (AEC; MLE-12 and primary AEC) and murine lung fibroblasts.

Results: Phospho-STAT-3 expression was increased in fibrotic tissue from systemic sclerosis patients, idiopathic pulmonary fibrosis patients, and mouse models of lung and skin fibrosis. STAT-3 inhibition by C-188-9 decreased fibrotic endpoints (collagen deposition by Sircol, expression of alpha-smooth muscle actin (SMA), and improved arterial oxygen saturation) in the IP bleomycin pulmonary fibrosis model. C-188-9 also decreased the development of dermal fibrosis in the SC bleomycin model as assessed by decreased dermal thickness, a reduction of alpha-SMA accumulation, and decreased collagen deposition. *In vitro* studies show that TGF-beta or IL-6 trans-signaling (IL-6/sIL-6R-alpha) were able to induce 1) EMT on primary AEC and MLE-12 cell line and 2) myofibroblast differentiation from fibroblasts. C-188-9 prevented TGF-beta and IL-6/sIL-6R-alpha induced EMT assessed by Col1a, alpha-SMA, Twist, and Snail mRNA levels and reduced myofibroblast differentiation as assessed by Col1a and alpha-SMA mRNA levels.

Conclusion: These findings demonstrate that STAT-3 contributes to the development of tissue fibrosis in the skin and the lung and plays a role in the development of myofibroblasts in vitro. Furthermore, these data suggest that STAT-3 may be a therapeutic target in the treatment of dermal and pulmonary fibrosis.

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ACR/ARHP Poster Session C
Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's - Clinical Aspects and Therapeutics II
Tuesday, October 29, 2013, 8:30 AM–4:00 PM

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Early Use of Prostacyclin Therapy Improves Transplant-Free Survival in Patients With Systemic Sclerosis-Related Pulmonary Arterial Hypertension Plus Interstitial Lung Disease. Elizabeth Volkmann[1], Rajan Saggar[1], Bryant Torres[1], Lynne Yoder[1], Robert Elashoff[1], Rajeev Saggar[2], Harsh Agrawal[1], Nabeel Borazan[3], Sarah Thomas[1] and Daniel Furst[1]. [1]University of California, Los Angeles, Los Angeles, CA, [2]St. Joseph's Hospital and Medical Center, Phoenix, AZ, [3]Rheumatology UCLA, Los Angeles, CA.

Background/Purpose: The leading causes of death in systemic sclerosis (SSc) are pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD). Use of PAH therapy in patients with both SSc-PAH and ILD is controversial and may not improve survival (1). This study investigates transplant-free survival in patients with SSc-PAH, both with and without ILD, treated aggressively with PAH therapies.

Methods: All SSc patients who had a right heart catheterization (RHC) diagnostic for PAH (mean pulmonary artery pressure (mPAP) greater than or equal to 25 mm Hg, pulmonary capillary wedge pressure (PCWP) less than or equal to 15 mm Hg, pulmonary vascular resistance (PVR) greater than or equal to 240 dynesxsecond/cm^5), between 2001–2012 were enrolled. ILD was defined as greater than 30% disease extent on high-resolution computed tomography (HRCT) or when disease extent 10–30%, forced vital capacity less than 70%. Kaplan-Meier and Cox proportional hazards models were used to analyze survival and identify prognostic variables.

Results: Of the 99 patients with SSc-PAH, 71 also had ILD. Patients with PAH+ILD were younger than patients with PAH alone (Mean 55 years vs. 60 years, respectively, p=0.07) and a smaller percentage were woman (70% vs. 93%, respectively, p=0.02). SSc type/disease duration, ethnicity, comorbidities, hemoglobin, creatinine, mPAP, PCWP, PVR, use of supplemental oxygen, and six-minute walk distance were similar between patients with PAH alone and PAH+ILD. Twenty-four percent of all patients started prostacyclin therapy within 6 months of the RHC, while 24% started prostacyclin therapy after 6 months of the RHC. The 1-, 2-, 3-year survival estimates were 72%, 59%, 50%, and 82%, 66%, 60%, for the PAH+ILD and PAH alone groups, respectively, p=0.5 (Figure 1). In the multivariate model, after controlling for potentially confounding variables, male gender (hazard ratio 0.6, p=0.008) and prostacyclin therapy initiation within 6 months of the RHC (hazard ratio 1.4, p=0.007) were the only factors significantly associated with transplant-free survival.

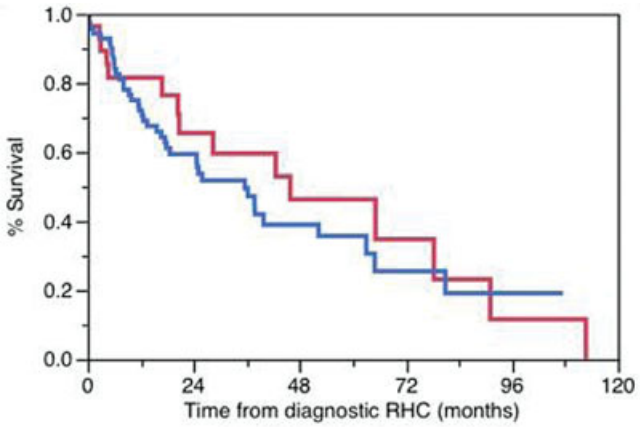

Figure 1. Kaplan-Meier survival curves demonstrating no significant difference in transplant-free survival for SSc-PAH patients with ILD (blue line) and without ILD (red line) (Log rank p-value 0.5).

Conclusion: Survival of SSc-PAH and ILD has improved compared with historical series (1); this may in part be due to aggressive use of prostacyclin therapy.

References:
(1) Le Pavec J, et al. Arthritis Rheum 2011;63:2456.

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Utility Of Autoantibody Testing For Predicting Risk Of Pulmonary Arterial Hypertension: A Retrospective Analysis In Routine Autoantibody Laboratory. Masataka Kuwana[1], Yuichiro Shirai[1], Hidekata Yasuoka[1], Tsutomu Takeuchi[1] and Kenichi Masui[2]. [1]Keio University School of Medicine, Tokyo, Japan, [2]National Defense Medical College, Tokorozawa, Japan.

Background/Purpose: Pulmonary arterial hypertension (PAH) is an intractable complication of connective tissue disease (CTD). Current guidelines recommend early detection and intervention for improvement of

outcomes. To achieve this goal, it is imperative to identify subgroups with high risk for developing PAH. Patients with systemic sclerosis (SSc) are known to have the highest risk for PAH. Serum autoantibodies, such as anticentromere, anti-U1RNP, anti-U3 RNP, and anti-Th/To, were also associated with PAH in certain CTD subgroups. However, little information is available for utility of autoantibody profiles for predicting PAH risk in patients with CTD. Here, we examined a role of autoantibody testing in identifying patients with PAH risk using a large-scale database of a routine autoantibody laboratory.

Methods: This study enrolled 6,162 patients, whose sera were sent to our autoantibody laboratory between 1995 and 2008 because of clinical suspicion of CTD. They were selected from 9,872 consecutive patients based on observation period >3 years, and availability of full clinical information on medical charts. Indirect immunofluorescence, double immunodiffusion, and RNA immunoprecipitation assay were routinely conducted to identify autoantibodies to centromere, topoisomerase I, Sm, U1RNP, SSA, SSB, Th/To, U3RNP, SRP, aminoacyl tRNA synthetase, and ribosome.

Results: During 6.6 ± 5.6 years of follow-up, 71 patients (1.2%) were diagnosed as having PAH confirmed by right heart catheterization. Mixed connective tissue disease (MCTD), SSc, and systemic lupus erythematosus (SLE) were clinical diagnosis associated with PAH (unadjusted odds ratio [OR] 10.8, 8.4, and 2.0, respectively). PAH also occurred in a small population of patients with primary Sjögren's syndrome (n = 7; 0.8%), rheumatoid arthritis (n = 3; 0.2%), or dermatomyositis (n = 1; 0.3%). Autoantibodies associated with PAH included those to centromere, U1RNP, Sm, SSA, SSB, and Th/To (unadjusted OR 4.5–6.6). Female gender and Raynaud's phenomenon were also identified as PAH risk factors (unadjusted OR 8.0 and 10.5, respectively). Multivariate logistic regression analysis revealed that MCTD, SSc, and SLE were independent PAH risk, indicating that the overall PAH risk could be explained primarily by clinical diagnosis. Interestingly, anti-SSA antibody without diagnosis of MCTD, SSc, or SLE was another independent PAH risk, indicating limited utility of the autoantibody status. When we further developed a multivariate logistic regression model by combining the diagnosis and autoantibody profile, PAH risk can be explained by 6 independent variables, including SSc with anticentromere (OR 578, 95% confidence interval [CI] 119–10409), MCTD (OR 397, 95% CI 81–7174), SLE with anti-U1RNP (OR 150, 95% CI 29–2743), SSc without anticentromere (OR 103, 95% CI 18–1923), anti-SSA without diagnosis of MCTD, SSc, or SLE (OR 56, 95% CI 11–1028), and SLE without anti-U1RNP (OR 42, 95% CI 6.8–813).

Conclusion: A combination of clinical diagnosis and autoantibody profiles effectively stratifies PAH risk in patients suspected to have CTD, and may aid in selection of patients who benefit from active screening program for PAH detection.

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Epoprostenol Rescue Therapy In Systemic Sclerosis-Associated Pulmonary Arterial Hypertension and Idiopathic Pulmonary Arterial Hypertension. Adrienne M. Roos[1], Christopher Pasarikovski[1], Amie T. Kron[1], John T. Granton[2], Peter Lee[3], John Thenganatt[4] and Sindhu R. Johnson[5]. [1]Toronto Scleroderma Research Program, Toronto Western Hospital, Mount Sinai Hospital, and University of Toronto, Toronto, ON, [2]Toronto Pulmonary Hypertension Programme, Toronto General Hospital and University of Toronto, Toronto, ON, [3]Mt. Sinai Hospital, Toronto, ON, [4]University Health Network Pulmonary Hypertension Programme, Toronto General Hospital, Divisions of Respirology and Critical Care Medicine, Toronto, ON, [5]Division of Rheumatology, Toronto Western Hospital, University Health Network Pulmonary Hypertension Programme, Toronto General Hospital, Mount Sinai Hospital and University of Toronto, Toronto, ON.

Background/Purpose: Epoprostenol has been demonstrated to improve hemodynamics, functional class, and six-minute walk distance (6MWD) in systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH) and idiopathic PAH (IPAH) patients. In contemporary practice, it is usually reserved for patients who have failed treatment with endothelin receptor antagonists and/or phosphodiesterase-5 inhibitors. The effect of epoprostenol rescue therapy on survival has not been evaluated. The objective of this study was to evaluate the role of intravenous epoprostenol as rescue therapy in the SSc-PAH and IPAH patients.

Methods: Patients attending the University Health Network Pulmonary Hypertension Program between 1998 and 2012 were included if they had a diagnosis of SSc-PAH and IPAH based on a mean pulmonary artery pressure (mPAP) of > 25 mmHg and a pulmonary capillary wedge pressure of <15 mmHg on cardiac catheterization, and had been treated with intravenous epoprostenol after treatment with endothelin receptor antagonists and/or phosphodiesterase-5 inhibitors for PAH. The primary outcome was survival. Survival was defined as the time from initiation of epoprostenol to death from any cause. Patients were censored as of May 1, 2012. Survival was evaluated using Kaplan Meier curves.

Results: 1140 patients were reviewed to identify 36 patients with SSc-PAH and 24 patients with IPAH treated with epoprostenol after failure with oral pulmonary hypertension specific therapies. 83% of SScPAH and 75% of IPAH patients were female. The mean (standard deviation) PAH duration prior to initiation of epoprostenol was 3.3 (5.7) years for SScPAH, and 2.1 (2.1) years for IPAH patients. Median 1-, 2-, 3-, 4-, 5-year survival for SSc patients was 85.7%, 60.7%, 53.6%, 46.1%, 42.3%; and for IPAH patients was 83.3%, 70.8%, 65.8%, 59.2%, 59.2%. There was no significant difference in survival between the SScPAH and IPAH patients treated with epoprostenol (p=0.13).

Conclusion: Our findings demonstrate desirable long-term survival and support the use of epoprostenol as rescue therapy for SSc-PAH and IPAH patients.

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Sex Disparities In Survival Of Systemic Sclerosis-Associated Pulmonary Arterial Hypertension and Idiopathic Pulmonary Arterial Hypertension Patients. Christopher Pasarikovski[1], John T. Granton[2], Peter Lee[3], Adrienne M. Roos[1], Amie T. Kron[1], Cathy Chau[4] and Sindhu R. Johnson[5]. [1]Toronto Scleroderma Research Program, Toronto Western Hospital, Mount Sinai Hospital, and University of Toronto, Toronto, ON, [2]Toronto Pulmonary Hypertension Programme, Toronto General Hospital and University of Toronto, Toronto, ON, [3]Mt. Sinai Hospital, Toronto, ON, [4]Toronto Scleroderma Research Program, Toronto Western Hospital, Mount Sinai Hospital, University of Toronto, Toronto, ON, [5]Toronto Western Hospital, Toronto General Hospital, Mount Sinai Hospital, and University of Toronto, Toronto, ON.

Background/Purpose: Systemic sclerosis (SSc) associated pulmonary arterial hypertension (PAH) and idiopathic PAH (IPAH) are conditions with poor survival. There is evidence to suggest that sex affects survival. The primary objective of this study was to evaluate the effect of sex on survival in SSc-PAH and IPAH. We secondarily evaluated the effect of sex on disease onset, time to diagnosis, disease progression and treatment.

Methods: Patients were included if they attended the Toronto Scleroderma Program or the University Health Network Pulmonary Hypertension Program; had a diagnosis of SSc-PAH or IPAH defined as a mean pulmonary artery pressure >25mmHg and age > 16 years. Sex was defined as self-reported biological and physiological characteristics at birth (male, female). The primary outcome was the time from diagnosis to death from all causes. Secondary outcomes were sex differences in age of diagnosis, disease duration and SSc manifestations. Cox proportional hazards model were used to evaluate survival.

Results: 52 male and 267 female SScPAH; and 47 male and 107 female IPAH patients were identified. Male SSc patients had a shorter mean (standard deviation) time from SSc diagnosis to PAH diagnosis (5.6 (8.7)) versus (8.4 (9.6)), p=0.047), increased frequency of renal crisis (19% versus 9%, p= 0.04), interstitial lung disease (67% versus 49%, p=0.02), and digital ulcers (29% versus 19%, p<0.001). Male IPAH patients had a higher frequency of diabetes (30% versus 12%). Despite adjusting for these differences, male SScPAH patients have decreased 1-, 2-, 3-, and 5-year survival (82.6%, 70.6%, 60.8%, 48.2%) compared to females (84.4%, 73.4%, 64.2%, 52.8%). Similarly, male IPAH patients have decreased 1-, 2-, 3-, and 5-year survival (93.4%, 87.9%, 84.8%, 77.7%) compared to females (94.5%, 91.0%, 88.7%, 83.2%).

Conclusion: Sex disparities appear to exist in survival of SSc-PAH and IPAH patients. Further investigation is needed to evaluate this disparity, mechanisms for disparity, and the role of a targeted screening and treatment approach.

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Pulmonary Hypertension In Systemic Sclerosis: Clinical Classification and Pulmonary Hypertension Subtypes. Monica Mohile[1], Mary Lucas[2], Virginia D. Steen[3], Thomas A. Medsger Jr.[2] and Robyn T. Domsic[2]. [1]University of Pittsburgh Medical Center, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA, [3]Georgetown University Medical Center, Washington, DC.

Background/Purpose: Pumonary hypertension (PH) is a significant complication of systemic sclerosis (SSc), with prevalence reports of 10–25%. Predictors of PH remain somewhat elusive. Our objective was to assess the pattern of PH timing and subtype development in limited versus diffuse cutaneous SSc.

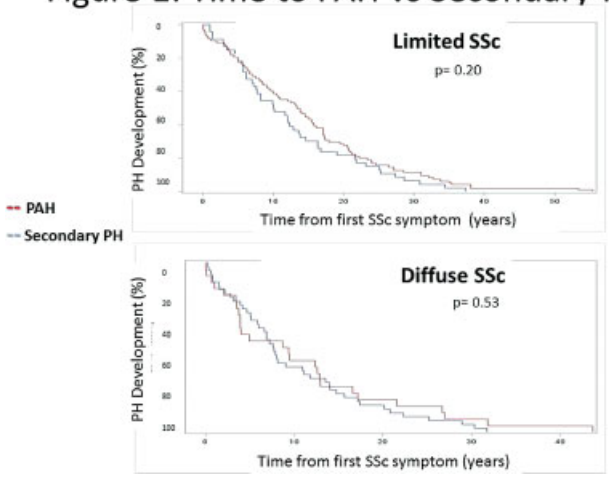
Methods: From our prospectively enrolled institutional scleroderma databank we performed a 10-year cross-sectional study of consecutive patients seen between January 1, 2000 and December 31, 2009. PH was defined as a mean pulmonary artery pressure (PAP) $>$ 25 mmHg on right heart catheterization (RHC) or transthoracic echocardiogram (TTE) with PAP $>$ 45 and PH diagnosed by a cardiologist. Descriptive statistics were used for baseline and PH characteristics, Kaplan Meier plots for time to development of PH and Cox proportional hazards for adjusted analysis.

Results: Of the 1,156 SSc patients included, 80% were female, the average age at first SSc symptom was 43.7 $\pm$ 14.2 years, and 44% had diffuse SSc. Two hundred thirteen (18%) had PH, of whom 122 (10% of total) had pulmonary arterial hypertension (PAH) and 90 (8% of total) had PH secondary to either ILD (PH-ILD) or cardiac involvement (PH-cardiac). 75% were confirmed by RHC; 25% did not have available RHC numbers in the hospital system but were confirmed as PH by cardiology evaluation. Prevalence of all PH was more common in limited (22%) vs diffuse SSc (14%; p=0.001). The profile of PH subtype was different, with 67% of limited SSc having PAH, compared to 37% in diffuse SSc ($p < 0.0001$). As shown in Table 1 approximately 5% of diffuse patients developed PAH with more secondary PH, whereas limited SSc patients developed predominantly PAH ($p =< 0.0001$). Patients with limited SSc developed all PH later in disease at a median 12.0 (IQR 5.7, 20.7), compared to 7.7 (3.5, 14.7) years since first SSc symptom in diffuse SSc (p=0.02), and this persisted after adjustment for age and gender (p=0.02). However there was no difference in the time to development of PAH compared to secondary PH in either diffuse or limited SSc (Figure 1).

Table 1. Prevalence of PH subtypes in limited and diffuse SSc

		Secondary PH		
	NoPH	PAH	PH-ILD	PH-cardiac
Limited cutaneous SSc	78%	15%	5%	2%
Diffuse cutaneous SSc	86%	5%	6%	3%

Figure 1: Time to PAH vs Secondary PH



Conclusion: These data suggest that although patients with limited SSc are more likely to develop PAH, the rate of PAH and secondary PH development is similar regardless of clinical subset. All SSc patients, including late diffuse SSc, should continue to be screened for all types of PH.

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Recommendations For Screening and Detection Of Connective-Tissue Disease Associated Pulmonary Arterial Hypertension. Dinesh Khanna[1], Heather Gladue[2], John D. Fitzgerald[3], Richard N. Channick[4], Lorinda Chung[5], Oliver Distler[6], Daniel Furst[7], Eric Hachulla[8], Marc Humbert[9], David Langleben[10], Stephen C. Mathai[11], Rajeev Saggar[12], Scott H. Visovatti[13] and Vallerie McLaughlin[2]. [1]University of Michigan Medical Center, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI, [3]UCLA School Med Rehab #32–59, Los Angeles, CA, [4]Massachusetts General Hospital, Boston, MA, [5]Stanford Univ Medical Center, Palo Alto, CA, [6]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [7]University of California in Los Angeles, Los Angeles, CA, [8]Claude Huriez University Hospital, Lille, France, [9]Centre Chirurgical Marie-Lannelongue, Le Plessis-Robinson, France, [10]McGill University, Montreal, QC, [11]Johns Hopkins University, Baltimore, MD, [12]St. Joseph's Hospital and Medical Center, Phoenix, AZ, [13]The University of Michigan, Ann Arbor, MI.

Background/Purpose: Pulmonary arterial hypertension (PAH) affects up to 15% of patients with connective tissue diseases (CTD) and is one of the leading causes of mortality in systemic sclerosis (SSc) and mixed connective tissue disease (MCTD). Previous recommendationswere developed as part of larger efforts in PAH and did not provide detailed recommendations in CTD-PAH. To develop recommendations for screening and early detection of CTD-PAH using rigorous data-driven and consensus-building methodology.

Methods: We performed a systematic review for the screening and diagnosis of PAH in CTD by searching available databases. Using the RAND/UCLA methodology, we developed case scenarios followed by 2 stages of voting—first one was voted anonymously by 10 international experts on 1 (inappropriate) −9 (appropriate) scale and 2nd voting after face-to-face meeting.

Results: The key recommendations include:

1. All patients with SSc should be screened for PAH.
2. MCTD or other CTD's with scleroderma features (referred hereon as scleroderma-spectrum disorders) should be screened similar to patients with SSc.
3. Screening of asymptomatic patients is not recommended for MCTD or other CTD patients without features of scleroderma.
4. RHC is mandatory for diagnosis of PAH.
5. Acute vasodilator testing is not required as part of the evaluation of PAH in patients with SSc, SSc-spectrum disorders, or other CTDs.
6. Initial screening evaluation in patients with SSc and scleroderma-spectrum disorders include pulmonary function test (PFT) including diffusion capacity carbon monoxide (DLCO), Transthoracic echocardiogram (TTE), NT- Pro BNP, and DETECT algorithm if DLCO% $<$ 60% and $>$3 years disease duration.
7. In SSc and SSc-spectrum disorders, TTE and PFT should be performed on an annual basis or TTE, PFT, and NT-Pro BNP if new signs or symptoms develop.

Recommendations for RHC for SSc and scleroderma-spectrum disorders

Non-invasive test	Threshold for RHC	Signs or symptoms* required for RHC
TTE	TR velocity of 2.5–2.8 m/s	Yes
	TR velocity of $>$2.8 m/s	No
	Right atrial (RA major dimension $>$53 mm) or right ventricular enlargement (Mid cavity RV dimension $>$35 mm), irrespective of TR velocity	No
PFTs	FVC/DLCO ratio $>$1.6 &/or DLCO $<$60%**	Yes
	FVC/DLCO ratio $>$1.6 &/or DLCO $<$60% & NT-Pro BNP $>$2 times upper limit of normal**	No
Composite measure	Meets DETECT algorithm in patients with DLCO $>$60% & disease duration $>$ 3 years	No

* Symptoms: dyspnea on rest or exercise, fatigue, pre-syncope/syncope, chest pain, palpitations, dizziness, lightheadedness. Signs: Loud pulmonic sound, peripheral edema **TTE without overt systolic dysfunction, greater than grade I diastolic dysfunction or greater than mild mitral or aortic valve disease or evidence of PH.

Conclusion: We provide consensus-based and evidence-driven recommendations for screening and early detection of CTD-PAH. It is our hope that these recommendations will lead to early detection of CTD-PAH and ultimately improve patient outcomes.

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Does Mycophenolate Mofetil (MMF) Have An Effect On Pulmonary Hemodynamics? Observations From The Pulmonary Hypertension Assessment and Recognition Of Outcomes In Scleroderma (PHAROS) Cohort. Lesley Ann Saketkoo[1], Matthew R. Lammi[1], Jessica K. Gordon[2], Paula Lauto[3] and Virginia D. Steen[4]. [1]LSU Scleroderma and Sarcoidosis Patient Care and Research Center, New Orleans, LA, [2]Hospital for Special Surgery, New York, NY, [3]LSU Health Sciences Center, New Orleans, LA, [4]Georgetown University Medical Center, Washington, DC.

Background/Purpose: Systemic sclerosis (SSc) related pulmonary hypertension (PH) carries a high mortality; with SSc pulmonary arterial hypertension (PAH) having a 4x higher mortality then idiopathic PAH. It is unknown whether immunosuppressant (IS) drugs, particularly mycophenoloate mofetil (MMF), have any effect on vascular remodeling in SSc PH since it has not been formally studied. This analysis looks at the possible effects of MMF in SSc patients who have developed PH.

Methods: PHAROS is a prospective registry designed to provide substantive data to recognize aspects of PH unique to SSc. Patients were stratified by history of MMF or No IS use (no MMF or other immunosuppressant drugs) at the time of the diagnosis of PH by right heart catheterization (RHC). Calculations are derived from non-parametric analyses using Mann-Whitney and Fisher's Exact as applicable followed by regression analyses.

Results: There were 39 SSc patients who had received MMF (mean duration 0.92 years) and 203 patients receiving No IS prior to diagnosis of PH. Patients treated with MMF when compared to the No IS group, were more likely to be younger, have diffuse SSc and have shorter disease duration. Patients treated with MMF had a significantly lower mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) with no difference in pulmonary capillary wedge pressure (PCWP) (Table 1). However, stratified analyses between diffuse and limited SSc patients on MMF revealed no significant differences in mPAP, PVR, PCWP nor in FVC, TLC, FEV/FVC nor DLCO (Table 2). In the group as a whole, MMF ($p=0.046$) and SSc subtype ($p=0.01$) were the only independent determinants of mPAP when adjusted for differences in age, FVC and disease duration.

Table 1. Comparison between SSc patients on No IS medications and MMF at time of first RHC. Continuous variables are reported as median, interquartile range; categorical values are proportional.

	No IS	MMF	p Value
n	203	39	
Age	60 (52,68)	54 (47,63)	*0.0143
Sex (% female)	84%	65%	0.6491
N (%) Limited SSc	144 (71%)	14 (35%)	*<0.0001
Time from 1st SSc Symptom (years)	11.2 (5.3,21.0)	6.9 (3.0,10.3)	*0.0004
mPAP	33 (23,44)	29 (25,35)	*0.0016
PVR	355 (242,692)	222 (162,344)	*0.0006
PCWP	11 (3,14)	11 (9,15)	0.7036
FVC	73.1 (64,88)	63.9 (48,84)	*0.0298
TLC	76.5 (66,93)	62.8 (47,80)	*0.0002
FEV/FVC	81 (75.37)	87 (81,93)	*0.0043
DLCO	37.5 (30,50)	34.3 (28,39)	0.0929
FVC:DLCO	1.94 (1.6,2.4)	1.85 (1.4,2.5)	0.6908
6MWD	338.3 (238,428)	396.2 (343,475)	*0.0298

Table 2. Comparison of patients on MMF by limited and diffuse subtypes.

	lcSSc on MMF	dcSSc on MMF	p Value
n	14	23	0.2185
Age	57.5 (50,53.8)	51 (40,63)	
Sex (% female)	64%	67%	1.0
Time from 1st SSc symptom (years)	8.4 (6.9,15.3)	4.1 (2.6,8.8)	*0.0176
Duration of MMF prior to RHC	0.47 (0.18,1.6)	0.55 (0.15,1.2)	0.9694
mRSS	3 (2,5)	16 (7,26)	*<0.0001
PH Meds at Time of RHC	36%	65%	0.1014
mPAP	29 (26,36)	29.0 (25.35)	0.7507
PVR	234 (140,466)	222 (166,340)	0.7495
PCWP	11.5 (9.8,16.5)	11.0 (9.15)	0.7621
FVC	75.9 (57.2,90.0)	61.7 (45.5,76.2)	0.1039
TLC	68,9 (54,7, 46,8)	60.3 (46.8,77.9)	0.1898
FEV/FVC	84.5 (79.0,88.5)	87.0 (81.8,93)	0.3181
DLCO	36.2 (31.4,40.2)	32.5(25.2,38.6)	0.2862
FVC:DLCO	2.04 (1.4,2.6)	1.73 (1.2,2.3)	0.5168
6MWD	417.1 (362,502)	388.8 (241,466)	0.3384

Conclusion: Patients treated with MMF compared to the No IS group had lower mPAP and PVR at time of the diagnosis of PH with no difference between groups in PCWP. Differences in mPAP between groups were not explained by differences in age, FVC, or disease duration. These data suggest that MMF could potentially play a role in pulmonary artery remodeling and modifying the severity of PH. These findings warrant prospective controlled investigations of MMF in SSc PH.

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Can Changes In NT-Probnp Predict Early Response To Therapy and Prognosis In Systemic Sclerosis Associated Pre-Capillary Pulmonary Hypertension? Vincent Sobanski[1], Bernadette Lynch[2], Benjamin E. Schreiber[3], Clive Handler[2], Christopher P. Denton[4] and John G. Coghlan[5]. [1]Royal Free Hospital, London, United Kingdom, [2]The Royal Free Hospital, London, United Kingdom, [3]National Pulmonary Hypertension Service, London, United Kingdom, [4]Royal Free and University College Medical School, London, United Kingdom, [5]The Royal Free Hospital NHS Foundation Trust, London, United Kingdom.

Background/Purpose: Pulmonary hypertension (PH) is a severe complication of systemic sclerosis (SSc), affecting 5–12% of patients. Despite recent progress in treatment, prognosis remains poor. Early therapeutic management and goal-oriented approach can improve long-term prognosis. Response to therapy is usually assessed by functional and hemodynamic parameters between 3–6 months after initiation of treatment. This study aimed to compare the changes in NT-proBNP with functional and hemodynamic parameters between baseline and 3–6 months after initiation of therapy.

Methods: A retrospective study, undertaken in a National Pulmonary Hypertension Centre, identified patients diagnosed with SSc associated pre-capillary PH on right heart catheterisation (RHC) (mean pulmonary arterial pressure (mPAP) $\geq$ 25mmHg and pulmonary capillary wedge pressure (PCWP) $\leq$ 15mmHg) between 1998 and 2012 (n=600). Patients were included if they had a second RHC between 3 and 6 months after the initial RHC diagnosing PH and if NT-proBNP results were available within 30 days prior to each RHC. 53 patients were identified. 6 patients were excluded (glomerular filtration rate $<$ 30 mL/min/1.73m^2). Changes in variables (Δ) between baseline and 3–6 months were calculated in absolute value, percentage of variation and logarithm of each value. Pearson or Spearman methods were used to estimate correlation coefficient, where appropriate. Patients were divided into two groups: D="NT-proBNP decreasing" and I/S="NT-proBNP increasing or stable" according to the difference in NT-proBNP levels between baseline and repeat RHC. Survival analyses were performed using Kaplan-Meier method and log-rank test.

Results: 47 patients (42 female and 5 male) were included. 83% had limited cutaneous SSc and 53% were anti-centromere antibody positive. The mean age at diagnosis of PAH was 62.1 $\pm$ 11.5 years; the mean time between

both RHCs was 3.6 ± 1.0 months and the mean follow-up after first RHC was 28.0 ± 15.4 months. Six-minute walking distance (6MWD − p=0.002), mPAP (p=0.003), cardiac index (p=0.034) and pulmonary vascular resistances (PVR – p<0.0001) significantly improved in the group D. There was a trend in decreasing for PVR in the I/S group (p=0.094). In the total population, ΔNT-proBNP was negatively correlated with Δ6MWD in percentage (R= −0.305, p=0.050). ΔNT-proBNP in percentage tended to correlate with ΔmPAP in percentage (p=0.090) or log (p=0.073). No correlation was found between ΔNT-proBNP in percentage or in log with PVR, cardiac output, cardiac index, venous oxygen saturation, right arterial pressure and PCWP. Survival was significantly better in patients with decreasing NT-proBNP in all patients with pre-capillary PH (p=0.045) and in patients with PAH (p=0.002). There was no difference for PH-ILD patients (p=0.658).

Conclusion: Patients with decreasing NT-proBNP presented a significant improvement in hemodynamic parameters at 3–6 months. No strong correlation was found between ΔNT-proBNP and changes in functional or hemodynamic variables. However, early changes in NT-proBNP seem to be associated with prognosis – especially in PAH patients.

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2582

Treatment Of Pulmonary Hypertension In Scleroderma Patients With Restricitive Lung Disease. Observations From The Pulmonary Hypertension Assessment and Recognition Of Outcomes In Scleroderma Cohort. Virginia D. Steen[1] and Robyn T. Domsic[2]. [1]Georgetown University Medical Center, Washington, DC, [2]University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Trials of therapy in pulmonary hypertension (PH) have generally excluded patients with significant interstitial lung disease, but many patients with systemic sclerosis(SSc) and PH have some interstitial lung disease. There are concerns that PH drugs may cause ventilation-perfusion mismatch and worsen PH, and it remains unclear if PH drugs improve outcomes for these patients. PHAROS, Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma, is a prospective observational multi-center cohort study of SSc-PH. Our objective is to describe the real-world experience of SSc-PH patients with restrictive lung disease treated with a single PH medication.

Methods: We included patients with PH defined as a mean pulmonary artery pressure (mPAP) ≥25mmHg on catheterization who had a FVC <70% predicted at the time of the diagnosis. Patients were grouped into 3 groups, based on the treatment during the first year following the PH diagnosis: No drug treatment, treatment with an endothelin receptor blocker antagonist (ERA), or andphosphodiesterase inhibitor (PDE). For this initial look at the data, patients treated with combination therapy and/or prostacyclins (PCA) were excluded. The primary outcome examined was one-year survival, with secondary outcomes of hospitalization, change in functional class, 6 minute walk and patient questionnaires at one year.

Results: Of the 266 patients with PH in PHAROS, 98 had a FVC <70% and were included. There were 26 receiving no therapy (No Drug), 19 receiving ERA and 33 treated with PDE. We excluded 18 treated with combination and 2 treated with PCAs alone. There were no significant differences in the demographics or the cardiopulmonary parameters between the 3 groups. These patients had striking restrictive disease with a mean FVC between 50 and 55% predicted. Although over survival was not statistically different between the 3 groups, patients in the PDE group had fewer deaths and a better 1 and 2 year survival than the No Drug group. (p<0.05). There were more patients in the PDE group who had an improvement compared to the ND group and neither treatment group had an increase in hospitalizations after starting the drugs (Table 1).

	No Drug n = 26	ERA n = 19	PDE n = 33
Age–yr, mean	54.5	57.2	56.8
Disease Duration yr, mean	10.1	8.3	9.2
% Female sex	70	79	62
% White race	76	63	64
% Diffuse cutaneous	42	63	42
FVC% predicted	52.2	49.9	55.5
DLCO % predicted	33.6	25.9	42.0
RHC m PAP	31.85	33.3	36
PVR (Woods)	293	343	419
Response in 1st year	23%	37%	43%
Hospitalizations	2	1	2
Deaths in 1st year	7	3	1
Survival, 1, 2 year	69%, 61%	82%, 64%	96%, 76%

Conclusion: SSc patients with PH and restrictive lung disease are being treated with PH drugs. Our observations suggest that some patients may respond favorably, without evidence of worsening PH. We strongly encourage further study of PH drugs in SSc-ILD patients in a controlled setting.

Disclosure: V. D. Steen, Gilead Science,, 2, Gilead Science, 5, Actelion Pharmaceuticals US, 2, Actelion Pharmaceuticals US, 8, Roche Pharmaceuticals, 2, Celgene, 2, Sanofi-Aventis Pharmaceutical, 2; **R. T. Domsic**, None.

2583

Long-Term Treatment With Endothelin Receptor Antagonist Increases Peripheral Blood Perfusion In Systemic Sclerosis Patients. Maurizio Cutolo[1], Barbara Ruaro[1], Elena Bernero[1], Francesca Ravera[1], Giuseppe Zampogna[1], Elisa Alessandri[1], Vanessa Smith[2] and Alberto Sulli[1]. [1]Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, [2]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium.

Background/Purpose: Systemic sclerosis (SSc) is characterized by progressive impairment of the microvascular system and decrease of peripheral blood perfusion (PBP) (1–3). The vasoactive peptide endothelin-1 (ET-1) seems to be implicated in these events (4). Laser Doppler flowmetry (LDF) is a technique to evaluate blood perfusion at peripheral sites, such as the central area of the fingertips (2). The aim of this study was to investigate long-term effects of ET-1 receptor antagonism on PBP evaluated by LDF technique in SSc patients.

Methods: Twenty-six SSc patients (mean age 62±12SD years, mean SSc duration 8±4 years) were enrolled during their programmed standard treatment protocols for digital ischaemia. At baseline (T0), 13 patients already receiving cyclic intravenous infusion of iloprost (average 80 mcg/day, for 5 continuous days, every three months), continued the treatment for further 3 years (ILO group: T1,T2,T3). The remaining 13 patients, although they continued the same cyclic intravenous iloprost treatment as the previous group, also received bosentan 125 mg twice a day for 3 years (ILO+BOS group: T1,T2,T3) since complaining digital ulcers. PBP was yearly evaluated in all SSc patients using LDF at both basal temperature and after heating of the LDF probe at 36°C to test microvascular dilation capacity. PBP was measured at the central area of the fingertips of the 2nd to 5thfinger bilaterally, scoring the average value as perfusion units (PU) (2). Non-parametric tests were used for the statistical analysis.

Results: A progressive and statistically significant increase of PBP was observed in the ILO+BOS group at basal temperature during the follow-up (median PU T0 51, T1 74, T2 70, T3 85, respectively, p=0.007); at 36°C, PBP significantly increased only during the first two years of follow-up (median PU T0 81, T1 104, T2 110, respectively, p=0.0003; T3 105). In contrast, not statistically significant PBP changes were observed in ILO group at both basal temperature (median PU T0 104, T1 78, T2 55, T3 44, p=0.70) and 36°C (median PU T0 126, T1 108, T2 109, T3 87, p=0.45). Gradient of PU between the evaluations at basal temperature and at 36°C was found progressively decreased during the followup in the ILO group, but not in the ILO+BOS group. Two SSc patients experienced new digital ulcers in the ILO+BOS group (15%), and four in the ILO group (31%). No serious side effects were observed. Transient increase of liver transaminases was managed by temporary discontinuation of bosentan treatment in two cases.

Conclusion: Long-term treatment with ET-1 receptor antagonist in combination with iloprost was found to significantly increase PBP in SSc patients, in contrast to the treatment with iloprost alone. This seems in agreement with the recent observation that long-term bosentan treatment reduces microvascular damage progression, as assessed by naifold capillaroscopy (5).

References:

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2584

Screening and Diagnostic Modalities For Systemic Sclerosis-Associated Pulmonary Arterial Hypertension: A Systematic Review. Heather Gladue[1], Nezam I. Altorok[1], Whitney Townsend[1], Vallerie McLaughlin[1] and Dinesh Khanna[2]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan Medical Center, Ann Arbor, MI.

Background/Purpose: Pulmonary arterial hypertension (PAH) affects patients with connective tissue diseases (CTD), especially systemic sclerosis (SSc) and MCTD. Despite this, there continues to be delay in screening and diagnosis of these patients. We undertook a systematic review to summarize the best evidence for screening and diagnosis of PAH in CTD.

Methods: A systematic search was performed in Pubmed, EMBASE, Web of Science and Scopus databases up to June 2012 with an experienced librarian, related to PH and CTD. We only focused on WHO group I PAH and excluded manuscripts that did not rule out interstitial lung disease (WHO group III) or left heart disease (WHO group II), or if the diagnosis of pulmonary arterial hypertension (PAH) was not made by RHC.

Results: We started with 2805 titles, 838 abstracts, and included 21 manuscripts. Twelve studies assessed the tricuspid regurgitation velocity (VTR) or equivalent right ventricular systolic pressure (RVSP) using transthoracic echocardiogram (TTE) as a threshold for RHC in patients suspected as having PAH. 11 of these studies were in SSc, and one pertained to SLE. The screening threshold for RHC was VTR >2.73 to >3.16 m/s without symptoms or 2.5 to 3.0 m/s with symptoms and resulted in 20–67% of patients having RHC proven PAH (Table). In the SLE study, VTR >3.0 m/s on TTE led to RHC in 3 patients and none had PAH. Three studies looked at pulmonary function tests and various DLCO% predicted cut-offs. These studies suggest that a low DLCO% 45–70% is associated with a 5.6–7.4% development of PAH, and the decline in DLCO% is associated with an increase in the specificity (For 60% cut off, spec= 45%, and for 50% cut off, spec=90%]) for PAH. Five studies looked at NT-ProBNP and a cut-off >209pg/ml has a high sensitivity (90–100%) and a specificity ranging from 45–95%.

Single studies looked at EKG findings, cardiac MRI, Chest X-ray, CT, autoantibodies, laboratory values and physical exam findings.

Screening Modality	Number of Studies	Conclusion
TTE (TR velocity)	12 (11 SSc, 1SLE)	Studies had various inclusion criterion. VTR ranges to prompt RHC • 2.73–3.16 m/s without PAH-associated symptoms • 2.5–3.16 m/s with symptoms
NT-ProBNP	5 studies (2 cohort, 3 case control) All SSc	Various Cut offs >236pg/ml sensitivity (45–93%) specificity (83–100%)
PFT's	4 studies (3 cohort, 1 case control) All SSc	Decreased DLCO was associated with PAH.
Composite Measures	3 cohort studies All SSc	1. DLCO >70.3% and FVC/DLCO ≥1.82 and NT-ProBNP ≥ 209.8pg/ml −100% sensitive and 100% specific. 2. DLCO/VA<70% and NT-ProBNP >97th percentile for age 75% sensitive and 97% specific. 3. Cochin RPS score (RPS=0.0001107(age) +0.0207818 (100-FVC) +0.04905 (150-DLCO/alveolar volume). A cut off of 2.73 sensitivity of 89.5 and specificity of 74.1% for PAH

Conclusion: Our systematic review shows that most evidence exists for use of TTE, pulmonary function tests, and NT-ProBNP for screening and diagnosis of PAH in CTD. These data will be used to develop guidelines for screening and diagnosis of PAH in CTD.

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2585

Left Ventricular Dysfunction Reflected By Higher Serum Brain Natriuretic Peptide Accounts For Poorer Prognosis Of Pulmonary Arterial Hypertension Associated With Systemic Sclerosis. Sumiaki Tanaka[1], Yoshiyuki Arinuma[1], Tatsuhiko Wada[1], Tatsuo Nagai[1], Jun Okada[2] and Shunsei Hirohata[1]. [1]Kitasato University School of Medicine, Sagamihara, Japan, [2]Kitasato Junior Collage of health and Hygienic Sciences, Minami-Uonuma, Japan.

Background/Purpose: Recentry, development of potent effective newer drugs for pulmonary arterial hypertension (PAH) have resulted in improving survival of the patients. However, the prognosis of patients with PAH associated with SSc remains still poor compared with that of patients without SSc. To explore the characteristics relevant to the poor survival of patients with PAH associated with SSc, we analyzed serum levels of brain natriuretic peptide (BNP).

Methods: We analyzed 2786 measurements of serum levels of BNP (pg/ml) obtained from 83 patient with PAH associated with CTDs, including 41 patients with SSc, and 42 patients with CTDs other than SSc (16 patients with SLE, 20 patients with MCTD and 6 patients with other CTDs), who had been diagnosed as PAH based on right heart catheterization test and followed between April 2001 and March 2013 in our hospital. For statistical analysis, we converted serum levels of BNP into logarithmic values based on the distribution. Comparison of serum levels of BNP between PAH with SSc and that with non-SSc CTDs was carried out using mixed effects model in which we set presence or absence of SSc, WHO-functional class (WHO-FC) as fixed effects, and patient as a random effect. Comparison of hemodynamics between PAH with SSc and that with non-SSc CTDs was similarly carried out.

Results: Significant deviation of the distribution of serum levels of BNP was observed between SSc and non-SSc CTDs (Figure). Thus, median (IQR) of serum level of BNP in SSc and non-SSc CTDs were 104.6 (52.5, 214) pg/ml, and 48.9 (19.9, 149.4) pg/ml, respectively. Mixed effects model showed that serum levels of BNP of each WHO-FC in SSc were significantly higher than those in non-SSc CTDs (Table). On right heart catheterization examinations, pulmonary capillary wedge pressure in SSc was significantly higher than that in non-SSc CTDs (8 (5.6, 11.0) mmHg, 6.3(5, 8) [median (IQR)], respectively; p=0.04), although there were no significant differences in mean pulmonary artery pressure, cardiac output, or pulmonary vascular resistance between both group.

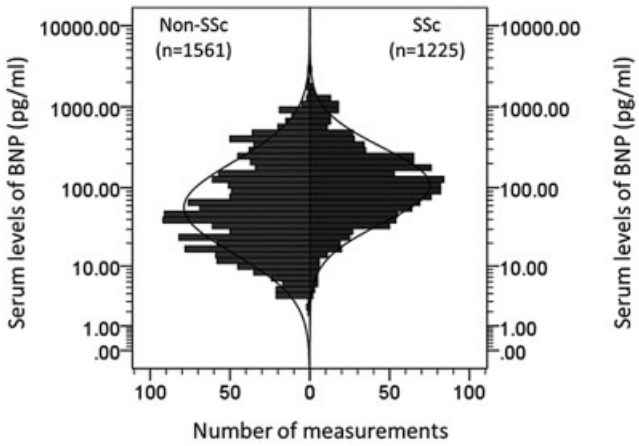

Table. Serum levels of BNP in PAH patients with CTDs

WHO-FC	serum levels of BNP(pg/ml)* PAH patients with non-SSc CTDs	PAH patients with SSc
I	35.0 (27.2–44.8)	54.0 (41.5–70)
II	67.1 (52.3–85.9)	103.5 (80.3–133.3)
III	108.3 (33.9–139.7)	167.1 (128.9–216.8)
IV	224.4 (170.0–297.9)	346.4 (261.6–458.6)

*Means (95% CI) were estimated with mixed effects models (fixed effect: SSc, WHO-FC(4), random effect; patient). SSc $p = 0.013$, WHO-FC: $p<0.0001$

Conclusion: Our results demonstrate that left ventricular dysfunction coexists with PAH associated with SSc, accounting for poor survival of PAH associated with SSc. Thus, special attention to this complication would be required in the management of patients with PAH associated with SSc using PAH-specific drugs.

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2586

Antinuclear Antibody Negative Systemic Sclerosis Patients Have Less Vasculopathic Disease Manifestations. Gloria Salazar[1], Shervin Assassi[1], Fredrick M. Wigley[2], Daniel E. Furst[3], Laura K. Hummers[2], Dinesh Khanna[4], John Varga[5], Elena Schiopu[6], Virginia D. Steen[7], Murray Baron[8], Marie Hudson[8], Janet E. Pope[9], Monique E. Hinchcliff[5], Marvin J. Fritzler[10], David B. Robinson[11], Robert W. Simms[12], Richard M. Silver[13], Tracy M. Frech[14], Barri J. Fessler[15], Jerry A. Molitor[16], Sara Zamanian[1], Niall Jones[17], John D. Reveille[1], Frank C. Arnett[1] and Maureen D. Mayes[1]. [1]University of Texas Health Science Center at Houston, Houston, TX, [2]Johns Hopkins University School of Medicine, Baltimore, MD, [3]UCLA Medical School, Los Angeles, CA, [4]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [5]Northwestern University Medical School, Chicago, IL, [6]University of Michigan Medical School, Ann Arbor, MI, [7]Georgetown University Medical Center, Washington, DC, [8]McGill University, Montreal, QC, [9]St Joseph Health Care, London, ON, [10]University of Calgary, Calgary, AB, [11]University of Manitoba, Winnipeg, MB, [12]Boston University School of Medicine, Boston, MA, [13]Medical University of SC, Charleston, SC, [14]University of Utah School of Medicine, SLC, UT, [15]University of Alabama at Birmingham, Birmingham, AL, [16]Univ of MN MMC108, Minneapolis, MN, [17]Rheumatology Clinic at 124th Street Medical Clinic, Edmonton, AB.

Background/Purpose: Systemic Sclerosis (SSc) is an autoimmune disease characterized by fibrosis of skin and internal organs, as well as vasculopathy and immune dysregulation.

Autoantibody formation is one of the hallmarks of SSc. Autoantibodies in patients with SSc carry considerable value in diagnosis and in predicting various clinical outcomes; however their role in the pathogenesis of SSc is unclear.

While the great majority of patients with SSc have circulating antinuclear antibodies (ANA) (90–95%), a small percentage is ANA negative (5–10%). The detailed demographic and clinical characteristics of patients without ANA have not been clearly explored.

The objective of this study was to examine the demographic and clinical characteristics of systemic sclerosis (SSc) patients without antinuclear antibodies (ANA) compared to ANA positive patients.

Methods: SSc patients enrolled in the Scleroderma Family Registry and DNA Repository were included. Relevant demographic and clinical data were entered directly by participating sites or by chart review. Autoantibodies were determined at one site utilizing commercially available kits.

Results: This study included 3249 patients, of whom 208 (6.4%) were ANA negative. The proportion of male patients was higher in the ANA negative group (OR 1.65 $p=0.008$).

ANA negative patients experienced significantly less vasculopathic manifestations of SSc. The percent predicted diffusion capacity of carbon monoxide (DLco) was higher in ANA negative patients (p=0.03). Seven ANA negative patients had pulmonary arterial hypertension (PAH) per right heart catheterization (RHC) versus 213 ANA positive (OR= 0.23 $p<0.001$) indicating that PAH was significantly less common in the ANA negative group. They also had less often telangiectasias and digital ulcers/ pits ($p=0.01$ and $p<0.001$, respectively).

Although, diffuse cutaneous involvement was more common, the modified Rodnan Skin Score (mRSS) was lower in the ANA negative group (2.4 points lower, $p=0.018$). Furthermore, they experienced more malabsorption (p=0.003). There was no difference in the frequency of pulmonary fibrosis and scleroderma renal crisis. All-cause mortality was also not different between the two groups (p=0.28).

The above observations remained significant after adjusting for potential confounders (age, disease duration, gender, disease type) (Table 1).

Table 1. Multivariable analysis of clinical parameters in systemic sclerosis (SSc) patients who are ANA negative compared with ANA positive patients.

	OR/coef	95% CI	*p*
Telangiectasias	0.59	0.38, 0.91	0.01
Digital ulcers and pits	0.38	0.24, 0.59	<0.001
MPAP per RHC	−5.58	−10.85, −0.32	0.04
PAH per RHC	0.28	0.11, 0.70	0.006

Conclusion: ANA negative patients constitute a distinct subset of SSc characterized by fewer vasculopathic features of the disease, a higher proportion of men, more frequent lower gastrointestinal involvement as well as higher proportion of diffuse cutaneous disease but less severity of skin fibrosis overall.

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2587 SEE ABSTRACT #2919

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Pulmonary Hypertension In Patients With Anti-U1-RNP Antibodies. Vincent Sobanski[1], Bernadette Lynch[2], Benjamin E. Schreiber[3], Svetlana I. Nihtyanova[4], Jennifer Harvey[1], Clive Handler[2], Christopher P. Denton[4] and John G. Coghlan[5]. [1]Royal Free Hospital, London, United Kingdom, [2]The Royal Free Hospital, London, United Kingdom, [3]National Pulmonary Hypertension Service, London, United Kingdom, [4]Royal Free and University College Medical School, London, United Kingdom, [5]The Royal Free Hospital NHS Foundation Trust, London, United Kingdom.

Background/Purpose: Pulmonary hypertension (PH) is a leading cause of morbidity and mortality in patients with connective tissue diseases (CTD). Patients with anti-U1-RNP antibodies belong to a heterogeneous group, including systemic sclerosis (SSc), systemic lupus erythematosus (SLE) or mixed connective tissue disease (MCTD). This study aimed to (i) describe the prevalence, clinical and hemodynamic characteristics of PH in U1-RNP positive patients and (ii) analyse survival and compare prognosis between the different CTDs associated with these antibodies.

Methods: In this National Pulmonary Hypertension database, more than 2000 patients had a right heart catheterisation (RHC) performed between 1998 and 2012. One hundred and twelve patients were tested anti-U1-RNP positive. Twenty-two patients did not have PH (mean Pulmonary Arterial Pressure [mPAP] $<$ 25 mmHg). In the 90 patients with PH, 10 had post-capillary PH (pulmonary capillary wedge pressure [PCWP] $>$ 15 mmHg). Eighty had pre-capillary PH (PCWP $\leq$ 15 mmHg). Six patients were excluded because of incomplete RHC data. Thirty-seven had PH due to lung disease (PH-ILD) and 37 had pulmonary arterial hypertension (PAH). Anti-U1-RNP positive patients with PH were compared with unselected U1-RNP negative patients also having PH: 387 SSc and 21 SLE. For binary variables, comparison between 3 PH groups was performed using Monte-Carlo method with Fischer test for comparison one by one. ANOVA was used to compare continuous variables with a normal distribution. Kruskal-Wallis test was used for non-parametric comparisons. Kaplan-Meier method with log-rank test was used for survival analysis. All statistical analyses were performed using SPSS for Microsoft Windows®.

Results: The proportion of patients with SSc, SLE or MCTD was not significantly different between the 3 groups of PH. Anti-Sm antibodies were only seen in PH-ILD (p=0.038). Six-minute walking distance and WHO FC were significantly better in PAH vs. PH-ILD (p=0.003 and p=0.007 respectively). Mean PAP was similar in 3 groups. In U1-RNP negative patients, mPAP was significantly higher in SLE than in SSc patients (p=0.003). In PAH patients, SLE patients had higher mPAP than others groups (p=0.023). When comparing U1-RNP positive vs. negative in SSc or SLE patients, no difference was observed in hemodynamic values. Among PH-ILD patients, U1-RNP negative SSc had lower DLCO than U1-RNP positive (p=0.001). MCTD patients had lower CI (p=0.007) and higher PVR (p=0.05) than U1-RNP negative SSc patients. SLE and MCTD had a better survival than SSc (p=0.005 and p=0.037, respectively). PH-SSc patients carrying the U1-RNP antibody tended to have a better survival than U1-RNP negative (p=0.065). This trend was found in PAH patients (p=0.068) but not in PH-ILD patients (p=0.225).

Conclusion: These data confirm that patients with anti-U1-RNP antibodies are heterogeneous. To our knowledge, this is the largest cohort of patients with PH and MCTD. It provides hemodynamic data for all patients at PH diagnosis. In this group, patients with SSc have the worse

prognosis. Interestingly, survival of patients fulfilling MCTD classification criteria is intermediate between SSc and SLE.

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Scleroderma Patients With Pulmonary Hypertension and Increased Pulmonary Capillary Wedge Pressure In The Pulmonary Hypertension Assessment and Recognition Of Outcomes In Scleroderma (PHAROS) Cohort. Matthew R. Lammi[1], Lesley Ann Saketkoo[2], Jessica K. Gordon[3], Paula Lauto[4] and Virginia D. Steen[5]. [1]Louisiana State University Health Sciences Center, Pulmonary and Critical Medicine, New Orleans, LA, [2]LSU HSC - New Orleans, Sections of Rheumatology and Pulmonary Medicine, New Orleans, LA, [3]Hospital for Special Surgery, New York, NY, [4]LSU Health Sciences Center, New Orleans, LA, [5]Georgetown University Medical Center, Washington, DC.

Background/Purpose: Systemic sclerosis (SSc) commonly leads to pulmonary hypertension (PH), which may be associated with left heart disease and an elevated pulmonary capillary wedge pressure (PCWP). Patients in this PH subgroup may have pulmonary artery pressures (PAP) in proportion to their elevated PCWP (pulmonary venous hypertension, "PVH") or higher than expected given their PCWP ("out-of-proportion PH"). It is not known what causes this difference in patients with SSc.

Methods: Baseline characteristics from 48 patients in the PHAROS registry (a prospective observational cohort of SSc patients at high risk for or with PH) who had a PCWP>15 on their inclusion right heart catheterization (RHC) were retrospectively analyzed. Using unpaired t-tests, characteristics of those who died before 2 years of follow-up (n=10) were compared to those who were alive at 2 years (n=20). Patients were divided into 2 groups based on their initial RHC diastolic pressure gradient (DPG=diastolic PAP minus PCWP): PVH (DPG ≤5mmHg) or out-of-proportion PH (DPG□5mmHg). Comparisons were made between groups using unpaired t-tests or Chi square. Kaplan-Meier analysis compared survival and time to first hospitalization between the 2 groups.

Results: At baseline, the mean PAP (mPAP) was 36.8±11.8 mmHg and the PCWP was 19.4±3.3mmHg. Univariate factors associated with death prior to 2 years are shown in the table. In multivariate analysis, the only independent factors associated with death prior to 2 years were lower 6MWD (p=0.01) and higher PCWP (p= 0.01). The out-of-proportion PH group (n=26) had higher baseline mPAP (42.7±13.0 vs. 29.7±3.7mmHg, p<0.0001), DPG (12.7±8.6 vs. 2.9±1.5mmHg, p<0.0001), and pulmonary vascular resistance (376±235 vs. 204±101 dynes/sec/cm^5, p=0.003) compared to the PVH group (n=22). Although there was no difference in baseline immunosuppression use overall, mycophenolate use was less common in the out-of-proportion PH group (8% vs. 37%, OR 0.15, p=0.027). There were no differences between the PVH and the out-of-proportion PH groups in age, sex, disease duration, pulmonary function, SSc subtype, or 6MWD (all p>0.05). There was no difference in 3-year survival between the 2 subgroups (PVH: 1-year=95%, 3-year=61%; out-of-proportion PH: 1-year=85%, 3-year=63%, p=0.73). There was a trend towards a shorter time to first hospitalization in the out-of-proportion PH group (p=0.13).

Table. Baseline characteristics in patients dying prior to 2 years of follow-up compared to those who survived for more than 2 years

Parameter	Death within 2 years	Survival > 2 years	p value
Age (years)	58.3 ± 15.5	54.1 ± 12.3	0.68
Sex (% female)	56%	85%	0.16
SSc disease duration (years)	8.9 ± 6.8	8.2 ± 8.4	0.83
Scleroderma type (%)			
Limited	40%	55%	0.71
Diffuse	50%	35%	
NYHA functional class			
I/II	30%	73%	p = 0.05
III/IV	70%	27%	
Immunosuppressant use at baseline (% yes)	20%	44%	0.40
6-minute walk distant (meters)	186 ± 96	366 ± 107	p = 0.002
Berg Dyspnea Score	5.7 ± 3.2	2.7 ± 2.0	p = 0.03
Mean pulmonary artery pressure (mmHg)	40.0 ± 9.8	32.7 ± 9.1	p = 0.05
Pulmonary capillary wedge pressure (mmHg)	22.9 ± 4.3	18.6 ± 2.4	p = 0.001

Conclusion: In patients with SSc-PH and a PCWP>15, lower 6MWD and higher PCWP were independently associated with an increased risk for death within 2 years. In SSc patients with a PCWP>15, those with out-of-proportion PH were less likely to be on mycophenolate (MMF) compared to those with pulmonary venous hypertension. The relationship between MMF and PH in SSc needs further investigation, as MMF's anti-fibrotic effects may theoretically decrease pulmonary artery remodeling in these patients.

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Laser Speckle Contrast Analysis A New Method To Evaluate Blood Perfusion in Different Skin Areas Of Systemic Sclerosis Patients: Comparison With Laser Doppler Flowmetry. Alberto Sulli[1], Barbara Ruaro[1], Giorgia Ferrari[1], Elena Bernero[1], Carmen Pizzorni[1], Vanessa Smith[2] and Maurizio Cutolo[1]. [1]Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, [2]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium.

Background/Purpose: In systemic sclerosis (SSc), blood perfusion (BP) may be evaluated by both laser speckle contrast analysis (LASCA) and laser Doppler flowmetry (LDF) techniques, as well as microangiopathy may be assessed by nailfold videocapillaroscopy (NVC) (1–3). This study aimed at investigating BP by LASCA in different skin areas of SSc patients, looking for any correlations with the extent of the nailfold microvascular damage. Correlations between LASCA and LDF analysis at fingertips were also checked.

Methods: Sixty-eight SSc patients and 68 sex and age matched healthy subjects were enrolled. The BP was assessed in the area of fingertips, periungual areas, dorsum and palm of both hands, as well as of face, forehead, tip of nose, zygomas and perioral region by LASCA, and scored as perfusion units (PU) (1). LDF was performed at the level of 2nd, 3rd, 4th, and 5th fingertip bilaterally (2), and average blood perfusion recorded as PU (2). NVC was performed in SSc patients and images classified and scored as previously reported (4–6). Non-parametric tests were used for the statistical analysis.

Results: Median BP was significantly lower in SSc patients when compared to healthy subjects at fingertips (86 vs 189 PU, respectively, p<0.0001), periungual areas (69 vs 140 PU, respectively, p<0.0001) and palms (77 vs 111 PU, respectively, p<0.0001). Conversely, both groups showed similar BP values at dorsum of hands and different areas of the face. The median BP gradient between fingertips and palm was lower in SSc patients than in healthy subjects (11 vs 67 PU, respectively, p<0.0001), as well as was the gradient between dorsum and periungual areas (25 vs 69 PU, respectively, p=0.0009). There was a statistically significant progressive decrease of BP in SSc patients with different NVC pattern of microangiopathy ("early", "active", or "late"), as well as a statistically significant negative correlation between microangiopathy evolution score (MES) and BP, at the level of fingertip areas (p<0.004), periungual areas (p<0.01) and palms (p<0.02), but not in the other areas. A positive correlation was detected between LASCA and LDF values at fingertip level, in all subjects (p<0.0001). LASCA, since evaluating large skin areas, is significantly less time consuming, is more accepted by patients and shows lower intra-operator variability than LDF (95% vs 88%).

Conclusion: This study shows that LASCA technique detects differences of BP at fingertips, periungual and palm areas between SSc patients and healthy subjects. Statistically significant correlations were observed between nailfold microangiopathy damage extent and BP at the level of fingertips, periungual and palm areas. LASCA positively correlates with LDF values at fingertips, but brings an higher reproducibility.

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Scleroderma Renal Crisis and Pulmonary Arterial Hypertension Are Very Rare In The Same Patient. Bernadette Lynch[1], Vincent Sobanski[1], Clive Handler[1], Benjamin E. Schreiber[2], John G. Coghlan[3], Voon H. Ong[4], Aine Burns[1] and Christopher P. Denton[5]. [1]The Royal Free Hospital, London, United Kingdom, [2]National Pulmonary Hypertension Service, London, United Kingdom, [3]The Royal Free Hospital NHS Foundation Trust, London, United Kingdom, [4]The Royal Free and University College Medical School, London, United Kingdom, [5]Department of Rheumatology, London, United Kingdom.

Background/Purpose: Systemic Sclerosis (SSc) is associated with occlusive vasculopathy resulting in digital ischaemia, telangiectasia, scleroderma renal crisis (SRC) and pulmonary arterial hypertension (PAH). SRC and PAH have similar histological features with neointimal proliferation and medial hyperplasia and shared pathogenic mechanisms are plausible. Pulmonary hypertension (PH) after SRC is frequently observed but generally due to post capillary mechanisms with elevated post capillary wedge pressure (WHO Group II). We have explored the association of PAH (WHO Group I) with SRC based upon shared histopathological features and possible similarities in pathogenesis.

Methods: Of more than 2000 SSc patients attending our institution between 1990–2013, 150 patients had a confirmed diagnosis of SRC of which six (4%) patients had a diagnosis of PAH (mean pulmonary arterial pressure ≥25mmHg and pulmonary capillary wedge pressure <15mmHg) following right heart catherisation. Estimated glomerular filtration rate (eGFR) was calculated using the 4-variable Modified Diet in Renal Disease (MDRD) equation. Demographic, clinical and haemodynamic parameters are expressed as mean ± SD.

Results: Two patients had diffuse cutaneous SSc (dcSSc) and 4 patients had limited cutaneous SSc (lcSSc). 5/6 (83%) demonstrated an immunofluoresecence and ENA reactivity consistent with anti-RNA polymerase III reactivity, confirmed by specific ELISA. All patients with SRC and PAH were female. PAH was diagnosed after SRC in all patients (49 vs 44 years old). 4/6 (66.7%) patients required dialysis. 2/6 (33.3%) patients who did not require dialysis had an eGFR of 26 and 44mls/min/1.73m^2. 2 patients recovered renal function at 6 and 14 months after the diagnosis of SRC. The mean mPAP (mean pulmonary arterial pressure) was 42 ± 12mmHg with a mean pulmonary capillary wedge pressure (PCWP) 9.3 ± 2.6mmHg and a cardiac index of 5.2 ± 0.8 L/min. 5 patients were treated with Bosentan and 1 patient with intravenous Iloprost. 3/6 (50%) patients died with a mean survival from date of diagnosis of SRC of 112 ± 30 months and a mean survival from date of diagnosis of PAH of 47 ± 17 months.

Conclusion: The presence of SRC and PAH in the same patient is very rare and PAH occurred after SRC in all patients at a mean of 5 years later. Temporal separation of SRC and PAH suggests that these complications may occur independently, but the frequent association with ARA suggests common susceptibility factors may be relevant.

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Clinical Significance Of Endothelial Vasodilator Function Evaluated By Endopat In Patients With Systemic Sclerosis. Naohiko Aozasa, Yoshihide Asano, Masaru Hatano, Ryosuke Saigusa, Kouta Takakuwa, Takehiro Takahashi, Tetsuo Toyama, Hayakazu Sumida, Atsushi Yao, Koichiro Kinugawa, Hisataka Maki, Toshiro Inaba, Hironori Muraoka, Shun Minatsuki, Issei Komuro and Shinichi Sato. University of Tokyo Graduate School of Medicine, Tokyo, Japan.

Background/Purpose: Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by initial vascular injuries and resultant fibrosis of skin and certain internal organs. Evidence has shown that vascular impairment in SSc may be a sign of endothelial dysfunction. The peripheral arterial tonometry (EndoPAT) is a device that is used to assess endothelial vasodilator function in a rapid and non-invasive fashion. Since its clinical significance has not been well established in SSc, we evaluated the association between the values of reactive hyperemia measured by EndoPAT and clinical features of SSc.

Methods: Thirty-three consecutive patients with SSc were studied, including 15 patients with limited cutaneous SSc (lcSSc) and 18 with diffuse cutaneous SSc (dcSSc). Clinical symptoms, such as swollen fingers, nailfold bleeding (NFB), pitting scars, digital ulcers, and Raynaud's phenomenon, were meticulously recorded. Reactive hyperemia peripheral arterial tonometry index (RHI) was measured using EndoPAT on all patients. Mean pulmonary artery pressure (mPAP) was measured by right heart catheterization. Correlations of RHI with various clinical symptoms, disease duration, laboratory data and disease subtypes were examined.

Results: RHI values were inversely correlated with mPAP ($r = -0.47$, $p < 0.01$), while positively correlated with %DLco ($r = 0.35$, $p < 0.05$). Furthermore, the values of RHI inversely correlated with disease duration in dcSSc patients ($r = -0.45$, $p < 0.05$), but not in lcSSc patients. Of note, RHI values were increased after one month of oral prednisolone in 4 patients with progressive skin sclerosis in whom skin stiffness was improved in response to the treatment.

Conclusion: Although mPAPs of all the patients enrolled in this study were less than 25 mmHg, the values of RHI were significantly and inversely correlated with mPAP, suggesting that the decreased RHI value reflects the reduction of the pulmonary vascular bed prior to the development of definite pulmonary arterial hypertension in SSc. Since skin sclerosis may affect the values of RHI, we have to be cautious to interpret the impact of prednisolone on endothelial function evaluated by EndoPAT in this disease.

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The Prognosis Of Scleroderma Renal Crisis In RNA-Polymerase III Antibody (ARA) Positive Compared To ARA Negative Patients. Bernadette Lynch[1], Henry Penn[2], Jennifer Harvey[3], Aine Burns[1] and Christopher P. Denton[4]. [1]The Royal Free Hospital, London, United Kingdom, [2]Northwick Park Hospital, Harrow, United Kingdom, [3]Royal Free Hospital, London, United Kingdom, [4]UCL Medical School, London, United Kingdom.

Background/Purpose: Scleroderma renal crisis (SRC) usually presenting with accelerated hypertension and acute kidney injury (AKI) is one of the most severe complications of Systemic Sclerosis (SSc). The presence of RNA-polymerase III auto-antibodies (ARA) is recognized as a strong risk factor for SRC but studies have not explored long-term outcomes in ARA positive cases compared to ARA negative cases.

Methods: Of more than 2000 SSc patients attending our institution between 1990–2013, 150 patients had a confirmed SRC. 80% patients had diffuse cutaneous SSc (dcSSc) and 20% patients had limited cutaneous SSc (dcSSc). ARA was measured by commercial ELISA or radio-immunoprecipitation. Patients were divided into two groups: ARA positive or ARA negative. Demographic and clinical parameters were compared between groups using Student's t-test or Chi-squared analyses where appropriate.

Results: 61/150 (41%) patients were ARA positive and significantly more likely to have dcSSc (88.3% vs 73.8%, p=0.032) than lcSSc compared to ARA negative patients. There was no significant difference in age of onset of SRC (51.2 vs 51.9 years) or the number of females (73% vs 79%) between the two groups. 50.8% of ARA positive patients required dialysis compared to 29.2% of ARA negative patients (p=0.07). The mean time to recovery of renal function was significantly longer in ARA positive patients (14.25 vs 8.27 months, p=0.032). Significantly more ARA positive patients were able to discontinue dialysis compared to ARA negative patients (53.3% vs 25.5%, p=0.01). ARA positive patients had a significantly better survival outcome (figure 1).

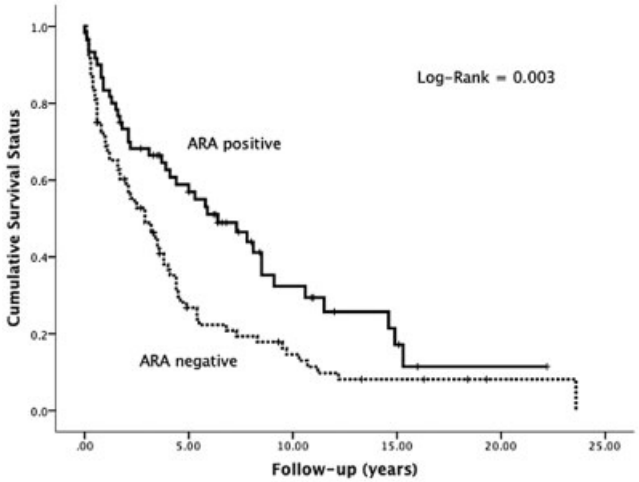

Figure 1. Kaplan Meier survival estimate showing the effect of ARA positive auto-antibodies in patients with SRC.

Conclusion: In SRC, although more ARA positive patients required dialysis they also had significantly greater capacity for long-term recovery and survival compared to ARA negative patients.

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Stabilisation Of Microcirculation In Early Systemic Sclerosis Patients With Diffuse Skin Involvement Following Rituximab Treatment. Vanessa Smith[1], Carmen Pizzorni[2], Valeria Riccieri[3], Saskia Decuman[4], Yves P. Piette[1], Ellen Deschepper[5], Filip De Keyser[1] and Maurizio Cutolo[6]. [1]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium, [2]Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, [3]Department of Internal Medicine and Medical Specialities, University Sapienza, Rome, Italy, [4]Department of Internal Medicine, Ghent University, Ghent, Belgium, [5]Biostatistics Unit, Department of Public Health, Ghent University, Ghent, Belgium, [6]University of Genova, Genova, Italy.

Background/Purpose: Microangiopathy in systemic sclerosis is progressive over time [1, 2]. This study assesses microangiopathic evolution by nailfold videocapillarocopic (NVC) analysis after two treatment course (month 0/6) with rituximab in early diffuse systemic sclerosis (dcSSc) patients.

Methods: Twelve months follow-up (open-label study) of six consecutive patients with early dcSSc. Patients received an infusion of two times 1000 mg rituximab at month 0 and 6, together with 100 mg methylprednisolone. All patients were on a stable dose methotrexate (10–25 mg/week) as background therapy since at least 12 weeks. Capillaroscopic assessment, clinical read outs (modified Rodnan skin score [mRSS], lung function and echocardiography) and disease activity score (DAS) were performed at 0, 3, 6 and 12 months.

Results: There was a clinical significant change in skin score with a mean (SD) mRSS of 24.8 (5.95) at baseline and 10.2 (1.17) at month 12 (Mixed Model Analyses [MMA] $p<0.001$) and a significant decrease in DAS, with a median of 3.8 at baseline (range: 2.0–7.0) and 0.5 at month 12 (range: 0.0–2.0) (MMA $p<0.001$). Indices of internal organ involvement remained stable. Semi-quantitatively scored NVC parameters remained stable showing no progression of the microvascular damage during the twelve months follow-up: mean score (SD) of capillary loss at baseline/12 months: 2.170 (0.408)/ 1.830 (0.408) (MMA $p=0.341$), mean score (SD) of giants at baseline/ 12 months: 0.670 (0.516)/ 1.17 (0.408) (MMA $p=0.093$), mean score of haemorrhages at baseline/12 months: 0.670 (0.516)/1.00 (0.000) (MMA $p=0.529$) and mean score of neoangiogenesis at baseline/12 months: 0.830 (0.408)/ 0.830 (0.753) (MMA $p=0.383$).

Conclusion: This is the first open pilot study to show that two immunosuppressive treatment courses with rituximab may not only have potential efficacy for skin and stabilisation of internal organ involvement but also additional stabilisation of microangiopathic parameters in early dcSSc.

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Microvascular Abnormalities In Patients With Early Systemic Sclerosis: Less Severe Morphological Changes Compared To Patients With Definite Disease. Cintia Camargo, Juliana Sekiyama, Maria I. Arismendi and Cristiane Kayser. Universidade Federal de São Paulo, São Paulo, Brazil.

Background/Purpose: To analyze the morphological and functional abnormalities of the microcirculation through widefield nailfold capillaroscopy (NFC), videocapillaroscopy and cutaneous microvascular blood flow measurement before and after cold stimulus, associated with vascular injury markers in patients with early systemic sclerosis (SSc), compared to primary Raynaud's phenomenon (PRP), definite SSc, and healthy controls.

Methods: Eighty patients with definite SSc (American College of Rheumatology criteria), 46 patients with early SSc (2001 LeRoy's criteria), 40 PRP patients, and 45 controls were included. The morphological abnormalities were evaluated through widefield nailfold capillaroscopy (NFC) (10–25x magnification), and videocapillaroscopy (200x magnification). The following parameters were analyzed in eight digits of the hands (excluding the thumb) by widefield NFC and videocapillaroscopy: number of capillaries/mm, enlarged, giant and ramified capillaries, microhaemorrhages, and avascular score. A score based on a semiquantitative rating scale (score 0–3) was used for each videocapillaroscopy parameter. Patients with scleroderma pattern were distributed into three patterns: early, active and late. Fingertip blood flow (FBF) was measured using laser Doppler imaging (LDI) at baseline and during 30 minutes after cold stimulus. Serum endothelin-1 (ET-1), von Willebrand factor (vWF) and transforming growth factor beta-1 (TGF-β1) were measured by ELISA.

Results: Patients with early SSc showed significantly higher number of capillaries/mm, and lower enlarged, giant capillaries and avascular score compared to patients with definite SSc in widefield NFC and videocapillaroscopy ($p<0.001$). Besides the number/score of enlarged capillaries, microhaemorrhages and avascular score were higher in patients with early SSc compared to patients with PRP and controls in both methods ($p<0.001$). Ninety-six percent of patients with definite SSc, and 76% of early SSc patients presented the scleroderma pattern using videocapillaroscopy. The early pattern was most frequently found among early SSc patients (37% in early SSc vs 17% in definite SSc, $p<0.01$). The active pattern was found in 63% of early SSc and in 60% of definite SSc. Interestingly, the late pattern was not observed in patients with early SSc, but was observed in 23% of definite SSc patients. FBF values before and after cold stimulus were significantly higher in controls compared to PRP, early SSc and definite SSc ($p<0.001$), with no difference between early and definite SSc. Serum levels of ET-1, vWF activity and TGF-β1 were similar between early and definite SSc.

Conclusion: Early SSc patients showed functional changes and serum vascular markers levels similar to patients with established disease. Nonetheless, the morphological changes were less severe in early SSc, suggesting a progression of the peripheral microangiopathy along different phases of the disease. These findings may have important implications in the management of patients with early disease.

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Association Between Nail Fold Capillaroscopy Abnormalities and Thermographic Assessment Of Peripheral Microvascular Dysfunction In An Unselected Cohort Of Patients Under Investigation For Symptoms Of Raynaud's Phenomenon. Bhavisha Vasta[1], Marina Scolnik[2], Darren Hart[1], Jacqueline A. Shipley[1], Sue Brown[1], Eleanor Korendowych[1], Neil J McHugh[3] and John D. Pauling[3]. [1]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [2]Rheumatology Section, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [3]Department of Pharmacy and Pharmacology, University of Bath, Bath, United Kingdom.

Background/Purpose: Nail fold capillaroscopy (NC) and infrared thermography (IRT) allow objective assessment of digital microvascular abnormalities in patients with Raynaud's phenomenon (RP) and have an important role in disease classification, particularly in systemic sclerosis (SSc). The relationship between NC appearances and assessment of digital microvascular function with IRT in an unselected population of patients with RP symptoms has not previously been explored.

Methods: A retrospective review of all patients investigated with both NC and IRT for symptoms of RP between August 2010 and November 2012 was undertaken. Thermographic assessment of the resting longitudinal thermal gradient of all fingers was undertaken by calculating the mean distal dorsal difference (DDD) at 23ºC (without prior knowledge of the clinical diagnosis or NC findings). NC images were reviewed (BV and MS) and categorized as normal, non-specific abnormalities and SSc-pattern abnormalities (Cutolo, Clin Exp Rheumatol. 2007). Indeterminate cases were reviewed by a 3rd assessor (JP) and consensus reached. A subsequent case note review was undertaken to categorize patients according to the following diagnoses; primary RP (no clinical features of connective tissue disease and ANA negative), SSc (sclerodactyly in conjunction with a SSc-specific autoantibody), fibromyalgia (FMS) (1990 criteria) and other diagnoses.

Results: One hundred and forty one patients were identified. NC appearances, IRT analysis and diagnoses are summarized in the accompany-

ing table. NC abnormalities were associated with a significantly lower median thermographic DDD indicating more severe peripheral microvascular function ($p=0.017$). There was no difference between thermographic findings of patients with non-specific and SSc-pattern NC abnormalities (possibly due to small patient numbers with SSc-pattern abnormalities). NC abnormalities were present in all patients with SSc and the majority (54.5%) had SSc-pattern changes. Patients with primary RP were significantly less likely to have NC abnormalities compared with SSc ($p<0.0001$). Non-specific NC abnormalities were identified in 15/46 (32.6) patients with primary RP but SSc-pattern abnormalities were not identified in any patients with primary RP. NC appearances were generally normal in FMS with only a small proportion of patients (3/18, 16.7%) exhibiting non-specific NC abnormalities.

	Normal NC appearance (n = 83)	Nonspecific NC changes (n = 48)	SSc-pattern NC changes (n = 10)
Median average DDD across all fingers, °C, median (IQR)	+0.15 (4.16)	−1.98 (4.21)	−2.09 (3.71)
p value vs. normal NC appearance (Mann Whitney U)		0.017	0.099
Proportion of patients with a mean DDD < −1, n (%)	35 (42.2)	25 (52.1)	7 (70)
Clinical diagnosis, n	31	15	0
Primary RP	0	5	6
SSc	15	3	0
FMS	37	25	4
Other rheumatic Diseases			

Conclusion: The presence of NC abnormalities is associated with thermographic evidence of more profound digital microvascular dysfunction in patients under investigation for symptoms of RP. The presence of NC abnormalities differs between primary RP and SSc. Despite a high reported prevalence of RP symptoms in FMS, the majority of patients have normal NC and thermographic findings.

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Acupressure For The Treatment Of Raynaud's Phenomenon: A Pilot Randomized Controlled Trial. Heather Gladue[1], Richard E. Harris[1], Veronica Berrocal[1], Pei-Suen Tsou[2], Gautam Edhayan[3], Ray Ohara[3] and Dinesh Khanna[4]. [1]University of Michigan, Ann Arbor, MI, [2]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [3]University of Michigan Medical School, Ann Arbor, MI, [4]University of Michigan Medical Center, Ann Arbor, MI.

Background/Purpose: Raynaud's phenomenon (RP) affects approximately 10% of the US population. The high cost, lack of efficacy, and side effects of conventional medical therapies necessitates the need for complementary or alternative options.

Objective: A pilot, randomized control trial (RCT) of acupressure vs. patient education for the treatment of RP.

Methods: A pilot single-center RCT of vasodilation acupressure, relaxation acupressure vs. RP education obtained from the Raynaud's Association (control). Patients with either primary (N = 15) or secondary (N = 8) RP were randomized from January through April by block randomization to the 3 groups for an 8 week period. Patients randomized to acupressure were instructed on how to self-perform at home by a single investigator and a DVD was provided with instructions. The primary endpoint was a decrease in the severity, frequency and duration of RP. All patients kept a daily Raynaud's diary, (recording the number and duration of attacks, pain, tingling and numbness on a 0–100 scale), and daily Raynaud's condition score. At baseline and 8 weeks, EndoPAT was performed to determine endothelial function, and serum was collected for biomarker analysis (VEGF, tPA, sE-Selectin, BFGF, VCAM-1, ICAM). Data analysis was conducted using the last observation carried forward and paired statistical analyses were used to assess difference.

Results: 23 patients were randomized and 9 discontinued prematurely (5 patients withdrew due to time restraints, 2 each for unrelated medical problems and lost to follow-up). Since there was no statistical difference between acupressure groups, they were combined and compared to the education group. 78% of patients were female, 96% were Caucasian, the mean age was 49.8 (SD=16) yrs; 5/16 patients in the acupressure group had secondary RP and 1/7 in the control group had secondary RP.. There was no statistical difference in the baseline characteristics between the acupressure groups vs. the control group. At the end of study, there were no statistical differences between the acupressure vs. education groups. However, there were trends in the patient reported severity of RP favoring acupressure groups (Table). In addition there were no significant differences in EndoPAT measurements or serum markers of vasculopathy. Sensitivity analysis using the completers showed similar results.

Table: Change from week 1 compared to week 8*

Variable	Group A+B	Control	P value
No of attacks	N: 12	N: 6	1.0
Mean (SD)	−6.3 (8.0)	−7.2 (12.8)	
Pain	N: 12	N: 6	0.12
Mean (SD)	−13.6 (30.1)	9.6 (27.6)	
Tingling	N: 12	N: 6	0.64
Mean (SD)	−5.3 (13.9)	−1.2 (7.5)	
Numbness	N: 12	N: 6	0.89
Mean (SD)	−10.5 (37.0)	1.1 (22.1)	
Average duration of attacks	N: 12	N: 6	0.08
Mean (SD)	−9.2 (18.7)	0.8 (11.2)	
RCS average for difficulty	N: 12	N: 5	0.72
Mean (SD)	−2.0 (2.4)	−0.6 (2.9)	
RCS average for pain	N: 12	N: 5	0.63
Mean (SD)	−1.4 (2.0)	−0.4 (3.0)	
Endopat	N: 14	N: 7	0.55
Mean (SD)	−0.1 (0.4)	−0.2 (0.8)	
Patient VAS	N: 16	N: 7	0.39
Mean (SD)	−1.6 (2.2)	−0.7 (2.0)	
MD VAS	N: 16	N: 7	1.0
Mean (SD)	−2.1 (2.0)	−1.9 (1.3)	

*Using LOCF.

Conclusion: Our pilot RCT showed that acupressure groups showed trends in improvement in symptoms associated with RP. However, there were no differences in the endothelial function and serum markers of vasculopathy. The parameters used to evaluate patients with RP have marked variability and supports the need for a composite measure to be developed for RP trials.

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2598

Timing and Outcome Of Transition From Primary To Secondary Raynaud's Phenomenon: A Capillaroscopic Based Study. Alberto Sulli[1], Giorgia Ferrari[1], Elena Bernero[1], Carmen Pizzorni[1], Vanessa Smith[2], Barbara Ruaro[1] and Maurizio Cutolo[1]. [1]Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, [2]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium.

Background/Purpose: Raynaud's phenomenon (RP) is classified as primary (PRP) or secondary (SRP) depending on its association with an underlying disease (1,2). PRP can evolve to SRP during followup (1,3). This is a prospective study to investigate timing and outcome of transition from PRP to SRP in a large cohort of patients, as well as to assess the progression of the nailfold scleroderma-patterns of microangiopathy in patients with isolated RP.

Methods: 2,853 patients with RP were investigated. Patients achieving a diagnosis of PRP at first visit (normal nailfold videocapillaroscopy (NVC), normal or negative laboratory findings including autoantibodies, absence of other clinical findings and exclusion of an underlying disease) were followed to monitor the appearance of specific morphological alterations at NVC, autoantibodies positivity, or clinical symptoms for a mean period of 52±40SD months (1,3). Nailfold microangiopathy was detected by NVC, and capillary abnormalities were classified according to different patterns of microangiopathy (4–5).

Results: At first visit, 797 (28%) patients out of 2,853 showed a NVC scleroderma-pattern, and got the diagnosis of SRP. Among the remaining 2,056 patients showing a normal capillaroscopy at baseline, 1,677 patients were lost during follow-up or not prospectively evaluable, whereas 379 patients were followed for a mean time of 52±40SD months. Among these last, 180 patients (47%) were positive for ANA, and 199 (53%) were ANA

negative (PRP patients). During the follow-up, the NVC scleroderma-pattern was diagnosed in 62 patients out of 379 (16%). In particular, it was found in 48 (27%) of the ANA-positive patients (27 "early", 4 "active", 9 "late", 8 "like" NVC scleroderma-pattern at the end of the follow-up): these patients achieved the diagnosis of systemic sclerosis (46 patients), UCTD (1 patient) and Sjogren syndrome (1 patient). NVC was found positive also in 14 (7%) of the ANA-negative patients (transition to SRP) (13 "early", and 1 "like" NVC scleroderma-pattern at the end of the follow-up): these patients developed systemic sclerosis (9 patients) and UCTD (5 patients). The time of transition from normal/not specific capillary alterations to "early" scleroderma-pattern was 37±29 months. In particular, in ANA-positive patients NVC became positive within 43±36SD months, while in ANA-negative patients in 18±16 months. The 132 ANA-positive patients with a not defined NVC pattern developed respectively systemic sclerosis (7 patients), UCTD (104 patients), MCTD (8 patients), autoimmune thyroiditis (6 patients), Sjogren syndrome (4 patients), antiphospholipid syndrome (1 patients), LES (1 patients).

Conclusion: This large cohort study demonstrates that 7% of patients initially diagnosed as affected by PRP may transit to SRP in a mean time of 37±29 months. The transition from normal NVC pattern to scleroderma-pattern was more frequent in ANA-positive patients (27%).

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2599

Safety and Effectiveness Of Mycophenolate In Systemic Sclerosis: A Systemic Review. Mohammed Omair[1], Abdulaziz Alahmadi[2] and Sindhu R. Johnson[3]. [1]Mount Sinai Hospital/University of Toronto, Toronto, ON, [2]Toronto Scleroderma Research Program, Division of Rheumatology, Mount Sinai Hospital, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, ON, [3]Toronto Western Hospital, Toronto General Hospital, Mount Sinai Hospital, and University of Toronto, Toronto, ON.

Background/Purpose: Mycophenolate reduces chronic allograft nephropathy and interstitial fibrosis by inhibiting TGF-β, which is an important molecule in the pathogenesis of systemic sclerosis (SSc). The main side effects observed are gastrointestinal disturbance, myelosuppression, and increased risk of infection. This maybe a limitation of its use in SSc patients since gastrointestinal involvement is very common. The objective of this study is to evaluate the safety, in particular gastrointestinal adverse events, of mycophenolate in SSc. Secondarily we evaluated the effectiveness of mycophenolate in SSc skin and lung disease.

Methods: A literature search of Medline, Embase, Cochrane Central Register of Controlled Trials, and CINAHL (inception - September 2012) was performed. Titles and abstracts were screened to identify studies that described the use of mycophenolate in SSc patients. Inclusion criteria included exposure to mycophenolate, and reporting of modified Rodnan skin score (MRSS), forced vital capacity (FVC), diffusing capacity of carbon monoxide (DLCO); or adverse events. The primary outcome was gastrointestinal events occurring after the initiation of mycophenolate. Secondary safety outcomes included myelosuppression, infection, malignancy, and death occurring after the initiation of mycophenolate.

Results: 616 citations were identified and 20 were included in the analysis. 477 patients have been exposed to mycophenolate. The mean disease duration ranged between 0.8–14.1 years. There were 89 non-lethal adverse events, of which 43 (48%) were gastrointestinal and 46 (52%) were non-gastrointestinal adverse events. The most commonly reported gastrointestinal events included diarrhea (n=18 (20%)), nausea (n=12 (13%)), and abdominal pain (n=3 (3%)). The most commonly reported non-gastrointestinal adverse events were infections (n=33 (37%), and 6 cytopenias (n=6, (7%)). The reported rate of discontinuation ranged between 8–40%. Seven observational studies report mycophenolate is effective improvement or stabilization in FVC, and 5 observational studies report stabilization or improvement in MRSS.

Conclusion: Observational studies report mycophenolate is effective in improving or stabilizing interstitial lung disease, and may be effective for skin involvement. However, gastrointestinal adverse events are common in SSc patients.

Disclosure: M. Omair, None; **A. Alahmadi**, None; **S. R. Johnson**, None.

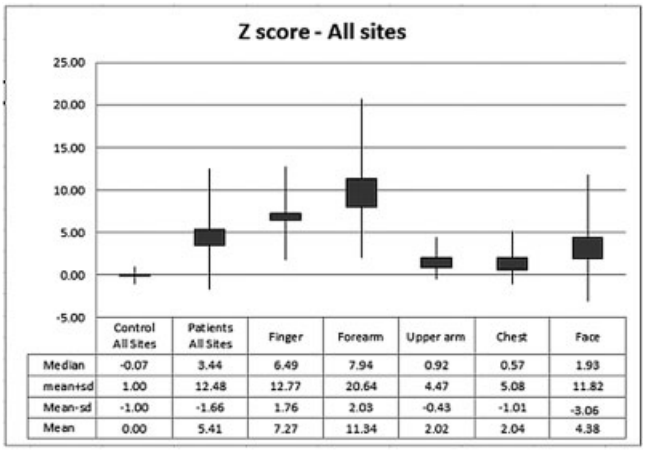
2600

Shear Wave Elastography: A Novel Quantitative Approach For Evaluating Scleroderma Skin. Ingeborg Sacksen, Mark H. Wener, P. Scott Pollock and Manjiri K. Dighe. University of Washington, Seattle, WA.

Background/Purpose: Systemic sclerosis (SSc) is a multi-system disease with both visceral and cutaneous fibrosis. Dermal elasticity is reduced and stiffness increased due to excessive dermal and subcutaneous deposition of collagen leading to increased skin thickness as well as hardening and tightening of the skin. Shear wave elastography (SWE) is an emerging, operator-independent technique, which can obtain quantitative stiffness values. We describe a novel quantitative approach for evaluating the skin in scleroderma using shear wave elastography

Methods: We evaluated the skin of thirteen patients with diffuse systemic sclerosis and ten healthy controls using an Aixplorer shear wave ultrasound instrument (SupersonicImagine, Bothell, WA). Each patient underwent a SWE exam of the right arm at multiple sites (3rd finger, extensor forearm, upper arm), sternum, and face. The images consist of a spectrum of translucent colored bands superimposed on B-mode ultrasonographic images indicative of soft and highly elastic tissue to hard and minimally elastic tissue. The mean stiffness values of skin (measured in kPa units) were obtained at each site by averaging 3 measurements made per image obtained.

Results: The skin of seven men and five women with diffuse systemic sclerosis as well as 10 healthy controls was evaluated. The mean and 1SD SWE stiffness measures were (in kPa): finger –SSc 98.3 (SD-56) vs control – 32.1, (SD- 11.8); forearm – SSc 89.6 (SD- 58.9) vs control – 18.3 (SD-6.9), upper arm – SSc 34.5 (SD-19.2) vs control 17.7(SD8.6), face: SSc 19.3 (SD-17.7) vs control 8.4(SD-2.7), chest –SSc 23.6 (SD-17.1) vs control 10.9(SD-6.0). Maximum (out of range high) values of 300kPA were obtained for 1 patient at the finger and two patients at the forearm. Two-tailed t –tests were performed between the means of patients and controls at each site. Statistical significance ($p<0.01$) was achieved at the finger, forearm, all sites combined, and ($p<0.05$) at the upper arm. Statistical significance was not reached for the chest ($p=0.056$) and the face ($p=0.08$). Z scores (based on the mean and SD of each site in controls) were calculated for patient measurements at each individual site and combined sites compared to controls. Z scores at all sites were above the mean for controls (see figure 1).



	Control All Sites	Patients All Sites	Finger	Forearm	Upper arm	Chest	Face
Median	-0.07	3.44	6.49	7.94	0.92	0.57	1.93
mean+sd	1.00	12.48	12.77	20.64	4.47	5.08	11.82
Mean-sd	-1.00	-1.66	1.76	2.03	-0.43	-1.01	-3.06
Mean	0.00	5.41	7.27	11.34	2.02	2.04	4.38

Conclusion: Shear wave elastography is a valid and feasible quantitative method for assessing abnormal elasticity of the skin in scleroderma patients. It adds a new dimension to the assessment of skin involvement in SSc, and is an objective, non-invasive tool for potential use in clinical trials. Studies comparing its performance to stage of disease, skin thickness, and mRss are ongoing.

Disclosure: I. Sacksen, None; **M. H. Wener**, None; **P. S. Pollock**, None; **M. K. Dighe**, None.

2601

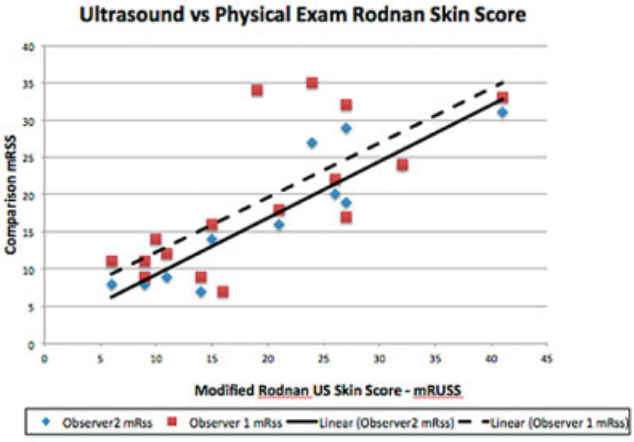
Modified Rodnan Ultrasound Skin Score: An Ultrasound Skin Scoring Approach In Systemic Sclerosis. Ingeborg Sacksen, P. Scott Pollock and Mark H. Wener. University of Washington, Seattle, WA.

Background/Purpose: Systemic sclerosis (SSc) is a multi-organ disease characterized by thickening, hardening and tightening of the skin. Skin

thickening is described by physical exam and measured semi-quantitatively as the modified Rodnan skin score (mRSS). Ultrasound (US) has been investigated to measure skin thickening, however, approaches to convert and relate US findings to mRSS's have not been adopted, in part because of the variability of normal skin thickness at different sites (as well as by age and gender). We present preliminary data reproducing a 17-point mRSS in scleroderma patients and controls by using mid frequency ultrasound (15mHz) and correlating it to physical exam findings. We propose development of an ultrasound adaptation of the mRSS: the Modified Rodnan Ultrasound Skin Score (mRUSS), which is easy to use, quantifiable, and allows ultrasound-based categorization of the skin in scleroderma patients.

Methods: We examined the skin of 16 patients (8 women) with diffuse cutaneous SSc and 10 healthy controls using a Sonosite M-Turbo 15mHz ultrasound machine operated by a single examiner. Each patient underwent a 17-point mRSS physical exam, and 12 patients had a second mRSS performed by an experienced rheumatologist. All patients then underwent a 17-point, comprehensive ultrasound skin exam at reproducible, predefined sites corresponding to the anatomic sites examined in the mRSS. The sites were: single sites on the face, chest wall, and abdomen, and bilateral 3rd finger, dorsum of the hand, extensor forearm, upper arm, thighs, lower legs, and the dorsal surface of the feet. Two dermal thickness measurements were taken from each image and averaged. The mean and standard deviation (SD) was calculated for controls at each site, and the z-score for each site calculated as [(skin thickness)-(mean control thickness at that site)]/(SD of control at that site)].

Results: Various cut-points were tested for translating the z-score to mRUSS's assigned to each anatomic site, and the best concordance between the overall mRSS and the overall mRUSS were obtained with the following criteria: z-score <1= mRUSS 0; z-score 1–3=mRUSS 1; z-score 3–5 =mRUSS 2; z-score >5 =mRUSS 3. Total mRUSS's were then correlated to the mRSS (physical exam). The correlation between observer 1 mRSS compared to US score (assuming this to be the gold standard) was.90 and.73 for observer 2 (less experienced provider) (see figure 1). The r-value comparing observer 1 to observer 2 was 0.97.



Conclusion: Use of mid frequency US (15-mhz) is a readily available, reproducible, objective method for evaluating skin thickness in scleroderma. The newly proposed mRUSS scoring system correlates well with the mRSS based on physical exam findings. These findings will require verification with more patients and by independent examiners, but they have promise for use of precise ultrasound measurements to generate a mRSS equivalent.

Disclosure: I. Sacksen, None; **P. S. Pollock**, None; **M. H. Wener**, None.

2602

Reduced Frequencies Of Circulating CD8 T Cells In Early Diffuse Cutaneous Systemic Sclerosis Is Associated With Worse Skin Scores. Marie Hudson[1], Maximilien Lora[2], Christopher Di Ioia[1], Solene Tatibouet[1], Sasha Bernatsky[3] and Ines Colmegna[4]. [1]McGill University, Montreal, QC, [2]McGill University Health Centre, Montréal, QC, [3]McGill University Health Center, Montreal, QC, [4]McGill University Health Centre, Montreal, QC.

Background/Purpose: Diffuse cutaneous systemic sclerosis (dcSSc) is associated with significant morbidity and mortality. Measurement of skin thickness (modified Rodnan skin score (mRss)) is a surrogate of dcSSc severity as an increase in this score is associated with involvement of internal organs and increased mortality. Recent studies have found that high levels of the profibrotic type-2 cytokine IL-13 are produced by peripheral blood effector CD8+ T cells from SSc patients and that IL-13-producing circulating CD8+ T cells express skin-homing receptors and induce a profibrotic phenotype in normal dermal fibroblasts. Although one study describes a reduction of the circulating CD8+ T cell subset in dcSSc, the clinical implications of this finding are unknown.

Methods: The frequencies of circulating CD4, CD8, CD20 and CD14 cells were determined by multi-parameter fluorescence-activated cell sorting (FACS) in peripheral blood mononuclear cells isolated from newly diagnosed, untreated dcSSc patients. Samples from patients with early onset, untreated seropositive rheumatoid arthritis were tested as controls. Clinical parameters recorded at the time of sample collection included: mRss, global assessment of activity, global assessment of severity, forced vital capacity and DLCO.

Results: Percentages and absolute counts of cell subsets isolated from dcSSc patients (n=10) with a mean age of 58±8.24 years and a mean disease duration of 2.7±1.8 years were compared with age matched early onset RA patients (n=10). The frequencies of the studied cell subpopulations was similar between RA and dcSSc except for the absolute number and percentage of the CD8+ fraction, which was lower among dcSSc (p=.007 and.03, respectively). Lower frequencies of CD8+ T cells were associated with higher mRss and higher global assessments of activity (p=.0037 and.0052, respectively). For an increase of 1 unit in the mRSS score (range 0–51) there was a decrease of 0.79 in absolute CD8+ T cells and for an increase of 1 unit in the global assessment of activity (range 0–10), there was a decrease of 0.75 in absolute CD8+ T cells.

Conclusion: Our findings suggest that early dcSSc have lower frequencies of peripheral blood circulating CD8+ T cells and that those are inversely associated with skin scores and disease activity. These findings are particularly relevant in light of recent evidence suggesting that skin homing – relocation IL-13-producing CD8+ T cells are directly involved in modulating dermal fibrosis in SSc, and emphasizes the need to prospectively assess the utility of reduced CD8+ T cell frequencies as a biomarker of dcSSc severity.

Disclosure: M. Hudson, None; **M. Lora**, None; **C. Di Ioia**, None; **S. Tatibouet**, None; **S. Bernatsky**, None; **I. Colmegna**, None.

2603

Are There Differences In Limited Systemic Sclerosis According To Extension Of Skin Involvement?. Marina Scolnik[1], Eliana Lancioni[2], Luis J. Catoggio[1], Mirtha Sabelli[2], Zaida Bedran[2], Carla Saucedo[2], Josefina Marin[2] and Enrique Soriano[1]. [1]Rheumatology Section, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.

Background/Purpose: There is consensus in classifying Systemic Sclerosis (SSc) according to extension of skin involvement as limited and diffuse, using the elbows and knees as "limits" to distinguish between them. Decades ago, Barnett classified SSc as Type 1(only sclerodactyly), Type 2 (acrosclerosis - distal but may reach up to elbows and/or knees plus face) and Type 3 (diffuse skin involvement). Patients with Type 2 had an intermediate degree of organ involvement compared to Type 1 (less) and Type 3 (more). This issue has not been recently addressed. We examined the characteristics of our patients with limited disease to see if we could find differences between Barnett Type 1 and Type 2 subsets.

Methods: electronic medical records of patients registered between years 2000–2011 with the problem: scleroderma, SSc or CREST and those with anti Scl-70, anticentromere or anti nucleolar antibodies in laboratory database were reviewed. Cases fulfilling ACR 1980 criteria were included and were classified as diffuse or limited according to LeRoy's criteria with limited being separated into sclerodactyly (only fingers) and acrosclerosis (fingers and up to elbows and/or knees) (Barnett's Types 1 and 2).

Results: 234 SSc patients (216 females) fulfilled criteria. Female/male ratio was 12:1; 24% had diffuse SSc and 76% limited (64% sclerodactyly and 12% acrosclerosis). Total follow up was 688 patients-years. Over half (55.1%) are still under our care and 17 died during this period. Ten year survival rate was 80% for limited and 70% for diffuse variants respectively (HR: 0.88 95% CI: 0.7–1.1). Table 1 shows clinical and serological profile of this cohort.

Anti Scl-70 was present in 16%, anticentromere in 53% and nucleolar ANA in 7% of overall patients. Within the limited group, several characteristics in the acrosclerosis (Type 2) group were more similar to the diffuse than the Type 1(sclerodactyly) patients. Duration of Raynaud was shorter, and they had significantly more anti Scl-70 and less anti centromere antibodies than those with Type 1. In particular, interstitial lung disease (ILD) was significantly more prevalent in Type 2 group, and similar to Type 3. Other characteristics did not reach statistical differences.

Table 1. Clinical and serological profile of this cohort

	Limited (n = 178)				
Type of systemic sclerosis	**Sclerodactyly (n = 149)**	**Acrosclerosis (n = 29)**	**p (sclero vs acro)**	**Diffuse (n = 56)**	**p (limited vs diffuse)**
Females, n (%)	142 (95.3)	25 (86.2)	0.06	49 (87.5)	0.13
Age at diagnosis, years mean (SD)	59.8 (15.2)	54.9 (16.2)	0.14	53 (18.3)	0.038
Duration of raynaud before diagnosis, years median (SD)	9.2 (3.4)	5.5 (1)	0.018	1.9 (0.8)	0.008
Anti Scl-70, %	6.4	39.3	<0.001	43.9	<0.001
Anticentromere, %	82.3	17.9	<0.001	4.8	<0.001
Nucleolar ANA, %	5.7	3.6	0.54	20.9	0.001
Other autoantibodies, %	26.1	23.5	0.54	25.9	0.76
GI involvement, %	65.9	81.3	0.22	64.3	0.45
Interstitial lung disease, %	17.1	50	<0.001	65.3	<0.001
Pulmonary hypertension with ILD,%	5.5	0	0.34	15.4	0.03
Pulmonary hypertension (without ILD), %	9.1	4.8	0.45	2.6	0.39
Echocardiographic abnormalities (other than PH), %	5.7	4.5	0.65	10	0.26
Digital ulcers, %	26.9	34.5	0.44	32.1	0.86
Renal Crisis, n	0	0		1	
Pregnancy after diagnosis, n	3	1		3	
Patient-year, years (SD)	462 (3.1)	81.2 (3.1)		144.8 (3.6)	
Currently followed, n (%)	88 (59.5)	15 (51.7)		26 (46.4)	
Died under our care, n	11	2		4	

Scl-70: anti-topoisomerase I; ANA: antinuclear antibodies; GI: gastrointestinal; ILD: interstitial lung disease; PH: pulmonary arterial hypertension

Conclusion: These results appear to confirm that extension of skin involvement within limited SSc may identify two different subsets with clinical and serologic characteristics. Indeed, Type 2 as defined by Barnett appears to have intermediate organ involvement, and serology may be more similar to the diffuse type.

Disclosure: M. Scolnik, None; **E. Lancioni**, None; **L. J. Catoggio**, None; **M. Sabelli**, None; **Z. Bedran**, None; **C. Saucedo**, None; **J. Marin**, None; **E. Soriano**, None.

2604

Longitudinal Assessment Of Scleroderma Skin By Optical Coherence Tomography: Preliminary Validation Of Sensitivity To Change Over-Time. Giuseppina Abignano[1], Lesley-Anne Bissell[1], Jason Britton[2], Daniel Woods[3], Maya H. Buch[1], Dennis McGonagle[1], Paul Emery[1] and Francesco Del Galdo[1]. [1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [2]Medical Physics Department, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [3]Michelson Diagnostics Ltd, Kent, United Kingdom.

Background/Purpose: Optical coherence tomography (OCT) has been shown to be a quantitative reliable tool to assess skin involvement in Systemic Sclerosis (SSc) (1). However the sensitivity to change over-time has not been evaluated. The present study aimed to compare skin assessment by OCT over-time in patients with SSc.

Methods: We performed 24 OCT scans of dorsal forearms on 12 sites of analysis from 7 SSc patients (6 with diffuse, 1 with limited subset according to Le Roy et al; mean disease duration at baseline= 8 ± 2.3 years) at 0 and 24 months. Clinical skin involvement was assessed using the modified Rodnan skin score (mRss). Minimum and Maximum Optical Density (Min and Max OD) of the mean-A scans were calculated employing Matlab software as previously described (1). Comparison of the local mRss and Min and Max OD at the 2 time-points was performed by two-tailed paired t-test employing GraphPrism software.

Results: Five sites of analysis with local mRss=0 did not change over 24 months. Accordingly, both Min and Max OD showed only an average −1.81% and −2.31% change, respectively ($p>0.05$) (1). On the contrary, in 5 sites of analysis mRss improved by 2 points (two sites with local score "2" improved to "0", three sites with local score of "3" improved to "1"). In these sites Min OD showed an increase of 29% (range=23–37%; $p=0.0005$) and Max OD of 29.8% (range=18–41%; $p=0.0027$). Furthermore, both Min and Max OD showed a trend forward a decrease (−3.54%, −5.41% respectively) at the 2 sites of analysis with worsening mRSS (one point increase) but the low sample size did not allow to perform a statistical evaluation.

Conclusion: Although preliminary for the low number of observations, this study provides the first evidence suggesting that OCT of the skin is sensitive to change over time and it changes consistently with mRss. Studies including a larger number of patients and sites of analysis with different grades of skin involvement and improvement/deterioriation of clinical score are needed to reach a definitive validation.

References:

1. Abignano et al. Ann Rheum Dis 2013.

Disclosure: G. Abignano, None; **L. A. Bissell**, None; **J. Britton**, None; **D. Woods**, Michelson Diagnostics Ltd, 3; **M. H. Buch**, None; **D. McGonagle**, None; **P. Emery**, None; **F. Del Galdo**, None.

2605

Quality Of Life and Psychosocial Aspects In Juvenile Localized Scleroderma. Roberta Culpo, Marco Ricca, Fabio Vittadello, Giuseppina Sequi, Francesco Zulian and Giorgia Martini. University of Padua, Padua, Italy.

Background/Purpose: Juvenile Localized Scleroderma (JLS) is a chronic, autoimmune disease, characterized by skin and subcutaneous tissues fibrosis, which can cause a poor quality of life and psychosocial and behavioural problems in affected children particularly when severe deformities such as face asymmetry, joint contractures, and growth disturbances of limbs develop. To date, quality of life and psychological aspects in JLS have been poorly investigated. Purpose: to evaluate quality of life and psychosocial aspects of patients with JLS as compared with healthy peers and identify specific disease characteristics possibly related to quality of life impairment and psychosocial problems.

Methods: Two types of questionnaires (Pediatric Quality of Life Inventory 4.0™ Generic Core Scales and Child Behaviour Check List (CBCL) 6–18/Youth Self Report (YSR) 11–18) were administered to 40 consecutive patients with JLS aged 6 to 18 years and their parents. Patients' demographic and clinical data were collected during medical examination and through the review of clinical records. Same questionnaires were administered to a control group of 44 healthy children and their parents.

Results: In PedsQL™ (children forms) no difference was found between JLS group and control group. In PedsQL™ (parents forms) children with JLS showed poorer quality of life as compared to control group (76.8 vs 84.8, $p=0.017$), especially in emotional area (64.5 vs 79, $p=0.004$). In CBCL/6–18 mean scores were lower in activity scale (35.2 vs 41.1, $p=0,006$) and higher in internalizing problems scale (58 vs 53.2, $p=0.026$) and depression scale (59.9 vs 55.9, $p=0.038$) in JLS group compared to control group. In YSR/11–18 mean scores were lower in social competence scale (44.2 vs 49.7, $p=0.007$) and in total competence scale (40.9 vs 42.4, $p=0.028$) and higher in internalizing problems scale (54.7 vs 50.9, $p=0.031$) in JLS group compared to healthy controls. Disease relapses, longer delay in correct diagnosis, onset of disease in adolescence and shorter disease duration significantly correlated with lower quality of life and psychosocial and behavioural problems.

Conclusion: Our study shows that quality of life is poorer in children with JLS compared to healthy peers. Emotional area and social activities are the most affected ambits and patients show also depressive and internalizing problems. Among patients with JLS, a greater need for psychological support is mainly related to disease relapses, longer diagnostic delay, shorter disease duration and onset in adolescence or pre-adolescence ages. Disease severity in terms of lesion extension or deformities and therapy related issues do not seem related to impairment in the investigated areas.

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2606 SEE ABSTRACT #2917

2607

Evaluation Of The Construct Validity Of The Patient-Reported Outcomes Measurement Information System (PROMIS®) Gastrointestinal (GI) Symptoms Measures In Systemic Sclerosis (SSc). Dinesh Khanna[1], Puja Khanna[1], Brennan Spiegel[2], Lin Chang[3], Gil Y. Melmed[4], Roger Bolus[5] and Ron Hays[2]. [1]University of Michigan Medical Center, Ann Arbor, MI, [2]University of California, Los Angeles, Los Angeles, CA, [3]David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA, [4]Cedar-Sinai Medical Center, Los Angeles, CA, [5]Research Solutions Group, Encinitas, CA.

Background/Purpose: As part of the National Institutes of Health PROMIS¨ roadmap initiative, we developed GI Symptoms measures that assess 8 domains: Gastroesophageal reflux (13 items), disrupted swallowing (7 items), diarrhea (5 items), bowel incontinence/soilage (4 items), nausea and vomiting (4 items), constipation (9 items), belly pain (6 items), and gas/bloat/flatulence (12 items). All scales are calibrated using a two-parameter IRT graded response model and scored on a T-score metric with a mean of 50 and SD of 10 in the U.S. general population. This paper evaluates the construct validity of the GI measures in patients with SSc.

Methods: 165 patients with SSc were administered the PROMIS GI Symptoms measures and UCLA SCTC GIT 2.0 instrument. GIT 2.0 has 5 symptom scales: reflux, distention/ bloating, diarrhea, constipation, and fecal incontinence. Product-moment correlations of the PROMIS GI measures with the GIT 2.0 symptoms scales were used to evaluate construct validity. In a subset of patients (N=37), both instruments were administered at 2 time points. F-statistics was calculated from one-way ANOVAs to assess responsiveness to change

Results: Patients with SSc GI involvement had scale scores 0.2–0.7 SD worse than US population. Hypothesized correlations were larger than other scales and in the right direction (Table). F-statistics were greater for 6 of 8 PROMIS scales (range 0.45 for belly pain to 3.21 for reflux scale) vs. GIT 2.0 except for diarrhea scale (0.67 vs. 0.98 for GIT 2.0) and constipation scale (1.37 vs. 1.79 for GIT 2.0).

Table. Product-moment correlations between PROMIS GI Symptoms scales and UCLA SCTC GIT scales

	Reflux	Distention/ bloating	Diarrhea	Constipation	Fecal incontinence
Reflux	**0.77**	0.44	0.13	0.25	−0.03
Disrupted swallowing	**0.61**	0.39	0.16	0.21	0.13
Nausea and vomiting	**0.66**	0.44	0.20	0.22	0.18
Belly pain	0.45	0.49	0.23	0.34	0.04
Gas/bloat/flatulence	0.46	**0.73**	0.30	0.29	0.10
Diarrhea	0.25	0.25	**0.65**	0.02	0.54
Constipation	0.37	0.32	0.05	**0.76**	−0.01
Fecal incontinence	0.12	0.11	0.43	−0.18	**0.87**

GIT 2.0 Reflux scale asks about reflux, dysphagia to solid foods, and nausea/ vomiting.

Conclusion: PROMIS GI Symptoms scales are significantly correlated with the hypothesized GIT 2.0 scales and 6 of 8 scales showed greater responsiveness to change than the GIT 2.0.

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Coeliac Disease In Scleroderma - Clinical Features, Frequency and Impact Of Screening In Scleroderma. Alfredo Guillén-Del Castillo[1], Vincent Sobanski[2], Jennifer Harvey[2], Christopher Denton[3] and Voon H. Ong[4]. [1]Hospital Universitari Vall d'Hebron, Barcelona, Spain, [2]Royal Free Hospital, London, United Kingdom, [3]Royal Free and University College Medical School, London, United Kingdom, [4]The Royal Free and University College Medical School, London, United Kingdom.

Background/Purpose: Recent studies suggest that coeliac disease (CD) affects 4–7% of Scleroderma (SSc) patients. This association however has not been well characterized in a large cohort of patients. We evaluate the key clinical features, nutritional complications, and clinical response after gluten free diet in SSc patients with CD (SSc-CD), compared with a group of SSc patients with gastrointestinal (GI) symptoms and negative coeliac antibodies.

Methods: This is a retrospective study of well-characterised cohort of 1920 SSc patients from 2008 to 2013 with data collected through clinical database and patient records including all SSc patients diagnosed with CD by duodenal biopsy (n=12), and 96 of 236 SSc patients with GI symptoms (chronic diarrhoea, bloating, constipation, discomfort, dysphagia, heartburn and faecal incontinence) and negative coeliac antibodies. 4 patients in the SSc-CD group had confirmed positive coeliac antibodies. Key demographic and clinical features including small bowel symptoms (chronic diarrhoea, bloating, constipation and discomfort) were examined.

Results: The prevalence of CD with positive coeliac antibodies in our SSc cohort with GI symptoms was 4/236 (1.69%). 92.6% were female, with median (interquartile range, IQR) of age at SSc onset of 45.0 (33.0 – 55.7) years, and 49.3 (41.0 – 55.7) years at CD diagnosis. 18.5% patients had diffuse subset and 66.7% of the patients were Caucasians. 33 (30.6%) had an overlap with another systemic autoimmune disease (17 had polymyositis-dermatomyositis, 8 rheumatoid arthritis, 5 Sjögren's syndrome, 3 others). A higher frequency of psoriasis was identified in 25% of SSc-CD patients compared with 2.1% (p=0.009) in negative-coeliac antibodies patients. SSc-CD patients had increased frequency of myopathy (33.3% vs 10.4%, p=0.04), and anti-Pm/Scl antibody (25.0% vs 3.1%, p=0.01). 88% of entire cohort had small bowel symptoms with no statistical differences between the two groups. Chronic diarrhoea was the most common symptom in 62.0% of patients. Upper endoscopy was performed in all SSc-CD patients and in 41.7% with negative-coeliac antibodies, with no statistical differences in frequency of esophagitis, gastritis, gastric antral vascular ectasia or macroscopic duodenitis. There were no differences in the prevalence of bacterial overgrowth or requirement for enteral/parenteral nutrition. Among all patients 44.4% had vitamin D deficiency, 40.7% iron deficiency and 7.4% osteoporosis. After gluten-free diet all SSc-CD patients had an improvement of small bowel symptoms. 50% of these patients achieved complete remission and the symptoms recurred in the remaining half with median (IQR) 5.0 (2.5 – 8.25) years. There was significant improvement in chronic diarrhoea (75% to 41.7%, p=0.04), abdominal distension or bloating (50% to 16.7%, p=0.04), and in weight loss (33.3% to 0%, p=0.04).

Conclusion: The clinical presentation of CD may be indistinguishable to SSc-GI disease and our study indicates that CD in this subgroup of SSc patients with GI involvement is no more common than the general population. The positive response to gluten-free diet suggests that screening for CD in selected SSc patients may be helpful.

Disclosure: A. Guillén-Del Castillo, None; **V. Sobanski**, None; **J. Harvey**, None; **C. Denton**, None; **V. H. Ong**, None.

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Dutch Translation and Validation Of The University of California, Los Angeles scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument 2.0. Jessica Meijs, Daisy Pors, Theodora P.M. Vliet Vlieland, Tom W.J. Huizinga and Annemie J.M. Schuerwegh. Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Gastrointestinal tract (GIT) involvement occurs in approximately 90% of the patients with systemic sclerosis (SSc) and leads to a decrease in health-related quality of life. To identify and evaluate GIT involvement in patients with SSc, the University of California Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument 2.0 (UCLA GIT 2.0) was developed. The UCLA GIT 2.0 consists of 34 items on 7-multi-item subscales. The total score averages 6 of 7 scales (excluding constipation) and ranges from 0 (no GIT problems) to 3 (most severe GIT problems) [1]. The aim of our study was to translate the UCLA GIT 2.0 from English into Dutch and validate the Dutch version.

Methods: First, the UCLA-GIT 2.0 questionnaire was translated according to international guidelines [2]. Secondly, the questionnaire was field-tested among 17 SSc patients. Then, in order to test internal consistency and validity, the final Dutch version was administered to SSc patients participating in a standardized, annual comprehensive medical assessment, compromising visits to health care professionals, laboratory and cardiopulmonary investigations, the SSc Health Assessment Questionnaire (SHAQ) and Short Form-36 (SF-36). The internal consistency was tested by computing Cronbach's alpha. For convergent and construct validity, Pearson correlations were computed between the Dutch UCLA-GIT and the SF-36 and SHAQ. ($r \leq 0.29$ is considered a small correlation, r 0.30 –0.49 a moderate, and $r \geq 0.50$ a strong correlation). To determine the reliability, the instrument was re-administered with an interval of two weeks to 27 of the patients, and the intraclass-correlation coefficient (ICC) was computed.

Results: Ninety-two patients were included. Patients were on average 53.8 (SD 15) years, mostly women (76%), Caucasian (82%) and 53% of the patients had limited cutaneous SSc. The median total UCLA GIT 2.0 score was 0.18 and a floor effect was seen (17% scored 0). Cronbach's alpha was ≥0.73 for all scales, except diarrhea (alpha=0.42). The total GIT score was weakly or moderately associated with the SF-36 mental component summary scale ($r=-0.247$, $p<0.05$), the SF-36 physical component summary scale ($r=-0.348$, $p<0.01$) and the SHAQ score ($r=0.287$, $p<0.01$). Correlations between the GIT subscale scores and the SF-36 subscale scores were strong with respect to the corresponding emotional wellbeing and social functioning scale ($r=-0.515$, $p<0.01$). The test-retest reliability was acceptable (ICC: 0.788).

Conclusion: The Dutch UCLA GIT 2.0 questionnaire showed good internal consistency, reliability and an acceptable construct validity according to comparisons with SF-36 and SHAQ. The Dutch translation will now be further validated with objective measures of GIT involvement.

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2610

A New Pathogenic Role Of BAFF As a Critical Mediator Of Skin and Lung Fibrosis In Experimental Bleomycin-Induced Pulmonary Fibrosis, Systemic Sclerosis and Idiopathic Pulmonary Fibrosis.

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Background/Purpose: Interstitial pneumonitis and lung fibrosis are frequent systemic complications of inflammatory arthritides, including systemic sclerosis (SSc), rheumatoid arthritis, or primary Sjögren's syndrome. B lymphocytes are involved in the pathogenesis of such lung involvement. BAFF (B-cell activating factor of the TNF family) plays a crucial role in autoreactive B-cell activation and survival. We therefore investigated the pathogenic role of BAFF in fibrosis

Methods: Levels of BAFF were assessed using ELISA in serum of 150 patients with SSc and 80 healthy controls and in bronchoalveolar lavage of 12 patients with idiopathic pulmonary fibrosis (IPF) and 7 controls. Cocultures of B lymphocytes, stimulated or not with BAFF, and skin fibroblasts from patients with SSc and controls were performed. Lung fibrosis induced by bleomycin (BLM) was compared in BAFF−/− knock-out, BAFF-R-Ig treated mice and wild type (WT) mice. Lung BAFF expression was compared in BAFF IL-1R1−/−, IL-17A−/−, IL-17RA−/− mice after BLM challenge. Levels of IL-17 secreted by lung cells isolated from BLM-treated mice were analyzed after stimulation with anti-CD3 and BAFF

Results: Serum BAFF level was significantly increased in SSc patients compared to controls (median 1.5 vs. 0.5; $p< 0.0001$). Patients with SSc and increased BAFF levels had a significantly higher incidence of pulmonary fibrosis assessed by lung CT scan (63% vs. 37%; $p< 0.005$). A significant increase in BAFF bronchoalveoar levels was observed in patients with IPF, especially in those with clinical exacerbation, compared to controls. Coculture of B lymphocytes and skin fibroblasts induced collagen secretion, which was further enhanced after BAFF stimulation. In the BLM model of lung fibrosis, a marked increase of BAFF, mainly secreted by infiltrating neutrophils, was detected in the bronchoalveolar lavage and in lung extracts. Inhibition of BAFF using BAFF-R-Ig or gene depletion (BAFF−/− mice) resulted in a marked decrease of lung fibrosis, assessed by histology, and quantification of TGF-beta and collagen by qPCR and ELISA. Interestingly, levels of BAFF were significantly decreased in IL-1R1−/−, IL-17A−/− and IL-17 RA−/− mice, in which lung fibrosis was significantly reduced after BLM challenge, compared to WT mice. In vitro, recombinant BAFF induced a dramatic increase in IL-17 secretion by lung cells isolated after BLM challenge.

Conclusion: These results confirm the implication of B lymphocytes and sheds light to a new pathogenic role of BAFF in fibrosis according to consistent results in the bleomycin model, SSc and IPF. Taken together, these results suggest the following scenario: i) BAFF is induced by IL-1β and IL-17, which are potent pro-fibrogenic cytokines; ii)BAFF in turn induces IL-17 secretion by Th17 cells in an amplification loop. This study adds to the rationale of evaluating the therapeutic interest of BAFF inhibition in systemic sclerosis, inflammatory arthritis-related lung fibrosis and idiopathic pulmonary fibrosis.

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2611 WITHDRAWN

2612

Epidemiology Of Cancer In Systemic Sclerosis. Systematic Review and Meta-Analysis Of Cancer Incidence, Predictors and Mortality.

Tatiana Nevskaya[1], Shelly Chandran[2], Adrienne M. Roos[1], Christopher Pasarikovski[1], Amie T. Kron[1], Cathy Chau[3] and Sindhu R. Johnson[4]. [1]Toronto Scleroderma Research Program, Toronto Western Hospital, Mount Sinai Hospital, and University of Toronto, Toronto, ON, [2]Toronto Scleroderma Research Program, Toronto Western Hospital, University of Toronto, Toronto, ON, [3]Toronto Scleroderma Research Program, Toronto Western Hospital, Mount Sinai Hospital, University of Toronto, Toronto, ON, [4]Toronto Western Hospital, Toronto General Hospital, Mount Sinai Hospital, and University of Toronto, Toronto, ON.

Background/Purpose: To improve our understanding of the epidemiology of cancer in systemic sclerosis (SSc) by evaluating the incidence, prevalence, relative risk of overall and site-specific malignancies in comparison with the general population, and cancer-attributable mortality.

Methods: MEDLINE, CINAHL, EMBASE and Cochrane Library (inception-May 2012) were searched. Estimates were combined using a random effects model. Consistency was evaluated using the I^2statistic.

Results: 4,876 citations were searched to identify 59 articles. The average incidence of malignancy in SSc was 14 cases/1000 person-years; the prevalence ranged between 4%-22%. Cancer was the leading cause of non-SSc related deaths with a mean of 38%. Overall SIR for all-site malignancy risk was 1.85 (95% CI 1.52, 2.25; $I^2$76%).There was a greater risk of lung (SIR 4.69, 95% CI 2.84, 7.75; $I^2$93%) and haematological (SIR 2.58, CI 95% 1.75, 3.81; $I^2$0%) malignancies, including non-Hodgkin's lymphoma (SIR 2.55, 95% CI 1.40, 4.67; $I^2$0%). SSc patients were at a higher risk of leukemia (SIR 2.79, 95% CI 1.22, 6.37; I^2 0%), liver (SIR 4.75, 95%CI 3.09, 7.31; $I^2$0%), cervical (SIR 2.28, 95% CI 1.26, 4.09; $I^2$54%) and oropharyngeal (SIR 5.0, 95% CI 2.18, 11.47; $I^2$58%) cancers. Risk factors include a-RNAP I/III positivity, male sex, and late onset SSc. Smoking and longstanding interstitial lung disease (ILD) increase the risk of lung cancer; longstanding gastroesophageal reflux disease with Barrett's esophagus and a positive family history of breast cancer, respectively, increase the risk of esophageal adenocarcinoma and breast cancer.

Conclusion: SSc patients have a two-fold increase in malignancy, and greater risk of lung and haematological malignancies that contribute significantly to mortality. Vigilance should be considered in SSc patients with a-RNAP I/III antibodies, male sex, smokers, late disease onset, a positive family history of breast cancer, long duration of ILD, Barrett's esophagus.

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NF-κB Pathway Is Depleted In Phagocytes From Behçet's Disease Patients Secondarily To Constitutive Phosphorylation Of The p65 Subunit. Sandro F. Perazzio[1], Paulo Vitor Soeiro Pereira[2], Alexandre W.S. Souza[3], Antonio Condino-Neto[2] and Luis Eduardo C. Andrade[1]. [1]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil, [2]ICB IV - Universidade de São Paulo, São Paulo, Brazil, [3]University Medical Center Groningen, Groningen, Netherlands.

Background/Purpose: Increased neutrophil activation has been previously shown in Behçet's disease (BD) patients and it is unclear whether neutrophil activation occurs constitutively or if it is secondary to a yet unknown stimulus or some serum or tissue soluble factor. NF-kB seems to modulate the immune response in BD and has been associated to apoptosis-related factors leading to apoptosis resistance in T cell subsets. The present study investigated the NF-kB pathway and its activation induced by TLR.

Methods: Neutrophils and peripheral blood mononuclear cells (PBMC) were obtained from patients with active BD (aBD; n=30), inactive BD (iBD; n=31), septic patients (SP; n=25), and healthy controls (HC; n=30). BD activity was established as Behçet's Disease Current Activity Form simplified (BDCAFs) score≥2. The functional analysis of the NF-kB pathway was performed by: 1) determining CD62L shedding after stimulation with specific ligands for TLR-2, -3, -4, -5, -7, and with *Streptococcus pneumoniae, Streptococcus sanguinis*, and *Candida albicans*; 2) the intracellular expression of phosphorylated NF-kB-p65 before and after stimulation with PMA, TLR-3, TLR-7, plasma from HC, aBD or iBD; 3) the intracellular expression of STAT3 before and after stimulation with PMA, IL-10, or plasma from HC or aBD.

Results: BD patients homogeneously presented very low CD62L shedding with all forms of stimulus, in contrast to the large dispersion observed in the other groups. The percent increase in CD62L shedding was more evident after activation by TLR3 in iBD (31±28%: p=0.022) and aBD (27±20%; p=0.029) than in SP (3.4±25%). In contrast, the activation by TLR7 was lower in iBD (27±23%; p=0.022) and aBD (32±27%; p=0.029) than in SP (74±39%). Neutrophils from aDB presented higher expression of phosphorylated NF-kB-p65 before stimuli (mean of intensity of fluorescence [MFI]=123.54±47.63 versus HC=69.43±39.29, p=0.050) and after PMA (MFI=194.10±97.18 versus HC=92.24±42.34, p=0.030) and TLR7 (MFI=135.76±45.92 versus HC=77.51±42.34, p=0.050). Monocytes from aDB also presented higher expression of phosphorylated NF-kB-p65 before stimuli (MFI=313.40±110.81 versus HC=135.98±87.61, p=0.018) and after PMA (MFI=372.80±145.01 versus HC=175.51±98.35, p=0.030) and TLR3 (MFI=320.40±117.39 versus HC=162.15±74.47, p=0.030). Phosphorylated NF-kB-p65 expression and CD62L shedding after human plasma and microbial stimuli, respectively, was equivalent for phagocytes from aBD, iBD, and HC. STAT3 expression in neutrophils and monocytes showed no difference among the aBD, iBD, and HC. There was no difference in medication use between aBD and iBD.

Conclusion: We originally showed that the NF-kB pathway of phagocytes is constitutively activated in BD patients and that there is additional increment after TLR stimuli. The low CD62L shedding of BD phagocytes may be due to exhaustion of the NF-kB pathway. These findings may underlie the characteristic hyperactivity of neutrophils in BD, represented by activation of the final pathway for several stimuli, like cytokines, chemoattractants and microorganisms, potentially involved in the pathophysiology of this disease.

Disclosure: S. F. Perazzio, None; **P. V. S. Pereira**, None; **A. W. S. Souza**, None; **A. Condino-Neto**, None; **L. E. C. Andrade**, None.

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Plasma Of Active Behçet's Disease Increases Oxidative Metabolism Profile Of Normal and Patients Phagocytes. Sandro F. Perazzio[1], Paulo Vitor Soeiro Pereira[2], Alexandre W.S. Souza[3], Antonio Condino-Neto[2] and Luis Eduardo C. Andrade[1]. [1]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil, [2]ICB IV - Universidade de São Paulo, São Paulo, Brazil, [3]University Medical Center Groningen, Groningen, Netherlands.

Background/Purpose: Behçet's disease (BD) exhibits several features suggestive of neutrophil hiperactivity. It is unclear whether neutrophil activation occurs constitutively or if it is secondary to yet unknown stimuli. Previous studies suggested a possible role for infectious agents and for unknown plasma factors in BD pathogenesis. The present study investigated the oxidative burst in phagocytes of patients with active BD (aBD) and inactive BD (iBD) in the presence of diverse stimuli.

Methods: Neutrophils and peripheral blood mononuclear cells (PBMC) were obtained from patients with aBD (n=30), iBD (n=31), septic patients (SP; n=25), and healthy controls (HC; n=30). BD activity was established as Behçet's Disease Current Activity Form Simplified (BDCAFs) score≥2. Oxidative burst was assessed by dihidrorhodamine (DHR) oxidation before and after stimulation with phorbol myristate acetate (PMA) or human plasma (from HC or aBD). H_2O_2 and O_2^- production was determined in neutrophils and PBMC by luminol/lucigenin luminescence intensity with or without stimulation with PMA, *Streptococcus pneumoniae, Streptococcus sanguinis*, *Candida albicans* or human plasma.

Results: There was no significant difference in medication use between aBD and iBD patients. Resting phagocytes from the four groups presented equivalent oxidative burst (DHR assay and H_2O_2/O_2^- production). However, aBD neutrophils produced more O_2^- when exposed to aBD plasma (median/range=96,297/19,202–298,941) compared to HC plasma (48,831/4,001–105,848; p=0.028) or non-stimulated (5,721/551–23,838; p<0.01). HC neutrophils also produced more O_2^- when stimulated by aBD plasma (93,452/12,242–226,932) versus HC plasma (36,225/8,432–79,461; p=0.028) versus non-stimulated (3,387/1,870–13,935, p<0.01). aBD neutrophils also produced more H_2O_2 when exposed to aBD plasma (404,045/24,825-1,408,347) compared to HC plasma (338,238/5,042–745,653; p=0.02) or non-stimulated (9,300/2,706–27,193; p<0.01). The same occurred with neutrophils from HC: aBD plasma (355,079/51,354–513,977); non-stimulated (15,092/4,959-47,814; p<0.01). PBMC from aBD produced more O_2^- when exposed to aBD plasma (39,208/9,656-315,306) compared to HC plasma (10,135/3,394-41,873; p=0.046) or non-stimulated (10,052/3,262-37,352; p=0.028). The same occurred with HC PBMC: 24,531/4,931–73,813; 3,661/1,697-28,992 (p=0.03); 1,994/928-5,532, respectively (p=0.02). Finally, H_2O_2 production in aBD PBMC was enhanced by aBD plasma (55,223/17,186–253,194) versus HC plasma (35,193/2,081–331,239; p=0.05) versus non-stimulated (18,690/2,340–78,728; p=0.046). The same was observed with HC PBMC: aBD plasma (10,357/4,024–75,036); HC plasma (2,502/975-7,810, p=0.028). H_2O_2 and O_2^- production after microbial stimuli was equivalent for phagocytes from aBD, iBD, and HC.

Conclusion: Phagocytes from BD patients were not constitutively activated and responded normally to microbial and PMA stimuli. Plasma from patients with active BD exerted a strong stimulus for H_2O_2 and O_2^- production. These findings warrant further studies in order to identify possible metabolic pathways involved in neutrophil activation in BD.

Disclosure: S. F. Perazzio, None; **P. V. S. Pereira**, None; **A. W. S. Souza**, None; **A. Condino-Neto**, None; **L. E. C. Andrade**, None.

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Serum Beta 2 Microglobulin and Its Association With Disease Activity in Patients With Behcet's Disease. Meltem Alkan Melikoglu[1] and Mehmet Melikoglu[2]. [1]Ataturk University Medical School, Rheumatology, Erzurum, Turkey, [2]Health Ministry Erzurum Regional Training and Research Hospital, Dermatology, Erzurum, Turkey.

Background/Purpose: β2-microglobulin (β2M) is a low-molecular weight protein, that is a constant component of human leukocyte antigen (HLA), which is secreted from all nucleated cells. Serum β2M levels increase in lymphoproliferative and autoimmune diseases related to the activities of B lymphocytes (1). The number of B cells secreting immunoglobulins increased in the active phase of Behçet's disease (2). The aim of this study was to evaluate a possible relation between B2M and Behcet's Disease (BD) clinical disease activity.

Methods: Seventy eight patients with BD were included in our study. Disease activity was evaluated with "BD Current Activity Form" (BDCAF) which offers an easy-to-complete, valid and reliable method of

assessing disease activity in BD. With this activity form, headache, mouth ulceration, genital ulceration, erythema, skin pustules, arthralgia, arthritis, new involvements in gastrointestinal system (GIS), eye, nervous system, major vessels and patient'-physician's assessments of the overall disease activity scores were analyzed. The levels of serum B2M of the patients were also measured. The independent samples t test and Pearson's correlation test were used to analyze the data.

Results: In the comparison of serum B2M levels of the patients with or without the components of BDCAF, no significant relation could be found between headache, mouth ulceration, genital ulceration, erythema nodosum, superficial thrombophlebitis, skin pustules, arthralgia, arthritis, new involvements in gastrointestinal system (GIS), nervous system, major vessels and patient'-physician's overall perception of disease activity. However, we found significantly higher levels of B2M in patients with uveitis than without eye involvement (p=0,032). Although each component of BDCAF did not show an association with B2M levels except from eye involvement, total BDCAF score was also found to be correlated with B2M levels (p□0,05).

Conclusion: Presence of a new developed eye involvement may be associated with higher levels B2M. Correlation between total disease activity score and B2M levels may contribute the overall disease activity perception in BD.

Disclosure: M. A. Melikoglu, None; **M. Melikoglu**, None.

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Ischemia-Modified Albumin: A Novel Marker of Vascular Involvement in Behcet's Disease? Erhan Capkin[1], Murat Karkucak[2], Mehmet Kola[3], Adem Karaca[2], süleyman Caner Karahan[4], Aysegul Sumer[4], Arzu Aydin Capkin[5], Ferhat Gokmen[2] and Refik Ali Sari[6]. [1]Rheumatolgy, Trabzon, Turkey, [2]Rheumatology, Trabzon, Turkey, [3]Oftalmology, Trabzon, Turkey, [4]BioChemistry, Trabzon, Turkey, [5]Dermatology, Trabzon, Turkey, [6]Immunology and Allergy, Trabzon, Turkey.

Background/Purpose: The etiology and pathogenesis of Behçet's disease (BD) are not yet well understood, but immunoregulatory abnormalities have been proposed as pathogenic mechanisms. Ischemia-modified albumin (IMA) is increased in diseases associated with oxidative stress, which plays an important role in the development of Behçet's disease. To investigate oxidative status and IMA levels in patients with Behçet's disease and their association with clinical and laboratory parameters

Methods: Thirty-five patients with Behçet's disease and 31 healthy controls matched for age and gender were enrolled. Patients' clinical and demographic characteristics were recorded. Serum IMA, malondialdehyde (MDA), total antioxidative status (TAS), total oxidative status (TOS) and oxidative stress index (OSI) levels were then evaluated.

Results: Serum IMA, MDA, TOS and OSI levels were significantly higher in patients with Behçet's disease than in the healthy control group. Serum TAS was significantly lower in patients with Behçet's disease than in the healthy controls. There was a statistically significant positive correlation between IMA levels and MDA, TOS, erythrocyte sedimentation rate and C-reactive protein levels. IMA levels were statistically significantly higher in patients with vascular involvement (p=0.016).

Conclusion: Our results demonstrate increased oxidative stress and decreased antioxidant capacity in patients with Behçet's disease. IMA levels were higher in patients with Behçet's disease than in healthy controls. IMA may be produced through an adaptive response to chronic hypoxia and oxidative stress, which may play a role in the systemic inflammation seen in Behçet's disease. IMA can be a useful guiding marker, particularly in patients with vascular involvement.

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Clinical Features Of 127 Patients With Behcet's Disease In Japan. Keisuke Nishimura[1], Jun Saegusa[1], Sho Sendo[1], Yoshinori Kogata[1], Goichi Kageyama[1], Seiji Kawano[1], Shunichi Kumagai[2] and Akio Morinobu[1]. [1]Kobe University Graduate School of Medicine, Kobe, Japan, [2]Shinko hospital, Kobe, Japan.

Background/Purpose: Behcet's disease (BD) is characterized by recurrent oral aphthae and any of several systemic manifestations including genital ulcer, ocular disease, skin lesions, gastrointestinal involvement, neurologic disease, vascular disease, or arthritis. BD is more common along the ancient silk road, including Japan. We present the disease profile of Japanese BD patients at Kobe University Hospital.

Methods: We retrospectively investigated the clinical features of 127 patients (63 males and 64 females) who fulfilled the International Criteria for Behcet's Disease (ICBD) and were treated in our hospital from April 2008 to May 2013. We assessed sex, age of onset, symptoms, complications, type of HLA and medications.

Results: Median age at diagnosis was 37.6 ±12.7 years old. Oral ulcers were the most common manifestation (97.6%), followed by genital ulcer (52.0%), ocular involvements (52.0%), papulopustular lesion (45.7%), erythema nodosum (43.3%), gastrointestinal manifestations (22.0%), vascular involvements (11.0%), and neurogenic diseases (5.5%). Ocular involvements were found to be significantly more frequent in males (male 63.5%, female 40.6%, $P=0.01$). The frequency of gastrointestinal manifestations was significantly higher in patients with vascular involvements ($P=0.007$), while patients with gastrointestinal manifestations showed a lower association rate with ocular involvements ($P=0.001$). Of the 127 BD patients, 2 patients were associated with spondyloarthropathy, one patient with giant cell arteritis and one with systemic sclerosis. The relationship of HLA and disease manifestations was studied in 54 patients (32.7% with HLA-B51 and 23.1% with HLA-A26). Ocular manifestations were significantly higher in patients with B51 than those without B51 ($P=0.03$). Colchicine was most commonly used for the treatment of BD (49.6%). TNFα inhibitor, infliximab, was used for patients with refractory ocular manifestations (n=21) and gastrointestinal manifestations (n=8). Only 3 patients had to be discontinued because of ineffectiveness or adverse events. The cumulative proportion of patients continuing infliximab therapy at 1 and 2 years was 95.8% and 84.3%, respectively. Pneumonia was the only severe adverse event.

Conclusion: A higher incidence of gastrointestinal manifestations was observed in Japanese patients with BD in our hospital. The frequency of gastrointestinal manifestations was significantly higher in patients with vascular involvements. Of the 127 BD patients, 25 patients (19.7%) were treated with infliximab, and the long-term infliximab treatment persistence rate was high.

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Bipolar Disorders May Represent a Primary Feature Of Behçet's Disease. Rosaria Talarico[1], Laura Palagini[2], Elena Elefante[1], Claudia Ferrari[1], Chiara Stagnaro[1], Chiara Baldini[1], Chiari Tani[1], Marta Mosca[3] and Stefano Bombardieri[1]. [1]Rheumatology Unit, Pisa, Italy, [2]Psychiatry Unit, Department of Neuroscience, Pisa, Italy, [3]Rheumatology Unit, University of Pisa, Pisa, Italy.

Background/Purpose: Frequency of psychiatric disorders in BD is a debated issue: while some experts attribute their presence to the chronicity of the illness, others think that they may be imputable to disease activity or to intrinsic features of the disease. The primary aims were to determine the frequency of psychiatric disorders in BD patients, both with neurological involvement or without; the secondary aims were: to investigate a possible association between disease activity/organ involvement and psychiatric profile of the BD patients and to compare the distribution of psychiatric disorders of patients with BD with those in patients with other chronic diseases.

Methods: One hundred and twenty BD patients with a diagnosis of BD according the ISG criteria were studied. Demographic profile of the cohort studied are summarized in Table 1. Psychiatric disorders evaluated were: bipolar disorder, obsessive-compulsive disorder, depression and sleep disorder. Age and sex matched disease controls of systemic lupus erythematosus (SLE) and chronic arterial hypertension were included. BD disease activity was evaluated by means of BD current activity form 2006 and clinician's overall perception of disease activity.

Results: Prevalence of psychiatric disorders are shown in Table 2. No correlations were found between the presence of psychiatric disorders and

disease activity; specifically either BD patients with an activity index ≤ 7 and ≥ 8 were equally characterized by a high prevalence of psychiatric disorders. Moreover, the occurrence of psychiatric disorders did not result correlating with a specific organ involvement. Comparing the frequency of bipolar disorder with the disease controls, the results have shown a significant difference in favor of bipolar disorder in BD ($p < 0.001$).

Table 1. Demographic profile.

	Neuro- BD	BD without neurological involvement
Number of patients	46	64
M/F	38/8	42/22
Mean age ± SD (min-max) (years)	43 ± 7 (15–68)	42 ± 8 (18–71)
Mean disease duration ± SD (min-max) (years)	9 ± 2 (3–28)	10 ± 2 (4–28)

Table 2. Prevalence of psychiatric disorders

psychiatric disorders	Neuro- BD n (%)	BD without neurological involvement n (%)
bipolar disorder	41 *(65)*	28 *(64)*
obsessive-compulsive disorder	29 *(46)*	20 *(43)*
depression	20 *(32)*	16 *(36)*
sleep disorder	5 *(11)*	10 *(16)*

Conclusion: Our results show a high frequency of psychiatric disorders in BD patients. This elevated prevalence both in BD patient with or without neurological involvement, independently from disease activity and significantly than in disease controls, strongly suggest that psychiatric disorders may represent a primary feature of BD.

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Suicidal Ideation Among Patients With Behcet's Syndrome. Didem Uzunaslan, Caner Saygin, Gulen Hatemi, Koray Tascilar, Hasan Yazici and Vedat Hamuryudan. Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey.

Background/Purpose: An increased frequency of depression has been reported in Behcet's syndrome (BS). While an increased suicidal ideation has been reported in other chronic rheumatologic conditions, this has not been studied in patients with BS. We aimed to evaluate the frequency of suicidal ideation among BS patients and to delineate the factors predicting an increase in suicidal ideation.

Methods: The frequency of suicidal ideation was evaluated with a standard questionnaire that was previously used (2), among BS patients with and without major organ involvement, and ankylosing spondylitis (AS) patients who attended our outpatient clinic for their routine visits and a group of healthy controls. We questioned whether the subjects 1) thought that life was not worth living, 2) thought about ending their lives within the previous year, 3) ever planned to end their lives and if yes, whether they had planned to end their lives before the onset of their disease. In addition, Beck depression inventory (BDI) and Behcet's disease quality of life (BDQoL) questionnaires were filled. Disease activity was assessed using the Behcet's disease current activity form (BDCAF) for BS patients and BASDAI and BASFI for AS patients.

Results: We surveyed 240 BS patients who had only mucocutaneous symptoms, 63 BS patients with active major organ involvement (30 eye, 31 vascular, 7 neurologic involvement), 50 patients with AS, and 106 healthy controls (Table). Number of subjects who answered affirmatively to the second and third questions were significantly higher among BS patients with active major organ involvement compared to the other groups ($p<0.001$ and $p=0.002$). Among BS patients with active major organ involvement, 9/27 with eye, ¼ with neurologic, 3/27 with vascular, and 3/5 with more than one type of major involvement had thought of ending their lives. 9/27 with eye, 2/4 with neurologic, 3/27 with vascular and 2/5 with more than one type of major involvement had planned to end their lives. BS patients with eye involvement had the highest frequency of answering positively to these 2 questions ($p<0.001$ for each). None of the drugs that were used seemed to be associated with suicidal ideation. For each of the questions regarding suicidal ideation, the BDCAF, BDQoL and BDI scores of BS patients were higher among those who answered positively. Regardless of suicidal ideation, the BDI scores of BS patients with active major organ involvement were higher than AS patients and healthy controls.

	BS major organ (n=63)	BS mucocutaneous (n=240)	AS (n=50)	Healthy controls (n=106)	p
M:F	36/27	83/157	14/36	77/29	< 0.001
Mean age ± SD	36 ± 12	38.2 ± 11	37.9 ± 10.3	36 ± 10.1	0.218
Thought about ending their lives	16/63 (25.4%)	21/240 (8.8%)	4/50 (8%)	7/ 106 (6.6%)	< 0.001
Ever planned to end their lives	16/63 (25.4%)	22/240 (9.2%)	4/50 (8%)	9/ 106 (8.5%)	0.002
Beck depression inventory scores	16.9 ± 11.4	10.9 ± 9	10.8 ± 10.1	9 ± 7.7	< 0.001

Conclusion: The frequency of suicidal ideation is increased among BS patients who have major organ involvement. This increase in suicidal ideation is correlated with higher disease activity and increased depression scores. Longitudinal studies are required for determining whether the frequency of suicidal ideation decreases with treatment and improvement in disease activity.

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Development Of De Novo Major Involvement During The Follow-Up In Behçet's Disease. Claudia Ferrari[1], Rosaria Talarico[1], Chiara Stagnaro[1], Anna d'Ascanio[1], Chiara Tani[1], Chiara Baldini[1], Marta Mosca[2] and Stefano Bombardieri[1]. [1]Rheumatology Unit, Pisa, Italy, [2]Rheumatology Unit, University of Pisa, Pisa, Italy.

Background/Purpose: Behçet's disease (BD) is globally characterized by a variable spectrum of disease profile: while prevalent mucocutaneous lesions and arthritis represent the only clinical features in patients with a benign disease subset, there are other patients who develop potentially sight or life-threatening manifestations, due to ocular, neurological or major vascular involvement. The primary aim of the study was to evaluate the incidence of the novo major involvement during the follow-up in a cohort of patients with BD; the secondary aim was to analyze the epidemiological profile and the long-term outcome of those patients who developed de novo major involvement.

Methods: One hundred and twenty patients were evaluated. The male/female ratio was 1.6:1, with a mean disease duration of 11±5 years. Their mean age was 42±9 years (min:18, max:77), while the mean age at disease onset was 25±4 years (min:10, max:58). The mean ± SD duration of follow-up at our centre was 8±2 (min:2, max:12) years. We have defined the development of de novo major involvement during the follow-up as the occurrence of severe ocular (anterior uveitis, posterior uveitis, retinal vasculitis), vascular (deep vein thrombosis, superficial vein thrombosis, arterial thrombosis, arterial aneurysm) or CNS (ischaemic pons-mesencephalon lesions and meningoencephalitis) involvement after a latency period from the diagnosis of at least 3 years

Results: At the time of diagnosis, the 52% of the cohort (n=62) presented a prevalent muco-cutaneous involvement. Among this sub group of patients, we observed that after at least 3 years from the diagnosis, 21 patients (34%) was characterized by the occurrence of de novo major involvement (i.e. ocular: 3; CNS: 9; vascular: 9). The demographic profile of this subgroup (male: 19, female: 2) was characterized by a mean age of 33±4 years (min 24-max 40) and a young age at disease onset. The long term outcome after a mean follow-up of 8 years has shown that the majority of these subjects presented during the disease course also relapsing attacks. Moreover, they were characterized by a bigger number of DMARDs (both traditional and anti TNF-alpha) compared to the other part of the cohort

Conclusion: As awaited, younger age and male sex represent predictive factors of poor long-term clinical outcome. We have found that ocular disease seems the organ involvement that more frequently has an onset before the first years of disease. Globally, he development of the novo major involvement during the course of BD represents an entity that may

confirm that a tight control is strongly recommended during the course of BD.

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Venous Claudication Is A Severe and Frequent Symptom In BEHCET'S Syndrome. SerdaL Ugurlu[1], Emire Seyahi[1], Veysel Oktay[2], Zerrin Yigit[2], Serdar Kucukoglu[2] and Hasan Yazici[1]. [1]Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [2]Cardiology Institute, University of Istanbul, Istanbul, Turkey.

Background/Purpose: In a previous cross-sectional questionnaire survey, we had shown that intermittent claudication was significantly more common among BS patients when compared to healthy controls, and had proposed that this was a "venous claudication" (1) rather than due to atherosclerotic vascular disease since a. a history of myocardial infarction or angina pectoris were not increased in frequency in the same group of patients as compared to age and sex matched healthy controls; and b. this intermittent claudication was specifically more common among males with venous thrombosis. The so called venous claudication is thought to be an exercise induced pain resulting from venous outflow impairment (1). With this study we aimed to 1. To reassess the frequency of venous claudication by a questionnaire survey and 2. To further study this venous claudication prospectively by a formal treadmill exercise in BS patients with and without venous thrombosis along with healthy controls.

Methods: We studied 59 BS patients with lower extremity venous thrombosis (LEVT), 42 BS patients without venous disease and 55 healthy controls. All patients and controls were male. Patients and controls with peripheral arterial disease were excluded. Intermittent claudication was assessed initially by Rose questionnaire. After this, patients were asked to walk in the treadmill at a set speed of 3.5 km/h and 10% inclination for 10 minutes. Patients who first experienced persistent symptoms consistent with venous claudication but still able to walk and those who had to give up the treadmill were noted. Pre and post-exercise ankle brachial pressure indices (ABPIs) were also measured.

Results: The mean ages of the patients and controls were similar (Table). Pre and post-exercise ABPIs did not differ between patients and controls. There were significantly more patients who described claudication in the questionnaire among those with LEVT (31 %) compared to those with no venous disease (5 %) and healthy controls (0 %) ($P<0.001$) (Table). Similarly, the number of patients who experienced claudication but still continued to walk on the treadmill were significantly more among those with LEVT. Finally, only those with LEVT had to stop the treadmill challenge due to claudication. Pre and post exercise ABPI's were similar among BS patients with LEVT. There was no relation between the presence of vena cava, iliac or femoral vein involvement and the presence of claudication or limitation of walking capacity.

Table. Severity and frequency of claudication

	BS patients with venous thrombosis n = 59	BS patients without thrombosis n = 42	Healthy controls n = 55	p
Age, mean ± SD, years	37 ± 7	34 ± 7	36 ± 9	0.346
Claudication as assessed by questionnaire, n (%)	18 (31)	2 (5)	0	< 0.001
Leg pain during the treadmill exercise (the patient continues to walk) n (%)	10 (17)	3 (7)	1 (2)	0.016
Claudication necessating the termination of the treadmill exercise, n (%)	6 (10)	0	0	0.006

Conclusion: Venous claudication seems to be a severe and frequent symptom being present in up to 1/3 of BS patients with major vein involvement. It clearly limits the walking capacity in 10 % of these patients even when tested in a treadmill set at low pace.

References:

1) Ugurlu S, et al.. Rheumatology (Oxford). 2008;47:472–5.

Disclosure: S. Ugurlu, None; **E. Seyahi**, None; **V. Oktay**, None; **Z. Yigit**, None; **S. Kucukoglu**, None; **H. Yazici**, None.

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Comparison Of Different Methods Of Skin Pathergy Test In Patients With Behçet's Syndrome. Aysegul Lacin, Cigdem Atan Uzun, Zafer Gunendi and Feride Gogus. Gazi University Faculty of Medicine, Ankara, Turkey.

Background/Purpose: Skin pathergy test (SPT) has a diagnostic value in Behçet's syndrome (BS). There are different descriptions of the test which may effect its positivity rate. We aimed to compare different methods of SPT in patients with Behçet's syndrome.

Methods: Patients with BS who fulfilled the International Study Group Criteria for Behçet's Disease and healthy volunteers were involved in the study. At 90% power (alpha= 0.5) for a 47% positivity rate for the oral method 20 patients and healthy volunteers were recruited (1). Pricks at five different sites were performed with a 20 gauge needle. i)subcutaneous ii) intradermal iii) intradermal with 0.1 cc of 0.09% saline solution iv) intravascular v) oral. The skin pathergy test was considered positive if there was a papule, pustule or oral aphtae (for the oral test) at the prick site after 48 hours. Sensitivity, specificity, positive and negative predictive values of SPT were calculated.

Results: All patients with Behçet's syndrome were positive for at least one SPT method where none of the healthy volunteers had a positive SPT. Among the five SPT methods subcutaneous and oral methods were most sensitive (70% and 60% respectively). All SPT methods showed 100% specificity and positive predictive value. Sensitivity and negative predictive values of SPTs are shown in Table 1.

Table 1. Sensitivity and negative predictive value of skin pathergy test methods

Skin Pathergy Methods	Sensitivity	Negative predictive value
Subcutaneous	%70	%77
Oral	%60	%71
Intradermal	%50	%67
Intradermal with saline	%50	%67
Intravascular	%20	%55

Conclusion: Subcutaneous method is the most sensitive test among SPTs. Oral method may be an alternative for subcutaneous SPT.

Reference:

1. Sharquie KE, Al-Araji A, Hatem A.Oral pathergy test in Behçet's disease Br J Dermatol. 2002 Jan;146(1):168–9

Disclosure: A. Lacin, None; **C. A. Uzun**, None; **Z. Gunendi**, None; **F. Gogus**, None.

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A CT Evaluation Of Pulmonary and Cardiac Lesions In BEHÇET'S Syndrome Patients Without Pulmonary Symptoms. Emire Seyahi[1], Deniz Cebi Olgun[1], SerdaL Ugurlu[1], Idil Hanci[2], Reona Takahashi[1] and Hasan Yazici[1]. [1]Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [2]Krankrenhaus Nordwest, Frankfurt am Main, Frankfurt, Germany.

Background/Purpose: In Behçet's syndrome (BS) patients with symptomatic pulmonary artery involvement (PAI) varying and multiple pulmonary parenchymal and cardiac lesions can be seen in thorax CT examinations (1). These lesions are pulmonary nodules of ≥ 1 cm (85 %), cavities (47 %), ground-glass opacities (45 %), mild pleural (45 %) and pericardial effusions (21 %), mediastinal lymphadenopathies (21 %) and intracardiac filling defects (28 %). Whether these pulmonary and cardiac abnormalities are exclusively observed in symptomatic BS with PAI or in vascular involvement without PAI have not been adequately studied. We now report the frequency of such lesions among BS patients with vascular disease but no PAI along with BS patients with no vascular disease at all.

Methods: Consecutive BS patients seen in the outpatient clinic between December 2011 and November 2012 were studied. Those with a disease duration of > 5 years were excluded. Contrasted thorax CT scans were obtained in BS patients with vascular disease along with BS patients with no vascular disease at all. Only patients with no prior history relevant with PAI or those with no pulmonary symptoms such as hemoptysis,

cough, chest pain and dyspnea were studied. CT scans were analyzed formally using a checklist by a radiologist who was blinded to the clinical diagnoses of the patients.

Results: We studied 49 (43 M/ 6 F) BS patients with vascular involvement and 35 (32 M/3 F) BS patients with no vascular involvement. Lower extremity deep or superficial vein thrombosis was present in all 49 patients with vascular involvement. The mean age (32 ± 7 years vs 33 ± 8 year, respectively) and disease duration (4 ± 3 years vs 3 ± 2 years, respectively) among patients with and without vascular involvement were similar. None of the patients had pulmonary artery aneurysms or thrombosis. Similarly, cavities, pleural or pericardial effusions, and intracardiac filling defects were not observed in any of the scans. The most common parenchymal lesions were nodules of < 1 cm, which were present in 61 % and 37 % patients with and without vascular involvement, respectively, (P = 0.029). Nodules of ≥ 1 cm were only present in 4 patients with vascular disease (8 %) and none of those with no vascular disease. Ground-glass opacities were present in 2 and 3 patients with and without vascular involvement, respectively. The frequency of pulmonary and cardiac lesions in the current study was much less when compared to that found in PAI.

Conclusion: Pulmonary parenchymal and cardiac lesions were rarely observed in BS patients with no pulmonary artery involvement. Although small pulmonary nodules (<1 cm) seemed to be more frequent among patients with vascular disease compared to those without, their significance remains to be further studied.

References:

1) Seyahi E et al. Pulmonary artery involvement and associated lung disease in Behçet disease: a series of 47 patients. Medicine (Baltimore). 2012;91:35–48.

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Evaluation of Asymptomatic Venous Disease By Venous Doppler Ultrasonography in Patients With Behcet's Disease. Fatma Alibaz-Oner, Emrah Karatay, Ihsan Nuri Akpinar, Tülin Ergun and Haner Direskeneli. Marmara University, School of Medicine, Istanbul, Turkey.

Background/Purpose: One of the major causes of mortality and morbidity in Behcet's disease (BD), especially in young males of Mediterranean origin, is vascular involvement. A limited data suggests also a high prevelance of venous insufficiency (VI) and some cases of asymptomatic thrombosis in BD. In this study, we aimed to investigate prospectively asymptomatic venous disease by venous doppler ultrasonography (US) in patients with BD without known vascular disease.

Methods: The study included 93 patients with BD (M/F: 45/48, age: 36.4±10 years), 97 patients with ankylosing spondylitis (AS)(M/F: 50/47, age: 37.5±9.5 years) and 43 healthy control subjects (M/F: 25/18, age: 34.7±4.5 years). Vessels of both upper and lower extremities were examined while the subjects were in supine position by venous doppler US. CEAP severity score was used to evaluate the severity of the venous insufficiency.

Results: Upper extremity veins were totally normal in all patients and controls. We also did not detect any "silent thrombosis" in study groups. Venous insufficiency findings in lower extremity were detected in 32.2% (n=30) in the BD group, 28.8% (n=28) in AS group and 9.3% (n=4) in the healthy control group. Both BD and AS patients had significantly higher VI rates than healthy controls (p=0.007 and 0.015). The rate of VI was similar between patients with BD and AS (p=0.64). Similarly, CEAP severity score in BD (0.34 (0–3)) was significantly higher than controls (0)(p=0.008), but similar to AS (0.18 (0–39)(p=0.18). No correlations were present between C-reactive protein elevations (>5 mg/L) and VI in patients with both BD (p=0.546) and AS (p=0.754).

Conclusion: A high prevelance of venous insufficiency was present in both BD and AS patients without asymptomatic thrombosis. Presence of VI also in AS, a disease without a major tendency to venous thrombosis, suggests that chronic inflammation might cause a mild insufficiency detected only by Power US in venous vessels. Long-term consequences of this finding requires further follow-up studies.

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Biologic Therapy In Refractory Uveitis Of Behcet's Syndrome: Switching and Dose Modification. Multicenter Study Of 124 Patients. F. Ortiz-Sanjuán[1], Vanesa Calvo-Río[1], Ricardo Blanco[2], Emma Beltrán[3], Juan Sánchez-Bursón[4], Marina Mesquida[5], Alfredo M. Adan[5], M Hernandez Grafella[3], E Valls Pascual[6], L Martínez-Costa[6], A Sellas-Fernàndez[7], Miguel Cordero-Coma[8], Manuel Diaz-llopis[9], David Salom[9], Jl García Serrano[10], Norberto Ortego[10], JM Herreras[11], Alejandro Fonollosa[12], A Aparicio[13], O Maíz[14], A Blanco[14], I Torre[15], Cruz Fernández-Espartero[16], V Jovani[17], D Peitado-Lopez[18], Esperanza Pato[19], J Cruz[20], J. Carlos Fernandez-Cid[20], Elena Aurrecoechea[21], M García[22], M Caracuel[23], Carlos Montilla[24], A Atanes[25], F Francisco[26], S Insua[27], S González-Suárez[28], A Sánchez-Andrade[29], F Gamero[30], Luis Linares[31], F Romero-Bueno[32], J García[33], AJ García González[33], Raquel Almodovar[34], E Minguez[35], C Carrasco Cubero[36], Alejandro Olivé Marqués[37], J Vázquez[38], O Ruiz Moreno[39], F Jimenez-Zorzo[39], J Manero[39], Javier Loricera[1] and Miguel Angel González-Gay[1]. [1]Hospital Universitario Marqués de Valdecilla. IFIMAV. Santander. Spain, Santander, Spain, [2]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain, [3]Hospital General Universitario, Valencia, Valencia, Spain, [4]Hospital de Valme. Sevilla, Sevilla, Spain, [5]Hospital Clínic of Barcelona, Barcelona, Spain, [6]Hospital Peset Valencia, Valencia, Spain, [7]Hospital Val d'Hebron. Barcelona, Barcelona, Spain, [8]Hospital de León, León, Spain, [9]Hospital Universitario La Fe de Valencia, Valencia, Spain, [10]Hospital San Cecilio. Granada, Granada, Spain, [11]Hospital Universitario, IOBA. Valladolid, Valladolid, Spain, [12]Hospital de Cruces. Bilbao, Baracaldo, Spain, [13]Hospital de Toledo., Toledo, Spain, [14]Hospital Donosti San Sebastian, San Sebastián, Spain, [15]Hospital Basurto. Bilbao, Bilbao, Spain, [16]Hospital Universitario de Móstoles. Madrid, Madrid, Spain, [17]Hospital General de Alicante., Alicante, Spain, [18]Hospital Universitario La Paz Madrid, Madrid, Spain, [19]Hospital Clínico San Carlos. Madrid, Madrid, Spain, [20]Hospital de Pontevedra, Pontevedra, Spain, [21]Hospital Sierrallana. Torrelavega, Torrelavega, Spain, [22]Hospital La Princesa. Madrid, Madrid, Spain, [23]Hospital de Córdoba., Córdoba, Spain, [24]Hospital Universitario de Salamanca, Salamanca, Spain, [25]HUCA La Coruña., A Coruña, Spain, [26]Hospital Doctor Negrín Canarias., Canarias, Spain, [27]Hospital Universitario Santiago de Compostela, Santiago de Compostela, Spain, [28]Hospital Cabueñes, Gijón, Gijón, Spain, [29]Hospital Lucus Augusti Lugo, Lugo, Spain, [30]Hospital San Pedro Alcantara Caceres, Caceres, Spain, [31]Hospital Universitario Virgen de la Arrixaca. Murcia, Murcia, Spain, [32]Fundación Jimenez Díaz. Madrid, Madrid, Spain, [33]Hospital 12 de Octubre. Madrid, Madrid, Spain, [34]Hospital Universitario Fundación Alcorcón. Madrid, Alcorcon. Madrid, Spain, [35]Hospital Clínico de Zaragoza, Zaragoza, Spain, [36]Hospital de Mérida, Mérida, Spain, [37]Hospital Germans Trias i Pujol. Badalona, Barcelona, Spain, [38]Hospital de Ferrol. A Coruña, A Coruña, Spain, [39]Hospital Universitario Miguel Servet. Zaragoza, Zaragoza, Spain.

Background/Purpose: Several situations can be observed in patients undergoing biologic therapy in uveitis associated to Behçet's syndrome (BS): **a)** Patients are switched to another therapy because of insufficient response (IR), toxicity, or change in the route of administration, **b)** remission is achieved and discontinuation or reduction of dose is performed.

Our aim was to study these situations in a large series of BS patients receiving biologic therapy.

Methods: Multicenter study of 124 patients with uveitis refractory to conventional therapy who required at least one biologic agent. Standard dose of Infliximab (IFX), generally 5 mg/kg/i.v. was given at 0, 2, 6 and then every 4–8 weeks, Adalimumab (ADA) 40 mg/sc/every other week, golimumab (Goli) 50 mg/4 weeks, tocilizumab (TCZ) 8 mg/kg/i.v./4 weeks and rituximab (RTX) 1g/i.v./15 days (2 doses) every 6 months.

Results: The biological agent used as the first choice was either IFX in 77 patients or ADA in 47. All the IFX-treated patients received the standard dose at weeks 0, 2, 6 and then every 4–8 weeks. Initial IFX dosage was: a) IFX at 5 mg/k/i.v. (69 cases) with a maintenance dose every: 4 weeks (n=15 cases), 6 weeks (16), 7 weeks (1) or every 8 weeks (37). b) 3 mg/kg (7 cases) with a maintenance dose every: 4 weeks (1 case), 6 weeks (1) or every 8 weeks (5). c) IFX 4 mg/kg (1 case) with a maintenance dose every 4 weeks. *Shortening* infusion times for *IFX administration* as the maintenance treatment *was required* in 5 cases because of IR. Initial IFX therapy was changed to another single biologic agent in 32 cases; 30 to ADA (because of IR [16 cases], decision of changing from *i.v. to subcutaneous* route of *administration* [5 cases] or toxicity [9 cases]), 1 to RTX because of infusional reaction, and 1 to etanercept because of toxicity. Initial ADA therapy was changed to another single biologic agent in 5 cases; 2 to Goli (because of IR or toxicity in 1 case each) and 3 to IFX (2 cases because of IR and 1 because of toxicity). In 3 cases there was a double biologic switching, 1 case from ADA to IFX and to Goli, 1 case from IFX to ADA and to Goli and 1 case from ADA to IFX and to TCZ. Improvement was achieved in: a) 14 of the 16 patients switched from

IFX to ADA due to IR; b) 3 of the 3 patients switched from ADA to another biologic due to IR. Persistent clinical remission was achieved in 66 (53.2%) patients and, the dose was reduced or the agent was discontinued. IFX was decreased from 5 to 3 mg/k/i.v. in 4 patients and the maintenance dose interval was increased in 23 cases. ADA maintenance dose interval was increased for more than two weeks in 13 patients. The biologic agent was discontinued in 26 cases (21 with IFX and 5 with ADA) that had clinically persistent remission. After a mean follow-up of 13.1 ± 9.2 months after biologic agent discontinuation, 21 of these 26 patients remained in remission while 5 of the 26 experienced a flare that led to the resumption of the therapy with same agent achieving remission again in all of them.

Conclusion: Switching of biologic agents may be useful. Once clinical remission is achieved, dose reduction or in some cases discontinuation of the biologic agent may be obtained.

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Infliximab For Sight-Threatening and Refractory Uveitis Of Behcet's Syndrome. Vedat Hamuryudan[1], Gulen Hatemi[2], Yilmaz Ozyazgan[2], Didar Ucar[2], Sebahattin Yurdakul[2], Emire Seyahi[2], Koray Tascilar[2], Serdal Ugurlu[2] and Hasan Yazici[1]. [1]Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey, [2]Behcet's Syndrome Research Center, Cerrahpasa Medical Faculty University of Istanbul, Istanbul, Turkey.

Background/Purpose: Uncontrolled studies suggest a beneficial effect of infliximab in the treatment of severe uveitis of BS. The majority of these studies had short observation periods.

Methods: The charts of 43 BS patients (33 men; age at the initiation of infliximab: 31±8.4 SD years) treated with infliximab (5 mg/kg) were reviewed retrospectively. All patients had severe, sight-threatening posterior uveitis of long-duration (82±50 SD months) refractory to previous treatments with multiple immunosuppressives (azathioprine=43, Cyclosporin A=42, Interferon alfa=38; duration of previous treatment: 62±43 SD months) and steroids. Efficacy was assessed by the change of visual acuity (LogMAR VA) and the decrease in the number of attacks under infliximab.

Results: The duration of infliximab treatment was 31±18 SD months (median 29 months). In 37 (86%) patients infliximab was combined with azathioprine (n= 26), azathioprine and cyclosporine A (n=10) or interferon alfa (n=1). Twenty-nine (67%) patients had no useful vision (LogMAR >1) in at least one eye at the time of initiation of infliximab. Five (17%) had gained useful vision of both eyes under infliximab. The mean VA (all patients) was maintained under infliximab (right eye: 0.83± 0.74 vs 0.84 ±0.79; left eye: 1.27±0.83 vs 1.13± 0.88). VA of the worse eye improved in 11 patients, remained stable in 24 and worsened in 8 patients under infliximab. Eleven patients (26%) had no attacks during previous treatment and were prescribed infliximab to protect the already compromised vision. The VA remained stable or improved in 10 patients and 9 patients remained attack free under infliximab. Thirty-two patients (74%) had attacks before infliximab. Eleven (34%) of them became attack free under infliximab. The number of uveitis attacks per year (all patients) under previous immunosuppressive treatment dropped from 1.9 ±3 to 0.3 ±0.6 in the right eye (p=0.0001) and from 2.5± 2.9 to 0.3 ±0.6 in the left eye (p=0.0001). There was also a significant decrease in the numbers of patients with hypopyon (11 and 3; x^2= 5.46, p=0.019), vascular infiltrations (23 and 12; x^2= 5.83, p=0.016), macular edema (8 and 1; x^2= 6.08, p=0.014), and retinal hemorrhages (7 and 0; x^2= 7.62, p=0.006) under infliximab. Infliximab treatment was terminated in 16 patients (adverse events =5, inefficacy =1, terminal eye disease = 4, unrelated reasons = 6). Fifteen of these patients received further treatment (biologics = 3, azathioprine =12) for 22±13 SD months and 12 of them remained attack free during this period. The adverse events causing discontinuation were pulmonary tuberculosis in 3 (at 17., 32., and 46. month of infliximab treatment, respectively), depression in 1, pneumonia in 1 patient.

Conclusion: Infliximab combined with immunosuppressives was useful in preserving visual acuity and in controlling the attacks of BS patients with refractory, sight-threatening uveitis at the long-term. Relapses were infrequent after discontinuation. Tuberculosis appears as a concern in prolonged treatment.

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Prognostic Factors Of Visual Function In The Treatment With Infliximab For Uveitis Of Behçet's Disease. Akihiko Nakabayashi[1], Toru Hirano[1], Yoshihiro Hishitani[1], Keisuke Hagihara[1], Kei Nakai[2], Kouji Nishida[2] and Atsushi Kumanogoh[1]. [1]Osaka University Graduate School of Medicine, Suita, Japan, [2]Osaka University Graduate School of Medicine, Suita, Japan.

Background/Purpose: Infliximab, a chimeric monoclonal antibody against TNF-α, is expected to improve prognosis of visual function in patients with severe and refractory uveitis of Behçet's disease. However, prognostic factors remain to be determined.

Methods: Observational study in one institute was conducted in the cohort of patients with Behçet's disease treated with infliximab. Outcome was defined as failure to recover above 20/50 of visual acuity (VA) at 2 year after the first administration of infliximab. Associations between outcome and baseline characteristics were assessed by bivariable analysis and logistic regression analysis to adjust confounding factors. Significance of each factor was assessed by likelihood ratio test.

Results: Infliximab was initiated in 28 patients between February 2007 and May 2012. Nineteen patients continued to receive infliximab beyond 2 year and could be assessed. Among 38 eyes of 19 patients, 18 eyes could not achieve 20/50 of VA (Figure). Bivariable analysis between the outcome and baseline characteristics demonstrated p-value (p) = 0.53 for sex, p = 0.19 for disease duration, p = 0.43 for HLA-B51, p = 0.97 for C-reactive protein (CRP), p < 0.0001 for VA at the first administration, p = 0.088 for deviation of VA during 6 months before the first administration, p = 0.48 for concomitant use of corticosteroids and p= 0.042 for concomitant use of immunosuppressants such as cyclosporine or methotrexate. Adjusted analysis with confounding factors such as sex, age, disease duration, VA at the first administration and concomitant use of immunosuppressants by logistic regression analysis revealed disease duration (p=0.024) and visual acuity (p < 0.0001) as significant factors (Table). Receiver operating characteristic (ROC) analysis demonstrated 16.5 months of disease duration and 20/140 of visual acuity (Area under the curve: 0.95) for candidate cutoff values.

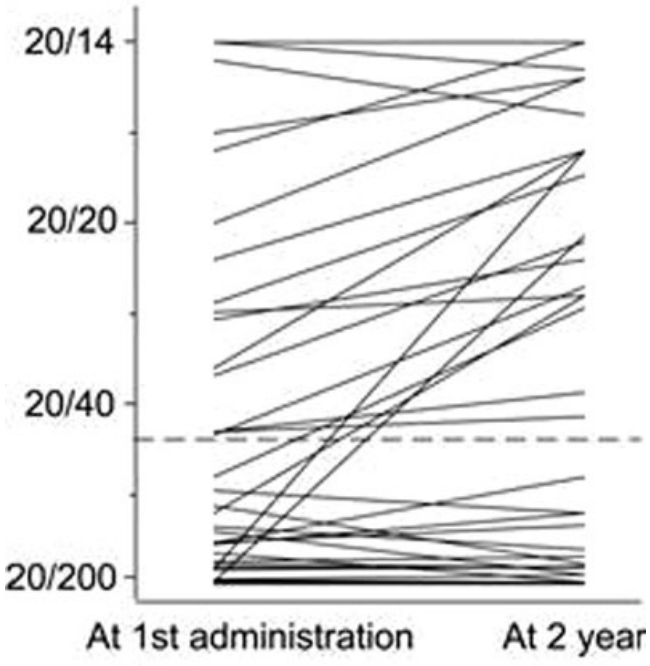

Figure. Change of visual acuity

Table. Contributable factors for visual acuity at 2 year

Factor	p-value
Sex	0.41
Age	0.42
Disease duration	0.024
Visual acuity	<0.0001
Immunosuppressants	0.64

*regression logistic analysis and likelihood ratio test

Conclusion: Disease duration and VA at the first administration of infliximab were the most contributable factors for the prognosis of visual function after 2 years. Cutoff values, 16.5 months of disease duration and 20/140 of VA suggest the importance of 'windows of opportunity' in treatment for uveitis of Behçet's disease.

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Immunogenicity Of Infliximab Modulates Efficacy and Safety In Behcet's Disease Patients With Uveitis. Mitsuhiro Takeno, Kayo Terauchi, Yohei Kirino, Ryusuke Yoshimi, Nobuhisa Mizuki, Etsuko Shibuya and Yoshiaki Ishigatsubo. Yokohama City University Graduate School of Medicine, Yokohama, Japan.

Background/Purpose: Infliximab (IFX) suppresses ocular attacks in Behcet's disease (BD) with uveitis, resulting in favorable long-term visual prognosis. However, some patients had ocular attacks which accumulate one or two weeks before the next IFX infusion, suggesting that the efficacy of IFX depends on the concentration. This study investigates IFX through levels and antibody toward IFX (ATI) in BD patients receiving IFX and analyzes the relationship of the pharmacokinetics with clinical efficacy and safety.

Methods: We retrospectively examined clinical courses of 20 BD patients (female 7, male 22 age 41.9 + 14.4 yo) who met the Japanese revised Behcet's disease Diagnositic criteria (2003) and received IFX because of refractory uveitis to conventional therapies including cyclosporine A. In principle, immunosuppressants were discontinued before introduction of IFX therapy. In the original regimen, IFX (5mg/kg) was given at 0, 2, 6 week, and thereafter every 8 weeks, but the intervals were shortened to 5 weeks after major ocular attacks occurred. The blood samples were drawn prior to the next infusion. IFX concentrations and ATI in the sera were determined by ELSIA.

Results: Mean duration was 6.4 + 5.8 years from the disease onset to initiation of infliximab therapy. A. Duration of IFX was 7 to 80 months. The therapy was discontinued in 2 patients because of infusion reaction and/or insufficient efficacy. Frequencies of ocular attacks (/6 months) were 2.6 + 2.1 and 0.4 + 0.5 before and after therapy, indicating that IFX suppresses ocular attacks significantly. During the therapy, total 29 ocular attacks occurred at 6.87 + 1.12 weeks after the last infusion, 1.43 + 1.53 weeks before the next infusion. The infusion interval was shortened from 5 to 7 weeks in 8 patients who experienced major ocular attacks. Thereafter, frequency of ocular attacks was reduced from 0.84 to 0.37/6months, while that was 0.10 in patients who continued to receive the infusions every 8 weeks. The mean IFX through level was 5.0 + 6.1 μg/ml but it was undetectable (less than 0.1μg/ml) in 7 patients. Of the 7 patients, 3 had recent ocular attacks, 6 showed extraocular symptoms, 6 had infusion reaction, and 6 had ATI. Shortening the infusion interval was associated with increased through level, leading to another remission in a patient. Besides 6 patients, ATI was also positive in one patient who had infusion reaction but no ocular attacks. Three of 4 patients who required admission due to infusion reaction were positive for ATI.

Conclusion: The present study suggests that low IFX trough level is also associated with ocular attacks, extraocular manifestations, and ATI, which is partially responsible for serious infusion reaction. Therefore, shortening the infusion interval and concurrent usage of immunosuppressants appear reasonable strategies to circumvent the issues.

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Is Complete Remission a Realistic Target With Current Therapeutic Options in Behçet's Disease? Fatma Alibaz-Oner[1], Gonca Mumcu[2], Zeynep Kubilay[1], Gülsen Ozen[3], Gülce Celik[1], Aslı Karadeniz[1], Meryem Can[1], Sibel Yılmaz Oner[1], Nevsun Inanc[4], Pamir Atagunduz[4], Tülin Ergun[1] and Haner Direskeneli[1]. [1]Marmara University, School of Medicine, Istanbul, Turkey, [2]Marmara University, Faculty of Health Sciences, Istanbul, Turkey, [3]Marmara University School of Medicine., Istanbul, Turkey, [4]Marmara University School of Medicine, Istanbul, Turkey.

Background/Purpose: The clinical course of Behcet's disease (BD) as a multi-systemic disorder with a remitting-relapsing nature is unsufficiently explored. As complete remission should be aimed in all inflammatory diseases, we investigated the frequency of complete remission in patients with BD in routine practice.

Methods: In this retrospective study, 258 patients with BD (F/M: 130/128, mean age: 41.1±11,5 years) classified according to ISG criteria were included. The demographic and clinical data for active organ manifestations and treatment protocols were evaluated, both for the current visit and in the last month. Patients having at least one of any disease manifestations were categorized as active.

Results: A total of 1757 visits of 258 patients were overviewed. Mean visit number was 6,8± 2,7 (range: 1–10) and mean follow-up duration was 45.8±36.5 months (2–165). One hundred twenty-five patients (48.4%) were of mucocutaneus type, whereas 133 patients (51.6%) had major organ involvement. When all visits combined, 19.8–43.9% of the patients were using immunosuppressives (IS), whereas 35.3–59.3% was under non-IS therapies such as colchicine or NSAIDs. There was also a group of noncompliant patients (6.4–45%) without any treatment in some visits. Patients were clinically active in 67.2% (n=1182) of the total visits (n=1757). Frequency of clinical activity increased to 75.6% (68.1– 90.3) when the month before the visit was also included. The major cause of the activity was aphthous ulcers (39.4–63.2%) with other mucocutaneous manifestations also commonly present (Genital ulcer: 3.5–27.1 %, erythema nodosum: 8.2–22.5%, papulopustular lesions: 18.2–33.7%, arthritis: 21.3–33.5%, uveitis: 0.5–8.5% and vascular involvement: 2.5–10.8%). No difference was observed between the frequency of activity of patients having ISs or non-IS therapies.

Conclusion: Although complete remission is the current, primary target in inflammatory rheumatological diseases such as rheumatoid arthritis or vasculitides, it is fairly difficult to achieve complete remission in BD with current therapeutic regimens. The reluctance of the clinicians to be aggressive for some BD manifestations with low morbidity, such as mucocutaneous lesions, might be influencing the continuous, low-disease activity state in BD patients.

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Low Medication Adherence Is Observed In Behcet's Disease. Gonca Mumcu[1], Ali Taze[1], Esra Kula[1], Semiha Yemez[1], Silay Eksi[1], Leyla Köksal[1], Fatma Alibaz-Oner[2], Sibel Yilmaz Oner[2], Pamir Atagündüz[2], Nevsun Inanc[2], Tülin Ergun[2] and Haner Direskeneli[2]. [1]Marmara University, Faculty of Health Sciences, Istanbul, Turkey, [2]Marmara University, School of Medicine, Istanbul, Turkey.

Background/Purpose: Symptom-control with reduction of mortality and morbidityare the main treatment goalsin Behcet's Disease (BD). However, similar to other chronic disorders, increased unnecessary visits, hospitalisation and medication costs are thought to originate from lack of adherence to medications of the treatment protocols in BD. Therefore, the aim of this study was to evaluate self-reported medication adherence in BD patients.

Methods: The study group was composed of 118BD patients(F/M:62/56, mean age:37.7±10.8 years) and disease control groups regarding 50

patients with Rheumatoid Arthritis (RA, F/M:37/13, mean age:39.9±10.4 years) and 58 patients with Familial Mediterranean Fever (FMF, F/M:39/19, mean age:34.4±11.9 years).

Medication adherence was evaluated by the Morisky scale that is a brief 4-item structured questionnaire. Each patient has a scale score ranging from "0" to "4" with low scores indicating better adherence. Trained interviewers (n=4) who were not involved in any disease assessment or treatmenthelped to individuals with visual impairment or illiterates in filling the questionnaire.

Results: The Moriskyscale score was similar in BD (2.05±0.99) and FMF (2.01±1.1) (p=0.99), whereas it was significantly lower in RA (1.54±1.05) than BD (p=0.021).In BD, no significant difference was present in the Morisky scale score according to gender (females:2.09±0.9vsmales: 2.0±1.02, p=0.60).The score of patients with major organ involvement (2.1±1.1) was also similar to mucocutaneous ones (1.9±0.9) (p=0.57) in males. In contrast, the score was lower in patients with major organ involvement (1.7±1.1) compared to patients with mucocutaneous involvement (2.29±0.8) in female BD patients (p=0.04). Moreover, a weak correlation was observed between the Morisky scale score and the number of medication (4.8±2.4, r:0.3 p=0.029).

Conclusion: Self-reported medication adherence was found to be low in BD patients. Medication adherence seems to be different according to gender in the frame of major organ involvement, suggesting that either the perception or consequences of disease-associated morbidity is associated to gender-related features in BD.

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Fertility In Behçet's Syndrome: Structured Interview In A Multidisciplinary Center. Caner Saygin, Didem Uzunaslan, Gulen Hatemi, Koray Tascilar and Hasan Yazici. Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey.

Background/Purpose: Behçet's Syndrome (BS) follows an active course during the child-bearing years in both men and women. Whether fertility is decreased among the BS patients due to the condition itself or to the frequently used medications like cyclophosphamide (CYC), azathioprine or colchicine is not clear. We aimed to determine the infertility rate, and the effect of drugs and types of organ involvement on fertility in BS patients.

Methods: We included BS patients with and without major organ involvement, familial Mediterranean fever (FMF), ankylosing spondylitis (AS) patients and healthy controls recruited from hospital staff. In order to show a 20% increase in infertility in BS with 0.05 alpha and 80% power, we calculated that each group should contain at least 125 individuals. Among patients who visited the clinic for routine controls, individuals with an even waiting list number were selected. A structured interview was performed by two physicians and medical records were reviewed. Infertility was defined as the inability to conceive after one year of unprotected intercourse. We compared the differences in the proportion of individuals who had never conceived in their lifetime, who had a successful conception but became infertile after disease onset, and individuals who conceived late or with assisted reproductive technology (ART), between BS and control groups. Finally infertility was separately assessed in a group of 62 patients who had used CYC and was compared to that observed among patients with major organ involvement who were CYC naïve. Multivariate logistic regression analysis was used to determine the association of infertility with involved organs and the drugs which were used.

Results: The numbers of subjects who were not able to ever conceive, who were not able to conceive only after disease onset, and who were able to conceive late or only with ART were not increased among patients with BS (Table). There were more FMF patients who conceived late or only with ART. Average number of children, miscarriages, terminations and ectopic pregnancies were not significantly different in patients with BS. Univariate logistic regression showed an increased risk of infertility with CYC (OR 6.1, %95 CI 0.7–54.2), however this effect was not confirmed in multivariate analysis. This was attributed to a type II error caused by the low number of patients who had used CYC. Finally the infertility was higher among the separate group of 62 CYC users as compared to the patients with major organ disease who were CYC naive (7/20 vs 3/60 among those who atttempted to conceive, p=0.002).

	BS major organ (n=190)	BS mucocutaneous (n=135)	FMF (n=126)	AS (n=129)	Healthy (n=125)	p
Mean age at diagnosis	29.2±8.6	30.8±9.4	28.7±11.9*	31.4±10.5	NA	0.012*
Never conceived despite attempts	4/156 (%2.6)	0/108	3/91 (%3.3)	3/100 (%3)	3/103 (%2.9)	0.502
Failed to conceive after disease onset	7/88 (%8)	5/49 (%10.2)	6/80 (%7.5)	6/66 (%9.1)	NA	0.95
Conceived late or only with ART	10/156 (%6.4)	9/108 (%8.3)	15/91 (%16.5)	6/100 (%6)	4/103 (%3.9)	0.014

Conclusion: Infertility rate is not appreciably increased among BS patients as compared to FMF patients, AS patients and healthy controls. Major organ involvement does not seem to affect this. CYC is the only drug which seems to decrease fertility in BS.

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Long Term Outcome Of Neuro-Behçet's Disease. Nicolas Noel[1], Remy Bernard[2], Bertrand Wechsler[1], Matthieu Resche-Rigon[2], Du Boutin[1], Jean-Charles Piette[1], Aurélie Drier[1], Didier Dormont[1], Patrice P. Cacoub Sr.[1] and David Saadoun[3]. [1]Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Paris, France, [2]Hopital Saint-Louis, Paris, France, [3]Pitié-Salpêtrière Hospital, APHP, Paris, France.

Background/Purpose: Neurological involvement occurs in 5.3 to up to 59% of patients with Behçet's disease (BD). Although the clinical and imaging features of neuro-Behçet's disease (NBD) have been extensively described, few studies have reported on the long term outcome, treatment and prognosis of NBD by multivariate analyses. Moreover, no large study has focused on the impact of immunosuppressants on the outcome of NBD. In this study, we sought to report the long-term outcome of neurological involvement in patients with Behçet's disease (BD).

Methods: Retrospective analysis of 115 patients fulfilling the International Criteria for BD [57% male with median [Q1-Q3] age of 37 [30–46] years] with neuro-Behçet's disease (NBD) after exclusion of cerebral venous thrombosis. Factors associated with relapses of NBD, dependence and mortality were assessed by multivariate analysis. The event-free survival was calculated using Kaplan-Meier curves and a multivariate Cox proportional hazard ratio model was performed.

Results: Seventy eight (68%) patients presented with an acute onset of NBD and 37 (32%) with a progressive course. The HLA B51 allele was carried by 49% of patients. Overall, 46/115 (40%) patients had a severe initial disability status, represented by a Rankin score ≥ 3. The 5 and 7 years event-free survival rate were of 65% and 53%, respectively. In multivariate analysis, HLA-B51 positivity was independently associated with the risk of relapses of NBD (OR=4.2 [1.6–10.9]). After a median follow-up of 73 [59–102] months, 21 (25.2%) patients became dependent or died. Factors independently associated with poor outcome were a paresis at onset (OR=6.47 [1.73–24.23]) and a brainstem location of inflammatory lesions on MRI (OR=8.41 [1.03–68.43]). All the 115 patients were treated with glucocorticosteroids, including 53/115 (46.1%) with cyclophosphamide and 40/115 (34.8%) with azathioprine. A trend towards a longer event-free survival was observed in severe NBD patients (i.e. Rankin score ≥ 3 at onset) receiving intravenous cyclophosphamide compared with those treated with azathioprine (p =0.06).

Conclusion: NBD is a severe condition in which HLA-B51 carriers seems to have a worse prognosis.

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Clinical Spectrum Of Cutaneous Vasculitis. Javier Loricera[1], Vanesa Calvo-Río[1], Francisco Ortiz-Sanjuan[1], Héctor Fernández-Llaca[1], Marcos A. González-López[1], Lino Álvarez[2], M. Carmen González-Vela[1], Domingo González-Lamuño[2], Cristina Mata[1], Javier Rueda-Gotor[3], Víctor M. Martínez-Taboada[4], Miguel Angel González-Gay[1] and Ricardo Blanco[3]. [1]Hospital Universitario Marqués de Valdecilla. IFIMAV. Santander. Spain, Santander, Spain, [2]Hospital Universitario Marqués de Valdecilla. IFIMAV. Santander, Santander, Spain, [3]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain, [4]Hospital Universitario Marqués de Valdecilla. IFIMAV., Santander, Spain.

Background/Purpose: Cutaneous vasculitis (CV) encompasses a large and heterogeneous set of syndromes characterized by inflammation of the skin vessels. The most common clinical manifestation is palpable purpura with leukocytoclastic vasculitis in biopsy. Our objective was to study clinical associations of a large series of patients with CV.

Methods: Study of 817 consecutive and unselected patients with CV of the same university hospital. The diagnosis required histological confirmation except in obvious cases like Henoch-Schönlein Purpura (HSP) in childhood. Primary vasculitic syndromes were classified according to the classification of Chapel Hill *(Jennette J et al. Arthritis Rheum 1994; 37:187)*.Secondary vasculitis were considered those due to malignancies, major infections and connective tissue diseases. The different clinical associations were studied according to different age groups, considering adults patients older than 20 years (Michel et al. J Rheumatol 1992; 19:721–8).

Results: Of 817 patients (457 men/360 women), 459 were adults (mean age±SD, 55.3±17.5 years) and 358 childrenyoung (mean age ± SD, 7.5 ± 4.2 years).Of the 358 children-young, 355 had primary VC: HSP (279 cases), cutaneous leukocytoclastic angiitis (CLA) (68) and urticarial vasculitis (8).Of the 459 adults, 369 had a primary CV: CLA (239), HSP(105), urticarial vasculitis (12) and mixed cryoglobulinemia (13 patients).The CV was a manifestation of a systemic necrotizing vasculitis in 13 adults; polyarteritis nodosa (3), microscopic polyangiitis (4), Wegener's disease (3) and Churg-Strauss syndrome (3).In addition, the CV was secondary to other processes in 77 adults: connective tissue diseases (34), severe infection (25), neoplasia (18).There were only three children-young patients, who had a secondary CV, a major infection (2 cases) and a connective tissue disease (1 case).Patients in which the CV was secondary to systemic necrotizing vasculitis, connective, serious infections or malignancies had clinical and laboratory data suggestive of this underlying disease.

Conclusion: CV in children in most cases (99.2%) is primary, usually HSP or CLA, and has a good prognosis. By contrast, in adults a 22.4% is due to malignancies, major infections, connective tissue diseases, systemic necrotizing vasculitis or cryoglobulinemic vasculitis. Therefore, clinical assotiations depends of age, being more serious in adults.

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Henoch-Schönlein Purpura: Clinical Spectrum Of The Disease In 417 Patients From A Single Center. F. Ortiz-Sanjuán[1], Vanesa Calvo-Río[1], Javier Loricera[1], C Mata[1], L Martín Penagos[1], L Alvarez[1], M. Carmen González-Vela[1], D González-Lamuño[1], Javier Rueda-Gotor[2], Héctor Fernández-Llaca[1], Marcos A. González-López[1], Susana Armesto[1], M. Enriqueta Peiró[1], M. Arias[1], Miguel Angel Gonzalez-Gay[1] and Ricardo Blanco[2]. [1]Hospital Universitario Marqués de Valdecilla. IFIMAV. Santander. Spain, Santander, Spain, [2]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain.

Background/Purpose: The severity of clinical features and the outcome in the different series of Henoch-Schönlein Purpura (HSP) shows great variability, probably due to selection-bias. Our aim was to establish the actual clinical spectrum of HSP in all age groups using an unselected and wide series of patients diagnosed at a single center.

Methods: Study of all consecutive patients classified as having HSP at a single center according to the criteria proposed by Michel et al (J Rheumatol 1992; 19: 721–8). HSP was pathologically confirmed in 110 cases by a skin biopsy showing the characteristic histological findings consistent with leukocytoclastic vasculitis. The remaining 307 patients without skin biopsy (mainly children) had typical non thrombocytopenic symmetric palpable purpura. In addition, all of them fulfilled the criteria proposed by Michel et al.

Results: We performed a retrospective review of 417 patients (240 men/177 women), with a median age at the time of disease diagnosis of 7.5 years (interquartile range-IQR: 5.3–20.1). Three-quarters of them (n=315) were children or young patients (age <20 years) and a quarter (n=102) were adults. The most frequent precipitating events were a previous infection (38%), usually an upper respiratory tract infection, and/or drug intake (18.5%) shortly before the onset of HSP. At disease onset the most common manifestations were skin lesions (55.9%), nephropathy (24%) gastrointestinal involvement (13.7%), joint symptoms (9.1%), and fever (6.2%). When the disease was fully established, the main clinical features were skin involvement (100%), mainly palpable purpura, gastrointestinal (64.5%), joint (63.1%), renal involvement (41.2%), fever (20.4%), constitutional syndrome (2.9%) and peripheral neuropathy (1.9%). The main gastrointestinal features were the typical colicky abdominal pain (64.5%), nausea and vomiting (14.4%), melena and or rectorrhagia (12.9%), and positive stool guaiac test (10.3%). Renal involvement (41.2%), usually behaving as a mild nephropathy; nephrotic syndrome (4.8%), nephritic syndrome (2.9%) and renal insufficiency (4.8%). The main laboratory data were leukocytosis (36.7%), anemia (8.9%) and increased of serum IgA levels (31.7%). The most frequent treatments used were corticosteroids (35%), nonsteroidal anti-inflammatory drugs (14%), and cytotoxic agents (5%). After a median follow-up of 12 (IQR: 2–38) months, complete recovery was observed in 346 patients (83.2%) and persistent, usually mild, nephropathy was observed in 32 cases (7.7%). Relapses were observed in 133 patients (31.9%).

Conclusion: Although HSP is a typical vasculitis affecting children and young people, it is not uncommon in adults. The prognosis is favorable in most cases depending mostly on renal involvement.

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IgA Vasculitis In Adults – a Rare and Benign Disease? Alojzija Hocevar[1], Jaka Ostrovrsnik[1], Vesna Jurcic[2] and Matija Tomsic[3]. [1]University Medical Centre Ljubljana, Ljubljana, Slovenia, [2]University of Ljubljana, Faculty of Medicine, Ljubljana, Slovenia, [3]University Medical Centre Ljubljana, Ljubljana, Slovenia.

Background/Purpose: IgA vasculitis (IgAV) is the most common vasculitis in children, with a defined epidemiology (14 cases/ 10^5children), clinical picture and generally favourable prognosis. In adults IgAV is less well characterized. It is assumed to be rare, with a higher incidence of renal involvement but overall a benign disease. Our aim was to better define IgAV in our adult patient population.

Methods: A retrospective chart analysis of adult patients diagnosed with IgAV at our rheumatological department between June 2010 and June 2013. The demographics, clinical data, treatment and outcome were recorded.

Results: 205 new cases of vasculitis were identified (Table 1). In 71 (34.6%) IgAV was histologically confirmed, 42 males (59.2%), 29 females (40.8%), mean age 58.2 ± 21.5. Prior infection was detected in 26/71 (36.6%) cases. Leukemia and primary biliary cirrhosis was coincidently diagnosed in one and two patients respectively. In 11 cases a new drug was introduced before the IgAV episode (mostly antibiotics).

Skin involvement was seen in all patients (purpura 71/71 cases, skin necrosis 32/71 (45.1%), bullous lesions 7/71 (9.8%)) and there was an isolated manifestation in 15 cases (21.1%). Arthritis was present in 16/71 (22.5%) and gastrointestinal involvement in 29/71 (40.8%; severe with bleeding or ileus in 9/71 (12.6%). 43/71 (60.6%) had renal involvement. Lung, heart and testicular involvement was rare - one case of each. The most common combination of symptoms was skin, gastrointestinal and renal involvement (18/71 cases; 25.3%).

No treatment (13/71) or local glucocorticoids (6/71) were sufficient in the isolated purpura. 52 patients (73.2%) received systemic glucocorticoid, 10/71 (14.1%) needed additional immunosuppression (9 cyclophosphamide (CyC), 1 mycophenolate mofetil), four received IVIG and two patients plasmapheresis in addition to CyC. None needed dialysis.

Two patients died due to active vasculitis, lung and gastrointestinal manifestation respectively and one due to cytomegalovirus infection. Two patients died shortly thereafter due to heart failure and pneumonia respectively.

Table 1. Newly diagnosed vasculitis from June 2010 to June 2013

TYPE	number	%
Takayasu arteritis	1	0.5
GCA	77	37.6
Isolated aortitis	3	1.5
PAN	2	1.0
Localized PAN	3	1.5
AAV (GPA and MPA)	18	8.8
EGPA	3	1.5
Cryoglobulinemic vasculitis	12	5.9
IgA vasculitis	71	34.6
Anti-GBM disease	1	0.5
Behçet disease	5	2.4
Cogan syndrome	2	1.0
SVV secondary to infection	3	1.5
Undetermined SVV	2	1.0
PCNSV	1	0.5
Vasculitis secondary to RA	1	0.5
TOTAL	205	

GCA - giant cell arteritis; PAN - polyarteritis nodosa; AAV - ANCA associated vasculitis; GPA -granulomatosis with polyangiitis; MPA - microscopic polyangiitis; EGPA - eosinophilic granulomatosis with polyangiitis; SVV - small vessel vasculitis; PCNSV - primary central nervous system vasculitis; RA - rheumatoid arthritis

Conclusion: In our adult patient population IgAV is the second most common vasculitis. Adult IgAV patients frequently need systemic immunosuppression. The most common clinical manifestation is concomitant skin, gastrointestinal and renal involvement. Heart and lung involvement is rare.

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IgA Vasculitis – The Second Most Common Systemic Vasculitis In Adults In Slovenia. Alojzija Hocevar[1], ŽIga Rotar[2], Jaka Ostrovrsnik[1], Vesna Jurcic[3], Jelka Lindic[1] and Matija Tomsic[4]. [1]University Medical Centre Ljubljana, Ljubljana, Slovenia, [2]University Medical Centre Ljubljana, 1000 Ljubljana, Slovenia, [3]University of Ljubljana, Faculty of Medicine, Ljubljana, Slovenia, [4]University Medical Centre Ljubljana, Ljubljana, Slovenia.

Background/Purpose: IgA vasculitis (IgAV) is assumed to be rare in adults. Reported annual incidence rates vary between 0.8 and 1.8 cases per 100,000 adults.[1] Our aim was to determine the incidence rate of histologically confirmed IgAV in our country.

Methods: A retrospective patient chart review of adult patients diagnosed with IgAV was performed at the departments of rheumatology, nephrology and dermatovenerology at an integrated secondary/tertiary university teaching hospital, which is the only hospital serving a region representing approximately a quarter of the national population. In order not to miss any cases managed by the few private dermatovenerology and nephrology outpatient clinics, the attached medical faculty's Institute of Pathology provided a list of all histologically proven cases of IaAV in the region. The annual incidence rate of histologically confirmed IgAV was calculated.

Results: From June 2010 to June 2013 48, 3, and 7 new cases of IgAV were identified at the departments of rheumatology, nephrology, and dermatovenerology, respectively in a well-defined region with a population of 517,445 white Caucasians aged 20 years or above. No additional cases were identified from records retrieved at the Institute of Pathology. The estimated annual incidence rate of IgAV is 3.7 (95% CI 2.2–5.7) per 100,000 adults. The largest proportion of cases were identified in the winter (31.0% cases) and the smallest in the spring (17.2% cases). Male to female ratio was 1.6.

Conclusion: The annual incidence rate of IgAV of 3.7 per 100,000 adults may be underestimated due to retrospective case ascertainment and inclusion of histologically confirmed cases only, yet IgAV none the less represents the second most common systemic vasculitis among adults in our population, second only to giant cell arteritis with an estimated annual incidence rate of 4.7 per100,000 adults, which is in striking discord with previous reports.[1]

Reference:

[1] Penny K, Fleming M, Kazmierczak D, Thomas A. An epidemiological study of Henoch-Schönlein purpura. Paediatr Nurs. 2010;22:30–5.

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Validation Study Of The International Classification Criteria For The Cryoglobulinemic Vasculitis. Luca Quartuccio[1], Miriam Isola[2], Laura Corazza[3], Soledad Retamozo[4], Manal Abdel-Moneim El-Menyawi[5], Elisa Gremese[6], Marco Sebastiani[7], Nicolo Pipitone[8], Teresa Urraro[9], Vincenza Conteduca[10], Christos Koutsianas[11], Benjamin Terrier[12], Mostafa Naguib Zoheir[13], Alessandra Ghinoi[14], Davide Filippini[15], Francesco Saccardo[16], Mohamed Nabil Salem[17], Salvatore Scarpato[18], Paolo Fraticelli[19], Antonio Tavoni[20], Eleonora Catarsi[21], Cesare Mazzaro[22], Pietro Pioltelli[23], Mervat Matar[5], Patrizia Scaini[24], Matija Tomsic[25], Norihiro Nishimoto[26], Dimitrios Vassilopoulos[27], Michael Voulgarelis[28], Gaafar M. Ragab[29], Carlo Salvarani[30], Armando Gabrielli[31], Patrice Cacoub[32], Loic Guillevin[33], Domenico Sansonno[34], Anna Linda Zignego[9], Gianfranco Ferraccioli[6], Athanasios G. Tzioufas[35], Manuel Ramos-Casals[36], Clodoveo Ferri[7], Maurizio Pietrogrande[37], Giuseppe Monti[16], Massimo Galli[38], Stefano Bombardieri[39] and Salvatore De Vita[1]. [1]Rheumatology Clinic, DSMB, University of Udine, Udine, Italy, [2]Institute of Statistics, DSMB, University of Udine, Udine, Italy, [3]Rheumatology Clinic, University of Udine, Udine, Italy, [4]Laboratorio de Enfermedades Autoinmunes Josep Font, IDIBAPS, Hospital Clínic, Barcelona, Spain, [5]Faculty of Medicine, Cairo, Egypt, [6]Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy, [7]University of Modena and Reggio Emilia, Modena, Italy, [8]Arcispedale S Maria Nuova, IRCCS, Reggio Emilia, Italy, [9]Center for Systemic Manifestations of Hepatitis Viruses (MASVE), Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy, [10]Department of Internal Medicine and Clinical Oncology, University of Bari, Bari, Italy, [11]Department of Pathophysiology, Medical School of Athens, Athens, Greece, [12]Cochin University Hospital, Paris, France, [13]Faculty of Medicine, Cairo University, Cairo, Egypt, [14]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [15]Rheumatology Unit, Ospedale Niguarda,, Milan, Italy, [16]Internal Medicine Unit, Saronno Hospital, Azienda Ospedaliera di Busto Arsizio, Saronno (VA), Italy, [17]Faculty of Medicine, Beni Swafe University, Beni Swafe, Egypt, [18]Rheumatology Unit, M. Scarlato Hospital, Scafati, Salerno, Italy, [19]Istituto di Clinica Medica, Università Politecnica delle Marche, Ancona, Italy, [20]Immunoallergology Unit, Pisa, Italy, [21]University of Pisa, Pisa, Italy, [22]Department of Internal Medicine, Pordenone General Hospital, Pordenone, Italy, [23]Hematology, S. Gerardo Hospital, Monza, Italy, [24]Nephrology, Spedali Civili di Brescia, Brescia, Italy, [25]University Medical Centre Ljubjana, Ljubljana, Slovenia, [26]Osaka Rheumatology Clinic, Osaka, Japan, [27]Athens University School of Medicine, Athens, Greece, [28]Department of Pathophysiology, Athens, Greece, [29]Faculty of Medicine, Cairo University, Giza, Egypt, [30]Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy, [31]Università Politecnica delle Marche, Ancona, Italy, [32]Hopital Pitié-Salpétrière, Paris, France, [33]Division of Internal Medicine, Hôpital Cochin, University Paris Descartes, Paris, France, [34]Section of Internal Medicine and Clinical Oncology, Department of Biomedical Sciences and Human Oncology, University of Bari, Medical School, Bari, Italy, [35]School of Medicine, National University of Athens, Athens, Greece, [36]Hospital Clínic, Barcelona, Spain, [37]Internal Medicine Unit, Policlinico San Marco, Bergamo, Italy, [38]Istituto di Malattie Infettive e Tropicali, Università di Milano c/o Ospedale L. Sacco, Milano, Italy, [39]Rheumatology Unit, University of Pisa, Pisa, Italy.

Background/Purpose: preliminary Classification Criteria for cryoglobulinemic vasculitis (CV) have been developed in 2011 by an European cooperative study, with an adequate methodology in a large number of real cases and controls (1). The aim of this study is to validate these classification criteria for CV.

Methods: Centres from Europe, United States, Japan and Egypt, were involved. A dedicated chart included: l) a validated questionnaire for CV (1); 2) the pattern of organ involvement (4 items: constitutional, articular, vascular and neurologic involvement); 3) laboratory tests (3 items: rheumatoid factor, complement C4 and serum monoclonal component), according to the preliminary criteria (1). New patients with CV (Group A) and controls (Group B), i.e., subjects with cryoglobulins but lacking CV based on the golden standard clinical judgment, were studied. A sample size of at least 140 patients for each group was estimated in order to obtain a sensitivity and a specificity of at least 90±5%, based on the previous results (1). Sensitivity and specificity were calculated by comparing Group A versus Group B. Finally, not for classification purposes, but to disclose whether the Criteria may be also clinically helpful in patients lacking serum cryoglobulins, but where CV is suspected (1), Group A was also compared with Group C, including patients with diseases mimicking CV, but without serum cryoglobulins.

Results: Six hundred forty-three patients were enrolled in 22 Centres (from Italy, Spain, France, Greece, Slovenia, Japan and Egypt). Major

organizative/local issues did not allow American experts to participate. Group A comprised 268 patients with CV, Group B 182 controls with serum cryoglobulins without CV, and Group C 193 controls without serum cryoglobulins. Notably, 20 patients showed type I cryoglobulinemia, 13 in Group A, and 7 in Group B. Group C included 108/193 (55.9%) systemic vasculitides, 100/108 (92.6%) were small vessel vasculitides. The classification criteria [positivity of at least 2/3 items among questionnaire (≥2/3 positive questions), clinical item (≥3/4 clinical manifestations), laboratory (≥2/3 tests)] showed 89.9% (95% CI 86.1–93.6) of sensitivity and 93.5% (95% CI 89.7–97.2) of specificity, replicating previous results (1). Sensitivity of 91.7% and specificity of 100% were observed in the subgroup of type I cryoglobulinemia. By the comparison of Group A vs. Group C, the Criteria showed a specificity 92.6% (88.8–96.5) and a sensitivity of 77.8% (72.6–83.0) when the laboratory item was positive (questionnaire + laboratory item; or clinical + laboratory item).

Conclusion: the International Classification Criteria for the CV have been validated in a new real cohort. High specificity and sensitivity were confirmed. Notably, in patients where CV is suspected on clinical grounds, but where cryoglobulins are negative by initial testing, or not yet available (patients who cannot be classified as CV, as positive serum cryoglobulinemia is a *conditio sine qua non* for classification) (1), the Criteria appear relevant to strengthen the suspicion for CV, and to optimize the follow-up.

1. De Vita S, et al. Ann Rheum Dis 2011;70(7):1183–90.

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Cryoglobulinemia Vasculitis With Or Without Associated Cryofibrinogenemia: A Different Phenotype? Martin Michaud[1], Guillaume Moulis[2], Jacques Pourrat[1], Benedicte Puissant[1], Antoine Blancher[1] and Laurent Sailler[3]. [1]Toulouse University Hospital, University of Toulouse, Toulouse, France, [2]Toulouse University Hospital, Clinical Pharmacology Department, University of Toulouse, UMR INSERM-UPS 1027, Toulouse, France, [3]Toulouse University Hospital, Toulouse, France.

Background/Purpose: Cryoglobulin (CryoGl) and cryofibrinogen (CryoFg) are cryoproteins, both responsible for well-described systemic vasculitis. Nevertheless, cryoglobulinemia may be associated with cryofibrinogenemia. Such mixed cryoprotein vasculitis (MCV) has not been properly described yet. This work aimed at determining whether the phenotype of MCV is different from CryoGl vasculitis.

Methods: Concomitant CryoGl and CryoFg dosages performed at our University Hospital from January 2011 to December 2012 were extracted and the corresponding medical files reviewed. We included all adult patients with systemic vasculitis associated with CryoGl with or without CryoFg. As in the CryoVas study, systemic vasculitis was defined by purpura or cutaneous ulcers, or other symptoms biopsy-proven associated with a detectable cryoprotein. Qualitative variables were compared with Fisher or chi^2 tests and quantitative variables with Student t-test or Wilcoxon-Mann-Withney test.

Results: Among 107 patients with cryoprotein positive dosage, 21 had MCV and 16 CryoGl vasculitis. Male:female sex ratio was respectively 1/2 and 5/3 ($p=0.8$). Mean age at diagnosis was respectively 58 ± 20 and 59 ± 16 years ($p=0.9$). Cutaneous manifestations (purpura, skin necrosis or ulceration and acrocyanosis) were similar in both groups as well as kidney (38 vs 31%) and peripheral nerve involvement (28 vs 32%). The frequency of rheumatic symptoms (arthralgia and/or myalgia) or of venous/arterial thrombotic events (43 vs 25%, $p=0.4$) was not different betweens both groups (51 vs 32%, $p=0.2$). Estimated glomerular filtration rate and cryoglobulin dosage were similar in both groups. As expected, α1 and α2globulin levels were higher in the MCV group ($p<0.05$). Decreased values of C3 and C4 were more frequent in the MCV group albeit not significantly (respectively, 29 vs 12% and 53 vs 35%). Regarding associated diseases, neoplasms tended to be 3 times more frequent in the MCV group (43 vs 12%, $p=0.07$) whereas the frequency of auto-immune disorders was similar in both groups (38% vs 50%, $p=0.5$). The use of systemic corticosteroids was more frequent in the MCV group (67 vs 31%, $p=0.03$), as well as exposure to immunosuppressives (47 vs 18%, $p=0.07$).

Conclusion: Cryofibrinogemnemia is associated with a more serious disease in cryoglobulinemic patients as they are associated with an increased use of corticosteroids and immunosuppressive drugs. Neoplasms should also be carefully searched in this group.

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Long-Term Outcome of Monoclonal (type 1) Cryoglobulinemia. Antoine Néel[1], François Perrin[1], Olivier Decaux[2], Thomas Dejoie[1], Maxime Halliez[1], Béatrice Mahé[1], Thierry Lamy[2], Fadi Fakhouri[1], Patrick Jego[2], Christian Agard[1], Cécile Vigneau[2], Lucienne Guenet[2], Bernard Grosbois[2], Philippe Moreau[1] and Mohamed Hamidou[1]. [1]Nantes University Hospital, Nantes, France, [2]Rennes University Hospital, Rennes, France.

Background/Purpose: To investigate long-term outcome of symptomatic type 1 cryoglobulinemia and its determinants.

Methods: Retrospective analysis of a prospective cohort from 2 French university hospitals. Patients with type 1 cryoglobulinemia were identified using laboratory databases. Inclusion criterion was the presence of persistent symptoms of cryoglobulinemia.

Results: Among 227 screened patients, 36 were included. Skin or vasomotor symptoms were the most frequent features (75%). Nephropathy and neuropathy occurred in 30% and 47% of cases, respectively. The underlying B cell lymphoproliferative disorder (LPD) was a gammopathy of unknown significance (MGUS) in 13 (36%) and a hematologic malignancy (HM) in 23 (64%; Waldenstrom macroglobulinemia (WM) in 12, low grade non-Hodgkin lymphoma (NHL) in 6, multiple myeloma (MM) in 4, and chronic lymphocytic leukemia (CLL) in 1). Severe manifestations affected half the patients and were more frequent with IgG cryoglobulins (82 vs 30% ($p=0,006$)). At last follow-up, 64% of patients had suffered no hematologic manifestation. Potent chemotherapeutic regimens were mainly used in HM. For patients with MGUS, WM or NHL, fludarabine or rituximab-based regimens appeared to yield better therapeutic responses. Five-year actuarial survival rate was 82 %. Older age and hemoglobin level < 12g/dL at diagnosis correlated with a poorer survival ($p<0.05$, Log-rank test). Nephropathy, infections, Richter's transformation and second malignancies were important sources of morbi-mortality.

Conclusion: Despite its limitations, this series provide novel information regarding type 1 cryoglobulinemia. Further studies are needed to improve its management. To date, therapeutic strategy should be tailored according to patient's characteristics (age, comorbidities, underlying LPD), and therapeutic target.

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VERY LONG-TERM Effects Of The "4 PLUS2 Infusion PROTOCOL" Of Rituximabalone In Patients With HCV-Associatedmixed Cryoglobulinemia With Diffusemembranoproliferative Glomerulonephritis, Severe Polyneuropathy and Necrotic Ulcersof Skin. Dario Roccatello[1], Savino Sciascia[1], Simone Baldovino[2] and Daniela Rossi[1]. [1]Centro di Immunopatologia e Documentazione su Malattie rare, Torino, Italy, [2]Centro di Ricerche di Immunologia Clinica ed Immunopatologia e Documentazione su Malattie Rare (CMID), Università di Torino, Torino, Italy.

Background/Purpose: Mixed cryoglobulinemia syndrome (MCs) is a systemic vasculitis characterized by multiple organ involvement due to the vascular deposition of IgMk/IgG cryoglobulins. B cells expansion usually triggered by HCV infection plays a central role in MCs.

Objectives: to evaluate the long term effects of B-cells depletion in MCs

Methods: Twenty seven patients, (mean age 60.2 [range 35–78] years, HCV infection in 96% of cases) with symptomatic type-II MCs with systemic manifestations, including renal involvement (diffuse membranoproliferative glomerulonephritis in 15 cases), peripheral neuropathy (26 cases) and large skin ulcers (9 case, in 7 necrotizing) were considered

eligible for Rituximab (RTX) therapy. RTX was administered at a dose of 375 mg/m2 on days 1, 8, 15 and 22. Two more doses were administered 1 and 2 months later. No other immunosuppressive drugs were added. Response was evaluated by assessing the changes in clinical signs, symptoms, laboratory parameters and electromyographic indices for a very long term follow-up (mean 54.3 months [12–96])

Results: Complete remission of pre-treatment active manifestations was observed in all the cases of skin purpuric lesions and non-healing vasculitic leg ulcers, and in 80% of cases of peripheral neuropathy. A significant improvement in the clinical neuropathy disability score was observed. Electromyography revealed that the amplitude of compound motor action potential had increased. Cryoglobulinemic glomerulonephritis, observed in 15 patients, significantly improved during the follow-up starting from the second month after RTX (serum creatinine from 2.2±1.9SD to 1.6±1.2SD mg/dl, p≤.05; 24-hour proteinuria from 2.3±2.1SD to 0.9±1.9SD g/24h, p≤.05). Significant improvement of serological hallmarks, such as cryocrit and low complement C4, were also detected (p≤.05). The safety of RTX was confirmed by the absence of side effects recorded during the mean 54-month follow-up. Re-induction was performed in 9 relapsed cases (after a mean of 31.1 months, range 12–54) with resolutive beneficial effects.

Conclusion: In this open prospective study, the "4 plus 2 infusion protocol" of RTX appeared to be very effective and safe in the treatment of patients with MCs-associated membranoproliferative nephritis, polyneuropathy and severe skin involvement

Disclosure: D. Roccatello, None; **S. Sciascia**, None; **S. Baldovino**, None; **D. Rossi**, None.

2641

Earlier Admission To Specialized Care, Intensified Treatment and Improved Outcome In Patients With Autoimmune Connective Tissue Disorders and Vasculitides In Germany 2011 Compared To 1995. Dörte Huscher[1], Katinka Albrecht[2], Katja Thiele[2], Sascha Bischoff[2], Jutta G. Richter[3], Ina Kötter[4], Wolfgang Ochs[5] and Angela Zink[6]. [1]Charité University Hospital and German Rheumatism Research Centre, a Leibniz Institute, Berlin, Germany, [2]German Rheumatism Research Centre, Berlin, Germany, [3]Heinrich-Heine-University, Duesseldorf, Germany, [4]ZIRS, Centre for Interdisciplinary Rheumatology Stuttgart, Stuttgart, Germany, [5]Rheumatology Practice Bayreuth, Bayreuth, Germany, [6]German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany.

Background/Purpose: Compared to rheumatoid arthritis and other arthritis-associated rheumatic diseases, autoimmune connective tissue disorders and vasculitides are still in the early stages of biological therapies. The study investigated whether health care and treatment with disease specific immunosuppressive drugs have changed in these indications. Furthermore, disease activity and outcomes of patients with autoimmune connective tissue diseases and vasculitides have been examined.

Methods: On average, a total of 3,900 patients with systemic lupus erythematodes (SLE), systemic sclerosis (SSc), primary Sjögren's syndrome (PSS), poly- and dermatomyositis (PM/DM), mixed connective tissue disease (MCTD), other connective tissue diseases (other CTD), polymyalgia rheumatica (PMR), primary systemic vasculitis, and other primary vasculitides (ICD10: I67.7, I77.6, L13.1, L95.0/8/9, M31.0/1/8/9, M35.2/6) were documented in the National Database of the German Collaborative Arthritis Centers in each of the years 1995 to 2011. Cross-sectional data of these years were analyzed to detect time trends.

Results: Between 1995 and 2011, the number of patients consulting a rheumatologist within six months after symptom onset increased from about 50% to 60%, especially patients with SLE and systemic sclerosis were seen earlier in specialized rheumatologic care. The overall percentage of patients receiving immunosuppressive drugs increased from 52.7% to 62.3%. High dose steroid use (>7.5 mg/d) decreased from 26.1% to 13.4%. In 2011, 3.5% of all patients received a biologic therapy, the most frequent use was seen in patients with other primary vasculitides (9.2%). Since 2005, the mean disease activity assessed by the physician (NRS 0–10) decreased from 3.0 to 2.2 and the percentage of patients with a high disease activity (7–10) from 7.6% to 1.8%. Overall, work participation (patients <65 years) remained stable (46.2% 1995, 49.4% 2011), but increased considerably in female patients with PSS, SSc and PMR (see Table 1).

	N		Mean age		Female		Immunosuppressive therapy		Mean disease activity (NRS 0–10)		Work participation (only patients <65 years)# female		male	
	1995	2011	1995	2011	1995	2011	1995	2011	1995	2011	1995	2011	1995	2011
SLE	1,432	946	43.1	46.3	89%	89%	69.6%	81.4%	3.0	2.2	45.6%	46.4%	55.3%	52.4%
SSc	317	317	55.7	57.5	86%	84%	42.9%	48.5%	3.8	3.1	36.5%	44.0%	–	–
PSS	320	200	53.1	57.9	93%	94%	43.7%	51.0%	3.2	2.5	44.2%	64.8%	–	–
DM/PM	143	94	50.7	54.9	76%	65%	65.9%	86.0%	3.1	2.4	43.2%	(41.7%)	–	–
MCTD/ overlap	329	165	47.4	50.0	89%	90%	68.8%	71.7%	3.4	2.4	47.0%	47.5%	–	–
other CTD	343	261	48.1	53.5	85%	86%	52.5%	54.5%	2.6	2.2	50.5%	63.0%	–	–
PMR	862	855	68.7	71.4	77%	67%	15.2%	28.6%	3.1	1.7	25.8%	40.0%	59.6%	60.0%
primary systemic vasculitis	292	435	50.6	60.3	52%	61%	72.0%	78.5%	3.1	2.3	31.1%	29.0%	63.0%	52.9%
other primary vasculitides	202	256	47.0	45.9	64%	45%	46.0%	57.6%	3.3	2.5	41.9%	(50.0%)	69.2%	(76.1%)

#For case numbers <50, percentages are given in brackets, for male patients with SSc, PSS, DM/PM, MCTD and other CTD case numbers were to low in both years for valid comparison.

Conclusion: Early rheumatologic care and immunosuppressive therapy have increased in patients with autoimmune connective tissue diseases and vasculitides during the past 15 years. Advancement in disease control and employment status in these rather infrequent chronic autoimmune diseases encourages to further improve disease outcomes and work participation.

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2642

A Novel Genetic Basis For Systemic Vasculitis: Polyarteritis Nodosa Caused By Recessive Mutations In An Immune-Related Gene. Reeval Segel[1], Pnina Elkan-Navon[2], Sarah B. Pierce[3], Tom Walsh[3], Judith Barash[4], Shay Padeh[5], Avraham Zlotogorski[6], Yackov Berkun[7], Isabel Voth[8], Philip Hashkes[2], Liora Harel[9], Eduard Ling[10], Fatos Yalcinkaya[11], Ozgur Kasapcopur[11], Paul F. Renbaum[2], Ariella Weinberg-Shukron[2], Barbara Schormair[12], Mordechai Shohat[13], Alan A. Rubinow[14], Elon Pras[5], Juliane Winkelmann[15], Mustafa Tekin[16], Yair Anikster[5], Mary-Claire King[3] and Ephrat Levy-Lahad[2]. [1]Hebrew University Medical School, Jerusalem, Israel, [2]Shaare Zedek Medical Center, Jerusalem, Israel, [3]University of Washington, Seattle, WA, [4]Kaplan Medical Center, Rehovot, Israel, [5]Sheba Medical Center, Ramat Gan, Israel, [6]Hadassah-Hebrew University Medical Center, Jerusalem, Israel, [7]Hadassah Medical Center, Mount Scopus, Jerusalem, Israel, [8]Technische Universitat Munchen Klinikum rechts der Isar, Munich, Germany, [9]Schneider Children's Medical Center, Tel Aviv University, Petach Tikvah, Israel, [10]Soroka University Medical Center and Ben-Gurion University, Beer-Sheva, Beer Sheva, Israel, [11]Ankara University, Ankara, Turkey, [12]Helmholtz Zentrum Munchen, Munich, Germany, [13]Rabin Medical Center, Beilinson Hospital, Petach Tikvah, Israel, [14]Hadassah Medical Center, Jerusalem, Israel, [15]Stanford University, San Francisco, CA, [16]Miller School of Medicine, University of Miami, Miami, FL.

Background/Purpose: Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis. Disease pathogenesis and possible genetic factors are poorly understood. We identified familial, mostly pediatric PAN, in twenty patients from six families, five of Georgian Jewish and one of German origin. Disease segregation was consistent with autosomal recessive inheritance.

Methods: Clinical data was collected from eight medical centers in Israel, Germany and Turkey. Exome sequencing was performed in six patients with familial PAN, four Georgian Jewish and two Germans. Targeted sequencing was done in another thirteen patients with familial PAN and in seventeen single cases: three of Gerogian Jewish and fourteen of Turkish origin. Mutations were assessed by impact on enzymatic activity in patient sera, analysis of protein structure, expression in mammalian cells, and biophysical analysis of purified protein.

Results: In most patients, disease onset was in early childhood and was most severe in those with onset in infancy. Skin manifestations almost universal: livedo reticularis, nodules, recalcitrant leg ulcers and acral necrosis. Raynaud's phenomenon, myalgia, arthralgia or arthritis were also common. Systemic involvement included gastrointestinal disease with significant weight loss and intestinal perforation, testicular pain, coronary and renal vasculitis with severe hypertension, peripheral neuropathy and brain strokes. Angiography demonstrated mesenteric, celiac, hepatic, or renal aneurysms, and infarcts in the renal cortex. There was a dramatically beneficial response to anti-TNF alpha blockade; life-saving in some cyclophosphamide refractory patients. All patients had recessive mutations in an immune-related gene, to be named at the meeting. Mutations in this gene have not been previously associated with any human phenotype. All Georgian Jewish cases were homozygous for this mutation, with variable phenotype; The German and the Turkish patients

were compound heterozygous for mutations in the same gene. In the endogamous Georgian Jewish population, the allele frequency was 0.05, reflecting high PAN prevalence. The other mutations were private or extremely rare. The missense mutations led to significantly reduced protein activity and secretion both in patient sera and in vitro. Protein activity was significantly reduced in patient sera.

Conclusion: Recessive loss-of-function mutations in an immune-related gene lead to PAN. Both population genetics and functional approaches were applied to demonstrate the causality of the founder allele. The mutations identified suggest blood vessels may be particularly vulnerable to impairment of the protein's catalytic, immune, and growth factor activities. A single-gene defect underlying a systemic vasculitis may provide new insights on disease pathogenesis and possibly help to develop new targeted therapy for PAN and other vasculitides.

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Midkine Is a Novel Prognostic Factor In Patients With Vasculitis Syndrome. Yoshie Kusunoki[1], Yutaka Okano[1], Natsuko Kusunoki[2], Natsuki Fujio[2], Mai Kawazoe[2], Emiko Shindo[2], Kotaro Shikano[2], Makoto Kaburaki[2], Sei Muraoka[2], Kanako Kitahara[2], Kaichi Kaneko[2], Nahoko Tanaka[2], Tatsuhiro Yamamoto[2], Kenji Takagi[2], Tomoko Hasunuma[2], Hirahito Endo[2] and Shinichi Kawai[2]. [1]Kawasaki Municipal Kawasaki Hospital, Kanagawa, Japan, [2]School of Medicine, Faculty of Medicine, Toho University, Tokyo, Japan.

Background/Purpose: Midkine (MK) is a heparin-binding growth factor, promotes growth, survival, and migration of various cells. Recently several reports show that MK may also play an important role in chronic inflammatory disorders including, kidney diseases, hypoxia-induced angiogenesis and rheumatoid arthritis. To evaluate the role of MK in vasculitis syndrome, we measured the serum level of MK in patients with vasculitis and detected the expression of MK in vasculitis tissues.

Methods: Thirty-two patients with active vasculitis syndrome (17 microscopic polyangiitis; MPA, 3 granulomatosis with polyangiits; GPA, 3 eosinophilic granulomatosis with polyangitis; EGPA, 4 giant cell arteritis; GCA, 3 Takayasu arteritis; TA and 2 polyarteritis nodosa; PAN) before treatment, and 10 healthy subjects as control were included in this study. Serum level of MK was measured by enzyme-linked immunosorbent assay (ELISA). Expression of MK was detected by immunohistchemical methods in several biopsy tissues of patients with vasculitis syndrome.

Results: Serum levels of MK in patients with vasculitis syndrome were significantly higher than that of healthy control (Vasculitis syndrome, 2014 (mean)±1839 (S.D.) pg/ml; Control 284 ± 57 pg/ml, (P <0.01). Mean age of vasculitis patients was 65.6±17.4, and disease duration was 2.2±1.6 months. Mean disease activity of these patients expressed by vsculitis activity score (BVAS) was 16.5±9.1 and mean vasculitis damage index (VDI) of these patients was 1.8±1.3. Both of BVAS and VDI of patients with vasculitis syndrome were not correlated with serum MK levels. Serum levels of MK in these patients with were; MPA:3615±4080,GPA: 960±23, EGPA: 989±698, GCA: 1080±997,TA:495±272, and PAN:507±102pg/ml. Levels of serum MK in patients with poor prognosis were significantly higher than that of patients with good prognosis (dead: 4608.0±4406.1pg/ml, survival: 1891.9±2933.4pg/ml, Mann-Whitney U test p<0.05). Optimal cut off value of serum MK as indicator of prognosis was 1797 pg/ml in patients with vasculitis syndrome using receiver operating characteristic curve analysis (high MK group n=22, low MK group n=10). Life table analysis of these patients by Kaplan-Meier method revealed that survival rate of high MK group was significantly shorter than that of low MK group (log-rank test P <0.05). All dead patients were complicated with pulmonary involvements. MK was detected in renal tubular epithelial cells, mesangial cells, but not in inflammatory cells and vascular cells in renal tissues of vasculitis patients. MK also highly expressed in dermal epithelial cells of vasculitis skin biopsy specimens.

Conclusion: It is suggested that MK might play an important role in pathogenesis of vasculitis syndrome. Since increased serum MK level was associated with poor prognosis, it might also be a novel prognostic factor of vasculitis syndrome.

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ACR Plenary Session III: Discovery 2013

Tuesday, October 29, 2013, 11:00 AM–12:30 PM

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Phase IB/Iia Study On Intravenous Administration Of Expanded Allogeneic Adipose-Derived Mesenchymal Stem Cells In Refractory Rheumatoid Arthritis Patients. JM Alvaro-Gracia[1], Juan A. Jover[2], Rosario Garcia-Vicuña[1], Luis Carreño[3], Alberto Alonso[4], Sara Marsal[5], Francisco J. Blanco[6], Víctor M. Martínez-Taboada[7], Peter C. Taylor[8], Federico Díaz-González[9] and Lydia Dorrego[10]. [1]Hospital Universitario de La Princesa, Madrid, Spain, [2]Hospital Clínico San Carlos, Madrid, Spain, [3]Gregorio Marañón Hospital, Madrid, Spain, [4]Hospital de Cruces, Bilbao, Spain, [5]Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [6]INIBIC-Hospital Universitario A Coruña. Rheumatology Division. Genomic Group, A Coruña, Spain, [7]Hospital Universitario Marqués de Valdecilla. IFIMAV., Santander, Spain, [8]University of Oxford, Oxford, United Kingdom, [9]University of La Laguna, Hospital Universitario de Canarias, La Laguna, Spain, [10]TiGenix, Tres Cantos, Spain.

Background/Purpose: Expanded adipose-derived stem cells (eASCs) are shown to have immune-modulatory effects both *in vitro* and in animal models of arthritis. eASCs are currently under investigation as potential treatments targeting auto-immune and inflammatory diseases such as Rheumatoid Arthritis (RA). The aim of the study was to determine the safety, feasibility and tolerance of intravenous (IV) administration of allogeneic eASCs in RA patients.

Methods: A 24-week, single blind dose-escalating study in RA patients under treatment with at least one non-biological DMARD and who previously failed treatment with at least two biologicals was conducted in 23 centers in Spain. Fifty-three patients with moderate to high disease activity (DAS28>3.2) were assigned to receive 1×10^6 eASCs/kg (cohort A: 20 patients), 2×10^6 eASCs/kg (cohort B: 20 patients), 4×10^6 eASCs/kg (cohort C: 6 patients) or placebo (Ringer's lactate solution: 7 patients). All patients received 3 IV eASC infusions at day 1, 8 and 15. Tolerability and treatment emergent adverse events such as Dose Limiting Toxicities (DLTs), serious adverse events (SAEs) and non-serious adverse events (AEs) were primary endpoints. ACR20/50/70, DAS 28, and SF-36 were secondary endpoints.

Results: Patient and disease characteristics were comparable for all three dose groups. Median disease duration was 13 years Repeated IV infusion of eASCs did not show any major safety signals and the dose-limiting safety signal was not identified Three serious adverse events were reported (lacunar infarction, peroneal palsy and fever of unknown origin) of which, lacunar infarction was possibly related and lead to discontinuation with patient recovery. Most frequent non-serious AEs (threshold: > 4%) in patients treated with eASCs, included pyrexia (19%), headache (13%), urinary tract infection (13%), upper respiratory tract infection (11%), nausea (11%), malaise, respiratory tract infection, vomiting and asthenia (6% each).

In secondary endpoints, a clear dose-response effect was not observed. Maximum clinical benefit in the ITT population was observed in cohort A. ACR20/50/70 responses were observed in 45/20/5% of patients in cohort A versus 28/14/5% of patients on placebo at month 1. At month 3, ACR responses were 25/15/5 and 0/0/0 in cohort A and placebo respectively. The DAS 28 good/moderate response was 10/35% in cohort A and 0/43% in the placebo group at month 1. These values were 20/20% and 0/0% at month 3 for cohort A and placebo respectively.

Conclusion: These early clinical results are the first to suggest that IV infusion of eASCs is well tolerated along 24 weeks and could be associated with clinical benefit in the treatment of refractory RA.

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2645

Pathological Roles Of The Anti-Oxidative Enzyme Peroxiredoxin 2 In Patients With Kawasaki Disease. Rie Karasawa[1], Toshiko Sato[1], Mayumi Tamaki[1], Mikiya Fujieda[2], Kazuhide Ohta[3] and Kazuo Yudoh[4]. [1]Institute of Medical Science, St. Marianna University School of Medicine, Kawasaki, Japan, [2]Department of Pediatrics, Kochi Medical School, Nankoku, Japan, [3]Department of Pediatrics, Kanazawa Medical Center, Kanazawa, Japan, [4]St. Marianna University School of Medicine, Kanagawa, Japan.

Background/Purpose: Anti-endothelial cell antibodies (AECA) are autoantibodies that are detected frequently in vasculitis caused by, for example, Kawasaki disease (KD)**.** However, AECA target molecules have been poorly identified, which hampers our understanding of the roles of AECA. We aimed to detect target proteins of AECA comprehensively by proteomics and investigate their clinical importance in patients with KD.

Methods: We separated proteins extracted from human umbilical vein endothelial cells (HUVECs) and HeLa cells by 2-dimensional electrophoresis and transferred them onto membranes. Antigens that were positive only in the HUVEC samples but not in the HeLa cell samples were detected by western blot, using serum samples from patients with vasculitis. Next, we identified the detected proteins by peptide mass finger-printing and characterized their antigenicity by preparing recombinant antigens and antibodies to them. Furthermore, we investigated the frequency, clinical significance, and pathological roles of AECA against individual identified target autoantigens.

Results: We identified 63 proteins, one of which was peroxiredoxin 2 (Prx2), an anti-oxidative enzyme. Using immunocytochemistry, antibodies against Prx2 were found to bind to the cell surface of live HUVECs. IgG antibodies to Prx2 were detected in 60% (18/30) of the patients with KD, but not in healthy controls. Furthermore, IgG antibodies to Prx2 were detected in all tested KD patients with coronary artery lesions. Stimulating endothelial cells (ECs) with anti-Prx2 antibodies resulted in increased H_2O_2levels in the cell lysates. The anti-Prx2 antibodies also increased various inflammatory cytokine secretions significantly; in particular, IL-6 in HUVECs and G-CSF in human coronary artery ECs. In addition, anti-Prx2 antibodies induced the increased expression of adhesion molecules, such as E-selectin and ICAM-1, on ECs. EC ELISA indicated that Prx2 proteins were released from ECs stimulated by inflammatory cytokines. By themselves, Prx2 proteins induced various inflammatory cytokine secretions, such as IL-6, IL-8, TNF-α and GM-CSF, from ECs, and the expression of adhesion molecules such as E-selectin and ICAM-1 on ECs. Interestingly, these effects of Prx2 proteins were enhanced significantly by the appearance of anti-Prx2 antibodies and were inhibited significantly by blocking Toll-like receptor 4 (TLR4) signaling with a TLR4-specific inhibitory peptide. Clinically, the duration of fever (>37.5°C) in KD patients was significantly longer in the anti-Prx2–positive group than in the anti-Prx2–negative group. There was no significant difference in inflammatory markers such as white blood cell counts and C-reactive protein between both groups.

Conclusion: IgG antibodies to Prx2 are expected to be useful markers for KD. Expression of endothelial adhesion molecules and inflammatory cytokine production are induced by the binding of anti-Prx2 antibodies to Prx2 proteins on ECs, and by the activation of TLR4 by extracellular Prx2 proteins, which could result in endothelial injury. Furthermore, anti-Prx2 antibodies may cause endothelial injury by inhibiting the anti-oxidative activity of intracellular Prx2 proteins.

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Cost-Effectiveness Analysis Of Triple Therapy Versus Etanercept Plus Methotrexate In Early Aggressive Rheumatoid Arthritis: Analysis Based On The TEAR Trial. Hawre Jalal[1], Jeffrey R. Curtis[2], Stacey Cofield[2], Larry W. Moreland[3], James R. O'Dell[4] and Kaleb Michaud[5]. [1]University of Minnesota, Minneapolis, MN, [2]University of Alabama at Birmingham, Birmingham, AL, [3]University of Pittsburgh, Pittsburgh, PA, [4]Omaha VA and the University of Nebraska Medical Center, Omaha, NE, [5]National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: The long-term cost-effectiveness of triple therapy (methotrexate [MTX], sulfasalazine [SSZ], hydroxychloroquine [HCQ]) disease modifying anti-rheumatic drugs (DMARDs) compared to a combination of MTX and anti-TNF therapy in patients with early rheumatoid arthritis (RA) is unknown. In this study, we used patient-level data from the Treatment of Early Aggressive RA (TEAR) trial and the National Data Bank for Rheumatic Diseases (NDB) to evaluate the cost-effectiveness of immediate combination therapy (with biologic or non-biologic DMARDs) versus stepping up to combination therapy at 6 months if disease activity persists despite MTX monotherapy.

Methods: We developed a Markov simulation model to estimate quality-adjusted life years (QALYs) and costs associated with the treatment strategies examined in the TEAR trial. We evaluated four strategies: immediate triple (IT), immediate etanercept (IE), step-up triple (ST), and step-up etanercept (SE). The step-up strategies involved switching those with persistent disease activity (DAS28 >= 3.2) from MTX monotherapy to MTX plus either etanercept or triple therapy at 6 months. The simulation model extends the 2-year trial to the life-time horizon, using parameters taken from longitudinal NDB data for therapy discontinuation rates, HAQ transitions, and DAS28-HAQ-QALY mappings as well as the published literature for direct and indirect cost estimates. Annual discontinuation rates of triple therapy and etanercept from the NDB were estimated to be 22% and 10%, respectively. Those who discontinued were assumed to continue to receive methotrexate. Markov health states were defined by DAS28. DAS28 score transitions were obtained directly from individual patients in the trial. Death was modeled as an additional state with background mortality estimated from the 2007 US Life Tables. HAQ scores were used as a secondary variable to estimate QALYs, RA-specific mortality, and direct and indirect costs (e.g., due to productivity loss). We assumed a 3-month cycle length, and discounted both costs and effectiveness by 3% annually.

Results: The etanercept strategies (SE and IE) were more costly than the triple strategies (ST and IT) mainly due to treatment costs [Table]. The lifetime benefits from IT, ST and SE were numerically similar (within 0.06 QALYs). Although IE was more effective than IT, the incremental cost-effectiveness ratio (ICER) of IE relative to IT was $837,100/QALY. These results were robust to parametric sensitivity analyses.

Table. Cost-Effectiveness Analysis of TEAR Strategies

Treatment Strategies	Cost ($)	Effectiveness (QALY)	Incremental Cost ($)*	Incremental Effectiveness (QALY)*	ICER ($/QALY)
Immediate Triple (IT)	152,400	9.991			Reference Strategy
Step-up Triple (ST)	154,900	9.928	2500	−0.063	Excluded (dominated by IT, more effective)
Step-up Etanercept (SE)	269,500	9.929	117,100	−0.062	Excluded (dominated by IT, more effective)
Immediate Etanercept (IE)	338,100	10.213	185,700	0.222	837,100

* Compared to IT

Conclusion: We used patient-level data from the TEAR trial, and then projected their lifetime costs and benefits using the NDB. The benefits from all strategies were comparable, but biologics strategies were almost twice more expensive than triple strategies, producing ICERs greater than what most healthcare settings find acceptable.

Disclosure: H. Jalal, None; **J. R. Curtis**, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, Abb Vie, 2, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, Abb Vie, 5; **S. Cofield**, None; **L. W. Moreland**, None; **J. R. O'Dell**, None; **K. Michaud**, University of Nebraska Medical Center, 3, National Data Bank for Rheumatic Diseases, 3.

2647

Recombinant Monoclonal Antibodies Derived From Single CD19+ Synovial B Cells Of RA Patients With Tertiary Lymphoid Structures Display a Strong Immunoreactivity Towards Citrullinated Histones. Elisa Corsiero[1], Michele Bombardieri[1], Emanuela Carlotti[1], Hedda Wardemann[2], William H. Robinson[3] and Costantino Pitzalis[1]. [1]William Harvey Research Institute, QMUL, London, United Kingdom, [2]Max Planck Institute for Infection Biology, Berlin, Germany, [3]Stanford University School of Medicine, Stanford, CA.

Background/Purpose: Rheumatoid arthritis (RA) is characterised by breach of self-tolerance towards citrullinated proteins. Around 40% of patients display synovial tertiary lymphoid structures (TLS) with functional B cell follicles supporting a germinal-centre response and local autoantibody production (1). However, the nature of the main (auto)antigenic reactivity of synovial B cells is unknown. Here we characterized the autoreactive B cell response of lesional B cells isolated from TLS+ RA synovium.

Methods: Single CD19+ B cells were FACS sorted from synovial cell suspension of 4 TLS+ RA patients. RNA was used to amplify Ig VH and VL genes and PCR products were cloned and expressed as recombinant monoclonal antibodies displaying identical specificity of the original B cells (2). Recombinant antibodies were then tested 1) to determine the frequency of polyreactive clones and 2) to define their immunoreactivity towards native and citrullinated antigens using a synovial antigen microarray platform (3).

Results: We obtained 139 individual VH sequences of which 33% were IgM, 40% IgG, 27% IgA and 175 VL sequences and we generated a total of 66 complete (H+L chains) recombinant monoclonal antibodies. Analysis of the VH gene somatic mutation rate showed evidence of antigen selection and intra-synovial clonal diversification. No skewed distribution of the VH and VL gene usage was observed. Around 30% of synovial monoclonal antibodies were reactive towards citrullinated histones in the antigen microarray, in particular citH2A and citH2B. This reactivity was confirmed by citH2A and citH2B ELISA. Moreover, reactivity towards the citrullinated form of fibrinogen was observed.

Conclusion: Here we provided novel evidence that highly mutated, locally differentiated B cells within RA synovial germinal centre-like structures display a strong immunoreactive bias towards citrullinated histones. This suggests that citrullinated histones are the main antigens driving in situ B cell activation and differentiation sustaining the humoral autoimmune response within the RA joints.

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2648

Characterization Of Histidyl-tRNA Synthetase Specific Th Cell Response In Blood and Broncheoalveolar Lavage (BAL) Of Myositis Patients. Inka Albrecht[1], Eddie James[2], Maryam Fathi[3], Maryam Dastmalchi[1], Jessica Herrath[1], Vivianne Malmström[4] and Ingrid E. Lundberg[5]. [1]Karolinska University Hospital, Department of Medicine, Solna, Unit of Rheumatology, Stockholm, Sweden, [2]Benaroya Research Institute, Seattle, WA, [3]Karolinska Institutet, Department of Medicine, Respiratory Medicine Unit, Stockholm, Sweden, [4]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [5]Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Idiopathic inflammatory myopathy is a rare chronic inflammatory disease that is associated with the presence of autoantibodies pointing to a contribution of adaptive immune responses to disease manifestation. One of the most frequent myositis-specific autoantibodies is raised against histidyl-tRNA synthetase (Jo1). This autoantibody can be detected in 20% of myositis patients and is associated with interstitial lung disease (ILD). ILD may precede myositis symptoms implicating that the autoimmune reaction may start in the lungs. The release of Jo1 and fragments thereof into the extracellular milieu is believed to trigger both activation of T cells by antigen-presenting cells and influx of CCR5 expressing cells e.g. dendritic cells and Th1 lymphocytes. So far, there is only limited knowledge about Jo1-reactive T cells in myositis patients.

Methods: A candidate T cell epitope was predicted from the N-terminal part of the Jo-1 protein. In order to identify and characterize Jo1 antigen-specific Th cells, we stimulated peripheral blood (n=9) and BAL cells (n=3) of myositis patients with either recombinant Jo1 protein or the 13aa peptide covering the predicted epitope. Subsequently, $CD3^+CD4^+$T cells were analyzed for up-regulation of CD40L by flow cytometry at day 5. In addition, T cells were examined for effector functions by measuring expression of intracellular cytokines. Finally we compared the phenotype of T cells in blood and BAL (n=4) by staining for Th1 associated chemokine receptors.

Results: Stimulation of cells from blood and BAL with Jo1 protein caused a high up-regulation of CD40L on $CD3^+CD4^+$ T cells. Thus, Jo1-specific $CD4^+$T cells can be detected in both blood and BAL fluid of myositis patients. Upon activation, Jo1-specific T cells mainly show Th1 effector functions as evident by IFNg expression.

Stimulation of cells with the 13aa peptide corresponding to our novel candidate T cell epitope also resulted in a high up-regulation of CD40L.

Moreover, Jo1-reactive T cells are highly enriched in the BAL fluid. Those antigen-specific T cells have a highly pronounced Th1 phenotype as around 60% produce IFNg in response to antigen stimulation compared to only 10% IFNg responders in the corresponding blood samples. Interestingly, BAL T cells were all (100%) positive for CXCR3 and CCR5, two chemokine receptors specifically expressed on Th1 cells. In contrast, $CD4^+$T cells derived from blood only showed 20% positivity for CCR5 and CXCR3 expression, respectively.

Conclusion: In this study, we were able to demonstrate presence of Jo1-reactive $CD4^+$ T cells in inflammatory myopathies and thus provide evidence that those T cells do react with epitopes on this autoantigen. Jo1 reactive $CD4^+$ T cells are also present in the lung and show here pronounced Th1 effector functions. Moreover, we were able to identify a novel T cell epitope of the histidyl-tRNA synthetase. This will open up new ways for studying disease mechanisms and might provide novel starting points for therapeutic intervention.

Disclosure: I. Albrecht, None; **E. James**, None; **M. Fathi**, None; **M. Dastmalchi**, None; **J. Herrath**, None; **V. Malmström**, None; **I. E. Lundberg**, None.

2649

Rituximab For The Treatment Of IgG4-Related Disease: A Prospective Clinical Trial. Mollie Carruthers[1], Mark Topazian[2], Arezou Khosroshahi[3], Thomas Witzig[4], Judith Oakley[1], Philip Hart[4], Lauren Kelly[1], Lori Bergstrom[4], Suresh Chari[4] and John Stone[5]. [1]Massachusetts General Hospital, Boston, MA, [2]Mayo Clinic, Rochester, MA, [3]Emory University School of Medicine, Atlanta, GA, [4]Mayo Clinic, Rochester, MN, [5]Massachusetts General Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: IgG4-related disease (IgG4-RD) is a multiorgan, fibro-inflammatory disorder. An open label pilot trial of rituximab (RTX) in IgG4-RD conducted at twocentershas enrolled 29 of the targeted 30 patients. We report preliminary results on28 patientsfollowed for a minimum of one month.

Methods: The trial was approved by institutional review boards at the Massachusetts General Hospital and Mayo Clinic. All patients had histopathologically-proven diagnoses of IgG4-RD, includingat least two out of the three major featuresoflymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis AND immunoperoxidase staining >10 IgG4+ plasma cells per HPF and a >40% IgG4/IgG ratio. All patients had active disease, based on the IgG4-RD Responder Index (IgG4-RD RI). Patients were treated with RTX(1000 mg) times two doses (days 0 and 15) but not treated with maintenance RTX. Patients received methylprednisolone 100 mg with each RTX dose. Trial visits were performed at 1, 3, 5, 6, 8, 10, and 12 months after the first rituximab infusion. The primary outcome was defined by three measures: 1) disease response (decrease of responder index of ≥2 points from baseline); 2) no disease flares before month 6; and, 3) no glucocorticoids between months 2 and 6. Complete remission was defined as an IgG4-RD RI disease activity score of zero.

Results: The organ system involvement among patients in the trial spanned the full spectrum of IgG4-RD, including the orbits, salivary glands, hypopharynx, lungs, lymph nodes, pericardium, pancreas, biliary tree, retroperitoneum, kidney, prostate, and others. The mean IgG4-RD RI at baseline was 12.7 (range: 5 – 36).The mean serum IgG4 concentration was 534 mg/dL (normal < 121; range: 22 – 4780), but 12 patients (43%) had normal values at baseline. Prednisone was used concomitantly with RTX at baseline for remission induction in only 2 of the 28 patients. Twenty-six of the 28 patients followed for at least one month and 22 of 24 followed for three months achieved steroid-free achieved disease responses (93% and 92% at these two timepoints, respectively). Among the

23 patients completing six months of follow-up to date, 20 (87%) have achieved the primary outcome. Only 2 of the 28 patients required an increase in prednisone dose after Month 1. Two patients were hospitalized during the study, one for Legionnaire's disease (pre-baseline infection) and the other for a cold agglutinin-mediated autoimmune hemolytic anemia. No serious adverse events related to rituximab were reported.

Conclusion: Rituximab has promise as a safe, effective treatment for IgG4-RD.Excellent disease responses have been observed to date despite the absence of concomitant glucocorticoid use in this trial.

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ACR Concurrent Abstract Session
Antiphospholipid Syndrome
Tuesday, October 29, 2013, 2:30 PM–4:00 PM

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Silent Ischemic Heart Disease In Patients With Primary Antiphospholipid Syndrome. Antonio R. Cabral[1], Gregoria Gómez-Hernández[2], Martha Morelos-Guzmán[3], Tatiana Rodriguez-Reyna[4], Carlos Alberto Núñez-Alvarez[5] and Jorge Vazquez-Lamadrid[3]. [1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubirán, Mexico, Mexico, [2]Instituto Nacional De Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, Mexico, [3]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico, [4]National Institute of Medical Sciences and Nutrition, Mexico City, Mexico, [5]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

Background/Purpose: Premature atherosclerosis in PAPS is still a matter of debate.

Patients and Methods: To determine the prevalence of ischemic heart disease in PAPS patients. *Inclusion criteria:* Patients ≥18 years of age included in the Patients Registry of the Department of Immunology and Rheumatology from our Institution with the diagnosis of PAPS (Sydney and Alarcón-Segovia et al classifications criteria). All patients gave their written informed consent. *Exclusion criteria:* creatinine >1.5 mg/dl, BP persistently >150/90 in spite of treatment, diabetes mellitus (I or II), dyslipidemia, SLE, positive anti-dsDNAcd (ELISA), positive antinucleosome antibodies (ELISA), asthma and/or pregnancy. All patients had a coronary CAT scan both at rest and under stress myocardial perfusión with adenosine (140 μg/kg/min for 3 minutes) with a 64 channel tomograph (G.E Milwaukee, USA). We also determined new aCL (IgG, IgA e IgM), anti-β_2GP-I (IgG, IgM e IgA), anti-dsDNA and anti-nucleosomes (all by ELISA). Lipid profile and serum creatinine were also newly determined. Our study was approved by the IRB of our Institution.

Results: We studied 24 patients (15 women) with PAPS with a mean age of 29 ± 9.8 years at time of study and 9.5 ± 5.5 years of disease duration. None of them had a history of coronary symptoms. We found that 14/24 patients (58%) had abnormal myocardial perfusion under stress with adenosine, 95% of them with normal coronary arteries. No valvular abnormalities were found. Only one patient (4%) had a previous EKG with ischemic abnormalities. The BMI for the whole group was 26.1 ± 4.5 kg/m^2 and 54% had history of cigarette consumption (TI= 9.7 ± 3.2). aCL y anti-β_2GP-I (any isotype) were positive in 86 and 96% of cases, respectively. We confirmed that no patient had positive anti-DNA, antinucleosomes nor hyperlipidemia.

Conclusion: We found no direct evidence of epicardial coronary atherosclerosis with aPL in PAPS patients, even after 10 years of follow-up. We also show a high prevalence of abnormal myocardial perfusión (58%) in PAPS patients with normal epicardial coronary arteries. Our study suggests silent myocardial ischemia perhaps due to endothelitis and/or microthrombosis in patients with primary antiphospholipid syndrome.

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2651

The Association Between Antiphospholipid Antibodies and Related Clinical Outcomes: A Critical Review Of The Literature. Cecilia B. Chighizola[1], Laura Andreoli[2], Alessandra Banzato[3], Guilherme Ramires de Jesus[4], Guillermo J. Pons-Estel[5], Doruk Erkan[6] and On Behalf of APS Action[7]. [1]Istituto Auxologico Italiano, University of Milan, Cusano Milanino, Italy, [2]Rheumatology Unit, University of Brescia, Brescia, Italy, [3]Department of Cardiac Thoracic and Vascular Sciences, University of Padua, Padua, Italy, [4]Department of Obstetrics, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil, [5]Department of Autoimmune Diseases, Institut Clìnic de Medicina i Dermatologia, Hospital Clìnic, Barcelona, Spain, [6]Hospital for Special Surgery, New York, NY, [7]APS ACTION, New York, NY.

Background/Purpose: AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking (APS ACTION) is an international network that has been created to design and conduct APS clinical trials. A basic need of APS ACTION was to accurately assess the relationship between antiphospholipid antibodies (aPL) and the different aPL-associated outcomes, i.e., pregnancy morbidity (PM, comprising pregnancy loss [PrL], early PrL, late PrL, intrauterine growth restriction [IUGR], pre-eclampsia [PEC], severe PEC, eclampsia [EC], and HELLP syndrome), stroke (ST), myocardial infarction (MI), and deep venous thrombosis (DVT).

Methods: The search for "aPL" and multiple keywords regarding the outcomes of interest was completed in PubMed. A total of 117 full-text papers assessing the rate of aPL positivity in patients and controls were retrieved; 97 of these studies statistically investigated the relationship between aPL and clinical outcomes. We analyzed the reported association between aPL and the clinical outcomes for each criteria test (anticardiolipin antibodies [aCL], anti-β_2-glycoprotein-I antibodies [a$\beta_2$2GPI], and lupus anticoagulant test [LA]), and then for all three criteria tests combined.

Results: The table reports the number of studies, median number of patients [IQR], and the association between aPL and related outcomes based on different aPL tests. There was a 25–100% association between aPL and clinical outcomes depending on the aPL type and outcome analyzed. However, the literature was impinged by several limitations including: a) only 12% of the studies used the three available criteria aPL tests; b) 4% used a cut-off conforming to international guidelines (low-titer cut-off was used in 22% and medium-titer cut-off in 8%); c) the sample sizes were rather small, with 64% including less than 100 patients; d) only 19% of the studies confirmed that aPL was persistent; and e) 57% of the studies did not have a prospective design.

OUTCOME (# of studies) (Median # of patients [IQR])	aCL (+) Association (N (+)/N, %)	ab2GPI (+) Association (N (+)/N, %)	LA (+) Association (N (+)/N, %)	Overall aPL (+) Association (N (+)/N, %)
PM				
- PrL (n: 9) (114 [48.25–213.75])	**7/8** (88%)	**3/4** (75%)	**7/7** (100%)	**8/9** (89%)
- Early PrL (n: 3) (113 [113–137])	**2/3** (66.6%)	**1/2** (50%)	–	**2/3** (67%)
- Late PrL (n: 7) (96 [26–158])	**6/8** (75%)	**2/3** (67%)	**5/6** (83%)	**5/7** (71%)
- IUGR (n: 3) (22 [14–36])	**1/3** (33%)	–	**0/1** (0%)	**1/3** (33%)
- PEC (n: 12) (87.5 31.75–216.75])	**5/11** (46%)	**0/1** (0%)	**3/5** (60%)	**5/12** (42%)
- Severe PEC (n: 8) (41.4 23.75–74.75])	**5/7** (71%)	**1/2** (50%)	**4/4** (100%)	**6/8** (75%)
- EC (n: 4) (25 [14–25.5])	**0/3** (0%)	–	**0/1** (0%)	**1/3** (25%)
- HELLP (n: 3) (44.5 [25.5–59.75])	**1/3** (33%)	**0/2** (0%)	**0/1** (0%)	**2/3** (67%)
ST (n: 21) (116.5 [81–189.25])	**15/21** (71%)	**2/4** (50%)	**6/9** (67%)	**10/21** (48%)
MI (n: 24) (90 [34–167])	**12/22** (55%)	**5/7** (71%)	**3/5** (60%)	**12/24** (50%)
DVT (n: 21) (122 [92–317])	**8/19** (42%)	**4/6** (67%)	**7/11** (64%)	**10/21** (48%)

Conclusion: The positive association between aPL and clinical outcomes included in the Updated Sapporo APS Classification Criteria is not supported by every study, the association is particularly weak for early PrL, IUGR, PEC, EC and HELLP Syndrome. Given the limitations of the literature, well-designed general population studies as well as large scale APS registries are warranted to further investigate the relationship between aPL and related manifestations. We hope that APS ACTION will help improving upon existing aPL/APS literature.

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2652

Ovarian Reserve In Women With Primary Antiphospholipid Syndrome. Lucas Yamakami[1], Paulo Serafini[2], Daniel B. Araujo[3], Eloisa Bonfá[4], Elaine P. Leon[4], Edmund C. Baracat[4] and Clovis A. Silva[5]. [1]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [2]MD; PhD, Sao Paulo, Brazil, [3]Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, Brazil, [4]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [5]University of São Paulo, São Paulo, Brazil.

Background/Purpose: Aging, smoking, obesity and surgery have been found to influence the quantity and quality of primordial follicles in ovaries and, ultimately, the ovarian reserve. Other conditions such as autoimmune oophoritis, ovarian ischemia and hemorrhage may also result in diminished ovarian reserve. Female primary antiphospholipid syndrome (PAPS) patients are susceptible to these complications but there is no systematic study assessing this ovary abnormality.

Methods: We screened 85 female patients between 18 to 40 years old with APS. Of these, 67 patients were excluded due to association with other autoimmune diseases (n=42), contraindication or unwillingness to stop hormonal contraceptive (n=21), current pregnancy or breastfeeding (n=3) and previous ovarian surgery (n=1). Therefore, a cross sectional study was conducted in 18 PAPS patients. Control group included 24 healthy volunteers recruited in primary care services according to the same inclusion and exclusion criteria. Complete ovarian function was assessed on the early follicular phase of the menstrual cycle, blinded to the other parameters of ovarian function. Ovarian reserve was assessed by: FSH, luteinizing hormone (LH), estradiol, anti-Müllerian hormone (AMH) and antral follicle count (AFC) in patients without hormonal contraception for at least 12 consecutive months. Anti-corpus luteum antibody (anti-CoL) was detected by immunoblot technique.

Results: Arterial thrombosis, venous thrombosis and pregnancy morbidity were observed in 17%, 83% and 33% of the PAPS patients, respectively. Lupus anticoagulant, anticardiolipin and anti-β2-GPI were detected in 67%, 83% and 11% of these patients. The mean of current age was similar between PAPS and controls (33.0 $\pm$ 5.0 vs. 30.4 $\pm$ 7.0 years old; p=0.189). Body mass index, smoking and the remaining demographic features were similar in both groups (p>0.05). Regarding ovarian reserve tests, the frequencies of low and very low AFC were significantly higher in PAPS patients compared to controls (56% vs. 22%, p=0.042; 37% vs. 9%, p=0.045, respectively). Trends to higher frequencies of reduced, low and negligible AMH levels were found in PAPS patients (p=0.08; p=0.07 and p=0.07; respectively). FSH, LH and estradiol were similar in PAPS patients and controls (p>0.05). Anti-CoL was solely observed in two PAPS patients (11% vs. 0%; p=0.177), one presented reduced ovarian reserve.

Conclusion: The present report was the first to identify a high prevalence of diminished ovarian reserve in PAPS patients reinforcing the need of fertility counseling and family planning. Further study is necessary regarding the mechanisms by which PAPS causes ovarian impairment, as well as the most appropriate fertility treatment for these patients.

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2653

Low Vitamin D Is Associated With Increased Risk of Venous Thrombosis in Systemic Lupus Erythematosus, Regardless of Lupus Anticoagulant Status. Michelle Petri and Hong Fang. Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Vitamin D deficiency is common in SLE. Vitamin D deficiency is also associated with activation of Tissue Factor. In cross-sectional studies, vitamin D deficiency is more common with APS and thrombosis. We determined whether vitamin D deficiency was associated with thrombosis in SLE.

Methods: 1131 SLE patients had a measure of 25-OH vitamin D. Twenty-seven% had a history of any thrombosis, 15% arterial thrombosis (defined as stroke, myocardial infarction, digital gangrene or other arterial thrombosis), and 17% venous thrombosis (defined as DVT or PE, or other venous thrombosis).

Results: Table 1 shows that low 25-OH vitamin D (<32 ng/ml) was associated with all thrombosis and with venous thrombosis, but not with arterial thrombosis.

Table 1. Association of 25-OH vitamin D level with thrombosis.

Variable	Number (%) with the characteristic: Vitamin D <32 (n=667)	Vitamin D ≥32 (n=464)	Adjusted p-value
All thrombosis	199 (30%)	105 (23%)	0.0017*
Arterial thrombosis	107 (16%)	63 (14%)	0.43**
Venous thrombosis	130 (19%)	59 (13%)	0.0004*
Same-day lupus anticoagulant	111 (17%)	62 (14%)	0.089§

*Adjusted for age at last assessment, ethnicity, gender, and history of lupus anticoagulant (LAC).
**Adjusted for age at last assessment, ethnicity, gender, history of LAC, history of hypertension, and history of hypercholesterolemia.
§Adjusted for age at last assessment, ethnicity, and gender.
Vitamin D deficiency was not associated with any gene signature (interferon, BAFF, neutrophil, or plasma cell).

Conclusion: Vitamin D deficiency in SLE is associated with venous (but not arterial thrombosis) in adjusted analyses that controlled for other risk factors, including lupus anticoagulant. Vitamin D deficiency is not associated with the interferon gene signature. Given that vitamin D deficiency is associated with Tissue Factor expression and that it is already known to be associated with thrombosis in antiphospholipid patients, this is another rationale for vitamin D measurement and supplementation in SLE. Clinical trials, already underway, in the general population may shed further light on the anti-thrombotic potential of vitamin D.

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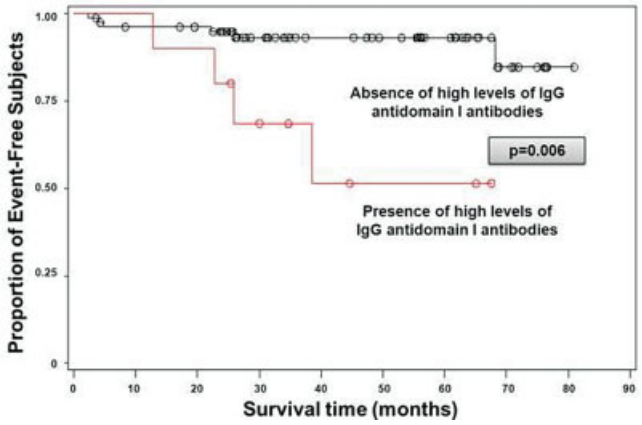
IgG Antibodies Directed Against Domain I Of β_2-Glycoprotein I Are Significant Predictors Of Thromboembolic Events In Patients With Antiphospholipid Antibodies. A Prospective Cohort Study. Stephane Zuily[1], Bas de Laat[2], Francis Guillemin[3], Pierre Kaminsky[4], Hilde Kelchtermans[5], Roger Albesa[6], Gary L. Norman[6], Anne-Christine Rat[7], Philip de Groot[8], Thomas Lecompte[9], Veronique Regnault[10] and Denis Wahl[1]. [1]CHU de Nancy, Vascular Medicine Division and Regional Competence Center For Rare Vascular And Systemic Autoimmune Diseases, Nancy, F-54000, France; Inserm, UMR_S 1116, Nancy, F-54000, France; Université de Lorraine, Nancy, F-54000, France, Nancy, France, [2]Biochemistry, CARIM, Maastricht University, The Netherlands; Clinical Chemistry and Hematology, UMC Utrecht, The Netherlands; Synapse BV, Maastricht, The Netherlands; Sanquin Research, Amsterdam, The Netherlands, Maastricht, Netherlands, [3]CHU Nancy, Clinical Epidemiology and Evaluation, Université de Lorraine, Paris Descartes University, APEMAC, EA 4360, Nancy, France, [4]Université de Lorraine, Nancy, F-54000, France; CHU de Nancy, Orphan disease unit, Nancy, F-54000, France;, Nancy, France, [5]Biochemistry, CARIM, Maastricht University, The Netherlands; Synapse BV, Maastricht, The Netherlands, Maastricht, Netherlands, [6]INOVA Diagnostics, San Diego, CA, [7]Université de Lorraine, Nancy, F-54000, France; Inserm, CIC-EC CIE6, Nancy, F-54000, France; CHU de Nancy, Clinical Epidemiology and Evaluation Department, Nancy, F-54000, France; CHU de Nancy, Rheumatology department, Nancy, France, [8]Clinical Chemistry and Hematology, UMC Utrecht, The Netherlands, Utrecht, Netherlands, [9]Inserm, UMR_S 1116, Nancy, F-54000, France; Université de Lorraine, Nancy, F-54000, France; CHU de Nancy, Haematology Laboratory, Nancy, F-54000, France; Division of Haematology, HUG, Geneva, Switzerland (current address), Geneva, Switzerland, [10]Inserm, UMR_S 1116, Nancy, F-54000, France; Université de Lorraine, Nancy, F-54000, France; CHU de Nancy, Contrat d'interface, Nancy, F-54000, France, Nancy, France.

Background/Purpose: Our objective was to prospectively determine the prognostic significance of laboratory variables regarding thrombotic events during follow-up, including novel assays IgG antibodies directed against domain I of β_2-glycoprotein I (antiDI) and IgG anti-phosphatidylserine-prothrombine (antiPS-PT) antibodies in patients with systemic lupus erythematosus (SLE) and/or antiphospholipid antibodies (aPL).

Methods: We performed a prospective cohort study in a French University Hospital and tertiary care center. Consecutive patients with SLE and/or aPL without ongoing anticoagulant treatment were enrolled. The outcome was the time to the first incident thrombotic event. Blood

was drawn at baseline. ELISA antiDI and antiPS-PT antibodies assays were performed together with traditional assays (lupus anticoagulant, anticardiolipin and anti-β_2-glycoprotein I antibodies).

Results: Ninety-two patients (median age 40 years [interquartile range IQR: 29–58]; 74 women) were followed-up for a median duration of 35 months (IQR: 26–62; 320 patient-years). Thrombosis during follow-up occurred in 11 patients (2 strokes, 1 myocardial infarction, 1 splanchnic arterial thrombosis, 2 pulmonary embolisms, 2 deep vein thromboses, 3 small vessels thromboses). Triple positivity, high levels of antiDI and of antiPS-PT antibodies were found in 17, 10 and 13 patients respectively. In univariate analysis, high levels of antiDI (HR=6.41 [CI95%; 1.72–23.89], p=0.006) and antiPS-PT antibodies (HR=3.62 [CI95%, 1.06–12.37], p=0.04) were significantly predictive of incident thrombotic event while triple positivity did not reach statistical significance (HR=3.09 [CI95%; 0.90–10.66], p=0.07). In multivariate analysis (stepwise method), high levels of antiDI antibodies remained the only laboratory variable significantly predictive of incident thrombotic events overtime.



Conclusion: High levels of IgG antibodies directed against the domain I of the β_2-glycoprotein I are significant predictors of thrombosis in patients with aPL and/or SLE.

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Therapeutic Effect Of β2GPI and Its Synthetic derivative Loaded Tolerogenic Dendritic Cells In Experimental Antiphospholipid Syndrome, Is Associated With miRNA 23b, 142-3p and 221 Expression and Tregs Upregulation. Miri Blank[1], Silvia S. Pierangeli[2], Honorio Torres-Aguilar[3] and Yehuda Shoenfeld[4]. [1]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, affiliated to Sackler Medical School, Tel Aviv University, Ramat Gan, Israel, [2]University of Texas Medical Branch, Galveston, TX, [3]National Center for Blood Transfusion, Mexico City, Mexico, [4]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Tel-Aviv, Israel.

Background/Purpose: The importance of beta-glycoprotein I (beta2GPI)-specific CD4+ T cells in the development of pathogenic processes in patients with antiphospholipid syndrome (APS) and APS mice models is well established. Tolerogenic dendritic cells (tDCs) have the potential to control the outcome of autoimmunity by modulating the immune response. Previously we showed that human tDCs induced with IL-10 and TGFbeta1, loaded with beta2GPI ameliorated effector/memory CD4+ T cells response in patients with APS in-vitro (Ann Rheum. Dis 2012). The aim of this study was to uncover the mechanisms that define the tolerogenic effect of beta2GPI or beta2GPI synthetic derivatives specific tDCs on experimental APS.

Methods: tDCs were generated *in-vitro* from naïve mice bone marrow cells in the presence of TGFbeta and IL-10, cDCs were supplemented with GM-CSF. All the DCs were LPS maturated, pulsed with beta2GPI or beta2synthetic derivatives control peptide and candidin and phenotyped by FACS. miRNA expression were defined by RT-PCR and MAPKs by MAPKs protein-arrays. beta2GPI T cell response to tDCs and cDCs by CFSC and FACS analyses. The tDCs and cDCs were subjected subcutaneously into mice with experimental APS induced by beta2GPI. $CD4^+CD25^+FOXP3^+$ Treg cells were analyzed by FACS. Adoptive transfer experiments were conducted by passive transfer of Tregs from the tDCs –injected mice to APS mice. Cytokine expression of IFNgamma, IL-17, TGFbeta and IL-10 by RT-CR.

Results: tDCs expressed miRNA 23b, 142-3p and 221, whereas cDCs were characterized in expression of miRNA 146a and miRNA155. tDCs specific to beta2GPI and its synthetic derivative were able to decrease b2GPI response manifested by decreased beta2GPI T cell response by 75%–87% while cDCs did not show any significant response, $p<0.001$. Moreover, we were able to show inhibition of circulating anti-beta2GPI antibodies titers ($p<0.002$) and inhibition of fetal loss by 67% was documented in tDCs recipient APS mice in comparison to 8% in the cDCs recipient mice, $p<0.02$. Enhanced expression of CD4+CD25+FOXP3+Tregs by 21% in tDCs injected mice in comparison to 5% in the cDCs injected APS mice was exemplified by FACS. Reduced expression of IFNgamma and L-17 by 5.2 times and enhanced expression of TGFbeta and IL-10 by 6.8 fold was illustrated by RT-PCR. A significant amelioration of all the above parameters were noticed as well in the Treg transferred-APS recipient mice (e.g decreased beta2GPI T cell response, circulating anti-beta2GPI antibodies, and IFNgamma/IL-17). tDCs uploaded with beta2GPI had beneficial effect on the therapeutic properties than the beta2GPI synthetic derivatives, $p>0.05$.

Conclusion: beta2GPI tDCS have the potential to ameliorate experimental APS by upregulation of Tregs and proinflammatory cytokines. beta2GPI tDCS may offer a novel approach for developing personalized therapy for APS patients.

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ACR Concurrent Abstract Session
Epidemiology and Health Services Research VI: Risk Factors in Rheumatic Disease Susceptibility
Tuesday, October 29, 2013, 2:30 PM–4:00 PM

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Performance Of Prediction Models For Rheumatoid Arthritis Serologic Phenotypes Among Women Using Family History, Genetics and Environmental Factors. Jeffrey A. Sparks[1], Chia-Yen Chen[2], Xia Jiang[3], Linda T. Hiraki[4], Lars Klareskog[5], Lars Alfredsson[3], Karen H. Costenbader[1] and Elizabeth W. Karlson[1]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Harvard School of Public Health, Boston, MA, [3]Karolinska Institutet, Stockholm, Sweden, [4]Brigham and Women's Hospital, Harvard School of Public Health, Boston, MA, [5]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Family history (FH) of autoimmunity, genetics, and environmental factors have been associated with RA. The area under the receiver operating characteristic curve (AUC) can measure the ability of prediction models to discriminate between cases and controls. We aimed to evaluate the performance of prediction models for RA based on family history, genetics, and environmental factors.

Methods: We developed RA prediction models in a nested case-control study within Nurses' Health Study (NHS) and replicated in women in the Epidemiological Investigation in RA (EIRA) study. NHS cases were validated by chart review and matched to controls by age, menopausal status and post-menopausal hormone use. EIRA new-onset RA cases were matched to controls by age and region. All cases were Caucasian and satisfied the 1987 ACR criteria for RA classification. FH data were obtained from questionnaires (NHS) and registries (EIRA). Serologic status was defined by +RF/ACPA for NHS and by +ACPA for EIRA. Weighted genetic risk scores were calculated for cases and controls based on 39 genetic markers associated with RA in prior studies. Logistic regression models were used to calculate the AUC and 95% confidence intervals (CI) for seropositive/ACPA+ RA and seronegative/ACPA- RA. Model components were based on family history (FH, first-degree relative with RA or lupus in NHS and RA in EIRA), environmental (E: age, smoking pack-years, body mass index, alcohol intake, education, and parity), genetic factors (G), and HLA shared epitope-smoking interaction (GEI). Analyses stratified by FH were performed using models based on E, G, and GEI components.

Results: We analyzed 492 cases and 501 controls in NHS women and 1,244 cases and 971 controls in EIRA women with FH data. The complete model (FH+E+G+GEI) for seropositive/ACPA+ RA had an AUC of 0.71 (95% CI 0.67–0.75) in NHS and 0.78 (95% CI 0.76–0.80) in EIRA (**Table 1**). For women with +FH, the complete model (E+G+GEI) had an AUC of 0.85 (95% CI 0.77–0.92) for seropositive RA in NHS and an AUC of 0.85 (95% CI 0.78–0.92) for ACPA+ RA in EIRA (**Table 2**). For seronegative/ACPA- RA with +FH, E+G+GEI models had an AUC of 0.85 (95% CI 0.63–0.72) in NHS and an AUC of 0.80 (95% CI 0.69–0.91) in EIRA.

Table 1. Areas under the receiver operating characteristic curves (AUC) for RA prediction models using family history (FH), environment (E), genetics (G), and gene-environment interaction (GEI) in the Nurses' Health Study (NHS) and the Epidemiologic Investigation of RA (EIRA) study.

	NHS AUC (95% CI)		EIRA AUC (95% CI)	
Models	**Seropositive RA**	**Seronegative RA**	**ACPA+ RA**	**ACPA- RA**
FH	0.58 (0.55–0.61)	0.59 (0.56–0.62)	0.53 (0.52–0.55)	0.51 (0.50–0.52)
E	0.65 (0.61–0.69)	0.58 (0.54–0.63)	0.69 (0.67–0.72)	0.65 (0.62–0.68)
G	0.59 (0.55–0.63)	0.58 (0.54–0.63)	0.72 (0.69–0.74)	0.53 (0.50–0.56)
FH+E	0.69 (0.65–0.73)	0.66 (0.61–0.70)	0.71 (0.68–0.73)	0.65 (0.62–0.68)
FH+E+G	0.70 (0.66–0.74)	0.68 (0.63–0.72)	0.78 (0.76–0.80)	0.65 (0.63–0.69)
FH+E+G+GEI	0.71 (0.67–0.75)	0.68 (0.63–0.72)	0.78 (0.76–0.80)	0.66 (0.63–0.69)

E models: age, cigarette smoking pack-years, body mass index, alcohol intake, education, and parity
FH models: family history
G models: weighted genetic risk scores based on 39 RA associated markers
GEI models: HLA shared epitope-cigarette smoking interaction

Table 2. Areas under the receiver operating characteristic curves (AUC) for RA prediction models stratified by family history (FH) using environment (E), genetics (G), and gene-environment interaction (GEI) in the Nurses' Health Study (NHS) and the Epidemiologic Investigation of RA (EIRA) study.

	NHS AUC (95% CI)			
	+FH		**-FH**	
Models	**Seropositive RA**	**Seronegative RA**	**Seropositive RA**	**Seronegative RA**
E	0.82 (0.74–0.90)	0.78 (0.68–0.87)	0.67 (0.62–0.71)	0.61 (0.55–0.66)
G	0.63 (0.52–0.75)	0.64 (0.52–0.75)	0.58 (0.54–0.63)	0.58 (0.53–0.62)
E+G	0.84 (0.77–0.92)	0.79 (0.70–0.88)	0.68 (0.64–0.72)	0.62 (0.57–0.67)
E+G+GEI	0.85 (0.77–0.92)	0.85 (0.77–0.92)	0.68 (0.64–0.73)	0.63 (0.58–0.68)

	EIRA AUC (95% CI)			
	+FH		**-FH**	
Models	**ACPA+ RA**	**ACPA- RA**	**ACPA+ RA**	**ACPA- RA**
E	0.77 (0.68–0.86)	0.78 (0.67–0.90)	0.69 (0.67–0.72)	0.65 (0.62–0.68)
G	0.74 (0.65–0.84)	0.57 (0.44–0.71)	0.71 (0.69–0.73)	0.53 (0.50–0.56)
E+G	0.84 (0.76–0.91)	0.80 (0.69–0.92)	0.77 (0.75–0.79)	0.65 (0.62–0.68)
E+G+GEI	0.85 (0.78–0.92)	0.80 (0.69–0.91)	0.77 (0.75–0.79)	0.66 (0.63–0.69)

E models: age, cigarette smoking pack-years, body mass index, alcohol intake, education, and parity
G models: weighted genetic risk scores based on 39 RA associated markers
GEI models: HLA shared epitope-cigarette smoking interaction

Conclusion: We have developed and replicated prediction models for RA in women using family history, environment, and genetics. These models had higher discrimination for seropositive/ACPA+ RA and performed best in stratified analysis for those with family history. For women with family history of RA or lupus, environmental and genetic data may be able to predict the development of RA.

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Interactions Between Cigarette Smoking, Body Mass Index and Inflammatory Cytokine Levels In Determining The Risk Of Developing Rheumatoid Arthritis. Elizabeth V. Arkema[1], Susan Malspeis[2], Bing Lu[2], Linda T. Hiraki[3], Elizabeth W. Karlson[4] and Karen H. Costenbader[5]. [1]Harvard School of Public Health, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]Brigham and Women's Hospital, Harvard School of Public Health, Boston, MA, [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [5]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Smoking and high body mass index (BMI) are risk factors for RA. Both are associated with increased systemic inflammation, with elevated C-reactive protein, interleukin (IL)-6, and tumor necrosis alpha (TNFα). We and others have previously reported that circulating plasma levels of IL-6 and TNFRII (a proxy for TNFα) are elevated years prior to RA onset. We hypothesized that there may be modification of the relationship between plasma levels of IL6 and TNFRII and the future risk of RA according to an individual's BMI and smoking history.

Methods: We conducted a nested case-control study using stored plasma samples from the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII), prospective cohort studies of U.S. female nurses. Cases were women diagnosed with RA at least 3 months after blood draw. We identified 3 controls for each case randomly chosen from subjects with stored blood, matched on year of birth, race, menopausal status/postmenopausal hormone use, time of day, blood draw fasting status and menstrual cycle timing. Smoking (pack-years) and BMI were obtained from the questionnaire cycle prior to blood collection. IL6 and TNFRII were measured by ELISA. Multivariable logistic regression models were used to calculate odds ratios (OR) and 95% CIs for RA risk associated with a 1 unit increase in log-TNFRII or log-IL6, adjusting for matching factors, alcohol intake, and menstrual regularity. We tested for multiplicative and additive interactions between cytokine levels, and smoking (never or $<$ 10 vs. $\geq$ 10 pack years) and BMI $<$25 (normal weight) vs. $\geq$25 kg/m2 (overweight).

Results: Among 62,439 women followed in the NHS cohorts with stored blood, incident RA was confirmed in 196 subjects, who were matched to 588 healthy participants. Mean age at RA diagnosis was 60.1 years (10.0 SD), 54% RF or anti-CCP seropositive. Mean duration until RA diagnosis was 7.6 years (4.5 SD). A significant association between IL6 and future RA risk was found (**Table**). The OR for TNFRII was elevated but non-significant. We observed a significant multiplicative interaction between TNFRII and BMI (p=0.02). The relationship between plasma TNFRII cytokine elevation and future RA risk was stronger among women with higher BMI than those of normal weight. We did not detect any significant additive or multiplicative interactions between IL6 and BMI, or IL6 or TNFRII and smoking.

Table. Odds Ratios for RA among Women in the Nurses' Health Studies Blood Cohort

	Odds Ratio (95%CI)
Smoking ($\geq$ 10 pack-years vs.$<$ 10 pack-years)	**1.78 (1.25, 2.52)**
BMI ($\geq$25 kg/m2 [overweight]) vs. $<$25 [normal weight])	**1.55 (1.11, 2.17)**
TNFRII	
TNFRII- per one unit increase	1.42 (0.78, 2.56)
Interaction between TNFRII and BMI (overweight vs. normal)	
RERI*	0.24 (−0.37, 0.85)
ROR**	**4.11 (1.29, 13.09)**
Interaction between TNFRII and Smoking ($\geq$ 10 pack-years vs. $<$ 10 pack-years)	
RERI*	−0.11 (−2.95, 2.73)
ROR**	1.65 (0.52, 5.29)
IL6	
IL6- per one unit increase	**1.32 (1.04, 1.68)**
Interaction between IL6 and BMI (overweight vs. normal)	
RERI*	0.24 (−0.48, 0.97)
ROR**	1.08 (0.68, 1.74)
Interaction between IL6 and Smoking ($\geq$ 10 pack-years vs. $<$ 10 pack-years)	
RERI*	0.89 (−0.17, 1.95)
ROR**	1.43 (0.88, 2.33)

TNFRII and IL6 were log-transformed in all models.
* RERI=additive interaction, relative excess risk due to interaction
** ROR= multiplicative interaction, ratios of odds ratios

Conclusion: In this large prospective cohort study of women with blood collected up to 14 years prior to the diagnosis of RA, a multiplicative interaction was found between high BMI and elevated TNFRII level in increasing the risk of RA. This suggests that BMI and TNFα elevation may belong to the same biologic pathway in RA pathogenesis.

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Dipeptidyl Peptidase-4 Inhibitors In Type 2 Diabetes May Reduce The Risk Of Autoimmune Diseases. Seoyoung C. Kim[1], Sebastian Schneeweiss[1], Robert J. Glynn[1], Michael Doherty[1], Allison Goldfine[2] and Daniel H. Solomon[3]. [1]Brigham and Women's Hospital, Boston, MA, [2]Joslin Diabetes Center, Boston, MA, [3]Harvard Medical School, Brigham and Women's Hospital, Division of Rheumatology, Division of Pharmacoepidemiology, Boston, MA.

Background/Purpose: Dipeptidyl peptidase-4 inhibitors (DPP4i), such as linagliptin, saxagliptin, and sitagliptin, are oral glucose-lowering drugs for type 2 diabetes mellitus (T2DM). DPP4 is a transmembrane glycoprotein widely expressed in various cells including fibroblasts, T lymphocytes, and macrophages, and has a co-stimulatory function in the immune response. Altered levels of DPP4 activity were noted in patients with autoimmune diseases (AD) such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), psoriasis, and multiple sclerosis (MS). The objective of this study was to estimate the incidence rate (IR) of systemic AD such as RA, SLE, psoriasis, MS, and IBD in patients with T2DM initiating a DPP4i drug compared to those initiating non-DPP4i oral hypoglycemic agents.

Methods: We conducted a population-based cohort study using commercial insurance claims data (2005–2011). Among patients aged ≥40 years with T2DM, two mutually exclusive exposure groups were selected: 1) DPP4i combination therapy (DPP4i and at least 1 other oral non-DPP4i drugs) and 2) non-DPP4i combination therapy (2 or more oral non-DPP4i drugs). Patients with a diagnosis of systemic AD, HIV, and cancer, and use of insulin-containing drugs or immunosuppressive drugs at baseline were excluded. Incidence rates (IRs) were calculated for RA, other AD and composite AD. RA and other AD were defined with ≥2 diagnosis codes that were ≥7 days apart and ≥1 prescription for disease-specific immunosuppressive drugs or steroids. Propensity score (PS)-matched Cox regression models compared the risk of RA or AD in DPP4i initiators compared to non-DPP4i initiators, controlling for baseline demographic factors, comorbidities, medications, and health care utilization. Sensitivity analyses matched on PS compared DPP4i combination therapy initiators separately to sulfonylurea combination therapy initiators and to thiazolidinediones combination therapy initiators.

Results: We included 58,275 patients starting DPP4i combination therapy 1:1 PS-matched to those starting non-DPP4i combination therapy. Risks of RA and other AD were significantly lower in the DPP4i group vs. non-DPP4i with the HR of 0.64 (95% CI 0.45–0.91) for RA, 0.53 (95% CI 0.39–0.73) for other AD, and 0.57 (95% CI 0.45–0.73) for composite AD (**Table**). In sensitivity analysis, the risk of other AD and composite AD was significantly reduced in initiators of DPP4i combination therapy compared to sulfonylurea combination therapy and thiazolidinediones combination therapy, but the risk of RA was not.

Table. Risk of autoimmune diseases associated with type 2 DM treatments: PS-matched 'as treated' analysis

	DPP4i (n=58,275)				Non-DPP4i (n=58,275)			
Outcome	Cases	Person-years (PY)	IR* (95% CI)	HR	Cases	Person-years (PY)	IR* (95% CI)	HR
RA	47	39,379	1.19 (0.88–1.59)	**0.64 (0.45–0.91)**	87	48,665	1.79 (1.43–2.21)	Ref
Other autoimmune diseases	59	39,361	1.50 (1.14–1.93)	**0.53 (0.39–0.73)**	129	48,615	2.65 (2.22–3.15)	Ref
Composite: RA or other autoimmune diseases	105	39,325	2.67 (2.18–3.23)	**0.57 (0.45–0.73)**	214	48,539	4.41 (3.84–5.04)	Ref

*Per 1,000 PY
The logistic model for PS includes age, sex, comorbidities, smoking, obesity, non-DM medications, number of DM meds, number of primary and specialist visits, and other health care utilization.

Conclusion: In this large cohort of T2DM patients, initiating DPP4i combination therapy was associated with a decreased risk of incident RA or other AD compared to those initiating non-DPP4i combination therapy. These results suggest possible pharmacologic pathways for reducing the incidence of AD.

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Antibodies To Citrullinated Enolase, Fibrinogen, and Vimentin Are Associated With Markers Of Endothelial Dysfunction In First-Degree Relatives Of Patients With Rheumatoid Arthritis: The Studies Of The Etiology Of Rheumatoid Arthritis. Jan M. Hughes-Austin[1], Kendra A. Young[2], Kevin D. Deane[3], Michael H. Weisman[4], Jane H. Buckner[5], Ted R. Mikuls[6], James R. O'Dell[7], Richard M. Keating[8], Peter K. Gregersen[9], Jeremy Sokolove[10], William H. Robinson[11], V. Michael Holers[3] and Jill M. Norris[2]. [1]University of California, San Diego, La Jolla, CA, [2]Colorado School of Public Health, Aurora, CO, [3]University of Colorado School of Medicine, Aurora, CO, [4]Cedars-Sinai Med Ctr, Los Angeles, CA, [5]Benaroya Research Institute, Seattle, WA, [6]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [7]University of Nebraska Medical Center, Omaha, NE, [8]The University of Chicago, Chicago, IL, [9]Feinstein Institute for Medical Research, Manhasset, NY, [10]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [11]Stanford University School of Medicine, Stanford, CA.

Background/Purpose: Among rheumatoid arthritis (RA) patients, antibodies to citrullinated protein antigens (ACPA) have been detected in atherosclerotic plaques. In particular, antibodies to citrullinated fibrinogen (cit-fib) have been associated with prevalent coronary artery calcium (*Sokolove, Arth Rheum 2013*). In the absence of RA, ACPA have been associated with cardiovascular disease (CVD) (*Cambridge, Atherosclerosis 2013*), suggesting that ACPA themselves may directly contribute to accelerated CVD recognized in RA. Therefore, we hypothesized that among RA-free first-degree relatives (FDRs) of patients with RA, ACPA are associated with markers of endothelial dysfunction, an indicator of initial vascular injury in CVD.

Methods: From the Studies of the Etiology of RA (SERA) (a multicenter prospective study of preclinical RA), 113 FDRs who had been positive for any of 5 RA-related antibodies (Abs): rheumatoid factor (RF), RF isotypes – IgM, IgG, IgA, or anti-cyclic citrullinated peptide (anti-CCP2) on at least one of their visits, and 100 FDRs who had never been Ab positive were selected, frequency matched on age, sex, and field center site. In cross-sectional testing of single samples obtained at the baseline exam, the following were measured: endothelial activation/injury markers: soluble intracellular adhesion molecule-1 (sICAM), soluble vascular cell adhesion molecule-1 (sVCAM) and E-selectin; and a panel of 15 ACPA (using Bio-Plex bead-based assay). ACPA were dichotomized as positive/negative based on cut-offs in 200 RA patients and 98 blood bank controls, and were developed using receiver operating characteristic (ROC) curves giving >90% specificity. Soluble VCAM was analyzed as a continuous variable; sICAM and E-selectin were log-transformed to approximate normality and were analyzed in log units. ANCOVA was used to evaluate associations between ACPA positivity and markers of endothelial dysfunction, adjusting for age, sex, race, body mass index, pack-years of smoking, and high sensitivity C-reactive protein.

Results: Among 193 FDRs with complete data and presented in detail in Table 1, sICAM was significantly higher in FDRs who were positive for ACPA to cit-enolase compared with those who were negative, with anti-cit-vimentin showing similar magnitude and marginal significance. sVCAM was significantly higher in those who were positive for antibodies to cit-fibrinogen and cit-vimentin. No significant associations were observed between ACPA and E-selectin.

Table. 1. Proportion of SERA FDRs with ACPA and associations of individual ACPA with markers of endothelial dysfunction

	n (%) positive n=193	Log ICAM		VCAM		Log E-selectin	
		B	p	B	p	B	p
Apolipo E (277–296) cit2 cyclic	33 (17)	0.0006 (0.09)	0.99	37.29 (44.8)	0.41	−0.04 (0.10)	0.65
Biglycan (247–266) cit cyclic	27 (14)	0.04 (0.10)	0.68	75.11 (48.9)	0.13	−0.03 (0.11)	0.75
Clusterin (221–240) cit	25 (13)	−0.03 (0.10)	0.76	62.49 (50.0)	0.21	−0.06 (0.11)	0.57
Enolase (5–21) cit	19 (10)	**0.24 (0.11)**	0.03	79.73 (56.9)	0.16	0.18 (0.12)	0.15
Fibrinogen A (211–230) cit cyclic	32 (17)	−0.04 (0.09)	0.69	39.85 (45.9)	0.39	−0.002 (0.10)	0.98
Fibrinogen A (41–60) cit3 cyclic	30 (16)	−0.02 (0.09)	0.84	75.10 (47.0)	0.11	−0.004 (0.10)	0.97
Fibrinogen A (556–575) cit cyclic	32 (17)	−0.04 (0.09)	0.70	**89.49 (45.7)**	0.05	−0.08 (0.10)	0.41
Fibrinogen A (616–635) cit3 cyclic	21 (11)	0.06 (0.11)	0.60	**130.59 (53.2)**	0.02	0.0007 (0.12)	1.00
Fibrinogen A cit	25 (13)	−0.02 (0.10)	0.86	15.96 (51.0)	0.75	−0.03 (0.11)	0.77
Filaggrin (48–65) cit2 cyclic	26 (14)	0.02 (0.10)	0.83	76.05 (49.0)	0.12	−0.01 (0.11)	0.91
Histone 2A (1–20) cit cyclic	40 (21)	−0.0003 (0.08)	1.00	55.68 (41.9)	0.19	−0.03 (0.09)	0.76
Histone 2B (62–81) cit cyclic	32 (17)	−0.07 (0.09)	0.41	67.76 (45.2)	0.14	0.02 (0.10)	0.87
Histone 2B–cit	8 (4)	0.04 (0.17)	0.80	116.93 (84)	0.17	0.22 (0.18)	0.22
Vimentin cit	10 (5)	−0.12 (0.15)	0.43	16.20 (76.9)	0.83	0.26 (0.17)	0.12
Vimentin (58–77) cit3 cyclic	8 (4)	**0.32 (0.17)**	0.05	204.17 (83.4)	0.02	0.31 (0.18)	0.09

*adjusted for age, sex, race, BMI, pack-years of smoking and high sensitivity C-reactive protein

Conclusion: In FDRs without classified articular RA, sICAM and sVCAM were higher in those who were ACPA positive. While cit-fib and cit-vimentin have been implicated in subclinical CVD in RA, and antibodies to a-enolase have been associated with vasculitis, our findings support the potential role of these ACPA in the initial insult in the development of CVD, even in the absence of clinical RA.

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Omega-3 Supplement Use Is Associated With a Reduced Risk Of Anti-Cyclic Citrullinated Protein Positivity In a Population Without Rheumatoid Arthritis, But At Risk For Future Disease. Ryan W. Gan[1], Kendra A. Young[1], Gary O. Zerbe[2], M. Kristen Demoruelle[3], Michael H. Weisman[4], Jane H. Buckner[5], Peter K. Gregersen[6], Ted R. Mikuls[7], James R. O'Dell[8], Richard M. Keating[9], Michael J. Clare-Salzler[10], Kevin D. Deane[3], V. Michael Holers[3] and Jill M. Norris[1]. [1]Colorado School of Public Health, Aurora, CO, [2]Colorado School of Public Health / University of Colorado Anschutz Medical Campus, Aurora, CO, [3]University of Colorado School of Medicine, Aurora, CO, [4]Cedars-Sinai Medical Center, Los Angeles, CA, [5]Benaroya Research Institute, Seattle, WA, [6]Feinstein Institute for Medical Research, Manhasset, NY, [7]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [8]University of Nebraska Medical Center, Omaha, NE, [9]The University of Chicago, Chicago, IL, [10]University of Florida, College of Medicine, Gainesville, FL.

Background/Purpose: Rheumatoid arthritis (RA) is characterized by systemic inflammation and circulating autoantibodies, which can be present in serum years prior to RA diagnosis and can define higher risk for future development of classified disease. In particular, the anti-cyclic citrullinated protein (anti-CCP) autoantibody is specific for RA, and its presence is strongly associated with future disease onset. While dietary intake of anti-inflammatory omega-3 (n-3) fatty acids *may* protect against development of RA and decrease the need for drugs to treat RA symptoms, the exact roles that n-3 fatty acids play prior to disease onset is unknown. We investigated the relationship between anti-CCP positivity and n-3 fatty acids, as measured by n-3 supplement use and erythrocyte membrane levels, in a population without RA, but increased risk for future RA.

Methods: The Studies of the Etiology of RA (SERA) is a multisite study of a cohort of first-degree relatives of RA probands (FDRs) and a cohort enriched with the HLA-DR4 genetic variant, both of which are RA-free, but at-risk for future RA. A nested case-control design was employed, with 30 cases defined as positive for anti-CCP2 autoantibody (Axis-Shield), and 48 controls always negative for any RA-related autoantibodies, frequency matched on age at study visit, sex, race, and study site. Antibody status, self-reported n-3 supplement use, and erythrocyte membrane levels of n-3 fatty acids (a biomarker for long-term fatty acid status measured by GC-MS) were obtained from a single cross-sectional visit. Logistic regression was used to assess the association between n-3 supplement use and CCP2 positivity, and test the association between a 1SD increase in membrane n-3 levels and CCP2 positivity. Mediation analyses assessed the percent of the association between self-report n-3 supplement use and CCP2 positivity mediated by membrane levels.

Results: Demographic characteristics were similar between CCP2 positive cases and controls. Subjects with CCP2 positivity were less likely than controls to self-report n-3 supplement use (OR: 0.14; 95% CI: 0.03–0.68). In addition, CCP2 positive subjects had lower erythrocyte membrane levels of certain n-3 fatty acids when compared to controls (Table). In mediation analyses, membrane n-3s explained ~9% of the association between supplement use and CCP2.

Table. The association between anti-CCP2 positivity and increasing levels of erythrocyte membrane n-3 fatty acids. Odds ratios reported correspond to a 1 SD increase in erythrocyte membrane n-3 fatty acid levels.

	Odds Ratio	95% CI	p-value
Self-Reported Use of n-3 Supplement*	0.14	0.03–0.68	0.01
Erythrocyte Membrane n-3			
Total n-3 fatty acid*	0.48	0.26–0.87	0.02
ALA(18:3n-3)*	0.90	0.56–1.45	0.67
EPA(20:5n-3)*	0.58	0.30–1.11	0.10
DPA(22:5n-3)*	0.65	0.40–1.05	0.67
DHA(22:6n-3)*	0.53	0.31–0.92	0.02
EPA + DHA*	0.51	0.29–0.92	0.03
EPA + DHA + DPA*	0.48	0.26–0.88	0.02

* Each row represents a separate model (i.e. the fatty acid variables are not adjusted for each other).

Conclusion: CCP2 positivity is inversely associated with self-reported n-3 supplement use and increasing levels of erythrocyte membrane n-3 fatty acid concentrations. These data suggest intake of longer chain n-3 fatty acids (EPA+DHA) may reduce the likelihood of developing anti-CCP2 antibodies, and potentially, the future development of RA. Only a small percentage of the association between n-3 supplement use and CCP2 positivity is explained by increasing levels of membrane n-3 fatty acids, suggesting other beneficial mechanisms, yet to be explored.

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Physical Activity, Adiposity, and The Risk Of Gout In Women: The Nurses Health Study. Hyon K. Choi[1], Lindsay C Burns[2], Yuqing Zhang[1], Sharan Rai[3] and Gary Curhan[4]. [1]Boston University School of Medicine, Boston, MA, [2]University of British Columbia, Vancouver, BC, [3]Arthritis Research Centre of Canada, Richmond, BC, [4]Harvard Medical School, Boston, MA.

Background/Purpose: There is a remarkable, increasing disease burden of gout and its associated cardiovascular (CV)-metabolic comorbidities in the US. While the benefits of physical exercise on CV-metabolic outcomes have been shown to extend beyond weight loss, such an independent impact on the risk of gout is unknown. We evaluated the potential impact of physical activity on the risk of incident gout in a large prospective cohort of women in the Nurses Health Study.

Methods: We examined the relation between physical activity, body mass index, and the risk of incident gout in 94,389 female participants with no history of gout at baseline. We used the American College of Rheumatology criteria to ascertain gout. Cox proportional hazards models were used to estimate the relative risk (RR) of incident gout after adjusting for the following variables in a time-varying manner: age, total energy intake, alcohol, body-mass index, use of diuretics, history of hypertension, history of chronic renal failure, and daily mean intake of meats, seafood, dairy foods, coffee, and total vitamin C.

Results: During 26 years of follow-up, we documented 846 confirmed incident cases of gout. An increasing level of physical activity was independently associated with a decreasing risk of gout. The multivariate relative risks (RRs) of gout were 1.00, 0.99, 0.90, 0.81, and 0.75 (95% CI, 0.58 to 0.97) (P for trend < 0.001) for physical activity levels from the lowest to the highest quintile (Table). In contrast, compared with BMI < 21, the multivariate RRs of gout were 1.71, 1.81, 2.91, 5.00, 6.77 (95% CI, 4.60 to 10.0) (P for trend < 0.001) for BMI categories of 21–22.9, 23–24.9, 25–29.9, 30–34.9, and ≥ 35, respectively. These findings persisted in subgroup analyses stratified by major factors such as intake of alcohol, dairy products, and sugary soda (all P values for interaction > 0.05).

Table 1. Relative Risk of Incident Gout According to Physical Activity

Physical Activity (hr/wk)	0	0.03–0.50	0.51–1.50	1.51–3.74	≥3.75	*P* for trend
No. of Cases	249	257	104	138	98	–
Person-Years	394096	251287	315926	299321	318665	–
Age-Adjusted RR (95% CI)	1.0	0.84 (0.66, 1.08)	0.70 (0.57, 0.86)	0.56 (0.44, 0.71)	0.44 (0.34, 0.56)	< 0.001
Multivariate* RR (95% CI)	1.0	0.94–0.74, 1.20)	0.82–0.67, 1.01)	0.70–0.55, 0.89)	0.59–0.46, 0.76)	< 0.001
Multivariate* + BMI-adjusted RR (95% CI)	1.0	0.99–0.78, 1.26)	0.90–0.73, 1.11)	0.81–0.64, 1.03)	0.75–0.58, 0.97)	0.012

Table 2. Relative Risk of Incident Gout According to BMI

Body Mass Index (kg/m^2)	< 21	21–22.9	23–24.9	25–29.9	30–34.9	≥35	*P* for trend
No. of Cases	33	75	99	304	248	173	–
Person-Years	322346	419510	441973	678320	262748	120362	–
Age Adjusted RR (95% CI)	1.0	1.80 (1.20, 2.71)	2.07 (1.40, 3.08)	3.80 (2.65, 5.45)	7.81 (5.42, 11.2)	12.8 (8.83, 18.7)	< 0.001
Multivariate* RR (95% CI)	1.0	1.70 (1.13, 2.57)	1.82 (1.22, 2.70)	2.94 (2.05, 4.23)	5.14 (3.55, 7.45)	7.07 (4.81, 10.4)	< 0.001
Multivariate* + Physical Activity-adjusted RR (95% CI)	1.0	1.71 (1.13, 2.58)	1.81 (1.22, 2.69)	2.91 (2.02, 4.18)	5.00 (3.45, 7.26)	6.77 (4.60, 10.0)	< 0.001

Abbreviations: RR= Relative Risk; CI = confidence intervals
* Adjusted for age, total energy intake, menopause, use of hormonal replacement, diuretic use, history of hypertension, and intake of alcohol, sugar-sweetened soft drinks, coffee, total meats, seafood, dairy foods, and total vitamin C

Conclusion: Our findings provide prospective evidence that increased physical activity is independently associated with a decreased risk of incident gout among women, beyond its impact on adiposity. In contrast, increased adiposity was independently associated with an increased risk of incident gout. These findings support the fundamental role of increased physical activity and weight control in the prevention of gout.

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ACR Concurrent Abstract Session
Health Services Research, Quality Measures and Quality of Care - Innovations in Health Care Delivery
Tuesday, October 29, 2013, 2:30 PM–4:00 PM

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Quality Of Care Predicts Disease Outcomes Among Patients With Systemic Lupus Erythematosus. Jinoos Yazdany[1], Laura Trupin[1], Patricia P. Katz[1], Gabriela Schmajuk[1] and Edward H. Yelin[2]. [1]University of California, San Francisco, San Francisco, CA, [2]UC San Francisco, San Francisco, CA.

Background/Purpose: Although measures to assess quality of care in systemic lupus erythematosus (SLE) are available, their relationship to long-term disease outcomes is unknown. Using a prospective, longitudinal cohort study, we examined the associations between high quality care and risks of increased SLE disease activity and damage.

Methods: Data derive from a longitudinal study of individuals with SLE, the UCSF Lupus Outcomes Study (LOS). Participants were followed from 2009 through 2012, responding to yearly telephone surveys. The primary outcomes in this study were clinically meaningful increases (>0.5 standard deviations) in 1) disease activity, defined as greater than or equal to 4 points on the Systemic Lupus Activity Questionnaire (SLAQ) between the 1st and 4th year of observation, and 2) disease damage, defined as greater than or equal to 2 points on the Brief Index of Lupus Damage (BILD) over the same time period. Both SLAQ and BILD have been validated for self-report in telephone surveys. Our primary independent variable was performance on 13 previously validated SLE quality measures, with a pass rate of greater than or equal to 85% (corresponding to the top quintile of performance, with pass rate defined as proportion of eligible recommended services received) considered indicative of high quality care. Using multivariable logistic regression, we examined the relationship between higher performance on quality measures and disease outcomes, adjusting for baseline disease activity and damage, age, gender, race/ethnicity, education, insurance source, health care utilization, specialties of providers seen, number of eligible quality measures, and follow-up time.

Results: Among 737 participants, the mean age at baseline was 50 years (SD 13), 93% were female, 63% were white; 41% had college degrees, and 15% had poverty-level incomes. Respondents were eligible for a mean of 5 quality measures (SD 2, range 2–11). There were 155 participants who had a clinically meaningful increase in SLAQ and 162 with an increase in BILD. In our models, we found no statistically significant relationship between performance on quality measures and changes in SLAQ score. However, receiving higher quality SLE care was significantly protective against increased disease damage (adjusted OR 0.4, 0.2–0.7; Table), even after adjusting for covariates, including baseline damage, disease activity, sociodemographic characteristics, insurance, health care utilization and number of eligible quality measures.

Table. Longitudinal relationship between higher performance on SLE quality measures and disease activity and damage, with adjustment for other health services and sociodemographic factors.

Characteristic	Increase in SLAQ by 4 or more points OR (95% CI)	Increase in BILD by 2 or more points OR (95% CI)
Higher performance (at least 85% fulfillment of eligible quality measures)	0.9 (0.5, 1.4)	**0.4 (0.2, 0.7)**
Eligible services in baseline year	.	.
2–3	Ref	Ref
4–6	1.2 (0.8, 1.9)	1.1 (0.7, 1.8)
7–11	1.6 (0.9, 2.9)	**1.9 (1.0, 3.6)**
Number of health care visits in baseline year (range 1–41)	1.0 (1.0, 1.0)	**1.0 (1.0, 1.1)**
Baseline BILD score	**1.2 (1.1, 1.3)**	**1.1 (1.0, 1.1)**
Baseline SLAQ score	**0.9 (0.9, 1.0)**	**1.1 (1.0, 1.1)**
Disease duration, per 10 years	0.9 (0.7, 1.1)	**1.9 (1.5, 2.5)**

BILD=Brief Index of Lupus Damage, SLAQ=Systemic Lupus Activity Questionnaire.
The model is also adjusted for age, sex, race/ethnicity, education, health insurance source and type, and the providers seen during the baseline year (rheumatologists vs. generalists).

Conclusion: In this community-based cohort of individuals with SLE, we illustrate for the first time a strong link between processes of care, defined by SLE quality measures, and the subsequent accumulation of disease damage, an important outcome. This suggests that improving quality of care has the potential to reduce accumulated damage in SLE even in advance of the development of new treatment options.

Disclosure: J. Yazdany, None; **L. Trupin**, None; **P. P. Katz**, None; **G. Schmajuk**, None; **E. H. Yelin**, None.

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Moving Towards Personalized Healthcare: A Patient Reported Outcome Based Algorithm Can Aid Rheumatologists and Patients In Monitoring Rheumatoid Arthritis In Daily Clinical Practice. Jos Hendrikx[1], Jaap Fransen[1], Alessandro Toniolo[2] and Piet L.C.M. van Riel[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Pfizer Pharmaceuticals, Rome, Italy.

Background/Purpose: Several Patient Reported Outcome (PRO)-based instruments to measure disease activity in Rheumatoid Arthritis (RA) exist, though an evidence base for their use in monitoring strategies is lacking. The objective of this study was to evaluate alerts generated by a PRO-based algorithm for monitoring patients with RA in the second year follow-up after diagnosis.

Methods: The algorithm (figure 1) monitors an easily attainable, equally weighted PRO-score of VAS general health, VAS disease activity and VAS pain. Red flags are generated in two instances:

1. the target level of disease activity is not met (set at a Patient Acceptable Symptom State value of 40mm)
2. change in disease activity (current level versus best moving average of 3 past visits) surpasses the early alert threshold (set at a Minimal Important Change value of 20mm)

Three consecutive red flags trigger an alert to the physician.

Data from patients with complete second year follow-up, included consecutively in the Nijmegen Early RA cohort between 2003–2011, were used. Weekly PRO-scores were interpolated, with addition of a random error component, based on the empirical individual patient data during the second year follow-up after diagnosis. Alerts were evaluated against DMARD/Biologic medication escalation registered in daily clinical practice. Escalation was defined as an increase in dose/frequency or start of new drug. Analyses were stratified according to DAS28 level at 12 months.

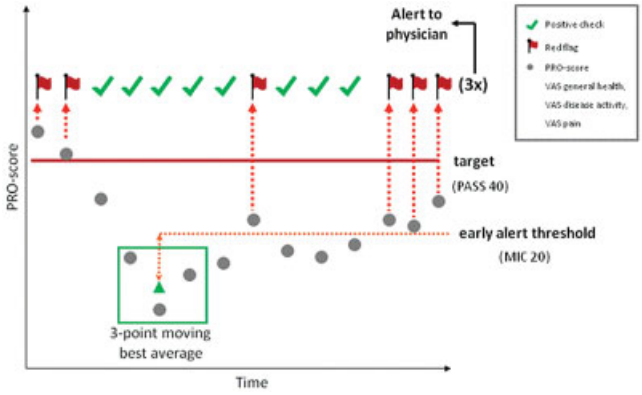

Figure 1. Preliminary PRO-based algorithm

Results: Data of 158 patients with RA were available for analysis. An overview of the algorithm performance is shown in table 1. The Negative Predictive Values (NPVs) represent the proportion of visits without medication escalation in all cases that the algorithm did not generate an alert. Overall, in 92.5% of visits where the algorithm did not generate an alert medication was also not escalated.

Table 1. preliminary algorithm results

	Visits	PPV	NPV	Sens	Spec	A priori chance of escalation
Total	693	14.0	92.5	55.7	61.5	10.1
	Stratified according to $DAS28_{12\ months}$					
DAS_{28} <2.6	277	6.0	95.9	38.5	70.5	4.7
DAS_{28} ≤3.2 & ≥2.6	101	16.7	95.4	66.7	67.4	8.9
DAS_{28} <5.1 & >3.2	282	18.3	86.8	54.5	55.0	15.6
DAS_{28} ≥5.1	33	13.8	100	100	13.8	12.1

PPV: Positive Predictive Value, NPV: Negative Predictive Value, Sens: Sensitivity, Spec: Specificity

Conclusion: The high NPVs indicate that, when using the algorithm, the chance of missing patients in need of medication escalation is very low. These findings provide evidence that an off-site monitoring system could aid in optimizing the number and timing of face-to-face consultations of patients with their rheumatologists. Further investigation into the optimal PRO-score, measurement frequency and algorithm parameter values to be used for off-site monitoring is warranted.

Disclosure: J. Hendrikx, Pfizer Inc, 2; **J. Fransen**, Pfizer Inc, 2; **A. Toniolo**, Pfizer Inc, 3; **P. L. C. M. van Riel**, Pfizer Inc, 2.

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Evaluation Of Osteoporosis Medication Starts In Patients Based On T-Score and FRAX® Absolute Fracture Risk Model In a Large Health Care System. Robert A. Overman and Chad L. Deal. Cleveland Clinic, Cleveland, OH.

Background/Purpose: The National Osteoporosis Foundation (NOF) 2008 guidelines recommend treatment for postmenopausal women (PMW) and men ≥ 50 if the T-score is ≤−2.5 at the hip or spine and in patients with osteopenia (T-score −1.0 to −2.5) if the WHO FRAX® 10-yr fracture risk is ≥3% for hip or ≥20% for major osteoporotic fractures. We evaluated treatment initiation in patients after DXA and compared treatment by rheumatologists to non-rheumatologists.

Methods: The Cleveland Clinic DXA registry was linked with the patient's electronic medical record using Explorys Inc. PMW and men ≥50 in the registry between 7/2009 and 12/2012, who were anti-osteoporosis medication (AOP) naïve, and had at least one office visit in the years pre and post-DXA were included. New use of AOPs; bisphosphonates, teriparatide, denosumab, raloxifene, calcitonin, and estrogen started within 90, 180, and 365 days post-DXA were collected through 2/2013. Subjects who did not exceed each post-DXA time period were not included in the analysis. Subjects were stratified into 6 groups based on T-score (osteoporosis or osteopenia); FRAX® 10-yr risk of major osteoporotic fracture or hip fracture, ≥20% and/or ≥3% (high-risk) or <20% and <3% (low-risk); and treatment by a rheumatologist or non-rheumatologist. Results are presented as % difference in treatment starts. Group comparisons were made using chi-square with p≤0.05 demonstrating statistical significance.

Results: Study subjects had a mean age of 70.9 (SD 10.5) and 80.8% (3456/4280) were female. The difference in treatment starts at 90, 180 and 365 days after initial DXA for rheumatologists and non-rheumatologists are presented in Table 1. The groups were osteoporosis at either spine or hip and FRAX® high-risk; osteoporosis and FRAX® low-risk; osteopenia and FRAX® high-risk. Rheumatologists were compared to non-rheumatologists. Treatment would be recommended for all 6 groups based on NOF guidelines. Rheumatologists started significantly more patients on AOP than non-rheumatologists at 180 and 365 days in patients with osteoporosis and FRAX ® high-risk, and at all-time points in patients with osteopenia and FRAX® high-risk. The greater number of AOP starts in rheumatologists indicate closer adherence to NOF guidelines for treatment.

Table 1. Percentage of osteoporosis treatment naïve patients started on osteoporosis therapy by Rheumatologists v Non-Rheumatologists based on time periods post-DXA

Treatment Initiation	Osteoporosis and FRAX® High-Risk (Rheum)	Osteoporosis and FRAX® High-Risk (Non-Rheum)	% diff	Osteoporosis and FRAX Low-Risk® (Rheum)	Osteoporosis and FRAX® Low-Risk (Non-Rheum)	% diff	Osteopenia and FRAX® High-Risk (Rheum)	Osteopenia and FRAX® High-Risk (Non-Rheum)	% diff
% within 90 Days (n/group n)	42.4 (70/165)	40.3 (546/1355)	2.1	32.4 (24/74)	42.4 (378/891)	−10.0	24.1 (58/241)	17.3 (269/1554)	6.8*
% within 180 Days (n/group n)	55.6 (85/153)	48.6 (613/1262)	7.0	45.7 (32/70)	51.2 (429/838)	−5.5	32.2 (75/233)	21.9 (316/1440)	10.3**
% within 365 Days (n/group n)	67.2 (90/134)	54.9 (594/1082)	12.3**	58.3 (35/60)	58.7 (423/721)	−0.4	40.5 (81/200)	27.8 (340/1225)	12.7**

Subjects who contributed at least the period days to the analysis were included in percentages for each row
Rheum = subjects who had at least one visit with a rheumatologist in the year before and after DXA
Non-Rheum = subjects not seen by a Rheumatologist in the year before and after DXA
FRAX® High-Risk = 10-yr risk of hip fracture ≥3% and/or 1-yr risk of major osteoporotic fracture ≥20%
FRAX® Low-Risk = 10-yr risk of hip fracture <3% and 10-yr risk of major osteoporotic fracture <20%
% diff = the difference in percent treated by rheumatologists vs. a non-rheumatology physician
*: p≤0.05 **: p≤0.01.

Conclusion: Rheumatologists started AOP therapy significantly more often in patients who would be recommended for therapy based on NOF guidelines. However, only 67.2% of rheumatology and 54.9% of non-rheumatology FRAX® high-risk with osteoporosis patients were started on AOP by 1-yr. In FRAX® high-risk with osteopenia patients only 40.5% of those treated by a rheumatologist and 27.8% of those not treated by a rheumatologist were started on therapy at 1-yr. These data indicate a care gap in osteoporosis treatment in both physician groups which needs to be addressed to improve quality of care.

Disclosure: R. A. Overman, None; **C. L. Deal**, None.

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Efficiency Gains For Rheumatology Consultation From An Electronic Referral System In a Safety Net Health System. Meghan M. Scheibe[1], John B. Imboden[2], Gabriela Schmajuk[2], Mary Margaretten[2], Jonathan D. Graf[2], Alice Chen[2], Edward H. Yelin[2] and Jinoos Yazdany[2]. [1]California Pacific Medical Center, San Francisco, CA, [2]University of California, San Francisco, San Francisco, CA.

Background/Purpose: Rheumatology care is a scarce resource in some settings. Health information technology holds promise in increasing the quality and efficiency of rheumatology referrals, but little information about its use for these purposes is available. The aim of this study was to determine the proportion of electronic referrals that are appropriate for pre-consultation exchange as well as to assess potential efficiency gains in a safety net health system.

Methods: The Electronic Referral System (eReferral) allows two-way electronic communication between referring and specialty providers for new patient referrals. Once a referral is initiated, several possible outcomes may result: either the patient is scheduled in rheumatology clinic, the consult is deemed not appropriate for rheumatology, more information is requested from the referrer to gauge the appropriateness of the consultation, or the question is answered entirely within the eReferral system without scheduling a clinic visit. The latter 3 constitute "pre-consultation exchange." We performed a retrospective study of a random sample of eReferrals for ambulatory rheumatology consultation between 2007–2012. A sample of approximately 10% of eReferrals (n=257) was reviewed. The primary clinical question and disposition for these referrals was recorded. Using a blinded adjudicated, structured review performed independently by two rheumatologists, we rated each eReferral for pre-consultation exchange using the categorization above.

Results: Between 2007–2012, 2383 eReferrals were sent to rheumatology. Of the 257 referrals examined in more detail, the top reasons for consultation are shown (Table). 156 (61%) eReferrals were rated as appropriate for pre-consultation exchange. The primary reasons pre-consultation exchange was recommended were: additional testing was needed to clarify or expedite the consultation request (37%), the clinical question was unclear (14%), or the consult was deemed not appropriate for rheumatology consultation (10%). Referrals for pain were most likely to be rated as appropriate for pre-consultative exchange and those for crystal arthropathies were the least likely (Table). Following the exchange, 49 (32%) eReferrals were able to be resolved without a clinic visit.

Table. Appropriateness of Rheumatology eReferrals for Pre-consultation Exchange in a Safety Net Setting.

Diagnosis	N (%) Top Reasons for eReferral	N (%) eReferrals recommended for immediate scheduling	N (%) eReferrals deemed appropriate for pre-consultation exchange
Potential inflammatory arthritis	42 (17%)	15 (35%)	27 (65%)
Rheumatoid arthritis	35 (14%)	15 (43%)	20 (57%)
Pain	31 (13%)	2 (6%)	29 (94%)
Systemic lupus erythematosus	20 (8%)	9 (45%)	11 (55%)
Crystal Arthropathy	17 (7%)	11 (65%)	6 (35%)

Conclusion: We evaluated eReferral, an innovative program designed to improve the quality and efficiency of specialty referrals. Over half of the referrals to rheumatology were rated as appropriate for pre-consultative exchange. In addition, one-third of the referrals were able to be resolved without a clinic visit, suggesting that using an iterative referral system that facilitates communication between referrers and specialists has the potential to improve the triage and efficiency of new patient visits in a busy

rheumatology practice, particularly in settings where rheumatologists are a scarce resource.

Disclosure: M. M. Scheibe, None; **J. B. Imboden**, None; **G. Schmajuk**, None; **M. Margaretten**, None; **J. D. Graf**, None; **A. Chen**, None; **E. H. Yelin**, None; **J. Yazdany**, None.

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Implementing a Personalized Health Plan To Improve Therapeutic Outcomes In Veterans With Gout. Astrud Lorraine Leyva[1], Una E. Makris[2] and Salahuddin Kazi[1]. [1]UT Southwestern Medical Center, Dallas, TX, [2]UT Southwestern Medical Center, VA Medical Center, Dallas, TX.

Background: Gout is a chronic crystal-induced arthritis that predominantly occurs among men with rising prevalence with advancing age. Patients with uncontrolled gout present with recurrent flares leading to unanticipated clinical encounters, i.e. phone calls, ER visits, and/or hospitalization. Given the patient population at the Dallas VAMC, it is appropriate to evaluate novel strategies for improving gout management. Outcomes in gout may be improved by eliciting goals of care from the patient.

The Dallas VA has adapted a personalized health plan (PHP) derived from Duke University's Integrative Medicine program that assesses patients' desired goals in 8 different domains, initially tested in diabetic patients. The purpose of this study is to pilot the PHP to facilitate achieving goal uric acid <6mg/dL in patients with uncontrolled gout.

Methods: We recruited consecutive patients at the VA rheumatology clinic with uncontrolled gout, defined by uric acid > 6mg/dL AND ≥ 1 acute gout flare(s) from July to September 2012. This project was reviewed by the VA IRB and considered to be a quality improvement project.

The initial interview focused on formulating a goal (congruent with gout management). Patients selected a goal, indicating their starting and desired status using a numerical scale (1–10). Continuous reinforcement was achieved by weekly phone calls (ALL). Uric acid levels were evaluated at baseline and at the end of the study period. An exit interview was conducted after 3 months; which included open ended questions regarding feedback for the PHP (see Table 1). Clinical encounters over 1 year were evaluated for trends and compared to non-PHP patients using a student's t-test.

Results: Thirty-six veterans meeting study criteria were approached; 13 agreed to participate and completed the 3 month study. Participants' average age was 59 ± 8.9 years, 5/13 were Non-Hispanic White, 7/13 African-American and 1/13 Hispanic. All but one selected a goal to increase physical activity or adjust diet. At completion of the study, 1 patient achieved his desired goal; 3/13 remained at the same level; 9/13 did not achieve, but approached, the goal, as seen in Table 1. 10/13 patients had a reduction in uric acid level, of which 8/10 reached the goal of ≤6mg/dL. Clinical encounter data did not significantly differ between PHP participants and non-participants.

Table 1.

Patient	Age	Race	Goal Pre → Post [desired]	Pre/Post Uric Acid	Quotes illustrating feedback for PHP
1	66	NHW	Increase physical activity 2 → 2 [10]	7.5/7.7	"Would have to change my expectation with 8, a little lower. I'd have a better chance of success with lower expectation"
2	73	H	Improve diet 3 → 5 [8]	12.6/6.1	"Makes me more aware to stay healthy and I'm eating better than I had been"
3	56	AA	Improve diet 7 → 10 [10]	4.3/4.1	"Having a doctor calling me and taking time to show their concern is really good"
4	57	NHW	Improve diet 4 → 5 [8]	8.0/6.0	"The weekly phone calls helped by re adjusting medications as problems came up"
5	43	AA	Stop alcohol use 3 → 8 [10]	12.7/10.9	"The program is a good reminder to stop drinking and source of education"
6	65	AA	Increase physical activity 3 → 4 [10]	8.6/5.3	"Having someone to talk to on a regular basis was good. Provided encouragement and answer questions as they come up"
7	60	AA	Increase physical activity 6 → 7 [10]	6.2/5.6	"How many doctors call you and ask if you are doing ok? It made me accountable to get out of bed."
8	45	AA	Increase physical activity 4 → 4 [10]	6.8/7.7	"Helpful to have someone concerned about you calling every week"
9	68	NHW	Increase physical activity 7 → 8 [10]	7.8/5.9	"Helps me stay an track"
10	65	NHW	Improve diet 6 → 8 [10]	8.5/5.6	"The program may be better calls were every 2 weeks"
11	53	AA	Increase physical activity 5 → 5 [10]	11.0/10.4	"Constant reminder to keep on working on my goal and to stay on medications"
12	53	NHW	Increase physical activity 5 → 7 [10]	8.4/5.9	"I like hearing from the doctor every week."
13	63	AA	Improve diet 5 → 6 [10]	6.8/4.1	"The depression is bad." The phone calls "it's like an uplift". "I have a better understanding of what gout brings on."

NHW = non-Hispanic white, AA = African American, H = Hispanic

Conclusion: This pilot study suggests that Veterans had a positive response to the gout PHP. Veterans indicated satisfaction with physician follow-up phone calls; however, this may not be feasible in a "real world" setting. Future studies evaluating the efficacy of the PHP in gout patients should include a control group, utilize technology for continuous reinforcement, measure unanticipated clinical encounters, and lastly, extend the duration of follow-up to allow behavioral, physical activity, or psychosocial change.

Disclosure: A. L. Leyva, None; **U. E. Makris**, None; **S. Kazi**, None.

2667

Fast-Track Pathway In Giant Cell Arteritis: A Cost-Effectivenss Analysis. Katerina Achilleos[1], Pravin Patil[1], Win Win Maw[1], Laura Bown[2], David Halsall[2], Charles Dobson[2], Christian Dejaco[1], Frances Borg[1], Sunil Gupta[3] and Bhaskar Dasgupta[1]. [1]Southend University Hospital, Westcliff-on-sea, United Kingdom, [2]National Health Service England, Leeds, United Kingdom, [3]Clinical Commissioning Group, Southend-on-sea, United Kingdom.

Background/Purpose: With incidence of 2.2 per 10,000 patient years, it is estimated that 12,000 new cases of Giant Cell Arteritis (GCA) are diagnosed every year in the UK of whom 20% lose sight permanently. This has significant implications on personal, social care and socioeconomic costs. A fast-track GCA pathway was introduced in 2012 aimed at reducing multiple referral routes, delayed review and treatment and improving outcomes. We report the cost effectiveness of this pathway.

Methods: A retrospective data analysis of 138 patients investigated for GCA (Jan 2009-Dec 2012), comparing costs of fast-track pathway (57 patients; Jan – Dec 2012) with the conventional referral route (81 patients; pre 2012) using the incremental cost effectiveness ratio (ICER). Data was collected from patient records, general practice and pathology databases along with telephone questionnaires. Direct costs included: GP appointments, investigations such as blood tests, scans and biopsies, outpatient appointments (Rheumatology, Eye Clinic and Neurology), A&E attendances, Inpatient stays, readmissions, drugs for treatment of GCA. Costing data for treatment and diagnosis costs was gathered from Reference Costs 2011/12, Prescription Cost Analysis 2012, and Unit Costs of Health and Social Care 2012. QOL was measured in 66 patients using the EQ5D. Health gains from diagnosis and treatment of GCA were quantified using Quality Adjusted Life Years (QALY's).

Results: The fast-track pathway has seen a reduction in number of GP appointments and cost of diagnosis and treatment. The difference in QALYs between patients with and without sight loss due to GCA was 0.2. Each patient that didn't lose vision gained on average 2.6 QALY's. The average cost of diagnosing and treating a patient with suspected GCA in the conventional pathway was ≤2,600, whilst in the fast-track; this was ≤1,675, a difference of ≤925 per patient. The ICER of implementing the fast-track pathway is -≤1,950 per QALY. Thus, there is an average cost saving to the NHS of ≤925 for each patient treated for suspected GCA.

Table 1. Patients with sight loss and the costs of treatment/diagnosis in the conventional and fast-track pathway

	Total number of patients suspected of having GCA	Total number of patients diagnosed with GCA	Number of patients with Sight loss	Average cost of diagnosis and treatment
Conventional pathway	81	46	17 (37%)	≤2,600
Fast-track pathway	57	33	3 (9%)	≤1,675

Conclusion: The fact-track pathway leads to a reduction in irreversible sight loss and is associated with reduced diagnosis and treatment costs. It results in 2.6 QALY's gained for each patient that does not suffer sight loss, suggesting that the fast-track pathway is more cost effective than the conventional pathway for management of early GCA. The ICER of implementing the fast-track pathway is -≤1,950 per QALY with an average cost saving to the NHS of ≤925 for each patient. Our results do not include the small educational/refresher costs and are preliminary but indicate that the Fast track GCA pathway should be 'rolled out' globally.

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2668

A Randomized, Double-Blind, Dose Ranging Study Comparing FX006, An Intra-Articular (IA) Sustained-Release Formulation Of Triamcinolone Acetonide (TCA), To An Approved Injectable Suspension Of TCA In Patients With Osteoarthritis (OA) Of The Knee.

Neil Bodick[1], Joelle Lufkin[1], Christina Willwerth[1], Pierre Lachance[2], Gregory Jasey[3], Anil Gupta[4], Anthony Chris[5], Marc Russo[6], Michael O'Mahony[7], Sam Henein[8], Louise Murdoch[9], Ferdinandus de Looze[10], David Hunter[11] and Michael Clayman[1]. [1]Flexion Therapeutics, Burlington, MA, [2]Clinique St-Louis (Recherche) Inc, Quebec, QC, [3]North Walkerville Orthopaedic Associates, Windsor, ON, [4]Anil K. Gupta Medicine Professional Corporation, Toronto, ON, [5]Aim Health Group, Waterloo, ON, [6]Hunter Clinical Research, Broadmeadow, Australia, [7]London Road Diagnostic Clinic and Medical Centre, Sarnia, ON, [8]SKDS Research Inc., Newmarket, ON, [9]Emeritus Research, Malvern East, Australia, [10]AusTrials Pty Limited, Sherwood, Australia, [11]Royal North Shore Hospital, St. Leonards, Australia.

Background/Purpose: FX006 is a novel sustained-release formulation of TCA in poly(lactic-co-glycolic) acid microspheres intended to maintain therapeutic concentrations in the joint up to 3 months following IA injection. In patients (pts) with OA of the knee, FX006 was compared to an approved injectable suspension of TCA (TCA IR) to identify a dose of FX006 to move forward into Phase 3.

Methods: Pts with baseline average daily pain intensity (ADP) of ≥5 to ≤9 on an 11 point Numeric Rating Scale (NRS) ranging from 0 (no pain) to 10 (pain as bad as you can imagine) were randomized (1:1:1:1) and treated with a single IA injection of FX006 (containing 10, 40 or 60 mg of TCA) or 40 mg of TCA IR. Pts were evaluated at 7 visits over 12 wks for efficacy, safety and PK. Primary endpoint: change from Baseline to each of Wks 8, 10 and 12 in the weekly mean of ADP. Secondary endpoints: time to onset of pain relief, WOMAC (pain, stiffness and function), responder status, and global impression of change.

Results: Pts (228) were randomized and treated (FX006 10 mg, n=58, FX006 40 mg, n=59, FX006 60 mg, n=60; TCA IR, n=51). Treatment arms were well balanced across demographic and baseline characteristics (mean baseline ADP: 6.5). FX006 40 mg was superior to TCA IR on weekly mean of ADP at Wk 5 to Wk 10 ($p<0.05$) (average pain reduction −0.9) (Figure 1). The 40 mg dose also demonstrated significant improvement over TCA IR ($p<0.05$) in secondary outcomes at Wk 8 (Table 1). Time to onset of pain relief was the same for FX006 40 mg and TCA IR. The 10 mg dose produced effects that were consistently improved relative to TCA IR but of lessor magnitude than those of the 40 mg dose. The 60 mg dose did not produce an improvement relative to the 40 mg dose. There were no related SAEs. AEs were generally mild and unrelated to study drug. Local knee-related AEs, lab assessments, ECGs and vital signs were unremarkable and similar across all treatments. Plasma PK across the FX006 doses were linear and dose-dependent. Peak plasma concentrations achieved with TCA IR were 10× of that seen with FX006 40 mg.

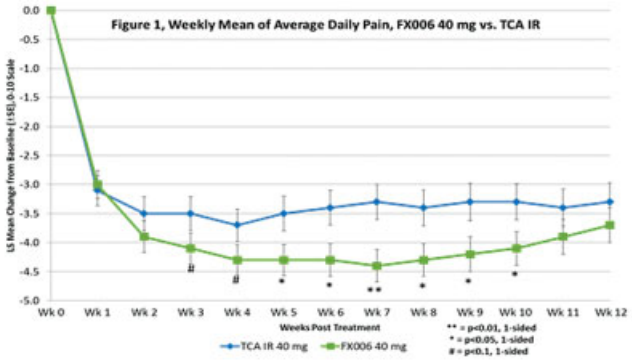

Table 1. Secondary efficacy endpoints at Week 8 comparing FX006 40 mg vs. TCA IR 40 mg

WOMAC A (pain) (0–4 Likert scale)	FX006 40 mg (n=59)	TCA IR 40 mg (n=51)
LSM change from baseline (SE)	−1.33 (0.098)	−0.96 (0.108)
LSMD vs TCA IR (90% CI)	−0.37 (−0.61, −0.13)	
1 sided p-value	0.0058	
WOMAC A1 (pain on walking) (0–4 Likert scale)		
LSM change from baseline (SE)	−1.2 (0.12)	−0.8 (0.13)
LSMD vs TCA IR (90% CI)	−0.4 (−0.7, −0.1)	
1 sided p-value	0.0098	
WOMAC B (stiffness) (0–4 Likert scale)		
LSM change from baseline (SE)	−1.49 (0.112)	−0.99 (0.124)
LSMD vs TCA IR (90% CI)	−0.49 (−0.77, −0.22)	
1 sided p-value	0.0018	
WOMAC C (function) (0–4 Likert scale)		
LSM change from baseline (SE)	−1.31 (0.096)	−0.94 (0.106)
LSMD vs TCA IR (90% CI)	−0.37 (−0.61, −0.14	
1 sided p-value	0.0049	
OMERACT-OARSI[a]		
n (%)	53 (89.8%)	32 (69.6%)
p-value	0.0118	
OR (90% CI)	3.9 (1.6, 9.3)	
Responder >30% Improvement[b]		
n (%)	47 (85.5%)	27 (62.8%)
p-value	0.0119	
OR (90% CI)	3.5 (1.5, 7.9)	
PGIC (1–7 Likert scale)		
LSM change from baseline (SE)	1.8 (0.16)	2.6 (0.17)
LSMD vs TCA IR (90% CI)	−0.7 (−1.1, −0.3)	
1 sided p-value	0.0013	
CGIC (1–7 Likert scale)		
LSM change from baseline (SE)	1.8 (0.16)	2.6 (0.17)
LSMD vs TCA IR (90% CI)	−0.7 (−1.1, −0.3)	
1 sided p-value	0.0013	

a n=59 for FX006 40 mg; n=46 for TCA IR
b n=55 for FX006 40 mg; n=43 for TCA IR
LSM = least squares mean; LSMD = least square means difference; WOMAC = Western Ontario and McMaster Osteoarthritis Index; OMERACT-OARSI = Outcome Measures in Rheumatoid Arthritis Clinical Trials- Osteoarthritis Research Society International; PGIC = Patient Global Impression of Change; CGIC = Clinical Global Impression of Change

Conclusion: In pts with OA of the knee, the 40 mg dose of FX006 demonstrated an amplified and prolonged therapeutic effect relative to TCA IR. A Phase 3 study of the 40 mg dose of FX006 is being planned.

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Treatment Of Knee Osteoarthritis Patients With Strontium Ranelate Reduces The Loss Of Cartilage Volume and Bone Marrow Lesions As Assessed By Magnetic Resonance Imaging: Data From The Phase III Strontium Ranelate Efficacy In Knee Osteoarthrtis Trial. Johanne Martel-Pelletier[1], Camille Roubille[1], Jean-Pierre Raynauld[1], François Abram[2], Marc Dorais[3], Philippe Delorme[1] and Jean-Pierre Pelletier[1]. [1]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [2]Imaging Research & Development, ArthroLab Inc., Montreal, QC, [3]StatSciences Inc., Notre-Dame de l'Île Perrot, QC.

Background/Purpose: This study aimed to evaluate in a subpopulation of osteoarthritis (OA) patients from the SEKOIA Phase III trial the disease-modifying (DMOAD) effect of strontium ranelate (SrRan) on the changes in knee OA cartilage volume and bone marrow lesions (BML) using magnetic resonance imaging (MRI).

Methods: Patients with knee OA (n=300) received placebo (n=112) or SrRan at 1 g/day (n=113) or at 2 g/day (n=105). The study included all randomised patients who received at least one dose of treatment and had at least two MRI examinations. MRI was performed at baseline and at 12, 24, and 36 months. The changes in cartilage volume loss and BML were assessed in the global knee and subregions. Missing values were imputed and the analyses were adjusted according to Bonferroni.

Results: Data showed no between-group differences at baseline with regard to demographics, clinical symptoms, or imaging characteristics. Treatment with SrRan at 2 g/day significantly decreased cartilage volume loss on the tibial plateau as early as 12 months (p=0.002), which persisted up to 36 months (p=0.003). The urinary CTX-II was found to be significantly decreased in both SrRan groups at 36 months. At baseline, the BML were detected mainly in the medial compartment where they were found at increased prevalence in the femur compared to the plateau. At 36 months, SrRan treatment at both 1 and 2 g/day significantly reduced the BML score change in the medial compartment (p=0.002 and p=0.001, respectively). Interestingly, patients treated with SrRan 2 g/day showed no increase in BML score in the medial femur, central condyle or plateau, and those treated with SrRan 1g/day showed no increase in the medial central condyle or plateau, while an increase (39%, 40%, and 17%, respectively) in BML score was found in the placebo group. In those patients with BML at baseline, SrRan 2 g/day significantly (p=0.023) decreased the cartilage loss at 36 months in the medial plateau.

Conclusion: In knee OA patients, treatment with SrRan 2 g/day was found to have a beneficial effect on both cartilage and subchondral bone by significantly reducing the cartilage volume loss in the tibial plateau and the progression of BML in the medial compartment. In turn, the decrease in BML in the medial tibial plateau was associated with a marked and significant reduction in cartilage volume loss at SrRan 2 g/day. These results from the MRI study support the DMOAD effect of SrRan reported using X-rays.

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Does Change In Femorotibial Cartilage Thickness Differ Between Acutely Anterior-Cruciate Ligament Injured Knees Treated With and Without Reconstructive Surgery. Wolfgang Wirth[1], Felix Eckstein[1], Martin Hudelmaier[1], Stefan Lohmander[2] and Richard Frobell[3]. [1]Paracelsus Medical University, Salzburg, Austria, [2]Department of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, [3]Lund University, Lund, Sweden.

Background/Purpose: An ACL tear is a serious knee injury, involving chronic alterations in joint biomechanics. The risk of developing knee OA after an ACL tear is elevated, but the driving mechanisms are not known. We tested the hypothesis that surgical reconstruction of an acute ACL tear would influence change in femorotibial cartilage thickness over the first five years after injury.

Methods: In a treatment RCT (the KANON-trial), 121 young (32 women, mean age 26.1 years) active adults with an acute ACL tear in a previously un-injured knee received similar rehabilitation. Baseline sagittal MR images were available for 117 participants, with year 2 and year 5 follow-up for each 112 of the 121 participants. 59 of those underwent an early ACL reconstruction (ACLR), 29 had a delayed ACLR, and 29 were treated with rehab alone. Cartilage thickness (ThC) was measured manually with blinding to time point and treatment using a dedicated software (Chondrometrics GmbH, Ainring, Germany). Primary outcome was the mean change in ThC for the entire femorotibial joint (FTJ); secondary outcomes were mean change in ThC for the medial and the lateral femorotibial compartments (MFTC/LFTC), the subregion with the largest ThC loss (ordered value 1 = OV1) and gain (OV16). ThC changes were analyzed using the t-test (crude differences) and analysis of covariance (differences with adjustment for age, sex & BMI).

Results: The cartilage thickness change over 5 years in the FTJ did not differ significantly between knees treated with early ACLR (+148μm, 95%CI: [+38, +258]μm), with delayed ACLR (+174 [+42, +306]μm), or with rehabilitation alone (+121 [−3,+246]μm, crude/adjusted p≥0.56/0.65). In addition, no significant differences were found for the periods between BL→Y2 and Y2→Y5. The change in FTJ ThC was largely driven by change in MFTC ThC (early ACLR: +132 [+77, +187] μm, delayed ACLR: +128 [+40, +216] μm, rehab alone: +82 [+19, +146] μm), but without significant differences between treatment groups over the entire 5 year period (p≥0.28/0.20) or for the sub-periods (p≥0.19/0.20). Smaller changes, not significantly different between treatment groups (p≥0.60/0.70), were observed in LFTC (early ACLR: +16 [−53, +85] μm, delayed ACLR: +46[−25, +116] μm, rehab alone: +39 [−46, +124] μm).

OV 1 was significantly more negative and OV 16 was significantly more positive over 5 years in knees treated with early ACLR than in knees treated with rehab alone (OV1: p=0.04/0.03; OV16: p=0.02/0.01). These differences were predominantly driven by changes occurring between BL→Y2 with OV1 being significantly more negative in knees with early (p=0.01/0.01) or delayed ACLR (p=0.04/0.04) compared to knees treated with rehab alone. No other significant differences were found for any period.

Conclusion: Change in mean femorotibial cartilage thickness over a five year period after acute ACL injury did not differ between knees treated with early or delayed ACL reconstruction or knees treated with rehabilitation alone. An early ACL reconstruction may induce greater magnitudes of subregional cartilage thickness change as compared to knees treated with rehabilitation alone but the clinical relevance of such change remains to be determined.

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The Relationship Between Toe-Out Angle During Walking and Risk Of Medial Knee Osteoarthritis Incidence: The Multicenter Osteoarthritis Study. K. Douglas Gross[1], Yuqing Zhang[2], Emily K. Quinn[1], Michael C. Nevitt[3], Neil A. Segal[4], Cora E. Lewis[5] and David T. Felson[2]. [1]Boston University, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]University of California, San Francisco, San Francisco, CA, [4]University of Iowa, Iowa City, IA, [5]University of Alabama, Birmingham, Birmingham, AL.

Background/Purpose: A previous study suggests a linear relationship between increased toe-out angle during walking and reduced risk of medial knee OA progression. Yet, gait lab findings indicate that both highly positive (toe-out) and negative (toe-in) angles can reduce medial knee load. The relationship of these angles with medial knee OA incidence has not been studied. We assessed the dose-response relationship of toe-out angle during walking with 2-year risk of incident medial knee OA.

Methods: The NIH-funded Multicenter Osteoarthritis Study (MOST) includes adults aged 50–79 years that have or are at risk of knee OA. Among 60-month participants, mean toe-out angle was measured during 4 self-paced walking trials using a 4.9 meter GAITRite walkway (14-day

retest ICC = 0.95). Readers scored medial joint space narrowing (JSN) on semiflexed knee x-rays using OARSI grades (weighted $\kappa = 0.81$). Among knees with medial JSN grade 0 at 60 months, incident cases had medial JSN ≥ 1 and $>$ lateral JSN grade at 84 months. With the middle quintile as a reference, logistic regression estimated the relative odds of medial OA incidence in each case-based quintile of toe-out angle while adjusting for age, BMI, walking speed, sex, race, clinic site, and non-independent knees of a single subject. We used a quadratic spline to smooth the curve and obtain a clear picture of the dose-response relationship. In sensitivity analysis, knees with pain during the walking exam were excluded.

Results: 1112 participants (mean age 66.6 +/− 7.6 yrs, BMI 29.6 +/− 5.3 kg/m^2, walking speed 1.19 +/− 0.19 m/sec, 61.1% female, 88.0% white, 55.7% Iowa clinic) contributed 1856 knees with a mean toe-out angle of 6.7 +/− 5.4° (range −11.0, 30.0°). After adjustments, the relative odds of incident medial knee OA had an n-shaped relationship with toe-out angle (p for trend < 0.01), such that the highest (9.8 to 30.0°) and lowest (−11.0 to 2.7°) quintiles had 11–25% reduced odds compared to the middle quintile (5.1 to 7.5°) (see table and figure). Results were unchanged in sensitivity analysis (p for n-shaped trend = 0.03).

	Toe-In −11.0, 2.7°	⟵ 2.8, 5.0°	5.1, 7.5°	7.6, 9.7° ⟶	Toe-Out 9.8, 30.0°	p for n shape trend
# knees	424	289	356	284	503	
% incident	3.3%	3.5%	3.9%	6.7%	3.4%	
Adj OR*	0.89	0.89	1.00	1.69	0.75	0.01
(95% CI)	(0.41, 1.92)	(0.38, 2.06)	(ref)	(0.85, 3.36)	(0.36, 1.60)	

*Adjusted for age, BMI, walk speed, sex, race, clinic, and non-independent knees

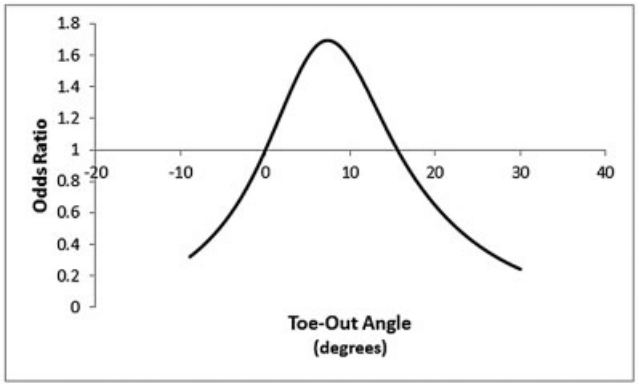

Figure. Quadratic spline depicting relative odds of medial knee osteoarthritis incidence by continuous measurement of toe-out angle during walking.

Conclusion: These results suggest that both highly positive (toe-out) and negative (toe-in) angles during walking are protective against medial knee OA incidence. Clinical trials should determine if gait training to alter toe-out angle is effective in preventing medial OA onset in at-risk knees.

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Associations Between Popliteal Artery Wall Thickness and Knee Structure In Adults Without Clinical Knee Disease: A Prospective Cohort Study. Yuanyuan Wang[1], Diaz Novera[1], Anita Wluka[1], Jessica Fairley[1], Graham Giles[2], Richard O'Sullivan[3], Andrew Teichtahl[1] and Flavia Cicuttini[4]. [1]Monash University, Melbourne, Australia, [2]University of Melbourne, Melbourne, Australia, [3]Epworth Hospital, Melbourne, Australia, [4]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, 3004, Australia.

Background/Purpose: There is evidence for a vascular contribution to the pathogenesis of osteoarthritis. The aim of this study was to examine the association between popliteal artery wall thickness, previously shown to be associated with risk of generalized osteoarthritis, and knee structural changes in an asymptomatic cohort.

Methods: 297 adults with no significant knee pain, injury, or history of clinical knee disease were recruited. Participants underwent knee magnetic resonance imaging at baseline and 2 years later. Popliteal artery wall thickness, knee cartilage volume and bone marrow lesions (BML) were assessed.

Results: Of 278 participants with valid popliteal artery wall thickness measurement, 254 (91.4%) completed the follow-up. After adjusting for age, gender, body mass index and tibial bone area, increased popliteal artery wall thickness was associated with reduced medial tibial cartilage volume (B = −6.7, 95% CI −12.9, −0.6, p = 0.03) and increased rate of medial tibial cartilage volume loss (B = 0.06, 95% CI 0.01, 0.12, p = 0.03). There was a trend for medial tibiofemoral BML getting worse in relation to increased popliteal artery wall thickness (odds ratio 1.07, 95% CI 0.99, 1.15, p = 0.07). No significant associations were observed in lateral tibiofemoral compartment.

Conclusion: Increased popliteal artery wall thickness was associated with adverse changes in knee structure, as evidenced by reduced medial tibial cartilage volume, increased rate of cartilage volume loss and a trend for BML worsening over 2 years. These findings suggest an association between vascular pathology and early knee structural changes, supporting the hypothesis that vascular health may play a role in the development of knee osteoarthritis.

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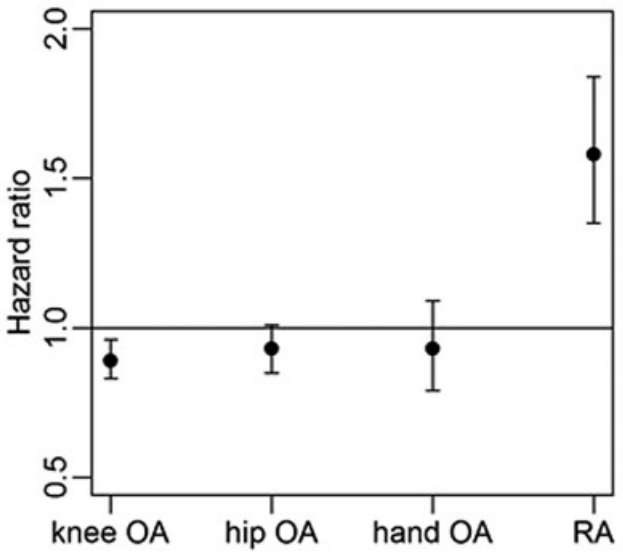
Mortality In Clinically Relevant Osteoarthritis and Rheumatoid Arthritis Compared With The General Population. Aleksandra Turkiewicz[1], Tuhina Neogi[2], George Peat[3] and Martin Englund[1]. [1]Department of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, [2]Boston University School of Medicine, Boston, MA, [3]Research Institute for Primary Care & Health Sciences, Keele University, Keele, United Kingdom.

Background/Purpose: There is strong evidence in support of increased mortality in patients with rheumatoid arthritis (RA), while the relation is more controversial in osteoarthritis (OA). Our aim was to assess mortality rates in patients with clinically relevant OA and RA, respectively, compared with those in the general population who have sought health care to minimize confounding.

Methods: We used a cohort study design within the Skåne Health Care Register in Sweden, which is a legislative, mandatory register based on physicians' International Classification of Diseases (ICD) 10 diagnostic codes. The register covers all primary and specialist health care as well as hospitalizations in southern Sweden (population 1.3 million). The Swedish population register contains information about vital events (births, deaths) and changes in residential address. We identified all patients aged ≥45 years having received the diagnosis of knee OA (ICD-10: M17), hip OA (M16), hand OA (M18, M15.1, M15.2, M19.0D, M19.1D, M19.2D), or RA (M05, M06) during 1999 to 2006. For RA patients we required at least two health care visits with the specific code registered, with at least one from a specialist in rheumatology or internal medicine. For OA we required at least one visit with the specific code registered. For the reference population aged ≥45, we required at least one visit with any diagnostic code (90% of the population had sought care during the period). Using the population register we followed all subjects from Jan 1st 2007 until relocation outside of the region, death, or Dec 31st 2011. We calculated mortality rates using the Cox proportional hazard model adjusted for age and sex, disposable income, marital status, and highest level of education reached (provided by Statistics Sweden). In a sensitivity analysis, we considered subjects who received a diagnosis of pain in a joint (M25.5, location unspecified) at age 55 or older as OA subjects in addition to the definition above.

Results: The hazard ratio of death for RA patients compared to general population was 1.58 (95% CI: 1.35–1.84). Patients with knee, hip or hand OA did not have increased risk of mortality compared with the general population, adjusted for age, sex and socioeconomic variables (Figure). The risk of death remained similar when OA in any joint (i.e., any combination of knee, hip, or hand) was assessed, or when pain in a joint at age ≥55 was additionally considered as OA. Effect estimates were similar in men and women (Table).



	Knee OA n=26 825	Hip OA n=14 557	Hand OA n=7 279	RA n=4 838	Reference population n=511 115
Age, mean (SD)	69.5 (11.8)	72.6 (10.8)	65.8 (10.2)	67.3 (11.0)	63.2 (12.3)
Women, n (%)	15 820 (590	8 449 (58)	5 666 (78)	3 459 (72)	269 118 (53)
Person time, years	122 982	65 498	34 532	21 399	2 386 221
Deaths, n	4 166	2 771	660	1 002	56 373
Mortality rate, per 100 000 person-years	3 388	4 231	1 911	4 682	2 362
HZ (95% CI)—adjusted for age, marital status, income and highest level of education reached					
Men	0.89 (0.79–1.00)	0.97 (0.85–1.10)	0.89 (0.65–1.21)	1.36 (1.04–1.79)	
Women	0.90 (0.82–0.98)	0.90 (0.80–1.01)	0.95 (0.79–1.15)	1.71 (1.41–2.06)	

Conclusion: We found no evidence of increased risk of mortality over 5 years in patients with doctor-diagnosed knee, hip or hand OA, compared with the general population, while increased mortality in RA was confirmed.

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ACR Concurrent Abstract Session
Pediatric Rheumatology - Clinical and Therapeutic Aspects III: Systemic Lupus Erythematosus and Other Disease Outcomes
Tuesday, October 29, 2013, 2:30 PM–4:00 PM

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Vitamin D Deficiency Is Common and Associated With Increased C-Reactive Protein In Children With Lupus: An Atherosclerosis Prevention In Pediatric Lupus Erythematosus Substudy. Angela B. Robinson[1], Vin Tangpricha[2], Eric Yow[3], Reut Gurion[1], Grace McComsey[1] and Laura E. Schanberg[4]. [1]Rainbow Babies and Children's Hospital / Case Medical Center, Cleveland, OH, [2]Emory University School of Medicine, Atlanta, GA, [3]Duke Clinical Research Institute, Durham, NC, [4]Duke University Medical Center, Durham, NC.

Background/Purpose: Epidemiologic associations suggest vitamin D may play a role in inflammation and progression of atherosclerosis. Using frozen serum, carotid intima medial thickness (CIMT) measurements, and other data from the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial, we assessed associations between 25-hydroxyvitamin D [25(OH)D] and measures of systemic lupus erythematosus (SLE) disease activity and cardiovascular risk.

Methods: Participants in the 3-year APPLE trial were randomized to placebo or atorvastatin and CIMT progression was measured. Serum collected at baseline and 1 year was used to measure 25(OH)D levels. Logistic regression models for vitamin D deficiency [25(OH)D levels < 20 ng/mL] at baseline were constructed to evaluate univariable and multivariable associations with baseline variables. Variables collected as part of the APPLE trial included (1) known risk factors for vitamin D deficiency, (2) SLE-specific factors including duration of illness, disease activity, high sensitivity C-reactive protein (hsCRP), and proteinuria, and (3) traditional cardiovascular risk factors including fasting lipids and baseline CIMT.

Results: 201/221 APPLE subjects had available samples and were included in the analysis; 61/201 (30%) had vitamin D deficiency at baseline. There was no change in 25(OH)D levels after 1 year of atorvastatin or placebo. In univariable analysis, baseline 25(OH)D deficiency was associated with season ($p < 0.01$), minority status ($p < 0.01$), body mass index ($p = 0.04$), duration of SLE ($p < 0.01$), SLICC damage index ($p = 0.04$), hsCRP ($p < 0.01$), mean-max IMT ($p = 0.01$), LDL-cholesterol ($p = 0.03$), and timed urine protein ($p = 0.03$). In multivariable modeling, vitamin D deficiency was associated with age, latitude, season, minority status, proteinuria, and hsCRP (see Table).

Table. Logistic modeling of vitamin D deficiency (25OHD $<$ 20ng/mL)

	Odds ratio	95% CI	P-value
Age	1.28	1.09, 1.50	0.002
Latitude	0.87	0.76, 0.99	0.034
Season			
1st quarter	2.83	0.87, 9.23	0.084
2nd quarter	1.23	0.45, 3.36	0.685
3rd quarter	0.57	0.19, 1.75	0.327
Minority status	17.47	5.22, 58.48	<0.001
Log timed urine proteinuria	2.47	0.96, 6.34	0.060
Log hsCRP	1.40	1.07, 1.83	0.015

Conclusion: Vitamin D deficiency is common in pediatric lupus and is independently associated with elevated hsCRP, a marker of inflammation which predicts higher general cardiovascular disease risk. Observed association differences between univariable and multivariable modeling may be related to confounding or loss of power and requires further study. The association between vitamin D deficiency and hsCRP is novel in the SLE population and suggests that vitamin D deficiency may independently contribute to heightened inflammation and cardiovascular risk in this population.

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Phase 2 Trial On Triptorelin For Ovary Protection In Childhood-Onset Systemic Lupus Erythematosus. Rina Mina[1], Andreas Reiff[2], Clovis A. Silva[3], Patricia Vega Fernandez[4], Gloria C. Higgins[5], Lisa F. Imundo[6], Marisa S. Klein-Gitelman[7], Calvin Williams[8], Carol A. Wallace[9], Nadia E. Aikawa[10], Shannen L. Nelson[11], Jun Ying[12], Susan R. Rose[13] and Hermine I. Brunner[14]. [1]Cincinnati Children's Hospital Medical Center/University of Cincinnati School of Medicine, Cincinnati, OH, [2]Children's Hospital Los Angeles, Los Angeles, CA, [3]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [4]Cincinnati Children's Hospital Medica Center, CINCINNATI, OH, [5]Nationwide Childrens Hosp, Columbus, OH, [6]Morgan Stanely Children's Hospital of New York-Presbyterian, Columbia University Medical Center, New York, NY, [7]Children's Memorial Hospital, Chicago, IL, [8]Medical College of Wisconsin, Milwaukee, WI, [9]Seattle Childrens Hosp & Research Institute, Seattle, WA, [10]Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, [11]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [12]University of Cincinnati, Cincinnati, OH, [13]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [14]PRCSG, Cincinnati, OH.

Background/Purpose: Gonadotoxicity is a known side effect of cyclophosphamide (CYC) therapy in childhood-onset systemic lupus erythematosus (cSLE). Gonadotropin releasing hormone (GnRH) agonists, such as triptorelin, can induce complete ovarian suppression (COS), which makes ovaries resistant to CYC gonadotoxicity. The aims of this research are to determine (1) the dose of triptorelin sufficient for reliable

COS in cSLE patients receiving CYC, and (2) the safety profile of triptorelin in cSLE.

Methods: This double-blind, placebo-controlled, dose-escalation RCT (phase I/II) recruited cSLE patients from 7 international centers (NCT00124514). All patients were female, aged ≤ 21 years and Tanner breast stage ≥ 2. They were randomized in a 4:1 fashion to receive either intramuscular triptorelin [μg/kg/dose: 25 (T1), 50 (T2), 75 (T3), 100 (T4)] or placebo every 4 weeks during CYC induction. The primary efficacy endpoint was the monthly dose of triptorelin that resulted in maintenance of COS which was defined *a priori* as (A) basal level of Follicle Stimulating Hormone (FSH) < 2 mIU/ml and of Luteinizing Hormone (LH) < 1 mIU/ml; or (B) FSH < 3 mIU/ml and of LH < 2 mIU/ml during GnRH Stimulation Testing (GAST). FSH and LH levels were drawn at the expected trough levels of triptorelin (27 days post administration). The triptorelin dose was escalated by 25% or at least 20 μg/kg until maintenance of COS was achieved (maximum=150 μg/kg/dose). Adverse events (AE) were graded according to the National Cancer Institute Common Toxicity Criteria, Version 2.

Results: Twenty-nine females were randomized (Placebo=6, T1= 9, T2=8, T3=5, T4=1). Of those who received triptorelin, 4 patients did not complete the study due to CYC discontinuation or withdrawal of consent. As expected, none of those in the placebo group achieved COS. A dose of 75 and 110 μg/kg maintained COS in 75% and 90% of the patients, respectively. There was no relationship between the triptorelin dose and the patients' age, Tanner stage, global disease activity, renal and hepatic function. None of the patients in T3 and T4 arms needed dose escalation of triptorelin while the converse is true for majority of patients in T1 and T2. AE were mild and the most common were hot flashes (24%), headache (14%), and insomnia (10%). Serious AE included hospitalization due to dehydration (Placebo=1), worsening of SLE disease activity (Placebo=1), and cutaneous vasculitis (T3=1).

Conclusion: This interim analysis supports that higher doses of triptorelin than previously suggested are needed for COS in adolescent females with cSLE who require CYC. Doses of intramuscular triptorelin at 110 μg/kg induce continuous COS between injections given every 28 days in almost all females, and thus likely provide ovarian protection. These high doses of triptorelin appear well tolerated.

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Increased Pulse Wave Velocity In Juvenile Idiopathic Arthritis Patients Compared To Controls From The General Population. Hanne A. Aulie[1], Anne Marit Selvaag[1], Vibke Lilleby[1], Oyvind Molberg[1], Anders Hartmann[2], Hallvard Holdaas[2] and Berit Flato[1]. [1]Department of Rheumatology, Oslo University Hospital, Rikshospitalet, Oslo, Norway, [2]Department of Nephrology (and specialised Endocrinology), Oslo University Hospital, Rikshospitalet, Oslo, Norway.

Background/Purpose: The aim of this study was to compare markers of subclinical cardiovascular disease (CVD) in adults with juvenile idiopathic arthritis (JIA) and controls, and assess the relation between arterial properties and JIA characteristics, received therapy, and traditional cardiovascular risk factors.

Methods: Eighty-seven JIA patients (median age 38.4 years), with persistently active disease at least 15 years after disease onset, registered by longitudinal follow-up, were reexamined after median 29 years and compared to 87 matched controls from the Norwegian population register. Pulse wave velocity (PWV), a direct measure of large arterial stiffness and augmentation index (AIx), a marker of arterial stiffness and wave reflection, were estimated. Linear regression analyses adjusted for age and gender were used to analyze the associations between arterial stiffness and traditional cardiovascular risk factors as well as disease characteristics. Linear multiple regression analyses were performed to identify predictors of arterial stiffness.

Results: PWV, systolic and diastolic blood pressures (SBP and DBP) were significantly higher in patients than controls (table). In patients, increased PWV was mainly related to DBP ($p < 0.001$), but was also associated with higher SBP ($p<0.001$), glucose ($p=0.001$), and pulse rate ($p=0.003$), lower high density lipoprotein cholesterol ($p=0.050$), and male gender ($p=0.013$). Higher AIx was determined by increased DBP ($p<0.001$), age ($p = 0.039$), female gender ($p < 0.001$), daily smoking ($p=0.024$), high sensitivity C- reactive protein (CRP) ($p=0.014$), and physician's global assessment of disease activity ($p=0.001$). Furthermore, AIx was associated with longer duration of active disease ($p=0.012$), higher CRP area under the curve ($p=0.006$), less vigorous physical activity ($p=0.004$), joint erosions ($p=0.016$), and therapy with prednisolone ($p<0.001$), nonsteroidal anti-inflammatory drugs ($p=0.036$), and methotrexate ($p=0.015$). Hypertension, daily smokers, and insulin resistance were more frequent in patients than controls ($p=0.039$, $p=0.043$ and $p=0.034$ respectively), but the traditional cardiovascular risk factors were more extensively related to increased AIx in controls.

Table.

	n	JIA patients	Controls	P (paired t-test)
Systolic blood pressure (mmHg)	87	119.4 ± 14.5	115.7 ± 9.8	0.050
Diastolic blood pressure (mmHg)	87	75.7 ± 10.3	72.7 ± ±8.2	0.029
Pulse (beats/ minute)	87	62.7 ± 10.7	61.8 ± 9.7	0.564
Pulse wave velocity (PWV) (m/s)	78	7.2 ± 1.0	6.9 ± 0.8	0.035
Augmentation index (AIx)	79	14.5 ± 10.8	12.0 ± 12.2	0.154

Conclusion: JIA patients with long-term active disease experienced increased arterial stiffness assessed by PWV. Traditional cardiovascular risk factors and the degree of disease activity and severity, treatment factors and physical activity influenced the arterial stiffness measured by PWV and AIx in these patients.

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Disease Progression Into Adulthood In Patients With Juvenile Idiopathic Arthritis – a Longitudinal 30 Year Follow-Up Study. Anne Marit Selvaag, Hanne Aulie, Vibke Lilleby and Berit Flatø. Department of Rheumatology, Oslo University Hospital, Rikshospitalet, Oslo, Norway.

Background/Purpose: The aim of the study was to assess disease activity and health status in a previously studied cohort of patients with juvenile idiopathic arthritis (JIA) 30 years after disease onset and reveal predictors of active disease.

Methods: A total of 254 patients with JIA, first referred to our hospital from 1980 to1985, were reexamined clinically after median 15 years of disease duration, and by mailed questionnaires after median 23 years. These patients were invited to attend the present study. All patients were assessed by questionnaires, and those with signs of active disease after 15, 23 and/or 30 years were invited to a clinical reexamination. Health status was measured by HAQ and SF-36, and disease activity by the clinical version of the juvenile arthritis disease activity score (cJADAS). Logistic regression analyses were used to assess predictors of persistently active disease and an unacceptable symptom state (cJADAS > 4.5).

Results: One hundred and seventy-one patients (67%) were included in the study. They were examined after a median of 30 (range 21–40) years of disease duration, median age 39 (range 28–45) years, 74% females.

After 30 years, 101 patients (59%) were in clinical remission off medication, 12 (7%) were in remission on medication and 58 (34%) had persistently active disease. Thirty-seven of 57 patients (65%) with active disease at 15 years follow-up had active disease at 30 years follow-up, and 20 patients (35%) went into remission on/off medication. Eighty-four of 97 patients (87%) in remission off medication at 15 years were in remission at 30 years follow-up. Patients in remission on medication at 15 years (n=17) tended to flare (n=9) or go into remission off medication (n=6).

The cJADAS score was median 1.9 for the total study group, and 43% (n=73) of the patients had a cJADAS score ≤ 1.0, 10 % (n=16) had cJADAS from 1.1 to 2.0, 18% (n=30) had cJADAS from 2.1 to 4.5, and 30% (n= 50) had cJADAS > 4.5.

Predictors of persistently active disease at 30 years follow-up were: being diagnosed with a JIA subgroup other than persistent oligo articular and systemic JIA (OR 4.1, 95%CI 1.5–11.5), being DR1 positive (OR 8.3, 95%CI 2.3–30.3), a short total time in remission (OR 9.0, 95% CI 3.0–26.7), and not being in remission at 15 years follow-up (OR 13.7, 95%CI 4.9–38.4). R^2=65%. Predictors of a cJADAS score > 4.5 at 30 years follow-up were physician's global score of disease activity at 15 years (OR 2.4, 95%CI 1.7–3.5) and daily smoking (OR 2.5, 95%CI 1.1–5.9). R^2=23%.

We compared disease activity at 15 years with that of 30 years follow-up for 90 patients. There were significant improvements in physicians global assessment of disease activity ($p=0.003$), number of active joints ($p=0.010$), ESR ($p=0.041$) and CRP ($p<0.001$), but no significant change in patient's global assessment, number of joints with limitation of motion, HAQ, or SF-36.

Conclusion: The overall remission rates were stable between 15 and 30 years. After 30 years, a third of the JIA patients had an unacceptable symptom state and a third was not in remission on or off medication. Physician's assessment of disease activity and inflammatory markers improved over the years, but patient reported disability and health status did not change.

Disclosure: A. M. Selvaag, The Norwegian Women's Public Health Association, 2; **H. Aulie**, None; **V. Lilleby**, None; **B. Flatø**, None.

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Medically Significant Infections Are Increased In Patients With Juvenile Idiopathic Arthritis Treated With Etanercept. Results From The British Society For Paediatric and Adolescent Rheumatology Etanercept Cohort Study. Rebecca Davies[1], Taunton R. Southwood[2], Lianne Kearsley-Fleet[1], Mark Lunt[1], Kimme L. Hyrich[3] and on Behalf Of The BSPAR Etanercept Cohort Study[1]. [1]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [2]Institute of Child Health, University of Birmingham and Birmingham Children's Hospital, Birmingham, United Kingdom, [3]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Sciences Centre, Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: The association between anti-TNF therapy and increased rate of infection are widely documented in adults with rheumatoid arthritis. Findings in children with juvenile idiopathic arthritis (JIA) have been less consistent and limited by small sample size and restricted follow up times. Dutch and German national registers documented low rates of serious infection (SI) in etanercept (ETN) treated patients with JIA, although one analysis has suggested more frequent SIs when ETN was used in combination with methotrexate (MTX). The aims of this analysis were (1) to compare rates of serious infection in JIA patients treated with ETN vs. MTX and (2) to compare the rates between ETN-MTX combination and ETN monotherapy.

Methods: To 31/5/2013, 677 ETN and 182 biologic-naive MTX control patients had been recruited to the BSPAR Etanercept Cohort Study, a UK national register established in 2004 to monitor the safety and effectiveness of ETN in children with JIA. All patients were followed by regular hospital questionnaires. Serious infections were defined as any infection regarded as medically significant by the patient's clinican. This on-drug analysis followed all patients until first SI, death, treatment discontinuation or last follow-up date, whichever came first. Cox proportional hazards models were used to compare rates of SI between cohorts. Adjustments were made for potential confounders including age, gender, co-morbidities, oral steroid use, disease duration, ILAR category (systemic versus non-systemic) and disease severity, using a propensity score stratified into deciles (PD). Missing baseline data were accounted for using multiple imputation.

Results: The ETN cohort were older (mean 10.6 v 7.8 years), with longer disease duration (4.6 v 1.2 years), and had a higher proportion of children with systemic arthritis (15% v 4%). Disease activity was similar between the cohorts. The mean duration of follow up was 2.4 years in the ETN cohort, and 2.6 years in the MTX cohort. A total of 120 first SI's were reported (99 ETN, 21 MTX). Patients on ETN had higher rates of SI than controls (PD adjusted HR 2.03 (1.12, 3.65)). The risk of SI did not differ between patients receiving ETN as monotherapy and those receiving ETN in combination with MTX (PD adjusted HR 1.24 (95 % CI 0.83, 1.86)) (Table).

Table. Patient characteristics and incidence of serious infection.

	MTX registered	On ETN	On ETN monotherapy	On ETN & MTX in combination
Subjects (n)	182	677	..	..
Exposure (person-years)	466	1498	827	671
Total serious infection, n	21	134	67	67
First serious infection, n	21	99	47	52
Upper respiratory tract, n	4	23	13	10
Skin & soft tissue, n	0	15	9	6
Lower respiratory tract, n	3	12	5	7
Varicella & zoster, n	5	14	7	7
Other Viral, n	6	11	3	8
Urinary tract, n	1	6	2	4
Bone/joint, n	0	2	1	1
Other or Not specified, n	2	16	7	9
SI incident rate/100 pyrs	4.5 [2.8, 6.9]	8.9 [7.5, 10.6]	8.1 [6.3, 10.3]	10.0 [7.7, 12.7]
SI PD adjusted HR*	ref	2.03 [1.12, 3.65]	1.96 [0.96, 4.00]	2.14 [1.12, 4.10]
	..	..	ref	1.24 [0.83, 1.86]

* Variables in PD: age, gender, Childhood Health Assessment Questionnaire (CHAQ), Juvenile Arthritis Disease Activity Score (JADAS), disease duration, co-morbidities, concurrent oral steroid use, ILAR category.

Conclusion: ETN therapy is associated with an increased risk of SI in JIA patients. This risk does not increase further for ETN-MTX patients compared to ETN monotherapy patients.

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Incidence Rates Of Serious Infections and Infection Subtypes Among Pediatric Systemic Lupus Erythematosus Patients Enrolled In Medicaid, According To Medication Use. Linda T. Hiraki[1], Candace H. Feldman[2], Mary Beth Son[3], Jessica M. Franklin[4], Michael A. Fischer[4], Daniel H. Solomon[5], Seoyoung C. Kim[6], Wolfgang C. Winkelmayer[7] and Karen H. Costenbader[8]. [1]Brigham and Women's Hospital, Harvard School of Public Health, Boston, MA, [2]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [3]Children's Hospital Boston, Boston, MA, [4]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, [5]Harvard Medical School, Brigham and Women's Hospital, Division of Rheumatology, Division of Pharmacoepidemiology, Boston, MA, [6]Brigham and Women's Hospital, Boston, MA, [7]Stanford University School of Medicine, Stanford, CA, [8]Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: We investigated incidence rates of serious infections and infection subtypes among children with SLE enrolled in Medicaid, the U.S. health insurance program for low-income children and parents.

Methods: We identified all children aged 3 to <18 years with SLE (≥3 ICD-9 codes of 710.0, each >30 days apart) in the Medicaid Analytic eXtract (MAX) from 2000–2006. This dataset contains all outpatient and inpatient Medicaid claims for enrollees in 47 U. S. states and the District of Columbia. Filled prescriptions were documented and patients were classified as ever/never users of corticosteroids (CS) and immunosuppressants (IS). We identified serious infections from hospital discharge diagnosis codes for all infections, and for specific subtypes of infections (bacterial, fungal and viral). We calculated incidence rates (IR) per 1000 person-years for number of infections ≥7 days following first prescription. Incidence rate ratios (IRR) (95% CI) were calculated comparing: 1) receipt of neither CS nor IS, 2) receipt of CS alone and 3) receipt of both CS and IS. We employed Poisson models, adjusted for age, sex and duration of enrollment in Medicaid.

Results: Of the 4,068 children identified with SLE. A total of 839 serious infections occurred in 457 children during 8,854 person-years. 2.9% of the children had ≥3 infections during their Medicaid enrollment. (**Table**) Incidence rates for all serious infections requiring hospitalization varied between 43 and 109 per 1000 children per year. Among children with SLE receiving CS alone, incidence rates were approximately twice as high for both all infections and for bacterial infections, and 5.2 times higher for viral infections, compared to those children not receiving CS or IS. Among children receiving both CS and IS, overall serious infection incidence rates were approximately 2.5 times higher, bacterial infections were 2.3 times higher, and viral infections were 7.5 times higher, compared to children not receiving either medication. Fungal infection incidence rates did not appear to be increased among users of CS or IS.

Table. Incidence Rates and Incidence Rate Ratios for Serious Infections among Children with SLE enrolled in Medicaid, 2000–2006

	All Infections		Bacterial Infections		Fungal Infections		Viral Infections	
	IR (95%CI)	IRR (95% CI)	IR (95% CI)	IRR (95% CI)	IR (95%CI)	IRR (95% CI)	IR (95%CI)	IRR (95% CI)
SLE								
No CS* or IS n=763**	43.6 (43.2, 44.0)	1.0 (ref)	37.9 (37.5, 38.2)	1.0 (ref)	3.6 (3.5, 3.7)	1.0 (ref)	2.1 (2.1, 2.2)	1.0 (ref)
CS* alone n=1211	86.5 (86.2, 86.8)	**1.97 (1.55, 2.53)**	71.2 (70.9, 71.5)	**1.90 (1.49, 2.41)**	3.7 (3.7, 3.8)	0.98 (0.71, 1.35)	11.2 (11.1, 11.3)	**5.16 (3.37, 7.90)**
CS* and IS n=1872**	109.0 (108.8, 109.2)	**2.48 (1.92, 3.22)**	88.5 (88.3, 88.7)	**2.32 (1.79, 3.00)**	4.4 (4.3, 4.4)	1.25 (0.92, 1.70)	15.7 (15.6, 15.8)	**7.51 (4.32, 13.06)**

Incidence rate ratios (IRRs) adjusted for age, sex and Medicaid enrollment duration. Incidence rates (IRs) and IRRs reported per 100,000 person years.
*CS: Corticosteroids: oral/IV prednisone, methylprednisolone, dexamethasone, hydrocortisone, prednisolone, cortisone.
**IS: Immunosuppressants: mycophenolate mofetil, oral/IV cyclophosphamide, azathioprine, cyclosporine, tacrolimus. Hydroxychloroquine not included.
Bacterial infections: cellulitis, endocarditis, pneumonia, pyelonephritis, septic arthritis, osteomyelitis, bacteremia, listerosis.
Fungal infections: systemic candidiasis, cryptococcosis, aspergillosis, histoplasmosis, pneumocystic carinii, .
Viral infections: cytomegaloviral disease, influenza, herpes zoster, varicella zoster.

Conclusion: We observed significant variation in incidence rates of serious infections among children with SLE. Those children with SLE who were receiving CS alone or in combination with IS, had much higher rates of bacterial and viral infections, compared to those children receiving neither CS nor IS. Viral infection rates were over 5 times higher among the children receiving these mediations than among those who were not.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects IV: Comorbidities in Rheumatoid Arthritis
Tuesday, October 29, 2013, 2:30 PM–4:00 PM

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Risk of Subsequent Infection among Rheumatoid Arthritis Patients Using Biologics. Huifeng Yun[1], Fenglong Xie[1], Elizabeth S. Delzell[1], Lang Chen[1], Emily Levitan[1], James Lewis[2], Kenneth G. Saag[1], Timothy Beukelman[1], Kevin L. Winthrop[3], John Baddley[1], Paul M. Muntner[1] and Jeffrey R. Curtis[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Pennsylvania, Philadelphia, PA, [3]Oregon Health & Science University, Portland, OR.

Background/Purpose: Much has been written about infections associated with biologic agents in patients with rheumatoid arthritis (RA). However, less is known about the risk of subsequent infections in RA patients who resume biologic therapy after a serious infection. To compare the subsequent risk of hospitalized infections associated with specific biologic agents among RA patients previously hospitalized for infection while receiving anti-TNF therapy.

Methods: Using Medicare data from 2006–2010 for 100% of beneficiaries with RA, we identified patients who were hospitalized with infection while on anti-TNF agents and who had US Medicare fee-for-service hospital, physician and prescription drug coverage continuously in the 6 months before the hospitalization discharge date and throughout follow up. Follow-up began 60 days after hospital discharge and ended at the earliest of subsequent infection, loss of Medicare coverage or after 18 months. We determined biologic exposure on each person-day during follow-up and treated exposure as time varying. Confounding was controlled through a person-specific infection risk score that was separately derived among new users of anti-TNF and non-biologic DMARDs. We calculated the incidence rate of subsequent hospitalized infection for each biologic and used cluster adjusted Cox regression to evaluate the association between specific biologics and subsequent infection, controlling for the decile of the infection risk score, types of anti-TNF use, steroid use during baseline, non-biologic DMARD use during baseline and coexisting biologic exposures.

Results: During follow-up of 10,794 hospitalized infections while exposed to anti-TNF therapy, we identified 7,807 person-years of exposure to target biologics and 2,666 subsequent hospitalized infections; of this exposure time 4% was on abatacept, 2% on rituximab and 94% on anti-TNFs, including 23% on etanercept, 18% on adalimumab and 53% on infliximab. Abatacept users had the lowest crude incidence rate of subsequent infection, and etanercept users had the highest. After adjusting for infection risk score decile, the original anti-TNF medication and other potential confounders, abatacept (hazard ratio (HR): 0.80, 95% CI: 0.64–0.99) and etanercept (HR: 0.83, 95% CI: 0.72–0.96) users had significantly lower risks of infection compared to infliximab users.

Table. Number of events, crude incidence rates (IRs) and adjusted Hazard Ratios (HR) for subsequent hospitalized infection by biologic*

Biologic Exposure	Events	PYs†	IR/100 PYs	Crude HR (95% CI)	Adjusted HR (95% CI)‡
Abatacept	88	333	26.5	0.88 (0.71–1.09)	0.80 (0.64–0.99)
Rituximab	38	133	28.5	0.93 (0.68–1.28)	0.85 (0.62–1.18)
Etanercept	661	1,831	36.1	1.07 (0.98–1.17)	0.83 (0.72–0.96)
Adalimumab	497	1,423	34.9	1.03 (0.93–1.14)	0.92 (0.79–1.07)
Infliximab	1382	4,087	33.8	1.0 (ref)	1.0 (ref)

*Biologic exposure was defined as the days' supply field from filled prescriptions to which was added a 30-day 'extension' period.
† Person years.
‡Adjusted for the decile of disease risk score, types of anti-TNF use before the index hospitalization, steroid dose during baseline, methotrexate use during baseline, infection type for the index hospitalization and concurrent biologic exposures during follow up.

Conclusion: Among RA patients who experienced a hospitalized infection while on anti-TNF therapy, the risk of subsequent hospitalized infection was lower for abatacept and etanercept than for other commonly prescribed biologic therapies.

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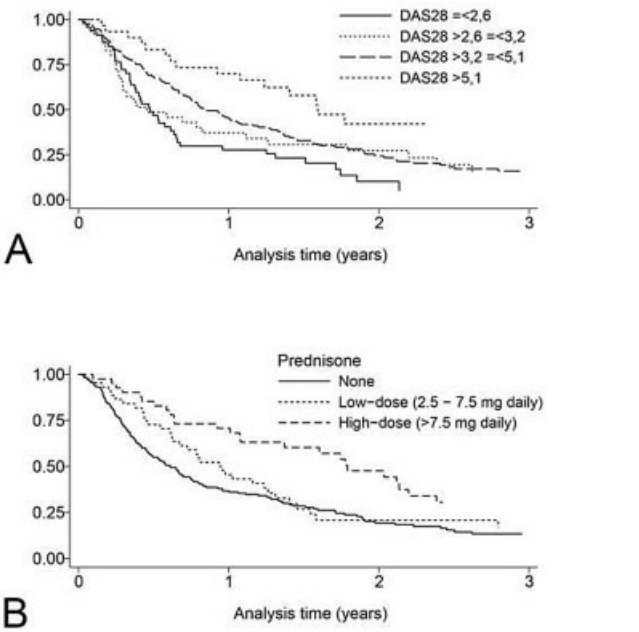
Reduced Fertility In Women With Rheumatoid Arthritis: Influence Of Disease Activity and Medication Use. Jenny Brouwer, Johanna MW Hazes, Joop SE Laven and Radboud JEM Dolhain. Erasmus University Medical Center, Rotterdam, Netherlands.

Background/Purpose: Many female rheumatoid arthritis (RA) patients who try to conceive have a time to pregnancy (TTP) longer than 12 months. During this period RA often cannot be treated optimally. As a result, a longer TTP may result in higher chance of permanent joint damage, with a negative impact on social roles. Thus far, no studies on possible causes of the prolonged TTP in RA patients have been reported. In order to optimize care for these women, we aimed to identify clinical factors associated with a prolonged TTP in RA patients.

Methods: From 2002 until 2010, a nationwide prospective cohort study on pregnancy in RA patients (PARA study) was performed. Women with RA according to the 1987 American College of Rheumatology (ACR) criteria were included preconceptionally or during first trimester. All preconceptionally included women were actively trying to become pregnant. To study the effect of various disease characteristics and medications on the TTP, we performed a multivariable Cox regression analysis.

Results: Two-hundred-forty-five patients were included. The mean age was 31.3±3.9 years. The TTP was longer than 12 months in 42% of patients, of whom 40 women(16%) had not gotten pregnant during the follow up period. A longer TTP was related to various variables. Hazard ratios for occurrence of pregnancy were 0.96 (95%CI 0.92–1.00) per year increase in age; 0.52 (0.38–0.70) for nulliparity; 0.81 (0.71–0.93) per

point increase in disease activity score (DAS28); 0.61 (0.45–0.83) for preconceptional prednisone use; and 0.66 (0.46–0.94) for non-steroidal anti-inflammatory drug (NSAID) use. Eighty-five patients used prednisone during the preconceptional period. The impact of prednisone use on TTP was dose-dependent, with a significant longer TTP when the daily dose was higher than 7.5 mg. TTP was not affected by smoking, disease duration, rheumatoid factor, anti-citrullinated protein antibodies, past methotrexate use, and preconceptional sulfasalazine use.



Survival curves showing the time to pregnancy (TTP) in RA patients with (**A**) various levels of disease activity, and (**B**) with different prednisone dosages. If women had not become pregnant at the last time of contact, the TTP was considered censored at the date of the last visit.

Conclusion: TTP in female RA patients is longer if patients are older or nulliparous, have higher disease activity scores, use NSAIDs or use prednisone in a daily dose higher than 7.5 mg daily. Treatment strategies during the preconceptional period should try to maximize suppression of disease activity, taking account of possible negative effects of NSAIDs use and use of higher doses of prednisone.

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2682

Incidence Trends and Predictors Of Orthopedic Surgery In Patients With Rheumatoid Arthritis – Results From a Well Defined Population. Korosh Hekmat[1], Lennart Jacobsson[1], Jan-Åke Nilsson[1], Minna Willim[1], Martin Englund[2], Ingemar F. Petersson[3] and Carl Turesson[1]. [1]Lund University, Malmö, Sweden, [2]Lund University, Lund, Sweden, [3]Musculoskeletal Scienes, Department of Orthopedics, Clinical Sciences, Lund, Sweden.

Background/Purpose: Orthopedic surgery is used effectively in many patients with severe rheumatoid arthritis (RA). The aim of modern pharmacologic treatment is to prevent joint destruction and reduce the need for orthopedic surgery. Our purpose was to investigate trends in the incidence as well as predictors for such procedures in a population-based sample of patients with RA.

Methods: The study was based on a dynamic cohort of all known patients from a defined geographical area with a clinical diagnosis of RA who fulfilled the 1987 American College of Rheumatology criteria for RA. A total of 2342 patients (68.7% women) were included. Questionnaires were sent to the RA patients in the register in 1997, 2002, 2005 and 2009(response rates 62–74 %) including visual analogue scales (VAS) for general health and pain and the health assessment questionnaire (HAQ). This register was linked to a regional health care register, which contains information on all inpatient and outpatient procedures in the area, to the national population register to add information on vitality and residential address, and to a regional register of patients with arthritis treated with biologics, which covers >90% of such patients in the region. The total follow-up was calculated for each calendar year from 1998 through 2011, and the annual incidence rate of orthopedic surgery procedures was estimated. The incidence rate for 1998–2001 was compared to those of 2002–2006 and 2007–2011. The impact of demographics and patient reported outcomes on the risk of future orthopedic surgery was analyzed using Cox proportional hazard models.

Results: The incidence of all orthopedic surgery procedures during the whole study period was 82,3/1000 person-years (95 % confidence interval (CI) 78,7–86,0). The incidence of all procedures declined significantly over time, with a decrease also for large joint surgery and small joint surgery (hand, wrist, foot and ankle surgery), when studied separately (Table). There was a decline in hip surgery, but not in knee surgery (Table). The incidence of large joint surgery was reduced already in 2002–2006 compared to 1998–2001, whereas a decline in small joint surgery was apparent only in the final period (2007–2011).

Female sex was a predictor of orthopedic surgery [age adjusted hazard ratio (HR) 1.50; 95 % CI 1.23–1.83). Greater disability, measured by HAQ, was associated with a higher rate of orthopedic surgery (HR per standard deviation 1.37; 95 % CI 1.25–1.50 adjusted for age, sex and duration of RA), and similar, although weaker, associations were observed for VAS pain and VAS global.

Table. Incidence of orthopaedic surgery procedures per 1000 person-years (95% CI)

	1998–2001	2002–2006	2007–2011	P for trend
Any orthopedic surgery	94.6 (87.3–102.2)	82.6 (76.7–88.8)	71.8 (66.1–77.8)	<0.001
Hip surgery	27.8 (23.9–32.0)	16.5 (14.0–19.4)	17.6 (14.8–20.7)	<0.001
Knee surgery	12.3 (9.8–15.3)	13.2 (10.9–15.8)	12.9 (10.6–15.6)	0.759
Any small joint surgery	43.8 (38.9–49.0)	43.4 (39.2–47.9)	30.5 (26.9–34.5)	<0.001
Any large joint surgery	48.5 (43.4–54.0)	37.9 (33.9–42.1)	39.3 (35.1–43.8)	0.009

Conclusion: The overall incidence of orthopedic surgery declined over time which coincides with increasing use of more intensive pharmacological treatment including the use of biologics. The decrease in large joint surgery predated that of small joint surgery. Improved management may reduce the need for orthopedic interventions in patients with RA.

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Application Of a Multi-Biomarker Disease Activity (Vectra® DA) Score For Assessing Rheumatoid Arthritis Patients With Fibromyalgia Or Low C-Reactive Protein. Yvonne C. Lee[1], James Hackett[2], Claire Alexander[3], Michelle A. Frits[1], Christine K. Iannaccone[1], Nancy A. Shadick[1], Michael E. Weinblatt[1], Oscar Segurado[3] and Eric H. Sasso[3]. [1]Brigham and Women's Hospital, Boston, MA, [2]Hackett & Associates, Inc., San Diego, CA, [3]Crescendo Bioscience Inc., South San Francisco, CA.

Background/Purpose: Clinical assessment of rheumatoid arthritis (RA) may be challenging if patients have fibromyalgia (FM) or if C-reactive protein (CRP) is low (≤1 mg/dL). A multi-biomarker disease activity (MBDA) blood test has been developed to assess RA disease activity with a score (range: 1–100) that is calculated using a validated algorithm for 12 serum protein biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL-40, leptin, resistin, SAA, CRP). The present study evaluated the role of the MBDA score for assessing disease activity in a cohort of established RA patients, including patients with concomitant FM or low CRP.

Methods: 208 RA patients from a prospective observational cohort were randomly selected for a substudy of pain in RA. For the present cross-sectional study, DAS28-CRP components, the Widespread Pain Index (to diagnose FM by a modified version of the 2010 ACR Diagnostic Criteria for FM), and the MBDA (Vectra‰ DA) score were evaluated for

the initial substudy visit. 198 patients with non-missing baseline MBDA score and DAS28-CRP components were included. Measures of disease activity were compared between patients with RA+FM vs. RA without FM using: t-test or Wilcoxon rank sum tests; multivariate adjustment for age, sex, race, BMI, RF-positivity and non-biologic DMARD use by linear regression or poisson regression (for SJC, TJC); and cumulative probability plots. CRP was compared to MBDA scores by cross-classification.

Results: Characteristics of the overall group (N=198) included: mean age 58.1 years, 84.8% female, 15.9 years mean duration RA, and 61.6%/60.6% taking a non-biologic/biologic DMARD. Patients with RA+FM (N=25) vs. RA alone (N=173) had similar CRP levels, MBDA scores and swollen joint counts (SJC), whereas the 25 RA+FM patients had significantly greater unadjusted values for patient global assessment (PGA) (median 50 vs. 15, $p<0.001$), DAS28-CRP (mean 3.6 vs. 2.8, $p<0.01$) and tender joint counts (TJC) (median 4.0 vs. 1.0, $p=0.04$). Multivariate adjustment gave similar results, but with a larger p-value for TJC ($p=0.30$). CRP levels were ≤1, >1 to 3, or >3 mg/dL in 93%, 6%, and 1% of the 198 subjects, respectively. Among those with low CRP (≤1 mg/dL), MBDA scores were low (≤29) in 51%, moderate (30–44) in 36% and high (>44) in 13%, with similar findings seen in the RA+FM and RA-alone groups. For those with low CRP, the TJC and SJC increased across low to high MBDA categories, suggesting that MBDA differentiated levels of joint inflammation when CRP was low.

Table 1. Disease activity measures for RA patients who met 2010 ACR diagnostic criteria for FM versus those who did not.

Disease Activity Index	RA + FM (N = 25)	RA without FM (N = 173)	Unadjusted P-value[1]	Adjusted P-value[2]
MBDA score	33	32	0.65	0.86
C-reactive protein (mg/dL)	2.0	1.6	0.84	0.72
Swollen joint count	1.0	1.0	0.38	0.40
Tender joint count	4.0	1.0	0.04	0.30
Patient global assessment	50	15	<0.001	<0.001
DAS28-CRP	3.6	2.8	<0.01	<0.01

Values for disease activity measures are unadjusted for covariates and are medians, except for MBDA score and DAS-28, which are means.
[1]P-values for unadjusted means by t-test; for unadjusted medians by Wilcoxon test.
[2]P-values for multivariate (covariate-adjusted) analysis.

Conclusion: Patients with RA+FM, vs. those with RA alone, had similar MBDA scores and CRP values, but significantly greater DAS28-CRP, mostly due to greater PGA. However, MBDA score differed from CRP because MBDA score detected moderate or high disease activity in nearly half of patients with low CRP (≤1 mg/dL). Further study is needed to determine the clinical meaning of discordance between CRP and MBDA scores.

Disclosure: Y. C. Lee, Forest Research Insitutute, 2, Merck Pharmaceuticals, 1, Novartis Pharmaceutical Corporation, 1, Cubist, 1, Elan Corporation, 1; **J. Hackett**, Crescendo Bioscience, Inc., 5; **C. Alexander**, Crescendo Bioscience, Inc., 1, Crescendo Bioscience, Inc., 3; **M. A. Frits**, None; **C. K. Iannaccone**, None; **N. A. Shadick**, MedImmune, 2, Crescendo Biosciences, 2, Amgen, 2, Abbott Immunology Pharmaceuticals, 2, Genentech and Biogen IDEC Inc., 2; **M. E. Weinblatt**, MedImmune, 2, Crescendo Bioscience, Inc., 2, Bristol Myers Squibb, 2, MedImmune, 5, Crescendo Bioscience, Inc., 5, Bristol Myers Squibb, 5; **O. Segurado**, Crescendo Bioscience, Inc., 1, Crescendo Bioscience, Inc., 3; **E. H. Sasso**, Crescendo Bioscience Inc., 1, Crescendo Bioscience Inc., 3.

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Impact Of Anti-Rheumatic Treatment On Immunogenicity Of Pandemic H1N1 Influenza Vaccine In Patients With Arthritis. Meliha C. Kapetanovic[1], Lars-Erik Kristensen[2], Tore Saxne[3], Teodora Aktas[4], Andreas Mörner[4] and Pierre Geborek[3]. [1]Dept of Clinical Sciences Lund, Section of Rheumatology, Lund University, Lund, Sweden, [2]Department of Clinical Sciences, Section of Rheymatology, University Hospital of Skåne, Lund, Sweden, [3]Lund University, Lund, Sweden, [4]Vaccinology Unit, Department of Diagnostics and Vaccinology, Swedish Institute for Communicable Disease Control, Solna, Sweden, Solna, Sweden.

Background/Purpose: An adjuvanted pandemic H1N1 influenza (pH1N1) vaccine (Pandemrix®) was reported as highly immunogenic resulting in seroconversion in 77–94% of adults after administration of a single dose. The aim of the present study was to investigate impact of different anti-rheumatic treatments on antibody response to pH1N1 vaccination in patients with rheumatoid arthritis (RA) and spondylarthropathy (SpA).

Methods: Patients with arthritis (n=291; mean age 57 years, 64% women) participated. Hemagglutination inhibition (HI) assay was performed on blood samples drawn before and after a mean (SD) of 8.3 (4) months following vaccination. A positive immune response i.e. seroconverstion was defined as negative prevaccination serum and post-vaccination HI titer ≥40 or a '4-fold increase in HI titer. There were 7 treatment groups: 1) RA on methotrexate (MTX); 2) RA on anti-TNF monotherapy; 3) RA on anti-TNF+MTX; 4) RA on other biologics (abatacept, rituximab, tocilizumab); 5) SpA on anti-TNF monotherapy; 6) SpA on anti-TNF+MTX and 7) SpA on NSAIDs/analgesics. Predictors of positive immune response were studied using logistic regression analysis.

Results: The percentage of patients with positive immune response in the different treatment groups were: 1) 42% 2) 53% 3) 43% 4) 20% 10%, 50% 5) 76% 6) 47% and 7) 59%, respectively. RA patients on rituximab had significantly lower ($p<0.001$) and SpA on anti-TNF monotherapy significantly better response rates compared to other treatment groups (p 0.001–0.033). Higher age ($p<0.001$) and current smoking predicted impaired immune response ($p=0.025$). Antibody titers 3–6 months after vaccination were generally lower compared to those within first 3 months but no further decrease in titers were observed 6–22 months after vaccination.

Conclusion: Rituximab treatment severely reduced antibody response to pH1N1 influenza vaccine. All other treatments groups showed lower although acceptable antibody response. Serological immunity seems to be stable for 22 months in the current patient population, with the exception of rituximab (and possibly abatacept) treated patients.

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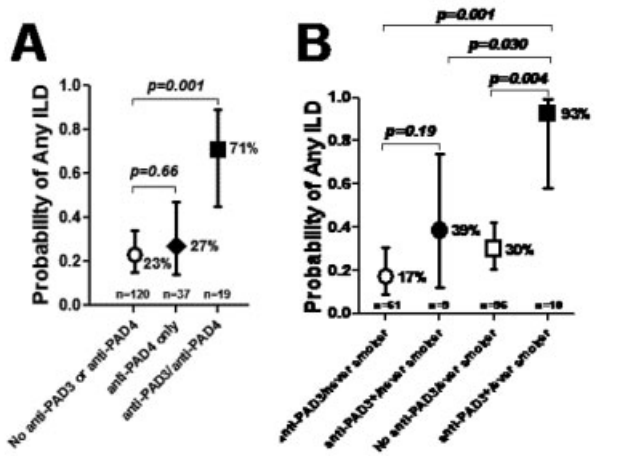
Anti-Peptidylarginine Deiminase 3/4 Cross-Reactive Antibodies Are Associated With Radiographic Interstitial Lung Disease In Rheumatoid Arthritis, An Effect Potentiated By Smoking. Jon T. Giles[1], Erika Darrah[2], Sonye K. Danoff[2], Cheilonda Johnson[2], Felipe Andrade[3], Antony Rosen[2] and Joan M. Bathon[4]. [1]Columbia University, College of Physicians & Surgeons, New York, NY, [2]Johns Hopkins University, Baltimore, MD, [3]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [4]Columbia University, New York, NY.

Background/Purpose: Antibodies targeting citrullinated proteins (ACPA) are implicated in the pathogenesis of interstitial lung disease (ILD) in rheumatoid arthritis (RA). Citrullinated proteins and the enzymes that catalyze citrullination, the peptidylarginine deiminases (PADs), are detected in RA-ILD lung tissue and in the lungs of heavy smokers. A subset of RA patients demonstrates cross-reactive antibodies against PADs 3 and 4 that have been shown to lower the calcium threshold required for PAD activation, an effect potentially relevant to the pathogenesis of RA-ILD. We sought to explore the association between anti-PADs and radiographic RA-ILD.

Methods: RA patients participating in a study of subclinical cardiovascular disease underwent multi-detector computed tomography (MDCT) of the chest with interpretation by a pulmonary radiologist for ILD features. A semi-quantitative ILD Score (ILDS; range 0–32) was calculated. Concurrent serum samples were assessed for antibodies against PAD by immunoprecipitation of S^{35}-labeled PAD3 and 4.

Results: Among the 176 RA patients studied [60% female, 86% Caucasian, mean age 59±9 years, 11% current smokers, median RA duration=8 years, median DAS28=3.7], any CT-ILD was observed in 58 (33%). Anti-PAD3/4 cross-reactive antibodies were detected in 19 (11%) and 37 (21%) had antibodies directed against PAD4 alone. In univariate analysis, the frequency of any CT-ILD among those with anti-PAD3/4 was 68%, vs. 27 and 29% among those with anti-PAD4 only and neither reactivity, respectively (crude OR=5.39; $p=0.001$ for the comparison of anti-PAD3/4 vs. no anti-PAD). The association was stronger after adjustment for relevant demographic and RA disease/treatment confounders

(Fig 1A: adjusted OR=7.22; p=0.001). Anti-PAD3/4 antibodies were significantly associated with all CT-ILD predominant patterns (i.e. ground glass, honeycombing, etc. . .) and quantitative ILD scores were significantly higher for the anti-PAD3/4 vs. the no anti-PAD group (median ILD score 2 vs. 0 units, respectively; p=0.020). The association of anti-PAD3/4 antibodies with CT-ILD was stronger in ever smokers than never smokers. Among never smokers, the adjusted frequency of any ILD was 39 vs. 17%, respectively, for those with vs. without anti-PAD3/4 (Fig 1B, never smokers: OR=3.01; p=0.19) compared with 93 vs. 30%, respectively, for ever smokers with vs. without anti-PAD3/4 (Fig 1B, ever smokers: OR=29.5; p=0.004, p-value for interaction<0.05).



Average probabilities and 95% confidence intervals are depicted. Associations adjusted for age, gender, current and past smoking (Panel A only), rheumatoid factor and CCP2 seropositivity, DAS28, current use of methotrexate and prednisone, RA duration, and total Sharp-van der Heijde Score.

Conclusion: The prevalence of CT-ILD was markedly higher among RA patients with anti-PAD3/4 antibodies, even after accounting for relevant confounders, particularly among ever smokers. Further mechanistic studies are needed to determine whether there is a biologic interaction between smoking and pulmonary hyper-citrullination facilitated by anti-PAD3/4 antibodies that contributes to ILD pathogenesis.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Novel Treatment Strategies in Rheumatoid Arthritis
Tuesday, October 29, 2013, 2:30 PM–4:00 PM

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Impact of Methotrexate Dose Reduction Upon Initiation of Adalimumab On Clinical and Ultrasonographic Parameters in Patients With Moderate to Severe Rheumatoid Arthritis. Gurjit S. Kaeley[1], Amy M. Evangelisto[2], Midori Jane Nishio[3], Shufang Liu[4] and Hartmut Kupper[5]. [1]University of Florida, Jacksonville, FL, [2]Arthritis, Rheumatic and Back Disease Associates, Voorhees, NJ, [3]Diablo Clinical Research, Walnut Creek, CA, [4]AbbVie Inc., North Chicago, IL, [5]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany.

Background/Purpose: Methotrexate (MTX) is the recommended first-line disease-modifying antirheumatic drug (DMARD) for the treatment of moderately to severely active rheumatoid arthritis (RA). Whether patients (pts) with inadequate response to MTX that begin combination therapy with adalimumab (ADA) can reduce MTX dose remains unclear. Clinical and ultrasonographic outcomes of MTX dose reduction when initiating ADA were examined.

Methods: MUSICA was a double-blind, randomized, parallel-arm study to examine the impact of MTX dose on disease outcomes and ultrasonographic signs in moderately to severely active RA pts who have failed prior synthetic DMARDs. The study enrolled 309 pts taking MTX ≥ 15 mg/week (wk) for ≥ 12 wks prior to enrollment. Patients blindly received either high (20 mg/wk) or low dose (7.5 mg/wk) MTX; all pts received open-label 40 mg ADA every other wk for 24 wks. Non-inferiority was assessed using the 95% confidence interval of the difference between high and low dose wk-24 outcomes. A 15% margin (0.56) of the high dose mean 24-wk 28-joint disease activity score (DAS28) was used as the primary endpoint. Ultrasound images acquired every 4 wks were independently read and scored blindly by 4 ultrasound-experienced rheumatologists. A 10-joint semi-quantitative scoring system incorporating OMERACT definitions for pathology (1) measured synovial hypertrophy, vascularity, and bony erosions.

Results: The study populations for both MTX dosages were well balanced for baseline demographics and disease characteristics and had overall age 54.8, 5.3 years RA disease duration, and a DAS28 of 5.8 (all means). Rapid improvement in clinical indices was seen in both groups after addition of ADA. After 24 wks of ADA combination therapy, pts receiving combination therapy with ADA displayed improvements consistent with other trials including low dose MTX. Differences in clinical and ultrasonographic outcomes comparing low vs high dose MTX were minimal. The primary endpoint, mean DAS28, did not meet non-inferiority criteria. Although outcomes favored maintaining 20 mg MTX, no statistically significant differences were detected for most clinical, functional, and ultrasound outcomes (**Table**). Statistically significant differences were only detected in wk-24 swollen joint count and physician's global assessment of disease activity. The number of adverse events (AEs), serious AEs, and infectious AEs were fewer in the low dose MTX arm.

Table. Week 24 Clinical, Functional, and Ultrasonographic Outcomes

Non-Inferiority Parameter	ADA + 7.5 mg MTX (N = 154)	ADA + 20 mg MTX (N = 155)	Difference (Low - High)
[a]DAS28(CRP)	4.11 (3.88, 4.34)	3.75 (3.52, 3.97)	0.37 (0.07, 0.66)
Clinical and Functional Outcomes*			***p* value**
ACR20, n/N (%)	86/151 (57.0)	95/154 (61.7)	0.395
ACR50, n/N (%)	45/151 (29.8)	58/154 (37.7)	0.145
ACR70, n/N (%)	20/151 (13.2)	31/154 (20.1)	0.114
HAQ-DI	0.98 ± 0.75	0.95 ± 0.78	0.476
HAQ-DI improvement ≥ 0.22, n/N (%)	96/151 (63.6)	101/154 (65.6)	0.707
TJC (0–68)	15.1 ± 16.0	13.5 ± 15.3	0.264
SJC (0–66)	9.6 ± 12.8	7.7 ± 10.5	0.028
PGA disease activity (100 mm VAS)	23.7 ± 21.3	19.0 ± 17.4	0.035
PtGA pain (100 mm VAS)	40.0 ± 27.9	36.4 ± 27.7	0.141
PtGA disease activity (100 mm VAS)	38.2 ± 27.5	33.8 ± 26.8	0.094
Ultrasound Outcomes			
Synovial hypertrophy	32.6 ± 7.2	32.9 ± 6.6	0.955
Synovial vascularity	4.43 ± 4.86	4.09 ± 4.53	0.779
Synovial vascularity improvement by 30%, n/N (%)	65/143 (45.5)	77/147 (52.4)	0.221
Synovial vascularity change from baseline	−1.52 ± 4.18	−1.46 ± 3.43	0.779
Bony erosions	1.36 ± 2.43	1.41 ± 2.01	0.598

[a]Primary endpoint, mean (95% CI).
*Mean ± SD unless noted otherwise. Means were calculated using last observation carried forward (LOCF).
ADA, adalimumab; MTX, methotrexate; DAS28, 28-joint disease activity score; CRP, C-reactive protein; ACR, American College of Rheumatology; HAQ-DI, disability index of the health assessment questionnaire; TJC, tender joint count; SJC, swollen joint count; PGA, physician's global assessment; VAS, visual analogue scale; PtGA, patient's global assessment.

Conclusion: Addition of ADA to MTX inadequate responders led to robust results consistent with prior studies. Compared to 20 mg MTX, lowering MTX weekly dose to 7.5 mg in combination with ADA resulted in small differences in clinical and ultrasonographic outcomes in RA pts. Statistically, non-inferiority was not met for mean DAS28. Based on the small differences in most outcomes, MTX dose reduction may be considered when initiating ADA therapy in MTX inadequate responders.

Disclosure: G. S. Kaeley, AbbVie Inc., 5; **A. M. Evangelisto**, AbbVie Inc., 2, AbbVie Inc., 8; **M. J. Nishio**, None; **S. Liu**, AbbVie Inc., 3, AbbVie Inc., 1; **H. Kupper**, AbbVie, 3, AbbVie, 1.

2687

Very High Remission Rates Are Achieved By Methotrexate and Intraarticular Glucocorticoids Independent Of Induction Therapy With Adalimumab; Year 2 Clinical Results Of An Investigator-Initiated Randomised, Controlled Clinical Trial Of Early, Rheumatoid Arthritis (OPERA). Kim Hørslev-Petersen[1], Merete L. Hetland[2], Peter Junker[3], Jan Pødenphant[4], Torkell Ellingsen[5], Palle Ahlqvist[6], Hanne M. Lindegaard[7], Asta Linauskas[8], Annette Schlemmer[9], Mette Y. Dam[10], Ib Hansen[11], Tine Lottenburger[6], Anette Jørgensen[10], Sophine B. Krintel[12], Johnny Raun[1], Christian G. Ammitzbøll[10], Julia Johansen[12], Mikkel Østergaard[13] and Kristian Stengaard-Pedersen[10]. [1]University of Southern Denmark, Graasten, Denmark, [2]DANBIO, Center for Rheumatology and Spine Diseases, Glostrup Univ Hospital, Glostrup, Denmark, [3]University of Southern Denmark, Odense, Denmark, [4]Copenhagen University at Gentofte, Hellerup, Denmark, [5]Silkeborg Regional Hospital, Silkeborg, Denmark, [6]University of Southern Denmark, Vejle, Denmark, [7]Odense University Hospital, Odense, Denmark, [8]Vendsyssel Hospital, Hjørring, Denmark, [9]Aalborg University Hospital, Aalborg, Denmark, [10]Arhus University Hospital, Aarhus, Denmark, [11]Viborg Hospital, Viborg, Denmark, [12]Copenhagen University and Glostrup Hospital, Copenhagen, Denmark, [13]Copenhagen University Hospital Glostrup, Copenhagen, Denmark.

Background/Purpose: In a double-blind placebo-controlled 2-year investigator-initiated trial of patients with early rheumatoid arthritis (RA), we investigated if additional adalimumab (ADA) for 1 year on top of an aggressive treat-to-target strategy with methotrexate (MTX) and intraarticular (i.a.) corticosteroid reduced disease activity. Previously published results *after 1 year* showed that >75% of patients in both groups achieved low disease activity, but remission rates and physical function were higher in the ADA group[1]. Here we present results from the 2nd year.

Methods: DMARD-naïve early RA patients (n=180) were randomized 1:1 to receive i.a. triamcinolone (40 mg/ml) in any swollen joint and MTX (20 mg/wk) for two years in combination with placebo-ADA (MTX+PLA) or MTX+ADA (40 mg eow) during the first year. Oral glucocorticoids were not allowed. ADA/PLA was withdrawn after 1 yr. During year 2, in both treatment arms, ADA (40 mg eow) was only (re)initiated in patients with recurrence of active disease (DAS28 CRP>3.2). Clinical response was assessed by DAS28(CRP), clinical disease activity index (CDAI), simplified disease activity index (SDAI) and ACR/EULAR remission criteria. Physical function was assessed by HAQ (health assessment questionnaire).

Results: Baseline characteristics were similar in the two groups: MTX+PLA/MTX+ADA: DAS28(CRP) 5.6(3.8–7.3)/5.5(3.8–7.8), p=0.53. After 2 years the median MTX dose and cumulated dose of i.a. triamcinolone were similar in the two groups (Table), and biologics were (re)initiated in 15%/17% of patients. During the 2nd year, disease activity (DAS28CRP, CDAI and SDAI) and HAQ scores decreased and ACR/EULAR remission rates increased in the MTX+PLA group. After 2 years, remission rates in MTX+PLA/MTX+ADA groups were: DAS28CRP remission: 69%/66%; CDAI remission: 55%/57%; SDAI remission: 54%/50%; ACR/EULAR(28 joints):44%/45% with no significant differences between MTX+PLA/MTX+ADA in any clinical outcome measure (p=0.36–1.00).

Table. Doses, disease activity, and remission rates at one and two years

	Year 1			Year 2		
Treatment	MTX+ 1st YR PLACEBO	MTX+ 1st YR ADA	P	MTX+ 1st YR PLACEBO	MTX+ 1st YR ADA	P
MTX dose mg/wk	20 (15–20)	20 (7.5–20)	0.17	20 (10–20)	20 (7.6–20)	0.33
I.a. triamcinolone (ml cumulated)	7 (2–18.8)	5.4 (1.8–17.4)	0.08	0 (0–7)	0 (0–7.7)	0.19
Triple DMARD	32 %	16 %	**0.018**	31 %	20 %	0.15
Biologics (open trial)	7 %	7 %	1.00	15 %	17 %	0.97
DAS28CRP	2.6 (1.7–4.7)	2.0 (1.7–5.2)	**0.009**	2.0 (1.7–4.5)	2.0 (1.7–4.4)	0.97
CDAI	3.9 (0–13.6)	1.9 (0–15.4)	**0.01**	1.9 (0.1–14.5)	2.2 (0–15.2)	0.75
SDAI	5.0 (0.8–20.2)	2.7 (0.7–30.4)	**0.006**	2.8 (0.7–19.0)	3.3 (0.7–17.7)	0.36
DAS28CRP<3.2	76%	80%	0.65	84%	83%	1.00
DAS28CRP<2.6	49%	74%	**0.001**	69%	66%	0.79
CDAI≤2.8	41 %	61 %	**0.01**	55 %	57 %	0.87
SDAI<3.3	36 %	57 %	**0.007**	54 %	50 %	0.66
ACR/EULAR Boolean (28)	30 %	48 %	**0.017**	44 %	45 %	1.00
ACR/EULAR Boolean (40)	29 %	49 %	**0.014**	44 %	42 %	0.91
HAQ	0.25 (0–1.44)	0.13 (0–1.5)	0.40	0.13 (0–1.63)	0.13 (0–1.5)	0.37

Values are medians (5%/95% percentiles) or percentage. We used Mann-Whitney or Pearson's chi-square tests. Analysis was by ITT with last observation carried forward. Completer analysis and ITT without imputations gave similar results.

Conclusion: An aggressive treat-to-target strategy of i.a. triamcinolone and methotrexate in early RA provided excellent disease control at 2 years' follow-up independent of 1 year induction therapy with adalimumab.

[1]Hørslev-Petersen K et al. Ann Rheum Dis Online First 7 mar 2013

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Methotrexate Dose Has Minimal Effects On Methotrexate-Related Toxicity In Patients With Early Rheumatoid Arthritis Treated In Combination With Adalimumab – Results Of Concerto Trial. Gerd R. Burmester[1], Alan J. Kivitz[2], Ronald F. van Vollenhoven[3], Stefan Florentinus[4], Piyalal M. Karunaratne[5], Hartmut Kupper[6], Maxime Dougados[7] and Roy M. Fleischmann[8]. [1]Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]Altoona Center for Clinical Research, Duncansville, PA, [3]The Karolinska Institute, Stockholm, Sweden, [4]AbbVie, Rungis, France, [5]AbbVie Inc., North Chicago, IL, [6]AbbVie Deutschland GmBH & Co KG, Ludwigshafen, Germany, [7]René Descartes University, Paris, France, [8]University of Texas Southwestern Medical Center, Dallas, TX.

Background/Purpose: Adalimumab is usually used in combination with 15–20 mg methotrexate (MTX) weekly in early rheumatoid arthritis (RA). Lower doses of MTX in combination with biologics have not been evaluated in controlled clinical trials. The objective of this study was to evaluate the MTX dose-response of MTX-related toxicities in patients (pts) with early RA receiving ADA in combination with MTX.

Methods: CONCERTO was a 26-week (wk), phase 3, double-blind, parallel-arm study in MTX-naive pts with active RA <1 year in duration. Pts were randomized 1:1:1:1 to open-label ADA 40 mg every other wk + blinded weekly oral MTX doses of 2.5, 5, 10, or 20 mg. All pts took 5 mg folic acid weekly throughout the study. Pts in the 20 mg arm started with 10 mg MTX, with bi-weekly increases of 2.5 mg through wk 8. MTX-toxicity related adverse events (AEs) were defined according to MTX prescribing information and recorded as AEs at each visit through wk 26. Laboratory data were summarized through wk 26.

Results: Of the 395 randomized pts, 358 (91%) completed 26 wks. The safety population included 98, 100, 99, and 98 pts in the 2.5, 5, 10, and 20 mg arms, respectively. 9 pts (2.3%) discontinued study drug due to an AE that was not necessarily MTX-related. Of the total population, the percentage of pts with any AE was 62, 59, 67, and 69%, any serious AE was 5, 2, 3 and 7%, and any infection was 20, 17, 24, and 35% in the 2.5, 5, 10, and 20 mg arms, respectively. Two infections in the 5 mg arm were serious AEs, appendicitis and sepsis, but did not result in study discontinuation and were not associated with MTX. The overall incidence of MTX-related AEs was low (Table). Infection and abnormal hair loss appeared to have a MTX dose relationship. No differences in mean change from baseline in hematocrit, neutrophil count, platelet count, ALT, or AST values were observed at wk 26 among the 4 doses of MTX. The percentage of pts with ALT values >upper limit of normal (ULN) that were associated with MTX at wk 26 were 3, 1, 6, and 6% in the 2.5, 5, 10, and 20 mg arms, respectively. Regarding AST, 4, 0, 3, and 3% in the 2.5, 5, 10, and 20 mg arms, respectively, had AST values >ULN.

Table. Adverse Events Reported by Investigators to be Associated with MTX

	ADA+2.5 mg MTX (N=98) n (%)	ADA+5 mg MTX (N=100) n (%)	ADA+10 mg MTX (N=99) n (%)	ADA+20 mg MTX (N=98) n (%)	Total (N=395) n (%)
Infection	6 (6.1)	7 (7.0)	11 (11.1)	13 (13.3)	37 (9.4)
Nausea &/or vomiting	6 (6.1)	3 (3.0)	13 (13.1)	8 (8.2)	30 (7.6)
Stomach pain/ discomfort	5 (5.1)	4 (4.0)	7 (7.1)	7 (7.1)	23 (5.8)
Abnormal hair loss	1 (1.0)	5 (5.0)	5 (5.1)	8 (8.2)	19 (4.8)
Excessive fatigue &/ or malaise	4 (4.1)	1 (1.0)	3 (3.0)	2 (2.0)	10 (2.5)
Dizziness	4 (4.1)	0	4 (4.0)	1 (1.0)	9 (2.3)
Oral ulcers	0	1 (1.0)	5 (5.1)	2 (2.0)	8 (2.0)
Fever &/or chills	0	1 (1.0)	3 (3.0)	0	4 (1.0)

Conclusion: Overall, the combination of ADA plus varying doses of MTX was well tolerated, and MTX-related AEs were infrequent. The frequency of infections and abnormal hair loss appeared to have a MTX-dose relationship. Serious infections were very rare and had no relationship to MTX. No differences in mean change from baseline in blood cell counts or transaminases were observed at wk 26 among the 4 doses of MTX.

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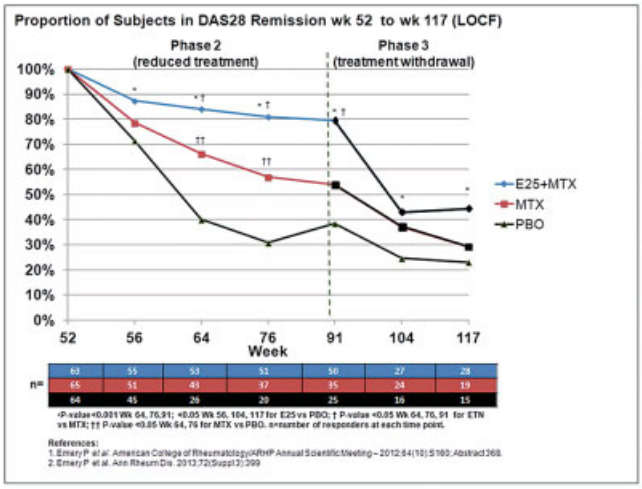
Assessing Maintenance Of Remission After Withdrawal Of Etanercept Plus Methotrexate, Methotrexate Alone, Or Placebo In Early Rheumatoid Arthritis Patients Who Achieved Remission With Etanercept and Methotrexate: The Prize Study. Paul Emery[1], Wolfgang Spieler[2], Maria Stopinska-Polaszewska[3], Nikolay I Korshunov[4], Jack Bukowski[5], Ronald Pedersen[5], Theresa Williams[6], Stefanie Gaylord[6] and Bonnie Vlahos[6]. [1]Institute Rheumatic and Musculoskeletal Medicine University of Leeds, Leeds, United Kingdom, [2]ZeFOR GmbH Zentrum für Forschung, Zerbst, Germany, [3]Family Physicians Specialists Clinic, Torun, Poland, [4]State Budgetary Healthcare Institution of Yaroslavl Region, Yaroslavl, Russia, [5]Pfizer Inc, Collegeville, PA, [6]Pfizer Inc., Collegeville, PA.

Background/Purpose: In the PRIZE study patients (pts) with early (mean 6 mos. since symptom onset) moderate-severe rheumatoid arthritis (RA), who achieved remission after open-label treatment with 50 mg etanercept (ETN) + 10–25 mg MTX (Phase 1)[1] were randomized to a double-blind 39-wk period of (25mg) ETN25+ MTX, MTX alone, or placebo (PBO, Phase 2)[2]; the study drugs were then withdrawn (randomized treatment remained blinded) and pts were monitored for an additional 26 weeks (Phase 3). Using patients who achieved remission in Phase 1, the objective of this analysis was to assess sustained remission and other clinical and safety outcomes in randomized pts (Phase 2) and subsequent withdrawal of drug treatments (Phase 3).

Methods: Pts with DAS28 remission (<2.6, n=193) began Phase 2 at wk 52; those maintaining DAS28 LDA by wk 91 (≤3.2, n=131) continued and had study drugs withdrawn (MTX tapered to week 95) through wk 117 (end of study). Remission and other standard clinical outcomes were assessed during Phase 2 and 3. LOCF was used for missing data. Fisher's exact test was used for significance.

Results: Between wks 52 and 91, the proportion of pts in the ETN25+MTX group who maintained DAS28 remission declined slower than those treated with MTX or PBO; at wk 117, significantly more pts in the ETN25+MTX group maintained remission relative to PBO following withdrawal of randomized treatment (Figure). Other outcomes had similar results. At the beginning of Phase 2, the proportions of pts in the ETN25+MTX group with DAS28 LDA, Boolean remission, ACR50/70 and normal HAQ (≤0.5) were 100%, 71%, 92%/83%, and 84%, respectively; MTX group: 100%, 72% 95%/87% and 86%, respectively; PBO group: 100%, 63%, 95%/82%, and 75%, respectively. At wk 91, the proportions declined to 89%, 68%, 78%/71%, and 78% (ETN25+MTX); 69%, 46%, 71%/62%, and 72% (MTX); 46%, 23%, 45%/37%, and 45% (PBO), respectively. After treatment withdrawal at wk 117, the proportions of pts who maintained these outcomes were 56%, 47%, 46%/41%, and 67% (ETN25+MTX), 43%, 25%, 38%/29%, and 59% (MTX), 37%, 16%, 35%/23%, and 40% (PBO), respectively. There were no unexpected safety findings.



Conclusion: Of the early RA pts with DAS28 remission at the beginning of Phase 2, those randomized to a reduced dose of ETN had a modest loss of efficacy in Phase 2, but randomization to PBO and withdrawal of ETN in Phase 3 both led to steep declines in all outcomes.

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Survival Of The Second Biologic After The First Tumor Necrosis Factor Alpha Inhibitor's Failure In The Treatment Of Rheumatoid Arthritis: Prospective Observational Data From Biorx. Si Registry. ŽIga Rotar[1] and Matija Tomsic[2]. [1]University Medical Centre Ljubljana, 1000 Ljubljana, Slovenia, [2]University Medical Centre Ljubljana, Ljubljana, Slovenia.

Background/Purpose: Current recommendations for management of RA propose a tumor necrosis factor alpha inhibitor (TNFi) for patients failing to achieve the treatment target with synthetic DMARDs. If 1st TNFi fails, a different TNFi, abatacept, rituximab (RTX) or tocilizumab (TCZ) are equally recommended. It has been shown that non TNFi biologics are at least as effective as the TNFi in this setting. Since there is little is known about the survival of 2nd biologic agent, we decided to investigate the survival of the 2nd biologic after switching from the 1st TNFi.

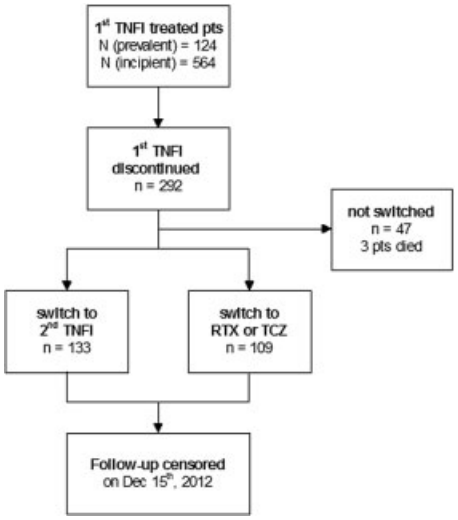

Figure 1.

Table 1.

Line of biologic DMARD	1st	2nd			
Biologic DMARD	**iTNF**	**iTNF**	**Rituximab**	**Tocilizumab**	
Patients	688	133	34	75	
iTNF used					
% adalimumab	43.6	33.8	/	/	
% etanercept	30.7	39.9	/	/	
% infliximab	10.7	9.8	/	/	
% certolizumab	9.9	15.0	/	/	
% golimumab	5.1	1.5	/	/	
Gender (% female)	81.5	78.2	76.5	90.7	*p*= 0.056‡
mean age at starting bio-DMARD [yr] (SD)	54.7 (11,5)	55.0 (11.4)	56.9 (12.2)	57.6 (11.3)	*p*= 0.272*
mean age at diagnosis [yr] (SD)	45.2 (11.8)	45.2 (11.4)	45.5 (11.8)	45.7 (12.0)	*p*= 0.948*
mean time to bioDMARD [yr] (SD)	9.8 (8.1)	9.9 (6.9)	10.6 (7.0)	11.9 (8.4)	*p*= 0.286†
% RF positive	81,8	81.2	91.2	77.3	*p*= 0.227‡
%ACPA positive	77.0	*73.7*	*96.5*	*74.5*	*p=0.008‡*
% with history of smoking	26.2	28.6	29.4	28.0	*p*=0.988‡
% current	15.1	18.9	23.5	18.7	*p*= 0.808‡
% past	11.1	9.8	5.9	9.3	*p*= 0.777‡
prior synth-DMARDs median (Q1;Q3)	3 (3;4)	4 (3;4)	4 (3;5)	4 (3;5)	*p*= 0.313†
% concomitatnt DMARD	82.0	72.2	79.4	80.0	*p*= 0.290‡
% methotrexate	71.1	*55.6*	*79.4*	*68.0*	*p=0.020‡*
mean methotrexate dose [mg] (SD)	17.4 (4.2)	16.8 (3.6)	17.6 (3.3)	16.1 (3.3)	*p*= 0.252*
% leflunomide	10.5	*15.8*	*0.0*	*12.0*	*p=0.044‡*
% concomitant prednisolone	45.3	48.1	41.2	52.0	*p*= 0.576‡
mean prednisolone dose [mg] (SD)	6.9 (3.4)	*7.3 (3.3)*	*7.7 (3.0)*	*5.7 (1.9)*	*p=0.011**
Mean baseline disease activity					
DAS28ESR (SD)	6.4 (1.0)	*6.1 (1.1)*	*6.3 (1.0)*	*6.5 (1.0)*	*p=0.043**
DAS28CRP (SD)	5.9 (1.0)	5.7 (1.1)	5.8 (1.1)	6.0 (1.0)	*p*= 0.139*
Promis HAQ (SD)	44.7 (24.3)	41.1 (22.7)	42.1 (25.0)	48.6 (23.7)	*p*= 0.094*
ESR [mm/h] (SD)	39.4 (22.6)	38.1 (24.2)	42.2 (25.5)	21.7 (25.1)	*p*= 0.469†
CRP [mg/L] (SD)	23.5 (28.2)	24.7 (27.1)	35.1 (37.7)	23.0 (2.4)	*p*= 0.404†
PGA (0–100) (SD)	66.9 (22.9)	66.0 (23.8)	64.1 (18.7)	70.5 (20.9)	*p*= 0.151†
Pain (0–100) (SD)	67.7 (22.0)	66.7 (21.5)	62.2 (21.9)	63.9 (22,3)	*p*= 0.678†
EGA (0–100) (SD)	62.0 (22.5)	59.9 (21.5)	63.3 (19.7)	65.7 (19.5)	*p*= 0.132†
TJC28 (SD)	14.3 (6.6)	*12.6 (6.9)*	*12.7 (6.9)*	*14.8 (6.2)*	*p=0.033†*
SJC28 (SD)	12.8 (5.5)	12.4 (6.7)	13.2 (5.3)	12.9 (5.8)	*p*= 0.632†

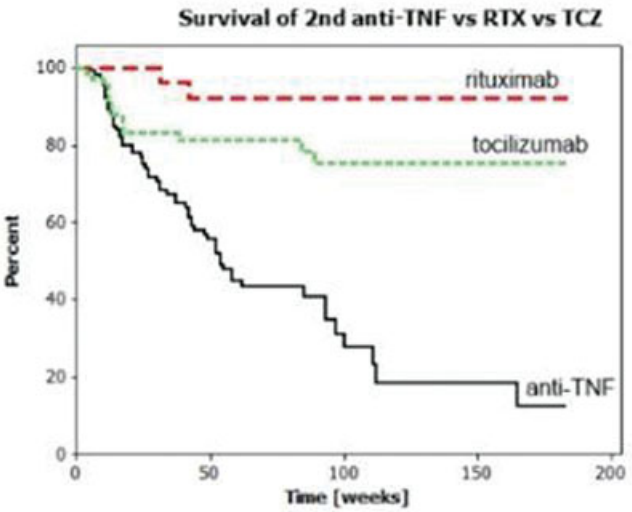

Figure 2.

Methods: Data was extracted from the mandatory nationwide registry of patients with rheumatoid arthritis treated with biologics on Dec 15th, 2012. Kaplan Meier survival analysis was performed. Statistical significance was determined using the Log-Rank and Wilcoxon tests.

Results: From the dataset collected between February 2007 and December 2012 we identified 688 RA patients who received TNFi as a first biologic. Flow of patients is depicted in Figure 1. Baseline patient characteristics are shown in Table 1. The 1st TNFi was stopped for inefficiency, adverse events, other reasons, and death in 73,4%, 16.7%, 8.7%, and 1.0%, respectively. Kaplan Meier survival curves for 2nd TNFi (as a group), RTX and TCZ are presented in Figure 2. 2nd TNFi failed due to insufficient efficacy in 90%, and adverse events in 8%.

Conclusion: After the 1st TNFi fails, a 2nd TNFi is more likely to fail earlier than RTX or TCZ (p=0.000). There is a trend of better survival of RTX vs TCZ, which did not reach statistical significance (p=0.057).

Disclosure: Rotar, None; **M. Tomsic**, None.

2691

Results Of The Strass Trial Regarding Impact Of Progressive Spacing Of Tnf-Blocker Injections In Rheumatoid Arthritis Patients In Das28 Remission: Is There a Difference Between Drugs - Adalimumab and Etanercept - Or Their Mode Of Use - Monotherapy Or Combination?

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Background/Purpose: The STRASS trial was an 18-month randomized controlled trial, conducted in established RA patients in DAS28 remission with etanercept (ETA) or adalimumab (ADA), comparing the impact of a DAS28-driven step-down strategy based on TNF-blocker injection spacing (S arm) to a maintenance strategy (M arm). It demonstrated that, although relapses were more frequent with the spacing strategy arm, no substantial increase in disease activity or structural damage progression occurred throughout the 18-month follow-up. We aimed to assess in a subgroup analysis if the feasibility of TNF-blocker injection spacing differs by molecule –ADA or ETA – and/or its use as monotherapy (MONO) or in combination with synthetic DMARD (COMBO).

Methods: Inclusion criteria were: ETA or ADA > 1 year, DAS28 remission > 6 months, no progression of structural damage on X-rays. Patients were randomized and followed every 3 months for 18 months. In the S arm, the inter-injection interval was increased every 3 months up to complete interruption at 4th step. In these stratified analyses, disease activity was assessed by DAS28 repeated measures and analyzed in a mixed linear model (GLM). Relapse, defined by DAS28 >2.6 and ΔDAS28 >0.6, was in a Cox model and statistical comparison by Wald chi-square test.

Results: 137 patients were included, 64 and 73 in the S and M arm (mean/%: age 55 yrs, female 78%, RA duration 9.5 yrs, ACPA+ 78%, erosive 88%, DAS28 1.8, HAQ 0.5). Sixty-three patients were treated with ADA and 74 with etanercept; 33 received the TNF-blocker as MONO (ADA 11, ETA 22) and 104 in combination with either methotrexate or leflunomide (ADA 52, ETA 52). There were no significant differences in either trial arm in disease activity between the ADA- and the ETA-treated populations, with mean DAS28 of 2.7 ±1.2 and 2.3 ±1.2 respectively (p=0.55). The relapse incidence was higher in the ADA than in ETA group: 77.4% vs. 60.3% (p=0.03). The median time to relapse was 12 months in the S arm and 18 months in the M-arm for ETA, and 9 months in the S arm, 18 months in the M-arm for ADA. Comparisons between the use of TNF-blockers as MONO or COMBO showed no significant differences in disease activity: mean DAS28 of 2.7 ±1.3 and 2.4 ±1.1 respectively (p=0.88), nor in relapse rates: 69.7% vs. 67.6% (p=0.8). The median time to relapse was 12 months in the S arm and 18 months in the M-arm for MONO, and 9 months in the S arm, 18 months in the M-arm for COMBO.

Conclusion: The molecule and the way TNF-blockers are prescribed do not influence RA disease activity control. However, the risk of relapse appears higher with ADA compared to ETA in this subgroup analysis.

(ClinicalTrials.gov n°: NCT00780793).

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Evidence That Fat Metaplasia Is a Key Intermediary In The Development Of Sacroiliac Joint Ankylosis Following Repair Of Erosions In Patients With Spondyloarthritis. Walter P. Maksymowych[1], Stephanie Wichuk[1], Praveena Chiowchanwisawakit[2], Robert GW Lambert[1] and Susanne Juhl Pedersen[3]. [1]University of Alberta, Edmonton, AB, [2]Mahidol University, Bangkok, Thailand, [3]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark.

Background/Purpose: Fat metaplasia is detected as bright signal on T1W MRI and has been shown to develop after resolution of inflammation in spine and sacroiliac joints (SIJ). Tissue with bright signal on T1W MRI, termed backfill (BF), may also fill areas of excavated sacral and iliac bone along the joint space and is thought to reflect repair of erosion. Imaging studies in the spine have indicated that fat metaplasia predicts development of new bone. We hypothesized that ankylosis in the SIJ develops following repair of erosion and that fat metaplasia is a key intermediary step in this pathway.

Methods: We used the SPARCC SIJ Structural Score (SSS) method to assess fat metaplasia (FAT), erosion (ER), BF, and ankylosis (ANK). This score relies on the T1W sequence and assesses 5 consecutive coronal slices anteriorly through the cartilaginous portion of the joint from the transitional slice. Lesions are scored dichotomously (present/absent) in SIJ quadrants (fat, erosion) or halves (backfill, ankylosis). Scoring ranges are: FAT (0–40), ER (0–40), BF (0–20), ANK (0–20). Four readers assessed 45 pairs of MRI scans blinded to time point (baseline, 2 years) from 45 cases in a prospective cohort receiving either standard (n=22) or anti-TNF (n=23) therapies. In a second study, two readers assessed 147 pairs of scans blinded to time point (baseline, 2 years) from cases either on standard (n=69) or anti-TNF (n=78) therapies. Univariate analyses and multivariate linear regression focused on identifying significant MRI predictors of change in BF and ANK scores, adjusted for age, sex, symptom duration, treatment, CRP (baseline and 2-year change), SPARCC SIJ inflammation score (baseline and 2-year change), and baseline SSS scores for FAT, ER, BF, and ANK.

Results: Using mean SSS scores for 4 readers in the 45 cases, resolution of ER was significantly associated with the development of BF ($p = 0.0082$) and new ANK ($p=0.045$) at 2 years. Using mean scores of two readers in the 147 cases, resolution of ER was significantly associated with the development of BF ($p<0.0001$), FAT ($p<0.0001$) and new ANK ($p=0.0001$) at 2 years. New ANK was also significantly associated with development of FAT ($p=0.0005$). Associations were also significant in both treatment groups. A decrease in ER score was a significant predictor for development of new BF in the multivariate regression model (adjusted $R^2 = 0.44$, F ratio 14.6, $p<0.0001$) (change in SSS erosion: $\beta = -0.74$, $t = -4.1$, $p=0.0001$). 31 (21.1%) of patients developed new ANK and these had significantly more resolution of ER than patients without new ANK ($p=0.014$, Mann-Whitney). Significant independent predictors of new ANK in the multivariate model (adjusted $R^2 = 0.24$, F ratio = 10.0, $p <0.0001$) were baseline BF score, decreased ER score and development of new FAT (Table).

	β coefficient	SE	t	p value
Age	−0.022	0.010	−2.25	0.026
BL SSS Backfill score	0.073	0.027	2.75	0.0068
Change in SSS Erosion score	−0.14	0.045	−3.11	0.0023
Change in SSS Fat score	0.20	0.058	3.36	0.001

Conclusion: Ankylosis in the SIJ develops following repair of erosion and fat metaplasia is a key intermediary step in this pathway.

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2693

Proof Of Concept: Enthesitis and New Bone Formation In Spondyloarthritis Are Driven By Mechanical Strain and Stromal Cells. Peggy Jacques[1], Stijn Lambrecht[1], Eveline Verheugen[1], Elin Pauwels[2], Marleen Verhoye[3], Annemie Van der Linden[3], George Kollias[4], Rik J. Lories[5] and Dirk Elewaut[6]. [1]Laboratory for Molecular Immunology and Inflammation, Ghent University, Ghent, Belgium, [2]UGCT, Ghent University, Ghent, Belgium, [3]University of Antwerp, Antwerp, Belgium, [4]Biomedical Sciences Research Center 'Alexander Fleming', Vari, Greece, [5]Laboratory for Skeletal Development and Joint Disorders, KU Leuven, Leuven, Belgium, [6]Department of Rheumatology Ghent University Hospital, Ghent, Belgium.

Background/Purpose: Spondyloarthritides (SpA) are characterised by both peripheral and axial arthritis. Hallmarks of peripheral SpA are the development of enthesitis, most typically of the Achilles tendon and plantar fascia, and new bone formation. This study was undertaken to unravel the mechanisms leading towards enthesitis and new bone formation in preclinical models of SpA. $TNF^{\Delta ARE}$ mice are an established model for SpA, characterized by an enhanced TNF messenger RNA stability, which leads to the development of peripheral and axial arthritis (sacroiliitis, spondylitis), and Crohn′s like ileitis.

Methods: To study the development of enthesitis in relation to mechanical strain, hind limb unloading of $TNF^{\Delta ARE}$ mice was performed, followed by histological analysis. Activation of extracellular signal-regulated kinase (Erk1/2) and p38 pathways in response to mechanical strain was studied on Achilles tendon lysates. In addition, $TNF^{\Delta ARE}$ mice were treated with small molecular inhibitors of Erk1/2 and p38. Since new bone formation does not occur in $TNF^{\Delta ARE}$ mice, the collagen antibody-induced arthritis model, which is also characterized by enthesitis, was used to study this particular feature. Hind limb unloading was again performed, followed by histological analysis and micro-CT.

Results: We demonstrated that the first signs of inflammation in $TNF^{\Delta ARE}$ mice were found at the entheses. Importantly, enthesitis occurred equally in the presence or absence of mature T and B cells, underscoring the importance of stromal cells. Hind limb unloading in $TNF^{\Delta ARE}$ mice significantly suppressed inflammation at the synovio-entheseal complex of the Achilles tendon compared to weight bearing controls. Erk1/2 signalling played a crucial role in mechanotransduction associated inflammation. Furthermore, new bone formation was strongly promoted at entheseal sites by biomechanical stress and correlated with the degree of inflammation.

Conclusion: These findings provide a formal proof of the concept that mechanical strain drives both entheseal inflammation and new bone formation in SpA.

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HLA-B27 Expression Prevents Tnfα-Induced Inhibition Of Bone Formation in Vitro In IFNγ/Tnfα-Treated Osteoblasts. Eva Yang, Grace Kwon, Robert A. Colbert and Gerlinde Layh-Schmitt. NIAMS NIH, Bethesda, MD.

Background/Purpose: HLA-B27 predisposes to ankylosing spondylitis (AS), an immune-mediated inflammatory disease associated with osteitis, bone loss, and dysregulated bone formation, most notably in the axial skeleton. Although the role of HLA-B27 is incompletely understood, it is thought to exert upstream pro-inflammatory effects. Recently however, it was shown that HLA-B27 promotes osteoclast development from monocytes in HLA-B27 transgenic rats. Given that MHC class I molecules can also be expressed in osteoblasts (OBs), we examined whether HLA-B27 alters the response of OBs to pro-inflammatory cytokines IFNγ and TNFα during differentiation and mineralization *in vitro*.

Methods: Wild type (WT), HLA-B7 (B7), and HLA-B27 (B27) transgenic rat calvarial OBs were harvested and differentiated in osteogenic medium for up to 3 weeks. Cultures were treated with rat IFNγ (100 ng/mL), TNFα (30 ng/mL) or both cytokines for up to 5 days of the 3-week culture period upon pre-calcified nodule formation, and collected for evaluation of gene (real-time PCR) and protein (immunoblotting) expression, and mineralization (alizarin red staining).

Results: IFNγ had no effect on mineralization while TNFα inhibited mineralization similarly for all 3 genotypes in a time- and dose-dependent

manner. TNFα also inhibited mineralization of IFNγ-treated WT and B7 OBs, similar to TNFα alone. In contrast, B27 OBs were refractory to the inhibitory effects of TNFα when cells were co-treated with IFNγ, exhibiting 3-fold higher mineralization than WT and B7 controls. HLA-B was synergistically upregulated at the mRNA and protein level by co-treatment with IFNγ and TNFα in both B7 and B27 OBs. Despite comparable upregulation of HLA-B27 and HLA-B7, only B27-expressing OBs exhibited activation of the unfolded protein response (UPR) as evidenced by induction of GRP78/BiP and CHOP, along with increased XBP1 mRNA splicing. B27-expressing OBs were responsive to TNFα as shown by RUNX2 degradation. However, RUNX2 degradation was incomplete in IFNγ/TNFα-treated B27-expressing OBs and RUNX2 binding to STAT1 was reduced compared to both WT and B7 controls.

Conclusion: This is the first demonstration to our knowledge that HLA-B27 expression can alter OB function as demonstrated in this transgenic animal model. Upregulation of HLA-B27 caused ER stress and activation of the UPR. In addition to its traditional role to maintain ER homeostasis, the UPR is also involved in development and differentiation and is activated during osteogenesis. Additionally, the ER chaperone BiP has been shown to affect mineralization processes, and IFNγ-activated STAT1 can inhibit mineralization through cytosolic sequestration of RUNX2. While the precise mechanism remains unclear, our studies strongly suggest that HLA-B27-induced UPR activation can affect OB function. The possibility that HLA-B27 expression and upregulation could interfere with TNFα-induced inhibition of bone formation might explain why patients with AS exhibit axial progression and develop ankylosis despite active inflammation.

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Host Genetic Background Disrupts The Relationship Between Microbiota and Gut Mucosal Tolerance Leading To Spondyloarthritis and Ileitis After a Dectin-1 Trigger. Linda Rehaume[1], Stanislas Mondot[2], Daniel Aguirre de Cárcer[2], Jared Velasco[1], Helen Benham[1], Sumaira Hasnain[3], Jaclyn Bowman[1], Merja Ruutu[1], Philip Hansbro[4], Michael McGuckin[3], Mark Morrison[2] and Ranjeny Thomas[1]. [1]University of Queensland Diamantina Institute, Brisbane, Australia, [2]CSIRO Livestock Industries, Brisbane, Australia, [3]Mater Medical Research Institute, Brisbane, Australia, [4]Center for Asthma and Respiratory Disease and Hunter Medical Research Institute, Newcastle, Australia.

Background/Purpose: Chronic inflammatory diseases known as spondyloarthropathies (SpA) including ankylosing spondylitis, psoriatic arthritis, reactive arthritis, and arthritis associated with inflammatory bowel disease, collectively affect 3% of the population, and are strongly heritable. Consistent with shared clinical features and genetic associations, the pathology of each disease is associated with microorganisms, and flares in bowel symptoms correlate with arthritic and spondylitic activity. However, it is not clear how the microbiome influences disease expression in SpA and how this relates to host genetic background. We sought to understand this in BALB/c wild type and ZAP-70^{W163C} (SKG) point-mutant mice with reduced T cell receptor signaling.

Methods: SKG and BALB/c mice housed under specific pathogen-free (SPF) or germ-free (GF) conditions were injected intraperitoneally with microbial 1,3-D beta-glucan (curdlan). Arthritis, spondylitis and ileitis were assessed histologically. Microbiome composition in serial fecal samples of mice cohoused from weaning was analyzed by 454 pyrosequencing.

Results: By analysis 8 weeks after curdlan, pathological severity of arthritis, spondylitis and ileitis depended on both genetic background and microbiome. Under SPF conditions, SKG mice developed severe spondylitis, arthritis and ileitis whereas curdlan-treated BALB/c developed mild arthritis and spondylitis, but no ileitis. Under GF conditions, SKG mice had reduced spondyloarthritis incidence and no ileitis. Thus development of ileitis was most sensitive to genetic background and associated microbiome i.e. absent in GF SKG mice and SPF BALB/c mice, highest incidence and severity in SPF SKG and intermediate in GF SKG mice colonized with a limited bacterial consortium. Initiation of ileal IL-23 expression, ER stress, depletion of goblet cells and IL-17 response in draining lymph nodes depended on presence of the microbiome. By pyrosequencing, microbiome content in turn depended on the genetic background of the host and the microbial response to beta-glucan over time. Consistent with transmissible suppressive microbes in BALB/c feces, ileitis but not arthritis or spondylitis severity was reduced in SKG cohoused with BALB/c mice.

Conclusion: Our data are consistent with impaired microbial homeostasis in SKG hosts where T cells express ZAP70^{W163C}, and provide a molecular basis for understanding the relationship between immune genetic susceptibility and development of SpA in response to an inflammatory environmental trigger, through host genetic effects on the gut microbiome. Modification of the microbiome presents a novel prophylatic strategy to attenuate genetic risk of SpA.

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Impaired Bacterial Clearance and An Exuberant Inflammatory Response Promote Chlamydia-Induced Reactive Arthritis In SKG Mice. Athan Baillet[1], Linda Rehaume[2], Helen Benham[2], Connor O'Meara[3], Charles Armitage[4], Marina Harvie[4], Geraldine Brizard[5], Jared Velasco[2], John V. Forrester[6], Mariapia Degli-Esposti[5], Kenneth Beagley[4] and Ranjeny Thomas[2]. [1]The University of Queensland, Brisbane, Australia, [2]University of Queensland Diamantina Institute, Brisbane, Australia, [3]Institute of Health & Biomedical Innovation, Biomedical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, Australia, [4]Institute of Health & Biomedical Innovation, Brisbane, Australia, [5]Lions Eye Institute, Nedlands, Australia, [6]Lions Eye Institute, Nedlands, Bahrain.

Background/Purpose: The sterile inflammatory arthritis associated with spondylitis, uveitis and rash, known as reactive arthritis, commences weeks after certain gastrointestinal or genitourinary infections, including Salmonella and Chlamydia in genetically-susceptible patients. Several potential mechanisms are proposed, including auto-immunity by molecular mimicry and persistent inflammation in response to intra-cellular live *Chlamydia*. ZAP-70^{W163C} mutant BALB/c mice (known as SKG), which exhibit reduced T cell receptor signaling, an autoreactive CD4+ T cell repertoire, relative lymphopenia and increased regulatory T cells are susceptible to spondyloarthritis after bacterial beta-glucan. *Chlamydia muridarum (Cmu)* is an obligate intracellular pathogen normally controlled by macrophages. We studied whether *Cmu* genital infection triggered reactive arthritis in SKG mice to explore the relationship between host immunity, bacterial clearance and joint inflammation.

Methods: SKG and BALB/c mice were genitally infected with mouse-adapted *Cmu* ($5\times10^2-10^6$ IFUs). Conjunctivis, lid swelling/thickening and arthritis were assessed weekly for 12 weeks post infection (wpi). Eye, skin and joint sections were scored after sacrifice. Bacterial load was quantified in genital swabs. *Cmu* Major Outer Membrane Protein (MOMP) antigen-specific cytokine production was assessed in splenocytes 1 wpi; cytokines were measured in serum, skin and joint explants at 12 wpi. Regulatory T cells (Treg) were depleted from FoxP3-DTR BALB/c or SKG mice. *Cmu* genomic ompA DNA was quantified by PCR in spleens, iliac lymph nodes and joints. Non parametric tests assessed statistical significance.

Results: SKG but not BALB/c mice developed typical histological features of chronic reactive arthritis, with and remained autoantibody-negative, from 5 weeks after genital infection. *Cmu* load in genital tract was significantly increased in SKG relative to BALB/c mice in the first week after infection, associated with impaired *Cmu* MOMP-antigen-specific T cell interferon (IFN)-gamma and increased TNF response. Arthritis severity was correlated with prior *Cmu* load and live *Cmu* infection was required for reactive arthritis, as no disease occurred after bacterial inactivation with UV or antibiotics. While depletion of regulatory T (Treg) cells from *Cmu*-infected Foxp3.DTR SKG mice prompted rapid bacterial clearance, it also hastened onset of severe arthritis, conjunctivitis and dermatitis, accompanied by increased MOMP-specific IFN-gamma production. *Cmu* DNA was detected in myeloid cells derived from spleen and lymph nodes draining the genital tract of both strains, confirming their capacity to transport Chlamydial inclusions from the site of infection to other organs. The proportion of myeloid cells was 2-fold higher in SKG relative to BALB/c mice and this, together with the increased bacterial load, increases the likelihood of systemic delivery of *Cmu* DNA to peripheral sites.

Conclusion: *Cmu* induced reactive arthritis results from an exuberant inflammatory response to a deficient early control of infection and incomplete inflammatory suppression by Treg in the setting of host genetic T cell receptor-ZAP70 signalling deficiency.

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Identification Of Genetic and Epigenetic Alterations In Spondyloarthritis. Tibor A. Rauch[1], Beata Tryniszewska[1], Andras Vida[1], Timea Ocsko[1], Sandor Szanto[2], Holly L. Rosenzweig[3], Matthew A. Brown[4], Gethin P Thomas[5], Katalin Mikecz[1] and Tibor T. Glant[1]. [1]Rush University Medical Center, Chicago, IL, [2]University of Debrecen, Debrecen, Hungary, [3]Oregon Health & Science University, Portland, OR, [4]University of Queensland Diamantina Institute, Brisbane, Australia, [5]University of Queensland Diamantina Institute, Woolloongabba, Australia.

Background/Purpose: Ankylosing spondylitis **(AS)** is the prototypic spondyloarthritis and affects approximately 0.2–0.5% of the human population. It is estimated that genetic risk factors contribute >90% of disease susceptibility, and the major genetic risk factor is HLA-B27. Approximately the other half of the genetic risk is composed by non-MHC traits. By generating interval-specific congenic (IVSC) strains utilizing the genetic combination of proteoglycan-induced SpA (PGISpA) in susceptible BALB/c mice and SpA-resistant DBA/2 mice (both carry the same MHC) we can identify non-MHC causative genes by excluding the effect of the MHC. These IVSC strains with overlapping chromosome (Chr) regions were used to narrow the (*Pgis2*) risk locus on mouse Chr2 (mChr2) to a small region syntenic with AS risk loci on human chromosomes 4 and 9.

Methods: PGISpA-resistant DBA/2 and –susceptible BALB/c strains were intercrossed, and then backcrossed with BALB/c mice until the entire *Pgis2* locus (mChr2) was from DBA/2 on a full BALB/c background. Congenic mice were tested for PGISpA, and then backcrossed to BALB/c strain. Recombination events were genotyped until partially overlapping DBA/2 intervals (n=12) completely covered the *Pgis2* locus. Heterozygous females and males with the same genomic intervals were intercrossed, homozygous offspring tested for PGISpA. Based on the overlapping Chr2 intervals, we narrowed a resistant (DBA/2 origin) to ~3.5 Mbp in size (mChr2:30.5–34.0 Mbp; syntenic with hChr9:129.−132.8 Mbp). All IVSC mice were tested with near infrared OsteoSenseTM 750 (Visen Medical) probe, spine histology, serum cytokines and cytokines in antigen-stimulated *in vitro* spleen cell cultures. The corresponding 3 Mbp genomic regions of PGISpA-resistant and –susceptible IVSC and parent strains (n=10) were sequenced by high-throughput methods and analyzed using the GeneSpring NGS program.

Results: We identified a total of 4,416 mutations within the 3.5 Mbp-long genomic region. The 3.5 Mbp region contains 70 protein-coding genes, 12 antisense transcripts (RNA) and 25 different forms (small nucloelar, miRNA) of non-coding RNAs. Mutations/indels were detected (93.38%) in three relatively small genomic regions affecting 3 (*Gpr107-Nsc1-Hmcn2*) genes and their intergenic regions, and two other genes (*St6galnac6* and *Lmx1b*). PGISpA was significantly reduced ($p<0.001$) in each IVSC strain carrying any of these three DBA/2 alleles. The *Gpr107-Nsc1-Hmcn2* triplet contained mutations affecting multiple transcription binding sites, the *Lmx1b* transcription factor has an in-frame 18-nucleotide deletion in exon 1, and the promoter region of the *St6galnac6* was hypermethylated in genomic regions of DBA/2 origin.

Conclusion: Although all three alleles affected PGISpA individually, it appears that an "epistatic triangle" exists among these alleles that protect against PGISpA. Overall, all mutations with predicted functional consequence are located in non-coding sequences underlining the critical role of epigenetic alterations in PGISpA (and perhaps in AS).

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ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Human Etiology and Pathogenesis II
Tuesday, October 29, 2013, 2:30 PM–4:00 PM

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The Treg/Th17 Imbalance Of Patients With Systemic Lupus Erythematosus Were Mediated By Mir-663 Through Down-Regulating TGF-β1 Secretion Of Bone Marrow-Derived Mesenchymal Stem Cells. Lingyu Geng, Xia Li, Xuebing Feng and Lingyun Sun. Department of Rheumatology and Immunology, the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China.

Background/Purpose: Systemic lupus erythematosus (SLE) patients exist an imbalance between CD4+CD25+FoxP3+ T regulatory (Treg) and IL-17-producing cells (Th17). Correction of this Treg/Th17 imbalance may have therapeutic impact for SLE patients. Our previous study demonstrated that bone marrow derived mesenchymal stem cells (MSCs) from SLE patients are defective in immune modulation, which might be involved in Treg/Th17 imbalance, but the mechanisms are not clear yet. As a computer predicted target of miR-663, Transforming growth factor-beta1 (TGF-β1) is an important negative immune regulatory factors secreted by MSCs which could modulate SLE Treg/Th17 imbalance. The aim of this study is to investigate whether miR-663 could contribute to SLE Treg/Th17 imbalance though directly down-regulating TGF-β1 mRNA of SLE BMSCs, to further understand the pathogenesis of SLE.

Methods: BMSCs were isolated, cultured and expanded from iliac crest bone marrow of four healthy controls and five SLE patients. MicroRNA expressions of BMSCs from were determined by MicroRNA array analysis. Real-time PCR was used to further determine the miR-663 expression and TGF-β1 mRNA level in MSCs, secretion of TGF-β1 was detected by ELISA. As a computer predicted target of miR-663, TGF-β1 was determined using the luciferase reporter assay system. MSCs were transfected with miR-663a, pre-miR-663a, and anti-miR-663a, and then co-cultured with PBMCs from SLE patients for 3 days respectively with PHA pre-stimulated, flow cytometry was used to detect their effect on percentage of Treg and Th17 cells.

Results: Mir-663 was significantly up-regulated(2.52- fold higher, $P<0.05$) in MSCs from SLE patients(n=5) compared to normal controls(n=4) by microRNA array analysis. The expression of miR-663 was further determined by RT-PCR, and the synthesis of TGF-β1 mRNAs was significantly lower(3.88- fold lower, $P<0.05$) in MSCs from SLE patients. Transfection of SLE MSCs with pre-miR-663a caused significant upregulation of miR-663a expression(8.33- fold higher, n=3, $P<0.01$) and markedly lower synthesis of TGF-β1 mRNA(1.52-fold lower, n=3, $P<0.05$), while transfection with anti-miR-663a markedly decreased the miR-663a expression (3.01- fold lower, n=3, $P<0.05$). The mean value of Treg/Th17 was significantly decreased in PBMCs from SLE patients compared to normal controls (0.48 ± 0.12vs0.65 ± 0.09, n=8, $P<0.01$). Compared to SLE MSCs, MSCs from normal controls exhibited a better immune suppression effect through up-regulating Treg/Th17 of SLE patients (0.68 ± 0.15vs0.54 ± 0.14, n=3, $P<0.05$), and transfection of normal MSCs with pre-miR-663a caused significant downregulation of Treg/Th17 compared to miR-663-control group(0.38 ± 0.07vs0.68 ± 0.15, n=3, $P<0.01$), while transfection with anti-miR-663a led to an opposite effect (0.76 ± 0.08vs0.68 ± 0.15, n=3, $P<0.05$).

Conclusion: SLE patients exist an imbalance between Treg and Th17 cells, which might be associated with down-regulated TGF-β1 secretion of bone marrow-derived mesenchymal stem cells mediated by miR-663.

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Transcription Factor RFX1 Regulates Th17 Differentiation and Its Role In The Pathogenesis Of Systemic Lupus Erythematosus. Ming Zhao, Gongping Liang, Qian Tang, Yang Yang, Yixin Tan and Qianjin Lu. Second Xiangya Hospital, Central South University, Changsha, China.

Background/Purpose: Recently, evidence is emerging that abnormal regulation of Th17 differentiation plays an important role in the pathogenesis of systemic lupus erythematosus (SLE). However, the molecular mechanisms are poorly understood. In our previous study, we found that transcription factor RFX1 expression was inhibited in SLE CD4+ T cells, which leads to overexpression of autoimmune-related genes CD11a and CD70. Here, we further investigate whether RFX1 regulates Th17 differentiation in SLE.

Methods: 40 SLE patients and 30 healthy controls were recruited. CD4+ T cells were isolated by magnetic beads. All patients fulfilled at least 4 of the SLE classification criteria of the American College of Rheumatology. RFX1 and cytokines expression levels were detected by real-time PCR, western blot and ELISA. CD4+ T cells were transfected with RFX1 expression plasmid (pSG-RFX1) or siRNA-RFX1 by nucleofector device in combination with the human T-cell nucleofector kit. Luciferase report gene assay and Chromatin Immunoprecipitation (ChIP) and Electrophoretic Mobility Shift Assay (EMSA) were used to confirm the target gene of RFX1. H3 acetylation levels and H3 lys9 (H3K9) tri-methylation levels in the promoter region of IL17A were measured by ChIP-qPCR.

Results: Compared with normal controls, RFX1 protein levels were decreased and IL17A mRNA levels were increased significantly in SLE CD4+ T cells. The IL-17A protein levels in serum of SLE patients were increased significantly. A negative correlation was observed between IL17A mRNA levels and RFX1 protein in SLE CD4+ T cells. Luciferase report gene assay, ChIP and EMSA showed that RFX1 can repress promoter activity of IL17A through binding the promoter of IL17A. Transfection of siRNA-RFX1 leads to up-regulated expression of IL17A through increasing H3 acetylation level and reducing H3K9 tri-methylation level in normal CD4+ T cells. In contrast, transfection of pSG-RFX1 inhibits expression of IL17A through reducing H3 acetylation level and increasing H3K9 tri-methylation level of IL17A promoter in SLE CD4+ T cells.

Conclusion: RFX1 is involved in repressing IL17A expression through regulating the epigenetic modifications in the promoter region of IL17A in CD4+T cells. Decreased RFX1 expression contributes to abnormal regulation of Th17 cells in SLE patients.

Disclosure: M. Zhao, None; **G. Liang**, None; **Q. Tang**, None; **Y. Yang**, None; **Y. Tan**, None; **Q. Lu**, None.

2700

Abnormal Mitochondrial Electron Transport Chain Activity At Complex I Is Regulated By Nitric Oxide and N-Acetylcysteine In Lupus Lymphocytes. Edward Doherty[1] and Andras Perl[2]. [1]SUNY Upstate, Syracuse, NY, [2]SUNY Upstate Medical University, Syracuse, NY.

Background/Purpose: Systemic lupus erythematosus (SLE) peripheral blood lymphocytes (PBL) show mitochondrial dysfunction, characterized by elevated mitochondrial transmembrane potential ($\Delta\Psi_m$) and mass and low ATP, attributed to elevated production of nitric oxide (NO) and reduced glutathione (GSH). To understand the molecular bases of mitochondrial dysfunction we tested activity of the electron transport chain (ETC) complexes I and IV. As N-acetylcysteine (NAC) reversed GSH depletion and improved disease activity in SLE, its target of impact in mitochondria was also investigated.

Methods: PBL from 65 SLE subjects and 30 healthy controls, matched for patients' age within ten years, gender, and ethnicity were studied. Mitochondrial respiration was measured using a Clark-type O_2 electrode (Oxygraph, Hansatech, Norfok, UK) in 1) freshly isolated PBL, 2) PBL rested overnight, 3) PBL exposed to NO donors NOC-9 or NOC-18, 4) PBL exposed to NAC, 5) PBL exposed to β-mercaptoethanol (BME). S-nitrosylation was assessed with a biotin switch kit (Cayman, Ann Arbor, MI). $\Delta\Psi_m$, mass, NO, $ONOO^-$, Ca^{2+}, and H_2O_2 stress were assessed by flow cytometry (Meth. Mol. Biol. 900:61–89, 2012).

Results: SLE PBL have increased respiration upon T cell activation (SLE: 4.157nmol/ml/min ±0.186, control: 3.655nmol/ml/min ±0.167; p=0.012). Digitonin-permeabilized SLE PBL also show increased respiration without exogenous substrates (SLE: 2.492 nmol/ml/min ± 0.196, control: 2.137 nmol/ml/min ± 0.153; p = 0.027) and with substrates of ETC complex IV (SLE: 7.722 nmol/ml/min ± 0.419, control: 7.006 nmol/ml/min ± 0.505; p = 0.028). SLE PBL had elevated mitochondrial mass (+10% ± 3% p = 0.002). When normalized to mitochondrial mass, SLE PBL exhibit 33% reduced respiration through complex I (p=0.036) and 81% enhanced respiration through complex IV (p = 0.036). As expected, exposure to NOC-18 increased NO (+158% ± 51% p = 0.005) and mitochondrial mass in normal PBL (+162% ± 68% p = 0.016). NO exposure selectively increased O_2 consumption by SLE PBL through complex I relative to healthy controls (SLE: 1.405 nmol/ml/min ± 0.206; Controls: 1.277 nmol/ml/min ± 0.150; p = 0.026). In contrast, NAC decreased both $ONOO^-$ (−37% ±0.04 p=0.0001) and H_2O_2 levels without (−45% ± 5% p=0.0005) or with co-incubation with NOC-18 ($ONOO^-$: −38% ±7% p=0.002; H_2O_2: −71% ±2% p=0.000004). Compared to NOC-18 alone, co-incubation with NAC also decreased NO (−92% p=0.014), $ONOO^-$ (−38% p=0.006), mitochondrial mass (−87% p=0.017), and Ca^{2+} (−52% p=0.042). Direct addition of NAC into the Oxygraph chamber inhibited respiration by 53% through complex I (p=0.004) but not complex IV. In contrast, BME failed to affect respiration at complex I, but it reduced respiration by 80% at complex IV (p=0.031). NAC also blocked respiration through complex I by 56% in SLE PBL (p=0.0001). Upon NO exposure, S-nitrosylation is increased in freshly isolated lupus PBL relative to matched healthy control PBL (p=0.002).

Conclusion: The results of this data suggest that SLE PBL have defective ETC activity at complex I. NAC helps maintain a reducing environment, possibly by directly blocking respiration at complex I.

Disclosure: E. Doherty, None; **A. Perl**, None.

2701

Spleen Tyrosine Kinase (Syk) Regulates Systemic Lupus Erythematosus T Cell Signaling. Alexandros P. Grammatikos[1], Debjani Ghosh[2] and Vasileios C. Kyttaris[3]. [1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [2]The Brody School of Medicine, East Carolina University, Greenville, NC, [3]BIDMC, Harvard Medical School, Boston, MA.

Background/Purpose: Systemic Lupus Erythematosus (SLE) T cells display an aberrant response to CD3/ TCR stimulation. The CD3/TCR complex in SLE is characterized by the substitution of the CD3 associated kinase Zap70 by Syk. The objective of this study is to better understand the role of Syk in the dysregulated SLE T cell phenotype.

Methods: A two-step approach was followed: (i) to examine whether increased Syk expression creates an SLE-like phenotype Syk was overexpressed in healthy blood-donor T cells; and (ii) to examine whether aberrant gene expression changes in SLE T cells can be corrected by Syk downregulation, SYK was silenced using a SYK-specific siRNA. Cells were lysed following 72h of incubation and expression levels of 36 genes previously associated with SLE measured in real-time PCR. Protein was also collected and expression changes confirmed in flow cytometry and western blot. Expression was normalized towards CD3E and GPADH for PCR and β-actin for western blot.

Results: Forced expression of Syk in normal T cells reproduced many of the aberrant gene expression changes seen in SLE. Expression of cytokine IL-21, cell surface molecule CD44, and intracellular molecules PP2A and OAS2 were found to increase in cells overexpressing SYK (fold increase over control transfected ±SEM: IL-21, 5.7±1.5; CD44, 4.2±2.2; PP2A, 1.5±1; OAS2, 1.5±0.3). Silencing of Syk in SLE T cells normalized the expression of the above molecules (fold decrease over control transfected ±SEM: IL-21, −1.9±0.2; CD44, −2.8±0.4; PP2A, −2.7±1.9; OAS2, −1.1±0.8).

Findings were confirmed at the protein level using flow cytometry (mean positive cells ±SEM: (i) empty vector vs. SYK overexpressing, IL-21, 7.9±1 vs. 13±2.3, p=0.05; CD44v6, 10.7±1.2 vs. 16±2.1, p=0.05; (ii) control vs. SYK siRNA transfected, IL-21, 18.6±2.4 vs. 11.4±1.6, p=0.03; CD44v6, 11.7±0.7 vs.7.6±1.2, p=0.05) and western blot (mean relative expression ±SEM: (i) empty vector vs. SYK overexpressing, OAS2, 0.91±0.1 vs. 1.39±0.2, p=0.05; PP2A, 0.49±0.1 vs. 1.23±0.3, p=0.05; (ii) control vs. SYK siRNA transfected, OAS2, 1.39±0.3 vs. 1.06±0.2; PP2A, 1.14±0.3 vs. 0.69±0.1).

Conclusion: Our data show that overexpression of Syk in healthy T cells recapitulates at least part of the SLE T cell phenotype. Syk overexpressing T cells may provide more help to B cells through IL21 secretion, have enhanced migration to tissues through CD44 upregulation and produce pro-inflammatory rather than counter-inflammatory cytokines. Inhibiting Syk in SLE T cells leads to the opposite effect, further underscoring Syk's potential as a therapeutic target in SLE.

Disclosure: A. P. Grammatikos, None; **D. Ghosh**, None; **V. C. Kyttaris**, None.

2702

Molecular Pathogenesis and Genetics Of Tartrate-Resistant Acid Phosphatase Deficiency In Systemic Lupus Erythematosus. Jie An[1], Tracy A. Briggs[2], Audrey Dumax-vorzet[2], Alice Wiedeman[1], Laurence Chaperot[3], Joel Plumas[3], Yanick J. Crow[2] and Keith B. Elkon[1]. [1]University of Washington, Seattle, WA, [2]University of Manchester, Manchester, United Kingdom, [3]Immunobiology & Immunotherapy of Cancers, La Tronche, France.

Background/Purpose: Biallelic mutations in ACP5, encodng tartrate-resistant acid phosphatase (TRAP), result in the immuno-osseous disorder spondyloenchondrodysplasia (SPENCD), characterized by a variety of autoimmune phenotypes – most particularly systemic lupus erythematosus (SLE). Importantly, patients with SPENCD demonstrate an upregulation of type 1 interferon (IFN) stimulated genes (ISGs – an "interferon signatures") similar to that observed in SLE. Since very little is known about the function of TRAP in immune cells, the objectives of our study were: a) to determine the consequences of TRAP deficiency in human immune cells, B) to identify substrates of TRAP, and c) to determine whether ACP5 mutations occur in 'idiopathic' SLE.

Methods: Unbiased substrates of TRAP were queried using a yeast 2 hybrid (Y2H) screen in a human macrophage cDNA library, and interaction of a candidate substrate, osteopontin (OPN) with TRAP was determined by confocal microscopy and immunoprecipitation-western blot analysis (IP-western). TRAP overexpression / knockdown was performed by transfection with cDNA / lentivirus shRNA, respectively. Expression of ISGs was

determined by quantitative PCR (qPCR). Phosphatase activity was quantified by colorimetry, and dephosphorylation of substrates by Liquid Chromatogram-tandem Mass Spectrometer (LC-MS/MS). Sequencing of ACP5 coding exons was undertaken in patients with SLE.

Results: OPN is a substrate for TRAP in Macrophase and pDC. TRAP interacted and co-localized with OPN as determined by Y2H, confocal microscopy and by IP-western. Consistent with these data, recombinant human TRAP (rhTRAP) dephosphorylated recombinant human OPN (rhOPN) by the release of free phosphate in an in vitro assay. LC-MS/MS demonstrated rhTRAP dephosphorylated rhOPN at two serine residues in vitro. To relate the functional significance of TRAP deficiency to IFN-α production, we knocked down TRAP expression in pDC and observed that TRAP specific shRNA, but not scrambled shRNA, increased the expression of ISGs as well as IL-6 following TLR9 stimulation. This was associated with increased nuclear translocation of IRF7 and P50 in TRAP KD pDC cells compared to control cells. Sequencing of ACP5 in 865 SLE patients and 511 controls revealed an excess of heterozygous ACP5 possibly pathogenic missense variants in SLE patients (11 adults in the lupus cohort compared to 2 in controls). These variants were predicted as pathogenetic since they were: coding, non-synonymous, occurred at a frequency of less than 1/300 in controls, were in residues conserved in mammalian species and were predicted to destabilize protein on in silico testing. Transient transfection of several mutants and patient serum assays revealed a significant reduction in TRAP enzyme activity.

Conclusion: Our findings indicate that TRAP and OPN co-localize, and that OPN is a substrate for TRAP in immune cells. Significantly, TRAP deficiency in pDCs leads to increased IFN-α production, providing at least a partial explanation for why ACP5 mutations cause lupus in the context of SPENCD. Detection of ACP5 missense variants in lupus patients suggests that impaired function of TRAP may play a role increasing susceptibility to adult-onset idiopathic lupus.

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2703

An Intronic *CR2* Polymorphism Associated With Systemic Lupus Erythematosus Alters CTCF Binding and *CR1* Expression. Jian Zhao[1], Brendan M. Giles[2], Rhonda L. Taylor[3], Gabriel A. Yette[2], Kara M. Lough[2], Lawrence J. Abraham[3], Hui Wu[1], Patrick M. Gaffney[4], Jennifer A. Kelly[4], Kenneth M. Kaufman[5], John B. Harley[6], Carl D. Langefeld[7], Elizabeth E. Brown[8], Jeffrey C. Edberg[9], Robert P. Kimberly[8], Daniela Ulgiati[3], Betty P. Tsao[1] and Susan A. Boackle[2]. [1]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [2]University of Colorado School of Medicine, Aurora, CO, [3]University of Western Australia, Perth, Western Australia, Australia, [4]Oklahoma Medical Research Foundation, Oklahoma City, OK, [5]Cincinnati Children's Hospital Medical Center and the University of Cincinnati, Cincinnati, OH, [6]US Department of Veterans Affairs Medical Center, Cincinnati, OH, [7]Wake Forest School of Medicine, Winston-Salem, NC, [8]University of Alabama at Birmingham, Birmingham, AL, [9]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by the production of antibodies to nuclear antigens, which form immune complexes that deposit in tissues and cause damage. Complement receptor 2 (CR2/CD21) is primarily expressed on B cells and follicular dendritic cells (FDC), and is required for normal humoral immune responses. Complement receptor 1 (CR1/CD35) is associated with CR2 on the B cell surface, and its cofactor activity is required for the conversion of iC3b to C3dg, the specific ligand for CR2. We previously identified *CR2* variants associated with decreased risk of SLE. To identify the causal variant(s) for the association, we conducted trans-ancestral fine-mapping of *CR2* and the surrounding genomic region.

Methods: Genotyped and imputed genetic variants located in a 57.6kb region spanning 5' of *CR2* to intron 1 of *CR1* were assessed for association with SLE in 15,750 unrelated case-control subjects from four ancestral groups using a logistic regression model adjusted for gender and global ancestry. Allele-specific functional effects of associated variants were determined using electrophoretic mobility shift assay (EMSA), chromatin immunoprecipitation (ChIP)-PCR, quantitative real-time PCR, and quantitative flow cytometry.

Results: The strongest association signal was detected at rs1876453, located in intron 1 of *CR2* ($P_{meta}=4.2\times10^{-4}$, OR 0.85), specifically when subjects with lupus were stratified based on the presence of dsDNA autoantibodies (case-control $P_{meta}=7.6\times10^{-7}$, OR 0.71; case-only $P_{meta}=1.9\times10^{-4}$, OR 0.75). Using EMSA, we demonstrated that the minor allele at rs1876453 altered the formation of several DNA-protein complexes, including one containing the highly conserved 11 zinc-finger protein CCCTC-binding factor (CTCF), which has pleiotropic effects on genomic organization, gene regulation, and alternative splicing. The allele-specific effects of rs1876453 on CTCF binding were confirmed by ChIP-PCR, with three-fold higher enrichment of the region surrounding this variant in the presence of the major allele ($p = 0.0178$). Although allele-specific effects of rs1876453 on B cell *CR2* mRNA or protein levels were not identified, levels of complement receptor 1 (*CR1/CD35)* mRNA and protein were significantly higher on the B cells of subjects harboring the minor allele ($p = 0.0248$ and $p = 0.0006$, respectively).

Conclusion: These data suggest that rs1876453 in *CR2* has long-range effects on gene regulation that decrease susceptibility to lupus. Since the minor allele at rs1876453 is preferentially associated with reduced risk of the highly specific dsDNA autoantibodies that are present in preclinical, active, and severe lupus, understanding its mechanisms will have important therapeutic implications.

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ACR Concurrent Abstract Session
Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's II: Pathogenesis, Animal Models, Genetics: Novel Signaling Pathways Mediating Fibrosis
Tuesday, October 29, 2013, 2:30 PM–4:00 PM

2704

Twist1 Regulates Transforming Growth Factor Beta Dependent Activation Of Fibroblasts In Fibrosis. Katrin Palumbo-Zerr[1], Andrea Liebl[1], Pawel Zerr[1], Michal Tomcik[2], Alfiya Distler[1], Christian Beyer[1], Oliver Distler[3], Georg Schett[4] and Joerg H. W. Distler[1]. [1]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Institute of Rheumatology, Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [3]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [4]University of Erlangen-Nuremberg, Erlangen, Germany.

Background/Purpose: Twist1 is a member of the tissue-restricted class B of basic-helix-loop-helix (bHLH) transcription factors acting as master regulators on different tissues. Twist1 is controlled by spatial-temporal expression, dimer choice and cellular localization. Twist1 was shown to be a regulator of mesenchymal transition (EMT). Moreover, Twist1 regulates pathways such as Wnt/βcatenin signalling and responses to hypoxia. The aim of the present study was to investigate the role of Twist1 in TGFβ signaling and in fibroblast activation in systemic sclerosis (SSc).

Methods: Twist1 expression was quantified in SSc patients and different mouse models of fibrosis by qPCR, Western Blot and IF. Collagen synthesis was quantified by qPCR and SirCol in fibroblasts overexpressing or lacking Twist1. Interaction of Twist1, E12 and Id was shown by Co-IP. ChIP assays were performed to analyze Twist1transcriptional binding. The role of Twist1 ***in vivo*** was evaluated using inducible, conditional knockout mice with either ubiquitinous (Ubc CreER) or fibroblast-specific (col1a2 CreER) depletion of Twist1. Mice were either challenged with bleomycin or infected with constitutively active TGFβ receptor I adenovirus (TBRI^{CA}).

Results: Twist1 mRNA was elevated by 330 % in the skin of SSc patients ($p = 0.002$). Consistently, Twist1 was increased by 490 % ($p = 0.008$) and by 349 % ($p = 0.001$) in bleomycin-induced and TBRI^{CA} mouse models, respectively. Induction of Twist1 was mediated by TGFβ in a Smad3 dependent manner ***in vitro*** and ***in vivo,*** as demonstrated using the selective TGFβ receptor I inhibitor SD208 and Smad3/4 siRNA. Twist1 overexpression fostered the pro-fibrotic effects of TGFβ and enhanced fibroblast differentiation and release of collagen. In contrast, fibroblasts lacking Twist1 ameliorated TGFβ signalling. Chronic stimulation with TGFβ upregulated Twist1 and E12 in fibroblasts, but resulted in an even more pronounced induction of Id1 and Id3. Id proteins have great affinity for E12 and compete against class bHLH factor Twist1 for E12 binding. Co-IP revealed a time dependent shift of Twist1/E12 heterodimers to Id/E12 and Twist1/Twist1 complexes. In addition, binding of Twist1 homodimers to the col1a1 and col1a2 promoter was demonstrated using ChIP assay. Mice lacking Twist1 in

fibroblasts were less sensitive to bleomycin induced dermal fibrosis with diminished dermal thickening (−69,3 %, $p < 0.0001$), myofibroblast counts (−62,3 %, $p < 0.0001$) and hydroxyproline content (−58,1%, $p < 0.0001$). Mice with ubiquitous Twist1 knockout were protected to a similar degree, highlighting that fibroblasts are the key-effector cells for Twist1 signalling in experimental skin fibrosis. Twist1 deficiency also protected from $TBRI^{CA}$ induced dermal fibrosis.

Conclusion: We identified Twist1 as an important downstream mediator of TGFβ in SSc. TGFβ induces Twist1 expression and stimulates its promoter binding, which triggers myofibroblast differentiation and release of collagen. Knockdown of Twist1 ameliorates the pro-fibrotic effects of TGFβ and ameliorates experimental fibrosis in different murine models of SSc. Thus our study characterizes Twist1 as a key-regulator of fibroblast activation in SSc.

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2705

Inhibition Of Microrna-155 Ameliorated Experimental Fibrosis By Suppressing Wnt and Akt Pathways. Qingran Yan[1], Qiong Fu[1], Jie Chen[1], Xinfang Huang[1], Nan Shen[2] and Chunde Bao[1]. [1]Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, [2]Shanghai Institute of Rheumatology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.

Background/Purpose: MicroRNA-155 plays a critical role in various physiological and pathological processes including cell proliferation and migration, epithelial- mesenchymal transition, as well as inflammation. Previous research found that miR-155 could promote the development of murine pulmonary fibrosis. The aim of this study was to evaluate the role of miR-155 in a bleomycin induced mouse model of systemic sclerosis (SSc) and to investigate the potential mechanisms involved.

Methods: miR-155 knock-out (KO) C57BL/6 and background controlled mice were given bleomycin subcutaneously every other day for 21days to induce experimental fibrosis. Dermal thickness and collagen deposition were determined histologically by Sirius red dying. Tissue fibroblast number was measured through α-smooth muscle actin (α-SMA) staining by immunohistochemistry. For in vitro study, primary murine skin fibroblasts were cultured and stimulated with TGF-β. siRNA was applied to inhibit miR-155 expression. Real-time PCR was used to compare collagen synthesis and activation marker expressions in miR-155 knockdown fibroblasts with controls. Collagen release was analyzed by Sircol assay. Major TGF-β induced profibrotic pathways were analyzed by Western Blot. Targets of miR-155 were predicted by bio-informatics and were confirmed by using dual luciferase report assay and Western blot.

Results: The expression level of miR-155 was significantly elevated in mice injected with bleomycin, as well as in fibroblasts stimulated by TGF-β. Compared with control mice, miR-155 KO mice displayed significantly less fibrosis in both skins and lungs, as well as less number of activated fibroblasts *in situ*. Consistent with the *in viv*o findings, miR-155-knockdown primary fibroblasts showed significantly reduced collagen synthesis and lower activation markers (fibronectin and α-SMA) upon TGF-β stimulation. Analysis of major TGF-β downstream pathways including Smad2/3, JNK, ERK, Wnt and Akt revealed that the activation of Wnt and Akt pathway were notably suppressed in miR-155-knockdown fibroblasts. These two pathways were also attenuated in the skin of miR-155 KO mice injected with bleomycin. Further bio-informatics and literature research suggested that miR-155 could directly target casein kinase I (CK-1) and Src homology 2-containing inositol phosphatase-1 (SHIP-1), which are negative regulators of Wnt and Akt pathway, respectively. We found miR-155 inhibition would result in an increased level of these two proteins in primary fibroblast. Further studies using dual luciferase reporter assay confirmed the direct interaction between miR-155 and 3'-UTR of CK-1 and SHIP-1.

Conclusion: Inhibition of miR-155 could ameliorate experimental fibrosis in a bleomycin induced SSc mouse model. miR-155 modulates profibrotic Wnt and Akt pathway by directly targeting CK-1 and SHIP-1, respectively. miR-155 is a potential target for therapeutic intervention in SSc.

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2706

Fli1 Haploinsufficiency Exacerbates Dermal Fibrosis Via Activation Of Fibroblasts, Endothelial Cells and Macrophages In Bleomycin-Treated Mice. Takashi Taniguchi[1], Yoshihide Asano[1], Kaname Akamata[1], Shinji Noda[1], Takehiro Takahashi[1], Yohei Ichimura[1], Tetsuo Toyama[1], Maria Trojanowska[2] and Shinichi Sato[1]. [1]University of Tokyo Graduate School of Medicine, Tokyo, Japan, [2]Boston University, Boston, MA.

Background/Purpose: Systemic sclerosis (SSc) is a multisystem autoimmune disorder with clinical manifestations resulting from immune activation, vascular injuries and fibrosis development. Previous reports suggest that deficiency of the transcription factor Fli1 (Friend leukemia integration-1) has a pivotal role in the pathogenesis of SSc. Although Fli1 deficiency activates fibroblasts and endothelial cells toward an SSc phenotype *in vitro*, $Fli1^{+/-}$ mice show no clinical symptoms similar to SSc, suggesting that some additional factors are required to develop SSc in those mice. To address this issue, we generated bleomycin (BLM)-induced SSc murine model using $Fli1^{+/-}$mice and evaluated their phenotype by focusing on fibroblasts, endothelial cells, and immune cells.

Methods: Wild type and $Fli1^{+/-}$ mice were used in the BLM model of scleroderma. Degree of dermal thickness and fibrosis were determined by histological analyses. The quantity of the collagen-specific amino acid hydroxyproline was measured. Immunohistochemistry and real-time PCR were conducted to evaluate the degree of inflammation and the expression of cytokines, growth factors, chemokines, and cell adhesion molecules. The influence of Fli1 deficiency on the phenotypical changes in dermal fibroblasts, endothelial cells, and macrophages were also evaluated *in vitro* by real-time PCR and TGF-b bioassay.

Results: BLM induced dermal fibrosis to a much greater extent in $Fli1^{+/-}$ mice than in wild type mice. In addition, upon BLM treatment, $Fli1^{+/-}$ mice exhibited higher mRNA levels of CCN2 in the lesional skin than wild type mice, while mRNA levels of TGF-b were comparable. On the other hand, Fli1 haploinsufficiency greatly activated dermal fibroblasts in response to BLM treatment partly due to the elevated expression of integrin aVb3 and aVb5 in those cells, leading to the activation of latent TGF-b on their cell surface. Upon BLM treatment, the lesional skin of $Fli1^{+/-}$ mice showed higher expression of IL-4, IL-6, IL-10, IFN-g, TNF-a, iNOS, arginase1, Fizz1, and Ym1 than that of wild type mice. The numbers of myofibroblasts, macrophages, and mast cells and the ratio of $CD4^+/CD8^+$ T cells were increased in the lesional skin of BLM-treated $Fli1^{+/-}$ mice relative to that of BLM-treated wild type mice. Moreover, Fli1 haploinsufficiency promoted M2 macrophage infiltration in the lesional skin of BLM-treated mice and also promoted M2 differentiation of peritoneal macrophages by IL-4 or IL-13 stimulation *in vitro*. As for endothelial cells, Fli1 haploinsufficiency modulated the expression of cell adhesion molecules toward the induction of Th2 skewed inflammation by BLM treatment, as shown by the lower expression of E-selectin and P-selectin and the higher expression of ICAM-1 and GlyCAM-1 in the lesional skin of $Fli1^{+/-}$mice than in that of wild type mice.

Conclusion: With BLM treatment, $Fli1^{+/-}$ mice exhibited exacerbated dermal fibrosis due to the phenotypical changes of fibroblasts, endothelial cells, and immune cells toward an SSc phenotype to a much greater extent than wild type mice. Some additional factors induced by BLM treatment may be required for $Fli1^{+/-}$ mice to develop an SSc phenotype.

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2707

Downregulation Of KLF5 and Fli1 Cooperatively Contribute To Distinct Manifestations Of Systemic Sclerosis *In Vitro* and *In Vivo*. Shinji Noda[1], Yoshihide Asano[1], Katsuhito Fujiu[1], Ichiro Manabe[1], Ryozo Nagai[1], Kaname Akamata[1], Takashi Taniguchi[1], Takehiro Takahashi[1], Yohei Ichimura[1], Tetsuo Toyama[1], Daisuke Tsuruta[2], Maria Trojanowska[3] and Shinichi Sato[1]. [1]University of Tokyo Graduate School of Medicine, Tokyo, Japan, [2]Osaka City University Graduate School of Medicine, Osaka, Japan, [3]Boston University, Boston, MA.

Background/Purpose: Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by initial vascular injuries and resultant fibrosis of skin and certain internal organs. Although the pathogenesis of SSc still remains unknown, our latest data have demonstrated that epigenetic suppression of transcription factor Fli1 is deeply involved in the constitutive activation of fibroblasts and endothelial cells in this disease. In murine

models, Fli1 haploinsufficiency results in increased expression of type I collagen at mRNA and protein levels in the back skin, but fibrosis does not occur at least partly because the expression of CTGF, which plays a critical role to establish and maintain tissue fibrosis, remains unchanged. Since our pilot studies have revealed that transcription factor KLF5 is a potent repressor of the CTGF gene and its expression is epigenetically suppressed in SSc dermal fibroblasts, we generated mice with heterozygous deletions of Fli1 and KLF5 and evaluated whether they recapitulated the clinical and histopathological features of SSc.

Methods: mRNA and protein levels of target molecules were determined by quantitative real-time PCR and by immunoblotting, immunohistochemistry and ELISA, respectively. Vascular structure in the back skin was visualized by FITC-dextran intravenously injected. Ultrastructue of collagen fibers was evaluated by electron microscopy. Auto-antibodies were detected by indirect immunofluorescence with Hep2 cells.

Results: $Klf5^{+/-}$;$Fli1^{+/-}$ mice (C57BL/6) were fertile, born in Mendelian ratio, and did not display any apparent early developmental abnormalities. Notably, these mice spontaneously recapitulated cardinal features of SSc, including peripheral vasculopathy, fibrosis of skin and lung, autoimmunity and inflammation. Dermal vascular abnormalities, including stenosis of arterioles with a moth-eaten pattern and bushy capillary tips, occurred around the age of 1 month prior to the development of dermal fibrosis with ultrastructural changes of collagen fibrils similar to those seen in SSc. Interstitial lung disease with B cell lymphoid aggregates and vascular changes characteristic of pulmonary arterial hypertension and pulmonary veno-occlusive disease appeared around the age of 2–4 months and progressed along with disease duration. Serum IL-6 levels and IL-6 mRNA levels in the skin and lung were elevated around the age of 2 months and splenic B cells secreted a greater amount of IL-6 in response to toll-like receptor 4 stimulation with LPS and/or T cell help in the form of an anti-CD40 antibody. Importantly, anti-nuclear antibodies were also detected.

Conclusion: These studies underscore the concept of epigenetic reprogramming underlying pathogenic changes in SSc and implicate the Fli1 and KLF5 pathways as central mediators of this disease.

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2708

The Hedgehog Transcription Factor Gli-2 Is a Novel Downstream Mediator Of The Pro-Fibrotic Effects Of Transforming Growth Factor-Beta. Barbora Sumova[1], Cinzia Cordazzo[2], Katrin Palumbo-Zerr[3], Clara Dees[4], Pawel Zerr[3], Oliver Distler[5], Georg Schett[4], Ladislav Senolt[6] and Joerg H. W. Distler[3]. [1]Department of Rheumatology of the First Faculty of Medicine, Institute of Rheumatology and Connective Tissue Research Laboratory, Prague, Czech Republic, [2]3Dipartimento Cardiotoracico e Vascolare, Laboratory of Respiratory Cell Biology, University of Pisa, Pisa, Italy, [3]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [4]University of Erlangen-Nuremberg, Erlangen, Germany, [5]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [6]Institute of Rheumatology, Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic.

Background/Purpose: Systemic sclerosis (SSc) is characterized by aberrant activation of fibroblasts with increased release of extracellular matrix components. TGFβ is a key-mediator of fibroblast activation in SSc. More recently, hedgehog signaling (Hh) has also been shown to induce tissue fibrosis in SSc. Gli-2 is activated by Hh signaling and induces the transcription of hedgehog target genes. Since the TGFβ and Hh signaling are both key drivers of fibroblast activation in SSc, the aim of this study was to investigate potential crosstalk between those two pathways in SSc.

Methods: The expression of Gli2 in the fibroblasts and tissue was analyzed by real- time PCR and IF staining. Collagen synthesis was quantified by real-time PCR and hydroxyproline assay. Selective knockdown strategies were used to evaluate the role of Gli2 in TGFβ signaling *in vitro* and *in vivo*. The interaction between Gli-2 and TGFβ signaling was analyzed using mice with inducible, fibroblast-specific knockout of Gli2 (Gli-2; Col1a2 CreER) and fibroblast-specific overexpression of a constitutively active TGFβ receptor I TBR (TBR; Col1a2 CreER). Cre mediated recombination was induced postnatally by injection of tamoxifen.

Results: The expression of Gli-2 was significantly increased in the skin of SSc patients compared to healthy controls. In particular, SSc fibroblasts expressed high levels of Gli-2. A prominent overexpression of Gli-2 in fibroblasts was also observed in mice overexpressing TBR. Consistently, stimulation with TGFβ increased the mRNA and the protein level of Gli2 in a time-dependent manner with maximal effects after 3 hours of stimulation (6-fold increase, $p<0.05$) and induced nuclear translocation of Gli2. Gli-2 knockout fibroblasts expressed lower levels of TGFβ targeted genes col1a2 (−47 %), CTGF (−30 %), Smad7 (−44 %), PAI-1 (−37 %) upon stimulation with TGFβ compared to control fibroblasts ($p<0.05$ each). The role of Gli-2 as a downstream mediator of TGFβ in fibroblasts was further analyzed *in vivo* using mice with fibroblast-specific depletion of Gli-2 and simultaneous overexpression of TBR. Fibroblast-specific overexpression of TBR in TBR; Col1a2 CreER mice induced progressive skin fibrosis. Fibroblast-specific, postnatal depletion of Gli-2 in Gli-2; Col1a2 CreER did not result in a basal skin phenotype. However, fibroblast-specific knockdown of Gli-2 protected from TBR induced fibrosis. Gli-2 × TBR; Col1a2 CreER mice treated with tamoxifen showed reduced dermal thickening (−30 %), decreased myofibroblast counts (−41 %) and lower hydroxyproline levels (−45 %) ($p<0.05$ each) compared to TBR; Col1a2 CreER mice.

Conclusion: We present here first evidence for a novel interaction of TGFβ and Hh signaling in fibrosis. TGFβ stimulates Hh signaling in a non-canonical manner by activation of the downstream transcription factor Gli-2. Fibroblast-specific knockdown of Gli-2 reduces the stimulatory effects of TGFβ on fibroblasts and ameliorates TBR-induced skin fibrosis, thereby demonstrating Gli-2 is as a novel downstream mediator of the pro-fibrotic effects of TGFβ.

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2709

Secreted Frizzled-Related Protein 4 Can Be Induced By Transforming Growth Factor-β, Is Regulated By Caveolin-1 and Can Induce Non-Canonical Wnt Signaling In Fibroblasts. Justin Gillespie[1], Giuseppina Abignano[1], Michael McDermott[1], Paul Emery[1] and Francesco Del Galdo[2]. [1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

Background/Purpose: Systemic Sclerosis (SSc) is a heterogeneous disease characterized by autoimmune activation, fibroproliferative vasculopathy, and tissue fibrosis of skin and multiple internal organs. Several studies have indicated that both caevolin-1 (CAV-1) and WNT/β-catenin signaling play important roles in the pathogenesis of tissue fibrosis. Indeed, CAV-1 is downregulated by 40% in SSc skin compared to healthy controls and, intriguingly, tissue expression studies with SSc skin biopsies show both upregulation of canonical WNT ligands[1,2] and consistent upregulation of Frizzled-Related Protein 4 (SFRP4), a putative WNT antagonist, at both mRNA at protein level[3,4]. To evaluate the role CAV-1 and TGFβ on the expression of SFRP4, and the effects of SFRP4 upon WNT signaling in fibroblasts.

Methods: Immortalized primary healthy (HC) and SSc fibroblasts were cultured in 10% DMEM and starved in 0.5% DMEM for 24hrs prior to stimulation with recombinant TGFβ (10ng/ml), WNT-3a/5a (100ng/ml) and/or SFRP4 (100–500ng/ml). Gene expression was quantified by SYBRgreen RTPCR and by western blot. CAV-1 siRNA was transfected at 5μM. Canonical WNT signaling was assessed by TOPFlash luciferase reporter activity. ELISA was used to measure both the level of Phospho-c-JUN from whole cell lysates, and the level of SFRP4 from SSc patient sera.

Results: In SSc fibroblasts, the basal expression of SFRP4 was increased at protein level and also by 264% at mRNA level compared to HC [$p<0.001$]. TGFβ stimulation upregulated SFRP4 mRNA by 170% [$P<0.01$] at 48hrs and by 348% [$P<0.01$] at 72hrs. TGFβ also induced a time-dependent increase of both SFRP4 and α-SMA protein expression, while reducing CAV-1. The siRNA-mediated silencing of CAV-1 was sufficient to induce a time-dependent increase in SFRP4 protein expression. WNT-3a induced a 600% increase in TOPFlash activity, while co-treatment with SFRP4 suppressed this activation by 59%. In contrast, SFRP4 induced a 260% increase [$p<0.001$] in c-JUN phosphorylation, a non-canonical WNT target, at 10 min in both HC and SSc fibroblasts. This was similar to the activity of the non-canonical WNT-5a ligand. Interestingly, basal Phospho-c-JUN was

increased by 180% [P<0.005] in SSc compared to HC fibroblasts. Further, SFRP4 treatment increased *COL1A1* expression by 26% in HCs at 500ng/ml, while in SSc fibroblasts SFRP4 induced both *COL1A1* and *α-SMA* by 49–50% with 100–500ng/ml SFRP4, respectively. Additionally, SSc sera levels of SFRP4 inversely correlated with diffusion lung capacity of carbon monoxide % (r=−0.29, P=0.01) and positively with mRSS in patients with normal lung function (r=0.40, p=0.006).

Conclusion: The increased expression of SFRP4 observed in SSc skin biopsies may be a direct consequence of CAV-1 downregulation by TGFβ in tissue fibroblasts. Given the non-canonical WNT activity of SFRP4, a TGFβ primed microenvironment may be responsible for shaping the phenotype of both fibroblasts and neighboring cells, through aberrant WNT pathway activation. Additionally, circulating SFRP4 may have potential as a biomarker of fibrosis. Investigation of the mechanisms linking CAV-1 expression and SFRP4 function will improve our understanding of the pathogenic role that aberrant WNT activation plays in SSc.

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ACR Concurrent Abstract Session
T-cell Biology and Targets in Autoimmune Disease
Tuesday, October 29, 2013, 2:30 PM–4:00 PM

2710

Deficiency Of The Protein Kinase Ataxia Telangiectasia Mutated Accelerates T Cell Aging In Rheumatoid Arthritis. Zhen Yang[1], Hiroshi Fujii[2], Eric L. Matteson[3], Jorg J. Goronzy[1] and Cornelia M. Weyand[1]. [1]Stanford University School of Medicine, Stanford, CA, [2]Tohoku University, Sendai, Japan, [3]Mayo Clinic, Rochester, MN.

Background/Purpose: T lymphocytes hold a pinnacle position in the pathogenesis of rheumatoid arthritis (RA) and through their longevity contribute to disease chronicity. The protein kinase Ataxia telangiectasia mutated (ATM) is traditionally considered critical in DNA damage repair and cell cycle checkpoint regulation. Recent studies have extended ATM function from the nucleus to the cytoplasm where it acts as an oxidative stress sensor and regulates cellular metabolism and apoptosis, affecting cellular fate decisions and survival. CD4 T cells from RA patients express low levels of ATM protein and are inefficient in repairing damaged DNA. Whether ATM deficiency affects reactive oxygen species (ROS) sensing, metabolic competence, apoptotic sensitivity as well as T cell functional differentiation is unknown.

Methods: Naïve T cells ($CD4^+CD45RO^-$) were purified from the blood of RA patients (n=59) and age-matched controls (n=62). T cell proliferation, cell cycle progression and IL-2 production was compared 48 and 72 hours following TCR ligation. Naïve-to-Memory conversion was monitored by cytometric phenotyping. Resting and activated T cells were loaded with fluorogenic dyes (DCF and DHE) to quantify H_2O_2 and O^{2-}production. The G2/M cell cycle checkpoint was measured with anti-phospho-Histone H3. Expression of ATM, p-ATM (Ser1981), AMPKa1, and p-AMPKa1 (Thr172) were quantified by immunoblotting. ATM signaling was blocked through the inhibitor ku-55933 or siRNA-mediated knockdown.

Results: Compared to age-matched control T cells, RA T cells produced low levels of ATM transcripts, ATM monomers and ATM dimers. In search for upstream signals triggering ATM activity, control and RA T cells were compared for the intracellular levels of H_2O_2 and O^{2-}. Both ROS were diminished in RA T cells. Reduced ATM signaling in RA T cells resulted in delayed histone H2Ax phosphorylation. ATM-deficient RA T cells passed through the G2/M cell cycle checkpoint without proper arrest, accelerating their differentiation into IL-2-producing effector cells. The modified cell cycle behavior led to the rapid conversion of naïve into memory T cells, depleting the naïve T cell reserve in RA patients. Abnormalities in cell cycle progression and T cell differentiation were reproduced in healthy T cells by blocking ATM signaling with ku-55933 or by siRNA-mediated ATM knockdown. Further downstream effects of insufficient ATM signaling in RA T cells included decreased activation of AMPK, a kinase critically involved in energy sensing and metabolic regulation.

Conclusion: Deficiency of ATM redirects cell cycle behavior, metabolic fitness and functional differentiation of RA T cells. ATM-low RA T cells fail to adhere to cell cycle checkpoints, proliferate faster and differentiate prematurely. Also, ATM deficiency impairs triggering of the energy sensor AMPK, leaving the cell without sufficient energy supply. Consequences include the depletion of the naïve T cell reserve, accelerated T cell aging and excessive production of T cell effector cytokines. Overall, these abnormalities in T cell homeostasis and function bias the immune system toward chronic non-resolving inflammation.

Disclosure: Z. Yang, None; **H. Fujii**, None; **E. L. Matteson**, None; **J. J. Goronzy**, None; **C. M. Weyand**, None.

2711

Self-Specific Polyclonal CD4 T Cells Enter a $FR4^{hi}$ $CD73^{hi}$ Anergic State To Prevent Immunopathology and Serve As a Reservoir For The Differentiation Of Protective $Foxp3^+$ Tregs. Lokesh Kalekar and Daniel L. Mueller. University of Minnesota Medical School, Minneapolis, MN.

Background/Purpose: Clonal anergy has been proposed as a mechanism to allow for peripheral recognition of self antigens, without the consequence of immunopathology. Model systems have confirmed that CD4 T cells can become unresponsive to self antigen stimulation, but there is currently no evidence for the existence of anergic CD4 T cells in the normal polyclonal repertoire.

Methods: Gene arrays were used to identify mRNAs specifically overexpressed in anergic ovalbumin (OVA)-specific OT-II TCR-transgenic CD4 T cells after adoptive transfer into healthy OVA-transgenic mice. Overexpression of anergy molecules was confirmed by multiparameter flow cytometry in anergic glucose-6-phosphate isomerase (GPI)-specific KRN TCR-transgenic CD4 T cells after adoptive transfer to self antigen-expressing healthy mice. Antigen-experienced polyclonal CD4 T cells expressing these anergy molecules were characterized by flow cytometry, purified, and tested for their capacity to cause immunopathology in lymphopenic hosts. Finally, adoptive transfer recipients of anergic polyclonal CD4 T cells were tested for evidence of autoantibody production and weight loss versus the generation of protective $Foxp3^+$ Tregs.

Results: Using microarrays to compare mRNA expression in naive, effector, and anergic OT-II CD4 T cells, we discovered that genes for folate receptor 4 (*Folr4*; FR4) and ecto-5'-nucleotidase (*Nt5e*; CD73) were greatly over-expressed following the induction of clonal anergy. Examination of KRN CD4 T cells following their initial adoptive transfer to GPI-expressing hosts confirmed up-regulation of FR4 and CD73 during the induction of anergy, and a reversal of this anergic state following adoptive transfer of $FR4^{hi}$ $CD73^{hi}$ anergic KRN T cells to TCRa-deficient lymphopenic hosts. Making use of these FR4 and CD73 anergy markers, 2–3% of the peripheral mature polyclonal CD4 repertoire was discovered to be anergic. Foxp3 was not expressed; however, CD69, PD-1, CTLA4, CD5, and Nur77 up-regulation suggested continuous engagement by high affinity TCRs on these tolerant T cells. Consistent with *in vivo* anergy induction in response to self antigen recognition, antigen-experienced ($CD44^{hi}$) insulin/I-A^{g7} tetramer-binding polyclonal CD4 T cells in NOD mice demonstrated high expression of FR4 and CD73. Adoptive transfer of $FR4^{hi}$ $CD73^{hi}$ polyclonal CD4 T cells to syngeneic TCRa-deficient lymphopenic hosts led to reconstitution of the $Foxp3^+$ Treg compartment. Remarkably, elimination of newly differentiated Tregs in these anergic CD4 T cell recipients led to fatal wasting disease and the production of autoantibodies.

Conclusion: Peripheral self antigen recognition in normal hosts drives autoreactive CD4 T cells into an anergic state that is associated with the up-regulation of FR4 and CD73. Anergic T cells remain in the peripheral repertoire, both as a threat to health upon anergy reversal as well as a reservoir of precursors for protective $Foxp3^+$ Tregs. A greater understanding of the role of anergy induction and reversal in the development of rheumatic diseases will offer new insights into strategies designed to restore self tolerance.

Disclosure: L. Kalekar, None; **D. L. Mueller**, None.

2712

Increased Soluble PD-1: A Link Between Generation Of Immunological Memory and Risk Of Disease Flare In Early RA. Stinne Greisen[1], Tue W. Kragstrup[1], Kristian Stengaard-Pedersen[2], Merete Lund Hetland[3], Kim Hørslev-Petersen[4], Malene Hvid[1] and Bent Deleuran[1]. [1]Aarhus University, Aarhus, Denmark, [2]Arhus University Hospital, Aarhus, Denmark, [3]The Danish Rheumatologic Database (DANBIO), Glostrup Hospital., Copenhagen, Denmark, [4]University of Southern Denmark, Graasten, Denmark.

Background/Purpose: Disturbances in the regulatory mechanisms of the immune system play a major role in rheumatoid arthritis (RA). Programmed Death 1 (PD-1) on lymphocytes negatively regulate T cell receptor (TCR)-

induced activation through interaction with two ligands (PD-L1 and PD-L2) on activated antigen-presenting cells, including fibroblasts. PD-1 exists in a soluble form (sPD-1), and is increased in chronic RA. Here, we investigate whether sPD-1 plays a role in the generation of immunological memory in early RA.

Methods: In a longitudinal set of steroid- and DMARD naïve RA patients (eRA) (n=76, <3 months of disease) we measured plasma levels of sPD-1 by ELISA (R&D systems) at baseline and after 3, 6 and 12 months of treatment with methotrexate (MTX) + placebo (PLA) or MTX + adalimumab (ADA). After 12 months of treatment, ADA/PLA was discontinued and patients were followed every third month for flare. sPD-1 was also measured in chronic RA (cRA) in plasma and synovial fluid (SF) (n=24, >8 years of disease). Data were expressed as median (IQR) and correlations were assessed by Spearman's rho. T cells were stimulated with anti-CD3/CD28 and co-cultured with RA fibroblast-like synoviocytes (FLS) for 3 days with addition of sPD-1 (20ng/ml), sPD-L1 (20ng/ml) or TNFα (10ng/ml). T cells were examined by flow cytometry for expression of PD-1, CD25, CD69 and proliferation, and FLS were examined for PD-L1 expression.

Results: The plasma levels of sPD-1 was increased in eRA (0.52 ng/ml (0.3–1.1 ng/ml)) compared with cRA (0.14 ng/ml (0.07 ng/ml −0.33 ng/ml), $p<0.001$) and decreased following treatment (0.26 ng/ml (0.2–0.6 ng/ml), $p<0.001$)). Treatment with ADA did not influence this decrease. Baseline sPD-1 correlated tightly with anti-CCP (r=0.42) and IgM-RF (r=0.60, both $p<0.001$). The correlation persisted at 3, 6 and 12 months. Patients with high baseline sPD-1 showed increased risk of disease flares ($p<0.05$). In cRA sPD-1 levels were increased in SF (0.31ng/ml, (0.14 ng/ml −0.73 ng/ml)) compared with plasma ($p<0.01$). T cell survival in FLS co-cultures was 76% when adding sPD-1 compared with 61% in controls. Stimulation with sPD-1 did not affect proliferation, CD25, CD69 or PD-1 expression by T cells. Co-culture with stimulated T cells increased PD-L1 expression on FLS from 2% to 45%. In co-cultures with TNFα, PD-L1 was expressed on nearly all FLS.

Conclusion: Plasma levels of sPD-1 were increased in eRA and decreased in response to treatment suggesting sPD-1 to be important for the initial phase of RA. The high concentrations found in SF points to a function of sPD-1 locally in the joint. The close association with IgM-RF and anti-CCP, the increased risk of flare with high sPD-1 in eRA plasma and the ability of sPD-1 to promote T cell survival in co-cultures with FLS support a role for sPD-1 in adaptive immunity and generation of immunological memory. Taken together, our findings suggest that sPD-1 is capable of blocking the PD-L1 binding-site on FLS, inhibiting the effects of the PD-1-induced TCR regulation and thereby increasing the risk of generating auto-reactive cells.

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2713

IL-21 Inhibited Follicular Regulatory T Cells To Promote Autoreactive Germinal Center Development In Autoimmune BXD2 Mice. Yanna Ding[1], Hui-Chen Hsu[2], Jun Li[1], PingAr Yang[1], Qi Wu[1], Allan J. Zajac[1] and John D. Mountz[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Birmingham VA Medical Center, Birmingham, AL.

Background/Purpose: Follicular T helper (Tfh) cells have been correlated with germinal center (GC) formation, autoantibody production and disease severity in human systemic lupus erythematosus (SLE). Follicular regulatory T cells (Tfr) are a regulatory CD4 T (Treg) subset that counteract Tfh cells and suppress GC B cell differentiation. We recently identified that interleukin 21 (IL-21) promotes Tfh differentiation in autoimmune BXD2 mice that develop spontaneous GCs. However, the role of IL-21 in regulating Tfr is unknown. The aim of this study is to determine the modulatory effects of IL-21 on Tfr/Tfh balance in BXD2 mice.

Methods: Real-time PCR analysis was used to determine the expression of Treg-related genes in sorted Tfr cells after *in vitro* cultured with IL-21 (50ng/ml) stimulation. Exogenous IL-21 was provided to BXD2-*Il21*$^{-/-}$ mice via adenovirus (Ad)-IL21 administration to investigate the effect of IL-21 on Tfr *in vivo*. Sorted Tfr cells from BXD2-*Il21*$^{-/-}$ mice were co-cultured with CD4 T cells and B cells *in vitro* as well as transferred into young BXD2 mice *in vivo* to determine the function of Tfr. FACS staining was used to determine the percent and phenotype of Tfh and Tfr. Confocal imaging analysis was used to visualize the distribution of Tfr cells and GCs. ELISA was used to determine serum levels of IL-21 and TGF-β1. ELISPOT was used to determine the generation of antibody producing B cells.

Results: GL-7^{+}Fas^{+} GC B cells and CXCR5^{+}ICOS^{+} Tfh cells were significantly reduced, but the frequency of FoxP3^{+}CXCR5^{+}ICOS^{+} Tfr cells was 2-fold higher in BXD2-*Il21*$^{-/-}$ mice than in wild-type BXD2 mice, although the frequencies of conventional Treg cells were equivalent. The Tfr cells in BXD2-*Il21*$^{-/-}$ mice expressed high level of other Treg markers including CTLA4, TGF-β1 and GITR. FoxP3^{+}Tfr cells were localized in spleen follicular areas of BXD2-*Il21*$^{-/-}$ mice. Transfer of Tfrs from BXD2-*Il21*$^{-/-}$ mice into BXD2 mice although decreased GC size and reduced IgM, it did not suppress IgG autoantibody producing B cells in the spleen. AdIL-21 administration to BXD2-*Il21*$^{-/-}$ mice increased GC B cells but decreased the serum TGF-β1, membrane TGF-β1 expression in Tfrs and the ratio of Tfr/Tfh in the spleen. *In vitro*, IL-21 decreased FoxP3^{+} and significantly reduced *Tgfb*, *Gitr* and *Il2* expression in Tfrs. IL-21 also counteracted Tfr-induced B cells death and inhibition of Tfhs.

Conclusion: The present study suggests that IL-21 positively promotes autoreactive GC reactions in BXD2 mice at least partially by decreasing Tfrs and compromising the suppressive function of Tfrs on B cells and Tfhs. The results further suggest that IL-21 can skew the balance between Tfr and Tfhs to favor Tfh differentiation. Thus, IL-21 blockage is necessary when developing a Tfr transferring therapeutic strategy to inhibit autoimmune GC response.

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2714

Commensal Intestinal Microbiota Drives Spontaneous Interleukin-1- and T Helper 17-Mediated Arthritis In Mice. Shahla Abdollahi-Roodsaz[1], Rebecca Rogier[2], Tom Ederveen[2], Harm Wopereis[3], Raish Oozeer[3], Marije I. Koenders[2] and Wim B. van den Berg[1]. [1]Rheumatology Research and Advanced Therapeutics, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Rheumatology Research and Advanced Therapeutics, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands, [3]Danone Research, Wageningen, Netherlands.

Background/Purpose: Altered composition of intestinal microbiota in recent-onset rheumatoid arthritis (RA) and possible efficacy of oral antibiotics suggest a role of intestinal microbiota in RA. This study aimed to investigate the involvement of commensal intestinal microbiota in T cell-dependent experimental arthritis.

Methods: IL-1 receptor antagonist deficient (IL-1Ra$^{-/-}$) mice spontaneously developing T cell-driven IL-17-dependent autoimmune arthritis were used. Intestinal and systemic T cell differentiation and arthritis development were studied in conventional and germ-free (GF) mice. Contribution of intestinal microbiota was investigated using oral broad-spectrum and selective antibiotic treatments via drinking water, combined with recolonization by specific microbiota. Multiplex 454 pyrosequencing of V5 and V6 hypervariable regions of fecal bacterial 16S rRNA was used to identify specific microbiota associated with arthritis.

Results: Compared to wild-type mice, small intestinal lamina propria of IL-1Ra$^{-/-}$ mice contained increased Th17 and to lower extent Th1 percentages, both of which significantly correlated with arthritis severity. Importantly, GF IL-1Ra$^{-/-}$ mice had a marked abrogation of arthritis along with reduced intestinal Th1 and in particular Th17. GF IL-1Ra$^{-/-}$ mice exhibited a notable decrease in IL-1β and IL-17 production by splenocytes upon CD3 and Toll-like receptor stimulations, suggesting abolishment of systemic Th17 response. Interferon γ was only detectable upon CD3 stimulation and was reduced as well.

Relevance of intestinal microbiota was underlined by significant long-term suppression of arthritis by one-week oral treatment with Metronidazole, Neomycin and Ampicillin (each 1g/l). Interestingly, recolonization of antibiotic-treated IL-1Ra$^{-/-}$ mice by segmented filamentous bacteria, previously reported as a prominent intestinal Th17 inducer, was sufficient to cause full-blown arthritis. Elimination of distinct intestinal microbiota subsets showed that arthritis is suppressed when Gram-negative, but not Gram-positive, bacteria are selectively eradicated, indicating members of intestinal Gram-negative commensals may drive arthritis.

High-throughput pyrosequencing revealed lower microbiota abundance (operational taxonomic units) and reduced species richness and diversity (Chao and Shannon indices, resp.) in arthritic IL-1Ra$^{-/-}$ compared to wild-type mice. The genus *Helicobacter*, belonging to Gram-negative bacteria, was found associated with arthritis severity (0.0% in wild-type versus 1.1 % in arthritic mice). The disease was further associated increased *Anaeroplama* and *Lactobacillus* accompanied by decreased *Bacteroidetes*. Valida-

tion of microbiota alterations and studies on T cell-modulatory and disease-inducing characteristics in GF mice are in progress.

Conclusion: The presence of commensal intestinal microbiota is critical for the development of autoimmune T cell-driven arthritis, probably via shaping the T cell differentiation by Gram-negative bacteria. Understanding the molecular and cellular mechanisms linking the intestinal T cell response with extra-intestinal disease may help identify novel therapeutic targets in RA.

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ARHP Concurrent Abstract Session
Clinical Practice/Patient Care
Tuesday, October 29, 2013, 2:30 PM–4:00 PM

2715 WITHDRAWN

2716

Support For Psychological State May Be Effective to Attain Remission Of Boolean-Based Definition Of Patient Global Assessment In Patients With Rheumatoid Arthritis. Mie Fusama[1], Kumiko Yukioka[2], Takanori Kuroiwa[2], Chikako Yukioka[2], Miyako Inoue[2], Tae Nakanishi[2], Norikazu Murata[2], Noriko Takai[3], Kayoko Higashi[4], Taro Kuritani[4], Keiji Maeda[4], Yasushi Miura[1], Hajime Sano[5], Masao Yukioka[2] and Hideko Nakahara[4]. [1]Kobe University Graduate School of Health Sciences, Kobe, Japan, [2]Yukioka Hospital, Osaka, Japan, [3]Yukioka College of Health Science, Osaka, Japan, [4]NTT West Osaka Hospital, Osaka, Japan, [5]Hyogo College of Medicine, Nishinomiya-city, Japan.

Background/Purpose: The patients with rheumatoid arthritis (RA) often do not meet patient global assessment (PGA) remission criterion despite a good clinical disease state and, therefore, PGA is not solely influenced by RA disease activity. It has been reported that PGA is a limiting factor for reaching remission. We evaluated whether psychological state influences on Boolean-based definition of PGA remission for patients with RA.

Methods: The patients with RA (n=112) were recruited. Disease activity was evaluated with swollen joint counts (SJC) and tender joint counts (TJC) and evaluator's global assessment (EGA), PGA, and patient pain (Pain VAS) were assessed with visual analog scale. Depression and anxiety were examined utilizing the Hospital Anxiety and Depression Scale-Depression (HADS-D) and the State-Trait Anxiety Inventory (STAI), respectively. General health status was evaluated with Sort Form-36 (SF-36). Comparison analyses were performed between remission group (VAS=<1cm) and non-remission group (VAS>1cm) in PGA, EGA, and pain VAS. Data analyses were performed utilizing Wilcoxon rank-sum test and Spearman correlation analysis.

Results: There was no significant difference in age, duration and PSL dosage between PGA remission group (n=35) and non-remission group (n=77) or EGA remission group (n=38) and non-remission group (n=74). SJC and TJC of remission groups were significantly lower in PGA and EGA ($p<0.0001$, $p<0.0001$, respectively). Among TJC, SJC and pain VAS, PGA was most significantly related to pain VAS ($r=0.9232$, $p<0.0001$), while EGA was related to SJC ($r=0.7725$, $p<0.0001$). STAI (State) and HADS-D were significantly lower in pain VAS remission group ($p=0.0018$, $p=0.0005$, respectively). STAI (State) was significantly lower in PGA remission group ($p<0.05$), while no significant difference was found between two groups in EGA ($p=0.2463$). Similarly in HADS-D, the number of patients with depression was significantly fewer in PGA remission group ($p<0.05$), while no significant difference was found between two groups in EGA ($p=0.2522$). In SF-36, all of the eight components improved significantly in PGA remission group. There was no significant difference in mental health between two groups in EGA ($p=0.1602$). PGA is related to pain VAS, in contrast EGA is related to SJC. The patients with pain VAS remission are less depressive and less anxious. The patients with PGA remission have depression or anxiety less than those with PGA non-remission. Moreover, mental health of SF-36 was significantly better in PGA remission group. On the contrary, there is no significant difference in anxiety, depression and mental health of SF-36 between two groups in EGA.

Conclusion: Discrepancy between PGA and EGA, which is supposed to reflect disease activity of RA, may be partially explained by the difference in psychological state, and support for psychological state may be effective for improvement of PGA. At present, clinical, radiological and functional remissions have been proposed as goal of treatment of RA. As PGA remission is a limiting factor for Boolean remission and PGA relates to psychological state, psychological remission might be important to attain true remission.

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2717

Fatigue in Rheumatoid Arthritis Is Associated With Modifiable Lifestyle Factors. Patricia P. Katz[1], Vladimir Chernitskiy[2] and David I. Daikh[1]. [1]University of California, San Francisco, San Francisco, CA, [2]University of California San Francisco, San Francisco, CA.

Background/Purpose: Fatigue has been identified as a major concern for individuals with rheumatoid arthritis (RA) and has been endorsed as a core outcome measure. However, in order to develop adequate treatments for fatigue, its sources need to be identified.

Methods: During home visits (n=160), assessments were made of fatigue (Fatigue Severity Index; FSI), self-reported sleep quality (Pittsburg Sleep Quality Index; PSQI), depression (Patient Health Questionnaire-9; PHQ9), usual levels of physical activity (International Physical Activity Questionnaire; IPAQ), RA disease activity (RA Disease Activity Index; RADAI), muscle strength (by hand-held dynamometer), functional limitations (Short Physical Performance Battery; SPPB), body composition (body mass index and percent fat mass by bioelectrical impedance), and pulmonary function (by spirometry). Blood was drawn to measure inflammatory markers (C-reactive protein [CRP], tumor necrosis factor-a [TNF], and interleukin-6 [IL-6]), RA-specific markers, anemia, and thyroid function, and information was collected on demographics, medication use, and smoking. The FSI average fatigue level over the past 7 days, rated on a 0–10 (no-severe fatigue) scale, was used as the outcome measure. Analyses were first conducted to evaluate bivariate relationships with fatigue. Multivariate analyses, including all variables significantly associated with fatigue in the bivariate analyses, were then conducted to identify independent predictors of fatigue.

Results: Mean age (±SD) was 59 (±11), mean disease duration was 21 (±13) years, and 85% were female. Mean FSI rating was 3.8 (±2.0; range 0–10). Significant bivariate relationships with fatigue are shown in the Table. No significant associations were found for age, sex, ethnicity, disease duration, knee extension or grip strength, TNF, IL-6, pulmonary function, or prednisone or biologic use (not shown). In multivariate analyses, obesity, RADAI, depression, and smoking remained significantly and independently associated with fatigue.

Table. Factors associated with fatigue

	Bivariate b (p)	Multivariate* b (p)
BMI obesity	1.56 (<.0001)	1.54 (.006)
Disease activity (RADAI)	0.68 (<.0001)	0.30 (.005)
Depressive symptoms (PHQ)	0.25 (<.0001)	0.12 (.002)
Sleep quality (PSQI)	1.21 (<.0001)	0.36 (.07)
Hip flexor strength	−0.03 (.004)	−0.006 (.52)
CRP	0.22 (.008)	−0.009 (.89)
Physical activity ≥150 minutes/week in moderate/vigorous activity	−1.20 (.0005)	−0.23 (.41)
Ever smoke	1.16 (.0008)	0.69 (.009)

* Multivariate model included all variables significantly associated with fatigue in bivariate analyses

In additional analyses, performing ≥150 minutes/week of moderate/vigorous physical activity was associated with lower odds of obesity (OR=0.29 [95% CI 0.15, 0.55]), lower depression score ($p=.002$), and better sleep quality ($p=.04$), suggesting that that physical activity may have an indirect association with fatigue, mediated by these factors.

Conclusion: In this cross-sectional study, much of RA fatigue appeared to arise from factors that are secondary to the disease process itself (obesity, poor sleep quality, and depression), but are commonly present in RA. In addition, physical inactivity appeared to play a role, although its effects were indirect. Further research is warranted to determine the time-ordering of the relationships and if interventions that target modifiable lifestyle factors such as physical activity improve fatigue.

Disclosure: P. P. Katz, None; **V. Chernitskiy**, None; **D. I. Daikh**, None.

2718

Exploring E-Health Ethics and Multi-Morbidity: A Qualitative Study Of Patient and Clinician Experiences Using Digital Media For Health Purposes. Anne F. Townsend[1], Paul Adam[2], Linda C. Li[3], Jenny Leese[4], Michael McDonald[1], Sheila Kerr[5], Gordon Whitehead[5] and Catherine L. Backman[4]. [1]University of British Columbia, Vancouver, BC, [2]Mary Pack Arthritis Centre, Vancouver, BC, [3]Arthritis Centre of Canada, Richmond, BC, [4]Arthritis Research Centre of Canada, Richmond, BC, [5]Consumer Advisory Board, Vancouver, BC.

Background/Purpose: E-Health can potentially transform and enhance health care delivery and empower patients. E-health includes a spectrum of digital health services and information communicated through the Internet and mobile technologies. As digital tools are embraced it is vital to examine emerging ethical issues. We apply a relational ethics lens to situations arising in e-health for patients with arthritis and their health care providers (HCP). Relational ethics emphasizes context, interdependence and relationships that facilitate or constrain meaningful self-direction. The prevalence of comorbidities in patients with arthritis amplifies the complexity of managing diseases concurrently for both patients and HCP. We explore their perspectives on the use of e-health technologies and how e-health use impacts the patient-physician relationship, and in so doing make ethical issues explicit.

Methods: This is Phase 1 of a 2-phase qualitative focus group (FG)/ interview study, informed by narrative and phenomenology to understand the 'lived experience' of e-health use. Eligible participants were: adults with multi-morbidity including arthritis and HCP with relevant caseloads, recruited via online ads, notices, and word of mouth. The FG guides were consistent across groups and organized around 4 areas: 1) E-health tools/devices; 2) descriptions of e-health experiences; 3) impact of e-health use on actions and decisions including patient-provider consultations; 4) a recap to check alignment and range of views. An iterative, constant comparative analysis began with independent open coding of transcribed data by at least 2 researchers; other team members discussed and clustered emerging codes; an ethical lens was then applied to clusters and key categories were identified and agreed upon by the wider team.

Results: 36 participants (18 patients, 18 HCPs) participated in 7 FG, 4 with patients and 3 with rehabilitation professionals and physicians (HCP). We interviewed 4 HCPs who were unable to attend a FG. Patients and HCP expressed similar views about e-health, though examples, emphasis and priorities varied. Predominant themes were: 1) Changing notions of trust (e.g. privacy was a concern but less so than expected; 2) Responsibilities (e.g. patients used e-health for tasks to prepare for consultations; 3) Partnerships (e.g. concordance); 4) Burden (e.g. searching for relevant information was time consuming and could be overwhelming.

Conclusion: There was evidence that fundamental aspects of patient-HCP relationships are shifting. It is critical to make the ethical issues in e-health explicit, as we track the transition towards empowered patients and receptive HCPs.

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2719

Urinary Angiostatin As Alternative To Biopsy In lupus Nephritis Patients Among Egyptian. Shereen Algergawy[1], Osama Alshaar[2] and Rania Zakaria[3]. [1]associate prof at benha university faculty of medicine rheumatology and rehabilitation department Egypt, cairo, Egypt, [2]benha university faculty of medicine, benha, Egypt, [3]benha university faculty of medicine, benha, Egypt.

Background/Purpose: Lupus nephritis (LN) is one of the most frequent manifestations of SLE and can be present in 60% of SLE patients. Kidney biopsy remains the basis of LN diagnosis. There is urgent need to identify biomarkers that alternative to renal pathology in lupus.

Aim: To study urinary angiostatin in SLE and investigate their possible role as indicative of renal involvement to be used as alternative to biopsy.

Methods: Angiostatin levels were measured in urine samples from 45 lupus patients and 14 healthy volunteers, renal biopsy was obtained from all patients

Results: SLE patients had elevated urinary angiostatin as compared to controls ($P < 0.001$). Levels of urinary angiostatin were higher in patients with an active LN (lupus nephritis) than those with inactive LN ($P < 0.001$). In patients with LN urinary angiostatin correlated with the renal score of the Systemic Lupus Erythematosus Disease Activity Index. Urinary angiostatin levels varied significantly and there is significant positive correlation ($P < 0.05$) levels with the activity and choronicty scores of the examined renal biopsies among the histopathological groups.

Conclusion: Urinary angiostatin is potentially useful markers of lupus activity. urinary angiostatin able to differentiate patients with active SLE from those with inactive disease.urinary levels are indicative of renal activity. Patients with Class IV lupus nephritis exhibited the highest levels of urinary angiostatin. Urinary angiostatin can be used as non invasive marker to detect renal involvement in lupus nephritis alternative to renal biopsy

Disclosure: S. Algergawy, None; **O. Alshaar**, None; **R. Zakaria**, None.

2720

Providing Comprehensive, Comparative Post-TJR Outcome Feedback To Surgeons For Quality Monitoring and Value Decisions. Patricia D. Franklin[1], Bruce Barton[1], Leslie R. Harrold[1], Wenjun Li[1], Regis O'Keefe[2], Jeroan Allison[1] and David Ayers[1]. [1]University of Massachusetts Medical School, Worcester, MA, [2]University of Rochester Medical Center, Rochester, NY.

Background/Purpose: With the CMS decision to publicly report hospital-specific post-operative total joint replacement (TJR) events and readmissions, surgeons and hospitals need comprehensive post-hospital data by which to manage and monitor outcomes. Currently, hospitals lack complete data on post-discharge events because patients seek care at multiple emergency rooms and hospitals. In addition, more than 40% of US TJR patients are under 65 years of age and are not captured in CMS data. To address this data void, we developed methods to capture comprehensive post-TJR medical and surgical events, as well as longitudinal patient-reported outcomes, and to report comparative data to participating surgeons and sites.

Methods: We established a national consortium of >120 diverse orthopedists representing all regions of the US with varied hospital and surgeon practices to ensure that data reflect typical US practice. We are enrolling >10,000 patients annually. Web-based and scannable paper data collection formats support efficient data gathering. Patients consent to participate and submit annual outcome assessments directly to us to assure complete reporting of hospital and emergency care. Post-TJR medical events are validated through chart review and CMS data (for those >65 years). Quarterly post-operative event rates and PROs are calculated for the national cohort, the individual surgeon, and site to deliver comparative feedback.

Results: A secure, HIPAA compliant MD website was established that presents summary and comparative descriptive statistics for primary TKR and THR for all of enrolled patients, specific to the site, and to the surgeon. A secure downloadable and printable report includes an Executive Summary of key outcome comparisons, as well as comprehensive tables of patient demographics, pre-operative medical and musculoskeletal comorbidities, post-operative events, and post-operative PROs enabling the providers to compare their outcomes to the other participating surgeons. Patient-level data are provided on request by the surgeon

Conclusion: In an era of public reporting of outcomes, surgeons and hospitals need a single comprehensive source of post-discharge medical events, readmissions, and PROs to manage and monitor all patient outcomes. We developed a secure web-site to return comparative data to providers. These data are used to demonstrate value in payer negotiations and to guide quality improvement efforts.

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2721

Exercise Therapy and Ultrasound Guided Glucocorticoid Injection In Patients With Painful Shoulder: A Randomised Controlled Trial. Karen Ellegaard[1], Robin Christensen[2], Sara Rosager Mortensen[1], Cecilie Bartholby[3], Søren Torp-Pedersen[4], Thomas Bandholm[5], Bente Danneskiold-Samsøe[4], Henning Bliddal[4] and Marius Henriksen[6]. [1]The Parker Institute, Copenhagen, Denmark, [2]Musculoskeletal Statistics Unit, The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, [3]The Parker Institute, Copenhangen, Denmark, [4]The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, Frederiksberg, Denmark, [5]Hvidovre Hospital, Copenhagen, Denmark, [6]The Parker Institute, Copenhagen University Hospital at Frederiksberg, Copenhagen F, Denmark.

Background/Purpose: SubAcromial Impingement (SAI) accounts for approximately 50% of all shoulder pain. The most commonly used treatments for SAI are glucocorticoid injection, exercise therapy or a combination of both. However the effect of exercise added to glucocorticoid injections is inadequately described in the peer reviewed literature. The aim of this study was to investigate the effectiveness of a standardized combination of exercise added to glucocorticoid injection compared to the glucocorticoid alone as the therapy for treatment of SAI.

Methods: Patients with unilateral SAI of minimum 4 weeks duration and thickened subacromial bursa (>2mm assessed by ultrasound) were included (NCT: 01506804). At baseline patients were randomized to two steroid injections into the painful shoulder separated by one week with subsequent 10 weeks exercise therapy of the involved shoulder (intervention group, IG), or two steroid injections into the painful shoulder separated by one week with subsequent 10 weeks exercise therapy of the un-involved shoulder (defined as sham-intervention, control group; CG). The patients were re-examined after the exercise program (at week 12) and again at week 26. Primary outcomes were change from baseline in shoulder pain at rest and during active shoulder abduction analyzed using intention-to-treat population with a non-responder imputation for missing data (i.e., baseline observation carried forward).

Results: 99 patients (58 females) with an average age of 49 years were randomised (49 IG/50 CG). In the IG, 17 participants were lost to follow-up; in the CG 18 were lost.

At the 12 week follow-up there were no statistically significant group difference in pain at rest (MD= 1.677 [95% CI −3.644 to 6.001], P=0.533); and during abduction (MD=2.230 [95% CI −6.462 to 10.921], P=0.612); both groups had decreased pain.. At the second follow up (26 weeks) the positive effect on pain at rest was maintained in the CG but decreased in the IG group; there was a trend towards a difference between groups (MD= 5.613 [95% −0.867 to 12.093], P=0.088). The beneficial effect on pain during active abduction was not different between groups at week 26 (MD= 2.234 [95% CI −6.754 to 11.224], P=0.623).

Conclusion: We found no beneficial effects of combined glucocorticoid injection and exercise therapy of the involved shoulder compared to injections combined with exercise of the uninvolved shoulder. In fact, the CG experienced a prolonged effect on pain at rest compared to the IG. This finding is in contradiction to other studies showing a positive effect of exercise in patients who have received glucocorticoid injection prior to exercise therapy.

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Rheumatology Research Foundation Special Session
2013 Rheumatology Research Foundation Edmond L. Dubois, MD Memorial Lectureship
Tuesday, October 29, 2013, 4:30 PM–6:00 PM

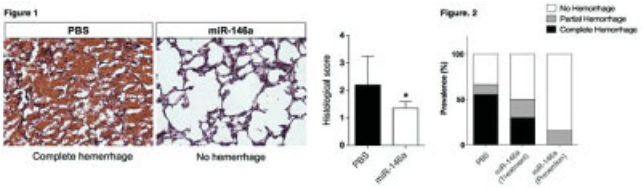
2722

In Vivo Administration Of MiR-146a Protects C57BL/6 Mice From Pristane-Induced Pulmonary Hemorrhage Via Suppressing Type I Interferon Response. Dong Liang[1], Shiyu Zhou[2], Zheng Liu[3], Zhengyuan Shan[1], Philip Brohawn[3], Yihong Yao[3], John B. Harley[1] and Nan Shen[4]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Shanghai Institutes for Biological Sciences Chinese Academy of Sciences & Shanghai Jiao Tong University School of Medicine, Shanghai, China, [3]MedImmune, LLC, Gaithersburg, MD, [4]Shanghai Institute of Rheumatology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.

Background/Purpose: miR-146a as an endogenous regulator plays a critical role in resolving acute inflammation. The risk-associated genetic variant in miR-146a promoter was linked to reduced expression of miR146a in the peripheral blood leukocytes of lupus patients. Our previous studies also showed that overexpression of miR-146a in PBMCs from patients with SLE suppressed coordinate activation of type I interferon (IFN) pathway. Pristane-induced lupus is a well established SLE murine model featuring abnormal activation of IFN pathway and unusual high penetrance of pulmonary capillaritis. This study explored a therapeutic potential of miR-146a in this induced murine model of lupus.

Methods: The C57BL/6 (B6) mice were intravenously injected with PBS or miR-146a via lateral tail veins. The peripheral bloods from 3, 7 and 14 days post Pristane injection were evaluated by real time PCR or gene expression profile analysis. For comparison, the B6 mice were categorized into 3 groups, receiving respectively 3 consecutive injections of PBS (control group, n=9) or miR-146a either 3 days before (prevention group, n =19) or 7 days after (treatment group, n=10) a single intraperiteneal injection of Pristane. The pulmonary hemorrhage was histologically investigated by HE staining 2 weeks post Pristane injection.

Results: The injections of miR-146a mimics (agomirs) resulted in a dramatic increase in the expression of peripheral blood miR-146a in both the prevention and treatment groups as compared to the control group receiving PBS. HE staining showed that miR-146a administration rendered mice resistant to Pristane-induced hemorrhagic pulmonary capillaritis (Fig. 1). While in the control group, 56% mice injected with Pristane developed complete pulmonary hemorrhage, the prevalence was reduced to 25% in the treatment group. Of note, the complete hemorrhage was completely blocked in prevention group (Fig. 2). Furthermore, qPCR revealed that miR-146a was significantly lower in mice with pulmonary hemorrhage compared with mice developing no hemorrhage ($p < 0.01$), and inversely correlated with expression of Mx1 ($p < 0.01$), an IFN-inducible gene. Gene expression profile analysis showed that miR-146a injection substantially suppressed the IFN response, accompanied by reduced production of multiple pro-inflammatory cytokines and chemokines.



Conclusion: Our study provides evidence that miR-146a plays a suppressive role in the Pristane-induced pulmonary hemorrhage in B6 mice. It also highlights a potential pathogenic role of type I IFN pathway activation in the development of pulmonary capillaritis in Pristane-induced murine lupus. These findings suggest that SLE patients with pulmonary hemorrhage may benefit from therapeutic intervention to induce miR-146a expression.

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2723

Role Of Interferon-Inducible RNA-Dependent Protein Kinase In The Pathogenesis Of Systemic Lupus Erythematosus. Aurélie De Groof[1], Benoît Van den Eynde[2], Frédéric A. Houssiau[1] and Bernard Lauwerys[1]. [1]Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium, [2]Institut de Duve, Université Catholique de Louvain, Brussels, Belgium.

Background/Purpose: PRKR (interferon-inducible RNA-dependent protein kinase) is an intracytoplasmic molecule that induces the production of interferon(IFN)-induced genes upon binding of double-stranded RNA viruses. PRKR is spontaneously over-expressed in PBMC from systemic lupus erythematosus (SLE) patients, and we previously demonstrated that in vitro exposure of SLE cells to 2-aminopurine (a pharmacological inhibitor of PRKR) results in a significant inhibition of IFN-induced genes and immunoglobulin production. In the present study, we wanted to further investigate the role of PRKR in the pathogenesis of SLE.

Methods: Intraperitoneal 2-aminopurine versus PBS injections were administered to $(NZB \times NZW)_{F1}$ mice three times a week for a period of 2 months. In addition, PRKR-KO mice were backcrossed in B6.Sle1.Sle2.Sle3 tricongenic SLE-prone mice, resulting in the generation of PRKR-KO versus

WT tricongenic animals. Exploratory studies on the role of PRKR in dendritic cell differentiation were performed using bone marrow cells from the original PRKR-KO mice versus Balb/c controls. The roles of 2-aminopurine and 6-mercaptopurine on IFN-induced gene expression were evaluated in TLR3-transfected HEK293 cells.

Results: While dsDNA antibody (Ab) titers and proteinuria significantly increase over time in PBS-treated $(NZB \times NZW)_{F1}$ mice, this is not the case in 2-aminopurine treated animals. 2-aminopurine therapy also results in a significant improvement of glomerulonephritis activity scores upon histological examination of the kidneys. Our first observations in PRKR-KO versus –WT SLE-prone mice indicate that dsDNA Ab titers display a significant increase from month 2 to month 10 in PRKR-WT B6.Sle1.Sle2.Sle3 mice, and this is not observed in their PRKR-KO littermates.

IL-4 and GM-CSF exposure of bone-marrow cells results in the generation of myeloid-derived dendritic cells (moDC). We observed that the percentage of bone-marrow-derived CD11c-positive cells was significantly decreased in PRKR-KO mice, compared to Balb/c age- and gender-matched animals. Similarly, CD86-positive CD11c cells were significantly less numerous in PRKR-KO compared to Balb/c animals.

Using 2-aminopurine and PRKR siRNA, we demonstrated that PRKR is involved in TLR3 signal transduction in TLR3-transfected HEK293 cells. Thus, poly I:C-induced expression of IFNβ and IFN-induced genes is abrogated in these cells upon PRKR blockade. Intriguingly, we found that exposure of these cells to 6 mercaptopurine resulted in the same inhibitory effects on IFNβ and IFN-induced gene expressio.

Conclusion: Our data indicate that PRKR, an intracytoplasmic danger-recognition molecule that has the ability to stimulate the expression of IFN-induced genes, is involved in the pathogenesis of SLE. The role of PRKR in the pathogenesis of the disease might be mediated by an increased differentiation and maturation of moDC, a hypothesis that we will verify in our PRKR-KO versus –WT SLE prone animals. Preliminary data indicate that the activity of PRKR is modulated by 6-mercaptopurine, the active metabolite of azathioprine.

Disclosure: A. De Groof, None; **B. Van den Eynde**, None; **F. A. Houssiau**, None; **B. Lauwerys**, None.

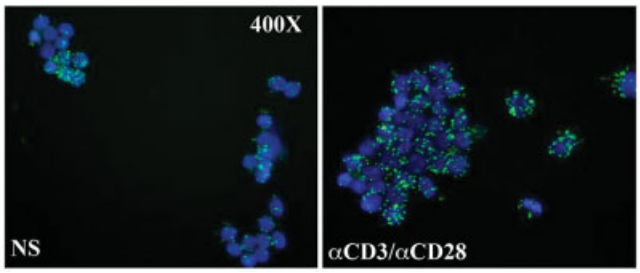
2724

cAMP Responsive Element Modulator (CREM)α Governs CD8 Expression and Contributes to the Generation of $CD3^+CD4^-CD8^-$ T Cells in Lupus. Christian M. Hedrich[1], José C. Crispín[1], Thomas Rauen[1], Christina Ioannidis[1], Tomohiro Koga[2], Noe Rodriguez Rodriguez[1], Sokratis A. Apostolidis[2], Vasileios C. Kyttaris[1] and George C. Tsokos[1]. [1]BIDMC, Harvard Medical School, Boston, MA, [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

Background/Purpose: $CD3^+CD4^-CD8^-$ "double negative" T cells are expanded in the peripheral blood of patients with systemic lupus erythematosus (SLE) and lupus-prone mice. Double negative T cells infiltrate tissues, induce immunoglobulin production and secrete pro-inflammatory cytokines. Although double negative T cells have been claimed to derive from $CD8^+$ T cells through down-regulation of CD8 surface co-receptors, the molecular mechanisms orchestrating this process remain unclear. The transcription factor cAMP responsive element modulator (CREM)α, that is overexpressed in T cells from SLE patients, has been demonstrated to *trans*-regulate lupus-relevant genes and orchestrate epigenetic remodeling in mature T cells. Thus, CREMα is a promising candidate in the search for molecular mechanisms in T cell pathology in SLE.

Methods: Primary human and murine T lymphocytes were isolated to assess epigenetic differences of the *CD8* cluster in $CD8^+$, $CD4^+$, and double negative T cells using MeDIP and ChIP techniques. CD8 mRNA and protein expression was monitored in response to forced expression or knock-down of CREMα. CREMα-mediated effects on chromatin conformation were assessed using over-expression and knock-down techniques, followed by MeDIP or ChIP. Interactions between CREMα and epigenetic modifiers were established using Co-IPs and proximity ligation assays (PLA).

Results: We link CREMα with transcriptional silencing of *CD8A* and *CD8B* in T cells from SLE patients and lupus prone MRL/lpr mice. CREMα *trans*-represses *CD8* and mediates chromatin remodeling of the *CD8* cluster through the recruitment of DNA methyltransferase (DNMT)3a and histone methyltransferase G9a.



Conclusion: We conclude that CREMα is essential for the expansion of double negative T cells in SLE and propose that CREMα may be utilized as disease biomarker and therapeutic target.

An interaction between CREMα and G9a has been established applying proximity ligation assays. *Ex vivo* isolated $CD8^+$ T cells exhibit interactions between CREMα and G9a that are enhanced after TCR-stimulation (120h). Nuclei are stained with DAPI, green signals represent CREMα:G9a interactions.

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2725

Regulation Of Aberrant CD4 T Cell Activation By Suppressor Of Cytokine Signaling-1 (SOCS1) Mimetic Peptide, Has Relevance To Human Systemic Lupus Erythematosus. Tenisha Wilson, Cristina Armbruster, Simone Bedoya, Howard M. Johnson, Westley H. Reeves, Yi Li, Ying Yi Zheng, Laurence Morel and Joseph Larkin III. University of Florida, Gainesville, FL.

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease, mediated by aberrantly activated CD4 T cells. Notably, suppressor of cytokine signaling-1 (SOCS1) regulates CD4 T cell activation. In addition, $SOCS1^{+/-}$ (SOCS1 deficient) mice develop lupus-like disease. Although murine studies implicate a relationship between decreased SOCS1 expression and increased lupus pathology, *the ability to translate these animal findings to human disease has not been established*. Therefore, the goals of this study were to (a) establish clinical relevance for SOCS1 deficiency in regard to *human* SLE and (b) establish the mechanism by which SOCS1 deficiency can lead to lupus development.

Methods: *Human:* qPCR was performed on PBMCs isolated from SLE patients (n=20) and healthy controls (HCs) (n=8) to assess SOCS1 expression, relative to GAPDH. SOCS1 expression was correlated with indicators of disease activity (monocyte CD64 MFI and C3 levels). *Mouse:* $SOCS1^{+/-}$ mice were studied prior to the onset of lupus disease. C57BL/6 mice served as wild-type (WT) controls. Naïve $CD4^+CD25^-$ T cells, isolated from spleen and LNs, were stimulated with anti-CD3 and anti-CD28 antibodies or only anti-CD3 antibody, with or without SOCS-1 KIR (mimetic peptide of SOCS1). Activation was assessed by flow cytometric analysis of CD25 and CD69. CFSE staining and ^3H Thymidine incorporation were employed to measure proliferation. Akt activation was measured by western blotting. For statistical comparisons between SLE patients and HCs and between $SOCS1^{+/-}$ and WT, the Mann-Whitney U test was performed. Spearman's correlation was used for correlation data.

Results: Similar to murine models of disease, SLE patients' PBMCs had reduced expression of SOCS1 in comparison to HCs. Additionally, SOCS1 expression was negatively correlated with monocyte CD64 expression and positively correlated with C3 levels. Mechanistic data revealed that stimulating $SOCS1^{+/-}$ naïve CD4 T cells with anti-CD3 antibody alone resulted in an elevated population of CD69 and CD25 expressing cells. In parallel with the elevated population of activated cells under this suboptimal T cell activation condition, these SOCS1 deficient cells also displayed enhanced ^3H thymidine incorporation and an increased $CFSE^{low}$ population - indicative of increased proliferation. The enhanced activation and proliferation was not due to an elevated population of memory T cells, but rather to a reduced requirement for Akt activation. Notably, SOCS1-KIR reduced the abnormal activation and proliferation.

Conclusion: SOCS1 deficiency is clinically relevant to human SLE. We also determined that SOCS1 deficient CD4 T cells do not require CD28-costimulation in order to undergo activation and proliferation. This has significant implications for lupus development, as SOCS1 deficient autoreactive T cells that have a reduced threshold for activation can activate

autoreactive B cells, which can perpetuate disease. Significantly, SOCS1-KIR has the capacity to restore the proper T cell activation threshold. Based on this data, we propose that SOCS1-KIR should begin to be explored as a potential candidate for the prevention/treatment of SLE.

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2726

A Polymorphism In The *Mif* Gene Is Associated With Cardiovascular Morbidity In Systemic Lupus Erythematosus – a Pilot Study. Eric F. Morand, Kathryn Connelly and Alberta Y. Hoi. Monash University, Melbourne, Australia.

Background/Purpose: Chronic inflammation is believed to be responsible for accelerated atherosclerotic cardiovascular disease (CVD) in patients with SLE. Macrophage migration inhibitory factor (MIF) is a pro-inflammatory molecule implicated in the etiology of both SLE and atherosclerosis via amplification of macrophage recruitment and activation. A single nucleotide polymorphism (SNP) in the *MIF* promoter regulates MIF expression and is associated with SLE risk, and an anti-MIF therapy is currently in Phase I trials in SLE. The association of *MIF* polymorphisms with CVD risk in SLE is unknown.

Methods: SLE patients (ACR criteria) attending a single centre were recruited fo a pilot study. Patients seen between 2007–2012 had disease activity (SLEDAI-2k) recorded at each visit, and organ damage (SLICC-SDI) recorded at baseline and annually. CVD was defined using the cardiovascular domains of the SLICC-SDI criteria. Genomic DNA was isolated from whole blood, amplified by PCR, and MIF-173*C genotype determined by restriction fragment length polymorphism.

Results: 153 SLE patients (80% female, median age 41y, disease duration 10y) were studied. The median (range) SDI and time-adjusted mean SLEDAI (AMS) were 1 (0–9) and 4 (0–22) respectively.

The distribution of MIF-173 genotypes observed was G/G(69%) G/C(28%) and C/C(3%), thus a MIF-173C SNP was present in 31%. Organ damage (SDI) in the overall population correlated with disease duration ($P<0.0001$) and disease activity (AMS; $P<0.0001$). The major finding was that CVD was increased among patients carrying a MIF −173*C allele. Among patients with SLE duration >10y, CVD was 13-fold more frequent among patients carrying a MIF -173*C allele (odds ratio 12.75 (95%CI 2.2–75.2), $p=0.0045$). A significant association was also detected when stroke was included (OR=6.13, 95% CI 1.4–26.9, $p=0.0204$), and when AMI and/or stroke were analysed independently (OR=6.06, 95% CI 1.2–31.0, $p=0.0375$). There was no significant difference in traditional risk factors in relation to MIF -173*C allele, and no association detected with renal or CNS disease, corticosteroid use, or the frequency of episodes of persistently active disease.

Conclusion: Although confirmation in larger cohorts is required, this pilot study suggests that carriage of the MIF-173C SNP is strongly associated with the risk of CVD in SLE. This suggests that anti-MIF therapy could alleviate SLE CVD risk in SLE.

Disclosure: E. F. Morand, None; **K. Connelly**, None; **A. Y. Hoi**, None.

2727

Immunologic and Inflammatory Markers Of Impending Disease Flare In Systemic Lupus Erythematosus Patients Not Taking Immunosuppressive Medications In The Biomarkers Of Lupus Disease (BOLD) Study. Joel M. Guthridge[1], Mikhail G. Dozmorov[1], Melissa E. Munroe[1], Krista M. Bean[1], Sudhakar T. Sridharan[2], Joan T. Merrill[1] and Judith A. James[3]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Pfizer Inc, Collegeville, PA, [3]Oklahoma Medical Research Foundation and University of Oklahoma Health Sciences Center, Oklahoma City, OK.

Background/Purpose: Systemic lupus erythematosus (SLE) is a clinically heterogeneous disorder characterized by a waxing and waning clinical course. Predictors of clinical disease flare have been difficult to identify, leading to cumulative damage, therapeutic toxicities and difficulties designing clinical trials. The goal of this study is to identify immunologic associations and pathogenic mechanisms of disease flares in SLE patients no longer taking immunosuppressive medications.

Methods: As part of the Biomarkers of Lupus Disease (BOLD) study, 41 SLE patients with moderately severe, but not organ-threatening disease activity were enrolled, background immunosuppressants (IS) stopped, intramuscular steroids given until disease suppression and then serially followed until clinical disease flare. SLE patients met > 4 ACR SLE classification criteria and had SLEDAI > 6 or BILAG >/= 2 B or 1 A scores at baseline. Peripheral blood specimens were collected at baseline, time of disease suppression and serially until they developed a significant enough flare to require new treatment (and minimum >/= 1 new BILAG B or SLEDAI increase of >/= 4 points). In addition to autoantibody levels and extensive immunophenotyping, 52 soluble inflammatory mediators, including cytokines, chemokines, and soluble receptors, using either xMAP multiplex technology or sandwich ELISA (BLyS and APRIL), were measured. Gene expression profiling, with globin depletion, was performed on a subset of baseline samples from SLE patients.

Results: Forty of 41 SLE patients flared within 24 weeks, with 21 patients flaring within 60 days (early) and 13 flaring greater than 90 days (late) after stopping background IS. Patients who flared early were more likely to be of African-American descent, while Native American patients were more likely to flare late. Compared to late flaring patients, Caucasian SLE patients who flared early overexpressed 69 genes (including MMP9, CD11b (ITGAM), and MYH9) and showed decreased expression of 20 genes, including HLA-DRB5 and IFI6 at baseline. SLE patients who flared early also had higher baseline expression levels of CD11b on neutrophils ($p=0.003$) and monocytes ($p=0.03$) and higher CD86 expression on B cells ($p=0.03$) (all races combined). SLE patients who flared more than 90 days after stopping medications had higher baseline plasma levels of IL-1RA ($p=0.03$) and TNFRI ($p=0.04$), as well as higher levels of BLyS ($p=0.01$), IL-7 ($p=0.03$) and IFNg ($p=0.04$) at the flare visit.

Conclusion: SLE patients who will flare earlier after withdrawal of ineffective immunosuppressants and transient steroid treatment have increased levels of activated B cells and increased expression of CD11b at baseline, while SLE patients who flared later have evidence of regulatory pathway engagement through secretion of IL1RA.

Disclosure: J. M. Guthridge, None; **M. G. Dozmorov**, None; **M. E. Munroe**, None; **K. M. Bean**, None; **S. T. Sridharan**, Pfizer Inc, 3; **J. T. Merrill**, Pfizer Inc, 5; **J. A. James**, Pfizer Inc, 5.

ACR Concurrent Abstract Session
Biology and Pathology of Bone and Joint II: Osteoclast Biology and Arthritis
Tuesday, October 29, 2013, 4:30 PM–6:00 PM

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The Small Ubiquitin Related Modifier-1 (SUMO-1) Regulates Osteoclast Differentiation *In Vitro* and *In Vivo*. Svetlana Frank[1], Daniel Umlauf[2], Olli A. Jänne[3] and Thomas Pap[4]. [1]University Hospital Münster, Muenster, Germany, [2]University Hospital Muenster, Muenster, Germany, [3]Univ Helsinki, Inst Biomed Physiol, Biomedicum, Helsinki, Finland, [4]University Hospital Münster, Münster, Germany.

Background/Purpose: Posttranslational modification of proteins by SUMO has been shown for a number of target molecules including transcription factors and is involved in a variety of cellular processes, including protein localization, transcriptional regulation, protein stability, cell survival and death. Previously, we have shown that the increased expression of SUMO-1 contributes to the inflammatory response in RA. Here, we investigated the role of SUMO-1 in osteoclastogenesis and studied the skeletal phenotype of *SUMO-1*$^{-/-}$ mice.

Methods: The skeletal phenotype of 8-week old *SUMO-1*$^{-/-}$ and wild type mice was investigated by μCT-analysis of trabecular bone in the lumbar spine and femora. L5 vertebral bodies from these mice mice were embedded into methylmetacrylate and analyzed using van Kossa and tartrate-resistant acid phosphatase (TRAP) staining. For *in vitro* experiments, bone marrow macrophages (BMMs) were isolated from *SUMO-1*$^{-/-}$ mice and wild-type controls. The cells were differntiated into osteoclasts in the presence of macrophage colony-stimulating factor and

receptor activator of nuclear factor k-B ligand (NF-kB). Osteoclast differentiation was characterized by staining for TRAP. Using PCR, the expression levels of DC-STAMP, Cathepsin K and Integrin β3 were analyzed. Proliferation and cell viability of BMMs was determined using CyQuant proliferation assay and MMT test. Osteoclast resorption capacity was analyzed using a calcium phosphate bone resorption assay.

Results: 8-weeks old *SUMO-1*$^{-/-}$ mice had a 20% higher trabecular bone volume fraction compared with wt mice. Moreover, trabecular thickness was higher and trabecular separation was lower in *SUMO-1*$^{-/-}$ mice. In addition, histological analyses revealed a significantly reduced number of osteoclasts in *SUMO-1*$^{-/-}$ mice *in vivo*. The loss of SUMO-1 was associated with impaired osteoclast differentiation and with impaired bone resorption capacity *in vitro*. In PCR analysis, we found a decreased expression of DC-STAMP, Cathepsin K and Integrin β3 in osteoclasts differentiated from *SUMO-1*$^{-/-}$ compared to wt mice. Proliferation and cell viability of BMMs were not affected by loss of SUMO-1. Using western blot analysis we found no differences in activation of MAPK p38 and p44/42 as well as in activation of NF-kB signaling in BMMs and osteoclasts in SUMO-1$^{-/-}$ and wt mice.

Conclusion: In our study, we found that *SUMO-1*$^{-/-}$ mice have high bone mass owing to a decrease in number and function of osteoclasts. These finding are most likely due to decreased expression of osteoclast markers contributing to osteoclast fusion and to osteoclast resorption capacity. These data suggest that SUMO-1 is involved predominantly in the regulation of bone mass by osteoclast formation and activity, and therefore may be an interesting target for treating diseases associated with bone loss.

Disclosure: S. Frank, None; **D. Umlauf**, None; **O. A. Jänne**, None; **T. Pap**, UCB, Servier, Abbott, Bioiberica, MSD, Pfizer, Eli Lilly, 5, UCB, Servier, Abbott, Bioiberica, MSD, Pfizer, Eli Lilly, 8.

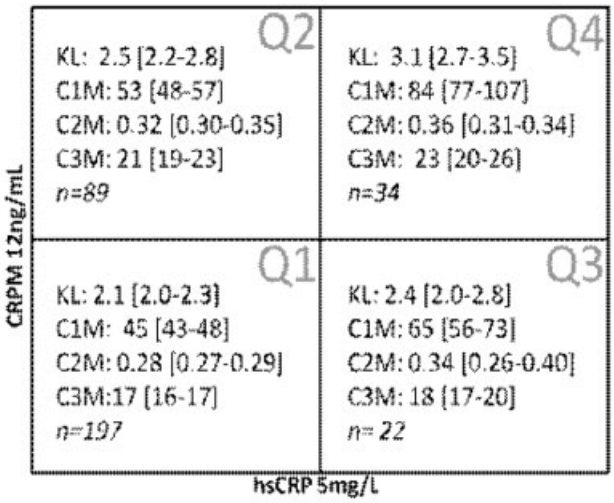
2729

Identification Of Osteoarthritis Patients With Chronic Inflammation Driven Disease Progression. Anne Sofie Siebuhr[1], Kristian Kjaer Petersen[2], Lars Arendt-Nielsen[2], Line Egsgaard[2], Thomas Navndrup Eskehave[3], Ole Simonsen[4], Claus Christiansen[1], Hans Christian Hoeck[3], Morten Asser Karsdal[1] and Anne C. Bay-Jensen[1]. [1]Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, [2]Center for Sensory-Motor Interaction, Aalborg, Denmark, [3]Center for Clinical and Basic Research and C4Pain, Aalborg, Denmark, [4]Frederikshavn Hospital, Frederikshavn, Denmark.

Background/Purpose: In osteoarthritis (OA) it is evident that a subset of patients experiences chronic tissue inflammation and may benefit from anti-inflammatory treatment. The systemic inflammation marker C-reactive protein (CRP) has shown limited use in predicting disease severity, progression or response to anti-inflammatory treatment. The aim of this study was to investigate whether OA patients can be segregated into groups dependent on the present or absence of systemic and/or chronic tissue inflammation and whether such groups have different levels of MMP driven tissue destruction.

Methods: A cross-sectional study of 342 patients: 281 patients had symptomatic knee OA and no planned total knee replacement (TKR) and 61 who underwent TKR. Serological biomarkers were measured by ELISA: high sensitive CRP (hsCRP), CRP degradation fragment (CRPM, chronic tissue inflammation), MMP-mediated degradation fragments of type I, II and III collagen; C1M (connective tissue), C2M (cartilage) and C3M (synovium). The associations between biomarkers and OA stage were investigated: Kellgren & Lawrence (KL) 0, Mild OA (n=12); KL1–2, Moderate OA (n=202); KL3–4, Severe OA (n=57); and KL3–4 with TKR (n=60). Cut-off values of CRPM and hsCRP were set as 12ng/mL and 5μg/mL (mean+2SD of controls). Patients were divided in quartiles (Q, fig) based on the cut-off values. Reference values of the biomarkers were recorded for healthy controls. Data are shown as mean [95%-CI].

Results: hsCRP was only elevated with TKR (5.9 [3.6–8.2] μg/mL) compared to controls. In contrast, the mean levels of the CRPM were twice as high in the OA groups (10–14ng/mL) compared to controls (5ng/mL). C1M and C2M were significantly elevated in the TRKs compared to Moderate ($p<0.001$) and Severe ($p<0.01$). There was no difference between patient and controls in C3M. Patients in Q4 (fig) had significantly higher KL compared to patients in Q1 ($p<0.0001$), Q2 ($P=0.017$) and Q3 ($p<0.0001$). C1M, C2M and C3M were lower in Q1 compared to all other quartiles. Comparing Q2 with Q3 showed that C1M was higher ($p=0.0005$) in Q3, but C3M was lower ($p=0.019$). Thus, the populations identified by systemic and chronic tissue inflammation have different structural integrity.



Conclusion: All OA patients had surprisingly high levels of chronic tissue inflammation. OA patients could be divided into quartiles or 2 separate groups: i) those who may benefit from anti-inflammatory treatment (Q3, Q4) and ii) those eligible for a more tissue centric treatment (Q1, Q2). Patients with high CRPM (Q2 and Q4) had higher levels of the tissue degradation markers C1M, C2M and C3M suggesting that they had elevated tissue turnover. In alignment, those OA patients undergoing TKR had even higher levels of tissue turnover markers, suggesting a distinct TKR serological phenotype. Clearly different types of OA with different levels and types of tissue destruction could be identified by CRPM, but not CRP.

Disclosure: A. S. Siebuhr, Nordic Bisocience, 3; **K. K. Petersen**, None; **L. Arendt-Nielsen**, None; **L. Egsgaard**, None; **T. N. Eskehave**, None; **O. Simonsen**, None; **C. Christiansen**, Nordic Bioscience Diagnostic, 1, Nordic Bioscience Diagnostic, 6; **H. C. Hoeck**, None; **M. A. Karsdal**, Nordic Bioscience, 1, Nordic Bioscience Diagnostic, 3; **A. C. Bay-Jensen**, Nordic Bioscience Diagnostic, 3.

2730

Netrin1 Is a Critical Autocrine Factor For Osteoclast Differentiation. Aranzazu Mediero[1], Bhama Ramkhelawon[1], Kathryn Moore[1], P. Edward Purdue[2], Steven R. Goldring[2] and Bruce N. Cronstein[3]. [1]NYU School of Medicine, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Netrins have been extensively studied for their role in axonal guidance during neural development. In addition, netrins are chemopulsants for a variety of non-neuronal cell types via binding to their receptors Unc5b and DCC. Although thought to suppress inflammation in several settings, netrin1, acting via Unc5b, inhibits macrophage migration directed by chemokines CCL2 and CCL19 to promote macrophage retention in and exacerbation of atherosclerotic plaque. We asked whether Netrin1 was expressed during osteoclast (OC) differentiation and whether it plays a role in OC differentiation.

Methods: DEXAscan and MicroCT analysis were performed on Netrin1 deficient mice (radiation chimeras) and wildtype (WT, radiation chimeras) littermates. OC differentiation was studied as M-CSF/RANKL-stimulated differentiation of murine bone marrow precursors to TRAP+/multinucleated cells, in the presence/absence of recombinant Netrin1 and Unc5b antibody. Netrin1, Unc5b and DCC expression were studied by RT-PCR and Western Blot in primary bone marrow-derived osteoclasts. Netrin1 immunostaining was performed in human tissue obtained following primary prosthesis implantation or after prosthesis revision.

Results: During OC differentiation cell-associated Netrin1 and Unc5b (but not DCC) protein expression increased by 30±2% and 98±4% respectively ($p<0.001$,n=4) and Netrin1 secretion increased by 66±2% ($p<0.001$, n=4). Consistently, RANKL stimulates an increase in Netrin1 and Unc5b mRNA expression during OC differentiation (25±4 and 3±0.5 fold change respectively $p<0.001$, n=4). Moreover, in Netrin1-deficient marrow precursors OC differentiation was diminished by 65±2% as compared to control ($p<0.001$, n=6), an effect reversed by addition of recombinant netrin1 to cultures (121±5% increased, $p<0.5$, n=4). An antibody to the netrin1 receptor Unc5b reduces OC formation by 57±6% ($p<0.001$, n=6) whereas an antibody to DCC had no effect on OC formation (5±4% reduction, p=NS

vs. control, n=6). Finally, DEXAscan and MicroCT analysis demonstrated an increase in bone mineral density (BMD), total volume (TV), bone volume (BV) and TV/BV in both cortical and trabecular bone in Netrin1 deficient mice when compared to WT ($p<0.01$ for all, n=5). Netrin1 immunostaining in human tissue biopsies reflect enhanced expression in tissue from implant revision when compared to primary implants.

Conclusion: The chemorepulsant Netrin1 is required for osteoclast differentiation and stimulates OC differentiation by an autocrine mechanism. This finding suggests that Netrin1 may be a novel target to reduce OC-mediated bone resorption and to prevent joint prosthesis loosening.

Disclosure: A. Mediero, Filed a patent on use of adenosine A2AR agonists to prevent prosthesis loosening (pending)., 9; **B. Ramkhelawon**, None; **K. Moore**, None; **P. E. Purdue**, None; **S. R. Goldring**, Boehringer Ingelheim, 2, Pfizer Inc, Bone Therapeutics, Fidia Pharma, Inc, Abbott Laboratories, 5; **B. N. Cronstein**, Canfite Pharma, 1, NIH, Gilead, Takeda, AstraZeneca, 2, NYU School of Medicine, 3, Merck-SeronoBristol-Myers Squibb, Novartis, CanFite Biopharmaceuticals, Cypress Laboratories, Regeneron (Westat, DSMB), Endocyte, Protalex, Allos, Inc., Savient, Gismo Therapeutics, Antares Pharmaceutical, Medivector, 5, Multiple patents on adenosine receptors and bone metabolism, pharmacology, 9.

2731

An Acetyl-Histone Mimetic Blocks Proinflammatory Activation Of Rheumatoid Arthritis Fibroblast-Like Synoviocytes. P. A. Kabala[1], A.M. Grabiec[1], C. Angiolilli[1], Nicholas Smithers[2], Jason Witherington[2], Paul Peter Tak[3], Rabinder Prinjha[2] and Kris A. Reedquist[1]. [1]Department of Clinical Immunology and Rheumatology Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]GlaxoSmithKline, Stevenage, United Kingdom, [3]Academic Medical Center / University of Amsterdam, Department of Clinical Immunology and Rheumatology & GlaxoSmithKline, Amsterdam, Netherlands.

Background/Purpose: Genetic backgrounds and environmental factors do not completely explain the etiology of disease and predisposition to rheumatoid arthritis (RA), and increasing attention has turned to the potential contributions of heritable epigenetic mechanisms such as DNA methylation, post-translational modifications of histones, and expression of non-coding microRNAs. Fibroblast-like synoviocytes (FLS) isolated from affected joints of RA patients maintain an aggressive phenotype *in vitro*, indicating potential alteration of epigenetic regulatory processes, and changes in global and gene-specific promoter DNA methylation and histone modification are observed in RA FLS. I-BET compounds, acetyl histone mimetics which interfere with reading of acetylated histones by BET family bromodomain proteins BRD2–4, prevent LPS-induced inflammatory gene expression in murine bone marrow-derived macrophages *in vitro*, as well as *in vivo* models of endotoxic shock and bacterial sepsis. This study was undertaken to assess the potential of I-BET to influence the inflammatory activation of RA FLS.

Methods: RA fibroblast-like synoviocytes (FLS) were treated with IL-1β or TNF in the presence or absence of increasing concentrations of I-BET, and IL-6 and IL-8 production measured by ELISA. Cellular viability was assessed using MTT assay and cell death ELISA kits. Activation of intracellular signaling pathways was examined by immunoblotting. Total RNA was extracted and mRNA expression of genes regulated by IL-1β or TNF in RA FLS was analyzed using a low density quantitative PCR custom array.

Results: BRD2–4 mRNA expression was readily detected in RA FLS. I-BET reduced RA FLS (n=6) production of IL-6 protein in response to IL-1β (1 μM, 70% reduction, $P < 0.001$) and TNF (50%, $P < 0.001$). IL-8 production in response to IL-1β (>75% reduction, $P <$. 0.001) and TNF (>70%, $P < 0.001$) was also inhibited. Similar effects were observed on IL-6 and IL-8 mRNA expression. Inhibition of IL-6 and IL-8 production was maintained when I-BET treatment was delayed 1–4 hours post-stimulation. I-BET had no effect on cell viability or survival, and failed to modulate IL-1β or TNF–induced activation of MAPK or NF-κB signaling pathways. Low density qPCR array analysis of 26 genes induced by IL-1β in RA FLS (n=3) demonstrated that I-BET reduced induction of 17 genes by >50%, including TNF (>80% suppression), MMP-1 (>90%), MMP-3 (90%), SELE (>80%), VCAM-1 (>60%), CXCL-6 (>75%), CXCL-9 (>95%) and CXCL-11 (>90%).

Conclusion: Our results demonstrate that disrupting the recruitment of BET family proteins to acetylated histones efficiently blocks RA FLS production of inflammatory mediators, including cytokines, chemokines and MMPs, in response to IL-1β and TNF. This study provides initial evidence that the development of synthethic compounds targeting interactions between epigenetic modifications, such as histone acetylation, and the proteins which interpret these modifications may have therapeutic potential in the treatment of RA.

Disclosure: P. A. Kabala, None; **A. M. Grabiec**, None; **C. Angiolilli**, None; **N. Smithers**, GlaxoSmithKline, 3; **J. Witherington**, GlaxoSmithKline, 3; **P. P. Tak**, GlaxoSmithKline, 3; **R. Prinjha**, GlaxoSmithKline, 3; **K. A. Reedquist**, GlaxoSmithKline, 2.

2732

Inhibition Of Autophagy Prevents Ovariectomy Induced Bone Loss. Neng-Yu Lin[1], Joerg H. W. Distler[1], Alfiya Distler[1], Christian Beyer[1], Georg Schett[2] and Oliver Distler[3]. [1]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]University of Erlangen-Nuremberg, Erlangen, Germany, [3]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland.

Background/Purpose: Autophagy is an essential, homeostatic process by which cells digest unnecessary or damaged organelles. Atg7 is essentially required for formation of the autophagosome. The DMARD chloroquine (CQ) has been identified to arrest autophagy function by blocking the fusion between autophagosomes and lysosomes. Accumulating evidence demonstrates that autophagy is involved in the pathology of varies diseases including infections, cancer and neurodegeneration and recent reports also linked autophagy to osteoclastogenesis and rheumatoid arthritis.

Methods: Systemic bone loss was induced by ovariectomy (OVX). Autophagy was modulated by genetic as well as pharmacologic approaches. For genetic inhibition of autophagy, we crossbred $Atg7^{fl/fl}$ mice with LysM Cre^{+} mice to generate $Atg7^{fl/fl} \times$ LysM Cre^{+} mice with selective inactivation of autophagy function in the monocyte lineage. For pharmacological inhibition, eight-week-old mice underwent daily intraperitoneal injection of 20mg kg^{-1} CQ for a total of 50 days. We applied Microcomputed tomography to analyze bone density *in vivo*. TRAP staining and bone histomorphometry were used to confirm osteoclast number in tissue. To assess osteoclast formation and activity *in vitro*, $Atg7^{fl/fl} \times$ LysM Cre^{+} BMCs and CQ treated BMCs were cultured on bone slices and analysed by the TRAP staining and Toluidine blue staining (n=6, for each group). To assess the autophagy effect on osteoblast activity *in vitro*, primary osteoblasts were treated with Cre Adenovirus and CQ to analyse ALP staining and measure osteoblast markers by RT-PCR.

Results: To investigate the effect of CQ on OVX-induced systemic bone loss, we analyzed the bone density (bone volume/trabecular volume; Bv/Tv) and the trabecular number (Tb. N.) at the proximal tibias. Bv/Tv and Tb. N. were strongly reduced in sham-treated OVX mice. The decreases in Bv/Tv and in Tb. N. were reduced by 76 % and 60% in CQ treated OVX mice (n=6, $p<0.05$ for both). Inhibition of autophagy by selective knockdown of Atg7 in monocytic cells ($Atg7^{fl/fl} \times$ LysM Cre-mice) also prevented OVX-induced osteoporosis and prevented OVX-induced decreases in Bv/Tv and in Tb. N.. Histomorphometric analyses demonstrated decreased osteoclast counts in CQ-treated mice and $Atg7^{fl/fl} \times$ LysM Cre-mice, respectively, compared to controls. Consistent with these *in vivo* results, inhibition of autophagy, either by treatment with CQ or by knockdown of Atg7, also prevented osteoclast differentiation and osteoclast mediated bone resorption *in vitro*. In contrast to the effects on osteoclasts, inhibition of autophagy by genetic or pharmacologic approaches did not inhibit osteoblast activity.

Conclusion: We demonstrate that inhibition of autophagy by genetic or by pharmacological approaches significantly reduced OVX-induced osteoporosis in mice. These findings identify the autophagy machinery as a potential target for the treatment of osteoporoses. Considering the potent anti-osteoporotic effects and the availability of approved inhibitors such as CQ, these findings may have direct translational implications.

Disclosure: N. Y. Lin, None; **J. H. W. Distler**, None; **A. Distler**, None; **C. Beyer**, None; **G. Schett**, Celgene, 2, Abbott Laboratories, UCB, Roche, 5; **O. Distler**, Sanofi, Active Biotech, Pfizer, Actelion, and Novartis, 2, Actelion, Sanofi-Aventis, Roche, Genentech, Active Biotec, medac, Novartis, Sinoxa, 4D Science, 5.

2733

Spontaneous Osteoarthritis In Mice By Genetic Deletion Of *Nfatc1* and *Nfatc2*. Susan Y. Ritter[1], Matthew B. Greenblatt[1], Kelly Tsang[1], Dorothy Z. Hu[2], John Wright[1] and Antonios O. Aliprantis[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Massachusetts General Hospital, Boston, MA.

Background/Purpose: Osteoarthritis (OA) was once viewed as a mechanical disease of "wear and tear", but recent advances suggest that OA results from active dysregulation of chondrocyte biology leading to catabo-

lism of the cartilage matrix. Little is understood regarding the transcription factors that regulate this catabolic program and ultimately the development of OA. Nuclear factor of activated T cells (NFATs) are a family of transcription factors with broad roles in vertebrate physiology including immune responses and tissue development. Since NFAT family members often display redundant functions and NFATc2-deficient mice were previously shown to develop OA at older ages, we tested the role of NFATc1 in OA.

Methods: Mice bearing two copies of a floxed allele of *Nfatc1* (*Nfatc1*$^{fl/fl}$) were crossed to *Col2-cre* mice to delete the gene in cartilage (*Nfatc1*^{col2} mice). *Nfatc1*^{col2} mice were analyzed in the destabilization of the medial meniscus (DMM) model of OA. The *Nfatc1*^{col2} strain was bred onto the NFATc2-deficient background to generate *Nfatc1*^{col2}*Nfatc2*$^{-/-}$ mice. These mice were analyzed by microCT, immunohistochemistry and quantitative real-time PCR (qPCR) of mRNA isolated from dissected cartilage tissue. mRNA purified from human cartilage tissue from joint replacement surgery was also interrogated for *NFATC1* and *NFATC2* expression by qPCR.

Results: *NFATc1*^{col2} mice were not more susceptible to OA in the DMM model than littermate controls, suggesting that in mice, NFATc1 deficiency is not sufficient to accelerate OA. In contrast, cartilage-specific ablation of *Nfatc1* in *Nfatc2*$^{-/-}$ mice led to a spontaneous, early onset, aggressive OA. The arthritis affects multiple joints including the knees, elbows and tarsal-metatarsal joints and is associated with subluxations. Histologically, joints from *Nfatc1*^{col2}*Nfatc2*$^{-/-}$ mice showed loss of proteoglycans, increases in collagen and aggrecan degradation products and eventual progression to cartilage effacement. MicroCT demonstrated increased osteophyte formation and changes to the subchondral bone in *Nfatc1*^{col2}*Nfatc2*$^{-/-}$ mice. Compared with littermate controls, cartilage dissected from the knee joints of *Nfatc1*^{col2}*Nfatc2*$^{-/-}$ mice showed increased expression of: *Mmp13, Adamts5, Col2a1 and Htra1*. Lastly, *NFATC1* expression is downregulated in paired lesional versus macroscopically normal cartilage samples from OA patients (1.63 vs. 2.72, $p=0.0065$ by paired t-test). No significant change was observed in *NFATC2* expression (2.44 vs. 2.06, $p=0.214$).

Conclusion: NFATs are suppressors of OA and regulating NFATs or their transcriptional targets in chondrocytes may lead to novel disease modifying OA therapies. The *Nfatc1*^{col2}*Nfatc2*$^{-/-}$ mice have a highly penetrant, early onset and severe OA phenotype, which could be an attractive platform for the preclinical development of treatments to alter the course of this disease.

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ACR Concurrent Abstract Session
Genetics and Genomics of Rheumatic Disease II
Tuesday, October 29, 2013, 4:30 PM–6:00 PM

2734

Epigenetic Control Of a Gene Regulatory Network Associated With Experimental Autoimmune Arthritis and Rheumatoid Arthritis. Andras Vida[1], Janos Gal[2], Gyorgyi Soos[2], Attila Balog[3], Laszlo G. Puskas[4], Katalin Mikecz[1], Tibor T. Glant[1] and Tibor A. Rauch[1]. [1]Rush University Medical Center, Chicago, IL, [2]Bacs-Kiskun County Hospital, Kecskemet, Hungary, [3]Albert Szent-Gyorgyi University, Szeged, Hungary, [4]Biological Research Center, Szeged, Hungary.

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune inflammatory disorder that mainly affects the synovial joints, leading to destruction of articular cartilage and bone. There is accumulating evidence for the involvement of epigenetic events in the pathogenesis of RA. Recent genome-wide DNA methylation studies have reported disease-associated changes in DNA methylation profile. However, methylation status-dependent molecular mechanisms that can potentially drive or amplify inflammatory processes in arthritis have not been explored.

Methods: We separated lymphocytes from mice with proteoglycan-induced arthritis (PGIA), an autoimmune model of RA, and surveyed arthritis-induced DNA methylation events at genome-wide level using a Methylated CpG Island Recovery Assay (MIRA)-chip method. In addition, we isolated RNA from lymphocytes of arthritic mice and from peripheral blood mononuclear cells (PBMC) of RA patients, and monitored the DNA methylation-dependent changes in gene expression levels by quantitative RT-PCR. Disease-associated DNA-protein interactions were analyzed using electrophoretic mobility shift assays. A cell culture-based in vitro transient expression system was employed to investigate the functional consequence of the binding of specific transcription factors to gene promoters.

Results: Using the MIRA-chip method, we detected arthritis-associated epigenetic changes that preferentially occurred in B cells from mice with PGIA. Specifically, hypomethylation of the promoter of the gene encoding the "zinc finger and BTB domain containing 38" (ZBTB38) transcription factor resulted in a sharp upregulation of ZBTB38 expression in lymphocytes of arthritic mice relative to non-arthritic animals. Expression of the ZBTB38 gene was also elevated in PBMC of RA patients as compared to its expression in healthy subjects. Moreover, ZBTB38 could facilitate its own transcription, and stimulate the expression of a number of other genes including those encoding transcription factors, pro-inflammatory cytokines, as well as receptors for chemokines and Toll-like receptors. Intriguingly, many of the ZBTB38-targeted genes, identified in this study, have been implicated in RA pathogenesis.

Conclusion: ZBTB38 is involved in an intricate gene regulatory network that seems to control inflammatory processes in RA. Exploration of epigenetic mechanisms involved in the regulation of a major RA-associated inflammatory pathway may lead to identification of new genes as novel biomarkers and potential drug targets for RA.

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2735

Integrative Analysis Of Multiple Omics Technologies Reveals a Novel Therapeutic Target For Rheumatoid Arthritis (RA). David L. Boyle[1], John Whitaker[1], Beatrix Bartok[1], Wei Wang[2] and Gary S. Firestein[1]. [1]UCSD School of Medicine, La Jolla, CA, [2]UCSD, La Jolla, CA.

Background/Purpose: Identifying novel therapeutic targets for immune-mediated disease has become increasingly challenging. We used an unbiased method to integrate multiple "omics" methodologies and evaluate the overlap between RA-associated genes identified in genome-wide association studies (GWAS), genes that are differentially expressed or genes that are differentially methylated in RA fibroblast-like synoviocytes (FLS). This analysis narrowed the search to a limited number of genes and allowed us to focus on Engulfment and Cell Motility Protein-1 (*ELMO1*), a gene not previously considered as a therapeutic target. We show how this novel candidate gene plays a key role in the pathogenic behavior of RA FLS.

Methods: Data were from three types of genome-wide RA assays were integrated: (i) for sequence variation we used the NCBI GWAS database and extracted all gene that were mapped to SNPs that had been implicated in RA susceptibility (www.genome.gov/gwasstudies/); (ii) for gene expression we used public microarray datasets of RA, OA, and normal (NL) FLS (Gene Expression Omnibus Database); (iii) for DNA methylation we used a set of differentially methylated genes that we previously identified in RA, OA, and NL FLS (Genome Medicine 5:40 2013). For functional studies, passage 4 to 6 RA FLS were cultured in medium or PDGF and migration was measured using a scratch assay. Cell invasion was determined by measuring cell invasion into Matrigel-coated transwell plates. Rac1 activation was determined by measuring the Rac1-GTP bound form of Rac1 by Western blot. Gene knockdown was performed using the siRNA and Amaxa technology.

Results: The integrative analysis of the three unbiased genome-wide approaches identified 6 genes as different in RA compared to controls (OA and normal) in all datasets. Of the overlapping genes, we were particularly interested in the cytoplasmic engulfment protein, *ELMO1*, as it was differentially methylated in the promoter region, differentially expressed, and associated with RA due to an intron-6 polymorphism. This protein can bind to Rac1 in activated cells and potentially alter cell movement. We first confirmed that ELMO1 is expressed in RA FLS and synovium as determined by qPCR. siRNA knockdown was then performed, which decreased ELMO1 expression by >90% compared to control siRNA. ELMO1 deficiency decreased PDFG-induced FLS migration by 40% ($p<0.02$). In an invasion assay, ELMO1 siRNA markedly decreased invasion of PDGF stimulated RA FLS into Matrigel matrix compared with control siRNA. The mechanism ELMO1 function was determined by determining the effect of ELMO1 deficiency on Rac1 activation. These experiments showed that ELMO1 siRNA decreased peak PDGF-induced Rac1 activation by 80%.

Conclusion: Integrative analysis of multiple unbiased genome-wide datasets is a novel method to identify potential therapeutic targets. One previously unanticipated target, ELMO1, emerged as a candidate gene in RA. ELMO1 plays a critical role as a regulator of FLS migration and matrix invasion by activating Rac1. These data show how one can use integrative studies to identify and validate novel therapeutic targets.

Disclosure: D. L. Boyle, None; **J. Whitaker**, None; **B. Bartok**, None; **W. Wang**, None; **G. S. Firestein**, None.

2736

High Density Microarray Analysis Identifies Novel Differentially Expressed Long Noncoding RNAs In Rheumatoid Arthritis Synovial Fibroblasts. Mojca Frank Bertoncelj[1], Michelle Trenkmann[1], Christoph Kolling[2], Beat A. Michel[3], Renate E. Gay[1] and Steffen Gay[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Schultess Clinic, Zurich, Switzerland, [3]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland.

Background/Purpose: Long noncoding RNAs (lncRNAs) have emerged as key regulators of gene expression. Recently, several new susceptibility loci were identified for rheumatoid arthritis (RA), mapping to noncoding genomic regions (Eyre et al., Nat Gen 2012). Furthermore, we showed that the lncRNA HOTAIR is epigenetically repressed in RA synovial fibroblasts (SF), enhancing their activated phenotype. The aim of the present study was to determine the global lncRNA expression in RASF and to identify differentially expressed (DE) lncRNAs in RASF with a potential role in the pathogenesis of RA.

Methods: Total RNA was isolated from cultured synovial fibroblasts (SF), passages 5–6, from 3 RA and 3 osteoarthritis (OA) age-matched female patients. Sample labeling and array hybridization were performed according to the Agilent One-Color Microarray-Based Gene Expression Analysis protocol. Fluorescently-labeled cRNA was hybridized to human LncRNA Array v3.0 (Arraystar) detecting 30,586 lncRNAs and 26,109 mRNAs. The arrays were scanned by the Agilent Scanner G2505C and analyzed by the Agilent Feature Extraction software. The Agilent GeneSpring GX v12.0 software was used for data processing. To identify DE transcripts the absolute fold change of normalized signal intensities between RASF and OASF was calculated (cut-off value 1.5, $p<0.05$). Gene ontology (GO) and pathway analysis were performed. Fourteen selected DE lncRNAs were confirmed by qPCR in a larger cohort of age- and gender-matched RASF and OASF (n=10 each) with normalization to GAPDH.

Results: The microarray analysis identified 225 DE RNA transcripts in RASF compared to OASF. Among these, 36 lncRNAs (x-fold range: 1.5–4.1) and 87 mRNAs (1.5–10.7) were significantly down-regulated, while 64 lncRNAs (1.51–3.5) and 38 mRNAs (1.5–3.3) were significantly upregulated in RASF. Among identified lncRNAs, small nucleolar RNA host gene 1 (SNHG1) (dCt±SD OASF: 6.92±0.29; RASF: 6.53±0.45, p=0.038) and RP11–39708.4 (dCt±SD OASF: 12.61±0.26; RASF: 12.07±0.69, p=0.042) were confirmed by PCR to be upregulated in RASF. Although their function is not known, it is of interest that RP11–39708.4 is a natural antisense transcript in the locus of fibroblast growth factor 14 and SNHG1 is a host gene for several small nucleolar RNAs, including SNORD22 and SNORD25–31. Among DE mRNAs, several transcripts linked to the pathogenesis of RA were found, such as interleukin 8, peroxisome proliferator-activated receptor (PPAR) gamma and sirtuin 1. Additionally, several novel DE mRNAs were identified, such as tumor protein p73, cell division cycle-associated protein 3 and chemokine-like receptor 1. DE mRNAs clustered to p53, Wnt and PPAR signaling and cell cycle-regulating pathways with significant enrichment of GO terms including cell adhesion molecules, cadherin and beta-catenin binding as well as mitosis and nuclear division.

Conclusion: In this study we identified novel DE lncRNAs in RASF, including SNHG1 and RP11–39708.4. This is the first study determining the global lncRNA profile in combination with differential expression of mRNAs in RASF, which will be a powerful tool to identify novel gene regulating pathways in RA.

Disclosure: M. Frank Bertoncelj, IMI-BT Cure, IAR Epalinges, EURO-TEAM, 2; **M. Trenkmann**, EURO-TEAM, IMI BTCure, IAR Epalinges, KFSP USZ, 2; **C. Kolling**, None; **B. A. Michel**, None; **R. E. Gay**, EURO-TEAM, IMI BTCure, IAR Epalinges, 2; **S. Gay**, EURO-TEAM, IMI BTCure, IAR Epalinges, 2.

2737

In Vivo MiR-146a Administration Ameliorates Murine Lupus Nephritis. Dong Liang[1], Shiyu Zhou[2], Zheng Liu[3], Zhengyuan Shan[1], Philip Brohawn[3], Yihong Yao[3], Indu Raman[4], Quan-Zhen Li[4], John B. Harley[1] and Nan Shen[5]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Shanghai Institutes for Biological Sciences Chinese Academy of Sciences & Shanghai Jiao Tong University School of Medicine, Shanghai, China, [3]MedImmune, LLC, Gaithersburg, MD, [4]University of Texas Southwestern Medical Center, Dallas, TX, [5]Shanghai Institute of Rheumatology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.

Background/Purpose: New Zealand black and white F1 (NZBW/F1) is a classic mouse model of systemic lupus erythematosus (SLE). Type I interferon (IFN) infusion accelerates lupus proteinuria and nephritis. miR-146a is a potent immune regulator to suppress inflammatory responses in T and dendritic cells. Potential involvement of this miRNA in lupus pathogenesis has been implicated in human SLE by both function and genetics. This study explored the novel functions and therapeutic potential of miR-146a in a mouse model of accelerated SLE.

Methods: At 15 weeks, NZBW/F1 mice were infused with IFNα delivered by subcutaneously implanted osmotic pumps. The miR-146a (n = 8) or PBS (n = 7) administration began one week before the IFNα infusion and lasted for 9 weeks. Age matched NZBW/F1 mice were used as negative controls (n=10). Urine samples were tested for proteinuria by dipstick. Blood sera were used for autoantibody profiling. Gene expression profile data were collected from peripheral blood RNAs of both miR-146a and PBS treated groups. At the end of 9-week intervention, the kidney tissues were harvested and renal damage was histologically investigated by HE and IgG1 staining.

Results: Administration of IFNα in NZBW/F1 mice resulted in an accelerated lupus. Proteinuria free survival rate differs between miR-146a treated and PBS-treated groups, with a significant delayed onset of proteinuria observed in the miR-146a-treated group ($p < 0.01$, Fig.1). IHC staining showed reduced IgG1 deposition in kidney tissues from mice treated with miR-146a, 9 weeks after miRNA treatment (Fig. 2). Gene expression profiling by microarray showed that miR-146a treatment decreased expression of immunoglobulin proteins (IgG1, IgG2b, IgM, and IgA). Consistent with these findings, autoantibody profiling of mouse sera showed that IFNα infusion triggered an induction of autoantibodies reactive with different glomerular or glomerular basement membrane antigens. However, the expression of some lupus relevant autoantibodies (anti-H3, anti-H4, anti-histone (total), anti-LC1, anti-MPO, anti-Ribophosphoprotein P1, anti-Sm-D1 and anti-U1-snRNP-BB') was significantly suppressed following miR-146a treatment.

Figure 1

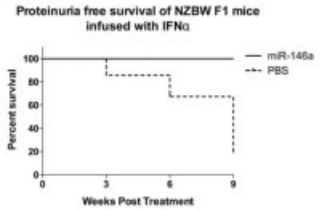
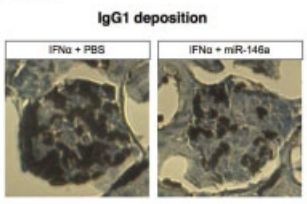


Figure 2



Conclusion: Overall, treatment with miR-146a attenuated lupus nephritis in the IFNα infused NZBW/F1 mice. The results are a proof of principal suggesting that interference with miR-146a may be a promising therapeutic strategy for treatment of lupus patients with renal involvement.

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2738

Microrna-Mediated Regulation Explains Allelic Risk Of *TLR7* Variant Predisposing To Systemic Lupus Erythematosis. Yun Deng[1], Jian Zhao[1], Jennifer M. Grossman[2] and Betty P. Tsao[1]. [1]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [2]UCLA David Geffen School of Medicine, Los Angeles, CA.

Background/Purpose: We identified a genome-wide significant association of the *TLR7* variant (rs3853839) with SLE susceptibility in multiple ancestries ($P_{meta} = 2.0\times10^{-19}$, OR =1.25), and the risk allele carriers exhibited elevated levels of *TLR7* mRNA and protein and more pronounced

type I interferon (IFN) signature in SLE PBMCs. At or near the location of this variant are targeted sequences for predicted multiple microRNA (miRNAs) binding sites that may affect transcript degradation, leading us to explore whether differential miRNA binding could explain allelic risk of *TLR7* for SLE.

Methods: Each of the six bioinformatically predicted miRNAs was co-transfected with the *TLR7* 3'UTR reporter construct carrying either the risk or non-risk allele of rs3853839 into HEK 293 cells to assess which miRNA inhibits luciferase activity. To test effects of miRNA(s) on regulation of endogenous *TLR7* expression and downstream IFN-α production, PBMCs from healthy donors were transfected with miRNAs or non-target control miRNAs for 24 hours, followed by stimulation with TLR7 agonist (CL097) for 24 hours to induce IFN-α production and measured in culture supernatants by ELISA. Cells were lysed for RNA extraction and mRNA levels of *TLR7* and IFN scores (*MX1*, *Ly6E*, *IFIT1* and *IFIT3*) were quantified by RT-PCR.

Results: Transfection of each of six miRNAs into HEK-293 cells showed that (1) only miR-3148 and miR-2278 could reduce luciferase activity driven by the *TLR7* 3'UTR construct containing either risk or non-risk allele of rs3853839; (2) allelic differences in reduction of luciferase activity were observed by overexpression of miR-3148 at increasing concentrations [reduction in non-risk allele vs. risk-allele construct: 13.2% vs. 4.8%, P =0.023 (6nM); 22.5% vs. 9.9%, P =0.0012 (12nM); 21.4% vs. 8.5%, P =0.0031 (48nM)], but only by overexpression of miR-2278 at the highest concentration [31.3% vs. 15.6%, P =0.039 (48nM)]. Expression levels of miR-3148, but not miR-2278, were inversely correlated with *TLR7* mRNA levels in PBMCs (R^2 = 0.255, P =0.001, and R^2 =0.086, P =0.08, respectively). Compared to the non-target control miRNA, preliminary results of overexpression of miR-3148 in PBMCs (n=15) led to 15% reduction in *TLR7* mRNA expression (P =0.003), resulting in a trend of decreased downstream production of IFN-α (P =0.07); whereas inhibition of miR-3148 led to 24% increase in *TLR7* mRNA expression (P =0.006) and a trend of increased production of IFN-α (P =0.09). Overexpression or inhibition of miR-3148 in PBMCs showed no significant difference in IFN scores.

Conclusion: Among the 6 tested miRNAs, miR-3148 and miR-2278 showed allelic difference in degradation of mRNA containing rs3853839, which results in increased expression of *TLR7* mRNA in risk-allele carriers. The inverse correlation between miR-3148 and *TLR7* mRNA levels and a trend of downregulation of IFN-α production in PBMCs *ex vivo* support miR-3148 regulates TLR7 expression and affects downstream IFN pathway. Our data suggests interactions between the genetic risk factor (rs3853839) and the epigenetic factor (miRNAs), implicating possibility of miRNA-based therapies to ameliorate SLE where excessive TLR7 activation exists.

Disclosure: Y. Deng, None; **J. Zhao**, None; **J. M. Grossman**, None; **B. P. Tsao**, None.

2739

Immunochip Analysis Identifies New Susceptibility Loci For Systemic Sclerosis: Implications For Pathogenesis. Maureen D. Mayes for the US Scleroderma GWAS Group[1], Lara Bossini-Castillo for the Spanish Scleroderma Group[2], Olga Gorlova[3], Jose Ezequiel Martin[2], Xiaodong Zhou[1], Wei Chen[3], Shervin Assassi[1], Jun Ying[3], John D. Reveille[1], Peter K. Gregersen[4], Annette T. Lee[4], Maria Teruel[2], Francisco David Carmona[5], Bobby P.C. Koeleman[6], Matthew A. Brown and the Immunochip Consortium[7], Christopher P. Denton[8], Murray Baron for the Canadian Scleroderma Research Group[9], Jasper Broen[10], T.R.D.J. Radstake[10] and Javier Martin[11]. [1]University of Texas Health Science Center at Houston, Houston, TX, [2]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Granada, Spain, [3]UT M.D. Anderson Cancer Center, Houston, TX, [4]Feinstein Institute for Medical Research, Manhasset, NY, [5]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Armilla (Granada), Spain, [6]Department of Medical Genetics, UMCU Utrecht, Utrecht, Netherlands, [7]University of Queensland Diamantina Institute, Brisbane, Australia, [8]Royal Free and University College Medical School, London, United Kingdom, [9]Jewish General Hospital, Montreal, QC, [10]University Medical Center Utrecht, Utrecht, Netherlands, [11]Instituto de Parasitologia y Biomedicina López-Neyra, IPBLN-CSIC, Granada, Spain.

Background/Purpose: The purpose of this study was to identify SSc risk *loci* shared with other autoimmune diseases on the Immunochip and to fine-map previously associated *loci*.

Methods: We genotyped 1,959 SSc cases and 3,582 controls of European ancestry from the United States and Spain using the Immunochip custom array containing 196,524 SNP variants within 186 known autoimmune risk *loci*. Ten SNPs were then chosen for replication in 4,017 SSc cases and 5,935 controls from 6 additional populations of European ancestry from the US, Canada, Europe and the UK for a combined population of 5,876 SSc cases and 9,517 controls.

Results: As noted in the Table below, we identified and validated 4 novel SSc risk *loci* including ***DNASE1L3*** at 3p14, ***SCHIP1 | IL12A*** at 3q25, ***ATG5*** at 6q21 and ***TREH/DDX6*** at 11q23. Remarkably, the association of the rs35677470 missense variant in the *DNASE1L3 locus* with the ACA+ subset of patients is the most significant non-HLA association with SSc revealed to date ($p = 2.70\times10^{-32}$ OR=2.00). In addition, we further refined the area of association for the *STAT4, IRF5/TNPO3 loci* and related an observed peak of association in the *PXK* gene to the novel *DNASE1L3 locus*.

Novel non-HLA loci associated with SSc and its subsets ($p < 5\times10^{-8}$) identified through Immunochip analysis.

Locus	SNP	Chr	Minor Allele	Comments	Phenotype	MAF Cases/CTRLs	*p*-value	OR
DNASE1L3	rs35677470	3p14	A	Missense Arg>Cys	All SSc	0.088/0.062	1.20×10^{-15}	1.43
					lcSSc	0.099/0.062	5.82×10^{-21}	1.6
					ACA+	**0.133/0.062**	$\mathbf{2.70\times10^{-32}}$	**1.99**
SCHIP1-I2A	rs77583790	3q25	A	Intergenic	All SSc	0.015/0.005	2.25×10^{-12}	2.54
					lcSSc	**0.016/0.005**	$\mathbf{3.60\times10^{-12}}$	**2.74**
					ACA+	0.016/0.005	2.24×10^{-8}	2.61
ATG5	rs9373839	6q25	G	Intronic	All SSc	0.241/0.185	2.16×10^{-8}	1.18
TREH/DDX6	rs7130875	11q23	G	Intergenic	All SSc	0.27/0.24	4.03×10^{-8}	1.17

Conclusion: The ***DNASE1L3*** association suggests that failure to clear apoptotic debris plays a role in SSc; that the ***IL12*** pathway is key to SSc susceptibility; that autophagy (***ATG5***), previously unreported in SSc, may be an important mechanism; and that ***DDX6***, which has been shown to regulate VEGF under hypoxic conditions may provide a clue to SSc vasculopathy.

Disclosure: M. D. Mayes for the US Scleroderma GWAS Group, None; **L. Bossini-Castillo for the Spanish Scleroderma Group**, None; **O. Gorlova**, None; **J. E. Martin**, None; **X. Zhou**, None; **W. Chen**, None; **S. Assassi**, None; **J. Ying**, None; **J. D. Reveille**, None; **P. K. Gregersen**, None; **A. T. Lee**, None; **M. Teruel**, None; **F. D. Carmona**, None; **B. P. C. Koeleman**, None; **M. A. Brown and the Immunochip Consortium**, None; **C. P. Denton**, None; **M. Baron for the Canadian Scleroderma Research Group**, None; **J. Broen**, None; **T. R. D. J. Radstake**, None; **J. Martin**, None.

ACR Concurrent Abstract Session
Innate Immunity and Rheumatic Disease
Tuesday, October 29, 2013, 4:30 PM–6:00 PM

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High Efficacy Of Toll-Like Receptor 4 Targeting In Murine and Humanized Models Of Rheumatoid Arthritis In Comparison With IL-1 and TNF Inhibitors. Shahla Abdollahi-Roodsaz[1], Marije I. Koenders[2], Leo A. Joosten[3], Fons A. van de Loo[2] and Wim B. van den Berg[1]. [1]Rheumatology Research and Advanced Therapeutics, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Rheumatology Research and Advanced Therapeutics, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands, [3]Department of Medicine, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands.

Background/Purpose: Increased expression of Toll-like Receptor (TLR) 4 and its endogenous agonists in rheumatoid joints suggest involvement in rheumatoid arthritis (RA). The aim of this study was to assess the therapeutic efficacy and downstream effects of TLR4 blockade in murine and humanized models compared with interleukin-1 (IL-1) and tumor necrosis factor (TNF) inhibitors.

Methods: Mice with established collagen-induced arthritis (CIA) systemically received TNF, IL-1 and TLR4 inhibitors (Enbrel, Anakinra and purified *B. quintana* LPS, resp., each 2 mg/kg/day) using osmotic minipumps. Severe combined immunodeficient (SCID) mice engrafted with active RA synovial tissue, and *ex vivo* synovial cultures served to translate the findings into RA.

Results: TLR4 blockade significantly suppressed clinical and histopathological manifestations of ongoing CIA to the same extent as IL-1 and TNF inhibitors. Targeting TLR4 substantially reduced serum IL-1β and IL-6, and was the only treatment capable of lowering serum TNFa. High-dose TLR4 inhibitor (8 mg/kg) was found significantly more

effective than high-dose Enbrel (10 mg/kg; $P < 0.05$ using Bonferroni's multiple comparison test). Importantly, TLR4 inhibition exceeded beneficial effects of TNF blocker by reducing serum IL-17 along with synovial gene expression of IL-23p19, IL-17 and the Th17-related transcription factor RORγt, while Th1 markers and type II collagen-directed T cell proliferation and antibody responses remained unaffected.

In intact RA synovial biopsies, TLR4 stimulation (100 ng/ml *E. coli* LPS) potently induced TNFα, IL-1β, IL-6 and IL-8 production *ex vivo*, indicating its functional relevance. When transplanted into SCID mice, one single i.p. injection of TLR4 agonist significantly increased IL-6 production by RA synovium *in vivo* and sustained the otherwise declining IL-8 levels for up to 7 days. Importantly, TLR4 activation clearly reversed the therapeutic efficacy of anti-TNF treatment in the humanized RA synovium-SCID model, suggesting involvement in anti-TNF non-responsiveness in subgroups of patients.

Therapeutic value of TLR4 targeting in RA was revealed by inhibition of TLR4 in the RA synovium-SCID model. Blocking endogenous TLR4 activation in this model resulted in substantial reduction of spontaneous IL-6 and IL-8 release and synovial inflammation, thereby equaling anti-TNF. In RA synovial explant cultures *ex vivo*, TLR4 blockade by either *B. quintana* LPS or the small molecule inhibitor TAK242 suppressed several inflammatory cytokines. High-density (phospho)protein microarray of synovial protein lysates showed 27% reduction in NFκBp65 phospho-Ser536, but not NFκBp105/p50, levels by TLR4 blockade. Interestingly, TLR4 inhibition suppressed synovial expression of multiple other key signaling molecules including TAK1 phospho-Thr187 and -Ser412 (26 and 23%, resp.), JAK1 phospho-Tyr1022 (22%), IRAK1 (22%), IRF3 (51%), Foxo3a (39%) and Btk (24%).

Conclusion: Data in murine and humanized models position TLR4 upstream to a number of inflammatory and pathogenic pathways. The findings including impact on IL-17 production and anti-TNF responsiveness collectively impel future research on TLR4 as a potential therapeutic target in RA.

Disclosure: S. Abdollahi-Roodsaz, None; **M. I. Koenders**, None; **L. A. Joosten**, None; **F. A. van de Loo**, None; **W. B. van den Berg**, None.

2741

Evidence That STAT3 controls NLRP3 inflammasome–dependent Release Of IL-1β and Pyronecrosis Through Regulation of mitochondrial activity. Jehad H. Edwan[1], Jae Jin Chae[2], Raphaela T. Goldbach-Mansky[3] and Robert A. Colbert[1]. [1]NIAMS NIH, Bethesda, MD, [2]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [3]National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD.

Background/Purpose: Self-activating NLRP3 mutations are responsible for cryopyrin-associated periodic fever syndromes (CAPS), the most severe form of which is neonatal-onset multisystem inflammatory disease (NOMID). Spontaneous inflammatory responses initiated by NLRP3 mutations promote inflammasome-mediated IL-1beta processing and release, and can induce a rapid cell death in a process known as pyronecrosis that is dependent on cathepsin B activation. Emerging evidence suggests a role for mitochondria in activation of the inflammasome, and mitochondrial STAT3 has been implicated in regulating cellular respiration. The aim of this study was to determine whether STAT3 is involved in IL-1b release and pyronecrosis.

Methods: We used whole blood cells from NOMID and healthy donors, THP-1 cells with STAT3 expression knocked down, THP-1 cells with NLRP3 expression knocked down, and monocytes derived from NRLP3 deficient mice. Cells were stimulated with LPS in the presence of inhibitors of STAT3, followed by ATP. Cell supernatants were collected and incubated with IL-1beta-capturing beads. Cells were fixed and permeabilized. Then beads were added back to cells, and the mixture of cells with beads was stained with anti-IL-1beta, CD14, CD16, and CD83 antibodies and then evaluated by flow cytometry. LPS stimulated cells were also evaluated using immunofluorescent, electron microscopy and western blot analysis. In addition, cell metabolism pathways were analyzed using an XF extracellular flux analyzer.

Results: By flow analysis we found that a small population of monocytes, which undergoes pyronecrosis and is characterized by CD14hi/CD16low and intracellular CD83 expression, is responsible for the majority of IL-1beta production and release. Using confocal microscopy to visualize pyronecrosis, we provided and evidence that this process is NLRP3 dependent. Blockade of STAT3 function with inhibitors leads to complete inhibition of IL-1beta processing and release, as well as pyronecrosis in NOMID and ATP-stimulated healthy donor monocytes and in THP-1 cells. Similarly, STAT3 knockdown in THP-1 cells significantly inhibited IL-1beta release and pyronecrosis. Enhancement of the mitochondrial membrane potential in STAT3 knockdown cells bypasses the effect of STAT3 knockdown, and leads to increased IL-1beta processing and release, which was reversed with inhibitors of oxidative phosphorylation and glycolysis.

Conclusion: Taken together, these data suggest a previously unrecognized role for mitochondrial STAT3 in mediating NLRP3 effects on pyronecrosis and IL-1beta release, and provide a novel therapeutic target for NOMID and other NRLP3-mediated inflammatory diseases.

Disclosure: J. H. Edwan, None; **J. J. Chae**, None; **R. T. Goldbach-Mansky**, None; **R. A. Colbert**, None.

2742

Blau Syndrome-Associated NOD2 Mutations Limit Production Of IL-6 and KC/IL-8 In Knock-In Mice and In Patients Suggesting a Loss Of Function Disease Mechanism. Jae Dugan[1], Eric Griffiths[1], Paige Snow[1], Holly L. Rosenzweig[1], Carlos D. Rose[2], Daniel Carr[1], James T. Rosenbaum[3] and Michael Davey[1]. [1]Dept. of Veterans Affairs Medical Center, Portland, OR, [2]Thomas Jefferson University/ AI duPont Hospital for Children, Wilmington, DE, [3]Oregon Health and Science University, Portland, OR.

Background/Purpose: Blau syndrome is an autosomal dominant disorder caused by mutations in nucleotide-binding oligomerization domain 2 (Nod2) and characterized by arthritis, dermatitis and uveitis. Nod2 binds muramyl dipeptide (MDP), a conserved structure from bacterial peptidoglycan, and activates NF-kB and MAPK signaling cascades. Prior *in vitro* studies using reporter assays indicated that Nod2 containing Blau mutations caused enhanced activation of NF-kB, suggesting a gain of function disease mechanism for Blau syndrome. However, studies with peripheral blood mononuclear cells (PBMCs) from patients with Blau syndrome stimulated with MDP show blunted cytokine responses. We tested the gain of function hypothesis *in vivo* by creating a knock-in mouse where a point mutation resulted in a change of arginine [R] to glutamine [Q] at position 314 (R314Q) of Nod2 (position 314 in mice corresponds to 334 in humans). Regulatory elements controlling Nod2 expression were not altered in this model.

Methods: Knock in mice were studied for systemic cytokine responses. Bone marrow derived macrophages (BMDM) from knock in mice were studied by western blot analysis for Nod2 expression and intracellular signaling, and by ELISA assays. Macrophages derived from patients with Blau syndrome were studied for cytokine responses to MDP and phosphorylation of p38 mitogen activated protein kinase (MAPK).

Results: R314Q heterozygous (+/m) and homozygous (m/m) mice did not spontaneously develop arthritis or dermatitis. BMDM from R314Q mice showed a reduction in full length (116 kD) Nod2 protein levels compared to wild type (WT) mice and they expressed an 80 kD protein that reacted with anti-Nod2 on western blotting. WT and mutant mice showed comparable amounts of Nod2 mRNA in BMDM and analysis of mRNA by PCR did not identify a splice variant. MDP treatment of BMDM showed reduced activation of NF-kB and p38 MAPK in +/m and m/m compared to WT mice that correlated with the copy number of mutated Nod2, with the greatest reduction in m/m mice. In response to *ip* MDP, reduced levels of IL-6 and KC were detected in the serum of +/m and m/m mice, also correlating with the copy number of the mutation. Macrophages derived from PBMCs of two patients with classic, familial Blau syndrome (a mother and son carrying an R334W mutation) showed negligible IL-6 and IL-8 production, and significantly reduced activation of p38 MAPK, in response to MDP compared to a healthy control.

Conclusion: These data indicate that R314Q-Nod2 mice as well as patients with Blau syndrome studied here have lost the ability to respond to MDP, a pathway that is dependent on Nod2. Rather than a gain of function as previously thought, the mutations cause a deficiency of Nod2-dependent responses to MDP and raise the possibility that Blau syndrome may fall within the spectrum of an immunodeficiency disease. This observation may provide insights into why granulomas form in Blau syndrome and it might have important implications for treatment.

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2743

Targeted Activation Of The Metabolic Super-Regulator AMP-Activated Protein Kinase (AMPK) Blunts Gouty Inflammation. Ru L. Bryan[1], Robert Terkeltaub[2] and Yun Wang[3]. [1]VA Medical Center/University of California San Diego, San Diego, CA, [2]VA Medical Ctr/University of California San Diego, San Diego, CA, [3]VA Medical Ctr, San Diego, CA.

Background/Purpose: Gout is associated with both multiple dietary triggers and metabolic co-morbidities, including obesity, metabolic syndrome, and diabates. AMP-activated protein kinase (AMPK) is a master regulator of energy homeostasis, and tissue AMPK activity is decreased by high fat diet and in diabetes, and is conversely increased by clarotic restraint, exercise, and several drugs in the clinic for arthritis (sodium salicylate, high dose aspirin, methotrexate) and by metformin. AMPK is a heterotrimeric complex compoased of an alpha catalytic subunit and two regulatory beta and gamma subunits. Phosphorylation at Thr-172 within the catalytic domain of the a subunit is critical for AMPK activity. Activation of AMPK exerts anti-inflamamtory effects partly by suppressing NF-kB activation. Thus, we assessed the function of AMPK in monsodium urate (MSU) crystal-induced inflammation *in vitro* and *in vivo*.

Methods: We added MSU crystals (0.2 mg/ml) for 18 h to bone marrow derived macrophages (BMDMs) from AMPKa1 knockout (KO) mice and C57BL/6 mice, and pre-treated with AMPK activators AICAR (1 mM) or highly AMPK selective A-769662 (0.25 mM). We analyzed conditioned media by ELISA for cytokines that drive gout arthritis, and cell lysates by Western blot for AMPK activity (phosphorylation of AMPKa). We also injected A-769662 (0.5 mM) one hour prior to injection of MSU crystals (3 mg) into mouse SQ air pouches *in vivo*, and collected samples 6 hrs later.

Results: MSU crystals decreased AMPK activity (phosphorylation of AMPKa Thr172) in BMDMs, and both AICAR and A-769662 inhibited IL-1b and CXCL1 induction by 75% ($p=0.0006$) and 88% ($p=0.0009$), respectively. Conversely, MSU crystal-induced production of IL-1b and CXCL1 was enhanced 1.5 to 2-fold in AMPKa1 knockout BMDMs. Colchicine at 10 nM concentration achieved by standard, low dose therapy for acute gout, up-regulated AMPK activity in BMDMs. Last, A-769662 attenuated inflammatory responses to MSU crystals *in vivo* by 72% reduction of number of infiltrating leukocytes ($p=0.04$) and decrease in IL-1b and CXCL1 in pouch fluid 60% ($p=0.003$) and 50% ($p=0.025$), respectively.

Conclusion: AMPKa1 deficiency enhances MSU crystal-induced macrophage IL-1b and CXCL1 release *in vitro*. Conversely, selective activation of AMPK by A-769662 markedly suppresses MSU crystal-induced inflammatory responses both *in vitro* and *in vivo*. We also established that nanomolar colchicine, in addition to certain other agents in the clinic for arthritis and diabetes, has the capacity to suppress gouty inflammation partly via AMPK activation. Our results indicate a novel, diet and drug targetable mechanism by which high fat diet, diabetes and the urate crystal by itself, are linked with heightened inflammatory potential of urate crystals in gout through decreased tissue activity of the metabolic super-regulator AMPK.

Disclosure: R. L. Bryan, None; **R. Terkeltaub**, Takeda, Savient, ARDEA, BioCryst, Novartis, Regeneron, Sobi, Pfizer, Abbvie, 5; **Y. Wang**, None.

2744

Caspase 8 Modulates The Polarisome To Prevent Lung Fibrosis In a Murine Ssc-Like Disease Model. Carla M. Cuda[1], Alexander Misharin[2], Gokhan Mutlu[2], Luisa Morales-Nebreda[2], GR Scott Budinger[2] and Harris R. Perlman[2]. [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Northwestern University, Chicago, IL.

Background/Purpose: Pulmonary fibrosis has emerged as the leading cause of death in patients with Systemic Sclerosis (SSc). Currently available therapies are only marginally effective in treating this devastating complication and even patients who respond to therapy are left with significant respiratory morbidity. Caspase-8 is a cysteine-aspartic acid protease was originally identified as a key initiator of the apoptotic death receptor pathway and was later found to suppress necrotic programmed cell death (necroptosis) by inhibiting the receptor-interacting serine/threonine kinase 1/3 (RIPK1/3). We discovered a non-apoptotic role for caspase-8 in limiting the activation of macrophages and dendritic cells by toll-like receptor (TLR) agonists via a mechanism that involves RIPK. This novel function of caspase-8 is independent of its apoptotic function; unlike mice lacking Fas or overexpressing the general-baculoviral caspase inhibitor p35 in macrophages and DCs, the loss of caspase-8 does not result in changes in macrophage or DC numbers or affect their survival after bone marrow transplantation into lethally radiated mice.

Methods: Mice lacking caspase 8 specifically in DCs or macrophages were generated ($Cre^{CD11c}Casp8^{flox/flox}$ $Cre^{LysM}Casp8^{flox/flox}$) and examined using the bleomycin and adenoviral TGF-β models of lung fibrosis Flow cytometric analysis was used to characterize macrophage and DC. Luminex-based assays detected cytokine levels.

Results: We show that mice deficient in caspase-8 specifically in macrophages and DCs (have markedly less lung fibrosis than their littermate controls following intratracheal treatment with either bleomycin or an adenovirus encoding an active form of TGF-β. In wild-type animals, we found that the development of fibrosis was accompanied by a polarization of interstitial macrophages into an alternatively activated or M2 phenotype while interstitial macrophages from animals lacking caspase-8 remained polarized toward an M1 phenotype. M2 polarized macrophages have been associated with the release of profibrotic mediators involved in tissue fibrosis and M2 polarized macrophages are found in the lungs of patients with pulmonary fibrosis.

Conclusion: These data suggest a new paradigm for fibrosis in which caspase-8 functions as a key component of a "polarisome" regulating the polarization of macrophages toward an M1 or M2 phenotype. Inhibiting the function of this polarisome in macrophages from patients with scleroderma may prevent the development of lung fibrosis.

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2745

Reshaping Inflammatory Macrophage Development and Functions by a Monosaccharide Analogue In Rheumatoid Arthritis. Jun Li[1], Hui-Chen Hsu[2], PingAr Yang[1], Qi Wu[1], Bao Luo[1], Amber L Rowse[1], David M. Spalding[1], James A Mobley[1], S. Louis Bridges Jr.[1] and John D. Mountz[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Birmingham VA Medical Center, Birmingham, AL.

Background/Purpose: Inflammatory macrophages (MΦs) play key roles in pathogenesis of rheumatoid arthritis (RA). Fucosylation, comprising the transfer of a fucose (6-Deoxy-L-galactose) to proteins, is regulated by fucosyltransferases (FUTs) and involved in inflammation, oncogenesis, and cell differentiation. We have observed upregulated *FUTs* in synovial tissues from RA compared to osteoarthritis (OA) subjects. The purpose of the study is to determine: *(i)* the major cell types that produce *FUTs*; *(ii)* the roles of fucosylation; *(iii)* the efficacy of rebuilding the immune homeostasis by using a fucose analogue in RA.

Methods: Twenty eight RA and OA subjects were recruited and the study is approved by UAB IRB. Q-PCR was performed to determine the expression of *FUTs* in synovial tissues and FACS sorted cells from RA synovial fluids. Inflammatory MΦs were polarized by GM-CSF using monocytes from human PBMC, synovial fluid, and mouse bone marrow. Cells were treated with a fucose analog, 2-Deoxy-D-galactose (2-D-gal, inhibited the fucosylation mediated by FUT1/2) at different time points. Antigen presenting function was studied by using Eα-GFP peptide, DQ-Ova, and denatured bovine collagen II (CII)-FITC. Proteomics analysis was carried out by LCMS. Cytoskeleton images and video were collected using a Nikon spinning disk confocal microscope. Collagen-induced arthritis (CIA) was established in DBA/1J mice. 2-D-gal (200 mg/kg BW, every 2–3 days) was administered via I.P.. FACS and histopathology analyses were performed 6 weeks posterior primary CII immunization.

Results: There is a highly positive correlation between *TNFα* with *FUTs* 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12 ($p=0.0001$ for all), but not *FUTs* 8 ($p=0.46$) and 13 ($p=0.47$) in human RA synovia. In sorted cells from RA synovial fluid, *FUTs* 1, 3, 5, 7, 9 were highly expressed in M1 inflammatory MΦ, but not in M2 MΦ, synovial fibroblasts, and T cells ($p<0.01$), whereas *FUTs* 8 and 13 were predominately expressed in synovial fibroblasts. This highly indicated that subsets of FUTs might associate with the inflammatory M1 MΦ characteristics. A fucose analog, 2-Deoxy-D-galactose (2-D-gal), precluded the differentiation of M1 MΦ. Phalloidin staining indicated 2-D-gal disrupted MΦ actin-based cytoskeleton. Furthermore, LCMS analysis revealed that plectin-10, an actin regulatory protein, is the major target of 2-D-gal in M1 MΦ. These data suggested a potential role of fucosylation in antigen processing. Indeed, 2-D-gal treatment of fully differentiated M1 MΦ for 2 days significantly reduced the uptake, processing and presentation of GFP-Eα (from I-Edα), DQ-OVA, and FITC-Collagen II (CII) antigens ($p<0.01$). Additionally, 2-D-gal skewed the M1 MΦ to M2 by increasing IL-10 secretion ($p<0.01$). *In vivo*, 2-D-gal treatment dramatically blocked bovine CII-induced arthritis (scores 9.5 ± 1.7 vs 0.5 ± 0.3, $p<0.01$) with reduced inflammatory MΦ in draining LN ($1.3\pm0.3\%$ vs $0.5\pm0.1\%$, $p<0.05$), decreased TNF-α (130 vs 39 pg/ml, $p<0.05$), and anti-CII in the serum.

Conclusion: Fucosylation, a hallmark of M1 MΦ, orientates MΦ polarization and function. 2-D-gal, a fucose analog restores the deranged M1 MΦ and leads to resolution of arthritis by inhibiting fucosylation of cytoskeleton molecules.

Disclosure: J. Li, Arthritis Foundation, 2; **H. C. Hsu**, NIH (1R01AI083705-01A2); Lupus Research Institute, 2; **P. Yang**, None; **Q. Wu**, None; **B. Luo**, None; **A. L. Rowse**, None; **D. M. Spalding**, None; **J. A. Mobley**, None; **S. L. Bridges Jr.**, None; **J. D. Mountz**, VA Merit Review Grant (1I01BX000600-01);NIH/NIAID (1AI 071110-01A1);Rheumatology Research Foundation, 2.

ACR Concurrent Abstract Session
Miscellaneous Rheumatic and Inflammatory Diseases I: Autoinflammatory Syndromes
Tuesday, October 29, 2013, 4:30 PM–6:00 PM

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A Novel Autoinflammatory Disorder Characterized By Ectodermal Dysplasia, Metaphyseal Chondrodysplasia, Growth Failure and Hyper-IgD In a Single Family. Edward J. Oberle and James W. Verbsky. Children's Hospital of Wisconsin, Milwaukee, WI.

Background/Purpose: Autoinflammatory disorders are characterized by chronic inflammation, and a variety of systemic complaints. Defects in the NF-kb essential modifier, or NEMO, are associated with an immune deficiency characterized by ectodermal dysplasia. We present a novel autoinflammatory disorder following an autosomal dominant pattern characterized by chronic inflammation, metaphyseal chondrodysplasia, ectodermal dysplasia with hypohidrosis, hyper-IgD and growth failure not associated with immune deficiency in a family.

Methods: Seven individuals from one family were identified. The proband, a male patient age 12 with known hypohydrosis, presented to our rheumatology clinic for chronic articular pain with bony hypertrophy of wrists, knees, and ankles. Standard labs were obtained including ESR, CRP, and CBC for all affected individuals. Plain radiographs and immunoglobulins were obtained from patient, father and sister. Films reviewed by two musculoskeletal radiologists. The proband underwent proximal tibial bone biopsy and marrow aspirate, as well as genetic testing for known autoinflammatory disorders.

Results: The proband, his father age 30, two brothers age 7 and 9, and his 2-year-old sister were all found to have ectodermal dysplasia, short stature and failure to thrive (Figure 1). The youngest affected was evaluated for fevers and elevated inflammatory markers from birth. The patient's father was admitted as a child for bone issues. All affected members exhibited chronically elevated ESR ranging between 64–118 mm/hr and elevated WBC. Radiographs of proband displayed symmetric lucent and sclerotic lesions of the metaphysis of distal radius/ulna, distal femora, and proximal and distal tibia/fibula (Figure 2). His father demonstrated widened metaphyses of distal ulna and tibia, but did not have lesions. Immunoglobulins were elevated in the patient and his father with IgD levels of 755 mg/L (<179 normal) and 600 mg/L, respectively. Bone biopsy of the proband was consistent with metaphyseal chondrodysplasia with marrow spaces consisting of loose fibrous stroma or cartilage, with scattered lymphocytes and plasmacytoid cells. Genetic testing was negative for mutations of CIAS1, LPIN2, MVK, IKBKG (NEMO), PSTP1P1, and TRAPS.

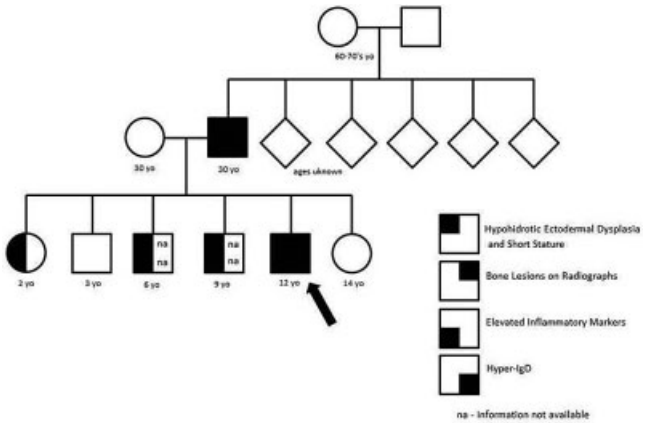

Figure 1. Pedigree.

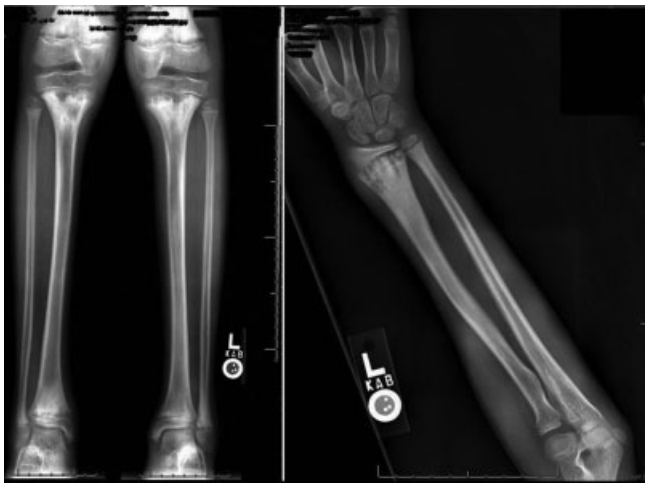

Figure 2. Proband radiographs.

Conclusion: We propose a novel, autoinflammatory disorder resulting in osseous abnormalities, ectodermal dysplasia and Hyper IgD.

Disclosure: E. J. Oberle, None; **J. W. Verbsky**, None.

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Canakinumab Treatment In Schnitzler's Syndrome: A Multi-Center Randomized Placebo-Controlled 4-Month Study. Karoline Krause, Karsten Weller, Martin Metz and Marcus Maurer. Dept. of Dermatology and Allergy, Allergie-Centrum-Charité, Charité – Universitätsmedizin Berlin, Germany, Berlin, Germany.

Background/Purpose: Schnitzler's syndrome (SchS) is an adult-onset autoinflammatory disease characterized by urticarial exanthema and monoclonal gammopathy in combination with episodes of fever, arthralgia, fatigue, and bone and muscle pain. Anti-IL-1 targeting therapies in small patient numbers including an open-label study with canakinumab (CAN) showed to be effective in reducing the clinical symptoms of SchS.

Methods: The current placebo-controlled study was designed to assess the effects of the selective anti-IL-1β humanized monoclonal antibody CAN on the clinical signs and symptoms of SchS in a larger patient cohort. A total of 20 patients with active disease enrolled in this multi-center trial. After a baseline period of up to 4 weeks, patients were randomized to receive a single CAN 150mg or placebo s.c. injection (day 0) and were evaluated for treatment response at day 7. This initial study period was followed by a 16-week open label phase with CAN injections upon confirmed relapse of clinical symptoms. Efficacy was determined by changes in the physician's global assessment (PGA; range 0–20), a combined symptom score which includes 5 key symptoms of SchS (urticarial rash, fever, fatigue, arthralgia and myalgia), measurement of the inflammation markers C-reactive protein (CRP) and serum amyloid A (SAA) as well as changes in quality of life assessment (SF-36).

Results: CAN was highly effective (P=0.001) in reducing median PGA total scores (14.0 to 2.0) within 7 days after first administration as compared to placebo treatment (15.0 to 13.0) in SchS patients. Also, significant (P<0.0001 – P<0.05) improvements were observed for each key symptom score. Median CRP reduced from 9.3mg/dL at baseline to 0.6mg/dL at day 7 in the CAN group vs increase from 3.0mg/dL to 5.0mg/dL for the placebo group. Similarly, median SAA levels reduced from 428mg/L to to 13mg/L for the CAN group vs increase from 160mg/L to 205mg/L for the placebo group. The median change from baseline between treatment groups for CRP (p=0.004) and SAA (p=0.002) was significant. Likewise, quality of life as measured by SF-36 significantly improved (P=0.001) for the CAN vs placebo groups at day 7. These improvements were maintained during the 16-week open label phase of the study. A total of 22 adverse events (AEs) were reported during the study including 3 serious AEs (2 hypertensive episodes in 1 patient and severe lumbago in another patient).

Conclusion: In this 4-month study, CAN s.c. injections significantly improved the clinical signs and symptoms of SchS, reduced inflammation

markers, and enhanced quality of life. CAN treatment may be considered a promising therapeutic option in these patients.

Disclosure: K. Krause, None; **K. Weller**, None; **M. Metz**, None; **M. Maurer**, Novartis Pharmaceutical Corporation, 2.

2748

Safety Results From The Beta Confident Registry In Canakinumab-Treated Patients With Cryopyrin-Associated Periodic Syndrome. Hal Hoffman[1], Jasmin B. Kuemmerle-Deschner[2], Philip N. Hawkins[3], T. van der Poll[4], Ulrich A. Walker[5], Michael Nebesky[6], Ken Abrams[7] and Hugh Tilson[8]. [1]University of California at San Diego, San Diego, CA, [2]University Hospital Tuebingen, Tuebingen, Germany, [3]University College London Medical School, London, United Kingdom, [4]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [5]Universitäts-Poliklinik, Felix-Platter Spital, Basel, Switzerland, [6]Novartis Pharma AG, Basel, Switzerland, [7]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [8]The University of North Carolina, Gillings School of Global Public Health, Chapel Hill, NC.

Background/Purpose: Cryopyrin-associated periodic syndrome (CAPS) comprises an extremely rare auto-inflammatory disorders, including familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease/chronic infantile neurological cutaneous and articular syndrome (NOMID/CINCA).[1] *NLRP3* gene mutation results in overproduction of IL-1β, leading to observed clinical symptoms of CAPS.[2] Canakinumab (CAN) is a selective anti-IL-1β monoclonal antibody, approved for the treatment of CAPS.[2,3] Here, we report the updated safety data for CAN in CAPS patients (pts) from the ongoing β-Confident Registry. The primary objective of the Registry is to monitor and further explore the overall safety of CAN, focusing primarily on serious infections, malignancies, hypersensitivity reactions, vertigo, and other selected adverse events in CAPS pts over a 5-year period (NCT01213641).

Methods: The Registry includes pts with CAPS and other auto-inflammatory disorders receiving CAN as part of regular medical care, after obtaining the written informed consent The study protocol does not mandate any visits or procedures, records all observed and reported adverse events (AEs) and serious adverse events (SAEs) or AEs potentially related to treatment with CAN. Cumulative safety data are reported, as incidence rate (number of events) per 100 patient-years (IR/100 pyr) from the date of first pt enrollment (November 19, 2009) until the data cut-off date (March 29, 2013). Additional safety data will be updated, as available, at the time of the conference presentation.

Results: A total of 245 pts were enrolled in the Registry at the current cut-off date, of which 229 patients reported a median duration of 50 weeks (range: 0.9 – 137.3) of prior treatment with CAN at the time of Registry enrollment. Of the total, 100 pts reported 238 AEs with an IR of 75.9/100 pyr. Infections with an IR of 20.7/100 pyr, were the most commonly observed AEs and included nasopharyringitis, rhinitis and urinary tract infections (UTI) among others. Eight pts reported 13 events of vertigo as AEs, resulting in an IR of 4.2/100 pyr, of which 8 were suspected to be CAN related. With regards to SAEs, 37 events were reported by 27 pts with an IR of 11.8 /100 pyr that included one fatal case of malignancy (metastatic rectal adenocarcinoma in a 76 yr MWS patient) and 12 events of serious infections. No case of hypersensitivity to CAN was reported. A total of 14 pts permanently discontinued CAN: 4 each due to pts preference and AEs, 3 due to lack of therapeutic effects, and 3 due to unspecified reasons.

Conclusion: No new or unexpected safety signals were reported to date in this ongoing Registry. Infections, as expected, were the most commonly occurring AEs and SAEs.

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1. Arthritis Res Ther 2011, 13:R34, 2. Lachmann et al. J Exp Med 2009, 206: 1029–1036, 3. Arthritis Rheum 2008;58:2443–2452

Disclosure: H. Hoffman, Novartis, Regeneron, Sobi Biovitrum, 5; **J. B. Kuemmerle-Deschner**, Novartis,, 2, Novartis,, 5; **P. N. Hawkins**, None; **T. van der Poll**, Novartis,, 5; **U. A. Walker**, Novartis,, 5; **M. Nebesky**, Novartis,, 3; **K. Abrams**, Novartis,, 3, Novartis,, 1; **H. Tilson**, Bio Soteria, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, HealthCore, Kendle, Merck, Novartis, 5, Glaxo Smith-Kline, Procter & Gamble, Other non-pharmaceutical holdings, 1.

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Amyloidosis and Its Related Factors In Patients With Familial Mediterranean Fever: A Nationwide Multicenter Study. Timucin Kasifoglu[1], Sule Yasar[1], Ismail Sari[2], Dilek Solmaz[2], Soner Senel[3], Hakan Emmungil[4], Levent Kilic[5], Sibel Yilmaz Oner[6], Fatih Yildiz[7], Sedat Yilmaz[8], Muhammet Cinar[8], Duygu Ersozlu Bakirli[9], Muge Aydin Tufan[7], Sema Yilmaz[10], Veli Yazisiz[11], Yavuz Pehlivan[12], Cemal Bes[13], Gozde Yildirim Cetin[14], Sukran Erten[15], Emel Gonullu[1], Tuncer Temel[1], Servet Akar[2], Kenan Aksu[4], Umut Kalyoncu[5], Haner Direskeneli[16], Eren Erken[7], Bunyamin Kisacik[12], Mehmet Sayarlioglu[17] and Cengiz Korkmaz[18]. [1]Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkey, [2]Dokuz Eylul University School of Medicine, Izmir, Turkey, [3]Kayseri Erciyes University School of Medicine, Kayseri, Turkey, [4]Ege University School of Medicine, Izmir, Turkey, [5]Hacettepe University School of Medicine, Ankara, Turkey, [6]Marmara University School of Medicine, Istanbul, Turkey, [7]Cukurova University School of Medicine, Adana, Turkey, [8]Gulhane School of Medicine, Ankara, Turkey, [9]Adana Numune Training and Research Hospital, Adana, Turkey, [10]Selcuk University School of Medicine, Konya, Turkey, [11]Akdeniz University School of Medicine, Antalya, Turkey, [12]Gaziantep University School of Medicine, Gaziantep, Turkey, [13]Bolu Izzet Baysal School of Medicine, Bolu, Turkey, [14]Kahramanmaras University School of Medicine, Kahramanmaras, Turkey, [15]Ataturk Training and Research Hospital, Ankara, Turkey, [16]Marmara University, School of Medicine, Istanbul, Turkey, [17]Ondokuz Mayis University School of Medicine, Samsun, Turkey, [18]Eskisehir Osmangazi University, Eskisehir, Turkey.

Background/Purpose: Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease that occurs worldwide and predominantly affects the populations arising from the Mediterranean origin. Secondary (AA) amyloidosis still remains the most devastating complication of FMF especially in untreated and noncompliant patients. However, pathogenesis and risk factors of amyloidosis still remains only partially understood in FMF. The primary aim of this study was to investigate the prevalence of amyloidosis and its related factors in a large number of FMF patients.

Methods: Fifteen centers from the different geographical regions of Turkey were included in the study. Detailed demographic and medical data based on structured questionnaire and medical records were collected. The diagnosis of amyloidosis was based on histological proof of congophilic fibrillar deposits in tissue biopsies.

Results: There were 2246 FMF patients. The male/female ratio was 0.87 (1049/1197). The mean ages of the patients were 33.6±0.25 years. Peritonitis was the most frequent clinical finding of the patients and it was present in 94.6% of the patients. The other clinical features were fever (91.9%), pleuritis (47.9%), arthritis (39.8%), erysipelas like erythema (ELE; 23.7%), myalgia (13%) and vasculitis (2.7%). Genetic testing was available in 1719 patients (76.5%). The most frequently observed genotype was homozygous M694V mutation which was present in 413 (24%) patients. Amyloidosis was present in 193 (8.6%) patients. Male sex, arthritis, M694V genotype, patients with end stage renal disease (ESRD), family history of amyloidosis and ESRD was significantly more prevalent in patients with amyloidosis compared with the amyloidosis negative subjects (Table 1). Patients with homozygous M694V mutations had significantly increased frequency of arthritis, ELE, amyloidosis, ESRD and family history of FMF and ESRD compared to the other genotypes.

Table 1. Comparison of patients with or without amyloidosis

	Amyloidosis (+) n=193	Amyloidosis (−) n=2053	*P*
Male sex	105, (54.4)	944, (46)	0.026
Peritonitis	170, (88.1)	1956, (95.3)	<0.001
Pleuritis	73, (37.8)	1002, (48.8)	<0.001
Arthritis	99, (51.3)	796, (38.8)	0.001
Patients with ESRD	101, (52.3)	10, (0.5)	<0.001
M694V homozygosity	90, (45.6)	323, (15.7)	<0.001
Delay in the diagnosis (years)	8	7	0.147
Family history of amyloidosis	54, (28)	428, (20.8)	0.027
Family history of ESRD	32, (16.6)	81, (3.9)	<0.001

Conclusion: In this nationwide study we revealed that 8.6% of our FMF patients had amyloidosis and homozygosity for M694V was the most common mutation in these patients. The latter finding confirms the association of homozygous M694V mutation with amyloidosis in Turkish FMF patients.

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Long-Term Efficacy and Safety Of IL1 Receptor Antagonist In Schnitzler's Syndrome: A French Multicenter Study. Antoine Néel[1], Agathe Masseau[1], Sebastien Barbarot[1], Benoit Henry[2], Pierre-Jean Weiller[3], Olivier Decaux[4], Xavier Kyndt[5], Xavier Puechal[6], Arnaud Hot[7], Pierre Pottier[1], Amar Smail[8], David Launay[9], Jean-Marie Berthelot[1], Eric Hachulla[9], Leonardo Astudillo[10], Pierre-Yves Hatron[9], Laurent Sailler[10], Aurelien Lorleac'h[11], Achille Aouba[12], Bérangère Cador[4], Renato Fior[13], Robin Dhote[14], Fabrice Bonnet[15], Jean-Dominique de Korwin[16] and Mohamed Hamidou[1]. [1]Nantes University Hospital, Nantes, France, [2]Pitié-Salpêtrière University Hospital, Paris, France, [3]La Timone University Hospital, Marseille, France, [4]Rennes University Hospital, Rennes, France, [5]Hospital of Valenciennes,, Valenciennes, France, [6]Hôpital Cochin, Paris, France, [7]Edouard Herriot University Hospital, Lyon, France, [8]Amiens University Hospital, Amiens, France, [9]Claude Huriez University Hospital, Lille, France, [10]Toulouse University Hospital, Toulouse, France, [11]Lorient Hospital, Lorient, France, [12]Necker University Hospital, Paris, France, [13]Antoine Béclère University Hospital, Clamart, France, [14]Avicenne University Hospital, Bobigny, France, [15]Bordeaux University Hospital, Bordeaux, France, [16]Nancy University Hospital, Nancy, France.

Background/Purpose: Schnitzler's syndrome is a rare late onset autoinflammatory disease which associates a chronic/recurrent urticarial skin rash, a monoclonal gammopathy (mostly IgM kappa), and a variable combination of intermittent fever, osteoarticular pain, sclerotic bone lesions, lymphadenopathy and/or hepatosplenomegaly. This chronic disease can significantly alter patients' quality of life through intermittent fever, rash, pain and sometimes profound weight loss or anaemia. Patients can also develop a hematologic malignancy (mainly Waldenström's macroglobulinemia). In recent years several case reports have underscored the efficacy of Anakinra but long-term follow-up data are scare. Further, a few patients who did not respond to IL1 blockade have been reported recently.

Methods: Retrospective analysis of a French multicenter cohort of 40 patients with Schnitzler's syndrome.

Results: In this cohort mean age at disease onset was 61y (53–74). Mean diagnostic delay was 3 years. Disease manifestations included urticarial rash (100%), intermittent fever (81%), weight loss (62%), bone and/or articular pain (86%) and anaemia (Hb<10g/dL; 46%). All patients had systemic inflammation and 80% had bone lesions. Monoclonal gammopathy was IgM kappa in 85% of cases. Mean follow-up was 9 years (2–35). Twenty eight patients (70%) received Anakinra. Thirteen of those were corticodependant (mean dose: 15mg/d) when Anakinra was introduced. All 28 patients experienced a dramatic improvement of all clinico-biological signs of disease activity. Mean hemoglobin level rose from 11,2 to 13,4 g/dL ($p<0.001$). At last follow-up, all patients remained on anti-IL1 therapy. A single patient was switched to Canakinumab, due to injection site reactions to anakinra. Eighty percent of patients were in complete remission under anti-IL1 monotherapy, 11% were in complete remission under anakinra plus low dose corticosteroids and 4% were in partial remission under anakinra monotherapy. Mean follow-up under anakinra was 40 months (2–73). No loss of effectiveness was observed. In case of treatment interruption most patients experienced disease flare within 24–48 h. Alternate day injections were sufficient to maintain remission in only 4 cases. Three cases of uncomplicated neutropenia were recorded. Six patients developed severe infections including pneumonia in 5 cases, with local predisposing factor in 4 (severe COPD in 3, enteral feeding in 1). Anakinra had no obvious effect on the monoclonal component. No lymphoproliferative disease occured. When last seen, all 12 patients without anakinra had an active disease with variable impact on quality of life. Their mean corticosteroids dosage was 7mg/d.

Conclusion: Anakinra is dramatically effective in Schnitzler's syndrome. Treatment failure should lead to reconsider the diagnosis. Long-term follow-up reveals no loss of effectiveness and a favourable safety and tolerance profile. Alternate day injections are rarely sufficient to maintain remission. The effects regarding the risk of malignant transformation remain undertermined.

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Recurrent Pericarditis In Children and Adolescents: Etiology, Presentation, Therapies, and Outcomes In a Multicenter Retrospective Cohort Of 100 Patients. Antonio Brucato[1], Massimo Imazio[2], Marco Gattorno[3], Antonella Insalaco[4], Chiara Di Blasi Lo Cuccio[1], Simona Marcora[5], Rolando Cimaz[6], Luca Cantarini[7], Luciana Breda[8], Manuela Marsili[8], Fabrizia Corona[9] and Alberto Martini[10]. [1]USC Internal Medicine, Ospedale Papa Giovanni XXIII, Bergamo, Italy, [2]Maria Vittoria Hospital, Torino, Italy, [3]G. Gaslini Institute, Genova, Italy, [4]Ospedale Pediatrico Bambino Gesù, Roma, Italy, [5]Ospedale Papa Giovanni XXIII, Bergamo, Italy, [6]A. Meyer Children's Hospital, Florence, Italy, [7]Policlinico Le Scotte, University of Siena, Siena, Italy, [8]University of Chieti G. D'Annunzio, Chieti, Italy, [9]Paediatric Department University of Milano, Milano, Italy, [10]Istituto G Gaslini, Pediatria II, Reumatologia, Genova, Italy.

Background/Purpose: Acute pericarditis is defined as at least 2 of the following criteria: typical chest pain (sharp and pleuritic, improved by sitting up and leaning forward), pericardial friction rub, suggestive EKG changes (widespread ST elevation or PR depression), new or worsening pericardial effusion. Pericarditis may recur in 15–30% of cases, and these children are frequently followed by pediatric Rheumatologists. In up to 68% of pediatric patients and in more than 80% of adult cases a specific etiology cannot be detected and pericarditis is considered idiopathic. Suggested explanations of recurrences include: insufficient dose and/or duration of non-steroidal anti-inflammatory drugs (NSAIDs), early corticosteroid treatment causing increased viral replication in pericardial tissue, too rapid tapering of corticosteroids, re-infection and exacerbation of the connective tissue disease.

Methods: Multicenter, retrospective cohort study including all consecutive cases of recurrent pericarditis of patients aged <18 years with at least 2 recurrences of pericarditis seen in referral centers in Italy. The study included 100 cases of recurrent pericarditis (median 13 years, range 1–17 years, 62 males).

Results: Pericarditis was idiopathic or viral in 87.0% of cases, post-pericardiotomy in 9.0% of cases; Familial Mediterranean Fever was diagnosed in 2.0% of cases, and a systemic inflammatory disease in 2.0% of cases. The majority of children had fever and CRP elevation at disease onset (96% fever, 98% CRP elevation), and pericardial effusion (57%), while pericardial rub (25%) and EKG changes (42%) were detected in a smaller percentage of patients. Corticosteroid-treated patients experienced more recurrences, side effects, and disease-related hospitalization (for all $p<0.05$). After a median follow up of 60 months (6–360 months), 470 recurrences were recorded (median 3, range 2–25). Duration of the active disease was unpredictable in the single patient and largely variable. Overall, 97% of cases had additional recurrences. ANA testing is ongoing. Additional adverse events during follow-up included: readmission in 74% of cases and cardiac tamponade in 13% of cases (in the first attacks). None of our patients diagnosed as having an idiopathic recurrent pericarditis developed a systemic autoimmune disease; 78% children were treated with NSAIDs, 62% with steroids and in 62% cases colchicine was added. Refractory cases (17%) were treated with immunosuppressant drugs (azathioprine, methotrexate, IVIG, Plaquenil), and 7 (7%) with Anakinra. Long term outcome was good, with no evolution in constrictive pericarditis, cardiomyopathy or systemic rheumatic diseases.

Conclusion: this is the largest ever published case-series of pediatric recurrent pericarditis. NSAIDs and colchicines remain the mainstay of the therapy while corticosteroids should be used with extreme caution, particularly in pediatric patients. In cortico-dependent cases anti-IL1 drugs proved to be very effective. The long term outcome is good.

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Good, Moderate and Poor Outcome Trajectories Of Pain Severity In Early Symptomatic Knee Osteoarthritis; 5 Year Follow-Up Of *Check* study. Janet Wesseling[1], Alex N. Bastick[2], Sita M.A. Bierma-Zeinstra[2] and Johannes W.J. Bijlsma[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Erasmus MC - University Medical Center, Rotterdam, Netherlands.

Background/Purpose: Knee pain is often the first sign of knee OA (osteoarthritis) and it is known that its course can be very different between patients over time. This study identifies distinct groups of patients with different trajectories of pain in symptomatic knee OA, and describes lifestyle and coping characteristics for each trajectory of pain. Lifestyle factors might be important elements for prevention, since they are modifiable in nature. Yet de role of lifestyle factors in different pain trajectories in early OA is unclear.

Methods: Longitudinal data of five years follow-up of the CHECK (Cohort Hip and Cohort Knee) study was used. Participants had pain of knee, were aged 45–65 years, and had not yet consulted their physician for these symptoms or the consultation occurred within 6 months before inclusion. Pain severity was measured with numeric rating scale (0–10). Latent class growth analysis identified homogenous subgroups with distinct trajectories of pain. Multinomial regression analysis was used to examine different lifestyle and coping characteristics between the trajectories.

Results: Longitudinal data of 5 years follow-up of 705 participants with symptomatic knee OA was analyzed. Three pain trajectories were identified based on their outcome: good, moderate and poor outcome. Participants with good outcome trajectory (n=222) had over time a slight decrease in pain severity and ended up with a low pain severity. Participants with moderate outcome trajectory (n=294) had a stable course of moderate pain over time. The poor outcome trajectory participants (n=189) had an increase of pain severity over time and ended up with severe pain. Compared to the good outcome group, participants in the moderate and poor outcome group were characterized by higher BMI (both OR's 1.1; p=0.01), smoking (moderate outcome group OR=1.7, p=0.1; poor outcome group OR= 2.3, p=0.02) by using passive coping strategies worrying (moderate outcome group OR= 2.3, p=0.01; poor outcome group OR=3.7, p<0.001) and resting (moderate outcome group OR= 1.5, p=0.1; poor outcome group OR=2.4, p=0.002). The passive coping strategy 'retreating' reduced the chance of belonging to the poor outcome group (moderate outcome group OR= 0.6, p=0.05; poor outcome group OR=0.5, p=0.01). Baseline radiographic features of OA did not differ between the trajectories and did not have an association with the trajectories. However change from baseline to follow-up of radiological features (Kellgren & Lawrence grade and osteophyte area) differed between poor and good outcome.

Conclusion: This study identified 3 trajectories of pain: good, moderate and poor outcome. Unhealthy lifestyle characteristics (high BMI and smoking) and passive coping strategies (worrying and resting) characterized the poor outcome group. The pain evolution of the participants in the poor outcome trajectory corresponds with an increase in radiological damage (Kellgren & Lawrence grade and osteophyte size). Distinguishing different trajectories could have implications for the treatment. Treatment for each pain trajectory in early OA might be tailored to lifestyle and coping characteristics.

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Relationship Of Pre-Radiographic MRI Lesions With Prevalent Frequent Knee Symptoms and Incident Persistent Knee Symptoms In Persons At Higher Risk For Knee Osteoarthritis. Leena Sharma[1], Joan S. Chmiel[1], Orit Almagor[2], Dorothy D. Dunlop[1], Marc C. Hochberg[3], Charles Eaton[4], C. Kent Kwoh[5], Rebecca D. Jackson[6], Joan M. Bathon[7], Ali Guermazi[8], Frank Roemer[9], Michel Crema[8], W. Jerry Mysiw[6] and Michael C. Nevitt[10]. [1]Northwestern University, Chicago, IL, [2]Northwestern University Medical School, Chicago, IL, [3]University of Maryland, Baltimore, MD, [4]Brown University, Providence, RI, [5]University of Pittsburgh, Pittsburgh, PA, [6]Ohio State University, Columbus, OH, [7]Columbia University, New York, NY, [8]Boston University, Boston, MA, [9]Klinikum Augsburg, Augsburg, Germany, [10]University of California, San Francisco, San Francisco, CA.

Background/Purpose: The clinical significance of pre-radiographic MRI lesions in persons at risk for knee OA is unclear. Understanding whether such lesions are inconsequential or early disease will aid prevention and disease-modifying strategy design. We hypothesized, in persons at risk but without radiographic OA, that cartilage damage, bone marrow lesions (BML), meniscal tear (MT), and meniscal extrusion (ME) are each associated with 1) prevalent frequent knee symptoms and 2) incident persistent knee symptoms.

Methods: The Osteoarthritis Initiative is a cohort study of men and women age 45–79 years with or at increased risk to develop knee OA. 850 participants were bilateral K/L 0 at 12 months. In their 12-month right knee (left if right inadequate) MR images, we assessed cartilage, BML, MT, and ME using a modified MOAKS system, blinding readers to hypotheses and all other data. At baseline, of the 850, 578 were without frequent knee symptoms (knee symptoms or medication use for knee symptoms most days of a month in the past 12 months). Incident persistent knee symptoms were defined as frequent knee symptoms at 2 consecutive annual OAI visits. Multiple logistic regression models evaluated associations between each lesion and 1) prevalent frequent symptoms and 2) incident persistent symptoms by 60 months, adjusting for age, gender, BMI, knee injury, and knee surgery.

Results: As shown in Table 1, cartilage damage, BML, and ME were each associated with prevalent frequent knee symptoms. As shown in Table 2, cartilage damage and BML (particularly patellofemoral), and MT were each associated with incident persistent symptoms.

Table 1. Pre-radiographic MRI Lesions and Risk of Prevalent Frequent Knee Symptoms

	Number of knees (1 knee per person)	Number of knees (row%) with frequent knee symptoms	OR (95% CI) Unadjusted	OR (95% CI) Adjusted for age, gender, BMI, previous knee injury, previous knee surgery
Cartilage damage (TF or PF)	642	178 (27.7%)	***1.81 (1.21, 2.69)***	***1.75 (1.16, 2.63)****
Cartilage damage (TF only)	118	27 (22.9%)	0.86 (0.54, 1.36)	0.78 (0.49, 1.26)*
Cartilage damage (PF only)	257	64 (24.9%)	0.98 (0.70, 1.37)	0.95 (0.67, 1.35)*
Cartilage damage (TF and PF)	266	87 (32.7%)	***1.73 (1.26, 2.40)***	***1.85 (1.32, 2.59)****
No cartilage damage *(TF or PF)*	208	36 (17.3%)	reference	reference
BML (TF or PF)	515	155 (30.1%)	***2.00 (1.42, 2.80)***	***1.95 (1.38, 2.76)****
BML (TF only)	79	21 (26.6%)	1.08 (0.64, 1.82)	1.04 (0.60, 1.79)*
BML (PF only)	289	84 (29.1%)	1.34 (0.98, 1.87)	1.38 (0.99, 1.92)*
BML (TF and PF)	147	50 (34.0%)	***1.68 (1.15, 2.47)***	***1.62 (1.09, 2.40)****
No BML (TF or PF)	335	59 (17.6%)	reference	reference
MT	180	51 (28.3%)	1.22 (0.84, 1.77)	1.22 (0.82, 1.81)*
No MT	670	163 (24.3%)	reference	reference
ME	117	39 (33.3%)	***1.58 (1.04, 2.41)***	***1.67 (1.08, 2.59)****
No ME	733	175 (23.9%)	reference	reference

n = 850 persons K/L 0 in both knees [mean age 59.6 years (8.8, SD), BMI 26.7 kg/m^2 (4.2), 475 (55.9%) women].
TF = tibiofemoral, PF = patellofemoral)
* BMI also significant

Table 2. Pre-radiographic MRI Lesions and Risk of Incident Persistent Knee Symptoms

	Number of knees (1 knee per person)	Number of knees (row%) with incident persistent knee symptoms	OR (95% CI) Unadjusted	OR (95% CI) Adjusted for age, gender, BMI, previous knee injury, previous knee surgery
Cartilage damage (TF or PF)	423	86 (20.3%)	***1.94 (1.13, 3.35)***	1.72 (0.98, 3.02)*
Cartilage damage (TF only)	84	13 (15.5%)	1.39 (0.65, 3.01)	1.17 (0.51, 2.73)*
Cartilage damage (PF only)	178	38 (21.3%)	***2.07 (1.12, 3.80)***	***1.98 (1.04, 3.75)****
Cartilage damage (TF and PF)	161	35 (21.7%)	***2.11 (1.14, 3.92)***	***2.00 (1.04, 3.84)***
No cartilage damage *(TF or PF)*	155	18 (11.6%)	reference	reference
BML (TF or PF)	337	75 (22.3%)	***2.09 (1.31, 3.33)***	***1.90 (1.18, 3.06)****
BML (TF only)	48	9 (18.8%)	1.69 (0.74, 3.84)	1.42 (0.58, 3.45)**
BML (PF only)	197	43 (21.8%)	***2.04 (1.22, 3.42)***	***1.82 (1.07, 3.08)***
BML (TF and PF)	92	23 (25.0%)	***2.44 (1.32, 4.49)***	***2.31 (1.24, 4.31)***
No BML (TF or PF)	241	29 (12.0%)	reference	reference
MT	109	30 (27.5%)	***2.03 (1.24, 3.30)***	***1.97 (1.17, 3.33)****
No MT	469	74 (15.8%)	reference	reference
ME	61	18 (29.5%)	***2.10 (1.16, 3.81)***	1.69 (0.90, 3.18)*
No ME	517	86 (16.6%)	reference	reference

*BMI also significant
**Previous surgery also significant
n = 578 persons K/L 0 in both knees and without frequent knee symptoms at baseline [mean age 59.3 years (9.0), BMI 26.6 kg/m^2 (4.3), 324 (56.1%) women].

Conclusion: In persons at higher risk but without any evidence of radiographic knee OA, cartilage damage, BML, ME, and BMI were associated with prevalent frequent knee symptoms, and cartilage damage, BML,

MT, and BMI with the new development of persistent symptoms by 5 years. These findings suggest that these lesions, in persons at higher risk for knee OA, are clinically significant and may represent early disease.

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Trajectory Of Cartilage Thickness Change During The Years Prior To Knee Replacement: Data From The Osteoarthritis Initiative. Felix Eckstein[1], Robert M. Boudreau[2], Zhijie Wang[3], Michael J. Hannon[3], Wolfgang Wirth[1], Sebastian Cotofana[1], Ali Guermazi[4], Frank Roemer[5], Michael C. Nevitt[6], Markus John[7], Christoph Ladel[8], David J. Hunter[9] and C. Kent Kwoh[2]. [1]Paracelsus Medical University, Salzburg, Austria, [2]University of Pittsburgh, Pittsburgh, PA, [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, [4]Boston University, Boston, MA, [5]Klinikum Augsburg, Augsburg, Germany, [6]University of California, San Francisco, San Francisco, CA, [7]Novartis Pharma AG, Basel, Switzerland, [8]Merck KG, Darmstadt, Germany, [9]University of Sydney, Sydney, Australia.

Background/Purpose: Knee replacement (KR) represents a clinically important and cost-effective endpoint of knee osteoarthritis (OA). We have shown previously that, in a year prior to KR, medial cartilage loss (measured quantitatively with MRI) was greater in knees with KR than in controls, who displayed the same (baseline) radiographic disease stage. The best discrimination was observed in the central medial tibia (cMT). However, the trajectory of the more long-term cartilage thickness change prior to KR is unknown. The purpose of this study therefore was to examine rates of cartilage loss up to 4 years prior to KR.

Methods: We studied knees from the Osteoarthritis Initiative (OAI) who received a KR between 12–60 month follow-up (12M–60M). Each knee with KR was matched with one control who did not receive a KR through 60M by sex, baseline KLG (0–1, 2, 3, 4 strata), and age (±5y). Sagittal 3T DESSwe MR images were used for segmenting the weight-bearing femoro-tibial cartilages (Chondrometrics GmbH), with blinding to acquisition order. The visit directly prior to KR (T0) and those 12, 24, 36, and 48 months prior to T0 (i.e. T-1 through T-4) were analyzed as available. Cartilage thickness in cMT was selected as the primary and that in the total medial compartment (MFTC) as the secondary endpoint. Comparisons included paired t-tests between case/control pairs, and conditional logistic regression model, with and without adjustment for pain and BMI at the beginning of the respective observation interval.

Results: 220 knees of 190 OAI participants received a KR up to 60M (37@24M, 60@36M, 58@48M, and 65 @60M). Of these, 189 (58 baseline KLG 0–2, 69 KLG3, and 62 KLG4) had MRIs for at least one longitudinal interval, and a matched control (age 64±8.7; BMI 29±4.5; 85 male; 104 female). Analysis of slopes of annual change from all available time points revealed significantly greater rates of cMT cartilage loss in KRs than in controls (n=189: 94±137 vs. 55±104μm; p=0.0017; odds ratio [OR] = 1.36 [95% CI: 1.11;1.66] without, and 1.34 [1.09;1.66] with adjustment for pain and BMI). Between T-1 and T0, cMT cartilage loss was 2.9× that in controls (n=152: 114±209 vs. 39±159μm; p=0.0007, OR 1.42 [1.14;1.75] without, and 1.48 [1.18;1.86] with adjustment). The difference was less in previous time intervals (≤1.7x), but stronger for the T-2 to T0 period (n=127: 209±281 vs. 61±156μm [3.4x]; p<0.0001, OR=1.61 [1.29;2.01] without, and 1.64 [1.30;2.06] with adjustment). However, no significant difference was observed during T-4 to T-2 (n=60: 119±255 vs. 125±175μm; p=0.86, OR=0.97 [0.71;1.33] without, and 1.21 [0.81;1.81] with adjustment). Results for MFTC were similar to those for cMT.

Conclusion: The rate of medial cartilage loss was substantially greater in knees with KRs than in those without during a two-year period prior to T0 (i.e. within 2 years proximate of the timing of the KR), even after matching for baseline radiographic disease status. During earlier time intervals (i.e. 4 to 2 years prior to T0) the rates of medial cartilage loss were not different between KRs and controls. This trajectory of cartilage thickness change resembles that observed for change in symptoms prior to KR.

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The Clinical Significance and Natural History Of Knee Bone Marrow Lesions Over 8 Years. Yi Chao Foong[1], Hussain Ijaz Khan[1], Dawn Aitken[1], Changhai Ding[1], Flavia Cicuttini[2] and Graeme Jones[1]. [1]Menzies Research Institute Tasmania, University of Tasmania, Hobart, 7000, Australia, [2]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, 3004, Australia.

Background/Purpose: There is increasing evidence to suggest that bone marrow lesions (BMLs) play a key role in the pathogenesis of OA. Whilst many studies have focused on short and medium term changes in BMLs, no study has explored BMLs over longer timeframes. The aim of this study was to describe the natural history of knee BMLs and their association with knee pain over eight years.

Methods: 199 subjects which consisted of 109 adult offspring of subjects who had a knee replacement and 90 controls who were initially matched by age and sex were studied. BMLs were measured at the two and ten year follow-ups using T2 weighted fat saturation MRI measuring the maximum area of the lesion at the medial and lateral tibial/femoral and patella sites. Knee pain was assessed by the Western Ontario and McMaster Universities Arthritis Index (WOMAC).

Multiple linear and logistic regression models were performed to investigate potential associations between BMLs and pain.

Results: At the two year follow-up, 64% of participants (n=128/199) had one or more BMLs, with a total of 231 BMLs present. Over eight years, of the 231 BMLs, 71% (164/231) increased in size, 8% (18/231) remained stable and 21% (49/231) decreased in size or resolved completely (Figure 1). Of those participants with no BMLs at baseline (71/199), 52% (37/71) developed one or more incident BMLs. In the whole sample, 31% of participants (62/199) developed a new BML at 1 site, 22% (44/199) at 2 sites, 9% (18/199) at 3 sites and 1% (2/199) at 4 sites or more. BML natural history did not vary between offspring and controls.

After adjusting for age, sex and BMI, the development of a new BML was associated with developing pain in those without pain at baseline (β=3.71, 95% CI 1.02–6.41). Those with a large BML at two years also had greater odds of having pain at ten years (OR=1.95, 95% CI 1.05–3.62). Eight year change in total BML size predicted an increase in total WOMAC pain in offspring but not controls (Table 1). The magnitude of the association in offspring was stronger in males as compared to females.

Table 1. Change in WOMAC pain score per change in BML size (linear regression)

	Univariable β (95% CI)	Multivariable* β (95% CI)	Females* β (95% CI)	Males* β (95% CI)
Total	0.46 (−0.17, 1.08)	0.47 (−0.16, 1.11)	0.14 (−0.58, 0.87)	**2.49 (0.86, 4.12)**
Controls	−0.09 (−0.71, 0.53)	−0.04 (−0.69, 0.60)	−0.14 (−0.93, 0.66)	1.56 (−1.10, 4.23)
Offspring	**2.68 (1.22, 4.13)**	**2.65 (1.20, 4.10)**	**2.22 (0.10, 4.34)**	**3.17 (1.04, 5.31)**

*Adjusted for age, sex, BMI.
βcoefficients are the change in pain score per unit change in BML size (cm^2).

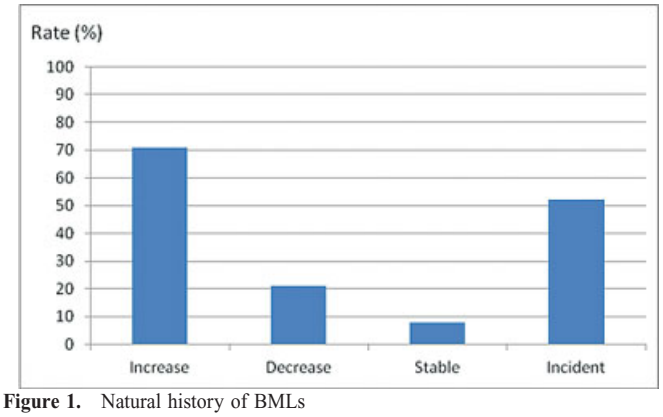

Figure 1. Natural history of BMLs

Conclusion: Over eight years, the proportion of BMLs increasing in size was more than triple those decreasing in size and stable BMLs were rare.

Incident BMLs were common, with slightly over half of our participants developing new BMLs, whilst one-fifth of BMLs resolved. Change in BML size was associated with pain only in those with a strong family history of OA, suggesting that knee pain associated with BMLs may have a genetic component.

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2756

Serum Periostin Is Associated With Prevalent Knee Osteoarthritis and Predicts Disease Progression In Women: The Ofely Study. Jean-Charles Rousseau[1], Elisabeth Sornay-Rendu[1], Cindy Bertholon[1], Patrick Garnero[2] and Roland Chapurlat[3]. [1]INSERM UMR 1033, Lyon, France, [2]INSERM, UMR 1033, Lyon and Cisbio Bioassays, Bagnols/Cèze, France, [3]INSERM UMR 1033 and Université de Lyon, Hôpital Edouard Herriot, Lyon, France.

Background/Purpose: Periostin (POSTN) is a secreted vitamin K-dependent (Gla-containing) protein produced by osteoblasts and chondrocytes. The aim of this study was to investigate the relationships between serum POSTN and both prevalent and incident knee osteoarthritis in women.

Methods: We investigated 753 women (mean age: 62.7 ± 11.2 yr) from the OFELY (Os des Femmes de Lyon) cohort, 19.3 % being premenopausal. Knee radiographs were performed and scored according to Kellgren & Lawrence at the ninth annual follow-up (baseline for this analysis) and 4 years later. Progression of knee OA was defined as an increase of the KL score ≥ 1 during the 4 years follow-up. Evaluation of the spine (X-rays), hip (self-reported) and hand OA (clinical exam) have been performed at the same visit. Serum POSTN was measured at baseline by ELISA (USCNK, China).

Results: Serum POSTN was significantly lower in the 110 women with a KL score ≥ 2 at baseline, compared to the 481 controls with a KL score < 2 (1118.9 ± 307 ng/ml vs 1182.3 ± 292 ng/ml, p = 0.018 after adjustment for age). During the 4 year follow-up, 181 women had a radiological progression in their knee OA. Baseline POSTN levels were significantly lower in progressors than in non progressors (1140 ± 296 vs 1182 ± 294 ng/ml, p = 0.039 after adjustment for age and for the presence of prevalent knee, spine, hip and hand OA**).** For each increase of one POSTN quartile, the risk of progression decreased by 0.82 (IC: 0.69–0.98, p = 0.034) after adjustment for age and for OA at the other anatomical sites.

Conclusion: We showed for the first time that serum POSTN is associated with prevalence and progression of knee OA in women. This biomarker may be of interest to study OA pathophysiology.

Disclosure: J. C. Rousseau, None; **E. Sornay-Rendu**, None; **C. Bertholon**, None; **P. Garnero**, None; **R. Chapurlat**, None.

2757

Metabolomics For The Identification Of Urinary Biomarkers In Knee Osteoarthritis Progression. Puja Saxena[1], Richard F. Loeser[2], Wimal Pathmasiri[3], Susan Sumner[3], Daniel Beavers[1], David J. Hunter[4] and Stephen P. Messier[5]. [1]Wake Forest University School of Medicine, Winston-Salem, NC, [2]Wake Forest School of Medicine, Winston-Salem, NC, [3]NIH Eastern Regional Comprehensive Metabolomics Resource Core, Research Triangle Park, NC, [4]University of Sydney, Sydney, Australia, [5]Wake Forest University, Winston-Salem, NC.

Background/Purpose: Obesity is an important risk factor for knee OA, not only due to effects of excess adipose tissue on joint loading, but also due to potential metabolic effects. It is not known if metabolic differences in people with OA might contribute to OA progression. The purpose of this study was to use a metabolomics approach to determine if a metabolic signature could distinguish overweight and obese adults with knee OA who exhibited radiographic progression during an 18 month exercise and/or weight loss intervention from those who did not progress.

Methods: Urine samples collected from 24 overweight or obese participants in the Intensive Diet and Exercise for Arthritis (IDEA) trial at baseline and at 18 months of follow-up were selected from two subgroups (n=12 each): a group that exhibited radiographic progression of knee OA and an age, race, sex, and BMI matched group who did not progress. Progression was defined as a decrease in medial joint space width of ≥ 0.7mm from baseline to 18 months (knees flexed at a 15° angle using a positioning device and the x-ray beam centered on the joint space). Non-progressors were defined as individuals who had a decrease in joint space width of ≤0.35mm.

Morning second void urine samples were collected at baseline and 18 months. After centrifuging and addition of internal standards, ^{1}H NMR spectra were acquired using a 950 MHz NMR spectrometer for each study sample and for a quality control sample prepared by pooling individual samples NMR data was processed by automated integration over the spectral window, and bins were normalized to the total intensity for each spectrum. Principal component analysis (PCA) and orthogonal partial least square discriminate analysis (OPLS-DA) were used to reduce the dimensionality and enable visualization of the separation of progressors and non-progressors. NMR bins that distinguished the study phenotypes were determined based on inspection of loadings plots and variable importance plots. Bins that distinguished the study groups were mapped to corresponding metabolites.

Results: The median age of this IDEA subgroup was 67 yrs. (range 60–78) and median BMI was 31.2 kg/m^2 (range 27.0–40.4). The mean minimum JSW change was −1.03 (SD=0.29, range −1.7 to −0.76) mm for progressors and 0.05 (SD=0.28 range −0.26 to +0.68)mm for non-progressors. After applying PCA, two outliers (non-progressors) with high levels of urine glucose were excluded. Using OPLS-DA, five urinary metabolites were determined that separated the progressors from non-progressors. At baseline, relatively higher levels of hippurate and glycolate and lower levels of lysine were identified in progressors. At 18 month follow-up, relatively higher levels of hippurate, glycolate, and sarcosine and lower levels of lysine and choline characterized the progressor group.

Conclusion: Metabolic differences were found for the first time to correlate with radiographic progression in overweight and obese adults with knee OA. These results merit further investigation in a larger sample set. Given that hippurate is a gut-flora derived metabolite, differences in the gut microbiome could be contributing to OA progression.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects V: Observational Studies in Rheumatoid Arthritis
Tuesday, October 29, 2013, 4:30 PM–6:00 PM

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Quantifying The Risk Of Incident Type II Diabetes Following Oral Glucocorticoid Therapy In Patients With Rheumatoid Arthritis: Association With Dose and Duration Of Use. William G. Dixon[1], Mohammad Movahedi[1], Marie-Eve Beauchamp[2], David W. Ray[3] and Michal Abrahamowicz[2]. [1]The University of Manchester, Manchester, United Kingdom, [2]McGill University, Montreal, QC, [3]Institute of Human Development, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Glucocorticoid (GC) therapy is widely used in patients with rheumatoid arthritis (RA). Its association with incident type II diabetes mellitus (DM) is accepted, but the extent of the risk and its relationship with GC dose and treatment duration in RA are not known.

Methods: Adult patients with RA were identified from a large UK primary care research database using a validated algorithm during the study period 1992–2009. Patients with prevalent DM at the time of their first code for RA were excluded. GC exposure was identified from oral GC prescriptions and was analysed using multivariable time-dependent Cox models with conventional exposure measures (eg on/off treatment) and a novel weighted cumulative dose (WCD) model that accounted for

past doses and treatment duration and timing. Incident DM was defined as a READ code for type II DM, at least two oral anti-diabetic prescriptions or abnormal blood results (blood sugar, HbA1C or glucose tolerance test). Hazard ratios (HR) associated with different GC patterns were adjusted for gender, age, family history of DM, hypertension, prior cumulative dose of oral GC, current DMARDs and ever NSAID use.

Results: 22,535 adult RA patients were included. 70% were female with a median age of 60 years (IQR 49–71). Median follow-up time per patient was 5.4 years. 2,324 patients were diagnosed with type II DM during follow-up: incidence 13.7 events/1000 person years (pyrs) in unexposed patients versus 21.8 events/1000pyrs after GC exposure. Ignoring dose and duration, the conventional HR was 1.42 (1.30–1.56) in ever GC users compared with non-users. This equates to one additional case of DM per year for every 172 patients who received GCs at some time in the past. The WCD model showed risk increased with increased dose and duration of recent use, especially in the past 8 months. 5mg prednisolone equivalent (PEQ) for past 1, 3 and 6 months were associated with HRs of 1.14, 1.36 and 1.46, respectively, compared to non-use. Doses more than eight months ago added little to the current risk of DM, e.g. increasing the duration of 5mg PEQ exposure from the past 6 to 12 months increased the HR to only 1.49 compared to non-use. Risk increased significantly with dose: 30mg PEQ for 1, 3 or 6 months generated HRs of 2.2, 6.3 and 9.8, respectively, compared to non-use. 5mg or 30mg PEQ for 6 months equates to one additional case for every 140 or 7 patients treated, respectively.

Conclusion: Oral GC therapy is a clinically important and quantifiable risk factor for incident Type II DM in patients with RA, influenced by dose and duration of exposure within the last eight months.

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2759

Can RA Registries Provide Contextual Safety Data For Modern RCTs? Kaleb Michaud[1], Johan Askling[2], Hisashi Yamanaka[3], Deborah Symmons[4], Marie Holmqvist[2], Thomas Frisell[2], George Reed[5], Dimitrios A. Pappas[6], Eiichi Tanaka[3], Eisuke Inoue[3], Suzanne M.M. Verstappen[4], Christopher Garwood[4], Laura Horne[7], Kathy Lampl[7], Niklas Berglind[8], Stefan Franzen[8], Fredrik Nyberg[9], Trung Tran[10], Meilien Ho[11] and Jeffrey D. Greenberg[12]. [1]National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE, [2]Karolinska Institutet, Stockholm, Sweden, [3]Tokyo Women's Medical University, Tokyo, Japan, [4]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [5]University of Massachusetts Medical School, Worcester, MA, [6]Columbia University, New York, NY, [7]AstraZeneca R&D Wilmington, Wilmington, DE, [8]AstraZeneca R&D Mölndal, Mölndal, Sweden, [9]AstraZeneca R&D, Mölndal, Sweden, [10]MedImmune LLC, Gaithersburg, MD, [11]AstraZeneca R&D Alderley Park, Macclesfield, United Kingdom, [12]NYU Hospital for Joint Diseases, New York, NY.

Background/Purpose: For ethical reasons, modern phase-III RCTs in rheumatoid arthritis (RA) have limited placebo exposure time, resulting in uncertainties when interpreting low frequency adverse events (AEs). We developed and implemented a novel method for providing contextual AE rates through coordinated analyses of 5 RA registries.

Methods: Participating observational registries included CORRONA (USA), CORRONA International (East Europe, India, Latin America), IORRA (Japan), NOAR (UK), and SRR (Sweden). By harmonizing AE definitions in a typical RA clinical trial program and corresponding available outcomes from the registries we defined specific outcomes in 4 areas: mortality, cardiovascular disease (CVD), infection, and malignancy. Each registry defined a primary cohort (all patients included from January 2000) for optimal sample size. To address comparability and potential bias several sub-cohorts were also defined for sensitivity analyses, based on disease activity, treatment, calendar time or duration of follow-up, and relevant RCT exclusions. Rates were standardized for the potential confounders age and sex, and in a sensitivity analysis also HAQ score to the distribution in a typical RA program.

Results: The primary cohorts included 57,251 RA patients (232,985 person-years [PY]) - mean (SD) baseline age 58.2 (13.8) years, 24.5% men, and RA duration 8.2 (11.7) years (Table 1). Some important demographic differences appeared; for example, smoking was most common in NOAR, and SRR had the highest proportion with early RA. Mean baseline HAQ and DAS28 were 0.88 (0.67) and 4.1 (1.5).

Specific outcome event rates were determined in each registry (Table 2). CVD rates varied the most with the lowest MI rate (0.09 per 100 PY) seen in IORRA and the highest (0.39) in SRR. Rates of hospitalized infections were quite consistent across registries. Sensitivity analysis returned higher mortality and MACE rates along with wider confidence intervals when standardized also for RCT HAQ levels. Additional sub-cohort analyses showed small and mostly consistent changes among registries.

Table 1. Baseline characteristics in 5 RA registries' primary cohorts.

Baseline characteristic	CORRONA	SRR	NOAR	CORRONA Int.	IORRA
Region	USA	West Europe		Other	
N	24,176	18,527	1,564	2,727	10,255
Age, >60 (%)	47.3	54.1	51.0	34.7	41.0
Gender, female (%)	76.0	70.3	69.9	84.7	82.2
Smoking, ever (%)	38.1	NA	66.9	26.5	37.7
RA duration, >5 yrs (%)	56.8	29.6	44.9	61.2	51.5
SJC, mean (SD)	4.3 (5.5)	6.3 (5.7)	5.8 (5.1)	2.9 (4.3)	2.8 (3.4)
TJC, mean (SD)	4.2 (5.8)	5.8 (5.8)	7.7 (8.3)	5.7 (6.7)	2.8 (3.8)
CRP, <10 mg/L (%)	72.4	47.3	37.8	64.9	62.8
DAS28, >3.2 (%)	58.3	75.9	75.0	67.4	70.5
HAQ, >1.1 (%)	35.0	39.2	54.5	49.3	30.3
RF^+ (%)	72.4	71.7	89.6	75.3	78.8
MTX from baseline (%)	64.6	71.5	33.8	68.9	74.7
Other nb-DMARDs from baseline (%)	30.1	22.4	24.2	52.8	76.2

Table 2. Standardized incidence rates (with 95% confidence intervals)* per 100 person-years of selected outcome events in 5 RA registries' primary cohorts.

Event	CORRONA	SRR	NOAR	CORRONA-INT	IORRA
All-cause mortality	0.42 (0.38, 0.46)	0.67 (0.63, 073)	0.80 (0.66, 0.98)	NA	0.74 (0.67, 0.81)
Major adverse cardiovascular events (MACE)	0.45 (0.40, 0.50)	0.77 (0.71, 0.83)	0.50 (0.39, 0.66)	0.36 (0.15, 0.81)	0.31 (0.26, 0.37)
Acute myocardial infarction (MI)	0.21 (0.18, 0.25)	0.39 (0.35, 0.43)	0.21 (0.14, 0.33)	NA	0.09 (0.07, 0.13)
Stroke	0.20 (0.17, 0.24)	0.31 (0.27, 0.35)	0.16 (0.10, 0.27)	NA	0.12 (0.09, 0.16)
Hospitalized congestive heart failure (CHF)	0.20 (0.11, 0.38)	0.16 (0.14, 0.19)	0.13 (0.07, 0.24)	0.42 (0.16, 0.92)	NA
Hospitalized infection	1.30 (1.18, 1.42)	1.62 (1.52, 1.72)	1.56 (1.30, 1.88)	1.51 (0.99, 2.24)	1.14 (1.05, 1.25)
Malignancies excluding non-melanoma skin cancer (NMSC)	0.64 (0.58, 0.71)	0.87 (0.80, 0.94)	0.77 (0.60, 0.99)	0.56 (0.27, 1.07)	0.65 (0.57, 0.75)
Solid malignancies	0.53 (0.47, 0.58)	0.86 (0.80, 0.94)	0.88 (0.70, 1.10)	0.37 (0.16, 0.81)	0.58 (0.49, 0.67)
Lymphomas	0.06 (0.04, 0.08)	0.06 (0.04, 0.08)	0.09 (0.03, 0.21)	NA	0.06 (0.04, 0.10)

* Standardized according to the age and sex distribution in a typical RA clinical trial program.
= Not Available. Too few events - incidence rates not calculated

Conclusion: While potential concern for bias may remain, we have successfully determined background safety rates that provide context for RCTs, through a coordinated approach between observational RA registries. This new approach may have utility to satisfy future regulatory requirements and support safety assessments.

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Incidence and Severity Of Myocardial Infarction In Subjects Receiving Anti Tumour Necrosis Factor Drugs For Rheumatoid Arthritis: Results From Linking the British Society For Rheumatology Biologics Register For Rheumatoid Arthritis and Myocardial Ischaemia National Audit Project. Audrey SL Low[1], Kimme L. Hyrich[2], Mark Lunt[3], Louise K. Mercer[1], Christopher Gale[4], Kath Watson[1], British Society for Rheumatology Biologics Registers (BSRBR) Control Centre Consortium[1], William G. Dixon[5], Deborah P. Symmons[3] and On behalf of the BSRBR[6]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Sciences Centre, Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom, [3]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [4]Department of Cardiology, York Teaching Hospital NHS Foundation Trust, York, United Kingdom, [5]The University of Manchester, Manchester, United Kingdom, [6]British Society for Rheumatology, London, United Kingdom.

Background/Purpose: Subjects with rheumatoid arthritis (RA) are at increased risk of myocardial infarction (MI) compared to subjects without RA, with the increased risk potentially driven by inflammation. Anti- tumour necrosis factor (TNFi) drugs may modulate the risk and severity of the MI. The aim of this analysis was to compare the risk and severity of MI in subjects treated with TNFi to non-biologic drugs (nbDMARDs) using linked data from BSRBR-RA (an ongoing prospective study of the safety of biologic therapy in RA) and the Myocardial Ischaemia National Audit Project (MINAP), a national database of hospitalisations with MI in England and Wales.

Methods: This analysis included subjects with RA starting TNFi (etanercept, infliximab, adalimumab) and a biologic-naïve comparator cohort receiving nbDMARDs recruited between 2001–2008; all followed via physician and patient questionnaires and flagged with the national death register. All subjects were also linked to MINAP using deterministic matching which provided both additional events and further event data regarding MI severity. Events from both datasets were verified using the American Heart Association/European Society of Cardiology criteria for MI with additional criteria of thrombolysis/angioplasty and MI listed as the underlying cause of death on death certificates, coded using International Classification of Diseases 10. When estimating incidence of MI, subjects were censored at first MI, death, 90 days following discontinuation of TNFi, last physician follow-up or 04/20/2010, whichever came first. The risk of MI was compared between subjects receiving nbDMARDs and TNFi using a Cox regression model, adjusted on deciles of propensity scores (PD) (Table). In a subset of MIs with additional event data from MINAP; MI phenotype and severity (using surrogates: cardiac arrest, peak creatine kinase (CK) levels and length of hospital stay) were compared between treatment groups using descriptive statistics.

Table.

	nbDMARD (n=3058)	TNFi (n=11200)	p-value
Years of follow-up per subject, median (IQR)	3.5 (1.8, 4.9)	5.3 (3.6, 6.4)	–
Person-years of exposure, pyrs	10337	55636	–
Number of verified MIs	58	194	–
Crude incidence rate of verified MIs from BSRBR & MINAP per 10,000 person-years (95% CI)	56 (43, 73)	35 (30, 40)	–
Risk of MI between nbDMARD and TNFi-treated subjects: Unadjusted HR (95%CI)	Referent	0.78 (0.58, 1.05)	–
Risk of MI between nbDMARD and TNFi-treated subjects: PD-adjusted HR (95% CI)	Referent	0.61 (0.41, 0.89)	–
Number of verified MIs with additional MINAP data	35	108	–
Phenotype of MI: n (%) of STEMI	16 (46)	53 (49)	0.32
Median peak CK, IU/L (IQR)	290 (172, 1598)	691 (150, 1293)	0.19
Cardiac arrest, n (%)	3 (8.6)	5 (4.7)	0.48
Median length of hospital stay, days (IQR)	6 (5, 9)	6 (4, 8)	0.46

Variables in PD: age, gender, disease duration, DAS28, HAQ score, steroid use, number of previous nbDMARDs, entry year to study, hypertension, diabetes, smoking, chronic lung disease, aspirin, statin, NSAID/COX2-inhibitor use, all at baseline.

Results: Using the linked data, a total of 252 verified first MIs were analysed: 58 in 3058 nbDMARD subjects and 194 in 11200 TNFi-treated subjects. The PD-adjusted hazard ratio (HR) of MI in TNFi referent to nbDMARD was 0.61 (95%CI 0.41, 0.89). The estimate was unchanged when all follow-up time following first dose of TNFi was included. There were 143 MIs (nbDMARD: 35, TNFi: 108) with additional MINAP data. No statistical differences were observed in MI severity when compared between nbDMARD and TNFi-treated subjects, although there was a trend towards higher peak CK levels recorded in TNFi-treated subjects (Table).

Conclusion: Subjects receiving TNFi drugs had a decreased risk of MI compared to subjects receiving nbDMARDs over the medium term which could relate to attributes of the drug itself or better overall disease control. The severity of MIs at presentation appears to be similar between both treatment groups.

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Comparative Risks Of Herpes Zoster Among RA Patients Switching Biologics In The U.S. Medicare Program. Huifeng Yun[1], Fenglong Xie[1], Elizabeth S. Delzell[1], Lang Chen[1], Emily Levitan[1], James Lewis[2], Kenneth G. Saag[1], Timothy Beukelman[1], Kevin L. Winthrop[3], John Baddley[1] and Jeffrey R. Curtis[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Pennsylvania, Philadelphia, PA, [3]Oregon Health & Science University, Portland, OR.

Background/Purpose: Several newer biologics have been approved for treatment of rheumatoid arthritis (RA) in the United States. However, their comparative risks of herpes zoster infection are not well understood. The objective of the present study is to evaluate whether the risks of herpes zoster infections associated with various biologics differ among Medicare RA population.

Methods: Using Medicare data from 2006–2011 for patients with RA, we identified new users of abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab. New users were defined specific to each drug as no use of that therapy in the prior 12 month 'baseline' period. To increase homogeneity of patients characteristics to allow comparison with biologics typically not used as first line agents, patients were required to have used another biologic during baseline (i.e. they were 'switchers'). Eligible subjects must have been continuously enrolled in Medicare Parts A, B and D in baseline and throughout follow up and could not have had zoster medications during baseline. Follow up started from the drug initiation date and ended at the earliest date of: zoster infection, a 30 day gap in current exposure, death, loss of Medicare coverage or Dec 31, 2011. We identified herpes zoster infection using physician diagnosis code and use of antiviral medication within 7 days. Confounding was controlled through a person-specific infection risk score that was separately derived among biologic-naïve new users of anti-TNF and non-biologic DMARDs. We calculated the incidence rate of herpes zoster infection for each biologic and compared their herpes zoster infection risks during follow-up using Cox regression adjusting for infection risk score decile, disability status, glucocorticoids use during baseline, methotrexate use during baseline, most recent biologic during baseline and Medicaid eligibility.

Results: Of 25,274 biologic switchers, 11.3% used etanercept, 15.9% adalimumab, 6.1% certolizumab, 4.4% golimumab, 12.6% infliximab, 29.0% abatacept, 14.5% rituximab and 6.3% tocilizumab. Among 24,237 patients who had no history of herpes zoster infection, we identified 336 herpes zoster infections yielding similar crude incidence rates across different biologics. After adjustment for potential cofounders and compared to infliximab users, the adjusted hazard ratios of all types of biologics were not significantly different from infliximab users. Among 1,037 patients with a history of herpes zoster infection during baseline, we identified 14 recurrent herpes zoster infections

yielding an incidence rate for recurrence of 2.1 per 100 person years. We did not have enough data to look at drug-specific associations with recurrent infection.

Table. Events, absolute incidence rate and adjusted hazard rate of herpes zoster infection by different types of biologics

Biologic Exposures	Events	Crude incidence rate per 100 py	Adjusted Hazard Ratio* (95% CI)
Abatacept	118	1.81	0.88 (0.61–1.28)
Adalimumab	40	1.69	0.96 (0.62–1.49)
Certolizumab	14	2.03	1.14 (0.64–2.04)
Etanercept	34	1.86	1.01 (0.65–1.58)
Golimumab	<11	1.74	0.97 (0.49–1.94)
Rituximab	60	1.99	0.94 (0.63–1.41)
Tocilizumab	15	2.11	0.92 (0.50–1.69)
Infliximab	45	1.69	1.00 (Ref)

*Adjusted for age, gender, infection risk score decile, steroid use during baseline, recent biologic use during baseline, original reason for Medicare coverage and Medicaid eligibility.

Conclusion: Among patients with RA, the risk for herpes zoster was similar across biologics, include those with non-TNF mechanisms of action.

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Rheumatoid and Psoriatic Arthritis Are Not Associated With Higher Risk Of Incident Diabetes Mellitus. Susan Mathew[1], Xiaoqin Tang[2], H. Lester Kirchner[3], Mary Chester M. Wasko[4] and Androniki Bili[1]. [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Center for Health Research, Danville, PA, [3]Geisinger Health System, Danville, PA, [4]Temple University School of Medicine, Pittsburgh, PA.

Background/Purpose: Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are chronic inflammatory conditions that are associated with increased risk of insulin resistance and cardiovascular disease (CVD). However, the evidence for the association of these conditions with incident diabetes mellitus (DM) has been inconsistent. The purpose of this study was to evaluate this association in a cohort of patients with physician entered diagnosis and laboratory values.

Methods: We studied a retrospective cohort of patients with RA or PsA from 1/1/2001 to 12/31/2012 with age- (± 2.5 years) and gender-matched non-rheumatic controls (NRC) in a tertiary health center. Data were extracted from electronic health records. RA and PsA were defined using ICD-9 codes 714.0 and 696.0, respectively, entered twice by a rheumatologist; with a primary care physician within the health system were included. Patients with prevalent DM were excluded. Patients were followed over time for development of DM, defined by ICD-9 250, random blood glucose >200 mg/dl, HgA1c ≥6.5% or use of anti-diabetic medications; a more stringent DM diagnosis, with DM defined as HgA1c ≥6.5%, was also examined. A Poisson regression model was used to estimate the incidence rate (IR) of DM per 1000 person-years for the RA and PsA groups separately compared to the NRC. Cox proportional hazard regression (HR) models, accounting for the correlation induced by matching, were used to estimate the association on developing incident DM after adjusting for age, gender, race, body mass index (BMI), hypertension, hyperlipidemia, ESR, number of office visits, number of drug classes, glucocorticoid, immunosuppressive agent and statin use in the year prior to cohort entry. For the primary outcome, our study had 80% power to detect a 25% difference in the risk for incident diabetes between the RA/PsA and NRC groups.

Results: 1502 RA patients, 359 PsA patients and 7887 NRC were included. Overall, the mean age of the cohort was 55 years; 70% were female, and 98% were Caucasian. RA patients on average were older, more likely to be female, taking steroids and immunosuppressive drugs, and had higher ESR and lower median BMI than PsA patients. Statin use was not different across all groups. During observation, there were 1195 incident diabetes cases: 199 in the RA, 47 in the PSA and 859 in the NRC, with IR 23.2, 23.0 and 17.7 respectively, with an incidence rate ratio (IRR) of 1.32 (1.13–1.54) and 1.30 (0.97–1.75) for RA and PsA respectively compared to NRC. The adjusted HR (95% CI) for DM was 1.14 (0.94–1.38) and 1.28 (0.94–1.75) for RA and PsA respectively compared to NRC. Defining DM as HgA1c ≥ 6.5%, there were 708 incident cases: 122 in the RA, 25 in the PsA and 561 in the NRC, with IR 13.8, 11.8 and 11.2 respectively and IRR 1.05 (0.70–1.57) and 1.22 (1.01–1.49) for RA and PsA respectively compared to NRC. The HR (95% CI) was 1.06 (0.87–1.30) and 1.12 (0.82–1.52) for RA and PsA respectively compared to NRC.

Conclusion: In this cohort, RA and PsA were not associated with increased risk of incident DM, defined by both clinical and stricter laboratory criteria. Our results suggest that an excessive burden of DM does not account for the high risk of CVD in these patients.

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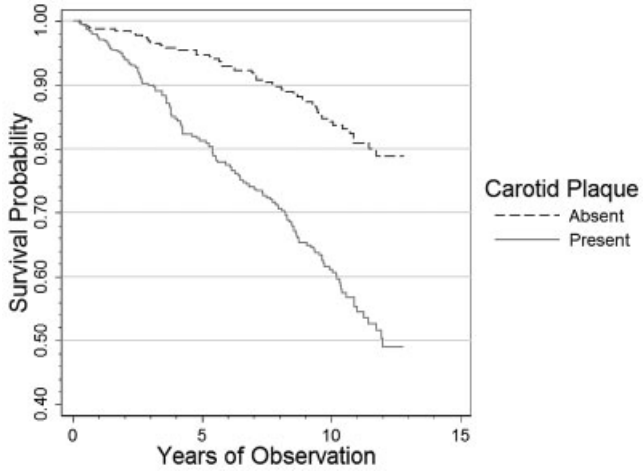
Carotid Atherosclerosis As a Predictor Of Mortality In Rheumatoid Arthritis. Inmaculada del Rincon[1], Roy W. Haas[1], Jose Felix Restrepo[1], Daniel F. Battafarano[2], Daniel H. O'Leary[3], Emily Molina[4] and Agustin Escalante[1]. [1]University of Texas Health Science Center, San Antonio, TX, [2]Brooke Army Medical Ctr, San Antonio, TX, [3]Tufts University-Boston Campus, Boston, MA, [4]University of Texas Health Science Center at San Antonio, San Antonio, TX.

Background/Purpose: Patients with rheumatoid arthritis (RA) have higher mortality than do persons of the same age and sex without RA. This is due in part to an increased risk of atherosclerosis and cardiovascular (CV) disease. The extent of atherosclerosis can be estimated non-invasively using high-resolution carotid ultrasound. In this study we examined the association of carotid atherosclerosis, as measured by carotid ultrasound, with mortality in a cohort of RA patients.

Methods: We recruited RA patients during a visit to their rheumatologist, and invited them to participate in a comprehensive clinical assessment that included a high-resolution carotid ultrasound. We also ascertained age, sex, RA duration, the CV risk factors and erythrocyte sedimentation rate (ESR), among other variables, using a predetermined protocol. After the assessment, we followed patients prospectively per protocol. We obtained a death certificate for all patients who died, from which we classified the causes of death using ICD9 codes. Deaths were classified as CV if the death certificate listed a CV condition, corresponding to ICD9 codes 390–459. We used standard time-to-event techniques to examine the association between the carotid ultrasound findings and all-cause and CV-mortality. Mortality rates are shown per 100 person-years. Rates and hazard ratios (HR) are shown with 95% confidence intervals.

Results: We recruited 1,328 RA patients, of whom 1,197 had a carotid ultrasound. We followed them prospectively over 6,500 person-years, during which 206 deaths occurred, for a mortality rate of 3.1 (2.7, 3.6). Death was attributed to a CV cause in 105 cases, for a CV mortality rate of 1.7 (1.4, 2.1). The presence of carotid plaque resulted in an increased all-cause mortality rate, 4.6 (3.9, 5.47), compared to 1.6 (1.2, 2.1) with absent plaque. The Figure shows a Kaplan Meier curve for all-cause mortality in patients with and without plaque ($P < 0.0001$, log rank test). Carotid plaque was also associated with an increased CV mortality rate, 2.7 (2.1, 3.4) vs. 0.8 (0.6, 1.2). The carotid intima-media thickness (IMT) was associated with increased all-cause mortality, with a HR of 2.28 per mm of IMT (2.00, 2.59), as well as CV mortality, with a HR of 2.26 per mm IMT (1.91, 2.68). The associations of both carotid plaque and the IMT with all-cause mortality were independent of age, sex, CV risk factors and the ESR. Their associations with CV mortality were independent of the all same variables, with the exception of the ESR.



Conclusion: Carotid atherosclerosis is significantly associated with mortality in RA, both all-cause and due to CV causes. The precise role of carotid ultrasound in mortality risk stratification and identification of candidates for intervention to reduce mortality in RA is an interesting area in need of study.

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ACR Concurrent Abstract Session

Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Efficacy of Approved Biologics I

Tuesday, October 29, 2013, 4:30 PM–6:00 PM

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Combination of Intra-Articular Steroid Injection and Tocilizumab More Effective Than Tocilizumab in Rapid Radiographic Progression Patients With Rheumatoid Arthritis. A Randomized, Open Label, x Ray Reader Blinded Study. Kensuke Kume[1], Kanzo Amano[1], Susumu Yamada[1], Toshikatsu Kanazawa[2], Hiroshi Komori[2], Hiroyuki Ohta[3], Noriko Kuwaba[4] and Kazuhiko Hatta[5]. [1]Hiroshima Clinic, Hiroshima, Japan, [2]Hiroshima Clinic, Hiroshima, Japan, [3]Hiroshima Clinic, Hiroshima, Japan, [4]Sanki Clinical Link, Hiroshima, Japan, [5]Hatta Clinic, Kure, Japan.

Background/Purpose: Treatment of rheumatoid arthritis (RA) should aim at full remission. However, recent publications described rapid radiographic progression (RRP) existed despite initial biologics and methotrexate combination therapy in early RA. In RRP, initial biologics and methotrexate might be inadequate. We reported that infliximab plus intra-articular steroid injection is more effective than infliximab in RRP patients in RA. How about other biologics? To compare remission and radiographic non-progression in RRP patients treated with tocilizumab or with tocilizumab plus intra-articular steroid injection.

Methods: We designed a single-blind (X ray reader and assessment physician), randomized controlled trial. We screened 32 RRP (CRP> 35mg/L, RF +, and ACPA+) early (disease duration<6 months) RA patients for inclusion. 28 were randomly allocated tocilizumab group (T group) or tocilizumab plus intra-articular steroid injection group (T plus I group). All patients were taking methotrexate (from 12 to 22mg a week). For T plus I group, palpate examinations of both MP and PIP joints, wrists, elbows, shoulders, and knees were performed every 4 weeks. If swollen joints were existed, intra-articular steroid injections were intensified in each swollen joints by clinician's decision. **Co-** primary endpoints were proportion of patients showing clinical remission (SDAI <3.3) and radiographic non-progression (Δ modified total Sharp score ≤0.5) at 52 weeks. Analysis was by intention-to-treat with last observation carried forward to missing data.

Results: The characteristics of each group at baseline were not significantly different. Clinical remission at 52weeks was achieved by more patients in the T plus I group (42%) than in the T group (25%) ($p<0.05$). Radiographic non-progression at 52 weeks was achieved by more patients in the T plus I group (41%) than in the T group (18%) ($p<0.05$). Especially, swollen and tender joints counts at 52 weeks are significantly improved T plus I group(SJC: 3.6±1.3, TJC:4.2±2.1) than T group.(SJC: 8.5±4.2, TJC: 6.2±3.5)(p $p<0.05$). However C reactive protein at 52 is not significantly difference each group (T plus I group: 0.21±0.12 mg/L, T group: 0.26±0.22 mg/L) ($p=0.67$).

Conclusion: Results of this reveal that combination of intra-articular steroid injection and tocilizumab can achieve a high clinical and radiological remission rate in early RRP RA.

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A Double-Blind Randomized Placebo-Controlled Trial Of Lovastatin in Patients with Rheumatoid Arthritis. Cynthia Aranow[1], John J. Cush[2], Marcy B. Bolster[3], Christopher C. Striebich[4], Maria Dall'Era[5], Meggan Mackay[1], Ewa Olech[6], Tracy M. Frech[7], J. Box[8], Richard M. Keating[9], Mary Chester M. Wasko[10], E. William St Clair[11], Alan Kivitz[12], Betty Diamond[1], Anne Davidson[1], Meagan Spychala[13], Ellen A. Goldmuntz[14] and Autoimmunity Centers of Excellence[15]. [1]Feinstein Institute for Medical Research, Manhasset, NY, [2]Baylor Research Institute and Baylor University Medical Center, Dallas, TX, [3]Medical University of South Carolina, Charleston, SC, [4]University of Colorado Denver, Aurora, CO, [5]University of California, San Francisco, San Francisco, CA, [6]Oklahoma Medical Research Foundation, Oklahoma City, OK, [7]University of Utah School of Medicine, SLC, UT, [8]Carolina Bone and Joint, Charlotte, NC, [9]The University of Chicago, Chicago, IL, [10]Temple University School of Medicine, Pittsburgh, PA, [11]Duke Unversity Medical Center, Durham, NC, [12]Altoona Center for Clinical Research, Duncansville, PA, [13]Rho, Inc., Chapel Hill, NC, [14]NIAID/NIH, Bethesda, MD, [15]National Institutes of Health, Bethesda, MD.

Background/Purpose: HMG-CoA reductase inhibitors (statins) are standard treatment for hyperlipidemia. In addition to lipid lowering abilities, statins exhibit multiple anti-inflammatory effects. The objectives of this study were to determine if treatment of patients with Rheumatoid Arthritis (RA) with lovastatin decreased CRP or reduced disease activity.

Methods: We conducted a randomized double blind placebo controlled 12 week trial. 64 patients with mildly active RA (defined as 2–8 tender joints and 1–6 swollen joints) and an elevated CRP (> 5mg/L) were randomized (1:1) to receive lovastatin 80mg or placebo. Patients could be on stable prednisone ≤ 10 mg, DMARDs and/or biologic therapy. The primary efficacy endpoint was the reduction in mean log CRP. Secondary endpoints included disease activity, RF and anti-CCP antibody titers. Safety was a co-primary endpoint; hepatic and muscle toxicities were of particular interest.

Results: Baseline features of the treatment groups were similar. The mean baseline CRP was 12.2 mg/L in the lovastatin arm and 12.6 mg/L in the placebo arm; mean baseline DAS-28 CRP was 3.5 and 3.6 in the lovastatin and placebo arms, respectively. No significant differences in mean log CRP reduction or % change in CRP from baseline between the two treatment arms were observed. No significant difference between the lovastatin and placebo arms was observed in a longitudinal model of the estimated mean log CRP. Disease activity assessed by DAS28 did not change from baseline in either lovastatin or placebo treated groups (−0.42 and −0.58, respectively, ns). At week 12, clinical responses were comparable in subjects receiving lovastatin or placebo: ACR 20 (29% vs.

40%) and Good/Moderate EULAR response (42% vs. 44%). Autoantibody titers were stable during the course of the study with no group differences. Although not statistically different, the frequency of subjects receiving biologic therapy was greater in the lovastatin treated group than placebo (59% vs. 38%). A post-hoc analysis of subjects not using biologic therapy (n=32) demonstrated a significantly greater proportion achieving ≥15% reduction in CRP from baseline in the lovastatin treated group (83%) compared to placebo (33%; p = 0.019). No analogous difference was observed in subjects receiving biologics (47% vs. 60%). The mean change from baseline CRP in subjects not using biologics was also numerically greater in subjects taking lovastatin (−4.75) than placebo (−2.00). Lovastatin was well tolerated with no serious safety concerns. Several subjects experienced transient reversible elevations of transaminases. Clinical myositis was not observed.

Conclusion: Statins were well tolerated in our patient population. This study showed no anti-inflammatory or clinical effects after 12 weeks of treatment with lovastatin. However, we observed a potential modest effect of lovastatin in subjects not using biologics, suggesting statins may be anti-inflammatory in selected patients.

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Improvement In Insulin Resistance Greater With The Use Of Infliximab Following Intensive Treatment Of Early Rheumatoid Arthritis. Lesley-Anne Bissell[1], Elizabeth Hensor[2], Sarah L. Mackie[2], Agata Burska[2], Jackie L. Nam[2], Lukasz Kozera[2], Helen I. Keen[2], Edith Villeneuve[2], Heike Eberl[3], Helena Donica[4], Philip G. Conaghan[5], Jacqueline Andrews[2], Paul Emery[6] and Ann W. Morgan[2]. [1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [2]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [3]Roche Molecular Diagnostics, Burgess Hill, United Kingdom, [4]Department of Biochemical Diagnostics, Medical University of Lublin, Lublin, Poland, [5]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [6]Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

Background/Purpose: Insulin resistance (IR), N-terminal pro-brain natriuretic peptide (NT-proBNP) and total cholesterol/high density lipoprotein cholesterol ratio (TC/HDL-C) profiles have been proposed as surrogate measures of CVD in RA, with some improving with suppression of disease activity. In early RA, few randomised controlled trials (RCTs) have compared the effects of DMARDs with TNFi on these biomarkers. A recent cohort study has linked TNFi to a reduced risk of diabetes. We aimed to determine whether TNFi had greater influence over DMARDs on homeostasis model assessment of IR (HOMA-IR), NT-proBNP and TC/HDL-C.

Methods: The Infliximab as Induction therapy for Early rheumatoid Arthritis (IDEA) multicentre double-blind RCT recruited 112 DMARD-naïve RA patients (pts) (1987 ACR criteria; 3–12 months duration). Pts were randomised 1:1 to IFX+MTX or MTX with single-dose 250mg IV methylprednisolone (MP) as induction therapy. Treatment was blinded to week 26 then guided using a treat to target (T2T) approach. 120mg IM MP was given in both groups at weeks 6, 14 and 22 if DAS>2.4 at that visit. A single centre conducted the CV sub-study. Fasting glucose, lipids, insulin and NT-proBNP were measured at baseline, week 26 (w26) and 78 (w78). Multiple imputation by chained equations, using predictive mean matching, created 20 datasets; linear regression analyses adjusted for baseline values. HOMA-IR (glucose*insulin/405) and NT-proBNP values were ln-transformed prior to analysis.

Results: CV biomarker data were available for 86 pts; 7 had known CVD and were excluded from the subsequent analysis. Of the 79 pts included (age 51.6 [range 19–75], 71% female, 57% RF+ve, 72% ACPA+ve), 38 received IFX and 41 MP. Baseline clinical characteristics were similar between the two groups, including CV risk factors. DAS44 remission rates did not differ between TNFi and DMARD groups at w26 (32% vs. 37%, p=0.956) and w78 (43% vs. 54%, p=0.593). In both groups the three surrogate CVD markers improved on average at w26 and w78 (see Table 1). TC/HDL-C or NT-proBNP did not differ, but the TNFi group showed greater improvement in HOMA-IR at w78. Adjusting for IA/IM steroid injection dose did not alter the result.

Table 1. Changes in surrogate measures of CVD over 78 weeks

	Baseline		Change at week 26			Change at week 78		
	MTX+IFX n=38	MTX+IV Steroid n=41	MTX+IFX	MTX+IV Steroid	Adjusted difference (95% CI), p-value	MTX+IFX	MTX+IV Steroid	Adjusted difference (95% CI), p-value
TC/HDL-C (mean (SD))	5.14 (1.60)	5.71 (2.26)	−0.67	−0.96	0.11 (−0.45, 0.66), p=0.709	−0.86	−1.01	−0.08 (−0.89, 0.73), p=0.838
HOMA-IR (geometric mean)*	2.17	2.54	FU/BL 0.68	FU/BL 0.69	IFX/IVS 0.87 (0.65, 1.16) p=0.333	FU/BL 0.51	FU/BL 0.87	IFX/IVS 0.51 (0.35, 0.76) p=0.001
NT-proBNP (geometric mean)*	82.47	62.92	FU/BL 0.80	FU/BL 0.82	IFX/IVS 1.06 (0.77, 1.46) p=0.708	FU/BL 0.85	FU/BL 0.88	IFX/IVS 1.06 (0.73, 1.52) p=0.768

*it was not possible to calculate SD in original units for log-transformed variables

Conclusion: Treatment of early RA was associated with improvement in TC/HDL-C, IR and NT-proBNP. To our knowledge this is the first double-blinded RCT to compare the change in HOMA-IR with TNFi versus non-TNFi in early DMARD-naive RA. We determined a greater long-term improvement in HOMA-IR in those treated with TNFi; on average at w78 HOMA-IR values were around half (0.51 times) as high as those treated with MTX/IV steroid. When implementing a T2T approach, there appears to be an advantage with the use of TNFi. Longer term follow up is underway to determine if these findings translate into reduced overt CVD.

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Tocilizumab In Combination Therapy and Monotherapy Versus Methotrexate In Methotrexate-Naive Patients With Early Rheumatoid Arthritis: Clinical and Radiographic Outcomes From a Randomized, Placebo-Controlled Trial. Gerd R. Burmester[1], William Rigby[2], Ronald F. van Vollenhoven[3], Jonathan Kay[4], Andrea Rubbert-Roth[5], Ariella Kelman[6], Sophie Dimonaco[7] and Nina Mitchell[7]. [1]Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]Dartmouth-Hitchcock Medical Center and Dartmouth Medical School, Lebanon, NH, [3]Karolinska Institute, Stockholm, Sweden, [4]UMass Memorial Medical Center and University of Massachusetts Medical School, Worcester, MA, [5]University of Cologne, Cologne, Germany, [6]Genentech, South San Francisco, CA, [7]Roche, Welwyn Garden City, United Kingdom.

Background/Purpose: Recent recommendations support intensive treatment of patients (pts) with early rheumatoid arthritis (RA) to achieve remission or low disease activity.[1–3] Tocilizumab (TCZ) was not previously studied exclusively in an early RA population. The purpose of this study was to assess the efficacy and safety of TCZ ± methotrexate (MTX) vs MTX in MTX-naive pts with early RA (defined as ≤2 y since diagnosis).

Methods: Pts were randomized 1:1:1:1 (double-dummy, double-blind) to receive TCZ 8 mg/kg (TCZ8) + MTX (primary intervention), TCZ8 monotherapy (TCZ8 MONO), TCZ 4 mg/kg (TCZ4) + MTX, or MTX for 104 wks. Pts received IV TCZ q4w, and MTX starting at 7.5 mg qw and escalating to 20 mg qw by wk 8. Inclusion criteria included RA duration ≤2 y, DAS28 >3.2, MTX-naive, elevated ESR or CRP, and presence of RF or anti-CCP antibodies or radiographic erosion(s). Primary endpoint was proportion of pts achieving DAS28 remission (DAS28 <2.6) at wk 24. Key secondary endpoints included mean changes from baseline (BL) to wk 52 in van der Heijde–modified Total Sharp Score (mTSS) and improvement in physical function (using HAQ-DI). A hierarchy of statistical testing was implemented to control the type 1 error rate for multiplicity. This trial is ongoing; 52-wk data are reported here.

Results: The intent-to-treat population consisted of 1157 pts. BL characteristics were similar in all treatment groups: mean RA duration, 0.4–0.5 y; mean DAS28, 6.6–6.7; mTSS, 5.66–7.72. Statistically significantly greater proportions of TCZ8 + MTX vs MTX pts achieved DAS28 remission and ACR20/50/70 responses at wks 24 and 52 ($p < 0.05$); statistically significant improvements in mean mTSS and HAQ-DI were also observed at wk 52 ($p < 0.05$; Table). TCZ8 MONO was also statistically significant for the primary endpoint of percentage of DAS28 remission responders in comparison to MTX at wk 24 ($p < 0.05$). Both TCZ8 MONO and TCZ4 + MTX exhibited numerically greater improvements vs MTX across key secondary endpoints and were more efficacious than MTX in preventing structural joint damage (Table). Adverse events (AEs) observed with TCZ were consistent with its known safety profile. Incidences of AEs and serious AEs were similar across groups, while serious infections were highest with combination therapy (Table). Overall, 9 deaths were observed across all groups; causes of death were variable.

Table. Primary and Selected Secondary Efficacy Endpoints (ITT Population) and Safety Data

	TCZ8+MTX n = 290	TCZ8 MONO n = 292	TCZ4+MTX n = 288	MTX n = 287
Efficacy				
DAS28-ESR remission (<2.6), 24 wks (%, OR)	44.8*** 4.77	38.7*** 3.70	31.9††† 2.72	15.0
ACR20	74.5*	70.2	73.6†	65.2
ACR50 24 wks (%)	56.9**	47.6	47.9	43.2
ACR70	38.6**	30.1	34.7†	25.4
Mean ΔmTSS, BL to 52 wks	0.08**	0.26†	0.42†	1.14
Mean ΔHAQ-DI, BL to 52 wks	−0.81*	−0.67	−0.75	−0.64
ACR/EULAR Boolean remission, 24 wks (%)	18.4[b]	14.2	16.7[b]	10.0
ACR/EULAR index (SDAI) remission, 24 wks (%)	28.5[b]	22.6	22.6	16.4
CDAI remission, 24 wks (%)	24.5[b]	20.5[b]	22.2[b]	13.2
Safety[a]				
Patients with AEs, n (%)	256 (88.3)	250 (85.6)	256 (88.6)	235 (83.3)
Patients with serious AEs, n (%)	31 (10.7)	25 (8.6)	29 (10.0)	24 (8.5)
Patients with serious infections, n (%)	10 (3.4)	8 (2.7)	11 (3.8)	6 (2.1)
Deaths, n(%)	2 (0.7)	1 (0.3)	4 (1.4)	2 (0.7)

ITT, intent-to-treat; OR, odds ratio.
efficacy comparisons versus MTX (MTX + placebo). ***$p < 0.0001$; **$p < 0.001$: *$p < 0.05$.
†††$p < 0.0001$ and †$p < 0.05$; these comparisons occurred after break in the hierarchical testing sequence.
[a]Analyses were based on safety population to 52 weeks (TCZ8 + MTX, n = 290; TCZ8 MONO, n = 292; TCZ4 + MTX, n = 289; MTX, n = 282); multiple occurrences of the same AE in a patient were counted only once.
[b]$p < 0.05$; ACR/EULAR Boolean remission, ACR/EULAR index (SDAI) remission, and CDAI remission were performed as post hoc exploratory analyses; therefore, p values were not adjusted for multiplicity.

Conclusion: TCZ is effective as combination therapy and monotherapy in MTX-naive pts with early active RA. TCZ resulted in greater improvements from BL in signs, symptoms, and physical function and in inhibition of structural joint damage in all treatment groups vs MTX alone. Of the 3 TCZ treatment groups, efficacy outcomes for TCZ vs MTX were consistently greatest in the TCZ8 + MTX group. The overall safety of TCZ was consistent with its known profile.

References:

1. *Arthritis Care Res* 2012;64:625; 2. *Ann Rheum Dis* 2010;69:631; 3.*Ann Rheum Dis* 2010;69:964

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Intravenous Golimumab Inhibits Radiographic Progression and Maintains Clinical Efficacy and Safety In Patients With Active Rheumatoid Arthritis Despite Methotrexate Therapy: 2-Year Results Of a Phase 3 Trial Of Intravenous Golimumab.

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Background/Purpose: To evaluate long-term clinical/radiographic efficacy of IV GLM 2mg/kg+MTX in active RA despite MTX through wk112.

Methods: 592 pts with active RA (≥6/66 SJC, ≥6/68 TJC, CRP≥1.0mg/dL, RF and/or anti-CCP positive) despite ≥3 months of MTX (15–25mg/wk) participated in this multicenter, randomized, double-blind, placebo (PBO)-controlled study. Pts were randomized to IV GLM 2mg/kg or PBO at wks0&4 and q8wks; all pts continued stable MTX. PBO pts with <10% improvement in SJC+TJC at wk16 could early escape to IV GLM 2mg/kg (wks16&20, q8wks). All PBO pts received IV GLM 2mg/kg starting at wk24. Primary endpoint was wk14 ACR20. Radiographs of hands and feet at wks 0, 24(wk16, early escape), 52, and 100 were scored by 2 independent readers and adjudicator (as needed) using the vdH-S score. Reading Session 2 included wk0, wk52, and wk100 scoresIn general, analyses at wks 24, 52, and 100 were performed using ITT methodology, with imputation for missing data.

Results: 82% of pts (486/592) continued through wk112; 106 pts d/c, mostly due to AEs(44pts) and few due to lack of efficacy (12pts). At wk14, significantly ($p<0.001$) larger proportions of GLM+MTX vs PBO+MTX pts had ACR20/50/70, DAS28-CRP good/moderate responses, and greater improvements in HAQ. Clinical improvements were maintained through wk100 (final efficacy visit), when ACR20/50/70 responses among all GLM+MTX-treated pts were 68.1%, 43.8%, and 23.5%, resp; DAS28-CRP moderate/good response was 81.9%; and median improvement from wk0 in HAQ was 0.5; 67.1% of GLM+MTX pts had improvement in HAQ ≥0.25 from baseline. GLM+MTX-treated pts continued to have significantly less radiographic progression based on vdH-S total and subscores vs PBO+MTX at wk24, and PBO+MTXàGLM + MTX at wk52 and wk100. Pts randomized to PBO+MTX who began GLM at wk16/24 demonstrated marked slowing of radiographic progression from wk24–52 and from wk52–100. Through wk112 (final safety visit), the mean follow-up for all GLM-treated pts was 96wks. AEs and serious AEs occurred in 79% and 18%, resp, of GLM-treated pts (vs 49% and 2% at wk24). 3 cases of TB and 2 serious opportunistic infections (cryptococcal pneumonia, intervertebral discitis) were reported through wk112. 6pts (1.0%) died: 1 PBO+MTX and 5 (0.8%) GLM+MTX (pneumonia/MI, dehydration, abdominal TB, unknown × 2). Through wk112, the proportion of infusions with infusion reactions was 0.4% and the proportion of pts with infusion reactions was 3.9% (vs. 1.1% and 3.5%, respectively, at wk24).

RADIOGRAPHIC PROGRESSION (mean ± standard deviation)	Placebo → GLM 2 mg/kg + MTX (n=197)	GLM 2mg/kg + MTX (n=395)	All GLM 2 mg/kg + MTX (n=592)
Baseline Total vdH-S	50.26 ± 59.85	47.59 ± 54.63	–
Total vdH-S change from baseline at wk24	1.09 ± 3.19	0.03 ± 1.90 ***	–
Total vdH-S change from baseline at wk52	1.22 ± 3.98	0.13 ± 3.11**	0.49 ± 3.46
Total vdH-S change from baseline at wk100	2.10 ± 7.42	0.74 ± 6.32**	1.19± 6.73
Total vdH-S change from wk24-wk 52	0.12 ± 2.44	0.15 ± 1.83	0.14 ± 2.06
Total vdH-S change from wk52-wk100	0.80 ± 3.03	0.58 ± 3.07	0.64 ± 3.06

**, ***p-value vs. placebo + MTX <0.01, 0.001, respectively. Pts with missing total vdH-S score at wk52 excluded.

Conclusion: IV GLM+MTX significantly inhibited radiographic progression (vdH-S scores) at wks 24,52 and 100. Among PBO-treated pts who began GLM at wk16/24, marked slowing of radiographic progression, to rates similar to pts randomized to GLM, was observed from wk24–52 and from wk52–100. IV GLM+MTX also significantly improved and maintained RA signs/symptoms in pts with active RA despite ongoing MTX and continued to demonstrate an acceptable safety profile through wk112.

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Clinical Remission After 52 Weeks Of Treatment Is a Predictor Of Adalimumab-Free Disease Control In Patients With Early Rheumatoid Arthritis: Hopeful 2 Study. Yoshiya Tanaka[1], Hisashi Yamanaka[2], Naoki Ishiguro[3], Nobuyuki Miyasaka[4], Katsuyoshi Kawana[5], Tadamichi Kubo[5], Aki Kuroki[5] and Tsutomu Takeuchi[6]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Tokyo Women's Medical University, Tokyo, Japan, [3]Nagoya Univeristy Graduate School of Medicine, Nagoya, Japan, [4]Tokyo Medical and Dental University, Tokyo, Japan, [5]AbbVie GK, Tokyo, Japan, [6]Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: Although it is possible to achieve remission or low disease activity (LDA) with the combination of methotrexate (MTX) and biologics for many patients with early rheumatoid arthritis (RA), it is uncertain whether disease is controlled following withdrawal of biologics. The purpose of this observational study was to assess the effect of withdrawal of adalimumab (ADA) on disease activity following treatment with MTX plus ADA, and to identify predictors of biologic-free disease control in patients with early RA.

Methods: Patients with early RA received blinded ADA 40 mg every other week (EOW) plus MTX 6–8 mg every week (EW) or MTX 6–8 mg EW alone for 26 weeks. Thereafter, all patients received open-label ADA 40 mg EOW plus MTX 6–8 mg EW for 26 weeks in the HOPEFUL 1 study. At week 52, patients could be enrolled in the 52-week observational, follow-up, HOPEFUL 2 study, during which time they received ADA plus MTX treatment (ADA-continued group), or MTX alone (ADA-withdrawal group) at the investigator's discretion. The primary outcomes of this study were disease activity score based on 28 joints count based on erythrocyte sedimentation rate (DAS28-ESR), Health Assessment Questionnaire-Disability Index (HAQ-DI), and modified total Sharp score (mTSS) at week 104. The factors correlated with the outcomes were also analyzed.

Results: Among 278 patients completing the 52-week HOPEFUL 1 study, 220 were enrolled in the HOPEFUL 2 study. At week 52, baseline characteristics including DAS28-ESR, HAQ-DI and mTSS were comparable between the ADA-continued (N=106) and ADA-withdrawal (N=114) groups. 70% and 50% from each group achieved low disease activity (LDA, DAS28-ESR<3.2) and clinical remission (DAS28-ESR<2.6), respectively. Table shows disease activity scores at week 104. Mean DAS28-ESR score at week 104 was significantly higher and the percentage of the patients who achieved LDA or clinical remission was significantly lower in the ADA-withdrawal group. There was no significant difference in HAQ-DI score and ΔmTSS in the two groups at week 104. In the ADA-withdrawal group, lower baseline CRP scores and lower DAS28-ESR scores at week 52 predicted LDA at week 104 in multivariate analysis. The cut-off point to sustain LDA through week 104 without using ADA was DAS28-ESR< 2.6 at week 52.

Table. Disease activity scores at week 104 in ADA-continued group and ADA-withdrawal group

	ADA-continued group	ADA-withdrawal group	P value
DAS28-ESR, Mean±SD	2.70±1.08	3.20±1.24	0.006
% of DAS28-ESR<3.2	72.5	55.8	0.021
% of DAS28-ESR<2.6	53.8	36.8	0.026
HAQ-DI, Mean±SD	0.20±0.29	0.26±0.39	0.609
ΔmTSS from week 52, Mean±SD	0.8±3.9	0.6±1.8	0.335

Conclusion: More patients who continued ADA therapy sustained LDA and clinical remission after 1 year. Nevertheless, half of ADA-withdrawal RA patients sustained LDA for 1 year. Achieving DAS28-ESR-remission after 52 weeks of treatment using ADA was the key determinant for biologic-free disease control in early RA patients.

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ACR Concurrent Abstract Session
Sjögren's Syndrome: Basic Science
Tuesday, October 29, 2013, 4:30 PM–6:00 PM

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Complex Functional Effects Within The HLA Contribute To Sjögren's Syndrome Pathogenesis and May Influence Both Transcriptional Regulation and Peptide Binding. Christopher J. Lessard[1], He Li[2], Indra Adrianto[2], John A. Ice[2], Mikhail G. Dozmorov[2], Roland Jonsson[3], Maureen Rischmueller[4], Gunnel Nordmark[5], Xavier Mariette[6], Corinne Miceli-Richard[7], Marie Wahren-Herlenius[8], Torsten Witte[9], Michael T. Brennan[10], Roald Omdal[11], Lars Rönnblom[5], Patrick M. Gaffney[2], Wan-Fai Ng[12], Nelson L. Rhodus[13], Barbara M. Segal[14], Jonathan D. Wren[2], R. Hal Scofield[15], Juan-Manuel Anaya[16], John B. Harley[17], Courtney G. Montgomery[2] and Kathy L. Sivils[1]. [1]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]University of Bergen, Bergen, Norway, [4]Queen Elizabeth Hospital, Adelaide, Australia, [5]Uppsala University, Uppsala, Sweden, [6]Bicêtre University Hospital, Le Kremlin Bicetre, France, [7]Université Paris Sud, Le Kremlin Bicêtre, France, [8]Karolinska Institutet, Stockholm, Sweden, [9]Medical University Hannover, Hanover, Germany, [10]Carolinas Medical Center, Charlotte, NC, [11]Stavanger University Hospital, Stavanger, Norway, [12]Newcastle University, Newcastle upon Tyne, United Kingdom, [13]University of Minnesota, Minneapolis, MN, [14]Hennepin County Medical Center, Minneapolis, MN, [15]US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [16]School of Medicine and Health Sciences, Universidad del Rosario. Center for Autoimmune Diseases Research (CREA), Bogotá, Colombia, [17]Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Background/Purpose: Primary Sjögren's syndrome (pSS) is a common, heterogeneous exocrinopathy. Etiology involves complex environmental, genetic and genomic influences driving innate and adaptive autoimmune responses. This study sought to integrate genome-wide association study (GWAS) and classical HLA allele associations in SS, and to explore this genetically complex region for insight into disease mechanisms through bioinformatic approaches.

Methods: Genotype data was collected for 1638 pSS cases and 6754 controls on Illumina Omni1-Quad or ImmunoChip arrays. HLA classical allele imputation was performed using HiBag with a certainty threshold of >80% to define relationships with single nucleotide polymorphisms (SNPs). A set of 9122 pSS associated SNPs (P<5×10E-5) were tested for enrichment using GenomeRunner to determine if the set of SNPs co-localize with various functional genomic elements such as specific transcription factor binding sites. A subset of SS associated SNPs that were significantly enriched in genomic locations near functional elements related to the transcriptional regulator, RFX5, were tested by expression quantitative trait locus (eQTL) analysis using the MATRIXeQTL package in R using transcript levels measured by Illumina WG-6 arrays in 133 subjects.

Results: After adjusting for the most significant GWAS variant (rs115575857 in HLA Class II; P=1.65×10E-114), we found a second independent effect peaking at rs116232857 (P=1.33×10E-96). Imputation and regression analyses identified the previously reported ancestral haplotype including DQB1*0201 (P=1.38×10E-95), DQA1*0501 (P=8.50×10E-94), and DRB1*0301 (P=2.19×10E-84) and indicated rs115575857 was synonymous with this haplotype. The association at rs116232857 persisted and

accounted for DQB1*0501, but DQB1*0501 could not account for rs116232857, suggesting rs116232857 either tags multiple functional effects or, alternatively, DQB1*0501 is a false positive. Statistically significant co-localization (P=1.53×10E-14) was observed showing that 160 HLA region variants are located within or near (100 bp) ChIP-seq peaks for RFX5, a key transcriptional regulator of HLA Class I and II loci. Further analyses of RFX5 related variants identified multiple eQTLs (P-values between 8.31×10E-11 and 4.54×10E-33) in both the Class I and Class II HLA loci and include HLA-DRB6, HLA-C, HLA-DPB1, HLA-DQA1, and HLA-A. Risk alleles for these eQTLs reside on both pSS associated haplotypes.

Conclusion: We conclude that the ancestral haplotype of DQB1*0201, DQA1*0501, and DRB1*0301 corresponds to our top GWAS effect, rs115575857 and the second independent effect at rs116232857 is novel. RFX5 was identified as a novel potential functional candidate as the RFX5 binding elements were enriched for pSS associated variants affecting HLA Class I and II expression levels. This work suggests that complex functional elements in the HLA region involved in both transcriptional regulation and peptide binding impact SS.

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The NKp30/B7H6 Axis Contributes To Pathogenesis In Primary Sjögren's Syndrome. Gaetane Nocturne[1], Sylvie Rusakiewicz[2], Damien Sene[3], Gunnel Nordmark[4], Maija-Leena Eloranta[5], Per Eriksson[6], Elke Theander[7], Helena Forsblad-d'Elia[8], Roald Omdal[9], Marie Wahren-Herlenius[10], Roland Jonsson[11], Lars Rönnblom[5], Joanne Nititham[12], Kimberly E. Taylor[13], Christopher J. Lessard[14], Kathy L. Moser[14], Jacques-Eric Gottenberg[15], Lindsey A. Criswell[12], Corinne Miceli-Richard[1], Laurence Zitvogel[16] and Xavier Mariette[17]. [1]Université Paris Sud, Le Kremlin Bicêtre, France, [2]IGR INSERM U1015, Villejuif, France, [3]Pitie-Salpetriere Hospital, Paris, France, [4]Uppsala University, Uppsala, Sweden, [5]Section of Rheumatology, Uppsala University, Uppsala, Sweden, [6]Rheumatology/AIR, Linköping University, Linköping, Sweden, Linköping, Sweden, [7]Lund University, Malmö, Sweden, [8]University of Gothenburg, Gothenburg, Sweden, [9]Stavanger University Hospital, Stavanger, Norway, [10]Karolinska Institutet, Stockholm, Sweden, [11]University of Bergen, Bergen, Norway, [12]University of California, San Francisco, Rosalind Russell Medical Research Center for Arthritis, San Francisco, CA, [13]University of California, San Francisco, San Francisco, CA, [14]Oklahoma Medical Research Foundation, Oklahoma City, OK, [15]Strasbourg University Hospital, Strasbourg, France, [16]IGR INSERM U1015, Villejuif, France, [17]Bicêtre University Hospital, Le Kremlin Bicetre, France.

Background/Purpose: NK cells are an important subset of cells involved in innate immunity. Their possible role has never been studies in pSS pathogeny. We aimed to assess the involvement of NCR3/NKp30, a NK-specific activating receptor regulating the cross-talk between NK and dendritic cells and type II IFN secretion, and its receptor named B7H6 in pSS pathogenesis.

Methods: First, a cohort of 584 pSS patients (ASSESS + KB cohort) and 451 controls of Caucasian ancestry, addressed by 48 AIMs, was used for exploratory genetic study. Nine single nucleotide polymorphisms (SNPs) within the 6p21.3 *NCR3* locus and 3 additional SNP proxies for *HLA-DR2,HLA-DR3* and *TNF-308* were genotyped. Two *NCR3* SNPs (rs11575837, rs2736191) and the SNP proxy for HLA-DR3 (rs2187668) were genotyped in the replication study that included 436 pSS Scandinavian patients and 441 healthy controls. Then, NKp30 mRNA levels were investigated in 102 pSS patients from the French ASSESS cohort according to their genotype. Second, we performed phenotypic characterization of NK cells in 38 pSS patients compared to 30 age-matched controls. The functional relevance of expression levels of NKp30 on NK cells was assessed by a cross-linking assay to analyze degranulation and IFN-γ secretion. Third, we assessed the presence of NK cells by immunohistochemistry (IHC) and transcriptional level of B7H6 within salivary glands. Last we investigated the NKp30-dependent cross-talk between NK cells and epithelial cells within salivary glands.

Results: Our case-control study of genetic polymorphisms of the NCR3/NKp30 gene demonstrated that the rare allele of the rs11575837 (G>A) residing in the promoter was protective for pSS and was associated with reduced gene transcription and function. We also demonstrated that circulating levels of NCR3/NKp30 were markedly increased among pSS patients compared with controls and correlated with higher NCR3/NKp30 IFN-γ secretion by NK cells. Excess accumulation of NK cells in minor salivary glands correlated with the severity of the exocrinopathy. B7-H6, the ligand of NKp30, was expressed by salivary epithelial cells and regulated by TNF-α triggering NKp30 mediated-effector functions.

Conclusion: These findings suggest that NK cells are involved in pSS pathogeny. Different levels of evidence (genetics, mRNA expression, function in blood, presence in the target organ as well as the ligand) demonstrate an NKp30-dependent inflammatory state in salivary glands. Blockade of the B7H6/NKp30 axis could be clinically relevant in pSS.

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2772

Identification Of a Sjögren's Syndrome-Associated Variant That Influences *OAS1* Isoform Switching. He Li[1], John A. Ice[2], Jennifer A. Kelly[2], Indra Adrianto[2], Stuart B. Glenn[2], Kimberly S. Hefner[3], Evan G. Vista[4], Donald U. Stone[1], Raj Gopalakrishnan[5], Glen D. Houston[1], David M. Lewis[1], Michael Rohrer[5], Pamela Hughes[5], John B. Harley[6], Courtney G. Montgomery[2], James Chodosh[7], James A. Lessard[8], Juan-Manuel Anaya[9], Barbara M. Segal[10], Nelson L. Rhodus[5], Lida Radfar[1], R. Hal Scofield[2], Christopher J. Lessard[1] and Kathy L. Sivils[2]. [1]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Hefner Eye Care and Optical Center, Oklahoma City, OK, [4]University of Santo Tomas, Taguig City, Philippines, [5]University of Minnesota, Minneapolis, MN, [6]US Department of Veterans Affairs Medical Center, Cincinnati, OH, [7]Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, [8]Valley Bone and Joint Clinic, Grand Forks, ND, [9]School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia, [10]Hennepin County Medical Center, Minneapolis, MN.

Background/Purpose: Sjögren's syndrome (SS) is a common, progressive autoimmune exocrinopathy characterized by symptoms of dry eyes and mouth present in 0.7–1% of the European population. Our previous gene expression profiling (GEP) study has demonstrated overexpression of transcripts induced by interferons (IFN) in SS patients. Here, we sought to identify and characterize underlying genetic contributions to dysregulation of IFN pathways in SS.

Methods: IFN signature genes of interest were selected from GEP studies performed in 180 SS cases and 73 controls using Illumina Human WG-6 v3.0 microarray data and evaluated for *cis*-expression quantitative trait loci (eQTL) in 222 subjects by integration with genome-wide association study (GWAS) data. Gene splicing patterns were evaluated using microarray data and supplemented with RNA-sequencing (RNA-seq) performed in 57 SS cases and 27 controls on the Illumina platform. Transcripts measured by RNA-seq were reconstructed using Cufflinks and the relative abundance of isoforms was compared across samples according to genotypes for loci of interest.

Results: GEP showed that *OAS1*, an IFN-inducible gene involved in inhibition of virus replication, was significantly overexpressed in SS patients. Multiple *cis*-eQTL were identified in *OAS1* with the most significant peaking at rs10774671, strengthening prior evidence of this variant for disease association ($P=6\times10^{-3}$) obtained in our large GWAS dataset consisting of 395 cases and 1975 controls. We further replicated this genetic association in an independent set of 648 cases and 2927 controls followed by meta-analysis using a weighted Z score ($P_{meta}=9\times10^{-6}$; OR=0.79). The rs10774671 A allele conferred risk, is a splice site variant located at the intersection between intron-5 and exon-6, and thus may switch the primary normal isoform, p46, to various alternatives. To characterize functional impact of this variant, we evaluated alternative splicing events using both microarray and RNA-seq data. Variation in splicing was detectable by a microarray probe that specifically recognizes a truncated form of *OAS1* (p42). Both microarray and RNA-seq showed that the risk allele A, which demolishes the splicing consensus sequence, was correlated with higher expression of p42 ($P_{micro}=2\times10^{-16}$ and $P_{seq}=1\times10^{-15}$). RNA-seq results also showed correlation of the A risk allele with higher proportions of p48 and p44 isoforms ($P=9\times10^{-8}$ and $P=4\times10^{-4}$, respectively), but a lower expression of the functionally normal isoform, p46 ($P=4\times10^{-30}$).

Conclusion: We identified *OAS1* as a novel candidate SS locus that confers risk through a functional eQTL at rs10774671. This splice site variant switches the primary p46 isoform to multiple alternatives with decreased OAS1 enzyme activity potentially contributing to reduced ability to inhibit viral replication. These results indicate the risk allele may cause vulnerability to viral infection that contributes to SS susceptibility.

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2773

Genome-Wide DNA Methylation Patterns In naïve CD4+ T Cells From Patients With Primary Sjögren's Syndrome. Nezam I. Altorok[1], Patrick S. Coit[1], Travis Hughes[1], Kristi A. Koelsch[2], R. Hal Scofield[3], Kathy L. Sivils[3], A. Darise Farris[4] and Amr H. Sawalha[1]. [1]University of Michigan, Ann Arbor, MI, [2]Oklahoma Medical Research Foundation, Okalahoma City, OK, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]Oklahoma Medical Research Foun, Oklahoma City, OK.

Background/Purpose: Primary Sjögren's syndrome (PSS) is a systemic autoimmune disease characterized by inflammation of the lacrimal and salivary glands and dryness of the eyes and mouth. There is evidence to suggest that PSS shares common pathogenic factors with other autoimmune diseases such as lupus, including common genetic susceptibility loci. Recent evidence strongly supports an epigenetic contribution to the pathogenesis of lupus, however, very little is known about the epigenetics of PSS.

Methods: We performed a genome-wide DNA methylation study in naïve CD4+ T cells in eleven PSS patients before receiving any treatment compared to age-, sex-, and ethnicity-matched healthy controls. Naïve CD4+ T cells were isolated from PBMCs by FACS or indirect labeling and magnetic bead separation. Cell purity was > 95%. DNA was isolated, and treated with sodium bisulfite. Cytosine methylation was quantified in more than 485,000 CpG sites that cover 99% of RefSeq genes, with an average of 17 CpG sites per gene region using the Illumina Infinium HumanMethylation450 BeadChip array. Differentially methylated CpG sites between PSS patients and controls with a fold difference ≥ 1.2 were identified. A false discovery rate (FDR) of 5% was applied to correct for multiple testing and differential methylation was considered statistically significant if the FDR corrected P value was ≤ 0.01.

Results: We identified 553 hypomethylated and 200 hypermethylated CpG sites in naïve CD4+ T cells from PSS patients compared to healthy matched controls, representing 311 hypomethylated and 115 hypermethylated gene regions. Hypomethylated genes in PSS include *LTA,* coding for Lymphotoxin α, which is involved in LTβ receptor signaling pathway, activation of follicular dendritic cells, and expression of interferon α. Other relevant genes such as *GSTM1, CD247*, *TNFSF25, PTPRC* and *PDCD1* were also hypomethylated. The interferon signature pathway was represented by hypomethylation of *STAT1*, *IFI44L*, and *IFITM1*. A group of genes encoding for members of the solute carrier proteins, which are membrane transport proteins that are important for maintenance of cell function were hypomethylated (*SLC11A1*, *SLC11A2*, *SLC22A23*, *SLC25A25*, *ALC25A3*, *SLC25A33*, *SLC6A20*), whereas, *SLC9A1*, which is important for the maintenance of PH homeostasis was hypermethylated in PSS patients compared to controls. In addition, the transcription factor *RUNX1* was hypermethylated in patients, suggesting an impact on the differentiation of hematopoietic stem cells, and possible connection to lymphoma predisposition. Gene ontology (GO) analysis of hypomethylated genes demonstrated enrichment of genes involved in lymphocyte activation (P= 1.10E-04), and immune response (P= 2.20E-03). GO terms for hypermethylated genes included antigen processing and presentation (P= 8.00E-06), and positive regulation of RNA metabolic process (P= 2.10E-02).

Conclusion: This is the first epigenome-wide DNA methylation study in PSS. Our data suggest wide-spread DNA methylation changes in naïve CD4+ T cells in PSS, and highlight several genes and pathways that may be involved in the pathogenesis of this disease and that will be the subject for our future investigation.

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2774

Distinct Role Of Plasmacytoid Dendritic Cells and Mast Cells In The Pathogenesis Of Sjögren's Syndrome. Jidong Zhao, Kunihiro Yamaoka, Satoshi Kubo, Shingo Nakayamada and Yoshiya Tanaka. University of Occupational and Environmental Health, Japan, Kitakyushu, Japan.

Background/Purpose: Sjögren's Syndrome (SS) is characterized by the destruction of the lacrimal and salivary grands due to autoreactive lymphocyte infiltration in the early phase and subsequent intralobular fibrosis and acinar atrophy at late phase of the disease. Involvement of plasmacytoid dendritic cells (pDCs) and mast cells (MCs) has been suggested, although their detailed role in pathology is poorly understood. The aim of this study was to investigate the role pDCs and MCs in the disease course of SS.

Methods: Lip biopsy specimen from 178 SS patients and 7 Sicca syndrome (Sicca) patients were analyzed. NanoZoomer Digital Pathology (NDP), a system to convert a histology slide into high-resolution digital slides and enables sequential pathological analysis of multiple sections and measurement of accurate specimen area was utilized for analysis. Density of pDCs and MCs (/mm^2) was measured with NDP and histological scoring was performed on lymphocytes infiltration, acinar atrophy and intralobular fibrosis. pDC, CXCL13 and CD68 were detected by immunohistochemistry and MCs were detected by toluidine blue staining. Histological stage was based on 'Greenspan grade'.

Results: Significant lymphocytes infiltration, acinar atrophy and intralobular fibrosis were observed in SS compared to Sicca patients with salivary gland destruction. Both, pDCs and MCs were significantly increased in SS compared to Sicca (12.6±10.2 vs 3.4±3.7, 43.7±21.8 vs 21.5±6.9). Positive correlation between density of pDCs with lymphocytes infiltration score (p□□0.02) and density of MCs with intralobular fibrosis score (p□□0.03) was observed in primary SS but not in secondary SS. Moreover, in the primary SS, density of CXCL13 positive infiltrating cells positively correlated with the degree of lymphocyte infiltration score and density of pDCs ($p<0.001$); by double immunostaining of anti-CXCL13 and anti-CD68, we found that most of CXCL13 positive infiltrating cells are from Macrophage(*57.8±22.1%*) and the localization of PDC and CXCL13 positive infiltrating cells are almost same around duct. On the other hand, no correlation was observed with secondary SS patients.

Conclusion: Our data suggests the specific role of pDCs in lymphocyte infiltration in primary SS. Correlation of CXCL13 expression, a chemoattractant for lymphocyte recruitement, with lymphocyte infiltration and density of pDCs further suggests the important role of pDCs. CXCL13 is induced by type 1 IFN, whereas pDCs are the major source of type 1 IFN. Therefore, it likely that type 1 IFN produced by pDCs in the early stage of the disease induces CXCL13 production of infiltrating cells, especially Macrophage, contributing to lymphocyte infiltration constructing germinal center. In addition, MCs seems to be involved in intralobular fibrosis which occurs in the mid to late stage of SS.

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2775

Adenosine A2b Receptor Agonist Bay60–6583 Restores Salivary Gland Function In a Mouse Model For Sjögren's Syndrome. Barbara Szczerba, Paulina Rybakowska, Paromita Dey, Harini Bagavant and Umesh Deshmukh. University of Virginia, Charlottesville, VA.

Background/Purpose: Primary Sjögren's syndrome (pSS) is a chronic autoimmune disorder mainly affecting the exocrine glands. However, it is now clear that both immune and non-immune mechanisms are responsible salivary gland dysfunction in this disorder. Thus, drugs capable of inducing immunosuppression as well as directly influencing salivary gland function would be highly desirable as therapeutics for SS. Adenosine is a major anti-inflammatory metabolite generated during tissue injury and it signals through four distinct G protein-coupled receptors, termed A1AR, A2aAR, A2bAR and A3AR. In addition it can have direct effects on different aspects of cellular metabolism. Thus, in this study we have tested the efficacy of adenosine A2b receptor agonist Bay60–6583 for restoration of salivary gland function in a mouse model for SS-like disorder.

Methods: The B6.Aec1Aec2 mouse model for SS-like disorder was used for this study. Gene expression of adenosine receptors on human and mouse submandibular gland cell lines, as well as mouse salivary glands was determined by real time PCR. ERK phosphorylation in cell lines treated with the drug and presence of serum autoantibodies were analyzed by western blotting. Mice with established glandular dysfunction were treated with the drug, 8 times, every third day by intraperitoneal route. Saliva production was measured following pilocarpine injection. Cytokine levels in sera were measured using Bioplex assay system. Formalin fixed salivary gland sections were stained with H and E and presence of inflammatory cell infiltrates quantified by Stereology.

Results: All adenosine receptors were expressed in the mouse salivary glands and in the mouse and human cell lines. Bay60–6583 readily induced ERK phosphorylation in the human and mouse cell lines. Mice treated with Bay60–6583 showed significant improvement in their saliva production than control (vehicle treated) mice. Salivary glands from drug treated mice showed significantly lower inflammatory cell infiltrates. Surprisingly, the inflammatory cytokine and autoantibody levels between the vehicle and drug treated mice were not different.

Conclusion: Our study has established for the first time the presence of functional adenosine receptors on salivary gland cells. The restoration of glandular function in drug treated mice demonstrates the potential of targeting adenosine receptors for therapeutic intervention in SS. Our study also demonstrates that in this mouse model, circulating inflammatory cytokine and autoantibody levels were dissociated from glandular dysfunction. This finding suggests that in some SS patients, biomarkers other than circulating cytokines and autoantibodies might be more relevant for following disease progression.

Disclosure: B. Szczerba, None; **P. Rybakowska**, None; **P. Dey**, None; **H. Bagavant**, None; **U. Deshmukh**, None.

ACR Concurrent Abstract Session

Spondylarthropathies and Psoriatic Arthritis: Clinical Aspects and Treatment: Clinical Features of Spondyloarthritis

Tuesday, October 29, 2013, 4:30 PM–6:00 PM

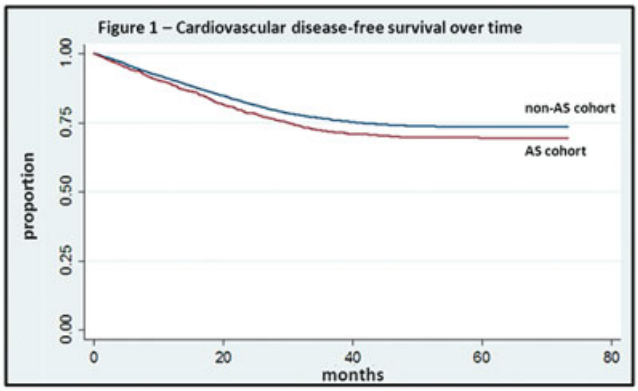
2776

Ankylosing Spondylitis Is Associated With An Increased Likelihood Of Cardiovascular Disease: A Nationwide Matched Cohort Study In Primary Care. Linda E. Dean[1], Gary J. Macfarlane[1], Alan G. MacDonald[2] and Gareth T. Jones[1]. [1]University of Aberdeen, Aberdeen, United Kingdom, [2]Aberdeen Royal Infirmary, Aberdeen, United Kingdom.

Background/Purpose: Cardiovascular disease (CVD) risk is well established in rheumatoid arthritis but less so in ankylosing spondylitis (AS). Due to a similar inflammatory profile, AS patients may be expected to be at increased risk of CVD, particularly ischemic heart disease, hyperlipidaemia and hypertension. Thus, the aim of this study was to determine whether there is an increased risk of CVD among persons with AS.

Methods: Design: matched cohort study. The Scottish Primary Care Clinical Informatics Unit collects demographic, diagnostic and clinical information from a nationally representative sample of general practices in Scotland, UK. As almost all UK residents are registered with a general practitioner and referrals to specialist services are made via this route, the database provides a source of nationwide health data. In April 2007, the database consisted of 3,256,108 patients, approximately 60% of the Scottish population. The 'exposed' cohort comprised all patients with a prior clinical diagnosis of AS (indicated by disease-specific codes). These patients were matched at a ratio of 4:1 to non-AS patients by age (+/− 1yr), gender and area-level deprivation. AS patients were followed up from date of diagnosis until either a CVD diagnosis or the end of follow-up period. Non-AS patients were assigned the same index date as their matched exposed patient and followed to the same end point. All those with a CVD diagnosis prior to the index date were excluded. Data was extracted on the following CVD outcomes: ischemic heart disease; congestive heart failure; cerebrovascular disease; cardiomyopathy; pericarditis; valvular disease; conduction disturbances; hyperlipidaemia; hypertension; atherosclerosis; and heart valve replacement. Differences in the occurrence of CVD between cohorts were examined using (a) Kaplan-Meier survival curves, and (b) Cox proportional hazards regression. Results were adjusted for smoking status and summarised as hazard ratios (HR).

Results: 1,964 AS patients, plus 7,856 matched non-AS patients, were identified (mean age 62yrs, 77% male). Median follow-up time was 16yrs (IQR 8–26). The risk of CVD, over time, is shown in Figure 1. Persons with AS were significantly more likely to receive a diagnosis of CVD than individuals without AS (HR 1.15; 95%CI 1.05–1.26) and, in particular, experienced a 20% increase in the risk of hypertension (1.20; 1.07–1.34). No significant individual associations were found with any of the other CVD diagnoses under investigation, including ischemic heart disease, heart failure or hyperlipidemia.



Conclusion: This large nationwide primary care cohort demonstrates an increased risk of CVD among AS patients which is evident from the time of diagnosis. Clinicians should be aware of the excess CVD risk in this patient group which may help inform their overall management, with the view to optimize long-term quality of life.

Disclosure: L. E. Dean, None; **G. J. Macfarlane**, Abbott Laboratories, 2, Pfizer Inc, 2; **A. G. MacDonald**, None; **G. T. Jones**, Abbott Laboratories, 2, Pfizer Inc, 2.

2777

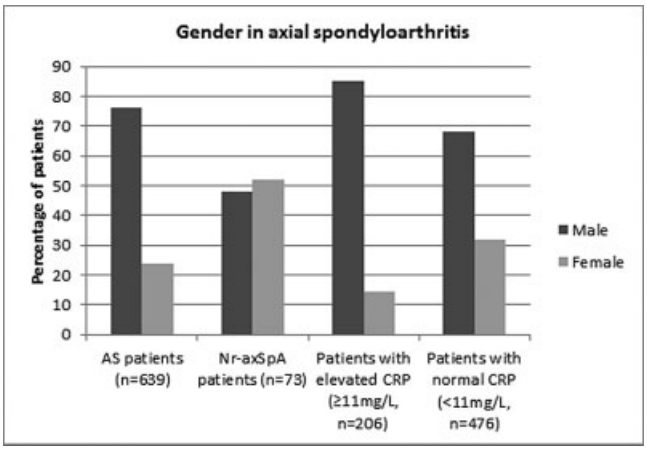
Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis: Part of a Common Spectrum Or Distinct Diseases? Analysis of a Longitudinal Prospective Cohort. Dinny Wallis[1], Nigil Haroon[1], Renise Ayearst[2], Adele Carty[1] and Robert D. Inman[1]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Historically ankylosing spondylitis (AS) has been defined by the modified New York classification criteria which require the presence of radiographic sacroiliitis. More recently the use of MRI has led to the identification of patients with features of axial spondyloarthritis (SpA) who do not fulfill the modified New York criteria (non-radiographic axial SpA, nr-axSpA). The natural history of axial SpA is not completely understood and current knowledge is drawn largely from European data. We aimed to compare the features of AS and nr-axSpA in a North American cohort.

Methods: Data were analyzed for all patients enrolled in a longitudinal spondyloarthritis cohort between January 2003 and December 2012 meeting modified New York criteria for AS or the ASAS classification criteria for nr-axSpA. Categorical variables were compared using Fisher's exact test with two-tailed p values. For continuous variables, a mean patient value was calculated based on all visits for that patient. Variables were compared using t-tests.

Results: 639 patients with AS and 73 patients with nr-axSpA were included. Of the nr-axSpA patients, 40 demonstrated inflammation on MRI, and 33 were classified according to ASAS clinical criteria for axial SpA (of whom 15 had MRI showing no inflammation and 18 did not have MRI). The proportion of male patients was higher in AS than in nr-axSpA (76.2% vs. 47.9%, $p<0.0001$). CRP and ESR levels were higher in AS than nr-axSpA (CRP 11.4 vs. 5.2, $p<0.0001$; ESR 13.7 vs. 9.9, $p=0.018$). Disease duration at last clinic visit was shorter in nr-axSpA than AS

(12.1y versus 17.7y, p=0.0002), providing some indirect support to the notion that nr-axSpA may represent a subset of axial SpA seen earlier in the course of the disease than AS. The proportions of patients receiving biologic therapy, non-steroidal anti-inflammatory drugs, disease modifying anti-rheumatic drugs and glucocorticoids were similar in AS and nr-axSpA. Further investigation of gender, inflammation and radiographic severity in the combined axial SpA cohort revealed that 31.9% of patients with a normal CRP were female, compared to only 14.6% of patients with an elevated CRP (p<0.0001). 96.6% patients with an elevated CRP had radiographic AS, compared to 86.8% of those with a normal CRP (p<0.0001). When data were analyzed for only the female patients, the difference in acute phase response between AS and nr-axSpA lost significance (CRP 9.4 versus 5.2, p=0.09; ESR 16.3 versus 11.5, p=0.07).



Conclusion: Analysis of this North American SpA cohort has identified some key differences between subsets of axial SpA, and highlights the influence of gender on inflammation and radiographic severity, thereby influencing the clinical classification of axial SpA patients.

Disclosure: D. Wallis, Janssen Pharmaceutica Product, L.P., 2; **N. Haroon**, Janssen Pharmaceutica Product, L.P., 5, Pfizer Inc, 5, Amgen, 5, Abbott Laboratories, 5; **R. Ayearst**, None; **A. Carty**, None; **R. D. Inman**, Abbvie, Janssen, Pfizer, UCB, 5.

2778

Mortality In United States Veterans With The HLA-B27 Gene. Jessica Walsh[1], Brian C. Sauer[1], Daniel O. Clegg[1], Grant W. Cannon[2], Xi Zhou[1] and Chiachen Teng[1]. [1]George E. Wahlen Veteran Affairs Medical Center, Salt Lake City, UT, [2]Salt Lake City VA and University of Utah, Salt Lake City, UT.

Background/Purpose: HLA-B27 (B27) is carried by in 6–8% of Americans and is strongly associated with spondyloarthritis (SpA). SpA has been associated with premature mortality. However, increased mortality was not suspected in B27 positive (B27+) individuals without SpA, until recently published data from the 2009 National Health and Nutrition Examination Survey reported a lower prevalence of B27 in randomly selected people older than 50, compared to younger people (7.3% vs. 3.6%, OR 0.4, CI 0.3–0.8). The purpose of this study was to better define the relationship between the B27 gene and mortality, by comparing mortality in B27+ and B27- veterans with clinically available B27 test results.

Methods: The Corporate Data Warehouse was used to identify veterans with available B27 test results. Mortality differences between B27+ and B27- veterans were compared with Cox proportional hazard ratios. Logistic regression was used to evaluate the relationships between death and covariates including age at B27 testing, sex, race, and SpA diagnoses codes from rheumatology encounters.

Results: Among 17,209,732 veterans, 32,327 had both available vital status data and B27 test results (Figure 1). The mean age at testing was 50.5 for B27+ and 50.1 for B27- veterans. Male gender was recorded in 92.9% of B27+ veterans and 88.3% of B27- veterans (Table 1). The hazard ratio comparing mortality in B27+ and B27- veterans was 1.16 (CI 1.04 – 1.30), after adjustment for age at B27 testing, sex, race, and SpA codes (Table 2).

Figure 1. Study population

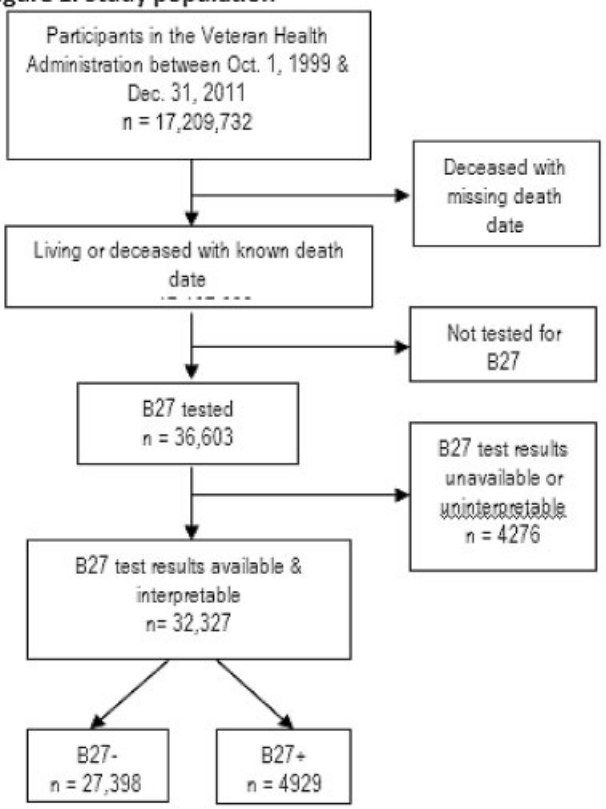


Table 1. Demographics, B27 testing, & spondylorthritis

	B27− n = 27,398 ± SD or (%)	B27 + n = 4929 ± SD or (%)
Age at B27 testing (mean)	50.1 ± 14.6	50.5 ± 14.3
Male gender	24,201 (88.3)	4578 (92.9)
Race		
White	19,321 (70.5)	3823 (77.6)
Black	5146 (18.8)	433 (8.8)
Other*	445 (1.6)	92 (1.9)
Unknown/declined to answer	2486 (9.1)	581 (11.8)
Years between B27 testing & study end or death (mean)	5.1 ± 3.3	5.3 ± 3.3
SpA ICD-9 code from a rheumatology encounter	2381 (8.7)	1717 (34.8)

*Other races included American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander

Table 2. Mortality in B27− and B27+ veterans

	Person time (Years after B27 testing)	Deceased (%)	Adjusted HR* (95% CI)	P
B27−	140,120	1981 (7.2)	Ref.	
B27+	26,060	411 (8.3)	1.16 (1.04–1.30)	0.01

*Adjusted for age at B27 testing, sex, race, & presence of SpA diagnoses codes

Conclusion: Mortality was higher in B27+ veterans than B27- veterans, and the difference was not explained by age, sex, race, or SpA diagnoses codes. The mortality difference was likely conservative because the B27- group may have been disproportionately enriched with conditions mimicking SpA that are associated with increased mortality, such as chronic pain or rheumatoid arthritis. Additional research is required to estimate survival in unselected individuals from the general population and to identify specific disease processes that contribute to premature mortality. Recognizing these diseases may provide mechanistic insights into B27 functions and may lead to interventions that improve survival in B27+ individuals.

Disclosure: J. Walsh, None; **B. C. Sauer**, None; **D. O. Clegg**, None; **G. W. Cannon**, None; **X. Zhou**, None; **C. Teng**, None.

2779

A Novel Evidence-Based Detection Of Undiagnosed Spondyloarthritis In Patients Presenting With Acute Anterior Uveitis: The DUET (Dublin Uveitis Evaluation Tool) Algorithm. Muhammad Haroon[1], Michael Anthony O'Rourke[2], Pathma Ramasamy[2], Conor Murphy[2] and Oliver FitzGerald[1]. [1]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [2]Royal Victoria Eye and Ear Hospital, Dublin, Ireland.

Background/Purpose: The prevalence of mostly undiagnosed underlying Spondyloarthropathy (SpA) is more than 60% among patients presenting with acute anterior uveitis (AAU). To date, there are no formal guidelines or referral pathways for AAU patients developed or endorsed by any international or national societies. The objectives of our study were: (1) to investigate the prevalence of undiagnosed SpA in patients presenting with idiopathic AAU; (2) to develop and validate an assessment algorithm for referral from Ophthalmologists of appropriate AAU patients to Rheumatology that will aid the early diagnosis of the SpA

Methods: All consecutive patients attending emergency department of local ophthalmology hospital with AAU, but who did not have a known diagnosis of SpA, were eligible to partake in this study. Patients with any other known cause of AAU were excluded.

DEVELOPMENT COHORT: The rheumatologic referral was made as per a test algorithm (Figure-1), and those who did not require a referral, remained part of the study as a control group; these patients also underwent detailed rheumatologic evaluation.

VALIDATION COHORT: To confirm the findings from the development cohort, we recruited a validation cohort with similar entry and exclusion criteria. Algorithm version-1 (revised form of test algorithm which is now named the DUET algorithm, figure-1) was used in this cohort to identify patients requiring rheumatologic referral.

Results: DEVELOPMENT COHORT: 104 consecutive patients from September 2011 through to June 2012 were recruited. However, 3 of these patients were lost to follow up prior to rheumatologic evaluation. After rheumatologic evaluation of the entire cohort (n=101), 41.6% (n=42) had undiagnosed SpA as per ASAS classification criteria. Our test algorithm was noted to have: sensitivity 100%, specificity 53.5%, PPV 61% and NPV 100%. Further regression analysis resulted in the development of the DUET algorithm which made the following improvements in the assessment of the development cohort: sensitivity 95%, specificity 98%, PPV 97.5%, NPV 96.6, positive LR 56.19, and negative LR 0.04.

VALIDATION COHORT: To obtain a 95% confidence interval of at least as narrow as ±10% or ±8% for all the statistics, a sample size of 44 or 69 participants, respectively, was deemed sufficient. Hence, consecutive 74 idiopathic AAU patients were recruited from November 2012 through to April 2013, but 2 of these patients were lost to follow-up. After rheumatologic evaluation of the cohort (n=72), 40% (n=29) were diagnosed with SpA, with the following performance of DUET algorithm - sensitivity 96%, specificity 97%, PPV 96.5, NPV 97.6, positive likelihood ratio 41.5 and negative likelihood ratio of 0.03

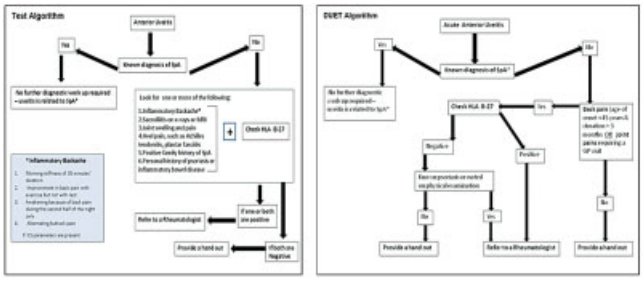


Figure 1.

Conclusion: Approximately 40% of patients presenting with idiopathic AAU have undiagnosed SpA. A simple to apply algorithm is described with excellent sensitivity and specificity.

Disclosure: M. Haroon, None; **M. A. O'Rourke**, None; **P. Ramasamy**, None; **C. Murphy**, None; **O. FitzGerald**, UCB, PFIZER, ABBOTT, ROCHE, MSD, BMS, 2, Janssen Pharmaceutica Product, PFIZER, ABBOTT, ROCHE, BMS, MSD, 5, Pfizer, ABBOTT, UCB, ROCHE, JANSSEN, 8.

2780

Cumulative Exposure To Elevated Inflammatory Markers Is Associated With Increased Burden Of Atherosclerosis In Psoriatic Arthritis Patients: A Cohort Study. Lihi Eder[1], Arane Thavaneswaran[1], Vinod Chandran[1], Richard J. Cook[2] and Dafna D. Gladman[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Waterloo, Waterloo, ON.

Background/Purpose: Cardiovascular morbidity is increased in patients with psoriatic arthritis (PsA). Traditional cardiovascular risk factors do not fully explain this excessive risk. It is unclear whether the cumulative burden of inflammation in the skin and the joints contribute to the development of atherosclerotic plaques. We aimed to investigate whether higher burden of arthritis and psoriasis over time is associated with the development of atherosclerotic plaques among patients with PsA.

Methods: A retrospective cohort analysis was conducted in patients attending a large PsA clinic. Patients were assessed at 6–12 month intervals according to a standard protocol. Information about demographics, medical history, musculoskeletal and skin examination, patient-reported outcomes and laboratory tests was collected at each visit. The cumulative effect of inflammation was measured by a time-adjusted arithmetic mean (AM) of all available measurements from the first visit to the clinic. The following variables were considered as predictors: Psoriasis Activity and Severity Index (PASI), Erythrocyte Sedimentation Rate (ESR), total leukocyte counts (TLC), Tender and Swollen joint count (TJC, SJC), C - reactive protein (CRP), Psoriatic Arthritis Disease Activity Score (PASDAS) and Disease Activity for PsA (DAPSA). Ultrasound assessment of the carotid arteries was performed and Total Plaque Area (TPA) was measured. This measure represented the extent of atherosclerosis and was considered the outcome of interest. TPA was stratified into 4 categories: 1) TPA=0 (no plaques), 2) $0<TPA\leq0.1$ cm^2, 3) $0.1<TPA\leq0.4$ cm^2, 4) TPA>0.4 cm^2. The association between the various AM variables and TPA categories was assessed using logistic ordinal regression model adjusted age and gender.

Results: A total of 235 patients with PsA were analyzed. Their mean age was 55.4±11.4 years and the duration of psoriasis and PsA were 27±13.5 and 16.2±11.7 years, respectively. 56.6% of the participants were males. Patients in higher TPA categories were older at the time of assessment ($p<0.001$), were more likely to be smokers ($p=0.008$), hypertensive ($p=0.002$), diabetics ($p<0.001$) and were older at the onset of psoriasis ($p<0.001$) and PsA ($p<0.001$). In a multivariable regression model adjusted for age and sex AM-ESR was associated with higher TPA categories (category 3 vs. 1 Odds Ratio (OR) 1.04, 95% Confidence Interval (CI) 1, 1.08, p=0.04, category 4 vs. 1 OR 1.05, 95% CI 1.01, 1.1, p=0.02). The following variables were also associated with higher probability of having severe atherosclerosis (being in TPA category 4 vs. 1): AM-TLC (OR 1.45, 95% CI 1.09, 1.92, p=0.01) and AM-DAPSA (OR 1.08, 95% CI 1.02, 1.14, p=0.009). A trend for an association was observed between AM-PASDAS and being in the highest TPA category (OR 1.73, 95% CI 0.97, 3.09, p=0.06). No significant association was found between AM-PASI, AM-CRP, AM-TJC, AM-SJC and damaged joint count and TPA category in multivariate analysis.

Conclusion: An exposure to increased cumulative inflammation is associated with development of atherosclerotic plaques among patients with PsA.

Disclosure: L. Eder, None; **A. Thavaneswaran**, None; **V. Chandran**, None; **R. J. Cook**, None; **D. D. Gladman**, None.

2781

The Disease Characteristics and Predictors Of Minimal Disease Activity On TNF Blockers- Results From A Longitudainal Observational Cohort. Amir Haddad[1], Arane Thavaneswaran[1], Ioana Ruiz Arruza[1], Vinod Chandran[1], Richard J. Cook[2] and Dafna Gladman[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Waterloo, Waterloo, ON.

Background/Purpose: A state of Minimal Disease Activity (MDA) has been defined and validated as a target for treatment in PsA. The purpose of the study is to identify disease characteristics and predictors of MDA in PsA patients treated with TNF blockers.

Methods: Patients fulfilled the CASPAR criteria and were followed regularly every 3–6 months and completed radiographic evaluation at 2-year intervals. TNFα blockers were prescribed when patients failed standard of care. Patients were considered in MDA when met at least 5/7 of the criteria defined by Coates et al[i].Sustained MDA was defined as MDA lasting for

≥ 12 months. Patients achieving MDA were compared to patients who did not achieve MDA. A proportional odds discrete time survival analysis model was applied adjusting for gender, age at visit, duration of PsA, presence of abnormal ESR and damaged joint count at each visit to identify predictors for MDA.

Results: Of the 306 patients treated with anti-TNF agents 23 were in MDA at baseline and 57 were prescribed anti-TNF agents prior to enrolment. 226 were in non-MDA state and constituted the study population. 145/226 patients achieved MDA after an average of 1.30 (1.68) years and for a mean duration of 3.46 (2.25) years. Patients who achieved MDA were more likely males (71.9% vs. 55.2%), younger at diagnosis (34.4 vs. 39.0 years), had a lower actively inflamed joint count (7.3 vs. 15.1), dactylitis (9.1% vs 13.9%), enthesitis (10.8% vs. 17.4% and tenosynovitis (9.2% vs. 21.7%), but more likely to have clinical damage (72.7% vs. 52.2%) and higher modified Steinbrocker score (25.5 vs. 11.5) as well as axial involvement (46.2% vs. 25%) at baseline compared to patients that didn't achieve MDA. Non-MDA patients had higher BMI (31.3 vs. 28.8), more were classified with functional class III/IV (33.3% vs. 10.1%) and had a lower SF-36 physical (28.1 vs. 43.9) and mental (41.9 vs. 49.9) component summary scores at baseline compared to the MDA group. HLA B*27 was found in 24.8% patients with MDA compared to 9.2% patients who didn't achieve MDA (P=0.007). The majority of patients in both groups were also treated with DMARDs and NSAIDs. No significant difference was found in disease duration, alcohol use, smoking, ESR, CRP or PASI score between the two groups. Patients who achieved MDA had less radiographic progression over time compared to patients without MDA. The survival analysis showed that after adjusting for characteristics at each visit male gender increased the odds of achieving MDA (OR=1.68 CI 1.11, 2.53, P=0.01), whereas an abnormal ESR lowered the odds of achieving MDA (OR=0.46 CI 0.27, 0.80, P=0.06). As for sustained MDA, only normal ESR was found to a predictor (OR 0.06 CI 0.03–0.15, P<0.0001).

Conclusion: 63% of the study group achieved MDA after an average duration of 1.3 years and those patients had less active disease at baseline but more damage with less radiographic progression over time. A normal ESR at each visit and male gender were predictors of MDA in patients treated with TNF blockers, the presence of HLA B*27 has a prognostic value also in identifying patients who achieve MDA.

[i] Ann Rheum Dis. 2010 Jan;69(1):48–53)

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ACR Concurrent Abstract Session
Vasculitis III
Tuesday, October 29, 2013, 4:30 PM–6:00 PM

2782

Retreatment With Rituximab In The Rituximab In ANCA-Associated Vasculitis (RAVE) Trial. Eli Miloslavsky[1], Ulrich Specks[2], Peter A Merkel[3], Philip Seo[4], Robert F. Spiera[5], Carol A. Langford[6], Gary S. Hoffman[7], Cees G.M. Kallenberg[8], E. William St Clair[9], Nadia Tchao[10], Linna Ding[11], David Ikle[12], Brett Jepson[12], Paul Brunetta[13] and John H. Stone[14]. [1]Massachusetts General Hopsital, Boston, MA, [2]Mayo Clinic, Rochester, MN, [3]University of Pennsylvania and VA Medical Center, Philadelphia, PA, [4]Johns Hopkins Vasculitis Center, Baltimore, MD, [5]Hospital for Special Surgery, New York, NY, [6]Cleveland Clinic, Cleveland, OH, [7]Cleveland Clinic Foundation, Cleveland, OH, [8]University Medical Center Groningen, Groningen, Netherlands, [9]Duke Unversity Medical Center, Durham, NC, [10]Immune Tolerance Network, Bethesda, MD, [11]NIAID, Bethesda, MD, [12]Rho, Chapel Hill, NC, [13]Genentech, So San Francisco, CA, [14]Massachusetts General Hospital, Boston, MA.

Background/Purpose: Retrospective studies have demonstrated that repeat rituximab treatment may be effective in re-inducing remission in relapsing ANCA-associated vasculitis. We analyzed data from the Rituximab in ANCA-associated vasculitis (RAVE) trial in order to determine the safety and efficacy of a second course of rituximab for relapsing granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA).

Methods: Randomized controlled trial comparing rituximab (RTX, n=99) to cyclophosphamide (CYC) followed by azathioprine (AZA, n=98) for remission induction. Patients who suffered a severe disease flare (BVAS/WG > 3 or one major BVAS/WG item) between 6 and 18 months were eligible for open label RTX (OLR) (375mg/m^2 once weekly times four).

Results: 17 patients received two courses of RTX. Baseline characteristics are presented in the table.

Characteristics of patients treated with open label RTX

	N = 17
Originally assigned to RTX	16 (94%)
PR3-ANCA positive	14 (82%)
GPA	15 (88%)
Newly diagnosed disease	6 (35%)
Mean time to OLR (range, days)	367 (225–556)
BVAS/WG at OLR (range)	4.8 (3–11)
Mean prednisone dose at OLR (range, mg)	8.4 (0–40)
Detectable B-cells at flare	16 (94%)
Rising ANCA at flare	14 (82%)

After retreatment, patients were followed for an average of 301 days (range 35–427). Treatment with OLR led to remission (BVAS/WG=0) in 15 of 17 patients (88%) by an average of 55 days (range 1–181). One patient with diffuse alveolar hemorrhage did not improve and died 7 weeks after the initial flare. Another patient reached a BVAS/WG of 1 before suffering a limited flare at 12 months after OLR.

Six months after OLR, 15 patients (88%) were in remission (BVAS/WG = 0), 8 (47%) had achieved complete response (BVAS/WG = 0 and prednisone ≤ 10mg/day) and 6 patients (35%) were in complete remission (BVAS/WG = 0 and prednisone = 0). After 12 months, 13 patients (76%) had achieved complete responses and 8 (47%) had reached complete remission. There were 4 limited and no severe flares among the 17 patients (BVAS/WG 2.5) over one year of follow up after OLR.

There were a total of 3 severe (grade ≥ 3) adverse events after OLR, including one death (described above), metastatic colon cancer, and severe sinusitis.

Conclusion: This prospective study indicates that retreatment of GPA or MPA flares with rituximab is effective in re-inducing remission.

Disclosure: E. Miloslavsky, Genentech Inc, 9; **U. Specks**, None; **P. A. Merkel**, None; **P. Seo**, None; **R. F. Spiera**, Roche Pharmaceuticals, g, 2; **C. A. Langford**, Bristol-Myers Squibb, 9, Genentech and Biogen IDEC Inc., 9; **G. S. Hoffman**, None; **C. G. M. Kallenberg**, Roche, 8; **E. W. St Clair**, None; **N. Tchao**, None; **L. Ding**, None; **D. Ikle**, Rho, 3; **B. Jepson**, Rho, 3; **P. Brunetta**, Genentech Inc, 3; **J. H. Stone**, Genentech and Biogen IDEC Inc., 2, Genentech and Biogen IDEC Inc., 5, Roche Pharmaceuticals, 2.

2783

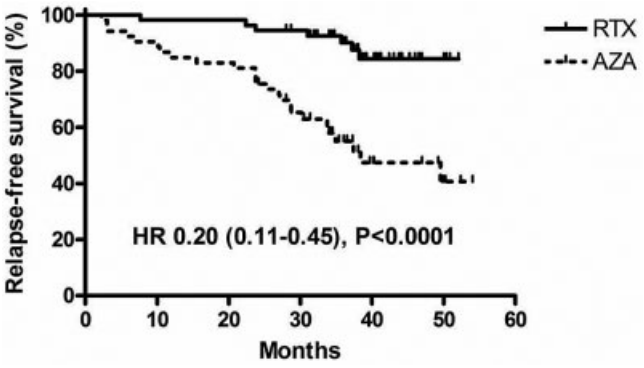
Rituximab Versus Azathioprine For Maintenance In Antineutrophil Cytoplasmic Antibodies-Associated Vasculitis: Follow Up At 39 Months. Benjamin Terrier[1], Christian Pagnoux[2], Alexandre Karras[3], Chahera Khouatra[4], Olivier Aumaître[5], Pascal Cohen[1], Francois Maurier[6], Olivier Decaux[7], Hélène Desmurs-Clavel[8], Pierre Gobert[9], Thomas Quemeneur[10], Claire Blanchard-Delaunay[11], Pascal Godmer[12], Xavier Puéchal[13], Luc Mouthon[14] and Loic Guillevin[15]. [1]Cochin University Hospital, Paris, France, [2]Division of Rheumatology, Mount Sinai Hospital, Toronto, ON, [3]Hôpital Européen Georges Pompidou, APHP, Paris, France, [4]CHU Lyon, Lyon, France, [5]Division of internal Medicine, Centre Hospitalier Universitaire, Hôpital Gabriel Montpied, Clermont–Ferrand, Clermont–Ferrand, France, [6]Division of internal Medicine, CHR Metz, Metz, Metz, France, [7]Rennes University Hospital, Rennes, France, [8]Hospices Civils de Lyon, Hôpital Louis Pradel, Lyon, France, [9]Centre Hospitalier d'Avignon, Avignon, France, [10]CHR de Valenciennes, Valenciennes, France, [11]Hôpital de Niort, Niort, France, [12]Department of Internal Medicine, Centre Hospitalier Bretagne Atlantique de Vannes, Vannes, France, [13]Hôpital Cochin, AP-HP, Université Paris Descartes, Sorbonne Paris Cité, Paris, France, [14]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, Paris, France, [15]Division of Internal Medicine, Hôpital Cochin, University Paris Descartes, Paris, France.

Background/Purpose: Rituximab was shown to be as effective as cyclophosphamide to induce remission in patients with ANCA-associated vasculitis (AAV). The prospective, randomized, controlled MAINRITSAN trial compared rituximab (RTX) to azathioprine (AZA) to maintain ANCA-associated vasculitis (AAV) remission. Once remission was obtained with a conventional regimen using corticosteroids and cyclophosphamide, patients were randomly assigned to receive a 500-mg RTX infusion on D1, D15, 5.5

months later, then every 6 months for a total of 5 infusions over 18 months, or AZA for 22 months at the initial dose of 2 mg/kg/d. The primary endpoint was the major relapse rate (EULAR/ACR criteria) at 28 months. This study demonstrated that 500 mg of rituximab (RTX) every 6 months was superior to azathioprine (AZA) to maintain ANCA-associated vasculitis (AAV) remission during the 28-month follow-up, with a similar profile of tolerance. This study describes the extended follow-up of patients included in the MAINRITSAN trial.

Methods: Extended follow-up was ascertained from the patients included in the trial. Data on relapse and survival were collected from physician records. All patients were analyzed according to the group to which they were randomized, except for 8 patients who were excluded from the extended follow-up because of severe violation to protocol.

Results: One hundred and nine patients were analyzed for the extension of follow-up. Median duration of follow-up was 38.6 months (IQR, 33.5–45.2 months). Seven out of 55 (12.7%) patients in the RTX arm and 26/54 (48.1%) patients in the AZA arm had at least one major relapse. Overall, the risk of major relapse remained significantly lower in the RTX arm compared to the AZA arm (hazard ratio 0.20, 95% CI 0.11 to 0.45, P<0.0001). During follow-up, 3 patients died in the AZA arm but none in the RTX arm. Causes of death were infection, cancer and mesenteric ischemia. Overall survival rate was better in the RTX arm compared to the AZA arm (P=0.07).



Conclusion: Despite relapses in the RTX arm after the end of the study period, RTX remains associated with a lower risk of relapse than AZA. RTX tends to be associated with a better overall survival compared to AZA.

Disclosure: B. Terrier, None; **C. Pagnoux**, None; **A. Karras**, None; **C. Khouatra**, None; **O. Aumaître**, None; **P. Cohen**, None; **F. Maurier**, None; **O. Decaux**, None; **H. Desmurs-Clavel**, None; **P. Gobert**, None; **T. Quemeneur**, None; **C. Blanchard-Delaunay**, None; **P. Godmer**, None; **X. Puéchal**, None; **L. Mouthon**, None; **L. Guillevin**, None.

2784

Mononeuritis Multiplex Predicts The Need For Immunosuppressive Or Immunomodulatory Drugs For Eosinophilic Granulomatosis With Polyangiitis, Polyarteritis Nodosa and Microscopic Polyangiitis Patients Without Poor-Prognosis Factors. Maxime Samson[1], Xavier Puéchal[2], Hervé Devilliers[3], Camillo Ribi[4], Pascal Cohen[5], Boris Bienvenu[6], Christian Pagnoux[7], Luc Mouthon[2], Loic Guillevin[8] and French Vasculitis Study Group (FVSG)[2]. [1]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France; Internal Medicine and Clinical Immunology, Hôpital du Bocage, Dijon, France, Paris, France, [2]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, Paris, France, [3]Internal medicine, Hôpital Général, Dijon, France, Dijon, France, [4]Immunology and Allergology, Internal Medicine, University Hospitals of Geneva, Geneva, Switzerland, Geneva, Switzerland, [5]Cochin University Hospital, Paris, France, [6]Division of Internal Medicine, Centre Hospitalier Régional Universitaire de Caen, Côte de Nacre, Caen, France, Caen, France, [7]Rheumatology, Mount Sinai Hospital, Toronto, Canada, Toronto, ON, [8]Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France.

Background/Purpose: Patients with eosinophilic granulomatosis with polyangiitis (EGPA), polyarteritis nodosa (PAN) or microscopic polyangiitis (MPA) without poor-prognosis factors, as defined by their 1996 Five-Factor Scores (FFS)=0, were included in 2 prospective CHUSPAN trials and initially received corticosteroids (CS) alone. Because some patients required add-on therapies (AT) during follow-up, baseline characteristics associated with their use were sought.

Methods: Patients' data were updated in 2012. Chapel Hill definitions classified EGPA, PAN and MPA. Analyzed AT were all cytotoxic agents, biologics (except omalizumab), intravenous immunoglobulins (IVIg) (>2 g/kg) and plasma exchange. Univariate and multivariate analyses were performed.

Results: The study included 193 patients (75 EGPA, 61 MPA and 57 PAN) initially treated with CS alone. Mean±SD overall follow-up was 97.6±39.6 months, with no difference among entities. During follow-up, 86/193 (24 PAN, 32 MPA and 30 EGPA) patients required AT (mean follow-up since CS onset: 23.3±34.1 months) because CS failed (37%), relapse (52%) or CS dependency (10%): 49 received IV cyclophosphamide (CYC), 13 oral CYC, 56 azathioprine, 15 methotrexate, 9 mycophenolate mofetil, 7 IVIg, 6 plasma exchange, 1 infliximab and 1 cyclosporine. The significant association of mononeuritis multiplex (MNM) with AT use (univariate analysis, Fig 1; P=0.008) was confirmed by multivariate analysis, with MM being the only factor independently associated with requiring AT (hazard ratio=1.81 [95% CI: 1.12–2.93]; P=0.02). AT prescription rates were comparable for the 3 entities. At last visit, 165/193 (85%) were alive, with 94 (57%) and 28 (17%), respectively, still taking CS and/or cytotoxic agent or biotherapy. Overall survival reached 90% at 7 years and was comparable for patients who had taken ≥1 AT vs those treated only with CS during follow-up (P=0.564). However, patients given ≥1 vs 0 AT had significantly higher Vasculitis Damage Indexes (VDI): 2.93±2.09 vs 1.96±1.40 (P<0.001), reflecting more frequent osteoporosis (33 vs 18%, P=0.013) or peripheral neuropathy (60 vs 38%, P=0.004).

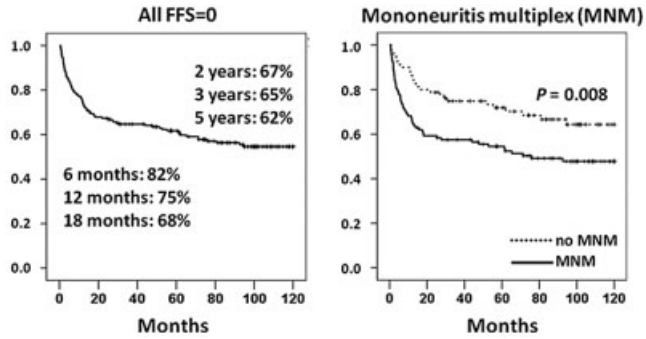


Figure 1. Probability of survival without prescription of new add-on therapies of 193 patients with EGPA, PAN or MPA without baseline poor-prognosis factors (FFS=0). P determined with log-rank test.

Conclusion: Despite the good and comparable overall survival of baseline-FFS=0 EGPA, PAN or MPA patients, 45% required AT, mostly those with MNM, and their VDI were significantly higher, indicating more sequelae than those of the other FFS=0 patients. Hence, this MNM subpopulation might be more likely to fail on CS alone, thereby supporting prospective evaluation of their initial cytotoxic agent use.

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2785

Urinary Inflammatory Cells Strongly Reflect the Disease Activity and Renal Function in Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis. Yoko Wada[1], Minoru Sakatsume[1], Masaaki Nakano[2] and Ichiei Narita[1]. [1]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [2]School of Health Sciences, Faculty of Medicine, Niigata University, Niigata, Japan.

Background/Purpose: The antineutrophil cytoplasmic autoantibody (ANCA)- associated vasculitides (AAVs) include microscopic polyangiitis (MPA), granulomatosis with polyangitis (GPA; formerly Wegener's), and eosinophilic granulomatosis with polyangitis (EGPA). These small-vessel vasculitides are characterized by necrotizing inflammation of the vessel wall, particularly affecting small arteries, arterioles, and capillaries in systemic organs, and the kidney is one of the most frequently involved organs. We have already reported that T cells and macrophages appear in the urine of patients with glomerulonephritis, accompanied by active cellular infiltration

such as cellular crescent formation and diffuse interstitial cell infiltration, but not in the urine of patients with glomerulonephritis without the active inflammatory lesions. In this study, we examined the correlation between the numbers of urinary inflammatory cells and disease activity in AAVs, and assessed the utility of urinary immune cell analysis.

Methods: Thirty patients with AAVs (MPA; n=26, GPA; n=3, EGPA; n=1), who had been referred to Niigata University Hospital between 2004 and 2012, were recruited for this study. The patients were divided into two groups according to clinical renal function (renal involvement (RI) group, n=24); non-renal involvement (non-RI) group, n=6)). Flow-cytometric analysis of urinary inflammatory cells was performed for each subject. Numbers of urinary T cells or macrophages were determined by multiplying the number of viable cells in the gated mononuclear cell region in each sample by the percentage of urinary CD3-positive or CD14-positive cells in the population, respectively. The numbers of urinary CD3-positive cells and CD14-positive cells, laboratory data including the titers of serum ANCA, serum creatinine and C-reactive protein, and the Birmingham vasculitis activity score (BVAS), were examined in each subject, and compared between the RI and non-RI groups. We then examined the correlations between the numbers of CD3-positive or CD-14-positive cells and laboratory data and BVAS by Spearman's rank correlation coefficient in all subjects.

Results: The total numbers of urinary CD3-positive cells and CD14-positive cells were significantly elevated (>120/ml urine) in all patients in the RI group and 5 of 6 patients in the non-RI group. The number of urinary CD3-positive cells was positively correlated with the titer of serum ANCA (r=0.41, p=0.02) and BVAS (r=0.38, p=0.038), while the number of urinary CD14-positive cells was positively correlated with serum Cr (r=0.38, p=0.038) and negatively correlated with eGFR (r=−0.38, p=0.03).

Conclusion: These results indicate the usefulness of urinary immune cell analysis for assessment of both kidney function and disease activity in patients with AAVs.

Disclosure: Y. Wada, None; **M. Sakatsume**, None; **M. Nakano**, None; **I. Narita**, None.

2786

Review Of The Expert Panel Methodology In The Diagnostic and Classification Criteria For Vasculitis Study: A Pilot Study. Cristina Ponte[1], Anthea Craven[2], Joanna Robson[2], Peter C. Grayson[3], Ravi Suppiah[4], Richard A. Watts[5], Peter A. Merkel[6] and Raashid A. Luqmani[2]. [1]Rheumatology and Metabolic Bone Diseases Department, Hospital de Santa Maria, CHLN and Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal, [2]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford, United Kingdom, [3]Section of Rheumatology & the Clinical Epidemiology Unit, Boston University School of Medicine, Vasculitis Center, Boston, MA, [4]Auckland District Health Board, Auckland, New Zealand, [5]Rheumatology Department Ipswich Hospital and University of East Anglia, Ipswich, United Kingdom, [6]University of Pennsylvania, Philadelphia, PA.

Background/Purpose: The Diagnostic and Classification Criteria for Vasculitis (DCVAS) Study is a multinational observational study to develop diagnostic criteria and to update classification criteria for the primary systemic vasculitides.

By 2015 the database will include clinical, laboratory and radiology data from over 2000 patients with vasculitis and 1500 comparator patients who present with features similar to vasculitis. To avoid the inherent circularity of using the submitting physician diagnosis as the gold standard, a reference diagnosis for each patient will be established using a combination of expert panel opinion and data-driven methods (e.g. machine learning algorithms).

The aim of this analysis was to evaluate the methodology by which the expert panel will assess individual patient data to establish the reference diagnosis.

Methods: By November 2012, 1662 patients had been recruited; 391 had complete 6 month follow-up data. Forty cases were randomly extracted and developed into clinical vignettes (CVs). The CVs were assessed for diagnoses by 6 independent experts using an online platform. Ten patients were assessed by all experts and the other 30 were each assessed by 2 of the 6 experts, randomly chosen. The experts first chose between primary vasculitis, secondary vasculitis, or other illness; then the respective major class (small-, medium-, or large-vessel vasculitis, or no predominant size vasculitis); and then the subtype or the specific disease for each category. For each answer a level of certainty (unlikely, possible, probable, definitive, or unknown) was provided. The diagnoses of the expert panel and the submitting physician were compared.

Results: The 40 clinical vignettes represented 26 women and 14 men, with a mean age of 62.5 ± 20.3 years (range 20–86 years). Data from all 120 CV reviews were available for analysis. Treating clinicians submitted a diagnosis of primary vasculitis in 32 patients (17 small-vessel, 1 medium-vessel, 13 large-vessel and 1 with no predominant size); secondary vasculitis in 2, and other illness in 6. The expert panel agreed with the submitted diagnosis of primary vasculitis in 97% of the cases (definite 54%, probable 35% and possible 8%). However, only 78% of the submitted patients with primary vasculitis were classified as having the same sub-type of vasculitis when compared with the expert panel diagnosis (9% could not be sub-typed within the correct major class of vasculitis, 9% classified the cases with another sub-type of the same major class, 3% chose another major class or diagnosis and 2% selected the unknown option). There was an intraclass correlation coefficient of 0.82 (confidence interval 0.57–0.95) in the 10 CVs assessed by the 6 experts, indicating low variability between evaluators.

Conclusion: An expert panel agreed with the individual submitting physician regarding a diagnosis of some form of primary vasculitis in nearly all cases, but disagreement about the exact form of vasculitis occurred in 22% of cases. Physician-based opinion may be more reliable for defining general categories of vasculitis than for defining specific subtypes. This exercise highlights the potential for diagnostic bias when using physician-opinion to define the gold standard diagnosis.

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2787

The Effect Of Smoking On The Clinical Expression Of ANCA-Associated Vasculitis. Neil Basu[1], Aladdin Mohammad[2], Richard A. Watts[3], Paul Gatenby[4], Luis F. Flores-Suarez[5] and Alfred Mahr[6]. [1]University of Aberdeen, Aberdeen, United Kingdom, [2]Skåne University Hospital, Lund, Sweden, [3]Rheumatology Department Ipswich Hospital and University of East Anglia, Ipswich, United Kingdom, [4]ANU Medical School, The Canberra Hospital, Canberra, Australia, [5]Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico, [6]Department of Internal Medicine, Hospital Saint-Louis, Paris, France.

Background/Purpose: It is well recognized that smoking has immunomodulatory effects in several chronic inflammatory disorders. For ANCA-associated vasculitis (AAV), which includes granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), the influence of smoking on disease risk and expression is not well understood. A small retrospective study suggested a protective effect of smoking on ENT manifestations. We investigated the relationship between smoking and AAV characteristics within two large, prospectively collected cohorts.

Methods: The analyses used data from newly-diagnosed patients with AAV who were enrolled in 4 international randomized controlled trials of the Europe Vasculitis Society (EUVAS). Disease characteristics at diagnosis (age, sex, diagnosis, ANCA subtype, system involvement, BVAS, creatinine, CRP) were compared according to smoking status (current versus non-current; ever versus never). The analyses were repeated for the cumulative disease characteristics of consecutive patients with AAV from the Vasculitis Quality of Life (VASQoL) study, a multi-center cross-sectional study involving rheumatology and renal clinics across the United Kingdom. Univariate analyses used Chi^2 and Mann-Whitney tests for categorical and continuous variables, respectively; logistic regression was used for age-adjusted analyses.

Results: Of the 535 EUVAS patients, smoking data was available for 342 (GPA/MPA ratio: 186/156; males: 57%; median age: 60 years) among which 36 (11%) were current smokers and 158 (46%) ever smokers. Of the 360 VASQoL patients (GPA/MPA ratio: 265/95; males: 49%; median age: 64 years), all with complete smoking data, 26 (7%) were current smokers and 191 (53%) were ever smokers. Compared with non-current smokers, current smokers were significantly more likely to have vasculitis-related gastrointestinal (GI) manifestations in the EUVAS and in the VASQoL cohorts (17% vs. 6% [p=0.026] and 12% vs. 4% [p=0.044], respectively). In addition, VASQoL current smokers were significantly more likely to experience cutaneous (48% vs. 28%, p=0.035) and less likely to experience ENT (44% vs. 64%, p=0.046) manifestations. No other differences in AAV characteristics, including anti PR3/MPO status, were observed in the EUVAS and VASQoL cohorts although current smokers were younger than non-current smokers (p=0.047 and p=0.021, respectively). Age-adjustment did

not alter the interpretation of the identified associations of current smoking with disease characteristics. Both EUVAS and VASQoL ever-smokers were more likely to be males (both $p<0.0001$) and older (both $p=0.02$) but ever-smoking was not associated with clinical AAV characteristics in either cohort.

Conclusion: These analyses of 2 independent AAV cohorts indicate that current smoking is positively associated with GI involvement, a finding which is in keeping with the established association between smoking and risk for Crohn's disease. The VASQoL data also replicated a previous report supporting that smokers less often present with ENT manifestations. The lack of phenotype-modifying effects of ever-smoking could suggest an acute immune-modulatory effect of smoking in AAV.

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ACR/ARHP Combined Session
ACR/ARHP Combined Pediatrics Abstract Session
Tuesday, October 29, 2013, 4:30 PM–6:00 PM

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Reliability and Responsivenss Of The Standardized Universal Pain Evaluations For Rheumatology Providers For Children and Youth (SUPER-KIDZ). Nadia Luca[1], Jennifer N. Stinson[1], Susanne M. Benseler[1], Brian M. Feldman[1], Dorcas Beaton[2] and Ahmed Bayoumi[3]. [1]Hospital for Sick Children, Toronto, ON, [2]Scientist, Institute for Work & Health, Toronto, ON, [3]Keenan Research Centre of the Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, ON.

Background/Purpose: Pain is the most common symptom in children and youth with juvenile idiopathic arthritis (JIA), however, currently there is no comprehensive validated pain measure for this population. The Standardized Universal Pain Evaluations for Rheumatology Providers for Children and Youth (SUPER-KIDZ) is a new multi-dimensional online pain tool, developed to fill this gap in clinical care. The objective of this study was to determine the test-retest reliability and responsiveness of the computerized 20-item version of the SUPER-KIDZ pain tool in children with JIA.

Methods: A single center prospective cohort study of JIA patients aged 8–18 years was performed. The SUPER-KIDZ questionnaire was administered to children expected to have stable pain for test-retest reliability analysis of each item using intra-class correlation coefficients (ICC) and weighted Cohen's kappa. Responsiveness of each SUPER-KIDZ item to change in pain was evaluated in patients undergoing intra-articular steroid injection(s) who are expected to have improvement in pain. Measures of responsiveness included standardized response mean (SRM), Wilcoxon signed rank test, linear mixed model regression, and receiver operating characteristic (ROC) curve analysis. Internal consistency of the three SUPER-KIDZ subscales (sensory, interference, emotional) was measured using ordinal reliability alpha and item-total correlation.

Results: Fifty-one children were included, of which 40 (78%) were female, and had a median of 3 active joints (1–5) and median physician global assessment of 2.5 cm (1.5–4) on 10 cm visual analog scale. Internal consistency was acceptable (ordinal $\alpha=0.73$–0.92) for the sensory, interference and emotional SUPER-KIDZ subscales. Good test-retest reliability (ICC or weighted kappa ≥ 0.80) was found for 15 SUPER-KIDZ items in at least one analysis. Reliability was strongest for the items on pain intensity, pain frequency, pain duration and physical function, and weakest for questions related to sleep, having fun, catastrophizing, and feeling angry. At 2 weeks post-injection, 16 items were responsive to change in pain (SRM=0.66–0.82, significant Wilcoxon signed rank and/or linear mixed model regression). ROC curve analysis of 9 items gave an area under the curve of ≥ 0.70, adequately distinguishing between improved and unimproved subjects. The questions less responsive to change in pain were those related to fatigue frequency and emotional function (feeling angry, cheerful, worried).

Conclusion: The majority of items of the new online SUPER-KIDZ tool have excellent test-retest reliability and responsiveness properties. The questions regarding fatigue and emotional function are less responsive to change after a joint injection procedure and could be tested after a cognitive intervention. If validity is demonstrated, this measure could be implemented as a standardized comprehensive pain tool for JIA patients, thereby fulfilling a longstanding gap in the care of patients with JIA.

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2789

Enhancing Uveitis Screening Compliance In Juvenile Idiopathic Arthritis Patients. Melissa S Oliver[1], Jennifer E. Weiss[2], Suzanne C. Li[2], Kathleen A. Haines[2], Ginger L. Janow[2], Esi Morgan DeWitt[3] and Yukiko Kimura[2]. [1]UMDNJ New Jersey Medical School, Newark, NJ, [2]Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [3]Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Background/Purpose: Chronic uveitis is one of the more severe morbidities associated with juvenile idiopathic arthritis (JIA). Risk of developing uveitis, and the frequency of uveitis screening visits, differs between the different JIA subtypes. Through participation in the Pediatric Rheumatology Care & Outcomes Improvement Network (PR-COIN), a quality improvement collaborative, we developed a uveitis screening tool for patients to bring to their ophthalmologist to improve communication between providers. This tool includes education for the family on uveitis. Our objective was to determine if use of this tool improved adherence to uveitis screening recommendations and documentation of uveitis screening.

Methods: A retrospective chart review was conducted of 243 JIA patients without uveitis identified from our Childhood Arthritis & Rheumatology Research Alliance Registry and PR-COIN databases in the 13 months before and after beginning our participation in PR-COIN. Collected data included demographics, documentation of the uveitis assessment, and documentation of patient education. Effectiveness of implementation of the screening tool was assessed by comparing compliance with uveitis screening in the two time periods. Continuous variables were summarized as median (interquartile range). Categorical variables were summarized as frequency (percent). Paired binary outcomes of screening compliance were examined using McNemar's test.

Results: Data from 184 patients were included (table 1). Patients were excluded if they did not follow up during the study period or if charts were unavailable for review. Prior to our participation in PR-COIN, 132 (71.7%) patients reported compliance with screening but only 50 (27%) patients had documentation of their uveitis screening visits. Following introduction of our uveitis screening tool, documentation of screening increased significantly to 45.7% (table2). Of the 184 patients, 52 (28%) were non-compliant by self-report prior to participation in PR-COIN. Of those 52 patients, 32 (61.5%) increased their compliance following implementation of our uveitis screening tool.

Table 1. Demographics and characteristics of JIA patients (n = 184)

Age at diagnosis (years)	
Median (Interquartile range)	9.3 (4.5–13.2)
Range: minimum - maximum	0.3–17.9
Female n (%)	127 (69.0)
Duration of JIA disease (years)	
Median (Interquartile range)	4.4 (3.0–7.5)
Range: minimum - maximum	0.7–18.0
JIA sub-type n (%)	
Polyarticular rheumatoid factor (−)	65 (35.3)
Oligoarticular, persistent	39 (21.2)
Enthesitis related arthritis	20 (10.9)
Systemic arthritis	19 (10.3)
Psoriatic arthritis	17 (9.2)
Oligoarticular, extended	13 (7.1)
Polyarticular rheumatoid factor(+)	11 (6.0)
ANA Positive n (%)	
Yes	50 (27.2)

Table 2. Summary of patient and ophthalmologist compliance before and after implementation of our uveitis screening tool (n = 184)

	13 months prior to joining PR-COIN n(%)	13 months after joining PR-COIN n(%)	P-Value[a]
Patient self-report of compliance with uveitis screening schedule n (%)	132 (71.7)	143 (77.7)	0.1308
Ophthalmologist documentation of eye exam on chart	50 (27.2)	84 (45.7)	0.0001

a, P-value is based on the McNemar's test performed on repeated binary outcomes

Conclusion: Since joining PR-COIN and implementing a uveitis education and communication tool, there was improvement in patient compliance with uveitis screening. There was significant improvement in documentation

by ophthalmology of the patient's visit. Simple tools such as a uveitis screening form can facilitate communication with the ophthalmologist and better educate JIA patients on the importance of uveitis screening, thus improving their care.

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2790

The Research In Arthritis In Canadian Children Emphasizing Outcomes (ReACCh Out) Cohort: Are We Achieving Clinically Important Outcomes? Deborah M. Levy[1], Shirley ML Tse[1], Elizabeth Stringer[2], Jaime Guzman[3], Roberta A. Berard[4], Karen Watanabe Duffy[5], Dax Rumsey[1], Mercedes O. Chan[3], Rosie Scuccimarri[6], Adam M. Huber[2], Lori B. Tucker[7], Rae SM Yeung[1], Ciaran M. Duffy[5], Kiem Oen[8] and The ReACCh Out Investigators[1]. [1]The Hospital for Sick Children and University of Toronto, Toronto, ON, [2]IWK Health Centre and Dalhousie University, Halifax, NS, [3]BC Children's Hospital and University of British Columbia, Vancouver, BC, [4]Children's Hospital of Western Ontario, London, ON, [5]Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa, ON, [6]Montreal Children's Hospital and McGill University, Montréal, QC, [7]University of British Columbia, Vancouver, BC, [8]Children's Hospital of Winnipeg and University of Manitoba, Winnipeg, MB.

Background/Purpose: Recent data suggests that achievement of inactive disease and early disease remission may result in improved outcomes for patients with juvenile idiopathic arthritis (JIA). Objectives of our study were to examine the probabilities of achieving i) active joint count (AJC)= 0; ii) inactive disease; and iii) disease remission for patients treated with contemporary treatments in a large prospective longitudinal inception cohort of patients with JIA.

Methods: ReACCh Out recruited consecutive patients diagnosed with JIA at 16 sites across Canada (Jan 2005 – Dec 2010), with prospective data collection every 6 months for the first 2 years, then yearly. Clinical information included the six ACR core outcome measures and medications. Inactive disease was defined as active joint count (AJC) =0, absence of systemic symptoms, enthesitis or uveitis and a physician global activity (PGA) of $<$ 1 cm on a 10 cm VAS. Remission was defined as $\geq$ 12 months with inactive disease with no anti-rheumatic or anti-uveitis medications. Descriptive statistics (median and interquartile range (IQR)) and Kaplan-Meier Survival analyses were examined; patients were censored at their last study visit or study end date.

Results: 1104 patients with newly diagnosed ($\leq$ 6 months) active JIA with $\geq$1 follow-up visit were analyzed. Patients were predominantly female (63%), age at diagnosis was 9.3 (3. 9, 13.0) years. Time from diagnosis to enrollment was 0.3 (0, 1.6) months. Follow-up to last visit or study end was 34.2 (21.5, 48) months. Patients were classified into ILAR subtypes at the 6 month visit: oligoarticular (416, 38%), polyarticular RF negative (235, 21%), polyarticular RF positive (46, 4%), psoriatic (64, 6%), enthesitis related arthritis (ERA) (157, 14%), systemic (sJIA)(76, 7%) and undifferentiated (110, 10%). Treatment received included intraarticular steroid injections in 46%, DMARDs in 55%, and biologics in 12%. Almost all patients (92%) achieved AJC=0 during the study period at a median of 7.0 mos (IQR 3.5, 13.3) from diagnosis. Patients with RF positive polyarthritis were last to reach AJC =0. Inactive disease was achieved by 81% of subjects at a median of 13.0 mos (IQR 7.7, 21.7) from diagnosis. Time to first episode of inactive disease was shortest in the oligoarthritis group, and longest in the RF positive polyarthritis group. Table 1 shows the time to achieve AJC =0 and inactive disease by JIA subtype. By survival analysis, the probability of disease remission by 4 years of disease was oligoarthritis (41%), polyarticular RF negative (8%), polyarticular RF positive (0%), psoriatic (47%), ERA (28%), sJIA (29%) and undifferentiated (30%).

Table 1. Disease duration (in months) to achieve outcomes

	AJC = 0		Inactive Disease	
	N	Median (IQR)	N	Median (IQR)
Oligoarthritis	412	5.9 (3.3, 10.0)	410	9.6 (6.8, 14.9)
Polyarticular RF negative	235	10.2 (5.0, 16.5)	232	14.9 (10.8, 27.3)
Polyarticular RF positive	46	10.0 (6.7, 20.2)	46	24.2 (13.5, 39.5)
Psoriatic	62	7.2 (4.7, 14.9)	63	12.6 (7.7, 18.1)
Enthesitis Related Arthritis	157	6.8 (3.0, 14.3)	153	16.0 (10.7, 24.5)
Systemic	75	3.6 (2.0, 11.3)	74	13.1 (6.7, 36.4)
Undifferentiated	110	6.4 (3.2, 15.9)	108	14.4 (9.4, 22.7)

Conclusion: Almost all patients achieve an AJC =0, and most attain inactive disease; however, the probability of remission remains low for the polyarticular subtypes.

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Telephone Consultation Usage In a Pediatric Rheumatology Clinic: Considerations In Optimizing Nursing Resources. Julie Lemieux[1], Audrey Tran[2], Vincent Brienza[3] and Roman Jurencak[3]. [1]Children's Hospital of Eastern Ontario, Ottawa, ON, [2]University of Western Ontario, London, ON, [3]University of Ottawa, Ottawa, ON.

Background/Purpose: Telephone consultation is essential to the delivery of patient care in the ambulatory care clinics at the Children's Hospital of Eastern Ontario (CHEO). Our objective was to quantify and analyze all telephone calls received by the pediatric rheumatology nurses at CHEO.

Methods: As per CHEO policy and procedure, all telephone calls nurses receive are documented on standard forms. Calls documented by the nursing staff in the Division of Pediatric Rheumatology over a six-month period from Jan 1, 2012 until June 30, 2012 were retrospectively analyzed for selected characteristics. An incoming call addressing a new concern relating to a specific patient was considered to be the index call. Index calls and all subsequent documented communications generated by the index call were then examined. Calls that only confirmed appointments and calls confirming that a message was received were excluded from analysis.

Results: 321 index calls were received during the study period (0.6 calls per clinic hour), generating a total of 780 follow-up calls. The most frequent patient diagnosis was juvenile idiopathic arthritis (57%) and most patients were 12–18 years old (52%). 79% of calls were placed by the patient's mother, while only 1% of callers were the patient themselves. 44% of calls lasted 1–5 minutes, 29% lasted 5–10 minutes and 27% lasted more than 10 minutes. The most common reasons for call were concerns relating to rheumatologic condition and medications taken (50%). Large number of calls was related to administrative issues such as requests for appointment change, prescription refills, etc (34%). Pain management was discussed in 29% of all calls. Nurses managed independently 40% of calls; when other health care providers were consulted, the physician was approached in 91% of cases. Only 8% of index calls resulted in an advanced clinic appointment.

Conclusion: This study provides a descriptive analysis of calls nurses receive in a tertiary care pediatric rheumatology clinic. While nursing telephone consultation is beneficial in providing inter-disciplinary patient care and in minimizing clinic visits, the associated workload is significant and utilization of this service needs to be optimized, including re-distribution of administrative calls. Teenage patients rarely call themselves and their independence needs to be encouraged.

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2792

Pediatric Rheumatology Care and Outcomes Improvement Network Demonstrates Performance Improvement On Juvenile Idiopathic Arthritis Quality Measures. Julia G. Harris[1], Esi Morgan DeWitt[2], Ronald M. Laxer[3], Stacy P. Ardoin[4], Beth S. Gottlieb[5], Judyann C. Olson[1], Murray H. Passo[6], Jennifer E. Weiss[7], Daniel J. Lovell[8], Tzielan C. Lee[9], Sheetal S. Vora[10], Nancy Griffin[2], Jason A. Stock[2], Lynn M. Darbie[2] and Catherine A. Bingham[11]. [1]Children's Hospital of Wisconsin, Milwaukee, WI, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]University of Toronto, Toronto, ON, [4]Ohio State University College of Medicine, Columbus, OH, [5]Cohen Children's Medical Center of New York, New Hyde Park, NY, [6]Medical University of South Carolina, Charleston, SC, [7]Hackensack University Medical Center, Hackensack, NJ, [8]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [9]Stanford University School of Medicine, Stanford, CA, [10]University of North Carolina Chapel Hill, Chapel Hill, NC, [11]Penn State Hershey Children's Hospital, Hershey, PA.

Background/Purpose: Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN) is a multi-site learning network designed to improve outcomes of juvenile idiopathic arthritis (JIA) care. Teams collect point of care data on measures of process of care and outcomes of care for the purposes of analysis to guide improvement activities. Eleven North American

pediatric rheumatology centers participate. This report illustrates our improvement in several JIA process quality measures (QMs).

Methods: Process of care QMs targeted for improvement include measurement of: arthritis-related pain, physician global assessment, joint count, health-related quality of life, physical function, as well as screening for uveitis, medication toxicity, and tuberculosis per guidelines. Outcome measures for JIA include clinical inactive disease, no or mild pain level, and optimal physical functioning. Network goals were determined for each process and outcome measure. Data are collected with IRB approval and informed consent, and the shared registry for data entry is the ACR's Rheumatology Clinical Registry. Site-specific and aggregate data are analyzed and displayed monthly via statistical process control charts allowing PR-COIN to track performance over time. Individual centers use established quality improvement methodology to reach and exceed pre-determined goals.

Results: Data from 3231 encounters for 905 JIA patients have been collected since April 2011. QMs with performance meeting or exceeding initial goals include: documentation of complete joint count every 180 days, measurement of arthritis-related pain at every visit, functional assessment every 180 days, and documentation of baseline toxicity labs. For PR-COIN network as a collective unit, QMs improved in five processes– measurement of functional ability, completion of ongoing medication toxicity labs, documentation of complete joint count, documentation of annual behavioral counseling, and measurement of health-related quality of life. All of these measures had a sustained shift above the baseline mean, demonstrating special cause. In addition, five sites have demonstrated individual improvement in at least one process QM.

Conclusion: PR-COIN sites are collectively and individually demonstrating significant improvements in JIA process of care QMs. Quality improvement efforts in PR-COIN are ongoing with the goal of improving the outcome for patients with JIA.

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Towards Developing a Rheumatology-Specific Transition Of Care Program. Rina Mina[1], Janalee Taylor[2], Pamela A. Heydt[3], Terry M. Moore[4], Julie V. Ranz[2], Mary Beth Burns[2], Paula G. Melson[5], Abigail Nye[2], Jill Segerman[2], Yolanda Farhey[6], John Houk[6], Avis Ware[6], Jennifer L. Huggins[2] and Lisa Vaughn[2]. [1]Cincinnati Children's Hospital Medical Center/University of Cincinnati School of Medicine, Cincinnati, OH, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Childrens Hospital Medical Center, Cincinnati, OH, [4]Cincinnati Chiildren's Hospital Medical Center, Cincinnati, OH, [5]Children's Hosp Medical Center, Cincinnati, OH, [6]University of Cincinnati, Cincinnati, OH.

Background/Purpose: Because of their considerable medical challenges, adolescents and young adults with pediatric-onset rheumatic diseases are often reliant on the health care system, and any interruption in their care could have serious consequences. Their successful transition of care from pediatric to adult health care systems is crucial for maintaining their health and health-related quality of life. As such, an organized transition of care program is highly important for these patients.

Our objective was to determine components of a transition program from pediatric to adult rheumatology care using survey method.

Methods: A checklist oriented towards developmentally appropriate goals for transition of care was formulated after review of existing literature and other transition checklists in use for other diseases. An online survey to gather approval for the checklist and resolve transition of care related questions was sent to members of the pediatric rheumatology multidisciplinary staff at Cincinnati Children's Hospital Medical Center and to its adult rheumatology counterpart at the University of Cincinnati. The participants included attending pediatric and adult rheumatologists on staff, fellows-in-training, nursing staff, physical and occupational therapists, and social worker. All have direct patient contact.

Results: Response rate was 84% (27 of 32). The respondents unanimously accepted the self-management transition checklist in terms of content and format. The checklist contained transition goals that reflected developmental skills of the patients. All respondents want the checklist to be incorporated into the patient's electronic chart.

From the pediatric rheumatology side, there was no agreement as to (1) the frequency of transition readiness assessment, and (2) at what age should the preparation phase of transition should commence. In addition, majority agreed on the (1) usefulness of scheduled independent visits for adolescent patients to (67%) and (2) necessity of actual doctor visit with an adult rheumatologist prior to the transfer-of-care.

The adult rheumatology staff and fellows unanimously thought that patients should be able to communicate independently to care providers and be informed about their disease. Majority (60%) of the adult rheumatology providers felt that they need more information and education about caring for patients with pediatric onset rheumatic diseases.

Conclusion: Agreement was reached on several relevant aspects of a transition of care checklist and program for patients with pediatric onset rheumatic disease. Validation of this checklist is ongoing as are interventional support to meet gaps in the transition process.

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Characterisation Of Antigens Driving *In Situ* Autoantibody Production In Human Lupus Tubulointerstitial Nephritis (TIN). Andrew Kinloch[1], Scott Henderson[1], Natalya Kaverina[1], Anthony Chang[1], D. James Haddon[2], Justin Jarrel[2], Carole Henry Dunand[1], Patrick C. Wilson[1], Paul Utz[2] and Marcus R. Clark[1]. [1]University of Chicago, Chicago, IL, [2]Stanford University School of Medicine, Stanford, CA.

Background/Purpose: We have demonstrated that the degree of tubulointerstitial nephritis (TIN) on diagnostic biopsy predicts progression to renal failure. TIN is associated with tertiary lymphoid structures, *in situ* B cell oligoclonal expansion and ongoing antigen-driven somatic hypermutation. These phenomena support the hypothesis that local antigen is driving in situ lymphocyte selection and activation. Therefore, we cloned and characterized the antigenic specificities of in situ selected antibodies in human TIN.

Methods: Human kidney biopsies with lupus TIN were stained for the proliferation marker ki-67 (6/8), or the post GC marker CD38 (1/8). Positive single cells were isolated by laser capture microscopy. An eighth sample was single cell sorted for $CD138^+$ plasmablasts. mRNA was purified and cDNA reverse transcribed. Matched IgG heavy and light chain variable regions were PCR amplified, cloned into human IgG1 heavy or light chain expression vectors and expressed as mAbs in HEK-293 cells. Antigen screening methods included clinical ELISAs, crithidia IIF (for DNA), human protein arrays (Invitrogen), confocal microscopy of HEp-2 cells. Antigens targeted in HEp-2 cells were sought by immunoprecipitation followed by mass spectrometry. Candidate antigen identity was confirmed by multi-color confocal microscopy, and purified antigen ELISAs and protein arrays. In situ expression pattern of target antigen was confirmed by immunofluorescence using kidney from lupus TIN and normal controls. Sera from lupus patients, with (n=40) and without nephritis (n=20), were tested for IgG reactivity with candidate antigens.

Results: 27 mAbs were generated. By HEp-2 analysis, 3/27 yielded nuclear speckled-patterns, 1/27 nucleolar-, 7/27 cytoskeletal-, 3/27 nuclear and cytoplasmic-, and 1/27 reacted with the golgi apparatus. None were DNA, Sm or RNP positive. Vimentin was confirmed as the dominant targeted antigen (40% of mAbs, from 7/8 patients), immunoprecipitated from HEp-2 cells, bound by TIN mAbs on arrays and ELISA, and yielding a co-staining pattern with an anti-vimentin antibody (V9, DAKO). Vimentin reactive TIN mAbs reacted strongly with both glomeruli and inflamed TI, but little with normal TI. Approximately 70% of serum samples reacted with vimentin by protein array and this tended to be more common in nephritis patients. Antigens targeted more strongly in nephritic serum included myosin and SSB (median % false discovery rate <.001).

Conclusion: Vimentin is an autoantigen upregulated during inflammation capable of driving in situ antibody production. These data support a model inwhich a positive feed-back loop of inflammation contributes to renal failure.

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B Cell Derived Cytokines Induce Glomerular Injury in Mice. Alfred Kim[1], Shreeram Akilesh[2], Jeffrey Miner[3] and Andrey Shaw[3]. [1]Washington Univ School of Med, St. Louis, MO, [2]University of Washington, Seattle, WA, [3]Washington University School of Medicine, Saint Louis, MO.

Background/Purpose: Renal involvment remains the leading cause of mortality for SLE patients, and is associated with proteinuria and foot process effacement. In subsets of LN patients, B cell depletion therapies have been efficacious in lowering disease activity including glomerulopathy. The contributions of B cells to proteinuria and foot process effacement remain unknown. The development of a murine model of B-cell induced proteinuria and identification of pathogenic factors would enhance our understanding of immune-based glomerular diseases.

Methods: The B cell model antigen model hen egg lysozyme (HEL) was biotinylated, complexed to avidin and injected into mice. Naïve HEL-specific B cells were then adoptively transferred and proteinuria assessed. Kidneys were processed for immunofluorescence and scanning electron microscopy (SEM). Cultured podocyte membrane ruffling was assessed with DIC videomicroscopy. IL-4 expression in mice was achieved by hydrodynamically injecting murine IL-4 in the piggyBac vector system.

Results: HEL embedded within the glomerular basement membrane (GBM) following IV injection. Proteinuria occurred after the transfer of naive HEL-specific B cells and associated with focal foot process effacement. No antibody or complement deposition was observed in proteinuric glomeruli. Intravital two-photon microscopy demonstrated that HEL-specific B cells arrested trafficking within glomeruli only in the presence of glomerular-localized HEL. This demonstrated that B cells were capable of inducing glomerular injury and proteinuria.

These data suggested cytokines secreted by activated B cells may be responsible for podocyte injury. Since foot process effacement is the histologic correlate of actin cytoskeletal rearrangement, we hypothesized that cytokines mediate podocyte injury through alterations in the actin cytoskeleton. We found that IL-4 induced unstable actin cytoskeletal changes leading to membrane ruffling. In addition, IL-4 generated foot process retractions on ex vivo fragments of renal cortex. Hydrodynamic DNA injection of wild-type mice with plasmid encoding IL-4 lead to proteinuria, which was reversed by JAK1/3 inhibition.

Conclusion: We developed a novel model of B cell-induced proteinuria with focal foot process effacement. B cell derived cytokines such as IL-4 induced alterations in foot process morphology, leading to proteinuria. Transgenic IL-4 mice are associated with glomerulosclerosis independent of autoantibody production. We believe that IL-4 plays a direct role in podocyte injury through disruptions in the actin cytoskeleton. This has important implications in developing therapies to preserve podocyte function, limiting glomerular injury.

Disclosure: A. Kim, ACR/RRF, 2; **S. Akilesh**, None; **J. Miner**, None; **A. Shaw**, None.

2796

Effects Of BAFF Inhibition On B Cell Selection In Murine SLE. Alexis Boneparth[1], Ramalingam Bethunaickan[2], Weiqing Huang[2] and Anne Davidson[2]. [1]Feinstein Institute for medical Research, Manhasset, NY, [2]Feinstein Institute for Medical Research, Manhasset, NY.

Background/Purpose: BAFF inhibition is a new B cell targeted therapy approved for the treatment of moderately active SLE. Although BAFF regulates selection of naïve autoreactive B cells, belimumab only modest decreases autoantibody titers. To determine whether BAFF inhibition alters the quality of the autoantibody response by affecting selection of autoreactive B cells we generated NZW/BXSB.yaa (W/B) mice bearing the 3H9 site directed Ig heavy chain transgene. An extra copy of TLR7 conferred by the *Yaa* locus accelerates disease in the males. 3H9 associates with diverse light chains to generate anti-DNA and anti-cardiolipin specificity. We have previously shown that the autoreactive B cell response in 3H9.W/B mice uses predominantly Vk5-43 and Vk5-48 light chains that confer autoreactivity in their germline configuration and that such 3H9/Vk5-expressing B cells are rare in the naïve repertoire but are expanded in germinal centers (GCs). Male W/B mice have defects in tolerance both at the GC entry checkpoint and in negative selection of B cells that acquire autoreactivity as a consequence of somatic mutation. We now wish to know whether BAFF inhibition influences either of these two checkpoints.

Methods: To create a physiologic setting in which autoreactive B cells compete for survival with non-autoreactive B cells, we generated 50% 3H9/50% wt W/B bone marrow chimeras in which transferred 3H9. $TLR7^{+/+}$ or $TLR7^{+/-}$cells are GFP+ and can be easily identified. To determine when negative selection of 3H9+ cells occurs, we enumerated the % 3H9+/GFP+ cells in immature bone marrow, transitional, marginal zone (MZ), follicular (Fo), GC and plasma B cells using flow cytometry. To investigate the effect of TLR7 dose and BAFF inhibitors on selection of the autoreactive B cell repertoire, we performed single cell PCR and sequencing to determine the repertoire of light chains associating with the 3H9 heavy chain in Fo, GC, and plasma cells.

Results: When competition from wt B cells is provided, significant deletion of 3H9 B cells occurs at the immature and transitional stage in the bone marrow regardless of TLR7 status or BAFF inhibition. Relative enrichment of 3H9 B cells occurs in the GC $TLR7^{+/+}$ compared with $TLR7^{+/-}$ chimeras. BAFF-R-Ig treatment significantly decreases B cell percentage and total numbers but does not decrease the percentage of immature or mature 3H9 B cells or mediate deletion of anergic cells. Data from single cell sorts of GFP+ B cells indicates comparable naïve B cell repertoires but a decrease in selection of high affinity anti-chromatin Vk5-48/

Jk4 light chains among TLR7$^{+/-}$ and BAFF-R-Ig treated mice compared with TLR7$^{+/+}$ untreated controls.

Conclusion: Preliminary data indicates that when competition is provided, negative selection of naïve 3H9+ cells appears to be TLR7 and BAFF independent. In contrast, although autoreactive B cells still entered the germinal centers in mice treated with BAFF inhibition, modest changes were observed in germinal center selection. Future studies will explore the specific effects of BAFF inhibition on B cells that acquire autoreactivity in the GC as a consequence of somatic mutation.

Disclosure: A. Boneparth, None; **R. Bethunaickan**, None; **W. Huang**, None; **A. Davidson**, GSK, 8, Eisai, 5.

2797

B-Lymphocyte Stimulator and A Proliferation Inducing Ligand In Lupus Nephritis: Low Serum Levels Of BLyS Predict Treatment Response. Ioannis Parodis[1], Agneta Zickert[1], Elisabet Svenungsson[1], Vivianne Malmström[1] and Iva Gunnarsson[2]. [1]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: B-lymphocytes have a pivotal role in the pathogenesis of Systemic Lupus Erythematosus (SLE). B-Lymphocyte Stimulator (BLyS) has an important role in the activation, differentiation and maintenance of activated B-cells. A PRoliferation Inducing Ligand (APRIL) is involved in the induction and maintenance of B- and T-cell responses. The aim of our study was to assess serum levels of BLyS and APRIL in patients with lupus nephritis (LN) and investigate how these levels are affected by immunosuppression.

Methods: Sixty-four patients with biopsy-proven LN (52 proliferative nephritis, PN, and 12 membranous nephritis, MN) and 64 gender- and age-matched controls were included in our study (mean age 34 years). The patients were treated with corticosteroids combined with cyclophosphamide (CYC, n=45), mycophenolate mofetil (n=11), rituximab (n=7) or azathioprine (n=1) and underwent a second renal biopsy after completed induction therapy. Serum was collected before and after induction treatment (mean time 8 months) for the patients and at recruitment for the controls. The mean proteinuria at baseline was 2.2 g/d. BLyS and APRIL levels were estimated by ELISA (R&D Systems and eBioscience, respectively). The renal biopsies were assessed according to the ISN/RPS classification system, as well as Activity Index (AI) and Chronicity Index (CI). We defined clinical response (CR) as ≥50% reduction in proteinuria, normal or improved renal function (≥25% increase of GFR) and inactive urinary sediment. For complete response the proteinuria at follow-up should be <0.2 g/d and for partial response between 0.2 and 2 g/d. We defined histopathological response (HR) as ≥50% improvement in AI for partial response and additionally demanded a lack of signs for active inflammation (ISN/RPS class I, II, III C or IV C) in the follow-up biopsy for complete response.

Results: BLyS levels were significantly higher in patients with LN than in controls ($p<0.001$), but remained unchanged after induction treatment ($p=0.99$). APRIL levels were significantly higher in patients compared to controls at baseline ($p=0.005$), but not at follow-up (0.14). This is consistent with a significant reduction of APRIL levels at follow-up ($p<0.001$). This decrease was more prominent in patients who received CYC ($p=0.006$). APRIL levels decreased significantly in both responding and non-responding patients. In the patient group with PN, the decrease of APRIL in non-responding patients was not statistically significant ($p=0.13$). Interestingly, the ROC-curve for BLyS by treatment response revealed a potential predictive power. Further analysis showed that low baseline levels of BLyS had high positive predictive value for both CR and HR.

Conclusion: We observed an overall decrease in serum levels of APRIL after immunosuppression. No decrease was found in non-responding patients with PN, implying that APRIL could be of importance in this subgroup. BLyS levels remained unchanged after immunosuppressive treatment, suggesting that conventional treatments do not affect BLyS-producing cells. However, low baseline levels of BLyS were found to predict both CR and HR, suggesting that BLyS should be evaluated as a potential biomarker of response in LN.

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Bone Marrow In Systemic Lupus Erythematosus Patients Contain a Highly Elevated Proportion Of Somatically Mutated, Activated Naive Cells Comprised Of Substantial Clonal Expansions. Jennifer Hom[1], Christopher Tipton[1], Christopher Fucile[2], Bridget Neary[1], Chungwen Wei[1], F. Eun-Hyung Lee[1], Alex Rosenberg[2] and Inaki Sanz[1]. [1]Emory University, Atlanta, GA, [2]University of Rochester, Rochester, NY.

Background/Purpose: Systemic lupus erythematosus (SLE) is a disease where autoreactive antibodies are produced as a result of abnormal B cell activation and broken self-tolerance. This activation is perhaps most prominently observed in elevated levels of circulating activated cells within the naïve compartment of SLE patients. The origin, diversity, and direct developmental consequences of this elevated activation are largely unclear though. In this study, we use a variety of multi-color flow cytometry panels to isolate and sort specific bone marrow (BM) and circulating B cell populations for immunoglobulin heavy chain (IGH) deep sequencing analysis. By developing a novel program to trace their inter-population relationships through mutational analysis, we aim to further characterize these cells and their contribution to the pathogenesis of SLE.

Methods: Peripheral blood and BM aspirates from healthy donors and volunteers with SLE were collected and sorted using several multi-color flow cytometry panels. The IGH gene was amplified from these cells using multiple sets of VH family-specific and isotype-specific primers. Deep sequencing was conducted using Illumina MiSeq technology, and results were analyzed using an internally developed analysis program that performs quality filtering, detailed mutational analysis, and identification and matching of clonal lineages.

Results: We found that a population of circulating mitotracker green (MTG) positive, CD23- activated naïve cells were highly elevated in flaring SLE patients, slightly elevated in non-flaring patients, and largely absent in healthy controls. This population was also identified in BM of SLE patients, and it was found to be highly elevated in all SLE samples. Deep sequencing analysis showed that unlike most other populations in the circulation and BM, this population was highly oligoclonal, with some clones accounting for greater than 5% of the total population. Sequences from these activated naïve cells were somatically mutated and typically found to be of lower VH mutation rates than memory and plasmablasts (PB), but higher than resting naïve cells. We found clonal relations between several circulating and BM B cell subsets and tracked the lineage maturation using mutation analysis. Surprisingly, the activated naïve fraction was highly related to PB and through mutational tree analysis, they were found to inhabit the more proximal portion of the same lineage branches as the more distal PB.

Conclusion: Our data suggest that in SLE, there is an expansion of activated MTG+, CD23- naive cells which may be an early implication of abnormal B cell activation as a result of damaged self-tolerance. We show that these cells are highly related to circulating and BM antibody-producing PB, which are typically also expanded in SLE.

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Identification Of IL-10 Producing Plasma Cells In Human and Its Deficiency In Systemic Lupus Erythematosus Patients. Xiaoqian Wang[1], James Roger[2] and Ignacio Sanz[3]. [1]Emory University, Allergy, Immunology and Rheumatology, Atlanta, GA, [2]University of Rochester, Rochester, NY, [3]Emory University School of Medicine, Atlanta, GA.

Background/Purpose: Regulatory B cells are active participants in down-regulating inflammation and autoimmunity, through the production of IL-10. Despite intensive studies in mice, there is only a paucity of data concerning the regulation of IL-10 production in human. The purpose of this study is to understand IL-10 production by human B cells and to explore the development of regulatory B cells either in healthy individuals or in patients with SLE.

Methods: Healthy controls (HC) (n=15) and SLE patients (n=20) fulfilling the American College of Rheumatology revised classification criteria were included in this study. Total B cells were purified with MACS-negative selection and different B cell subsets were obtained by sorting. IL-10 producing B cells were identified with intracellular staining, Elispot, and dual color Flurospot assay. Elisa was used to determine the level of IL-10 in B cell cultures.

Results: In vitro and ex vivo analysis determined for the first time, that human plasma cells (PC: CD19+CD27++CD38++CD138+) and plasmablasts (PB: CD19+CD27++CD38^{++}CD138^{-}) are major sources of IL-10. This cytokine was secreted from PB and PC generated in vitro from cultured memory cells using Elispot assay and intracellular flow cytometry. Both assay identified 1–2% of IL-10 positive PB/PC. Similarly, ex vivo analysis of unstimulated B cell subsets sorted 7 days after flu vaccination of HC identified PB and PC as the only source of IL-10 and up to 1% of PC and PB are able to produce IL-10. In contrast, circulating PB and PC spontaneously expanded in the circulation of active SLE patients failed to produce IL-10 ex vivo. In vitro stimulation of purified B cell subsets with CpGDNA and IL-2 coupled with CFSE labeling identified the IgD(+)CD27(+) non-switched memory B-cell subpopulation as the main IL-10-producing precursor B cell in a division-linked fashion. Of interest, IL-10 production from stimulated B cells was significantly lower in SLE patient (380.1±60.94 pg/ml) than in HC (857.6±97.06 pg/ml) ($p<0.001$), in direct correlation with the reduction in non-switched memory cells typical of this disease. In contrast, SLE patients with normal distribution of B cell subsets had normal IL-10 secretion.

Conclusion: We provide the first description of spontaneous IL-10 production by human PB and PC in HC and its deficiency in SLE. These findings suggest that IL-10 could negatively regulate antibody secreting cells in an autocrine fashion that would be deficient in SLE thereby enhancing autoantibody production. Our data also identify non-switched memory B cells as an important source of potent regulatory B cells and indicate that the decrease of this population typically observed in SLE may be a major contributor to the deficiency of regulatory IL-10 in this autoimmune disease.

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ACR Concurrent Abstract Session
Imaging in Rheumatoid Arthritis
Wednesday, October 30, 2013, 9:00 AM–10:30 AM

2800

Dose-Response Effects Of Denosumab, a Novel Subcutaneous RANKL Inhibitor, On The Progression Of Bone Erosion In Japanese Patients With Rheumatoid Arthritis Treated With Methotrexate: Results Of Phase II DRIVE Study—A Twelve Month Placebo Controlled, Randomized, Double Blind Study. Tsutomu Takeuchi[1], Yoshiya Tanaka[2], Naoki Ishiguro[3], Hisashi Yamanaka[4], Toshiyuki Yoneda[5], Harry K. Genant[6] and Désirée van der Heijde[7]. [1]Keio University School of Medicine, Tokyo, Japan, [2]University of Occupational and Environmental Health, Kitakyushu, Japan, [3]Nagoya University Graduate School of Medicine, Nagoya, Japan, [4]Institute of Rheumatology Tokyo Women's Medical University, Tokyo, Japan, [5]Indiana University School of Medicine, Indianapolis, IN, [6]University of California, San Francisco, CCBR-Synarc, Newark, Tiburon, CA, [7]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Denosumab is a fully human monoclonal antibody (IgG_2 subclass) that binds specifically to RANKL. It inhibits osteoclast-induced bone resorption by preventing the binding of RANKL to RANK, thereby inhibiting progression of marginal bone erosion at the joints where inflammatory cytokines are highly expressed, stopping structural joint damage. In this study, we evaluated the dose-frequency of denosumab for safety and efficacy in Japanese patients with RA.

Methods: DRIVE Study (AMG162-D-J201) was a placebo-controlled, 4-arm randomized (1:1:1:1), double-blind, parallel-group study in patients receiving methotrexate treatment. Denosumab 60 mg (every 6 months (Q6M), 3 months (Q3M), or 2 months (Q2M)) or placebo was administered subcutaneously for 12 months. The primary endpoint was change in the bone erosion score assessed by the modified Sharp-van der Heijde method from baseline to 12 months. One-tailed Shirley-Williams's test were performed and differences were considered significant when $p<0.025$.

Results: Among 350 patients enrolled, 346 (placebo, n=88; Q6M, n=86; Q3M, n=85; Q2M, n=87) were treated with the study drugs (Table 1), and 35 (placebo n=6; Q6M, n=8; Q3M, n=13; Q2M, n=8) were discontinued.

Table 1. Baseline demographics and characteristics of Japanese patients with RA.

Characteristic	Placebo N = 88	Denosumab 60 mg Q6M N = 85	Denosumab 60 mg Q3M N = 82	Denosumab 60 mg Q2M N = 85
Female	76 (86.4)	65 (76.5)	59 (72.0)	66 (77.6)
Age (years)	57.0 ± 10.6	54.4 ± 10.6	52.0 ± 11.7	54.6 ± 10.5
Disease duration (years)	2.3 ± 1.3	2.2 ± 1.3	2.3 ± 1.3	2.3 ± 1.4
Rheumatoid factor positive	60 (68.2)	59 (69.4)	56 (68.3)	57 (67.1)
MTX dose (mg)	7.6 ± 1.8	8.0 ± 2.0	8.4 ± 2.2	8.3 ± 2.0
DAS28-CRP	3.5 ± 0.9	3.2 ± 0.9	3.3 ± 0.9	3.3 ± 0.8

Data presented are Mean ± SD or n (%).

Changes in the bone erosion score (deltaERO) at Month 12 were 0.99 ± 2.69 in placebo, 0.27 ± 0.98 in Q6M (Compared with placebo, p=0.0082), 0.14 ± 0.53 in Q3M (p=0.0036), and 0.09 ± 1.52 in Q2M ($p<0.0001$) (Figure 1). Percentages of patients without increase in ERO (≤0) at Month 12 were 62.5% in placebo, 78.8% in Q6M (p=0.0173), 80.5% in Q3M (p=0.0099), and 83.5% in Q2M (p=0.0019).

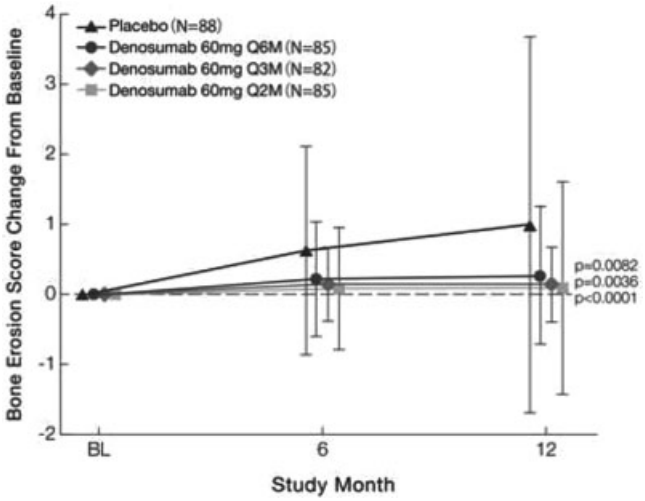

Figure 1. Mean (± SD) Bone Erosion Score Change From Baseline (Full Analysis Set)

No significant differences in the types and the overall incidence of adverse events (AEs) were observed among denosumab-treated groups and the placebo group. No hypocalcemia, osteonecrosis of the jaw, or atypical femoral fracture were observed.

Conclusion: Greater suppression of the bone erosion from baseline to 12 months and the less erosive progression were observed after denosumab treatment in all doses compared with placebo, with lower progression rates in groups with shorter dosing interval. Denosumab was well tolerated in Japanese patients with RA and shortening the dosage interval did not increase AE incidence.

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2801

Comparative Longitudinal Analysis Of Periarticular Bone Structure In Patients Treated With Methotrexate In Combination Of Either TNF Blockers Or Tocilizumab. Sebastian Kraus, Matthias Englbrecht, Juergen Rech, Roland Kocijan, Georg A. Schett and Stephanie Finzel. University of Erlangen-Nuremberg, Erlangen, Germany.

Background/Purpose: Inhibition of tumor necrosis factor alpha (TNFi) and interleukin-6 receptor (IL6Ri, tocilzumab) are among the most potent therapeutic strategies in patients with rheumatoid arthritis (RA) and have shown to retard structural bone damage. Comparative longitudinal studies on the impact of TNFi or IL-6i on periarticular bone damage in RA, however, have not been performed.

Methods: Observational study on 54 patients with RA receiving TNFi (N=25) or IL6Ri (N=29) in combinaton with methotrexate over one year. All patients received baseline and one-year follow-up examination of the 2nd–4th metacarpophalangeal and wrist joints for presence of erosions and osteophytes using high-resolution peripheral quantitative computed tomography (HR-pQCT). Erosions and osteophytes were quantified both numerically and metrically at baseline and one year follow-up. Demographic and disease specific characteristics such as age, gender, disease duration and -activity were recorded.

Results: Both cohorts were comparable for age, gender, disease duration and –activity, autoantibody status as well as baseline bone damage. At baseline 185 erosions (MCP:N=136; wrist:N=49) and 340 osteophytes (MCP:N=248; wrist:N=92) were detected in the 29 patients of the IL-6i group and 123 erosions (MCP:N=84; wrist;N=39) and 270 osteophytes (MCP: N=176; wrist: N=94) were detected in the 25 patients of the TNFi group. Erosion numbers significantly increased in the MCPs (+0.321mm^3, t(83)=−2.92, p=0.004) and tended to increase in the wrist joints: (+0.13mm^3, t(48)=−0.52, p=0.096) in the TNFi group, whereas they remained constant in IL-6i treated patients both in wrist and MCP joints. No significant volumetrical change of erosive changes of erosions was observed in either group. Osteophyte numbers (TNFi:+0.27mm, t(175)=−6.99, p<0.001; IL6i:+ 0.1mm, t(245)=−3.49, p=0.001) and size (TNFi: +0.19mm, t(174)=−7.01, p<0.0001; IL-6i:+0.08mm, t(247)=−3, p=0.003) in the MCP joints significantly increased in both groups. In the wrists, osteophytes increased both in size (+0.9mm, t(96)=2.49, p=0.015) and numbers (+0.19mm, t(93)=−3.14, p=0.002) in the TNFi group while remaining constant in size and increasing in numbers (+0.185mm, t(91)=−3, p=0.004) in the IL-6i group.

Conclusion: This study suggests that IL-6Ri allows an even better control of structural bone damage than TNFi in patients with erosive RA. Furthermore, the observation that HR-pQCT allows detecting structural progression in TNFi treated RA patients is important and indicated that high-level imaging technology allows very detailed analysis of changes of bone composition in RA patients, which could be valuable to improve the monitoring of strucrural effects of anti-rheumatic drugs.

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A Treat-To-Target Strategy With Methotrexate and Intra-Articular Triamcinolone With Or Without Added Adalimumab Reduces Synovitis, Osteitis and Tenosynovitis and Halts Structural Damage Progression In Early Rheumatoid Arthritis: The Opera Magnetic Resonance Imaging Sub-Study. Mette Bjørndal Axelsen[1], Iris Eshed[2], Kim Hørslev-Petersen[3], Kristian Steengaard-Petersen[4], Merete L. Hetland[5], Jakob M. Møller[6], Peter Junker[7], Jan Pødenphant[8], Torkell Ellingsen[9], Palle Ahlquist[10], Hanne M. Lindegaard[11], Asta Linauskas[12], Annette Schlemmer[13], Mette Yde Dam[14], Ib Hansen[15], Hans Chr Horn[16], Christian G. Ammitzbøll[17], Anette Jørgensen[17], Sophine B. Krintel[18], Johnny Raun[19], Julia S. Johansen[20], Niels Steen Krogh[21] and Mikkel Østergaard[5]. [1]Copenhagen University, Copenhagen, Denmark, [2]Sheba Medical Center, Tel Hashomer, Israel, [3]South Jutland Hospital, Graasteen, Denmark, [4]Aarhus University Hospital, Aarhus, Denmark, [5]Copenhagen University Hospital Glostrup, Copenhagen, Denmark, [6]Copenhagen University Hospital at Herlev, Copenhagen, Denmark, [7]Odense University Hospital, Odense C, Denmark, [8]Copenhagen University at Gentofte, Hellerup, Denmark, [9]Diagnostic Centre Region Hospital Silkeborg Denmark, 8600 Silkeborg, Denmark, [10]Vejle Regional Hospital, Vejle, Denmark, [11]Odense University Hospital, Odense, Denmark, [12]Vendsyssel Hospital, Hjørring, Denmark, [13]Aalborg University Hospital, Aalborg, Denmark, [14]Silkeborg Regional Hospital, Silkeborg, Denmark, [15]Viborg Hospital, Viborg, Denmark, [16]Vejle Hospital, Vejle, Denmark, [17]Arhus University Hospital, Aarhus, Denmark, [18]Copenhagen University Hospital at Glostrup, Glostrup, Denmark, [19]University of Southern Denmark, Graasten, Denmark, [20]Herlev Hospital, Herlev, Denmark, [21]ZiteLab ApS, Copenhagen, Denmark.

Background/Purpose: The aim was to investigate if a treat-to-target strategy with methotrexate and intra-articular glucocorticoid suppressed synovitis and osteitis, and halted structural damage progression in early rheumatoid arthritis (ERA), and if added adalimumab provided an additional effect, as judged by magnetic resonance imaging (MRI).

Methods: In a double-blinded placebo-controlled investigator-initiated trial, 180 DMARD naïve ERA patients were randomized 1:1 to methotrexate, intra-articular glucocorticoid injections and placebo/adalimumab (1). Eighty-five patients (placebo/adalimumab: 43/42) had contrast-enhanced MRI of the right wrist and the 2nd–5thmetacarpohalangeal joints at months 0, 6 and 12. Synovitis, osteitis, tenosynovitis, bone erosion and joint space narrowing (JSN) were scored with validated methods (2–4).

Results: Synovitis, osteitis and tenosynovitis scores decreased highly significantly (p<0.0001) during the 12-months follow-up, with change scores of mean −3.7 (median −3.0[range −13;11]), −2.2 (−1 [−31;32]) and −3.3 (−1[−31; 32]), respectively. No overall change in MRI erosion and JSN scores were observed, with change scores of 0.1 (0 [-16;13]) and 0.2 (0 [-3;4]), respectively. See table for status scores. Clinical disease activity scores and patient-related measures decreased highly significantly during follow-up (table). Among MRI, clinical and biochemical outcome measures, the tenosynovitis score at month 6 was the only measure that differed significantly between the treatment groups; placebo group: 3.9 (2 [0;18])/the adalimumab group: 1.3 (0 [0;11]), Mann-Whitney: p<0.035. Furthermore, the osteitis score decreased significantly from month 0 to month 6 and 12 in the adalimumab group, but not in the placebo group, Wilcoxon; p≤0.002 and p≥0.062, respectively.

Table. MRI and clinical status values for patients in the placebo and the Adalimumab treatment groups at 0, 6 and 12 months, mean (median [range])

	0 months	6 months	12 months
Synovitis (0–21)			
Placebo group	8.2 (8 [0–19])	4.9 (4 [0–13])***	4.7 (4 [0–15])***
Adalimumab group	7.6 (7 [0–21])	5.0 (5 [0–13])**	4.8 (4 [0–15])*
BME (0–69)			
Placebo group	6.2 (1 [3–35])	**3.9 (0 [0–35])^{NS}**	**3.5 (0 [0–36])^{NS}**
Adalimumab group	4.3 (1 [0–34])	**1.4 (0 [0–11])****	**2.1 (0 [0–31])***
Tenosynovitis (0–30)			
Placebo group	7.3 (5 [0–26])	**3.9 (2 [0–18])***	**2.0 (0 [0–20])****
Adalimumab group	5.2 (3 [0–23])	**1.3 (0 [0–11])*****	**1.6 (0 [0–30])***
Erosions (0–30)			
Placebo group	12.5 (6 [0–64])	11.6 (5 [0–49])^{NS}	13.7 (6 [0–61])^{NS}
Adalimumab group	10.9 (8 [0–43])	9.9 (8 [0–30])^{NS}	10.3 (8 [0–30])^{NS}
JSN (0–84)			
Placebo group	(0 [0–8])	(0 [0–9])^{NS}	1.4 (0 [0–12])^{NS}
Adalimumab group	0.6 (0 [0–7])	0.6 (0 [0–7])^{NS}	0.9 (0 [0–7])^{NS}
DAS28			
Placebo group	5.3 (5.2 [3.5–8.1])	2.7 (2.5 [1.7–5.0])***	2.6 (2.3 [1.7–4.6])***
Adalimumab group	5.4 (5.4 [3.3–7.5])	2.6 (2.4 [1.7–6.0])***	2.4 (2.0 [1.7–4.7])***

Values are presented as mean (median [range]). The numbers in bold writing indicate differences between treatment groups. Between baseline and follow-up visit differences were tested using Mann-Whitney's test: .^{NS}: Not significant; *≤0.005; **≤0.001; ***<0.0001.

Conclusion: A treat-to-target strategy with methotrexate and intra-articular glucocorticoid in ERA patients effectively decreased synovitis, osteitis and tenosynovitis and halted structural damage progression judged by MRI. The addition of Adalimumab provided further suppression of osteitis and tenosynovitis.

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Can Ultrasonographic Findings Predict Response To Tumor Necrosis Factor-α Inhibitor Treatment In Rheumatoid Arthritis? Nevsun Inanc[1], Gülsen Ozen[2] and Haner Direskeneli[1]. [1]Marmara University, School of Medicine, Istanbul, Turkey, [2]Marmara University School of Medicine, Istanbul, Turkey.

Background/Purpose: Tumor necrosis factor-α inhibitors (TNFi) are highly effective in patients with rheumatoid arthritis (RA), while not effective in all, with predictors of response being necessary. Although genetic, inflammatory and serologic biomarkers are under major investigation for this purpose, little is known about the predictive value of ultrasonographic parameters in RA. We aimed to investigate the ability of ultrasonographic parameters to predict which patients with RA will benefit from the treatment with TNFi in terms of EULAR response

Methods: Biologic naive RA patients starting treatment with TNFi were examined longitudinally by ultrasonography (US) (both Gray-Scale [GS] and Power Doppler [PD]) of 28 joints according to standard scans of EULAR guideline and clinically (tender/swollen joint counts, DAS28 and HAQ scores) at baseline and after 3 and 6 months. US examinations were performed by an experienced sonographer (NI) using a MyLab 70 US machine (Esaote, Italy) equipped with 6–18 and 4–13 MHz broad band multi-frequency linear transducer. US synovitis GS and PD signals were semiquantitatively graded from 0 to 3. Total PD and GS synovitis scores of all sites are recorded as sum scores of PD and GS, respectively. The clinical response was evaluated according to the EULAR response criteria at 3rd month. Potential ultrasonographic predictors of response were identified using multivariate binary logistic regression models.

Results: The study cohort consisted of 42 RA patients (F/M=33/9, mean age 49.0±10.7 years) with a mean disease duration of 9.1±7.5 years and mean baseline DAS28 score of 5.5±1.0. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (CCP) positivity were 76.2% and 64.3%, respectively. Baseline characteristics of TNFi responders (30/42) and non-responders (12/42) are shown in Table 1. Swollen joint count ($p= 0.05$), sum scores of baseline PD ($p= 0.048$), GS ($p= 0.048$) and PD+GS ($p= 0.046$) differed significantly between responders and non-responders. Baseline PD sum score was the only ultrasonographic parameter in the multivariate analysis predicting which patients achieve good/moderate EULAR response with TNFi at 3rd month ($p= 0.004$). The mean PD+GS, PD and GS sum scores decreased significantly from baseline to 3 months ($p<0.001$ for all parameters) whereas decrease between 3rd and 6th months was nonsignificant for all US parameters ($p=0.128$, $p=0.266$, $p= 0.105$, respectively).

Table 1. Baseline characteristics of TNFi responders and nonresponders

	Responders (n=30)	Non-responders (n=12)	p Value
Age (years)	48.8 ± 10.6	**49.6 ± 11.5**	0.81
Disease duration (years)	8.0 ± 7.2	**11.9 ± 7.8**	0.13
Treatment delay (months)	32.2 ± 51.0	**35.2 ± 38.2**	0.85
RF titer (IU/mL)	166.4 ± 233.9	**295.1 ± 586.8**	0.31
Anti-CCP titer (U/mL)	78.7 ± 147.0	**232.2 ± 457.5**	0.10
DAS28	5.5 ± 0.9	**5.5 ± 1.3**	0.99
Pain VAS (0-100 mm)	66.0 ± 21.7	**79.2 ± 16.7**	0.067
ESR (mm/h)	43.7 ± 20.7	**40.0 ± 22.5**	0.61
CRP (mg/L)	27.2 ± 34.1	**28.6 ± 28.4**	0.90
Tender joint count (0–28)	8.0 ± 6.8	**12.0 ± 9.5**	0.12
Swollen joint count (0–28)	5.7 ± 5.0	**9.8 ± 7.8**	0.05
HAQ score	1.1 ± 0.6	**1.3 ± 0.4**	0.22
Prednisolone dose, mg/day	5.7 ± 3.1	**5.8 ± 2.2**	0.93
Sum score of PD (0–84)	12.5 ± 9.8	**20.1 ± 13.2**	0.048
Sum score of GS (0–84)	16.1 ± 11.7	**25.7 ± 15.6**	0.048
Sum score of PD+GS (0–168)	29.0 ± 21.4	**45.6 ± 28.5**	0.046

The values were presented as mean±SD

Conclusion: Our data underline that baseline PD scores, despite similar clinical features, can predict which patients will respond to TNFi therapy. Ultrasonographic response to TNFi treatment can be achieved substantially in the first 3 months. Beyond 3rd month changes in US scores are mostly nonsignificant.

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2804

Radiological Outcome Of Joints With MRI Detected Subclinical Inflammation In Early Arthritis Patients. A. Krabben, W. Stomp, J. A. B. van Nies, T.W.J. Huizinga, D. van der Heijde, J.L Bloem, M. Reijnierse and A. H. M. van der Helm-van Mil. Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Extremity-MRI is becoming important in Rheumatoid Arthritis (RA) research as it is a sensitive tool to assess inflammation. Inflammation is measured by three features: bone marrow edema (inflammation of bone), synovitis and tenosynovitis. Part of the inflammatory lesions detected by MRI are subclinical, indicating that these were not observed by physical examination. The relevance of subclinical inflammation detected by MRI in a population of early arthritis patients for to the disease course is not known. In this study we investigated the relevance of subclinical inflammation on MRI in early arthritis patients for radiological joint damage.

Methods: 179 early arthritis patients (median symptom duration of 15 weeks) included in the Leiden Early Arthritis Clinic underwent a 68-tender and 66-swollen joint count (including MCP, wrist and MTP joints) and a 1.5T MRI of the MCP (2–4), wrist and MTP (1–5) joints at the most painful side at baseline. Synovitis and bone marrow edema were scored according to the RAMRIS method; tenosynovitis at the wrists and MCP joints was also determined. Scoring was performed by two readers and the average scores were studied. Radiographs of hands and feet were made at baseline and after one year of follow-up and scored according to the Sharp-van-der-Heijde scoring method (SHS).

Results: 1,790 small joints of 179 patients were studied. Of these joints 1,525 (85%) were not swollen at physical examination. Of all clinically non-swollen joints, any subclinical inflammation was present on MRI in 25%; 15% had bone marrow edema, 15% synovitis and 18% tenosynovitis. When evaluating these clinically non-swollen joints in relation to the radiographs at year-1, 7% of the joints had SHS ≥1 and 2% SHS progression ≥1.

The subclinical inflamed joints were evaluated with progression of radiological joint damage over the first year (SHS progression ≥1) as outcome. When comparing the non-swollen joints with and without any inflammation on MRI, 4% versus 1% had SHS progression ≥1, (RR 3.5 (1.3–9.6)). For bone marrow edema this was 6.5% versus 1% (RR 5.3 (2.0–14.0), for synovitis this was 5% versus 1% (RR 3.4 (1.2–9.3)) and for tenosynovitis this was 4% versus 1% (RR 3.0 (0.7–12.7)). Hence, although radiological progression was infrequent, it was significantly increased in joints with subclinical synovitis or bone marrow edema. For comparison we studied the outcome of the swollen joints. 8% of all swollen joints had SHS progression ≥1 over the first year, indicating that the frequency of progression in subclinical inflamed joints almost equaled the frequency of progression in clinically swollen joints.

Conclusion: Joints with subclinical inflammation detected by MRI have an increased risk of progression in structural damage in early arthritis. This points to the relevance of subclinical inflammation for the disease outcome in RA.

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2805

Synovial Explant Inflammatory Mediator Production Is Associated With Synovitis While Not With Bone Marrow Edema In Rheumatoid Arthritis: A Cross Sectional Study. Martin Andersen[1], Mikael Boesen[2], Karen Ellegaard[1], Robin Christensen[1], Kalle Söderström[3], Søren Torp-Pedersen[1], Bente Danneskiold-Samsøe[1], Else Marie Bartels[1], Nina Vendel[4], Niels H. Søe[5], Pieter Spee[3], Ulrik GW Mørch[6], Lars Karlsson[3] and Henning Bliddal[1]. [1]The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, Frederiksberg, Denmark, [2]Department of Radiology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, Frederiskberg, Denmark, [3]Translational Immunology, Biopharmaceutical Research Unit, Måløv, Novo Nordisk, Denmark, Måløv, Denmark, [4]Department of Anaesthesiology, Intensive Care and Operations, Gentofte University Hospital, Denmark, Hellerup, Denmark, [5]Department of Orthopedics, Section of Hand Surgery, Gentofte University Hospital, Denmark, Hellerup, Denmark, [6]Biomarkers, Søborg, Novo Nordisk, Denmark, Søborg, Denmark.

Background/Purpose: Synovitis and bone damage may represent two distinct but overlapping pathological processes in rheumatoid arthritis (RA).

Whereas the bulk of synovial cells contribute to general joint inflammation, the interplay between synovial cells, neighboring cartilage and bony tissue at the margins of the joint contribute to bone degradation(1). The aim of this study was investigate if the levels of inflammatory cytokines interleukine 6 (IL-6), interleukine 8 (IL-8), macrophage chemo-attractant protein 1 (MCP-1) and macrophage inflammatory protein 1 beta (MIP-1b), which all play key roles in RA pathology, correlate with disease intensity and/or can discriminate between key pathological processes in RA.

Methods: Fifty-seven synovial sites from the hand joints of twenty-five RA patients were evaluated by color Doppler ultrasound (CDUS, 52 synovial sites) and/or high field magnetic resonance imaging (MRI, 39 synovial sites) and subsequently synovectomized by a needle-arthroscopic procedure. Synovial tissue was cultured for 72h, and the concentration of Il-6, Il-8, MCP-1 and MIP-1b in the culture supernatants were measured by Multiplex immunoassays. Ultrasound Doppler was determined as the color fraction. MRI bone marrow edema, synovitis, and erosion score were estimated by the rheumatoid arthritis magnetic resonance score [RAMRIS]. The concentrations of inflammatory mediators were compared to imaging data from the individual sites using repeated samples from the same patients. Since data was clustered within patients, a mixed linear model was applied for the statistical analysis. Parsimony in the statistical model was achieved omitting covariates with ($P>0.1$) from the model.

Results: Ultrasound color fraction and the RAMRIS synovitis score were statistically associated with the release of MCP-1 ($P=0.004$ and $P=0.04$, respectively), IL-8 ($P=0.04$ and $P=0.04$, respectively), and MIP-1b ($P=0.01$ and $P=0.05$, respectively), but not with IL-6 ($P=0.29$ and $P=0.21$, respectively). IL-6 was the only supernatant mediator, which was associated to the RAMRIS erosion component ($P=0.002$). There were no statistically significant associations between mediator release and the RAMRIS bone marrow edema component: MCP-1($P=0.07$), IL-6 ($P=0.93$), IL-8 ($P=0.40$) and MIP-1b ($P=0.96$).

Conclusion: Levels of IL-8, MCP-1, MIP-1b were significantly associated with clinical assessment of synovitis, but not bone erosion, indicating that these molecules play key roles in general inflammation in the joint, and underlining their potential as biomarkers to measure levels of synovitis. In contrast, levels of IL-6 significantly associted with clinical assessment of bone erosion, indicating that this cytokine, which is known to have direct activating effects on osteoclasts, has potential as a biomarker for measuring bone destructive activity in RA patients.

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Disclosure: M. Andersen, Novo Nordisk, 3; **M. Boesen**, None; **K. Ellegaard**, None; **R. Christensen**, Abbott, Axellus A/S, Bristol-Myers Squibb, Cambridge Weight Plan, Norpharma, Pfizer, and Roche, 5, Axellus A/S, Cambridge Weight Plan, Mundipharma, and Roche, 2, Abbott, Axellus, Bayer HealthCare Pharmaceuticals, Biogen Idec, Bristol-Myers Squibb, Cambridge Weight Plan, Ipsen, Laboratoires Expanscience, MSD, Mundipharma, Norpharma, Pfizer, Roche, and Wyeth, 8; **K. Söderström**, Novo Nordisk, 1, Novo Nordisk, 3; **S. Torp-Pedersen**, None; **B. Danneskiold-Samsøe**, None; **E. M. Bartels**, None; **N. Vendel**, None; **N. H. Søe**, None; **P. Spee**, Novo Nordisk, 1, Novo Nordisk, 3; **U. G. Mørch**, Novo Nordisk, 1, Novo Nordisk, 3; **L. Karlsson**, Novo Nordisk, 1, Novo Nordisk, 3; **H. Bliddal**, None.

ACR Concurrent Abstract Session
Infection Related Rheumatic Diseases
Wednesday, October 30, 2013, 9:00 AM–10:30 AM

2806

Low Risk Of Hepatitis B Virus Surface Antigen Seroreversion In HBsAg Negative/Anti-Hbc Positive Carriers Undergoing Rituximab For Rheumatoid Arthritis. Valentina Varisco[1], Mauro Vigano'[2], Alberto Batticciotto[1], Pietro Lampertico[3], Antonio Marchesoni[4], Patrizia Gibertini[4], Raffaele Pellerito[5], Guido Rovera[5], Roberto Caporali[6], Monica Todoerti[6], Michele Covelli[7], Antonella Notarnicola[7] and Piercarlo Sarzi-Puttini[1]. [1]Rheumatology Unit, L. Sacco University Hospital, Milan, Italy, [2]San Giuseppe hospital, University of Milan, Milan, Italy, [3]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy, [4]Istituto Ortopedico Gaetano Pini, Milano, Italy, [5]Ospedale Mauriziano, Turin, Italy, [6]Rheumatology, IRCCS Policlinico San Matteo Foundation and University of Pavia, Pavia, Italy, [7]D.I.M.I.M.P, Rheumatology Unit—University of Bari, Bari, Italy.

Background/Purpose: B cell-targeted therapy using rituximab (RTX), anti-CD20 monoclonal antibody, is an effective treatment for Rheumatoid arthritis (RA). However, the safety of such therapy in hepatitis B surface antigen (HBsAg) negative/anti-hepatitis B core antigen (anti-HBc) positive recipients is unknown. The aim of this study is to evaluate the risk of HBsAg seroreversion in this kind of patients.

Methods: We retrospectively reviewed 306 patients of our multicentre database affected by RA and treated with RTX from August 2006 to December 2011 in 5 italian outpatient rheumatologic Clinics. Complete serological screening for HBV status before the first administration of RTX and adequate post-treatment follow-up were available in 35 HBsAg negative/anti-HBc positive patients who did not undergo antiviral prophylaxis with Lamivudine. All patients (75% female, median age 60 years, median disease duration 8 yrs, 100% serum HBV DNA negative by sensitive PCR assay, 87% anti-HBs positive) has been treated with one or more disease-modifying anti-rheumatic drugs (83% MTX, 26% CYS, 80% PDN, 8% LEF, 6% AZA) and were eligible for RTX therapy according to the international guidelines. RTX was administered for a median of 3 cycles (range: 1–8) and was ongoing in 76% of cases. Clinical and laboratory examinations, including serum HBsAg and serum HBV DNA were assessed every 6 months or in case of alanine aminotransferase (ALT) elevation and at the end of the follow-up period.

Results: During a median follow-up of 45 months (range: 12–80) 27% of patients had anti-HBs titer reduction (2 patient with a complete lost of anti-HBs levels). All patients remained viremic free except one (3%) who had an increase of serum HBV DNA (from undetectable to 24 and 44 IU/mL, 1 week apart) not associated to either HBsAg seroreversion or ALT increase. The mild virological breakthrough occurred 5 months after the first RTX administration and required Lamivudine treatment which successfully suppressed viral replication. Another patient (3%) had an ALT flare which was not related to HBV reactivation.

Conclusion: A retrospectively review of our multicentre experience suggest that in RA patients HBsAg negative/anti-HBc positive treated with RTX, Lamivudine prophylaxis should be avoid using an adequate monitoring of HBsAg or HBV DNA levels.

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Management Of Vertebral Osteomyelitis: A Randomized Clinical Trial Comparing 6 Versus 12 Weeks Of Antibiotic Treatment. Louis Bernard[1], Aurélien Dinh[2], Idir Ghout[3], Valérie Zeller[4], Bertrand Issartel[5], Nadia Belmatoug[6], Michel Dupon[7] and Denis Mulleman[8]. [1]University hospital of Tours, Tours, France, [2]University hospital of Paris, Garches, France, [3]University Hospital of Paris, Boulogne, France, [4]La Croix Saint Simon Hospital, Paris, France, [5]Clinique du Tonkin, Lyon, France, [6]University hospital of Paris, Clichy, France, [7]University Hospital of Bordeaux, Bordeaux, France, [8]CHU Trousseau Tours, Tours, France.

Background/Purpose: As for most of bone and joint infection, optimal treatment duration for vertebral osteomyelitis (VO) is unknown. In an era of increasing bacterial resistance, we compare the effectiveness of 6 and 12 weeks antibiotic treatment.

Methods: We carried out anational, open blind, randomized controlled non-inferiority multicentre trial in 2 parallel groups comparing 6 versus 12 weeks of antibiotic treatment duration.

Adult patients with clinical and radiologic diagnosis of VO (MRI or CT) and a reliable microbiological identification (positive and significative blood culture or needle biopsy) were recruited since 2007 to 2011. At one year, after the end of antibiotic therapy, cure was define as the absence of clinical and biological signs related to VO without the need for additional or alternative antibiotic therapy.

Results: 359 patients were randomized, 175 in the group 12 weeks treatment group and 176 in the group 6 weeks; 240 (69%) were male with mean age 61 years old. Eight patients were secondarily excluded. Median

duration between first symptoms and diagnosis was 49 (1–80) days; 182 (52%) patients were febrile at diagnosis and 237 (68%) had positive blood culture. Infective endocarditis was present in 70 (20%) cases. Main bacteria involved were *Staphylococcus aureus* (n=143, 41%), Coagulase negative-*Staphylococci* (n=52, 15%) and *Streptococcus non enterococcus* (n=63, 18%).

At baseline, characteristics were similar in both group of treatment duration. During follow up, difference was non significative in both groups regarding median duration of parenteral antibiotictherapy, median length of hospitalization stay, most frequent antibiotics for oral treatment (rifadin and fluoroquinolon). Adverse events occurred in 100 cases of whom 26 deaths. In the intention to treat analysis, cure rates in the 6 weeks treatment group and in the 12 weeks treatment group were respectively 91% (159/171) and 91% (160/176)with a difference non significative between the two groups.

Conclusion: We have demonstrated in this large multicentre randomized clinical trial that 6 weeks of antibiotic treatment duration is as effective as 12 for VO.

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2808

Favorable Outcome Of Hepatitis E Virus Infection In Patients With Inflammatory Arthritides Treated With Immunosupressants. Hélène Bauer[1], Cécile Luxembourger[2], Sophie Fournier[2], Alain G. Cantagrel[3], Jean Marie Peron[2], Anne Marie Roque Afonso[4], Pascal Claudepierre[5], S. Fabre[6], Christophe Hudry[7], Guillaume Lefevre[8], Antoine Martin[9], Laurent Messer[10], Béatrice Pallot Prades[11], Christian Roux[12], Christelle Sordet[13], Claire Veissier[14], Daniel Wendling[15], Jacques-Eric Gottenberg[13] and Jean Sibilia[16]. [1]CHU de Hautepierre, Strasbourg, France, [2]CHU de Toulouse, Toulouse, France, [3]Centre Hospitalier Universitaire de Toulouse, Toulouse, France, [4]virologie hôpital Paul Brousse, Villejuif, France, [5]Henri Mondor Teaching Hospital, AP-HP, Créteil, France, [6]CHU MONTPELLIER, Montpellier, France, [7]Hopital Cochin, Paris, France, [8]Lille University Hospital, Internal Medicine Department, Lille, France, [9]Centre Hospitalier De St Brieuc, St Brieuc, France, [10]Hopitaux Civils de Colmar, Colmar, France, [11]CHU St Etienne, St Etienne, France, [12]CHU L' Archet University Nice, Nice, France, [13]Strasbourg University Hospital, Strasbourg, France, [14]CHU de Bordeaux, Bordeaux, France, [15]University Hospital, Besancon, France, [16]CHU Hautepierre, Strasbourg, France.

Background/Purpose: In inflammatory rheumatic diseases, the prevalence, clinical presentation and outcome of hepatitis E, an ubiquitous viral infection, remain unknown. We therefore addressed these issues in a large retrospective study. The main objective of this study was to investigate the severity of acute hepatitis E and the risk of chronic viral replication in patients suffering from inflammatory rheumatisms and treated with immunosuppressive drugs.

Methods: All French rheumatology and internal medicine practitioners registered on the Club Rhumatisme et Inflammation (nearly 2,000 physicians),were repeatedly sent newsletters asking to report observations of acute hepatitis E virus (HEV) infection in patients with inflammatory arthritides. They were subsequently sent a standardized and detailed questionnaire on baseline characteristics of the patients and the course of HEV infection.

Results: Nineteen observations of hepatitis E were collected. They occurred in patients with rheumatoid arthritis (n = 9), axial spondyloarthritis (n = 4), psoriatic arthritis (n = 3), juvenile idiopathic arthritis (n =1), Jaccoud arthropathy (n = 1) and undifferentiated arthritis (n = 1), treated with methotrexate (n = 13), anti-TNFα therapy (n = 6), rituximab (n = 4), abatacept (n = 3) or tocilizumab (n = 1). Eight patients were treated with corticosteroids with a median dose of 4.5 mg/d. Most of the patients had few symptoms, except asthenia. A woman, suffering from psoriatic arthritis treated with cyclosporine developed a bilateral Parsonage Turner syndrome, which was considered as an extrahepatic HEV-related manifestation. All of the patients had acute elevation of aspartate and alanine aminotransferase levels, and 7 patients also had moderate cholestasis. Two patients had an acute hepatic failure with decreased prothrombin time. The hepatitis E diagnosis either relied on positive PCR detection for HEV RNA (n = 13 patients), or on positive IgM result without PCR assessment (n = 2) or with negative PCR for HEV (n = 4). No other aetiology of the hepatitis could be found, except in 1 patient who had a HEV and HAV coinfection. Mean current follow-up is 13.4 months (standard deviation: 8.8 months). Treatment of HEV infection included the discontinuation of immunosuppressants in 18 out of 19 patients (adalimumab was maintained in 1 patient) and ribavirine in 5 patients. Liver enzymes normalized within 1 month in 7 patients, 3 months in 6 patients, and 4 months in 2 patients. Ten previously positive PCR tests were repeated and all became negative within 3 months after HEV infection.Among the 15 patients with a follow-up of at least 3 months, all are considered to be cured by their clinicians and an immunosuppressant (the same as before HEV infection in 14 patients, etanercept in 1 patient) could be reinitiated in all of them with no viral reactivation.

Conclusion: The diagnosis of acute hepatitis E should be considered in patients with inflammatory arthritides treated with immunosuppressants and elevated liver enzymes. The outcome of HEV infection is usually favourable, after transient discontinuation of immunosuppressants associated or not with ribavirin, with no reported evolution towards chronicity.

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2809

Prevalence and Clinical Presentation Of Lyme Arthritis In a Large Cohort Of Patients With Recent-Onset Arthritis. Jeska K. De Vries-Bouwstra, Nathalie D. van Burgel, Tom Vreeswijk, Aloys C. M. Kroes, Tom W. J. Huizinga and Annette H. M. van der Helm-van Mil. Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Lyme arthritis is a relatively uncommon form of arthritis that is relevant to identify because it requires specific therapy. The presents study aimed to describe 1. the seroprevalence of Lyme antibodies, 2. the prevalence of Lyme arthritis, and 3. the diagnostics accuracy of serologic testing for *Borreliae* among patients with recent-onset arthritis in The Netherlands.

Methods: The present study included all patients who presented to the Leiden Early Arthritis Clinic during the period of February 1993 to April 1997 (cohort 1) and the period July 2003 to June 2008 (cohort 2). In sera from cohort 1, antibodies against *Borreliae* were detected by the IgG and IgM flagellin-Enzyme Immune Assay (EIA). All available positive samples were retested with the IgG/IgM C6 EIA. In cohort 2, the C6 Lyme EIA Kit was used. All positive EIA results from both cohorts were confirmed by the *Borrelia* Europe LINE blot and a second EIA, the Liaison® *Borrelia burgdorferi* IgG (VlsE) and IgM (VlsE+OspC). The clinical records of the patients with positive or equivocal serology were thoroughly studied; Lyme disease was not diagnosed in case of a clear alternative diagnosis. The proportion of patients with Lyme arthritis was determined, as well as the diagnostic accuracy of *Borrelia* serology.

Results: Of 1180 patients with recent-onset arthritis, 53 patients had positive serology, indicating a seroprevalence of 4,5% (Figure 1 and 2). Eight cases of definite Lyme arthritis (0.7%) were identified These patients were characterized by younger age, and typically presented with monoarthritis or oligoarthritis including a knee. Retrospectively, possible Lyme arthritis was diagnosed in seven (0,6%) patients. In the remaining patients with positive or equivocal serology different clinical diagnoses were made (rheumatoid arthritis n= 14; spondylarthritis n= 11; systemic inflammatory disease n= 3; osteoarthritis n= 2; other n=8). Based on the low prevalence of Lyme arthritis, the positive predictive value of serology for Lyme disease was low (10–28%). By selecting patients with a higher prior chance of Lyme disease, eg in patients presenting with an oligo- or monoarthritis of large joints, the positive predictive value increased to 67%.

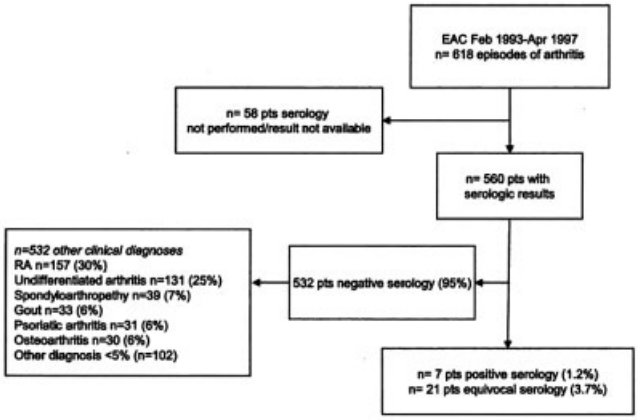

Figure 1: serologic results cohort 1; EAC= Early Arthritis Clinic; pts = patients

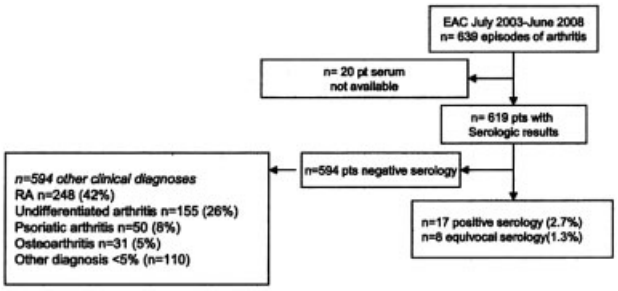

Figure 2: serologic results cohort 2; EAC= Early Arthritis Clinic; pts = patients

Conclusion: The prevalence of Lyme arthritis among patients with recent-onset arthritis in The Netherlands is low, 0.7%. Although sensitivity and specificity of Lyme serology are reported to be good, serologic testing for Lyme arthritis contributes poorly to clinical decision making in patient with recent-onset arthritis due to the low a priori chance on Lyme arthritis.

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2810

Follow-Up Testing Of Interferon-Gamma Release Assays For The Diagnosis Of Hidden Tuberculosis Infection In Patients Receiving Tumor Necrosis Factor Alpha Antagonists. Chan-Nam Son, Tae-Hwan Kim, Il-Hoon Sung, Jae-Bum Jun and Dae-Hyun Yoo. Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea.

Background/Purpose: Anti-tumor necrosis factor alpha (Anti-TNFα) therapy is often used in patients with rheumatic diseases who do not respond to conventional treatment. Risk of tuberculosis infection is high in patients receiving anti-TNFα treatments. Therefore, tuberculosis infection prophylaxes are recommended prior to anti-TNFα therapy if a tuberculin skin test or interferon-gamma release assay (IGRA) is positive. However, little data is available on the conversion of IGRAs in patients with rheumatic diseases who received anti-TNF treatment. We evaluated the utility of follow-up IGRAs for the diagnosis of latent tuberculosis infection and newly developing tuberculosis in patients receiving TNFα antagonists.

Methods: The study participants (n=117) were enrolled from September 2008 to August 2012, among ankylosing spondylitis (AS) and rheumatoid arthritis (RA) patients registered in tertiary care center. These patients had a negative IGRA screening before receiving anti-TNFα therapy and were evaluated by follow-up IGRA for detection of latent and newly developing tuberculosis until May 2013. We retrospectively examined data of the subjects according to age, gender, tuberculosis prophylaxis, IGRA conversion and TNFα blockers, including type and treatment duration. The QuantiFERON-TB Gold In-Tube test was used for the initial and follow-up screenings to detect tuberculosis infection.

Results: The median interval between initial and follow-up IGRAs in patients was 20.5 months, and the median age was 38.9 years. Of the 117 patients (92 AS and 25 RA), 105 patients (89.7%) showed consistently negative results, and IGRA conversion was found in 12 patients (10.3%). Among the 92 AS patients, IGRA conversion was found in 7 patients (7.6 %). Among the 25 RA patients, 5 patients with positive conversion (20%) were found. One RA patient developed extrapulmonary tuberculosis. IGRA conversion rate was higher in older patients ($\geq$ 40 years) (24.4%) than it was in younger patients ($<$ 40 years) (1.4%) ($p < 0.05$) (Table 1). AS patients were younger and used anti-TNFα inhibitors for extended time period. IGRA conversion rate was not significantly different between AS (7.6%) and RA (20%) ($p = 0.13$).

Table 1. Patients characteristics and interferon-gamma release assay (IGRA) conversion rate.

Characteristics	All (N=117)	Conversion (N=12)	Adjusted OR	95% CI	p-value
Diagnosis					
AS	92 (78.63)	7 (7.61)	0.42	(0.06–3.07)	0.394
RA	25 (21.37)	5 (20.00)	1.00		
Age, yrs, mean (SD)					
<40	72 (61.54)	1 (1.39)	1.00		
≥ 40	45 (38.46)	11 (24.44)	21.19	(2.12–211.57)	0.009*
Gender					
Male	76 (64.96)	6 (7.89)	1.00		
Female	41 (35.04)	6 (14.63)	0.34	(0.05–2.30)	0.271
TNFα antagonists					
Etanercept	43 (36.75)	7 (16.28)	1.00		
Adalimumab	37 (31.62)	1 (2.70)	0.19	(0.02–1.96)	0.164
Infliximab	37 (31.62)	4 (10.81)	0.53	(0.11–2.47)	0.418
Duration of TNFα inhibitor therapy					
< 2 yrs	74 (63.25)	5 (6.76)	1.00		
≥ 2 yrs	43 (36.75)	7 (16.28)	2.31	(0.46–11.70)	0.313
Tuberculosis prophylaxis					
No	102 (87.18)	8 (7.84)	1.00		
Yes	15 (12.82)	4 (26.67)	1.70	(0.25–11.54)	0.590

*$p < 0.05$

Conclusion: In patients with rheumatic diseases receiving TNFα blocker, IGRA conversions were observed. Patients with old age had higher IGRA conversion rate than patients with young age. These data suggest that follow-up IGRAs may identify false negative results of screening test and detect latent tuberculosis reactivation and new developing tuberculosis in patients receiving TNFα blockers in Korea. Larger-scaled studies may be needed for further evaluation about follow-up IGRAs.

Disclosure: C. N. Son, None; **T. H. Kim**, None; **I. H. Sung**, None; **J. B. Jun**, None; **D. H. Yoo**, None.

2811

Disease Characteristics and Treatment Patterns In US Veterans With Rheumatoid Arthritis and Concomitant Hepatitis C Infection. Ruchika Patel and Joshua Baker. University of Pennsylvania, Philadelphia, PA.

Background/Purpose: The prevalence of concurrent rheumatoid arthritis (RA) and hepatitis C (HCV) is estimated at 0.02%, affecting around 40,000 Americans. To our knowledge, no existing studies evaluated disease characteristics and treatment patterns in RA patients with and without HCV infection. Our aim was to evaluate disease characteristics, component and composite measures of disease activity, and treatment patterns in HCV-positive subjects with RA compared to HCV-negative subjects with RA in a large national registry

Methods: We utilized the Veterans Affairs Rheumatoid Arthritis Registry (VARA) to identify subjects with RA and concomitant HCV. Subjects who were identified by the physician to have comorbid HCV infection at the time of enrollment were considered HCV-positive. The registry includes baseline and longitudinal measures that are updated and entered into the VARA database by the treating physicians at routine clinical visits. Differences in disease characteristics, disease activity measures, and treatment patterns were assessed over the first 5 clinical visits. Chi^2 tests and T-tests or ranksum tests of significance were utilized for group comparisons. Linear and logistic regression analyses assessed group differences after adjustment for potential confounders (age, race and days from enrollment).

Results: Of 1870 registry participants, 53 were identified with concomitant HCV (2.8%). At enrollment, HCV-positive subjects were younger [60.7 $\pm$5.9 vs. 67.1 $\pm$11.1 ($p<0.0001$)], more likely to be African American (62% vs. 38%, $p=0.001$) and to smoke ($p=0.001$). Other disease characteristics (anti-citrullinated protein antibodies, erosions and disease duration) were similar between groups. At enrollment, HCV-positive subjects had greater DAS28 [4.7 $\pm$1.85 vs. 4.0 $\pm$1.61 ($p=0.05$)], tender ($p=0.001$) and swollen joint counts ($p=0.006$). By visit 2, there were no observed group differences in disease activity. During the five-visit period, HCV-positive patients had more frequent follow up [12.1 $\pm$ 5.3 vs. 17.4 $\pm$ 11.8 ($p=0.009$)]. No differences were observed in patient global score, global evaluator score,

Multidimensional Health Assessment Questionnaire (MD-HAQ), ESR, or CRP. At baseline, methotrexate use was less common among HCV-positive subjects (Table 1). By visit 2, subjects with HCV were more likely to use prednisone and, by visit 4, were more likely to use hydroxychloroquine. These differences in medications use persisted through the fifth visit (Table 1).

Table 1. Medication use among HCV-positive and HCV-negative subjects with Rheumatoid Arthritis at enrollment and over the initial 5-visits in VARA. Odds of use is adjusted for group differences in age, race, and days from enrollment for each visit.

Visit #	HCV− (%)	HCV+ (%)	Odds Ratio (95% CI)
Hydroxychloroquine			
1	28	34	1.26 (0.71–2.27)
2	28	36	1.23 (0.68–2.25)
3	26	42	1.59 (0.87–2.93)
4	25	43	1.91 (1.00–3.67)*
5	23	42	2.29 (1.12–4.68)*
Sulphasalazine			
1	12	21	1.68 (0.84–3.34)
2	13	21	1.43 (0.71–2.89)
3	13	23	1.58 (0.79–3.16)
4	12	19	1.16 (0.55–2.46)
5	11	21	1.69 (0.78–3.59)
Methotrexate			
1	45	21	0.32 (0.16–0.62)*
2	47	21	0.24 (0.12–0.47)*
3	43	19	0.20 (0.01–0.40)*
4	40	15	0.15 (0.07–0.34)*
5	36	15	0.16 (0.07–0.37)*
Prednisone			
1	37	40	1.14 (0.65–2.01)
2	38	55	1.85 (1.02–3.38)*
3	34	49	1.44 (0.78–2.66)
4	31	53	2.32 (1.16–4.67)*
5	28	48	2.41 (1.13–5.14)*
Anti-TNFs			
1	19	26	1.38 (0.73–2.60)
2	19	30	1.67 (0.89–3.13)
3	19	40	2.32 (1.25–4.29)*
4	17	30	1.71 (0.88–3.33)
5	17	26	1.46 (0.72–2.98)

* P value < 0.05

Conclusion: At enrollment, HCV-positive subjects were younger, more likely to be African American, smoke, had higher joint counts, and were less likely to be prescribed methotrexate. Our data suggest more frequent follow up and use of prednisone and hydroxychloroquine over time among subjects with RA and concomitant HCV, may result in comparable early disease control compared to RA subjects without HCV.

Disclosure: R. Patel, None; **J. Baker**, None.

ACR Concurrent Abstract Session
Medical Education
Wednesday, October 30, 2013, 9:00 AM–10:30 AM

2812

A Rheumatology Objective Structured Clinical Examination Using Challenging Patient Scenarios Shows Trainee Use Of Medical Jargon Correlates Inversely With Patient Perceptions Of Professionalism. Jessica Berman[1], Juliet Aizer[2], Anne R. Bass[2], Anne Davidson[3], Edward Dwyer[4], Theodore R. Fields[2], Jane Kang[4], Leslie Kerr[5], Svetlana Krasnokutsky-Samuels[6], Deana M. Lazaro[7], Stephen A. Paget[2], Julie S. Schwartzman-Morris[8] and Michael H. Pillinger[9]. [1]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, [2]Hospital for Special Surgery Weill Cornell Medical College, New York, NY, [3]Feinstein Institute for Medical Research, Manhasset, NY, [4]Columbia School of Medicine, New York, NY, [5]Mount Sinai School of Medicine, New York, NY, [6]NYU School of Medicine, New York, NY, [7]Brooklyn VA, Brooklyn, NY, [8]Albert Einstein College of Medicine, Bronx, NY, [9]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: For 8 years, the New York City Rheumatology Objective Self Assessment Clinical Exam (NYC-ROSCE) has been used to assess trainee competencies such as patient care and communication. Most recently, we have refocused the NYC-ROSCE to assess professionalism, using a validated professionalism questionnaire. This year we asked which individual skills were most likely to correlate with overall achievement in the area of professionalism.

Methods: The 2012 NYC-ROSCE included 5 patient-centered stations focusing on rheumatic disease. For the first time, stations were designed to challenge fellows with patient psychosocial dilemmas, in order to assess specific aspects of the patient-doctor relationship including physician professionalism. Rheumatology trainees (n=28) and faculty MD-evaluators (n=32) from 6 NY rheumatology training programs participated. Professional actors (n=30) were trained to role-play patients. Quantitative assessments of the trainees were made at each station (9-point Likert scale) by patient- and MD-evaluators in the areas of: maintaining composure, partnering with the patient, being open and honest, professionalism, empathy and accountability. Qualitative free text comments were solicited after each station, regarding the strengths and weaknesses of each fellow's performance during the encounter. In addition, trainees rated their own performance after each encounter. Immediate oral feedback on professionalism was given to each trainee by both patient-actors and MD-evaluators.

Results: When assessing professionalism, MD-evaluators tended to rate trainees lower (6.74+/−0.58) than patient-actors (7.12+/−0.78), suggesting that physicians and patients may apply different criteria when assessing professionalism during observed encounters. Trainee self-evaluations for professionalism were in the range of the MD-evaluators rather than the patient-actors (6.70+/−1.16). MD-evaluators also tended to give lower ratings for accountability (6.32+/−0.82) than patient-actors (6.68+/−0.85) or the trainees themselves (6.53+/−1.04). In contrast, ratings of empathy were found to be closely in agreement for trainees (6.62+/−1.04), MD-evaluators (6.58+/−0.69) and patient-actors (6.55+/−1.05. MD-evaluators most often commented on the trainees' word choice and body language, ability to formulate a clear plan, ability to recognize and address patient's fears, and the need to actively partner with the patient. For all evaluators, excessive use of medical jargon was most often cited as the area that needed improvement. The use of jargon correlated inversely with the ratings of professionalism for MD-evaluators and patient-actors.

Conclusion: The introduction this year of new and challenging patient encounters allowed us to assess which patient-centered traits most contributed to perceptions of achievement in the area of professionalism. We found that our evaluators considered the ability to minimize medical jargon to be one of the most important markers of the competency of professionalism. This finding suggests that patients view communication as correlating most strongly with their doctor's professionalism.

Disclosure: J. Berman, None; **J. Aizer**, None; **A. R. Bass**, None; **A. Davidson**, None; **E. Dwyer**, None; **T. R. Fields**, Takeda Pharmaceuticals, 8, Takeda Pharmaceuticals , 9, Savient Pharmaceuticals, 8, Pfizer Pharmaceuticals, 8; **J. Kang**, None; **L. Kerr**, None; **S. Krasnokutsky-Samuels**, None; **D. M. Lazaro**, None; **S. A. Paget**, None; **J. S. Schwartzman-Morris**, None; **M. H. Pillinger**, None.

2813

Expert Panel Consensus On Content Of a Rheumatology Objective Structured Clinical Examination. Lisa G. Criscione-Schreiber[1], Marcy B. Bolster[2], Beth L. Jonas[3], Richard Sloane[1], Jeffrey Hawley[4] and Kenneth S. O'Rourke[5]. [1]Duke University Health System, Durham, NC, [2]Massachussetts General Hospital, Boston, MA, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC, [4]Duke University School of Nursing, Durham, NC, [5]Wake Forest School of Medicine, Winston-Salem, NC.

Background/Purpose: Rheumatology objective structured clinical examinations (ROSCEs) are assessment tools to evaluate learner performance in simulated clinical experiences. ROSCEs allow standardization of learner assessment in competencies that are challenging to measure in other ways. While several regional groups in the United States conduct ROSCEs, none have been validated for use across programs. We aimed to establish agreement among subspecialty experts regarding the important benchmarks for rheumatology fellows to achieve in 11 theoretical ROSCE stations.

Methods: First, each author independently created a grid listing important attributes to assess in 11 possible ROSCE stations. The grids were combined (by LCS) into a 173-item checklist survey to assess the importance of each item for future use in ROSCEs. IRB exemption was granted to send the survey by email to 37 expert rheumatologists, defined as individuals who have helped create and administer regional ROSCEs. Participants in the expert

panel survey rated the importance of each item using a 5-point Likert scale (1=not important to 5=very important). Minimum and maximum scores, the mean, standard deviation, and lower 95% confidence level for the mean were calculated for each survey item. Consensus for high importance was predefined as a lower bound of the 95% CI ≥ 4.0.

Results: 11 individuals completed the expert panel survey. 123 of the 173 items (71%) met statistical cutoff for consensus to retain, distributed among the 11 proposed stations. Several items were rejected that had population means of ≥ 4.0 but did not meet the pre-determined definition for consensus. The percentage of retained items for individual stations ranged from 23.5 to 100% (Table). All items were retained for the core interpersonal and professionalism items included as part of general patient counseling and for x-ray interpretation tasks. Only 23% of items were retained for a station involving rehabilitation medicine, and 46% of items for a microscope use/synovial fluid analysis station.

Table. Item retention summary. Items were retained if statistical analysis revealed a lower bound of the 95% CI ≥ 4.0.

Station	Number of items assessed	Number of items retained	Agreement score range	Percentage of items retained
Phone call from primary care provider	18	10	1.98–5	55.5%
X-rays	19	19	4.19–5	100%
Non-formulary request letter to insurance company	16	12	3.03–5	75%
Osteoporosis/DXA interpretation	17	14	2.98–4.74	82.4%
Rehabilitation	17	4	2.51–4.6	23.5%
General counseling	13	13	4.08–5	100%
Counseling: anti-Ro+ woman pre-conception	13	11	3.13–5	84.6%
Counseling: new scleroderma	11	8	3.13–4.6	72.7%
Counseling: new biologic for RA	14	9	3.34–5	64.3%
Knee arthrocentesis	20	16	3.18–5	80%
Microscope synovial fluid	15	7	2.70–5	46.7%
Total	173	123	1.98–5	71.1%

Conclusion: In this single round expert panel survey, we established national consensus on 123 items to assess on 11 proposed ROSCE stations. This study represents the first use of such rigorous methods to establish checklist content agreement for an OSCE in any medical field. Next steps include 1) defining behavioral anchors (milestones) for performance on individual stations and 2) finalizing checklists and station manuals that can be shared among rheumatology programs nationally to improve the validity of regional OSCEs and initiate use in programs without regional collaborators. Use of these checklists by regional rheumatology groups will create the framework for collection of summary data and perhaps eventual creation of a high-stakes rheumatology OSCE.

Disclosure: L. G. Criscione-Schreiber, None; **M. B. Bolster**, American College of Rheumatology, 6, Rheumatology Research Foundation, 6, American College of Rheumatology, 6; **B. L. Jonas**, None; **R. Sloane**, None; **J. Hawley**, None; **K. S. O'Rourke**, None.

2814

The Resident-Fellow Interaction: Limiting Barriers and Maximizing Learning. Eli Miloslavsky[1], Amy Sullivan[2], Jeremy Richards[2], Jakob I. McSparron[3], David Roberts[2] and Alberto Puig[4]. [1]Massachusetts General Hopsital, Boston, MA, [2]Beth Israel Deaconess Medical Center, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]Massachusetts General Hospital, Boston, MA.

Background/Purpose: Subspecialty fellows may play an important role in Internal Medicine (IM) residents' education and career specialty choice (Horn 2008). This may be particularly important in rheumatology where a projected workforce shortage may require the expansion of the current training capacity (Deal 2007), and over 75% of fellows decide to pursue a career in rheumatology during residency (Kolasinski 2007). In this context, fellows may be underutilized as clinical teachers and role models, possibly due to the existence of barriers to an effective resident-fellow interaction (Miloslavsky 2010).

To our knowledge, the working relationship between IM subspecialty fellows and IM residents has not been examined. We conducted a study to determine the barriers and facilitating factors to the IM resident-fellow interaction on the wards.

Methods: We conducted 4 focus groups: IM residents at the Massachusetts General Hospital (MGH) and the Brigham and Women's Hospital (BWH), IM fellows at BWH/MGH, and IM fellows at MGH who received teaching awards. There were 32 participants from all residency classes and 7 IM subspecialties including rheumatology. Four investigators analyzed focus group transcripts via a theory driven immersion-crystallization process using activity theory (Engestrom 2011).

Results: Five themes of barriers were identified:

- Intrinsic: residents' and fellows' expectations of each other; absence of familiarity/personal relationship between residents and fellows; interest and availability (fellows - willingness to see the consult, residents - being available/interested in discussing the consult); knowledge (residents - patient history, fellows - subject matter).
- Logistical: resident work hours (e.g. frequent patient handoffs); primary team structure (e.g. team-based care model, de-regionalized teams).
- Attending-related: primary team attending (role in formulating the consult question, communication); consult attending (role modeling).
- Workload: resident and fellow patient census and the duration/complexity of the consult.
- Teaching: time available to teach and fellows' teaching skills.

Focus group participants cited increasing familiarity/personal relationships between residents and fellows as a critical variable in improving the interaction. Other means of overcoming barriers included limiting fellow pushback on residents' consult requests, standardizing fellows' and residents' expectations about the consult interaction, and improving fellows' teaching skills.

Positive and negative feedback loops appear to be important in the resident-fellow interaction, with positive interactions strengthening future ones and negative interactions creating additional barriers.

There was broad agreement between fellows from different subspecialties and residents with respect to both barrier and facilitating factors.

Conclusion: The resident-fellow interaction faces multiple barriers from both systems and personal domains, however many of these barriers may be modifiable. Future efforts should focus on implementing strategies to overcome these barriers. Such efforts may enhance IM residents' rheumatologic clinical skills and potentially influence their career choice.

Disclosure: E. Miloslavsky, Genentech Inc, 9; **A. Sullivan**, None; **J. Richards**, None; **J. I. McSparron**, None; **D. Roberts**, None; **A. Puig**, None.

2815

Preliminary Entrustable Professional Activities in Muscloskeletal Ultrasound For Rheumatology Fellowship Training. Amy C. Cannella[1], Eugene Y. Kissin[2], Gurjit S. Kaeley[3], Jay B. Higgs[4], Kelly J. Caverzagie[5] and Karina D. Torralba[6]. [1]Omaha Veterans Affairs Hospital and University of Nebraska Medical Center, Omaha, NE, [2]Boston University, Boston, MA, [3]University of Florida, Jacksonville, FL, [4]San Antonio Military Medical Center, Fort Sam Houston, TX, [5]University of Nebraska Medical Center, Omaha, NE, [6]Loma Linda University, Loma Linda, CA.

Background/Purpose: As part of the Next Accreditation System (NAS), the Accreditation Council for Graduate Medical Education (ACGME) has mandated a change in the evaluation of postgraduate trainees by including the development of Entrustable Professional Activities (EPAs) for each specialty and subspecialty. EPAs are the routine professional activities which define a profession. They also provide a means of framing the 6 ACGME competencies in a way that allows them to be meaningful to learners and faculty. The American College of Rheumatology (ACR) is developing EPAs for Rheumatology training. Although not currently an ACGME requirement, many fellowship programs have incorporated Musculoskeletal Ultrasound (MSUS) in their curricula. We seek to define EPAs for MSUS in rheumatology as an initial step towards the development of standardized curriculum and assessment tools.

Methods: A group of educators utilized a modified nominal group technique (NGT) to develop EPAs for MSUS. A literature search was completed on MSUS education, certification, best practices and curriculum development to generate a list of potential EPAs specific for MSUS in rheumatology, framed within the ACGME competency and milestone vernacular.

Each item was rated for inclusion as an EPA using a Likert scale, where 1 represented the least agreement and 9 represented the most agreement. A median score of 7–9 was considered to have highest agreement, 4–6 was intermediate agreement, and <3 was rejected. An initial postal round was followed by a teleconference call, where each group member had the opportunity to discuss, defend or dispute the item. A second round was then completed to develop a final list of EPAs.

Results: 35 initial EPAs were developed for scoring in each round. In the postal round, 24 and 11 EPAs met criteria for highest and intermediate agreement, respectively. In the final round, 19 EPAs met criteria for highest agreement and included concepts such as indications, limitations and proper performance of MSUS. Eight EPAs met criteria for intermediate agreement, and included concepts such as communication with referring providers and patients regarding MSUS findings. The remaining 8 EPAs were rejected for reasons such as redundancy with predicted sub-specialty EPAs, and a lack of specificity for MSUS. As a result of conferencing, several EPAs were merged into single EPAs to enhance cohesiveness and included concepts such as combining patient positioning with other strategies to obtain optimal images, and approaches to self-reflection and self-directed learning. Out of the initial 35 items, a final list of 16 EPAs was developed for MSUS in Rheumatology.

Conclusion: A preliminary set of EPAs specific for the practice of MSUS in rheumatology was developed. These EPAs are the initial step in the development of assessment tools for determination of MSUS competency for a rheumatology fellow in training. Further studies will include validation of these EPAs by a larger group of educators and practitioners of MSUS.

Disclosure: A. C. Cannella, None; **E. Y. Kissin**, None; **G. S. Kaeley**, None; **J. B. Higgs**, None; **K. J. Caverzagie**, None; **K. D. Torralba**, None.

2816

Pilot Phase Outcomes From The ACR/Carra Inter-Institutional Mentoring Program In Pediatric Rheumatology. Peter A. Nigrovic[1], Eyal Muscal[2], Lakshmi N. Moorthy[3], Sampath Prahalad[4], Marisa S. Klein-Gitelman[5], Meredith P. Riebschleger[6], B. Anne Eberhard[7] and Rayfel Schneider[8]. [1]Boston Children's Hospital, Boston, MA, [2]Baylor College of Medicine, Houston, TX, [3]Robert Wood Johnson Medical School-UMDNJ, New Brunswick, NJ, [4]Emory Children's Center, Atlanta, GA, [5]Children's Memorial Hospital, Chicago, IL, [6]University of Michigan Health System, Ann Arbor, MI, [7]Cohen Children's Hospital Medical Center, New Hyde Park, NY, [8]Pediatric Rheumatology Collaborative Study Group (PRCSG), Cincinnati, OH.

Background/Purpose: In pediatric rheumatology, the small size of many academic programs translates into limited mentoring options for early career physicians. To address this "mentorship gap," the American College of Rheumatology (ACR) and the Childhood Arthritis and Rheumatology Research Alliance (CARRA) joined together to develop **AMIGO, the ACR/CARRA Mentoring Interest Group**, that now enrolls more than 80 pediatric rheumatology fellows and junior faculty in the US and Canada. We report program evaluation data from the AMIGO pilot project, launched in November 2011 with 20 mentor-mentee dyads.

Methods: Mentees and mentors participating in the AMIGO pilot phase were surveyed via online questionnaire 17 months after initial match to determine dynamics of contact and perceived benefit in domains relevant to professional success and work-life balance.

Results: Of 20 initial matches, 19 were still functioning while one had dissolved due to departure of the mentee from North America. Ninety-five percent of the participants reported at least two substantial interactions. Total mentoring time was estimated at under 60 minutes by approximately half of respondents, though 20% reported more than 3 hours of interaction. Thirty-one percent of participants rated the quality of the match as good and 51% as excellent (defined as 'excellent overlap of mentee needs and mentor experience'). All mentees considered the mentoring helpful in providing career guidance, with substantial benefit also in scholarship, and job satisfaction. Benefits reported by mentors included improvement of their mentoring skills and development of their academic portfolios. Both mentees and mentors reported improved connectedness to the wider pediatric rheumatology community. All participants favored continuation of the program (**Table 1**).

Table 1. Pilot survey data at 17 months after initiation of a mentoring program

	Mentees (n, %)	Mentors (n, %)	Overall (n, %)
Responses (%)	18/19 (95)	19/19 (100)	37/38 (97)
Benefit to mentee			
Career path/job search	18 (100)	13 (68)	31 (84)
Research/scholarship	12 (67)	10 (53)	22 (59)
Job satisfaction	13 (72)	12/17 (71)	25/35 (71)
Work-life balance	8 (44)	12/18 (67)	20/36 (56)
Benefit to mentors			
Mentoring skills	NA	12/18 (67)	NA
Professional portfolio	NA	8/17 (47)	NA
Enhanced connection to community	14/17 (82)	14 (75)	28/36 (78)
Should AMIGO be continued?	18 (100)	19 (100)	37 (100)

Conclusion: The success of the pilot AMIGO program indicates that a North American inter-institutional mentoring program in pediatric rheumatology is feasible. Participants identified benefits to both mentees and mentors in multiple domains, most prominently in career guidance, a core goal of the program. Although longer-term evaluation of the full AMIGO program is needed, the success of the pilot program suggests that AMIGO could serve as a model for mentoring more broadly within the ACR and potentially in other medical subspecialties.

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2817

Objective Assessment Of Musculoskeletal Physical Examination Skills During Continuing Education Programs For Primary Care Providers Adds Significant Information Not Obtained Through Self-Assessment. Andrea M. Barker[1], Michael J. Battistone[1], J Peter Beck[1], Jorie Butler[2], Marissa Grotzke[1], Timothy A. Huhtala[1], Amy C. Cannella[3], David I. Daikh[4], Meika A Fang[5], Antonio A. Lazzari[6], Pedro Roldan[7], Joan Marie Von Feldt[8] and Grant W. Cannon[1]. [1]Salt Lake City VA and University of Utah, Salt Lake City, UT, [2]Salt Lake City VA, Salt Lake City, UT, [3]Omaha Veterans Affairs Hospital and University of Nebraska Medical Center, Omaha, NE, [4]University of California, San Francisco, San Francisco, CA, [5]VA Greater Los Angeles Healthcare System, Los Angeles, CA, [6]Boston VA Medical Center, Boston, MA, [7]Leesburg VA CBOC, Leesburg, FL, [8]Univ of Pennsylvania/Philadelphia VAMC, Philadelphia, PA.

Background/Purpose: Self-assessment is the most frequently used method in the evaluation of continuing medical education (CME) programs. This multi-institutional project was designed to examine convergent validity of learners' self-assessment competency ratings with their scores on a 2-station objective structured clinical examination (OSCE) during a musculoskeletal (MSK) CME program.

Methods: The VA Salt Lake City Health Care System developed a 3-day MSK Mini-Residency program in collaboration with six other VA facilities. This program for primary providers emphasizes physical examination and clinical management of common shoulder and knee disorders. Curriculum was introduced through focused didactics followed by small group hands-on practice sessions involving simulated patients. At the conclusion of the program, participants completed a self-reported competency assessment utilizing a 5-point Likert scale and an OSCE for both the shoulder and knee with a rater unaware of the self-reported competency. Self-assessment ratings were classified as low (<4.0), medium (4.0–4.5), and high (>4.5). OSCE ratings were classified with the same numerical boundaries based on a weighted scoring system for each component of the physical exam and then percentage of exam completed correctly (low <80%, medium 80%-90%, high >90%).

Results: A total of 107 and 109 participants completed all components of the shoulder and knee assessments, respectively. Over half the participants were rated high on both self-assessment and OSCE for the shoulder, though correlation was weak (Pearson coefficient = 0.28). For the knee, the OSCE ratings were more variable with approximately one-third of participants in each category while the majority of the participants assessed themselves as being highly competent. Correlation was again weak (Pearson coefficient = 0.05).

Table 1. Self-assessment ratings compared to OSCE ratings for shoulder.

SHOULDER		OSCE Rating			
	Low	Med	High		
Self-Assessment Rating	Low	0	1 (0.9%)	0	1 (0.9%)
	Med	5 (4.7%)	8 (7.5%)	10 (9.3%)	23 (21.5%)
	High	9 (8.4%)	18 (16.8%)	56 (52.3%)	83 (77.6%)
		14 (13.1%)	27 (25.2%)	66 (61.7%)	107

Table 2. Self-assessment ratings compared to OSCE ratings for knee.

KNEE		OSCE Rating			
	Low	Med	High		
Self-Assessment Rating	Low	0	0	1 (0.9%)	1 (0.9%)
	Med	13 (11.9%)	7 (6.4%)	8 (7.3%)	28 (25.7%)
	High	26 (23.9%)	28 (25.7%)	26 (23.9%)	80 (73.4%)
		39 (35.8%)	35 (32.1%)	35 (32.1%)	109

Conclusion: Following an intense MSK CME program, the majority of participants rated themselves as highly competent for the shoulder and knee. However, correlation of self-reported competency and OSCE rating was weak, particularly for the knee. Greater variability in the knee OSCE rating and correlation coefficient may be due to the exam maneuvers being more technically difficult to perform as they require more "hands-on" skills of the examiner. These data suggest that an OSCE should be included in evaluation of participants in CME programs to assess competency in the clinical skills being taught.

Disclosure: A. M. Barker, None; **M. J. Battistone**, None; **J. P. Beck**, None; **J. Butler**, None; **M. Grotzke**, None; **T. A. Huhtala**, None; **A. C. Cannella**, None; **D. I. Daikh**, None; **M. A. Fang**, None; **A. A. Lazzari**, None; **P. Roldan**, None; **J. M. Von Feldt**, None; **G. W. Cannon**, None.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Animal Models II
Wednesday, October 30, 2013, 9:00 AM–10:30 AM

2818 WITHDRAWN

2819

Administration Of a Multi-Epitope Citrullinated Peptide Attuneuates adjuvant Induced Arthritis In Rats Via Induction Of Immune Tolerance.
Howard Amital[1], Smadar Gertel[2] and Yehuda Shoenfeld[3]. [1]Sheba Medical Center,Tel-Hashomer, Tel-Aviv University, Tel-hashomer, Israel, [2]Sheba Medical Center, Tel-Hashomer, Israel, [3]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Affiliated to Sackler Faculty of Medicine, Tel-Aviv University,Tel-Aviv, Tel-Aviv, Israel.

Background/Purpose: Antigen-induced peripheral tolerance is a potentially efficient and specific therapeutic approach to attenuate autoimmunity. Citrullinated peptides are major targets of disease-specific autoantibodies in Rheumatoid Arthritis (RA). Currently, citrullinated peptides serve primarily as biomarkers for the diagnosis of RA by measuring titers of anti-citrullinated protein antibodies.

In an attempt to develop a citrullinated peptides-based specific immunotherapy for RA, we previously showed the potential of two citrullinated peptides (citrullinated-filaggrin and citrullinated-β-fibrinogen) to up-regulate TGF-β mRNA expression and concomitant expansion of regulatory T cell population. In addition, our citrullinated peptides reduced the expression of inflammatory cytokines (INF-γ, TNF-α and IL-17), reduced the percentage of pathogenic IL-17$^+$ cells and increased the apoptosis rate of T cells following incubation with RA-derived peripheral blood mononuclear cells (PBMC).

In view of the multiplicity of citrullinated target autoantigens in RA we tailored a multi-epitope citrullinated peptide (Cit-ME) derived from major prevalent citrullinated autoantigens (citrullinated filaggrin, fibrinogen, vimentin and collagen type II). The later was tested for treatment of adjuvant induced arthritis (AIA) via immune tolerance induction by attenuating the disease manifestations.

Methods: Seven days following induction of AIA in Lewis female rats we administrated Cit-ME (300mg/rat) by 8 subcutaneous injections given on alternate days. Clinical scoring was performed once a week during the experiment. At the end of the experiment rats spleens were analyzed for apoptosis of CD4$^+$ T cells by flow cytomety.

Results: Treatment with Cit-ME ameliorated the clinical score of the diseased arthritic rats.

Rats treated with the Cit-ME had significantly less arthritic symptoms compared to untreated rats at day 21 (Figure 1). Amelioration of disease manifestations was associated with increased apoptosis rate of T cells.

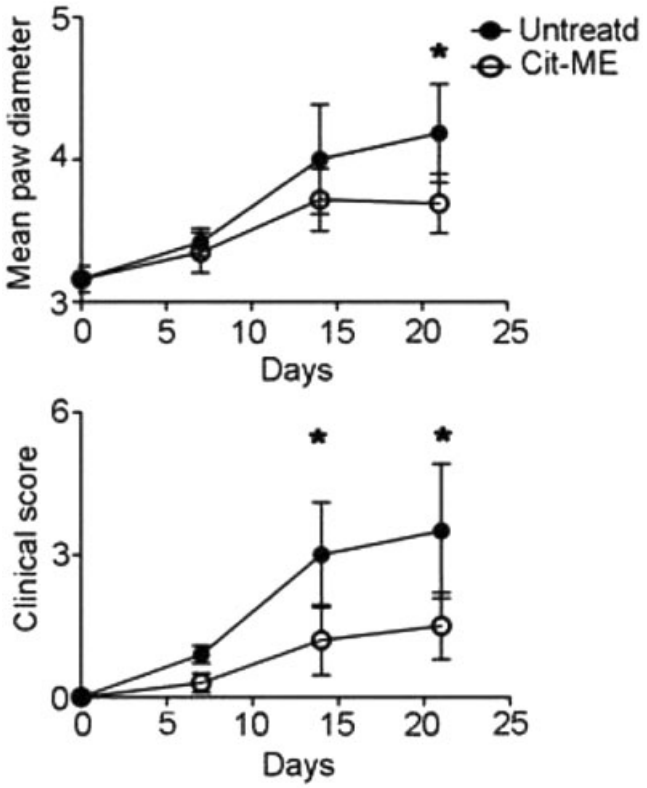

Figure 1. Treatment with Cit-ME suppressed Adjuvant induced arthritis (AIA) clinical score in Lewis rats

Conclusion: We demonstrated that citrullinated peptides induced immune tolerance in an experimental model of AIA.

Disclosure: H. Amital, None; **S. Gertel**, None; **Y. Shoenfeld**, None.

2820

Disease-Regulated Local Interleukin-10 Gene Therapy Diminishes Synovitis and Articular Cartilage Damage In Experimental Arthritis.
Eline A. Vermeij[1], Mathijs G.A. Broeren[1], Miranda B. Bennink[1], Onno J. Arntz[2], Inger Gjertsson[3], Wim B. van den Berg[1] and Fons A.J. van de Loo[1]. [1]Rheumatology Research and Advanced Therapeutics, Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [3]Department of Rheumatology and Inflammation Research, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden, Gothenburg, Sweden.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic destructive autoimmune disease and in most patients the disease follows an intermittent course with periods of exacerbation and remission. Today's treatment is based on continuous immunosuppression, irrespective of the patient's inflammatory status. An attractive alternative treatment would provide a disease-regulated therapy that offers flexible drug delivery, high during flares and low during remission. To explore this concept we expressed the anti-inflammatory cytokine interleukin (IL)-10 gene under the control of an inflammation dependent promoter in a mouse model of RA, the streptococcal cell wall arthritis (SCW).

Methods: C57Bl6/N mice were injected intra-articularly in the knee joint with lentiviral vectors expressing a luciferase reporter or the therapeutic protein IL-10. The disease-regulated proximal promoters of S100a8, Cxcl1, Mmp13, Saa3, IL-1b, and TSG6 were selected from endogenous genes differentially regulated in the inflamed synovium of arthritic mice. The constitutive PGK promoter was used as a positive control. Arthritis was

induced by injection of 25μg SCW into the knee joint cavity 4 days after lentivirus injection. At 1, 4, and 7 days after arthritis induction, in-vivo bioluminescent imaging was performed or mice were sacrificed and knee joints were dissected for either histological analysis, or RNA isolation for qPCR analysis.

Results: The 6 disease-regulated promoters all showed a different activation profile during the course of the disease. Two promoters were selected for IL-10 overexpression in the SCW model; the Saa3 promoter which showed an immediate and high upregulation at day 1 after arthritis induction, and the MMP13 promoter which showed a delayed response and peaked at day 4. For both regulated promoters, overexpression of IL-10 showed significant less synovitis at day 4 after arthritis induction (decrease from 2.2±0.2 to 1.6±0.2) and significant less cartilage proteoglycan (PG) depletion at day 4 (decrease from 2.6±0.2 to 1.3±0.2) and day 7 (decrease from 2.2±0.3 to 0.7±0.3) after arthritis induction. At day 4, IL1-Ra and SOCS3 genes were upregulated by Saa3-IL10, whereas at day 7 both Saa3-IL10 and MMP13-IL10 caused an upregulation of IL1Ra and SOCS3 gene expression. IL-1Ra is known to counteract the detrimental effects of IL-1 on cartilage damage and SOCS3 can inhibit the JAK/STAT pathway and subsequent inflammation. Therefore, these IL-10 induced changes in gene expressions can explain the diminished synovitis and PG depletion. Probably because IL-10 is expressed in the synovial tissue at day 1 of SCW arthritis without any treatment, a major therapeutic difference between the MMP13 and SAA3 promoter was not evident in this study.

Conclusion: Local inflammation-dependent IL-10 gene therapy suppresses experimental arthritis and is a promising strategy in the development of novel treatments for RA.

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2821

Evaluation Of Selective Manipulation Of The CD28 Co-Stimulation Pathway In The Rhesus Monkey Model Of Collagen-Induced Arthritis. Michel P.M. Vierboom[1], Elia Breedveld[1], Bert 't Hart[1], Flora Coulon[2] and Bernard Vanhove[3]. [1]Biomedical Primate Research Centre, Rijswijk, Netherlands, [2]Institut National de la Santé et de la Recherche Médicale, Nantes, France, [3]INSERM UMR-S 1064, Nantes, France.

Background/Purpose: T-cells are important in the pathogenesis of rheumatoid arthritis (RA). T-cell activation depends on at least two signals. Next to the first signal that is provided by the binding of the T-cell receptor (TCR) to a peptide bound by an MHC molecule it requires a second signal provided by one or more co-stimulatory pathways. If only the first signal is present without co-stimulation T cells become anergic. One of the most important pathways, which is of therapeutic interest is that between CD80/86 on antigen-presenting cells and CD28 on naïve T-cells. This interaction is necessary for T-cell activation. Intervention in this pathway has resulted in clinical success in the treatment of RA as demonstrated by treatment with the CD80/86 antagonist CTLA4-Ig (Abatacept). Here we present the beneficial result of treatment with a novel CD28 antagonist, which blocks CD28 instead of CD80/86, in a nonhuman primate model of inflammatory arthritis.

Methods: FR104, is a monovalent and pegylated humanized Fab' antibody fragment directed against CD28. FR104 functions as a CD28 antagonist that prevents the interaction between CD28-CD80/86 without inhibiting the interaction with CTLA-4 and PDL-1, thereby promoting immune regulation. FR104 is a primate specific antibody and safety and efficacy was tested in a collagen-induced arthritis (CIA) model in the rhesus monkey. The rhesus CIA model is an autoimmune-mediated model of polyarthritis with inflammation and erosion of joints that shares several important cellular and histopathological features with (RA). Treatment with either Vehicle (N=5) or FR104 (N=7) started at the day of induction and continued weekly until day 42 (7 administrations)

Results: Treatment with FR104 prevented the development of clinical arthritis leading to a significant disease free survival compared to placebo treated animals. This was supported by unchanged production of cartilage breakdown products and minimal histological changes. This was associated with a suppressed production of CRP and IL-6. Treatment with FR104 also resulted in a robust suppression of collagen type II-specific proliferation and antibody (IgM/IgG) production and prevented the development of joint swelling and the subsequent destruction of cartilage and bone.

Conclusion: FR104 was well tolerated after the multiple dosing in this nonhuman primate model of arthritis. Treatment resulted in a robust suppression of collagen specific immune responses and inhibited the development clinical arthritis. In addition it prevented the development of neutralizing antibodies, a phenomenon that is regularly observed in the model with treatments targeting inflammatory cytokines like IL-6. The current study demonstrated the strong potential of CD28 as a therapeutic target of antagonist antibodies in a range of inflammatory disorders, including RA.

Disclosure: M. P. M. Vierboom, None; **E. Breedveld**, None; **B. 't Hart**, None; **F. Coulon**, None; **B. Vanhove**, Effimmune, 9.

2822

IKKε Deficiency Prolongs Neutrophil Survival Paradoxically Prolonging Inflammation In The Absence Of a Type I Interferon Response. Maripat Corr[1], Christopher Chung[2], Seong-Kyu Kim[3], D. L Boyle[2] and G. S. Firestein[2]. [1]Univ of California-San Diego, La Jolla, CA, [2]UCSD School of Medicine, La Jolla, CA, [3]Catholic University of Daegu School of Medicine, Daegu, South Korea.

Background/Purpose: Deficiency of the IKK-related kinases IKKε synergizes with the anti-inflammatory effects of IFNβ in a murine model of arthritis, and this effect is mediated by IL-1Ra. To further explore the relationship between IFN signaling and IKKε, IKKε null mice were intercrossed with IL1Ra or type I interferon receptor deficient mice and evaluated in the passive K/BxN model of arthritis.

Methods: IKKε null, *Il1rn* (which encodes IL-1Ra) null, IL1Ra/IKKε null, IFNAR1 null, IFNAR1/IKKε null and wild type mice were injected with 150 ul of pooled K/BxN sera on day 0. Clinical response and histologic scores were assessed. Gene expression was measured by quantitative PCR. Mice were injected intraperitoneally with thioglycollate. The peritoneal lavage was evaluated for cell counts. The number and viability of neutrophils was determined by flow cytometry. Gene expression and protein production were tested by qPCR and western blot respectively.

Results: IKKε null mice had a modestly attenuated course of arthritis (area under the curve [AUC] for ankle diameter=5.1 vs. 5.9 for wild type controls, $P<0.05$). In contrast IFNAR1 null mice (AUC 6.3 vs. 5.9, $P<0.05$) and $Il1rn^{-/-}$ mice (AUC 11.4 vs. 5.9 $P<0.01$) had more severe serum transfer arthritis than wild type mice. The IL1Ra/IKKε null had arthritis similar (AUC 12.1) to the $Il1rn^{-/-}$ mice (AUC 11.4). Unexpectedly, IFNAR1/IKKε null mice (AUC 7.9, $P<0.05$) had even greater disease severity than the IFNAR1 null (AUC 6.3) mice. The ankle histology scores in each strain correlated well with the clinical course. Of interest, quantitative PCR of arthritis paws showed a significant increase in the neutrophil chemotactic protein GCP2 in the IFNAR1 (98+10) and IFNAR1/IKKε (81+11) null compared to the WT (19+1) mice ($p<0.05$). There was no difference in IL-6, IL-1β, IL-1a or IFNb in the IL1Ra/IKKε null or IFNAR1/IKKε null mice compared to the individual knockout controls. Concordant with higher GCP2 expression mice deficient in IFN signaling recruited higher numbers of neutrophils into the peritoneum after thioglycollate challenge: 4.6+1 (WT), 6.1+2 (IKKε), 15.8+4.8 (IFNAR1) and 13.5+2.8 (IFNAR1/IKKε) $\times 10^6$ neutrophils ($p<0.05$). The neutrophils recovered from the IFNAR1/IKKε mice, however, expressed higher mRNA and protein levels of the anti-apoptotic protein Mcl1 than those of the individual knockout controls, suggesting that the deficient neutrophils had defective apoptosis.

Conclusion: IKKε deficiency did not offset increased severity in IL-1Ra deficiency supporting a direct role of IL-1Ra in reducing arthritis. Surprisingly, IKKε deficiency increased disease severity in the IFNAR null mice, most likely due to increased neutrophil recruitment and prolonged survival.

Disclosure: M. Corr, NIAMS-NIH, 2, UCSD, 3; **C. Chung**, None; **S. K. Kim**, None; **D. L. Boyle**, NIH, 2; **G. S. Firestein**, NIH, 2.

2823

FLIP Deficiency In Dendritic Cells Promotes Spontaneous Inflammatory and Erosive Arthritis. Qi Quan Huang[1], Harris R. Perlman[1], Robert Birkett[2], Renee E. Koessler[1], Syamal K. Datta[3] and Richard M. Pope[4]. [1]Northwestern University, Chicago, IL, [2]Northwestern University Medical School, Chicago, IL, [3]Northwestern University FSM, Chicago, IL, [4]Northwestern Univ Med School, Chicago, IL.

Background/Purpose: FLIP is an anti-apoptotic protein induced by chronic inflammation. In this study a mouse line with FLIP deleted in CD11c+ dendritic cells (DCs), that spontaneously develops arthritis, was employed to define the potential role of tolerance induction and adaptive immune.

Methods: Mice with FLIP deficient in DC (*Flip* $^{f/f}$, *CD11c* $^{cre/+}$ or KO) were generated by crossing *Flip* $^{f/f}$ with *CD11c*^{cre} transgenic mice. Immune cells in lymphoid organs were analyzed by Flow-cytometry employing multi-fluorochrome-conjugated antibodies. Arthritis was evaluated by joint swelling and/or deformity. Pathology was analyzed by histologic HE staining. The levels of IgG and cytokines were determined by ELISA and serum rheumatoid factors (RF) by rabbit IgG-ELISA. *In vivo* antigen presentation was determined by T cell proliferation to OVA, monitored by CFSE labeled CD4+ T cells from OTII mice. All data are analyzed comparing with gender matched littermate controls.

Results: The KO mice spontaneously developed progressive, erosive arthritis, starting at 6 weeks of age and reaching ≥ 80% incidence at ≥ 4 months. For mice at ≥ 5 months, histological examination of knees, ankles, and paws demonstrated increased joint inflammation with neutrophils, macrophages and lymphocytes, bone erosion, pannus formation and cartilage destruction ($p < 0.05$-0.001). Further, increased TNFα, IL-1β, IL-6, IL-10, CXCL5, INF-g and RANKL, but reduced OPG, were present in ankle homogenates ($p < 0.001$). Old KO mice expressed increased circulating INF-γ, IgG1 and RF ($p < 0.05$-0.001). All 5 month KO mice developed lymphadenopathy with increased B cells and plasmablasts. Examination of 4 week old (young) KO mice, prior to the onset of arthritis, demonstrated reduction in the size and number of cells in the thymus. The subset of DCs expressing high CD11c and MHCII and were CD8+ were significantly reduced in the thymus, as well as the spleen, and lymph nodes (LN) young mice ($p < 0.05$-0.001). Further, single positive CD4+ or CD8+ T cells, the ratio of CD4:CD8 cells and CD4+/CD25+/Foxp3+ Treg cells were reduced ($p < 0.05$-0.001) in the thymus of young KO mice. CD3+,CD4+ and CD3+,CD8+ cells were reduced and B cells were increased in the LNs of young mice. In the LNs of old KO mice CD11c DC and CD3+,CD8+ cells normalized, while CD3+,CD4+ and B cells were increased. Finally, the young *Flip* $^{f/f}$, *CD11c* $^{cre/+}$ mice demonstrated reduced *in vivo* antigen presentation properties, identified by reduced CD4+ T proliferation in response to OVA.

Conclusion: These observations suggest that reduction of FLIP in DC results in reduced positive and negative selection, reduced Tregs and increased B cells, IFN-g, and autoantibodies. DCs expressing high levels of CD11c and MHCII are necessary for normal tolerance development and restraining the occurrence of inflammatory arthritis.

Disclosure: Q. Q. Huang, None; **H. R. Perlman**, None; **R. Birkett**, None; **R. E. Koessler**, None; **S. K. Datta**, None; **R. M. Pope**, None.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects VI: Cardiovascular Disease in Rheumatoid Arthritis
Wednesday, October 30, 2013, 9:00 AM–10:30 AM

2824

Urinary Microalbumin Is Associated With Arterial Stiffness In Patients With Rheumatoid Arthritis. Karima Becetti[1], Annette Oeser[1], Joseph F. Solus[2], Paolo Raggi[3], C. Michael Stein[2] and Cecilia P. Chung[1]. [1]Vanderbilt University, Nashville, TN, [2]Vanderbilt Medical Center, Nashville, TN, [3]University of Alberta, Edmonton, AB.

Background/Purpose: Rheumatoid arthritis (RA) is associated with an increased risk for cardiovascular disease (CVD). Urinary microalbumin is a risk factor for CVD in the general population, but its association with CVD in RA is less well defined. Thus, we examined the association between urinary microalbumin and CVD, using coronary artery calcium (CAC) and augmentation index (AIX), measures of coronary atherosclerosis and vascular stiffness, respectively.

Methods: In a cross-sectional study, we evaluated 136 patients with RA and 79 controls with no diabetes or clinical history of CVD. MA was defined as urine albumin to creatinine ratio (UACR) > 30mg/g in a spot urine. Traditional CVD risk factors such as age, gender, smoking, family history of CVD, body mass index (BMI), hypertension, and lipids were recorded, and insulin resistance (defined using the homeostasis model assessment), metabolic syndrome and Framingham risk scores were calculated. Disease duration, DAS 28 score and inflammatory markers, including vascular cell adhesion molecule-1 (VCAM-1), interleukin-10 (IL-10), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), tumor necrosis factor-a (TNF-a), and cystatin-C, were measured in RA. Subclinical atherosclerosis was assessed using electron beam computer tomography, and arterial stiffness using AIX. We compared traditional risk factors, UACR and measures of subclinical CVD between RA and controls using Wilcoxon rank sum and Fisher's exact test. The association between MA and CAC and AIX was adjusted for age, sex and race using linear or logistic multivariate analyses as appropriate.

Results: Patients with RA had a higher UACR [median (IQR): 7.6mg/g (4.0–15.5) than controls (5.6 (3.3–9.0), p=0.02). The presence of MA was significantly associated with HTN in RA (p=0.01). No significant association was observed with age, gender, smoking, HOMA-IR, or metabolic syndrome. In RA, but not controls, there was a significant association between AIX and log transformed UACR, β coefficient of 1.9 (95% CI 0.4–3.4), p=0.01. The association remained significant after adjusting for age, sex, and race. CAC was not significantly associated with UACR in RA or controls [Table]. UACR was significantly associated with higher levels of VCAM-1 (ρ=0.2, p=0.01) and lower levels of IL-10 (ρ=−0.2, p=0.02) in RA.

Table. Association between UACR and subclinical CVD in RA and controls:

		UACR			
		Unadjusted		Adjusted for age, sex, and race	
		b coef. (95% CI)	P value	b coef. (95% CI)	P value
AIX	RA	1.9 (0.4–3.4)	0.01	1.5 (0.1–2.8)	0.03
	Controls	−1.3 (−3.6–1.0)	0.26	−0.9 (−2.8–1.0)	0.34
		R (95% CI)	P value	OR (95% CI)	P value
CAC	RA	0.9 (0.7–1.2)	0.64	0.7 (0.5–1.1)	0.13
	Control	0.6 (0.4–1.1)	0.11	0.7 (0.4–1.3)	0.31

Conclusion: Urinary microalbumin is increased in patients with RA compared to controls and is associated with increased arterial stiffness as measured by AIX in RA, independent of other CVD risk factors. MA is not associated with CAC. In RA, urinary microalbumin is associated with higher levels of VCAM-1, which mediates the adhesion of inflammatory cells to vascular endothelium, and with lower levels of IL-10, an anti-inflammatory cytokine.

Disclosure: K. Becetti, None; **A. Oeser**, None; **J. F. Solus**, None; **P. Raggi**, None; **C. M. Stein**, NIH, 2; **C. P. Chung**, Vanderbilt Physician Development Award, 2.

2825

The Influence Of Early Menopause On Cardiovascular Risk In Women With Rheumatoid Arthritis. Emily Pfeifer, Cynthia S. Crowson, Shreyasee Amin, Sherine E. Gabriel and Eric L. Matteson. Mayo Clinic, Rochester, MN.

Background/Purpose: Lifetime exposure to female sex hormones may play a role in the development and severity of rheumatoid arthritis (RA). These same hormones have also been found to play a role in the development of cardiovascular disease (CVD) in women. Since RA is associated with an increased risk of CVD, the purpose of this study was to determine if early menopause, representing a surrogate for lower lifetime exposure to female sex hormones, affects the risk of developing CVD in women with RA.

Methods: A population-based inception cohort of 600 women with RA who first fulfilled 1987 ACR criteria for RA between 1955 and 2007 was assembled and followed until death, migration or 12/31/2008. Age at menarche, gravidity, parity, age at menopause, and duration, if any, of hormone replacement therapy (HRT), along with occurrence of CVD (including coronary artery disease, heart failure, cerebrovascular disease and peripheral vascular disease) was ascertained by review of medical records. Cox proportional hazard models were used to compare women within this cohort who underwent early menopause, defined as natural or artificial menopause at age ≤ 45 years, to those within the cohort who did not undergo early menopause.

Results: This study included 600 women with RA age ≥ 45 years at diagnosis, of whom 199 experienced early menopause (mean age ± SD: 64.3 ± 12.0 years; 67.x % rheumatoid factor (RF) positive) and 401 did not (mean age: 62.8 ± 11.4 years; 64.9% RF positive). The mean age at menopause in those who experienced early menopause was 40.9 ± 5.0 years,

while in those who did not the mean age at menopause was 50.7 ± 2.8 years. Among women without prior CVD, 73 with early menopause and 132 without early menopause developed CVD during a mean follow-up of 11.8 years. Women who underwent early menopause were at significantly higher risk for developing CVD when compared to women who did not experience early menopause (hazard ratio (HR): 1.41; 95% CI: 1.05–1.91, adjusted for age, calendar year of RA diagnosis and cardiovascular risk factors including smoking status, body mass index at RA diagnosis, diabetes mellitus and hypertension). This difference remained significant when age of menopause was defined as the end of HRT for women with artificial menopause who started HRT therapy at the time of artificial menopause (HR: 1.40; 95% CI: 1.03–1.88). CVD risk was increased in women with higher gravidity and parity (HR 1.06 per pregnancy increase; 95% CI 1.004–1.12 and HR 1.07 per 1 birth increase, 95% CI 1.01–1.14 respectively). There was a strong non-linear relationship between gravidity and parity and cardiovascular outcomes, whereby the increase risk of CVD was detected only at very high values (>7) of gravidity and parity. No associations were found between the development of CVD and cause of early menopause (natural vs. artificial), the use of HRT or the length of time on HRT.

Conclusion: The risk of CVD in women with RA was significantly higher in those who experience early menopause, and like other known risk factors should increase clinician concern for development of CVD in these patients. Further investigation is needed to determine the role that female sex hormones play in the development of CVD in women with RA.

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2826

Performance Of Five Current Risk Algorithms In Predicting Cardiovascular Events In Rheumatoid Arthritis Patients. Elke.E.A. Arts[1], Calin Popa[1], Alfons A. den Broeder[2], Anne G. Semb[3], Tracey Toms[4], George Kitas[4], Piet L.C.M. van Riel[1] and Jaap Fransen[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Sint Maartenskliniek, Nijmegen, Netherlands, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]Dudley Group of Hospitals NHS Trust, Russells Hall Hospital, Dudley, United Kingdom.

Background/Purpose: Cardiovascular risk in rheumatoid arthritis (RA) is increased. The cardiovascular (CV) risk algorithms used in the general population may underestimate the risk of cardiovascular disease (CVD) in the RA population[1]. This study was undertaken to assess the predictive ability of 5 established CV risk models for the 10-year risk of fatal and non-fatal CVD in European patients with Rheumatoid Arthritis

Methods: Included were the Framingham risk score (FRS), the Systematic Coronary Risk Evaluation score (SCORE), the modified SCORE according to the EULAR recommendations for CV risk[2] (M-SCORE), the Reynolds risk score (RRS) and the QRisk II risk score. Prospectively collected data from the Nijmegen early RA inception cohort were used. Patients with CVD prior to enrollment were excluded. Discriminatory ability for CV risk prediction was estimated by the area under the receiver operating characteristic (ROC) curve. Calibration was assessed by comparing the observed versus expected number of events using Hosmer-Lemeshov tests and calibration plots. Sensitivity and specificity were calculated for the cut-off values of 10% and 20% predicted risk

Results: In total, n=1050 patients were included. During follow-up, 145 patients developed a CV event. The mean±SD age was 54±13.8 years, 66% were female and 74% were rheumatoid factor positive. Areas under the ROC curve were 0.75 (95% CI; 0.71–0.80), 0.75 (95% CI;0.71–0.80), 0.76 (95% CI; 0.73–0.80), 0.75 (95% CI; 0.71–0.79) and 0.77(95% CI; 0.73–0.80) for the SCORE, M-SCORE, FRS, Reynolds and QRisk II respectively, indicating moderate to good discrimination between patients with and without a CV event. All five models underestimated CV risk at low and middle observed risk levels, and overestimated CV risk at high observed risk levels (Fig. 1). For the 10% and 20% cut-off values used as indicators for CV preventive treatment, sensitivity ranged from 66–87% and 43–67% respectively and specificity ranged from 44–57% and 67–81% respectively. Depending on the model, 13% to 35% of observed CV events occurred in RA patients who were classified as low risk (<10%) for CVD.

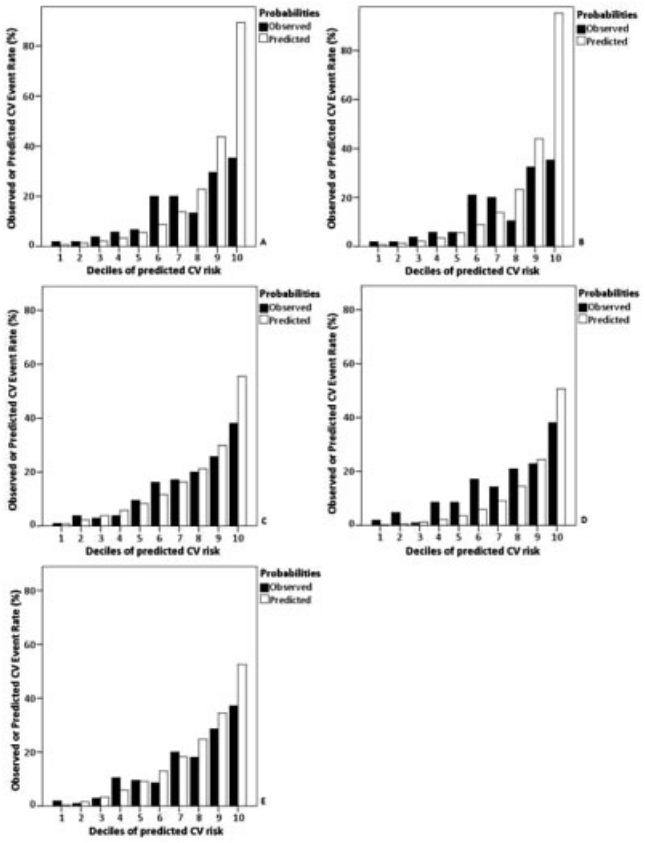

Figure 2. Observed (closed bars) versus predicted (open bars) CV event rate (%) in deciles of predicted risk, for the SCORE (A), M-SCORE (B), FRS (C), Reynolds (D) and QRisk II (E) risk algorithms.

Conclusion: Established risk models generally underestimate CV risk in RA patients. There is an unmet need for development of a RA-specific CV risk model.

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1. Crowson CS, Matteson EL, Roger VL, et al. Usefulness of Risk Scores to Estimate the Risk of Cardiovascular Disease in Patients With Rheumatoid Arthritis. Am J Cardiol. 2012;**10**:420–24.
2. Peters MJ, Symmons DP, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis. 2010;**69**:325–31.

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2827

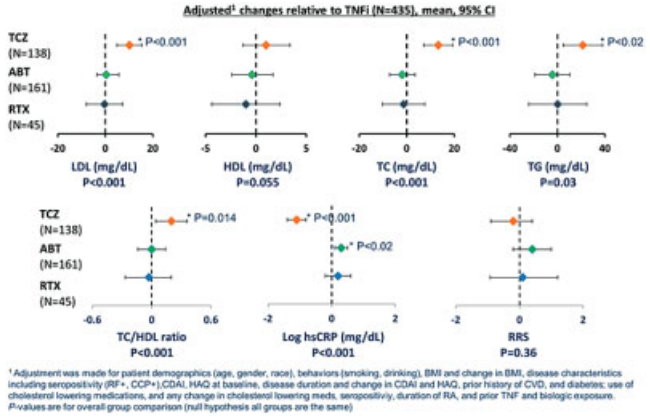
Effect Of Biologic Agents On Lipids and Cardiovascular Risk In Rheumatoid Arthritis Patients. Dimitrios A. Pappas[1], Ani John[2], Jeffrey R. Curtis[3], George W. Reed[4], Jeffrey D. Greenberg[5], Ashwini Shewade[2], Daniel H. Solomon[6], Joel M. Kremer[7] and Tanya Sommers[4]. [1]Columbia University, New York, NY, [2]Genentech Inc., South San Francisco, CA, [3]University of Alabama at Birmingham, Division of Clinical Immunology and Rheumatology, Birmingham, AL, [4]CORRONA, Inc., Southborough, MA, [5]New York Hospital for Joint Diseases, New York, NY, [6]Harvard Medical School, Brigham and Women's Hospital, Division of Rheumatology, Division of Pharmacoepidemiology, Boston, MA, [7]Albany Medical College and The Center for Rheumatology, Albany, NY.

Background/Purpose: The risk for cardiovascular disease (CVD) is increased in patients (pts) with RA. The interplay between traditional CV risk factors and inflammatory burden may be responsible for this increased CVD risk. Therefore, CVD risk scores incorporating measures of inflammation such as the Reynolds risk score (RRS) may be more appropriate than the Framingham risk score or total cholesterol/HDL ratio to predict CVD risk in pts with rheumatoid arthritis (RA), though not yet validated for RA pts

(Ridker, 2007, 2008). This study investigated the effects of biologics on lipids, CRP and CVD risk using RRS.

Methods: Pts with moderate disease activity (CDAI >10) initiating a biologic DMARD participated in a comparative effectiveness prospective study (CERTAIN) nested within CORRONA. Characteristics, including LDL, HDL, total cholesterol (TC) (desirable < 200) and triglycerides (TG), high sensitivity C-reactive protein (hsCRP) and RRS in pts initiating a TNF-α inhibitor (TNFi) or non-TNFi (rituximab [RTX], abatacept [ABT] or tocilizumab [TCZ]), were measured at baseline and at 3 months. Linear, mixed effect regression models were fit to compare the effect of biologics on lipids, CRP and RRS outcomes after 3 months of therapy. In all models adjustment took place for the baseline levels of the outcome, biologically plausible covariates and other characteristics that were imbalanced among the four groups of medications.

Results: 779 initiations of a biologic were analyzed: 435 (55.8%) TNFi, 45 (5.8%) RTX, 161 (20.7%) ABA and 138 (17.7%) TCZ. Overall baseline characteristics: 75.9% women, 86.3% Caucasian, 65.5% seropositive. Mean ± SD age was 55.9 ± 13.3 years, RA disease duration 8.8 ± 9.5 years; CDAI 28.6 ± 12.7. 35.9% of pts were biologic naïve and 24.6% received anti-hyperlipidemic therapy. History of prior CVD was present in 8.0% of pts; 7.8% had diabetes mellitus and 41% were obese (BMI > 30). The adjusted effect of biologic agents on lipid levels, CRP and RRS after 3 months of treatment are summarized in Figure 1. ABT and RTX had a similar effect on lipid levels compared to TNFi after 3 months while TCZ increased TC, LDL and TG levels compared with TNFi after 3 months. Significantly different changes in CRP were observed across different biologics at 3 months. For CVD risk, as measured by RRS, ABT, RTX and TCZ had a similar effect compared with TNFi.



Conclusion: Our study showed that there was a differential effect on lipid levels and CRP when compared amongst biologics with different mechanisms of action. However, these changes did not translate to an increased CVD risk as measured by RRS. In order to better understand CV risk in RA, long term outcome studies are needed to evaluate the interplay among lipids, inflammation and other CVD risk factors.

Ridker P, et al. JAMA 2007;297:611; Ridker P, et al. Circulation 2008;118;22

Disclosure: D. A. Pappas, CORRONA, 3, Novartis, 5; **A. John**, Genentech, 3; **J. R. Curtis**, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **G. W. Reed**, CORRONA, 3; **J. D. Greenberg**, CORRONA, 1, Astra Zeneca, Corrona, Novartis, Pfizer, 5; **A. Shewade**, Genentech, 3; **D. H. Solomon**, Amgen, Lilly, CORRONA, 2, Pfizer, Novartis, Lilly, BMS, 9, UpToDate, 7; **J. M. Kremer**, CORRONA, 1, CORRONA, 3; **T. Sommers**, CORRONA, 3.

2828

The Performance Of The Original and An Updated Cardiovascular Risk Algorithm (SCORE) In Patients With Rheumatoid Arthritis. Elke.E.A. Arts[1], Calin Popa[1], Alfons A. den Broeder[2], Anne Grete Semb[3], Tracey Toms[4], George Kitas[4], Piet L.C.M. van Riel[1] and Jaap Fransen[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Sint Maartenskliniek, Nijmegen, Netherlands, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]Dudley Group of Hospitals NHS Trust, Russells Hall Hospital, Dudley, United Kingdom.

Background/Purpose: Cardiovascular (CV) risk in rheumatoid arthritis (RA) is increased. The CV risk algorithms for the general population may underestimate the risk of cardiovascular disease (CVD) in RA patients[1]. The objective of this study was to test the performance of the original and updated SCORE risk algorithm for the prediction of the 10-year risk of CVD in RA patients.

Methods: Data from the Nijmegen early RA inception cohort (n=1017) were used. The systematic coronary risk evaluation algorithm (SCORE) recalibrated for the Dutch population was used as a basis for the new model. This algorithm was recalibrated in this cohort (SCORE recalibrated) by first adjusting the weights of only the risk factors that were included in the original SCORE (age, gender, smoking, systolic blood pressure and total cholesterol: HDL ratio) and in the following this step the original SCORE was updated (SCORE updated) by including other risk factors as assessed in univariate and multivariate Cox proportional hazard regression analysis (significant at p-value <0.2). Predictive performance was assessed by the area under the receiver operating characteristic (ROC) curve and by comparing the observed versus expected number of CV events using Hosmer-Lemeshov tests and calibration plots.

Results: During follow-up, 144 patients had a CV event. In addition to the risk factors of the original SCORE, the updated model included BMI, diabetes, hypertension and high disease activity (DAS28>5.1) at baseline. Areas under the ROC curve were 0.72 (95% CI; 0.68–0.77, 0.71 (0.67–0.75), 0.75 (0.71–0.79), for the original, the recalibrated and the updated SCORE respectively (figure 1A), indicating moderate to good discrimination. The agreement between the observed and the predicted CV events was poor for the original score which underestimated CV risk at low and middle observed risk levels, which was confirmed in the Hosmer and Lemeshow (H-L) test that indicated poor model fit (p< 0.001). The updated SCORE still showed some underestimation (figure 1B) in the low-middle risk groups (≤ 20% CV risk) and overestimation in the highest risk groups, but overall model fit and predictive accuracy improved (H-L test p=1.0).

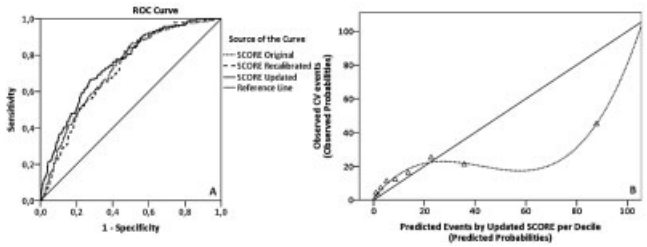


Figure 1. Panel A: ROC-curves for the different SCORE algorithms. Panel B: Calibration plot of the updated SCORE. Depicted are the observed events versus predicted events (observed versus predicted probabilities).

Conclusion: CV risk predictions according to the updated SCORE risk algorithm were more accurate compared to the original SCORE risk algorithm, particularly in the low and intermediate CV risk groups. The next step will be to externally validate these results in a different cohort.

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1. Crowson CS, Matteson EL, Roger VL, Therneau TM, Gabriel SE. Usefulness of Risk Scores to Estimate the Risk of Cardiovascular Disease in Patients With Rheumatoid Arthritis. Am J Cardiol. 2012.3

Disclosure: E. E. A. Arts, None; **C. Popa**, None; **A. A. den Broeder**, None; **A. G. Semb**, Merck/Schering-Plough, Abbott, BMS, Pfizer/Wyeth, Genentech and Roche, 5; **T. Toms**, None; **G. Kitas**, None; **P. L. C. M. van Riel**, None; **J. Fransen**, None.

2829

Statin Adherence and Risk Of Mortality In Patients With Rheumatoid Arthritis: A Population-Based Study. Mary De Vera[1], Michal Abrahamowicz[2] and Diane Lacaille[3]. [1]Arthritis Research Centre of Canada, Richmond, BC, [2]McGill University, Montreal, QC, [3]Arthritis Research Centre of Canada, University of British Columbia, Richmond, BC.

Background/Purpose: Poor adherence with statin therapy is associated with increased mortality in the general population, but no corresponding data are available among patients with rheumatoid arthritis (RA). Since cardiovascular diseases (CVD) are the primary cause of excess mortality in RA, RA-specific data are highly relevant to RA clinical care. We evaluated the impact of statin adherence on risk of mortality in individuals with RA.

Methods: We conducted a cohort study of all incident statin users in a population-based cohort of RA identified from physician billing data, fol-

lowed from May 1996 to March 2010 using administrative health data. Each individual's observational time was divided into 90-day periods from the date of the first statin prescription until date of death or end of follow-up. For each period, we calculated the proportion days covered (PDC) of statin use and created three adherence categories: high adherence (PDC $\geq$ 0.80), poor adherence (0 < PDC < 0.80), and non-use (PDC = 0). Outcomes evaluated include deaths due to all causes and due to any CVD. We used Cox's proportional hazards analyses, modeling risk of death, with statin adherence as a time-dependent variable representing adherence in the current 90 day interval. We considered the following covariates: age, gender, comorbidities (e.g. acute myocardial infarction, cerebrovascular accidents, infections), use of diabetes, hypertension, and congestive heart failure medications, and use of medications known to influence cardiac risk (e.g. hormone replacement therapy), measured at baseline. Markers of RA severity and RA medication use that could influence mortality risk (DMARDs, glucocorticosteroids, methotrexate and rate of RA-related medical visits) were also included as time-dependent covariates. Covariates were included in the final model if they were significant predictors of death or if they had a confounding effect on the association between statin adherence and death.

Results: The cohort of RA patients with incident statin use included 6,525 individuals with 36,097 person-years of follow-up (60% females; mean age 67 years). We documented 1,193 deaths overall with 386 due to CVD. Adjusted HRs for statin adherence status in the current period and mortality risk are summarized (Table).

Statin Adherence Status	CVD Mortality aHR (95% CI)	All Cause Mortality aHR (95% CI)
High adherence (PDC≥0.80) *ref*	1.00	1.00
Poor adherence (0<PDC<0.80)	1.70 (1.27, 2.28)	1.69 (1.42, 1.99)
Non-use (PDC=0)	1.54 (1.21, 1.95)	1.83 (1.60, 2.08)

Conclusion: These population-based data indicate that RA patients who are poorly adherent with statins have a higher risk of death from CVD and from all causes. Findings emphasize the importance of discussing adherence with statin therapy during health care professional encounters with RA patients.

Disclosure: M. De Vera, None; **M. Abrahamowicz**, None; **D. Lacaille**, None.

ACR Concurrent Abstract Session
Systemic Lupus Erythematosus Clinical Aspects: Pregnancy
Wednesday, October 30, 2013, 9:00 AM–10:30 AM

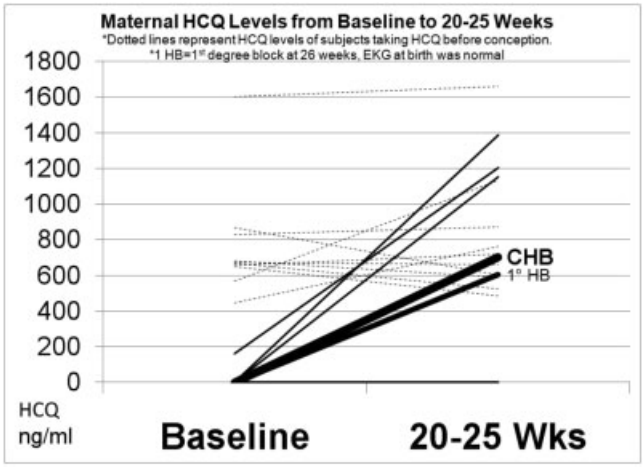
2830

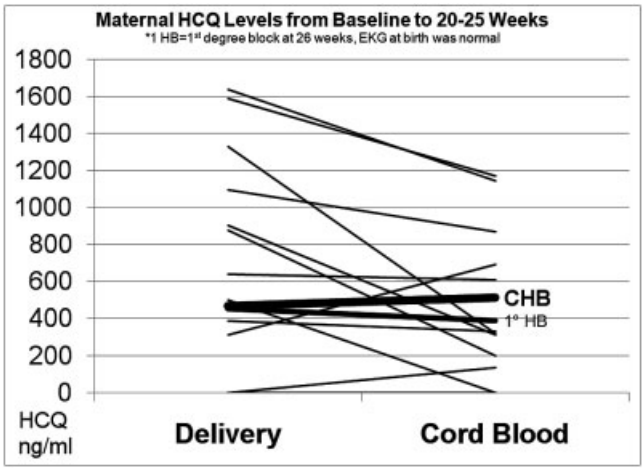
First Stage Of a Simon's Two-Stage Optimal Approach Supports Placental Transfer Of Hydroxychloroquine and a Reduced Recurrence Rate Of The Cardiac Manifestations Of Neonatal Lupus. Peter M. Izmirly[1], Nathalie Costedoat-Chalumeau[2], Amit Saxena[1], Amanda Zink[1], Zoey Smith[1], Deborah Friedman[3] and Jill P. Buyon[1]. [1]New York University School of Medicine, New York, NY, [2]Hopital Cochin, Paris, France, [3]New York Medical College, Valhalla, NY.

Background/Purpose: A previous case control study suggested that hydroxychloroquine (HCQ) might prevent the development of cardiac Neonatal Lupus (cardiac NL) in anti-SSA/Ro antibody (ab) exposed fetuses of SLE mothers. In a subsequent study the use of HCQ reduced the nearly 10 fold increased recurrence rate of cardiac NL in an international cohort of anti-SSA/Ro ab women. Based on these encouraging data, an open label prospective study was initiated to evaluate whether HCQ reduces the recurrence rate of cardiac NL

Methods: A Phase II trial using a Simon's two-stage optimal approach was employed to allow for early stopping due to absence of treatment efficacy. In this first stage of the study, 19 anti-SSA/Ro ab pregnant patients with a previous child with cardiac NL (1st degree block excluded) were enrolled and if 3 or more children with cardiac NL were born, the study would be terminated for inefficacy. The protocol called for initiation of HCQ by 10 weeks gestation. Serial echocardiograms (echos) to evaluate for the development of the primary (2nd or 3rd degree block) and secondary (1st degree block) outcomes were performed. Maternal and cord blood HCQ levels were evaluated to assess treatment adherence, pathobiology and efficacy.

Results: Eighteen pregnancies in 17 women have been completed. Seventeen babies (including a set of twins) had normal serial fetal echos and normal EKGs at birth. One pregnancy resulted in a primary outcome of 3rd degree block. In this pregnancy, the echo at 20 weeks revealed 2nd degree block which progressed 2 days later to 3rd degree. The neonate was not paced until 4.5 months of age. Another pregnancy resulted in a secondary outcome of a prolonged fetal PR interval > 150 msec at 26 weeks for which the mother was treated with 3 days of 4mg dexamethasone. The PR interval normalized and the EKG at birth was normal. In the one ongoing pregnancy, all echos through 37 weeks were normal (notable since the most vulnerable period for complete block is 18–24 weeks). Overall, the rate of recurrence of cardiac NL was 5.3%. Figure 1 reveals that therapeutic HCQ levels can be achieved by the mid second trimester in mothers who were not previously on HCQ prior to conception. Figure 2 substantiates cord blood levels of HCQ.





Conclusion: These prospective data affirm that HCQ may prevent the recurrence of cardiac NL. The feasibility of the strategy using the Simon's two-stage design was substantiated. Moreover, the study unequivocally demonstrates that measurable HCQ levels can be reached prior to the vulnerable period and are present in the cord blood, reflective of placental transfer.

Disclosure: P. M. Izmirly, None; **N. Costedoat-Chalumeau**, None; **A. Saxena**, None; **A. Zink**, None; **Z. Smith**, None; **D. Friedman**, None; **J. P. Buyon**, NIH, 2.

2831

Increased Risk Of Autism Spectrum Disorders In Children Born To Women With SLE: Preliminary Data From The OSLER Cohort. Evelyne Vinet[1], Susan Scott[2], Christian A. Pineau[1], Lawrence Joseph[3], Ann E. Clarke[1], Eric Fombonne[4], Robert W. Platt[3] and Sasha Bernatsky[1]. [1]McGill University Health Center, Montreal, QC, [2]McGill University Health Centre, Montreal, QC, [3]McGill University, Montreal, QC, [4]Oregon Health and Sciences University, Portland, OR.

Background/Purpose: Recent experimental data suggest in utero exposure to maternal antibodies and cytokines as important risk factors for autism spectrum disorders (ASD). Interestingly, women with SLE display autoantibodies (e.g. anti-N-methyl-D-aspartate receptor and antiphospholipid antibodies) and cytokines (e.g. interleukin-6), which, in animal models, alter fetal

brain development and induce behavioural anomalies in offspring. To date, no one has specifically assessed the risk of ASD in children of SLE mothers. Using the "Offspring of Systemic Lupus Erythematosus mothers Registry (OSLER)", we aimed to determine if children born to SLE mothers have an increased risk of ASD compared to children born to mothers without SLE.

Methods: OSLER is a large population-based cohort, which includes all women who had ≥1 hospitalization for delivery after SLE diagnosis, identified through Quebec's universal healthcare databases (1989–2009). OSLER also includes a randomly selected control group of women, matched at least 4:1 for age and year of delivery, who did not have a diagnosis of SLE prior to or at the time of delivery. We identified children born live to SLE mothers and their matched controls, and ascertained ASD based on ≥1 hospitalization or physician visit with a relevant diagnostic code, through to end of database follow-up.

We performed multivariate analyses to adjust for maternal demographics, sex and birth order of child, and obstetrical complications. In a subsample analysis of children with maternal public drug coverage throughout pregnancy, we further assessed relevant in utero medication exposures.

Results: 509 women with SLE had 719 children, while 5824 matched controls had 8493 children. Mean maternal age and follow-up were respectively 30.3 [standard deviation (SD) 5.0] and 9.1 (SD 5.8) years. Children born to women with SLE had more records of ASD diagnoses compared to controls [1.4% (95% CI 0.8, 2.5) vs 0.6% (95%CI 0.5, 0.8)]. Mean age at ASD diagnosis was slightly younger in offspring of SLE mothers (3.8 years, 95%CI 1.8, 5.8) as opposed to controls (5.7 years, 95%CI 4.9, 6.5).

In multivariate analyses (Table 1), children born to women with SLE had substantially increased risk of ASD versus controls (HR 2.31, 95%CI 1.03, 5.16). In the subsample of children with maternal drug coverage (n=1925), in utero medication exposures were rare in the 18 ASD cases: none were exposed to antimalarials, antidepressants, or immunosuppressants, while only one case born to a SLE mother and another born to a control mother were respectively exposed to corticosteroids and anticonvulsants.

Table 1. Multivariate analyses of the risk of autism spectrum disorders (ASD) in SLE mothers versus controls (n=9212)

Covariates	Multivariate HR[a] for ASD (95% CI)
Maternal SLE	
No	Reference
Yes	2.31 (1.03, 5.16)
Education level	
High school or less	Reference
College or more	0.87 (0.51, 1.49)
Race/ethnicity	
Other	Reference
Caucasian	1.22 (0.66, 2.23)
Preterm birth	
No	Reference
Yes	1.44 (0.59, 3.54)
Small for gestational age	
No	Reference
Yes	1.75 (0.82, 3.72)
Gestational diabetes	
No	Reference
Yes	2.38 (0.85, 6.66)

[a] Matching for maternal age, calendar year, and accounting for birth order and sex; hazard ratio (HR); confidence interval (CI); systemic lupus erythematosus (SLE)

Conclusion: Compared to children from the general population, children born to women with SLE have a substantially increased risk of ASD. Our findings are supported by previous experimental data and should prompt further research on the potential role of SLE-related autoantibodies, such as N-methyl-D-aspartate receptor antibodies, in ASD.

Disclosure: E. Vinet, None; **S. Scott**, None; **C. A. Pineau**, None; **L. Joseph**, None; **A. E. Clarke**, None; **E. Fombonne**, None; **R. W. Platt**, None; **S. Bernatsky**, None.

2832

The Effect Of Maternal Antimalarial Intake During Pregnancy On The Risk Of Neonatal Lupus. Julie Barsalou, Edgar Jaeggi and Earl D. Silverman. The Hospital for Sick Children, University of Toronto, Toronto, ON.

Background/Purpose: Neonatal Lupus (NLE) results from passive transfer of anti-Ro and/or anti-La antibodies to the fetus during gestation. It has been suggested that prenatal exposure to hydroxychloroquine (HCQ) reduces the risk of cardiac NLE through disruption of toll-like receptors signalling. The effect of HCQ on the risk of extra-cardiac NLE has not been specifically studied. The aim of this study was to assess if maternal intake of HCQ or chloroquine throughout pregnancy reduces the risk of NLE in the offspring. We hypothesized that these drugs would confer protection against NLE.

Methods: A case-control study was performed on a large single-center cohort of NLE and unaffected children, on whom prospective data has been collected since 1984. Inclusion criteria were: (1) first child born from a mother positive for anti-Ro and/or anti-La antibodies with a diagnosis of either cutaneous lupus, systemic lupus erythematosus, Sjogren's syndrome, dermatomyositis or rheumatoid arthritis and, (2) assessment of the child in the NLE clinic at least once in his first 6 months of life. Descriptive statistics and logistic regressions were performed.

Results: The study population consisted of 220 children, of whom 62 were exposed to HCQ or chloroquine throughout gestation (Table). NLE was diagnosed in 98 patients; 12 had cardiac NLE (11 congenital heart block and 1 cardiomyopathy). Neutropenia (n=41) was the most frequent extra-cardiac NLE feature followed by hepatitis (n=36), skin involvement (n=32), thrombocytopenia (n=4) and extraventricular obstructive hydrocephalus (n=4). One hundred and twelve children did not develop NLE. Ten children were classified as having no cardiac NLE involvement but could not be diagnosed as true unaffected children as one or more blood test components were missing. No statistically significant protective effect of HCQ or chloroquine exposure was found on the risk of NLE (OR 0.79; p=0.45). Similar results were found when extra-cardiac NLE cases were analyzed separately (OR 0.85; p=0.60). Only 1 of 62 children exposed to HCQ or chloroquine developed cardiac-NLE compared to 11 of 158 unexposed children (OR 0.22; p=0.19). On multivariable logistic regression, anti-La titer ≥100 U/mL was the only significant predictor of NLE (OR 2.23; p=0.03). The mother's age, diagnosis, intake of azathioprine, anti-Ro titers ≥50 U/mL and the child's gender did not significantly impact on the risk of NLE.

Table. Characteristics of mothers of NLE cases and unaffected children

	NLE (n=98)	Unaffected children (n=112)	p value
Mothers			
Age at birth of child	31.7 ± 4.8	32.2 ± 4.6	0.44
Diagnosis			0.13
SLE or cutaneous lupus	71 (72)	93 (83)	
Sjogren's syndrome	20 (21)	12 (11)	
Others	7 (7)	7 (6)	
Anti-Ro ≥50 U/mL*	62 (67)	63 (66)	0.96
Anti-La ≥100 U/mL§	26 (28)	14 (14)	0.01
On HCQ or chloroquine	26 (27)	35 (31)	0.45
On azathioprine	5 (5)	13 (12)	0.09
On prednisone	28 (29)	40 (36)	0.32
Older child with CHB	1 (1)	2 (2)	1.00

Mean±SD; n (%)
*n=93 NLE and 95 unaffected children; §n=94 NLE and 103 unaffected children

Conclusion: In the largest single-center case-control study of children born to anti-Ro and/or anti-La antibody positive women diagnosed with a connective tissue disease, HCQ or chloroquine exposure throughout gestation did not result in a significantly lower risk of NLE. High titers of anti-La antibodies in the mother were associated with an increased risk of NLE.

Disclosure: J. Barsalou, GlaxoSmithKline, 9; **E. Jaeggi**, None; **E. D. Silverman**, None.

2833

Increased Cardiac Septal Defects In Children Born To Women With Systemic Lupus Erythematosus: Results From The OSLER Study. Evelyne Vinet[1], Susan Scott[2], Christian A. Pineau[2], Ann E. Clarke[3], Robert W. Platt[3] and Sasha Bernatsky[1]. [1]McGill University Health Center, Montreal, QC, [2]McGill University Health Centre, Montreal, QC, [3]McGill University, Montreal, QC.

Background/Purpose: Cardiac septal defects, which include atrial septal defects (ASD) and ventricular septal defects (VSD), are the most frequent congenital heart anomalies in the general population. Uncontrolled small studies of children born to women with SLE suggest a potentially increased prevalence of structural heart defects, such as ASD and VSD. In a large population-based study, we aimed to determine if offspring born to mothers

with SLE have an increased risk of ASD and VSD compared to offspring born to mothers without SLE.

Methods: The "Offspring of SLE mothers Registry (OSLER)" includes all women who had ≥1 hospitalization for delivery after SLE diagnosis, identified through Quebec's universal healthcare databases (1989–2009). OSLER also includes a randomly selected control group of women, matched at least 4:1 for age and year of delivery, who did not have a diagnosis of SLE prior to or at the time of delivery. We identified children born live to SLE mothers and their matched controls, and ascertained ASD and VSD based on ≥1 hospitalization or physician visit with a relevant diagnostic code, within the first 12 months of life.

We performed multivariate analyses to adjust for maternal demographics, sex and birth order of child, and maternal co-morbidities. In a subsample analysis of children with maternal public drug coverage throughout pregnancy, we further adjusted for relevant maternal medications

Results: 509 women with SLE had 719 children, while 5824 matched controls had 8493 children. Compared to controls, children born to women with SLE experienced more ASD [2.9% (95%CI 1.9, 4.4) vs 0.8% (95%CI 0.6, 1.0) and VSD [1.7% (95%CI 1.0, 2.9) vs 0.7% (95%CI 0.5, 0.9)]. Among children with cardiac septal defects, those born to SLE mothers had more repair procedures compared to controls [9.7% (95%CI 3.4, 24.9) vs 4.4% (95%CI 1.9, 9.9)].

In multivariate analyses (n=9212), children born to women with SLE had a substantially increased risk of both ASD (OR 3.36, 95%CI 1.99, 5.70) and VSD (OR 2.48, 95%CI 1.20, 4.76) compared to controls. In addition, offspring of SLE mothers had a substantially increased risk of having a cardiac septal defect repair compared to controls (OR 4.90, 95%CI 1.11, 21.73).

When accounting for the possibility of detection bias by excluding children with ≥ 1 fetal echocardiography (n=331), adjusted effect estimates were similar to the primary multivariate analysis results for both ASD (OR 2.48, 95%CI 1.26, 4.87) and VSD (OR 2.09, 95%CI 0.96, 4.53). In the subsample analysis further controlling for relevant maternal medications (n=1925), though a trend remained for increased risk of ASD and VSD (combined) for offspring of SLE mothers versus controls, due to reduced sample size the 95% CI was wide and included the null value (both ASD and VSD combined; OR 1.83, 95%CI 0.59, 5.69).

Conclusion: Compared to children from the general population, children born to women with SLE have an increased risk of ASD and VSD, as well as an increased risk of having a cardiac septal defect repair. The effect of SLE on cardiac septal defects does not seem to be explained by detection bias and might be independent of medication exposures.

Disclosure: E. Vinet, None; **S. Scott**, None; **C. A. Pineau**, None; **A. E. Clarke**, None; **R. W. Platt**, None; **S. Bernatsky**, None.

2834

Maternal data Analysis Of The French Registry Of 205 Cases Of Immune Congenital Heart Block (neonatal lupus). Kateri Levesque[1], Nathalie Morel[2], Gaëlle Guettrot-Imbert[3], Mohamed Hamidou[4], Jean Loup Pennaforte[5], Pauline Orquevaux[5], Jean-Charles Piette[6], Christophe Deligny[7], Zahir Amoura[6], Olivier Meyer[8], Olivier Fain[9], Agathe Masseau[4], Holly Bezanahary[10], Pascal Cathebras[11], Elizabeth Diot[12], Yves Dulac[13], Loic Guillevin[14], Eric Hachulla[15], Jean-Louis Pasquali[16], Anne Besancon-Bergelin[17], Bernard Bonnotte[18], Jérome Lebidois[19], Alice Maltret[20], Elisabeth Villain[20] and Nathalie Costedoat-Chalumeau[1]. [1]Hopital Cochin, Paris, France, [2]COCHIN, Paris, France, [3]Centre Hospitalier de Clermont-Ferrand, Clermont-Ferrand, France, [4]Nantes University Hospital, Nantes, France, [5]CHU Reims, Reims, France, [6]CHU Pitié-Salpêtrière, Paris, France, [7]Centre hospitalier Universitaire de Fort de France, Fort de France, Martinique, [8]Bichat University Hospital, Paris, France, [9]Internal Medicine, Jean Verdier Hospital, Bondy, France, [10]University Hospital of Limoges, Limoges, France, [11]University Hospital St Etienne, St Etienne, France, [12]Department of Internal Medicine, Hôpital Bretonneau, Centre Hospitalier Régional Universitaire de Tours, Tours, France, Tours, France, [13]University Hospital Toulouse, Paris, France, [14]Division of Internal Medicine, Hôpital Cochin, University Paris Descartes, Paris, France, [15]University Hospital Lilles, Lille CEDEX, France, [16]Hôpitaux Universitaires de Strasbourg, Hôpital civil, Service de médecine interne et immunologie clinique, Strasbourg, France, [17]Internal Medicine, Le Mans Hospital, Le Mans, France, [18]Centre Hospitalier de Dijon, Dijon, France, [19]Cardiac Institute, Paris, France, [20]Groupe Hospitalier Necker - Enfants Malades, Paris, France.

Background/Purpose: Congenital heart block (CHB) occurs in 1 to 2 % of pregnancies exposed to anti-SSA antibodies. Few data are available regarding the risk of the mothers of fetuses/children with CHB to develop an autoimmune disease.

Methods: The inclusion criteria in the French registry of neonatal lupus are the positivity of anti-SSA and/or anti-SSB antibodies and a manifestation of neonatal lupus. In this retrospective study, we analyzed the data of the mothers who had a foetus/child with CHB.

Results: 184 mothers of 205 fetuses/children with CHB were included: 99.5% (183) had anti-SSA antibodies and 69.6% (128) had anti-SSB antibodies.

At the time of their first diagnosis of CHB, 136 mothers (73.9%) were asymptomatic. The 48 mothers (26.1%) with an auto-immune disease had a systemic lupus erythematosus (SLE, n=20, associated with antiphospholipid syndrome with venous thrombosis in 2 cases), a sjogren syndrome (n=12), an undifferentiated connective tissue disease (UCTD, n=10), a rheumatoid arthritis (n=3), a idiopathic thrombocytopenic purpura (n=1), an auto-immune hepatitis (n=1) and a systemic scleroderma (n=1). Clinical manifestations of SLE mainly included cutaneous and articular manifestations and only 8 mothers had more severe manifestations (renal, neurological, pericarditis, hematological). Only one had received cyclophosphamide.

After a median follow up period of 8.8 years [1 day-36.5 years], 75 mothers (40.8%) remained asymptomatic. The 109 mothers (59.2%) with an autoimmune disease had a Sjogren syndrome (n=42), an SLE (n=37, including 2 associated with an antiphospholipid syndrome), an UCTD (n=20), a rheumatoid arthritis (n=3), an SLE associated with a Sjogren syndrome (n=2), a idiopathic thrombocytopenic purpura (n=2), an auto-immune hepatitis (n=1), a systemic scleroderma (n=1) and a primary obstetrical antiphospholipid syndrome (n=1).

Conclusion: At the time of the CHB diagnosis in their offspring, a third of the mothers had a diagnosis of autoimmune disease. During the follow up period, another third developed an autoimmune disease. The remaining third was still asymptomatic after a median follow up period of 8.8 years [1 day-36.5 years].

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Safety Of Gardasil® Vaccine In Systemic Lupus Erythematosus. J. Patricia Dhar, Lynnette Essenmacher, Renee Dhar, Ardella Magee, Joel Ager, Malini Venkatram, Harpreet Sagar and Robert Sokol. Wayne State University, Detroit, MI.

Background/Purpose: Cervical neoplasia is increased in women with SLE presumably due to cervical infection with oncogenic Human Papillomavirus (HPV) types which persist in an immunosuppressed host. Vaccinating women with SLE against HPV is thus an important part of health prevention in this population. Gardasil® immunizes against the HPV types that cause the majority of cervical cancer (types 16 and 18) and genital warts (types 6 and 11), and has been shown to be protective against these HPV-related diseases.

Methods: For this ongoing trial, twenty women ages 18–50 years with a history of mild to moderate SLE and minimally active or inactive SLE disease received Gardasil® at the standard dosing schedule (0, 2 months, 6 months). This study was approved by the Human Investigation Committee at Wayne State University and the U.S. Food and Drug Administration. Patients were excluded if they had active disease (SELENA-SLEDAI >2), a history of severe disease, deep venous thrombosis, were on >400 mg/day of hydroxychloroquine, were on >15 mg/day of prednisone, or had active infections. To date, 20 patients have completed the second vaccine shot. Patients were monitored for adverse events (AE), SLE flare, and generation of thrombogenic antibodies and thrombosis.

Results: The women in the study were predominantly African-American (75%), mean age 39 years with mean age at diagnosis of SLE at 29.8 years. All patients met American College of Rheumatology (ACR) criteria for SLE; 25% had a history of smoking, 95% had 4 or more sexual partners, 35% had a history of sexually transmitted diseases, and only 21% used condoms on a regular basis. History of abnormal pap smears occurred in 40%, ranging from ASCUS (atypical glandular cells of undetermined significance) to CIN 3 (cervical intraepithelial neoplasia grade 3). Most of our patients had multiple comorbidities in addition to SLE. Vaccine site reactions (VSRs) occurred in 50%, 90% being mild, with the most common reaction being pain. This

compares favorably to data from the current prescribing label showing frequency of VSRs in normal women to be 83.9% for Gardasil® vs. 75.4% for controls. For the non-vaccine site adverse events (nvAE), 90% of our cohort experienced at least one nvAE; there were 105 nvAEs reported from 18 patients and 90% of these nvAEs were mild. There was one serious AE related to underlying osteoarthritis and cervical disc disease. The most common nvAEs reported were musculoskeletal (n=28) followed by cardiopulmonary (n=25), headache (n=21), and dermatologic (n=19). None of the nvAEs were related to vaccine or SLE. There was no flare of SLE, thrombosis, or generation of thrombogenic antibodies in any patient.

Conclusion: Preliminary data from our study shows that Gardasil® vaccine is safe to use in women with SLE. Vaccine site reactions are not increased in SLE patients. Other than vaccine site reactions, there were no related short term adverse events. Gardasil® vaccine administration did not result in any lupus flare or thrombosis. Women with SLE should be immunized with Gardasil® vaccine as part of their health prevention program, particularly since this population is at increased risk for HPV-related cervical dysplasia.

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ACR Concurrent Abstract Session
Spondylarthropathies and Psoriatic Arthritis: Clinical Aspects and Treatment: Clinical and Imaging Aspects of Axial Spondyloarthritis
Wednesday, October 30, 2013, 9:00 AM–10:30 AM

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Development of a Health Index in Patients With Ankylosing Spondylitis (ASAS HI)—Final Result of a Global Initiative Based On the International Classification of Functioning, Disability and Health (ICF) Guided By Assessment of Spondyloarthritis International Society (ASAS). Uta Kiltz[1], Désiréé van der Heijde[2], Annelies Boonen[3], Alarcos Cieza[4], Gerold Stucki[5], Muhammad Asim Khan[6], Walter P. Maksymowych[7], Helena Marzo-Ortega[8], John D. Reveille[9], Simon Stebbings[10], Cristina Bostan[11] and Juergen Braun[1]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Maastricht University Medical Center, Maastricht, Netherlands, [4]University Southampton, Southampton, United Kingdom, [5]University of Lucerne, Lucerne, Switzerland, [6]Case Western Reserve University Hospital, Cleveland, OH, [7]University of Alberta, Edmonton, AB, [8]Leeds Musculoskeletal Biomedical Research Unit and University of Leeds, Leeds, United Kingdom, [9]Univ of Texas Health Science Center at Houston, Houston, TX, [10]University of Otago, Otago, New Zealand, [11]Paraplegic Research Unit, Nottwil, Switzerland.

Background/Purpose: The impact of ankylosing spondylitis (AS) on a patient's life can be considerable. Patients suffer from pain, stiffness and fatigue, are limited in their activities, and restricted in social participation. The International Classification of Functioning, Disability and Health (ICF) is a model to systematically classify and describe functioning, disability, and health in human beings. However no ICF-based patient-reported outcome measure has been developed. the objective is to develop a measure to assess health in patients with AS, the ASAS (Assessments of SpondyloArthritis international Society (ASAS)) Health Index, based on the Comprehensive ICF Core Set for AS.

Methods: Development has been performed in five phases.

Table 1. Phases of development for the ASAS Health Index

	Phase	Objectives	Methods
Ia	Preparatory	Development of a pool of items representing the categories of the Comprehensive ICF Core Set for AS	Linkage of various assessment tools for functioning and health to ICF categories
Ib	Patient meeting	Patient preference and weighting of the items per ICF category	Relative weight to each item, patients distributed 100 points per ICF category.
II	1st postal patient survey	Item reduction (within and across ICF categories)	Factor Analysis, Rasch Analysis, Spearman rank correlation coefficient
III	Expert consultation	Agreement on item reduction	Nominal Consensus Process
IV	2nd postal patient survey	Validation of the draft version and further item reduction	Testing psychometric properties Rasch Analysis
V	Consensus Meeting	Agreement on a final version	Nominal Consensus Process

Results: Phase 1: The item pool contained 251 items in 44 categories. Phase 2 was performed based on data collected along an international cross sectional study among 1915 AS patients (mean age 51.2±3.6, 53% male, BASDAI 5.5±2.4) in 4 continents. For 82 items of the *functioning* part a unidimensional scale, fit to the Rasch model and absence of Differential Item Function (DIF) could be confirmed. Phase 3: An expert committee selected 50 functioning items using predefined selection criteria. Phase 4: An international cross sectional study with 628 AS patients (mean age 48.5±14.2, 51.6% male, BASDAI 5.6±2.3) was conducted in 4 continents. Misfit was identified in 4 items and DIF in 15 items. More than 50% of the items showed a residual correlation between each other above a value of 0.2 in the initial round. Phase 5: Based on results of the analyses in step 4, the consensus members agreed on 17 final items. In the 17 items fit to the model, no residual correlation and absence of constant DIF could be confirmed with a Person-Separation Index of 0.82. The item location has been shown to be 0.00 ± 1.84 with a fit residual of 0.06 ± 1.24 and the person location has been shown to be 0.01 ± 1.80 with a fit residual of −0.30 ± 0.67. The chi-square probability was 0.73.

Conclusion: The ASAS HI measure contains 17 dichotomous items addressing categories of pain, emotional functions, sleep, sexual functions, mobility, self-care, community life and employment. In covering much of the ICF Core Set for AS, these items represent a whole range of abilities of patients with AS. The questionnaire will be translated and further tested for sensitivity to change. ASAS HI can be used in clinical trials and clinical practice as a new composite index that captures relevant information on the health status of the patients.

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2837

Higher Disease Activity Leads To More Damage In The Early Phases Of Ankylosing Spondylitis: 12-Year Data From The OASIS Cohort. Sofia Ramiro[1], A.M. van Tubergen[2], Désirée van der Heijde[3], Carmen Stolwijk[2], Maxime Dougados[4], Filip Van den Bosch[5] and Robert Landewé[6]. [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Maastricht University Medical Center, Maastricht, Netherlands, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France, [5]Gent University Hospital, Gent, Belgium, [6]Academic Medical Center Amsterdam & Atrium Medical Center, Heerlen, Netherlands.

Background/Purpose: For years, it was unclear if inflammation and radiographic progression were related in ankylosing spondylitis (AS), but studies were only of short follow-up and not analysed optimally. We here present a true longitudinal analysis on the long-term relationship between disease activity and radiographic damage.

Methods: Patients from the Outcome in AS International Study (OASIS) were followed-up for 12 years, with biannual clinical and radiographic assessments. Two readers independently scored the x-rays according to the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) and scores were averaged. Disease activity measures include the BASDAI, ASDAS-CRP, CRP, ESR, patient's global assessment and spinal pain. The relationship between disease activity measures and radiographic damage was investigated using generalized estimating equations. Auto-regressive models with 2-year time-lags were used and analyses were adjusted for potential confounders. Different models were constructed: model 1 – with ASDAS as a continuous measure; model 2 – with ASDAS disease activity states; model 3 – with BASDAI continuous and CRP; model 4 – with BASDAI categories and CRP; model 5 – with patient global and CRP; model 6 – with spinal pain and CRP. Models were repeated replacing CRP by ESR. Model fit was compared using the quasi-likelihood information criterion (QIC). Interactions were tested for gender and disease duration.

Results: A total of 185 patients were included (70% males, mean (SD) age: 43(12) years, mean symptom duration: 20(12) years and 83% HLA-B27 positive). All disease activity measures, except ESR, were significantly longitudinally associated with radiographic progression (Table). Neither medication (NSAIDs, NSAID score or biologicals), nor the presence of extra-articular manifestations (uveitis, psoriasis or IBD) were confounding this relationship. The models with ASDAS had the best fit (i.e. lowest QIC): An increase in one ASDAS-unit led to an increase in 0.72 mSASSS-units and a 'very high disease activity state' (i.e. ASDAS>3.5) compared to inactive disease (i.e. ASDAS<1.3) represented an additional progression of 2.31

mSASSS-units per 2 years (Table). Results were consistent across all disease activity measures. The effect of ASDAS on mSASSS was higher in males vs females (β 0.98 vs −0.06) and in patients with shorter vs longer (<18 vs ≥18 years) disease duration (0.84 vs 0.16).

Table. Longitudinal relationship between disease activity measures and radiographic damage*

Variable	Univariable regression β (95% CI) (N = 174 - 185)	Multivariable regression 1 β (95% CI) (N = 183)	Multivariable regression 2 β (95% CI) (N = 183)	Multivariable regression 3 β (95% CI) (N = 184)	Multivariable regression 4 β (95% CI) (N = 184)	Multivariable regression 5 β (95% CI) (N = 184)	Multivariable regression 6 β (95% CI) (N = 184)
Previous mSASSS (0–72)	–	1.03 (1.01; 1.05)	1.03 (1.01; 1.05)	1.03 (1.01; 1.05)	1.03 (1.01; 1.05)	1.03 (1.01; 1.05)	1.03 (1.01; 1.05)
BASDAI (0–10)	0.24 (0.09; 0.40)	§	§	0.21 (0.06; 0.37)	§	§	§
ASDAS	0.72 (0.41; 1.04)	0.72 (0.41; 1.04)	§	§	§	§	§
ASDAS disease activity states							
- Moderate vs inactive (≥1.3 and <2.1 vs <1.3)	0.57 (−0.56; 1.69)	§	0.57 (−0.56; 1.69)	§	§	§	§
- High vs inactive (≥2.1 and <3.5 vs <1.3)	0.91 (−0.17; 1.99)	§	0.91 (−0.17; 1.99)	§	§	§	§
- Very high vs inactive (≥3.5 vs <1.3)	2.31 (1.11; 3.51)	§	2.31 (1.11; 3.51)	§	§	§	§
BASDAI disease activity states							
- Moderate vs inactive (≥2 and <4 vs <2)	−0.19 (−0.98; 0.60)	§	§	§	−0.29 (−1.09; 0.52)	§	§
- High vs inactive (≥4 and <6 vs <2)	1.13 (0.30; 1.97)	§	§	§	1.06 (0.21; 1.90)	§	§
- Very high vs inactive (≥6 vs <2)	1.11 (0.12; 2.11)	§	§	§	0.82 (−0.19; 1.84)	§	§
CRP (mg/l)	0.02 (0.01; 0.04)	§	§	0.02 (0.00; 0.04)	0.02 (0.01; 0.04)	0.02 (0.00; 0.04)	0.02 (0.00; 0.04)
Patient's global assessment (0–10)	0.20 (0.08; 0.32)	§	§	§	§	0.17 (0.05; 0.29)	§
Pain (0–10)	0.25 (0.12; 0.38)	§	§	§	§	§	0.22 (0.00; 0.04)
QIC of the model		5349	5458	5665	5579	5664	5473

*All models are time-lagged (2 years) and auto-regressive
§ Not included in the model

Conclusion: In AS disease activity is unequivocally longitudinally associated with radiographic progression. ASDAS is the best measure to reflect this relationship. The effect of disease activity on radiographic damage is more pronounced in men and in the earlier phases of the disease. These findings may give support to use ASDAS as a treat-to-target.

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Relationship Between Active Inflammatory Lesions In The Spine and Sacroiliac Joints and Development Of Fatty Lesions On Whole-Body MRI In Patients With Early Axial Spondyloarthritis—Long-Term Data Of The Esther Trial. In-Ho Song[1], Kay-Geert A. Hermann[2], Hildrun Haibel[3], Christian Althoff[4], Denis Poddubnyy[3], Joachim Listing[5], Anja Weiss[6], Ekkehard Lange[7], Bruce Freundlich[8], Martin Rudwaleit[9] and Joachim Sieper[10]. [1]Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany, [2]Charité Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany, [3]Charité Universitätsmedizin Berlin, Berlin, Germany, [4]Charite Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany, [5]German Rheumatism Research Center, Berlin, Germany, [6]German Rheumatism Research Centre, Berlin, Germany, [7]Pfizer Pharma AG, Berlin, Germany, [8]University of Pennsylvania, Philadelphia, PA, [9]Endokrinologikum Berlin, Berlin, Germany, [10]Charité Universitätsmedizin Berlin, Campus Benjamin-Franklin, Berlin, Germany.

Background/Purpose: In patients with early axial spondyloarthritis (SpA) with evidence of active inflammation on magnetic resonance imaging (MRI) in the spine and/or sacroiliac (SI-)joints at baseline [1] we previously reported about the relationship between inflammation and the development of fatty lesions in the subchondral bone marrow [2]. We now assessed this relationship in the spine and SI-joints on MRI in these patients with 3 years of continuous treatment with etanercept (ETN).

Methods: Wb-MRIs of those 40 patients who reached the end of year 4 were scored for active inflammation (osteitis) and fatty lesions in the SI-joint quadrants and spine vertebral units (VUs). For this analysis we pooled the data of the patients who were continously treated with ETN for 3 consecutive years. Scoring was performed by two radiologists, blinded for treatment arm and MRI time point. Fatty lesions were scored for absence or presence according to our recently published score [2]. For this analysis, the presence or absence of osteitis and fatty lesions were only counted if both scorers agreed.

Results: New fatty lesions did not develop at all in sites (quadrants or VUs) where there was no osteitis at baseline.

New fatty lesions at year 2 (Y2) or Y3 primarily developed in SI-joint quadrants in which osteitis disappeared between baseline (BL) and Y2, this was the case in 28.6% quadrants (10 out of 35) (see Figure 1, section A2). In the spine only 1 VU developed a new fatty lesion in which osteitis disappeared between BL and Y2/Y3.

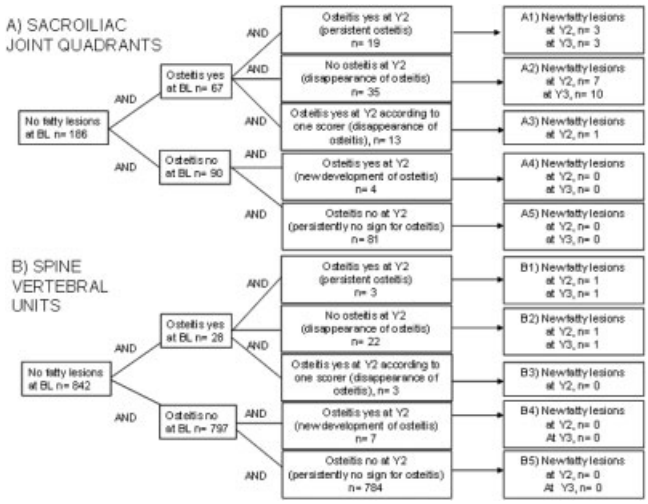

Figure 1. Development of new fatty lesions depending on the presence of inflammation on magnetic resonance imaging related to sacroiliac joint quadrants and spine vertebral units (VUs) with no fatty lesions at baseline (BL). Y= year; n= number of sites (SI-joint quadrants or spine vertebral units)

Persistent osteitis at Y2 or new development of osteitis (occurred rarely) was associated with a low rate of new development of fatty lesions, 16% (3/19) and 33% (1/3) for SI-joint and spine, respectively (A1, B1). New onset of osteitis at Y2 was not associated with new fatty lesions.

At baseline 74 SI-joint quadrants and 26 spine VUs showed fatty lesions. Until Y2 and Y3 only in 3 SI-joint quadrants and 0 VUs fatty lesions disappeared.

The mean spine fatty lesion scores were 1.1 (2.1) at BL, 1.4 (2.5) at Y2 and 1.3 (2.3) at Y3. The mean SI-joint fatty lesion scores were 4.6 (6.3), 5.2 (6.4) and 4.7 (6.3), respectively.

Conclusion: Our data indicate a strong relationship between presence of inflammation and new development of fatty lesions. Furthermore there was no increase of fatty lesions over continous treatment of axial SpA patients with etanercept over 3 years.. Whether this is predictive of stopping radiographic progression needs to be further investigated.

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[1] Song I.-H. et al. Ann Rheum Dis. 2011 Apr;70(4):590–6.
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Effects Of Treatment On Spinal Fat Lesions As Assessed By MRI With The Fat Spondyloarthritis Spine Score. Susanne Juhl Pedersen[1], Zheng Zhao[2], Stephanie Wichuk[3], Robert GW Lambert[3] and Walter P. Maksymowych[3]. [1]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [2]Department of Rheumatology, University of Alberta and PLA General Hospital, Beijing, PR China, Beijing, China, [3]University of Alberta, Edmonton, AB.

Background/Purpose: Fat lesions develop after resolution of inflammation in the spine (1), and have also been shown to predict development of new syndesmophytes (2). Consequently, spinal fat lesions may constitute an

important measure of treatment efficacy and a surrogate for structural damage progression. The aim of this study was to investigate the effects of different treatments on development of fat lesions on spinal MRI.

Methods: A total of 135 patients with axial spondyloarthritis (SpA) had MRIs performed with a mean (SD) follow-up of 1.7 (0.8) years. Patients either received no anti-inflammatory treatment (n=12), or were treated with non-steroid anti-inflammatory drugs (NSAIDs) only (n=55), tumor-necrosis-factor-alpha (TNFα) inhibitor only (n=15) or NSAIDs and TNFα inhibitor in combination (n=53). Spinal fat lesions were assessed by the Fat Spondyloarthritis Spine Score (FASSS), where fat lesions are scored based on anatomical location and recorded dichotomously (present/absent) at each vertebral endplate (3). Scoring range per disco-vertebral unit (DVU) for the cervical spine is 0–8, and for the thoracic and lumbar spine: 0–24, resulting in a total score range of 0–456 for all 23 DVUs. Two rheumatologists evaluated pairs of scans blinded to clinical, biochemical or imaging data. Inter-class correlation coefficients were 0.96 (CI 95% 0.94–0.97) for baseline and 0.86 (0.80–0.90) for change scores.

Results: Patients treated only with NSAIDs had significantly shorter disease duration, lower CRP and structural damage on X-rays as assessed by mSASSS as compared to patients treated with TNFα inhibitor alone or in combination with NSAIDs (results not shown, Mann-Whitney test). Patients treated only with NSAIDs had lower FASSS at baseline (p=0.03) and had less change (p=0.01) as compared to patients treated only with TNFα inhibitors (Table 1). Furthermore, significantly more patients treated only with NSAIDs decreased or had no change in FASSS score during follow-up as compared to patients receiving no anti-inflammatory treatment (p=0.009) or TNFα inhibitor alone (p=0.03) (Table 1) (Chi2 test).

Table 1. FASSS baseline and change scores, and number and frequency of patients with decrease/no change or increase in FASSS scores stratified according to treatment.

	FASSS scores		Change in FASSS score	
Treatment group	**Baseline**	**Change**	**Decreased/ no change**	**Increased**
1: No anti-inflammatory treatment (n=12)	10.3 (0; 187)	2.0 (−1; 9.5)	2 (16.6)	10 (83.3)
2: NSAIDs only (n=55)	11.5 (0; 115)	0 (−9.5; 50)	32 (58.2)	23 (41.8)
3: TNFα inhibitor only (n=15)	18.5 (1; 118)	8.5 (−8; 51)	4 (26.7)	11 (73.3)
4: NSAIDs and TNFα inhibitor (n=53)	10.0 (0; 93)	1.5 (−35.5; 34)	21 (39.6)	32 (60.4)

Results are provided a median (range) or N (%).

Conclusion: Treatment with NSAIDs is associated with a lower propensity to develop fat lesions which could be associated with their effects on new bone formation.

References:

1. Chiowchanwisawakit et al. ARD 2010; 2. Chiowchanwisawakit et al. AR 2011; 3. Østergaard et al. J Rheum 2009

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Predictors Of Spinal Mobility Progression In A Multi-ethnic Cohort Of Patients With Ankylosing Spondylitis. Roozbeh Sharif[1], Trisha M. Parekh[1], Lianne S. Gensler[2], MinJae Lee[3], Mohammad Rahbar[4], Laura A. Diekman[4], Michael H. Weisman[5], Michael M. Ward[6], Shervin Assassi[3] and John D. Reveille[3]. [1]University of Texas Medical Branch, Galveston, TX, [2]University of California, San Francisco, San Francisco, CA, [3]University of Texas Health Science Center at Houston, Houston, TX, [4]The University of Texas Health Science Center at Houston, Houston, TX, [5]Cedars-Sinai Medical Center, Los Angeles, CA, [6]NIAMS/NIH, Bethesda, MD.

Background/Purpose: Clinicians utilize several different clinical measurements (metrology) in patients with Ankylosing Spondylitis (AS) to assess the spinal mobility. We aimed to examine the pattern of change in metrology over time and to evaluate the factors associated with these changes.

Methods: In a prospective study, we included participants from a multi-ethnic, multi-center cohort of AS patients meeting modified New York criteria. The primary outcomes were eight individual clinical measurements, recorded at baseline and follow up visits every 6 months: cervical rotation and flexion, occiput to wall distance, chest expansion, modified Schober, lateral lumbar spinal flexion, and hip internal/external rotation. The independent variables included demographic, health habits, medications, radiologic and the patient-perceived functional limitation index (Bath AS Functional and Disease Activity Indices [BASFI & BASDAI]). Mixed models that accounted for correlation of repeated measures longitudinally as well as interaction with time were conducted to examine whether the spinal mobility pattern is changed by each of independent variables among AS patients.

Results: Overall, 611 patients, including 177 female (29%) and 462 (75.7%) non-Hispanic white were followed up to 4 years. The univariable analyses are shown in table 1. Age, sex, disease duration, smoking habits, radiologic severity and patient perceived functional limitation and disease activity indices at baseline were associated with metrology over time. However, ethnicity and treatment with NSAID and anti-tumor necrosis factor (TNF)-α medications at baseline did not correlate with metrology over time among AS patients. Multivariable analysis indicated that after adjusting for age, sex, employment status, BASFI and BASRI at baseline, age>40 at enrollment associated with worse outcome among all measurements, except hip rotation. Gender, race, and educational status were not associated with the longitudinal changes in metrology. Smoking at baseline visit was associated with greater worsening of lateral flexion and cervical flexion and rotation. Moreover, being employed as well as lower BASDAI, BASFI, and BASRI score at baseline were associated with slower progression over time, across all eight metrology indices.

Table 1. Univariable longitudinal analysis of demographic and clinical factors associated with deterioration of mobility over time among patients with ankylosing spondylitis

Predictor factor	**Cervical flexion**	**Cervical rotation**	**Chest expansion**	**Hip external rotation**	**Hip internal rotation**	**Lateral lumbar spine flexion**	**Occiput to wall**	**Schober test**
Age ≥40 years	**−24.4 (<0.001)***	**−29.6 (<0.001)**	**−1.2 (<0.001)**	**−1.6 (0.003)**	**−2.8 (<0.001)**	**−4.9 (<0.001)**	**−3.7 (<0.001)**	**−0.9 (<0.001)**
Sex, male	**−9.1 (0.001)**	**−7.3 (0.040)**	−0.3 (0.065)	0.6 (0.557)	**−2.8 (<0.001)**	**−1.5 (0.006)**	**3.2 (<0.001)**	**−0.3 (0.026)**
Ethnicity, non-Hispanic white	1.8 (0.761)	−0.3 (0.908)	**0.6 (0.011)**	0.1 (0.319)	−0.3 (0.291)	0.6 (0.604)	−0.1 (0.662)	0.2 (0.393)
Educational level, college degree or above	−1.1 (0.814)	−0.5 (0.530)	0.3 (0.057)	1.3 (0.254)	1.8 (0.104)	0.9 (0.244)	**−2.3 (0.027)**	**0.3 (0.029)**
Employment status, disabled	**−23.2 (<0.001)**	**−33.5 (<0.001)**	**−1.4 (<0.001)**	**−2.6 (0.001)**	**−3.8 (<0.001)**	**−4.9 (<0.001)**	**5.6 (<0.001)**	**−1.3 (<0.001)**
Smoking, current smoker	**−11.2 (<0.001)**	**−13.8 (<0.001)**	**−0.6 (<0.001)**	−0.5 (0.126)	**−1.4 (0.006)**	**−2.3 (<0.001)**	**3.0 (<0.001)**	**−0.4 (<0.001)**
Disease duration, 17 years	**−24.9 (<0.001)**	**−33.4 (<0.001)**	**−1.1 (<0.001)**	−0.2 (0.797)	**−2.2 (0.004)**	**−4.9 (<0.001)**	**4.2 (<0.001)**	**−1.1 (<0.001)**
History of joint surgery	**−20.6 (<0.001)**	**−34.4 (<0.001)**	**−0.8 (<0.001)**	**−5.0 (<0.001)**	**−4.9 (<0.001)**	**−3.8 (<0.001)**	**2.5 (<0.001)**	**−0.8 (<0.001)**
BASFI** ≥26	**−20.1 (<0.001)**	**−27.4 (<0.001)**	**−1.4 (<0.001)**	**−3.3 (<0.001)**	**−4.5 (<0.001)**	**−4.8 (<0.001)**	**3.9 (<0.001)**	**−1.2 (<0.001)**
BASDAI$^{\beta}$ ≥4	**−4.9 (0.034)**	**−9.6 (0.001)**	**−0.5 (0.005)**	**−2.6 (<0.001)**	**−1.7 (0.011)**	**−1.2 (0.018)**	1.4 (0.206)	**−0.4 (0.002)**
BASRI$^{\gamma}$ ≥6	**−35.7 (<0.001)**	**−43.8 (<0.001)**	**−2.0 (<0.001)**	**−1.3 (0.022)**	**−4.4 (<0.001)**	**−7.4 (<0.001)**	**6.5 (<0.001)**	**−1.7 (<0.001)**
mSASSS$^{\alpha}$≥5	**−35.5 (<0.001)**	**−43.7 (<0.001)**	**−1.9 (<0.001)**	**−1.2 (0.078)**	**−3.9 (<0.001)**	**−7.4 (<0.001)**	**6.2 (<0.001)**	**−1.7 (<0.001)**
NSAID$^{¥}$	6.3 (0.786)	6.9 (0.241)	0.1 (0.121)	1.2 (0.344)	−0.2 (0.434)	1.2 (0.972)	−0.6 (0.665)	0.3 (0.343)
Anti TNF-α agent use	−2.6 (0.838)	−4.1 (0.616)	**−0.1 (0.012)**	**−1.4 (0.048)**	−0.5 (0.364)	−0.2 (0.538)	0.2 (0.210)	0.1 (0.161)

* mean difference (p-value) ; **BASFI: Bath AS Functional Index ; $^{\beta}$BASDAI: Bath AS Disease Activity Index $^{\gamma}$BASRI: Bath Ankylosing Spondylitis Radiology Index $^{\alpha}$mSASSS: modified Stoke Ankylosing Spondylitis Spine Score and $^{¥}$NSAID: Nonsteroidal anti-inflammatory drugs

Conclusion: Demographics and disease severity indices at baseline were independent correlates of the worsening of clinical measurements among patients with AS. Further studies are encouraged to identify whether reversing the potentially modifiable factors such as smoking cessation can slow the rate of progression.

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Inflammation and Structural Progression In The Sacroiliac Joints Of Patients With Axial Spa Treated With Adalimumab Or Placebo As Assessed By The Berlin and The Spondyloarthritis Research Consortium Of Canada MRI Methods. Susanne Juhl Pedersen[1], Denis Poddubnyy[2], Inge Juul Sørensen[3], Anne Gitte Loft[4], Jens Skjødt Hindrup[5], Gorm Thamsborg[6], Karsten Asmussen[7], Elka Kluger[8], Jesper Nørregaard[9], Torben Grube Christensen[10], Anne G. Jurik[11], J.M. Møller[12], Thomas Skjødt[13], Dorrit Mikkelsen[14] and Mikkel Østergaard[15]. [1]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [2]Charité Universitätsmedizin Berlin, Berlin, Germany, [3]Hvidovre Hospital, Copenhagen, Denmark, [4]Department of Rheumatology, Sygehus Lillebaelt, Vejle, Denmark, [5]Gentofte Hospital, Copenhagen, Denmark, [6]Glostrup Hospital, Copenhagen, Denmark, [7]Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, [8]King Christian 10th Rheumatism Hospital at Gråsten, Graasten, Denmark, [9]Hørsholm Hospital, Hørsholm, Denmark, [10]MD, Slagelse, Denmark, [11]Aarhus University Hospital, Aarhus, Denmark, [12]Copenhagen University Hospital in Herlev, Copenhagen, Denmark, [13]Vejle Hospital, Vejle, Denmark, [14]Aabenraa Hospital, Aabenraa, Denmark, [15]Copenhagen University Hospital Glostrup, Copenhagen, Denmark.

Background/Purpose: To investigate changes in inflammation and structural progression in the sacroiliac joints (SIJs) in patients with axial spondyloarthritis (SpA) during treatment with adalimumab and placebo in a randomized double-blind placebo-controlled trial, as assessed by two different MRI methods.

Methods: Fifty-one patients with axial SpA were treated with adalimumab 40 mg (n=26) or placebo (n=25) sc. e.o.w. for 12 weeks, followed by an open label extension phase of 36 weeks where all patients received adalimumab. MRIs of the SIJs were performed at weeks 0, 12, 24 and 48. Two rheumatologists evaluated the images in random order, blinded for clinical, biochemical and other imaging data with either the Berlin method (reader DP)(1) or the SPondyloArthritis Research Consortium of Canada (SPARCC) MRI Sacroiliac Joint Inflammation (2) and Structural Score (reader SJP)(2). By the Berlin method scoring ranges are: Inflammation (INF): 0–24, fat (FAT): 0–24, erosions (ER): 0–6, sclerosis (SCL): 0–2, and ankylosis (ANK): 0–2. In the SPARCC method scoring ranges are: inflammation (INF): 0–60, fat (FAT): 0–50, erosions (ER): 0–40, backfill (BF): 0–20, ankylosis (ANK): 0–20. The structural lesions are defined according to standardized and validated definitions (Morpho) (3).

Results: According to the Berlin method, INF decreased significantly in the adalimumab group from week 0 to 12 (Wilcoxon-Pratt; $p=0.01$), while the placebo group decreased from week 0 to 24 ($p<0.01$), i.e when patients had received 12 weeks of open-label adalimumab (Table 1). Berlin scores for FAT, ER, ANK and SCL did not change in any of the groups. According to the SPARCC method, INF decreased significantly in both treatment groups ($p<0.05$) from baseline to all time points. In patients treated with adalimumab, FAT increased from week 0 to 24 and 48 ($p<0.03$) and BF increased from week 0 to 12 ($p<0.02$). ANK increased from week 0 to 48 in both treatment groups ($p<0.03$), and ER decreased from week 0 to 24 and 48 ($p<0.02$) in the placebo group. At baseline, no differences between the treatment groups as assessed by the two scoring methods, besides that SPARCC ANK was higher in patients treated with adalimumab (Mann-Whitney; $p<0.05$) (Table 1). At week 12, INF was significantly lower in the adalimumab group than the placebo group, both by the Berlin ($p<0.003$) and the SPARCC ($p<0.002$) methods, and ER was lower when assessed by the SPARCC method ($p<0.01$).

Table 1. Berlin and SPARCC MRI scores for inflammation and structural lesions in the SIJs

	Berlin					
	Adalimumab			Placebo		
	0	12	24	0	12	24
INF	1 (0–14)	0 (0–6)*	1 (0–6)	2 (0–18)	2 (0–24)	1 (0–10)*
FAT	15 (1–24)	16 (1–24)	15.5 (1–24)	12 (2–24)	13 (2–14)	13 (3–24)
ER	3 (0–6)	3 (0–6)	2 (0–6)	4 (0–6)	4 (0–6)	4 (0–6)
SCL	0 (0–2)	0 (0–2)	0 (0–2)	2 (0–2)	2 (0–2)	2 (0–2)
ANK	0 (0–2)	0 (0–2)	0.5 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)

	SPARCC					
	Adalimumab			Placebo		
	0	12	24	0	12	24
INF	0.5 (0–37)	0 (0–17)*	0 (0–18)*	5 (0–39)	4 (0–40)*	2 (0–26)**
FAT	15 (0–50)	17 (0–50)	17.5 (0–50)	9 (0–41)	9 (0–41)	10 (0–45)
ER	0 (0–8)	0 (0–4)	0 (0–13)	2 (0–20)	2 (0–20)	0 (0–8)**
BF	3.5 (0–20)	4.5 (0–20)*	4.5 (0–20)	4 (0–15)	6 (0–15)	7 (0–17)
ANK	3 (0–20)	3.5 (0–20)	4 (0–20)	0 (0–20)	0 (0–20)	0 (0–20)

Results are median (range). *$p<0.05$; **$p<0.01$; Wilcoxon-Pratt test.

Conclusion: After 12 weeks of therapy, SIJ inflammation was lower in adalimumab than placebo treated patients. The Berlin and SPARCC methods are both sensitive for changes in inflammation, while the SPARCC method may be more sensitive for changes in structural lesions.

References:

1: Song et al. Ann Rheum Dis 2011. 2. Maksymowych et al. Arthritis Rheum. 3: Weber et al. Arthritis Rheum 2010.

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ARHP Concurrent Abstract Session
Education/Community Programs
Wednesday, October 30, 2013, 9:00 AM–10:30 AM

Cochrane Systematic Review Of Self-Management Education Programs For People With Osteoarthritis. Féline P.B. Kroon[1], Lennart R.A. van der Burg[1], Rachelle Buchbinder[2], Richard H. Osborne[3] and Veronica Pitt[4]. [1]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Monash Department of Clinical Epidemiology at Cabrini Hospital, Department of Epidemiology and Preventive Medicine, Monash University, Malvern, Victoria, Australia, [3]Deakin University, Melbourne, Australia, [4]National Trauma Research Institute, The Alfred Hospital, Monash University, Melbourne, Australia.

Background/Purpose: We performed a Cochrane systematic review to determine the effectiveness of self-management education programs (SMPs) for people with osteoarthritis (OA).

Methods: Published randomised controlled trials of SMPs delivered to people with OA were included up to 17 January 2013. We excluded studies of SMPs that did not have a reproducible structured format or that treated participants solely as passive recipients of care. Studies comparing different types of SMPs without a control group were excluded. We extracted data about SMP content using the domains of the Health Education Impact Questionnaire (heiQ) and considered contextual factors and participant characteristics relevant to health equity issues using PROGRESS-Plus and the Health Literacy Questionnaire. Main comparisons were SMPs versus attention control or usual care. Main outcomes were self-management skills, positive and active engagement in life, pain, global OA scores, function, quality of life and withdrawal rates.

Results: Twenty-nine trials (6753 participants) were included: SMP vs attention control (5 trials, N=937), usual care (17 trials, N=3738), information alone (4 trials, N=1251) or another intervention (7 trials, N=919). Most SMPs included elements of skill and technique acquisition (94%), health directed activity (85%) and self-monitoring and insight (79%). Most trials did not provide enough information to assess health equity issues; 8 included mainly Caucasian, educated females and only 4 provided any information on participants' health literacy. All studies were at high risk of performance and detection bias for self-reported outcomes.

Compared with attention control, there was low to moderate quality evidence that SMPs may not result in significant benefits at 12 months. Although there was a small difference in pain favouring SMPs (low quality evidence, 3 trials, N=575): SMD −0.26 (95% CI −0.44 to −0.09), this is unlikely to be of clinical importance, and there were no between-group differences for any of the other measured main outcomes, e.g. self-management skills (low quality evidence, 1 trial, N=344): MD 0.4 points (95% CI −0.39 to 1.19), withdrawal rates (moderate quality evidence, 5 trials, N=937): RR 1.11 (95% CI 0.78 to 1.57).

Compared with usual care, there was moderate quality evidence (11 trials, N=1706), of small but clinically unimportant benefits favouring SMPs up to 21 months. Differences favoured SMPs for self-management skills (absolute improvement 12.8% (2.4% to 23.2%), pain (SMD −0.19 (95% CI −0.28 to −0.1)), function (SMD −0.18 (95% CI −0.27 to −0.09)) and global osteoarthritis symptoms (SMD −0.28 (95% CI −0.39 to −0.17)) but there were no between-group differences in quality of life (SMD 0.02 (95% CI −0.09 to 0.13)) or positive and active engagement in life (SMD 0.01 (95% CI −0.2 to 0.21). There was low quality evidence (16 trials, N=3738) of similar withdrawal rates (RR 0.99 (95% CI 0.74 to 1.33)).

Conclusion: Although we found small statistically significant effects in a few outcomes favouring SMPs over attention control or usual care, these were of doubtful clinical importance. Our results challenge the current endorsement of SMPs in osteoarthritis treatment guidelines.

Disclosure: F. P. B. Kroon, None; **L. R. A. van der Burg**, None; **R. Buchbinder**, None; **R. H. Osborne**, None; **V. Pitt**, None.

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An Education Needs Assessment: Findings From Surveys Of Patients and Caregivers. Elizabeth M. Badley[1], Monique A. Gignac[2], Lynn Moore[3], Christina H. Chan[2], Xingshan Cao[4] and Julie Bowring[2]. [1]University of Toronto, Toronto, ON, [2]Toronto Western Research Institute, University Health Network, Toronto, ON, [3]The Arthritis Society, Toronto, ON, [4]Arthritis Community Research and Evaluation Unit, Toronto Western Research Institute, Toronto, ON.

Background/Purpose: Getting trustworthy information to patients with arthritis is a challenge facing health professionals and organizations concerned with arthritis. This study examined the perceptions of individuals with arthritis and family members of those with arthritis to learn about where they most frequently sought and received information about arthritis and their perceptions of the trustworthiness of arthritis information.

Methods: The Arthritis Society in Canada contracted a survey research organization to conduct parallel national surveys in June 2012 of adults living with arthritis and adults caring for individuals with arthritis. Respondents completed on-line or telephone interviews asking about their (or their relative's) arthritis; where and when they sought information about arthritis; their attitudes toward different sources of information; and any actions taken to manage arthritis.

Results: 1300 patients were surveyed (inflammatory arthritis (IA) = 399; osteoarthritis (OA) = 560, other arthritis = 341). Overall results did not differ by type of arthritis. The mean severity of arthritis (1–10 scale) was 5.4 and the major reported impact was being no longer able to do many of the things they used to enjoy (76%). The majority of participants had been given their arthritis diagnosis by a general practitioner and only a minority by a rheumatologist (17% of those with IA). Information provided at the time of diagnosis concerned mainly medical management: 17% reported getting no arthritis information. The most cited reason for looking for information was wanting to know more to help better manage arthritis symptoms. Topics included managing pain other than with medication (32%), medications for arthritis symptoms (30%), exercising safely (23%), and diet for good health (22%). Top changes made as a result of information were starting to exercise (22%), changes to diet (22%), and adjustments to lifestyle to deal with pain (21%). The two top sources of information were health care professionals and the internet. Only a minority of participants (30%) used The Arthritis Society online or print media. Health care professionals were viewed as a trustworthy source, but not easy to access, with the opposite view about the internet. The Arthritis Society online was viewed as trustworthy, easy to access and as providing current information. Only 13% of patients had attended a self-management or education programs. When asked about reasons for not attending, 30% expressed no interest and 27% did not answer. Overall, the findings from the 319 caregivers surveyed were similar to those of patients.

Conclusion: The findings reveal opportunities for arthritis organizations to help meet arthritis information needs. Major reasons for looking for information were related to how to live better with arthritis and a substantial proportion of individuals reported taking action as a result. Trustworthy information was not found to be easy to access. Providing this online is an opportunity for arthritis organizations. Many people sought advice from health professionals, especially family doctors who would also benefit from information to help patients better manage arthritis in their daily lives.

Disclosure: E. M. Badley, None; **M. A. Gignac**, None; **L. Moore**, None; **C. H. Chan**, None; **X. Cao**, None; **J. Bowring**, None.

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The assessment of education requirements for patients with rheumatoidarthritis, based on the Polish version of the Educational Needs Assessment Tool (Pol-ENAT). Matylda Sierakowska[1], Malgorzata Klepacka[1], Stanislaw Sierakowski[2], Justyna Sierakowska[3], Piotr Leszczynski[4], Maria Majdan[5], Marzena Olesinska[6], Wojciech Romanowski[7], Małgorzata Bykowska-Sochacka[8], Slawomir Jeka[9], Mwidimi Nondosi[10] and Elzbieta Krajewska-Kulak[1]. [1]Medical University of Bialystok, Bialystok, Poland, [2]Medical University in Bialystok, Bialystok, Poland, [3]University of Bialystok, Bialystok, Poland, [4]Medical University in Poznan and J. Strus, Poznan, Poland, [5]Medical University in Lublin, Lublin, Poland, [6]Institute of Rheumatology, Warsaw, Poland, [7]Poznań Centre of Rheumatology in Srem, Srem, Poland, [8]Dr. Jadwiga Titz-Kosko Regional Hospital for Rheumatic Diseases in Sopot, Sopot, Poland, [9]Clinic of Rheumatology and Connective Tissue Diseases University Hospital No 2 in Bydgoszcz Collegium Medicum UMK in Torun, Bydgoszcz, Poland, [10]University of Leeds, Leeds, United Kingdom.

Background/Purpose: Chronic rheumatic diseases lead to large deficits in physical, mental and social functioning. Only an early diagnosis, followed by the implementation of comprehensive and individualized therapeutic approach, enable to avoid the disease's negative consequences. The person with rheumatic disease needs advice and support in order to face the problems of everyday life, as well as suffering associated with the disease. Nurse/educator should attempt to raise the level of resourcefulness and independence of the patient, in order to help him or her in dealing with the consequences of disease.

PURPOSE: -to assess the learning needs of patients with RA.

-to determine the impact of socio-demographic variables on the level of knowledge about the disease.

-to assess the relationship between the deficit of knowledge about RA and the degree of pain, felt fatigue, morning stiffness of joints, the overall assessment of disease activity as well as the functional efficiency.

Methods: The study was conducted in seven rheumatologic centers in Poland, on 277 patients with RA. The inclusion criterion was to consider a classification of RA according to ARA in 1987, and the patient's age ≥ 18 years.

The method applied in the study was a diagnostic survey with a use of the questionnaire for evaluation of educational needs Pol-ENAT (0–4); HAQ disability index (0–3); analog scales (0–100) (overall disease activity of pain, fatigue, morning stiffness).

Results: Most of the respondents were women N = 214 (77%). Mean age was 13.01 ± 53.28 years, and disease duration 10.63 ± 13.71 years. More than one third of respondents had a high school education (38%, N = 105). The average value of the severity of disease activity (0–100 mm) was 54.16 ± 21.33, 54.93 ± 23.17 pain and fatigue, 52.97 ± 21.98. HAQ index - 1.40 ± 0.66, with an upward trend with duration of disease ($p \leq .05$).

The analysis of the questionnaire ENAT (0–4) demonstrated that the study group was in relatively high demand for education about the disease (2.5), self-care (2.4), and methods of coping with pain (2.3). The greatest interest in education was declared by respondents from the youngest group, with disease duration of 10 years ($p \leq .05$).

There was a positive correlation between the demand for knowledge about the movement and felt morning stiffness (Spearman $R=0.204$, $p \leq 0.05$) and disease activity ($R=0.127$, $p \leq 0.05$); self-care and the perceived morning stiffness ($R=0.1823$, $p \leq 0.05$); assistance /support and the perceived morning stiffness ($R=0.1194$, $p \leq .05$).

Conclusion: Respondents, especially from the youngest group and with an early RA, declare lack of knowledge about the disease as well as a desire to improve it.

- Patients want to know more about the disease, particularly on the subject of inflammatory process, methods of self-care and methods of coping with pain.
- The level of functionality is significantly reduced with the duration of disease, while the demand for knowledge about the course of disease and treatment, as well as dealing with pain and emotions decreases.
- The intensity of morning joints stiffness and the increased disease activity is combined with the greater demand for knowledge concerning the physical activity, self-care and the possibilities of help/support.

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"Work It" Recruitment: Lessons Learned From An Arthritis Work Disability Prevention Randomized Trial. Rawan Alheresh[1], Saralynn H. Allaire[2], Michael P. Lavalley[3], Mary Vaughan[1], Rebecca Emmetts[1] and Julie J. Keysor[1]. [1]Boston University Sargent College, Boston, MA, [2]Boston Univ School of Medicine, Boston, MA, [3]Boston University, Boston, MA.

Background/Purpose: Participant recruitment is a critical component of randomized controlled trials, particularly large ones with long term outcomes like work disability. Recruitment needs to be cost-effective; but few guidelines are available to estimate recruitment costs. The objective of this study is to evaluate the recruitment methods to date of the "Work-It Study", a large randomized controlled trial examining the effects of a work barrier problem-solving intervention delivered by physical and occupational therapists on preventing work disability among persons with arthritis or rheumatic conditions.

Methods: Recruitment approaches included: 1) rheumatology and medical registries (displaying brochures in practices, mailing physician letters to patients, and mailing letters to persons in a medical registry), 2) social media (Facebook, LinkedIn, and Patientslikeme) and 3) community advertising (Craigslist, flyers, newspapers, direct marketing, and other (support groups, professional associations, and arthritis foundation events)). Recruitment costs were calculated by summing printing, mailing, and personnel costs. Percentages were calculated for screened eligible, enrolled, and yield (# enrolled/ #participants contacted), as available. Cost per enrolled participant in each recruitment approach was calculated. The different approaches were compared in terms of yield and cost-effectiveness. A 20-month recruitment time period was used for all approaches.

Results: 440 people were screened, with 74% eligible; 190 were enrolled to date (58% of screened eligible; 54% of targeted sample); average cost per subject enrolled was $115 (see Table 1 for details). Letters to patients and community approaches resulted in the highest numbers of enrolled participants. Social media generated zero participants enrolled. Yield for mailings ranged from 1–5%; the medical registry had the highest yield. Costs per-participant enrolled were lowest for medical registry, physician letters, flyers, and 'other' approaches; displaying brochures, newspapers, and direct marketing had the highest cost per-participant enrolled. Though cost-effective, physician letters and patient registries would require large numbers of persons to be contacted to meet the desired sample size of 350 (n=8750 and n=7000 respectively). With the exception of direct marketing, community advertising approaches can generate participants but longer time periods would be needed to recruit (e.g., approximately 4 years would be needed to recruit 350 participants).

Table 1. Yield and cost of rheumatology, medical database registry, and community advertising recruitment methods in the Work-It Study

	Rheumatology offices and medical databases			Community advertising					Total
	Brochure displayed in rheum practices	Letters sent to patients from rheum MDs	Medical registry	News papers	Flyers	Craigslist	Direct Market	Other	
Participants contacted	–	650	108	–	–	–	1975	–	–
Screened (% screened eligible)	20 (60%)	38 (74%)	12 (67%)	128 (70%)	43 (58%)	112 (75%)	41 (78%)	57 (75%)	440 (74%)
Enrolled (% from screened eligible)	9 (75%)	25 (89%)	6 (75%)	50 (56%)	13 (52%)	40 (48%)	20 (63%)	27 (63%)	190 (58%)
Yield	–	4%	5%	–	–	–	1%	–	–
Cost per enrolled	$300[a]	$71[b]	$17c	$185[d]	$91[e]	$53[f]	$177[g]	$28[h]	$115
Total costs	$2696[a]	$1780[b]	$100[c]	$9258[d]	$1181[e]	$2125[f]	$3533[g]	$762[h]	$21,435

[a]Payment to rheumatology practice, printing, brochures
[b]Payment to rheumatologists, printing, brochures, supplies, stamps
[c]Registry fees
[d]Advertising fees
[e]Staff time, printing
[f]Posting fees
[g]Direct marketing fees, printing, supplies, stamps
[h]Printing

Conclusion: Direct mailings to patients from rheumatology practices and medical registries are the most cost-effective approaches but may not be feasible given the low yield. Physician willingness to support these methods is essential. Community advertising is feasible but may take longer time periods if large sample sizes are needed.

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Baseline Work Participation Of a Novel Intervention To Prevent Work Disability Among Persons With Arthritis: The "Work it" Study. Rawan Alheresh[1], Saralynn H. Allaire[2], Michael P. Lavalley[3], Mary Vaughan[1] and Julie J. Keysor[1]. [1]Boston University Sargent College, Boston, MA, [2]Boston Univ School of Medicine, Boston, MA, [3]Boston University, Boston, MA.

Background/Purpose: People with arthritis are at risk of work disability. Job accommodation and educational programs delivered before imminent work loss can minimize work disability, yet are not widely implemented. The Work It Study is a randomized controlled trial testing the efficacy of a work barrier problem solving program delivered by physical and occupational therapists to prevent work loss over a two year period among people with arthritis and rheumatological conditions (i.e. lupus, fibromyalgia and scleroderma) who are concerned about their ability to continue working due to their health. The purpose of this abstract is to describe the baseline work participation status of the subjects.

Methods: Eligibility criteria: age 23–65, self-report of physician diagnosed arthritis or rheumatic condition, report of "any concern about working now or in the near future due to your health", working at least 15 hours a week, plans to continue working, and work or live in Massachusetts. Subjects were recruited through community sources, rheumatology offices, and a medical registry. Work participation was measured at baseline. Self-reported data collected by telephone included i) work status/work hours, ii) number days off from work due to arthritis, iii) Work Limitation Questionnaire (WLQ), iv) WHO Health and Work Performance Questionnaire (HPQ), and v) Work Maintenance Self-Efficacy Questionnaire (WMSEQ). Other baseline data included visual analogue scales of pain, fatigue, stress, and job satisfaction, physical function (Health Assessment Questionnaire) and demographics (e.g., age, gender, ethnicity, education, and marital status), self-report diagnosis of arthritis or rheumatological condition.

Results: 428 people screened to date; 177 completed baseline data collection and were randomized. The mean age of the sample is 50 years old, 65% are white, and the majority are female. All participants were employed at baseline and worked 36.7 hours a week on average and had 3.4 days away from work due to arthritis in the past 3 months. The WLQ- output demand scale score showed respondents were limited on-the-job 48% of time in the past two weeks (SD=27.9; 0 least limited, 100 most limited). The HPQ presenteeism score was 1.04 (SD=0.34; 0.25 least productive, 2.0 most productive). The WMSEQ score was 2.85 (SD=0.70; 0 least confident, 3 most confident). Demographic and clinical variables are listed in Table 1.

Table 1. Descriptive statistics of the Work-It sample (n=177)

Variable	Mean or Percent
Age (in years)	49.9 (SD: 10.9)
Sex	
Female	77.8%
Male	22.2%
Race	
White	65.4%
Black	24.6%
American Indian/ Alaska Native	2.23%
Asian/other pacific Islander	2.79%
Mixed/Other	5.03%
Education	
Some high school	1.7%
High school	11.7%
Some college	25.0%
College	30.0%
Some graduate	5.0%
Graduate	26.7%
Marital Status- Married	35.0%
Self-Reported Arthritis or Rheumatic Condition	
Osteoarthritis	40.4%
Rheumatoid Arthritis	23.6%
Lupus	12.3%
Fibromyalgia	12.3%
Psoriatic Arthritis	3%
Other	8.4%
Pain VAS* (0 the least, 10 the most)	6.2 (SD: 2.16)
Fatigue VAS* (0 the least, 10 the most)	6.8 (SD: 1.98)
Stress VAS* (0 the least, 10 the most)	6.3 (SD: 2.55)
Job Satisfaction* VAS (0 the least, 10 the most)	6.5 (SD: 2.76)
HAQ** Score (0 the least, 3 the most)	0.82 (SD: 0.47)

* Visual Analogue Scale
**HAQ: Health Assessment Questionnaire, the higher score indicates greater disability

Conclusion: To date, the Work It sample seems to have presenteeism work limitations and high pain, fatigue, and stress. Thus, participants seem to be at risk of increasing work disability over the upcoming few years.

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The Employment Experience Of People With Arthritis: Findings From An On-Line Survey. Monique A. Gignac[1], Elizabeth M. Badley[1], Lynn Moore[2], Julie Bowring[1] and Xingshan Cao[3]. [1]Toronto Western Research Institute, University Health Network, Toronto, ON, [2]The Arthritis Society, Toronto, ON, [3]Arthritis Community Research and Evaluation Unit, Toronto Western Research Institute, Toronto, ON.

Background/Purpose: Understanding the employment experience and needs of people with arthritis is growing in importance as baby boomers make up an increasing proportion of the workforce. This study examined the impact of arthritis on employment with an emphasis on 1) at-work productivity and absenteeism and 2) benefits, treatment, workplace practices and policies that might help sustain employment.

Methods: In September 2012 The Arthritis Society, Canada, commissioned a survey research organization with expertise in large panel designs to carry out an online, national survey of adult Canadians with arthritis. Questions asked about demographic factors, arthritis diagnosis, work status, and for those who were working, benefits, workplace policies and accommodations available, disclosure of health to employers, and the perceived impact of arthritis treatment at work.

Results: 1057 individuals were surveyed (mean age 57 years, 69% women, inflammatory arthritis (IA) = 414, osteoarthritis (OA) = 351, other = 292). 10.4% were on disability leave and 41.7% of respondents reported working in the past week (<54 years 62.2%, 55–64 years 38.0%, 65+ 16.4%) of whom 2/3 reported no productivity losses in the past week, and 80% had missed no time from work in the past month. Nevertheless, 66% of participants reported going to work even when they felt unwell because of their arthritis, 41% reported difficulty managing symptoms and their jobs, 41% said arthritis make it difficult to carry out work responsibilities or to travel to and from work (30%). Slightly more people with IA than OA reported difficulties, but there were few age differences. 83% of those currently employed had at least one workplace benefit, including health benefits or insurance (63%), flexible working hours (34%), or ability to work from home (30%). 46% had not told their supervisor about their arthritis—mainly because they felt their symptoms were under control or there was no point because nothing could be done to improve their situation. Among those who had disclosed, only 37% had discussed ways to better manage working with arthritis (17.4% of all workers). Among those employed 57% (more with OA than IA) reported that treatment (including prescription medication) did not have a positive impact on their work life. Overall 37% of respondents reported that challenges in accessing treatment (including physical and occupational therapy or massage therapy) had an impact on work—including having to leave the workforce, reduce work hours, or modify job responsibilities.

Conclusion: Although arthritis often did not affect productivity or work attendance, many experienced some difficulty managing both their arthritis and their jobs. There were few age differences and many similarities between IA and OA. Giving the aging workforce it is positive that older workers were not more likely to miss time from work or be less productive than younger workers, and a significant minority were employed after the age of 65. However the lack of disclosure and discussion of better ways to manage arthritis and work, and challenges in accessing therapy are concerning and point to the need for proactive initiatives to help sustain employment and to work well.

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2848

A Randomised Controlled Trial (RCT) of Telephone Delivered Cognitive Behaviour Therapy (tCBT) and Exercise In The Management Of Chronic Widespread Pain (CWP): Identifying Long-Term Outcome and Who Benefits From Which Treatment. Gary J. Macfarlane[1], Marcus Beasley[1], Philip Keeley[2], Karina Lovell[2], Philip Hannaford[1], Deborah PM Symmons[2], Steve Woby[3], Gordon J. Prescott[1] and The MUSICIAN study team[4]. [1]University of Aberdeen, Aberdeen, United Kingdom, [2]University of Manchester, Manchester, United Kingdom, [3]Pennine Acute Hospital NHS Trust, Manchester, United Kingdom, [4]Universities of Manchester and Aberdeen, Manchester and Aberdeen, United Kingdom.

Background/Purpose: CWP is challenging for rheumatologists to manage and results from long-term epidemiological studies demonstrate that improvement in symptoms is uncommon. Recent reviews have, however, suggested that non-pharmacological therapies such as behaviour therapy and exercise may be effective, at least in the short-term. The aim of the current study is to determine whether tCBT, exercise, or both treatments combined deliver long-term health benefits to patients with CWP in comparison to treatment as usual (TAU) and to characterise patients who benefit from each specific treatment.

Methods: A 2 × 2 factorial RCT. Patients with CWP were identified from a population screening survey of 45, 994 adults in the UK. Eligible individuals met the ACR definition of CWP and reported disability. They had consulted their family physician in the last year with pain, and with no cause identified which required specific treatment. Participants were randomly assigned to a) 8 sessions of tCBT over 6 weeks, and refresher sessions at 3 and 6 months, b) an individually tailored exercise programme with monthly review over 6 months at a local fitness centre c) a combination of these treatments, or d) TAU. Participants were followed up at the end of treatment and 3 and 24 months later. The primary outcome was self reported "change in health since entering the study" and a positive outcome was at least 6 ("I felt much better") on a scale from 0 ("I feel very much worse") to 7 ("I feel very much better"). Analysis was intention-to-treat with longitudinal logistic regression using generalised estimating equations (GEE). Results are presented as Odds ratios (OR) with 95% Confidence Intervals (CI). Additional models were run to assess the effect of baseline characteristics in predicting the response to the specific treatments received.

Results: A total of 442 persons (median age 57 years, 69% female) entered the study and 361 persons (82%) provided information at final follow-up. At 24 months post-treatment, the proportion of patients reporting a positive outcome was: tCBT 35.4%, Exercise 29.4%, combined treatment 31.2%, TAU 12.8%. Response, after adjustment for age, sex, baseline psychological distress, pain intensity and disability was significantly more likely for exercise (OR 2.5, 95% CI (1.2, 5.4), tCBT (3.6; 1.7–7.6) and the combination (2.9; 1.4,6.0) compared to TAU. Baseline characteristics associated with significantly greater response to tCBT (compared to those not receiving tCBT) were: high psychological distress, a passive coping style, high intensity and/or disabling pain and moderate levels of fatigue. Older persons responded significantly better to the exercise intervention, although this was evident at the end of treatment but not subsequently.

Conclusion: A six month programme of exercise or tCBT is associated with long-term improvements in the health of patients with CWP. The size of effect was similar with each treatment, and there was no advantage in subjects receiving both. However we identified specific characteristics associated with response to tCBT which can potentially allow future targeting of therapy.

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2849

Medication Adherence and Healthcare Costs Among Patients With Fibromyalgia: Combination Medication Versus Duloxetine, Pregabalin, and Milnacipran Initiators. Nicole Marlow, Kit Simpson, James Zoller and E. Baron Short. Medical University of South Carolina, Charleston, SC.

Background/Purpose: The combined use of prescription drugs (Rx) with complementary mechanisms of action has been described for treating fibromyalgia (FM). We examined medication adherence and healthcare costs for combination Rx (duloxetine/milnacipran with pregabalin) initiators vs. duloxetine, pregabalin, and milnacipran initiators among privately insured patients with FM.

Methods: Our retrospective cohort study used population-based claims data for the South Carolina Blue Cross Blue Shield State Health Plan (SHP). Patients with FM aged ≥18 years, with Rx initiation during 7/2007 – 6/2010, and SHP enrollment for 12-months pre- and post-index periods were included (combination Rx: N=491, pregabalin: N=1270, duloxetine: N=1460, milnacipran: N=167). Medication initiation was defined as no pill coverage for the Rx in the prior 90 days, and the index-date was defined as the Rx initiation date. Medication adherence measures included high adherence (medication possession ratio ≥80%) and total supply days; healthcare costs comprised direct medical expenditures. Propensity score stratification methods were used to control for selection bias due to differing demographic and clinical characteristics as well as Rx history during the 12-months pre-index. Multivariable regression models that incorporated adjustment for propensity score quintiles were used to compare post-index outcomes, including logistic regression models for high adherence, negative binomial regression models for total supply days, and generalized linear models with a log-link and gamma distributions for expenditures.

Results: Mean age at Rx initiation was 55 years, and 81% were women. Odds ratios for high adherence were significantly increased ($p<0.001$) among the combination Rx cohort vs. the duloxetine (1.89), milnacipran (3.99), and pregabalin (2.01) cohorts. Rate ratios for total supply days were significantly higher ($p<0.0001$) for combination Rx vs. duloxetine (1.14), milnacipran (1.34), and pregabalin (1.31). Expenditures for total healthcare and the initiated Rx were significantly higher ($p<0.05$) for combination Rx vs. duloxetine ($20488 vs. $16202; $2989 vs. $1315; respectively), milnacipran ($21401 vs. $17457; $2877 vs. $717), and pregabalin ($20530 vs. $17516; $2941 vs. $898). However, there were no significant differences observed for direct medical care expenditures (inpatient and/or outpatient services) for combination Rx vs. duloxetine ($11767 vs. $10531, respectively), milnacipran ($11869 vs. $10776), and pregabalin ($11429 vs. $11160), indicating costs neutrality.

Conclusion: Medication adherence was considerably better for combination Rx initiators. Furthermore, expenditure results showed that the use of polypharmacy for combination Rx did not produce a substantial burden to the healthcare system regarding services for direct medical care, indicating that it was safe and well tolerated by patients. Overall, our results suggest important benefits for patients with FM who use combination Rx as part of their multi-modal treatment regimen. Clinical practice guidelines for FM should continue to evolve with the availability of new therapies as well as emerging evidence from population-based naturalistic studies.

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Once Daily Controlled-Release Pregabalin In Fibromyalgia Patients: A Phase 3 Double-Blind, Randomized Withdrawal, Placebo-Controlled Study. Lesley M. Arnold[1], Pierre Arsenault[2], Cynthia Huffman[3], Jeffrey L. Patrick[4], Michael Messig[4], Marci L. Chew[4], Luis Sanin[4], Lynne Pauer[4] and Andrew Clair[4]. [1]University of Cincinnati College of Medicine, Cincinnati, OH, [2]Université de Sherbrooke, Sherbrooke, QC, [3]Meridien Research, Tampa, FL, [4]Pfizer Inc, New York, NY.

Background/Purpose: Pregabalin (PGB) is currently approved for the treatment of fibromyalgia (FM) for twice daily dosing over a range of 300–450 mg/day. A pregabalin controlled-release (PGB CR) formulation was developed to enable once daily (QD) dosing.

Methods: The study involved 4 phases: baseline (BL; 1 week), single blind (SB; 6 weeks), double blind treatment (DB; 13 weeks), and a 1-week double blind taper. The SB starting dose was 165 mg/day and was escalated during the first 3 weeks, up to 495 mg/day based on efficacy and tolerability. Dosing was QD following an evening meal. Patients with ≥50% reduction in average daily pain score at the end of SB compared to BL were randomized (1:1) in the DB phase to continue PGB CR treatment at the optimized dose (330 to 495 mg/day) or to matching placebo (PBO). The primary endpoint (EP) of time to Loss of Therapeutic Response (LTR) was assessed during DB and defined as < 30% pain response relative to BL (SB) or discontinuation due to lack of efficacy or an adverse event (AE). Secondary endpoints included measures of pain relief, global assessment, functional status, tiredness, and sleep. A total of 290 SB patients were planned to provide the 74 LTR events needed to achieve 90% power to detect a difference in the primary EP. However, there was insufficient power, a priori, to detect differences in the secondary endpoints of this study.

Results: 441 patients, ≥18 years of age, meeting the American College of Rheumatology 1990 criteria for FM (Wolfe F, et al. *Arthritis Rheum*. 1990; 33(2):160–172) were enrolled. The majority were white (80%), female (89%) and an average age of 48 years. Of the 441 patients, 121 (27%) completed SB, had ≥50% pain response and were treated in DB. Seventy-five LTR events occurred. The median time from randomization to LTR (Kaplan-Meier analysis) was 58 days in the PGB CR group and 22 days in the PBO group ($p=0.021$). During the DB phase 34/63 (54.0%) PGB CR and 41/58 (70.7%) of PBO patients met LTR criteria. There was no statistically significant difference between DB treatments for the secondary endpoints with the exception of benefit from treatment; a domain of the Benefit, Satisfaction and Willingness to Continue scale: more patients reported "much benefit" in the PGB CR group ($p=0.0296$). While not significant, trends favoring PGB CR treatment were seen in the Fibromyalgia Impact Questionnaire Total Score, Patient Global Impression of Change, and the Sleep Quality domain of the Subjective Sleep Questionnaire. In PGB CR patients the most common AEs during SB were dizziness, somnolence, and headache; and during DB were dizziness, peripheral edema, and insomnia. The most common AEs in PBO patients were dizziness, somnolence, dry mouth, and peripheral edema. The majority of AEs were mild to moderate in severity. Five patients experienced serious adverse events (SAE) during SB and 1 event (glossitis) was considered related to PGB CR; 2 PGB CR patients experienced an SAE during DB. No deaths occurred.

Conclusion: PGB CR was effective in improving the time to and the number of LTR events in FM patients. PGB CR was well-tolerated in most patients and results were consistent with the known safety profile of PGB.

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The Polysymptomatic Distress Scale As a Measure Of Disease and Practice Severity In Fibromyalgia. Frederick Wolfe[1], Don L. Goldenberg[2], Brian T. Walitt[3] and Winfried Häuser[4]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]Newton-Wellesley Hosp, Newton, MA, [3]Washington Hospital Center, Washington, DC, [4]Klinikum Saarbrücken, Saarbrücken, Germany.

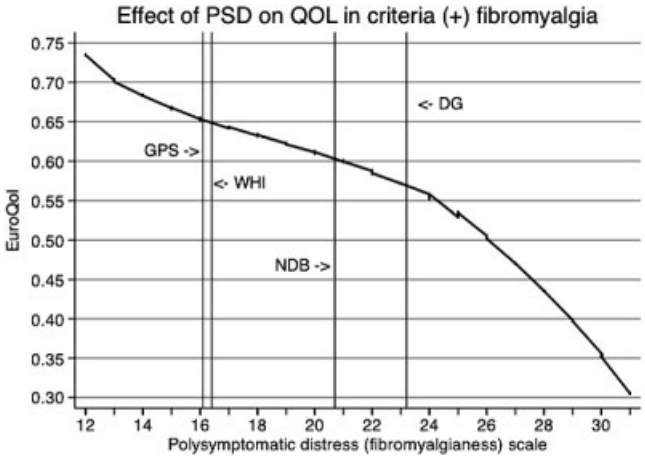
Background/Purpose: The 2010 American College of Rheumatology (ACR) fibromyalgia (FM) criteria created a scale for the measurement of severity of pain extent—the 0–19 Widespread Pain Index (WPI), and a symptom scale—the 0–12 Symptom Severity scale (SS). Subsequent research and clinic usage combined the scales by summing them into the polysymptomatic distress (PSD) or fibromyalgianess scale, a 0–31 overall measure of pain extent and symptom distress. We investigated the value of the PSD scale in capturing severity of illness, and also applied the PSD scale to determine relative severity of subjects with criteria (+) FM in different settings: epidemiological studies—844 persons in the Women's Health Initiative (WHI) and 52 in the German general population (GPS), and in clinical studies —1036 patients from the National Data Bank for Rheumatic Diseases (NDB) study of FM, and 64 from the tertiary referral practice of Dr. Don Goldenberg (DG). We hypothesized that DG's patients would have the most severe FM and persons in the GPS epidemiological study the least severe FM. We also investigated whether values of the PSD would have clinical relevance as measures of severity.

Methods: We measured the mean scores of PSD in ACR 2010 (survey) criteria (+) FM subjects. We calculated the SF-36 Physical and Mental Component Summary scores (PCS/MCS), the EuroQol quality of life score, the Health Assessment Questionnaire (HAQ) functional disability score, the

VAS pain scale, and the percentage of disabled patients, using data from the NDB at the 4 quartiles of the PSD.

Results: Severity of illness was related to PSD scores (Table 1) and Figure 1, and patients with higher mean PSD scores and in higher PSD quartiles demonstrated more severe illness. The quartile differences were large and clinically significant, and can also be seen clearly in the figure. By PSD, persons in the community (GPS and WPI) had the least severe illness, while illness was most severe in the tertiary referral practice (DG). From left to right, vertical lines in the figure represent PDS means for GPS, WHI, NDB and DG.

Quartile (Range)	PSD	SF-36 PCS	SF-36 MCS	EuroQol	HAQ	VAS Pain	Disabled (%)
Q1 (12–16)	14.5	32.5	41.5	0.66	1.05	5.5	25
Q2 (17–20)	18.4	31.2	39.8	0.61	1.18	5.9	30
Q3 (21–25)	23.2	29.3	40.0	0.59	1.29	6.5	36
Q4 (26–31)	28.0	27.5	34.5	0.43	1.59	7.4	43



Conclusion: There is a considerable range of severity that can be observed among FM patients, and the PSD appears to be an easy-to-use assessment tool. Thus, much of the difference between patients is hidden when we simply diagnose FM. Patients in clinical practice have greater severity of illness compared with community subjects. This information regarding differential severity in the community compared with practice, sheds light on the role of self-selection and self-referral, and allows placing clinical and epidemiological data into perspective.

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Real-Life Assessment Of The Validity Of Patient Global Impression Of Change In Fibromyalgia. John S. Sampalis[1], Mary-Ann Fitzcharles[2], Peter A. Ste-Marie[2], Emmanouil Rampakakis[1] and Yoram Shir[2]. [1]McGill University, Montreal, QC, [2]McGill University Health Centre, Montreal, QC.

Background/Purpose: Assessing fibromyalgia (FM) is challenging due to the lack of hard outcomes and the need to rely on patient-reported symptoms. Completion of questionnaires by patients may be fraught with inaccuracy, and meaningful interpretation of results can only be performed with due consideration of the clinimetric properties and weaknesses of instruments. Global rating of change scales represent a practical method of measuring disease severity and treatment outcomes, and may be particularly useful in routine clinical practice. This analysis assessed the validity of Patient Global Impression of Change (PGIC) in patients treated in routine clinical care.

Methods: FM patients from a prospective cohort at a tertiary care multidisciplinary clinic with at least one follow-up (FUP) assessment were included. Disease severity at treatment initiation and FUP was measured with pain visual analog scale, patient global assessment (PGA), Fibromyalgia Impact Questionnaire (FIQ), Health Assessment Questionnaire (HAQ), McGill Pain Questionnaire (MPQ), and body map. PGIC was assessed at FUP. Between-group differences in disease severity improvement were assessed for statistical significance with one-way analysis of variance. Linear regression was used to assess the association between different measures. Parameter correlation was assessed with the Spearman's rank coefficient (rho).

Results: 167 patients (91% female) were included with a mean (SD) age of 48.8 (9.8) years, disease duration of 10.8 (10.2) years, and FUP duration of 30.0 (15.3) months. Patients rating their condition as much/moderately/little worse vs. same vs. little/moderately/much better since treatment began experienced significant ($P \leq 0.001$) differences in change in pain (1.03 vs. 0.31 vs. −1.31), PGA (0.67 vs. 0.90 vs. −1.18), body map (2.62 vs. 1.29 vs. −3.82), FIQ (6.52 vs. −0.32 vs. −10.73), and HAQ (0.20 vs. 0.06 vs. −0.19). However, no significant differences were observed between-groups in MPQ (−0.66 vs. −1.88 vs. −6.58; $P=0.086$). In correlation analysis, PGIC showed a statistically significant ($P<0.001$) weak positive correlation with improvement in MPQ (rho=0.250), pain (rho=0.387), PGA (rho=0.327), body map score (rho=0.287), and HAQ (rho=0.343) and moderate positive correlation with FIQ improvement (rho=0.423). Regression analysis showed that a significant ($P<0.01$) positive association exists between improvement in all disease severity measures and PGIC. Interestingly, upon adjusting for improvement in disease activity measures, FUP duration had a significant ($P<0.05$) impact on PGIC with patients followed for a longer period reporting a greater improvement in their condition compared to patients followed for shorter periods.

Conclusion: The results of this analysis suggest that, overall, a weak correlation exists between PGIC and improvement in standard FM outcome measures. Furthermore, FUP duration was identified as a significant confounder of patient perception of disease improvement which could be due to recall bias or survival bias. Altogether, these results have important implications for FM management and designing new instruments assessing outcomes in FM.

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ACR Concurrent Abstract Session
Orthopedics, Low Back Pain, Rehabilitation and Mechanisms of Pain in Arthritis
Wednesday, October 30, 2013, 11:00 AM–12:30 PM

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Restricting Back Pain and Subsequent Mobility Disability In Community-Living Older Persons. Una E. Makris[1], Liana Fraenkel[2], Ling Han[3], Linda Leo-Summers[3] and Thomas M. Gill[4]. [1]UT Southwestern Medical Center, VA Medical Center, Dallas, TX, [2]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare System, New Haven, CT, [3]Department of Medicine, New Haven, CT, [4]Yale University, New Haven, CT.

Background/Purpose: Although back pain is common and costly, few longitudinal studies have evaluated the association between back pain, severe enough to restrict activity (hereafter referred to as restricting back pain), and the development of disability in mobility. Older persons who lose independent mobility have higher rates of morbidity and mortality, and experience a poorer quality of life. The objective of this study is to evaluate restricting back pain and subsequent mobility disability, both dynamic conditions that recur in older persons.

Methods: We evaluated the 709 participants (mean age 77.3 years, range 70–96, 63% women) of the Precipitating Events Project, a prospective study of community-living persons, aged 70+ years, all non-disabled at baseline, who completed monthly telephone assessments of restricting back pain and who were at risk for developing mobility disability for up to 159 months. Restricting back pain was defined as staying in bed for at least half a day and/or cutting down on one's usual activities due to back pain. Mobility disability was defined as needing help with or inability to complete any of the following three tasks in any given month: walking a 1/4 mile, climbing a flight of stairs, lifting or carrying 10 pounds. The event rate for mobility disability was estimated using a GEE Poisson model. A recurrent events Cox model was used to evaluate the associations between the occurrence of restricting back pain (yes/no) and subsequent (within one month) mobility disability. The model was adjusted for fixed-in-time (sex, education, ethnicity) and time-varying covariates (age, chronic conditions, BMI, depressive symptoms, cognitive impairment, hip weakness, and physical frailty defined by slow gait speed) that were updated every 18 months. In a secondary analysis, these models were re-run after excluding participants who had mobility disability at baseline. We ran a final set of analyses, focusing on the

relationship between restricting back pain and mobility disability that persisted for at least two months.

Results: The event rate for mobility disability was 7.26 per 100-person months (95% CI 6.89,7.64) with a median duration of 2 (interquartile range: 1–4) months. Overall, 213 (30%) of the 709 eligible participants reported one or more of the three disabilities at baseline and recovered at some point during the follow-up. The frequency of each of the three mobility disability items at baseline was 20.2% for walking a 1/4 mile, 6.6% for climbing stairs, and 19% for lifting/carrying 10 pounds. After adjusting for covariates, restricting back pain was strongly associated with subsequent mobility disability, with a hazard ratio (HR) (95% CI) of 3.23 (2.87,3.64) in the primary analytic sample, HR 3.71 (3.22,4.27) after omitting subjects with baseline mobility disability, and HR 3.64 (3.15,4.20) in the analyses evaluating longer duration of mobility disability.

Conclusion: In this longitudinal study, restricting back pain was independently associated with subsequent mobility disability among older persons. Interventions implemented to decrease or prevent restricting back pain may reduce the likelihood of mobility disability.

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2855

Association Of Back Pain With Functional Limitations In Patients With Knee and Hip Osteoarthritis. Adam P. Goode[1], Hayden B. Bosworth[2], Cynthia Coffman[2], Amy Jeffreys[2], Eugene Z. Oddone[2], William S. Yancy Jr.[2] and Kelli D. Allen[2]. [1]Duke University, Durham, NC, [2]Duke and Durham VA Medical Center, Durham, NC.

Background/Purpose: Back pain, most commonly occurring in the lower back, is a prevalent condition and common reason for both decreased function and quality of life. The influence of back pain on physical function among patients with osteoarthritis (OA) has received little attention. This study examined association of back pain with functional outcomes in patients with hip and / or knee OA.

Methods: Participants (n=300) were patients enrolled in a clinical trial of a combined patient and provider intervention for managing OA at the Durham Veterans Affairs Medical Center (mean age = 61.1 (SD 9.2), 90.7% male, 50.0% non-white – primarily African American). All measures were taken from baseline surveys and tests. Self-reported presence of back pain was measured with a single item from the Self-Administered Comorbidity Questionnaire. Functional outcomes included the Satisfaction with Physical Function Questionnaire (scores range −3 to +3, with higher scores indicating greater satisfaction), disease specific knee and/or hip function (Western Ontario and McMasters University Osteoarthritis Index physical function subscale; range 0–68), and the Short Physical Performance Battery (SPPB) consisting of walking, balance and chair stands tests, with scores ranging from 0 (worst performance) to 12 (best performance). Simple linear regression models examined the association of back pain with each functional measure (separately), and then multivariable models were fit, including all covariates. Covariates included participant age, race (white vs. non-white), gender, self-rated health (excellent, very good, or good vs. fair or poor) and number of joints with knee and/or hip OA (1–4).

Results: Back pain was present in 75.3% of patients. In bivariate analyses, back pain was associated with less Satisfaction with Physical Function (b= −0.64; 95% CI −1.06, −0.22; p<0.01), worse WOMAC function scores (b= 5.10; 95% CI = 1.70, 8.50; p=0.003), and worse SPPB scores (b= −0.73; 95% CI −1.31, −0.15; p=0.01). In the multivariable models, back pain remained significantly associated with Satisfaction with Physical Function scores (b= −0.49; 95% CI −0.89, −0.10; p=0.02) and WOMAC physical function scores (b= 4.1; 95% CI 0.90, 7.30; p=0.01), but not SPPB scores (b= −0.51; 95% CI −1.1, 0.04; p=0.07).

Conclusion: Among patients with hip and knee OA, back pain was highly prevalent. Back pain was associated with worse functional outcomes, specifically Satisfaction with Physical Function and WOMAC function scores. These results highlight that back pain is associated with lower extremity functional limitations above and beyond decreased function related to knee and/or hip OA. Because of its high prevalence and added impact on physical function, back pain is an important issue to identify and address among patients with OA.

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Influence Of Mechanical Symptoms On Treatment Outcomes For Meniscal Tear In The Setting Of Osteoarthritis. Jeffrey N. Katz[1], John Wright[1], Lisa A. Mandl[2], Brian Cole[3], Laurel Donnell-Fink[1], Ali Guermazi[4], Morgan Jones[5], Bruce Levy[6], Scott Martin[1], Robert Marx[2], Anthony Miniaci[5], Kurt P. Spindler[7], Rick Wright[8] and Elena Losina[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Hospital for Special Surgery, New York, NY, [3]Rush University, Chicago, IL, [4]Boston University, Boston, MA, [5]Cleveland Clinic, Cleveland, OH, [6]Mayo Clinic, Rochester, MN, [7]Vanderbilt University, Nashville, TN, [8]Washington University, Saint Louis, MO.

Background/Purpose: Clinicians are challenged to identify those patients with knee pain, osteoarthritis (OA) and imaging evidence of a meniscal tear (MT) who are likely to benefit from arthroscopic partial meniscectomy (APM). Traditionally, clinicians have recommended that patients with "mechanical symptoms" (e.g. locking, clicking, catching) consider APM. The MeTeOR (MT in OA Research) Trial demonstrated similar symptomatic relief in persons treated with APM and those treated initially with physical therapy (PT), with referral for APM if PT did not relieve pain. We analyzed MeTeOR data to compare improvement in mechanical symptoms between subjects that received APM and those that received PT; and to examine whether frequency of baseline mechanical symptoms influenced pain relief at 6 month follow-up.

Methods: MeTeOR is a seven-center RCT of APM vs. standardized PT in subjects age 45+ with symptomatic MT and OA. The baseline survey asked about 5 mechanical symptoms (clicking, catching, popping, locking, giving way), each with 5 responses ("never" to "several times a day"). We summed these 5 items to create a mechanical symptom score. We used t-tests to compare patients who had surgery (at the outset or after crossing over) vs. those treated with PT with respect to changes in mechanical symptom score from baseline to 6 months. We compared baseline mechanical symptom scores with changes over 6 months in WOMAC Pain using correlations (presented as crude r-squared). We used multivariable linear regression with an interaction to assess whether the association between baseline mechanical symptom score and improvement in WOMAC Pain over 6 months differed between subjects treated with APM vs. those treated with PT.

Results: 351 subjects participated, 57% female, mean age 58.The baseline mean mechanical symptom score was 10.4 (SD 4.9) and mean WOMAC Pain 41.0 (SD 17.8, possible range 0–100 with 0=best). Subjects improved in WOMAC Pain over 6 months by a mean of 21.4 points (SD 18.7). Improvement over 6 months in mechanical symptom score was greater among subjects treated with APM (0.82 SD's) than among those treated with PT (0.42 SD's; p=0.01). However, improvement in mechanical symptom score explained just 8% of variability in improvement in WOMAC Pain. We did not find an association between baseline mechanical symptom score and improvement in WOMAC Pain (r-squared <0.02 for both APM- and PT-treated subjects.) Associations between individual symptom frequencies (e.g. locking, catching) and change in WOMAC pain and function scores were also negligible. The association of baseline mechanical symptom score and change in pain score did not differ between subjects receiving APM and those receiving PT (p for interaction=0.44).

Conclusion: While mechanical symptom scores improved more following APM than following PT, MeTeOR data did not support the clinical teaching that frequent mechanical symptoms at baseline predict greater pain relief following APM than following PT. Thus, clinicians should not rely upon the frequency of mechanical symptoms to predict pain relief following APM but can advise their patients that mechanical symptoms are more likely to resolve with surgery than without.

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The Role Of FAM173b As a Newly Identified Regulator Of Chronic Pain. Hanneke Willemen[1], Annemiek Kavelaars[2], Rafael González Cano[3], Cobi Heijnen[2] and Niels Eijkelkamp[1]. [1]UMC Utrecht, Utrecht, Netherlands, [2]MD Anderson Cancer Center, Houston, TX, [3]University of Granada, Granada, Spain.

Background/Purpose: Chronic pain is a major debilitating problem in many inflammatory diseases including rheumatoid arthritis and osteoarthritis. Pain is an important problem during active disease but often continues during minimal disease activity or even after sustained remission. Chronic pain is often difficult to treat and new insights into the mechanisms underpinning the development of chronic pain are needed. Recently we have identified involvement of the 5p15.2 region that includes the coding region for CCT5 and FAM173b in chronic widespread pain (CWP). The minor allele frequency of two highly correlated SNPs (rs13361160 and rs2386592) annotated to the 5p15.2 region were associated with a 30% increased risk for CWP. 130 associated SNPs were identified that were in linkage disequilibrium with these two top SNPs and included one non-synonymous SNP (rs2438652) located in the coding region in the FAM173B gene. Here we examined the role of FAM173b in regulating chronic inflammatory pain.

Methods: FAM173b antisense oligonucleotides (asODN) were injected intrathecally to establish in vivo knockdown of FAM173b in sensory neurons. Transient inflammatory hyperalgesia was induced by intraplantar injection of a low dose of carrageenan in mice. Chronic inflammatory hyperalgesia was induced by intraplantar injection of Complete Freund Adjuvant (CFA). Development of hyperalgesia was assessed by using the Hargreaves' method to determine heat sensitivity, while Von Frey hairs were used to assess mechanical sensitivity.

Results: FAM173b is upregulated in the lumbar spinal cord and dorsal root ganglion after peripheral inflammation induced by intraplantar CFA. Knockdown of FAM173b by intrathecal injection of FAM173b antisense oligodeoxynucleotides reduced the intensity of transient carrageenan-induced inflammatory thermal and mechanical hyperalgesia. Importantly, FAM173b knockdown during established chronic CFA-induced hyperalgesia completely attenuated CFA-induced persistent thermal and mechanical hyperalgesia. Mechanistically, intrathecal FAM173b asODN treatment completely prevented CFA-induced increase in Iba1+ microglia/macrophages with an activated phenotype in the spinal cord and DRG. Moreover, FAM173b asODN treatment reduced spinal cord and DRG Iba1 mRNA expression. Intrathecal FAM173b asODN prevented CFA-induced upregulation of the pro-inflammatory cytokine TNF-a in the lumbar spinal cord and dorsal root ganglia. In contrast, FAM173b asODN did not affect CFA-induced increase in BDNF mRNA expression in the DRG.

Conclusion: We have identified an as yet unrecognized role for FAM173b in chronic inflammatory pain. We propose that FAM173b promotes spinal cord and DRG microglia/macrophages activation and subsequent pro-inflammatory cytokine production leading to persistent inflammatory pain.

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Inhibition Of Chronic Pain By IL4–10 Synerkine Is Superior To IL-4 Or IL-10 Monotherapy: A Novel Strategy To Restrain Pain In Rheumatic Diseases. Niels Eijkelkamp[1], Sarita Hartgring[2], Cristine Steen-Louws[1], Hanneke Willemen[1], Qiu-Ling Mao-Ying[3], Cobi Heijnen[3], Erik Hack[1], Annemiek Kavelaars[3] and J.A.G. van Roon[2]. [1]UMC Utrecht, Utrecht, Netherlands, [2]University Medical Center Utrecht, Utrecht, Netherlands, [3]MD Anderson Cancer Center, Houston, TX.

Background/Purpose: Chronic pain is a major problem in many diseases, including RA and OA, arising from inflammation or structural damage. It is often associated with glial cell-mediated inflammatory responses in the spinal cord leading to enhanced pain perception (hyperalgesia), which is difficult to treat. Moreover, therapeutic options are limited. Despite the potential of IL4 and IL10 to inhibit inflammation and pain in experimental models, clinical studies were disappointing, likely due to poor bioavailability. We developed a novel option to inhibit multiple inflammatory responses by constructing an IL4/IL10 fusion protein (IL4–10 synerkine). This synerkine is a novel biologic that combines the distinct characteristics of IL4 and IL10, with an increased mass and anticipated improved bioavailability. Strong anti-inflammatory potential of the synerkine was demonstrated in human in vitro assays. Our objective was to investigate the capacity of IL4–10 synerkine to treat chronic pain induced by inflammation or nerve damage.

Methods: IL4–10 synerkine, injected intrathecally (it), was tested in 3 mouse models of chronic pain. First, chronic inflammatory hyperalgesia was induced by intraplantar injection of carrageenan. Secondly, we used mice with a cell-specific reduction of ~50% in GRK2 level in microglia/macrophages (LysM-GRK2+/− mice) that develop persistent inflammatory hyperalgesia after a single intraplantar injection of IL-1b, while WT mice develop a transient hyperalgesia. Thirdly, chronic neuropathic pain was induced by spared nerve injury (SNI). Hyperalgesia was assessed by Hargreaves test to determine heat withdrawal latencies and Von Frey hairs to determine mechanical thresholds. To demonstrate surplus value of the synerkine, IL-4 and IL-10 mono and combination therapies were tested.

Results: Intraplantar injection of carrageen induced profound persistent hyperalgesia in WT mice. A single it. injection of IL4–10 synerkine completely inhibited established carrageenan-induced persistent hyperalgesia (for 40, 100 and 200 ng all $p<0.001$) for at least 2 days. The highest dose of IL4–10 synerkine significantly inhibited hyperalgesia for 4 days ($p<0.05$). Injection of IL4, IL10, or a combination (100 ng) only modestly inhibited hyperalgesia (30–40%) for 1 day. It. administration of IL4–10 synerkine also dose-dependently inhibited IL-1β-induced persistent hyperalgesia in LYSM-GRK2+/− mice. Single injections of 100 ng and higher, completely prevented the development of IL-1β-induced hyperalgesia in LYSM-GRK2+/− mice ($p<0.001$). Moreover, it shortened the duration of transient IL-1β-induced hyperalgesia in WT mice. Interestingly, IL4–10 synerkine also inhibited mechanical hypersensitivity in the SNI neuropathic pain model, although for shorter time periods (6 hours).

Conclusion: IL4–10 synerkine, next to its strong anti-inflammatory properties, also robustly relieves hyperalgesia in models for inflammatory and neuropathic pain, superior to IL4 or IL10 mono or combination therapy. These data underscore the potential of IL4–10 synerkine to inhibit immunopathology and pain in inflammatory and degenerative rheumatic diseases.

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Pain Pathway Activation In Dorsal Root Ganglia and Dorsal Horn In a Murine Surgical Model Of Osteoarthritis. Rachel E. Miller[1], Phuong Tran[1], Richard J. Miller[2] and Anne-Marie Malfait[1]. [1]Rush University Medical Center, Chicago, IL, [2]Northwestern University, Chicago, IL.

Background/Purpose: Using a surgical mouse model of osteoarthritis (OA), destabilization of the medial meniscus (DMM), we monitor pain and associated pathways over a period of 16 weeks post surgery. We observed longitudinal changes in pain-related behaviors as joint disease progresses, with concomitant molecular changes in the innervating DRG (Miller et al, 2012, PNAS). Specifically, mice develop progressive mechanical allodynia in the ipsilateral hindpaw over the first 4 weeks, while locomotive changes indicative of chronic pain appear 8 weeks after DMM. It has been hypothesized that activation of microglia in the dorsal horn (DH) – a dynamic process that contributes to pain through further neuronal activation - is dependent on signaling molecules (ie MCP-1 and fractalkine (CX3CL1)) that originate in DRG neurons and are transported to the DH, where they can act on microglia (Miller et al, 2009, Handb Exp Pharmacol). Our previous work has focused on MCP-1/CCR2 signaling in DRG neurons after DMM surgery. Here, we examined fractalkine expression in the DRG and activation of microglia and neurons in the DH following DMM surgery.

Methods: Animal procedures were approved by Rush University Medical Center. DMM or sham surgery was performed in the right knee of 10-week old male wild-type C57BL/6 mice. Pain-dependent behaviors were assessed at 0, 4, 8, and 16 weeks post surgery. Mechanical allodynia in the hind paw was assessed with von Frey fibers. Locomotion was assessed using a LABORAS platform, as described (Miller et al, 2012, PNAS). Eight weeks post DMM, L3-L5 DRG were harvested (these DRG contain neurons that innervate the knee joint) and cells were cultured for 4 days; supernatants were collected for CX3CL1 ELISA. For immunohistochemistry, mice were perfused transcardially with paraformaldehyde; L3-L5 DRG were dissected out or the spinal column was decalcified prior to spinal cord sectioning of the L3-L5 levels. Anti-Iba1 or anti-cFos was used to examine microglia or neuronal activation, respectively, in the dorsal horn.

Results: In order to investigate whether changes in the DRG and DH of the spinal cord correlated with observed changes in locomotion, we focused on the 8-week post surgery time point.

Eight weeks post DMM, cultured DRG cells produced elevated levels of CX3CL1 protein compared to age-matched naïve DRG ($p<0.05$). In addition, the DH in DMM mice showed markedly higher expression of Iba1 (marker of microglial activation) and of cFos (marker of neuronal activation) compared to age-matched naïve mice.

Conclusion: This is the first report of increased fractalkine release by DRG neurons in a model of osteoarthritis, which may contribute to cellular activation in the DH. Microglia and neuronal activation in the DH has been reported in murine mono-iodoacetate (MIA) arthritis (Ogbonna et al, 2013, Eur J Pain) and in non-disease-related animal models of nerve injury. Longitudinal assessments of these dorsal horn changes are currently underway. This will yield insight into how pain signaling spreads from the peripheral to the central nervous system in osteoarthritis.

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ACR Concurrent Abstract Session
Pediatric Rheumatology - Pathogenesis and Genetics
Wednesday, October 30, 2013, 11:00 AM–12:30 PM

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Mir-26a, Mir-30b and HER2: New Players On Lupus Nephritis Pathogenesis. Patrícia Costa-Reis, Pierre Russo and Kathleen E. Sullivan. The Children's Hospital of Philadelphia, Philadelphia, PA.

Background/Purpose: microRNAS (miRNAs) are noncoding RNAs responsible for post-transcriptional gene silencing. These key regulatory molecules control the expression of multiple genes, so its dysregulation can contribute to sustained pathology. Our goal was to study the miRNA pattern of lupus nephritis (LN) in order to better understand its pathogenesis and to identify clinically relevant pathways.

Methods: RNA was extracted from paraffin embedded kidney samples of controls (n=6) and patients with LN (n=18) and post-streptococcal glomerulonephritis (n=2). Molecular digital detection of miRNAs was performed, analyzed on R, and confirmed by qRT-PCR. Gene expression of human kidney cells lines, submitted to knockdowns of the miRNAs of interest using lentivirus, was studied with GeneChip® 2.0 ST Arrays. Off-target lentivirus were used as controls. Immunohistochemistry, immunofluorescence and western-blots for HER2 were performed.

Results: There was a kidney LN specific miRNA signature, which, according to IPA® pathway analysis, mainly reflected cell proliferation and inflammation. miR-26a and miR-30b were found to be significantly decreased in LN ($p=0.002$; $p=0.008$, respectively). Furthermore, miR-26a levels inversely correlated with proteinuria ($p=0.005$), casts ($p=0.031$) and the presence of crescents ($p=0.030$), a sign of kidney cell proliferation. PPARCG1A, which is involved in type 1 interferon pathway, was found to be highly increased in mesangial cells submitted to miR-26a knock-down. Finally, HER2, a protein that regulates miR-26a and miR-30b levels in breast cancer cell lines, was found to be highly increased in the glomeruli and tubular compartments of LN patients. HER2 was found to be expressed in human podocytes, tubular and mesangial cell lines and its expression was increased by α-interferon ($p=0.002$).

Conclusion: The kidneys of LN patients have a specific miRNA pattern, characterized by a significant decrease of miR-26a and miR-30b. These miRNAs were previously found to be key regulators of cell proliferation in several malignancies and miR-26a was found to reduce cancer cell progression and cause tumor-specific apoptosis *in vivo*. Our data indicate that these miRNAs also regulate cell proliferation in LN. Interestingly, it was previously shown that trastuzumab, a monoclonal antibody against HER2, produces therapeutic actions by up-regulating miR-26a and miR-30b in breast cancer cell lines. Since we demonstrated that HER2 was highly increased in the kidneys of LN patients, blocking HER2 with trastuzumab may be a new promising pathway to decrease cell proliferation and damage in this disease. miR-26a, miR-30b and HER2 are, therefore, three new interesting players on LN pathogenesis.

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Accounting For Parental Load and Identification Of Multiple Risk Variants For Anti-Ro Congenital Heart Block Through High-Density Genotyping Of Immune-Related Loci. Robert M. Clancy[1], Jill P. Buyon[1], Nathalie Costedoat-Chalumeau[2], Antonio Brucato[3], Kateri Levesque[2], Véronique Ramoni[4], Miranda C. Marion[5], Mary Comeau[5], Satria Sajuthi[6], Paula S. Ramos[7], Robert P. Kimberly[8], Timothy D. Howard[6] and Carl D. Langefeld[5]. [1]New York University School of Medicine, New York, NY, [2]Hopital Cochin, Paris, France, [3]USC Internal Medicine, Ospedali Riuniti, Bergamo, Italy, [4]Rheumatology University of Pavia, Pavia, Italy, [5]Wake Forest University Health Sciences, Winston-Salem, NC, [6]Wake Forest School of Medicine, Winston-Salem, NC, [7]Medical University of South Carolina, Charleston, SC, [8]University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Anti-Ro associated congenital heart block (CHB) exhibits a 33% concordance rate in monozygotic twins, 17.5% recurrence of disease and a high sibling risk ratio (lamda s=3000). Given the strong maternal genetic influence on anti-Ro antibody production and the proposed pathogenesis of injury which implicates fetal innate immune responses, the Immunochip (SNP array for fine mapping 186 genomic regions previously connected to at least one of 12 autoimmune diseases) was selected to explore associations between immune-related variants and CHB. Pedigrees inclusive of affected and unaffected children and their parents were included in an attempt to untangle maternal from fetal contributions.

Methods: Caucasian CHB children (n=170) and nuclear family members (n=435) from three Registries (U.S., France, Italy) were genotyped. Sera from the mothers of all probands were confirmed to react with either 52kD SSA/Ro, 60kD SSA/Ro, or 48kD SSB/La. In 96%, 2nd or 3rd degree block was present; the remaining 4% had an isolated cardiomyopathy. Out-of-study controls (n=1087) were called together with CHB pedigree data. After standard QC, association analyses were computed using logistic regression for case-control and pedigree disequilibrium tests (PDT) for pedigree-based tests; the latter accounts for genetic maternal immune load. P-values were genomic control adjusted and genome-wide significance was assessed using the false discovery rate P-value (FDR-P<0.05). Primary inference is based on the FDR-P for the case-control analysis, conditional on the PDT/TDT P-value being <0.05.

Results: There were 18 SNPs inside and 25 SNPs outside the HLA region that met the dual criteria, case-control FDR-P<0.05 (i.e., genome-wide significance) and PDT/TDT P<0.05. The strongest association was inside the extended HLA region within an intronic region of *GABBR1* (rs29252: FDR-P=2×10E-10, OR=6.2) which encodes an inhibitory neurotransmitter receptor whose ligation resists ischemia/reperfusion-injury and fibrosis. Detailed imputation-based four digit HLA analyses are underway. Outside the HLA region the primary associations included rs3739706 [FDR-P=0.0009, OR=1.9] within *LPAR1* which encodes a lysophosphatidic acid G-protein-coupled receptor with a role in endothelial cell differentiation; rs62092154 [FDR-P=0.0026, OR=4.8] within *SLC14A2* (encodes a urea transporter, which in addition to being expressed in the kidney, is also expressed in the heart and increased in heart failure); rs8063008 [FDR-P=0.00598, OR=0.46] with an intergenic on 16q24 and numerous associations on 2p14 within FLJ16124 (e.g., rs7575614: FDR-P=0.02, OR=2.7), a region rich in regulatory elements. Interestingly, rs473024 showed evidence of association [FDR-P=0.01, OR=1.8] and is located within *MAGI2*, a gene identified in an imprinted gene expressed in human placenta.

Conclusion: Analysis with the Immunochip yielded numerous regions strongly associated with CHB, even after accounting for potential parental load. These associations corroborate the genetic influence on CHB and suggest a link between immune responses and exuberant fibrotic replacement of the atrioventricular node and in some cases a cardiomyopathy.

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Autoantigen Microarray Analysis Of Sera From New-Onset Pediatric Systemic Lupus Erythematosus Patients: A Distinct Autoantibody Profile Associated With Class III/IV Lupus Nephritis. Imelda Balboni[1], David Haddon[2], Vivian Diep[2], Cindy Limb[2] and Paul Utz[2]. [1]Stanford University School of Medicine, Palo Alto, CA, [2]Stanford University School of Medicine, Stanford, CA.

Background/Purpose: Systemic lupus erythematosus (SLE) is a heterogeneous systemic autoimmune disease characterized by the production of autoantibodies directed against highly-conserved nuclear antigens. 15–20% of SLE patients develop disease in childhood or adolescence, and pediatric (pSLE) patients often have more severe disease onset and organ system involvement. Autoantigen microarray technology allows the comprehensive analysis of autoantibodies directed against hundreds of antigens with minimal amounts of sera. The purpose of this study was to characterize the spectrum of autoantibody reactivity in a cohort of new-onset pSLE patients and to identify an autoantibody profile that could serve as a biomarker for class III/IV lupus nephritis.

Methods: New-onset pediatric rheumatology patients meeting the revised ACR diagnostic criteria for SLE were eligible for this study. The study was approved by the Stanford University Institutional Review Board and informed consent was obtained prior to participation in the study. Demographic and clinical data at disease onset were collected. Sera from 51 pSLE patients and 20 healthy age- and sex-matched controls were evaluated using an 1128-feature antigen microarray manufactured with approximately 135 antigens. Microarrays were probed with 1:200 dilutions of serum and a Cy5-conjugated goat-anti-human IgG secondary antibody, scanned with a GenePix 4000 scanner, and analyzed using GenePix 6.1 software to determine median fluorescence intensity minus background for each antigen. Significance Analysis of Microarrays (SAM) software was used to determine differences in autoantibody reactivity between pSLE patients and controls, and between pSLE patients with and without proliferative nephritis. Enzyme-linked immunosorbant assays (ELISAs) were performed to confirm autoantibody reactivity identified by microarray.

Results: SAM identified increased reactivity against 50 autoantigens in sera from new-onset pSLE patients compared to controls, with a false discovery rate of zero. In addition to reactivity against classically-described SLE autoantigens, reactivity against several basement membrane and extracellular matrix proteins was identified. Subgroup analysis comparing patients with class III or IV lupus nephritis to patients without significant nephritis demonstrated increased reactivity against several autoantigens including double-stranded DNA, C1q, histones, collagen and aggrecan in patients with proliferative nephritis. ELISAs confirmed a significant association between proliferative nephritis and reactivity against double-stranded DNA ($p=0.0037$), histones H2B ($p=0.047$) & H1 ($p=0.02$), C1q ($p=0.0005$), and type IV collagen ($p=0.0051$).

Conclusion: New-onset pSLE patients demonstrate a broad spectrum of autoantibodies directed against many autoantigens, including those not classically associated with SLE. Subgroup analysis of pSLE patients with and without nephritis revealed a distinct autoantibody profile that could serve as a biomarker for proliferative nephritis. We are currently developing a composite score, based on these autoantibodies and clinical data, to test on an additional cohort of pSLE patients.

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2863

Copy Number Variations Of Complement C4A and C4B Genes Are Genetic Risk Factor and Disease Modification Factor, Respectively, For Juvenile Dermatomyositis. Anjali Patwardhan[1], Katherine Lintner[1], Lisa G. Rider[2], Frederick W. Miller[2], Terrance O'Hanlon[2], Yee Ling Wu[1], Bi Zhou[1], Huanyu Wang[1], David Newsom[1], Peter White[1], Charles H. Spencer[3] and C. Yung Yu[1]. [1]The Research Institute at Nationwide Children's Hospital and The Ohio State University, Columbus, OH, [2]NIEHS, NIH, Bethesda, MD, [3]Nationwide Childrens Hospital, Columbus, OH.

Background/Purpose: Juvenile Dermatomyositis (JDM) is a systemic and inflammatory vasculopathy that affects mainly proximal muscles and skin in children. It is a rare but severe autoimmune disease featuring the presence of autoantibodies against the translational machinery for protein synthesis. Proteolytic products of antibody-mediated complement activation are often observed in affected tissues of JDM. The causal factors for JDM are unknown, but genetic variants of the HLA are strongly implicated, particularly in haplotypes with HLA-DR3. Recently, differential copy number variations (CNVs) for the HLA-associated complement C4A and C4B genes were demonstrated in healthy subjects and autoimmune disease patients. A deficiency of C4A is strongly associated with HLA-DR3 and systemic autoimmunity. Our objective is to investigate CNVs of total C4, C4A, and C4B on the pathogenesis of JDM.

Methods: The study population included 56 JDM patients (53 Whites, 3 Blacks) and 577 geographically matched healthy subjects, recruited upon informed consents according to IRB-approved protocols. The mean ($\pm$SD) age for JDM disease diagnosis was 7.91 ± 4.27 years old. Calcinosis, lipodystrophy, and skin ulceration were observed in 19.6%, 9.1% and 16.1% of patients, respectively. Genomic DNA, PAXGENE RNA, and EDTA-plasma were isolated from peripheral blood samples. Gene copy numbers (GCN) for total C4, C4A, and C4B were determined by genomic Southern blot and TaqMan-based, realtime qPCR. Global gene expression array were determined using PAXGENE RNA and Agilent SurePrint G3 8×60K microarrays. The expression of IFI44 was determined by SYBR-Green based qPCR using PAXGENE RNA and GADPH as standard.

Results: Among White subjects, the GCNs vary from 2 to 6 for total C4, 0 to 5 for C4A, and 0 to 4 for C4B. There were significant decreases in JDM (vs. controls) for GCNs of total C4 (cases: 3.42 ± 0.72, controls: 3.85 ± 0.69; $p=0.00007$, t-test) and C4A (cases: 1.74 ± 0.86, controls: 2.10 ± 0.76; $p=0.0009$, t-test). Remarkably, 43.4% of the JDM patients had a heterozygous or homozygous deficiency of C4A, compared to 18.5% in controls ($p=0.00008$, X^2analysis). The odds ratio (95% CI) for C4A deficiency in JDM was 3.37 (1.88– 6.04). Intra-group comparison of clinical presentations revealed that patients with calcinosis and lipodystrophy both had significantly higher GCN of C4B ($p=0.001$, Fisher's exact), reflecting a role of C4B in complement-mediated tissue injuries. Global gene expression studies using peripheral blood RNA (19 JDM, 8 controls) and Agilent microarrays revealed up-regulation of genes typical for interferon-α response signature and down-regulation for chemokine genes. SYBR-green labeled qPCR on transcripts for IFN-α response gene IFI44 showed a 4.7 and 2.6-fold increase in expression among patients with and without a C4A deficiency, respectively, vs. controls ($p=0.004$, t-test).

Conclusion: A deficiency of C4A is a common genetic risk factor for JDM with medium to high effect size. Peripheral blood RNA from JDM exhibited upregulation of IFN-α response gene IFI44, particularly among C4A deficient patients. Among established JDM patients, normal/high GCN of C4B was associated with disease complications, including calcinosis and lipodystrophy.

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2864

Whole Exome Sequencing In Pediatric Patients With Early Onset Rare Immunodysregulatory Diseases That Present With Fever and Systemic Inflammation. Adriana Almeida de Jesus[1], Julie Niemela[2], Yin Liu[1], Steven Boyden[3], Ivona Aksentijevich[4], Daniel L. Kastner[4], Thomas A. Fleisher[2], Raphaela Goldbach-Mansky[1] and Zuoming Deng[1]. [1]National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD, [2]Laboratory Medicine, NIH Clinical Center, Bethesda, MD, [3]National Human Genome Research Institute, NIH, Bethesda, MD, [4]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD.

Background/Purpose: WES (Whole Exome Sequencing) has increasingly become the tool of choice in translational research, providing molecular diagnoses in Mendelian diseases and identifying important genes in key biological pathways. Here we report using WES to investigate the molecular basis of a group of rare diseases presenting with autoinflammatory phenotypes that are characterized by perinatal onset of fever and systemic and organ specific inflammation.

Methods: Total blood DNA was extracted and whole exome sequencing was performed using human exome capture by Agilent V4 (51Mbp) exome enrichment kit, followed by next generation sequencing using Illumina HiSeq2000. We have developed a bioinformatics pipeline to process WES data and an integrated workflow to analyze variants in family trios or quartets. Using the pipeline, we were able to assess the quality of WES data and check discrepancies in sample gender and family relatedness.

Results: The number of coding variants per sample in our WES studies ranged from 19,000 to 25,000, correlating with exome coverage and sample ethnicity. The Transition to Transversion ratios (Ti/Tv) varied from 2.98 to

3.27 with a median of 3.15 after excluding a poorly performed batch. Other QC metrics such as heterozygous to homozygous ratio, synonymous to nonsynonymous ratio and indel percentage are all within expected ranges for WES. Concordance in two pairs of technical replicates was 97.25%. In total, 42 subjects were sequenced, including 14 patients and their parents (trios). Five probands were male (35.7%), 10 probands were Caucasian (56.3%), 3 were Hispanic and 1 had other ethnicity. All patients presented with immune dysregulatory clinical phenotypes including chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) in 1 patient and neonatal onset multisystem inflammatory disease (NOMID) in 4 patients. The remained 9 probands presented with undifferentiated complex clinical phenotypes characterized by early-onset fever, skin rashes and organ-specific inflammatory involvement. On average, the novel variants (defined as not present in dbSNP137) count for about 2% of all variants in each sample. The variant annotation, analysis and filtering workflow has allowed us successfully identify *de novo* mutations in 5 trios. In 2 patients we identified disease-causing mutations in previously known genes, *PSMB8 and PSMA3* in 1 patient and NLRP3 in 1 patient, causing CANDLE and NOMID syndromes, respectively. In one patient we found a disease causing *de novo* mutation in a gene previously not associated with human disease with sufficient data to claim causality and in two patients we have found previously non-described variants that are suggestive of causing disease but functional studies are currently underway in the other families to confirm the pathogenicity of the mutations in these families. All mutations described were confirmed by Sanger sequencing.

Conclusion: Our results suggest that WES can be used as an effective tool in translational research of rare immunodysregulatory diseases.

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Gene Expression Profiles Of Fibroblast-Like Synoviocytes In Early Stage Of Oligoarticular Juvenile Idiopathic Arthritis Are Different In Extended Versus Persistent Course. AnneMarie C. Brescia[1], Megan M. Simonds[2], Suzanne M. McCahan[2], Paul T. Fawcett[2] and Carlos D. Rose[1]. [1]Thomas Jefferson University/ AI duPont Hospital for Children, Wilmington, DE, [2]Nemours/AI duPont Hospital for Children, Wilmington, DE.

Background/Purpose: Our goal is the identification of informative synovial biomarkers to predict persistent vs extended course in oligoarticular JIA patients.

Methods: Stored remnant synovial fluid samples obtained from patients undergoing medically indicated arthrocenteses were retrieved. Using our clinical database, JIA samples were separated into two groups: (1) oligoarticular JIA with persistent course (PR), (2) oligoarticular JIA with extended course (E). All samples were from steroid-naïve joints and all samples from E were obtained prior to extension. Primary cultures of fibroblast-like synoviocytes (FLS) were established for each subject. RNA from cultured passage 3–6 FLS were isolated, amplified and hybridized to Affymetrix Human GeneChips using the Affymetrix protocol. Expression values were determined with GC-RMA. Global gene expression of FLS from 5 PR and 9 E samples were obtained. Data was filtered for log2 expression >4 in all samples of either PR or E, then for absolute value of 1.5-fold change to reveal 3231 probesets. Of these, LIMMA revealed 39 probesets with statistically significant differential expression between PR vs E FLS ($p<0.05$), shown in heatmap (Figure 1).

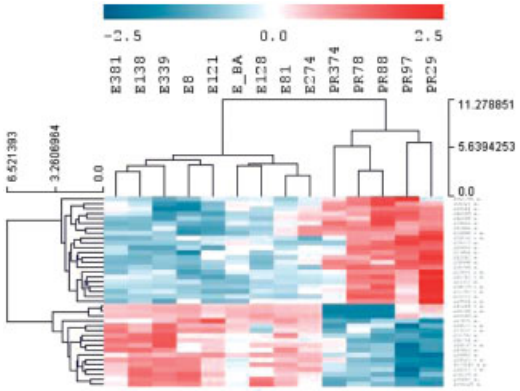

Figure 1

Results: Hierarchical clustering of the 39 probesets revealed samples from the different courses cluster together, with all the E to the left of the heatmap. Importantly, the E were all taken from the very first sample available, which preceded extension in all patients, highlighting that there are detectible differences in the gene expression of the FLS early in the course in the patients whose disease is destined to extend. These 39 probesets represent 32 unique genes. PR overexpressed 19 genes, including known biomarkers for other diseases, AURKA, CCNB1, PLAUR and the secreted protein IGFBP6, in addition to another secreted protein, COL5A1. E overexpressed 13 genes, including known biomarkers for other diseases, XIST and secreted protein GDF5, which is important in inflammatory and apoptotic pathways and activates macrophages within the TNFa pathway.

Conclusion: We were able to demonstrate differential gene expression in FLS from JIA patients who remained PR vs those who were destined to extend, demonstrating detectible difference early in disease which may be useful for prediction. The differentially expressed proteins, especially secreted proteins, provide a starting point for development of biomarkers to distinguish between PR and E JIA using aspirated synovial fluid.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects VII: Remission, Flare and Outcome Measures in Rheumatoid Arthritis
Wednesday, October 30, 2013, 11:00 AM–12:30 PM

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Determining The Absolute Change In The Clinical Disease Activity Index (CDAI) To Define a Minimally Important Difference. Jeffrey R. Curtis[1], Shuo Yang[1], Lang Chen[1], Janet E. Pope[2], Edward C. Keystone[3], Boulos Haraoui[4], Gilles Boire[5], J. Carter Thorne[6], Diane Tin[6], Carol A. Hitchon[7], Clifton O. Bingham III[8] and Vivian P. Bykerk[9]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]St Joseph Health Care, London, ON, [3]Mount Sinai Hospital/University of Toronto, Toronto, ON, [4]Centre Hospitalier de l'Université de Montréal, Montreal, QC, [5]Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, [6]Southlake Regional Health Centre, Newmarket, ON, [7]University of Manitoba, Winnipeg, MB, [8]Johns Hopkins University, Baltimore, MD, [9]Hospital for Special Surgery, New York, NY.

Background/Purpose: Simplified measures to quantify rheumatoid arthritis (RA) disease activity are increasing in use in clinical practice. However, the absolute minimally important difference (MID) in some of these measures, such as the clinical disease activity index (CDAI), has not been well defined in real-world settings, especially for early RA patients (ERA) with low or moderate disease activity. To determine the MID for improvement of the CDAI in a "real world" setting using an observational cohort of patients with ERA.

Methods: Data from the Canadian CATCH cohort of patients with ERA were used to identify pairs of rheumatology visits spaced 3 months apart occurring within 12 months of cohort entry. Patients with concomitant fibromyalgia (8% of cohort) were excluded. Absolute change in CDAI was examined between visit pairs and correlated with relevant changes corresponding to MIDs in patient self-reported improvement (better vs. same/worse), patient pain (>1 vs. <= 1, and >2 vs. <= 2) and HAQ (>0.22 vs. <= 22, and >0.30 vs. <= 0.30). The 10th and 90th percentile of the CDAI distributions for EULAR good response vs. non-response in DAS28 ESR (>1.2 vs. < 0.6 units improvement) were used to determine proposed CDAI cutpoints to define MID, overall and stratified by initial CDAI disease activity categories (low < 10; moderate 10<=-<=22; high > 22). Discrimination of these cutpoints was examined using area under receiver operator curves (AUROC). These CDAI cutpoints were used to describe the Sensitivity (Se), Specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) of the CDAI cutpoints for patient pain and HAQ.

Results: A total of 1191 unique CATCH patients (mean± SD age 53.5± 15.1 years; 72% women, median RA disease duration 5.8 ± 3.0 months and contributed 3262 visit pairs within 12 months of enrollment. Among those with available serologic results (91% of cohort for RF, 67% of cohort for anti-CCP), 70% were RF positive and 60% anti-CCP antibody positive.

Overall, there was excellent discrimination between DAS28 responders using a CDAI cutpoint of 5 units; the AUROC was 0.87. CDAI cutpoints for patients who started in low, moderate, or high disease were 2, 6, and 10,

respectively. The Se, Sp, PPV and NPVs shown in the Table showed acceptable performance characteristics using these proposed CDAI cutpoints.

Improvement in	CDAI Cutpoint and Starting Disease Activity	Sensitivity	Specificity	PPV	NPV
Patient self-reported improvement (better vs. same/worse)	5 (all data)	76	53	56	74
	2 (low)	84	58	42	90
	6 (moderate)	76	82	57	72
	11 (high)	82	73	88	63
Pain (>1 vs. <=1)	5 (all data)	45	85	55	80
	2 (low)	33	92	54	83
	6 (moderate)	46	75	52	70
	11 (high)	52	77	71	61
Pain (>2 vs. <=2)	5 (all data)	29	93	62	77
	2 (low disease)	15	96	54	80
	6 (moderate)	24	88	55	66
	11 (high)	40	85	73	58
HAQ (> 0.22 vs. <= 0.22)	5 (all data)	57	80	69	71
	2 (low disease)	28	87	40	79
	6 (moderate)	46	73	58	64
	11 (high)	70	64	77	55
HAQ (> 0.30 vs. <= 0.30)	5 (all data)	48	87	74	69
	2 (low disease)	17	93	44	78
	6 (moderate)	36	81	59	62
	11 (high)	63	72	80	53

Conclusion: These minimally important absolute differences in CDAI can be used to evaluate improvement and increase the usefulness of this clinical simplified disease activity measure in real-world settings.

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Using Patient Reported Outcomes Measurement Information System Instruments To Identify Disease Flares In People With Rheumatoid Arthritis. Susan J. Bartlett[1], Ana-Maria Orbai[2], Trisha Duncan[2] and Clifton O. Bingham III[2]. [1]Johns Hopkins School of Medicine, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD.

Background/Purpose: Rheumatoid arthritis (RA) is associated with unpredictable episodes of disease worsening that may prompt consideration of treatment change. Core RA Flare domains have been ratified by OMERACT, but the optimal PRO instruments have not been determined. PROMIS offers population-normed measures to assess physical, emotional, and social health, including RA Flare domains. PROMIS use in RA is limited and has not been evaluated for flare detection

Methods: Data are from the baseline visit of the first 125 RA pts enrolled in an ongoing study integrating PROs into routine RA care. Pts were asked whether they were in a significant RA flare, flare duration and severity, and completed selected PROMIS CATs (pain, fatigue, physical function, and social roles/activities), along with MHAQ, pain, fatigue, pt global VAS, change from last visit and pt acceptable symptom state. MD global and joint counts were also recorded. Flare vs. no-flare groups were compared using t-tests and χ^2.

Results: Participants (N=126) were mostly female (79%) and white (86%) with a mean (SD) age of 56 (13) and RA duration of 12 (9) yr; 10% were diagnosed ≤ 2 yr. 20% reported a current flare with a mean severity of 6.0 (2.5)(0=none; 10=worst); 52% reported duration >14 d. Compared to others, flaring pts were more likely to rate RA worse than the prior visit (OR 7.6; 95% CI 2.9, 19.7) and current symptom state unacceptable (OR 5.6; 95% CI 2.2, 14.4). Flare was not associated with age, sex, race, RA duration, or education. Pts reporting flare had significantly higher PROMIS pain and fatigue scores, and lower physical function as well as participation in and satisfaction with social roles and activities (Table). Traditional PROs (pain, fatigue, pt global VAS, MHAQ) and clinical disease activity indicators (CDAI, MD Global, joint counts) were also significantly higher in the flare group.

	Flare (n=25)		No Flare (n=100)		
	Mean	SD	Mean	SD	p value
Pain					
100 mm VAS	53.6	25.8	25.0	26.5	.000
PROMIS Pain Intensity	50.7	7.0	43.0	7.8	.000
PROMIS Pain Interference	59.9	6.8	51.3	9.7	.000
Fatigue					
100 mm VAS	59.8	24.2	34.8	30.6	.000
PROMIS Fatigue	58.2	7.0	53.3	10.6	.032
Physical Function					
MHAQ	0.5	0.4	0.3	0.4	.014
PROMIS Physical Function†	37.9	6.2	44.2	9.0	.001
Social Roles and Activities†					
PROMIS Participation	46.4	7.6	50.7	9.3	.037
PROMIS Satisfaction	42.8	9.6	49.8	10.2	.002
Patient Global	47.0	24.4	24.1	25.7	.000
AM Stiffness 30 min	52%		31%		.049
Stiffness Intensity*	1.8	0.7	1.2	0.8	.001
Stiffness Interference**	1.8	0.9	1.2	1.1	.002
CDAI	14.8	10.5	6.8	7.0	.001
Swollen joints (28)	5.0	5.5	1.9	2.8	.000
Tender joints (28)	3.0	4.4	1.2	2.7	.017
MD Global	25.5	22.8	12.6	13.9	.013

†Higher scores reflect greater impairment. *0=none, 4=very severe; **0=never, 4=always

Conclusion: Patient reports of RA flares are associated with significantly higher PROMIS scores, legacy measures and clinical disease activity indicators, providing evidence of convergent validity of PROMIS instruments. Results suggest PROMIS measures can assess RA Flare domains and identify pts in flare, with shifts of 0.4–1 SD between groups. Prospective studies are ongoing to assess responsiveness of PROMIS for RA improvement and worsening. Beyond flare detection, selected PROMIS measures may aid in RA self-monitoring, and in the case of worsening, could signal the need for additional clinical assessment.

Disclosure: S. J. Bartlett, None; **A. M. Orbai**, None; **T. Duncan**, None; **C. O. Bingham III**, OMERACT, 6, PCORI, 2.

2868

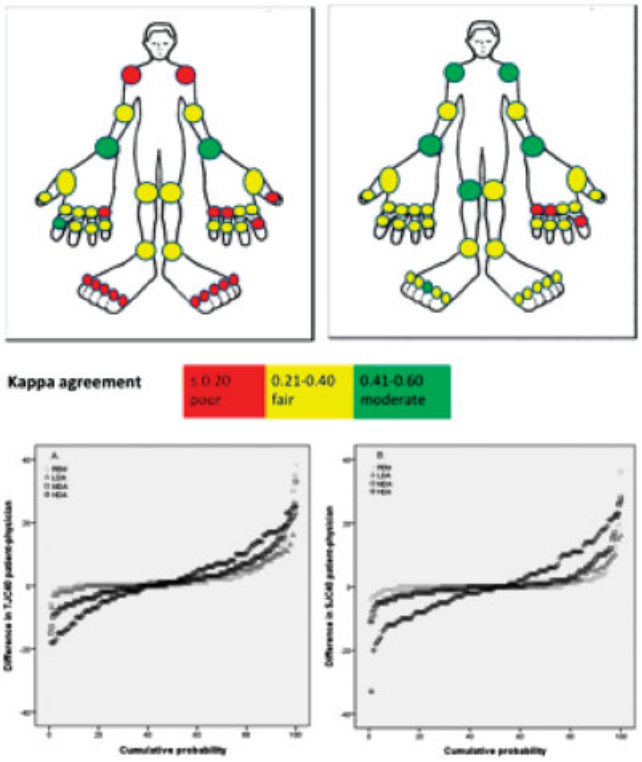
Reliability and Validity Of Patient-Reported Joint Counts and Determinants Of Disagreement With The Physician In Recent Onset Rheumatoid Arthritis. Karen Visser[1], Janet E. Pope[2], Ernest Choy[3], Clifton O. Bingham III[4], Susan J. Bartlett[5], Gilles Boire[6], Carol A. Hitchon[7], J. Carter Thorne[8], Boulos Haraoui[9], Diane Tin[8], Edward Keystone[10] and Vivian P. Bykerk[11]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]St Joseph Health Centre, London, ON, [3]Cardiff University, Cardiff, ENGLAND, United Kingdom, [4]Johns Hopkins University, Baltimore, MD, [5]Johns Hopkins School of Medicine, Baltimore, MD, [6]Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, [7]University of Manitoba, Winnipeg, MB, [8]Southlake Regional Health Centre, Newmarket, ON, [9]Institut de Rhumatologie de Montréal, Montreal, QC, [10]University of Toronto, Toronto, ON, [11]Hospital for Special Surgery, New York, NY.

Background/Purpose: Patient-reported joint counts (JCs) might improve the efficiency and consistency of disease monitoring, self-management and early recognition of changes in disease activity in rheumatoid arthritis (RA).

To assess the reliability and validity of patient-reported JCs as compared to physician JCs in recent onset RA and to identify determinants of disagreement.

Methods: Data from 795 recent-onset (< 1 year) RA patients from the Canadian early arthritis cohort (CATCH) were used. Patient-reported tender (T) and swollen (S) JCs were derived from a 40-joint homunculus and the 16-joint RA-disease-activity-index (RADAI) mannequin. Physician JCs were abstracted from the TJC68 and SJC66. Inter-rater reliability of patient TJCs and SJCs as compared with corresponding physician JCs was assessed, using intra-class correlation coefficient (ICC) two-way random effects model. Agreement on activity of joint areas was assessed by kappa. Pearson correlation coefficients were determined between the patient JCs counts separately and incorporated into the patient-disease-activity-score (pDAS) and routine-assessment-of-patient-index-data (RAPID4) with DAS28 and health assessment questionnaire (HAQ). Determinants of disagreement with the physician (over- or underestimation >=1 joint) were identified by multinomial logistic regression.

Results: The reliability of the patient TJC40 was moderate (ICC 0.61; 95%CI 0.51–0.69), with lower ICC for the 16 joint RADAI-derived TJC (ICC 0.51; 95%CI 0.21–0.68) and patient SJC40 (ICC 0.52; 95%CI 0.46–0.57). Positive agreement among joint regions ranged from 47%-82% (kappa 0.26–0.51) for tenderness and from 33%-60% (kappa 0.10–0.44) for swelling, being highest for tenderness in large joints (figure 1). Differences between patient and physician JCs were lowest in patients in DAS28 remission or low disease activity (figure 2). Determinants of disagreement on TJC were lower age, male gender, higher DAS28, disability and depressed mood. Disagreement on SJC was associated with male gender and higher DAS28. Correlations of DAS28 and HAQ with the PDAS (r 0.90; r 0.73, resp.) and RAPID4 (r 0.72; r 0.85, resp.) were higher than with the separate patient SJC40 (r 0.54; r 0.47, resp.) and TJC40 (r 0.57; r 0.54, resp.).



Conclusion: In recent onset RA, patient-reported JCs demonstrate moderate reliability and validity. Patient JCs can be incorporated in patient-reported outcomes in studies addressing remission induction and treatment withdrawal strategies to investigate their ability to detect changes in disease activity and discriminate flares.

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2869

Changes In Patient-Reported Joint Counts and Composite Indices Can Identify Flare Of Disease Activity In Recent Onset Rheumatoid Arthritis.

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Background/Purpose: Patient-reported joint counts (JCs) have been identified as core domains for assessment of flare in rheumatoid arthritis (RA) [1].

To assess the responsiveness and discriminative validity of patient-reported JCs, separately and incorporated in composite patient-reported outcomes (PROs), for worsening of disease activity in early RA (ERA).

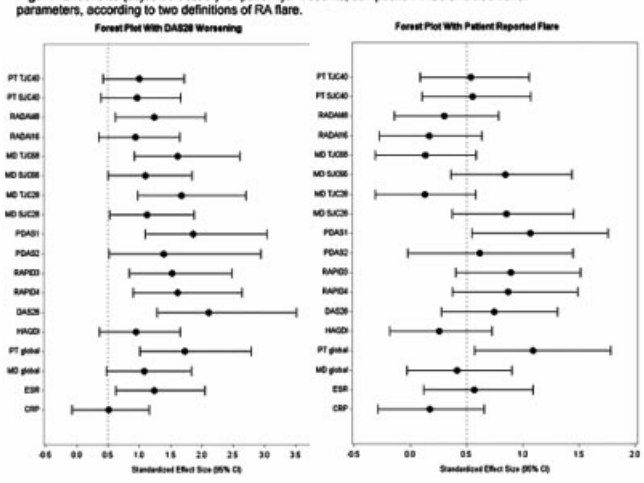
Methods: Paired data from ERA patients in the Canadian early arthritis cohort (CATCH) who prospectively completed OMERACT preliminary flare questions twice over a 3-month interval between 12/2011 and 4/2013 were used. Patients reported tender (T) and swollen (S) JCs on a 40-joint homunculus and the 16-joint RA-disease-activity-index (RADAI) mannequin. Physicians assessed the TJC68, SJC66 and global assessment (MDGA). Flare was defined as: a worsening in DAS28 >1.2 (or > 0.6 if DAS28 >= 3.2) and patients answering: 'Are you having a flare at this time?' with no changing to yes. Median changes in patient JCs were compared between patients in a flare or not by Wilcoxon signed rank test. Discrimination of flare vs. non-flare for the patient JCs separately and incorporated into the patient-disease-activity-scores (pDAS1 and pDAS2) and routine-assessment-of-patient-index-data (RAPID4) was assessed via effect sizes (ES) and compared with ES of traditional parameters.

Results: Of 115 eligible patients, 90% fulfilled the ACR 2010 RA criteria, 79% were female, mean (SD) age was 55 (15) years and symptom duration 5 (3) months. At the initial assessment, 46%/15% of the patients were in DAS28 remission/low disease activity, with a median (IQR) patient SJC40 and TJC40 of 1 (0–3) and 3 (1–10), respectively. Mean physician SJC66 and TJC68 were 1.9 (SD 3.3) and 4.6 (SD 6.6). After 3 months, 16 (14%) patients reported a flare and 26 (23%) experienced a flare according to the DAS28 definition. DAS28 flare was associated with a significant increase in patient JCs and PROs, physician JCs, HAQ, MDGA and ESR (Table). The composite PROs, RADAI48, physician TJCs, ESR, MDGA and patient global best discriminated flare from non-flare (ES>1) (Figure). Flare according to the patient statement was associated with a significant increase in PDAS1, RAPID3 and 4, DAS28 and ESR and was discriminated best by the PDAS1, RAPID3 and 4, and physician SJC (ES>0.8).

Table. Median (interquartile range) change in patient joint counts, composite PROs and traditional parameters, for patients experiencing a flare or not according to two definitions.

	DAS28 worsening				Patient reported flare			
	Flare n=16		Non-flare n=99		Flare n=26		Non-flare n=89	
Variables	Median change (IQR)	p-value	Median change (IQR)	p-value	Median change (IQR)	p-value	Median change (IQR)	p-value
Patient SJC40	2 (0–7)	0.013	0 (−2–0)	0.006	0 (0–4)	0.116	0 (−2–0)	0.008
Patient TJC40	4 (0–12)	0.018	0 (−4–1)	0.003	1 (−2–4)	0.184	0 (−4–1)	0.008
RADAI TJC16	3 (0–4)	0.017	−0.5 (−2–1)	0.109	0 (−2–4)	0.548	0 (−2–1)	0.460
RADAI TJC48	6 (2–12)	0.003	0 (−3–1)	0.010	1 (−4–6)	0.290	0 (−3–1)	0.087
PDAS1	1.2 (0.8–2)	<0.001	−0.1 (−0.7–0.4)	0.005	0.7 (0.2–1.3)	0.004	−0.1 (−0.8–0.3)	0.005
PDAS2	0.6 (0.4–1.2)	0.004	−0.2 (−0.5–0.3)	0.303	0.4 (−0.2–1.1)	0.091	0 (−0.6–0.4)	0.459
RAPID3	1.7 (0.9–2.7)	<0.001	−0.1 (−0.9–0.5)	0.043	1.3 (−0.1–2.3)	0.002	−0.1 (−1.0–0.5)	0.026
RAPID4	1.4 (0.9–2.0)	<0.001	−0.1 (−0.7–0.4)	0.050	1.1 (−0.1–1.8)	0.004	−0.1 (−0.7–0.4)	0.050
MD SJC66	1 (0–2)	0.065	0 (−2–0)	<0.001	0 (0–1)	0.203	0 (−2–0)	<0.001
MD TJC68	4 (2–8)	0.001	−1 (−3–0)	<0.001	1 (−4–3)	0.834	0 (−2–1)	0.057
MDGA	0.1 (0–2)	0.031	0 (−1.5–0)	<0.001	0 (−1–1)	0.993	0 (−1.4–0)	<0.001
DAS28	1.5 (1.4–2.4)	<0.001	−0.2 (−1.1–0.2)	<0.001	0.6 (−0.1–1.4)	0.041	−0.2 (−1–0.3)	0.005
HAQ	0.1 (0–0.4)	0.005	0 (−0.1–0)	0.148	0 (−0.1–0.4)	0.299	0 (−0.1–0.1)	0.265
ESR	7 (3–10)	<0.001	−2 (−5–2)	0.037	4 (−2–6)	0.038	−2 (−5–2)	0.097
CRP	0.2 (0–3)	0.160	0 (−2–1)	0.279	0 (−2–2)	0.448	0 (−2–1)	0.454

Figure. Effect size (adjusted 95%CI) for patient joint counts, composite PROs and traditional parameters, according to two definitions of RA flare.



Conclusion: In ERA, a change in patient-reported JCs can identify worsening of disease activity and detect flares, with highest discriminative validity when used in composite indices. Patient derived composite indices incorporating patient JCs should be considered in developing a comprehensive definition of RA flare.

Reference: 1. Bartlett SJ, Ann Rheum Dis 2012;71(11):1855

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2870

Higher Disease Activity and Serum Levels Of Angiogenic Factors In Patients With Rheumatoid Arthritis In Clinical Remission With Synovitis On Ultrasound. Julio Ramirez[1], Virginia Ruiz-Esquide[2], Isaac Pomés[1], Raquel Celis[1], Jaume Pomés[1], Sonia Cabrera[1], M. Victoria Hernández[2], Oscar M Epis[3], Jose L. Pablos[4], Raimon Sanmarti[5] and Juan D. Cañete[1]. [1]Hospital Clínic, Barcelona, Spain, [2]Hospital Clinic, Barcelona, Spain, [3]Ospedale Niguarda Cà Granda, Milano, Italy, [4]Instituto de Investigación Hospital 12 de Octubre, Madrid, Spain, [5]Hospital Clínic of Barcelona, Barcelona, Spain.

Background/Purpose: To identify and characterize subclinical synovitis in patients with rheumatoid arthritis in clinical remission using power Doppler ultrasound and serum levels of angiogenic factors.

Methods: We selected patients with rheumatoid arthritis in clinical remission (defined as DAS28-ESR<2.6) tested by two independent rheumatologists. Clinical, epidemiological, demographic and serological data were analyzed. Ultrasonography of knees and hands (wrists, metacarpophalangeal [MCP], proximal interphalangeal [PIP], flexor and extensor tendons of the hand) was performed by a radiologist with an ultrasound scanner (Acuson Antares, Siemens AG, Erlangen, Germany) with a linear probe of 10.5 MHz. Synovial hypertrophy and power Doppler signal were scored (grades 0–3). Synovial hypertrophy >2 plus power Doppler signal was classified as active synovitis.

Serum levels of angiogenic factors were determined by Quantibody® Human Array (RayBiotech, Inc, Norcross, GA, USA).

Results: Fifty-five patients were included of whom 25 (45.4%) met criteria for active synovitis. The most-affected joints were the wrist and second MCP. Patients with active synovitis on ultrasound had significantly higher DAS28-CRP (p=0.020) and only 12% were taking oral glucocorticoids (< 5 mg/day) compared with 40% of patients without active synovitis. No other clinical differences were found (Table 1). Patients with active synovitis had significantly-higher serum levels of angiogenic factors: angiopoietin-2 (p=0.038), VEGF-D (p=0.018), PIGF (p=0.043), SDF-1 (p=0.035), MMP-2 (p=0.027) and bFGF (p=0.007) (Table 1).

Table 1. Clinical, demographic and biological data of the 55 patients, stratified according the presence or not of active synovitis as defined by ultrasound*.

	All n=55	HS + Doppler (active synovitis) n=25	No HS+Doppler (no active synovitis) n=30	p-value
Age (years)	52 (44–62)	51 (43–61)	55 (46–65)	0.275
Women, n (%)	42 (76)	17 (68)	25 (83)	0.155
Disease duration (months)	90.0 (56.2–150.3)	86.3 (57.1–166.9)	93.7 (50.8–148.9)	0.649
RF, n (%)	39 (71)	18 (72)	21 (70)	0.555
ACPA, n (%)	47 (86)	23 (92)	24 (80)	0.193
DAS283v-ESR	2.03 (1.67–2.44)	2.24 (1.88–2.57)	1.92 (1.55–2.21)	0.060
DAS283v-CRP	1.42 (1.37–1.59)	1.54 (1.38–1.71)	1.40 (1.17–1.49)	0.020
mHAQ	0.1 (0.0–0.4)	0.1 (0.0–0.3)	0.0 (0.0–0.4)	0.564
ESR (mm/1h)	9 (6–16)	10 (7–20)	9 (6–12)	0.493
CRP (mg/dL)	0.10 (0.03–0.35)	0.11 (0.03–0.50)	0.09 (0.04–0.27)	0.722
Glucocorticoids, n (%)	15 (27)	3 (12)	12 (40)	0.020
Biological Therapy, n (%)	23 (42)	9 (36)	14 (47)	0.301
DMARDs, n (%)	44 (80)	21(84)	23 (77)	0.233
ANG-2 (pg/mL)	726 (579–1027)	880 (659–1152)	702 (525–881)	0.038
VEGF-D (pg/mL)	32096 (17759–239749)	63479 (26346–600000)	27544 (9813–87872)	0.018
PlGF (pg/mL)	288 (147–994)	452 (180–1501)	237 (115–730)	0.043
SDF-1 (pg/mL)	280 (115–1648)	750 (157–3420)	165 (80–1127)	0.035
MMP-2 (pg/mL)	2738 (1909–4109)	3762 (2101–5779)	2403.5 (1870–3448)	0.027
bFGF (pg/mL)	314 (267–521)	383 (285–762)	295 (260–327)	0.007

*Data are expressed as median (IQR) or as percentage. HS: synovial hypertrophy; RF: rheumatoid factor; ACPA: anti-citrullinated protein/peptide antibodies; DAS28: disease activity score; mHAQ: modified Health Status Questionnaire; ESR: erythrocyte sedimentation rate; DMARD: disease modifying anti-rheumatic drugs. ANG-2: angiopoietin-2; VEFG: vascular endothelial growth factor; PIGF: Placental Growth Factor. SDF: Stromal-cell derived factor-1; MMP-2: matrix metalloproteinase-2; bFGF: basic fibroblast growth factor.

Conclusion: Around half of patients with RA in clinical remission presented active synovitis on ultrasound. These patients have greater disease activity and higher serum levels of angiogenic factors. These findings are clinically and physiopathologically consistent and may help identify active synovitis in RA patients in clinical remission.

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Validation Of The FLARE Self-Report Questionnaire For Assessing FLARE Out Of The Clinical Visit In Rheumatoid Arthritis. Jacques Morel[1], Jean-Marie Berthelot[2], Arnaud L. Constantin[3], Michel De Bandt[4], Philippe Gaudin[5], Olivier Vittecoq[6], Jean Francis Maillefert[7], Olivier Meyer[8], Thao Pham[9], Alain Saraux[10], Elisabeth Solau Gervais[11], Elisabeth Spitz[12], Daniel Wendling[13], Francis Guillemin[14] and Bruno Fautrel[15]. [1]Lapeyronie Hospital, Montpellier, France, [2]Nantes University Hospital, Nantes, France, [3]Purpan University Hospital, Toulouse, France, [4]Centre hospitalier Universitaire de Fort de France, Fort de France, Martinique, [5]CHU Hôpital Sud, Grenoble Teaching Hospital, Echirolles, France, [6]Department of Rheumatology, Rouen University Hospital & Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen Cedex, France, [7]Rheumatology, Dijon, France, [8]Bichat University Hospital, Paris, France, [9]Sainte Marguerite Hospital, Marseille, France, [10]CHU de la Cavale Blanche, Brest Cedex, France, [11]CHU de Poitiers, Poitiers, France, [12]APEMAC-EA4360, Metz, France, [13]University Hospital, Besancon, France, [14]CHU Nancy, Clinical Epidemiology and Evaluation, Université de Lorraine, Paris Descartes University, APEMAC, EA 4360, Nancy, France, [15]Paris 6 – Pierre et Marie Curie University; AP-HP, Rheumatology, Pitié-Salpêtrière Hospital, - GRC-UPMC 08 – EEMOIS, Paris, France.

Background/Purpose: Defining flare in rheumatoid arthritis (RA) raises a complex issue related to the difference in perception or concept of flare between patients or health professionals. Altogether, defining a worsening in RA should clearly not depend on physicians' perspectives only. The Strategy of Treatment in Patients with Rheumatoid arthritis (STPR) group developed a self-administered questionnaire (FLARE) to detect a past or present RA flare to be used to identify patients whose appointment should be anticipated or treatment revised (Berthelot et al, ARD 2011). Purpose: To validate the measurement properties of the FLARE self-administered questionnaire.

Methods: the validation study was conducted in a prospective trial of RA patients with 3 main objectives to determine: 1) the truth of the tool.The internal validity was measured with a principal component factor analysis, the external validity evaluated by Spearman correlation coefficients with the DAS28, rheumatoid arthritis impact of disease [RAID], routine assessment of patient index data [RAPID], and HAQ scores. The measurement invariance was assessed with Rasch analysis; 2) the reliability by intra-class correlation coefficients (ICC) and Bland et Altmann);and 3) the feasibility of using this score in daily practice. To be included patients should be at least 8 years old, have RA according to ACR criteria 1987 and/or 2012, evolving for more than 6 months. RA treatments (DMARDs, symptomatic treatments including stéroids) should be stable for at least 2 months. Patients were examined at baseline and 3 months and questionnaires were filled in 2 days before and at M3 clinical visit.

Results: 207 patients were recruited from 13 centres: 78.7% women, 57.7 years old, 84.4% RF+, 78.7% ACPA+, DAS28 was 2.9, CRP was 5.7 mg/l and 81.2% had erosive disease. At baseline, mean FLARE score (SD) – arithmetic mean of the 13 subscales – were 2.1 (+/−2.1) and 2.4 (+/−2.3) in groups 2 and 3 respectively.

Flare score internal validity was fair, with scores left-skewed. A substantial floor effect (1.7%), but no ceiling effect (0.7%), were observed.

The principal component factor analysis evidenced 2 dimensions of the FLARE questionnaire , one dealing with physical items and the other with emotional items. Partial credit model analysis further confirmed that one item on steroid treatment was inadequate.

Flare scores were correlated with DAS28 (0.43; p<0.0001) and (0.40; p<0.0001), RAID (0.69; p<0.0001) and (0.69; p<0.0001), RAPID3 (0.70; p<0.0001) and (0.70; p<0.0001, HAQ (0.47; p<0.0001) and (0.39; p<0.0001) in physical and emotional dimension respectively.

FLARE questionnaire was reproducible in both physical (ICC=0.91 [95%CI 0.88–0.94[) and emotional (ICC=0.93 [95%CI 0.90–0.95]) dimensions.

Conclusion: FLARE self-administered questionnaire is highly reproducible. Internal validity is fair with a good correlation with other questionnaires assessing disease activity, functional status and quality of life. This self-administered questionnaire may represent a tool to detect flare between visits to the physician.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis - Pathogenetic Pathways
Wednesday, October 30, 2013, 11:00 AM–12:30 PM

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Long Noncoding RNA Nron Regulates The Cytoplasmic-Nuclear Shuttling and Activity Of NFAT5 In Rheumatoid Arthritis Synovial Fibroblast. Kunihiko Umekita[1], Michelle Trenkmann[1], Christoph Kolling[2], Beat A. Michel[3], Renate E. Gay[1], Steffen Gay[1] and Mojca Frank Bertoncelj[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Schultess Clinic, Zurich, Switzerland, [3]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland.

Background/Purpose: Long noncoding RNAs (lncRNAs) are critical regulators of gene expression and of major biological processes, such as cell migration, proliferation and invasion. The lncRNA NRON, Noncoding Repressor of Nuclear factor of activated T cells (NFAT), was recently shown to repress the cytoplasmic-nuclear translocation and function of NFAT1–4 transcription factors. It is unknown, however, whether NRON can regulate the function of NFAT5, which was reported to influence the migration and proliferation of rheumatoid arthritis synovial fibroblasts (RASF).

Here we investigated the expression and regulation of NRON in RASF and analyzed its role in regulating the function of NFAT5.

Methods: The expression of NFAT5 protein in RA (n=3) and osteoarthritis (OA) (n=3) synovial tissues was analyzed by immunohistochemistry. RASF were transfected with siRNA targeting NRON (n=4) or NFAT5 (n=4) using Lipofectamine 2000. Gene expression in SF was measured by quantitative real-time PCR with normalization to GAPDH or β2-microglobulin. Successful silencing of NFAT5 in SF was confirmed by Western blotting using α-tubulin for normalization. The secretion of IL-6 was measured by ELISA. Immunofluorescence microscopy was used to investigate the cytoplasmic- nuclear trafficking of NFAT5 in RASF transfected with siNRON or stimulated with TNFα (10ng/ml). The formation of stress fibers in SF after silencing of NRON was assessed by phalloidin staining. Migration of SF was analyzed by scratch assay.

Results: The expression of NFAT5 protein was increased in RA compared to OA synovial tissues. The constitutive levels of NFAT5 mRNA (mean dCt±SD: 5.1±0.5 vs 5.8±0.7, p= 0.01) and NRON (mean dCt±SD: 11.7±0.7 vs 13.0±0.5, p= 0.01) were significantly up regulated in RASF (n=15) compared with OASF (n=11). The expression of NRON significantly correlated with the levels of NFAT5 mRNA in RASF (R=0.71, p=0.003). Furthermore, silencing of NFAT5 in RASF resulted in a down regulation of NRON (x-fold±SD: 0.57±0.3, p=0.07, n=4), indicating that NFAT5 regulates the expression of NRON in RASF. Stimulation of RASF with TNFα (2h) also significantly decreased the expression of NRON (by 26.9±25%, p= 0.02, n=7). Importantly, down regulation of NRON in RASF after silencing or TNFα stimulation was accompanied by the translocation of NFAT5 protein from the cytoplasm to the nucleus and by up regulation of NFAT5 target genes, including IL-6 (x-fold±SD: 3.0±2.2, p=0.03, n=4) and MMP-13 (x-fold±SD: 4.7±2.0, p= 0.03) mRNAs. The levels of IL-6 protein also significantly increased by silencing of NRON compared to control (mean±S.D: 1676±479 vs 2433±504 pg/mL, p= 0.007, n=5). Furthermore, silencing of NFAT5 resulted in a significant down regulation of MMP-13 mRNA (x-fold±SD: 0.58±0.2, p=0.02, n=4). The formation of stress fibers (n=3) and the migratory abilities of RASF (n=4) were increased after silencing of NRON.

Conclusion: Our data indicate that the lncRNA NRON regulates gene expression profiles, stress fiber formation and migration of RASF in a NFAT5-dependent manner and can therefore significantly contribute to the pathogenic characteristics of activated synovial fibroblasts in RA.

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The Ion Channel TRPV2 Is New Suppressor of Arthritis Severity and Joint Damage. Teresina Laragione[1], Max Brenner[1], Christine Beeton[2] and Percio Gulko[1]. [1]Hosftra North Shore-LIJ School of Medicine, Manhasset, NY, [2]Baylor College of Medicine, Houston, TX.

Background/Purpose: Rheumatoid arthritis (RA) is a common and chronic disease associated with increased risk of developing disability. Disease remission is still rarely achieved and better treatments are needed. The fibroblast-like synoviocyte (FLS) has a central role in the formation of synovial hyperplasia and in articular damage. The FLS *in vitro* invasive properties through Matrigel correlate with disease severity and joint damage in rodents and patients with RA, yet, little is known about the genes regulating RA severity, FLS invasion and joint damage. We have identified significantly increased levels of the non-selective cation channel Trpv2 (transient receptor potential vanilloid subfamily, type 2 channel) in highly invasive FLS obtained from arthritis-susceptible DA rats. In this study we characterize the role of this ion channel in arthritis.

Methods: Trpv2 was knocked-down using siRNA, or was stimulated with the specific agonist O-1821, and its role in FLS invasion determined in Matrigel invasion assays over 24 hours. For the *in vivo* studies, C57BL/6 mice received KRN serum intra-peritoneal to induce arthritis. After the onset of arthritis animals were assigned to receive either O-1821 or control vehicle BID.

Results: Knock-down of Trpv2 with siRNA unexpectedly significantly increased FLS invasion by nearly 4-fold suggesting that this gene is a suppressor of invasion. We next used the Trpv2-specific agonist O-1821 to treat FLS from DA rats and RA patients. O-1821 significantly reduced invasion by as much as 90% (p<0.01). O-1821 was then used to treat KRN serum-induced arthritis in C57BL/6 mice and it significantly reduced arthritis severity scores and preserved a nearly normal joint histology.

Conclusion: We have identified a new regulator of arthritis severity and joint damage *in vivo*, and show that at least part of Trpv2 activity involves suppression of the invasive properties of FLS both in rodents and patients with RA. These new discoveries should provide the basis for the development of new drugs targeting Trpv2 to better preserve joint architecture and improve outcome in RA.

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Biological Roles of C5orf30 In Rheumatoid Arthritis Synovial Fibroblasts. Munitta Muthana[1], Holly Davies[1], Sachin Khetan[2], Gbadebo Adeleke Adeleke[2], Sarah Hawtree[1] and Anthony G. Wilson[1]. [1]University of Sheffield, Sheffield, United Kingdom, [2]Dr, Sheffield, United Kingdom.

Background/Purpose: A recent genome wide association study identified the variant rs26232 in the first intron of an uncharacterized gene *C5orf30* as a rheumatoid arthritis susceptibility variant. In addition, it has been associated with severity of radiological joint damage suggesting a role in tissue breakdown[1]. To date there is no function assigned for *C5orf30* and neither the gene or protein show homology to any known functional sequences. However, *C5orf30* is highly conserved in chimpanzee, dog, cow, mouse, chicken, and zebrafish (orthologs). The aim of this study is to determine the biological role of *C5orf30* in rheumatoid arthritis synovial fibroblast.

Methods: Immunohistochemistry on synovial samples was used to determine expression of *C5orf30* including co-localisation using antibodies to macrophages (CD68), fibroblasts (5B5), T (CD3) & B (CD19) cells. Real time PCR and western blotting were used to examine *C5orf30* transcript and protein levels in fibroblast-like synovial cells (FLS stimulated with TNF & hypoxia). To investigate gene function siRNA was used to knockdown either *C5orf30* or a non-targeting control (NTC) in synovial FLS *in vitro*.

Results: Confocal microscopy revealed *C5orf30* to be strongly expressed in both the nuclear and cytoplasmic compartment of synovial lining cells including macrophages and fibroblasts, but not T & B cells. *C5orf30* was undetectable in arthroscopy sections obtained from osteoarthritis or control synovium. *C5orf30* was expressed in FLS and was found to be up-regulated by hypoxia (8-fold) and down-regulated by TNF (0.5-fold). We found that $C5orf30^{KD}$ compared to the NTC increased the number of invading FLS using the Matrigel invasion assay ($p=0.01$) and increased FLS migration using a scratch assay ($p=0.02$) ($n=6$). Preliminary gene profiling studies suggest that multiple gene sets involved in cell proliferation, intracellular signal transduction, angiogenesis, and immune and inflammatory pathways were significantly modified following $C5orf30^{KD}$.

Conclusion: *C5orf30* knockdown increased FLS migration and invasion into matrigel suggesting *C5orf30* is negatively regulating cellular invasion. Together this identifies a potentially novel pathway mediating tissue damage in RA. We are currently performing proteomic and gene profiling (after *C5orf30* KD) studies in order to work out the biology of this important marker in the pathogenesis and severity of RA.

[1]Teare, M.D., et al (*in press*). Allele dose association of the *C5orf30* rs26232 variant with joint damage in rheumatoid arthritis, Arthritis and Rheumatism.

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Metabolic Profiles of Synovial Fibroblasts. Sabrina Kapoor[1], Andrew Filer[2], Christopher D. Buckley[3], Karim Raza[1] and Stephen Young[1]. [1]University of Birmingham, Birmingham, United Kingdom, [2]Rheumatology Department, Birmingham, United Kingdom, [3]School of Immunity and Infection, MRC Center for Immune Regulation, Birmingham, United Kingdom.

Background/Purpose: Synovial fibroblasts play a key role in the persistence of inflammation and joint destruction in rheumatoid arthritis (RA). Cell function and proliferation are highly dependent on availability of nutrients and their metabolism. In the joint, fibroblasts have limited access to nutrients within a poorly vascularised hypoxic tissue and yet expansion of fibroblast numbers is a feature of the RA joint. This suggests fibroblasts may adapt their metabolism to this environment and this altered function may be involved in preventing the resolution of chronic inflammation.

We used NMR spectroscopy to assess differences in metabolite fingerprints in fibroblasts from patients with established RA, early arthritis and healthy controls, and determine how cytokine production by fibroblasts relates to their metabolic profile.

Methods: Fibroblasts were cultured from synovial biopsies from 6 newly presenting, disease-modifying drug naïve patients with established RA (>12 week symptom duration), 6 healthy controls (HC), and patients with arthritis of ≤12 weeks duration whose disease resolved ($n=6$) or evolved into RA ($n=6$) at follow-up. Cell metabolites were extracted for analysis using 1D ^{1}H-NMR spectroscopy and secreted IL6 measured by ELISA. NMR spectra were analysed using partial least squares discriminant analysis (PLSDA) and partial least squares regression (PLS-R) to correlate the metabolite profiles with 1) IL6 production by fibroblasts and 2) the level of CRP, at the time of synovial biopsy, in the serum of patients whose fibroblasts were being assessed.

Results: We were able to distinguish the metabolic profiles of fibroblasts from HC and early RA (sensitivity 67%, specificity 67%), HC and established RA (sensitivity 67%, specificity 50%) and resolving arthritis and early RA (sensitivity 67%, specificity 83%). The IL6 production of fibroblasts from patients with inflammatory arthritis was clearly distinct from that of healthy controls. There was a strong correlation between the metabolic profile of synovial fibroblasts and their IL6 production ($p<0.001$) with several metabolites (in particular citrate, carnosine, pyroglutamate, alanine and lactate) contributing. In patients with inflammatory arthritis the fibroblast metabolic profile correlated strongly ($p<0.001$) with patient serum CRP at the time of synovial biopsy, with several metabolites (in particular cholesterol, fatty acids, leucine, citrate and pyroglutamate) contributing.

Conclusion: There was a significant association between the metabolomic fingerprint of synovial fibroblasts and their IL 6 production, suggesting that IL6 production drives or is driven by significant changes in metabolism. There was also a significant association between CRP levels in the patients' serum and the metabolic profile of their synovial fibroblasts suggesting that fibroblasts retain their metabolic fingerprint during culture ex vivo and that this is strongly related to systemic measures of inflammation in patients with clinical synovitis.

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Key Rheumatoid Arthritis-Associated Pathogenic Pathways Revealed By Integrative Analysis Of Rheumatoid Arthritis Omics Datasets. John Whitaker[1], Wei Wang[2] and Gary S. Firestein[1]. [1]UCSD School of Medicine, La Jolla, CA, [2]UCSD, La Jolla, CA.

Background/Purpose: Genome-wide analysis of RA has independently evaluated DNA sequence variation, differential RNA expression, and differential DNA methylation. Each approach alone implicates promising pathways and networks in the pathogenesis of disease. Prioritizing high value pathways from a large set of candidates can be difficult. To address this limitation, we performed an integrative analysis of genome wide association study (GWAS) as well as DNA methylation and RNA transcriptomics for cultured fibroblast-like synoviocytes (FLS). We then identified genes that found in at least two of these sets and evaluated whether they are enriched in the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways.

Methods: Data were from three types of genome-wide RA assays: (i) for sequence variation we used the NCBI GWAS database and extracted all gene that mapped to SNPs that had been implicated in RA susceptibility (www.genome.gov/gwasstudies/); (ii) for gene expression we used public microarray datasets of RA, OA, and normal (NL) FLS lines (Gene Expression Omnibus Database (GSE 29746)); (iii) for DNA methylation we used a set of differentially methylated genes that we previously identified in 11 RA, 11 OA, and 6 NL FLS (Genome Medicine 5:40, 2013). We then overlapped the gene sets and identified those with two or three forms of evidence, termed the multi-evidence genes (MEGs). The significance of MEGs in KEGG human pathways was determined and resulting p-values represented the fraction of randomly selected background gene sets that were at least as enriched in genes found in the tested pathway as the DMG set. A q-value was calculated to correct for multiple comparisons and a threshold of 0.05 determined significance.

Results: 357 MEGs in RA FLS were identified for KEGG analysis. 14 out of 271 KEGG pathways were significantly enriched with MEGs. Perhaps most interesting, evaluation of MEGs identified a 3.88-fold enriched in the KEGG "rheumatoid arthritis" pathway (q = 1.4e-02) with 7 out 89 genes: ANGPT1, CSF2, CTLA4, HLA-DQA1, HLA-DQA2, HLA-DRA and HLA-DRB1. Involvement of this pathway strongly suggests that the MEGs are highly relevant to RA. At least four additional immunological pathways relevant to RA were also significantly enriched in the MEGs set. For example, the KEGG 'Cell adhesion molecules' pathway is 4.59-fold enriched (q = 2.00E-04) with 12 out of 129 genes in the MEGs set. The KEGG 'Cytokine-cytokine receptor interaction' pathway is 2.98-fold enriched (q =1.63e-03) with 15 out of 248 genes labeled in the MEGs set. The KEGG 'Antigen processing and presentation' pathway is 4.42-fold enriched (q =1.53e-02) with 6 out of 67 genes labeled as DMGs in the MEGs set. The KEGG 'Jak-STAT signaling pathway' pathway is 2.84-fold enriched (q =4.10e-02) with 8 out of 139 genes labeled in the MEGs set.

Conclusion: Pathway analysis demonstrates non-random identification of RA related genes through the integrative analysis of multiple genome-wide datasets. The identified genes and pathways, such as those involved with cytokines and Jak-STAT, are likely dysregulated in the disease and reflect the pathogenesis of disease. Therefore, genes identified in the pathways identified through integrative analysis could be novel targets for treatment of RA.

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Potential Of Integrating Human Genetics and Electronic Medical Records For Drug Discovery: The Example Of *TYK2* and Rheumatoid Arthritis. Dorothee Diogo[1], Katherine P. Liao[2], Robert S. Fulton[3], Robert R. Graham[4], Jing Cui[2], Jeffrey D. Greenberg[5], Stephen Eyre[6], John Bowes[7], Annette T. Lee[8], Dimitrios A. Pappas[9], Joel M. Kremer[10], Anne Barton[6], Marieke J.H. Coenen[11], Xavier Mariette[12], Corrine Richard-Miceli[13], Helena Canhão[14], João E. Fonseca[15], Niek de Vries[16], Fina Kurreeman[17], Ted R. Mikuls[18], Yukinori Okada[1], Isaac Kohane[19], Joshua C. Denny[20], Jane Worthington[6], Soumya Raychaudhuri[1], Timothy W. Behrens[21], Michael F. Seldin[22], Peter K. Gregersen[8], Elaine R. Mardis[3] and Robert M. Plenge[1]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]The Genome Institute, Washington University School of Medicine, Saint Louis, MO, [4]Genentech, Inc., South San Francisco, CA, [5]NYU Hospital for Joint Diseases, New York, NY, [6]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [7]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [8]Feinstein Institute for Medical Research, Manhasset, NY, [9]Columbia University, College of Physicians and Surgeons, New York, NY, [10]Center for Rheumatology, Albany Medical College, Albany, NY, [11]Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [12]Bicêtre University Hospital, Le Kremlin Bicetre, France, [13]Hôpital Bicêtre, Université Paris-sud, Paris, France, [14]Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa and Rheumatology Department, Centro Hospitalar de Lisboa Norte, EPE, Hospital de Santa Maria, Lisboa, Portugal, [15]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal, [16]Division of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Center / University of Amsterdam, Amsterdam, Netherlands, [17]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [18]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [19]on behalf of i2b2; Brigham and Women's Hospital, Boston, MA, [20]Department of Biomedical Informatics, Vanderbilt University School of Medicine, Nashville, TN, [21]Genentech, Inc, South San Francisco, CA, [22]Department of Biochemistry and Molecular Medicine, University of California, Davis, CA.

Background/Purpose: Human genetics has the potential to identify promising drug targets for complex traits such as rheumatoid arthritis (RA). Genes with a series of disease-associated functional alleles mimic the effect of pharmacological modulation, thereby allowing estimates of efficacy and toxicity before clinical trials in humans.

Methods: To search for genes with alleles that protect from RA susceptibility, we sequenced the protein-coding exons of 845 genes in 1,118 RA cases and 1,118 matched controls, and investigated excess of potentially damaging variants in controls compared to RA patients by gene-based association tests. We replicated findings at one gene, *TYK2*, by direct genotyping in two large datasets (9,372 RA cases and 18,868 controls). To investigate phenotypes that serve as proxies for potential adverse drug events, we performed a phenome-wide association study (PheWAS) with RA-associated *TYK2* variants and clinical data from electronic medical records (EMR).

Results: We demonstrate that multiple protein-coding variants in *tyrosine kinase 2* (*TYK2*), including variants reported to be loss-of function (LOF), independently protect from RA risk ($P=0.0018$ in sequencing, $P=1.6\times10^{-27}$ in replication genotyping). Using EMR clinical data from 3,102 individuals, we observe an enrichment of associations with *TYK2* LOF alleles for diagnoses related to infections.

Conclusion: Our findings identify a series of LOF alleles in *TYK2* that protect against RA and are associated with increased risk of clinical diagnoses that may be considered adverse drug events, suggesting that drugs that inhibit TYK2 may be an effective treatment in RA with predictable side effects.

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The Importance Of Germinal Center-Like Structures In Primary Sjögren's Syndrome Salivary Glands Beyond Lymphoma Risk. Elke Theander[1], Thomas Mandl[2], Rolf Liedholm[3], Roland Jonsson[4], Malin V. Jonsson[4] and Gunnar Warfvinge[3]. [1]Lund University, Malmö, Sweden, [2]Skåne University Hospital Malmo, Lund University, Sweden, Malmö, Sweden, [3]Skåne University Hospital Malmö, Lund University, Malmö, Sweden, [4]University of Bergen, Bergen, Norway.

Background/Purpose: The association between germinal center (GC)-like structures and lymphoma in primary Sjögren's syndrome (pSS) has been demonstrated recently (1). Here we present a comprehensive analysis of associations between these GC-like structures in minor salivary glands and other disease characteristics.

Methods: One-hundred-and-sixty biopsies from pSS patients fulfilling the 2002 AECG criteria were evaluated by re-examining the original diagnostic minor salivary gland biopsies for the presence of ectopic lymphoid structures, defined as a densely packed dark zone and a less densely packed light zone in association with focal sialadenitis in otherwise normal glands. Demographic and disease characteristics were extracted from the Malmö pSS database. T-test and χ^2 statistics were applied as appropriate.

Results: Thirty-eight (23.8%) of 160 biopsies were GC-positive, with similar frequency in both genders. Age at diagnosis was slightly lower in GC-positive patients (48.3(12.9) vs 53.8(12.8) yrs respectively, ns. The frequency of anti-SSA/SSB antibodies was significantly higher in GC-positives (79% vs 61%, $p=0.045$), with a trend towards higher prevalence of RF. ANA frequency was similar. During follow-up systemic manifestations were reported cumulatively in 71% of GC-positive and 49% of GC-negative patients ($p=0.019$). The presence of additional autoimmune phenomena (presence of either autoimmune diseases such as thyroiditis, celiac disease, primary biliary cirrhosis, etc, or additional autoantibodies such as centromere, anti-DNA, anti-cardiolipin, anti-thyroid, etc, was overrepresented in GC-positives (50% vs 27%, $p=0.011$). As expected, GC-formation was associated with lymphoma development (12% vs <1%, $p=0.011$). There were no significant differences between GC-positive and GC-negative patients with regard to complement levels, IgG levels, or ESR.

Stimulated sialometry was significantly lower in patients with GC-like structures (2.40 (2.33) vs 3.39 (3.29) ml/5 min, $p=0.013$). Ultrasonography of major salivary glands demonstrated more often pSS typical hypoechoic lesions in those with GC-like structures (67% vs 35%, $p=0.012$). Other exocrine function tests such as unstimulated whole sialometry, Schirmer test and van Bijsterveld score resulted in trends towards more severe disease in GC-positives. No difference was demonstrated regarding subjective dryness.

Conclusion: Beyond being a strong predictor of lymphoma development, GC-like structures in minor salivary glands predict systemic disease manifestations and worse exocrine performance as well as higher grade of morphological destruction assessed by ultrasonography. The simultaneous presence of additional autoimmune phenomena may be a marker of general GC-formation not restricted to the salivary glands and thus characterize a separate pSS phenotype with potentially severe and complicated disease.

1. Theander E et al. Ann Rheum Dis 2011;70:1363–8.

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Prognostic Value Of Minor Salivary Gland Assessments In Primary Sjögren's Syndrome. Anna Risselada, A.A. Kruize, J.A.G. van Roon, F.P.J.G. Lafeber and J.W.J. Bijlsma. University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: Salivary gland assessment is important for diagnosing primary Sjögren's syndrome (pSS), as the lymphocytic focus score (LFS) is part of pSS classification criteria. Quantitative immunohistology

(QIH) is another technique used for assessing pSS in which the percentage of immunoglobulin-specific plasma cells is measured, with IgA <70% and/or IgM >10% as positive criteria. Our objective was to investigate the prognostic value of minor salivary gland assessment (LFS and QIH) for disease severity of pSS.

Methods: Medical charts of all patients with pSS according to the 2002 classification criteria who attended our outpatient clinic for at least one year from 1998 to July 2011 were analyzed. In total, 174 patients had documented minor salivary gland histology and were included for this analysis. Histology results (LFS and percentages of IgA, IgM and IgG plasma cells) were compared with disease outcomes as non-Hodgkin lymphoma (NHL) and clinical scores: cumulative EULAR Sjögren's Syndrome disease activity index (ESSDAI) and the number of extraglandular manifestations (EGM) during disease course.

Results: Mean age at pSS diagnosis was 47 ± 14 years and median follow-up after biopsy was 105 months (range 10 – 408). LFS ≥1 were seen in 99%, <70% IgA-positive plasma cells in 90%, and >10% IgM-positive plasma cells in 71% of patients, respectively. The number of foci correlated to a decrease in the percentage of IgA-positive plasma cells (R=0.315, p=0.0001), but not to the percentage of IgM- or IgG-positive plasma cells.

NHL developed in 16 patients (9%). The mean LFS was significantly higher in patients with NHL (3.0 ± 0.9 versus 2.3 ± 1.1; p=0.021). The threshold of ≥3 foci had a positive predictive value of 16% for development of lymphoma, and a negative predictive value of 98% (OR 7.9; p=0,008). QIH results could not predict lymphoma development.

Only LFS ≥3 contributed significantly and independently to NHL development in a hierarchical multiple regression model, correcting for presence of anti-SSA/SSB antibodies (beta 0.244; p=0.017). Cumulative ESSDAI and EGM were significantly correlated to LFS, a decreased percentage of IgA-positive and an increased percentage of IgM-positive plasma cells (R range 0.166–0.284; p≤0.04), but not to the percentage of IgG-positive plasma cells.

Conclusion: Routinely performed minor salivary gland assessments have important prognostic value. The number of lymphocyte foci can be used to identify patients with increased lymphoma risk.

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Impact Of Different End Points On The Patient Cohort Size Needed To Demonstrate The Efficacy Of a Therapeutic Intervention In Pss. A Post Hoc Analysis Of The Tears Study (Tolerance and efficacy of Rituximab in primary Sjogren Syndrome study). Valerie devauchelle-Pensec[1], Sandrine jousse-Joulin[2], Xavier Mariette[3], Jean-Marie Berthelot[4], Aleth Perdriger[5], Eric Hachulla[6], Xavier Puechal[7], Véronique le Guern[8], Jean Sibilia[9], Jacques-Eric Gottenberg[9], Laurent Chiche Sr.[10], Vincent Goeb[11], Gilles Hayem[12], Jacques Morel[13], Charles Zarnitsky[14], Jean Jacques Dubost[15], Jacques-Olivier Pers[16], Divi Cornec[16], Raphaèle Seror[17], Emmanuel Nowak[18] and Alain Saraux[19]. [1]Brest Occidentale university, Brest, France, [2]CHU de la Cavale Blanche, Brest, France, [3]Bicêtre University Hospital, Le Kremlin Bicetre, France, [4]Nantes University Hospital, Nantes, France, [5]Hôpital Sud, Rennes, France, [6]Internal Medicine, Lille CEDEX, France, [7]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, Paris, France, [8]Cochin Hospital, Paris, France, [9]Strasbourg University Hospital, Strasbourg, France, [10]Internal Medicine, CHU Marseille, Marseille, France, [11]Amiens University Hospital, Amiens, France, [12]Bichat Hospital, Paris, France, [13]Lapeyronie Hospital, Montpellier, France, [14]Le Havre General Hospital, Le Havre, France, [15]CHU G.-Montpied, Clermont-Ferrand, France, [16]Brest Occidentale University, Brest, France, [17]Bicetre university hospital, LE Kremlin-Bicetre, France, [18]CHU Brest, Brest, France, [19]Université Brest Occidentale, Brest, France.

Background/Purpose: To calculate the sample sizes needed in future randomized controlled trials (RCTs) testing a therapeutic intervention in pSS, methodologists usually rely on data obtained from previous studies. To evaluate the reverse influence of each usual criteria on the number of patients needed to demonstrate the efficacy of rituximab in pSS, we have done a post hoc analysis on the multicenter, randomized, double-blind, placebo-controlled trial TEARS.

Methods: 122 Patients were assigned to receive either RTX infusions (1g) or placebo (P) at weeks 0 and 2. All patients fulfilled the new American-European Consensus Group criteria for pSS, had an active disease as assessed by mean values of the 2 highest visual analog scales (VAS) ≥50 evaluating dryness, pain, fatigue and global, and had either a recent and a biologically active pSS or at least one extra-glandular manifestation. Results concerning the primary end point (improvement of at least a 30 mm on 2 of 4 VAS) and secondary end points have shown a statistically improvement of the disease on global VAS score (continuous data) but not on the primary criteria and discrete variables, excepting VAS sicca). We also evaluated in a single centre (Brest, France) the echostructural changes (parotid and submandibular) using a semi-quantitative scoring (0 to 4). Here, we report the impact of various end points on the sample size calculated using EpiInfo. Analysis was made only when the proportion of patient improved in the RTX group was higher to the one obtained in the placebo group.

Results: The table shows the proportion of patients improved depending on the chosen cut-off of four VAS evaluating dryness, pain, fatigue and global disease or ultrasound and the number of patients needed to demonstrate a significant difference considering that the same proportions should be observed in a future study. At week 24, the more important clinical differences between the P group and the RTX group were observed with sicca VAS; the cut-off chosen between 20 or 30 mm gave quite similar results. ESSDAI improvement 'was observed in 9/54 (17%) in the P group vs 12/61 (20%) in the R group. Ultrasonographic changes seemed to be the most sensitive end point in terms of sample size needed to demonstrate an effect of RTX. Nevertheless, the US changes were not associated with the mean VAS improvement registered between W0 and W24 and the number of patient evaluated was low.

VAS improvement	≥10 mm P vs R; sample needed	≥20 mm P vs R; sample needed	≥30 mm P vs R; sample needed
Disease	18/53 (34%) vs 31/60 (52%) N: 258	13/53 (24%) vs 21/60 (35%) N: 574	12/53 (23%) vs 9/60 (15%)
Pain	21/54 (39%) vs 26/60 (43%) N: 4844	18/54 (33%) vs 15/60 (25%)	13/53 (24%) vs 8/60 (13%)
Fatigue	15/54 (28%) vs 29/60 (48%) N: 204	9/54 (17%) vs 17/60 (28%) N: 486	5/53 (9%) vs 11/60 (18%) N: 494
Sicca	15/53 (28%) vs 32/60 (53%) N: 136	11/53 (21%) vs 24/60 (40%) N: 204	6/53 (11%) vs 16/60 (27%) N: 212
Number of VAS improved ≥30 mm	**≥1**	**≥2**	**≥3**
	26/59 (44%) vs 30/63 (48%) N: 4972	16/59 (27%) vs 18/63 (29%) N: 16024	13/59 (22%) vs 12/63 (19%)
Improvement of the ultrasonographic grade	**≥1 grade**		
	1/14 (7%) vs 7/14 (50%) N: 42		

Conclusion: In future RCTs in pSS, ultrasound salivary gland changes could represent the most sensitive end point for pSS study, followed by sicca and fatigue. Nevertheless, ultrasound improvement was not associated with any clinical improvement. Change in a single VAS can be used but assesses only one domain of the patients's complaints. Change in ESSDAI could be the most logical end-point reflecting all the domains of activity of the disease but its change appeared low in the TEARS study.

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Ultrasonographic Salivary Glands Response To Rituximab In Primary Sjögren Syndrome Patients In the Tolerance and Efficacy Of Rituximab In Primary Sjogren Syndrome Study Is Not Associated With The Anatomopathology Changes. Sandrine Jousse-Joulin[1], Valerie Devauchelle-Pensec[2], Divi Cornec[3], Simon Gestin[4], Luc Bressollette[3], Thierry Marhadour[5], Jacques-Olivier Pers[3], Emmanuel Nowak[4] and Alain Saraux[6]. [1]Brest university medical school, EA 2216, UBO and CHU de la Cavale Blanche,, Brest, France, [2]Brest Occidentale university, Brest, France, [3]Brest Occidentale University, Brest, France, [4]CHU Brest, Brest, France, [5]CHU de la Cavale Blanche, Brest, France, [6]CHU Brest et Université Bretagne Occidentale, Brest, France.

Background/Purpose: We conducted a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of Rituximab (RTX) in active pSS patients in France (TEARS study) and we evaluated, in a single centre (Brest, France), the echostructural and vascularisation changes in this population.

Methods: The TEARS study included pSS patients with scores above 50 mm on at least two of four visual analog scales (VASs) evaluating dryness, pain, fatigue, and global disease. They were randomly assigned (1:1) to RTX (1 g at weeks 0 and 2) or placebo (PBO). Patient had recent-onset (<10 years) biologically active pSS and/or systemic pSS. 28 pSS patients had ultrasonographic examination and a salivary gland biopsy before the first infusion (placebo or RTX) and at 24 weeks follow up. Both parotid and submandibular glands were assessed. The echostructure of each gland was scored using a semi quantitative scoring (0 to 4) (figure 1). We also evaluated the size of each glands and the vascularisation using the resistive index of the transverse facial artery of the parotid glands before and after stimulation with lemon juice. Concerning the echostructural scoring of each gland, we considered an improvement if the score of the glands was improved by one point or more and the comparison between the RTX and placebo group were obtained using the Fisher's exact test. Difference of size (mm) and resistive index before and after treatment (RTX or PBO) were evaluated using the non parametric Wilcoxon test.

Results: Parotid echostructural scoring was improved in 50% of pSS patients in the RTX group versus 7% in the placebo group (p=0.03). Table 1 shows the changes of grade before and after treatment in both RTX and PBO groups. The US submandibular scoring was also improved in 35% of pSS patients in the RTX group compared to 16% in the placebo but the difference was not statistically significant (p= 0.16). There were no changes concerning the size of each gland in RTX or placebo groups (figure 2). Regarding the modifications between week 0 and week 24 of lemon stimulation response, measured by resistive index variation before and after stimulation, the two groups were not different. 35 had a Chisholm score evaluation before and after treatment, 16 a focus score evaluation and 28 an ultrasound evaluation. At least one parotid gland had an improvement in 2/14 in the P group versus 7/14 in the R group. At least one submandibular gland had an improvement in 1/14 in the PBO group versus 7/14 in the R group (p: 0.03). Focus score was lower after treatment in 3/10 in both PBO and R groups. Similarly, 3/18 had an improvement of their Chisholm score in the P group versus 2/17 in the R group (NS). The concordance between both submandibular and parotid glands US score and focus score was low (kappa<0.1).

Conclusion: In our pSS population treated by RTX or PBO, ultrasound evaluation showed a more important improvement of the echostructure of the salivary glands in treated patients than in the placebo group. In contrast, RTX did not modify neither sizes of the salivary glands nor vascularisation inside the glands. Ultrasonographic improvement was not associated to anatomopathologic changes of the minor salivary gland labial biopsy.

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2882

B-Cell Depletion Modulates T-Helper Cell Balance In Patients With Primary Sjögren's Syndrome. WH Abdulahad[1], FGM Kroese[1], Gwenny Verstappen[2], MG Huitema[1], PM Meiners[1], A Vissink[1] and H Bootsma[1]. [1]University Medical Center Groningen, Groningen, Netherlands, [2]University of Groningen and University Medical Center Groningen, Groningen, Netherlands.

Background/Purpose: B-cell depletion therapy with a chimeric anti-human CD20 antibody (rituximab; RTX) is an effective treatment modality for patients with primary Sjögren's syndrome (pSS). However, the mechanisms through which RTX exerts its effects on pSS have not been fully elucidated. Alterations in T-helper (Th) cell homeostasis may contribute to the therapeutic effect of RTX as Th cell subset imbalances are involved in the emergence of autoimmune diseases. The current study assessed the influence of RTX on Th1/Th2/Th17 balance in peripheral blood of pSS patients.

Methods: Twenty-eight patients with pSS, diagnosed according to the American-European Consensus Group criteria, were treated on days 1 and 15 with RTX (1000 mg i.v.). The absolute numbers of circulating Th1/Th2/Th17 cell subsets were examined in fresh blood samples by 6-color flow cytometry at baseline and at 5, 16, 24 and 36 weeks after treatment. Expression patterns of chemokine receptors $CXCR3^+CRTh2^-CCR4^-CCR6^-$, $CXCR3^-CRTh2^+CCR4^+CCR6^-$ and $CXCR3^-CRTh2^-CCR4^+CCR6^+$ were used for distinction between Th1, Th2 and Th17, respectively. In addition, numbers of Th1/Th2/Th17 cells were analyzed based on their associated cytokines IFNg/IL-4/IL-17 upon *in vitro* stimulation of thawed PBMCs. Sixteen matched healthy individuals were studied in parallel as controls (HCs).

Results: At baseline, compared to HCs, pSS patients showed a significant decrease in numbers of circulating Th1-cells, and a significant increase in Th17-cells. In contrast, no differences were seen in numbers of Th2 cells between HCs and pSS patients. Following RTX treatment, numbers of circulating Th1 and Th2 subsets in pSS patients at 5, 16 and 24 weeks were comparable to their baseline values, whereas a significant decrease was observed in Th17 cells at week 5 post-treatment. Importantly, RTX treatment induced a significant decrease in number of IL-17 producing Th-cells at weeks 16 and 24 as compared to baseline, whereas IFNg and IL-4 producing Th-cells remained unchanged. Importantly, numbers of IL-17 producing Th-cells increased again and reached their baseline value by 36 weeks post RTX-treatment. This coincides with a reconstitution of B cells in peripheral blood of pSS patients.

Conclusion: B cell depletion therapy in pSS influences Th cell homeostasis affecting Th17 cells in particular. Recovery of Th17 cells coincides with B cell repopulation indicates that B cells modulate the pro-inflammatory Th17 responses. Reduction in Th17 responses post RTX-treatment may contribute to the observed clinical outcome of RTX in pSS patients.

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2883

Clinical Characteristics of Rheumatoid Arthritis Patients with Secondary Sjögren's Syndrome and Association with Joint Damage. Lindsay E. Brown[1], Michelle A. Frits[2], Christine K. Iannaccone[2], Michael E. Weinblatt[2], Nancy A. Shadick[2] and Katherine P. Liao[2]. [1]Massachusetts General Hospital, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Secondary Sjögren's syndrome (sSS) is a common extra-articular manifestation of rheumatoid arthritis (RA). However, the clinical characteristics of this subgroup of patients are not well characterized. In addition, whether sSS is associated with worse outcomes such as joint damage remains unclear. This study aims to characterize sSS patients in an RA cohort and determine whether there is an association between sSS and worse joint damage.

Methods: We conducted a cross-sectional study in an observational cohort of RA patients at a large academic center. We included all subjects with >=1 year of follow-up. Subjects with comorbid diseases, which can also result in sicca symptoms, e.g. sarcoidosis, viral hepatitis,HIV/AIDS, were excluded from the analysis. Subjects were considered to have sSS if they were reported as having sSS by their rheumatologist at recruitment into the cohort (baseline) and had the diagnosis confirmed by manual chart review. Fifty subjects without sSS were also reviewed to determine the negative predictive value (NPV) of having no sSS reported at baseline. The primary outcome was Sharp scores associated with bilateral hand radiographs at baseline. We conducted univariate analyses on potential clinical variables associated with sSS, e.g. age, gender, race, ACPA or RF positivity, DAS28-CRP, methotrexate and anti-TNF use at baseline. We constructed a linear regression model to determine the association of sSS status and baseline Sharp score, adjusted by age, gender, RA disease duration and variables significant from the univariate analyses.

Results: We studied 829 RA subjects, mean age was 57 years, 83% female, mean RA duration 13 years, 63% ACPA positive; fifty-seven subjects (7%) had sSS (the NPV of not having sSS if not reported at baseline was 100%). We observed a female predominance (98%) and a significantly higher

percentage of African-Americans subjects (10%) with sSS than the general RA cohort; subjects with sSS also had a significantly higher DAS28-CRP at baseline in the univariate analysis (**Table 1**). Having sSS at baseline was associated with higher Sharp scores (p=0.01), adjusted for age, gender, disease duration and variables significant from the univariate analyses (African American race, RF positive, baseline DAS28-CRP) (**Table 2**).

Table 1. Clinical characteristics of subjects with Secondary Sjögren's Syndrome (sSS) in the RA cohort (n=829).

Clinical characteristics	sSS, n=57 (6.9%)	No sSS, n=772 (93.1%)	p-value
Age, mean yrs (SD)	57.2 (10.5)	56.9 (13.7)	0.869
Female gender (%)	98.3	81.4	0.001
Disease duration, mean yrs (SD)	16.1 (10.8)	13.5 (12.4)	0.13
Race (%)			
Caucasian	84.2	93.7	0.004
African American	10.5	3.8	0.02
ACPA positive (%)	70.4	61.7	0.20
RF positive (%)	80.0	62.1	0.008
Baseline DAS28-CRP, mean (SD)	4.36 (1.7)	3.89 (1.6)	0.03
Baseline Sharp score, median (IQR)	48.0 (82.0)	17.0 (61.0)	0.002
Anti-TNF at baseline, %	45.6	35.8	0.14
MTX at baseline, %	57.9	46.3	0.10

Table 2. Association between sSS at baseline and joint damage (as measured by Sharp scores*).

Clinical variable	Beta coefficient (SE)	p-value
Age, yrs	0.02 (0.007)	0.18
Female gender	−0.13 (0.23)	0.62
Disease duration, yrs	0.04 (0.007)	<.0001
African-American race	−0.78 (0.32)	0.02
RF positivity	0.76 (0.19)	<.0001
Baseline DAS28-CRP	0.18 (0.05)	0.0003
Presence of sSS	**0.43 (0.17)**	**0.01**

*Sharp scores were non-normally distributed and were categorized into quintiles (Q1: <1, Q2: ≥1 and <10, Q3: ≥10 and <32.5, Q4: ≥32.5 and <81.5, Q5: ≥81.5 units)

Conclusion: In our RA cohort, sSS affected a significantly higher proportion of women and African Americans than the overall cohort. RA subjects with sSS had worse joint damage, suggesting that sSS may a marker of more aggressive disease.

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ACR Concurrent Abstract Session
Spondylarthropathies and Psoriatic Arthritis: Clinical Aspects and Treatment: Imaging in Axial Spondylarthropathies: Challenges, Advances
Wednesday, October 30, 2013, 11:00 AM–12:30 PM

2884

Prevalence Of Structural Lesions Seen On MRI-Spine In Patients With (Possible) Axial Spondyloarthritis (axSpA) Included In The SPACE-Cohort. Manouk de Hooge[1], Rosaline van den Berg[1], Victoria Navarro-Compán[1], Monique Reijnierse[1], Floris van Gaalen[1], Karen Fagerli[2], Maureen C. Turina[3], Maikel van Oosterhout[4], Roberta Ramonda[5], Tom Huizinga[1] and Désirée van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [4]GHZ Hospital, Gouda, Netherlands, [5]University of Padova, Padova, Italy.

Background/Purpose: Little is known about the prevalence of structural lesions (erosions, syndesmophytes, fatty lesions) on MRI of the spine (MRI-spine) in patients with chronic back pain. Therefore the purpose of our study was to investigate the prevalence of structural lesions on MRI-spine in patients with chronic back pain.

Methods: Patients with back pain (≥3 months, ≤2 years, onset <45 years) recruited from 5 participating centres in Europe were included in the SPondyloArthritis Caught Early (SPACE)-cohort. Patients underwent MRI-spine scored independently by 3 blinded, well-calibrated readers for presence of erosions, fatty lesions and (bridging) syndesmophytes on T1-weighted images (STIR images viewed simultaneously). Fatty lesions suggestive of spondylitis were scored when visible on ≥2 consecutive slices. For erosions and syndesmophytes, suggestive of spondylitis, the presence on ≥1 slice was sufficient. Agreement of 2/3 readers was used. The prevalence of structural lesions was calculated based on several cut-offs.

Results: All patients with complete MRI-spine data were included for analysis (n=306). All patients were grouped according to the ASAS axSpA criteria; imaging arm (fulfilling the modified New York criteria (mNY+) and not fulfilling the modified New York criteria (mNY-)) and clinical arm, possible SpA (patients not fulfilling the ASAS axSpA criteria but with 1 SpA feature with a LR+ of ≥6 or 2 SpA features with a LR+ <6) and no-axSpA. Prevalence of fatty lesions was the highest of all structural lesions in the spine in all subgroups. With a cut-off of ≥3 fatty lesions, the 'false-positive' rate in the no-axSpA group was low (6.5%) with still a considerable prevalence in the imaging and radiographic axSpA groups. The prevalence of erosions and syndesmophytes was generally low (see the table).

	ASAS axSpA, n=126				
	Imaging-arm				
	mNY+ n=26	mNY− n=46	Clinical-arm, n=54	Possible axSpA, n=116	No-axSpA, n=64
Fatty lesions ≥1	9 (34.6%)	18 (39.1%)	8 (14.8%)	19 (16.4%)	8 (12.5%)
Fatty lesions ≥2	5 (19.2%)	14 (30.4%)	6 (11.1%)	12 (10.3%)	7 (10.9%)
Fatty lesions ≥3	4 (15.4%)	11 (23.9%)	3 (5.6%)	10 (8.6%)	3 (4.7%)
Fatty lesions ≥4	4 (15.4%)	9 (19.6%)	2 (3.7%)	5 (4.3%)	2 (3.1%)
Fatty lesions ≥5	4 (15.4%)	7 (15.4%)	2 (3.7%)	4 (3.4%)	2 (3.1%)
Fatty lesions ≥6	3 (11.5%)	5 (10.9%)	2 (3.7%)	3 (2.6%)	2 (3.1%)
Fatty lesions ≥7	3 (11.5%)	4 (8.7%)	2 (3.7%)	3 (2.6%)	2 (3.1%)
Erosions ≥1	5 (19.2%)	11 (23.9%)	9 (16.7%)	20 (17.2%)	10 (15.6%)
Erosions ≥2	2 (7.7%)	6 (13.0%)	5 (9.3%)	10 (8.6%)	7 (10.9%)
Erosions ≥3	1 (3.8%)	2 (4.3%)	2 (3.7%)	3 (2.6%)	4 (6.3%)
Erosions ≥4	0	1 (2.2%)	0	3 (2.6%)	0
Erosions ≥5	0	0	0	1 (0.9%)	0
Syndesmophyt ≥1	5 (9.3%)	10 (21.7%)	1 (3.8%)	17 (14.7%)	7 (10.9%)
Syndesmophyt ≥2	1 (1.9%)	2 (4.3%)	0	8 (6.9%)	3 (4.7%)
Syndesmophyt ≥3	1 (1.9%)	0	0	2 (1.7%)	2 (3.1%)

Conclusion: The prevalence of fatty lesions on MRI-spine is the highest of any structural lesions in all subgroups. Fatty lesions with a cut-off of '3 are primarily present in patients fulfilling the ASAS axSpA criteria, infrequent in possible axSpA patients and no-axSpA patients. Erosions and syndesmophytes in the spine are equally present in all groups. Fatty lesions are the only type of structural lesions that can potentially discriminate between patients with and without axSpA.

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2885

Erosions and Sclerosis, But Not Squaring, Predict The Development Of New Syndesmophytes: A 12-Year Longitudinal Analysis (OASIS). Sofia Ramiro[1], A.M. van Tubergen[2], Désirée van der Heijde[3], Carmen Stolwijk[2], Maxime Dougados[4], Filip Van den Bosch[5] and Robert Landewé[6]. [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Maastricht University Medical Center, Maastricht, Netherlands, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France, [5]Gent University Hospital, Gent, Belgium, [6]Academic Medical Center Amsterdam & Atrium Medical Center, Heerlen, Netherlands.

Background/Purpose: Erosions, sclerosis and squaring are included in the modified Stoke Ankylosing Spondylitis (AS) Spine Score (mSASSS). However, their value in predicting the development of new syndesmophytes has not been established, and their value in the mSASSS has been argued. We aimed at analysing the effect of erosions, sclerosis and squaring on the development of new syndesmophytes over 12 years.

Methods: Biannual radiographs from patients with AS (mNY criteria) followed in OASIS (up to 12 years) were included. Two readers (R1 and R2) independently scored the x-rays according to the mSASSS and separately registered all the items with a score of 1 (erosions, sclerosis and squaring, or any combination) per vertebral corner (VC). The progression from erosions, sclerosis and squaring to new (bridging) syndesmophytes (either score of 2 or

3 in the mSASSS) in a 2-year period and over the 12 years was investigated by means of a multilevel (adjusted for time, reader and cervical/lumbar spinal region) auto-regressive and time-lagged longitudinal model, using generalized estimating equations. Interactions with reader and spinal region were investigated.

Results: 211 patients were included in this analysis (mean age 43 (SD 13) years old, 71% male, 85% HLA-B27 positive, 11.5 (SD 9.1) years since diagnosis and 20.5 (SD 11.6) years since symptom onset, 4.4 (SD 1.8) radiographs per patient). A total of 921 radiographs were included in this analysis, with a total of 20509 VCs (R1) and 20568 VCs (R2) evaluable. Of these, erosions were scored in 1% for R1 (2.5% R2), sclerosis in 0.3% for R1 (1.7% R2), squaring in 6.5% for R1 (5.1% R2) and syndesmophytes in 25% for R1 (27% R2). The presence of erosions, sclerosis and squaring together had, compared with a normal VC, a risk for the development of new syndesmophytes over a 2-year period of 2.0 (Table). There was a significant interaction with 'spinal region' (OR cervical spine: 3.1; OR lumbar spine: 1.3). There was no significant difference between the readers. Separately, the presence of erosions or the presence of sclerosis, but not the presence of squaring, gave an increased risk for new syndesmophytes, Squaring was predictive of the development of new syndesmophytes in the cervical spine only (Table).

Table. Longitudinal effect (GEE) of erosions, sclerosis and squaring on the development of new syndesmophytes over 12 years (adjusted for spinal region and reader)

		Multivariable GEE models with syndesmphytes as the outcome* OR (95% CI)	Same model, but with results stratified for spinal region or reader if significant interactions OR (95% CI)
	Factor: Erosion, sclerosis and/or squaring (score of 1 in mSASSS)	2.0 (1.7–2.3)	
Stratification	*- Cervical spine*		*3.1 (2.5–3.9)*
	- Lumbar spine		*1.3 (1.0–1.6)*
	- Reader 1		*No significant interaction*
	- Reader 2		
	Factor: Erosions	2.1 (1.6–2.8)	
Stratification	*- Cervical spine*		*No significant interaction*
	- Lumbar spine		
	- Reader 1		*No significant interaction*
	- Reader 2		
	Factor: Sclerosis	5.1 (3.9–6.8)	
Stratification	*- Cervical spine*		*No significant interaction*
	- Lumbar spine		
	- Reader 1		*15.3 (9.2–25.5)*
	- Reader 2		*3.9 (2.8–5.5)*
	Factor: Squaring	1.3 (1.0–1.6)	
Stratification	*- Cervical spine*		*8.5 (2.1–34.7)*
	- Lumbar spine		*1.1 (0.8–1.4)*
	- Reader 1		*1.6 (1.2–2.1)*
	- Reader 2		*1.0 (0.6–1.4)*

* Adjusted for spinal region and reader (each row reflects the OR for main predictor of the model, all different models).

Conclusion: Erosions and sclerosis occur rarely on X-rays, but if so, are predictive for the development of new syndesmophytes. Therefore, these lesions not only seem to precede the development of syndesmophytes, but are also correctly included in the mSASSS. The possibility of excluding squaring from the mSASSS in the lumbar spine may be considered.

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2886

Prevalence Of Structural Lesions On MRI Of The Sacroiliac Joints In Patients With Early Axial Spondyloarthritis and Patients With Back Pain. Rosaline van den Berg[1], Manouk de Hooge[1], Victoria Navarro-Compán[1], Monique Reijnierse[1], Floris van Gaalen[1], Karen Fagerli[2], Maureen Turina[3], Maikel van Oosterhout[4], Roberta Ramonda[5], Tom Huizinga[1] and Désirée van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [4]GHZ Hospital, Gouda, Netherlands, [5]University of Padova, Padova, Italy.

Background/Purpose: Little is known about the prevalence of structural lesions on MRI in the SI joints (MRI-SI) in recent onset axial spondyloarthritis (axSpA) patients and patients with back pain of other origin. Therefore, we investigated the prevalence of structural lesions on MRI-SI in these patients.

Methods: Patients with back pain (≥3 months, ≤2 years, onset <45 years) from the 5 centers the SPondyloArthritis Caught Early (SPACE)-cohort were included. Patients underwent MRI-SI. Available MRIs-SI were scored by 3 well-calibrated readers independently for ankylosis, sclerosis, erosions, and fatty lesions (MRI T1-weighted images; STIR images viewed simultaneously). Erosions, sclerosis and fatty lesions were defined according to the MORPHO definition[1] (≥1 lesion on ≥2 consecutive slices or ≥2 lesion on 1 slice); ankylosis as 1 lesion on ≥1 slice. Lesions were considered present if 2/3 readers agreed. Prevalence based on several cut-offs of structural lesions was calculated. Patients were grouped according to the ASAS axSpA criteria[2][imaging-arm (mNY+, mNY-), clinical arm], no-SpA and possible SpA.

Results: Patients with MRI-SI data were included (n=299). If defined as ≥1, all structural lesions except ankylosis were frequent in all groups; in decreasing frequency in mNY+, MRI+mNY-, clinical arm, possible SpA and no-SpA (table). The higher the cut-offs, the better discrimination between the imaging-arm and no/possible SpA, with the clinical arm close to no/possible SpA. To define a proper cut-off for the presence of structural lesions in axSpA, the false-positive percentage in no-SpA patients should be low. We defined possible cut-offs based on the acceptance of ≤10% (italics) and ≤5% (bold) false-positives (table). E.g. if ≥4 structural lesions are present, false-positives are 6.0% and 5.2% respectively, with a frequency of 61.5% and 43.5% in the mNY+ and MRI+mNY- subgroups.

	AxSpA (ASAS), n=123				
	mNY+ (n=26)	mNY− (n=46)	Clinical arm (n=51)	Possible SpA n=116	No SpA n=60
Fatty lesion ≥1, n (%)	*11 (42.3)*	*12 (26.1)*	*7 (13.7)*	*8 (6.9)*	*6 (10.0)*
Fatty lesion ≥2, n (%)	**11 (42.3)**	**10 (21.7)**	**6 (11.8)**	**7 (6.0)**	**2 (3.3)**
Erosion ≥1, n (%)	*18 (69.2)*	*30 (65.2)*	*11 (21.6)*	*22 (19.0)*	*5 (8.3)*
Erosion ≥2, n (%)	**13 (50.0)**	**24 (52.2)**	**3 (5.9)**	**8 (6.9)**	**3 (5.0)**
Sclerosis ≥1, n (%)	**1 (3.8)**	**3 (6.5)**	**1 (2.0)**	**2 (1.7)**	**2 (3.3)**
Ankylosis ≥1, n (%)	**2 (7.7)**	**1 (2.2)**	**0 (0.0)**	**1 (0.9)**	**1 (1.7)**
Fatty lesion and/or erosion ≥1, n (%)	19 (73.1)	32 (69.9)	14 (27.5)	28 (24.1)	11 (18.3)
Fatty lesion and/or erosion ≥3, n (%)	*16 (61.5)*	*20 (43.5)*	*6 (11.8)*	*9 (7.8)*	*6 (10.0)*
Fatty lesion and/or erosion ≥4, n (%)	*16 (61.5)*	*18 (39.1)*	*5 (9.8)*	*4 (3.4)*	*4 (6.7)*
Fatty lesion and/or erosion ≥5, n (%)	**16 (61.5)**	**18 (39.1)**	**3 (5.9)**	**4 (3.4)**	**0 (0.0)**
Any structural lesion ≥1, n (%)	20 (76.9)	36 (78.3)	16 (31.4)	34 (29.3)	14 (23.3)
Any structural lesion ≥4, n (%)	*16 (61.5)*	*20 (43.5)*	*7 (13.7)*	*7 (6.0)*	*5 (8.3)*
Any structural lesion ≥5, n (%)	**16 (61.5)**	**20 (43.5)**	**5 (9.8)**	**6 (5.2)**	**2 (3.3)**
Any structural lesion, no ankylosis ≥1, n (%)	19 (73.1)	35 (76.1)	15 (29.4)	29 (25.0)	13 (21.7)
Any structural lesion, no ankylosis ≥4, n (%)	*16 (61.5)*	*19 (41.3)*	*6 (11.8)*	*6 (5.2)*	*5 (8.3)*
Any structural lesion, no ankylosis ≥5, n (%)	**16 (61.5)**	**19 (41.3)**	**4 (7.8)**	**5 (4.3)**	**1 (1.7)**
Any structural lesion, no sclerosis ≥1, n (%)	20 (76.9)	32 (69.6)	16 (31.4)	32 (27.6)	12 (20.0)
Any structural lesion, no sclerosis ≥3, n (%)	*17 (65.4)*	*21 (45.7)*	*7 (13.7)*	*11 (9.5)*	*6 (10.0)*
Any structural lesion, no sclerosis ≥5, n (%)	**16 (61.5)**	**19 (41.3)**	**4 (7.8)**	**4 (3.4)**	**1 (1.7)**

Italics represents ≤10% false-positives in the group of no SpA patients. **Bold** represents ≤5% false-positives in the group of no SpA patients

Conclusion: Prevalence of erosions, sclerosis and fatty lesions on MRI-SI is high in axSpA patients but also in no-SpA patients. Higher cut-offs than ≥1 lesion are needed to reduce false-positives; also with higher cut-offs structural lesions are frequent in early axSpA patients. These data suggest that with appropriate cut-offs, structural lesions might be helpful in defining sacroiliitis on MRI.

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The Spondyloarthritis Research Consortium Of Canada MRI Sacroiliac Joint Structural Score: A Method For Reliable Detection Of Structural Progression. Walter P. Maksymowych[1], Stephanie Wichuk[1], Praveena Chiowchanwisawakit[2], Robert GW Lambert[1] and Susanne Juhl Pedersen[3]. [1]University of Alberta, Edmonton, AB, [2]Mahidol University, Bangkok, Thailand, [3]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark.

Background/Purpose: With increasing focus on effective treatment intervention in early spondyloarthritis, there is an unmet need for reliable assessment of structural progression in the sacroiliac joints (SIJ) but radiography is unreliable for detecting change and lacks responsiveness. There has been limited validation of MRI-based scores for structural lesions in the SIJ, primarily based on cross-sectional data and recording fat metaplasia, but it is unclear whether change in structural progression can be reliably detected and change in which specific MRI lesions is most consistently detected over time.

Methods: The SPARCC SIJ Structural Score (SSS) method for assessment of structural lesions on T1WSE MRI scans is based on: 1. Standardized and validated definitions (MORPHO) for fat metaplasia, erosion, backfill, and ankylosis, 2. Anatomical matching of all time points according to the transitional semi-coronal SIJ slice, defined as the first slice in the cartilaginous portion that has a visible portion of the ligamentous joint when viewed from anterior to posterior, 3. Dichotomous scoring (present/absent) of lesions in SIJ quadrants (fat, erosion) or halves (backfill, ankylosis) using a direct online data entry system based on schematics of the SIJ, 4. Assessment of 5 consecutive slices from the transitional slice anteriorly through the cartilaginous portion of the joint. Scoring ranges are: fat metaplasia (0–40), erosion (0–40), backfill (0–20), ankylosis (0–20). Four readers independently assessed 20 pairs of MRI scans from 20 cases (baseline, 2 years) blinded to time point (exercise 1). In exercise 2, 15 pairs of scans from exercise 1 were randomly scored with an additional 30 new pairs of scans from 30 cases (baseline, 2 years) to assess consistency of change in reliability data. This nested study design addresses the limitation for assessment of reliability posed by differences in progression rates between different study samples since changes in progression are typically small. Inter-observer reliability was assessed by intra-class correlation coefficient (ICC3,1).

Results: Mean (SD) for baseline scores were 3.4(4.0), 3.1(3.4), 3.7(4.3), and 5.3(7.9) for fat, erosion, backfill and ankylosis, respectively. Corresponding mean (SD) change scores were 0.2 (1.4), −1.3 (2.1), 0.5 (2.5), and 0.1(1.1). Consistently very good reliability was observed for detection of 2-year progression in ankylosis. Consistently good reliability was also evident for detection of change in backfill. Reliability was least consistent for detection of change in erosion.

Table. ICC [95% CI] values

		Fat metaplasia		Erosion		Backfill		Ankylosis	
	Readers	Status		Change		Status		Change	
Exercise 1 (n = 20)	All	0.72 [0.54–0.86]		0.68 [0.49–0.84]		0.60 [0.39–0.79]		0.59 [0.38–0.78]	
	N = 15*	0.71 [0.49–0.87]		0.59 [0.34–0.81]		0.67 [0.43–0.85]		0.61 [0.37–0.82]	
Exercise 2 (n = 45)	All	0.78 [0.69–0.86]	0.86 [0.74–0.93]	0.44 [0.29–0.60]	0.76 [0.34–0.76]	0.62 [0.49–0.75]	0.98 [0.96–0.99]	0.39 [0.24–0.56]	0.64 [0.65–0.90]
	N = 15*	0.80 [0.62–0.92]	0.90 [0.79–0.86]	0.42 [0.16–0.70]	0.72 [0.51–0.88]	0.53 [0.28–0.78]	0.98 [0.95–0.99]	0.32 [0.07–0.63]	0.84 [0.70–0.94]
			0.79 [0.53–0.77]		0.56 [0.41–0.69]		0.98 [0.97–0.99]		0.98 [0.51–0.76]
			0.76 [0.57–0.90]		0.58 [0.33–0.80]		0.97 [0.94–0.99]		0.84 [0.70–0.94]

* Cases read in both exercises

Conclusion: The SPARCC MRI SSS method is a reliable scoring method for detecting structural progression, especially ankylosis, even though progression is small.

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Frequent Detection Of Inflammation and Fat Infiltration Suggestive Of Spondyloarthritis On MRI Of The Entire Spine In Healthy Subjects and Patients With Mechanical Back Pain. Ulrich Weber[1], Zheng Zhao[2], Veronika Zubler[1], Stanley Chan[3], Robert GW Lambert[3], Mikkel Ostergaard[4], Susanne Juhl Pedersen[5], Kaspar Rufibach[6] and Walter P. Maksymowych[3]. [1]Balgrist University Hospital, Zurich, Switzerland, [2]Department of Rheumatology, University of Alberta and PLA General Hospital, Beijing, PR China, Beijing, China, [3]University of Alberta, Edmonton, AB, [4]Copenhagen Center for Arthritis Research, Glostrup, Denmark, [5]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [6]rePROstat, Basel, Switzerland.

Background/Purpose: Mechanical back pain (MBP) patients and healthy subjects may show spinal MRI lesions suggestive for spondyloarthritis (SpA) such as corner inflammatory lesions (CIL) or corner fat lesions (CFL). There are few data about their frequency and whether they may result in a false positive classification of controls as having SpA. We aimed to assess the frequency of false positive classification as SpA in controls consisting of MBP patients and healthy volunteers, and to evaluate which MRI lesion type had the highest impact on misclassification.

Methods: The study sample comprised 2 independent cohorts A/B of 130 consecutive patients with back pain ≤50 years newly referred to 2 university clinics, and 20 healthy controls (HC). Patients were classified according to clinical examination and pelvic radiography as having non-radiographic SpA (nr-axSpA; n=50), ankylosing spondylitis (AS; n=33), or MBP (n=47). Age-matched healthy controls in cohort A were recruited according to the Nordic Questionnaire from hospital staff of the same clinic that also recruited the SpA patients. Spinal MRI scans were assessed by 4 blinded readers according to the Canada-Denmark MRI definitions for spinal lesions [1, 2]. Bone marrow edema (BME) and fat infiltration (FI) were reported in the central and lateral compartment of 23 discovertebral units. Readers recorded presence/absence of SpA and their level of confidence in this conclusion by global evaluation of the MRI scans (T1SE and STIR sequences) on a 0–10 scale (0 = definitely not SpA; 10 = definite SpA). The mean number (percentage) of controls misclassified as having SpA by ≥1 of 4 readers and the principal spinal lesions indicative of SpA were analysed descriptively

Results: 33.9%/28.0% of MBP patients in cohorts A/B, and 26.3% of healthy subjects in cohort A were misclassified as having SpA by global assessment of MRI of the entire spine. Both BME and FI in varying percentages were the most important MRI lesions leading to this misclassification. The mean number of CIL and CFL observed in controls was lower than in SpA patients.

Mean percentage of false positive controls, principal MRI lesions responsible for misclassification, and mean number for CIL and CFL on spinal MRI in cohort A/B.

	Cohort A (n=62)				Cohort B (n=88)		
Cohort Group	nr-axSpA	AS	MBP	HC	nr-axSpA	AS	MBP
Number of subjects	19	9	14	20	31	24	33
Classification as SpA (%) Confidence range 5–10	51.3	72.2	33.9	26.3	48.4	72.9	28.0
BME most important (%)	79.5	76.9	52.6	52.4	23.3	47.1	16.2
FI most important (%)	17.9	23.1	26.3	23.8	66.7	45.7	62.2
CIL (mean)	3.4	6.4	1.3	1.4	2.2	4.1	0.9
CFL (mean)	3.9	6.8	3.2	2.8	6.5	14.3	3.0
Classification as SpA (%) Confidence range 8-10	35.5	55.6	14.3	7.5	31.5	62.5	10.6

Conclusion: 26% to 34% of healthy controls and patients with MBP were misclassified as having SpA by evaluation of MRI of the spine alone. Misclassifications with high confidence ranged from 8% to 14%. Caution is warranted if a classification of SpA is based on MRI of the spine alone.

References:

[1] Lambert R et al. J Rheumatol 2009;36 suppl 84:3. [2] Ostergaard M et al. J Rheumatol 2009;36 suppl 84:18.

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Bone Marrow Edema and Structural Lesions In The Sacroiliac Joint In a Large Cohort Of Patients With Axial Spondyloarthritis, Chronic Low Back Pain and Healthy Controls. L. van Hoeven[1], J.J. Luime[1], P.D.M. de Buck[2], J.M.W. Hazes[1] and A.E.A.M. Weel[3]. [1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]MC Haaglanden, Den Haag, Netherlands, [3]Maasstad Hospital, Rotterdam, Netherlands.

Background/Purpose: MRI of the sacroiliac joint (SIJ) is included in the ASAS classification criteria for axial spondyloarthritis (axSpA) to identify patients at an earlier stage of the disease. However, the diagnostic utility is discussed since there are only few MRI data of patients with chronic low back pain and healthy populations. Therefore, we investigated the frequencies of bone marrow edema (BME) and structural lesions (SL) in a large cohort of axSpA patients, chronic low back pain (CLBP) patients and healthy controls (HC). Furthermore, to assess the added value of structural lesions for the sensitivity of a MRI of the SIJ (MRI-SIJ).

Methods: A cross-sectional study (CaFaSpA 2) was set up among primary care patients with CLBP aged 18–45 years (n=579) and healthy controls (n=79). The healthy controls were oversampled towards physical active controls and therefore included 25 runners. Also 4 women with pregnancy related pelvic pain were included. In all participants a MRI-SIJ was obtained. MRIs-SIJ were scored by one out of two experienced radiologist, blinded for clinical status. MRI evaluation followed ASAS recommendations for BME and SL, (ankylosis, sclerosis, erosions and fatty lesions).[1] The outcome was reported by descriptive statistics. To analyze the added value of SL as a MRI positive feature we tested the sensitivity and specificity.

Results: 95 out of 579 CLBP patients fulfilled the ASAS classification criteria for axSpA.[2] BME was observed in 71% of the axSpA patients, in 5% of the CLBP patients and in 14% of the HC. This resulted in a sensitivity of 71% and a specificity of 95%. No relationship between physical activity or pregnancy related back pain and BME frequency was observed.

The frequencies of structural lesions were 25%, 7%, and 8% for respectively, axSpA patients, CLBP patients and HCs. The sensitivity of the MRI, based only on the presence of BME, is 71%, with a 95% specificity. Adding the structural lesions as an MRI positive feature would increase the sensitivity to 84%, with a slight decrease in specificity, 88%.

Table 1. Patients characteristics and frequencies of BME and structural lesions (SL) on MRI-SIJ

	ASAS aSpA patients (n=95)			CLBP patients (n=484)	Healthy controls (n=79)
	Radiographic SpA (n=24)	Nonradiographic SpA (n=71)	Total (n=95)		
Male n (%)	6 (25)	36 (42)	36 (38)	202 (42)	33 (42)
Age yrs (sd)	38.6 (5.8)	36.8 (6.6)	37.3 (6.5)	35.8 (7.1)	36.9 (7.4)
CLBP duration yrs (sd)	9.3 (9.9)	9.6 (7.4)	9.5 (8.1)	9.2 (7.7)	NA
BME n (%) *	8 (33)	59 (83)	67 (71)	24 (5)	11 (14)
SL n (%) °	16 (67)	8 (11)	24 (25)	36 (7)	6 (8)
BME or SL n (%)	19 (79)	61 (86)	80 (84)	57 (12)	15 (19)

*BME lesion present on at least two consecutive slices or more than one signal on a single slice.
° Fat depositions, sclerosis, erosions or ankylosis.

Conclusion: Bone marrow edema on MRI will be seen in 5% to 14% of the chronic low back pain patients and healthy controls. Structural lesions will be seen in 7% to 8% of these populations. The added value of structural lesions in diagnosing axSpA is promising, since it increases the sensitivity and therefore facilitates the diagnostic utility of MRI-SIJ.

1. Sieper J ARD 2009;68 Suppl 2:ii1–44.
2. Rudwaleit M ARD;2009;68:777–83.

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ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Animal Models
Wednesday, October 30, 2013, 11:00 AM–12:30 PM

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Novel Selective Inhibitors Of Nuclear Export (SINE) Decrease Type I Interferon Activation and Deplete Autoreactive Plasma Cells In The Kidney In Murine Lupus. Teresa Owen[1], Javier Rangel-Moreno[1], Boris Klebanov[2], Yosef Landesman[2], Michael Kauffman[2], Sharon Shacham[2] and Jennifer H. Anolik[1]. [1]University of Rochester Medical Center, Rochester, NY, [2]Karyopharm Therapeutics Inc., Natick, MA.

Background/Purpose: There is great interest in developing new treatment approaches for SLE, but the biologic therapies under investigation over the past several years have yielded disappointing results. SINE are orally available, well tolerated XPO1 (Exportin 1/CRM1) antagonists that are in human phase 1 clinical trials and show potent activity and tolerability in hematologic malignancies. We hypothesized that SINE would be efficacious in murine lupus through the combined targeting of interferon alpha production by plasmacytoid dendritic cells (pDCs) and autoantibody production by plasma cells (PCs).

Methods: Nephritic NZB/W F1 lupus-prone female mice, with elevated serum anti-dsDNA antibodies and established proteinuria, were treated with the SINE KPT-251 or vehicle control by oral gavage (n=9 per group). Proteinuria was monitored, and kidney histology assessed (0–4+ scale). Spleen, bone marrow (BM), and kidney were harvested, cells analyzed by flow cytometry, and antibody secreting cells (ASCs) enumerated by ELIspot. Serum samples and RNA were collected for Luminex assay and qPCR. Effects on pDC production of IFN were assessed using in-vitro cultures with BM cells stimulated with CpG 2216 10ng/ml for 5 hours.

Results: SINEs inhibit the production of IFN alpha by pDCs in a dose dependent fashion: pDC% positive for IFN no drug 10.5%, 3.125 uM 12.1%, 6.25 um 9%, 12.5 um 3.8%, and 25 uM 1.2%. IFN regulated chemokines in the serum of SINE treated lupus mice were decreased (MCP-1: 250+/−290 pg/ml vehicle vs. 54+/−26 pg/ml SINE, p=0.049), as was the PC survival factor IL6 (192+/−50 pg/ml vehicle vs. 11+/−23 pg/ml SINE, p=0.045). SINEs prevented nephritis progression with a statistically significant reduction in urine protein levels in the treated group ($p<0.05$ beginning at 5 weeks) and significantly reduced both IgG and anti-DNA ASCs in the spleen (81% reduction for anti-DNA, p=0.0048) and BM (63% reduction for anti-DNA, p=0.07). In the spleen, GC B cells (PNA+FAS+) and T follicular helper cells (CD4+CXCR5+ICOS+PD1+) were dramatically reduced (p =0.0016 and p=0.0051, respectively). Moreover, nephritis was improved histologically (GN score 3.3+/−1.2 vehicle vs. 1.0+/−0 SINE; lymphoid infiltrate score 1.3+/−0.6 vehicle vs. 0+/− SINE). There was also a dramatic reduction in autoreactive PCs in the kidney (98% reduction for anti-DNA, $p<0.0001$). We are presently examining the kidney tissue for IFN regulated genes and PC survival factors.

Conclusion: The combined reduction in IFN activation, GCs, and autoreactive plasma cells suggests that SINEs alter both the generation of PCs and the kidney PC niche with beneficial effects on nephritis. The mechanisms underlying these effects, including potential inhibition of NFkB signaling, are under investigation.

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Loss Of Caspase 8 Exacerbates Dendritic Cell Activation In a MyD88- and RIPK1-Dependent Manner That Is Controlled By Inhibitory Molecules Transcribed By IRF3. Carla M. Cuda[1], Alexander V. Misharin[2], Rana Saber[2] and Harris R. Perlman[2]. [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Northwestern University, Chicago, IL.

Background/Purpose: Previous studies implicate dendritic cells (DCs) in the initiation and persistence of systemic lupus erythematosus (SLE). While DCs from SLE patients exhibit elevated activation, the factors responsible remain unknown. To this end, we recently identified that caspase 8, an enzyme known to initiate apoptosis and/or suppress necroptosis (by inhibition of RIPK signaling) in a multitude of cells, is a novel DC-specific inhibitor of inflammatory processes independent of DC survival.

Methods: Mice lacking caspase 8 specifically in DCs were generated ($Cre^{CD11c}Casp8^{flox/flox}$). $Cre^{CD11c}Casp8^{flox/flox}$ mice were also crossed with $MyD88^{flox/flox}$, $IRF3^{-/-}$ or $IRF7^{-/-}$ mice to determine the role of these molecules in disease development. Flow cytometric analysis was used to characterize DC populations in mixed bone marrow chimeras and BrdU pulse assays. Bone marrow derived DCs were cultured with TLR agonists +/− necrostatin-1 (RIPK1 inhibitor), 1MT (indoleamine 2,3-dioxygenase (IDO) inhibitor), zIETD-FMK (caspase 8 enzymatic inhibitor). Luminex based assays detected cytokine and transcription factor DNA binding levels.

Results: $Cre^{CD11c}Casp8^{flox/flox}$ develop a SLE-like disease characterized by splenomegaly, lymphadenopathy, autoantibodies, glomerulonephritis, immune complex deposition in the kidney, proteinuria, an interferon signature, and early mortality. Loss of caspase 8 in DCs does not affect their survival, as there are equal numbers of $Cre^{CD11c}Casp8^{flox/flox}$ and WT DCs in mixed bone marrow chimeras, there is no change in DC turnover rate using BrdU pulse assays, and bone marrow derived DCs display similar levels of death independent of caspase 8 or RIPK1. However, caspase 8-deficient DCs are highly activated, leading to lymphocyte hyperactivation in a paracrine manner. Immune complexes containing self nucleic acids activate TLR7/9, which require the adaptor MyD88 for subsequent up-regulation of proinflammatory gene expression. The increased activation of $Cre^{CD11c}Casp8^{flox/flox}$ DCs is controlled by a MyD88-dependent mechanism, as DC-specific loss of MyD88 in $Cre^{CD11c}Casp8^{flox/flox}$ mice reduces disease, and caspase 8 defi-

cient DCs display a hyperresponsiveness to TLR7/9 ligation with increased DNA binding activity of IRF independent of caspase 8's enzymatic activity. Additionally, blocking RIPK1, but not IDO, signaling dampens TLR7/9 induced secretion of proinflammatory cytokines in caspase 8 deficient DCs. Despite caspase 8's known inhibitory role on IRF3 activity, deletion of IRF3, but not IRF7, in $Cre^{CD11c}Casp8^{flox/flox}$ mice exacerbates rather than ameliorates SLE-like disease, indicating that IRF3 transcribes inhibitory molecules that attempt to control the activation induced by the loss of caspase 8.

Conclusion: DC-specific loss of caspase 8 induces an SLE-like disease initiated by heightened DC activation via a MyD88- and RIPK1-dependent unknown mechanism. This constitutive activation is dampened by IRF3-specific transcription of unknown molecules possessing inhibitory functions, thereby uncovering novel roles for caspase 8 and IRF3 and highlighting potentially useful targets for autoimmune disease therapy.

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Masp-1/3 Deficient MRL/Lpr Mice Lack The Alternative Complement Pathway Activation and Are Protected From Development Of Lupus-Like Glomerulonephritis. Takeshi Machida, Natsumi Sakamoto, Teizo Fujita, Minoru Takahashi and Hideharu Sekine. Fukushima Medical University School of Medicine, Fukushima, Japan.

Background/Purpose: Complement has both protective and pathogenic functions in lupus due to a balance between its role in the clearance of immune complexes (ICs) and apoptotic cells and its role in inflammation. The classical pathway is thought to contribute to IC and apoptotic cell clearance, whereas the alternative pathway is a key mediator of renal inflammation. Mannose-binding lectin (MBL)-associated serine proteases (MASPs)-1 and -3 are responsible for activation of the alternative pathway by activation of complement factor D which is required to cleave C3b-bound factor B to Bb (the C3 convertase (C3bBb)) during the alternative pathway activation. The aim of this study was to investigate the role of essential components of the alternative pathway, MASP-1/3, on lupus-like renal disease in MRL/*lpr* mice.

Methods: MASP-1/3 gene-knockout MRL/*lpr* mice were generated by backcrossing MASP-$1/3^{-/-}$C57BL/6 mice for seven generations to MRL/lpr mice, a mouse strain that spontaneously develops lupus-like disease. Alternative pathway activity in serum was measured by zymosan assay. Sera were analyzed every 2 weeks for total IgG, IgG anti-dsDNA autoantibodies, and C3 levels by ELISA. Urinary excretion of albumin was also determined. Kidneys were collected at 24 weeks for histologic evaluation.

Results: Sera from WT MRL/*lpr* mice showed significant C3 deposition on zymosan particles, whereas sera from MASP-$1/3^{-/-}$ MRL/*lpr* mice failed. Interestingly, compared to WT MRL/*lpr* mice, MASP-$1/3^{-/-}$ MRL/*lpr* mice had significantly increased levels of serum total IgG. However, there was no statistically significant difference of serum IgG anti-dsDNA antibody levels between the two groups. Serum C3 levels in WT MRL/*lpr* mice decreased as the mice aged. In contrast, serum C3 levels in MASP-$1/3^{-/-}$mice were maintained, and were significantly higher than those in the WT group at and after week 16. There was no significant difference in glomerular IgG deposition levels between WT and MASP-$1/3^{-/-}$ groups. Importantly, minimal or no glomerular C3 deposition was observed in MASP-$1/3^{-/-}$ MRL/lpr mice, while it was ready evident in WT MRL/*lpr* mice. Unlike WT MRL/*lpr* mice, none of MASP-$1/3^{-/-}$ MRL/*lpr* mice developed albuminuria (no more than 100 micro-g/day/mouse) until 24 weeks of age. Pathological analysis revealed minimal or no glomerular disease in MASP-$1/3^{-/-}$ MRL/*lpr* mice; however, there was no significant reduction in interstitial nephritis compared to WT MRL/*lpr* mice.

Conclusion: Unlike WT MRL/*lpr* mice, MASP-$1/3^{-/-}$ MRL/*lpr* mice lacked activity of the alternative pathway, and had maintained serum C3 levels, no albuminuria, and minimal or no glomerular C3 deposition and glomerular pathologic changes. Thus, inhibition of the alternative pathway protects against the development of glomerular disease in lupus-prone MRL/*lpr* mice. MASP-$1/3^{-/-}$ MRL/*lpr* mice, however, had no significant reduction in interstitial nephritis, suggesting that the pathological mechanism of interstitial kidney disease was distinct from that of glomerular disease in MRL/*lpr* mice.

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Intestinal Microbiota Plays a Critical Role In The Production Of Antinuclear Antibodies In Lymphopenia-Induced Autoimmunity. Toshiki Eri[1], Kimito Kawahata[1], Mitsuru Imamura[1], Takeyuki Kanzaki[2], Lisa Akahira[1], Kazuya Michishita[1], Makoto Dohi[1], Takeshi Tokuhisa[3] and Kazuhiko Yamamoto[1]. [1]Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [2]Yamanashi Prefectural Central Hospital, Yamanashi, Japan, [3]Graduate School of Medicine, Chiba University, Chiba city, Chiba, Japan.

Background/Purpose: Production of antinuclear autoantibodies (ANAs) is one of the major characteristics of the systemic autoimmune diseases, such as systemic lupus erythematosus (SLE), but the mechanisms of their production are not known. Past studies showed athymic nude BALB/c mice developed spontaneous ANAs and lupus-like autoimmunity, and lymphopenic transfer model mice, in which $CD4^+CD25^-$ cells were transferred into nude mice, produced various autoantibodies including ANAs and anti-parietal cells antibodies, and organ specific autoimmune diseases. Here, using these mouse models, we investigated the mechanisms of the ANA production, in terms of the differentiation of transferred T cells into follicular helper T (T_{FH}) cells via lymphopenia-induced homeostatic proliferation (LIP). Moreover, by depleting intestinal microbiota by antibiotics administration, we elucidated the role of intestinal microbiota in this system.

Methods: $CD4^+$T cell subsets from wild-type BALB/c mice were adoptively injected into athymic BALB/c nude mice, with or without depleting recipient mice of their intestinal microbiota by orally administering broad-spectrum antibiotics in drinking water. Immunoprecipitation, immunofluorescent staining, and ELISA were performed to detect ANAs. Flowcytometry and immunostaining were performed to detect germinal center formation, and differentiation of transferred T cells.

Results: This lymphopenic mouse transfer model induced high titer IgG-type ANA production early and at high rates. Clinically important autoantibodies in SLE, such as anti- double strand-DNA, Sm, U1-RNP antibodies, were also detected by ELISA. Class switching and ANA production were enhanced when regulatory T cells-depleted $CD4^+$ T cells were transferred into. We identified IL-21-producing PD-1^+ T_{FH}cells which develop from conventional T cells during LIP and drive germinal center reactions with aberrant B cell responses. Depletion of intestinal microbiota resulted in significant reduction of both spontaneously occurring ANAs in nude mice and enhanced ANAs in lymphopenic transfer model. LIP and differentiation into TFH cells of transferred conventional T cells were also substantially impaired by microbiota depletion.

Conclusion: This study reveals that ANA production by nude mice is enhanced by LIP-T_{FH} cells. The novel insight that intestinal microbiota plays a critical role in both spontaneous and induced ANA production, would help to understand the immunopathogenesis of systemic autoimmune diseases. Moreover, the further investigation into the crosstalk between intestinal microbiota and the innate and adaptive immune systems may lead to a new therapeutic approach to systemic autoimmune diseases.

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Triggering Receptor Expressed on Myeloid Cells 1 In Systemic Lupus Erythematosus. Laurie Davis[1], Yong Du[2], Tianfu Wu[2] and Chandra Mohan[3]. [1]UT Southwestern Medical Center, Dallas, TX, [2]University of Texas, Southwestern Medical Center at Dallas, Dallas, TX, [3]University of Texas Southwestern Medical Center, Dallas, TX.

Background/Purpose: In healthy individuals, TREM-1 proteins are cell surface receptors expressed by hematopoietic cells of the myeloid lineage. TREM-1 is a potent amplifier of proinflammatory responses. TREM-2 acts to downregulate inflammatory cytokines and is associated with suppressive macrophages. In prior studies increased soluble TREM-1 (sTREM-1) levels in serum accurately correlated with sepsis. TREM-1 hyper-expression has been observed in auto-inflammatory responses, such as rheumatoid arthritis and inflammatory bowel disease. In both sepsis and arthritis models, TREM-1 inhibitors prevent tissue destruction caused by inflammation. We posit that TREM-1 plays a significant role in regulating SLE renal disease and that TREM-1 is involved in the amplification of the inflammatory response.

Methods: We have explored TREM-1 expression and function in a murine anti-glomerular basement membrane antibody-induced nephritis (anti-GBM) model which shares a number of relevant pathogenic features with

lupus nephritis. Mice were pre-sensitized on day −5 (5 days before induction of anti-GBM) with rabbit IgG (250 μg/mouse) in adjuvant. On day 0, the mice received anti-GBM serum; 200μg of total IgG in a 300μl volume intravenously per mouse. After induction of anti-GBM disease, urine was collected from 129/SvJ and B6 mice at different timepoints and sTREM-1 was assessed by ELISA. Renal disease was measured by proteinuria and renal pathology. The impact of a TREM-1 inhibitory peptide (LP17) was assessed.

Results: In the anti-GBM model, 129/SvJ mice developed severe GN, whereas B6 mice did not. Renal macrophages from 129/SvJ mice expressed elevated TREM-1 compared to B6 mice. Anti-GBM disease induced elevated urine sTREM-1 levels in 129/SvJ versus control B6 mice. After induction of anti-GBM disease, urine was collected from 129/SvJ and B6 mice at different timepoints and sTREM-1 was assessed by ELISA. Elevated sTREM-1 levels were detected in the urine of 129/SvJ mice from day 7 through day 21. In the anti-GBM model, TREM-1 blockade with an inhibitory peptide ameliorated renal inflammation compared to control peptide. TREM-1 blockade inhibited proteinuria, as well as renal disease as measured by GN class, severity of tubulointerstitial disease, crescent formation, and inflammatory cell infiltrates. Elevated sTREM-1 levels were detected in serum of spontaneous murine lupus (SLN) models compared to controls and in SLN renal biopsies. Finally, elevated sTREM-1 levels were detected in serum of SLE patients with nephritis and TREM-1 was detected in renal biopsies from SLE patients but not controls.

Conclusion: These studies suggest that the TREM-1 hyper-expression in the nephritis prone 129/SvJ strain has critical pathogenic relevance, and that TREM-1 is amenable to therapeutic targeting for nephritis. These studies could have important implications in the understanding of pathogenic mechanisms driving SLE renal disease. More specific assays for nephritis, such as TREM-1 as a prognostic indicator of disease, might greatly enhance quality of therapeutic management for SLE nephritis.

Disclosure: L. Davis, None; **Y. Du**, None; **T. Wu**, None; **C. Mohan**, None.

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Bacterial Amyloids Promote Type I Interferon Production and Accelerate Autoimmunity. Paul Gallo, Glenn Rapsinski, Cagla Tukel and Stefania Gallucci. Laboratory of Dendritic Cell Biology, Temple Autoimmunity Center, Temple University School of Medicine, Philadelphia, PA.

Background/Purpose: Infection is a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE). This is largely due to the use of potent immunosuppressive therapy, but may also stem from inherent immune dysregulation. Curli is a bacterial amyloid that serves as a component of enteric bacterial biofilms including those of *Escherichia coli* and *Salmonella enterica* serovar Typhimurium. Patients are exposed to curli during urinary tract infections, gastrointestinal infections, and sepsis. Nucleic acids are also an integral part of curli biofilms as treatment with DNases leads to biofilm dissociation. Here we studied the immune response to nucleic acid-containing curli amyloids in the context of murine SLE.

Methods: Curli amyloid was isolated from *Salmonella* bacterial cultures. *In vitro* studies were performed using bone marrow-derived dendritic cells (BMDCs) from wild type and lupus-prone mice. BMDCs were activated with a dose titration of curli amyloid. Synthetic curli was used to study the role of nucleic acids in the immune response. *In vivo* studies were performed using lupus-prone NZBW-F1 mice. To simulate a chronic bacterial infection, eight 6-week-old mice were injected intraperitoneally (i.p.) with curli or PBS three times a week for 5 weeks and monitored for autoantibody production.

Results: We found that curli amyloids from bacterial cultures contain abundant nucleic acids and that exogenous DNA enhances amyloid fibrillization. BMDCs strongly respond to curli, producing large quantities of IL-12, IL-6, and IL-10. Curli also induces expression of IFN-β and IFN-simulated genes, with BMDCs from lupus-prone mice over-expressing these genes compared to wild type. Using both natural and synthetic curli, we found that curli and nucleic acids synergize to activate DCs. Lupus-prone NZBW-F1 mice injected i.p. with curli, compared to PBS, produce high quantities of anti-dsDNA and anti-chromatin autoantibodies within 2 weeks of the first injection.

Conclusion: The bacterial amyloid curli contains nucleic acids which are integral to the immune response to bacterial biofilms. Curli is a potent activator of dendritic cells and can rapidly accelerate autoimmunity in lupus-prone mice. This work suggests that nucleic acid-containing bacterial amyloids are an important environmental trigger for lupus and that curli injection may be useful as a novel method to accelerate murine lupus.

Disclosure: P. Gallo, None; **G. Rapsinski**, None; **C. Tukel**, None; **S. Gallucci**, None.

2896

Damage In Systemic Lupus Erythematosus Is a Potentially Modifiable Outcome: Results From The Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort. Ian N. Bruce[1], Aidan O'Keefe[2], Li Su[3], Vernon Farewell[3], John G. Hanly[4], Susan Manzi[5], Murray B. Urowitz[6] and Systemic Lupus International Collaborating Clinics (SLICC)[7]. [1]Arthritis Research UK Epidemiology Unit and NIHR Manchester Musculoskeletal Biomedical Research Unit, The University of Manchester, Manchester, United Kingdom, [2]University of Cambridge, Cambridge, United Kingdom, [3]MRC Biostatistics Unit, Cambridge, United Kingdom, [4]Dalhousie University and Capital Health, Halifax, NS, [5]West Penn Allegheny Health System, Pittsburgh, PA, [6]University of Toronto, Toronto Western Hospital, Toronto, ON, [7]Toronto Western Hospital, Toronto, ON.

Background/Purpose: Irreversible damage is an important outcome in patients with SLE. We aimed to study damage accrual in early SLE. We examined the rate of accrual and factors that determine the development and progression of damage as well as the relationship between damage and survival.

Methods: The SLICC Inception Cohort Study includes patients from 31 centres in 11 countries in North America, Europe, and Asia. The cohort was recruited from 2000–2011 and enrolled within 15 months of their 4th 1987 ACR criteria. Damage was measured annually by the SLICC/ACR damage index (SDI). A multi-state model for transitions among damage states was used. Initial modelling was based on a proportional hazards analysis and assumed common explanatory variables effects across selected transition rates. We assessed the relative rates of transition using maximum likelihood estimation. The Kaplan-Meier method was used to estimate the probabilities relating to time until first worsening of SDI score. Cox regression analysis was performed with patient survival as the outcome against damage scores over time.

Results: We recruited 1722 patients. The mean (SD) age at cohort entry and number of visits was 35.0(13.4) years and 4.25(2.72) respectively. At baseline, 600 (34.8%) patients had at least one item of damage rising to 51.1% (178/348) by 6 years follow-up. 1502 patients, including 1337 (89%) females were analysed for SDI change over time. Patients with initial damage were more likely to increase their SDI at each follow-up visit [SDI 0 vs ≥1 ($p<0.01$)].

Multivariate models for transitions from no damage to damage and increase(s) in pre-existing damage were comparable; age, USA African race/ethnicity, SLEDAI score, steroid use and hypertension were all associated with increasing damage (Table 1). For transition from SDI 0 to >=1, male gender (Relative Transition Rates [95%CI]: 1.48 [1.06, 2.07]) and USA Caucasian race/ethnicity (1.68 [1.08, 2.46]) were associated new damage and Asian race/ethnicity with lower rates of new damage (0.60 [0.39, 0.93]). Increase in pre-existing damage was reduced in patients taking antimalarials (0.63 [0.44, 0.89]). Each point increase in SDI score was associated with an increased risk of death (HR [95%CI]: 1.46 [1.18, 1.81]).

Table 1. Analysis of factors significantly associated with accrual of damage in SLE patients either from no damage to damage (SLICC 0 to 1) or accrual in pre-existing damage (SLICC 1 to >1).

	Multivariate Relative Transition Rates (95% CI)	
Covariate	**SLICC 0→1**	**SLICC 1→1**
Gender (male)	**1.48 (1.06 ,2.07)**	**1.12 (0.86 ,1.46)**
Age diagnosis*	**1.30 (1.12 ,1.52)**	**1.00 (0.87 ,1.14)**
(Age diagnosis)^2	**1.12 (1.03 ,1.23)**	**1.07 (1.00 ,1.14)**
Caucasian USA	**1.63 (1.08 ,2.46)**	**1.26 (0.90 ,1.78)**
African USA	**1.58 (1.03 ,2.43)**	**2.40 (1.76 ,3.27)**
Asian	**0.60 (0.39 ,0.93)**	**0.95 (0.65 ,1.39)**
Steroid Use (Y/N)	**1.64 (1.21 ,2.21)**	**1.43 (1.12 ,1.84)**
Antimalarial Only	0.81 (0.53 ,1.22)	**0.63 (0.44 ,0.89)**
Immunosupp and AM	1.06 (0.69 ,1.62)	0.83 (0.60 ,1.16)
Hypertension (Y/N)	**1.71 (1.27 ,2.31)**	1.61 (1.28 ,2.03)
SLEDAI/3**	**1.17 (1.07 ,1.27)**	1.10 (1.03 ,1.16)

*Standardised age, **increase in rate for each SLEDAI increase of 3

Conclusion: Early damage in SLE is an important stratification factor that predicts future damage and mortality. We found a number of modifiable risk factors for damage (disease activity, hypertension, steroid use and a protective

effect of antimalarial use). An integrated intervention strategy to address these may improve long-term outcomes in SLE patients.

Disclosure: I. N. Bruce, Glaxo Smith Kline, 2, Roche Pharmaceuticals, 2, UCB, 5, BMS, 5; **A. O'Keefe**, Glaxo Smith Kline, 2; **L. Su**, Glaxo Smith Kline, 2; **V. Farewell**, Glaxo Smith Kline, 2; **J. G. Hanly**, None; **S. Manzi**, None; **M. B. Urowitz**, None; **S. L. I. C. C. (SLICC)**, GlaxoSmithKline, 2, Bristol-Myers Squibb, 2, Human Genome Sciences, Inc., 2.

2897

The Risk Of Deep Vein Thrombosis and Pulmonary Embolism In Systemic Lupus Erythematosus: A Population-Based Cohort Study. J. Antonio Avina-Zubieta[1], Eric C. Sayre[2], Diane Lacaille[1] and John M. Esdaile[1]. [1]Arthritis Research Centre of Canada, University of British Columbia, Richmond, BC, [2]Arthritis Research Centre of Canada, Richmond, BC.

Background/Purpose: Previous hospital-based studies have shown that patients with systemic lupus erythematosus (SLE) have an increased risk of cardiovascular disease, but limited population-based data are available on the risk of deep venous thrombosis (DVT) and pulmonary embolism (PE). We estimated the population-based risk of newly recorded DVT and PE among incident cases with SLE compared to controls from the general population using physician-billing and hospitalization databases that cover the entire population of the province of British Columbia, Canada (~ 5 million).

Patients and Methods: Our data include all visits to health professionals and all hospital admissions from Jan 1, 1990 to Dec 31, 2010 and all dispensed medications from Sept 1, 1995 to Dec 31, 2010 for all individuals. We conducted a retrospective matched cohort study among patients satisfying at least one of the following criteria: **a)** diagnosis of SLE in adults on at least two visits within a two-year period between Jan 1996 and Dec 2010 by a non-rheumatologist physician; **b)** diagnosis of SLE on at least one visit by a rheumatologist or from hospitalization. To increase specificity we excluded cases that were not confirmed by a rheumatologist if they were seen at a later point. Ten non-SLE controls matched by birth year, sex and calendar year of follow-up were selected from the general population for each case. Outcomes: incident PE, DVT, and PE or DVT events based on hospitalization records (for PE and DVT), outpatient visits (DVT) or death certificates (all outcomes). For non-fatal outcomes, we also required the use of anticoagulant medication within six-months of the event as part of all outcome definitions. We estimated relative risks (RRs) comparing SLE with age-, sex- and entry time-matched comparison cohorts, adjusting for potential cardiovascular risk factors.

Results: Among 5,031 incident SLE cases, 72, 72 and 121 developed a first time DVT, PE, and PE or DVT event, respectively (incidence rates = 3.4, 3.4 and 5.8 per 1,000 person years, respectively) (see table). Compared with the age, sex, and entry-time-matched controls, the RRs were 5.2 (95% CI; 3.8 – 6.9), 4.6 (95% CI; 3.5 – 6.2) and 4.8 (95% CI; 3.8 – 6.0) for DVT, PE, and DVT or PE, respectively. After adjusting for covariates the results remained similar (see table). The risk of developing DVT, PE or either event was highest within the first year following diagnosis of SLE, decreasing over time and persisting after 5 years.

Table. Risk of Incident PE, DVT or DVT or PE according to SLE Status

	SLE n = 5,031	Non-SLE n = 50,310
Incidence Rate Ratios of DVT		
DVT events, N	72	136
Incidence Rate/1000 Person-Years	3.4	0.7
Age-, sex-, and entry time-matched RRs (95% CI)	5.2 (3.8–6.9)	1.0
<1 year of disease duration	8.6 (4.9–15.1)	1.0
1–4.9 years of disease duration	4.7 (2.9–7.4)	1.0
5+ years of disease duration	3.4 (1.8–6.2)	1.0
Multivariable RR (95% CI)	3.9 (2.8–5.6)	1.0
Females	4.0 (2.7–5.9)	1.0
Males	4.0 (1.8–9.1)	1.0
Incidence Rate Ratios of PE		
PE events, N	72	150
Incidence Rate/1000 Person-Years	3.4	0.7
Age-, sex-, and entry time-matched RRs (95% CI)	4.6 (3.5–6.2)	1.0
<1 year of disease duration	14.9 (8.4–26.8)	1.0
1–4.9 years of disease duration	3.4 (2.1–5.4)	1.0
5+ years of disease duration	2.2 (1.1–4.2)	1.0
Multivariable RR	3.5 (2.5–4.8)	1.0
Females	3.4 (2.3–4.9)	1.0
Males	3.9 (1.6–9.4)	1.0
Incidence Rate Ratios of DVT or PE		
DVT and PE events, N	121	247
Incidence Rate/1000 Person-Years	5.8	1.2
Age-,sex-, and entry time-matched RRs (95% CI)	4.8 (3.8–6.0)	1.0
<1 year of disease duration	11.8 (7.8–17.8)	1.0
1–4.9 years of disease duration	3.9 (2.7–5.5)	1.0
5+ years of disease duration	2.3 (1.4–3.9)	1.0
Multivariable RR	3.6 (2.8–4.7)	1.0
Females	3.6 (2.7–4.8)	1.0
Males	3.6 (1.9–7.0)	1.0

Conclusion: This large population-based study indicates an increased risk of DVT and PE in patients with SLE. Our results support the need for increase monitoring for these complications in SLE patients, especially within the first year of disease onset.

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2898

Atherosclerosis In Systemic Lupus Erythematosus (SLE) and Controls, -An Analysis Of SLE Subgroups. Johanna Gustafsson[1], Kerstin Jensen-Urstad[1], Marie Herlitz-Lindberg[1], Sonia Möller[1], Susanne Pettersson[1], Iva Gunnarsson[1], Anders Larsson[2] and Elisabet Svenungsson[1]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Akademiska Hospital, Uppsala, Sweden.

Background/Purpose: Atherosclerosis is often assumed to be the main underlying cause of premature vascular events (VE) among patients with systemic lupus erythematosus (SLE) and accelerated atherosclerosis is frequently considered to be a general feature of SLE, though not confirmed in all studies. Since SLE is a very heterogeneous disease we studied the occurrence of atherosclerosis in unselected and in predefined subgroups of SLE patients. Individually matched population controls were used as comparators.

Methods: 281 SLE patients and 281 population controls, individually matched for age, sex, and region of living were included. All were investigated clinically including CVD risk factors and inflammatory biomarkers. The same investigator performed B-mode ultrasonography of carotid arteries. Mean intima media thickness (mIMT) and plaque occurrence (local IMT>1mm) were tabulated. Paired analyses were performed.

Results: In both groups: mean age was 48±14 years, 93% were females.

Patients had slightly thicker mIMT than controls (0.59±0.01 vs 0.57±0.01, p=0.003), but plaque occurrence did not differ, 20% and 16% respectively.

Manifest CVD (ischemic heart, cerebro- and peripheral vascular disease) was more common in patients (12 % vs. 1 %, p<0.0001).

Patients had lower high (HDL), low density lipoprotein (LDL) and albumine, but higher triglycerides (TG), apoB/A, C-reactive protein, homocysteine, cystatin C, creatinine, tumor necrosis factor receptor (TNFR) 1 and 2, and vascular cell adhesion molecule-1 (p<0.005 for all). Patients were more often on antihypertensive-, lipid-lowering, aspirin and warfarin treatments (p<0.05 for all).

Among SLE patients, after age adjustment: Manifest CVD was associated with plaques (p<0.0001), but not with mIMT (p=0.3).

mIMT was associated with smoking, sBP, HDL(negatively), LDL, TG, apoB/A, and glucose(p<0.05 for all).

Plaques were positively associated with smoking, sBP, TG, albumine, cystatin C, nephritis, TNFR 1 and 2, SLICC>1, and antihypertensive treatment, and negatively associated with leukopenia (p<0.05 for all).

Multivariable-adjusted models: In patients, age, sBP and apoB/A remained associated with mIMT (p<0.05 for all). Age, sBP and manifest CVD remained for plaques (p<0.05).

Stratified analyses: Analysis of SLE subgroups (nephritis(*112+112*), SSA/SSB(*131+131*) and anti phospholipid (aPL) (*75+75*)-positivity) compared to individually matched controls revealed that patients diagnosed with nephritis selectively had more plaques than their respective controls (p=0.008) and mIMT was was also thicker in the nephritis group (p=0.006). Thicker mIMT was also present in the SSA/SSB and aPL subgroups (p<0.05).

Conclusion: This is, to our knowledge, the largest study of atherosclerosis in SLE patients/matched population controls. Manifest CVD was more common among patients, but enhanced occurrence of atherosclerotic plaques was not a general feature of SLE as it was essentially confined to patients with a history of nephritis. mIMT was slightly thicker in patients, a more general SLE feature, but not associated with manifest CVD in this study. Our results imply that renal disease is an important driving factor behind accelerated atherosclerosis in SLE.

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2899

Outcome Of Incidental Silent Strokes In Systemic Lupus Erythematosus. Jamal Mikdashi University of Maryland School of Medicine, Baltimore, MD.

Background/Purpose: Silent strokes are brain infarcts that lack clinically overt stroke-like symptoms and fail to come to clinical attention. The prevalence of incidentally detected acute/subacute silent brain infarcts (SBIs) in systemic lupus erythematosus (SLE) is not known. Our aim is to determine the prevalence of SBIs in SLE and examine their outcome.

Methods: Consecutive subjects drawn from the Maryland Lupus Cohort, aged 18–50 years who underwent a cranial MRI between 2000 and 2010 were included. A total of 376 eligible patients were identified: 30 did not undergo diffusion-weighted MR imaging and 32 patients had inadequate follow-up, leaving a study population of 314 patients. Incidental silent stroke was ascertained when focal T2 hyperintense lesions ≥3 mm on diffusion-weighted imaging with corresponding apparent diffusion coefficient defects were identified. Demographic and clinical data for SLE patients with SBIs (n=86) were compared to SLE patients with no SBIs (n=228). The primary outcome was recurrent stroke and cognitive dysfuction determined at mean follow up of 24 months. A forward stepwise Cox regression model was used to determine factors associated with recurrent stroke or cognitive dysfunction in SBIs patients. Significant variables; age, ethnicity, smoking, alcohol intake, and cardiovascular risk factors were included in the model. SLE disease activity (SLEDAI), damage (SDI) and duration of SLE were adjusted for during analyses.

Results: 86 of 314 (27.4 %) subjects had SBIs with a mean age (SBIs=37.3 +/− 12.1 years, No SBIs=34.7 +/− 14.7 years), women (SBIs=80 %, No SBIs=80 %), African American (SBIs=70 %, No SBIs= 65 %), and mean duration of SLE (SBIs= 9.0 + 3.6, No SBIs= 6.9 + 2.8 years). Hypertension (SBIs= 80 %, No SBI= 65 %), migraine with aura (SBIs 10.4 %, No SBIs= *2.6 %),* and cardiovascular disease (SBIs= 11.6 %, No SBIs =1.7 %) were more frequent among patients with SBIs. There were no significant statistical differences among both groups with respect to baseline SLEDAI or SDI. SBIs were small and subcortical (basal ganglia 46.5%, cerebellum 23.4%, globus pallidus 7.0%, corpus callosum 4.7%).

Recurrent stroke occurred among SBIs patients (29%) and among those with no SBIs (6.5%), (p= 0.004). Independent predictors of recurrent stroke in SBIs patients included, anti-phospholipid syndrome [OR 12.0; 95% CI: 1.2–203.1].

A majority of the subjects with SBIs had significant cognitive impairment compared to no SBIs patients (60 % v 22%). SBIs patients had poorer memory and cognitive performance in all domains as compared to no SBI patients, including executive function, working memory, language, attention, and visuospatial abilities, but significantly in global cognition (48 % v 20 %) and information processing speed (42 % v 15 %). Independent predictors of cognitive dysfunction in SBIs patients included baseline presence of extensive white matter hyperintensity lesions in the periventricular and subcortical regions [OR: 10.1; 95 % CI: 1.1–98.4].

Conclusion: Silent strokes are prevalent in SLE, and are associated with recurrent strokes and cognitive dysfunction. Identifying novel risk factors that shed light on SBIs pathogenesis in SLE may offer potential therapeutic targets.

Disclosure: J. Mikdashi, None;

2900

Predictors Of Damage Accrual Over a 2 Year Period In a Large Multi-Racial/Ethnic Lupus Cohort. Megan E. B. Clowse[1], Jennifer M. Grossman[2], Joan T. Merrill[3], Anca Askanase[4], Olga Dvorkina[5], Michael D. Lockshin[6] and Cynthia Aranow[7]. [1]Duke University Medical Center, Durham, NC, [2]UCLA David Geffen School of Medicine, Los Angeles, CA, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]New York University School of Medicine, New York, NY, [5]SUNY Downstate Medical Center, Brooklyn, NY, [6]Hospital for Special Surgery, New York, NY, [7]The Feinstein Institute, Manhasset, NY.

Background/Purpose: Clinical experience and some previous research suggest that patients with lupus who live in more socio-economically vulnerable conditions fair worse than other patients. We sought to identify factors associated with damage accrual using the Lupus Clinical Trials Consortium, Inc. (LCTC) Lupus Data Registry, a patient registry of SLE in 16 lupus centers in North America.

Methods: The LCTC Lupus Data Registry began enrollment in 2010. We compared lupus patients who had accumulated ≥2 points in the SLICC Damage Index (SDI) over 2 years to those who had not with respect to demographics, features of disease, and factors that may enhance socio-economic vulnerability. A Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between a ≥2 point change in SDI and factors that were statistically significant in a univariate analysis. A most parsimonious model was created using a backwards-selection process, keeping all variables in the multivariable model that had a p-value <0.10.

Results: 1,478 patients with documented SDI scores at both enrollment and follow-up contributed a total of 2,503 person-years of follow-up (mean 1.77 years). 91.4% were female, 37.4% were non-Hispanic Caucasian, 34.0% were non-Hispanic African-American, and 8.2% reported Hispanic ethnicity.

In univariate analysis, higher baseline damage, higher baseline lupus disease activity (SLEDAI), longer duration of SLE, and more ACR classification criteria were each associated with a ≥2point increase in SDI. Prior treatments with immunosuppressants or with high dose prednisone were also associated with damage accrual while hydroxychloroquine use at enrollment was protective against damage accrual.

Among socioeconomic characteristics, there was no association between rate of damage accrual and educational attainment, marriage status, and insurance status; however, a two-fold increase in the rate of damage accrual was observed for those not working compared to those who either were working or were students (RR 2.06, 95% CI 1.42–3.01). After adjusting for the other socioeconomic characteristics, this association remained (RR 2.34, 95% CI 1.53–3.56).

In the multivariable model, work was no longer significantly associated with the rate of damage accrual. Additional factors losing significance in the multivariable model included duration of SLE, number of ACR criteria, high dose prednisone, and prior immunosuppressant use. Baseline SDI (p<0.0001) and SLEDAI (p=0.0036) remained significantly associated with the rate of damage accrual.

Conclusion: Baseline SDI and SLE activity were associated with damage accrual. Socio-economic factors did not demonstrate independent associations, contrary to our perceived clinical experience. The cross-sectional relationship between work and damage may in fact be a result rather than a cause of severe illness and damage.

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2901

Standardized Incidence Ratios For Cancer After Renal Transplant In Systemic Lupus Erythematosus and Non-Systemic Lupus Erythematosus Recipients. Rosalind Ramsey-Goldman[1], Amarpali Brar[2], Moro Salifu[2], Ann E. Clarke[3], Rahul M. Jindal[4] and Sasha Bernatsky[3]. [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]SUNY Downstate, Brooklyn, NY, [3]McGill University, Montreal, QC, [4]Uniformed Services University and George Washington University, Washington, DC.

Background/Purpose: Differentiating between effects of drugs vs. disease activity on cancer risk in SLE is difficult. Because all renal transplant recipients are on similar immunomodulatory medications, we hypothesize that additional cancer risk due to SLE itself would manifest as a higher cancer risk in SLE vs. non-SLE transplant recipients.

Methods: A cohort of 143,652 renal transplant recipients contributing 585,420 patient-years of follow-up were identified between 2001–2009 from the United States Renal Data System, USRDS. Patients were stratified by primary cause of renal failure: SLE (n=4289 [3%], contributing 18,435 patient-years) and non-SLE (n=139,361 [97%], contributing 566,985 patient-years). ICD 9 cancer codes were identified from Medicare physician claims. All cancers and individual cancer types were expressed as incidence per 100,000 patient-years. The expected number of cancers was derived from SEER general population cancer data from 2000–2009, accounting for age and sex. Standardized incidence ratios, SIRs, were calculated by dividing the observed by the expected number of cancers and 95% confidence intervals were generated.

Results: We identified 10,160 cancers occurring 3 months post transplant in this cohort. Tables 1 and 2, indicate a 3–4 fold increased cancer risk over-all in renal transplant recipients, vs. the general population. SIRs were similar in SLE vs. non-SLE transplant recipients for many specific cancers, with increased risks (compared to the general population) for lip/oropharyngeal, Kaposi, renal, lymphoma, colorectal, breast, and decreased risk (compared to the general population) for prostate. The SIRs for neuroendocrine and melanoma were increased in SLE vs. non-SLE transplant recipients. In contrast, the SIR for lung was decreased in SLE vs. non-SLE transplant recipients.

Table 1. SIRs for Cancer in SLE Renal Transplant Recipients vs. General Population

Cancer	Observed Cases/100,000 person-years	Expected Cases/100,000 person-years	Standardized Incidence Ratio (SIR)	95% Confidence Interval (CI)
All Cancers	1622	466	3.5	2.1–5.7
Lip/Oropharyngeal	781	11	72.6	57.3–92.0
Kaposi	38	0.6	62.2	35.2–141.1
Neuroendocrine*	163	5	42.8	30.7–50.2
Renal	217	14	15.4	12.3–21.7
Lymphoma	293	22	13.1	9.0–14.6
Colorectal	222	49	4.5	3.2–6.1
Melanoma	27	20	2.1	1.6–2.8
Breast	255	127	2.0	1.1–3.1
Lung	43	65	0.7	0.6–1.0
Prostate	54	163	0.7	0.01–1.0

Table 2. SIRs for Cancer in Non-SLE Renal Transplant Recipients vs. General Population

Cancer	Observed Cases/100,000 person-years	Expected Cases/100,000 person-years	Standardized Incidence Ratio (SIR)	95% Confidence Interval (CI)
All Cancers	1739	469	4.0	2.4–5.7
Lip/Oropharyngeal	665	11	58.1	36.2–80.1
Kaposi	0.6	42	72.5	55.2–89.9
Neuroendocrine*	74	5	14.3	4.1–24.6
Renal	142	14	10.1	7.6–12.6
Lymphoma	194	22	9.0	7.4–10.5
Colorectal	150	50	2.8	2.2–3.4
Melanoma	22	20	1.0	0.7–1.25
Breast	280	127	2.1	1.3–2.8
Lung	90	64	1.4	1.0–1.7
Prostate	65	163	0.4	0.2–0.5

* Neuroendocrine tumors include carcinoid tumors, islet cell tumors, medullary thyroid carcinoma, Merkel cell, secondary neuroendocrine, pheochromocytoma

Conclusion: Cancer risk in transplant recipients is high and surveillance may need to be tailored to the indication for transplant. Different methods of cancer ascertainment using physician claims data vs. tumor registries and inclusion of different SLE patient populations, restriction to those with severe SLE renal disease vs. our multinational cohort, may explain higher SIRs for cancer seen in SLE renal transplant recipients than in our previous multinational SLE cohort study evaluating cancer risk.

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ACR Concurrent Abstract Session
Systemic Sclerosis, Fibrosing Syndromes and Raynaud's – Pathogenesis, Animal Models and Genetics: Pathogenesis of Systemic Sclerosis
Wednesday, October 30, 2013, 11:00 AM–12:30 PM

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Key Roles For Interferon and Macrophage Activation In Progressive Lung Fibrosis Associated With Systemic Sclerosis. Romy Christmann[1], Giuseppina Stifano[1], Claudia Borges[2], Carlos Carvalho[3], Ronaldo Kairalla[3], Edwin R. Parra[3], Avrum Spira[1], Robert W. Simms[1], Percival Sampaio-Barros[3], Vera L. Capelozzi[3] and Robert Lafyatis[1]. [1]Boston University School of Medicine, Boston, MA, [2]CEUMA University, Sao Luis do Maranhao, Brazil, [3]University of Sao Paulo School of Medicine, Sao Paulo, Brazil.

Background/Purpose: Interstitial lung disease associate with Systemic Sclerosis(SSc-ILD) is one of the leading causes of mortality. We analyzed the gene expression of lung tissue in a prospective cohort of SSc-ILD compared to control lungs and to two prospective clinical parameters in order to understand molecular pathways implicated in progressive lung disease.

Methods: Lung tissue was obtained by open lung biopsy in 28 consecutive SSc-ILD patients and 4 controls. High-resolution computerized tomography(HRCT) and pulmonary function tests(PFTs) were performed on baseline and 2–3 years after treatment that was based on lung histologic classification. SSc lung RNA was available from 11 diffuse and 10 limited SSc patients. Microarray analysis was performed and the results correlated (Pearson's) with changes in HRCT score(FibMax) and PFTs values. Quantitative polymerase chain reaction(qPCR) and immunohistochemistry(IHC) were used to confirm differential levels of mRNA and protein levels. Interferon receptor alpha-1(IFNAR) deficient mice were submitted to a systemic bleomycin-lung fibrosis murine model. The study was approved by the Institutional Review Boards from both universities (Brazil and USA).

Results: Despite treatment, cyclophosphamide for non-specific interstitial pneumonia(NSIP) and intense anti-reflux treatment for centrilobular fibrosis-(CLF), most of SSc-ILD patients progressed based on delta FibMax($p<0.01$). Lung microarray data distinguished SSc-ILD from healthy controls. Macrophage markers, chemokines, collagen, TGF-beta- and interferon-regulated genes that were upregulated in SSc-NSIP were strongly correlated to the delta FibMax. IHC confirmed the collagen(Col1a1), interferon(OAS1 and IFI44), and macrophage(CCL18 and CD163) signatures and the positive correlation with delta FibMax was confirmed by qPCR in a larger group of SSc-NSIP patients: Col1a1 ($r^2=0.39$; $p<0.01$); IFI44 ($r^2=0.44$; $p<0.01$); OAS1 ($r^2=0.36$; $p<0.01$); CD163 ($r^2=0.24$; $p<0.03$), and CCL18 ($r^2=0.42$; $p<0,01$). Several genes were correlated with both the delta FibMax ($r>0.4$) and delta %FVC ($r<-0.1$), including interferon and macrophage markers; chemokines; and heat-shock proteins. IFNAR-deficient compared to wild-type mice exposed systemically to bleomycin developed a milder fibrotic score at day 21st. Several profibrotic genes, such as SPP1(osteopontin), LOX(protein-lysin oxidase), and PAI-1(serpine-1); macrophage markers (arginase-1 and chitinase-3) were blocked or partially blocked in IFNAR-deficient mice.

Conclusion: These results highlight the major pathogenic pathways relevant to progressive pulmonary fibrosis in SSc-ILD: macrophage activation, and upregulation of TGF-beta- and IFN-regulated genes. The importance of IFN was further supported here in a murine systemic lung-fibrotic model. These findings support the notion that blocking one or more of these pathways may be the best treatment approach for SSc-ILD.

Disclosure: R. Christmann, None; **G. Stifano**, None; **C. Borges**, None; **C. Carvalho**, None; **R. Kairalla**, None; **E. R. Parra**, None; **A. Spira**, None; **R. W. Simms**, None; **P. Sampaio-Barros**, None; **V. L. Capelozzi**, None; **R. Lafyatis**, None.

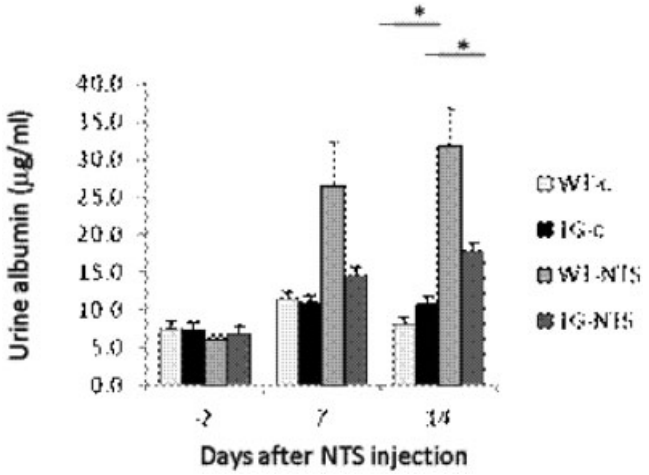
2903

Perturbed Response To Experimental Renal Injury In a TGFβ Dependent Mouse Model Of Scleroderma. Emma Derrett-Smith, Mark Neal, David J. Abraham, Alan Salama, Mark A. Little and Christopher P. Denton. UCL Medical School, London, United Kingdom.

Background/Purpose: Scleroderma renal pathology is predominantly vascular and fibrotic without major inflammatory features. Accelerated hypertension and rapidly progressive renal dysfunction are hallmarks of scleroderma renal crisis. No current animal model of scleroderma (SSc) develops this complication. The TβRIIΔk-fib transgenic mouse model of SSc has a systemic vascular phenotype comprising hypertension and large vessel adventitial fibrosis without constitutive renal disease. However, the response to long-term further elevation of blood pressure or an inflammatory renal insult has not been studied. We have therefore explored the link between altered TGFb bioactivity, vasospasm and inflammatory stress on the systemic vascular endothelium using nitric oxide synthase inhibition and the nephrotoxic nephritis model using this strain.

Methods: Histological assessment of cardiac and renal architecture, immunostaining for microvessel density and inflammatory cells and assessment of microalbuminuria by ELISA were performed on adult male transgenic (TG) and littermate wildtype (WT) animals (n=6) treated with either the NO synthase inhibitor L-NAME for 20 weeks, or a single dose of nephrotoxic serum with pre-immunisation. Biochemical analysis of the TGFb signalling pathway was performed assessing RNA and protein using whole organ isolates, and by immunostaining of tissue sections. Results were compared to appropriate control groups.

Results: Increased cardiac mass, and an increase in cardiac collagen measured by qPCR and Sircol® assay in TG and WT treated groups demonstrated that L-NAME treatment successfully induced hypertensive stress in this strain. Whole kidney lysates from L-NAME treated TG animals showed upregulated expression of Col1a1 (TG untreated copy number 3937±315, TG treated 6319±48, $p<0.05$) and Pai-1 (TG untreated 410±57, TG treated 740±74, $p<0.05$), and glomerulosclerosis was present on sirius red staining in the TG treated group, suggesting that these animals exhibited an enhanced renal fibrotic response when compared to WT treated animals. No other structural vascular changes were identified. In contrast, by day 14, TG animals had developed significantly less proteinuria following treatment with nephrotoxic serum (NTS) when compared with WT littermates (figure 1). Examination of PAS stained samples showed increased severity and number of damaged glomeruli in WT treated mice compared with TG.



Conclusion: This mouse model of scleroderma demonstrates exaggerated fibrotic response to hypertensive injury and is relatively resistant to experimental glomerulonephritis. This is likely to be a consequence of increased tissue levels of TGFb. Both of these processes may underpin the unique vascular pathology seen in scleroderma renal crisis, this mouse strain provides a platform for further studies of renal injury in scleroderma.

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2904

Gadolinium-Based Compounds Induce NLRP3-Dependent IL-1β Production and Peritoneal Inflammation. Jonathan Kay[1], Lukas Bossaller[2], Christian Schmidt-Lauber[2], Hani H. Abujudeh[3], Gregory Vladimer[2], Eicke Latz[2], Katherine A. Fitzgerald[2], Ann Marshak-Rothstein[2] and Ellen M. Gravallese[2]. [1]UMass Memorial Medical Center and University of Massachusetts Medical School, Worcester, MA, [2]University of Massachusetts Medical School, Worcester, MA, [3]Massachusetts General Hospital and Harvard Medical School, Boston, MA.

Background/Purpose: Nephrogenic systemic fibrosis (NSF) is a progressive iatrogenic fibrosing disorder that develops in patients with chronic kidney disease following administration of gadolinium (Gd)-based contrast agents (GBCA) for imaging studies. In the setting of impaired renal clearance of GBCA, Gd deposits in various tissues and fibrosis develops. However, the precise mechanism by which Gd induces systemic fibrosis is incompletely understood. Because other profibrotic agents, such as silica and asbestos, activate the NOD-like receptor protein 3 (NLRP3) inflammasome and thereby initiate a cellular response associated with IL-1β release, we evaluated the effects of various Gd-containing compounds on inflammasome activation.

Methods: Bone marrow derived macrophages (BMDM) from wild type (WT), *NLRP3*$^{-/-}$ and *ASC*$^{-/-}$ mice were exposed to each of three Gd-containing compounds: $GdCl_3$ (free Gd salt), and Omniscan® and Gd-diethylenetriaminepentaacetic acid (Gd-DTPA) (chelated forms of Gd). IL-1β release into in culture media was quantified by ELISA and the extent of IL-1β processing was determined by ELISA and Western blot analysis. Inflammasome activation and regulation was determined in macrophages polarized to an M1 or M2 phenotype using ELISA, qRT-PCR and NanoString nCounter analysis. Finally, WT and *NLRP3*$^{-/-}$ mice were injected intraperitoneally (i.p.) with either 500 μM Gd-DTPA or phosphate buffered saline (PBS) and recruitment of inflammatory cells to the peritoneum was analyzed by FACS.

Results: All three Gd-containing compounds induced concentration-dependent IL-1β secretion. $GdCl_3$ was the most potent activator, leading to the release of detectable levels of IL-1β at a concentration of 2.5 μM. Gd-DTPA and Omniscan® also induced IL-1β production but at 200- and 4000-fold higher concentrations, respectively. For all three substances, Western blot analysis confirmed that pro-IL-1β was processed to mature IL-1β. None of the Gd-containing reagents induced IL-1β release by BMDM from *ASC*$^{-/-}$ or *NLRP3*$^{-/-}$ mice, in which inflammasome activation is impaired, demonstrating that IL-1β secretion is induced through engagement of the NLRP3 inflammasome. Furthermore, after priming with low doses of LPS, Gd-containing compounds activated IL-4-polarized (M2) macrophages more effectively than IFNγ-polarized (M1) macrophages, since the M1 macrophages preferentially expressed genes (CD40, SOCS1, STAT1, and STAT3) known to downregulate inflammasome signaling. Mice injected i.p. with Gd-DTPA exhibited both a relative and an absolute increase in the number of inflammatory monocytes and granulocytes recruited to the peritoneal cavity, as compared to PBS-injected mice. This effect was markedly reduced in *NLRP3*$^{-/-}$ mice, as compared to WT mice.

Conclusion: Both free Gd and GBCA activate the NLRP3 inflammasome in macrophages and induce IL-1β secretion *in vitro* and the recruitment of neutrophils and inflammatory monocytes *in vivo*. The preferential activation by Gd of M2 macrophages, which promote wound healing and fibrosis, is consistent with the predominantly fibrotic presentation of NSF and may be clinically relevant.

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2905

Demethylation of ITGAL (CD11a) regulatory sequences in CD4+T lymphocytes of Systemic Sclerosis. Yaoyao Wang[1], Ye Shu[2], Qing Wang[1], Ming Zhao[1], Gongping Liang[1], Qianjin Lu[1] and Rong Xiao[1]. [1]Second Xiangya Hospital, Central South University, Changsha, China, [2]Hunan Children's Hospital, Changsha, China.

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune connective tissue disease epitomized numerous cellular and humoral immunological abnormalities. The immune system undoubtedly plays a pivotal role in SSc pathogenesis. And a growing body of evidence indicates that alterations to epigenetic DNA methylation patterns contribute to many autoimmune diseases including SSc. CD11a, a subunit of the lymphocyte function-associated antigen 1alpha LFA-1 (CD11a/CD18)with costimulatory functions by adhesive interactions between T cells and other immune system cells including macrophages, dendritic cells and B cells plays a central role in inflammatory and immune responses. CD11a is overexpressed due to hypomethylation of its regulatory elements in CD4+ T cells from patients with several autoimmune diseases. However, it is unknown whether aberrant expression and methylation of CD11a occur in T cells from patients with SSc. We aimed to compare the CD11a expression level and the methylation status of the CD11a promoter and enhancer regions in CD4+ T cells from SSc patients, healthy controls (HC) and CD4+ T cells with DNA methylation inhibitors.

Methods: CD11a expression in CD4+T cells from patients with SSc and healthy control subjects was measured by flow cytometry and real-time reverse transcription polymerase chain reaction. Related DNA methylation modifier enzymes such as DNA methyltransferases (DNMTs), Methyl DNA binding domain proteins (MBDs) and Ten-eleven translocation protein-s(TETs) were measured by RT-PCR. Bisulfite sequencing was used to determine the methylation status of the CD11a promoter and flanking regions in CD4+ T cells from SSc and HC and in CD4+ T cells with DNA methylation inhibitors. Detection of CD4+T cell proliferation and autologous B cell IgG antibodies was performed using commercially available kits. Modified Rodnan total skin score(MRTSS) and Valentini Scleroderma Disease Activity Index (SDAI) for Systemic Scleroderma patients were performed.

Results: Elevated CD11a expression were observed in CD4+T cells from patients with SSc. Expression of TET1 was significantly increased but DNMT1, MBD3, and MBD4 were significantly down-regulated in SSc CD4+T cells relative to controls. Expression of DNMT1 mRNA was negatively correlated with transcript level of CD11a. The methylation levels of the DNA regulatory sequences of CD11a were reduced in patients with SSc compared with HC, and there was a significant inverse correlation

between the average methylation level and CD11a mRNA expression in patients with SSc. Treatment with a DNA methylation inhibitor decreased CD11a regulatory sequences methylation contribution to CD11a overexpression and increased B cell costimulation and subsequent immunoglobulin over-production. Further more, transcript level of CD11a was positively correlated with disease activity.

Conclusion: Demethylation of CD11a regulatory elements contributes to CD11a overexpression and results in T cell autoreactivity and B cell immunoglobulin overproduction in CD4+T cells from patients with SSc correlating with disease activity.

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2906

Peripheral Blood Mononuclear Cells Co-Cultured With Autologous Skin Fibroblasts Up-Regulate IL-17A and Play Anti-Fibrotic Effects In Systemic Sclerosis. Serena Vettori[1], Giuseppe Pasquale[2], Michele Iudici[1], Giovanna Cuomo[1], Giusi Barra[2], Barbara Russo[1], Raffaele De Palma[2] and Gabriele Valentini[1]. [1]Rheumatology Unit, Second University of Naples, Naples, Italy, [2]Immunology Unit, Second University of Naples, Naples, Italy.

Background/Purpose: IL-17A has been recently implicated in the pathogenesis of systemic sclerosis (SSc). Therefore, we explored its expression and effects in peripheral blood mononuclear cells (PBMCs) co-cultured with autologous skin fibroblasts.

Methods: PBMCs and autologous skin fibroblasts from 5 patients with early (disease duration < 3 years) diffuse (dc) SSc were co-cultured in presence of IL-2 20U/ml in a 1:10 ratio. Separate cultures of PBMCs with IL-2 20U/ml and unstimulated fibroblasts were used as controls. The expression of IL17A, IL1B, IL4, and TGFB1 mRNA was analyzed in co-cultured and control PBMCs after 10 days by real-time PCR. The expression of IL17RA, CCL2, CCL3, CXCL1, COL1A1, COL3A1, CTGF, TGFBR2, and SMAD3 mRNA was analyzed in co-cultured and control fibroblasts. Chemokine production was further investigated at the protein level in culture surnatants by multiplex suspension fluorescence-based immunoassay.

Results: Real-time PCR analysis showed an increased expression of IL17A in co-cultured PBMCs by 11.5 fold ($p < 0.01$). No significant difference was found in the expression of IL1B, IL4, and TGFB1 mRNA between co-cultured and control PBMCs. Consistently with IL17A up-regulation in co-cultured PBMCs, mRNA levels of IL17RA were increased by 4.3 fold in co-cultured fibroblasts ($p < 0.05$). In order to clarify whether this up-regulation ensued in the formation of a functional receptor, we analyzed the expression of CCL2, CCL3, and CXCL1 mRNA, which are IL-17A target genes, in co-cultured fibroblasts. Indeed, CCL2, CCL3, and CXCL1 were up-regulated by 11.9 fold, 773.26 fold, and 13 fold respectively ($p < 0.05$). This induction was confirmed at the protein level in surnatants from co-cultures (CCL-2 25014 pg/ml; CCL-3 2227 pg/ml; CXCL-1 605.8 pg/ml) compared to control PBMCs (CCL-2 2821 pg/ml; CCL-3 199.1 pg/ml; CXCL-1 2.4 pg/ml) and control fibroblasts (CCL-2 2894 pg/ml; CCL-3 21.56 pg/ml; CXCL-1 3.1 pg/ml) ($p < 0.05$). Lastly, we investigated the effects of co-cultured PBMCs on the expression of pro-fibrotic genes in fibroblasts. We found that COL1A1, COL3A1, and CTGF mRNA was down-regulated by 0.33 fold, 0.24 fold, and 0.31 fold respectively ($p < 0.05$). In addition, we also found a down-regulation by 0.78 fold of TGFBR2 and by 0.79 of SMAD3 mRNA, suggesting that co-cultured PBMCs may interfere with the TGF-beta pathway hyperactivity in SSc fibroblasts.

Conclusion: Here we show for the first time that PBMCs from early dcSSc patients co-cultured with autologous skin fibroblasts over-express IL17A and exert anti-fibrotic effects in vitro. The simultaneous up-regulation of IL17RA and IL-17A target genes in the co-cultured fibroblasts suggests that IL-17A pathway is active in early dcSSc fibroblasts. These findings are paralleled by the down-regulation of TGF-beta signalling components. We previously showed that in co-cultures performed with PBMCs and autologous skin fibroblasts from early dcSSc patients T cells are expanded and kill autologous fibroblasts. Taken together, our novel data support the hypothesis that immune system may be primarily aimed to control fibroblast activation in the early phases of the disease, potentially opening new therapeutic approaches in SSc.

Disclosure: S. Vettori, None; **G. Pasquale**, None; **M. Iudici**, None; **G. Cuomo**, None; **G. Barra**, None; **B. Russo**, None; **R. De Palma**, None; **G. Valentini**, None.

2907

D1398G Variant Of Hepatocyte Growth Factor Receptor—A Potential Biomarker Of Severe Interstitial Lung Disease In African American Scleroderma Patients. Ilia Atanelishvili, Tanjina Akter, Richard M. Silver and Galina S. Bogatkevich. Medical University of SC, Charleston, SC.

Background/Purpose: Interstitial lung disease (ILD) is a major complication and leading cause of mortality in scleroderma (SSc, systemic sclerosis). The morbidity and mortality rates in African American scleroderma patients are higher when compared with SSc patients of other races. We previously demonstrated that hepatocyte growth factor (HGF) is reduced in BALF and plasma from African American SSc-ILD patients compared with white SSc-ILD patients. Moreover, in African American SSc fibroblasts the anti-fibrotic effects of HGF are compromised due to a deficiency in phosphorylation of the HGF receptor (cellular mesenchymal-epithelial transition factor, c-MET). The present study was undertaken to identify potential inhibitory mutations in c-MET gene extracted from lung fibroblasts with impaired phosphorylation of the HGF receptor.

Methods: Lung tissue was collected postmortem from SSc patients who fulfilled the ACR criteria for SSc and had evidence of lung involvement. SSc-ILD was confirmed by histological examination of postmortem lung tissue. Lung fibroblasts were isolated using standard procedures. RNA samples from lung fibroblasts were prepared by QIAGEN RNeasy® kit; c-MET gene was extracted by QIAGEN OneStep RT-PCR Kit. The coding exons of c-MET were PCR amplified and sequenced on both strands on ABA Prism 377 Genetic Analyzer using taq dye terminator chemistry at our university's DNA Sequencing Core. The sequence data were analyzed by BLASTN 2.2.18 using CCDS 47689. D1398G c-Met mutant was created using the QuickChange Site-Directed Mutagenesis XL kit from Stratagene; c-Met wild type and D1398G adenoviruses were generated by AdEasy Vector System, Quantum Biotechnology. HGF receptor phosphorylation, connective tissue growth factor (CTGF) and collagen content were studied by immunoblotting.

Results: We have identified six variants of c-Met unique for lung fibroblasts with non-functional HGF receptor. All of them are located in the C-terminus of the c-Met gene. We found that 100% of cell lines with non-functional HGF receptor carry the D1398G variant of c-Met gene; approximately 20% of all tested SSc lung fibroblasts contain C1379W and V1380G variants of c-Met gene; approximately 10% of cells with reduced HGF receptor function contain H1366P, L1351W, or E1350D variants of c-Met gene. None of these mutations was found in the c-Met gene isolated from SSc lung fibroblasts containing functional c-Met receptor. Lung fibroblasts isolated from African American SSc-ILD patients with D1398G variant of c-Met gene and normal lung fibroblasts transfected with D1398G c-Met mutant were characterized by limited effects of HGF on CTGF and collagen and by reduced HGF receptor phosphorylation on tyrosine 1238, 1252, and 1253.

Conclusion: D1398G variant of c-Met gene results in defective HGF signaling in lung fibroblasts. The occurrence of D1398G in African American SSc-ILD patients may explain in part a pathophysiologic link between African American race and poor pulmonary outcomes in SSc patients.

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ARHP Concurrent Abstract Session
Research and Health Services
Wednesday, October 30, 2013, 11:00 AM–12:30 PM

2908

The Roles Of Nurse Practitioners and Physician Assistants In Rheumatology Practices In The United States. Erika Brown[1], Asaf Bitton[1], Liana Fraenkel[2], Hsun Tsao[3], Jeffrey N. Katz[1] and Daniel H. Solomon[4]. [1]Brigham and Women's Hospital, Boston, MA, [2]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare System, New Haven, CT, [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [4]Harvard Medical School, Brigham and Women's Hospital, Division of Rheumatology, Division of Pharmacoepidemiology, Boston, MA.

Background/Purpose: A recent workforce study of rheumatology in the US suggests that during the next several decades the demand for rheumatology services will outstrip the supply of rheumatologists. Mid-level providers working in rheumatology, such as nurse practitioners (NPs) and physician

assistants (PAs), may be able to alleviate projected shortages, but national data on their current roles and responsibilities are sparse.

Methods: We administered a nation-wide survey to mid-level rheumatology providers during 2012 through the Association of Rheumatology Health Professionals and Society of Physician Assistants in Rheumatology. E-mails and mailed invitations with the survey were sent with one follow-up reminder. The survey contained questions regarding demographics, training, level of practice independence and responsibilities, disease modifying antirheumatic drug (DMARD) prescribing, use of objective RA outcome measures, and knowledge and use of Treat to Target strategies.

Results: The invitation was sent to 482 eligible mid-level providers via e-mail and 90 via US mail. We received a total of 174 (30%) responses, 47% from NPs and 51% from PAs (2% missing). The mean age was 46 (±11) years, and 83% were female. Nearly 75% had ≤10 years of experience, and 53% received formal training in rheumatology training. Sixty-three percent reported having their own panel of patients. Respondents reported seeing patients in the context of follow-up visits (98%), initial consults (74%), and urgent visits (89%). They described a variety of practice responsibilities, with the top five being: performing patient education (98%), adjusting medication dosages (97%), conducting physical exams (96%), treating patients (96%), and starting patients on medications (94%). Over 90% felt very or somewhat comfortable diagnosing RA and a similar percentage prescribed DMARDs (see Table). Forty-nine percent reported using DAS, CDAI, SDAI, and/or RAPID disease activity measures for RA and 56% reported that their practices used Treat to Target strategies.

Table. Survey Responses

	Total
Confidence diagnosing RA[1]	
Very confident	76.9%
Somewhat confident	21.3%
Not particularly confident	1.2%
Not at all confident	0.6%
Manages patient treatment[2]	
Yes	94.6%
No	5.4%
Knows of TTT[2]	
Yes	77.8%
No	22.2%
Practice uses TTT[3]	
Yes	75.4%
No	24.6%
Outcomes measures used[4]	
DAS	21.5%
CDAI	12.8%
SDAI	0.6%
HAQ	37.8%
RAPID	23.3%
Patient global	25.0%
Physician global	21.5%
Uses any outcomes measure	48.6%

Abbreviations: DAS = Disease Activity Score; CDAI = Clinical Disease Activity Index; SDAI = Simple Disease Activity Index; HAQ = Health Assessment Questionnaire; RAPID = Routine Assessment of Patient Index Data; TTT = Treat to Target Totals varied due to missing data: [1]N = 169; [2]N = 167; [3]N = 130; [4]N = 172

Conclusion: Most NPs and PAs responding reported substantial patient care responsibilities, working independently; many reported using disease activity measures and treat to target strategies. These data suggest the potential opportunity of expanding the use of NPs and PAs as practitioners in rheumatology to reduce the projected workforce shortages and meet current RA treatment recommendations.

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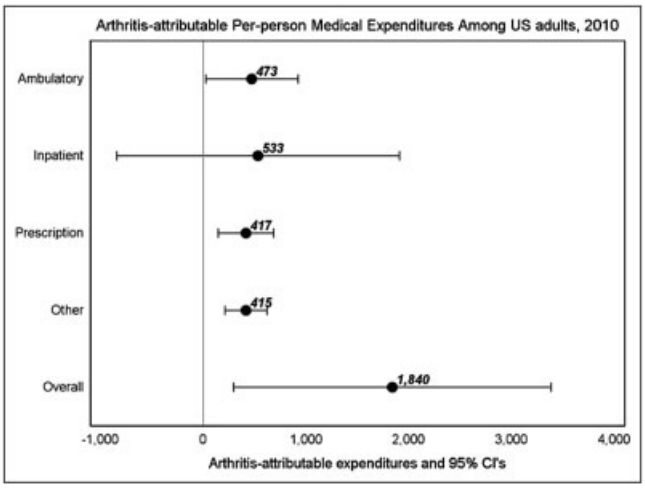
2909

2010 Medical Care Expenditures Among US Adults With Arthritis. Miriam Cisternas[1], Louise Murphy[2], David Pasta[3], Edward H. Yelin[4] and Charles G. Helmick[5]. [1]MGC Data Services, Carlsbad, CA, [2]CDC, Atlanta, GA, [3]DMA Corporation, Palo Alto, CA, [4]UC San Francisco, San Francisco, CA, [5]Centers for Disease Control and Prevention, Atlanta, GA.

Background/Purpose: Using data from the 2010 Medical Expenditure Panel Survey (MEPS), we estimated total and arthritis-attributable medical care expenditures among US adults age 18 years and over with arthritis.

Methods: Arthritis was identified using an ICD-9-CM based definition of doctor-diagnosed arthritis. We estimated total and arthritis-attributable expenditures (the national sum and per–person mean) overall and for four categories: ambulatory care (office-based and hospital outpatient); inpatient care; prescriptions; and other (emergency room visits, home health care, vision aids, dental visits and medical devices). Arthritis-attributable expenditures were calculated using multi-stage regression models that adjusted for demographics (age, sex, race, Hispanic ethnicity, and education), health insurance coverage (any private, public only, or none), and nine costly comorbid conditions.

Results: In 2010, total medical care expenditures among adults with arthritis were $9,262 per person, (national sum = $566 billion), representing half of all expenditures among US adults in MEPS. Across categories, inpatient expenditures were highest ($2,972 per person), accounting for 32% of total medical expenditures among people with arthritis. National arthritis-attributable expenditures totaled $112.4 billion (mean per person = $1,840 [Figure]), and represented 10% of all national expenditures among US adults in MEPS, with inpatient expenditures comprising the largest portion of arthritis-attributable costs (29%). The national sum of arthritis-attributable expenditures were $33 billion for inpatient care, $29 billion for ambulatory care, $25 billion for prescriptions, and $25 billion for other services.



Figure

Conclusion: Analysis of US adults in 2010 showed that their arthritis-attributable medical care costs comprised 10% of all medical care expenditures nationally and total costs (including non-arthritis expenditures) for the arthritis population comprised half of all medical expenditures. This illustrates both the substantial economic impact of arthritis itself as well as the impact of comorbid conditions that occur in the 27% of the adult population living with arthritis. Population aging and increasing prevalence of obesity imply that these expenditures will increase in the future and suggest the need for intervention strategies such as weight management and increasing physical activity that prevent the adverse effects of arthritis including pain and disability.

Disclosure: M. Cisternas, None; **L. Murphy**, None; **D. Pasta**, None; **E. H. Yelin**, None; **C. G. Helmick**, None.

2910

Differences In Abatacept Use In Rheumatoid Arthritis Patients Across Europe: A Pan-European Database Analysis Of Abatacept In European RA Registries. David Neto[1], Axel Finckh[2], Florenzo Iannone[3], Estíbaliz Loza[4], Elisabeth Lie[5], Piet L.C. Van Riel[6], Merete L. Hetland[7], Karel Pavelka[8], Jacques-Eric Gottenberg[9], Xavier Mariette[10] and Carl Turesson[11]. [1]University of Geneva, Geneva, Switzerland, [2]Geneva University Hospital, Geneva, Switzerland, [3]D.I.M.I.M.P, Rheumatology Unit - University of Bari, Bari, Italy, [4]Spanish Society of Rheumatology, Madrid, Spain, [5]Diakonhjemmet Hospital, Oslo, Norway, [6]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [7]Copenhagen University Hospital Glostrup, Copenhagen, Denmark, [8]Department of Clinical and Experimental Rheumatology, Charles University, Prague, Czech Republic, [9]Strasbourg University Hospital, Strasbourg, France, [10]Bicêtre University Hospital, Le Kremlin Bicetre, France, [11]Skåne University Hospital, Malmö, Sweden.

Background/Purpose: Several European registries have pooled data of patients (pts) who received Abatacept (ABA) for rheumatoid arthritis (RA) to

acquire new knowledge about performance of ABA in clinical care in different settings.

The objective of this study was to analyze potential heterogeneity in pts initiating ABA across different European countries.

Methods: This is a cohort study of 8 longitudinal, observational, national RA registries from different European countries: ARTIS (Sweden), ATTRA (Czech Republic), BIOBADASER (Spain), DANBIO (Denmark), GISEA (Italy), NORDMARDS (Norway), ORA (France), SCQM (Switzerland), which have been described elsewhere. Inclusion criteria for this project were a diagnosis of RA and registered initiation of treatment with ABA. Key demographic variables, disease characteristics at ABA initiation, time on ABA treatment and reasons for discontinuation were collected from all registries and analyzed using descriptive statistics. Crude ABA drug retention was analyzed using Kaplan-Meier curves and log rank test.

Results: A total of 4041 pts were included, contributing 5980 pt-yrs of follow-up (median 1 year per patient; interquartile range [IQR]: 0.40–2.3). Pts in the different national registries had similar demographic characteristics (Table). More heterogeneity existed for RA disease characteristics: disability (by HAQ ranged from 0.9 (NORDMARDS) to 1.5 (ATTRA)) and disease activity (by DAS28 ranged from mean 4.2(SCQM) to mean 5.7(ATTRA)). The greatest difference across registries existed regarding treatment history prior to ABA initiation: the median number of prior inadequate responses (IR) on conventional DMARDs varied between a median of 1 ([IQR: 1–2], SCQM) and 4 ([IQR: 2–5 or 6], ATTRA, DANBIO); the number of prior IR on Biologics (*90%* anti-TNF agents) before first ABA initiation also varied between a median of 1 (SCQM) and 3 (DANBIO).

Registers (N)	NORDMARD (52)	SCQM (506)	ATTRA (215)	GISEA (375)	ORA (1032)	ARTIS (1019)	DANBIO (315)	BIOBADASER + Granada (487 + 40)
Follow-up (pt-years)	49.9	332.9	340.5	476.4	1748.5	1531.4	411.4	1089
Male %	13.5	21.0	20.9	13.3	20.9	20.7	19.0	19.7
Age (Yr), (Mean±SD)	51.3 ± 12.6	59.0 ± 13.2	50.1 ± 12.5	56.5 ± 12.8	58.1 ± 13.7	58.6 ± 12.4	56.0 ± 12.5	57.1 ± 12.7
RF %	59.6	71.6	70.1	73.6	71.3	–	84.3	87.3
Anti-CCP %	48.9	63.2	74.7	81.5	69.8	–	59.3	–
Disease Duration (Yr), (Mean ± SD)	14.8 ± 9.7	9.5 ± 13.2	11.2 ± 8.4	10.6 ± 8.5	15.6 ± 10.1	9.6 ± 12.4	11.4 ± 9.6	13.4 ± 11.2
Disability (HAQ), (Mean ± SD)	0.9 ± 0.5	1.1 ± 0.5	1.5 ± 0.5	1.4 ± 0.8	1.2 ± 0.7	1.3 ± 0.7	1.4 ± 0.7	–
DAS28-ESR, (Mean ± SD)	5.4 ± 1.1	4.2 ± 1.0	5.7 ± 1.1	5.0 ± 1.3	5.3 ± 1.3	5.1 ± 1.4	4.9 ± 1.2	–
Smoker %	23.1	24.0	22.8	22.3	9.8	–	63.5	11.5
BMI (kg/m^2), (Mean ± SD)	24.0 ± 4.1	25.9 ± 5.1	25.5 ± 4.9	25.8 ± 5.0	–	24.8 ± 1.5	26.3 ± 5.6	–
CRP (mg/l), (Mean ± SD)	24.2 ± 34.2	13.9 ± 16.3	25.7 ± 29.3	3.9 ± 6.6	2.5 ± 3.3	19.6 ± 26.5	–	–
ESR (mm/h), (Mean ± SD)	36.4 ± 28.1	25.9 ± 20.3	38.3 ± 24.3	34.4 ± 23.4	35.6 ± 27.7	30.4 ± 23.0	–	–
N° past c. DMARDs, (Median [IQR])	3 [2–4]	1 [0–2]	4 [2–5]	2 [2–3]	3 [2–4]	1 [1–2]	4 [3–6]	–
N° past Biologics, (Median [IQR])	2 [2–3]	1 [0–2]	–	1 [1–2]	2 [1–3]	2 [1–3]	3[2–4]	2 [1–4]
ABA drug retention med (yrs), (Median [IQR])	0.9 [0.5–2]	0.9 [0.8–1.1]	3.1 [2.6–3.9]	< 4 [3.7–∞]	1.8 [1.5–2.0]	1.0 [0.9–1.0]	1.3 [1.0–1.7]	2.6 [2.4–2.8]

We found significant differences in drug survival for ABA ($p < 0.001$; log rank test). The median drug retention ranged from > 4 years in GISEA, to around 1 year in SCQM, NORDMARDs or ARTIS. When examining only drug discontinuation for ineffectiveness the same trends were found (not shown).

Conclusion: Patient characteristics at ABA initiation varied across European countries, probably reflecting differences in eligibility criteria and prescription patterns. There were also large differences in ABA drug retention, with a trend to shorter ABA maintenance in countries with relatively liberal access to biologics. National differences need to be accounted for when analyzing pooled data from several national registries.

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2911

The Challenge To Develop a Multidimensional Computerized Adaptive Test For Fatigue In Rheumatoid Arthritis. Stephanie Nikolaus[1], Christina Bode[1], Erik Taal[1], Cees A.W. Glas[1] and Mart A.F.J. van de Laar[2]. [1]University of Twente, Enschede, Netherlands, [2]Medisch Spectrum Twente & University of Twente, Enschede, Netherlands.

Background/Purpose: Computerized adaptive testing (CAT) provides the possibility to measure patient reported outcomes precisely at individual level. As items are selected based on the previous answer of a patient, the number of items needed to achieve the same level of precision as obtained in a traditional questionnaire can be up to 40% less. Multidimensional CAT has the further advantage that simultaneous measurement of multiple dimensions increases the efficiency of the adaptive item selection procedure. Aim of the study was the development of a multidimensional CAT for fatigue in rheumatoid arthritis (RA) whereby the perspectives of patients as well as modern psychometrics were included. Reporting on its construction is informative for health professionals since multidimensional CATs are still rare in health care and clear guidelines for their development are lacking.

Methods: For the construction of a CAT, an item pool has to be developed and calibrated according to item response theory (IRT). Our item pool was based on interviews with patients and existing fatigue questionnaires. It was examined for content validity by a Delphi study and examined with IRT and factor analysis to explore its statistical dimensionality structure and to fit a multidimensional IRT model. It contained 196 items and three dimensions of fatigue: severity, impact and variability of fatigue. Based on a functional script, and the item information gained by IRT analyses, software was constructed and provided as online application. Responses to the CAT were simulated for about 1000 virtual persons to determine start- and stopping rules. The first version of the CAT was tested for its usability by patients.

Results: Simulations showed that the standard error for each of the dimensions was acceptably low under the following conditions: test length of 20 items, at least two random start items per dimension and at least five items per dimension. A low standard error is desirable as it indicates high measurement precision. The first version of the CAT was checked for programming problems and a usability test was conducted with 15 patients with RA. They filled in the CAT while thinking aloud and were interviewed about their experience with the new instrument. Patients' comments were positive; they experienced the CAT as clear, short and innovative. Some patients noticed that several items of the dimension "severity" were formulated in a similar way. The first version of the CAT fatigue RA will be demonstrated in this presentation.

Conclusion: This study provided the first version of a multidimensional CAT for fatigue in RA. In this presentation, further important issues for the construction of a multidimensional CAT will be discussed since the thorough development of measurement instruments is essential for precise and reliable assessment of patient reported outcomes. Only then, an instrument will be able to provide benefits for further research, possible interventions and/or the enhancement of the communication between patients and health professionals. At the moment, a validation study is taking place to examine the psychometric properties of the multidimensional CAT in more detail.

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2912

Integrating Patient Electronic Health Records With An Electronic Data Capture System In a Biologics Registry For Inflammatory Arthritides. Inge C. Olsen, Espen A. Haavardsholm, Tore K. Kvien, Ellen Moholt and Elisabeth Lie. Diakonhjemmet Hospital, Oslo, Norway.

Background/Purpose: The NORwegian Disease Modifying Anti-Rheumatic Drugs (NOR-DMARD) registry has since 2000 been registering DMARD use and response in five different Norwegian rheumatology departments (ref). Almost 5,000 biologic treatment courses in 3,500 patients have been included so far, together contributing with 19,000 study visits. Clinical information was previously recorded on paper, but from May 2012 an electronic data capture (EDC) system has been implemented.

Methods: A commercial EDC system, Viedoc™, has been set up in order to capture study data using electronic case report forms (e-CRFs). All centers have implemented a structured electronic health record (EHR), GoTreatIt™, which facilitates the export of un-identified source data. The workflow of a new patient is as follows:

1. The patient is included into the EDC system with patient information such as patient initial, date of birth and biologic treatment, and a visit is initiated with some information not collected in the EHR.
2. The EDC system generates a unique patient number, which is then registered in the EHR. This key enables the transfer from one system to the other.
3. Study data are then registered in the EHR, both by the treating physician/nurse (e.g. DAS28, ASDAS) and the patient (e.g. MHAQ, RAID).

Once a month each center extracts data in an XML-format from the site's EHR system. The contents of the extracted data are pre-specified and in accordance with the study protocol and e-CRF. The trial data manager uses a SAS program to parse the XML-files to a flat file format readable in the EDC system. The SAS program also runs a validation check against patient numbers, dates of birth and visit dates. We then import the flat files into the EDC system using the system's import routine, merging by patient number. The system facilitates an audit trail, so any changes are registered. A patient's e-CRF with all collected data is then accessible for both site and trial data management.

Results: From May 2012 to June 2013, 1697 patients on biologic treatment have been successfully included into the EDC system. A Contract Research Organization (CRO) NOK handled the previous paper-CRF system at a price of 115 NOK (20 USD) per visit/CRF. The money saved from this contract has already made the shift into EDC profitable, taken the set-up and licensing costs of the EDC system into consideration. In addition to this, the paper CRF system required considerable manual resources at each participating center, including entering, copying and mailing of completed CRFs and administration of inclusion IDs.

Conclusion: We have developed a novel methodology where we gather patient′s health record information from five different centers into a central trial database. We avoid time-consuming handling of paper-CRFs and eliminate data entry errors since we import source data directly into the study database. Compared to a standard e-CRF solution we gain efficacy effects because we avoid redundant registration, i.e. both in the patient journal and in the e-CRF system.

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2913

The Validity Of Patient-Reported Short-Term Complications Following Total Hip and Knee Arthroplast. Leslie R. Harrold[1], David Ayers[1], Regis O'Keefe[2], Courtland Lewis[3], Vincent Pellegrini[4] and Patricia D. Franklin[1]. [1]University of Massachusetts Medical School, Worcester, MA, [2]University of Rochester Medical Center, Rochester, NY, [3]Hartford Hospital, Hartford, CT, [4]Medical University of South Carolina, Charleston, SC.

Background/Purpose: Given the absence of national longitudinal data on patients who undergo total joint arthroplasty (TJA) and the limitations of hospital databases to capture information on patients who seek post-TJA care elsewhere, there is growing interest in using patient self-report to identify complications following surgery. We examined the concordance between patients self-report of potential short-term complications with review of available medical records.

Methods: Patients undergoing primary hip or knee arthroplasty from 7/1/11 through 12/3/12 participating in a tertiary care center were identified. Patients completed a 6-month post-operative survey regarding evaluation at an emergency department, day surgery or hospitalization for possible medical or mechanical complications following primary TKA/THA. We reviewed available inpatient and outpatient medical records and examined the sensitivity, specificity, positive predictive values and negative predictive values for patient-self report and medical records.

Results: There were 328 patients who had 339 surgeries and completed the 6-month questionnaire. Patients reported 46 medical encounters (emergency department, day surgery or inpatient care): 15 were excluded as they were hospitalizations >90 days following surgery or unlikely to be related to TJA (e.g., tooth extraction) resulting in a 10% possible event rate; 12% of the events occurred at hospitals different from the surgical hospital. Review of medical records revealed 6 additional medical encounters that patients had not mentioned including 3 hospitalizations following surgery (2 for leg pain and 1 for cellulitis) and 3 emergency department visits where no complications from TJA were identified. Patient self-report of emergency department, day surgery and inpatient care for possible complications was both sensitive (91%) and specific (100%). The positive predictive value was 100% and negative predictive value 99%.

Conclusion: We examined the concordance between patients' self-report of possible complications following surgery with review of available medical records and found a sensitivity of 91% and positive predictive value of 100% suggesting this approach may be used to augment current hospital post-discharge surveillance procedures. Patients appropriately reported medical care signifying potential adverse events following TJA. Given the new public reporting requirements of all post-TJA discharge complications, patient reported post-operative events may augment current hospital-specific surveillance procedures.

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ACR Concurrent Abstract Session
Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's - Clinical Aspects and Therapeutics III
Wednesday, October 30, 2013, 11:00 AM–12:30 PM

2914

Serum Proteins and Whole Blood Transcripts Suppressed By An Anti-Type I Interferon Receptor Monoclonal Antibody In Subjects With Systemic Sclerosis. Xiang Guo[1], Brandon W. Higgs[1], Christopher Kane[1], Chris, A. Morehouse[1], Zheng Liu[1], Liangwei Wang[1], Stephen Yoo[1], Yihong Yao[1], Lorin Roskos[2] and Wendy White[1]. [1]MedImmune, LLC, Gaithersburg, MD, [2]MedImmune, Gaithersburg, MD.

Background/Purpose: To identify serum markers that are modulated by an investigational human IgG1κ monoclonal antibody directed against subunit 1 of the type I interferon receptor (IFNAR1), MEDI-546, in systemic sclerosis (SSc) subjects.

Methods: An open-label single- and multiple-dose phase 1a clinical trial was conducted to evaluate the safety, tolerability, pharmacokinetics, immunogenicity, and pharmacodynamics (PD) of MEDI-546 in SSc patients (NCT00930683). Affymetrix whole genome arrays were used to measure transcript expression in whole blood before and after administration of MEDI-546, and a 5 gene type I IFN signature was used to assess the type I IFN activity and PD effects of MEDI-546 in SSc patients. Serum levels of 93 proteins were measured in 47 SSc patients and compared to 20 healthy controls to determine dysregulated analytes in SSc subjects using a Luminex-based immunoassay platform. Next, this same panel of analytes was used to determine the effects of MEDI-546 by comparing pre- and post-dose samples.

Results: Comparison of serum proteins between SSc subjects and healthy controls identified 35 dysregulated proteins, multiple of which were found to be associated with clinical/laboratory measurements, such as modified Rodnan Total Skin Score (mRTSS) and serum levels of collagen synthesis markers (PINP and PIIINP). Administration of MEDI-546 resulted in suppression of 8 proteins, among which 6 are type I IFN-inducible. Reduction of CXCL10 and soluble CD40L levels were significantly correlated with type I IFN gene signature suppression by MEDI-546. These two proteins are associated with T cell activation and movement, along with CXCL11 and IL2RA that also demonstrated significant down-regulation post-administration of MEDI-546. Furthermore, paired comparison of whole blood microarray data, pre- and post-MEDI-546 administration identified a list of differentially regulated transcripts enriched in regulatory functions by various IFN-related proteins, T cell receptor (TCR), nuclear factor of activated T cells (NFATC2), and CD40L. Thus, both proteomics and transcriptomic results suggest a suppressive effect of MEDI-546 in T cell activation and tissue infiltration. Using serum levels of CXCL10, CXCL11, soluble IL2R, and CD40L, we defined a protein index suppressible by type I IFN blockage. This index exhibited significant correlation with mRTSS and PIIINP levels at baseline, and down-regulation in the index was significantly associated with suppression of type I IFN gene signature post administration.

Conclusion: Our study demonstrated a robust overexpression of multiple serum proteins in SSc patients, particularly those with an elevated type I IFN gene signature score. Type I IFN blockade by MEDI-546 resulted in significant suppression of multiple type I IFN-associated proteins, particularly those related to T cell activation and

movement. A protein index suppressible by type I IFN blockage may serve as a responsive or predictive marker for type I IFN-targeted therapy in SSc subjects, which shall be examined in future clinical trials.

Disclosure: X. Guo, AstraZeneca, 3, AstraZeneca, 1; **B. W. Higgs**, MedImmune LLC, 3, AstraZeneca, 1; **C. Kane**, AstraZeneca, 1, AstraZeneca, 3; **C. A. Morehouse**, MedImmune LLC, 3; **Z. Liu**, MedImmune LLC, 3, AstraZeneca, 1; **L. Wang**, AstraZeneca, 1, MedImmune, 3; **S. Yoo**, AstraZeneca, 1, MedImmune, 3; **Y. Yao**, MedImmune, 3, AstraZeneca, 1; **L. Roskos**, AstraZeneca, 3, AstraZeneca, 1; **W. White**, AstraZeneca, 3, AstraZeneca, 1.

2915

Effect Of Menopause On Skin Thickening In Systemic Sclerosis. Evelyne Vinet[1], Sasha Bernatsky[1], Christian A. Pineau[1], Marie Hudson[2], Murray Baron[2] and the Canadian Scleroderma Research Group[3]. [1]McGill University Health Center, Montreal, QC, [2]McGill University, Montreal, QC, [3]McGill University Health Centre, Montreal, QC.

Background/Purpose: Menopause, characterized by a low estrogenic state, is associated with skin thinning, due to decreased extracellular matrix protein deposition by fibroblasts. Although systemic sclerosis (SSc) most commonly occurs near the end of the reproductive period and predominantly affects women, no one has investigated the impact of menopause on skin involvement in women with SSc. Thus, we aimed to evaluate the effect of menopause on skin thickening, as measured by the modified Rodnan skin score (MRSS), in women with SSc

Methods: We identified women with either limited or diffuse SSc, aged ≥ 18 years, enrolled within the Canadian Scleroderma Research Group (CSRG) cohort, between 2004–2011. As part of the CSRG cohort, subjects undergo annual assessments with standardized questionnaires and physical examinations.

We performed multivariate regression analyses using generalized estimating equation (GEE) to determine the effect of menopause on the MRSS, adjusting for relevant covariates (Table 1).

Table 1. Multivariate analysis of covariates' effect on the modified Rodnan skin score

Covariate	Multivariate effect estimate (95% CI[a])
Menopausal status	
Premenopausal	Reference
Postmenopausal	−2.62 (−4.44, −0.80)
Disease subtype	
Diffuse	Reference
Limited	−12.10 (−13.81, −10.39)
Menopause*disease type	2.04 (0.20, 3.88)
Time since baseline (years)	0.19 (0.04, 0.34)
Disease duration at baseline (years)	−0.05 (−0.07, −0.03)
Age at disease onset (years)	0.02 (−0.01, 0.05)
Race/ethnicity	
White	Reference
Black	−4.6 (−10.11, 0.91)
Other	−0.46 (−1.42, 0.50)
Smoking	
Never	Reference
Ever	−0.08 (−0.71, 0.55)
Oral contraceptive pill	
Past/never	Reference
Current	−0.60 (−3.03, 1.83)
Hormone replacement therapy	
Past/never	Reference
Current	−0.43 (−1.74, 0.88)
DMARDs[b]	
Past/never	Reference
Current	1.08 (0.22, 1.94)
Cyclophosphamide	
Never	Reference
Ever	0.73 (−0.60, 2.06)

[a]Confidence interval. [b]disease modifying antirheumatic drugs

Results: We identified 1070 women with SSc, contributing a total of 3546 observations over the study period. Of these women, at baseline, 65% had limited disease and 35% diffuse disease. At cohort entry, mean age and mean disease duration were respectively 55.5 [standard deviation (SD) 11.7] and 11.2 (SD 9.6) years, and 72% of subjects had already reached menopause. Overall, at baseline, the mean MRSS was 9.6 (SD 9.1), and in pre- and postmenopausal women, it was respectively 12.0 (SD 10.5) and 8.7 (SD 8.4).

In multivariate analyses (Table 1), we observed a substantial effect of postmenopausal status on the mean MRSS in women with diffuse disease subtype [-2.62 units, 95% confidence interval (CI) −4.44, −0.80] and significant interaction between menopausal status and disease subtype (2.04 units, 95% CI 0.20, 3.88). The effect of postmenopausal status on the mean MRSS was smaller in women with limited SSc (−0.58, 95% CI −1.50, 0.34).

In a multivariate analysis restricted to women with early disease (i.e. baseline disease duration less than 5 years), we observed a larger effect of postmenopausal status on the mean MRSS (compared to premenopausal status) both in women with diffuse (−3.36 units, 95% CI −5.87, −0.85) and limited SSc (−1.45, 95% CI −3.21, 0.31), as opposed to the effect estimates observed in the overall sample.

Conclusion: Our results suggest that menopause has a substantial effect on skin thickening in diffuse SSc, with postmenopausal status being associated with a lower mean MRSS compared to premenopausal status. This effect might be more pronounced in early disease (i.e. baseline disease duration of less than 5 years). Our findings should prompt further research on the role of estrogen on skin disease progression in SSc.

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2916

Anti-Fibrillarin Antibodies Are Associated With More Severe Gastrointestinal Involvement and Poorer Survival. Shervin Assassi[1], Marie Hudson[2], Maureen D. Mayes[1], Jennifer Walker[3], Murray Baron[2], Wendy Stevens[4], Karen Patterson[5], Tiffany Graham[1], Solene Tatibouet[2], James Wick[6], Matt Stephenson[6] and Marvin J. Fritzler[6]. [1]University of Texas Health Science Center at Houston, Houston, TX, [2]McGill University, Montreal, QC, [3]Flinders Medical Centre, Adelaide, Australia, [4]St Vincent's Hospital, Melbourne, Australia, [5]Institute of Medical and Veterinary Science, North Adelaide, Australia, [6]University of Calgary, Calgary, AB.

Background/Purpose: Anti-fibrillarin (U3-RNP) antibodies (AFA) are a relatively specific biomarker for systemic sclerosis (SSc). Previous studies have indicated a higher prevalence of AFA among African American patients. The examination of demographic and clinical correlates of AFA has been hampered by its low prevalence. Our objective was to examine the clinical correlates of AFA in a large study population consisting of three well-characterized SSc cohorts from Canada, Australia, and the USA.

Methods: A total of 1596 SSc patients enrolled in the Canadian Scleroderma Research Group (CSRG), the Australian Scleroderma Interest Group (ASIG), and the Genetics versus Environment In Scleroderma Outcome Study (GENISOS) were included in this study. AFA were determined by a line immunoassay (EUROLINE, Euroimmun, Lübeck, Germany). In addition to demographic data, associations with clinical data including modified Rodnan Skin Score (mRSS), history of digital ulcers/pits, calcinosis, arthritis, telangiectasia, scleroderma renal crisis, gastrointestinal (GI), pulmonary manifestations and pulmonary function test parameters were examined. An association with the overall mortality was also examined by Cox regression analysis

Results: The mean (± SD) age at enrollment and disease duration were 55 (± 12.8) and 9.5 (± 9.2) in the overall study population. Diffuse cutaneous involvement was present in 606 patients (38.6%). The study population was multi-ethnic consisting of 1,106 white, 71 African descent, 90 Hispanic, 48 Asian, and 39 Native North-American, and 8 Australian Aboriginal patients. A total of 52 patients (3.3%) had AFA. These antibodies were more common among African descent (OR: 2.92, p= 0.033) and Native North-American patients (OR=4.4, p=0.008).

In the multivariate analysis after adjustment for age at enrollment and ethnicity, patients with AFA had more frequently bacterial overgrowth requiring antibiotics (OR=2.5, p=0.048). There were also trends for an association with diffuse cutaneous involvement (OR=1.78, p=0.057) gastroesophageal reflux disease (OR=2.56, p=0.074) and need for parenteral nutrition (OR=3, p=0.099).

In Cox regression analysis after adjustment for age at enrollment and ethnicity, patients with AFA had poorer survival (HR: 2.36, $p<0.001$). This relationship remained significant even after addition of disease type to the model (HR: 2.28, $p<0.001$).

AFA were not associated with vascular, renal, or pulmonary manifestations of disease.

Conclusion: This large international study confirmed the association of AFA with African decent ethnicity and GI involvement. The large, well-characterized study population allowed us to make the following novel observations: AFA are associated with Native North-American ethnicity, diffuse cutaneous involvement, and poorer survival. The more severe GI involvement might explain partially the observed poorer survival in this serological subtype of SSc patients.

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2917

Mortality, Recurrence, and Hospital Course of Patients With Systemic Sclerosis Related Acute Intestinal Pseudo-Obstruction. Chris T. Derk[1], Nora Sandorfi[2], Shivani Purohit[3] and Christopher Mecoli[1]. [1]University of Pennsylvania, Philadelphia, PA, [2]Thomas Jefferson Univ Med Coll, Philadelphia, PA, [3]Rheumatology Division, Department of Medicine, Thomas Jefferson University, Philadelphia, PA.

Background/Purpose: Acute intestinal pseudo-obstruction is a rare gastrointestinal manifestation of SSc with little data existing as to the demographics, clinical course, outcomes and mortality of this disease. With this study we attempt to describe the mortality, recurrence and hospital course of these patients.

Methods: We undertook a retrospective chart review of patients admitted at two University Medical Centers in the city of Philadelphia over an 11.5 year period (1/2001-6/2012). Medical records were searched using ICD codes for SSc in combination with ICD codes for intestinal obstruction and fecal impaction. The medical records were then reviewed for those patients who were identified as true cases of pseudo-obstruction and we collected information regarding demographic data, laboratory and radiological studies, hospital presentation and course, medical and surgical treatment, outcomes and mortality. Continuous variables were analyzed by student's unpaired two-tailed t test while categorical variables by Fisher's exact test.

Results: A total of 1,733 admissions of SSc patients to the two hospitals were identified during the time period in question. 103 admissions had ICD codes matching our search criteria and from them 64 admissions were identified as true acute intestinal pseudo-obstruction cases in 37 unique SSc patients. From these cases 73% had spontaneous resolution with conservative measures of IV hydration and bowel rest, 11% underwent surgical resection and 26% required permanent total parenteral nutrition (TPN). Hospital course was for a mean of 12+12.5 days and there was 10% mortality. In a subgroup analysis of patients who had recurrent episodes of pseudo-obstruction this was more commonly seen in women ($p=0.01$), associated with symptoms of nausea at presentation ($p=0.04$) and resulted more often to the use of prolonged TPN ($p<0.0001$). Mortality was higher in male patients ($p=0.014$) who had low hemoglobin ($p<0.00008$) and serum albumin ($p<0.001$). Patients who underwent surgery were more likely to die as compared to patients who did not ($p<0.005$). A prolonged hospital stay was more often related to the use of a nasogastric tube ($p<0.05$) and surgical resection ($p<0.05$).

Conclusion: Acute intestinal pseudo-obstruction is a rare cause of hospitalization of SSc patients (64/1733 (3.7%) admissions). This is the largest study attempting to characterize this subpopulation of SSc patients. Based on our results most patients have spontaneous resolution with conservative measures such as bowel rest and IV hydration. Women were more likely to have recurrences and these patients were more likely to suffer from nausea at their presentation, and progressed to need permanent TPN. Mortality was higher in males especially in those patients with a low hemoglobin and serum albumin at presentation. Patients who underwent a surgical resection had a higher mortality and a more prolonged hospital stay.

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Survival After Lung Transplantation In Systemic Sclerosis. A Systematic Review. Irfan Y. Khan[1], Lianne G. Singer[2], Marc de Perrot[3], John T. Granton[4], Shaf Keshavjee[3], Cathy Chau[5], Amie T. Kron[6] and Sindhu R. Johnson[7]. [1]Pulmonary Hypertension Programme, University Health Network, University of Toronto, Toronto, ON, [2]Division of Respirology, University of Toronto; and Toronto Lung Transplant Program, University Health Network, Toronto, ON, [3]Toronto Lung Transplant Program, Division of Thoracic Surgery, University Health Network, University of Toronto, Toronto, ON, [4]Toronto Pulmonary Hypertension Programme, Toronto General Hospital and University of Toronto, Toronto, ON, [5]Toronto Scleroderma Research Program, Toronto Western Hospital, Mount Sinai Hospital, University of Toronto, Toronto, ON, [6]Toronto Scleroderma Research Program, Toronto Western Hospital, Mount Sinai Hospital, and University of Toronto, Toronto, ON, [7]Division of Rheumatology, Toronto Western Hospital, University Health Network Pulmonary Hypertension Programme, Toronto General Hospital, Mount Sinai Hospital and University of Toronto, Toronto, ON.

Background/Purpose: Lung transplantation is a life-saving option for systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH) and interstitial lung disease (SSc-ILD) patients. Yet, there is risk of post-transplantation mortality. The objective of this study was to evaluate survival of SSc patients post-lung transplantation. We secondarily evaluated SSc lung transplant recipient characteristics, and compared post-lung transplantation survival of SSc patients to non-SSc patients (idiopathic PAH, and ILD).

Methods: A systematic review of MEDLINE, EMBASE, Cochrane Central Registry of Controlled Trials and CINAHL (all inception to 2012) was performed to identify studies evaluating post-lung transplant survival in SSc compared to non-SSc patients. Two reviewers independently abstracted study and survival data using a standardized form.

Results: 226 citations were screened to identify 7 observational studies reporting SSc patients who underwent single lung, double lung, or heart-lung transplantation. Mean age at transplantations ranged 46–53 years. SSc post-transplantation survival ranged 69%–91% at 30-days, 69%–85% at 6-months, 59%–93% at 1-year, 49%–80% at 2-years, and 46%–79% at 3-years. ILD post-transplant survival was 80% at 30-days, 80%–90% at 6-months, 59%–83% at 2-years, and 69% at 3-years. IPAH post transplant survival was 79% at 30-days, 79%–90% at 6-months, and 74%–90% at 1-year. The reporting of overlapping cohorts potentially including the same patients precluded meta-analysis. Causes of death in SSc patients, when reported, included graft failure (n=6), infection (n=8), cardiac events (n=3), hemorrhagic stroke (n=1), respiratory failure (n=3), malignancy (n=2), pulmonary hypertension (n=1), complications of bronchiolitis obliterans syndrome (BOS) (n=1), anesthetic complication (n=1), and scleroderma renal crisis (n=1). There were no reports of recurrence of SSc in the lung allograft.

Conclusion: SSc survival post-lung transplantation is very good, and improving with time. The short-term and intermediate-term survival post-lung transplantation are similar to IPAH and ILD patients requiring lung transplantation. Future researchers should delineate the access process for lung transplantation and report the occurrence of acute rejection, infection, bronchiolitis obliterans syndrome, renal dysfunction and dialysis, gastroparesis, and need for tube feeding.

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The Clinical Utility Of Flow-Mediated Dilation In Systemic Sclerosis. Tracy M. Frech[1], Ashley Walker[2], Zachary Barrett-Okeefe[2], Russell Richardson[2], D. Walter Wray[2] and Anthony Donato[2]. [1]Salt Lake City VAMC, Salt Lake, UT, [2]University of Utah, Salt Lake, UT.

Background/Purpose: In systemic sclerosis (SSc, scleroderma) vasculopathy can result in the end-stage manifestation of a digital ulcer (DU). We hypothesized that bedside flow mediated dilatation (FMD) with ultrasound Doppler, which inexpensive, easy to use, and can directly measure endothelial function, could be used in SSc patients to identify features of patients at risk for DU.

Methods: 38 consecutive SSc patients were recruited from SSc Clinic and compared to 51 healthy controls (HC) which were age and body mass index (BMI) matched from the Veteran's Affair Medical Center Utah Vascular

Research Lab. Duplex ultrasonography was utilized to assess baseline vascular parameters forearm blood flow and brachial artery diameter. Afterward a blood pressure cuff was inflated to suprasystolic pressures (240 mmHg) distal to the ultrasound probe on the forearm and brief ischemia was induced for 5 minutes. Following cuff release measure of vascular reactivity (peak reactive hyperemia and hyperemia area under the curve [AUC]), brachial artery FMD (cm and % vasodilation) were obtained. A T-test was used to measure these continuous variables between SSc and HC, as well as SSc patients with DU and without DU.

Results: The SSc population's mean age was 54±3, with a BMI of 27±1, 33 were female, and 34 were white. Mean mRSS was 8; 31 with limited and 7 with diffuse cutaneous skin distribution. Mean duration of Raynaud's was 14.9 years and SSc (first non-Raynaud's symptom) was 11 years. Vasculopathy manifestations included 13 with DU, 6 with pulmonary arterial hypertension, and 1 with scleroderma renal crisis; 31 of these patients were on treatment with vasodilators. The age-matched HC group mean age was 51±2, with a BMI of 24±1 and included 42 females. None of the HC group had a history CVD, diabetes or respiratory disease and were not on prescription medication. None of the subjects in either group used tobacco.

Baseline vascular differences were seen in SSc patients displaying elevated forearm blood flow ($p=0.05$) and smaller brachial artery diameter ($p=0.002$) (Figure 1) versus age-matched healthy controls. Post-forearm occlusion, significant differences were seen in hyperemia ($p=0.00001$), shear stress ($p=0.002$), brachial artery FMD (cm, $p=0.001$ and %, $p=0.01$) compared to healthy controls (Figure 2). Within the SSc population brachial artery flow mediated dilation was significantly different between those with DU and without DU (cm, $p=0.05$ and %, $p=0.05$), whereas other parameters were similar ($p>0.31$).

Conclusion: Utilizing a non-invasive ultrasound technique developed for FMD we identified that SSc patients have significantly altered vascular structure and function which includes: smaller brachial artery diameter, blunted vascular reactivity, attenuated endothelial mediated dilation, despite an increased forearm flow at baseline. SSc patients with DU have a significantly attenuated endothelial mediated dilation, despite having an otherwise similar vascular structure and function profile to those SSc patients without DU. We believe that FMD has potential has clinical utility for identify SSc patients at risk for DU and monitoring response to endothelial-based therapeutics.

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